# Studies on the Diastereoselective Barbier-Type Reactions for the Construction of Unnatural Amino Acid Derivatives Having Contiguous Stereocenters

*A Thesis*

*Submitted for the Degree of*

**Doctor of Philosophy**

*By*

*Nayyar Ahmad Aslam*

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*Department of Chemical Sciences,*
*Indian Institute of Science Education and Research (IISER) Mohali,*
*Sector 81, Knowledge City, S. A. S. Nagar, Manauli PO, Mohali, 140306.*
*Punjab, India.*

*Dedicated to*

***MY BELOVED PARENTS***

***AND NAUGHTY BROTHERS***

***(EZAZ AND FAKHAR).....***

# Declaration

I hereby declare that the matter embodied in this thesis entitled "*Studies on the Diastereoselective Barbier-Type Reactions for the Construction of Unnatural Amino Acid Derivatives Having Contiguous Stereocenters*" is the result of investigations carried out by me under the supervision of **Dr. S. Arulananda Babu** at the Department of Chemical Sciences, Indian Institute of Science Education and Research (IISER) Mohali, SAS Nagar Mohali, India. This work has not been submitted in part or full for the award of any degree, a diploma or a fellowship to any other university or institute. Whenever contributions of others are involved, every effort is made to indicate it clearly with due acknowledgements. In keeping with the general practice in reporting scientific observations, acknowledgements has been made whenever the work was described based on the findings of other investigators. Any omission that might have occurred due to oversight or error in judgment is regretted. A complete bibliography of the books and journals referred to is given at the end of the thesis.

**Nayyar Ahmad Aslam**

Date:

Place:

In my capacity as the supervisor of the candidate's thesis work, I certify that the above statements by the candidate are true to the best of my knowledge.

**Dr. S. Arulananda Babu**

*Associate Professor*

*Department of Chemical Sciences*

*Indian Institute of Science Education and Research Mohali*

Date:

Place:

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## List of publications from thesis work

- **Aslam, N. A.**; Rajkumar, V.; Reddy, C.; Yasuda, M.; Baba, A.; Babu, S. A.* *Eur. J. Org. Chem.* **2012**, 4395.

  Title: Indium-mediated addition of γ-substituted allylic halides to *N*-aryl α-imino esters: diastereoselective production of β,β'-disubstituted α-amino acid derivatives with two contiguous stereocenters.

- **Aslam, N. A.**; Babu, S. A.*; Arya, J. S.; Yasuda, M.; Baba, A. *Tetrahedron* **2013**, *69*, 6598.

  Title: Chelation-controlled diastereoselective construction of *N*-aryl-, *N*-acyl/tosylhydrazono β-substituted aspartate derivatives via Barbier-type reaction.

- **Aslam, N. A.**; Babu, S. A.* *Tetrahedron* **2014**, *70*, 6402.

  Title: Direct lactonization of α-amino γ,δ-unsaturated carboxylic acid esters via olefin activation: stereo- and regioselective production of homoserine lactone scaffolds having contiguous stereocenters.

- **Aslam, N. A.**; Babu, S. A.*; Rani, S.; Mahajan, S.; Solanki, J.; Yasuda, M.; Baba, A. *Eur. J. Org. Chem.* **2015**, 4168.

  Title: Diastereoselective construction of 3-aminooxindoles with adjacent stereocenters: stereocontrolled addition of γ-substituted allylindiums to isatin ketimines.

- **Aslam, N. A.**; Babu, S. A.* Manuscript under preparation.

  Title: Stereoselective addition of α-halo esters to isatin-derived *tert*-butylsufinylketimines under Reformatsky/Barbier-type reaction conditions: synthesis of enantiomerically enriched oxindolinyl β-amino acid derivatives.

## List of publications as a co-author

- Rajkumar, V.; **Aslam, N. A.**; Reddy, C.; Babu, S. A.* *Synlett* **2012**, 549.

  Title: Unactivated norbornenes in [3+2] cycloadditions: remarkably stereocontrolled entry into norbornane-fused spirooxindolopyrrolidines, spiro-1,3-indandionolylpyrrolidines and spirooxindolopyrrolizidines.

- Reddy, C.; Babu, S. A.*; **Aslam, N. A.**; Rajkumar, V. *Eur. J. Org. Chem.* **2013**, 2362.
  Title: Construction of functionalized carbocycles having contiguous tertiary carbinol and all-carbon stereogenic centers.
- Naveen; **Aslam, N. A.**; Babu, S. A.*; Singh, D. K.; Rana, A. *Synlett* **2014**, *25*, 2201.
  Title: Magnetically separable nano $Fe_3O_4$ catalyzed direct azidation of allylic and benzylic alcohols followed by copper-catalyzed click reaction.
- Reddy, C.; Babu, S. A.*; **Aslam, N. A.** *RSC Advances* **2014**, *4*, 40199.
  Title: Indium-assisted aluminium-based stereoselective allylation of prostereogenic α,α-disubstituted cycloalkanones and imines.
- Naveen; Babu, S. A.*; Kaur, G.; **Aslam, N. A.**; Karanam, M. *RSC Advances* **2014**, *4*, 18904.
  Title: Glaser–Eglinton–Hay sp–sp coupling and macrocyclization: construction of a new class of polyether macrocycles having a 1,3-diyne unit.
- Naveen; Babu, S. A.*; **Aslam, N. A.**; Sandhu, A.; Singh, D. K.; Rana, A. *Tetrahedron* **2015**, 71, 7026.
  Title: Direct azidation of allylic/benzylic alcohols and ethers followed by the click reaction: one-pot synthesis of 1,2,3-triazoles and 1,2,3-triazole moiety embedded macrocycles.

## Patent applications filed

- Inventors: Srinivasarao Arulananda Babu and Nayyar Ahmad Aslam. Patent Application No. 2811/DEL/2011. Dt 27th September, 2011 entitled *"Stereoselective Preparation of β,β-Disubstituted and β,β,β-Trisubstituted α-Amino Acid Derivatives at Least With Two Contiguous Stereocenters.*"

- Inventors: Srinivasarao Arulananda Babu and Nayyar Ahmad Aslam. Patent Application No. 295/DEL/2013. Dt 2nd February, 2013 entitled *"A Stereoselective Method of preparation of β-Alkyl N-Substituted Aspartic Acid Derivatives*."

- Inventors: Srinivasarao Arulananda Babu and Nayyar Ahmad Aslam. Patent Application No. 3400/DEL/2013, Dt 20th Nov 2013 entitled *"Process for the Preparation of Homoserine Lactones Derivatives*."

## Book chapter

- Babu, S. A.*; Padmavathi, R.; **Aslam, N. A.**; Rajkumar, V. *Recent Developments on the Synthesis and Applications of Natural Products-Inspired Spirooxindole Frameworks* in Studies in Natural Products Chemistry, 2015, vol. 46, chap. 8, pp 227.

## Conferences/Symposia

- Oral presentation entitled "Barbier-Type In-Mediated Addition of *γ*-Substituted Allylic Halides to *N*-Aryl-*α*-Imino Esters: Diastereoselective Production of *γ,δ*-Unsaturated-*β,β′*-Disubstituted-*N*-Aryl *α*-Amino Acid Derivatives" **N. A. Aslam,** V. Rajkumar, C. Reddy, M. Yasuda, A. Baba, S. A. Babu at the *7th Junior National Organic Symposium (J-NOST)* held at the Indian Institute of Science Education and Research (IISER) Mohali, S. A. S. Nagar Mohali, India (14-17 December, 2011).

- Participated in the *7th RSC-CRSI Symposium in Chemistry* held at the Banaras Hindu University (BHU), Varanasi, India (31st January, 2013).

- Poster presentation entitled "Indium-Mediated Exceedingly Diastereoselective Protocol for the Construction of Functionalized Aspartic Acid (*α*-Amino Acid) Derivatives with Two Contiguous Stereocenters" **N. A. Aslam**, Arya J. S. and S. A. Babu at the *15th CRSI National Symposium in Chemistry* held at the Banaras Hindu University (BHU), Varanasi, India (1-3 February, 2013).

- Participated in the *National Seminar on Crystallography 43A* held at the Indian Institute of Science Education and Research (IISER) Mohali, S. A. S. Nagar Mohali, India (28-30 March, 2014).

- Participated as nominated candidate in the *3rd Summit of South Asian Science Academies and AASSA (Association of Academies and Societies of Sciences in Asia) General Assembly* held at the Indian National Science Academy (INSA), New Delhi, India (13-17 October, 2014).

# Contents

# Preamble

The synthesis of urea by Friedrich Wöhler in 1828 and acetic acid by Hermann Kolbe in 1845, initiated a field of chemical science that has evolved remarkably during the past decades and resulted in a number of achievements that have strongly contributed to the well-being of the modern societies. In this process, the 19$^{th}$ century witnessed the birth of the "synthetic organic chemistry (or) organic synthesis discipline" that started a new era in the field of chemical sciences.[1] Imprecise categorization of synthetic organic chemistry can give rise to mainly two subdivisions which often overlap and mingle into each other; development of synthetic methodologies and application of the methodologies in the synthesis of target molecules. Nevertheless, the eventual goal is always to contribute towards the synthesis of simple or more complex molecules with biological or physical significance.[2]

Paul A. Wender gave a description for an ideal organic synthesis, which states that the target molecule is prepared from readily available, inexpensive starting materials in one simple, safe, environmentally acceptable and resource-effective operation that proceeds quickly and in quantitative yield.[3a] Though, in many occasions, it is almost impossible to practice an ideal synthesis; however, the ideal synthesis as a concept can inspire and guide us to develop new synthetic methodologies by touching the boundaries of an ideal organic synthesis. The best example of an ideal synthetic organic chemist is the *Nature*, which performs multistep-cascade reactions with the maximum selectivity control.[3b] Notably, implementation of such kind of cascade approaches in the chemical production requires thorough knowledge of individual transformation steps and the mechanism of the reactions. Furthermore, optimization of each step is required, (a) to find out an ideal reaction condition, (b) to obtain the excellent conversion and chemo-, regio- and stereoselectivity, (c) to minimize the formation of side products and (d) to maximize the yield of the final product.

Attempting to be a part of such community of synthetic chemists, in this thesis work, efforts have been put forth to present a tiny contribution to the vast field of synthetic organic chemistry. Precisely, the work discussed in this thesis deals with the development of simple routes for the stereoselective synthesis of certain new classes of unnatural amino acid derivatives.

### 2.1. Non proteinogenic (unnatural) amino acids.

Amino acids are vital to life as they are building blocks of peptides, proteins and a number of natural products and exhibit several important and diverse functions.[4] Amino acids are also used as additives in food products, pharmaceuticals and agrochemicals.[5] Notably, amino acids constitute an important class of molecules which serve as building materials, synthetic reagents or catalysts in chemical sciences.[6a,b,7-12]

Research on proteins, peptides and related systems is considered as important and fundamental areas of science. However, the fundamental building blocks of proteins and peptides are a small number of proteinogenic amino acids.[6c] Therefore, to understand and study or mimic the chemistry of proteins and peptides, in the past decades, a vast amount of synthetic work dealing with the synthesis of unnatural amino acids has been reported. In addition to the synthetically derived unnatural amino acid derivatives, several non-proteinogenic amino acids called as unusual amino acids are also found in the nature. However, they are not naturally encoded or found in the genetic code of organisms.[7] Some of the unusual amino acids are produced by microorganisms and have evolved to interfere with biochemical pathways of other organisms. Thus, in spite of not being encoded by the genetic code as proteinogenic amino acids, many non-standard amino acids are found in proteins (see Figure 1 for representative examples of structurally modified unusual amino acids). The unusual amino acids which are formed by post translational modifications, are often essential for the function or regulation of a protein.[8] For example, carboxyglutamic acid[8a] (**1a**, Figure 1) formed by carboxylation of glutamate provides better binding ability to calcium ions in gamma-carboxy glutamate. In the case of 4-hydroxyproline[8b] (**1b**, Figure 1), the hydroxyl group is critical for proline to stabilize the triple helical structure of collagen through additional water mediated hydrogen bonds, which in turn helps to maintain the connective tissues. Certain amino acid analogues prop up translational errors that result in irregular protein synthesis and have been used to understand the effects of protein misfolding in a variety of physiological and pathological situations.[9] For example, canavanine (**1i**, Figure 1) and azatidine-2-carboxylic acid (**1j**, Figure 1) exhibit greater degree of dose dependent toxicity to primary rat neurons culture as compared to astrocytes.[9a]

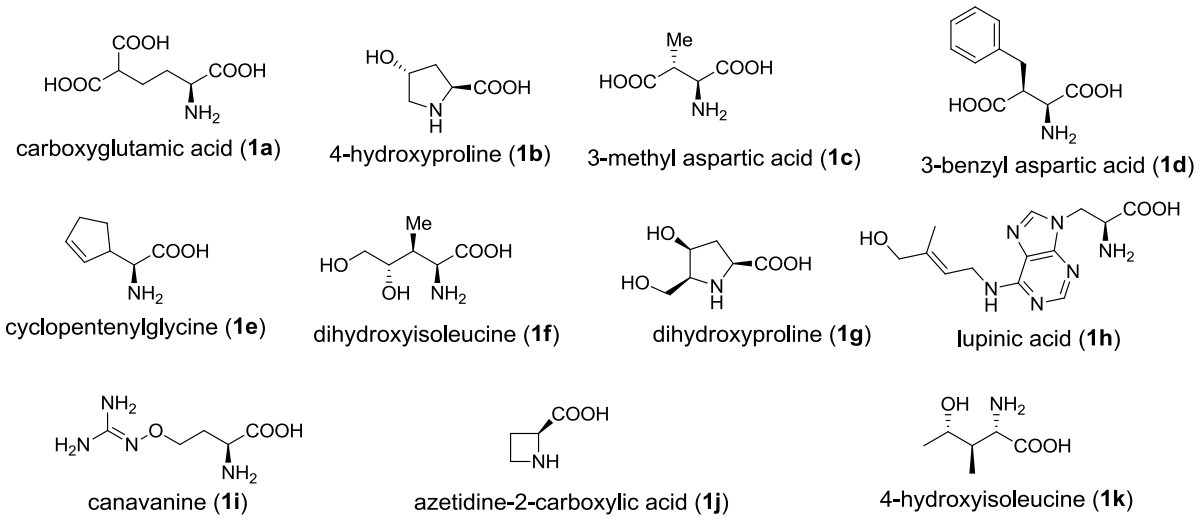



**Figure 1.** Structurally modified amino acids.

In particular, amongst the families of structurally modified amino acids, the β,β'-disubstituted α-amino acid family is relatively well known.[10a] The β,β'-disubstituted α-amino acids are also one of the prevalent substructures found in a large number of natural products;[4,10a-c] e.g. 4-hydroxyisoleucine (**1k**), halipeptin A (**2a**), nikkomycin B (**2b**), salinosporamide A (**2c**), cyclomarine C (**2d**), furanomycin (**2g**), celogentin, lysobactin, papuamides, tamandarin B and callipeltin A (Figures 1 and 2). Several β,β'-disubstituted α-amino acids are found to exhibit a wide range of biological activities[10a] (e.g. cytotoxic, anti-HIV, antiviral, proteosome inhibition, antidiabetic, etc). Along this line, the β-alkyl aspartates which belong to the family of β-substituted α-amino acids (unnatural amino acid derivatives) constitute an important class of nonproteinogenic α-amino acid systems. Several β-alkyl aspartates have been reported to exhibit diverse biological and biochemical actions.[11] For example, (a) 3-methyl aspartic acid[11g] (**1c**) occurs as a component of certain members of the highly toxic microcystin and nodularin families of natural products and cyclic peptides (which are known to be powerful inhibitors of several serine and threonine phosphatases), and (b) 3-benzyl aspartic acid (**1d**) acts as blocker of excitatory amino acid transporters (EAAT).[11a,h]

The functions and properties of native peptides vary from highly specific antibiotics or cytotoxic antitumor drugs to hormones, neurotransmitters, immunomodulators, etc.[12] For example, cecropin-melittin hybrid peptide,[12b] protect fish against infection caused by the fish pathogen *Vibrio anguillarum*. Granulocyte-colony stimulating factor (G-CSF)[12c] is a

glycoprotein that stimulates the bone marrow to produce white blood cells and stem cells and release them into the bloodstream, thereby acting as an immunomodulator. Despite the potential utility as therapeutic agents, there are problems connected with the use of natural peptides, due to the low stability against proteolysis, resulting in a short duration of *in vivo* activity and a low bioavailability.[13] One way to overcome some of the disadvantages of native peptides is to use the modified peptides, called as peptidomimetics, which are constituted from unnatural amino acids. For example, the incorporation of β,β'-disubstituted unnatural amino acids in a peptide chain results in higher stability against proteases and increased levels of lipophilicity and bioavailability.[14] Additionally, by incorporating the unnatural amino acids in a peptide chain, it is found that the conformational rigidity of the peptide chain also increases, which is expected to be helpful in increased selectivity towards biological receptors.[14]

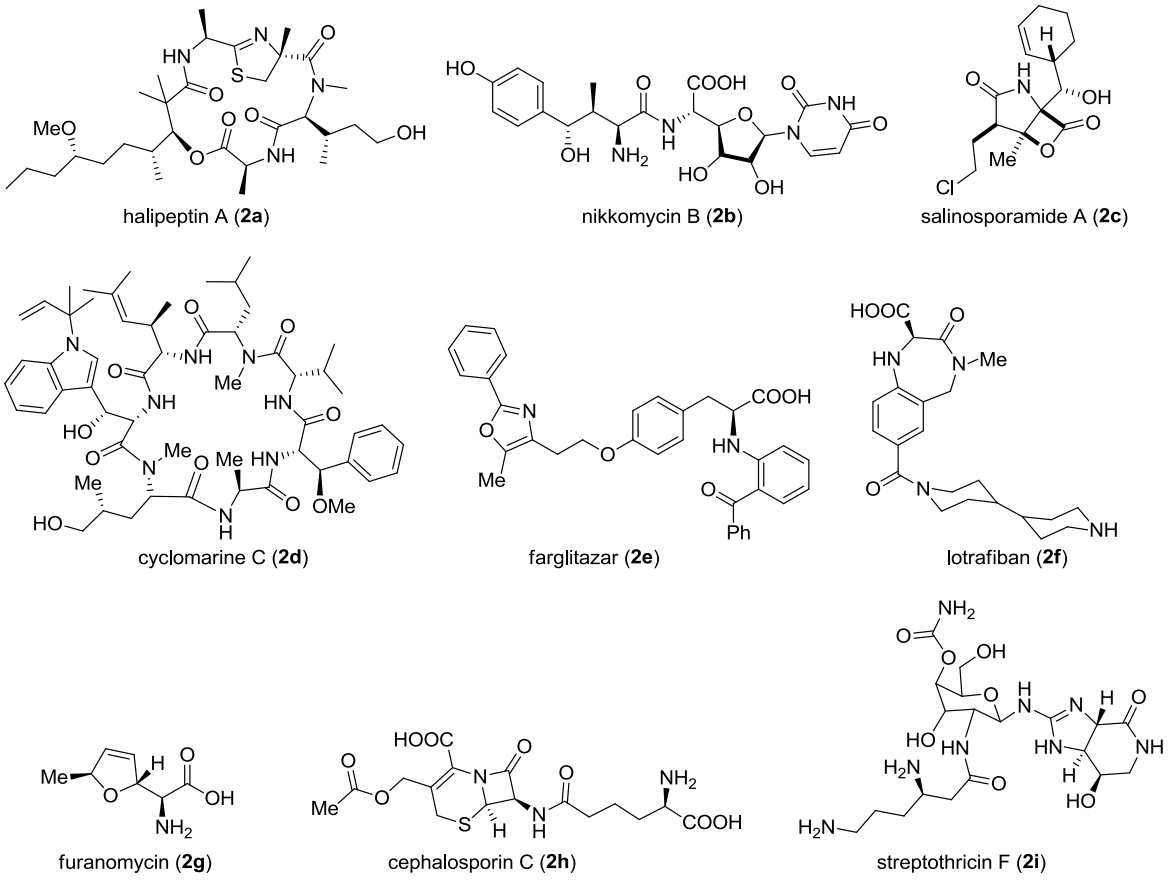



**Figure 2.** Natural products with unnatural amino acid component as their sub-structural unit.

### *N*-Protected α-amino acids.

*N*-Protected α-amino acids containing peptides, isolated from a variety of sources[10c] and secondary metabolites of these peptides (e.g. vancomycin, cyclosporin, actinomycin D) have gained pharmaceutical importance due to the physical properties and chemical stability bestowed by the *N*-protected α-amino acids present in their structures.[10c] Additionally, the *N*-protected α-amino acids also form the core framework of various medicinal agents.[11f] Many of the *N*-protected α-amino acid derivatives are reported to display promising biological activities,[4,10,11] e.g. opaviraline (**2n**) acts as the non-nucleoside reverse transcriptase inhibitor, farglitazar (**2e**) function as the insulin sensitizer, lotrafiban (SB-214857; **2f**) acts as anticoagulant factor Xa inhibitor and platelet aggregation inhibitor GP IIb/IIIa antagonist (Figures 2 and 3).

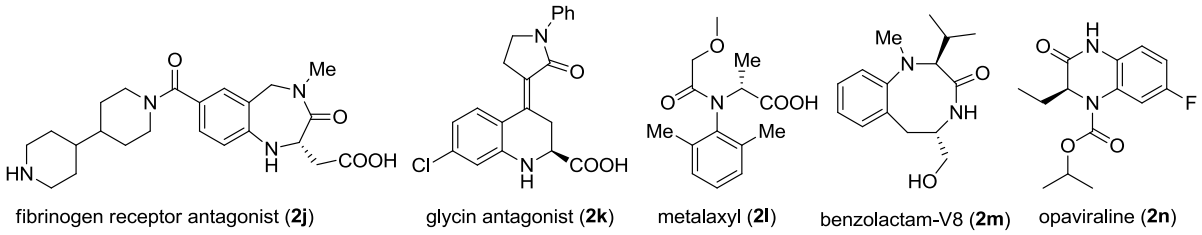



**Figure 3.** *N*-Aryl-α-amino acids as part of potential biologically important molecules.

Specifically, *N*-aryl-α-amino acids constitute the common core structural unit for a number of synthetically challenging and medicinally important agents. These agents include protein kinase C (PKC) activators, indolactam-V,[10f] and its analogue benzolactam-V8 (**2m**);[10g] Ciba's phenylamide fungicide, (*R*)-metalaxyl (**2l**);[10h] fibrinogen receptor antagonist SB 214857 (**2j**);[10i] angiotensin-converting-enzyme inhibitors (ACE inhibitors);[10j] and antiulcer agents[10k] (Figure 3). It is worth to mention that a large number of synthetically derived unnatural amino acids are also used to control the plant growth and plant diseases.[14]

As a result, the synthesis and evaluation of the biological properties of unnatural amino acids considered as an important research area of chemical biology and drug discovery, which has received considerable attention over a long period.[10-15] Due to the immense biological importance and because of their value as synthetic building blocks, numerous synthetic methods have been developed for the synthesis of several unnatural amino acids and their

derivatives and a vast amount of literature reports are available in this regard.[4,18-46] In view of the theme of this thesis work, the representative background works, especially, related to synthesis of β-substituted α-amino acid and β,β'-disubstituted α-amino acid derivatives have been presented in the following sections.

### 2.2. Synthetic approaches towards unnatural amino acid derivatives.

As mentioned earlier, amongst the family of synthetically derived unnatural amino acids, the β-substituted α-amino acid and β,β'-disubstituted α-amino acid derivatives are relatively popular and it is worth to mention that the β-substituted α-amino acid and β,β'-disubstituted α-amino acid derivatives are prevalent in a large number of natural products.[4,10] Given the importance of the β-substituted α-amino acid and β,β'-disubstituted α-amino acid derivatives, several methods have been reported in the literature dealing with their synthesis (Figure 4).[10a-c,10l] Some of the outstanding synthetic approaches dealing with the synthesis of β-substituted unnatural amino acid derivatives are presented in the subsequent sections with the main emphasis on Barbier- type metal mediated nucleophilic addition reactions.

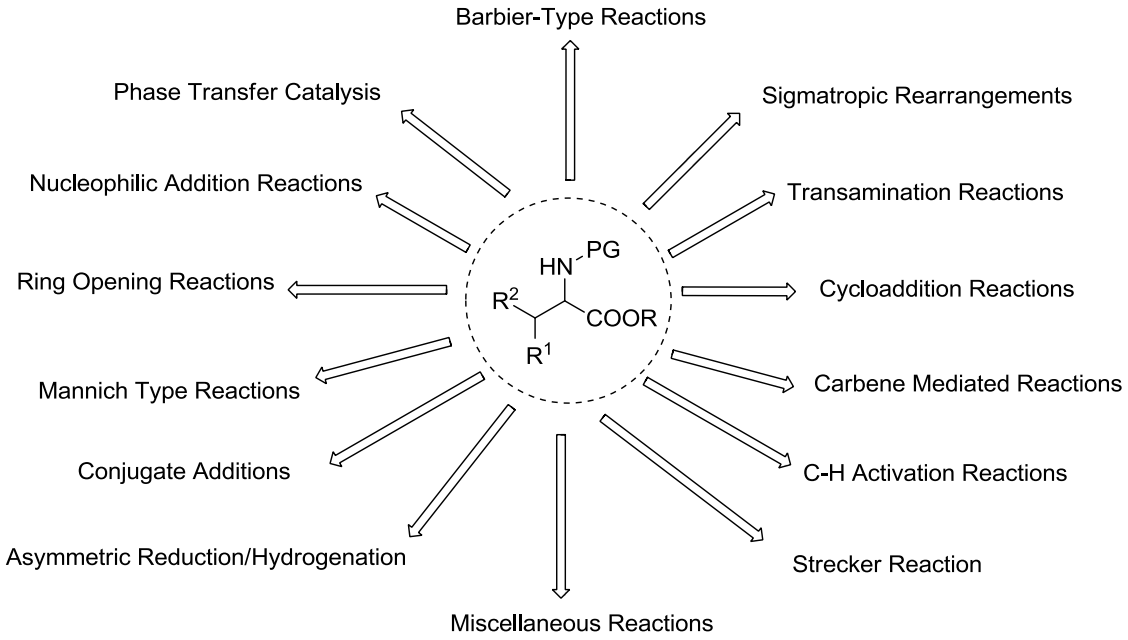
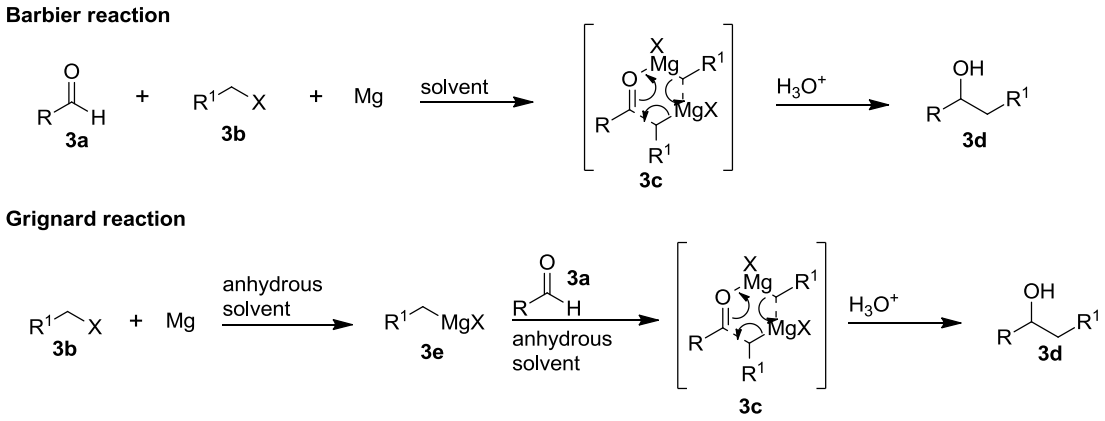



**Figure 4.** Synthetic approaches towards β-substituted α-amino acid and β,β'-disubstituted α-amino acid derivatives.

### 2.2.1. Barbier- and Reformatsky-type reaction and their application for the synthesis of β-substituted α-amino acid and β,β'-disubstituted α-amino acid derivatives.

Construction of carbon–carbon bond is one of the key transformations in synthetic organic chemistry. The nucleophilic addition to carbonyl groups and imines is one of the most exercised C–C bond forming reactions.[16,17] Barbier reaction[16a] (formally an equivalent of Grignard reaction) is a single step reaction, which involves the direct addition of an alkyl halide **3b** to a carbonyl compound **3a** in the presence of magnesium metal in a one-pot manner (Scheme 1). On the other hand, Grignard reaction[16b] is a two-step reaction, which involves the addition of an organomagnesium reagent **3e** that is separately prepared from the corresponding organohalide **3b** and magnesium metal, to a carbonyl compound **3a** (Scheme 1). The Grignard reaction was accompanied with some drawbacks, such as (a) it requires the use of an anhydrous solvent and (b) inability to tolerate a number of common functional groups such as those containing acidic protons (e.g. -OH, -$NH_2$, -COOH). On the other hand, especially, the Barbier-type allylation procedure,[17,18] which is typically mediated by indium, zinc, tin or bismuth does not require anhydrous conditions.[16c,d]



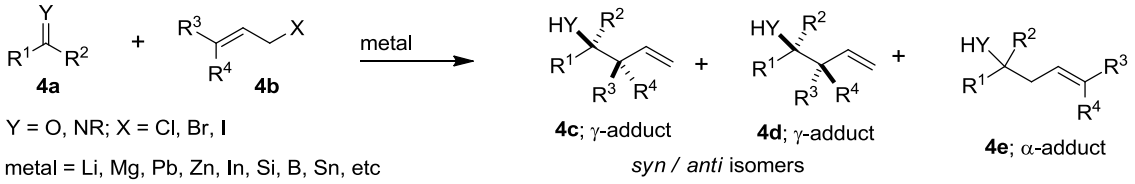

**Scheme 1.** Barbier and Grignard reactions.

### Indium-mediated Barbier-type allylation reactions.

Among the organometallic reagents used in the reactions involving the organometallic nucleophilic addition to carbonyl and imino groups, the addition of allylmetals is considered as a fundamental C-C bond forming method, which is widely used for synthesizing functionalized acyclic- or cyclic- homoallylic alcohols/amines (Scheme 2).[17,18] Notably, the

synthetic step involving the addition of allylmetals to carbonyl (C=O) and imino (C=N) functional groups is considered as one of the important step in multistep synthesis.[17] This is because, after the allylation reaction, the olefin moiety present in the products (homoallylic alcohols/amines) can be subjected to a wide range of functional group transformations such as ring closing metathesis, dihydroxylation, hydrogenation, cycloaddition, ozonolysis and hydration, etc.[17,18]

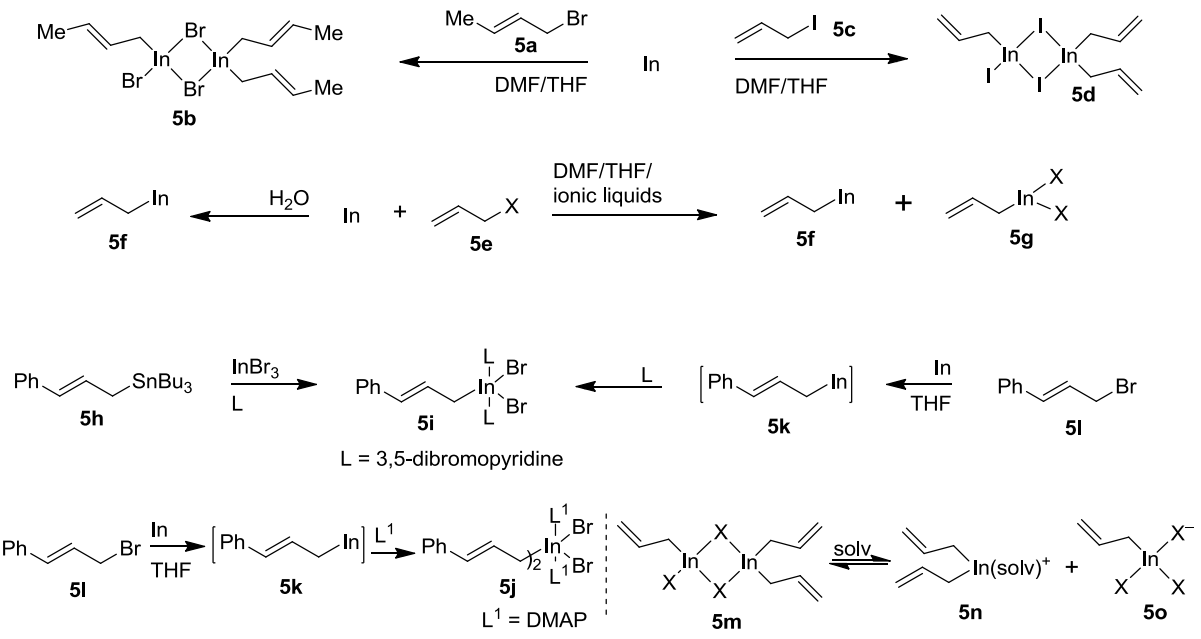
A variety of allylmetal reagents prepared using metals, such as Li,[25] Mg,[21] Sn,[22] Zn,[20] Bi,[19] Mn,[24] Pb,[26] Ce,[27] Cr,[24a-d] Ti,[23] B,[17g] etc have been very well studied for performing, typically, the Barbier-type allylation of the carbonyl and imino functional groups.[17-27] Alternatively, in recent years, the Barbier-type reaction of allylmetals with carbonyl and imino functional groups, involving some of the above mentioned metals along with other metals[17-27] such as In, Ga, Zn, Sn and Bi, etc, has been well documented. It is worth to mention that Barbier-type reaction protocol has an advantage as the prior preparation of allylmetal reagents is not required and the reaction can be performed by directly reacting the substrate, metal powder and allyl halide. Amongst the metals used for performing the Barbier-type allylation reaction, the indium metal-based Barbier-type addition of allylic reagents to carbonyl and imino systems has been well appreciated.[17,18] Often the indium metal-based Barbier-type addition of allylic reagents to carbonyl and imino systems has offered satisfactory yields of the corresponding homoallylic alcohols/amines with very high regio- as well as stereoselectivity and has been applied for the synthesis of a variety of functionalized molecules containing one or more stereocenters (Scheme 2).[17,18]




**Scheme 2.** Barbier-type reactions of carbonyl compounds and imines.

Many studies have been carried out to explore the identity of the allylindium species in the Barbier type allylation reaction and the nature of the reactive allylindium species has yet to be fully confirmed.[28] It was proposed that indium-mediated allylation in aqueous medium proceeds on the metal surface with a single electron transfer (SET) from the metal to the allyl

bromide to generate a reactive radical anion species.[28a] This proposal lost its probability with time, because of the evidences put forth by advanced studies. Madsen and Fristrup *et al.* eradicated the involvement of radicals in the rate determining step and claimed that the Barbier-type allylation in aqueous media proceeds through a discrete allylmetal species which subsequently reacts with a carbonyl group involving a cyclic transition state.[28b] A computational study further supported the involvement of a six-membered transition state. This conclusion was supported by the earlier work of Madsen and Norrby *et al.*, where the Hammett study performed by the authors did not give any indication on the involvement of radical mechanism, but an organometallic reagent was suggested to be involved in the reaction.[28c] Subsequent studies led to the general acceptance that the allylindium intermediate is involved in the reactions as predicted by Araki and Chan.[28d,28g]




**Scheme 3.** Plausible allylindium species (**5b**, **5d**, **5f**, **5g**, **5k**, **5n**, **5o**).

Araki *et al.* proposed the formation of allylindium sesquihalide $allyl_3In_2X_3$ (**5b** or **5d**) in polar organic solvents such as THF or DMF (Scheme 3).[28d,28e] Their proposal is based on the observance of two sets of allylic methylene signals at $\delta$ 1.75 and 2.02 ppm with a relative intensity of 2:1 in the proton NMR spectrum, when indium was mixed with an allyl halide. This proposal is in agreement with results obtained by Gynane and Worrall in 1974 from the

insertion of indium into an alkyl halide.[28f] Chan and Yang proposed the allylindium$^{I}$ **5f** as the reactive species in the indium-mediated allylation reaction based on the $^{1}$H NMR study (Scheme 3).[28g]

Later, Chan *et al.* indicated that the reaction of allyl bromide with metallic indium (in polar organic solvent or in ionic liquid) produces a mixture of two allylindium species, namely allyl-In$^{I}$ (**5f**) and allyl-In$^{I}X_2$ (**5g**) at the initial stage (Scheme 3)[28h] with predominance of allylindium dihalide (allyl-In$^{I}X_2$, **5g**) as the reaction proceeds. The formation of indium$^{I}$ instead of indium$^{III}$ intermediate is consistent with the observation that indium has a relatively low first ionization potential but relatively high second or third ionization potentials.[28i] On the basis of these observations, Chan and Yang hypothesized that two types of allylindium species were in fact produced in DMF and one of the species corresponds to allylindium$^{I}$. They thought that the signal observed at δ 2.02 ppm as earlier, might be allylindium$^{III}$ dibromide or its dimer; because allylindium$^{III}$ dibromide prepared from the insertion of In$^{I}$Br into allyl bromide also displayed the same signal at δ 2.02 ppm, which is also consistent with what Araki[28k] had observed in the preparation of allylindium$^{III}$ diiodide from the reaction of In$^{I}$I with allyl iodide in THF. Hence, they proposed that the two species formed, either in organic solvent or ionic liquid, are allylindium$^{I}$ and allylindium$^{III}$ dibromide. Few years later, Preite and Pérez-Carvajal[28j] observed an analogous phenomenon in their studies and arrived at the same conclusion as Chan and Yang.

Recently, Baba and co-workers studied the allylindium species generated from different methods through X-ray crystallographic analysis.[28l-28n] When cinnamyl bromide (**5l**) was treated with indium in THF, $^{1}$H NMR monitoring showed the presence of two types of allylindium species, subsequently they managed to solve the X-ray structure of these allylindium species upon complexing them separately with two different pyridine ligands (L and L$^{1}$) (Scheme 3). The X-ray crystallographic analysis indicated the formation of a cinnamylindium$^{III}$ dibromide complex (**5i**) and a dicinnamylindium$^{III}$ bromide complex **5j**. In addition, authenticity of the cinnamylindium$^{III}$ dibromide complex **5i** was further confirmed by the fact that its NMR signals were identical to those of authentic cinnamylindium$^{III}$ dibromide (**5i**), synthesized *via* transmetalation between tributyl-(cinnamyl)stannane (**5h**) and $InBr_3$, followed by complexation with ligand (L). Crystals of allylindium$^{III}$ dibromide

and diallylindium$^{III}$ bromide were also obtained in a similar manner.[28m] Because the actual organoindium species formed in the reaction were isolated and analyzed by X-ray crystallography, findings of the Baba group may be more convincing and conclusive.

Lately, a new method attempting at determination of the allylindium species in DMF, THF, and water, based on a combination of electrospray-ionization mass spectrometry, temperature-dependent $^1$H NMR spectroscopy and electrical conductivity measurements, was reported by Koszinowski.[28o] The results obtained suggested the presence of allylindium$^{III}$ species **5m**, which undergoes solvolytic heterolytic dissociation to yield ions such as $InR_2(solv)^+$ (**5n**) and $InRX_3^-$ (**5o**) (Scheme 3).

NMR study conducted by Bowyer and co-workers showed that indium reacted with allyl halide in a ratio of 2:3 in aqueous media, likely pointing to the generation of an allylindium$^{III}$ compound under the conditions.[28p] Singaram[28q,28r] also suggested that an allylindium$^{III}$ species is the active allylating intermediate in a polar aprotic solvent based on the NMR study.

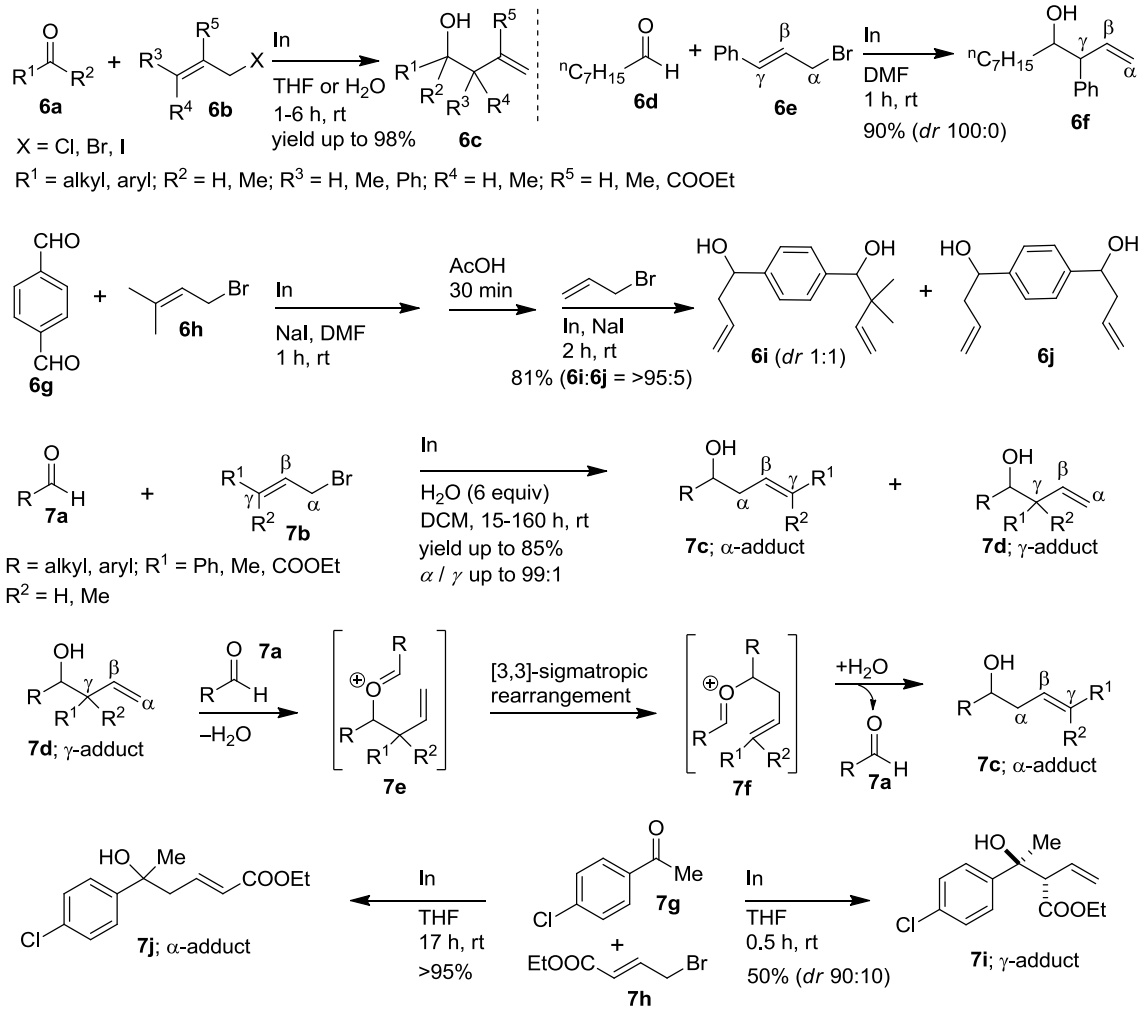
On the basis of the above contributions from several groups to depict the nature of the allylindium species, it can be summarized that allylindium$^{III}$ dihalide ($RInX_2$) and diallylindium$^{III}$ halide ($R_2InX$), instead of an allylindium sesquihalide ($R_3In_2X_3$), are most probable active allylindium species formed during allylation reactions both in organic solvents and in aqueous media. However, formation of a transient allylindium$^{I}$ cannot be overlooked.[28]

**Indium-mediated Barbier-type allylation of carbonyl compounds.**

The first report for the use of indium in organic synthesis appeared in literature from Rieke's[29] group, which revealed the use of activated indium powder for the Reformatsky-type reaction. Later, Araki and co-workers performed indium-mediated allylation of a variety of aldehydes and ketones in THF or DMF, which gave the corresponding homoallylic alcohols **6c** (Scheme 4).[28d,30] Chan and co-workers demonstrated the attractiveness of allylindium additions to carbonyl compounds **6a** by performing the reaction in water (Scheme 4).[28a] Various other researchers have also shown that no inert atmosphere or dry solvent is required to carry out the indium-mediated allylation reaction.[31]

**Chemo- and regioselective indium-mediated Barbier-type allylation of carbonyl compounds.**

Reaction of one of the identical functional groups located in the same molecule would be a very important selectivity concept. In this regard, Baba[32a] and co-workers developed a one-pot sequential double allylation of dicarboxaldehyde **6g** with two different allyl groups, which gave unsymmetrical bis-homoallylic alcohols **6i** and **6j** (Scheme 4). The difficulty in avoiding the formation of **6j** was overcome by quenching the monoallylated indium homoallylic alkoxide species with AcOH prior to introduction of the second allyl group.




**Scheme 4.** Chemo- and regioselective Barbier-type allylation of carbonyl compounds for the synthesis of homoallylic alcohols (**6c**, **6f**, **6i**, **7c**, **7d**, **7i**, **7j**).

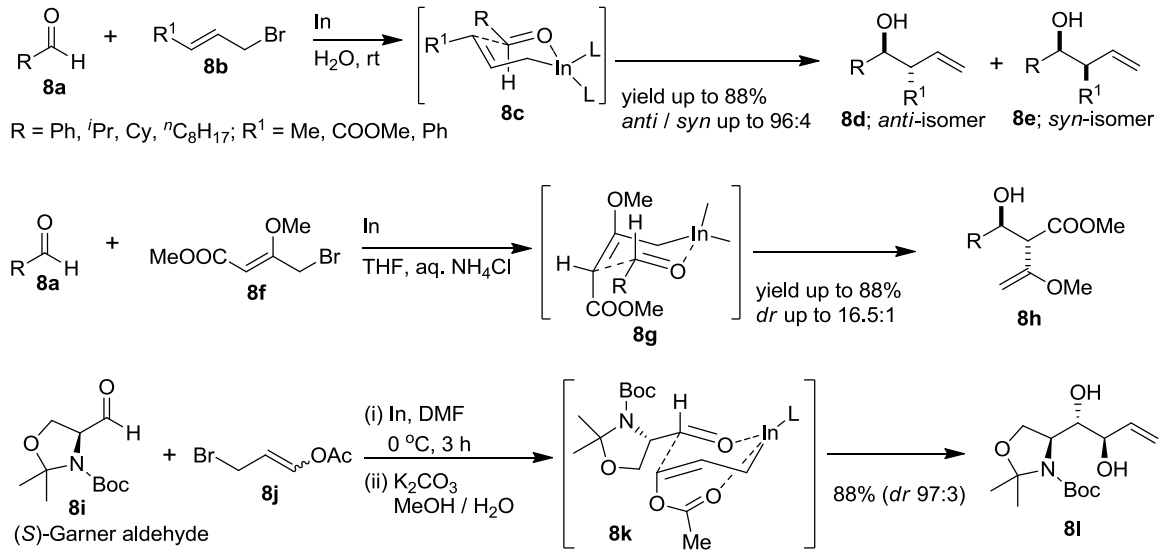
Allylation of carbonyl compound using γ-substituted allyl halide can form either α-adduct or γ-adduct. Araki[28d] *et al.* showed that reaction of the cinnamyl bromide (**6e**) with carbonyl compound **6d** proceeded exclusively at the γ-position of the allyl halide **6e** to give γ-substituted homoallylic alcohol **6f** as the sole product, regardless of steric effect of the γ-substituent (Scheme 4). Loh[32b-32d] and co-workers found a general method to prepare α-adduct **7c** by using just 6 equiv of water. The allylation of carbonyl compounds **7a** worked well in DCM with a variety of allyl halides **7b** irrespective of their substitution pattern and gave the α-adducts **7c** with high selectivities (Scheme 4). As shown by the mechanistic study, the reaction proceeded normally to give the γ-adduct **7d**. After stirring the reaction for a longer time period, the initially formed γ-adduct **7d** underwent a 2-oxonia-[3,3]-sigmatropic rearrangement with **7a** to furnish the corresponding α-adduct **7c** with high regioselectivity. Baba[32e] *et al.* also observed a similar kind of phenomenon which involves the complete conversion of γ-adduct **7i** formed from a ketone **7g** and ethyl 4-bromocrotonate (**7h**) into the α-adduct **7j**, when the reaction time was extended from 0.5 to 17 h (Scheme 4).

**Stereoselective indium-mediated Barbier-type allylation of carbonyl compounds.**

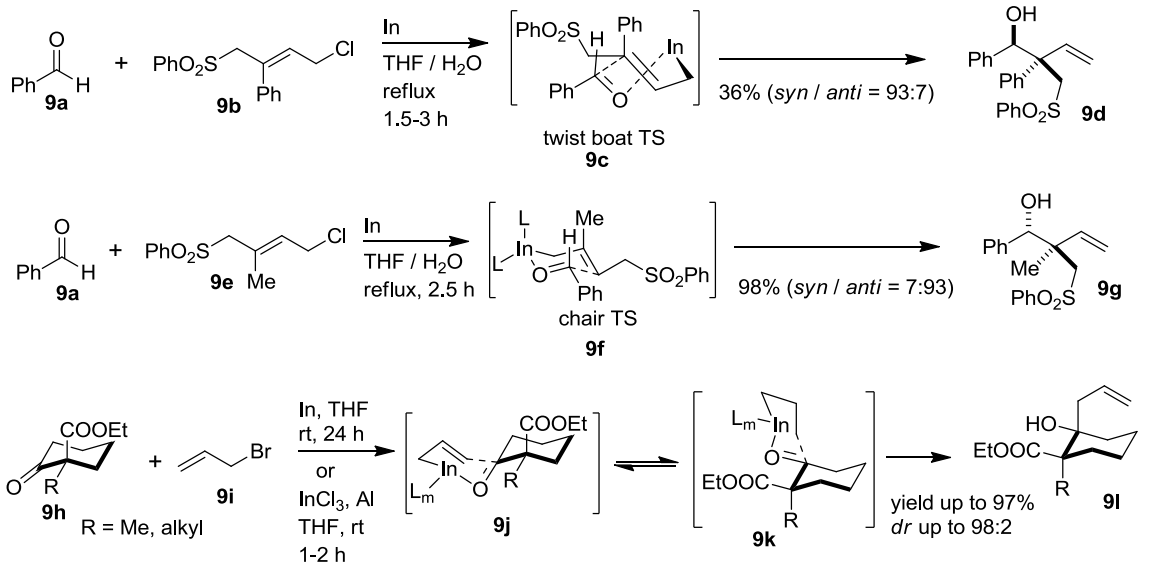
The addition of a γ-substituted allylindium reagent to a carbonyl compound can give two diastereomers (*anti* or *syn* isomer; e.g. **8d** or **8e**) of γ-adduct (Scheme 5). Chan's group[33a] conducted an earliest study with regard to the diastereoselective allylation, the reaction of allyl bromide (**8b**) bearing a small γ-substituent (R = Me) with **8a** furnished a mixture of both *anti* (**8d**) and *syn* (**8e**) isomers in equal proportions. Whereas the use of a γ-substituted allyl bromide with a bulky γ-substituent (R = Ph or COOR) gave **8d** with good to excellent *anti* selectivities. Acyclic or Zimmerman−Traxler[33b,33c,28b] transition state **8c** was proposed to account for the observed diastereoselectivities (Scheme 5).

Paquette[34a] *et al.* carried out the indium-mediated allylation of aldehydes **8a** in aqueous media, which gave the β-hydroxyesters **8h** with good selectivity (Scheme 5). 3-Bromo-1-acetoxy-1-propene (**8j**) underwent the allylation with aldehydes in the presence of indium in THF to give the corresponding monoprotected 3,4-diols in good yields and selectivity.[34b-e] Allylation of aliphatic aldehyde furnished the *anti* adduct, whereas the allylation of α,β-unsaturated aldehyde gave the *syn* adduct. When the protocol was applied to (*S*)-Garner

aldehyde (**8i**), the *anti*−*anti* diastereomer **8l** was obtained as the major product with high diastereoselectivity. A justification for the stereochemical outcome was proposed, assuming bicyclo[3.2.2]nonane-type TS structure **8k** on the basis of steric grounds (Scheme 5).[34d]




**Scheme 5.** Stereoselective indium-mediated Barbier-type allylation of carbonyl compounds for the synthesis of homoallylic alcohols (**8d**, **8h**, **8l**).



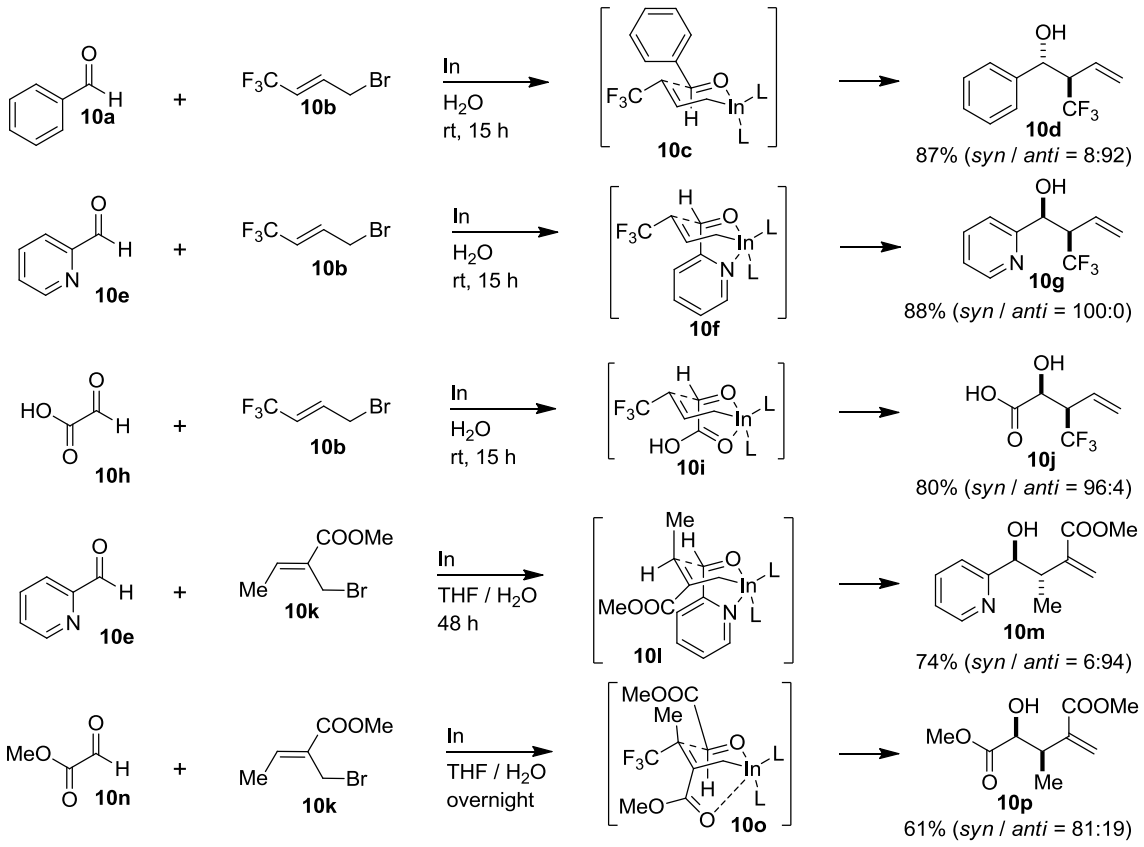

**Scheme 6.** Stereoselective indium-mediated Barbier-type allylation of carbonyl compounds for the synthesis of homoallylic alcohols (**9d**, **9g**, **9l**).

Koo's group studied the allylation of aldehydes by using haloallylic sulfone as allylating agent.[35a,b] The indium-mediated reaction of the haloallylic sulfone **9b** or **9e** and aldehyde **9a** proceeded efficiently in THF/$H_2O$ (Scheme 6). The diastereoselectivity was found to be mostly dependent on the R substituent irrespective of the geometry of the C=C bond. When the substituent was a methyl group, the reaction preferred a chair conformation in the indium-coordinated six-membered cyclic transition state **9f** to give the *anti* product **9g** as the major isomer. On the other hand, *syn* isomer **9d** was obtained as the major isomer when the substituent was a phenyl group, suggesting the involvement of a transition state **9c** (Scheme 6). A highly stereoselective protocol is reported by our group[35c] for customizing functionalized carbocyclic hydroxy esters **9l** containing contiguous stereocenters. The observed stereoselectivity in the diastereofacial selective indium-mediated addition of allyl bromide (**9i**) to hindered α,α-disubstituted cycloalkanones **9h** was accounted with a plausible reaction pathway involving the fleeting TS **9j** and **9k** (Scheme 6). We[35d] also reported the use of a catalytic amount of $InCl_3$ in combination with $Al^0$ for the allylation of a variety of α,α-disubstituted cycloalkanones **9h**. The stereoselective $InCl_3$-catalyzed Al-based allylation gave the corresponding β-hydroxy esters **9l** with moderate to excellent diastereoselectivity (Scheme 6).

**Chelation-controlled indium-mediated Barbier-type allylation of carbonyl compounds.**

Loh and Li disclosed[36a,b] an exceptionally diastereoselective indium-mediated allylation of aldehydes with 1,1,l-trifluoro-4-bromo-2-butene (**10b**), which afforded the *anti* β-trifluoromethylated homoallylic alcohols **10d** and water media was proved to be superior to DMF in inducing better diastereoselectivity (Scheme 7). Conversely, the allylation of 2-pyridinecarboxylaldehyde (**10e**) and glyoxylic acid (**10h**) gave products **10g** and **10j** with *syn* stereochemistry. This abnormal phenomenon is largely indicative of the adoption of a Cram-chelation[36c,d] (or anti-Felkin-Anh[37]) transition states **10f** and **10i** in the reaction, which involves coordination of the pyridine and C=O to the allylindium species, in respective cases (Scheme 7). Paquette[38a] performed a comprehensive study on the chelation phenomenon involving the reaction of 2-pyridinecarboxaldehyde (**10e**) and methyl glyoxalate (**10n**) with different allyl halides (Scheme 7).[38a] A noteworthy example is the use of thermally stable methyl (*Z*)-2-(bromomethyl)-2-butenoate (**10k**), in such case a competitive chelation of

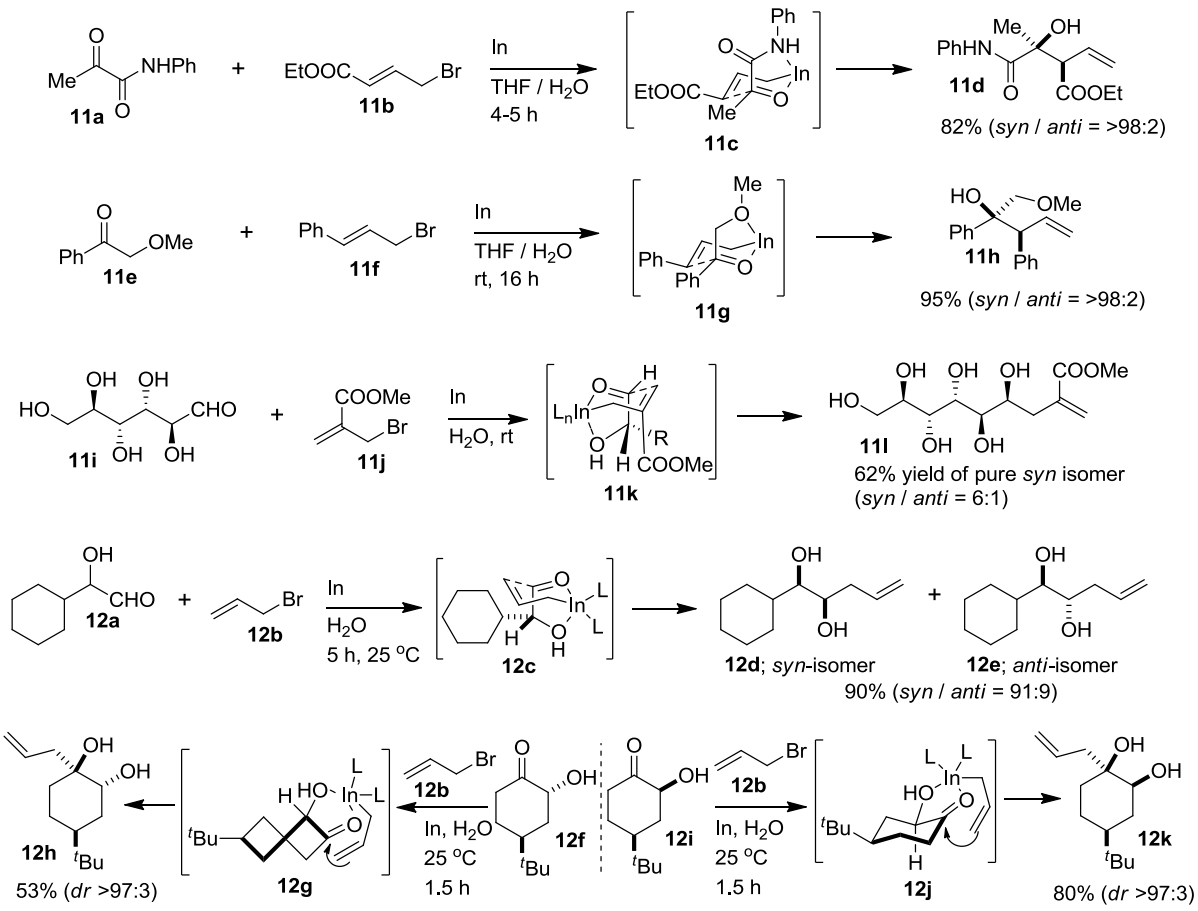
allylindium reagent with ester functionality may be envisioned. When 2-pyridinecarboxaldehyde (**10e**) was employed as substrate, a preferential formation of the *anti* adduct **10m** was observed, reflecting the involvement of chelation-controlled TS **10l**. Interestingly, the use of glyoxylic ester **10n** led to the predominant production of the corresponding *syn* adduct **10p** involving the transition state **10o**.




**Scheme 7.** Chelation-controlled indium-mediated Barbier-type allylation of carbonyl compounds for the synthesis of homoallylic alcohols (**10d**, **10g**, **10j**, **10m**, **10p**).

Kumar[38b] *et al.* reported the allylation of α-ketoamide (**11a**; 2-oxo-*N*-phenylpropanamide) afforded the allylated product **11d** with excellent *syn* selectivity, involving chelation-controlled TS **11c** (Scheme 8). Baba's group[32e] showed the allylation of ketones with allyl halides such as cyclohexenyl halides, cinnamyl halides and ethyl 4-bromocrotonate with high diastereoselectivity. The choice of solvent medium was crucial in this reaction. The reaction of a ketone **11e** bearing a chelating group (OMe) with cinnamyl bromide (**11f**) occurred more effectively in THF/water media rather than in an organic solvent (Scheme 8). A chelation-

controlled transition state **11g** was proposed by the authors to explain the observed *syn* stereoselectivity. Chan and Li[38c] also reported the chelation controlled indium-mediated allylation of unprotected carbohydrate (**11i**; D-(+)-mannose) with 2-bromomethylacrylate (**11j**) in water. Interestingly, the allylated product **11l** was obtained with *dr* 6:1 *syn/anti* (with respect to the newly generated hydroxy group and the C-2 hydroxyl group of mannose, Scheme 8). The observed *syn* selectivity was explained *via* the plausible transition state **11k** involving either Cram-chelation model or by Felkin−Anh model.[38c,38d]




**Scheme 8.** Chelation-controlled indium-mediated Barbier-type allylation of carbonyl compounds for the synthesis of homoallylic alcohols (**11d**, **11h**, **11l**, **12d**, **12h**, **12k**).

Paquette[39a,39b] *et al.* achieved a highly diastereoselective allylation of α-hydroxyaldehyde **12a** which led to the construction of *syn* 1,2-diol **12d** in water (Scheme 8). This high *syn*-diastereoselectivity was explained through the Cram-chelation transition state **12c**. Notably, the results also revealed that the presence of water does not compete with the hydroxy group

in coordination with the allylindium species (Scheme 8). Paquette's group[39c] reported the allylation of unprotected 2-hydroxycyclohexanones **12f** and **12i** possessing α-hydroxy substituent (Scheme 8). It is noteworthy to mention that in the case of substrate **12f**, a proposed twist-boat conformation **12g** was adopted in order to facilitate the chelation and the allyl group attacks from the equatorial direction to afford the *trans* 1,2-diol **12h**. While in the case of **12i**, it is suggested that the product **12k** could be formed *via* the transition state **12j** (Scheme 8).

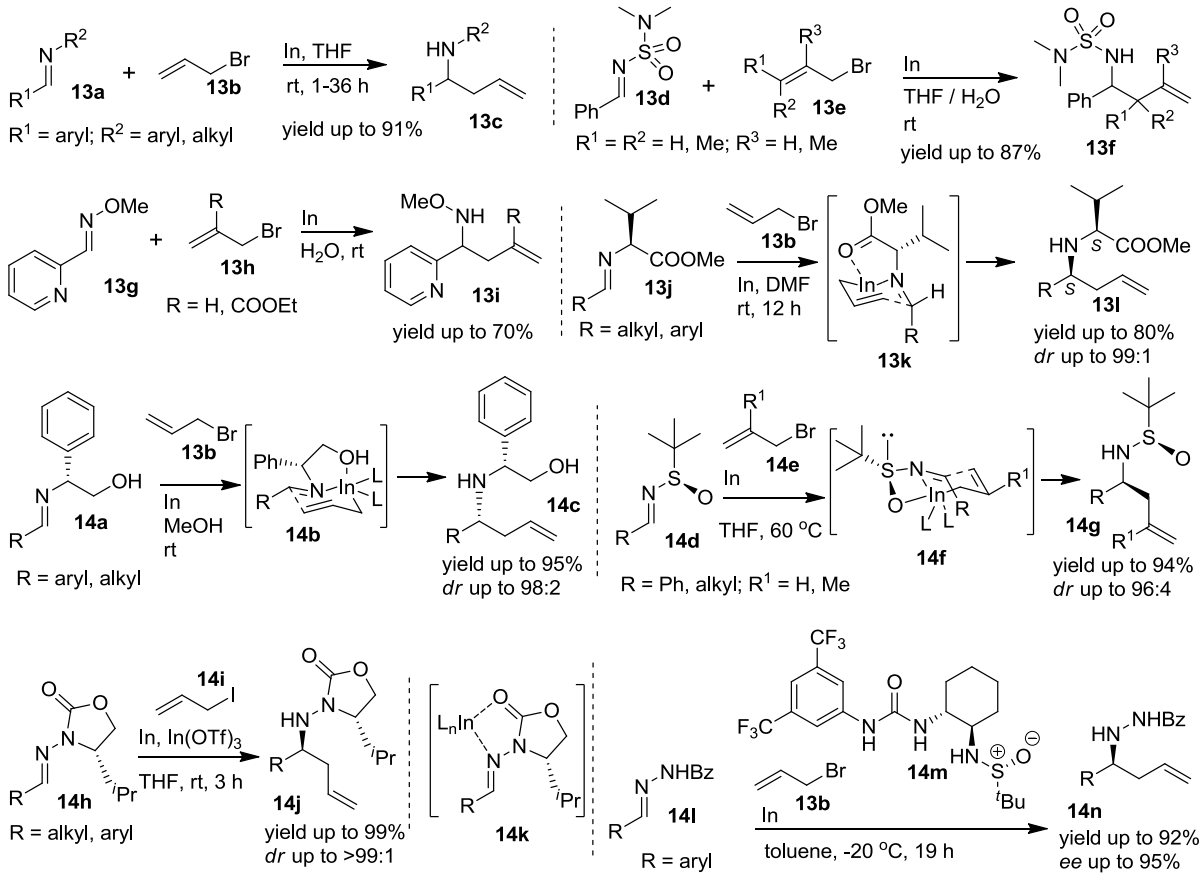
**Indium-mediated Barbier-type stereoselective allylation of imino systems.**

The Barbier-type In-mediated non-stereoselective and stereoselective additions of simple or unsubstituted allylic halides to the C=N bond systems, such as aldimines, ketimines, hydrazones, oximes and sulfonimines have been well-studied.[40-42] This approach provides an easy access to racemic or enantiomerically pure homoallylic amines possessing one stereocenter.

Mosset[40a] was the first to use the fascinating properties of indium enabling the allylation of aldimines **13a** under simple Barbier type conditions to yield homoallylic amines **13c** (Scheme 9). Barbier-type In-mediated allylation of an *N*,*N*-(dimethylsulfamoyl)-protected aldimine **13d** with allyl bromide (**13e**) was investigated by Minnaard and Leino[40b] for the preparation of homoallylic sulfamides **13f** (Scheme 9). Ricci[40c] *et al.* reported the indium-mediated allylation of oxime ether **13g** derived from 2-pyridinecarboxaldehyde afforded the homoallylic oximes **13i** (Scheme 9). Loh[40d] and co-workers described the first asymmetric allylation of an imine system utilizing chiral auxiliary with a synthetically useful level of diastereocontrol. The allylation of imines **13j** derived from *L*-valine methyl ester in the presence of indium afforded the product (*S*,*S*)-diastereomer **13l** (Scheme 9). The observed diastereoselectivity was accounted *via* the chelation-controlled TS **13k**.

Vilaivan[40e,f] and co-workers reported the indium-mediated allylation of imines **14a** (derived from chiral (*R*)-phenylglycinol) in methanol, which resulted several enantiomerically pure homoallylic amines **14c** with good to excellent diastereoselectivities (Scheme 9).[40f] Foubelo and Yus[41a] reported that the indium-mediated allylation of enantiomerically pure *N*-*tert*-butylsulfinyl imines **14d** in THF at 60 °C gave the corresponding enantiomerically pure *N*-

*tert*-butylsulfinyl amines **14g**. The observed high diastereoselectivity was explained *via* the transition state **14f** (Scheme 9). Further, Lin[41b,c] and co-workers revealed that by adding NaBr as an additive, the above reactions can be performed in water at room temperature to get improved yields and diastereoselectivities.




**Scheme 9.** Synthesis of homoallylic amines (**13c**, **13f**, **13i**, **13l**, **14c**, **14g**, **14j**, **14n**) *via* indium-mediated Barbier-type allylation of imines.

Cook[41d] and co-workers showed the indium-mediated allylation of valinol-based hydrazones **14h** afforded the corresponding enantiomerically pure homoallylic hydrazones **14j** with good to excellent diastereoselectivities (Scheme 9). It was postulated that the Lewis acid chelated hydrazone **14k** acts as an activated substrate and the chelation effect restricts the conformational mobility affording the product with high selectivity (Scheme 9). Jacobsen[41e] *et al.* showed the bifunctional urea-catalyzed highly enantioselective allylation of acyl hydrazone substrates **14l** gave the enantiomerically pure homoallylic acyl hydrazine **14n** with excellent yield and enantioselectivity (Scheme 9).

As mentioned earlier, the synthetic step involving the addition of allylmetals to carbonyl (C=O) and imino (C=N) functional groups considered as important methods in multistep synthesis. Because the olefin moiety present in the products (homoallylic alcohols/amines) can be subjected to a wide range of functional group transformations.[17,18] Especially, the olefin moiety present in the products (homoallylic alcohols/amines) can be subjected to the ring closing metathesis (RCM) reaction[43] to synthesize functionalized cyclic olefins.

The ring closing metathesis reactions with nitrogenated compounds (e.g. homoallylic amines) have been studied in detail.[44a] Particularly, several biologically relevant scaffolds such as alkaloids, peptidomimetics and other compounds were synthesized *via* ring closing metathesis reactions[44b,c] in the presence of a Grubbs' ruthenium carbene catalyst (Figure 5).[45]

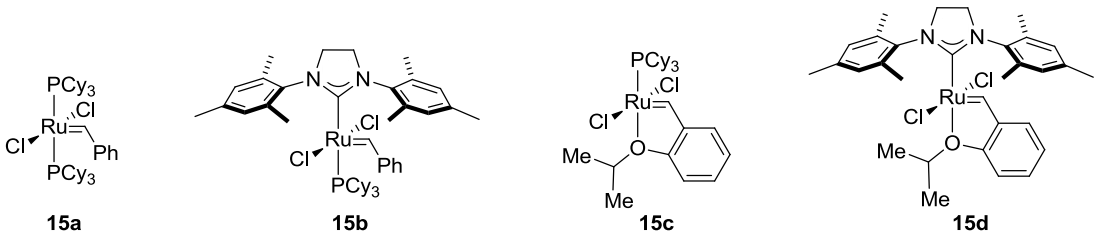
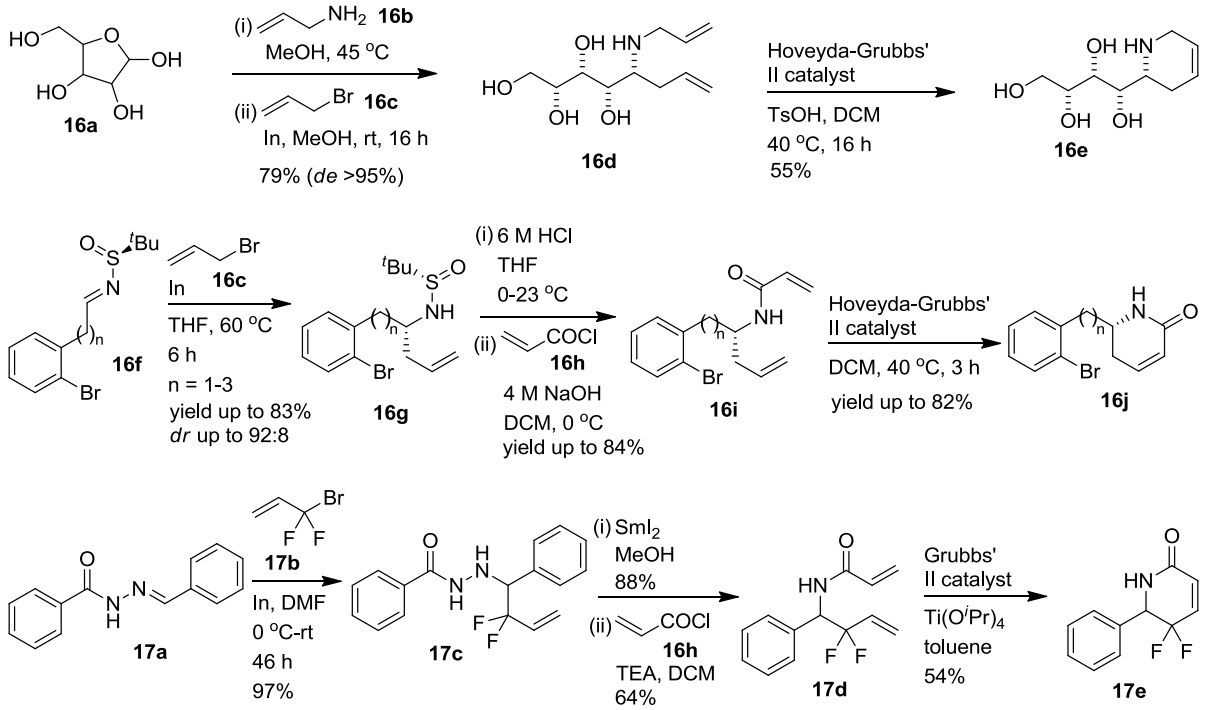



**Figure 5.** Ru-catalysts used for performing the ring closing metathesis (RCM): 1st generation Grubbs' catalyst (**15a**), 2nd generation Grubbs' catalyst (**15b**), 1st generation Hoveyda Grubbs' catalyst (**15c**) and 2nd generation Hoveyda Grubbs' catalyst (**15d**).

Behr[46a] *et al.* demonstrated a straightforward indium-mediated allylation of unprotected glycosylamines generated from condensation of D-pentoses **16a** and allylamine (**16b**) afforded the homoallylaminopolyols **16d** (*syn* isomer), which was then subjected to the ring closing metathesis reaction to afford the optically active 1,2,3,6-tetrahydropyridine **16e** (Scheme 10). Foubelo[46b] *et al.* reported a highly diastereoselective addition of allylic indium to enantiopure *o*-bromophenyl sulfinyl imines **16f**. Then, the homoallylic amine derivatives **16g** were transformed into lactams **16j** *via* ring closing metathesis reaction (Scheme 10). Qing[46c] *et al.* reported the indium-mediated *gem*-difluoroallylation of *N*-acylhydrazone **17a** with 3-bromo-3,3-difluoropropene (**17b**) gave the α,α-difluorohomoallylic hydrazide **17c**, which was used as a starting material to synthesize the *gem*-difluoro-δ-substituted α,β-unsaturated lactam **17e** (Scheme 10).



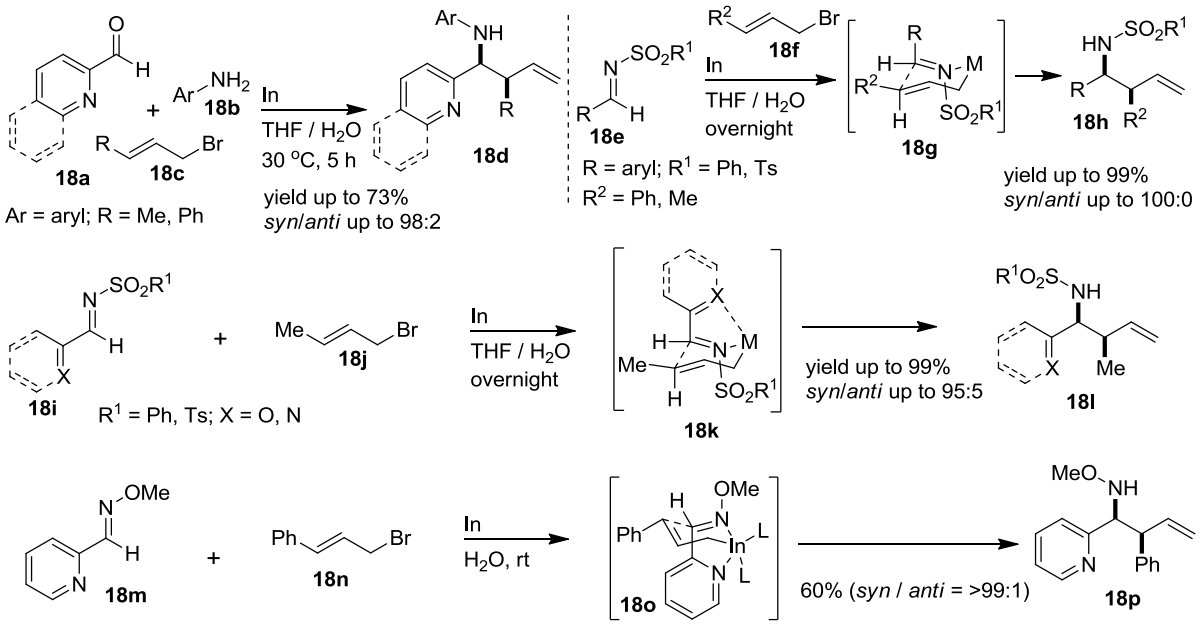

**Scheme 10.** Indium-mediated Barbier-type allylation of imines followed by the RCM reaction of the homoallylic amines (**16d**, **16g**, **17c**).

**Indium-mediated stereoselective Barbier-type allylation of imino systems and construction of homoallylic amines possessing two vicinal stereocenters.**

Though the Barbier-type In-mediated stereoselective addition of simple allyl halides (e.g. allyl bromide and prenyl bromide) to C=N bond systems and the synthesis of homoallylic amines possessing one stereocenter are well explored, however, there exists only limited reports dealing with the Barbier-type In-mediated stereoselective addition of γ-substituted allylic halides (e.g. cinnamyl bromide and crotyl bromide) to C=N bond systems and the synthesis of homoallylic amines possessing two vicinal stereocenters.[47-51]

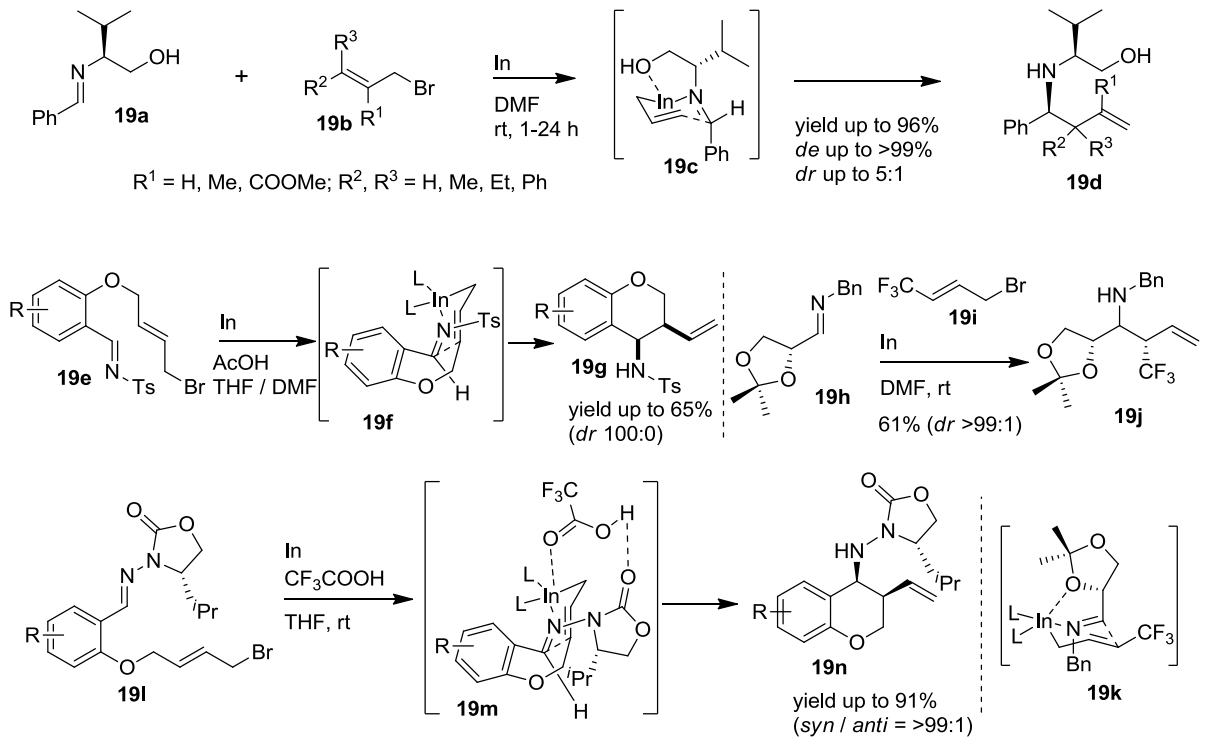
Kumar[48a] *et al.* reported the indium-mediated allylation of imines (generated *in situ* from 2-pyridinecarboxaldehyde (**18a**) with aryl amines **18b**) with crotyl- or cinnamyl bromides (**18c**) occurred in aqueous media and gave the corresponding homoallylic amines **18d** (*syn* isomer) possessing two stereocenters with good to excellent diastereoselectivities (Scheme 11). Chan and Lu[48b,48c] showed the indium-mediated allylation of sulfonimine **18e** in THF/$H_2O$ furnished the homoallylic sulfonamides **18h** (Scheme 11). The indium-mediated crotylation

or cinnamylation of **18e** selectively gave the γ-adduct **18h** depending on the solvent system and the observed stereoselectivity was accounted *via* the cyclic transition state **18g**. The crotylation of sulfonimines **18i** bearing a proximal chelating group led to the construction of *syn* isomers **18l** and the observed stereoselectivity was accounted *via* a chelation-based TS **18k** (Scheme 11).[48c] Similarly, the cinnamylation of oxime ether **18m** led to the construction of *syn* isomer **18p** and in this case also the observed stereoselectivity was accounted *via* the chelation-based TS **18o** (Scheme 11).[48d]




**Scheme 11.** Indium-mediated synthesis of homoallylic amines (**18d**, **18h**, **18l**, **18p**) with two vicinal stereocenters.

Yanada, Kaieda, and Takemoto[48e] reported the indium-mediated allylation of enantiopure imine system **19a** led to the construction of homoallylic amino alcohols **19d** with exceptionally high asymmetric induction. The observed stereoselectivity was accounted *via* the chelation-based TS **19c** (Scheme 12). The indium-mediated allylation of (*R*)-*N*-benzyl-2,3-*O*-isopropylideneglyceraldimine (**19h**) with 4-bromo-1,1,1-trifluoro-2-butene (**19i**) gave the homoallylic amine **19j** with excellent diastereoselectivity and the observed stereoselectivity was accounted *via* the chelation-based TS **19k** (Scheme 12).[49a]



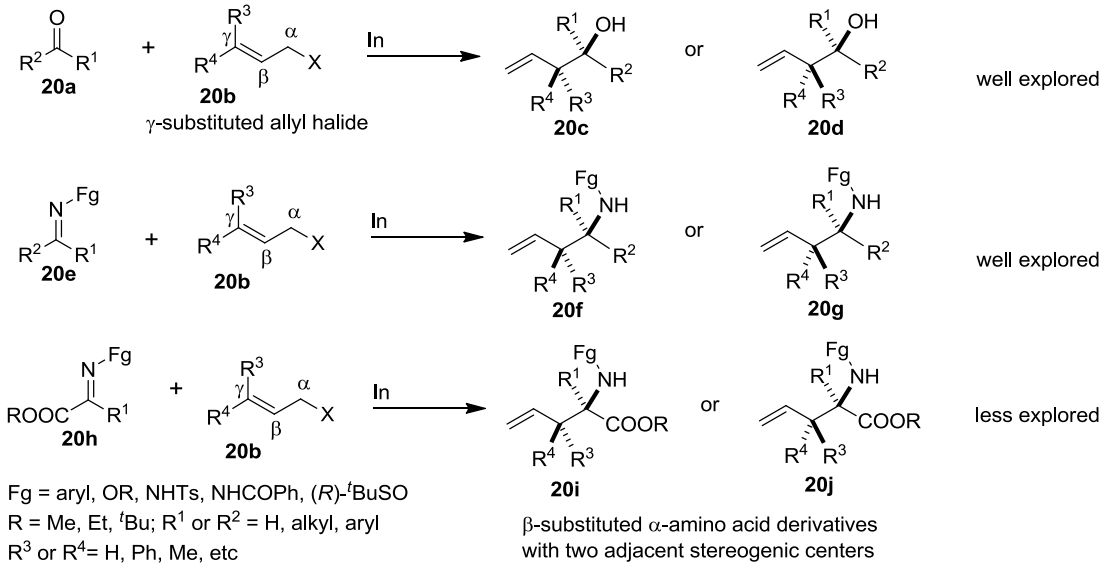

**Scheme 12.** Indium-mediated construction of homoallylic amines (**19d**, **19g**, **19j**, **19n**) with two vicinal stereocenters.

Kang[48f] and co-workers reported the intramolecular cyclization of the substrate **19e** embedded with both imine and allyl bromide moieties in the presence of indium and acetic acid which led to the assembling of chromanes **19g** possessing two stereocenters with *cis* stereochemistry. The observed stereoselectivity was accounted *via* the chair like transition state **19f** illustrated in Scheme 12. Similarly, Cook's group reported the indium-mediated intramolecular allylation of the substrate **19l** in the presence of trifluoroacetic acid, which gave the product **19n** bearing a chromane framework possessing two stereocenters with *cis* stereochemistry (Scheme 12).[49b]

**Stereoselective synthesis of β-substituted α-amino amino acid derivatives *via* allylation of imino systems.**

Regardless of the existing developments on the indium-mediated stereoselective addition of allylic halides to C=N systems,[17,40-51] a survey of the literature indicated that especially, the theme of In-based addition of simple or γ-substituted allylic reagents to C=N bond systems

affording the α-amino acid derivatives possessing two vicinal stereocenters is relatively less explored (Scheme 13).[17,50,51]

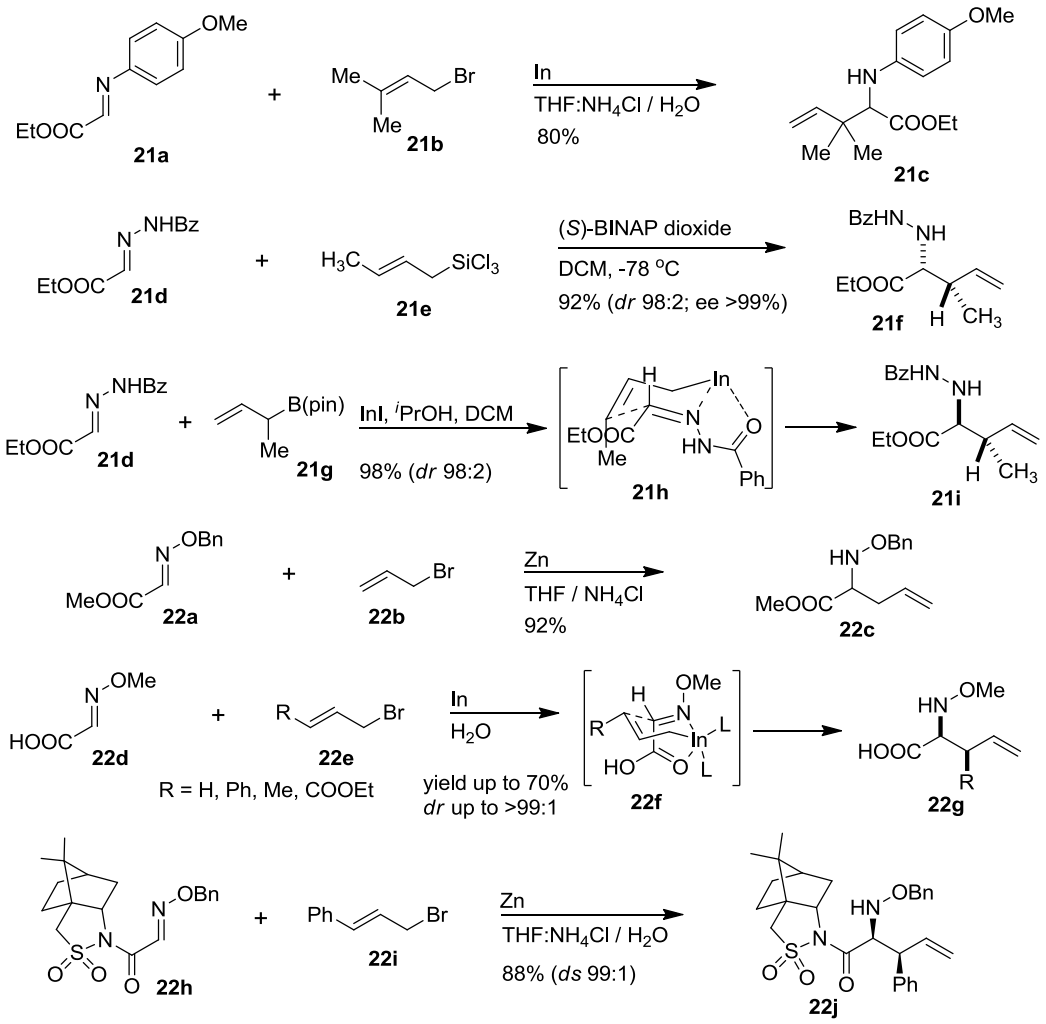



**Scheme 13.** Indium-mediated stereoselective Barbier-type allylation.

Formerly, Kang[42a] and co-workers have reported the Barbier-type In- or Zn-mediated addition of γ,γ′-dimethyl allyl halide **21b** to *N*-aryl α-imino ester **21a** in aqueous media (Scheme 14). This protocol gave an access to γ,δ-unsaturated β,β′-dimethyl *N*-aryl α-amino acid derivative **21c** bearing only one stereocenter. This reaction clearly indicates that the addition of the α- and/or γ-substituted allylmetals to C=N bond of α-imino esters **21a** would be one of the direct methods to obtain the unnatural γ,δ-unsaturated β,β′-disubstituted α-amino acid derivative **21c**. However, in this regard, there exists only a few significant reports dealing with the stereoselective production of β,β'-disubstituted α-amino acid derivatives possessing two vicinal stereocenters. Kobayashi[50a,b] *et al.* reported a magnificent methodology comprising the diastereoselective crotylation of α-hydrazono ester **21d** using silicon as well as boron (**21e** and **21g**) reagents and the production of β-substituted α-amino acid derivatives **21f** and **21i** with the excellent diastereocontrol for respective isomers (Scheme 14).

Ritson *et al.* reported[50h] the allylation of the *O*-functionalized oxime **22a** in THF/$NH_4Cl$ mixture with allyl bromide (**22b**) in the presence of zinc. The reaction afforded the

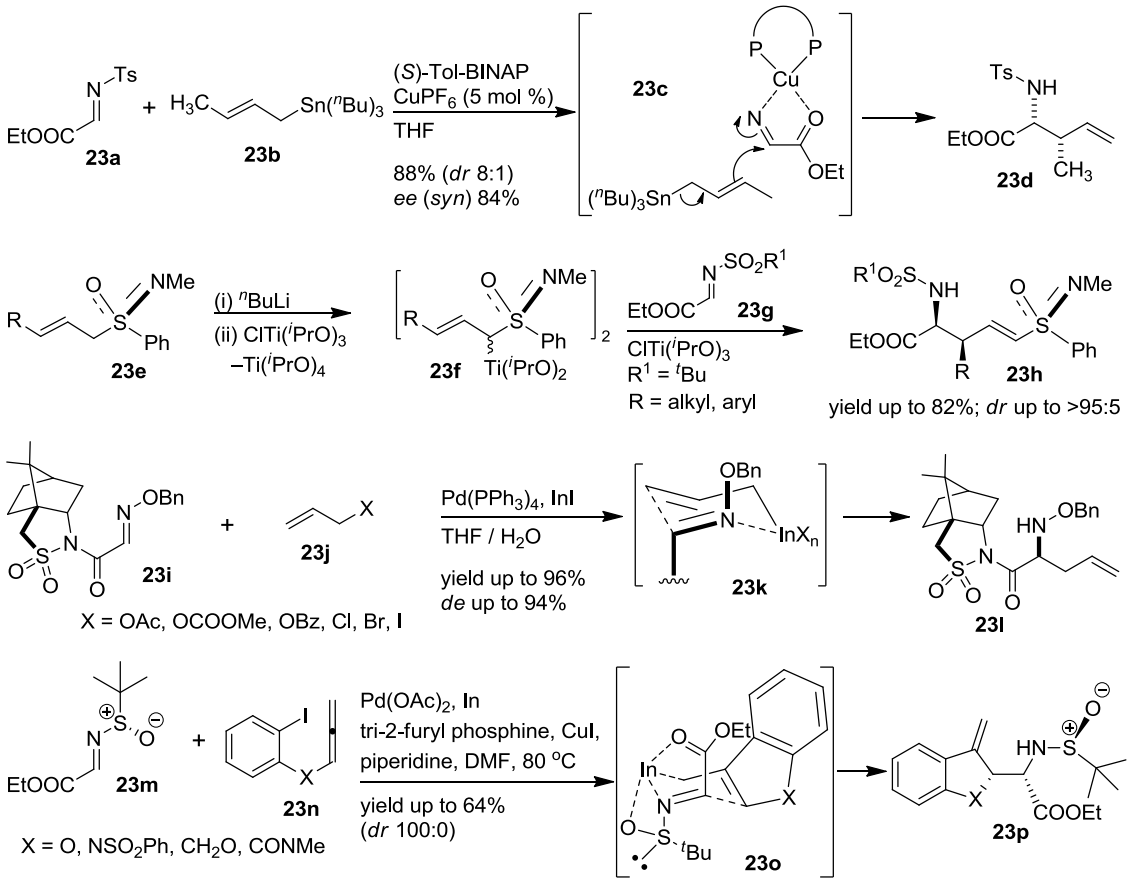
corresponding α-amino acid precursor **22c** (Scheme 14). Similarly, Ricci and co-workers showed[40c] that the indium-mediated diastereoselective allylation of oxime ether **22d** (derived from glyoxylic acid) in aqueous media successfully gave an access to a variety of β-substituted α-amino amino acids **22g** with promising yield and excellent diastereoselectivity (Scheme 14).




**Scheme 14.** Synthesis of β-substituted α-amino acid- and β,β'-disubstituted α-amino acid derivatives (**21c**, **21f**, **21i**, **22c**, **22g**, **22j**).

Hanessian[50i] reported the Barbier type reaction of sultam derivative of *O*-benzyl glyoxylic acid oxime (**22h**) with cinnamyl bromide (**22i**) in the presence of zinc powder in aqueous ammonium chloride, which successfully gave the enantiomerically pure allylglycine analogues **22j** with satisfactory yields and synthetically useful diastereoselection (Scheme

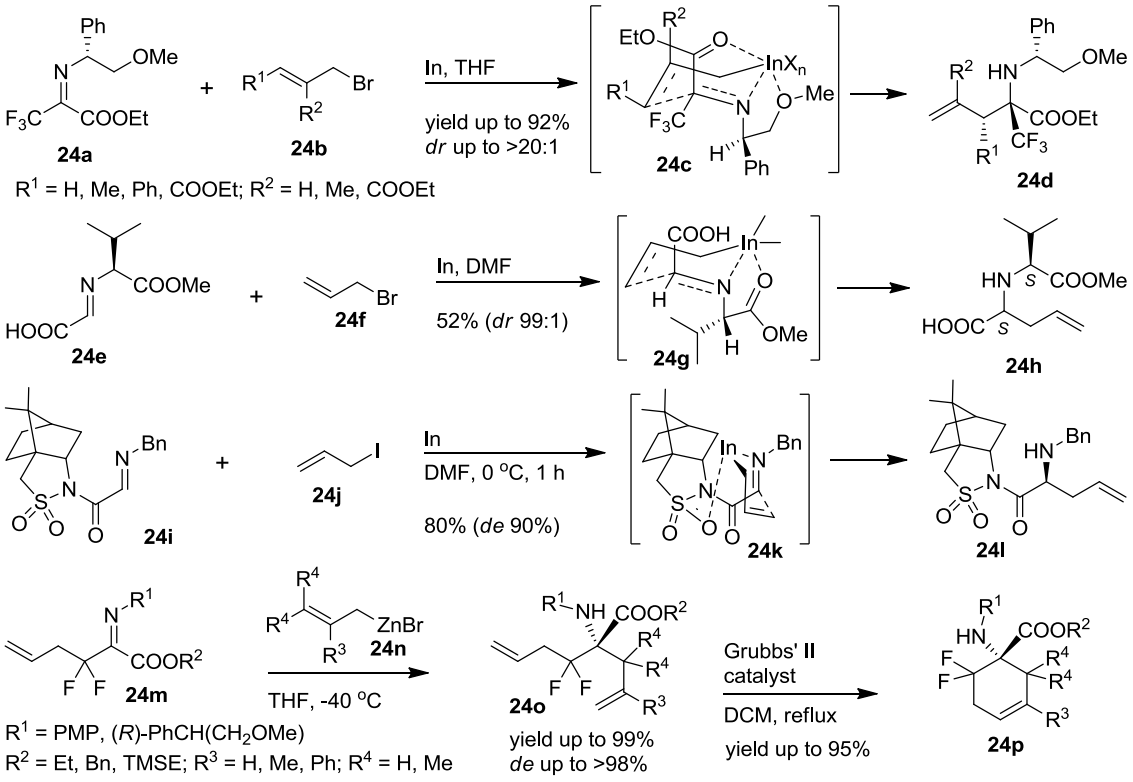
14). Naito[50j] also reported a similar kind of methodology involving indium mediated allylation of *O*-benzyl glyoxylic acid oximes.




**Scheme 15.** Synthesis of β-substituted α-amino acid- and β,β'-disubstituted α-amino acid derivatives (**23d**, **23h**, **23l**, **23p**).

Jørgensen and co-workers demonstrated[50e] the addition of tributyl crotyl tin (**23b**) to *N*-tosyl α-imino ester (**23a**) in the presence of a copper catalyst which afforded the β-substituted α-amino acid derivative **23d** (Scheme 15). A highly diastereoselective allylation protocol was established by Raabe's group[50f,g] using titanium reagents. The reaction demonstrated the allylation of *N*-sulfonimino esters **23g** using titanium allylating reagent **23f** which was prepared *in situ* from allylic sulfonimide **23e**, gave the β-substituted α-amino acid derivatives **23h** with high diastereoselectivity (Scheme 15). Takemoto's group[50k] reported the synthesis of α-amino acid derivative **23l** *via* the allylation and propargylation of glyoxylic oxime ether **23i** in the presence of a catalytic amount of palladium(0) catalyst and indium(I) iodide.

Allylation of glyoxylic oxime ether **23i** proceeded in the presence of water to give the α-amino acid derivative **23l** with excellent diastereoselectivity (Scheme 15). Grigg *et al.* described[50l] an efficient synthesis of functionalized α-amino acid derivatives **23p** *via* the diastereoselective palladium-catalyzed indium-mediated allylation of enantiomerically pure *N*-sulfinyl-α-imino ester **23m** by interfacing the process with catalytic cyclization–anion capture (Scheme 15).




**Scheme 16.** Synthesis of β-substituted α-amino acid- and β,β'-disubstituted α-amino acid derivatives (**24d**, **24h**, **24l**, **24o**, **24p**).

Zhang and co workers demonstrated[50m] that the indium-mediated allylation of chiral imine **24a** derived from trifluoropyruvate, gave the fluorinated quaternary α-amino acid derivatives **24d** in excellent yield and diastereoselectivity (Scheme 16). The authors proposed the chelated transition state **24c** for the observed excellent diastereocontrol. Loh[40d] also established a highly stereoselective one-pot Barbier-type allylation methodology. The preparation of chiral amino acid **24h** was shown from the reaction of **24e** and **24f** involving the TS **24g** (Scheme 16). Cho[41l] *et al.* devised a diastereoselective method for the preparation

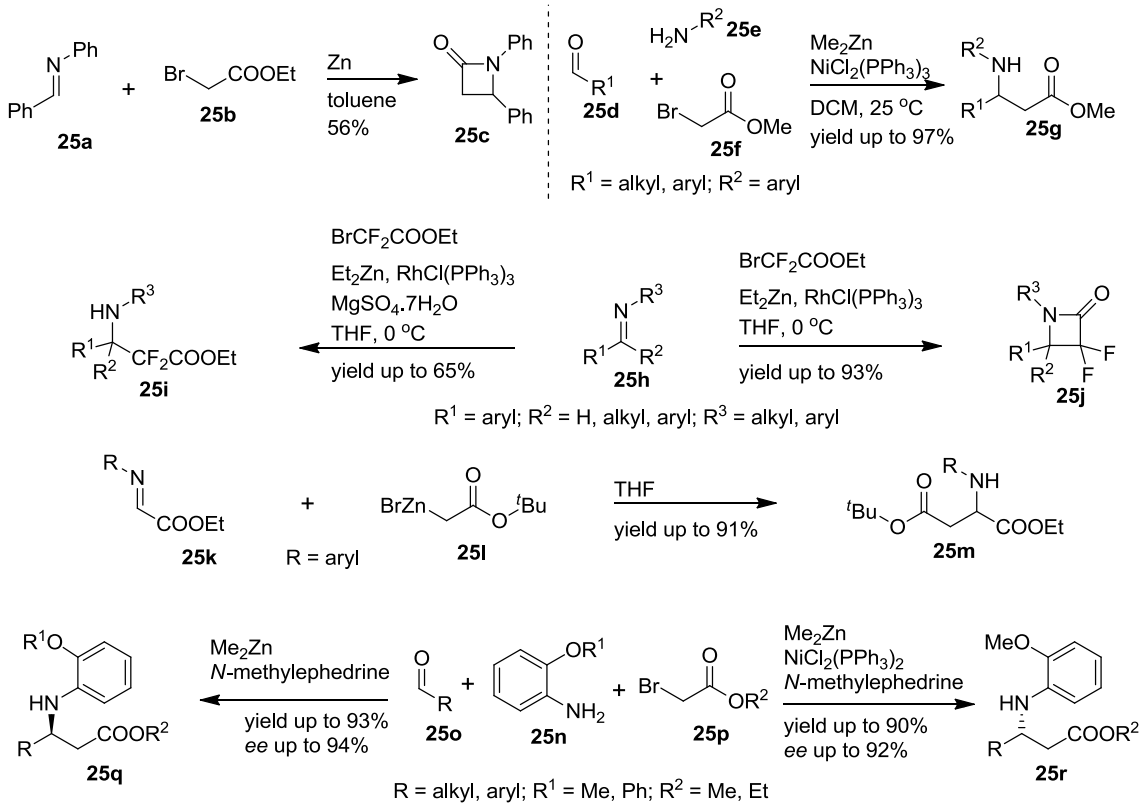
of α-amino acid derivative **24l**. The reaction of imines of *N*-glyoxyloylbornane-10,2-sultam (**24i**) with allyl iodide (**24j**) in the presence of indium in DMF furnished the corresponding α-amino camphor sultam derivative **24l** with high diastereoselectivity (Scheme 16). Fustero[51a] and co-workers described a stereoselective method for the synthesis of cyclic β,β'-difluorinated α-amino acid derivatives **24o**. The diastereoselective addition of allylzinc reagents **24n** to fluorinated α-imino esters **24m** (prepared using (*R*)-phenylglycinol methyl ether auxiliary) gave the β,β'-difluorinated α-amino acid derivatives **24o**, which were subjected to ring closing metathesis reaction (RCM to obtain the desired cyclic β,β'-difluorinated α-amino acid derivatives **24p** as shown in Scheme 16.

**Reformatsky-type reactions for the synthesis of α- or β-amino acid derivatives.**

In addition to the Barbier-type stereoselective addition of allylic halides to C=N systems (e.g. α-imino ester systems) affording the α-amino acid derivatives; Reformatsky-type reaction[52] is an important and complimentary procedure for synthesizing the α- or β-amino acid derivatives.[53-61]

Imino-Reformatsky reaction was first described by Gilman,[53] in which the Zn-mediated reaction of an imine **25a** with an α-halo ester **25b** directly afforded the β-lactam **25c** (Scheme 17). Although, the imino-Reformatsky reaction has great potential in synthetic chemistry, however this protocol lagged behind until recently, because of the drawback of producing a mixture of β-amino esters and β-lactams. Still the future of the imino Reformatsky reaction is expected to be bright as recently the problem of getting mixture of β-amino esters and β-lactams was claimed to be solved by various researchers.[54] After the invention of the imino-Reformatsky reaction, enormous efforts have been invested to capitalize the imino-Reformatsky protocol for the direct construction of β-amino acids.[53-61] Adrian Jr. and co-workers have developed[54] a highly efficient three component nickel-catalyzed Reformatsky-type reaction between an aldehyde **25d**, an amine **25e** and an α-halo ester **25f**, which afforded the β-amino esters **25g** in astonishing yield (Scheme 17). Ando and Kumadaki demonstrated[55a] the formation of difluoro-β-lactams **25j** from corresponding imines **25h** *via* the rhodium-catalyzed Reformatsky-type reaction (Scheme 17). The outcome of the reaction can be switched to 3-amino-2,2-difluorocarboxylic esters **25i** by adding the hydrated salt of magnesium sulphate to the reaction mixture. Lou and co workers[55b] demonstrated the

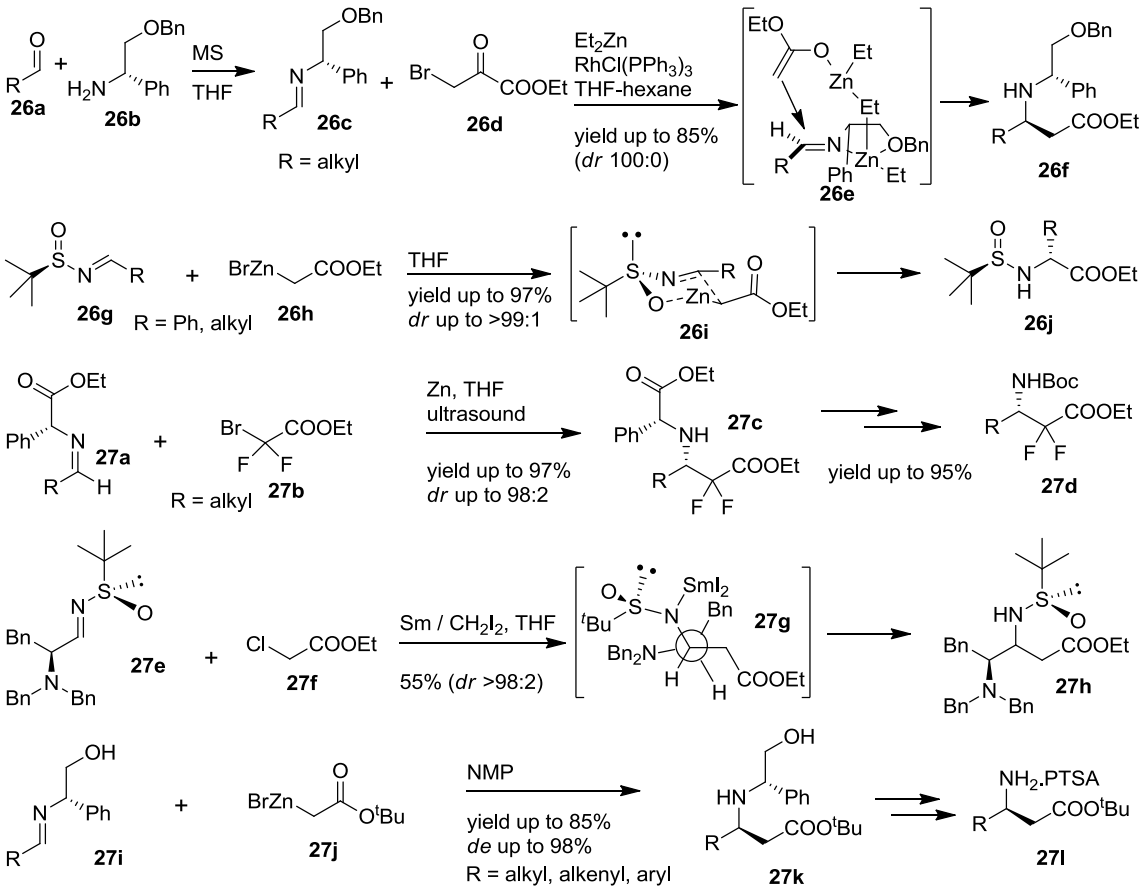
synthesis of orthogonally protected aspartic acid derivatives **25m** with desirable yields *via* Reformatsky reaction of **25k** with commercially available Reformatsky reagent **25l** (Scheme 17). Cozzi demonstrated[56] a highly enantioselective catalytic one-pot three-component imino-Reformatsky reaction which afforded the diversely substituted β-amino esters **25q** and **25r** having stereochemistry complementary to each other (Scheme 17). Attainment of opposite stereochemical outcome during the reaction was entirely dependent on the reaction conditions.




**Scheme 17.** Stereoselective synthesis of β-lactams and α- or β-amino acid derivatives (**25c**, **25g**, **25i**, **25j**, **25m**, **25q**, **25r**).

Honda *et al.* demonstrated[57a] the diastereoselective Rh-catalyzed Reformatsky-type three component reaction of amines **26b**, aldehydes **26a** and ethyl bromoacetate (**26d**), which successfully afforded enantiomerically pure β-amino esters **26f** (Scheme 18). A bimetallic chelation directed addition of α-halo ester was proposed by the authors as shown in the TS **26e** in Scheme 18. Poon[58a] *et al.* described the scalable stereoselective synthesis of β-amino ester derivatives **26j** from *N*-*tert*-butyl-sulfinylaldimines **26g** and zinc enolate **26h** (Scheme

18). Apart from this, diastereocontrol has been efficiently achieved in the Reformatsky type reactions by many research groups for the construction of a range of β-amino acid derivatives using a large variety of chiral auxiliaries.[58] Duggan[58c] *et al.* developed a sonocatalyzed imino-Reformatsky reaction of **27a** (derived from (*R*)-phenylglycine ethyl ester auxiliary) and the stereoselective preparation of difluoro-β-amino acid derivatives **27d** with magnificent yield and diastereoselectivity (Scheme 18).



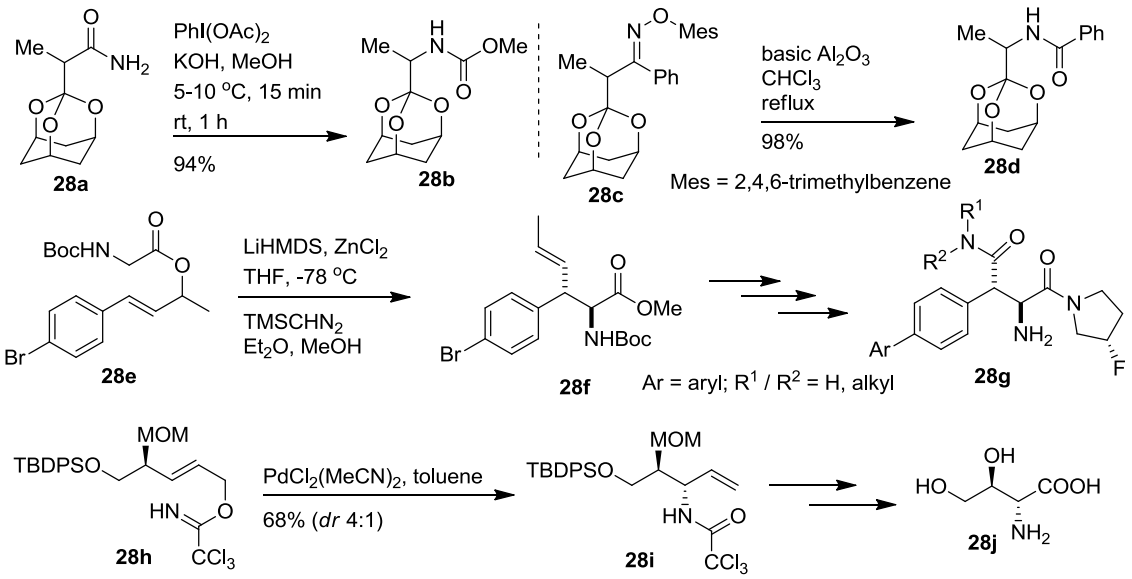

**Scheme 18.** Reformatsky reaction-based stereoselective synthesis of β-amino acid derivatives (**26f**, **26j**, **27d**, **27h**, **27k**).

Concellón[58d] showed the $SmI_2$-based reaction of ethyl chloroacetate (**27f**) with the α-dibenzylamino-*N*-*tert*-butanesulfinimine (**27e**) which gave the corresponding enantiopure 3,4-diamino acid derivative **27h** with very high diastereoselectivity (Scheme 18). Awasthi and Clark have demonstrated the scalable synthesis of β-amino esters **27k** with excellent yield and stereoselectivities *via* the Zn-mediated Reformatsky-type reaction between zinc

enolate of *tert*-butyl bromoacetate (**27j**) and aryl, alkyl and alkynyl chiral imines **27i** (derived from (*S*)-phenylglycinol) (Scheme 18).[59]

Notably, the diastereoselective Reformatsky reactions are also employed in the total synthesis of natural products. Few of the recent literature reports cover the application of the coupling reaction to the stereoselective synthesis of acyclic or cyclic fragments as well as biologically active molecules, including fluorinated moieties.[61]

### 2.2.2. Sigmatropic rearrangement-based synthesis of functionalized unnatural α-amino acid derivatives.

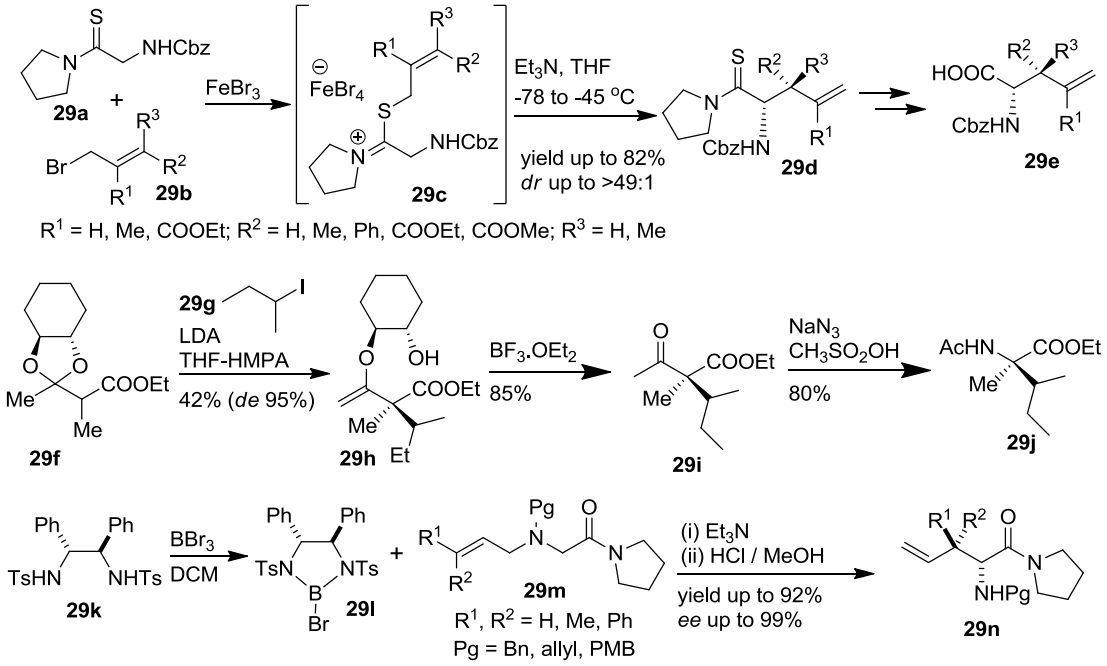



**Scheme 19.** Synthesis of unnatural amino acid derivatives (**28b**, **28d**, **28f**, **28g**, **28j**).

Sigmatropic rearrangement is one of the fundamental rearrangement reactions in synthetic organic chemistry. Several unnatural amino acid derivatives have been synthesized utilizing the concept of sigmatropic rearrangement and some representative examples are given in this section. Chandrasekhar[62a] *et al.* designed controlled approaches to α-amino acid derivatives **28b** and **28d** *via* two classical reactions, such as the Beckmann and the Hofmann rearrangements. The methodology was demonstrated on the precursor substrates **28a** and **28c** having the 2,4,10-trioxaadamantane moiety (Scheme 19). Edmondson's[62b] group showed the Kazmaier's[62c] enolate-Claisen rearrangement of **28e** as a key step for the synthesis of various β-amide substituted phenylalanine derivatives **28g** (Scheme 19) and also revealed that the

synthesized derivatives can function as DPP-IV inhibitors. Sutherland[62d,62e] and co-workers reported the stereoselective synthesis of (2*R*,3*S*)-2-amino-3,4-dihydroxybutyric acid (**28j**; an α-amino acid originate from Lyophyllum ulmarium) involving the transition metal-catalyzed MOM-ether directed aza-Claisen rearrangement of an allylic trichloroacetimidate **28h** (Scheme 19).

Hruby *et al.* developed[63a] a thio–Claisen rearrangement method for preparing *anti*-β-functionalized γ,δ-unsaturated α-amino acid derivatives **29e**. Initially, the thioamide **29a** was subjected to allylation *via* Friedel Crafts alkylation type reaction resulting into the formation of an intermediate **29c** which further got transformed into thio–Claisen rearrangement products **29d** with excellent diastereoselectivities. The resulting rearrangement products **29d** were converted into nonproteinogenic amino acid derivatives **29e** (Scheme 20).



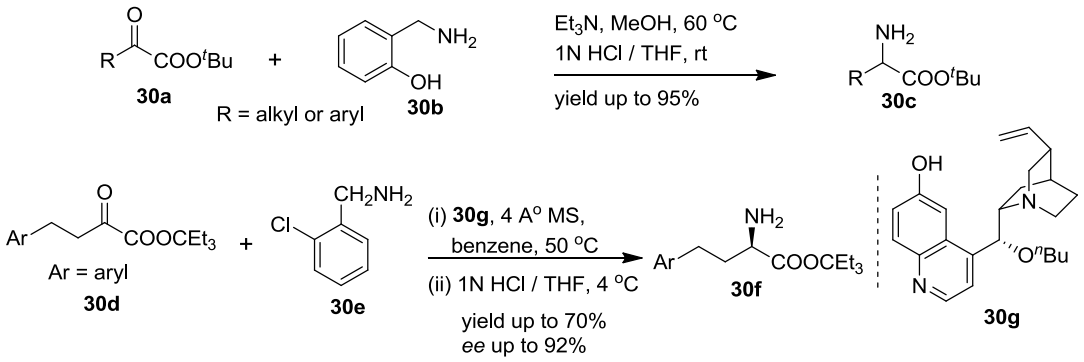

**Scheme 20.** Synthesis of α-amino acid derivatives (**29e**, **29j**, **29n**).

Suemune[63b] *et al.* described the diastereoselective alkylation of ethyl 2-methylacetoacetate **29f** (connected with (*S*,*S*)-cyclohexane-1,2-diol as an acetal chiral auxiliary) which gave the enol ether **29h**, which was transformed into α-keto ester **29i**. Then, the α-keto ester **29i** was converted into optically active α-alkylated α,α-disubstituted amino acid **29j** *via* the Schmidt

rearrangement (Scheme 20). Somfai's[63c] group demonstrated the first asymmetric [2,3]-sigmatropic rearrangement of achiral allylic amines **29m** through quaternization of the amines **29m** with an enantiomerically pure diazaborolidine **29l** (which was formed by mixing the chiral ligand **29k** and $BBr_3$) followed by the treatment with $Et_3N$ which afforded homoallylic α-amino acid derivatives **29n** (Scheme 20).

### 2.2.3. Synthesis of unnatural α-amino acids *via* transamination reactions.

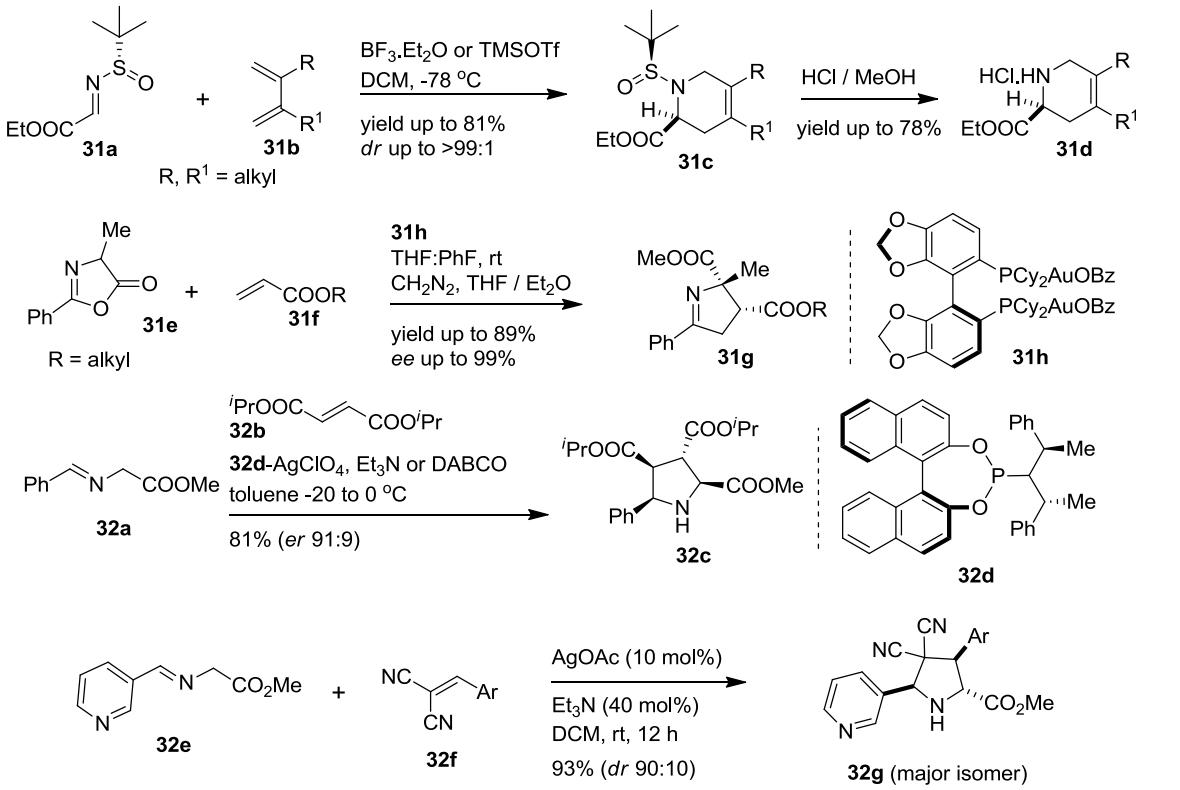
Shi's[64a] group described the base-catalyzed transamination of α-keto esters **30a** with *o*-hydroxy benzylamine (**30b**) to construct a wide variety of α-amino esters **30c** (Scheme 21). Shi's group published a series of papers[64b-64d] on biomimetic transamination of α-keto esters **30d** using *o*-chloro benzyl amine (**30e**) in the presence of chiral base **30g** derived from quinine. A wide variety of α-amino esters **30f** containing various functional groups were synthesized with high enantioselectivity (Scheme 21).




**Scheme 21.** Synthesis of α-amino acid derivatives (**30c** and **30f**).

### 2.2.4. Synthesis of functionalized unnatural α-amino acid derivatives *via* cycloaddition reactions.

Gautun[65a] *et al.* described the diastereoselective aza-Diels–Alder reactions of ethyl (*S*)-*N*-(*tert*-butanesulfinyl)iminoacetate (**31a**) with different dienes **31b** in the presence of Lewis acids. Reactions of unactivated dienes with stoichiometric amounts of TMSOTf afforded the aza-Diels–Alder adducts **31c** in modest yields with diastereoselectivities up to 99% (Scheme 22). Cleavage of the sulfinyl group under acidic condition gave the optically active non-proteinogenic α-amino acid derivatives **31d**.



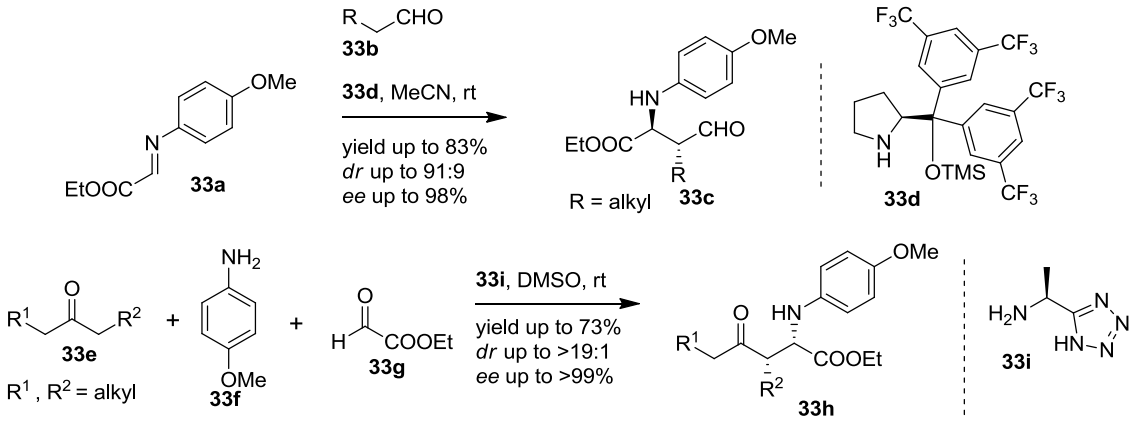

**Scheme 22.** Synthesis of α-amino acid derivatives (**31d**, **31g**, **32c**, **32g**).

Toste[65b] and co-workers showed an enantioselective [3 + 2] dipolar cycloaddition reaction between azalactone **31e** and acrylate esters **31f** in the presence of the chiral gold catalyst **31h** which yielded the substituted amino acid precursors **31g** (Scheme 22). Nájera[65c] *et al.* described the 1,3-dipolar azomethine cycloaddition between imine **32a** and dipolarophile **32b** catalyzed by chiral monodentate phosphoramidite (**32d**)–silver complex which afforded the substituted proline derivative **32c** (Scheme 22). Recently, our group[65d] described the diastereoselective synthesis of nornicotine analogs **32g** (proline derivatives) comprising the 1,3-dipolar azomethine cycloaddition between imine **32e** and Knoevenagel adduct **32f** (Scheme 22).

### 2.2.5. Synthesis of functionalized unnatural α-amino acid derivatives *via* Mannich-type reactions.

Jørgensen[66a] *et al.* showed the organo-catalyzed route for the construction of the α-amino acid derivatives **33c** *via* the Mannich-type reaction of **33a** and **33b** (Scheme 23). Similarly,

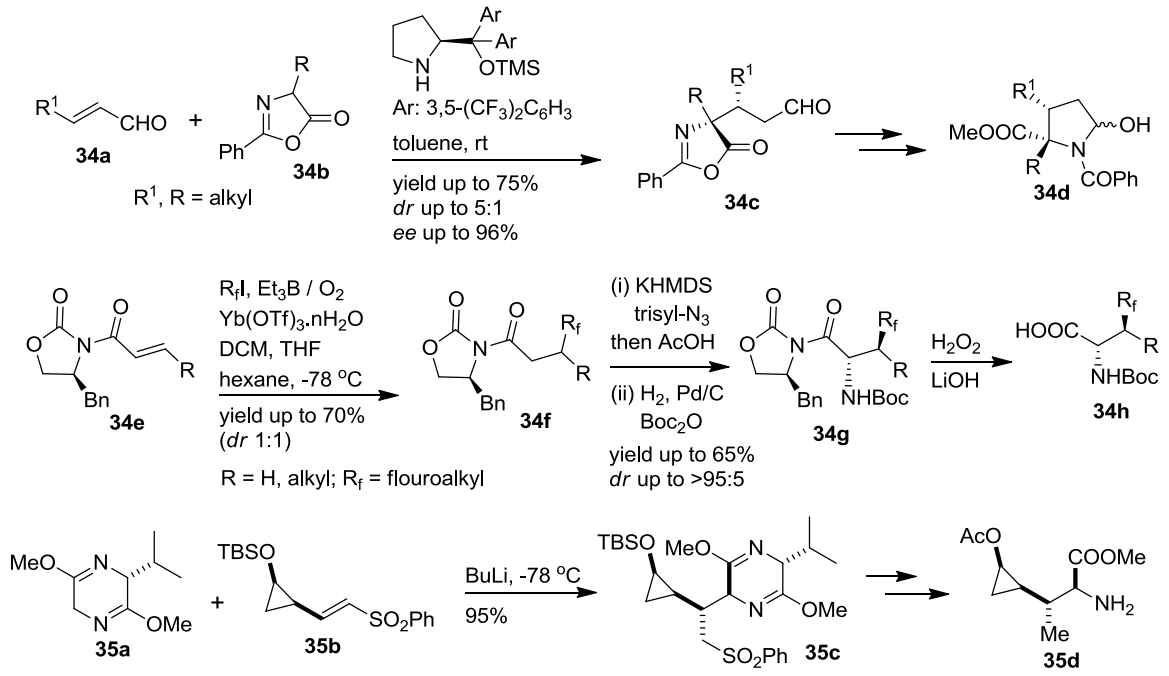
Barbas III reported[66b] the synthesis of α-amino acid derivatives involving the Mannich-type reaction. Córdova's group[66c] reported the three-component asymmetric Mannich reaction between ketones **33e**, *p*-anisidine (**33f**) and ethyl glyoxalate (**33g**) catalyzed by an acyclic chiral amine **33i** which gave the corresponding amino acid derivatives **33h** (Scheme 23).




**Scheme 23.** Synthesis of α-amino acid derivatives (**33c** and **33h**).

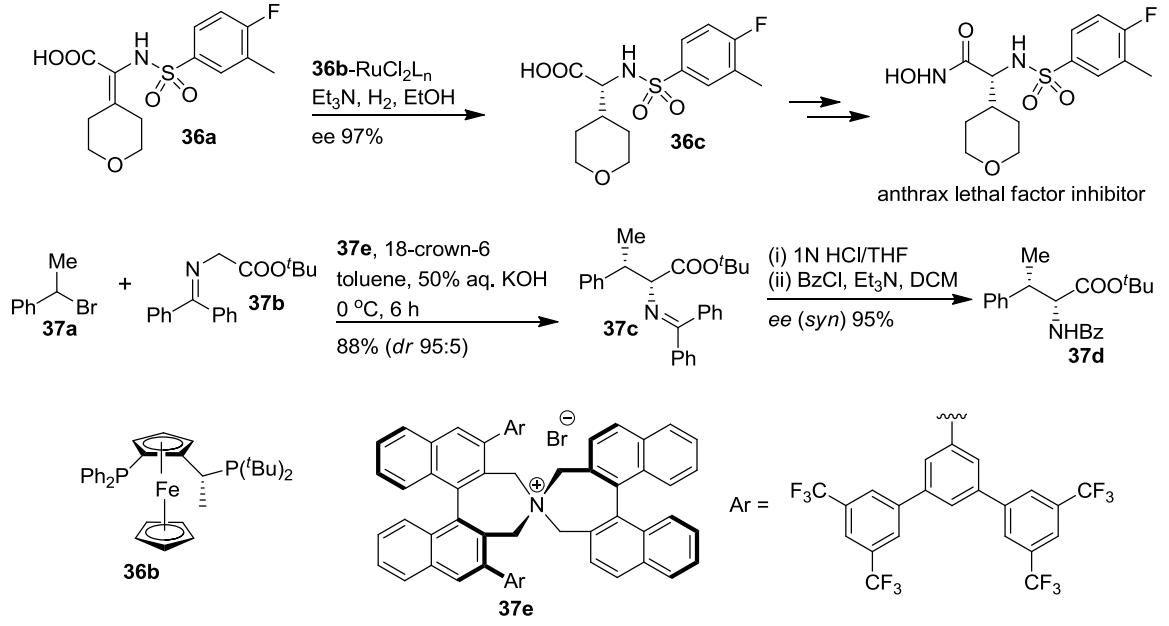
### 2.2.6. Synthesis of functionalized unnatural α-amino acid derivatives *via* conjugate additions.

Jørgensen[67a] *et al.* reported an organocatalytic conjugate addition reaction of an α,β-unsaturated aldehyde **34a** and azalactone **34b** with proline-derived catalyst that afforded the product **34c**, which was further hydrolyzed to provide the corresponding protected amino acids **34d** (Scheme 24). Koksch and Czekelius[67b] *et al.* described the conjugate hydrofluoroalkylation of the α,β-unsaturated acyl-oxazolidinones **34e** and the importance of the protocol by preparing the enantiomerically pure β-trifluoromethylated amino acid derivatives **34h** (Scheme 24). Díez[67c] *et al.* devised a unique approach for the synthesis of glutamic acid analogues **35d** in which the diastereoselective addition of cyclopropanol vinyl sulfone **35b** to the lithiated Schöllkopf bislactim ether **35a** provided an access to the α-amino acid derivative precursors **35c** (Scheme 24).




**Scheme 24.** Synthesis of α-amino acid derivatives (**34d**, **34h**, **35d**).

### 2.2.7. Synthesis of functionalized unnatural α-amino acid derivatives *via* asymmetric reduction and hydrogenation.



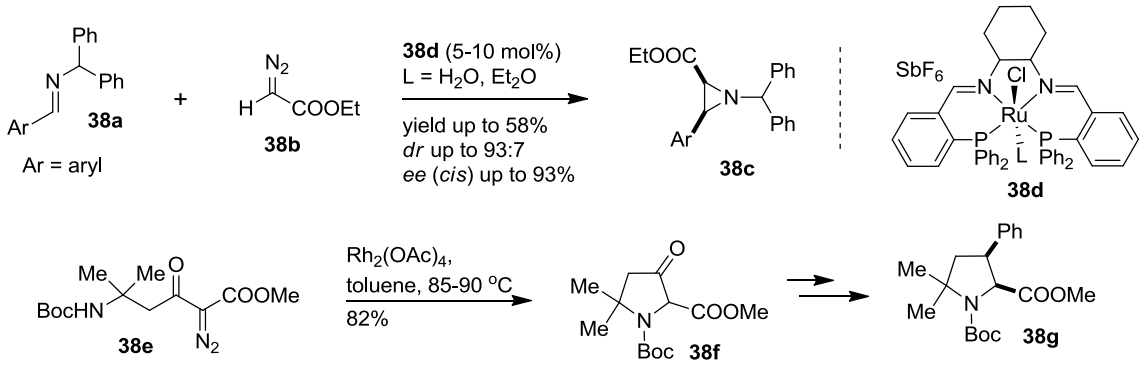

**Scheme 25.** Synthesis of α-amino acid derivatives (**36c** and **37d)**.

Shultz[67d] *et al.* demonstrated a highly enantioselective Ru-catalyzed hydrogenation of *N*-sulfonylated-α-dehydroamino acids **36a** (Scheme 25) which successfully afforded the *N*-sulfonylated amino acids **36c**. Further, the process was used for the synthesis of an anthrax lethal factor inhibitor (LFI). Ishida's[67e] and Chandrasekhar's[67f] groups also showed the synthesis of enantiopure unnatural amino acid derivatives involving hydride reduction and reductive amination strategies, respectively.

### 2.2.8. Synthesis of functionalized unnatural α-amino acid derivatives *via* phase transfer catalyst-based reactions.

Maruoka[68a] *et al.* described the stereoselective synthesis of β-alkyl α-amino acid derivative **37c** *via* the phase transfer catalyst-based alkylation of glycinate Schiff base **37b** with secondary alkyl halide **37a** under the influence of the chiral quaternary ammonium bromide **37e** and 18-crown-6 (Scheme 25). The *syn* isomer of β-alkyl α-amino acid derivative **37c** was selectively converted into the corresponding *anti* isomer, allowing the preparation of all the stereoisomers of β-alkyl α-amino acid derivatives. Along this line, Jørgensen's[68b] and Takemoto's[68c] groups also showed the synthesis of enantiopure polyfunctionalized amino acid derivatives involving the phase transfer catalysts.

### 2.2.9. Synthesis of functionalized unnatural α-amino acid derivatives *via* carbenes.

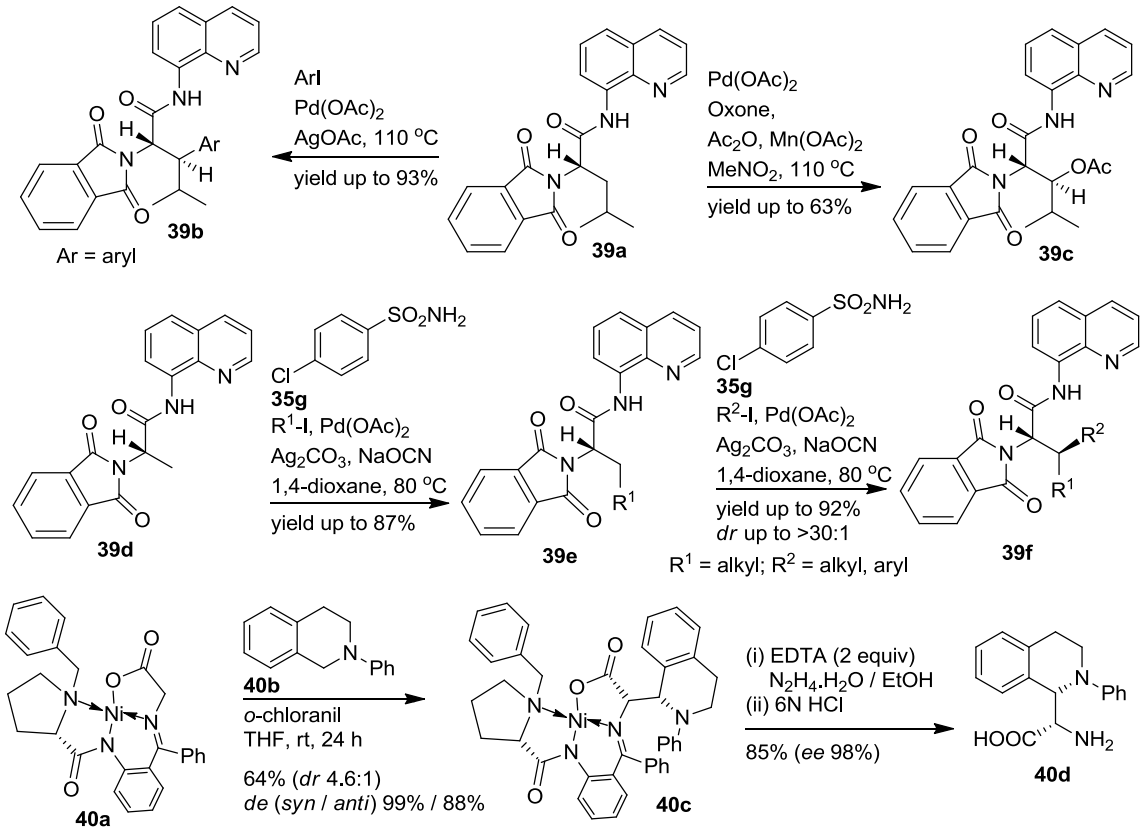



**Scheme 26.** Synthesis of α-amino acid derivatives (**38c**, **38f**, **38g**).

Mezzetti[68d] *et al.* reported the enantioselective Rh-catalyzed aziridination of imines **38a** with ethyl diazoester **38b** (carbene source), which gave the substituted aziridine-based amino acid systems **38c** (Scheme 26). The proposed reaction mechanism[68d] implied the carbene transfer

from an intermediate diazoalkane complex rather than from a carbene complex. Cativiela[68e] developed a versatile method for the preparation of racemic δ,δ-dimethylproline and δ,δ-dimethyl-β-phenylproline derivatives **38g**. Cativiela showed that the treatment of an α-diazo-β-oxo ester **38e** with rhodium diacetate followed by the intramolecular N–H insertion of the metal carbenoid generated *in situ* led to the formation of δ,δ-dimethyloxoproline system **38f**. Further functional group transformation on the δ,δ-dimethyloxoproline system **38f** successfully afforded the δ,δ-dimethyl-β-phenylproline derivative **38g** (Scheme 26).

### 2.2.10. Synthesis of functionalized unnatural α-amino acid derivatives *via* C-H activation reactions.



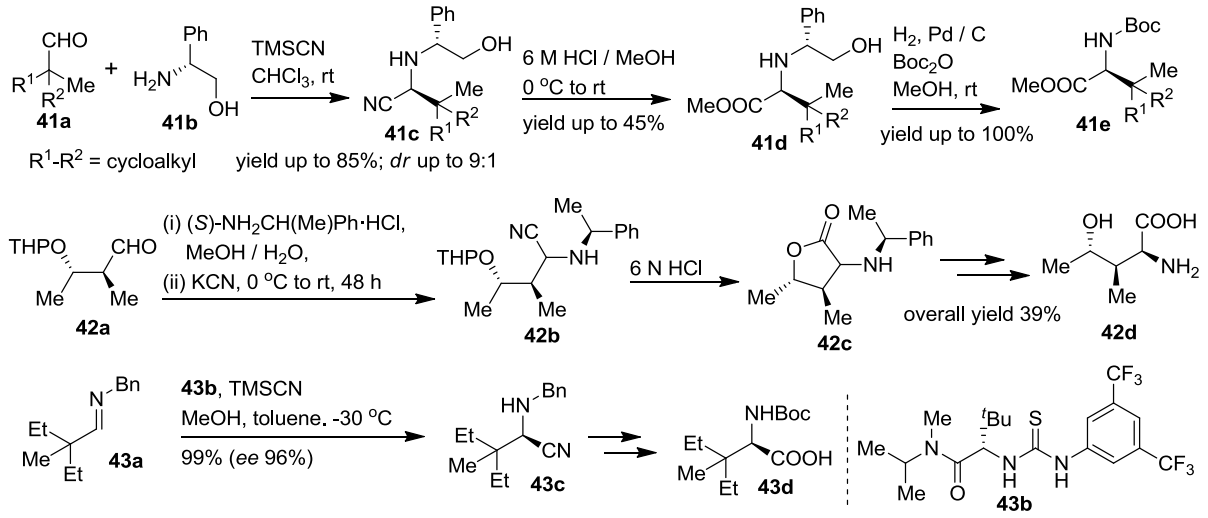

**Scheme 27.** Synthesis of α-amino acid derivatives (**39b**, **39c**, **39e**, **39f**, **40d**).

Corey[69a] *et al.* discovered a method in which *N*-phthaloyl α-amino acid amides of 8-aminoquinoline **39a** was selectively acetoxylated or arylated *via* C-H activation at the β-carbon. This method provided an easy access to a broad range of unnatural (*S*)-α-amino acid derivatives **39b** and **39c** (Scheme 27). Shi[69b] *et al.* developed the palladium-catalyzed

stereoselective synthesis of various β,β'-disubstituted α-amino acids **39f** through a sequential C($sp^3$)-H functionalization approach using the 8-aminoquinoline auxiliary (Scheme 27). Shi[69c] *et al.* also described a method for diastereoselective fluorination of β-methylene C($sp^3$)−H bonds of α-amino acid derivatives with the help of picolylamine based directing group. The process led to the formation of an array of β-fluorinated α-amino acid derivatives. Along this line, Chen[69d] *et al.* reported the Pd-catalyzed alkylations of methylene C($sp^3$)−H bonds of *N*-phthaloyl α-amino acid amides of 8-aminoquinoline. Liu[69e] *et al.* devised the C-H activation of amine **40b** with chiral nickel (II) glycinate **40a** using *o*-chloranil as the oxidant that afforded the adduct **40c** *via* the oxidative crossdehydrogenative coupling (CDC) reaction. Product **40c** was further transformed into an amino acid system **40d** (Scheme 27).

### 2.2.11. Synthesis of functionalized unnatural α-amino acid derivatives *via* Strecker reaction.

Arasappan[70a] *et al.* developed an efficient route towards the synthesis of amino acid derivatives **41e** containing β-quaternary center *via* the diastereoselective Strecker reaction of imine generated from aldehydes **41a** and (*R*)-phenylglycinol (**41b**). The addition products **41c** were subjected to hydrolysis and hydrogenolysis to afford the amino acid derivatives **41e** (Scheme 28).



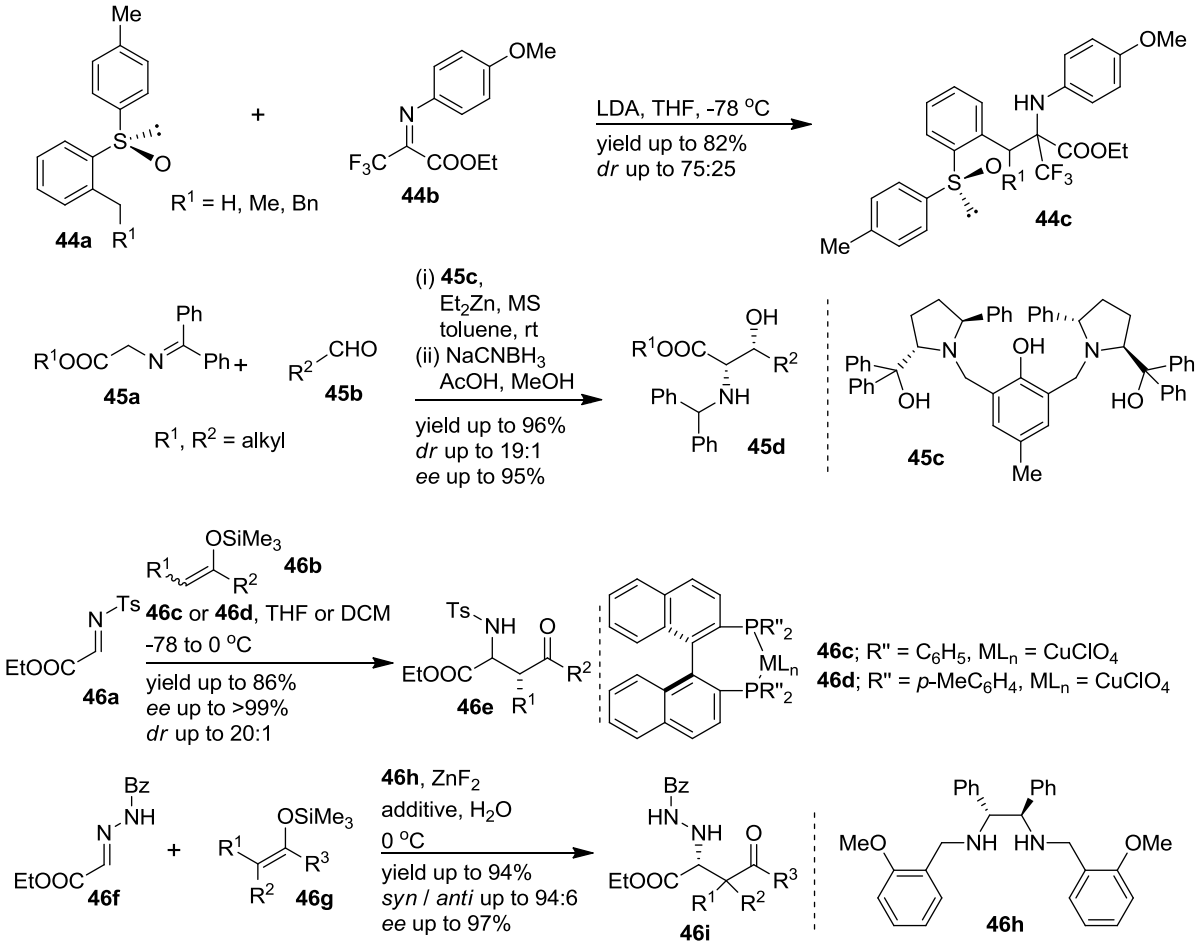

**Scheme 28.** Synthesis of α-amino acid derivatives (**41d**, **41e**, **42d**, **43d**).

Sasaki[70b] *et al.* reported the synthesis of optically pure (2*S*,3*R*,4*S*)-4-hydroxyisoleucine (**42d**) involving the asymmetric Strecker reaction of an imine generated from an aldehyde **42a** and

(*S*)-α-methylbenzylamine as a key step (Scheme 28). Jacobsen[70c] *et al.* reported the synthesis of highly enantiomerically enriched unnatural amino acid **43d** using a chiral thiourea catalyst **43b** to control the hydrocyanation of imine **43a** (Scheme 28).

### 2.2.12. Synthesis of functionalized unnatural α-amino acid derivatives *via* nucleophilic addition reactions.

Fustero[70d] *et al.* described the diastereoselective addition of chiral 2-*p*-tolylsulfinylbenzyl carbanions **44a** to trifluoromethyl α-imino ester **44b** to afford a series of fluorinated quaternary α-amino acid derivatives **44c** (Scheme 29). Trost[70e] *et al.* reported a zinc−prophenol (**45c**) catalyzed direct asymmetric aldol reaction between glycine Schiff bases **45a** and aldehydes **45b** for obtaining the *syn*-β-hydroxy-α-amino esters **45d** (Scheme 29).

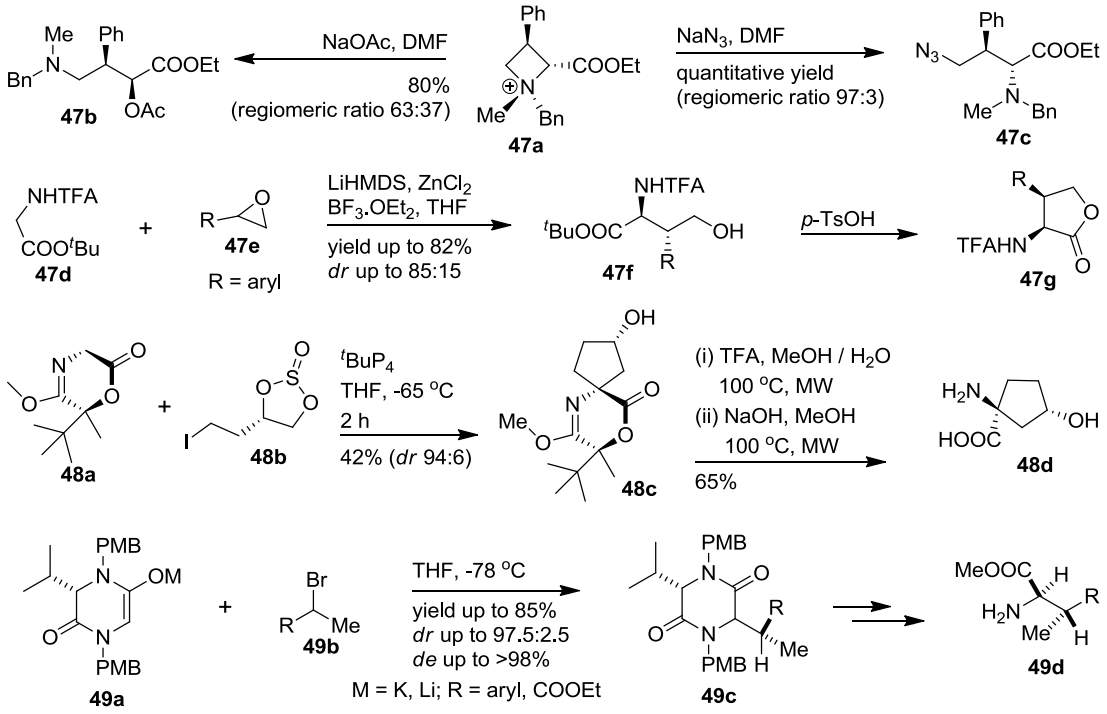



**Scheme 29.** Synthesis of α-amino acid derivatives (**44c**, **45d**, **46e**, **46i**).

Lectka's[70f] group reported the synthesis of unnatural amino acids through the catalytic, asymmetric alkylation of α-imino ester **46a** with enol silanes **46b** using the chiral transition metal-phosphine complexes **46c**/**46d** as the catalysts (Scheme 29). Kobayashi[70g] *et al.* developed an organo-catalyzed efficient enantio- and diastereoselective Mannich-type reactions of a hydrazono ester **46f** with silicon enolates **46g** in water medium to obtain the *syn* or *anti* adducts **46i** from (*E*)- or (*Z*)-silicon enolate (Scheme 29).

### 2.2.13. Synthesis of functionalized unnatural α-amino acid derivatives *via* ring opening reactions.

Couty's[71a] group showed the ring-opening of enantiopure azetidinium salts **47a** (which was prepared by alkylation of the corresponding azetidine with methyl trifluoromethanesulfonate) by the treatment of azetidinium salts with an array of nitrogen or oxygen nucleophiles (Scheme 30).




**Scheme 30.** Synthesis of α-amino acid derivatives (**47b**, **47c**, **47f**, **48d**, **49d**).

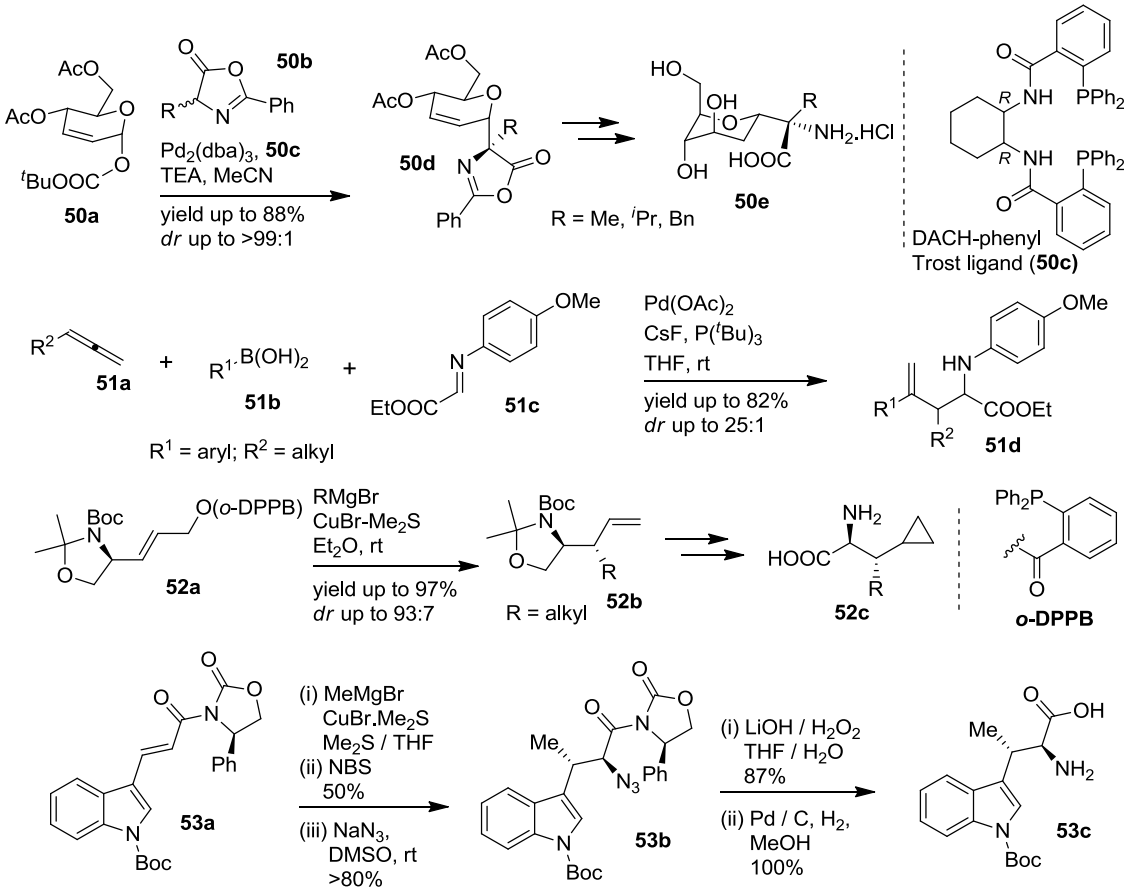
Regioselective opening occurred at the C-4 position of azetidinium ion **47a** with azide, which afforded the β-substituted α-amino acid derivative **47c**. On the other hand, the C-2 ring

opening of azetidinium ion **47a** by the attack of acetate afforded the γ-amino acid derivative **47b**. Kazmaier[71b] *et al.* performed a regioselective ring opening reaction of aryl epoxides **47e** with amino acid ester enolates **47d**. This method gave a direct access to β-hydroxymethyl phenylalanine derivatives **47f** (Scheme 30).

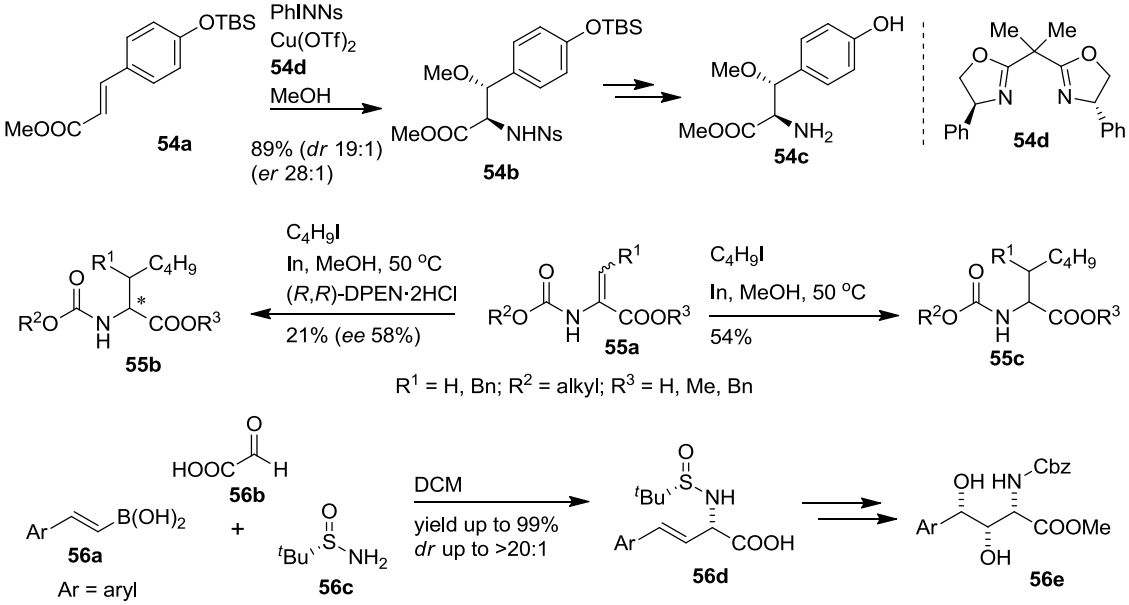
### 2.2.14. Miscellaneous methods for synthesis of unnatural α-amino acid derivatives.

Wanner and Kulig[71c] reported the synthesis of all four stereoisomers of 1-amino-3-hydroxy-cyclopentane-1-carboxylic acid (**48d**) based on a chiral glycine equivalent **48a** (Scheme 30). The phosphazenic base $^{t}BuP_4$ mediated alkylation of (*S*)- and (*R*)-glycine equivalent with the respective stereoisomers of 4-(2-iodoethyl)-1,3,2-dioxathiolan-2-oxide (**48b**) was considered to be the crucial step of the performed synthetic sequence. Davies[71d] *et al.* showed highly enantioselective alkylations of enolates of (*S*)-*N*,*N*'-bis-(*p*-methoxybenzyl)-3-iso-propylpiperazine-2,5-dione (**49a**) with **49b** which afforded the substituted diketopiperazines **49c** containing two new stereogenic centers (Scheme 30). Deprotection followed by hydrolysis of **49c** provided a route to the homochiral methyl 2-amino-3-aryl-butanoates and 3-methyl-aspartates **49d**.

Giacomo and Serra[71e] *et al.* reported the stereoselective synthesis of α-D-*C*-mannosyl-(*S*)-amino acid derivatives **50e**. The Pd-catalyzed reaction of 4,6-di-*O*-acetyl α-pseudoglucal carbonate **50a** with racemic alanine-, valine-, and phenylalanine-derived azalactones **50b** gave the corresponding (4*S*)-4-α-D-C-mannosyl-2-phenyloxazol-5(4H)-one derivatives **50d** which were transformed into the α-D-*C*-mannosyl-(*S*)-amino acid derivatives **50e** (Scheme 31). Malinakova[71f] *et al.* demonstrated a Pd(II)-catalyzed three-component coupling of boronic acids **51b**, allenes **51a** and ethyl iminoacetate **51c**, which gave highly substituted unnatural α-amino acid derivatives **51d** (Scheme 31). Breit[72a] *et al.* reported the diastereoselective synthesis of β-substituted α-amino acids **52c** *via* a copper-mediated *o*-DPPB directed allylic substitution reaction with Grignard reagents. (Scheme 31). Hruby's[72b] group synthesized (2*S*,3*S*)-β-methyltryptophan **53c** with the aid of an oxazolidinone chiral auxiliary. Michael addition of **53a** with methyl magnesium bromide and CuBr–$Me_2S$ in methyl sulfide was carried out to afford the *trans* Michael addition product which was further converted into an azide **53b**. Hydrolysis of the chiral auxiliary and hydrogenation of **53b** gave (2*S*,3*S*)-β-methyltryptophan (**53c**; Scheme 31).

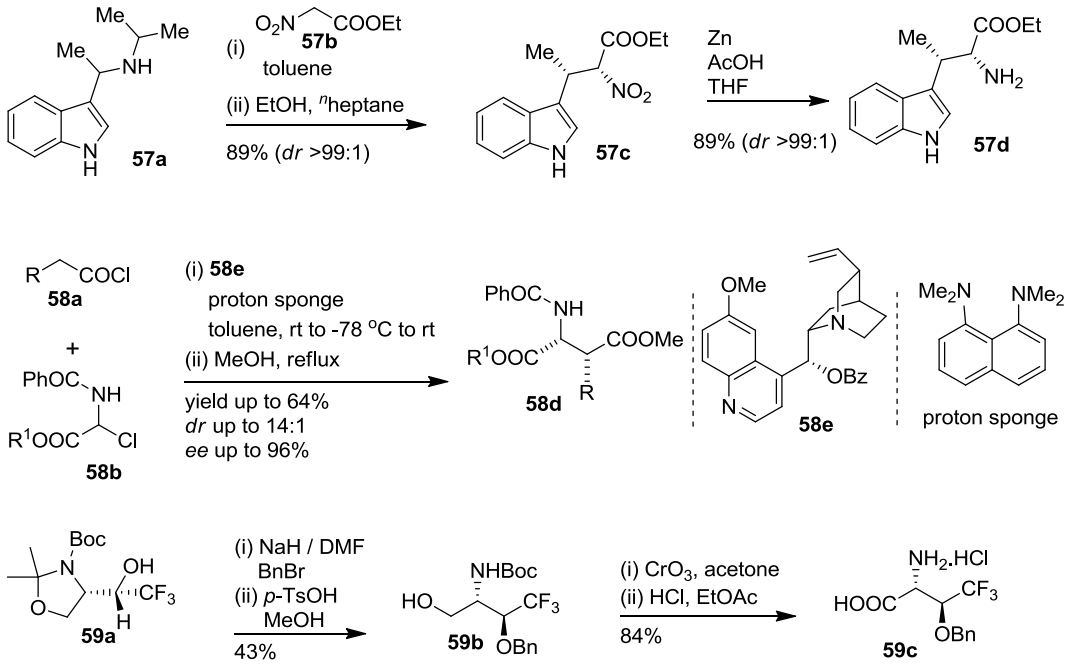



**Scheme 31.** Synthesis of α-amino acid derivatives (**50e**, **51d**, **52c**, **53c**).




**Scheme 32.** Synthesis of α-amino acid derivatives (**54c**, **55c**, **56e**).

Lipton[72c] *et al.* synthesized the nonproteinogenic amino acid (2*R*,3*R*)-β-methoxytyrosine derivative **54c** (**54c** is a constituent of several cyclic depsipeptide natural products, Scheme 32). The synthesis of **54c** started with aziridination of **54a**. The aziridine thus formed was dissolved in methanol to give **54b**. The compound **54b** was further converted into (2*R*,3*R*)-β-methoxytyrosine derivative **54c** (Scheme 32). Jiang[72d] *et al.* reported the HZSM-5-supported palladium-catalyzed amidocarbonylation reaction of aldehydes for the construction of *N*-acylated amino acid derivatives. Szymoniak[73a] *et al.* described a simple and stereoselective method for the preparation of (*Z*)-2-substituted 1-aminocyclopropanecarboxylic acid derivatives involving the stereoselective Ti-mediated coupling reaction.




**Scheme 33.** Synthesis of α-amino acid derivatives (**57d**, **58d**, **59c**).

Yajima[73b] *et al.* reported the synthesis of racemic and optically pure β-perfluoroalkyl α-amino acid derivatives **55b** and **55c** involving the In-mediated addition of perfluoroalkyl radicals to dehydroamino acid derivatives **55a** followed by asymmetric protonation (Scheme 32). Hutton[73c] *et al.* demonstrated the Petasis reactions of substituted styrenylboronic acids **56a**, glyoxylic acid (**56b**) and *tert*-butylsulfinamide (**56c**) to produce β,γ-dehydrohomoarylalanine derivatives **56d**. Subsequent asymmetric dihydroxylation gives the corresponding protected β,γ-dihydroxyhomoarylalanines **56e** (Scheme 32).

Sawai[74a] *et al*. developed the C–C bond forming reaction of **57a** with ethyl nitroacetate (**57b**) to give **57c** as mixture of diastereomers. The subsequent reduction of nitro group of major diastereomer of **57c** using zinc in THF/acetic acid successfully proceeded without epimerization to provide *rac-threo*-β-methyltryptophan ethyl ester (**57d**; Scheme 33). Lectka[74b] *et al.* reported a catalytic asymmetric procedure for the preparation of β-substituted α-amino diacid ester **58d** from *N*-acyl-α-chloroglycine esters **58b** and acid chlorides **58a** in the presence of cinchona alkaloid catalyst **58e** (Scheme 33). Miller[74c] *et al.* described an efficient synthesis of the non-proteinogenic amino acid (2*R*,3*S*)-4,4,4-trifluoro-*O*-benzyl-threonine (**59c**). Starting with commercially available (*S*)-Garner's aldehyde, the desired amino acid **59c** was prepared as its hydrochloride salt in five steps (Scheme 33).

## 2.3. 3-Substituted-3-aminooxindoles and oxindole-based unnatural amino acid derivatives.

Oxindole framework having a tetra-substituted carbon stereocenter (C3-carbon) is a promising bioactive heterocyclic scaffold[75-77] and present as the core unit in several pharmaceutical lead compounds, synthetic and naturally occurring oxindoles.[75-78] Oxindole molecules possessing a heteroatom (N or O or S) at the C3 position are considered as important heterocyclic building blocks, e.g. convolutamydine A (**60j**),[79a] spirobrassinin (**60i**)[79b] and chartellines A-C (**60a**-**60c**)[79c,79d] (Figure 6). Several 3-amino oxindole derivatives were reported to exhibit a variety of biological activities.[80] The 3-amino-2-oxindole molecule AG-041R (**60d**)[80a,80b] was reported to function as a gastrin/CCK-B receptor antagonist and the 3-amino-2-oxindole (**60k**) was reported to work as HIV protease inhibitor.[78d] The thiazolidinone spiro-fused to indolin-2-one (**60e**) function as inhibitors of the *Mycobacterium tuberculosis* protein tyrosine phosphatase B.[80c] The spirotetrahydro β-carboline (**60g**) was reported to act as the potential antimalarial agent.[80d] The spirooxindole spiroindolinone (**60f**) was found to act as the antagonists of CRTH2[80e] (Figure 6). AstraZeneca's spirohydantoin[80f,80g] was reported to function as a TRPV1 antagonist for chronic pain control. The 3-aminooxindole molecule SSR-149415 (**60h**),[80h-80j] was reported to control anxiety and depression.

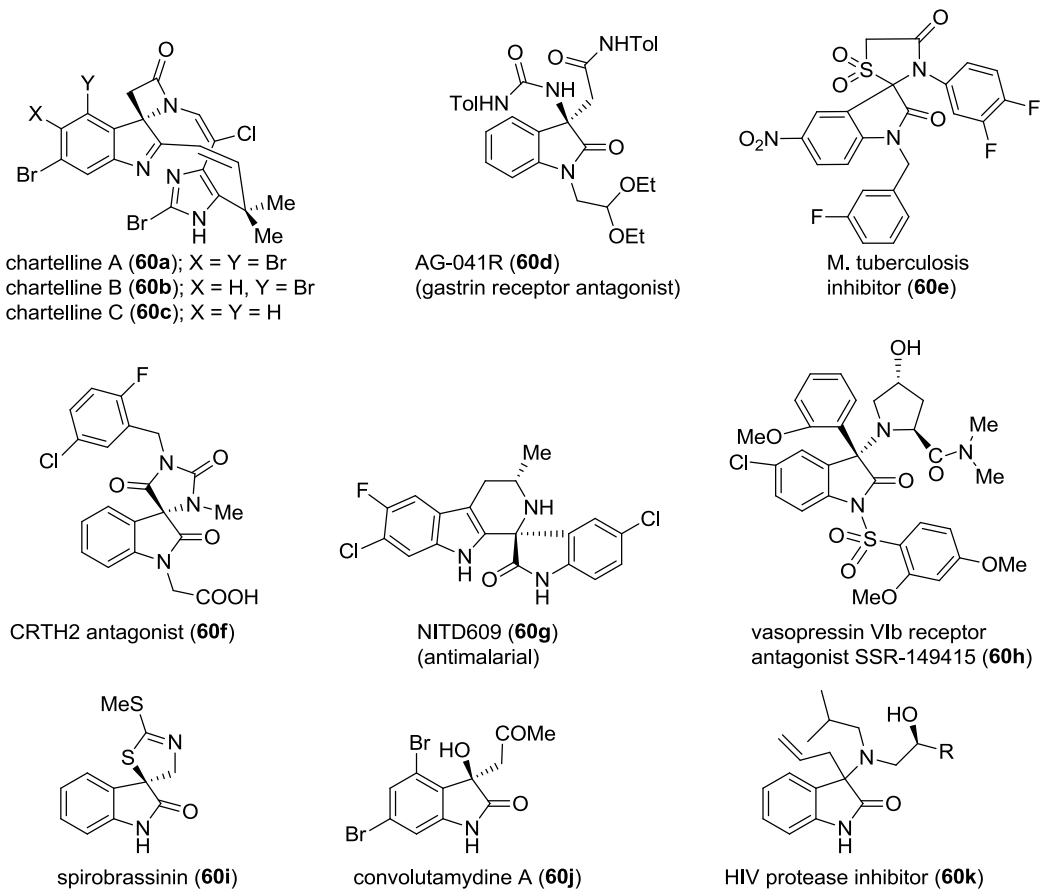
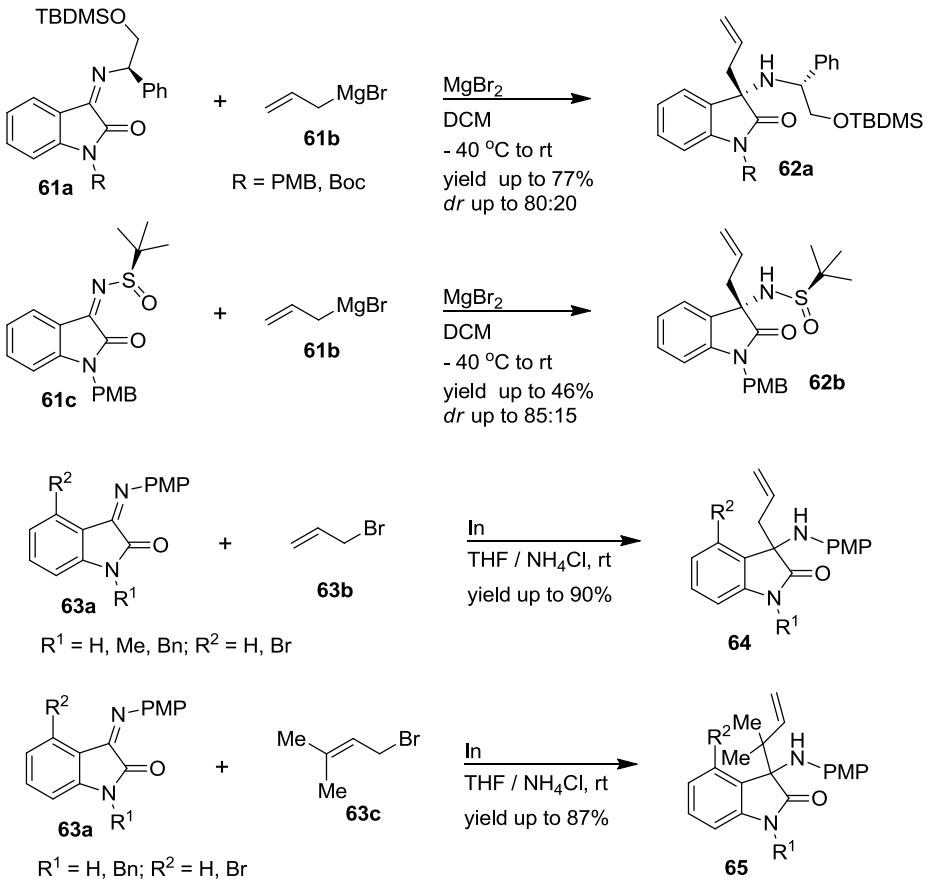



**Figure 6.** Biologically relevant compounds having 3-amino-oxindole core unit.

Due to their synthetic utility and biological activities, several methods have been developed for synthesizing, especially, 3-aminooxindole molecules which includes, nucleophilic addition of organometallic agents to isatin-derived ketimines,[81] alkylation of 3-aminooxindoles,[82] amination of 3-substituted oxindoles,[83] intramolecular arylation,[84] Mannich reaction[85] and other transformations[86] have been devised to synthesize 3-substituted 3-aminooxindoles.

Noticeably, the metal-mediated addition of carbon nucleophiles to ketimines derived from isatin represents a straightforward route to 3-substituted-3-aminooxindoles, however, only limited reports are available which deal with the metal-mediated addition of carbon nucleophiles to ketimines derived from isatin. Formerly, Silvani[81a] *et al.* described the addition of allylmagnesium bromide (**61b**) to imino-isatins **61a** to give 3-allyl-3-aminooxindoles **62a** (yield up to 77% and *dr* up to 80:20, Scheme 34). The same group also

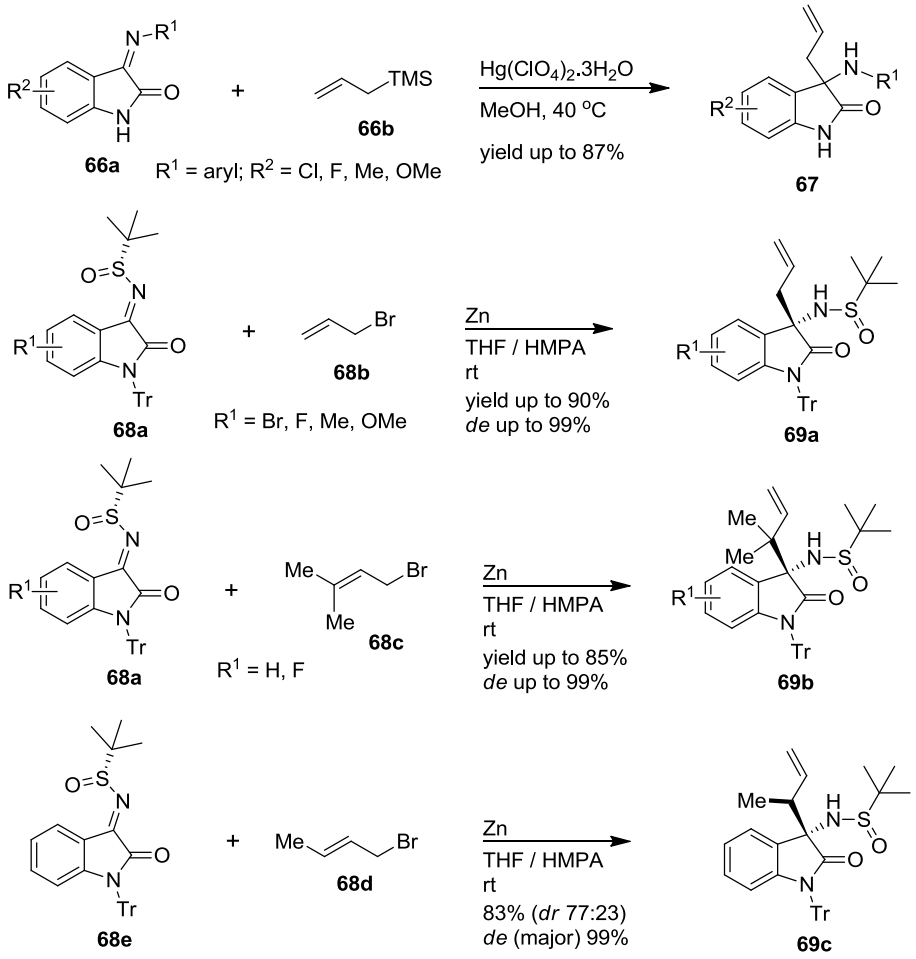
reported the synthesis of 3-allyl-3-aminooxindoles **62b** *via* the addition of allylmagnesium bromide (**61b**) to chiral imino-isatin **61c** having a chiral auxiliary.




**Scheme 34.** Construction of homoallylic-3-amino oxindoles (**62a**, **62b**, **64**, **65**).

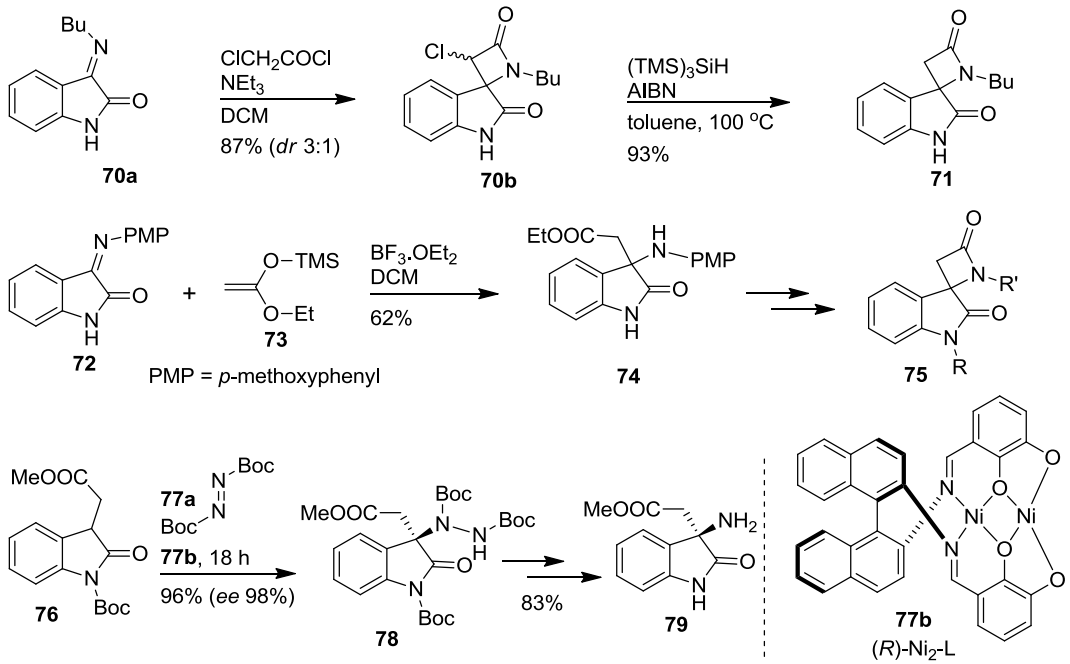
Successively, Alcaide and Almendros[81b] group reported the allylation of isatin ketimines **63a** with allyl bromide (**63b**) which gave 3-allyl-3-aminooxindoles **64** with one stereocenter (Scheme 34). They also carried out the addition of prenyl bromide (**63c**) to isatin ketimines **63a** which gave the γ-addition product 3-(2-methylbutene)-3-aminooxindoles **65** (Scheme 34). Along this line, Zhou[81c] *et al.* demonstrated $Hg(ClO_4)_2 \cdot 3H_2O$-catalyzed Sakurai–Hosomi allylation of isatin ketimines **66a** using allyltrimethylsilane (**66b**) (Scheme 35). After that, Xu[81d] and co-workers reported the Zn-mediated addition of allyl bromide (**68b**) to isatin ketimines **68a** derived from chiral *N*-*tert*-butanesulfinamide. They have also shown the prenylation of isatin ketimines **68a** afforded the γ-addition product 3-(2-methylbutene)-3-aminooxindoles **69b**. Xu[81d] and co-workers also showed an example of crotylation of *N*-*tert*-

butanesulfinyl isatin ketimine **68e**, which gave the corresponding enantiomerically enriched quaternary 3-aminooxindole **69c** as diastereomers (*dr* 77:23, Scheme 35).




**Scheme 35.** Construction of homoallylic-3-amino oxindoles (**67**, **69a**, **69b**, **69c**).

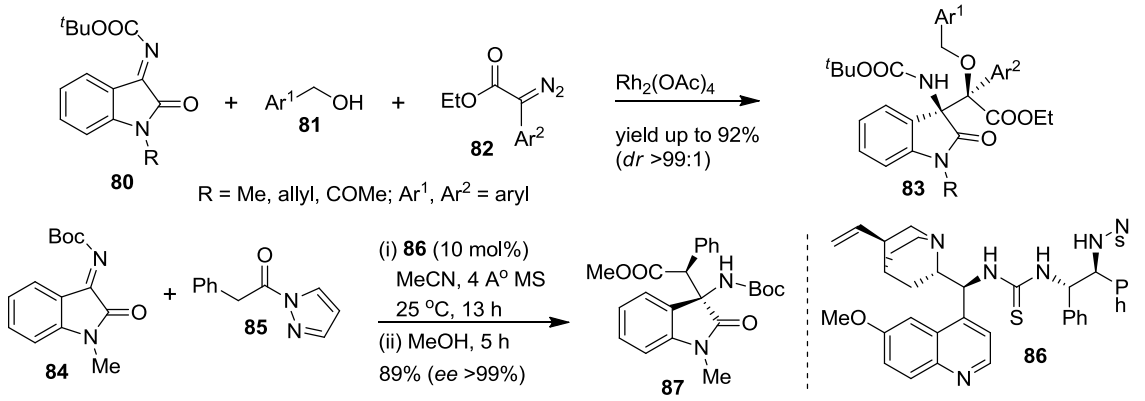
Apart from these reports, Barbier-type or Grignard-type diastereoselective addition of substituted allyl halides with isatin-ketimines and the stereoselective synthesis of 3-allyl-3-amino oxindoles having vicinal stereogenic centers is not explored well.[81] Furthermore, the addition of allyl metal derived from ethyl 4-bromocrotonate with isatin ketamine would be an interesting study to accomplish the synthesis of oxindole-based unnatural amino acid derivatives with multiple stereocenters. A literature survey revealed that there have been only few reports dealing with the construction of oxindole-based unnatural amino acid derivatives, especially, oxindole derivatives appended with a β-amino acid motif.[87]




**Scheme 36.** Synthesis of oxindolinyl β-amino acids/lactams (**71**, **74**, **75**, **79**).

Weinreb[87a] *et al.* demonstrated the construction of spirocyclic β-lactam moieties **71** as a model system for the synthesis of chartelline alkaloids using a Staudinger imine–ketene cycloaddition as one of the key steps (Scheme 36). Nishikawa and Isobe[87b] showed the Mannich reaction of isatin imine **72** with ketene silyl acetal **73** which gave the β-amino ester **74** followed by the formation of β-lactam **75** (Scheme 36). Matsunaga and Shibasaki[87c] reported an enantioselective amination of 3-alkylsubstituted oxindoles **76** with azodicarboxylates **77a** to give 3-aminooxindoles **78** with the help of $Ni_2$-Schiff base chiral complex **77b**. The product **78** was converted to oxindolinyl β-amino acid methyl ester **79** (Scheme 36).

Reddy[87d,87e] and co-workers reported the stereoselective synthesis of oxindole-derived α-alkoxy β-amino acid derivatives **83** with excellent diastereoselectivity involving a three-component reaction of isatin ketimine **80**, benzyl alcohol **81** and methyl 2-diazoarylacetate **82** (Scheme 37). The synthesis of 2-oxindole-based chiral β-amino acid ester **87** was reported by Sha and Wu[87f] involving the Mannich-type reaction of *N*-Boc ketimine **84** with pyrazoleamide **85** catalyzed by chiral thiourea organocatalyst **86** (Scheme 37).




**Scheme 37.** Construction of oxindole-based β-amino acids (**83** and **87**).

### 2.4. Homoserine lactone scaffolds (α-amino butyrolactone scaffolds).

Homoserine γ-lactone skeletons (γ-butyrolactones) are a common feature in certain biological analogs including antiallergic, immunosuppressant and antineoplastic agents.[88,89] Several *N*-protected homoserine γ-lactones were employed in numerous biological studies and have served as precursors of various non-proteinogenic amino acid derivatives and organic molecules.[90] Nealson's[91a] and Eberhard's[91b] groups independently described the cell density phenomenon of bioluminescence in bacteria and identified the signaling component as *N*-(3-oxohexanoyl) homoserine lactone.[91c]

Many bacterial species control their physiology in response to the change in their population size by the activation of complex signaling pathways called quorum sensing (QS).[92a] Quorum sensing is cell to cell communication phenomena between bacteria by sensing the level of a chemical signal using small diffusible molecules, also known as autoinducers. *N*-acylated derivatives of *L*-homoserine lactone (AHLs or *N*-AHLs) act as autoinducers in Gram-negative bacteria to achieve quorum sensing (Figure 7).[93-96] Revealing the mechanism of the quorum sensing process could be highly beneficial to figure out the secrets of other signaling processes and provide potential hints to develop new anti-infective strategies. In this regard, significant amount of work related to the synthesis and testing of various homoserine lactone analogs has already been reported. [93-96]

The native or non-native homoserine lactone analogs examined so far have been assembled (a) by varying the acyl unit while keeping the lactone skeleton unchanged and (b) from the

amino acid resources having one stereocenter e.g. the relatively very expensive homoserine γ-lactone or L-homoserine and L-aspartic acid or L-methionine.[97a-97c] Enormous methods are available for synthesizing the native or non-native homoserine lactone analogs having no other substituents at the β- or γ-carbons of homoserine lactones.[97d-97h]

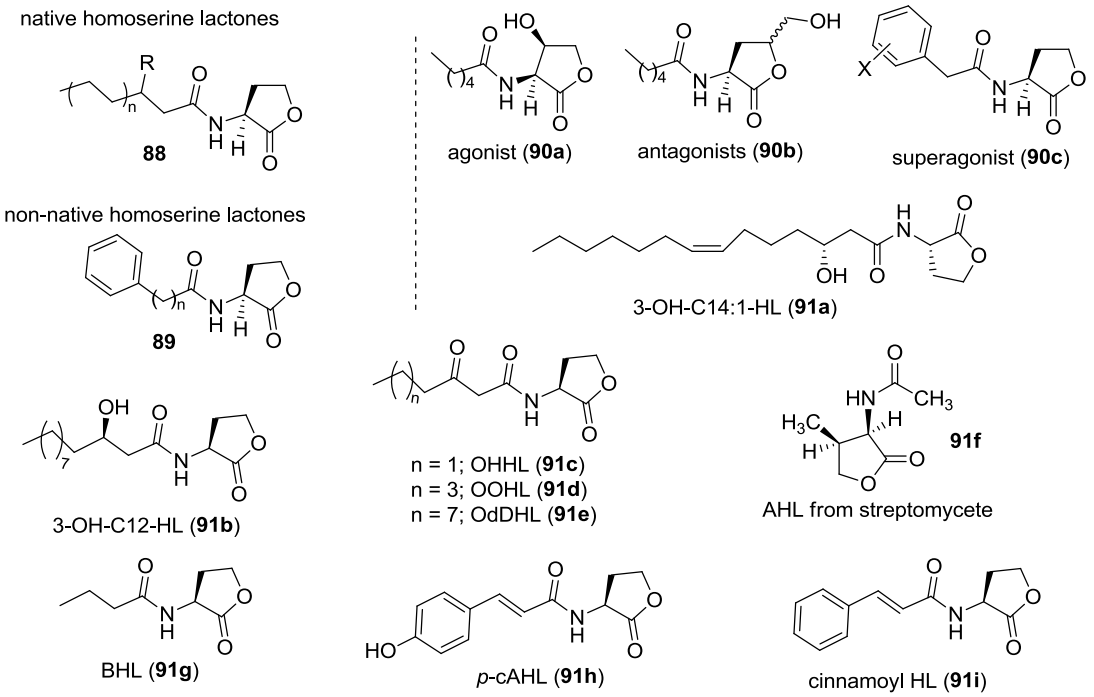
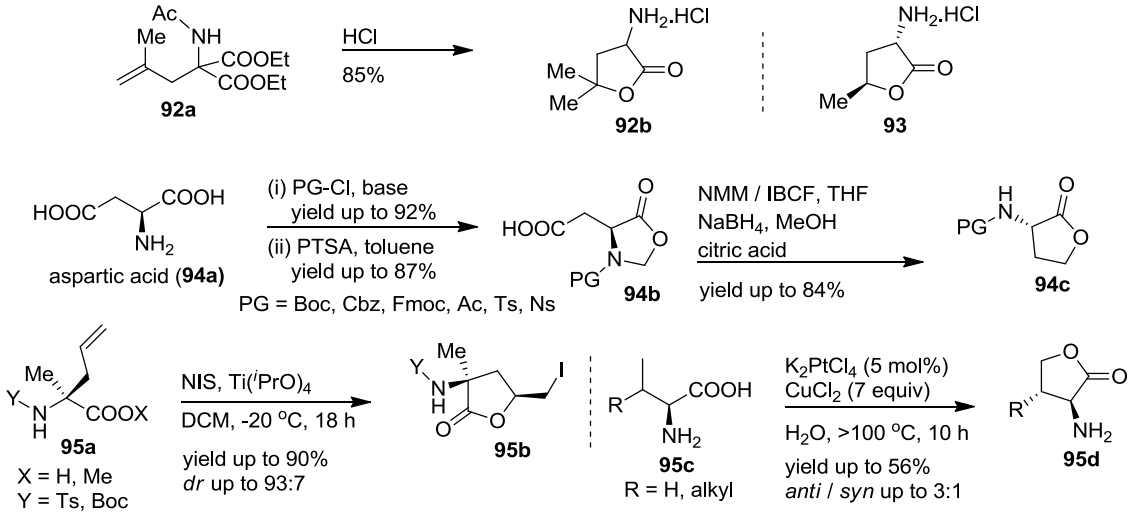



**Figure 7.** Native and non native homoserine lactones (AHLs).

Some of the representative literature methods available for synthesizing the native or non-native homoserine lactone analogs are outlined here. Formerly, Fillman[97a] *et al.* reported the synthesis of γ-hydroxyleucine lactone hydrochloride (**92b**) as an intermediate during the hydrochloric acid promoted hydrolysis of methallylacetamido malonic ester **92a** into γ-hydroxyleucine (Scheme 38). Similarly, the lactone hydrochloride **93** was also synthesized as an intermediate during the synthesis of γ-hydroxynorvaline by Roumestant[97b] (Scheme 38). Schwan[97c] *et al.* revealed the preparation of (*S*)-*N*-protected homoserine γ-lactones **94c** by converting *L*-aspartic acid (**94a**) to an oxazolidinone **94b** followed by selective reduction and acid-catalyzed or microwave assisted cyclization (Scheme 38).

Scrimin and Licini[97d] reported highly chemo- and stereoselective synthesis of the γ-lactones **95b** *via* iodolactonization of (*S*)-allylalanine derivatives **95a** (Scheme 38). Sames's[97e] group

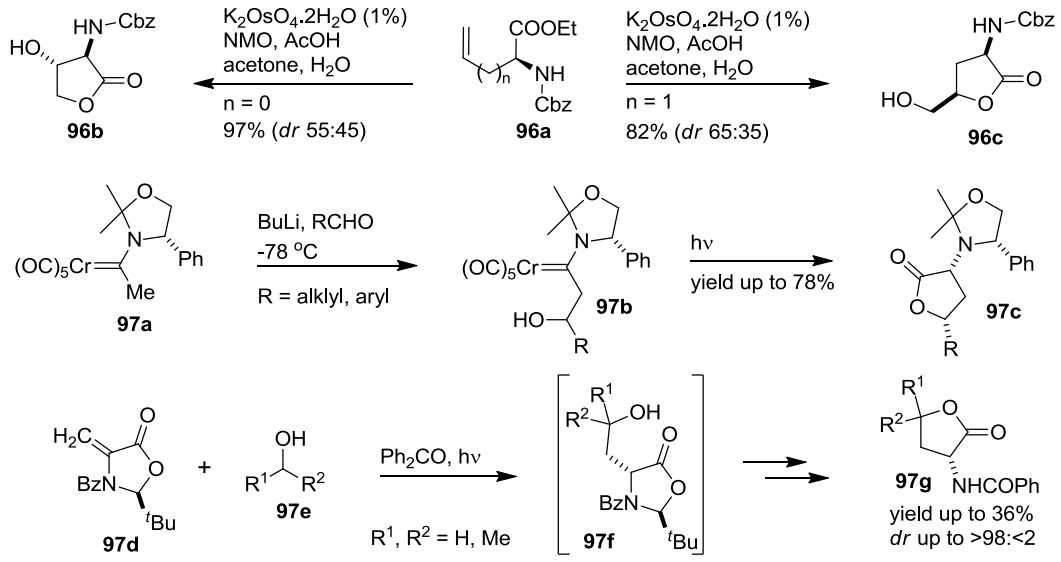
revealed the regio- and stereoselective C-H bond functionalization of amino acids **95c** giving the lactones **95d** (Scheme 38). Neilsen[97f] and co-workers synthesized the new class of homoserine lactone-based autoinducers **96b** and **96c** having substituent at the 3- and 4-positions of the lactone ring from α-substituted amino acids **96a** (Scheme 39).




**Scheme 38.** Synthesis of homoserine lactone analogues (**92b**, **93**, **94c**, **95b**, **95d**).

Hegedus[97g] *et al.* demonstrated the preparation of 4-substituted 2-aminobutyrolactones **97c** using aldol reaction of optically active chromium aminocarbene complexes **97a**. Photolysis of the aldol product **97b** gave optically active 4-substituted 2-aminobutyrolactones **97c**, which were hydrolyzed to obtain γ-hydroxy α-amino acids (Scheme 39). Pyne[97h] *et al.* reported the synthesis of optically active homoserine derivatives **97g** *via* the photoinduced radical addition of alcohols **97e** or ethers with chiral 4-methyleneoxazolidin-5-one **97d** (Scheme 39).

A literature survey revealed that there exist only limited reports dealing with the stereoselective construction of *N*-protected homoserine γ-lactones having substituents at the β- or γ-carbon. Therefore, a part of the thesis work deals with a straightforward stereoselective lactonization protocol which enables the introduction of some substituents at the β- or γ-carbon of the lactone ring with high degree of stereocontrol.



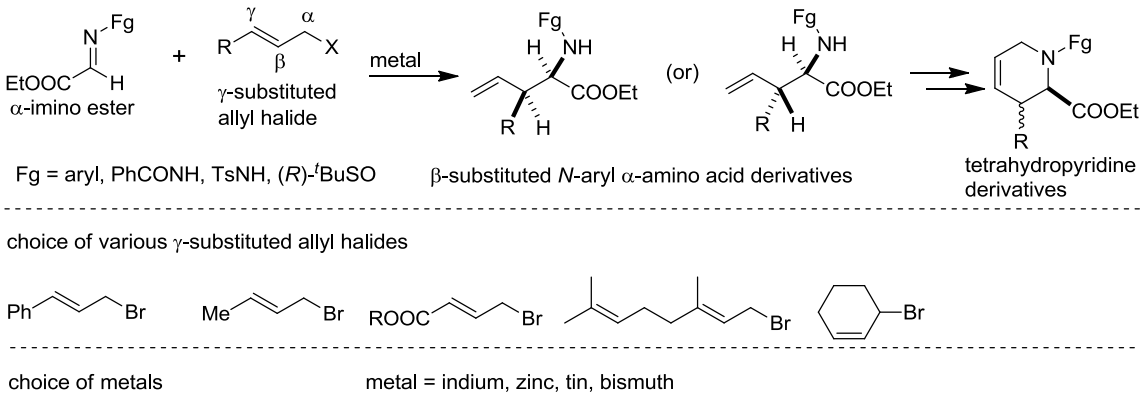

**Scheme 39.** Synthesis of homoserine lactone analogues (**96b**, **96c**, **97c**, **97g**).

It is apparent from the above illustrated examples in various sections that a variety of strategies exist for the synthesis of unusual or unnatural amino acids and related scaffolds. Moreover, a concise survey in the literature revealed that there have been continuous efforts on the synthesis and chemistry of unnatural amino acid derivatives and there exist numerous bioactive molecules having the unnatural amino acid moieties. Furthermore, unnatural amino acid derivatives having multiple stereocenters are recognized as common structural units in a range of naturally existing biologically relevant compounds.

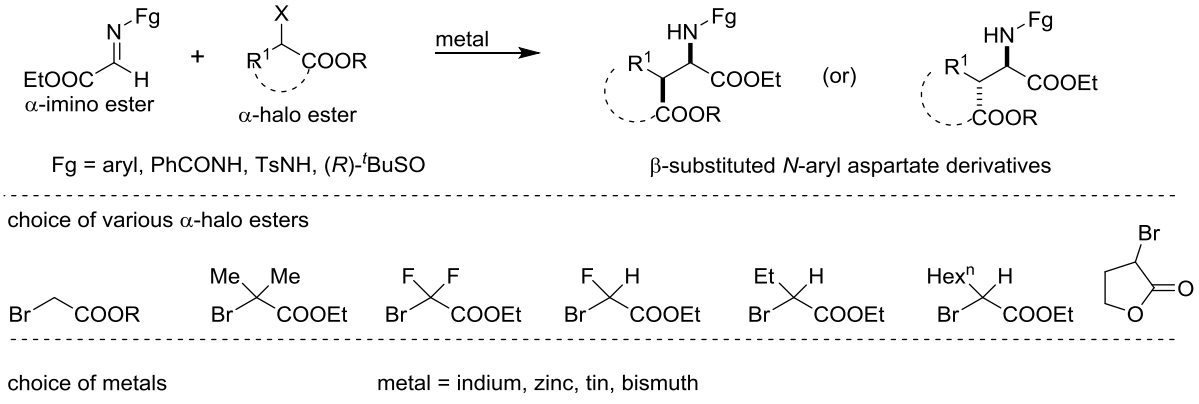
Conceptually, the Barbier type reactions represents a valuable strategy for the construction of unnatural amino acid derivatives starting from relatively simple precursors. Hence, efforts to approach the naturally existing amino acid based bioactive molecules and other synthetic unnatural amino acid scaffolds *via* Barbier-type reactions with high degree of stereocontrol would be an interesting and appealing method to explore.

**3.1. Objective 1.** Inspired by the encouraging developments on the construction of unnatural amino acid analogs, the foremost objective of the present work is to explore the metal-mediated addition of substituted alkyl halides to imine systems for synthesizing new β-substituted unnatural amino acid derivatives.

***Objective 1a. Diastereoselective Barbier-type addition of γ-substituted allyl halides to α-imino esters and construction of β-substituted N-aryl α-amino acid derivatives.***




***Objective 1b. Diastereoselective Reformatsky-type addition of α-halo esters to α-imino esters and construction of functionalized aspartic acid derivatives.***



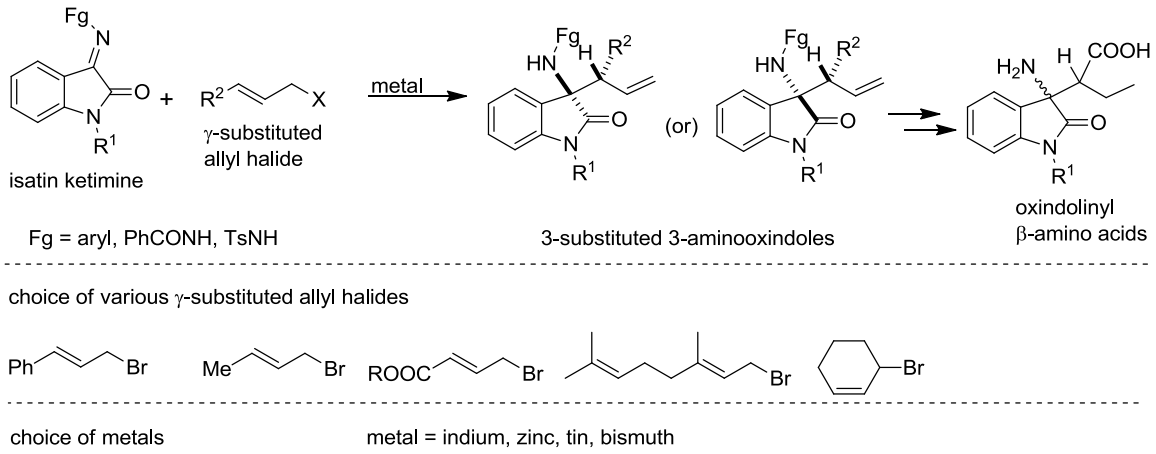

Especially, it was planned to examine (a) the indium-mediated Barbier-type reaction and the reactivity pattern of the addition of a variety of γ-substituted allyl halides to α-imino ester systems (objective 1a); (b) the indium-mediated Reformatsky-type reaction and the reactivity

pattern of the addition of various α-halo esters to α-imino ester systems (objective 1b); and (c) the stereoselective construction of new classes of highly functionalized *N*-aryl α-amino acid derivatives having two vicinal stereocenters *via* the indium-mediated Barbier and Reformatsky-type reactions.

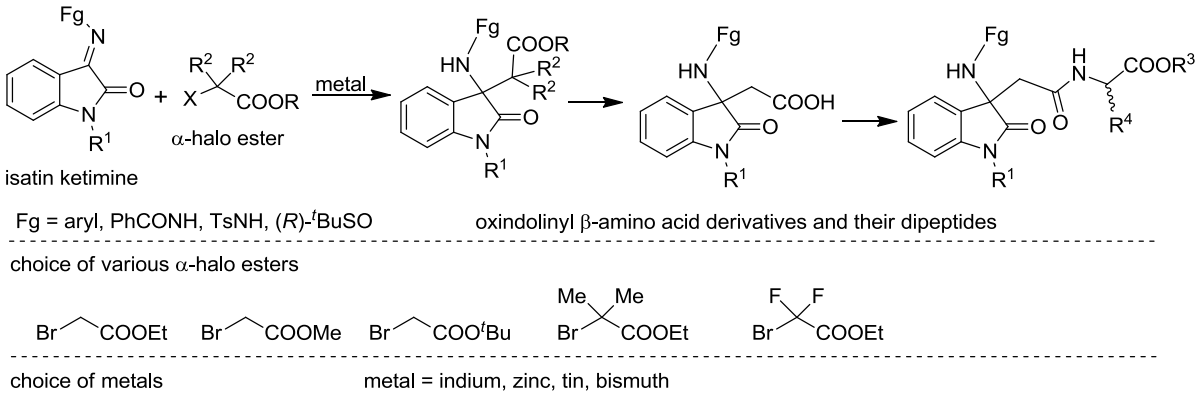
After obtaining the unnatural amino acid derivatives from the corresponding Barbier- or Reformatsky-type reactions, further synthetic transformations are expected to afford various functionalized amino alcohols, *N*-aryl-tetrahydropyridine derivatives and other valuable synthetic intermediates.

**3.2. Objective 2.** Considering the importance of oxindole molecules containing a heteroatom (N or O or S) at the C-3 position, it was envisioned to investigate (a) the diastereoselective construction of 3-aminooxindole systems (oxindole-based homoallylic amines) having two adjacent stereocenters *via* the indium-mediated Barbier-type reaction of a variety of γ-substituted allylic halides with the C=N bond of isatin ketimines (objective 2a); (b) the indium-mediated Barbier-type reactions of alkyl 4-bromocrotonate to isatin ketimine for synthesizing new classes of oxindole-based β-amino acid derivatives possessing two vicinal stereocenters (objective 2a); and (c) the indium- or zinc-mediated Reformatsky-type reactions of α-halo esters with isatin ketimines for synthesizing new classes of oxindole-based β-amino acid derivatives (objective 2b).

***Objective 2a. Barbier-type addition of γ-substituted allyl halides to isatin ketimines and construction of 3-amino-oxindole-based β–amino acid derivatives.***



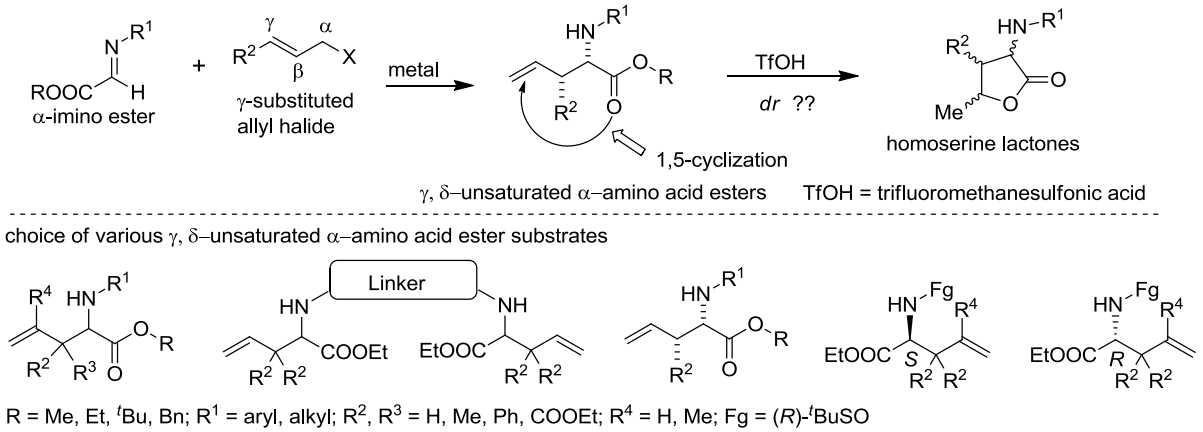
***Objective 2b. Reformatsky-type addition of α-halo esters to isatin ketimines and construction of 3-amino-oxindole-based β–amino acid derivatives.***




After obtaining the oxindole-based β-amino acid derivatives from the Reformatsky-type reactions, further synthetic transformations are expected to afford various oxindole moiety-appended amino alcohols, dipeptide derivatives and other valuable synthetic intermediates.

**3.3. Objective 3.** Given the importance of homoserine lactones (a class of amino acid derivatives) due to their widespread biological applications and usefulness as versatile synthetic building blocks, as a part of the objective of this thesis, it was envisioned to explore (a) the triflic acid-promoted intramolecular stereo- and regioselective direct lactonization of α-amino γ,δ-unsaturated carboxylic acid esters (objective 3); and (b) the stereoselective synthesis of new class of homoserine lactones having multiple stereocenters.

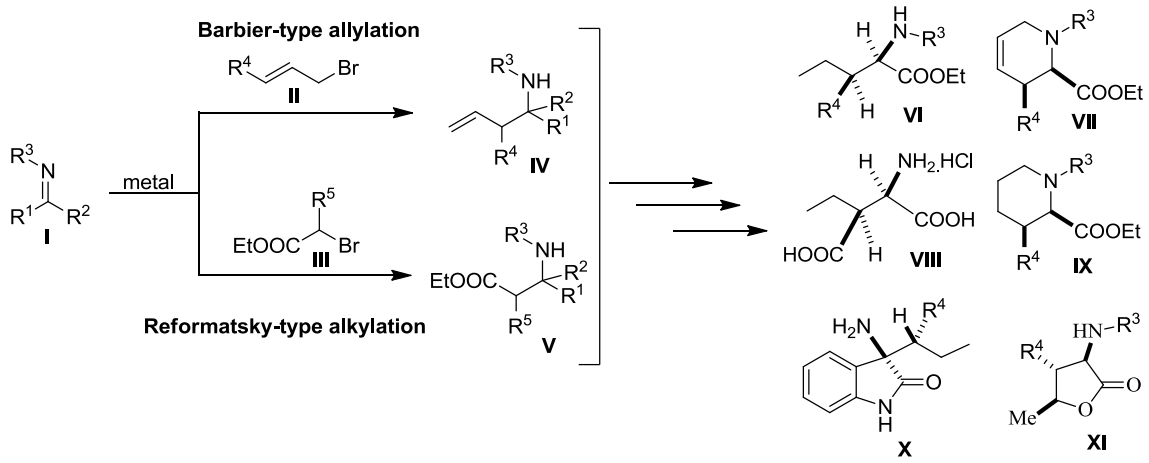
***Objective 3. Stereoselective construction of homoserine lactones possessing multiple stereogenic centers.***



### 4.1. Outline of results and discussion.

In an initial subsection, a brief description about devising and synthesis of starting materials used in the work to explore the diastereoselective Barbier-type reactions for the construction of unnatural amino acid derivatives has been provided. The next subsection deals with the indium-mediated Barbier-type reaction and the reactivity pattern of addition of various γ-substituted allylic halides such as *E*-cinnamyl bromide, *E*-crotyl bromide, cyclohexenyl bromide, geranyl bromide and *E*-alkyl 4-bromocrotonate to *N*-aryl α-imino- and *N*-acylhydrazono esters. Then, the next subsection deals with the indium-mediated Reformatsky-type addition of α-halo esters or α-halo lactone to *N*-aryl α-imino esters.

Subsequent subsection deals with the indium-mediated Barbier-type addition of various γ-substituted allylic halides such as *E*-cinnamyl bromide, *E*-crotyl bromide, cyclohexenyl bromide, geranyl bromide and *E*-alkyl 4-bromocrotonate to ketimines and hydrazones derived from isatins. Along this line, next subsection deals with the Reformatsky-type addition of α-halo esters to the ketimines of isatins and enantiomerically enriched ketimines derived by the condensation of enantiomerically pure *tert*-butyl sulfinamide and isatin.




**Scheme 40.** Brief outline of the results and discussion part.

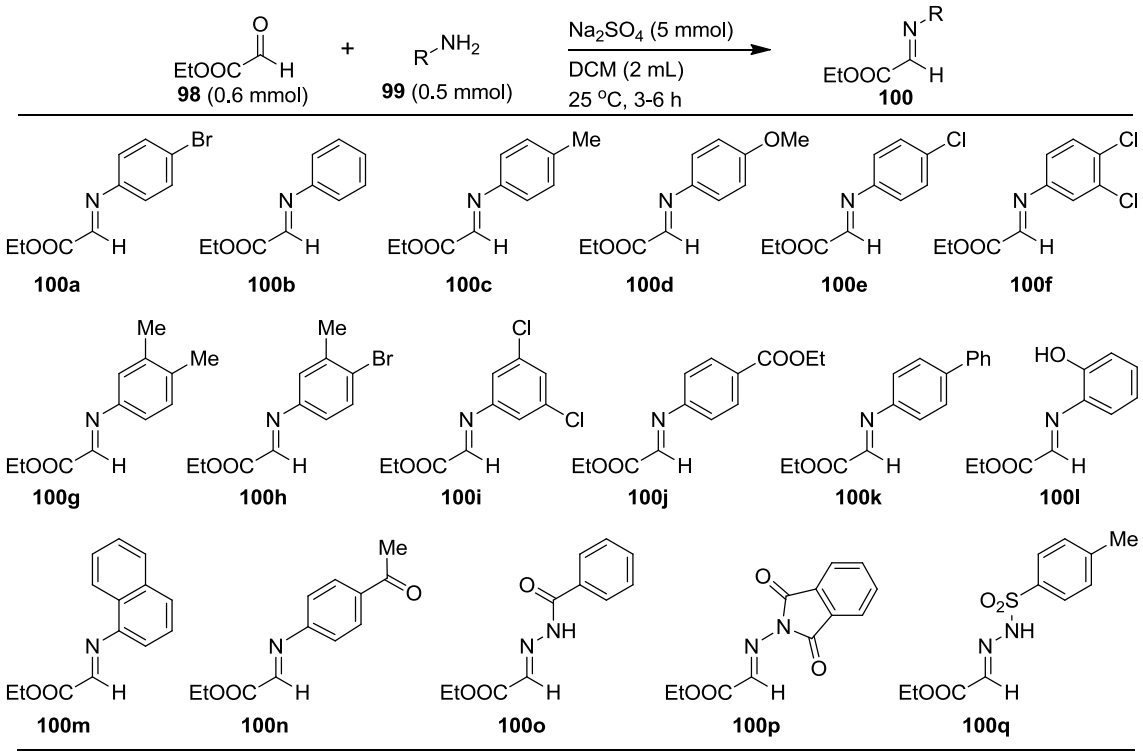
The final subsection deals with the diastereoselective construction of new homoserine lactones (γ-butyrolactone structural motifs) *via* triflic acid-mediated stereoselective direct lactonization of a variety of α-amino γ,δ-unsaturated carboxylic acid esters (Scheme 40).

In all the above mentioned processes, (a) extensive screening of the reaction conditions was carried out to obtain the products with high stereoselectivity for the respective series, (b) the stereochemistry of the synthesized products was unambiguously established from the X-ray structures of representative compounds, and (c) the mechanism and observed high diastereoselectivities in the reactions involving the metal-mediated addition of γ-substituted allylic halides or α-halo esters with *N*-protected α-imino esters or isatin ketimines were accounted by using chelation-controlled TS in concurrence with the literature reports.

### 4.2. Design and synthesis of required starting materials.

#### 4.2.1. Preparation of α-imino esters.

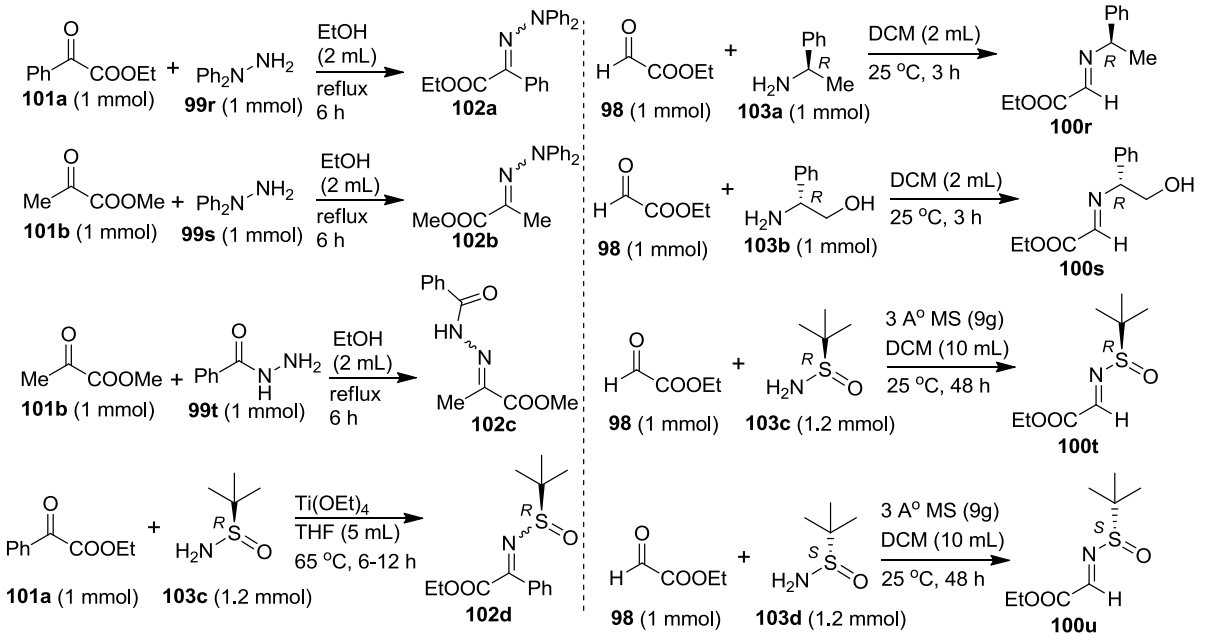
**Table 1.** Synthesis of α-imino- or hydrazono esters **100a-q**.




To study the diastereoselective construction of unnatural amino acid derivatives *via* the Barbier- and Reformatsky-type reactions of various γ-substituted allyl halides with imines (C=N systems), in particular, α-imino esters and ketimines derived from 2,3-dioxoindoles (isatins) were chosen as suitable substrates. Accordingly, a library of α-imino and hydrazono

esters as well as isatin ketimines and isatin hydrazones was prepared from the corresponding primary amines and hydrazides using the standard methods available in literature.[98,99,102,103]

Various anilines having electron-donating and electron-withdrawing groups, tosylhydrazide and benzoylhydrazide were utilized for the synthesis of various *N*-protected α-imino esters **100a-n**, *N*-benzoylhydrazono esters **100o**, *N*-phthaloylhydrazono ester **100p** and *N*-tosylhydrazono ester **100q** from ethyl glyoxalate (**98**) and all these reactions were carried out using the standard literature procedures (Table 1).[98,100a] The α-imino esters **100a-n** as well as hydrazono esters **100o-q** thus formed were used immediately without further purification.



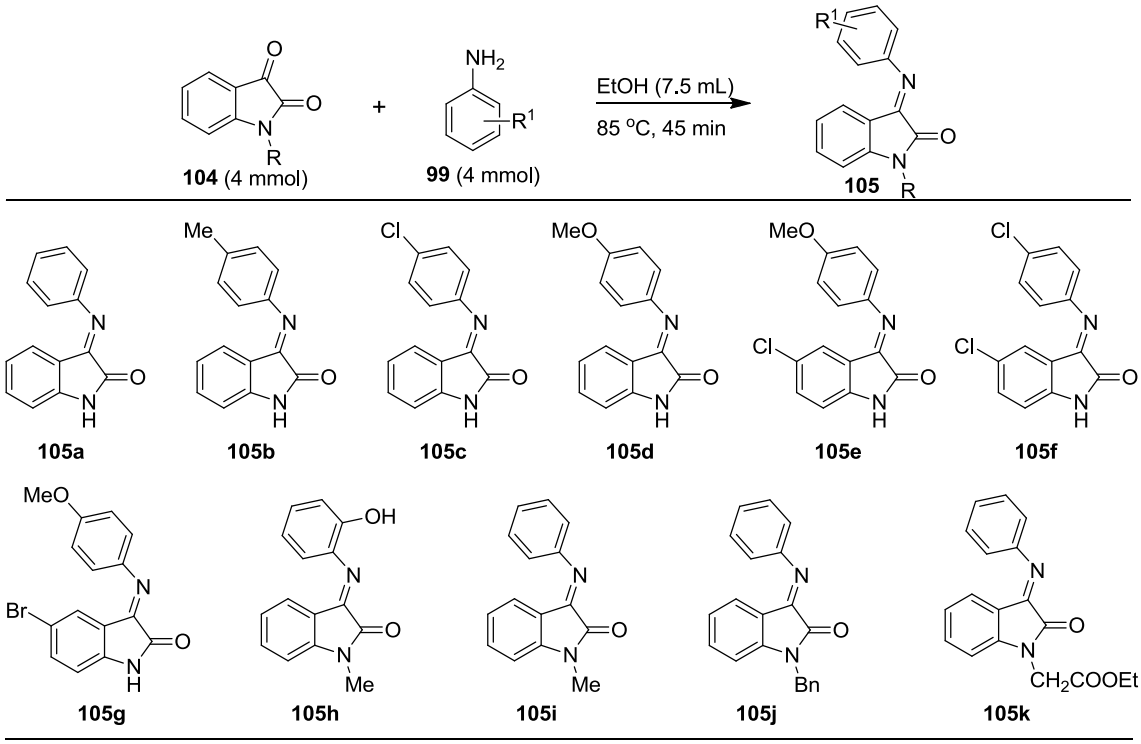

**Scheme 41.** Synthesis of α-hydrazono esters and sufinylimine esters (**100r-100u** and **102a-102d**).

Subsequently, hydrazono esters **102a-c** were synthesized from ethyl 2-oxo-2-phenylacetate (**101a**) and methyl 2-oxopropanoate (**101b**) using the standard reaction conditions (Scheme 41).[99,100b] Enantiomerically enriched α-imino ester **100r-100u** were prepared by reacting **98** with (*R*)-1-phenylethanamine (**103a**), (*R*)-2-amino-2-phenylethanol (**103b**), (*R*)-2-methylpropane-2-sulfinamide (**103c**) and (*S*)-2-methylpropane-2-sulfinamide (**103d**) in DCM by using the procedure reported in the literature (Scheme 41).[98,100c,101a-c] Similarly, enantiomerically enriched α-imino ester **102d** was prepared by reacting **98** with (*R*)-2-

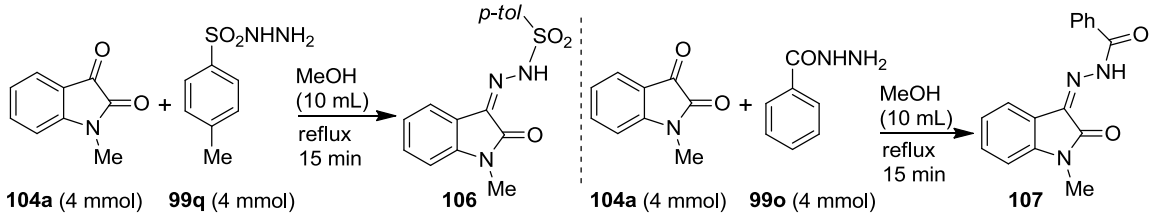
methylpropane-2-sulfinamide (**103c**) in the presence of $Ti(OEt)_4$ in THF by using the procedure reported in the literature (Scheme 41).[100b,101d]

### 4.2.2. Preparation of isatin ketimines.

**Table 2.** Synthesis of isatin ketimines **105**.



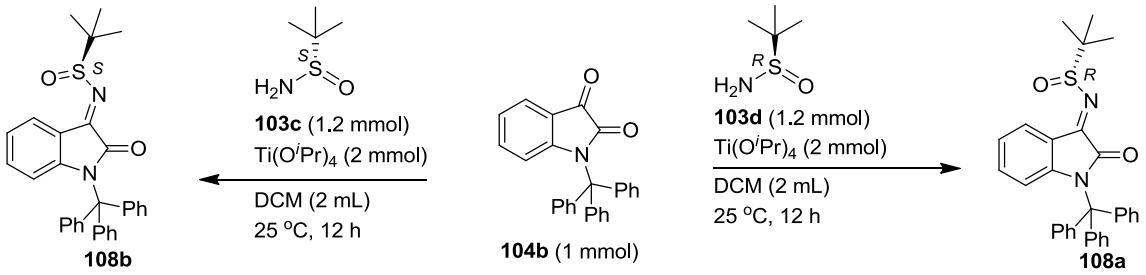

Then, an assorted number of anilines having electron-donating and electron-withdrawing groups, tosylhydrazide (**99q**) and benzoylhydrazide (**99o**) were reacted with various isatins **104** to afford a variety of isatin ketimines **105a-k** (Table 2),[102] isatin *N*-tosylhydrazone **106** and isatin *N*-benzoylhydrazone **107** (Scheme 42).[103]




**Scheme 42.** Synthesis of isatin hydrazones (**106** and **107**).

The synthesis of isatin ketimines **105a-k** and isatin hydrazones **106** and **107** was performed by using the procedures reported in the literature and the compounds **105a-k, 106** and **107** were characterized by matching the characterization data with the literature data. [102,103,105a]

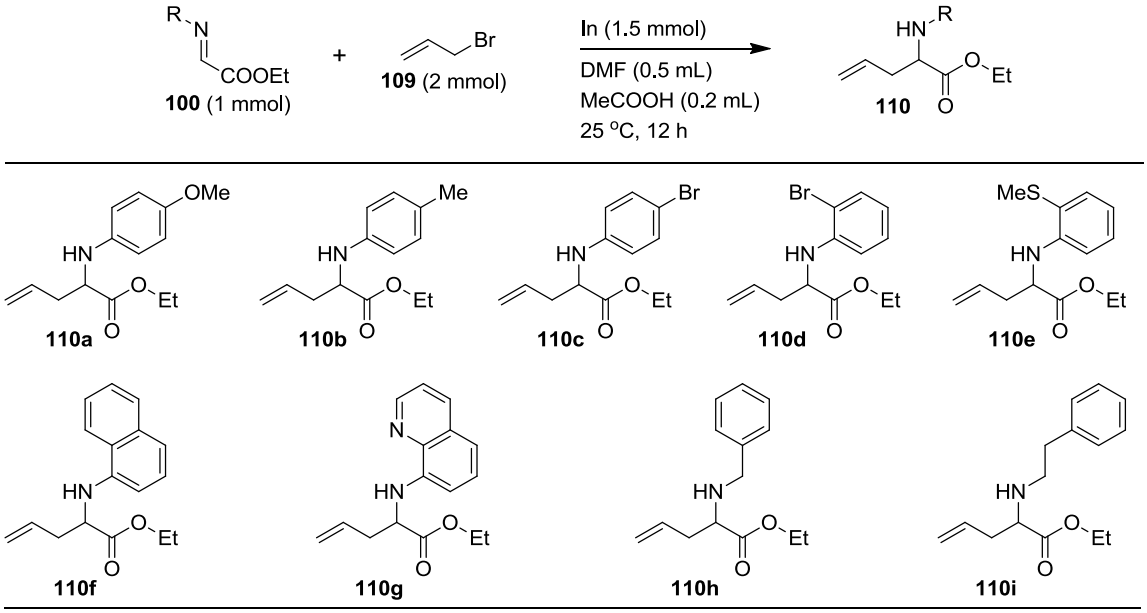
Next, enantiomerically enriched sulfinyl imines **108a**,**b** were synthesized by reacting isatin **104b** with *R* or *S* 2-methylpropane-2-sulfinamide **103c** and **103d** in the presence of $Ti(O^iPr)_4$ by using the procedure reported in the literature (Scheme 43).[104] The compounds **108a**,**b** were characterized by matching the characterization data with the literature data.[105b]




**Scheme 43.** Synthesis of sufinylimines of isatin (**108a** and **108b**).

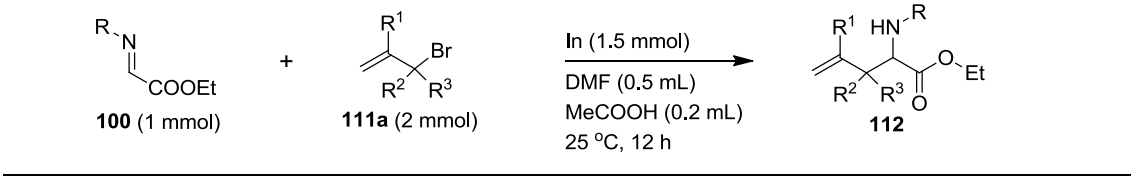
### 4.2.3. Synthesis of *N*-protected allyl glycine esters as precursors for lactonization.

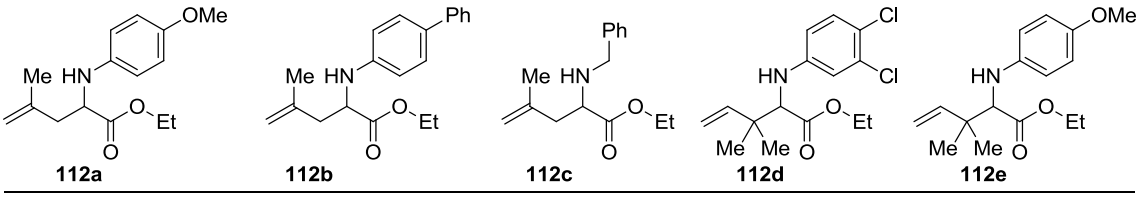
**Table 3.** Synthesis of *N*-protected allyl glycine esters **110**.



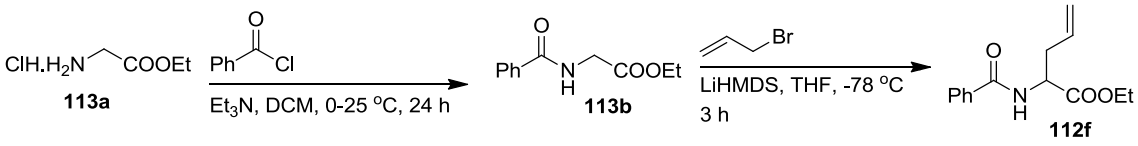
A library of *N*-protected allyl glycine esters **110a-i**, **112a-e** were prepared by reacting the corresponding α-imino esters **100** with different allyl bromides in the presence of indium under reported reaction conditions (Tables 3 and 4).[42a] Similarly, *bis N*-protected allyl glycine esters **115a-d** (having two units of 2-amino-pentenoic acid esters linked *via* a linker) were also made from the indium-mediated allylation of *bis* α-imino esters **114** (Table 5).[42a]

**Table 4.** Synthesis of *N*-protected allyl glycine esters **112**.



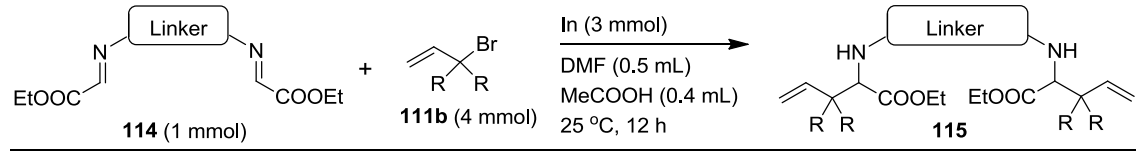




*N*-benzoyl allyl glycine ester **112f** was also prepared to explore the compatibility of stereoselective lactonization process with the starting materials having acyl *N*-protection (Scheme 44).[105c,d]




**Scheme 44.** Synthesis of *N*-benzoyl allyl glycine ester **112f**.

**Table 5.** Synthesis of *bis N*-protected allyl glycine esters **115**.



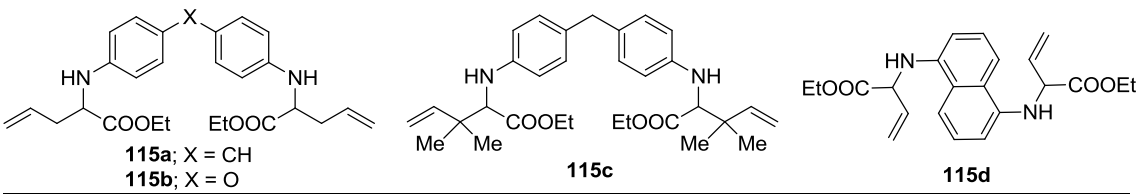
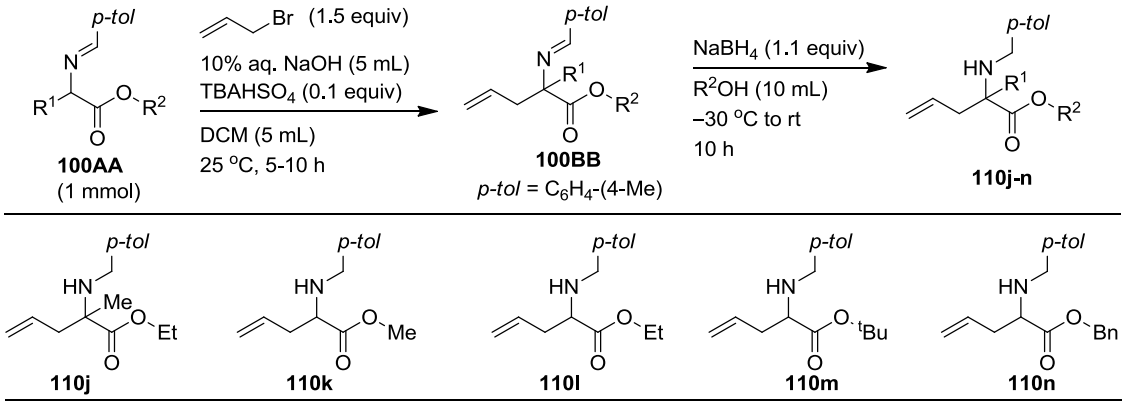
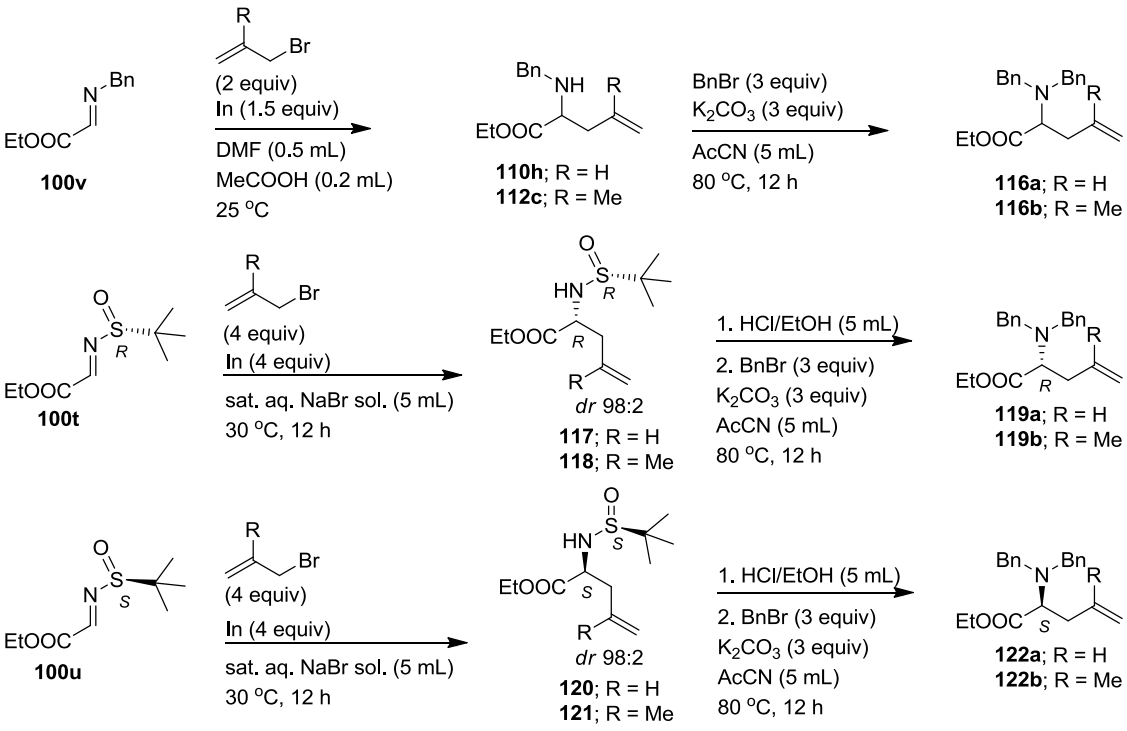



**Table 6.** Synthesis of *N*-protected allyl glycine esters **110j**-**110n**.



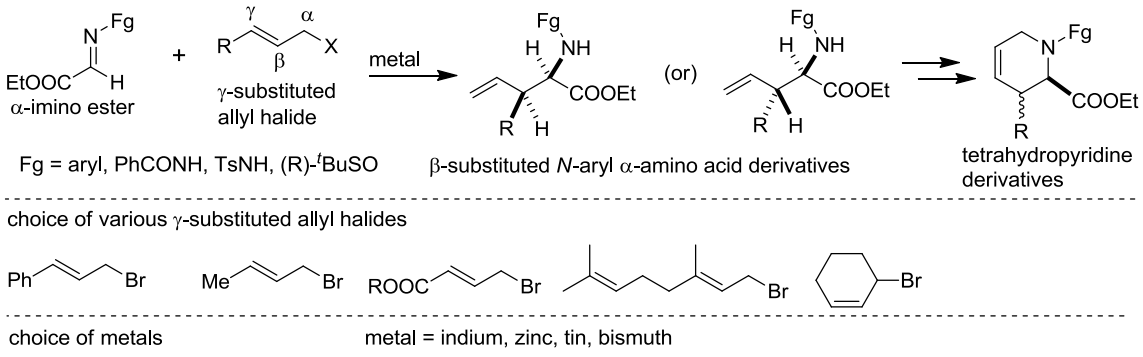

**Scheme 45.** Synthesis of *N*-protected allyl glycine esters **116a**, **116b**, **119a**, **119b**, **122a**, **122b**.

Additionally, a variety of *N*-protected allyl glycine esters **110j**-**n** having an easily removable *p*-methylbenzyl protecting group were constructed starting from their respective imino ester precursors **100AA** *via* the base-mediated allylation strategy (Table 6).[106] Along this line, racemic 2-amino-pent-4-enoic acid ester derivatives **116a**,**b** were synthesized from their

respective precursors involving a series of reaction sequences by using the literature procedures (Scheme 45).[42a] Furthermore, enantiomerically enriched 2-amino-pent-4-enoic acid ester derivatives **119a**,**b** and **122a**,**b** were assembled from their respective precursors involving a series of reaction sequences by following the procedures reported in the literature (Scheme 45).[41b]

### 4.3. Studies on the diastereoselective indium-mediated Barbier-type allylation and Reformatsky-type reactions of *N*-aryl α-imino esters.

#### 4.3.1. Diastereoselective indium-mediated Barbier-type allylation of *N*-aryl α-imino esters.



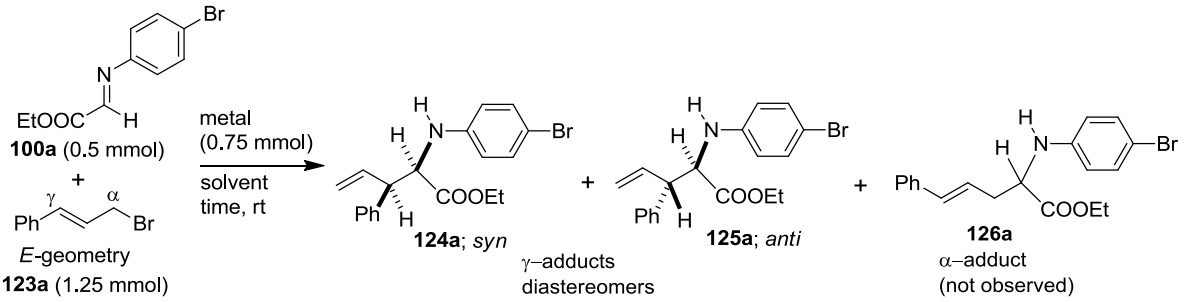

**Scheme 46.** Diastereoselective Barbier-type addition of γ-substituted allyl halides with α-imino esters and construction of β-substituted *N*-aryl α-amino acid derivatives.

At the outset, it was envisaged that the addition of γ-substituted allylindiums to α-imino esters will affect the construction of two contiguous stereogenic centers and the synthesis of highly functionalized γ,δ-unsaturated β,β′-disubstituted *N*-aryl α-amino acid derivatives having more than one stereocenter as illustrated in Scheme 46.

To begin with, optimization reactions were performed to find out the best reaction conditions comprising the indium-mediated addition of γ-substituted allyl halide such as *E*-cinnamyl bromide (**123a**) to α-imino ester **100a**. A mixture of **100a** and *E*-cinnamyl bromide (**123a**) was treated with indium metal powder in anhydrous *N*,*N*-dimethylformamide (DMF) and the mixture was stirred at room temperature for 2 h, which afforded γ-adduct **124a** having two vicinal stereocenters in 42% yield with an excellent diastereoselectivity *(dr* 98:2; entry 1,

Table 7). The product **124a** was characterized by the NMR and X-ray analysis and was found to be the *syn* stereoisomer (Figure 8).

**Table 7.** Optimization of reaction conditions. Diastereoselective addition of **123a** to **100a**.

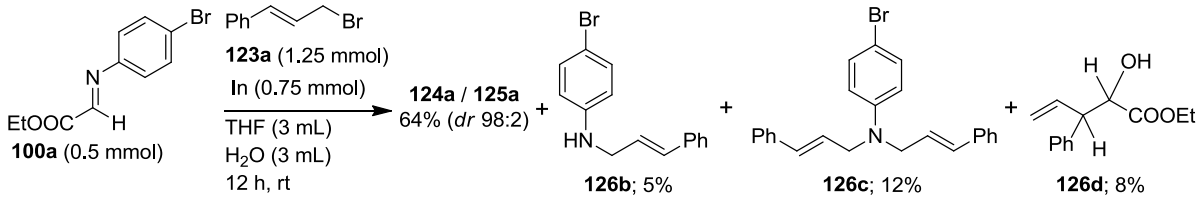



| entry | metal | solvent (mL) | time (h) | **124a** / **125a**; yield (%) (*dr*)[a] |
|---|---|---|---|---|
| 1 | In | DMF (1.5) | 02 | 42 (98:2) |
| 2 | In | DMF (1.5) | 12 | 48 (98:2) |
| 3 | In | THF (3) | 12 | 52 (98:2) |
| 4 | In | THF (3) | 12 | 53 (98:2)[b] |
| 5 | In | THF (3) | 12 | 55 (98:2)[c] |
| 6 | In | DMF (1.5) : $H_2O$ (1.5) | 12 | 47 (98:2) |
| 7 | In | THF (2) : $H_2O$ (4) | 12 | 53 (98:2) |
| 8 | In | THF (4) : $H_2O$ (2) | 12 | 50 (98:2) |
| 9 | In | THF (3) : $H_2O$ (3) | 05 | 47 (98:2) |
| 10 | In | THF (3) : $H_2O$ (3) | 12 | 64 (98:2) |
| 11 | In | THF (3) : $H_2O$ (3) | 12 | 38 (98:2)[b] |
| 12 | In | THF (3) : $H_2O$ (3) | 12 | 67 (98:2)[d] |
| 13 | In | THF (3) : $H_2O$ (3) | 24 | 63 (98:2)[e] |
| 14 | In | THF (3) : $H_2O$ (0.2) | 12 | 66 (98:2) |
| 15 | In | THF (0.2) : $H_2O$ (3) | 12 | 50 (98:2) |
| 16 | In | THF (3) : sat. aq. $NH_4Cl$ (3) | 12 | 38 (98:2) |
| 17 | In | THF (3) : sat. aq. $NH_4Cl$ (3) : MeCOOH (0.18) | 12 | 40 (98:2) |
| 18 | Zn | THF (3) : $H_2O$ (3) | 12 | 27 (98:2) |
| 19 | Zn | THF (3) : sat. aq. $NH_4Cl$ (3) | 12 | 5 |
| 20 | Zn | THF (3) : sat. aq. $NH_4Cl$ (3) : MeCOOH (0.18) | 12 | 26 (98:2) |
| 21 | Sn | THF (3) : $H_2O$ (3) | 12 | 5 |

[a] Isolated yields are given and the ratio of (*syn* / *anti*) diastereomers (calculated from the NMR spectra of the crude reaction mixture) is reported in the parenthesis. The product **126a** was not observed in any of the reaction. [b] The reaction was carried out at 80 $^oC$. [c] The reaction was carried out at −10 to 0 $^oC$. [d] The reaction was carried out at 5 $^oC$. [e] Indium powder was added in 3 portions (each portion was added after every 4 h).

It is worth to mention that indium-mediated addition of γ-substituted allyl halide *E*-cinnamyl bromide (**123a**) to α-imino ester **100a** selectively afforded the γ-adduct and the indium-mediated reaction of *E*-cinnamyl bromide (**123a**) to α-imino ester **100a** did not afford the corresponding α-adduct **126a**.[32] Next, when the indium-mediated reaction of **100a** and **123a** was extended to 12 h, the product **124a** was obtained in 48% yield (entry 2, Table 7). The cinnamylation of **100a** in anhydrous tetrahydrofuran afforded the product **124a** in 52% yield (entry 3, Table 7). There was no effect of increasing or lowering the reaction temperature in the yield of **124a** (entries 4 and 5, Table 7). It is well documented in the literature that the allylindium compounds are tolerant to water or protogenic solvents and the indium-based allylation of carbonyls or imines were performed in water media.[31,38,40,48,50h-50j] In the present work, employment of DMF/$H_2O$ mixture as solvent for the reaction successfully afforded the product **124a** in 47% yield (entry 6, Table 7). After that, various THF/$H_2O$ combinations were examined which were also found to promote the formation of the *syn* isomer **124a**, bearing two contiguous stereocenters (entries 7–10, Table 7). Reaction at ambient temperature for 12 h reaction time gave the product **124a** in 64% yield (*dr* 98:2; entry 10, Table 7). The reaction in THF/water at 80 °C as well as at 5 °C gave the product **124a** in 38% and 67% yield, respectively (entries 11 and 12, Table 7). Whereas, portion wise addition of indium powder to the reaction in THF/water at ambient temperature gave 63% of the product **124a** (entry 13, Table 7). Furthermore, small amount of water in THF or small amount of THF in water gave the product **124a** in 66% and 50% yield, respectively (entries 14 and 15, Table 7). Use of saturated ammonium chloride alone and in combination with acetic acid did not improve the yield of **124a** (entries 16 and 17, Table 7). Employment of Zn and Sn, in place of indium, failed to yield the product **124a** in satisfactory yields (entries 18-21, Table 7). Therefore, indium metal powder and THF/water system were found as the best choice for the diastereoselective synthesis of **124a** (*syn* isomer) having two contiguous stereocenters. Notably, the product **126a** (α-adduct) was not obtained in any of the above reactions. Though the formation of α-adduct from the addition of γ-substituted allyl halide such as *E*-cinnamyl bromide (**123a**) to carbonyls or imines in anhydrous solvents is reported in the literature,[32b-32e] the corresponding α-adduct **126a** was not obtained in the present reaction system. It is also worth to mention that in the present reaction system, solvent has no significant role on the diastereoselectivity of the products formed. However, apart from the

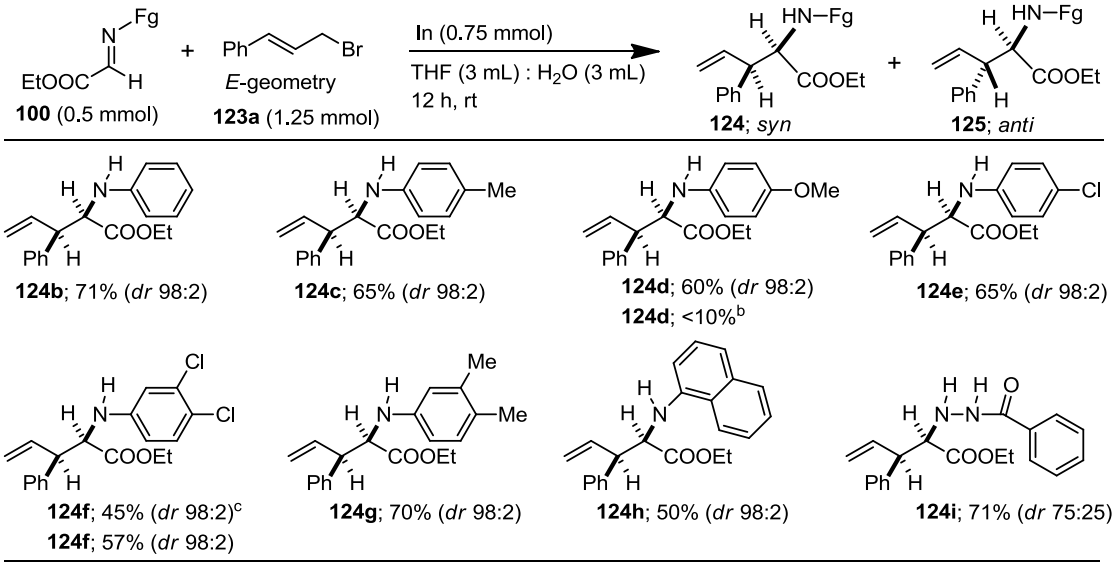
main product **124a**, minor by-products **126b**, **126c** and **126d** were detected in the indium-mediated reaction of **100a** with **123a**. In one of the optimization reaction condition (entry 10, Table 7 and Scheme 47), the minor by-products **126b**, **126c** and **126d** were completely isolated from the column chromatography purification.




**Scheme 47.** Indium-mediated cinamylation of α-imino ester **100a**.

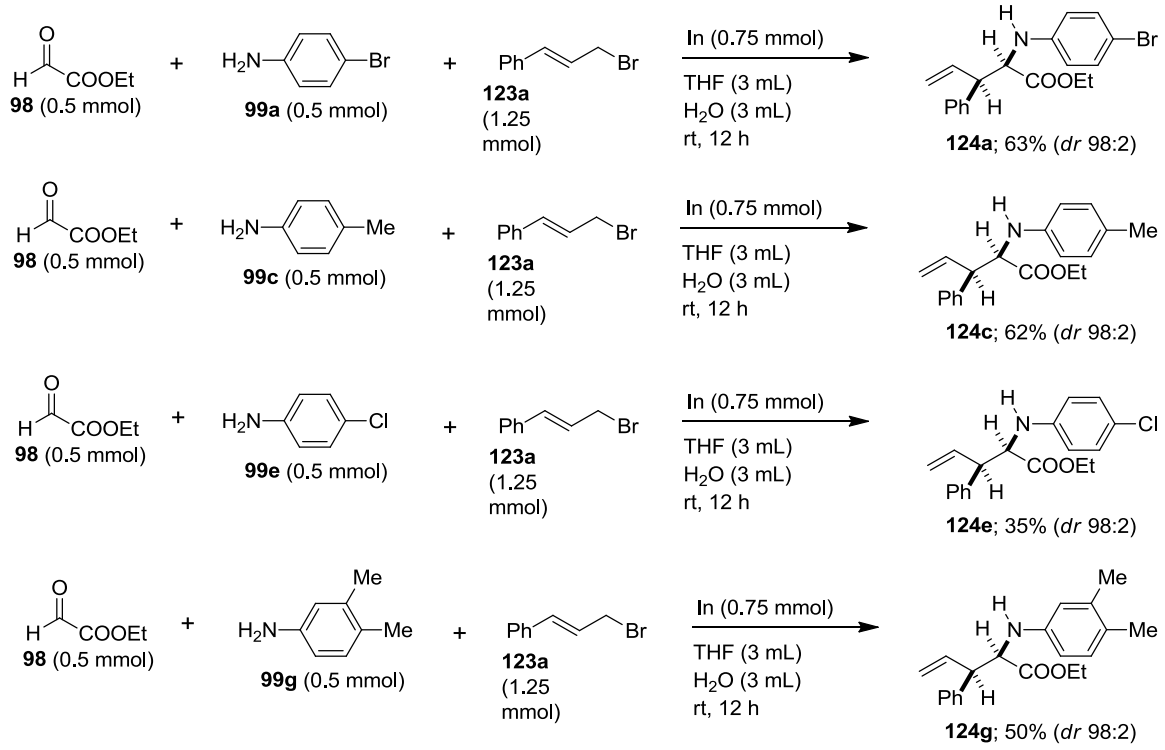
Correspondingly, the compounds **126b** and **126c** were identified as *N*-allylated compounds of 4-bromoaniline and the compound **126d** was identified as homoallyl alcohol of ethyl glyoxalate. The α-imino ester **100a** was hydrolyzed under the reaction condition (entry 10, Table 7, Scheme 47) and subsequently, the compounds **126b**, **126c** and **126d** were formed from 4-bromoaniline and ethyl glyoxalate. For all other reactions shown in Table 7, the attention was paid to isolate the main product **124a** and the corresponding minor products were not isolated in pure form (Scheme 47).

**Table 8.** Synthesis of γ,δ-unsaturated β,β′-disubstituted *N*-aryl α-amino acid derivatives **124**.[a]




[a] Isolated yields are given and the ratio of (*syn* / *anti*) diastereomers (calculated from the NMR spectra of the crude reaction mixture) is reported in the parenthesis. [b] The reaction was carried out in $H_2O$ (3 mL). [c] The reaction was carried out with **123a** (1 mmol).

The scope of the Barbier-type cinnamylation was tested by using various α-imino esters **100**, prepared from anilines with electron donating and withdrawing groups (Table 8). The indium-mediated cinnamylation of various α-imino esters **100** furnished the respective α-amino acid derivatives **124b**–**g** (*syn* isomers, *dr* 98:2; Table 8). The cinnamylation of **100d** in water as solvent produced unsatisfactory result and the corresponding product **124d** was obtained in <10% yield (Table 8). The cinnamylation of **100m** prepared from the condensation of ethyl glyoxalate and α-naphthylamine gave the *syn* isomer **124h** (Table 8). The Barbier-type addition of **123a** to α-hydrazono ester **100o** in the presence of indium afforded the product **124i** with moderate diastereoselectivity (*dr* 75:25; Table 8).




**Scheme 48.** Synthesis of γ,δ-unsaturated β,β′-disubstituted *N*-aryl α-amino acid derivatives (**124a**, **124c**, **124e**, **124g**) *via* one-pot multicomponent cinnamylation.

Next, the synthesis of γ,δ-unsaturated β,β′-disubstituted *N*-aryl α-amino acid derivatives without the prior preparation of the corresponding α-imino esters was envisioned. Accordingly, the Barbier-type cinnamylation comprising a three-component one-pot reaction of ethyl glyoxalate (**98**), aniline (**99**) and cinnamyl bromide (**123a**) in the presence of indium powder was carried out. The three-component one-pot reactions of ethyl glyoxalate (**98**),

anilines **99a**,**c**,**e**,**g** and cinnamyl bromide (**123a**) in the presence of indium powder in THF / water successfully afforded the respective products **124a**, **124c**, **124e** and **124g** in 35-63% yields with very high diastereoselectivity (*syn* isomers, *dr* 98:2; Scheme 48).

Based on single crystal X-ray structure analyses of compounds **124a**, **124e** and **124i**, the stereochemistry of the vicinal stereocenters of the compounds **124a**, **124e** and **124i** was found to be *syn* (Figure 8). Consequently, the stereochemistry of other adducts listed in the Tables 7 and 8 and Scheme 48 was also assigned based on the X-ray structure analyses of representative products **124a**, **124e** and **124i** coupled with the similarity in their NMR spectral patterns.

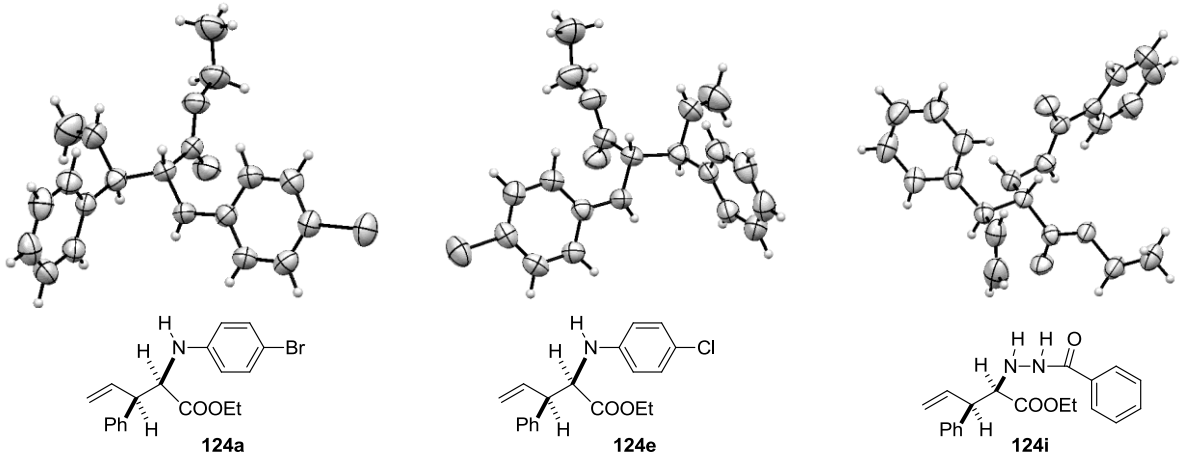
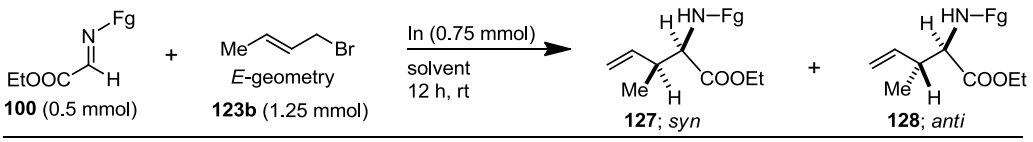
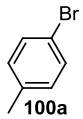
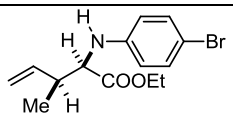
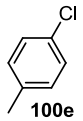
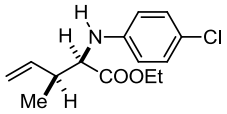
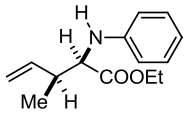
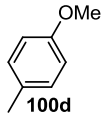
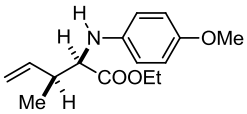
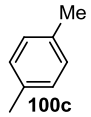
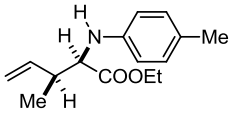
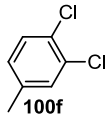
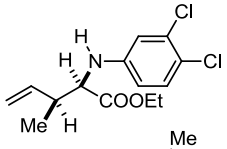
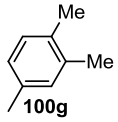
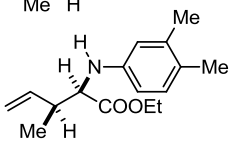
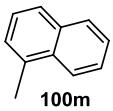
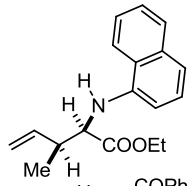
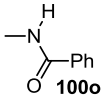
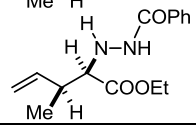



**Figure 8.** X-ray structures of **124a**, **124e** and **124i**.

After investigating the indium-mediated cinnamylation of α-imino esters **100**, the addition of the crotyl bromide (**123b**) to α-imino esters **100** was studied (Table 9). Optimization reactions were carried out to find out the best reaction conditions comprising the indium-mediated addition of crotyl bromide to α-imino ester **100a**. The reaction of crotylindium formed *in situ* from crotyl bromide (**123b**) and indium with **100a** in THF/water gave the α-amino acid derivative **127a** (*syn* isomer) with two vicinal stereocenters in 61% yield with very high diastereoselectivity (*dr* 98:2; entries 1-3, Table 9). The crotylation of α-imino ester **100e** in THF/water successfully afforded α-amino acid derivative **127b** (*syn* isomer) having two vicinal stereocenters in 60% yield with very high diastereoselectivity (*dr* 98:2; entry 4-6, Table 9).

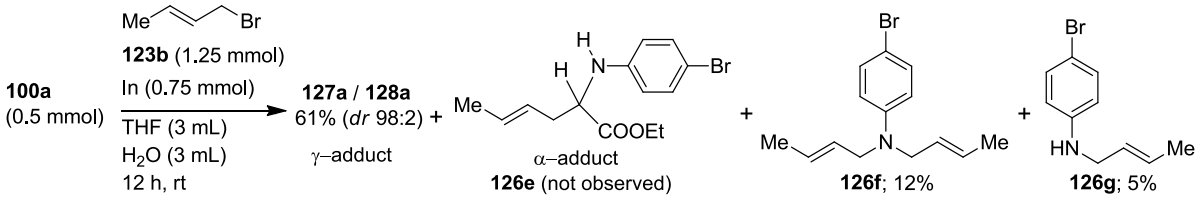
**Table 9.** Synthesis of *N*-aryl α-amino acid derivatives *via* crotylation of α-imino ester **100**.




| entry | —Fg | solvent (mL) | product | **127** / **128**; yield (%) (*dr*)[a] |
|---|---|---|---|---|
| 1 |  **100a** | THF (3) : $H_2O$ (3) |  | **127a**; 43 (98:2)[b] |
| 2 | | THF (3) : $H_2O$ (3) | | **127a**; 61 (98:2) |
| 3 | | THF (3) : $H_2O$ (3) | | **127a**; 62 (98:2)[c] |
| 4 |  **100e** | THF (3) : $H_2O$ (3) |  | **127b**; 60 (98:2) |
| 5 | | THF (4) : $H_2O$ (2) | | **127b**; 52 (98:2) |
| 6 | | THF (2) : $H_2O$ (4) | | **127b**; 46 (98:2) |
| 7 |  **100b** | THF (3) : $H_2O$ (3) |  | **127c**; 54 (98:2) |
| 8 |  **100d** | THF (3) : $H_2O$ (3) |  | **127d**; 59 (98:2) |
| 9 | | DMF (2) | | **127d**; 82 (75:25)[d] |
| 10 |  **100c** | THF (3) : $H_2O$ (3) |  | **127e**; 59 (98:2) |
| 11 |  **100f** | THF (3) |  | **127f**; 43 (98:2) |
| 12 | | THF (3) : $H_2O$ (3) | | **127f**; 49 (98:2) |
| 13 |  **100g** | THF (3) : $H_2O$ (3) |  | **127g**; 48 (98:2) |
| 14 |  **100m** | THF (3) : $H_2O$ (3) |  | **127h**; 40 (98:2) |
| 15 |  **100o** | THF (3) : $H_2O$ (3) |  | **127i**; 65 (75:25) |

[a] Isolated yields are given and the ratio of (*syn* / *anti*) diastereomers (calculated from the NMR spectra of the crude reaction mixture) is reported in the parenthesis. [b] The reaction time was 6 h. [c] The reaction time was 24 h. [d] The reaction time was 2 h.

Then, the indium-mediated crotylation of α-imino esters **100b**–**d** gave the respective α-amino acid derivatives **127c**–**e** (*syn* isomers) having two vicinal stereocenters with very high diastereoselectivity (*dr* 98:2; entries 7–10, Table 9). The crotylation of **100d** in DMF gave the product **127d** in 82% yield with moderate diastereoselectivity (*dr* 75:25; entry 9, Table 9). Furthermore, the crotylation of α-imino esters **100f**,**g** also furnished the respective *syn* isomers **127f**,**g** (entries 11–13, Table 9). The crotylation of **100m** prepared from α-naphthylamine gave the *syn* isomer **127h** in only 40% yield (entry 14, Table 9). Along this line, the crotylation of the α-hydrazono ester **100o** successfully gave the product **127i** in 65% yield with moderate diastereoselectivity (*dr* 75:25; entry 15, Table 9).

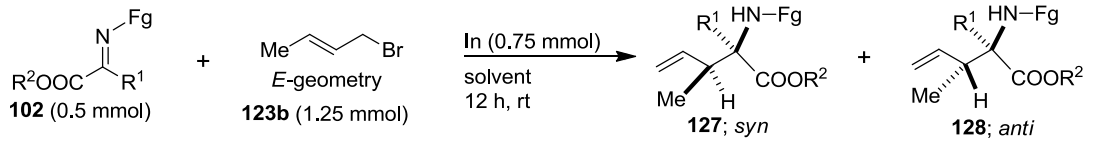


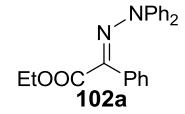
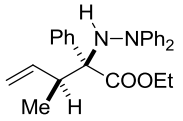
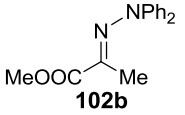
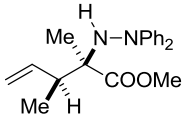
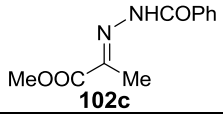
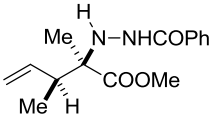

**Scheme 49.** Indium-mediated crotylation of α-imino ester **100a**.

Similar to the process comprising the cinnamylation of α-imino esters (Tables 7 and 8), the corresponding α-adduct **126e** was not obtained in the indium-mediated crotylation of α-imino esters **100** in THF/water. However, apart from the main product **127a**, the formation of other minor by-products **126f** and **126g** was observed (Scheme 49). The by-products **126f** and **126g** were isolated and identified as *N*-allylated products of 4-bromoaniline similar to the case of cinnamylation (Scheme 48). For all other reactions shown in Table 9, the attention was paid to isolate the main product **127a** and the corresponding minor products were not isolated.

Then, the addition of indium-mediated crotyl bromide (**123b**) to hydrazono esters **102a-c** (prepared from ethyl benzoylformate and methyl pyruvate, Table 10) was explored. The indium-mediated reaction of crotyl bromide (**123b**) with hydrazono esters **102a** and **102b** in anhydrous THF or THF/water (1:1) did not afford the corresponding products (entries 1–3, Table 10).

**Table 10.** Stereoselective crotylation of α-imino esters **102a-c**.




| entry | 102 | solvent (mL) | product | 127 / 128; yield (%) (*dr*)[a] |
|---|---|---|---|---|
| 1 |  | THF (3) |  | **127j**; 0 |
| 2 | **102a** | THF (3) : $H_2O$ (3) | | **127j**; 0 |
| 3 |  **102b** | THF (3) : $H_2O$ (3) |  | **127k**; 0 |
| 4 |  **102c** | THF (3) |  | **127l**; 81 (70:30) |
| 5 | | THF (3) : $H_2O$ (3) | | **127l**; 63 (72:28) |

[a] Isolated yields are given and the ratio of (*syn* / *anti*) diastereomers (calculated from the NMR spectra of the crude reaction mixture) is reported in the parenthesis.

Though an exact reason is not clear for the failure of the crotylation of hydrazono esters **102a** and **102b**, however, it is assumed that the hydrolysis of esters **102a** and **102b** could have happened under the experimental condition and the crotylindium might be having a poor reactivity with the electrophilic center of **102a** and **102b**. Surprisingly, the crotylation of **102c** in THF as well as THF/water afforded the product **127l** in 81% and 63% yields, respectively, with moderate diastereoselectivity (entries 4-5, Table 10).

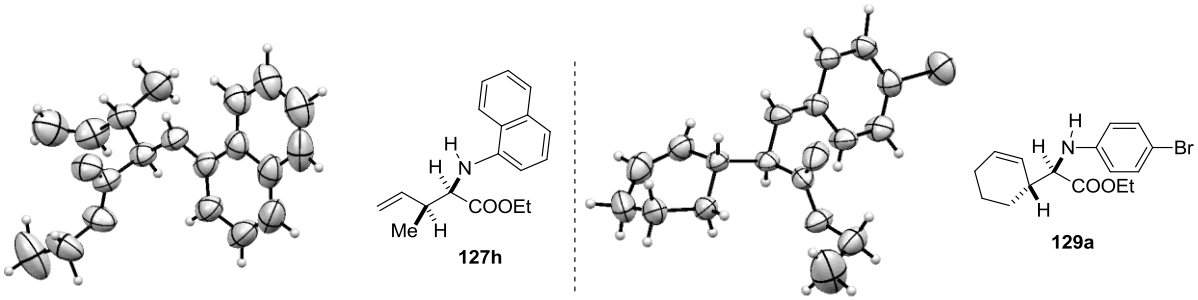
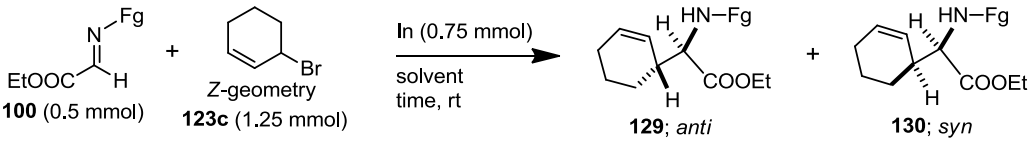


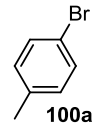
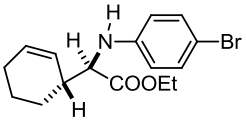
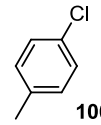
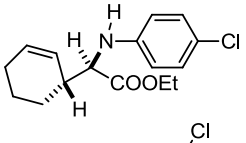
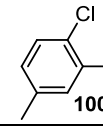
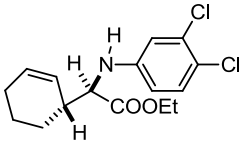

**Figure 9.** X-ray structures of **127h** and **129a**.

The observed moderate diastereoselectivity of **127l** may be due to the involvement of less rigid cyclic TS in the crotylation of **102c**. Based on the single crystal X-ray structure analysis

of the compound **127h**, the stereochemistry of the vicinal stereocenters of the compound **127h** was found to be *syn* (Figure 9). Consequently, the stereochemistry of other adducts listed in Tables 9 and 10 was also assigned based on the X-ray structure analysis of representative product **127h** coupled with the similarity in their NMR spectral patterns.

**Table 11.** Synthesis of *N*-aryl α-amino acid derivatives *via* cyclohexenylation of **100**.

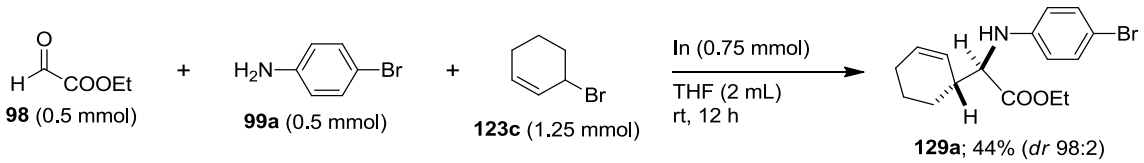



| entry | Fg | solvent (mL) | time (h) | product | **129** / **130**; yield (%) (*dr*)[a] |
|---|---|---|---|---|---|
| 1 |  **100a** | THF (3) : $H_2O$ (3) | 12 |  | **129a**; < 5 |
| 2 | | THF (3) : $H_2O$ (3) | 24 | | **129a**; < 5 |
| 3 | | THF (3) | 12 | | **129a**; 50 (98:2) |
| 4 | | THF (3) | 12 | | **129a**; 40 (98:2)[b] |
| 5 |  **100e** | THF (3) | 12 |  | **129b**; 37 (98:2) |
| 6 | | THF (3) | 24 | | **129b**; 45 (98:2) |
| 7 |  **100f** | THF (3) | 24 |  | **129c**; 45 (98:2) |

[a] Isolated yields are given and the ratio of (*syn* / *anti*) diastereomers (calculated from the NMR spectra of the crude reaction mixture) is reported in the parenthesis. [b] This reaction was carried out using Zn dust (2 mmol) instead of In.

Then, it was envisaged to optimize the reaction conditions for the Barbier-type indium-mediated direct addition of cyclohexenyl bromide (**123c**) to the α-imino esters **100** (Table 11). Unlike the indium-mediated reactions of cinnamyl- or crotyl bromide with α-imino esters **100** in THF / water, the indium-mediated addition of **123c** to **100a** in THF / water system failed to give the products **129a**/**130a** (entries 1 and 2, Table 11). The reason for the failure of the indium-mediated addition of **123c** to **100a** in THF / water system could be attributed to the instability of the cyclohexenylindium in water. However, indium-mediated direct addition of cyclohexenyl bromide (**123c**) to **100a** in anhydrous THF was successful and gave the corresponding amino acid derivative **129a** (*anti* isomer) bearing two vicinal stereocenters with very high diastereoselectivity (*dr* 98:2; entry 3, Table 11). Similar result

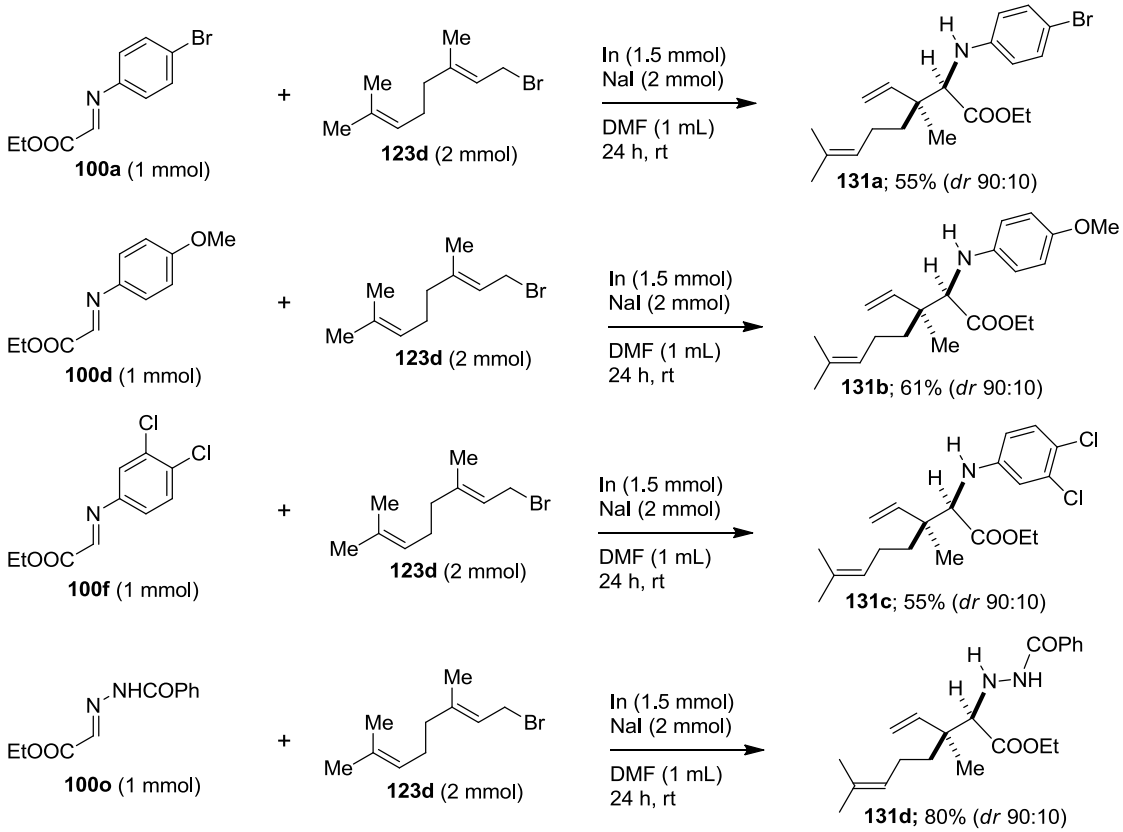
was obtained from the reaction of **100a** with **123c** in the presence of zinc powder instead of indium (entry 4, Table 11). Next, the indium-mediated direct addition of cyclohexenyl bromide (**123c**) to **100e,f** in anhydrous THF gave the corresponding amino acid derivatives **129b,c** (*anti* isomers) bearing two vicinal stereocenters with very high diastereoselectivity (*dr* 98:2; entries 5-7, Table 11). Additionally, the one-pot treatment of cyclohexenyl bromide (**123c**), 4-bromo aniline (**99a**), and ethyl glyoxalate (**98**) mediated by indium in THF also successfully gave the product **129a** in 44% yield with very high diastereoselectivity (*dr* 98:2; Scheme 50).




**Scheme 50.** In-mediated one-pot multicomponent cyclohexenylation.

Based on single crystal X-ray structure analysis of the compound **129a**, the stereochemistry of the vicinal stereocenters of the compound **129a** was found to be *anti* (Figure 9). Consequently, the stereochemistry of other adducts listed in the Table 11 was also assigned based on the X-ray structure analysis of representative product **129a** coupled with the similarity in their NMR spectral patterns.

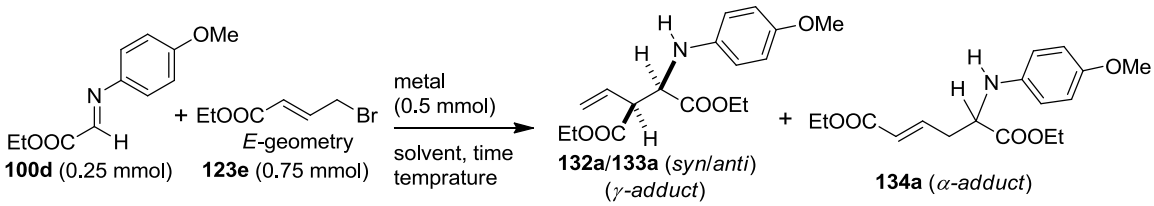
Subsequently, the reactivity pattern of γ-substituted allylindiums generated from geranyl bromide (**123d**) with α-imino esters (**100**) was explored to synthesize highly functionalized γ,δ-unsaturated β,β′-disubstituted *N*-aryl α-amino acid derivatives (**131**) having more than one stereocenter as illustrated in Scheme 51. The indium-mediated reactions of geranyl bromide (**123d**) with α-amino esters **100a**, **100d** and **100f** were performed in DMF, which led to the stereoselective synthesis of β,β'-disubstituted derivatives **131a**–**c** (*dr* 90:10) bearing a terpene unit and two contiguous stereocenters (including an all carbon quaternary center) in 55-61% yield (Scheme 51). The geranylation of α-hydrazono ester **100o** also occurred to give the respective product **131d** in 80% yield with very good diastereoselectivity (*dr* 90:10; Scheme 51). NaI was used as an additive in these reactions since the reactions were not fruitful in the absence of NaI, perhaps because of the lesser reactivity of geranyl bromide towards indium.




**Scheme 51**. Stereoselective geranylation of α-imino esters **100**.

Furthermore, the indium-mediated addition of ethyl 4-bromocrotonate (**123e**) to α-imino ester **100d** was investigated to synthesize *N*-aryl β-vinyl aspartic acid derivative having two vicinal stereocenters. At first, the optimization reactions were performed to find out the best reaction condition to obtain the γ-adducts **132a/133a** from the indium-mediated addition of ethyl 4-bromocrotonate (**123e**) to α-imino ester **100**. The reaction of α-imino ester **100d**, ethyl 4-bromocrotonate (**123e**) and indium powder in dry DMF at 30 $^{o}$C for 12 h furnished the diastereomers **132a** (γ-adduct) in 70% yield with very high diastereoselectivity (*dr* 90:10) and also the corresponding α-adduct **134a** in 25% yield (entry 1, Table 12). A similar regioselectivity was observed when the reaction was carried out in THF or 1,4-dioxane or toluene (entries 2-4, Table 12). The reaction of α-imino ester **100d**, ethyl 4-bromocrotonate (**123e**) and indium powder in 1,2-DCE or MeOH or DMSO gave only the diastereomers **132a** (γ-adducts) in 25-63% yields with *dr* up to 85:15 (entries 5-7, Table 12). The addition of **123e** to **100d** in THF-water mixture exclusively gave the γ-adduct **132a** (*syn* isomer) in 46% yield with an excellent diastereoselectivity (*dr* 98:2; entry 8, Table 12).

**Table 12.** Optimization of the reaction conditions for the diastereoselective addition of **123e** with α-imino ester **100d**.




| entry | metal | solvent (mL) | temp ($^{o}$C) | time (h) | **132a** / **133a**; yield (%) (*dr*)[a] | **134a**; yield (%) |
|---|---|---|---|---|---|---|
| 1 | In | DMF (1) | 30 | 12 | 70 (90:10) | 25 |
| 2 | In | THF(1) | 30 | 12 | 40 (70:30) | 25 |
| 3 | In | 1,4-dioxane (1) | 30 | 24 | 30 (82:18) | 13 |
| 4 | In | toluene (1) | 30 | 24 | 31 (81:19) | 25 |
| 5 | In | 1,2-DCE (1) | 30 | 24 | 25 (76:24) | ND |
| 6 | In | MeOH (1) | 30 | 12 | 40 (69:71) | ND |
| 7 | In | DMSO (0.5) | 30 | 12 | 63 (85:15) | ND |
| 8 | In | THF (1) : $H_2O$ (1) | 30 | 12 | 46 (98:02) | ND |
| 9 | In | EtOH (1) : $H_2O$ (1) | 30 | 12 | 53 (98:02) | ND |
| 10 | In | DMF (1) : $H_2O$ (1) | 30 | 12 | 60 (98:02) | ND |
| 11 | In | EtOH (1) | 30 | 03 | 66 (>95:05) | ND |
| 12 | In | EtOH (1) | 30 | 06 | 91 (>95:05) | ND |
| 13 | In | EtOH (1) | 30 | 24 | 90 (>95:05) | ND |
| 14 | In | EtOH (1) | -5 | 06 | 95 (>95:05) | ND |
| 15 | In | EtOH (1) | 80 | 06 | 51 (>93:05) | ND |
| 16 | In | EtOH (1) | 30 | 06 | 95 (>95:05)[b] | ND |
| 17 | In | EtOH (1) | 30 | 06 | 92 (>95:05)[c] | ND |
| 18 | In | EtOH (1) | 30 | 06 | 77 (94:06)[d] | ND |
| 19 | In | EtOH (1) | 30 | 06 | 91 (>95:05)[e] | ND |
| 20 | In | EtOH (1) | 30 | 06 | 84 (>95:05)[f] | ND |
| 21 | Sn | EtOH (1) | 30 | 06 | 65 (>95:05) | 23 |
| 22 | Zn | EtOH (1) | 30 | 06 | 25 (>95:05) | ND |
| 23 | Bi | EtOH (1) | 30 | 06 | 65 (>95:05) | ND |

[a] Isolated yields are given and the ratio of (*syn* / *anti*) diastereomers (calculated from the NMR spectra of the crude reaction mixture) is reported in the parenthesis. [b] 20 mol% of NaI was added as an additive. [c] 20 mol% of KI was added as an additive. [d] 20 mol% of $I_2$ was added as an additive. [e] 20 mol% of MeCOOH was added as an additive. [f] The reaction was carried out using **100d** (0.5 mmol), **123e** (1.5 mmol) and indium powder (0.75 mmol). ND = Not Detected.

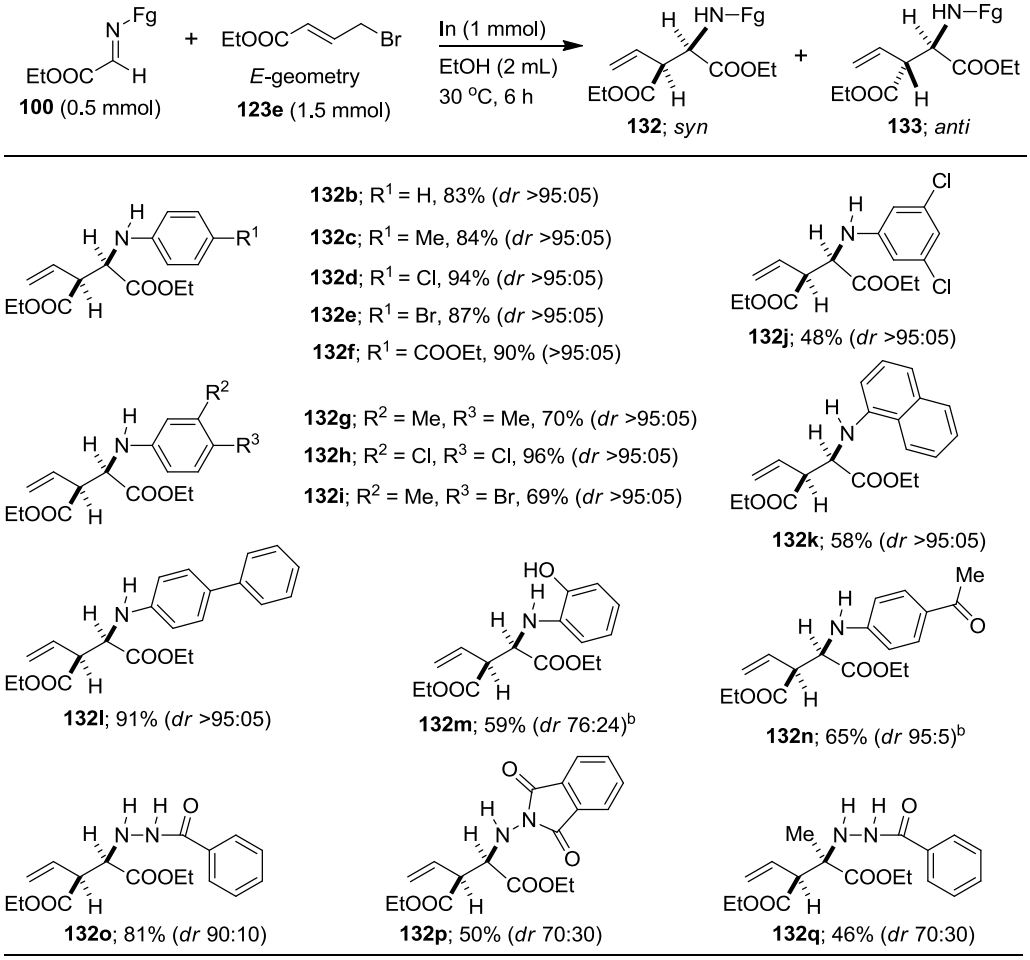
Use of EtOH/water and DMF/water solvent media could not improve the yield of the reaction to an appreciable amount (entries 9-10, Table 12). The indium-mediated reaction of **123e** to **100d** in EtOH underwent smoothly (entries 11-20, Table 12). The γ-adduct **132a** (*syn* isomer) was obtained from the reaction of **123e** with **100d** in EtOH at 30 $^{o}$C in 91% yield

with very high diastereoselectivity (*dr* >95:5; entry 12, Table 12) and in this case, the corresponding α-adduct **134a** was not obtained. Some more optimization reactions were also performed to improve the yield of the product **132a**. Lowering the temperature of reaction of α-imino ester **100d**, ethyl 4-bromocrotonate (**123e**) and indium powder in EtOH to -5 $^{o}$C exclusively gave the γ-adduct **132a** in 95% yield (*dr* >95:5; entry 14, Table 12). Yield of the reaction of **100d** with **123e** in the presence of indium in EtOH got diminished at higher temperature (entry 15, Table 12). The reaction of α-imino ester **100d**, ethyl 4-bromocrotonate (**123e**) and indium powder in the presence of NaI as an additive gave the γ-adduct **132a** in 95% yield (*dr* >95:5; entry 16, Table 12). Employment of the additives like KI and acetic acid did not alter the course of reaction much (entries 17 and 19, Table 12). Use of iodine as an additive decreased the yield of the reaction (entry 18, Table 12). Decrease in the amount of indium in the reaction gave the product **132a** with decreased yield (entry 20, Table 12). Use of other metals such as Sn, Zn and Bi gave the γ-adduct **132a** in 65%, 25% and 65% yields (*dr* >95:5), respectively (entries 21-23, Table 12).

Next, the scope and generality of the indium-mediated Barbier-type addition of ethyl 4-bromocrotonate (**123e**) to various *N*-aryl α-imino- and *N*-acyl/tosylhydrazono esters (**100**, **102c**) was tested (Table 13). The indium-mediated addition of ethyl 4-bromocrotonate (**123e**) to various α-imino esters **100** synthesized from various anilines having electron withdrawing and electron donating groups in EtOH afforded the respective β-vinyl aspartate derivatives **132b-j** (*syn* isomers) having two contiguous stereocenters with very high diastereoselectivity (*dr* >95:5; Table 13). The indium promoted addition of ethyl 4-bromocrotonate (**123e**) to **100m** in EtOH furnished the product **132k** in 58% yield with very high diastereoselectivity (*dr* >95:5; Table 13). The indium-mediated addition of ethyl-4-bromocrotonate (**123e**) to *N*-biphenyl α-imino ester **100k** furnished the corresponding *N*-biphenyl β-vinyl aspartate **132l** in very high yield and diastereoselectivity (*dr* >95:5; Table 13). The reaction of the α-imino ester **100l** derived from 2-hydroxyaniline provided the product **132m** in 59% yield with moderate diastereoselectivity (*dr* 76:24; Table 13). The observed moderate diastereoselectivity could be due to the disturbance caused by the hydroxyl group in the aromatic ring in the chelation-assisted TS. Interestingly, the indium-promoted addition of **123e** to the α-imino ester **100n** derived from 4-acetylaniline provided the product **132n** (*syn*

isomer, *dr* 95:5) with very high diastereoselectivity and chemoselectivity as the acetyl group was unaffected in the indium-mediated addition of **123e** to the α-imino ester **100n** (Table 13).

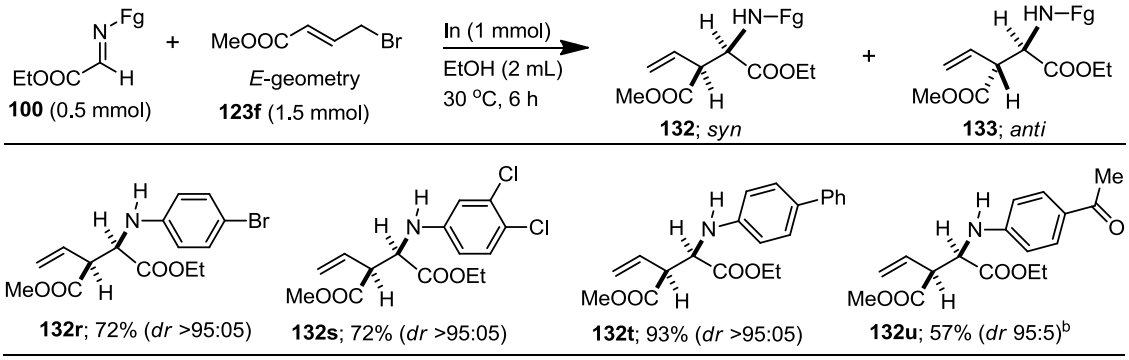
**Table 13.** Diastereoselective synthesis of *N*-aryl β-vinyl aspartic acid esters **132b-q**.[a]



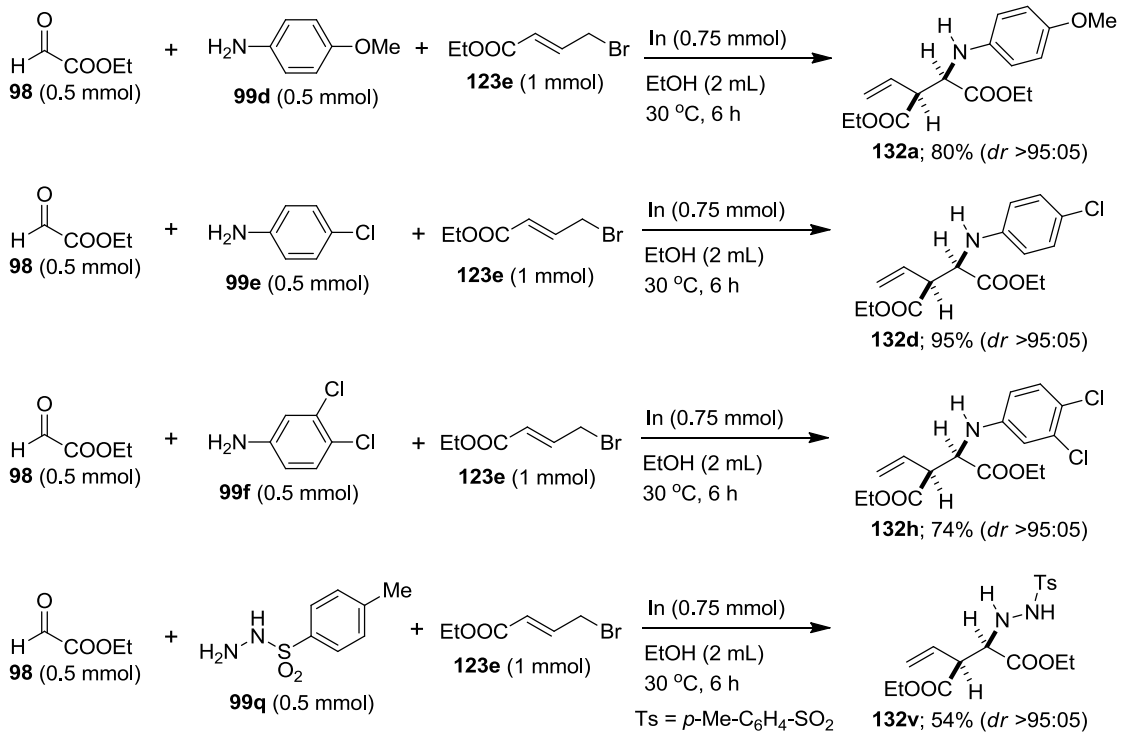

[a] Isolated yields are given and the ratio of (*syn* / *anti*) diastereomers (calculated from the NMR spectra of the crude reaction mixture) is reported in the parenthesis. [b] The reaction was performed using **100** (0.25 mmol), **123e** (0.75 mmol) and indium powder (0.5 mmol).

Subsequently, the reaction of the ethyl 4-bromocrotonate (**123e**) with *N*-acylhydrazono esters **100o**, **100p** and **102c** in the presence of indium metal powder in EtOH furnished the functionalized β-vinyl aspartate derivatives **132o** (81%, *dr* 90:10), **132p** (50%, *dr* 70:30) and **132q** (50%, *dr* 70:30), respectively (Table 13). The products **132p** and **132q** were obtained with moderate diasteroselectivity and perhaps, this is due to the involvement of less rigid cyclic TS.

**Table 14.** Diastereoselective synthesis of orthogonally protected aspartic acid esters **132r-u**.[a]




[a] Isolated yields are given and the ratio of (*syn* / *anti*) diastereomers (calculated from the NMR spectra of the crude reaction mixture) is reported in the parenthesis. [b] The reaction was performed using **100** (0.25 mmol), **123f** (0.75 mmol) and indium powder (0.5 mmol).




**Scheme 52**. One-pot diastereoselective and regioselective synthesis of *N*-aryl β-vinyl aspartic acid derivatives.

Then, the synthesis of orthogonally protected *N*-aryl β-vinyl aspartic acid derivatives having two vicinal stereocenters was envisaged. Accordingly, the indium-mediated Barbier-type reaction of α-imino ester with methyl 4-bromocrotonate (**123f**) was explored. The addition of

methyl 4-bromocrotonate **123f** with α-imino esters **100a**, **100f**, **100k** and **100n** in the presence of indium powder in EtOH successfully gave the orthogonally protected β-vinyl aspartate derivatives **132r-u**, respectively (*syn* isomers, *dr* >95:5; Table 14).

Next, the synthesis of *N*-aryl β-vinyl aspartic acid derivatives having two vicinal stereocenters without the prior preparation of the corresponding α-imino esters was envisioned. Accordingly, the Barbier-type reaction comprising a three-component one-pot reaction of ethyl glyoxalate (**98**), aniline (**99**) and ethyl 4-bromocrotonate (**123e**) in the presence of indium powder was explored. The three component Barbier-type reactions of ethyl glyoxalate (**98**), anilines **99d-f**,**r** and ethyl 4-bromocrotonate (**123e**) in the presence of indium metal were performed, which successfully led to the construction of respective β-alkyl aspartate derivatives **132a**, **132d** and **132h** (*syn* isomers) with high degree of stereocontrol (*dr* >95:5; Scheme 52). Similarly, the one-pot indium mediated three component reaction of ethyl glyoxalate (**98**), *p*-toluenesulfonyl hydrazide (**99q**) and ethyl 4-bromocrotonate (**123e)** in EtOH exclusively afforded the *syn* isomer **132v** (γ-adduct with very high diastereoselectivity (*dr* >95:5; Scheme 52).

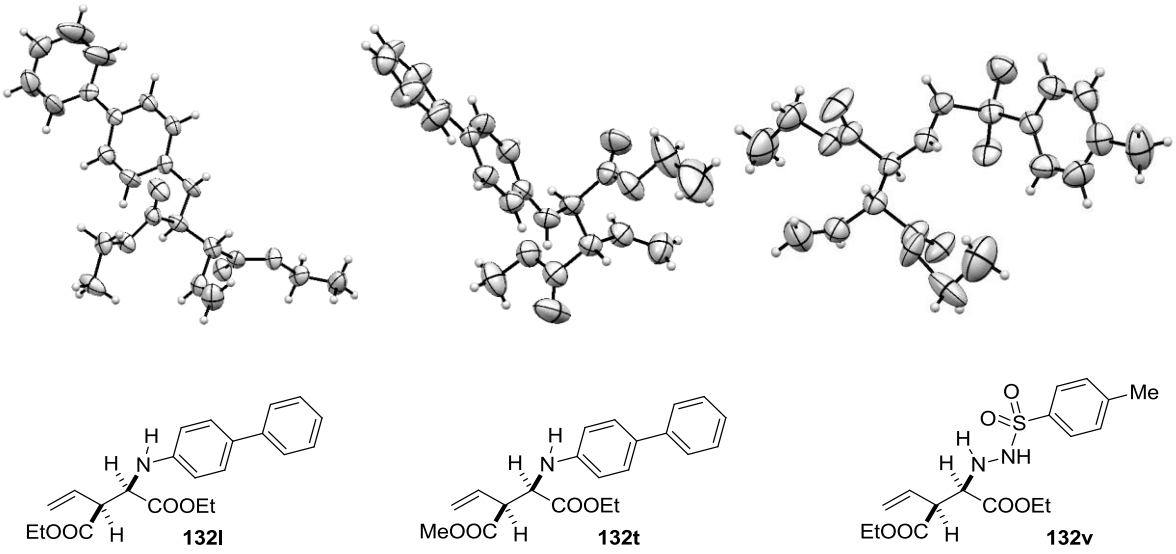



**Figure 10.** X-ray structures of **132l**, **132t** and **132v**.

Based on single crystal X-ray structure analysis of the compounds **132l**, **132t** and **132v**, the stereochemistry of the vicinal stereocenters of the compounds **132l**, **132t** and **132v** was found

to be *syn* (Figure 10). Consequently, the stereochemistry of other adducts listed in the Tables 12-14 and Scheme 52 was also assigned based on the X-ray structure analysis of representative products **132l**, **132t** and **132v** coupled with the similarity in their NMR spectral patterns.

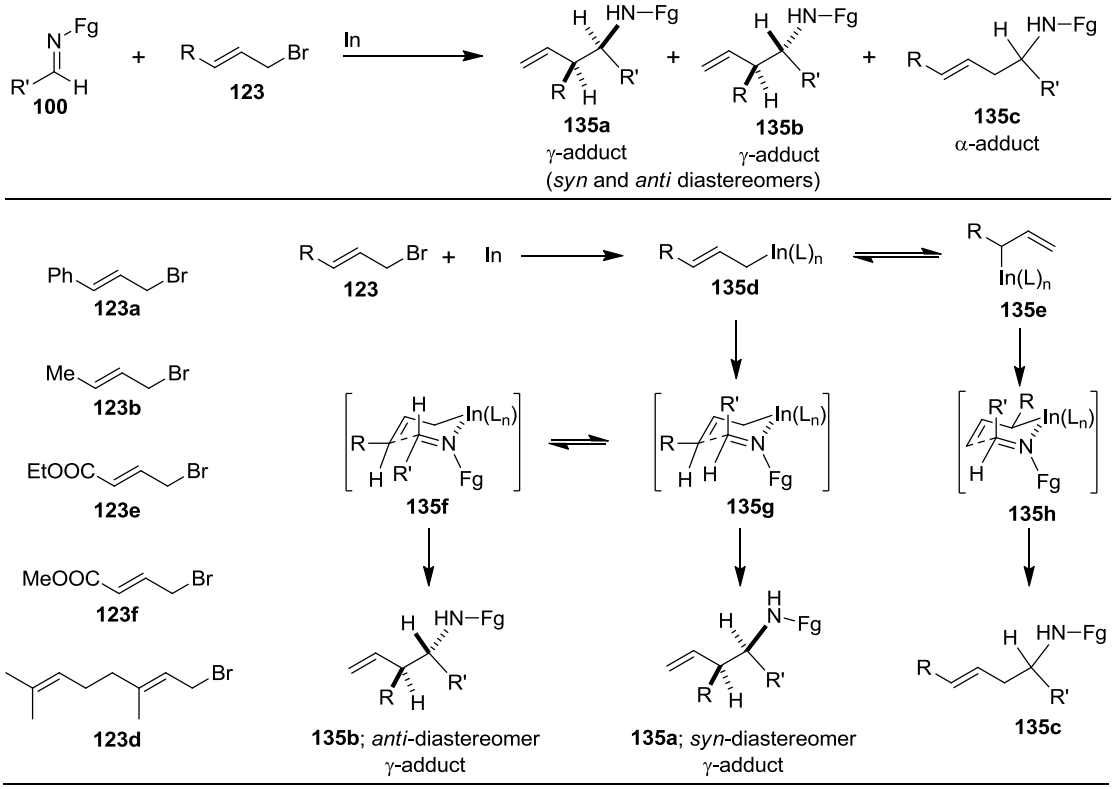
### 4.3.2. Discussion on the observed regio- and diastereoselectivity in the indium-mediated addition of γ-substituted allyl halides to α-imino esters.

To account for the reactivity and selectivity patterns of γ-substituted allyl halides with carbonyl (C=O) and imine (C=N) functionalities, various plausible mechanisms have been reported in the literature.[32-39,48-50] The coupling of an allylindium species **135d** which exists in equilibrium with its regioisomeric species **135e** with an imine considered to proceed through the plausible Zimmerman type transition states (**135f-135h**; Scheme 53). In the case of allyl bromides having a bulky γ-substituent (e.g. silyl or *tert*-butyl), the reaction affords α-adducts *via* the preferred TS **135h**. While in other cases, the metal-mediated addition of γ-substituted allyl halides with imines affords γ-adducts *via* the favoured cyclic transition states **135f** or **135g** and the diastereoselectivity is also governed by the steric size of the substituent on the imine systems.[33a,48d,36b] Thus, the regio- and diastereoselectivity can be explained by the preferred Zimmerman type transition state (Scheme 53).[28b,33b,33c]

Generally, very high diastereoselectivities were obtained when the indium-mediated allylation of C=O and C=N bonds of compounds were performed in protogenic solvents (e.g., aqueous or alcoholic media).[17,18,38a,39,41a,48] Given the fact that the allylindium species formed are tolerant to protogenic solvents,[28a,31] in the Barbier-type reactions comprising indium-mediated addition of γ-substituted allyl halides to α-imino esters described here, the aqueous/alcohol media promotes the fast quenching of the transient indium amide,[16d,17m,28a] which is formed after the addition of the corresponding allylindium to α-imino ester. Moreover, the very high degree of stereocontrol and diastereoselectivity observed in these reactions revealed that the addition of allylindiums to α-imino esters seems to be kinetically controlled.[17,18,38a,39,41a,48]

Furthermore, the stereoselective addition of allylindiums to C=O and C=N bonds of compounds having the heteroatom-based functional groups (e.g. OR or $NR_2$, carbonyl

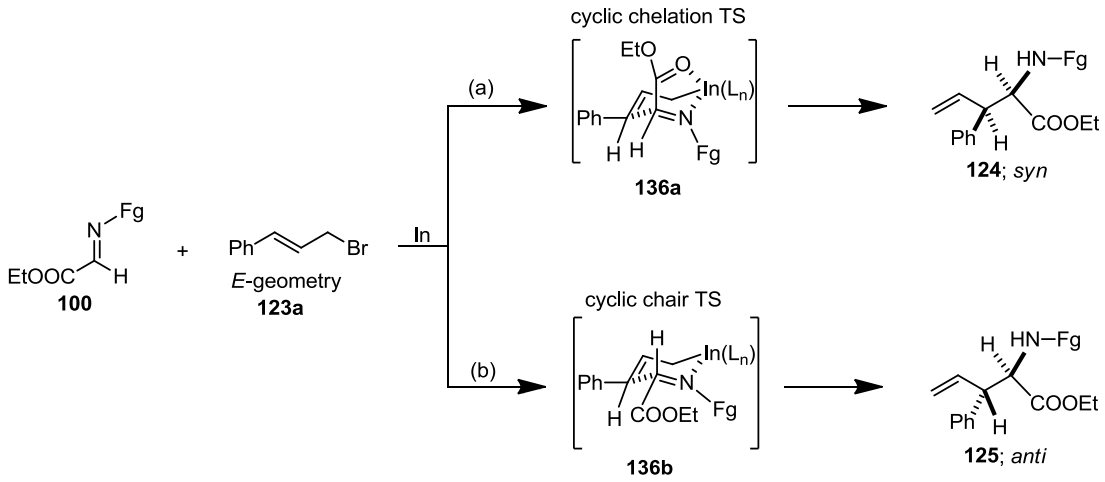
oxygen, etc) at the α-carbon has been well documented.[33-39,48-50] Various research groups proposed the involvement of the chelation-assisted TS for the observed very high diastereoselectivity in the addition of allylindiums to C=O and C=N bonds of compounds having the heteroatom-based functional groups (e.g. OR or $NR_2$, carbonyl oxygen, etc) at the α-carbon. It is assumed that the involvement of a chelation-assisted and rigid TS is an essential factor for obtaining the high degree of diastereoselectivity irrespective of the solvent system used to carry out the reaction.[17,18,38a,39,41a,48]




**Scheme 53.** Plausible transition states (**135f**, **135g**, **135h**) for the regio- and diastereoselectivity.

It is also worth to mention regarding the nature of the allylindium species involved in the allylation reactions. The involvement of both the indium$^{I}$ and indium$^{III}$ species was assumed to be possible as proposed in various reports.[28] Various groups, observed the formation of two discrete species from allylic halides and indium with the help of $^{1}$H NMR studies and the addition of both the species to a carbonyl compound revealed that one species was more reactive than the other species.[28a-28i] The nature of the active indium species remains elusive

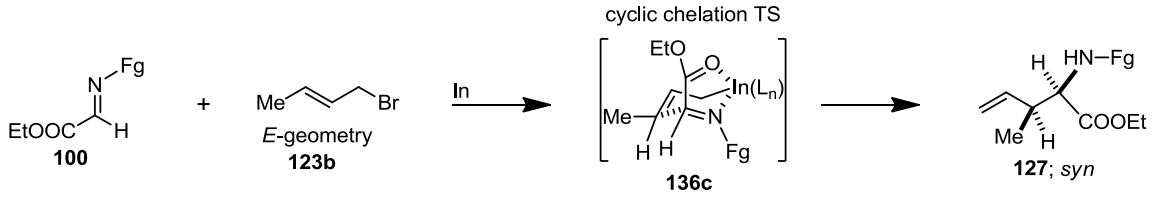
because of its fleeting character. Recent reports strongly suggest the involvement of an $In^{III}$ species in the TS (proposed by Singaram,[28q,28r] Baba[28l-28n] and Koszinowski[28o]), however, in the present reactions, the involvement of an $In^{I}$ species (proposed by Chan[28a,28g,28h] and Hilt[28s]) is also very likely as a chelation-controlled rigid TS, essential for obtaining very high degree of diastereoselectivity, might favor a low-valent indium species.




**Scheme 54.** Plausible transition states (**136a** and **136b**) for the observed diastereoselectivity in the cinnamylation of α-imino esters.

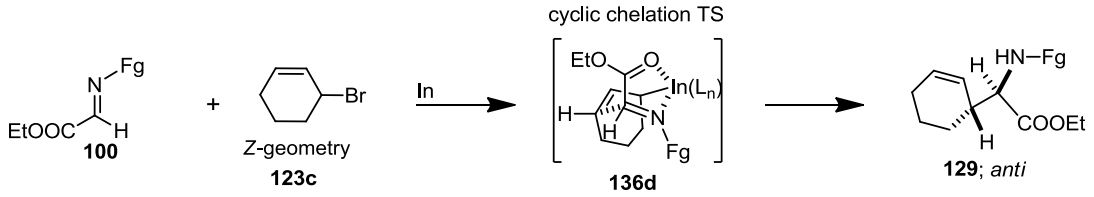
In concurrence with the literature reports, the present study also involves the indium-mediated allylation of C=N bond of α-imino ester having the heteroatom-based functional group i.e. COOEt at the α-carbon. Accordingly, the observed very high degree of diastereoselectivity in the reaction of the indium-mediated addition of γ-substituted allyl halide such as *E*-cinnamyl bromide (**123a**) to α-imino esters **100** and the exclusive formation of *syn* isomers **124** (confirmed from the X-ray structures of **124a**, **124e** and **124i**; Figure 8) could be elucidated *via* the proposed chelation-assisted TS **136a** (Scheme 54).[17,18,33-39,48-50] On the other hand, the corresponding product with *anti*-stereochemistry is expected to form from the non-chelated cyclic chair TS **136b** (Scheme 54).

Similarly, the observed very high degree of diastereoselectivity in the reaction of the indium-mediated addition of *E*-crotyl bromide (**123b**) to α-imino esters **100** and the exclusive formation of *syn* isomers **127** (confirmed from the X-ray structure of **127h**; Figure 9) could be accounted *via* the proposed chelation-assisted TS **136c** (Scheme 55).[17,18,33-39,48-50]




**Scheme 55.** Plausible transition state (**136c**) for the observed diastereoselectivity in the crotylation of α-imino esters.

The indium-mediated addition of 3-bromocyclohexene (**123c**) to α-imino esters **100** gave the products **129** with *anti* stereochemistry with very high degree of stereocontrol. The observed very high degree of diastereoselectivity and the exclusive formation of *anti* isomers **129** (confirmed from the X-ray structure of **129a**; Figure 9) could be accounted *via* the proposed chelation-assisted TS **136d** (Scheme 56).[17,18,33-39,48-50]

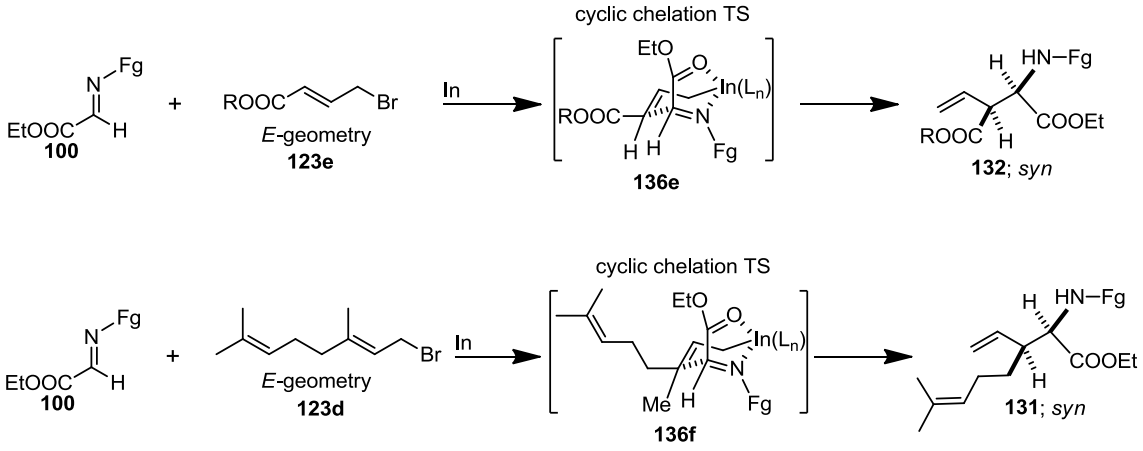



**Scheme 56.** Plausible transition state (**136d**) for the observed diastereoselectivity in the cyclohexenylation of α-imino esters.

Next, the indium-mediated addition of ethyl 4-bromocrotonate (**123e**) or methyl 4-bromocrotonate (**123f**) to α-imino esters **100** furnished the products **132** with *syn* stereochemistry with very high degree of stereocontrol. The observed very high degree of diastereoselectivity and the exclusive formation of *syn* isomers **132** (confirmed from the X-ray structures of **132l**, **132t** and **132v**; Figure 10) could be explained *via* the proposed chelation-assisted TS **136e** (Scheme 57).[17,18,33-39,48-50]

Along this line, the exclusive formation of *syn* isomers **131** from the addition of *E*-geranyl bromide (**123d**) to α-imino esters **100** could be accounted *via* the proposed chelation-assisted TS **136f** (Scheme 57). Noticeably, the reaction of α-imino esters with allyl halides having *E*-geometry, such as, cinnamyl bromide or crotyl bromide or ethyl/methyl 4-bromocrotonate gave the corresponding γ-adducts **124**/**127**/**132** in which the *N*-aryl moiety and the respective

groups Ph/Me/COOEt obtained from the corresponding allyl halides were found to be *syn*. In analogy, the stereochemistry of the products **131** obtained from geranyl bromide having *E*-geometry was proposed based on the *syn* stereochemistry of the products **124**/**127**/**132** (major isomers) which were obtained from the other γ-substituted allylic halides, e.g. cinnamyl bromide, crotyl bromide, ethyl 4-bromocrotonate having the *E*-geometry.



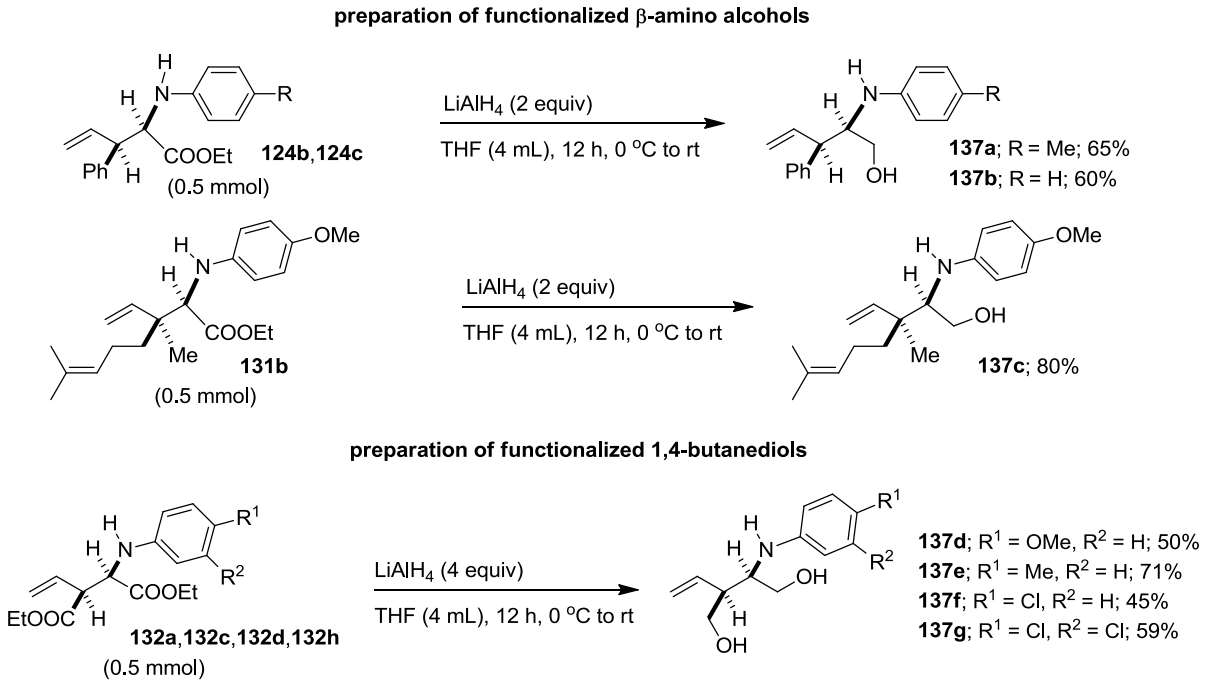

**Scheme 57.** Plausible transition states (**136e** and **136f**) for the observed diastereoselectivity in the crotonate addition and geranylation of α-imino esters, respectively.

### 4.3.3. Scope and utility of the *N*-aryl α-amino acid derivatives obtained from the indium-mediated addition of γ-substituted allyl halides to α-imino esters.

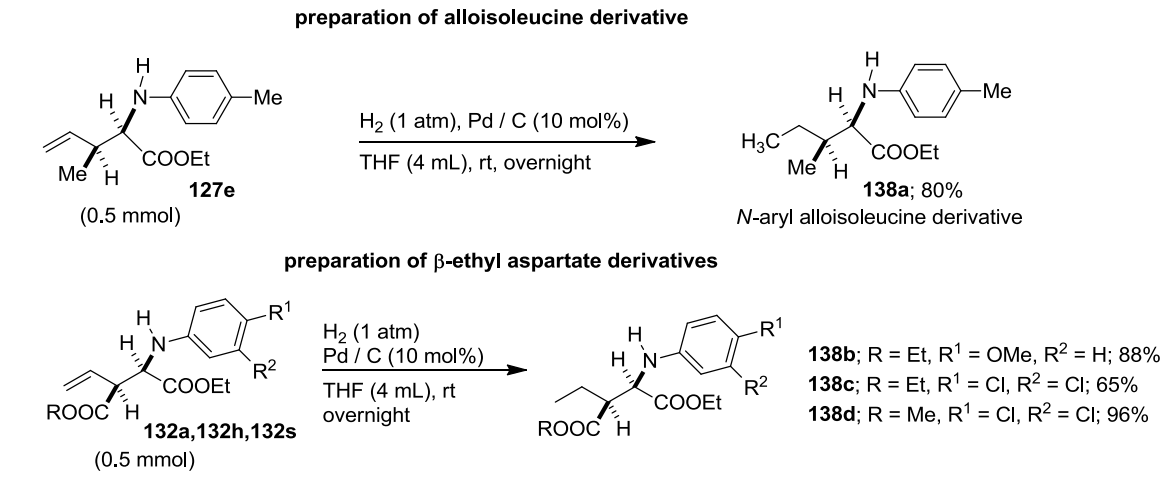
The indium-mediated addition of various γ-substituted allyl halides such as, cinnamyl bromide or crotyl bromide or ethyl/methyl 4-bromocrotonate to α-imino esters led to the construction of several γ,δ-unsaturated β,β′-disubstituted *N*-aryl α-amino acid derivatives **124**, **127**, **129**, **131** and **132** with high degree of stereocontrol. To elaborate the scope of this protocol and to obtain different synthetic intermediates, it was envisioned to perform additional synthetic transformations using the representative compounds from the pool of amino acid derivatives **124**, **127**, **129**, **131** and **132**. Accordingly, the synthetic transformations performed using the representative compounds from the pool of amino acid derivatives **124**, **127**, **129**, **131** and **132** are delineated in Schemes 58-62.

Reduction of the representative compounds **124b**, **124c**, and **131b** gave the respective functionalized δ,ω-unsaturated *N*-aryl β-amino alcohols **137a**–**c** bearing two contiguous

stereocenters. Additionally, reduction of the representative compounds **132a**, **132c**, **132d** and **132h** afforded the corresponding functionalized 1,4-diols **137d-g** having two contiguous stereocenters (Scheme 58).



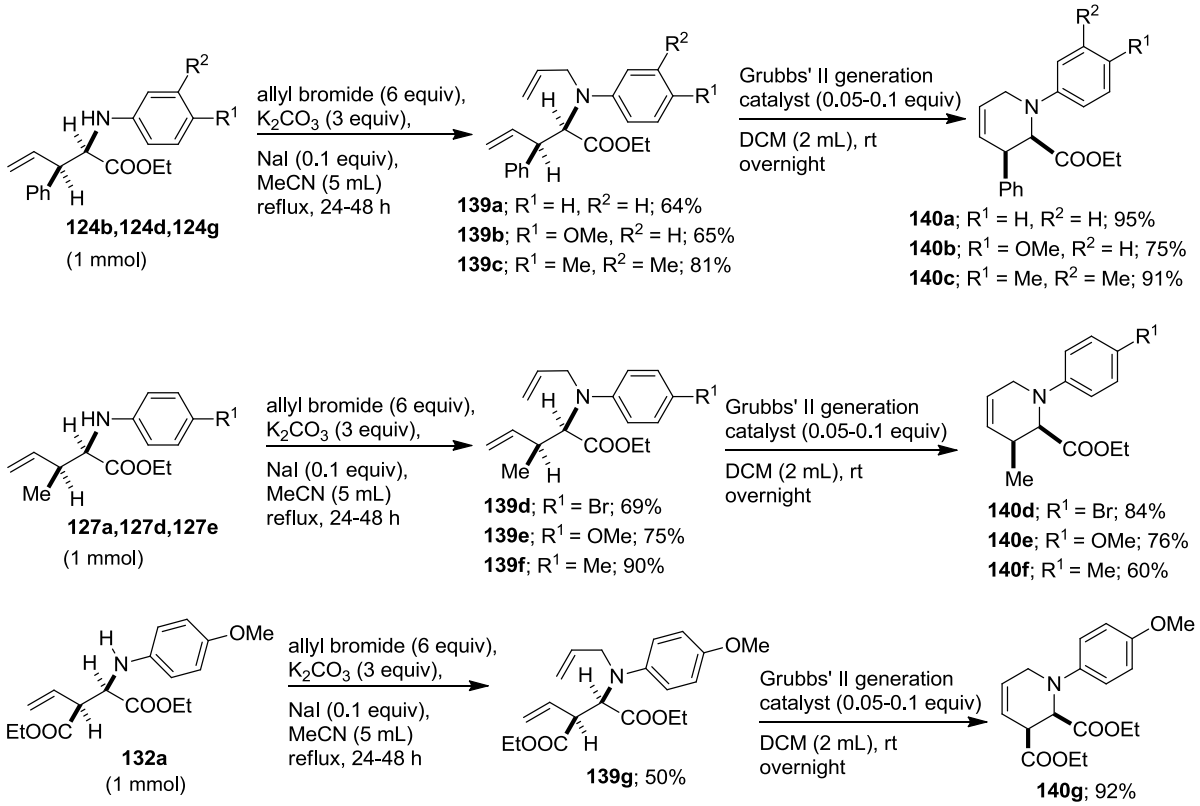

**Scheme 58.** Synthesis of β-amino alcohols (**137a-137g**).



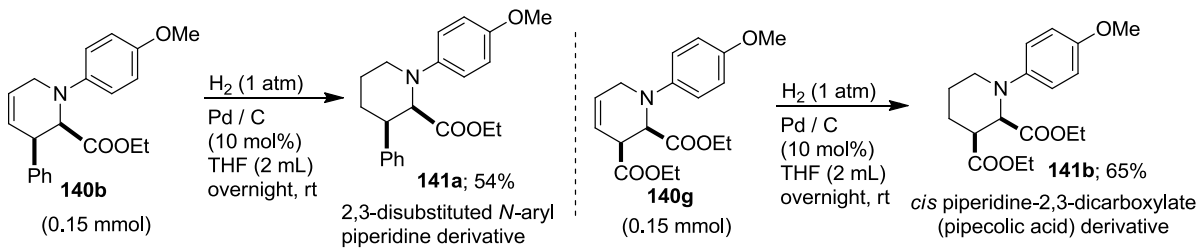

**Scheme 59.** Synthesis of β-ethyl unnatural α-amino acid derivatives (**138a-138d**).

In this line, the catalytic olefin hydrogenation of the compound **127e** (*syn* isomer) was carried out to accomplish the synthesis of a novel *N*-aryl alloisoleucine derivative **138a** (Scheme 59). Next, catalytic olefin hydrogenation of representative aspartate derivatives **132a**, **132h** and **132s** led to the synthesis of *N*-aryl β–ethyl aspartate derivatives **138b-d** (*syn* isomers, Scheme 59).

Subsequently, It was envisaged to construct various 2,3-disubstituted *N*-aryltetrahydropyridine derivatives bearing two contiguous stereocenters using the representative compounds from the pool of amino acid derivatives **124**, **127**, **129**, **131** and **132** (Scheme 60). Accordingly, the *N*-allylation of the secondary amine group of the compounds **124b**, **124d**, **124g**, **127a**, **127d**, **127e** and **132a** led to the assembling of *N*-allylated γ,δ-unsaturated β,β'-disubstituted *N*-aryl α-amino acid derivatives **139a-g**. Further, the ring closing metathesis of the compounds **139a-g** in the presence of a catalytic amount of Grubbs' II generation catalyst[45] successfully led to the production of various 2,3-disubstituted *N*-aryltetrahydropyridine derivatives **140a-g** bearing two contiguous stereocenters in very good yields (Scheme 60).

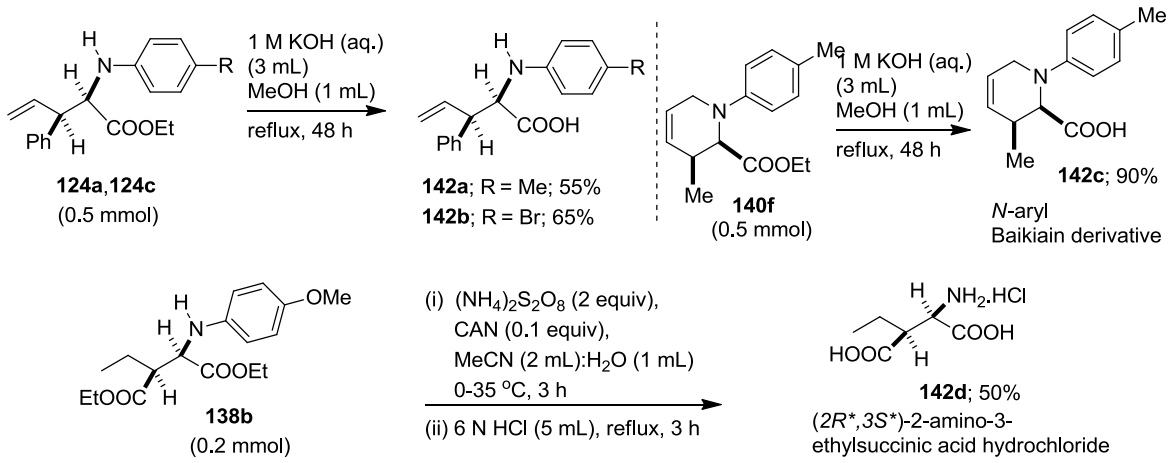



**Scheme 60.** Synthesis of cyclic unnatural amino acid derivatives (**140a-140g**).




**Scheme 61.** Synthesis of pipecolic acid derivatives (**141a** and **141b**).

Subsequently, the hydrogenation of a representative compound **140b** was performed to give the 2,3-disubstituted *N*-aryl piperidine derivative **141a** (Scheme 61). Similarly, the hydrogenation of the compound **140g** gave the pipecolic acid derivative **141b**[107a] (Scheme 61).




**Scheme 62.** Synthesis of phenylalanine derivatives (**142a** and **142b**), *N*-aryl baikiain acid derivative (**142c**) and β–ethyl aspartic acid hydrochloride (**142d**).

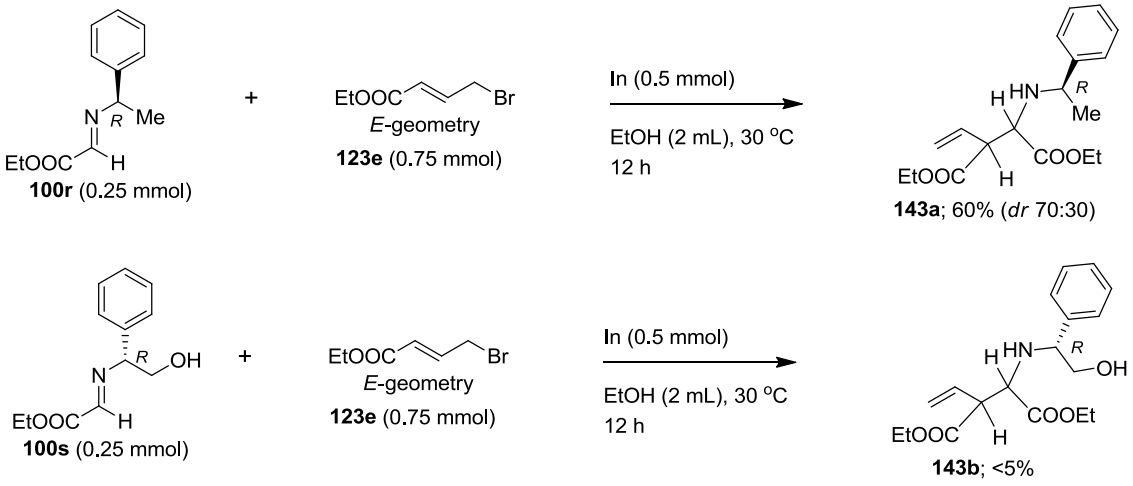
Then, the alkaline hydrolysis of compounds **124a** and **124c** gave the respective unnatural β,β'-disubstituted *N*-aryl α-amino acids **142a** and **142b** and the compounds **142a** and **142b** were obtained as single diastereomers (Scheme 62). Successively, hydrolysis of the compound **140f** was performed to give the 3-methyl-1-(*p-tolyl*)-1,2,3,6-tetrahydropyridine-2-carboxylic acid **142c**. The NMR spectrum of **142c** revealed that the compound **142c** is obtained as a mixture of diastereomers (*dr* 80:20) after the hydrolysis of **140f** and this is due to the occurrence of epimerization under the alkaline hydrolysis condition. It is worth to mention that the synthesized compound **142c** is an analogue of *N*-aryl baikiain acid (Scheme

62).[107b] Then, the deprotection of the amine group of **138b**, *i.e.* removal of the *p*-methoxyphenyl group followed by the ester hydrolysis reaction afforded the new unnatural amino acid β–ethyl aspartic acid hydrochloride **142d** (Scheme 62).

### 4.3.4. Synthesis of enantiomerically enriched γ,δ-unsaturated β,β′-disubstituted α-amino acid derivatives from the indium-mediated Barbier-type allylation of α-imino esters.

Asymmetric addition of carbon nucleophiles to α-imino esters or oximes having chiral auxiliary represents a straightforward route to chiral α-amino acid derivatives. As many reports are available with satisfactory results, none of them deals directly with the synthesis of chiral aspartate derivatives with two vicinal centers.[40d,41m,50i-50m,51a]

Therefore, it was envisioned to disclose an effective method for the highly diastereoselective synthesis of enantiomerically enriched γ,δ-unsaturated β,β′-disubstituted aspartic acid derivatives through the coupling of allylindium generated *in situ* with enantiopure imines (**100r**-**100u**). This method would be a convenient route to obtain a series of enantiopure β,β′-disubstituted aspartic acid and related derivatives.

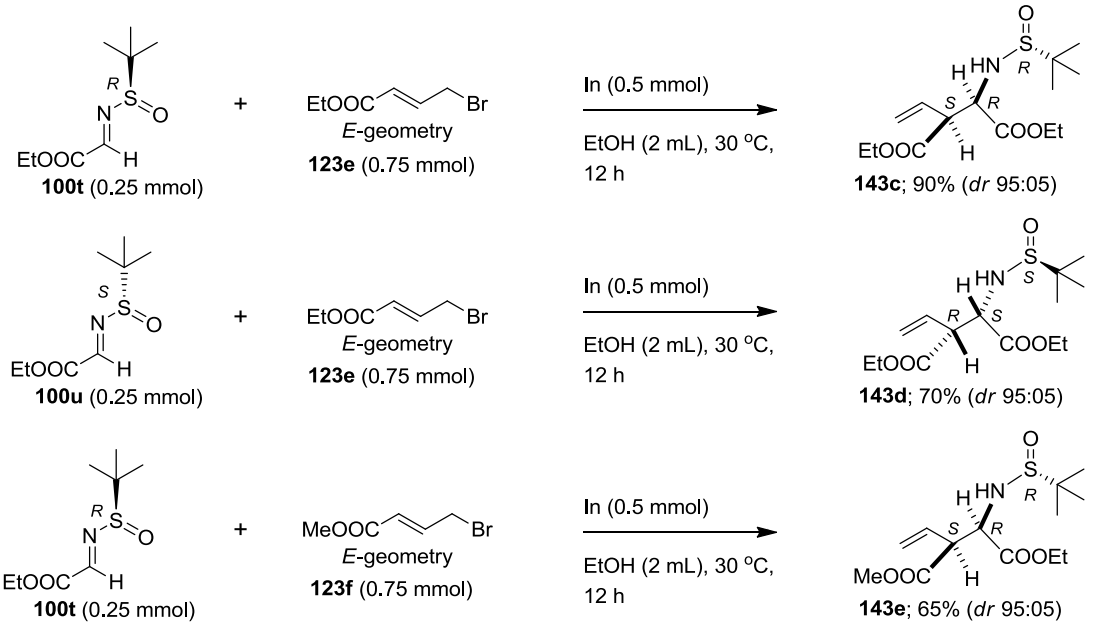



**Scheme 63.** Diastereoselective synthesis of enantiopure β-vinyl aspartic acid derivatives (**143a** and **143b**).

At first, the indium mediated Barbier-type allylation of enantiopure α-imino ester **100r** derived from (*R*)-1-phenylethanamine (**103a**) was investigated by reacting **100r** with **123e** (Scheme 63). The reaction of **123e** with **100r** in EtOH gave the chiral aspartate derivative

**143a** in 60% yield with moderate stereoselectivity (*dr* 70:30; Scheme 63). Similarly, the reaction of **123e** with **100s** (derived from (*R*)-2-amino-2-phenylethanol; **103b**) did not give the corresponding chiral aspartate derivative **143b** (Scheme 63).

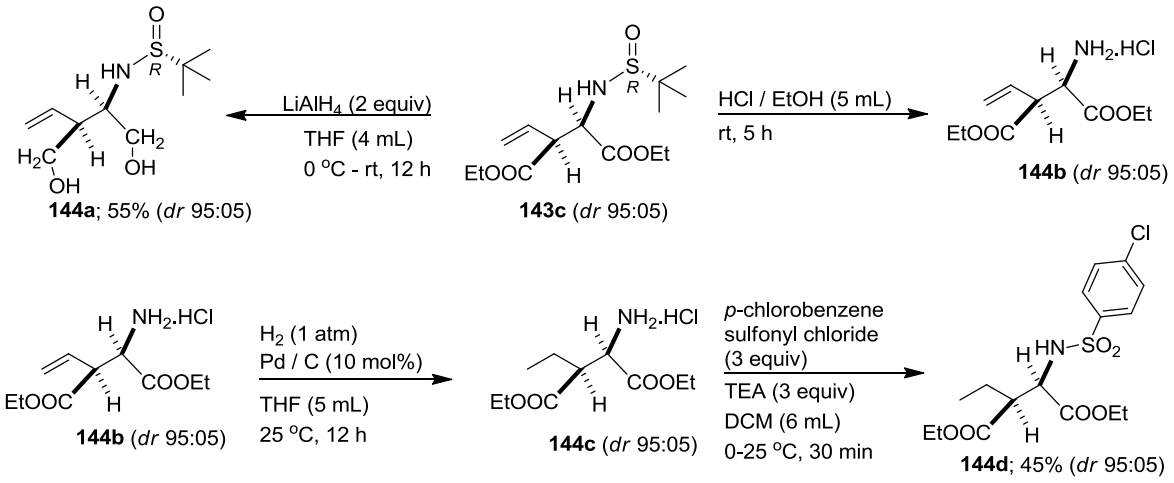
Moving ahead in search of a better chiral auxiliary, the Barbier-type allylation of enantiopure α-imino ester **100t** and **100u** (derived from (*R*) and (*S*)-2-methylpropane-2-sulfinamide, respectively) was investigated by reacting **100t** and **100u** with **123e** and **123f** in the presence of indium metal powder (Scheme 64). The reaction of **123e** with **100t** in the presence of indium in EtOH gave the enantiopure aspartate derivative **143c** in 90% yield with an excellent stereoselectivity (*dr* 95:05; Scheme 64). Similarly, reaction of **123e** with **100u** gave the aspartate derivative **143d** in 70% yield with an excellent stereoselectivity (*dr* 95:05; Scheme 64). Furthermore, the reaction of **100t** with **123f** underwent smoothly under similar reaction conditions to provide **143e** having orthogonally protected ester groups with an excellent stereoselectivity (*dr* 95:05; Scheme 64).




**Scheme 64.** Diastereoselective synthesis of enantiopure β-vinyl aspartic acid derivatives (**143c-e**).

The enantiomerically enriched β-vinyl aspartic acid derivatives **143c-143e** (major isomers) were obtained as liquid samples and it was not possible to assign the stereochemistry of the

vicinal stereocenters. To establish the stereochemistry of the major compounds, some functional group transformations were tried to obtain a solid compound from a representative compound **143c** (*dr* 95:5). At first, the reduction of the ester groups present in the compound **143c** (*dr* 95:5) was performed, which afforded the corresponding amino alcohol **144a** as a liquid (Scheme 65). Then, it was envisaged to remove the chiral auxiliary from a representative compound **143c** (*dr* 95:5) and to obtain a new derivative of **143c** as a solid that could be recrystallized and characterized by the X-ray structure analysis. Accordingly, the enantiopure compound **143c** (*dr* 95:5) was treated with HCl dissolevd in EtOH and without purification the resulted compound **144b** was subjected to catalytic olefin hydrogenation to afford the compound **144c**. Then, without further purification the compound **144c** was treated with *p*-chlorobenzene sulfonyl chloride in DCM and this reaction afforded the compound **144d** as a solid sample. The ratio of diastereomers, presented in the parenthesis in case of compounds **144a-d**, was calculated from the NMR spectra of the corresponding crude reaction mixture.




**Scheme 65**. Functional group transformations using enantiopure β-vinyl aspartic acid derivative **143c**.

The compound **144d** was recrystallized and subjected to the single crystal X-ray structure analysis. The stereochemistry of the vicinal stereocenters of the compound **144d** was found to be *syn* from the single crystal X-ray structure of the compound **144d** (Figure 11). Consequently, the stereochemistry of the vicinal stereocenters of the compounds **143c-143e** (major isomers) was assigned to be *syn* based on the X-ray structure of **144d**.

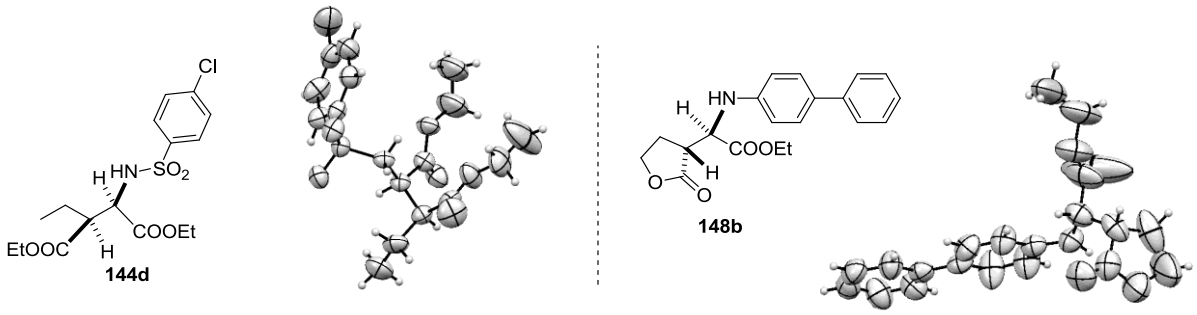
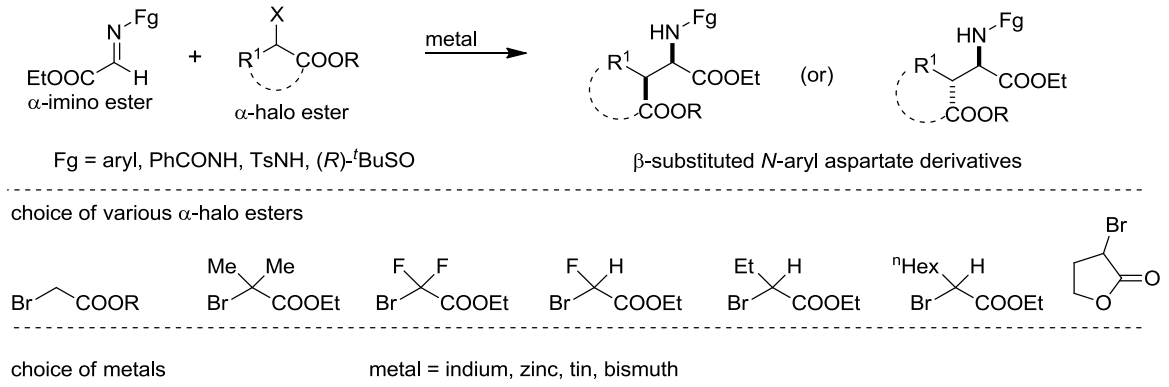



**Figure 11.** X-ray structures of **144d** and **148b**.

### 4.3.5. Indium-mediated Reformatsky-type addition of α-halo esters to α-imino esters and synthesis of aspartate derivatives.

In line with the objective of the present work and after investigating the indium-mediated Barbier-type allylation of α-imino esters for the synthesis of γ,δ-unsaturated β,β′-disubstituted α-amino acid derivatives, it was envisioned to explore the indium-mediated Reformatsky-type reactions of α-halo esters **145** with *N*-aryl α-imino esters **100** for synthesizing aspartate derivatives (Scheme 66).

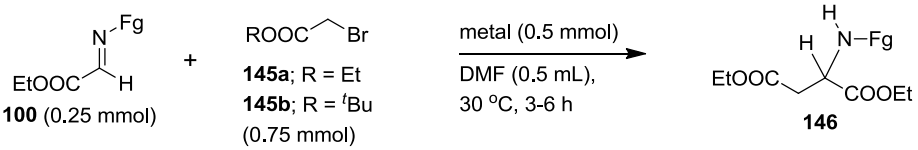


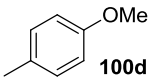
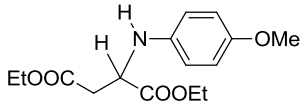
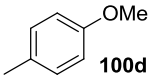
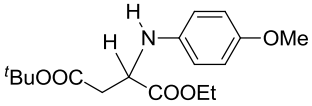
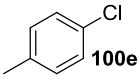
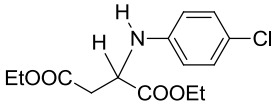
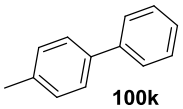
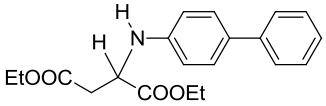
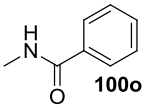
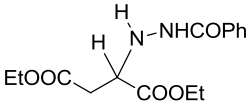

**Scheme 66.** Diastereoselective Reformatsky-type addition of α-halo esters to α-imino esters and construction of functionalized aspartic acid derivatives.

To begin with, optimization reactions were performed to find out the best reaction conditions for the Reformatsky-type reactions of α-halo esters **145a**,**b** with *N*-aryl α-imino esters **100** (Table 15). The reaction of α-halo ester **145a** with the α-imino ester **100d** in DMF in the presence of indium metal gave the aspartate derivative **146a** in 65% yield (entry 1, Table 15).

Employment of other metals, such as Zn, Bi and Sn provided the product **146a** in 5-41% yields (entries 2-4, Table 15). The reaction of the α-halo ester **145b** with **100d** at 80 °C furnished the product **146b** in 40% yield (entry 5, Table 15). Then, the addition of **145a** to other α-imino esters successfully afforded the aspartic acid derivatives **146c-e** in 60-69% yields (entries 6-8, Table 15).

**Table 15.** Reformatsky-type addition of α-halo esters **145** to α-imino esters **100** and synthesis of aspartic acid derivatives **146**.

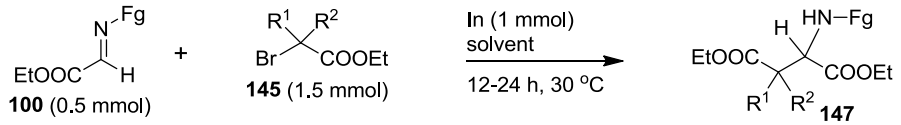


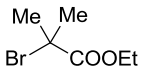
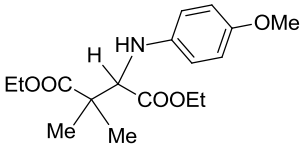
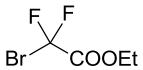
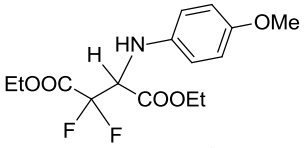
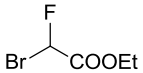
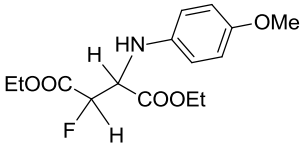
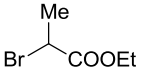
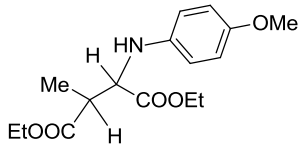
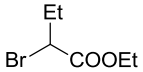
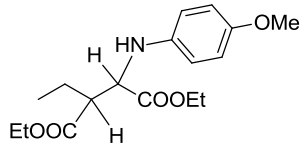
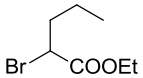
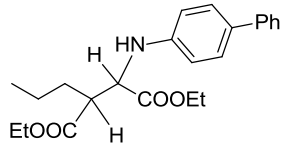
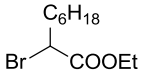
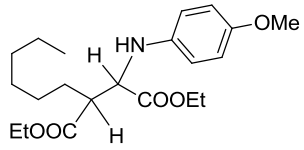

| entry | —Fg | metal | product | **146**; yield (%)[a] |
|---|---|---|---|---|
| 1 |  | In |  | **146a**; 65 |
| 2 | | Zn | | **146a**; 41 |
| 3 | **100d** | Bi | | **146a**; <5 |
| 4 | | Sn | | **146a**; 38 |
| 5 |  **100d** | In |  | **146b**; 40[b] |
| 6 |  **100e** | In |  | **146c**; 69 |
| 7 |  **100k** | In |  | **146d**; 67[c] |
| 8 |  **100o** | In |  | **146e**; 60[c] |

[a] Isolated yields are given. [b] The reaction was carried out at 80 °C. [c] The reaction was carried out at 0 °C for an initial 1 h then at 30 °C for 10 h.

Next, the indium-mediated addition of the substituted α-halo ester **145c** to the α-imino ester **100d** in THF or DMF gave the β,β-dimethyl aspartate derivative **147a** in very good yield (entries 1 and 2, Table 16). The reaction of the α-halo esters **145d** and **145e** with the α-imino ester **100d** in the presence of indium powder afforded the β, β'-difluoro- and β-fluoro aspartates **147b** and **147c**, in 40 and 59% yield, respectively (entries 3 and 4, Table 16).

**Table 16.** Reformatsky-type addition of α-halo esters **145** to α-imino esters **100** and synthesis of aspartic acid derivatives **147**.



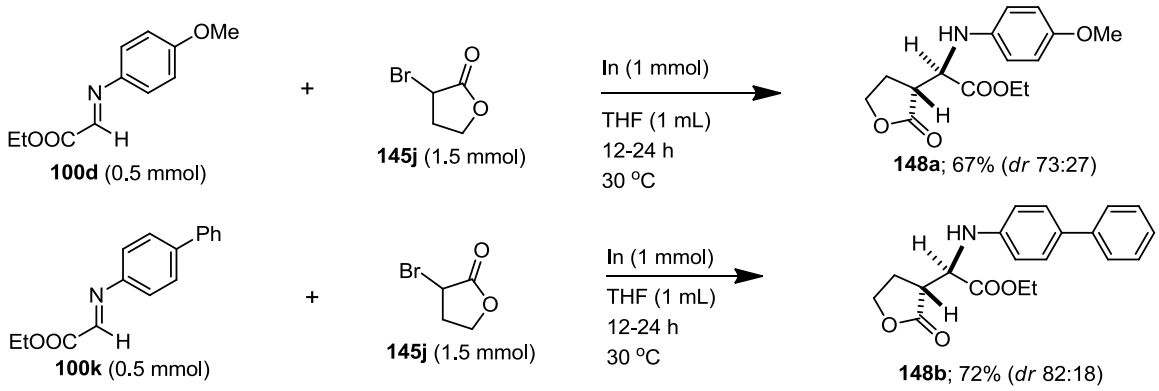

| entry | solvent | 145 | 100 | product | 147; yield (%) (*dr*)[a] |
|---|---|---|---|---|---|
| 1 | DMF (0.5 mL) |  **145c** | **100d** |  | **147a**; 78 |
| 2 | THF (1 mL) | | | | **147a**; 85 |
| 3 | THF (1 mL) |  **145d** | **100d** |  | **147b**; 40[b] |
| 4 | THF (1 mL) |  **145e** | **100d** |  | **147c**; 59 (60:40)[b] |
| 5 | DMF (1 mL) |  **145f** | **100d** |  | **147d**; 66 (65:35)[b] |
| 6 | THF (1 mL) |  **145g** | **100d** |  | **147e**; 62 (65:35) |
| 7 | THF (1 mL) |  **145h** | **100k** |  | **147f**; 50 (60:40) |
| 8 | THF (1 mL) |  **145i** | **100d** |  | **147g**; 35 (80:20)[c] |

[a] Isolated yields are given and the ratio of (*syn* / *anti*) diastereomers (calculated from the NMR spectra of the crude reaction mixture) is reported in the parenthesis. [b] The reaction was done at 75 °C. [c] Indium was first allowed to react with **145i** for 2 h, then the organoindium was added to **100** slowly.

Then, it was envisioned to perform the diastereoselective indium-mediated reaction of substituted α-halo esters (**145f-i**) with the α-imino esters **100** to obtain the corresponding aspartate derivatives with vicinal stereocenters. The indium-mediated reaction of ethyl 2-

bromopropanoate (**145f**) with the α-imino ester **100d** at 75 $^{o}$C gave the product **147d** in 66% yield with low diastereoselectivity (*dr* 65:35; entry 5, Table 16). Similarly, the reaction of ethyl 2-bromobutyrate (**145g**) with the α-imino ester **100d** in the presence of indium gave the product **147e** in 62% yield with low diastereoselectivity (*dr* 65:35; entry 6, Table 16). The reaction of ethyl 2-bromopentanoate (**145h**) with the α-imino ester **100k** also gave the corresponding product **147f** as diastereomers in 50% yield with low diastereoselectivity (*dr* 60:40; entry 7, Table 16). There was a notable improvement in the diastereoselectivity in the indium-mediated reaction of ethyl 2-bromooctanoate (**145i**) with **100d**, which gave the product **147g** in only 35% yield with good diastereoselectivity (*dr* 80:20; entry 8, Table 16).

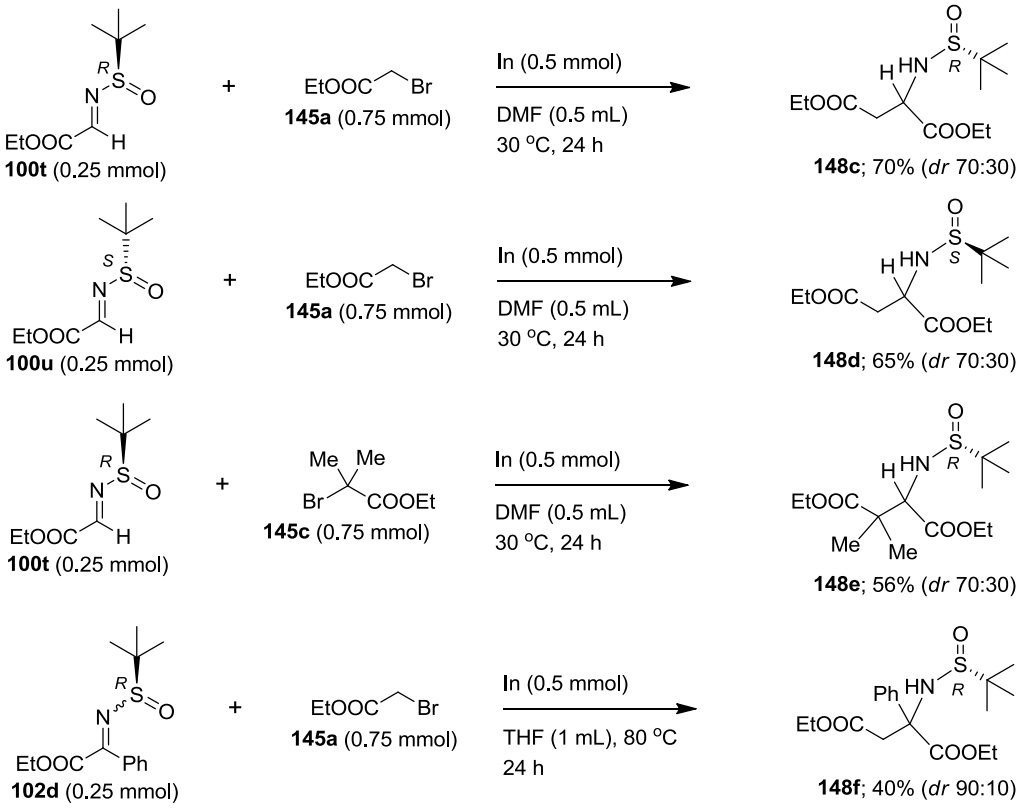
Furthermore, the indium-mediated reactions of the α-imino esters **100d** and **100k** with α-bromo-γ-butyrolactone (**145j**) furnished the corresponding β-substituted aspartate lactones **148a** (67%, *dr* 73:27) and **148b** (72%, *dr* 82:18) with relatively good diastereoselectivity (Scheme 67). The formation of the products **147c-g** with relatively low diastereoselectivity might be due to the involvement of a less rigid cyclic TS in the respective Reformatsky reactions. The respective compounds **147c-g** were obtained as liquids and mixture of diastereomers and hence, the stereochemistry of the compounds **147c-g** were not assigned. The major isomer of the compound **148b** (*dr* 82:18) was isolated in pure form and the stereochemistry of the products **148a** and **148b** was assigned based on the single crystal X-ray structure of the major diastereomer of **148b** (Figure 11).




**Scheme 67.** In-mediated addition of α-bromo γ-butyrolactone (**145j**) to **100**.

It was envisaged that due to the enormous value of enantiomerically pure molecules, there is a scope to explore the synthesis of enantiomerically enriched aspartic acid derivatives from

the indium-mediated Reformatsky-type reactions of α-halo esters **145** with α-imino esters **100**. Accordingly, the Reformatsky-type reactions of the α-halo esters **145** with enantiomerically pure α-imino ester **100t** (prepared using (*R*)-2-methylpropane-2-sulfinamide chiral auxiliary) or **100u** (prepared using (*S*)-2-methylpropane-2-sulfinamide chiral auxiliary) in DMF gave the corresponding enantiomerically enriched aspartate derivatives **148c** and **148d** with moderate diastereoselectivity (Scheme 68). Similarly, the enantioselective indium-mediated Reformatsky-type reactions of α-halo ester **145c** with enantiopure α-imino ester **100t** and α-halo ester **145a** with enantiopure α-imino esters **102d** afforded the corresponding enantiomerically enriched aspartate derivatives **148e** and **148f** (Scheme 68). Though, the stereochemistry of the chiral auxiliary part is known the stereochemistry of the respective major isomers of compounds **148c-f** could not be assigned since the respective compounds **148c-f** were obtained as liquids and mixture of diastereomers.

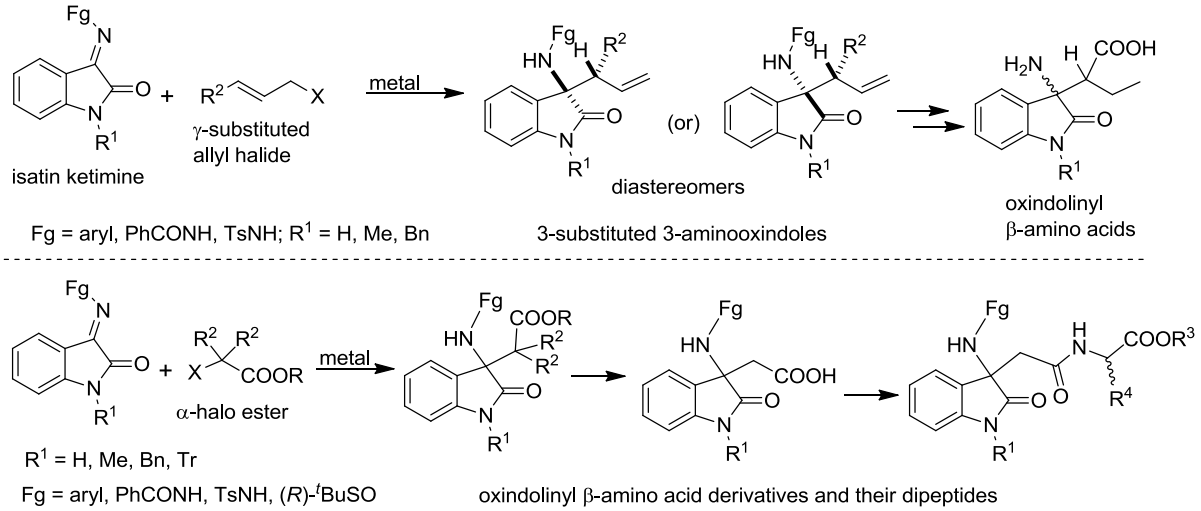



**Scheme 68.** Enantioselective synthesis of aspartic acid derivatives (**148c-f**).

## 4.4. Stereoselective construction of various 3-amino-2-oxindole scaffolds *via* the indium-mediated Barbier-type and Reformatsky-type reactions.

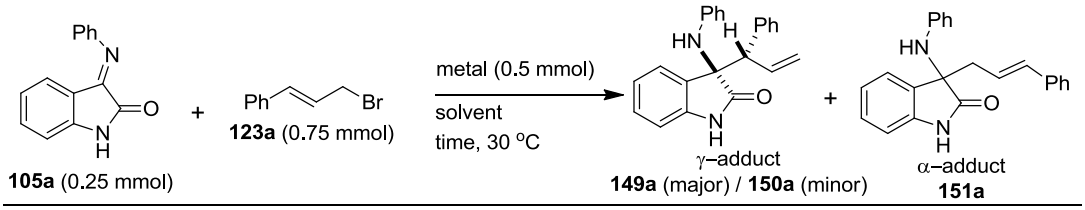
### 4.4.1. Diastereoselective indium-mediated Barbier-type allylation of isatin ketimines.

Considering the importance of oxindole molecules containing a heteroatom (N or O or S) at the C-3 position,[79-80] it was envisioned to investigate the diastereoselective construction of 3-aminooxindole (oxindole-based homoallylic amine) systems having two adjacent stereocenters *via* the Barbier-type metal-mediated addition of γ-substituted allylic halides to the C=N bond of isatin ketimines. Along this line, it was envisioned to explore the synthesis of oxindole-based unnatural β-amino acid derivatives possessing vicinal stereocenters *via* the Barbier- and Reformatsky-type reactions as delineated in Scheme 69. The metal-mediated Grignard- or Barbier-type allylations of ketimines derived from isatins and the synthesis of 3-amino-oxindole based homoallylic amines possessing one stereocenter has been well documented.[81] However, the diastereoselective indium-mediated addition of γ-substituted allyl halides to ketimines derived from isatins and the construction of 3-amino-oxindole based homoallylic amines and β–amino acid derivatives possessing vicinal stereocenters have not been explored well.




**Scheme 69.** Barbier-type addition of γ-substituted allyl halides and α-halo esters to isatin ketimines and construction of 3-amino-oxindole-based β–amino acid derivatives.

**Table 17.** Optimization of reaction conditions. Diastereoselective synthesis of 3-substituted-3-amino-oxindole **149a**.




| entry | metal | solvent (mL) | time (h) | **149a** / **150a**; yield (%) (*dr*)[a] | **151a**; yield (%) |
|---|---|---|---|---|---|
| 1 | In | THF (2) | 24 | 59 (86:14) | 20 |
| 2 | In | DMF (0.5) | 24 | 30 (50:50) | 65 |
| 3 | In | 1,4-dioxane (1) | 24 | 65 (90:10) | ND |
| 4 | In | EtOH (2) | 06 | 78 (95:5) | ND |
| 5 | In | THF (1) : $H_2O$ (2) | 24 | 30 (95:5) | ND |
| 6 | In | THF (2) : $H_2O$ (0.2) | 24 | 53 (95:5) | ND |
| 7 | In | THF (0.2) : $H_2O$ (2) | 24 | 83 (95:5) | ND |
| 8 | In | THF (0.2) : $H_2O$ (2) | 36 | 83 (95:5) | ND |
| 9 | In | THF (0.2) : $H_2O$ (2) | 12 | 80 (95:5) | ND |
| 10 | In | THF (0.2) : $H_2O$ (2) | 06 | 80 (95:5) | ND |
| 11 | In | THF (0.2) : $H_2O$ (2) | 03 | 65 (95:5) | ND |
| 12 | In | THF (0.2) : $H_2O$ (2) | 1.5 | 60 (95:5) | ND |
| 13 | In | THF (0.2) : $H_2O$ (2) | 03 | 13 (-)[b] | ND |
| 14 | In | THF (0.2) : $H_2O$ (2) | 03 | 70 (95:5)[c] | ND |
| 15 | In | DMF (0.2) : $H_2O$ (2) | 03 | 13 (-) | ND |
| 16 | Zn | THF (0.2) : $H_2O$ (2) | 03 | 23 (95:5) | ND |
| 17 | Sn | THF (0.2) : $H_2O$ (2) | 06 | < 5 (-) | ND |

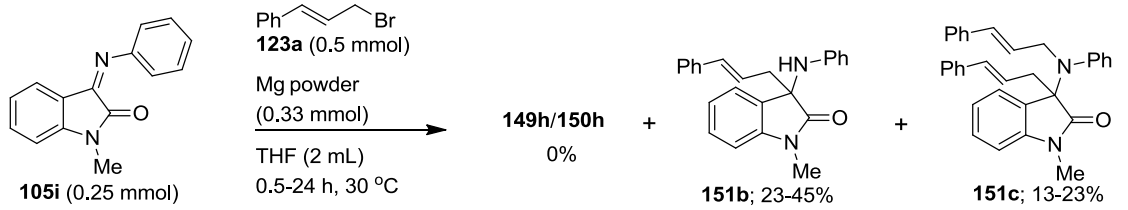
[a] Isolated yields are given and the ratio of (*syn* / *anti*) diastereomers (calculated from the NMR spectra of the crude reaction mixture) is reported in the parenthesis. [b] The reaction was carried out at 70 °C. [c] The reaction was carried out at 5 °C. ND = Not Detected.

At first, the Barbier-type reaction of isatin ketimines with γ-substituted allylic halides was examined and various optimization reactions were performed comprising the indium-mediated addition reaction of γ-substituted allyl halide such as *E*-cinnamyl bromide (**123a**) to isatin ketimine **105a** to obtain the 3-aminooxindole **149a** (γ-adduct) having contiguous stereocenters with very high diastereoselectivity. A mixture of isatin ketimine **105a**, cinnamyl bromide (**123a**) and indium metal powder in anhydrous THF was stirred at 30 °C

for 24 h. Then, the reaction was quenched with water, extracted with ethyl acetate and concentrated in vacuum to afford a crude reaction mixture. Column chromatographic purification of the reaction mixture gave the 3-aminooxindoles **149a**/**150a** (γ-adducts) as diastereomers in 59% yield with very good diastereoselectivity (*dr* 86:14) and also the 3-aminooxindole **151a** (α-adduct) in 20% yield (entry 1, Table 17). Performing the same reaction in *N*,*N*-dimethylformamide (DMF) afforded the diastereomers **149a**/**150a** in 30% yield (*dr* 50:50) and the α-adduct **151a** in 65% yield (entry 2, Table 17). The indium-mediated addition reaction of **123a** with **105a** in 1,4-dioxane afforded the 3-aminooxindole diastereomers **149a**/**150a** in 65% yield with very high diastereoselectivity (*dr* 90:10; entry 3, Table 17) and the α-adduct **151a** was not obtained in this reaction. The reaction of isatin ketimine **105a** with **123a** in the presence of indium in EtOH gave the diastereomers **149a**/**150a** with an improved yield and diastereoselectivity (78%, *dr* 95:5; entry 4, Table 17). Subsequently, the reaction of isatin ketimine **105a**, cinnamyl bromide (**123a**) and indium metal powder was tested in various THF-water combinations (entries 5-7, Table 17). The THF-water (0.2:2) combination smoothly promoted the indium-mediated addition reaction of **123a** with **105a** and 3-aminooxindoles **149a**/**150a** were obtained in good yields (up to 83%) with very high diastereoselectivity (*dr* 95:5; entries 7-12, Table 17). Notably, the α-adduct **151a** was not obtained in these reactions (entries 5-12, Table 17). The indium-mediated addition reaction of **123a** with **105a** at 70 $^{o}$C gave the diastereomers **149a**/**150a** in very low yield **(**13% entry 13, Table 17). On the other hand, the reaction of **105a** with **123a** in THF-water at 5 $^{o}$C gave the diastereomers **149a**/**150a** in 70% yield (*dr* 95:5; entry 14, Table 17). The indium-mediated addition reaction of **123a** with **105a** in a mixture of DMF-water furnished the diastereomers **149a**/**150a** in very low yield **(**13%; entry 15, Table 17). The addition reaction of **123a** with **105a** in the presence of Zn or Sn metal powder instead of In metal powder provided the diastereomers **149a**/**150a** in 23 and <5% yield, respectively (entries 16-17, Table 17).

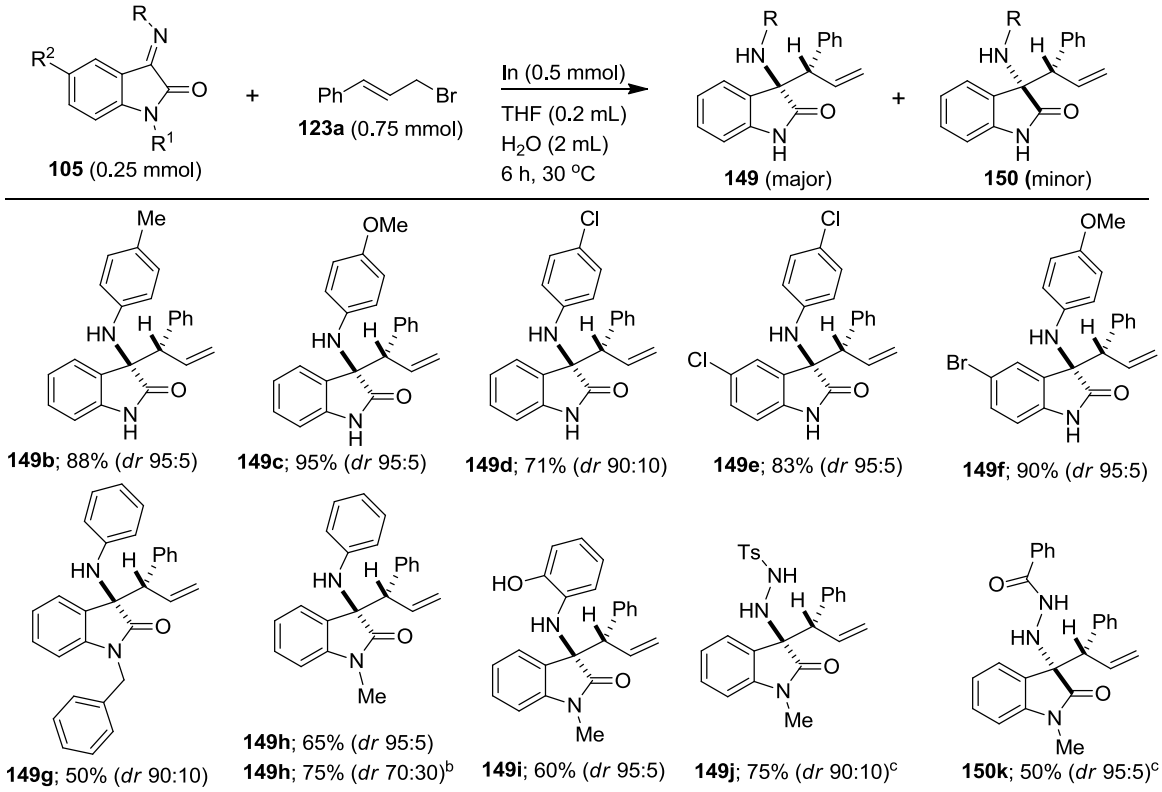
Additionally, it was envisaged to perform the Barbier-type reaction of isatin ketimine **105i** with *E*-cinnamyl bromide (**123a**) in the presence of Mg powder instead of In powder. Accordingly, a mixture of **105i**, **123a** and Mg powder in anhydrous THF was stirred at 30 $^{o}$C. After the standard work-up procedure and purification of the crude reaction mixture afforded the products **151b** and **151c** (Scheme 70). Notably, the reaction of **105i**, **123a** and Mg powder

did not afford the expected γ-adducts **149h**/**150h**. Thus, In metal powder and THF-water (0.2:2) system are the best reaction conditions for the diastereoselective Barbier-type reaction of isatin ketimine with γ-substituted allylic halide **123a** and for synthesizing the oxindole-based homoallylic amine **149a** bearing two vicinal stereocenters.




**Scheme 70**. Mg-mediated addition of **105i** and **123a**. Formation of **151b** and **151c**.

**Table 18.** Diastereoselective synthesis of 3-substituted-3-amino-oxindoles **149b-j** and **150k**.[a]




[a] Isolated yields are given and the ratio of (*syn* / *anti*) diastereomers (calculated from the NMR spectra of the crude reaction mixture) is reported in the parenthesis. [b] The reaction was carried out in EtOH. [c] The reactions was carried out with **106** or **107** (0.25 mmol), **123a** (0.63 mmol) and indium powder (0.38 mmol) in a mixture of THF (0.5 mL) and $H_2O$ (1 mL) for 24 h. In all these reactions, the corresponding α-adducts were not detected.

After finding the optimized reaction conditions, the generality of the protocol comprising the Barbier-type cinnamylation of isatin ketimines was explored and the diastereoselective synthesis of a number of cinnamylated 3-aminooxindoles was accomplished (Table 18). The indium-mediated cinnamylation of various isatin ketimines prepared from diversely substituted anilines and isatins in THF-water media successfully gave the corresponding cinnamylated 3-aminooxindoles **149b-i** having two vicinal stereocenters in 50-95% yields and excellent diastereoselectivity (*dr* up to 95:5; Table 18). The In-mediated Barbier-type cinnamylation of isatin ketimine **105h** having a free hydroxyl group also smoothly underwent the addition reaction in THF-water media to afford the product **149i** in 60% yield with high diastereoselectivity (*dr* 95:5; Table 18).

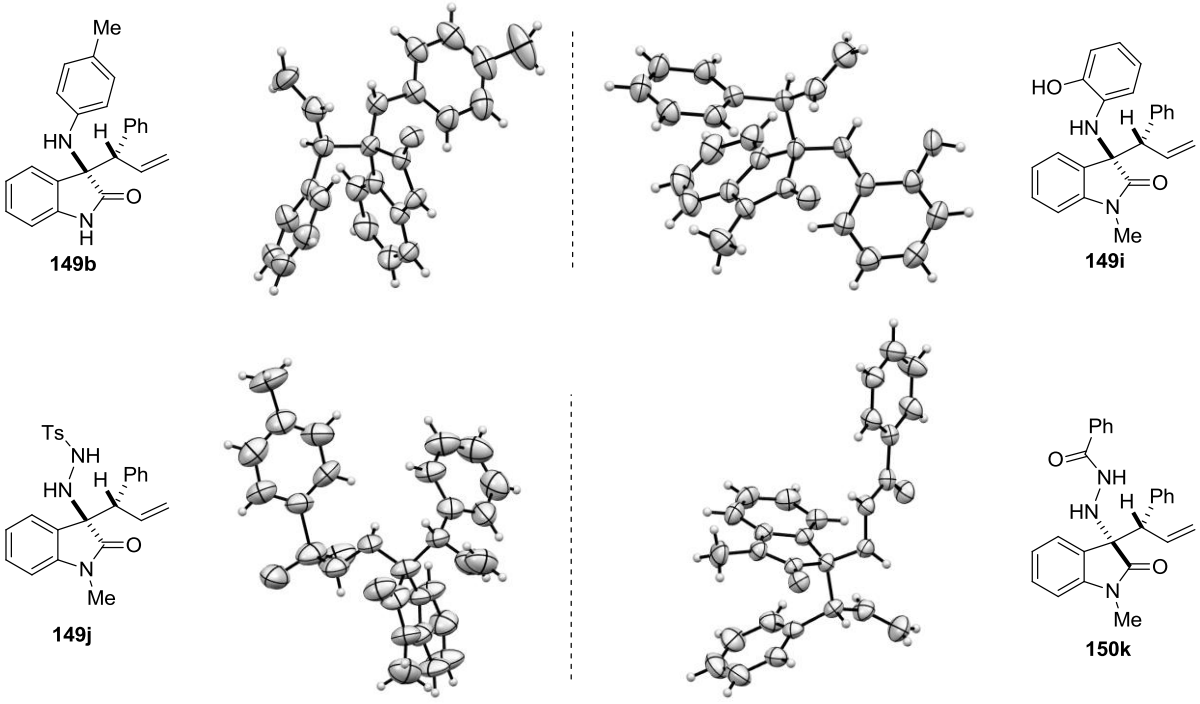
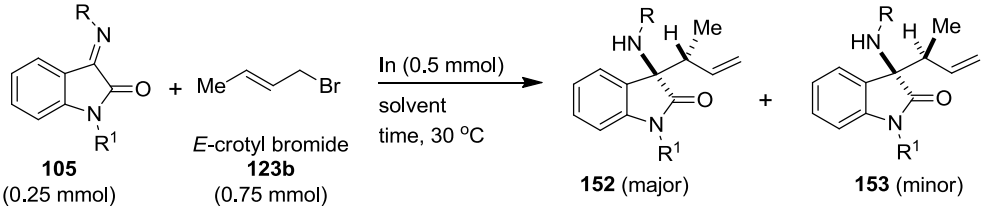


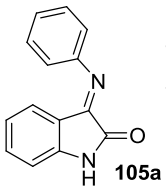
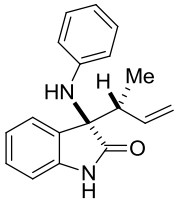
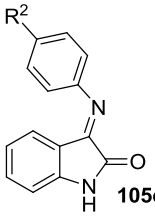
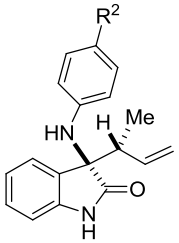
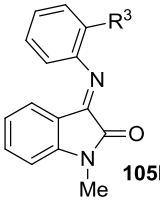
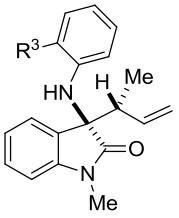

**Figure 12**. X-ray structures of **149b**, **149i**, **149j** and **150k** (major isomers).

Next, the cinnamylated 3-aminooxindole **149j** having two vicinal stereocenters was obtained from the indium-mediated cinnamylation of tosylhydrazone **106** (derived from *N*-methyl isatin) in 75% yield with high diastereoselectivity (*dr* 90:10; Table 18). Similarly, the indium-mediated cinnamylation of benzoylhydrazone **107** furnished the corresponding cinnamylated 3-aminooxindole **150k** having two adjacent stereocenters in 50% yield with

good diastereoselectivity (*dr* 95:5; Table 18). The stereochemistry of the cinamylated 3-amino oxindoles **149a-j** and **150k** was assigned on the basis of the X-ray structures of representative major isomers of **149b**, **149i**, **149j** and **150k** (Figure 12).

**Table 19.** Diastereoselective synthesis of 3-substituted-3-amino-oxindoles **152a-e**.[a]




| entry | imine | solvent (mL) | time (h) | product | **152** / **153**; yield (%) (*dr*)[a] |
|---|---|---|---|---|---|
| 1 |  **105a** | DMF (0.5) | 03 |  | **152a**; 95 (60:40) |
| 2 | | THF (1) | 06 | | **152a**; 66 (60:40) |
| 3 | | THF (0.2) : $H_2O$ (2) | 06 | | **152a**; 65 (70:30) |
| 4 | | EtOH (1) | 06 | | **152a**; 56 (60:40) |
| 5 |  **105c**,**105d** | THF (0.2) : $H_2O$ (2) | 06 |  | **152b**; $R^2$ = Cl; 80 (68:32) |
| 6 | | THF (0.2) : $H_2O$ (2) | 06 | | **152c**; $R^2$ = OMe; 60 (70:30) |
| 7 |  **105h**,**105i** | THF (0.5) : $H_2O$ (2) | 12 |  | **152d**; $R^3$ = H; 70 (69:31) |
| 8 | | THF (0.5) : $H_2O$ (2) | 12 | | **152e**; $R^3$ = OH; 75 (60:40) |

[a] Isolated yields are given and the ratio of (*syn* / *anti*) diastereomers (calculated from the NMR spectra of the crude reaction mixture) is reported in the parenthesis.

After investigating the indium-mediated cinnamylation of isatin ketimines **105**, the Barbier-type In-mediated direct addition of crotyl bromide (**123b**) to isatin ketimines **105** was studied (Table 19). Optimization reactions were carried out to find out the best reaction conditions comprising the indium-mediated addition of crotyl bromide (**123b**) to isatin ketimine **105a**. The-indium mediated reaction of isatin ketamine **105a** with crotyl bromide (**123b**) in various solvents such as DMF, THF, THF/water mixture and EtOH afforded the 3-aminooxindoles

**152a/153a** (γ-adducts) as a mixture of diastereomers in 56-95% yield with moderate diastereoslectivity (*dr* up to 70:30; entries 1-4, Table 19). Amongst the solvent systems employed, only the THF/water media was found to afford the 3-aminooxindoles **152a/153a** (γ-adducts) in moderate diastereoslectivity (*dr* up to 70:30). Subsequently, the indium-mediated reactions of crotyl bromide with other isatin ketimines **105c**, **105d**, **105h** and **105i** were carried out in THF/water solvent media to afford the corresponding crotylated 3-amino-oxindoles **152b-e** in 60-80% yields with moderate diastereoselectivity (*dr* up to 70:30; entries 5-8, Table 19). When compared to the cinnamylation of isatin ketimines, the crotylation of isatin ketimines gave the 3-aminooxindoles **152** with moderate diastereoselectivity. The reason for the relatively low diastereoselectivity in the In-mediated reactions of crotyl bromide (**123b**) to isatin ketimines **105** might be due to the involvement of a less rigid cyclic TS and the smaller size of the methyl group (in crotyl bromide) when compared to the phenyl group in case of cinnamyl bromide. The stereochemistry of the crotylated 3-amino oxindoles **152a-e** was assigned on the basis of the X-ray structures of the representative major isomers of **152d** and **152e** (Figure 13).

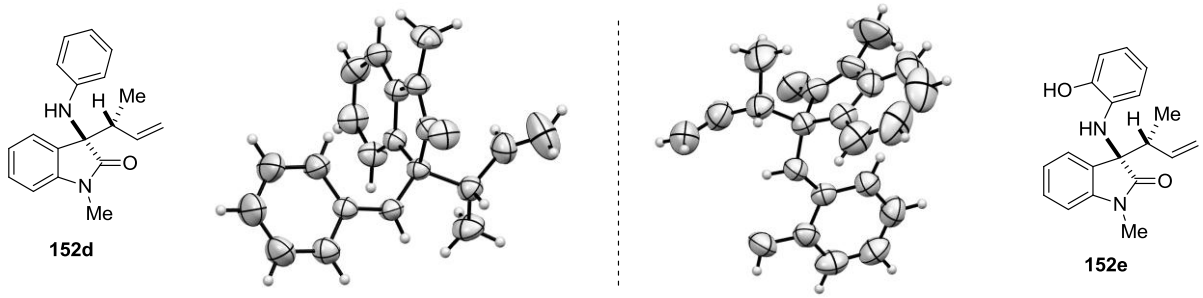
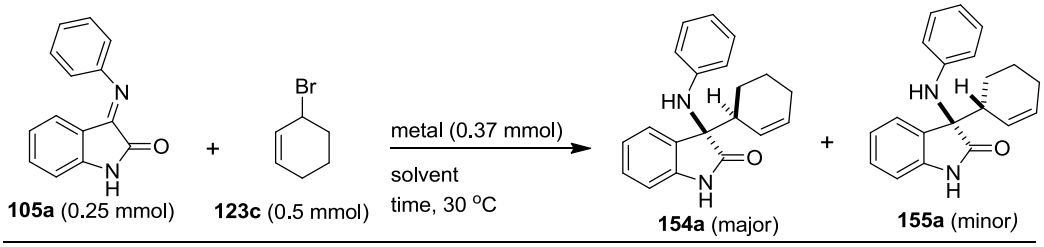



**Figure 13.** X-ray structures of **152d** and **152e** (major isomers).

Then, it was envisaged to examine the Barbier-type indium-mediated direct addition of cyclohexenyl bromide (**123c**) to isatin ketamine **105a** to obtain the 3-cyclohexenyl-3-aminooxindole **154a** having adjacent stereocenters (Table 20). At first, we performed various optimization reactions to find out the best reaction conditions for synthesizing the 3-cyclohexenyl-3-aminooxindole **154a** with very high diastereoselectivity (Table 20). The reaction of isatin ketimine **105a**, cyclohexenyl bromide (**123c**) and indium powder in THF or 1,4-dioxane or DMSO or EtOH gave the 3-cyclohexenyl-3-aminooxindole diastereomers **154a**/**155a** in 34-65% yields with moderate to good diastereoselectivity (*dr* up to 80:20;

entries 1-4, Table 20). The indium-mediated addition of cyclohexenyl bromide (**123c**) to **105a** in toluene or THF/water media failed to give the diastereomers **154a**/**155a** (entries 5 and 6, Table 20). The addition of cyclohexenyl bromide (**123c**) to isatin ketamine **105a** underwent smoothly in DMF and gave the 3-cyclohexenyl-3-aminooxindole diastereomers **154a**/**155a** in good yields (up to 91%) and diastereoselectivity (*dr* up to 80:20; entries 7-9, Table 20). To get better diastereoselectivity, the reaction was carried out in DMF at 5 $^{o}$C, which furnished the diastereomers **154a**/**155a** in 93% yield (*dr* 79:21; entry 10, Table 20).

**Table 20.** Diastereoselective synthesis of 3-cyclohexenyl 3-aminooxindole **154a**.



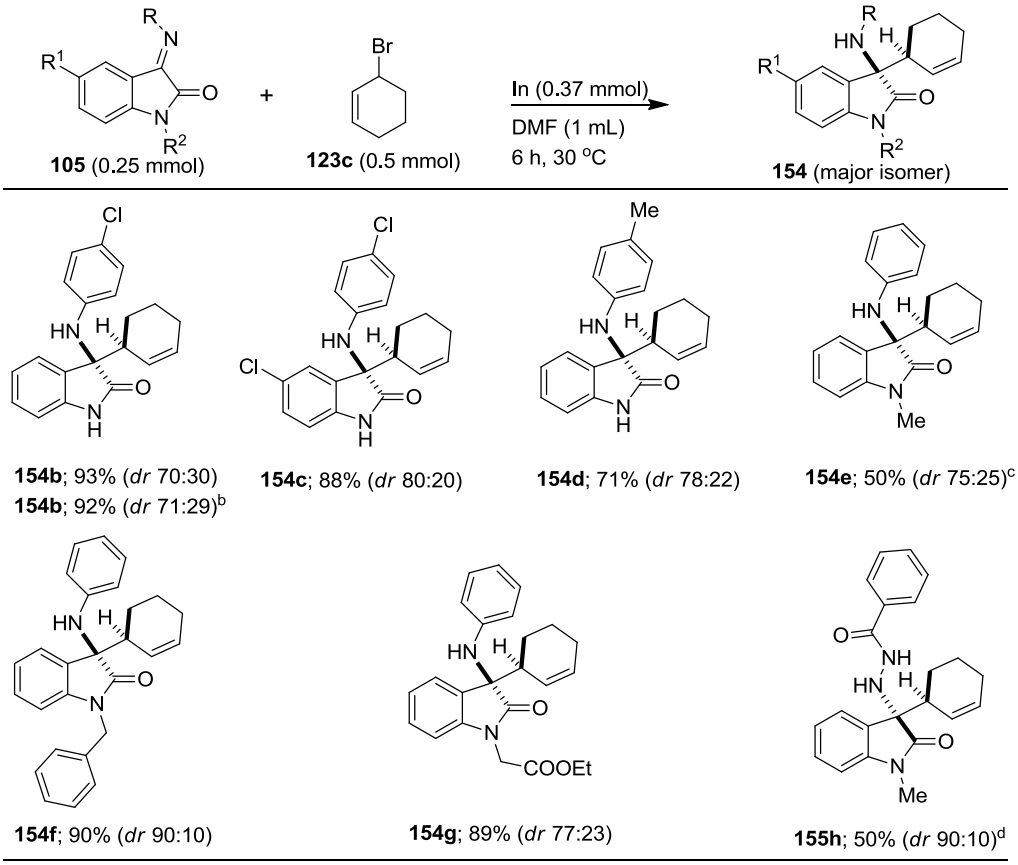

**105a** (0.25 mmol) + **123c** (0.5 mmol) → **154a** (major) + **155a** (minor)

| entry | metal | solvent (mL) | time (h) | **154a** / **155a**; yield (%) (*dr*)[a] |
|---|---|---|---|---|
| 1 | In | THF (2) | 06 | 34 (60:40) |
| 2 | In | 1,4-dioxane (1) | 12 | 36 (80:20) |
| 3 | In | DMSO (0.5) | 12 | 57 (67:33) |
| 4 | In | EtOH (0.5) | 12 | 65 (77:23) |
| 5 | In | toluene (2) | 12 | ND |
| 6 | In | THF (0.5) : $H_2O$ (0.5) | 12 | ND |
| 7 | In | DMF (0.5) | 12 | 91 (80:20) |
| 8 | In | DMF (0.5) | 06 | 90 (80:20) |
| 9 | In | DMF (0.5) | 03 | 75 (79:21) |
| 10 | In | DMF (0.5) | 06 | 93 (79:21)[b] |
| 11 | In | DMF (0.5) | 06 | 23 (67:33)[c] |
| 12 | In | DMF (0.5) | 06 | 90 (80:20)[d] |
| 13 | In | DMF (0.5) | 06 | 92 (80:20)[e] |
| 14 | Bi | DMF (0.5) | 06 | 14 (-) |
| 15 | Sn | DMF (0.5) | 06 | 32 (58:42) |
| 16 | Zn | DMF (0.5) | 06 | 80 (82:18) |

[a] Isolated yields are given and the ratio of (*syn* / *anti*) diastereomers (calculated from the NMR spectra of the crude reaction mixture) is reported in the parenthesis. [b] The reaction was carried out at 5 $^{o}$C. [c] The reaction was carried out at 80 $^{o}$C. [d] The reaction was carried out with **105a** (0.25 mmol), **123c** (0.5 mmol) and metal powder (0.5 mmol). [e] The reaction was carried out with **105a** (0.25 mmol), **123c** (0.75 mmol) and metal powder (0.5 mmol).

On the other hand, the reaction in DMF at 80 $^{o}$C afforded the product **154a**/**155a** in only 23% yield and low diastereoselectivity (*dr* 67:33; entry 11, Table 20). Increased equivalents of indium powder or 3-bromocyclohexene (**123c**) did not improve the diastereoselectivity (entries 12 and 13, Table 20). Employment of Bi or Sn powder instead of indium was ineffective (entries 14 and 15, Table 20). The use of Zn powder instead of indium powder for the addition of cyclohexenyl bromide (**123c**) to isatin ketimine **105a** in DMF furnished the 3-cyclohexenyl-3-aminooxindole **154a**/**155a** in 80% yield with good diastereoselectivity (*dr* 82:18; entry 16, Table 20) and the result of this reaction was comparable to that of the indium-based reaction (entry 7, Table 20).

**Table 21.** Diastereoselective synthesis of 3-cyclohexenyl-3-aminooxindoles **154b-g** and **155h**.[a]




[a] Isolated yields are given and the ratio of (*syn* / *anti*) diastereomers (calculated from the NMR spectra of the crude reaction mixture) is reported in the parenthesis. [b] The reaction was carried out using zinc dust. [c] The reaction was carried out in EtOH. [d] In this case the major isomer is **155h** and the minor isomer is **154h**.

After finding the optimized reaction conditions for the addition of cyclohexenyl bromide (**123c**) to isatin ketimine **105a**, the generality of the reaction was explored (Table 21). The Barbier-type addition of cyclohexenyl bromide (**123c**) to various isatin ketimines **105** in the presence of indium powder in DMF gave the corresponding 3-cyclohexenyl-3-aminooxindole scaffolds **154b-g/155b-g** with moderate to good diastereoselectivities (*dr* up to 90:10; Table 21). When the reaction of cyclohexenyl bromide (**123c**) with isatin ketimine **105c** was performed in the presence of Zn as well as In and the yield and diastereoselectivity obtained for **154b/155b** were comparable. In the case of Zn, the product **154b/155b** was obtained in 92% yield with *dr* 71:29. In the case of indium, the product **154b/155b** was obtained in 93% yield with *dr* 70:30. Notably, the reaction of cyclohexenyl bromide (**123c**) with isatin ketimine **105i** in EtOH also gave the product **154e/155e** in 50% yield with *dr* 75:25 (Table 21). The indium-mediated cyclohexenylation of benzoylhydrazone **107** (derived from *N*-methyl isatin) in DMF afforded the corresponding 3-cyclohexenyl-3-aminooxindole scaffolds **155h/154h** having two contiguous stereogenic centers in 50% yield with good diastereoselectivity (*dr* 90:10; Table 21).

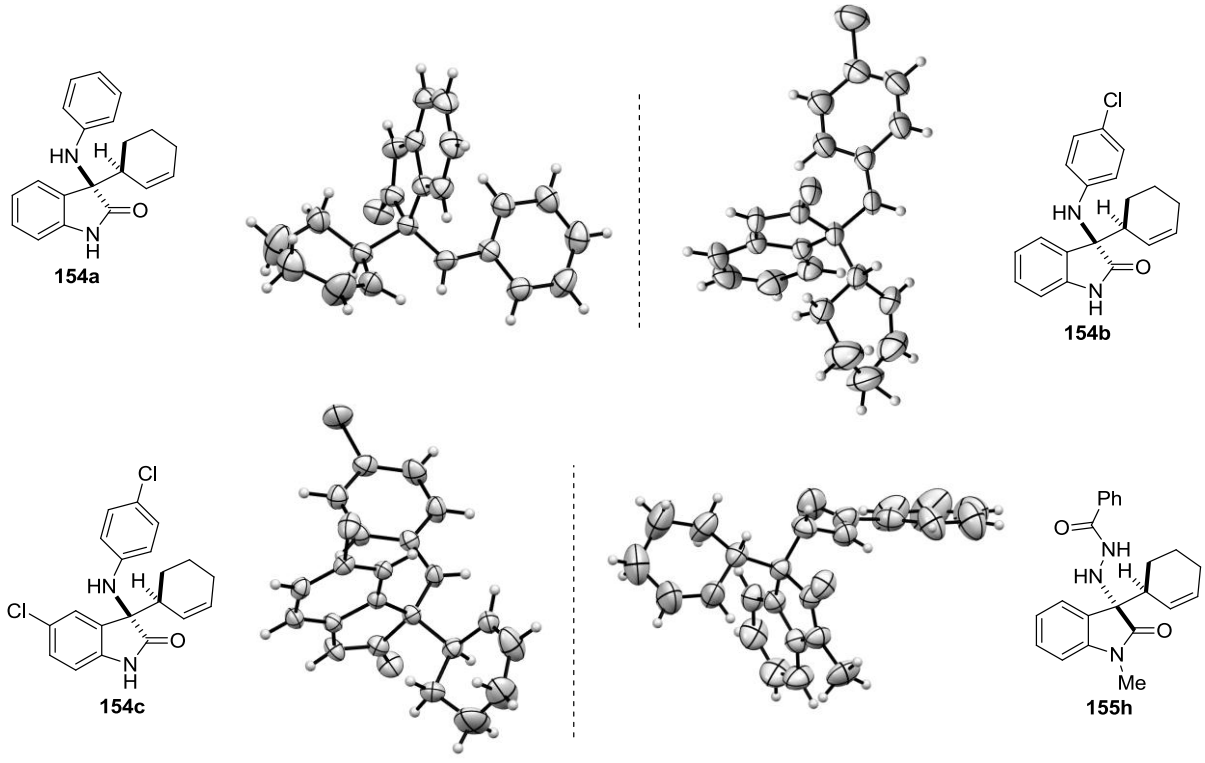
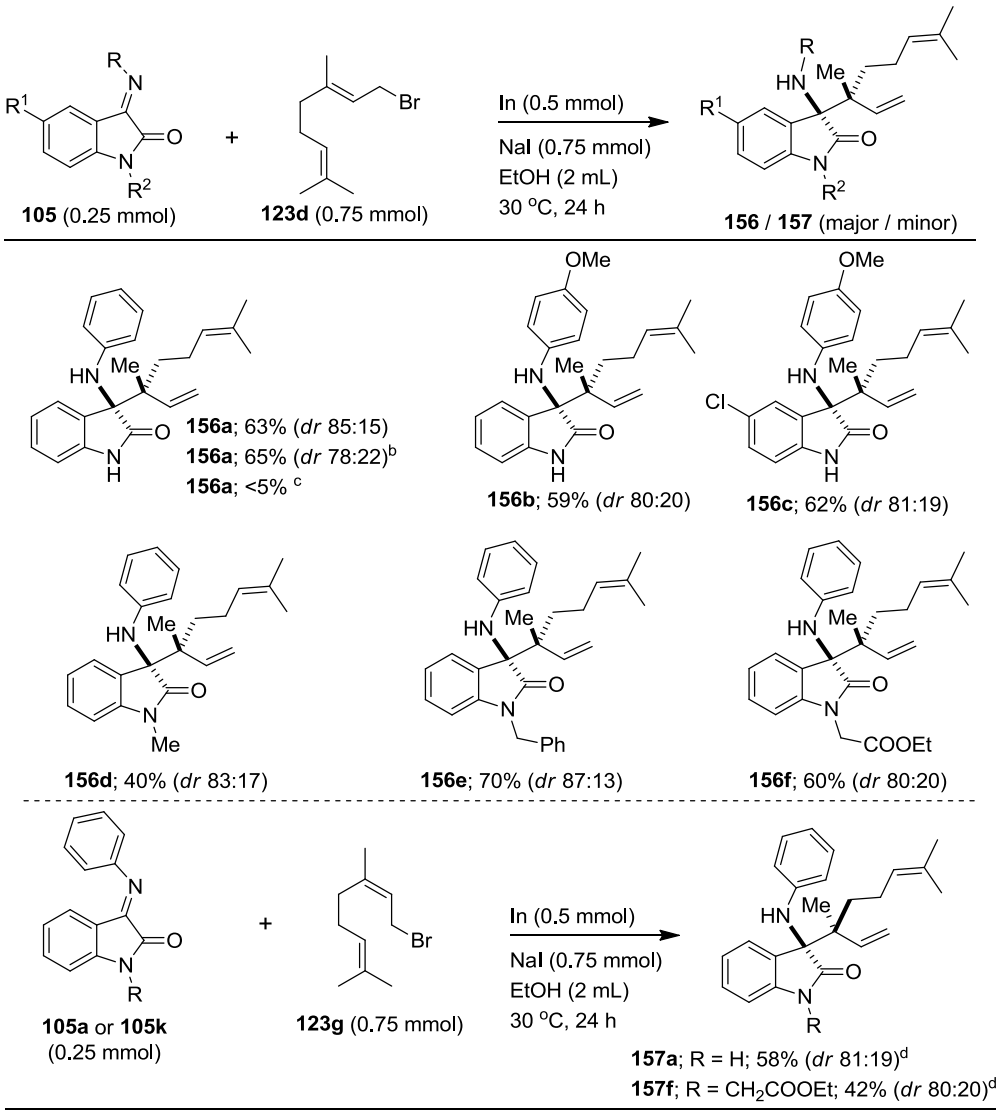



**Figure 14**. X-ray structures of **154a**, **154b**, **154c** and **155h** (major isomers).

**Table 22.** Stereoselective synthesis of 3-aminooxindole scaffolds **156a-f**/**157a**,**f**.[a]

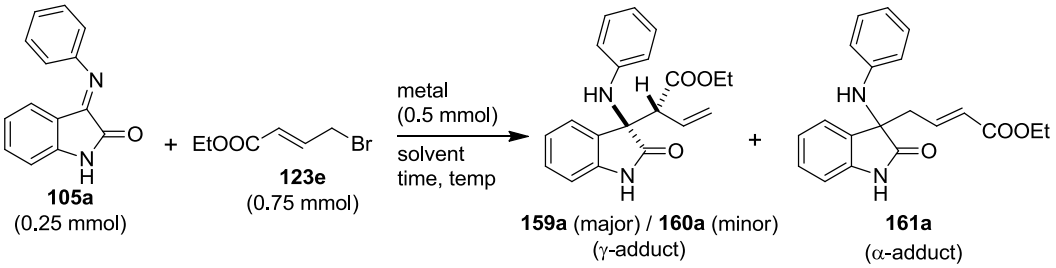



[a] Isolated yields are given and the ratio of (*syn* / *anti*) diastereomers (calculated from the NMR spectra of the crude reaction mixture) is reported in the parenthesis. [b] The reaction of **105a** with geranyl bromide (**123d**) was carried out in THF and the corresponding α-adduct **158a** was obtained in 10% yield in addition to the diastereomers **156a**/**157a**. [c] The reaction was carried out in DMF. [d] In this case, the major isomer is **157** and the minor isomer is **156**.

The stereochemistry of the 3-cyclohexenyl-3-aminooxindole scaffolds **154a-g** and **155h** was assigned on the basis of the X-ray structures of the representative major isomers of **154a**, **154b**, **154c** and **155h** (Figure 14). Consequently, it was envisaged to explore the reactivity pattern of geranyl bromide (**123d**, *E*-geometry) with isatin ketimines **105** for synthesizing 3-aminooxindole scaffolds bearing a terpene unit and two contiguous stereocenters.

Accordingly, the indium-mediated reaction of **105a** with *E*-geranyl bromide (**123d**) in the presence of sodium iodide as an additive in EtOH as a solvent at 30 $^{o}$C was performed. This reaction afforded the 3-aminooxindole scaffolds **156a/157a** in 63% yield with very good diastereoselectivity (*dr* 85:15; Table 22). Use of THF instead of EtOH for the same reaction resulted in slight decrease in diastereoselectivity of **156a**/**157a** (*dr* 78:22; Table 22).

**Table 23.** Optimization of the addition of ethyl 4-bromocrotonate (**123e**) to **105a**.



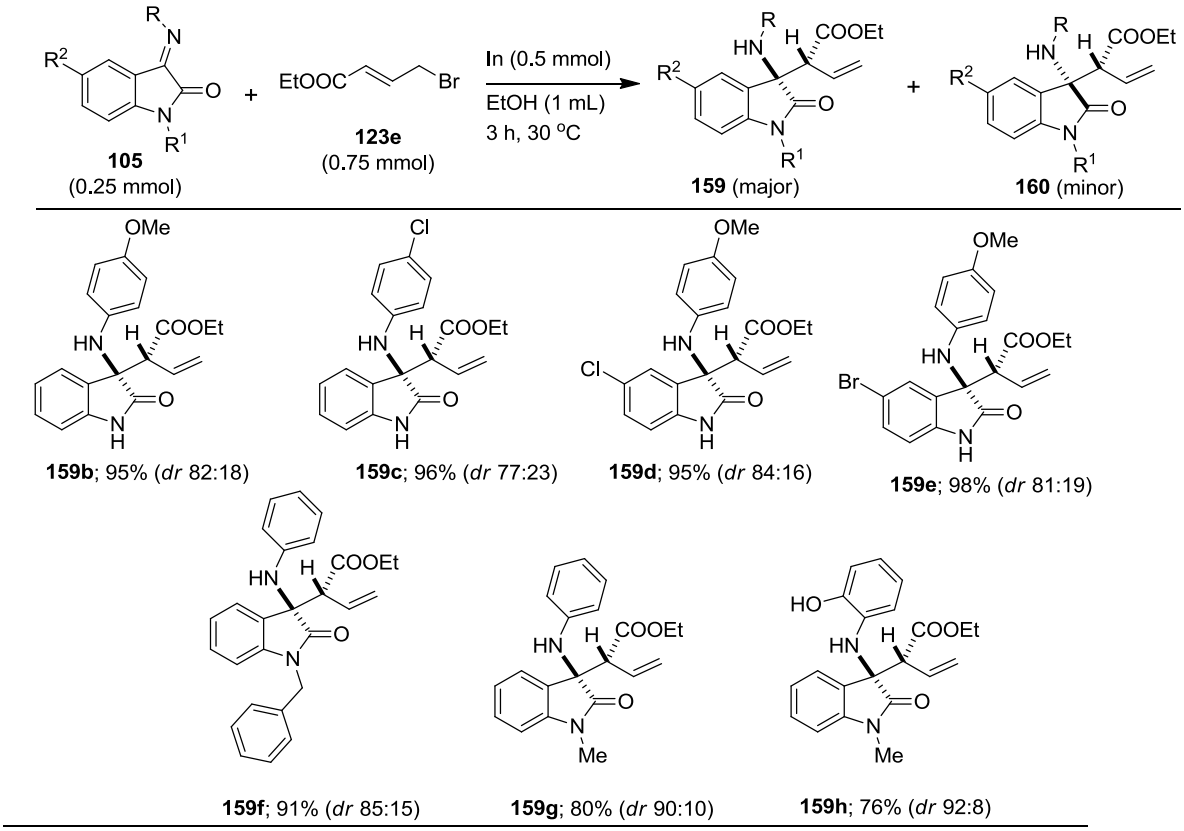

| entry | metal | solvent (mL) | temp ($^{o}$C) | time (h) | **159a** / **160a**; yield (%) (*dr*)[a] | **161a**: yield (%) |
|---|---|---|---|---|---|---|
| 1 | In | THF (2) | 30 | 24 | 30 (77:23) | 40 |
| 2 | In | DMF (0.5) | 30 | 12 | 53 (72:28) | 42 |
| 3 | In | 1,4-dioxane (1) | 30 | 12 | 75 (73:27) | 20 |
| 4 | In | EtOH (1) | 30 | 12 | 93 (81:19) | - |
| 5 | In | EtOH (1) | 30 | 06 | 93 (82:18) | - |
| 6 | In | EtOH (1) | 30 | 03 | 93 (82:18) | - |
| 7 | In | EtOH (1) | 0 | 03 | 92 (82:18) | - |
| 8 | Zn | EtOH (1) | 30 | 12 | >5 | - |
| 9 | Bi | EtOH (1) | 30 | 12 | 10 (-) | - |
| 10 | Sn | EtOH (1) | 30 | 12 | 10 (-) | - |

[a] Isolated yields are given and the ratio of (*syn* / *anti*) diastereomers (calculated from the NMR spectra of the crude reaction mixture) is reported in the parenthesis.

The reaction of geranyl bromide **123d** with isatin ketimine **105a** in DMF did not work. Then, the generality of this In-based Barbier-type addition of geranyl bromide (**123d**) to various isatin ketimines **105** was elaborated and various examples of 3-substituted-3-aminooxindole scaffolds bearing a terpene unit and two contiguous stereocenters **156b-f**/**157b-f** were obtained as mixture of diastereomers with good diastereoselectivity (*dr* up to 87:13; Table 22). Along this line, the reaction of neryl bromide (**123g**, *Z*-geometry) with the corresponding isatin ketimines **105a** and **105k** in the presence of indium powder and sodium iodide in EtOH

at 30 °C was performed and this reaction successfully gave the corresponding 3-substituted-3-aminooxindole scaffolds **157a**,**f**/**156a**,**f** as mixture of diastereomers with good diastereoselectivity (Table 22).

**Table 24.** Diastereoselective synthesis of oxindole-based β-amino esters **159b-h**.[a]




[a] Isolated yields are given and the ratio of (*syn* / *anti*) diastereomers (calculated from the NMR spectra of the crude reaction mixture) is reported in the parenthesis.

After investigating the indium-mediated Barbier-type cinnamylation, crotylation, cyclohexenylation and geranylation of isatin ketimines, it was envisioned to explore the indium-mediated Barbier-type reactions of ethyl 4-bromocrotonate (**123e**) to isatin ketimine **105a** for synthesizing oxindole-based β-amino esters. A number of reactions were performed to find out the optimized reaction condition to obtain the oxindole-based β-amino esters **159a** (γ-adduct) having contiguous stereogenic centers with high diastereoselectivity. A mixture of isatin ketimine **105a**, ethyl 4-bromocrotonate (**123e**) and indium metal powder was stirred in various solvents such as THF, DMF and 1,4-dioxane, which furnished the oxindole-based β-

amino ester **159a/160a** (γ-adducts) as diastereomers having two contiguous stereocenters (30-75%, *dr* up to 80:20; entries 1-3, Table 23). Notably, in these reactions the corresponding α-adduct **161a** was also obtained in 20-42% yield (entries 1-3, Table 23).

Encouragingly, the indium-mediated reaction of isatin ketimine **105a** with ethyl 4-bromocrotonate (**123e**) in EtOH cleanly afforded the oxindole-based β-amino ester **159a/160a** (γ-adducts) as diastereomers in very high yield (up to 93%, *dr* up to 85:15; entries 4-7, Table 23). Lowering the reaction temperature to 0 $^{o}$C could not improve the diastereoselectivity much (*dr* 86:14; entry 7, Table 23). Noticeably, the-adduct **161a** was not observed when the reaction was performed in EtOH (entries 4-7, Table 23). Employment of other metal powders such as Zn, Bi and Sn for the Barbier-type addition of ethyl 4-bromocrotonate (**123c**) to isatin ketimine **105a** was ineffective (entries 8-10, Table 23).

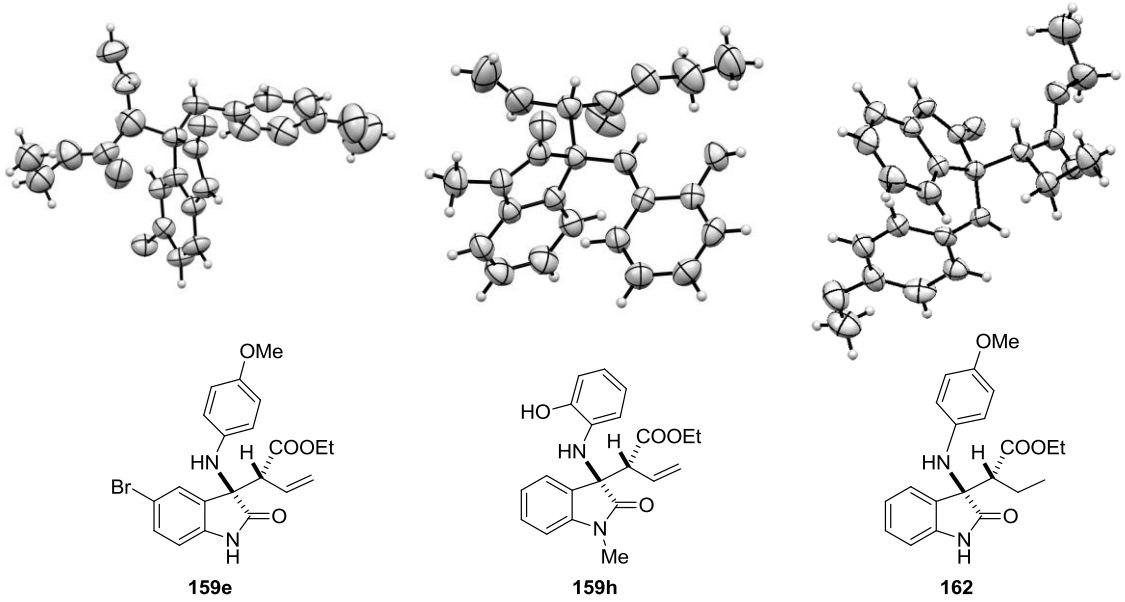
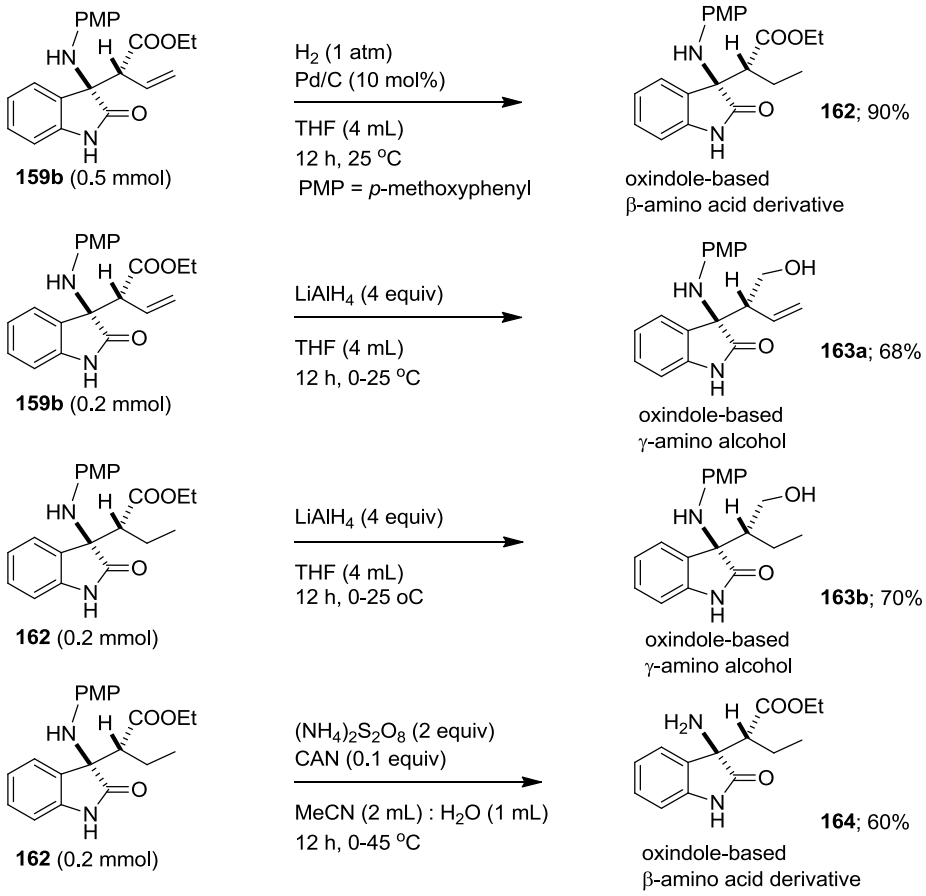



**Figure 15.** X-ray structures of **159e**, **159h** and **162** (major isomers).

Then, the generality of this indium-based Barbier-type addition of ethyl 4-bromocrotonate (**123e**) to various isatin ketimines **105** was elaborated and various examples of oxindole-based β-amino ester scaffolds bearing two contiguous stereocenters **159b-h** (major isomers) were obtained with very high diastereoselectivity (*dr* up to 95:5; Table 24). Notably, the indium-mediated reaction of ethyl 4-bromocrotonate (**123e**) with isatin ketimine **105h** having a free OH group in EtOH appreciably gave the corresponding product **159h** (76%, *dr* 92:8;

Table 24). The major isomers were isolated in pure form in most of the reactions and the stereochemistry of the products **159a-h** was assigned based on the X-ray structures of representative major isomers of **159e** and **159h** (Figure 15).




**Scheme 71.** Synthetic transformations of oxindole-based β-amino ester scaffolds.

The indium-mediated addition of ethyl 4-bromocrotonate to isatin ketimines led to the construction of oxindole-based β-amino ester derivatives **159a-h** with high degree of stereocontrol. To explore the scope of this protocol and to obtain different synthetic intermediates, it was envisioned to perform additional synthetic transformations using the representative compounds from the pool of oxindole-based β-amino ester derivatives **159a-h** (Scheme 71). The catalytic olefin hydrogenation of the oxindole-based β-amino ester derivative **159b** led to the synthesis of **162** and the stereochemistry of the compound **162** was confirmed from the X-ray structure analysis (Figure 15). The reduction of the oxindole-based β-amino ester derivatives **159b** as well as **162** using $LiAlH_4$ gave the corresponding

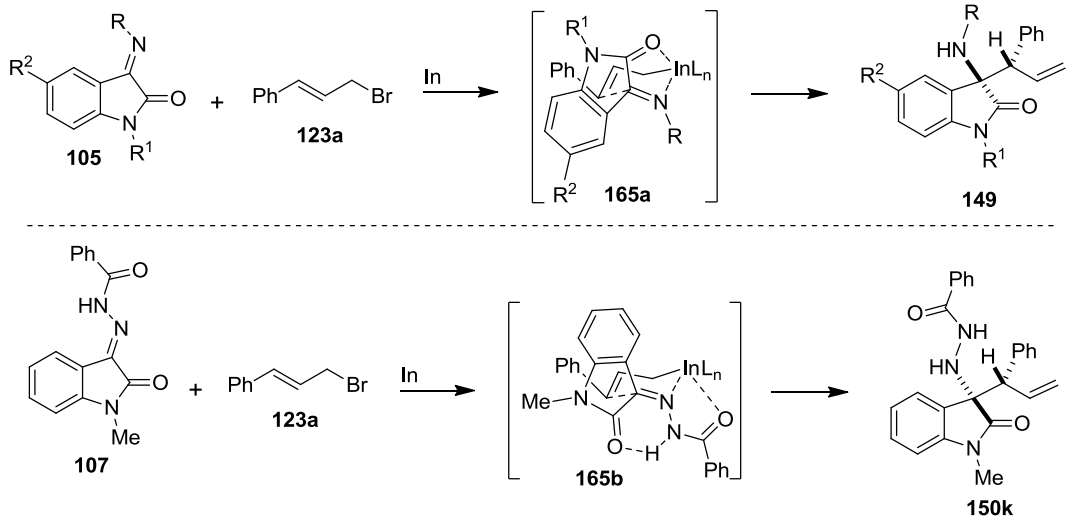
oxindole-based γ-amino alcohols **163a** and **163b** having adjacent stereocenters. Deprotection of the *p*-methoxy phenyl group (PMP group) from substrate **162** led to the production of 3-aminooxindole substrate **164** equipped with two contiguous stereocenters (Scheme 71).

### 4.4.2. Discussion on the observed regio- and diastereoselectivity in the indium-mediated addition of γ-substituted allyl halides to isatin ketimines.

Various research groups proposed the involvement of the chelation-assisted TS for the observed very high diastereoselectivity in the addition of allylindiums to C=O and C=N bonds of compounds having the heteroatom-based functional groups (e.g. OR or $NR_2$, carbonyl oxygen, etc) at the α-carbon. It is assumed that the involvement of a chelation-assisted and rigid TS is an essential factor for obtaining the high degree of diastereoselectivity irrespective of the solvent system used to carry out the reaction.[17,18,38a,39,41a,48] However, the reaction in protogenic solvents (e.g. aqueous or alcoholic media) afforded very high degree of diastereoselectivity.[17,18,38a,39,41a,48] Given the fact that the allylindium species formed are tolerant to protogenic solvents,[28a,31] it is believed that the aqueous/alcohol media promotes the fast quenching of the transient indium amide that formed after the allylation reaction.[16d,17m,28a] The very high degree of diastereoselectivity observed in the In-based allylation reactions revealed that the addition of allylindiums to C=O and C=N bonds seems to be kinetically controlled.[17,18,38a,39,41a,48] The nature of the active indium species remains elusive because of its fleeting character. Recent reports strongly suggest the involvement of an $In^{III}$ species in the TS (proposed by Singaram,[28q,28r] Baba[28l-28n] and Koszinowski[28o]), however, in the present reactions, the involvement of an $In^{I}$ species (proposed by Chan[28a,28g,28h] and Hilt[28s]) is also very likely as a chelation-controlled rigid TS, essential for obtaining very high degree of diastereoselectivity, might favor a low-valent indium species.

With regard to the present work, with some minor de*via*tions, in general, the addition of γ-substituted allyl halides to isatin ketimines underwent smoothly in protogenic solvent systems such as THF/water and EtOH and afforded the corresponding allylated products with very high diastereoselectivity. The very high diastereoselectivities obtained in the indium-mediated γ-substituted allyl halides with isatin ketimines are perhaps due to the involvement

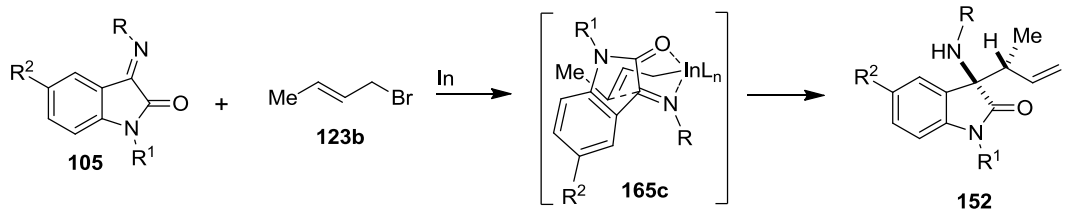
of chelation-assisted TS as proposed in the following discussions (Scheme 72-76), however, the involvement of more than one possible TS cannot be ignored as delibrated in the literature.[17,18,38a,39,41a,48] Additionally, in general, the geometry of the C=N bond of isatin ketimines (predominant isomers) reported to be *E*.[105] We have also obtained the X-ray structure of **105i** and **105k** . The stereochemistry of C=N bond in **105i** and **105k** was found to be *E* from the X-ray structure analysis. The observed high diastereoselectivities in the indium-mediated addition of γ-substituted allyl halides to isatin ketimines may be independent of the *E*/*Z* ratios of C=N bond of the isatin ketimines. This assumption is supported by the literature reports dealing with the stereoselective addition of the γ-substituted allylmetals to C=N bond of ketimine systems, in which very high diastereoselectivites were obtained.[17,18, 41h,50m]




**Scheme 72**. Plausible transition states (**165a** and **165b**) for the observed diastereoselectivity in the cinnamylation of isatin ketimines.

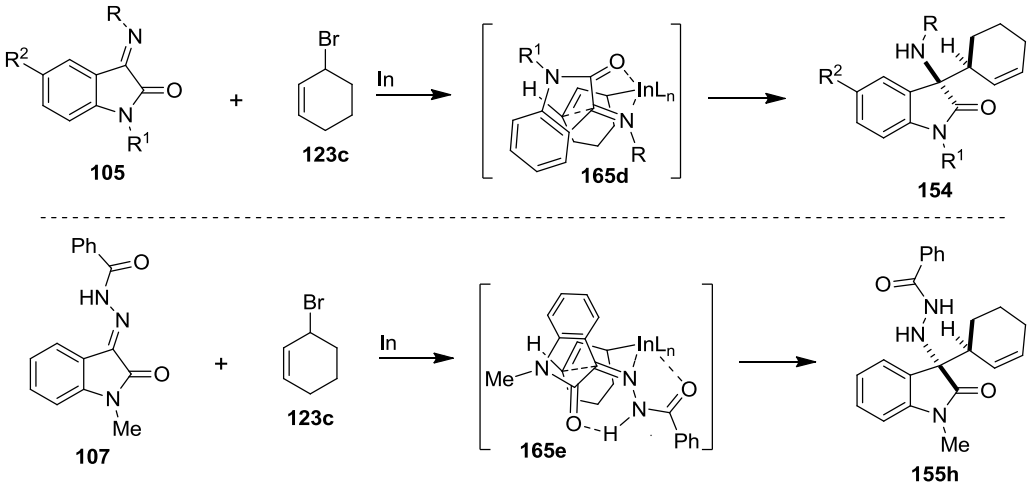
In concurrence with the literature reports, the present study also involves the indium-mediated allylation of C=N bond of isatin ketimines having the heteroatom-based functional group i.e. CONH at the α-carbon.[33-39,48-50] Accordingly, the observed very high degree of diastereoselectivity in the reaction of the indium-mediated addition of γ-substituted allyl halide such as *E*-cinnamyl bromide to isatin ketimines and the exclusive formation of the major isomers of 3-aminooxindoles **149a-j** (confirmed by the X-ray structures of **149b**, **149i**,

and **149j**; Figure 12) could be exemplified *via* the chelation-assisted TS **165a** (Scheme 72). Similarly, the formation of the major isomer of 3-aminooxindole **150k** (confirmed by the X-ray structure; Figure 12) from the cinnamylation of benzoylhydrazone **107** could be accounted *via* the plausible TS **165b** (Scheme 72). The plausible TS for the exclusive formation of the major isomer of 3-aminooxindole **150k** was proposed based on a literature report that revealed the addition of allylboronic acid to hydrazone system in which the authors proposed a TS involving hydrogen bonding for the observed diastereoselectivity.[47d]



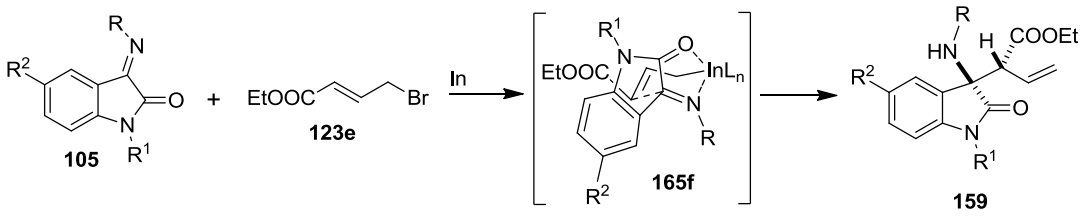

**Scheme 73**. Plausible transition state (**165c**) for the observed diastereoselectivity in the crotylation of isatin ketimines.

Similar to the cinnamylation case, the formation of the major isomers of crotylated 3-aminooxindoles **152a-e** (confirmed by the X-ray structures of **152d** and **152e**; Figure 13) in the indium-mediated crotylation of isatin ketimines could be explained *via* the chelation-assisted TS **165c** (Scheme 73).[17,18,33-39,48-50]




**Scheme 74**. Plausible transition states (**165d** and **165e**) for the observed diastereoselectivity in the cyclohexenylation of isatin ketimines.

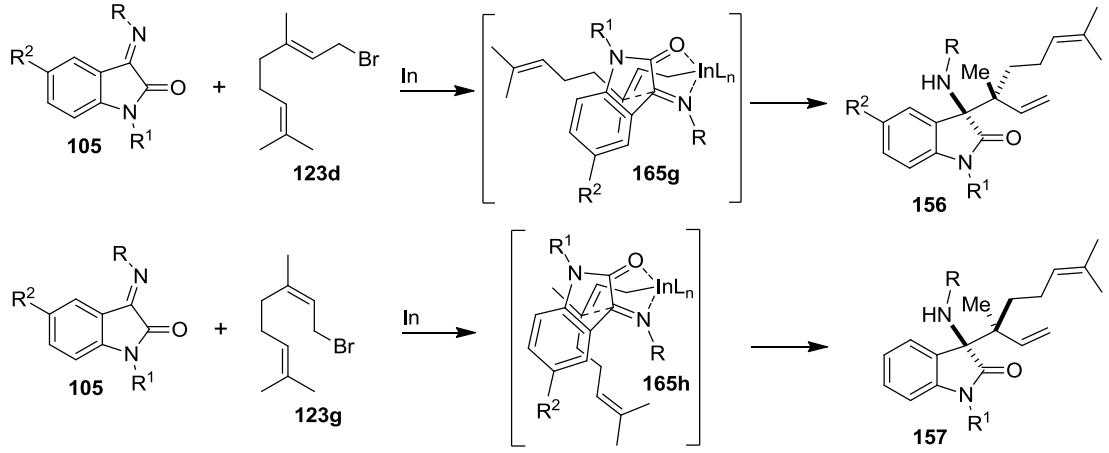
The exclusive formation of the major isomers of 3-cyclohexenyl 3-aminooxindole **154a-f** (confirmed by the X-ray structures of **154a**, **154b** and **154c**; Figure 14) could be exemplified *via* the chelation-assisted TS **165d** (Scheme 74).[17,18,33-39,48-50] As discussed earlier, similar to the stereochemistry of the cinnamylated product **150k**, which was obtained from the cinnamylation of the benzoylhydrazone **107**, the stereochemistry of the product 3-cyclohexenyl 3-aminooxindole **155h** (major isomer, confirmed by the X-ray structure; Figure 14) obtained in the cyclohexenylation of **107** could be accounted *via* the TS **165e** (Scheme 74), which presumably involves the hydrogen bonding.[47d]




**Scheme 75**. Plausible transition state (**165f**) for the observed diastereoselectivity in the crotonate addition to isatin ketimines.

The exclusive formation of the major isomers of oxindole-based β-amino acid derivative **159a-h** (confirmed by the X-ray structures of **159e** and **159h**; Figure 15) could be exemplified *via* the chelation-assisted TS **165f** (Scheme 75).[17,18,33-39,48-50] The reaction of isatin ketimines with allyl halides having *E*-geometry, such as, cinnamyl bromide or crotyl bromide or ethyl 4-bromocrotonate gave the corresponding γ-adducts **149**/**152**/**159** in which the *N*-aryl moiety and the respective groups Ph/Me/COOEt obtained from the corresponding allyl halides were found to be *anti*. The reaction of isatin ketimines with allyl halides having *Z*-geometry, such as, cyclohexenyl bromide gave the corresponding γ-adducts **154** in which the *N*-aryl moiety and the respective group (-$CH_2$-) obtained from the cyclohexenyl bromide were found to be *syn*. In analogy, the stereochemistry of the products **156** obtained from geranyl bromide having *E*-geometry and **157** obtained from neryl bromide having *Z*-geometry, were proposed based on the *anti* stereochemistry of the products **149**/**152**/**159** (major isomers) which were obtained from the γ-substituted allylic halides, e.g. cinnamyl bromide, crotyl bromide, ethyl 4-bromocrotonate having the *E*-geometry and the *syn* stereochemistry of the products **154** (major isomers) which were obtained from cyclohexenyl

bromide having the *Z*-geometry, respectively. Further, the observed diastereoselectivity in the geranylation/nerylation also could be accounted *via* the chelation-assisted TS model **165g**/**165h** as proposed for the cinnamylation/crotylation/cyclohexenylation/crotonylation (Scheme 76).




**Scheme 76**. Plausible transition states (**165g** and **165h**) for the observed diastereoselectivity in the geranylation and nerylation of isatin ketimines.

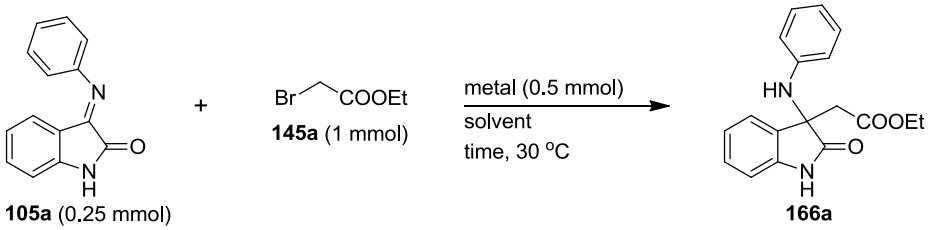
### 4.4.3. Zinc-mediated Reformatsky-type addition of α-halo esters to isatin ketimines.

In line with the objective of the present work and after investigating the indium-mediated Barbier-type allylation of isatin ketimines, it was envisioned to explore the indium- or zinc-mediated Reformatsky-type reactions of α-halo esters **145** with isatin ketimines **105** for synthesizing oxindolinyl β-amino esters.

At first, various reactions were performed to find out the best reaction conditions for obtaining oxindolinyl β-amino esters. To a mixture of isatin ketimine **105a** and ethyl bromoacetate (**145a**) in THF was added zinc metal powder and the reaction mixture was stirred at 30 $^{o}$C for 24 h to yield the product **166a** in 67% yield (entry 1, Table 25). The reaction of **105a** with **145a** at 80 $^{o}$C gave the product **166a** in 77% yield (entry 2, Table 25). The zinc-mediated addition of **145a** to **105a** in acetonitrile gave the product **166a** in only 25% yield (entry 3, Table 25). The zinc-mediated addition of **145a** to **105a** in 1,4-dioxane or EtOH failed to give the product **166a** (entries 4 and 5, Table 25). The zinc-mediated addition of **145a** to **105a** in DMF furnished the product **166a** in 92-93% yields (entry 6, Table 25).

Addition of **145a** to **105a** in the presence of indium instead of zinc in DMF or THF gave the product **166a** in 93 and 92% yields, respectively (entries 7 and 8, Table 25). The Reformatsky-type addition of **145a** to **105a** in the presence of Bi and Sn metal powder afforded the product **166a** in <5% and 60% yields, respectively (entries 9 and 10, Table 25). The addition of **145a** to **105a** with lesser amount of zinc or reduced amounts of ethyl bromoacetate **145a** gave the product **166a** in moderate yields (entries 11-13, Table 25). It is worth to mention that both zinc and indium metal aptly promoted the Reformatsky-type reactions of α-halo ester **145** with isatin ketimine **105a** and afforded the oxindolinyl β-amino ester **166a** in comparable yield (entry 6 and 7, Table 25).

**Table 25.** Synthesis of oxindole-based β-amino ester **166a**.



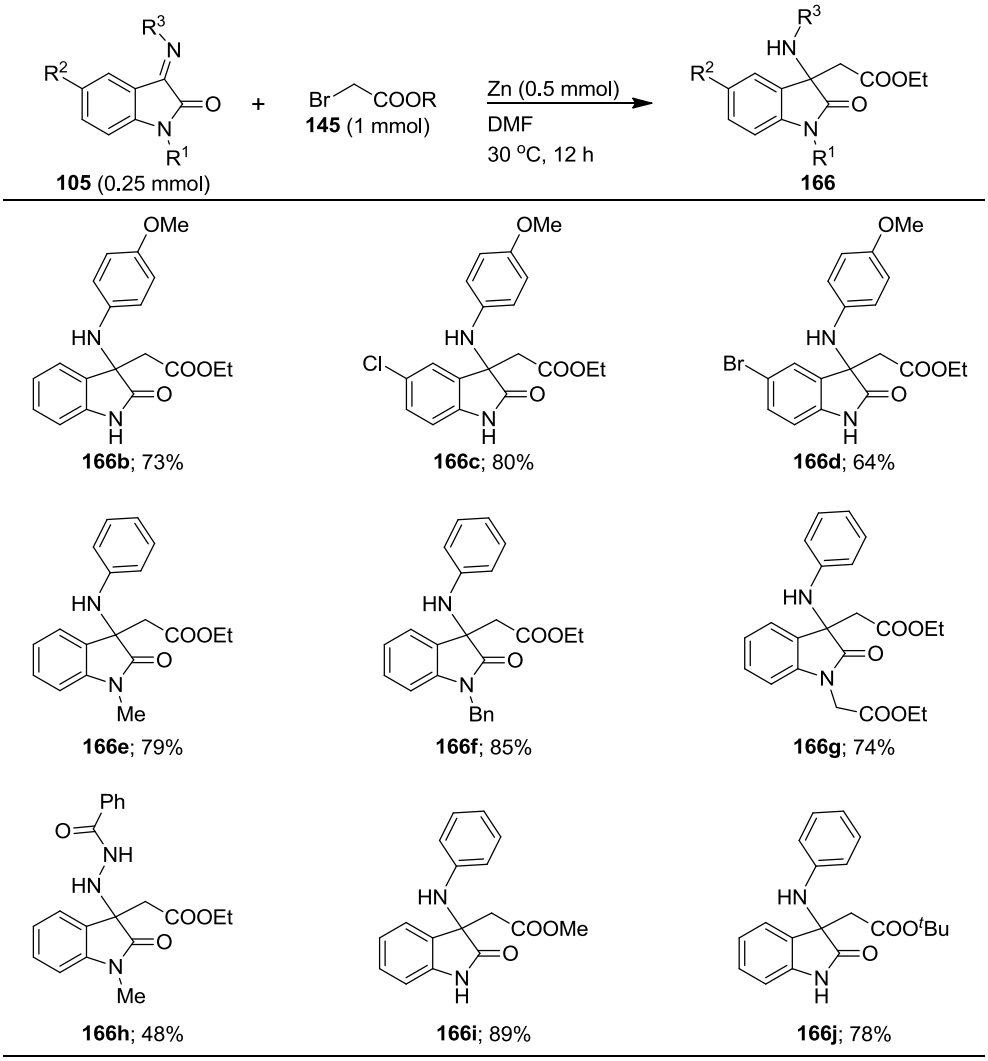

| entry | metal | solvent (mL) | time (h) | **166a**; yield (%)[a] |
|---|---|---|---|---|
| 1 | Zn | THF (1) | 24 | 67 |
| 2 | Zn | THF (1) | 24 | 77[b] |
| 3 | Zn | MeCN (1.5) | 24 | 25 |
| 4 | Zn | 1,4-dioxane (1) | 24 | <5 |
| 5 | Zn | EtOH (1) | 24 | <5 |
| 6 | Zn | DMF (0.5) | 24 (12) | 92 (93) |
| 7 | In | DMF (0.5) | 24 | 93 |
| 8 | In | THF (2) | 24 | 92 |
| 9 | Bi | DMF (0.5) | 24 | <5 |
| 10 | Sn | DMF (0.5) | 24 | 60 |
| 11 | Zn | DMF (0.5) | 24 | 56[c] |
| 12 | Zn | DMF (0.5) | 12 | 45[d] |
| 13 | Zn | DMF (0.5) | 12 | 66[e] |

[a] Isolated yields are given. [b] The reaction was carried out at 80 °C. [c] Zn (0.375 mmol) was used. [d] **145a** (0.5 mmol) was used. [e] **145a** (0.75 mmol) was used.

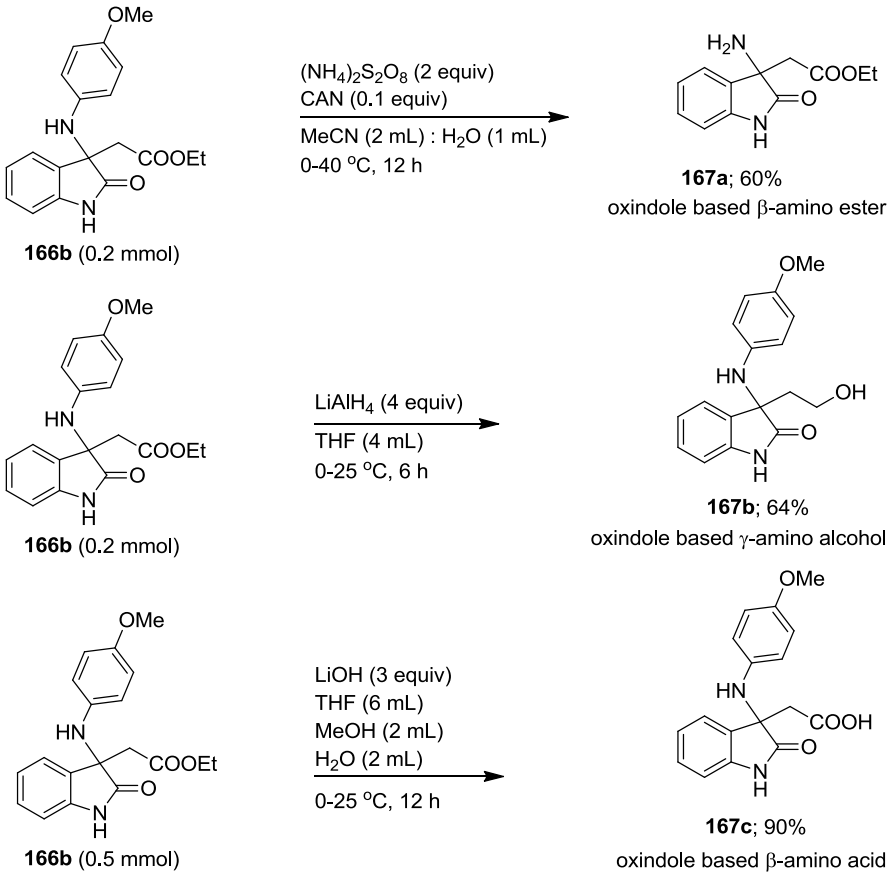
After finding the optimized reaction conditions for obtaining the oxindolinyl β-amino ester **166a** *via* the Zn-mediated Reformatsky-type reaction, various oxindolinyl β-amino esters

**166b-j** (Table 26) were prepared in good yields (48-89%) by using the optimized condition as shown in Table 25 (entry 6).

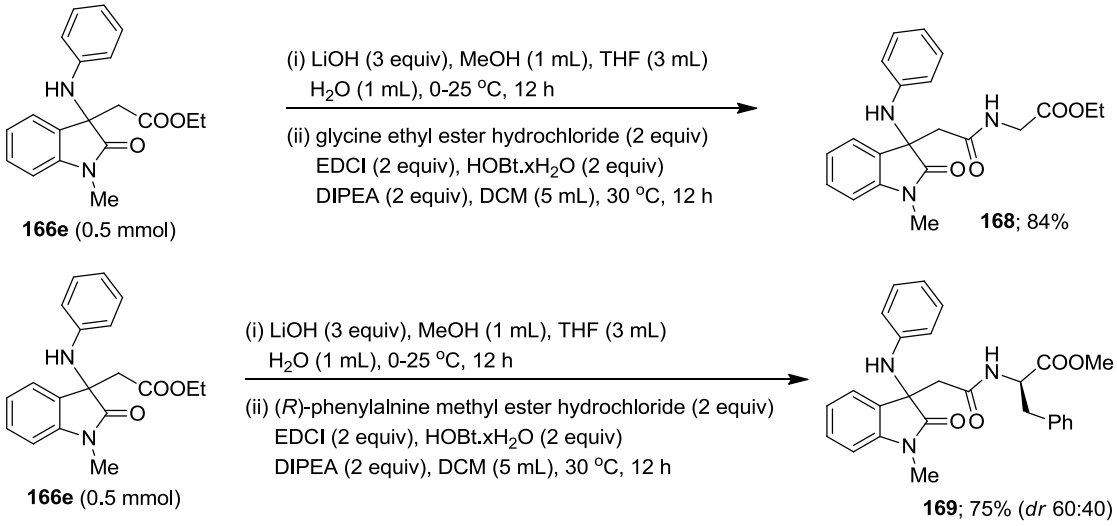
**Table 26.** Synthesis of oxindole-based β-amino esters **166b-j**.




Then, to show the usefulness of the products obtained from the Zn-mediated Reformatsky-type reaction of α-halo ester **145** with isatin ketimines **105**, various synthetic transformations were carried out by using a representative compound **166b** (Scheme 77). Deprotection of the *p*-methoxy phenyl group from **166b** successfully produced ethyl 2-(3-amino-2-oxoindolin-3-yl)acetate (**167a**) (Scheme 77). The $LiAlH_4$-promoted reduction of the oxindole-based β-amino ester **166b** led to the assembling of the corresponding oxindole-based γ-amino alcohol **167b**. Next, alkaline hydrolysis of the compound **166b** successfully gave the *N*-protected oxindolinyl β-amino acid **167c** (Scheme 77).

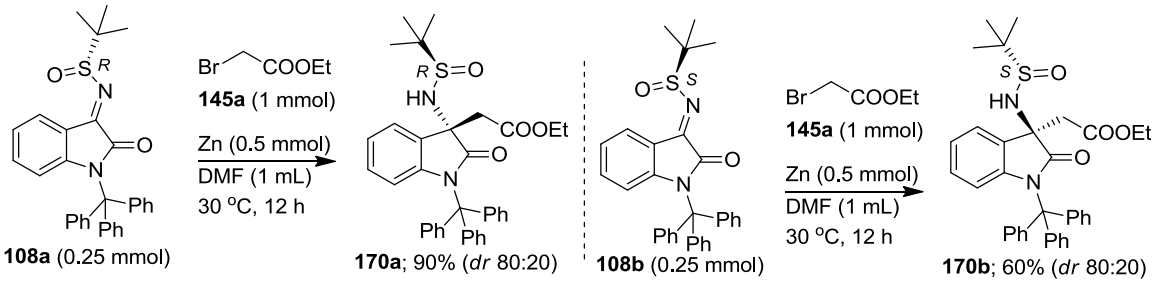



**Scheme 77.** Synthetic transformations of oxindole-based β-amino ester scaffold **166b**.




**Scheme 78.** Synthesis of oxindole moiety appended dipeptide derivatives **168** and **169**.

Subsequently, it was decided to further elaborate the utility of the products obtained from the Zn-mediated Reformatsky-type reaction of α-halo ester **145** with isatin ketimines **105**. In this regard, it was envisaged to synthesize oxindole moiety appended dipeptide derivatives starting from a representative oxindolinyl β-amino ester **166e**. Accordingly, oxindolinyl β-amino ester **166e** was subjected to the alkaline hydrolysis reaction followed by the EDC driven peptide bond formation with glycine ethyl ester hydrochloride to afford the oxindole moiety appended dipeptide derivative **168** (Scheme 78). Similarly, the substrate **166e** was subjected to the alkaline hydrolysis reaction followed by the EDC driven peptide bond formation with (*R*)-phenylalanine methyl ester hydrochloride to afford the oxindole moiety appended dipeptide derivative **169** (Scheme 78).




**Scheme 79.** Synthesis of oxindole-based chiral β-amino ester scaffolds (**170a** and **170b**).

It was envisaged that due to the immense value of enantiomerically pure oxindole derivatives in organic chemistry, exploring the synthesis of enantiomerically enriched oxindole-based β-amino esters from the Reformatsky-type reaction would be a valuable task. Reformatsky-type reaction of enantiomerically enriched isatin ketimine **108a** (derived from isatin and (*R*)-*tert*-butylsulfinamide) with **145a** in the presence of zinc in DMF at 30 °C successfully gave the enantiomerically enriched oxindolinyl β-amino ester scaffold **170a** in 90% yield with good diastereoselectivity (*dr* 80:20; Scheme 79).

The stereochemistry of the major isomer of enantiomerically enriched oxindolinyl β-amino ester scaffold **170a** was unambiguously assigned on the basis of X-ray structure analysis of the major isomer of **170a**. Similarly, the Zn-mediated Reformatsky-type reaction of enantiomerically enriched isatin ketimine **108b** (derived from isatin and (*S*)-*tert*-butylsulfinamide) with **145a** afforded the enantiomerically enriched oxindolinyl β-amino

ester scaffold **170b** in 60% yield with good diastereoselectivity (*dr* 80:20; Scheme 79). The stereochemistry of the major isomer of enantiomerically enriched oxindolinyl β-amino ester scaffold **170b** was unambiguously assigned on the basis of X-ray structure analysis of the major isomer of **170b** (Figure 16). These successful attempts dealing on the synthesis of enantiomerically enriched oxindolinyl β-amino ester scaffolds (**170a** and **170b**) need to be further elaborated and in this regard, additional works are in progress in our research group.

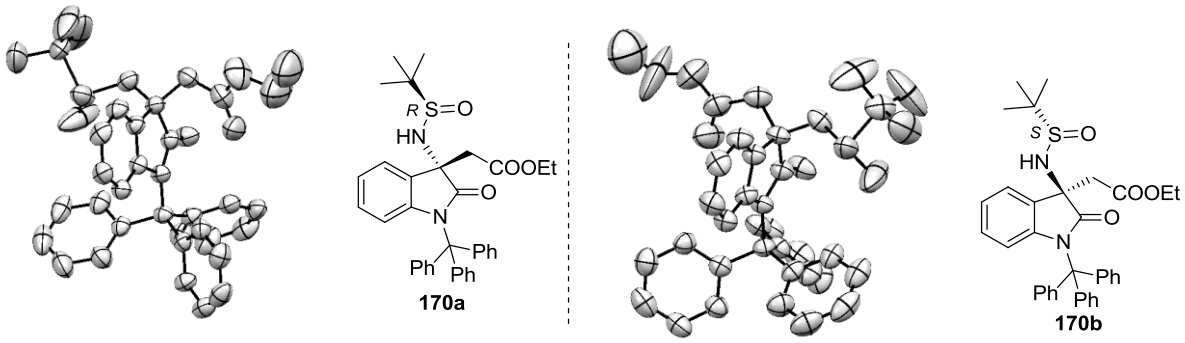
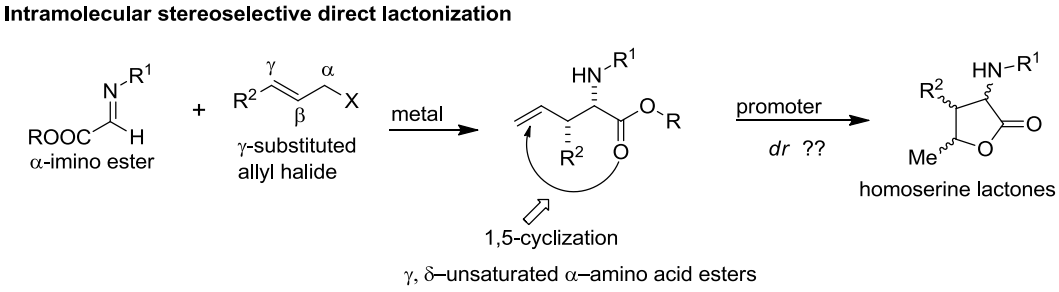



**Figure 16.** X-ray structures of major isomers of **170a** and **170b.** The unit cell contains two molecules and only one molecule is shown here and hydrogens are omitted for better visualization.

### 4.5. Triflic acid-mediated diastereoselective synthesis of homoserine lactone scaffolds.



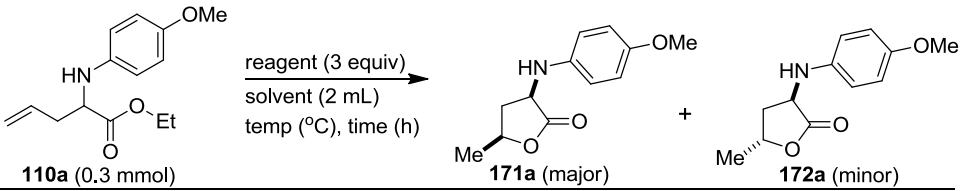

**Scheme 80.** Stereoselective construction of homoserine lactones possessing multiple stereogenic centers.

Homoserine lactones (α-amino butyrolactones, a class of amino acid derivatives) are highly privileged class of synthetic targets due to their widespread biological applications and usefulness as versatile synthetic building blocks.[88-90] Notably, *N*-acylated derivatives of *L*-homoserine lactone (AHLs or *N*-AHLs) act as autoinducers in Gram-negative bacteria to

arbitrate the quorum sensing process.[92] Though a significant amount of work related to the synthesis of various homoserine lactone analogs having one stereocenter in the lactone part and testing for their biological activities were already reported.[93-97] However, still there is a scope for the new methods revealing the synthesis of homoserine lactone analogs having multiple stereocenters with stereocontrol.

Consequently, it was decided to explore the stereoselective synthesis of homoserine lactone analogs having multiple stereocenters and the lactonization reaction starting from easily accessible γ,δ-unsaturated α-amino esters **110**/**116**, which were synthesized from the indium-mediated Barbier-type allylation of α-imino esters **100** (Scheme 80).

**Table 27.** Optimization of the reaction conditions for direct lactonization of **110a**.




**110a** (0.3 mmol) **171a** (major) **172a** (minor)

| entry | reagent | solvent | temp (°C) | time (h) | **171a** / **172a**; yield (%)[a] | (*dr*)[92b] |
|---|---|---|---|---|---|---|
| 1 | TfOH | DCM | 25 | 24 | N.D. | - |
| 2 | TfOH | DCM | 40 | 24 | N.D. | - |
| 3 | TfOH | THF | 70 | 24 | N.D. | - |
| 4 | TfOH | MeCN | 80 | 24 | 22 | 80:20 |
| 5 | TfOH | DCE | 85 | 24 | 45 | 80:20 |
| 6 | TfOH | 1,4-dioxane | 110 | 24 | 36 | 80:20 |
| 7 | TfOH | toluene | 110 | 24 | 67 | 81:19 |
| 8 | TfOH | DMF | 120 | 24 | N.D. | - |
| 9 | TfOH | DMSO | 130 | 24 | N.D. | - |
| 10 | TfOH | toluene | 110 | 24 | 65[b] | 81:19 |
| 11 | TfOH | toluene | 110 | 24 | 69[c] | 81:19 |
| 12 | TfOH | toluene | 110 | 06 | 30 | 81:19 |
| 13 | TfOH | toluene | 110 | 12 | 50 | 81:19 |
| 14 | PTSA | toluene | 110 | 24 | N.D. | - |
| 15 | $CH_3COOH$ | toluene | 110 | 24 | N.D. | - |
| 16 | TFA | toluene | 110 | 24 | N.D. | - |
| 17 | camphor-10-sulfonic acid | toluene | 110 | 24 | N.D. | - |
| 18 | $BF_3.Et_2O$ | toluene | 110 | 24 | 18 | 85:15 |
| 19 | $In(OTf)_3$ | toluene | 110 | 24 | 42[d] | 81:19 |
| 20 | TfOH | toluene | 110 | 24 | 0[e] | - |
| 21 | TfOH | toluene | 110 | 24 | 15[f] | - |

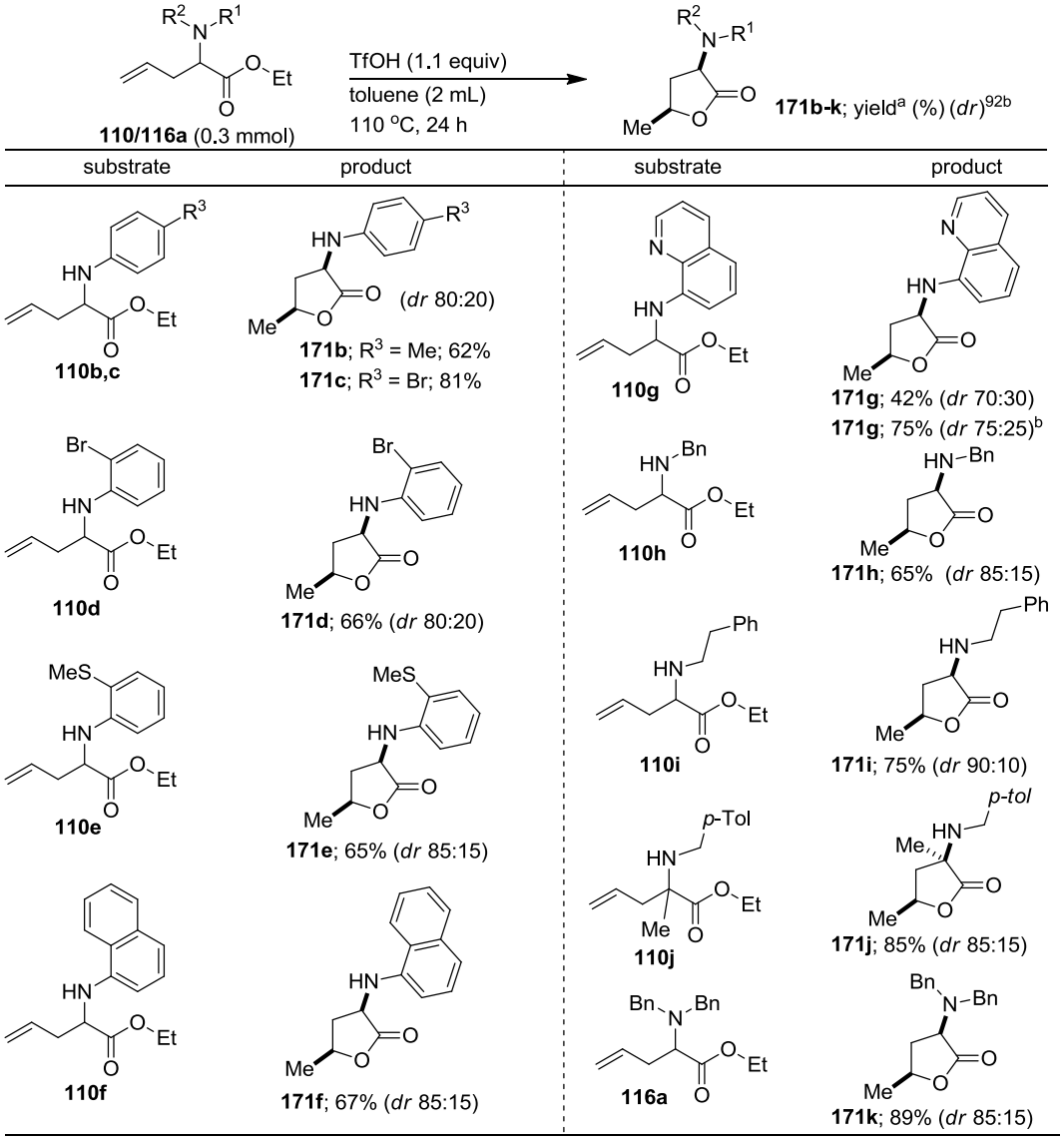
[a] Isolated yields are given. [b] 2 equiv of TfOH was used. [c] 1.1 equiv of TfOH was used. [d] 2 equiv of $In(OTf)_3$ was used. [e] 10 mol% of TfOH was used. [f] 50 mol% of TfOH was used. N.D. = Not Detected/Not formed.

The lactonization of γ,δ-unsaturated carboxylic acids under various procedures is well documented.[93-97] However, the lactonization reaction involving the γ,δ-unsaturated carboxylates (γ,δ-unsaturated carboxylic acid esters) would be an ideal procedure,[93-97] since in this procedure there is no need to prepare the γ,δ-unsaturated carboxylic acids. Because, sometimes handling the carboxylic acids is a challenging task. Based on the literature work, it was intended that the direct lactonization of γ,δ-unsaturated α-amino esters **110**/**116** would be highly possible to carry out and the stereoselective synthesis of homoserine lactone analogs having multiple stereocenters is also an achievable task (Scheme 80).

To begin with, several reactions were carried out to find out the best reaction conditions and suitable promoter for promoting the direct lactonization of the γ,δ-unsaturated α-amino ester **110a**. The lactonization of **110a** was tried in DCM or THF in the presence of triflic acid as a promoter, however, the reaction failed to give any product (entries 1-3, Table 27). The reaction of **110a** (1 equiv) and TfOH (3 equiv) in MeCN at refluxing temperature gave the α-amino γ-butyrolactones scaffolds **171a**/**172a** as diastereomers in 22% yield with good diastereoselectivity (*dr* 80:20; entry 4, Table 27). Similarly, heating a mixture of **110a** (1 equiv) and TfOH (3 equiv) in 1,2-DCE or 1,4-dioxane afforded the homoserine lactone derivatives **171a**/**172a** in 45 and 36% yields, respectively, with good diastereoselectivity (*dr* 80:20; entries 5 and 6, Table 27). Utilization of toluene as solvent for the reaction of **110a** (1 equiv) with 3 equiv of TfOH at 110 $^{o}$C for 24 h afforded the homoserine lactone derivatives **171a**/**172a** with improved yield (67%, *dr* 81:19; entry 7, Table 27). However, the lactonization of **110a** in DMF or DMSO was ineffective (entries 8 and 9, Table 27). When the lactonization of **110a** (1 equiv) was performed in toluene at 110 $^{o}$C for 24 h with lesser equiv of TfOH (2 equiv or 1.1 equiv), there was no significant change in the yield and diastereoselectivity of **171a**/**172a** (entries 10 and 11, Table 27). The lactonization of **110a** (1 equiv) in toluene at 110 $^{o}$C in the presence of TfOH (3 equiv) for reaction time of 6 and 12 h resulted in the significant decrease in yield of **171a**/**172a** (entries 12 and 13, Table 27). The lactonization of **110a** with other acids such as PTSA, AcOH, TFA and CSA failed to give the products **171a**/**172a** (entries 14-17, Table 27). Further, the lactonization of **110a** with Lewis acids such as $In(OTf)_3$ or $BF_3{\cdot}OEt_2$ gave the products **171a**/**172a** in only 42% and 18% yields (*dr* 81:19; entries 18 and 19, Table 27). The lactonization of **110a** in the presence of

catalytic amounts of triflic acid furnished the products **171a**/**172a** in very low yield (entries 20 and 21, Table 27).

**Table 28.** Triflic acid-mediated diastereoselective synthesis of α-amino γ-butyrolactones (homoserine lactones) **171b-k**.

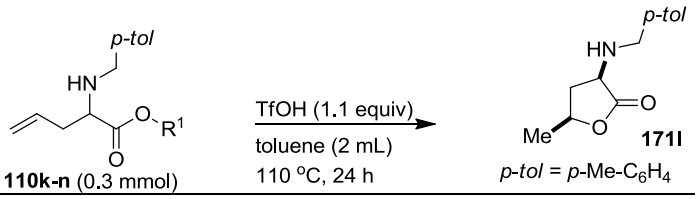



[a] Isolated yields are given. [b] 2.2 equiv of TfOH was used.

Succeedingly, it was envisioned to explore the generality of the triflic acid-mediated direct lactonization of several 2-amino-pent-4-enoic acid esters. In this regard, several 2-amino-pent-4-enoic acid esters **110b-j** (having different aryl- or naphthyl- or quinolinyl ring or alkyl/Bn group as protecting group for the amine functionality) and **116a** (having two Bn

group as protecting group for the amine functionality) were assembled by using the literature procedures.[42a] Then, the compounds **110b-g** were subjected to the triflic acid-mediated direct lactonization reaction to afford various *N*-arylated homoserine lactone derivatives **171b-171g** having two stereocenters in moderate to very good yields with appreciable diastereoselectivity (*dr* up to 85:15; Table 28). Similarly, the reaction of **110h-j** (*N*-benzyl, *N*-phenethyl and *N*-*p*-methylbenzyl 2-amino-pent-4-enoic ester derivatives) with triflic acid yielded the respective homoserine lactone derivatives **171h-j** containing two stereocenters in 65-85% yield with very good diastereoselectivity (*dr* up to 90:10; Table 28). The reaction of ethyl 2-(dibenzylamino)pent-4-enoate (**116a**) led to the assembling of **171k** in 89% yield with very good diastereoselectivity (*dr* up to 85:15; Table 28).

**Table 29.** Triflic acid-mediated lactonization of **110k-n**. Effect of various ester groups.



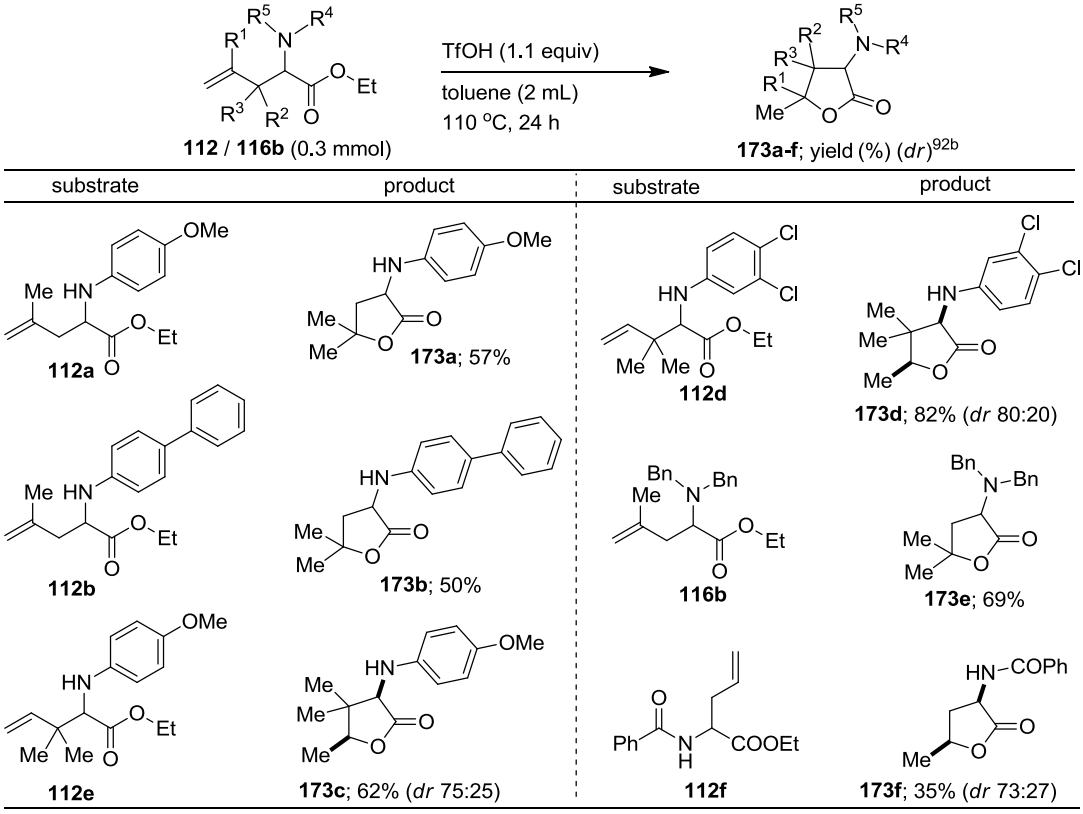

| substrate | **171l** / **172l**; yield (%) (*dr*)[92b] |
|---|---|
| **110k**; $R^1$ = Me | 73% (75:25) |
| **110l**; $R^1$ = Et | 71% (80:20) |
| **110m**; $R^1$ = $^t$Bu | 72% (80:20) |
| **110n**; $R^1$ = Bn | 69% (77:23) |

Further, the effect of ester functionality on the TfOH-mediated lactonization process was tested by using various 2-amino-pent-4-enoic acid ester derivatives **110k-n** having different alkyl groups (R = Me, Et, *tert*-butyl and Bn). The TfOH-mediated lactonization **110k-n** smoothly afforded the homoserine lactone derivative **171l** in 69-73% yields. There was no significant change in the diastereoselectivity by changing the alkyl groups (R = Me, Et, *tert*-butyl and Bn) in the starting material (**110k-n**) for the lactonization process (Table 29).

Subsequently, it was envisioned to elaborate the scope of the lactonization protocol to obtain homoserine lactone derivatives **173a-e** possessing substitutions at the β and γ-positions by using the γ,δ-unsaturated α-amino acid esters **112/116b** having substitutions at the β and γ-positions (Table 30). Accordingly, The triflic acid-promoted direct lactonization of various 2-

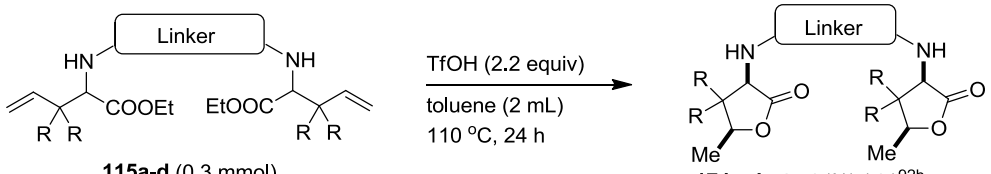
amino-pent-4-enoic acid esters **112/116b** underwent smoothly to afford the corresponding homoserine lactone derivatives **173a-e** containing substitutions at the β and γ-positions (Table 30). It is worth to mention that the construction of *N*-benzoylated homoserine lactone derivative **173f** was also achieved but with relatively low yield and moderate diastereoselectivity (35%, *dr* 73:27; Table 30).

**Table 30.** Triflic acid mediated diastereoselective synthesis of α-amino γ-butyrolactones (homoserine lactones) **173a-f**.



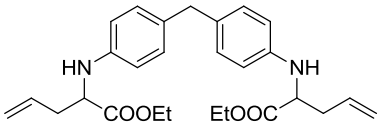
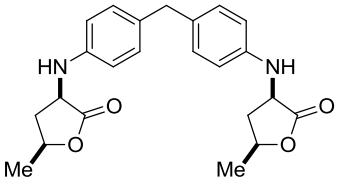
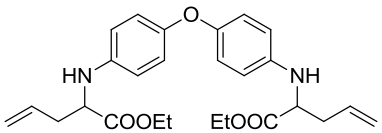
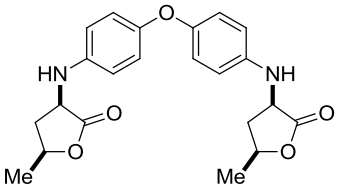
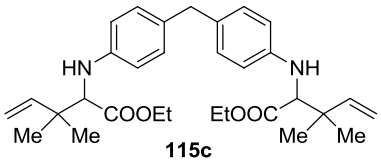
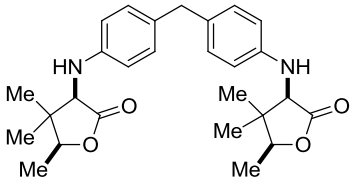
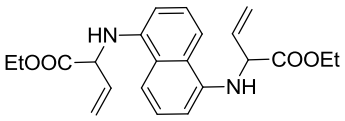
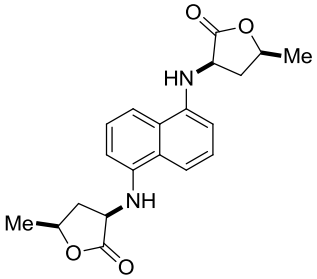

Then, it was intended to investigate the triflic acid-mediated direct lactonization of the *bis*-allylated substrates **115a-d** (Table 31). The substrates **115a-d** were constructed by using a linker and two units of 2-amino-pent-4-enoic acid esters from their respective imines (Table 5). Table 31 reveals the triflic acid-mediated lactonization reactions of substrates **115a-d** led to the stereoselective synthesis of compounds **174a-d** with good diastereoselectivity (*dr* up to 81:19). The compounds **174a-d** contain two lactone units linked *via* different linkers.

**Table 31.** Triflic acid mediated diastereoselective synthesis of α-amino γ-butyrolactones (homoserine lactones) **174a-d**.




**115a-d** (0.3 mmol)

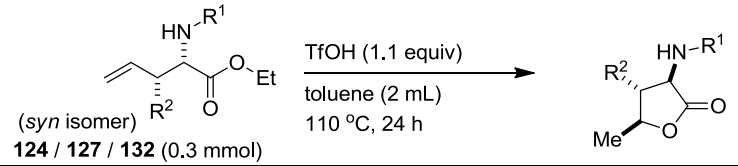
**174a-d**; yield (%) (*dr*)[92b]

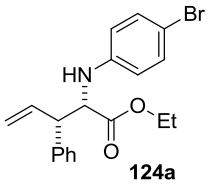
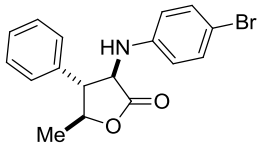
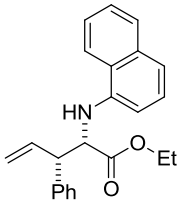
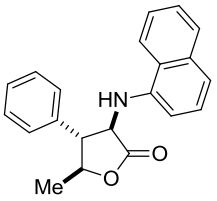
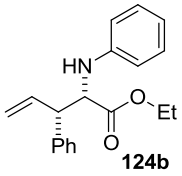
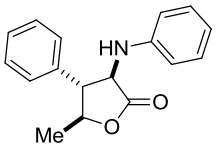
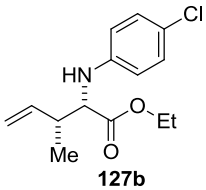
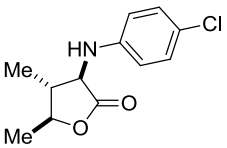
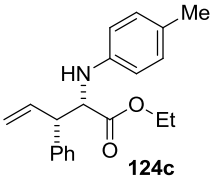
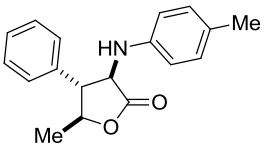
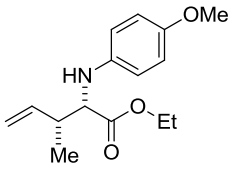
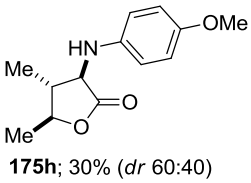
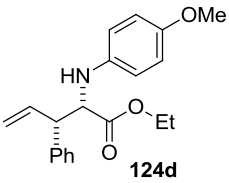
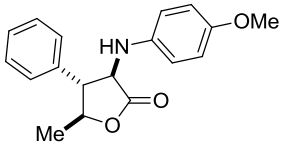
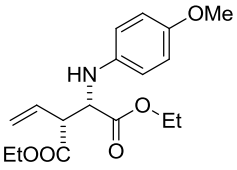
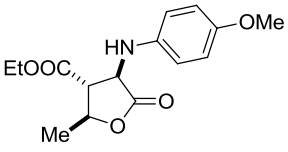
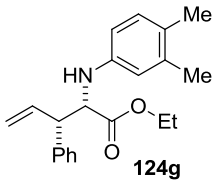
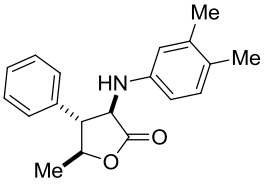
| substrate | product |
|---|---|
|  **115a** |  **174a**; 85% (*dr* 76:24) |
|  **115b** |  **174b**; 51% (*dr* 80:20) |
|  **115c** |  **174c**; 44% (*dr* 81:19) |
|  **115d** |  **174d**; 40% (*dr* 80:20) |

Furthermore, it was planned to extend the generality of the stereoselective lactonization protocol and get densely substituted lactones possessing substitutions at the β and γ-positions and three contiguous stereogenic centers. The synthesis of densely substituted lactones **175a-**

**i** can be achieved by treating the γ,δ-unsaturated α-amino acid esters **124/127/132** (*syn* isomers) having substitutions at the β and γ-positions with TfOH.

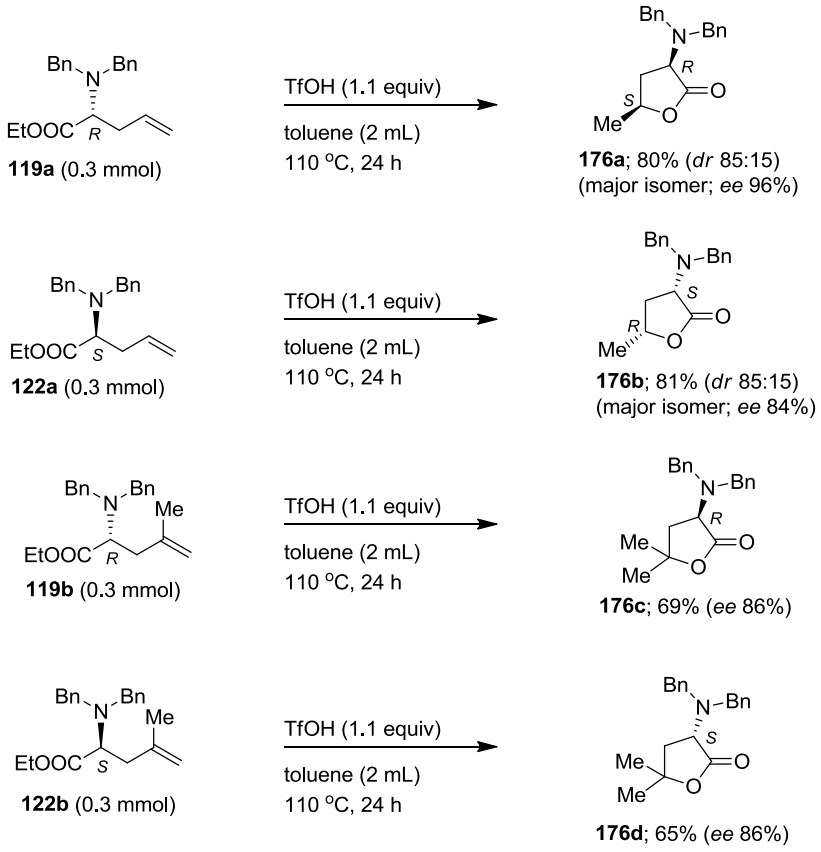
**Table 32.** Triflic acid mediated diastereoselective synthesis of α-amino γ-butyrolactones (homoserine lactones) **175a-i**.




| substrate | product | substrate | product |
|---|---|---|---|
|  **124a** |  **175a**; 70% (*dr* 98:2) |  **124h** |  **175f**; 69% (*dr* 95:5) |
|  **124b** |  **175b**; 84% (*dr* 80:20) |  **127b** |  **175g**; 50% (*dr* 67:33) |
|  **124c** |  **175c**; 70% (*dr* 81:19) |  **127d** |  **175h**; 30% (*dr* 60:40) |
|  **124d** |  **175d**; 67% (*dr* 80:20) |  **132a** |  **175i**; 0% |
|  **124g** |  **175e**; 46% (*dr* 95:5) | | |

Accordingly, the triflic acid-promoted direct lactonization of various 2-amino-pent-4-enoic acid esters **124/127/132** (*syn* isomers) proceeded smoothly and successfully afforded the corresponding homoserine lactone derivatives **175a-h** (*dr* up to 98:2) containing substitutions at the β-position (e.g. Me or Ph) and γ-position (Me) with very good regio- and stereocontrol

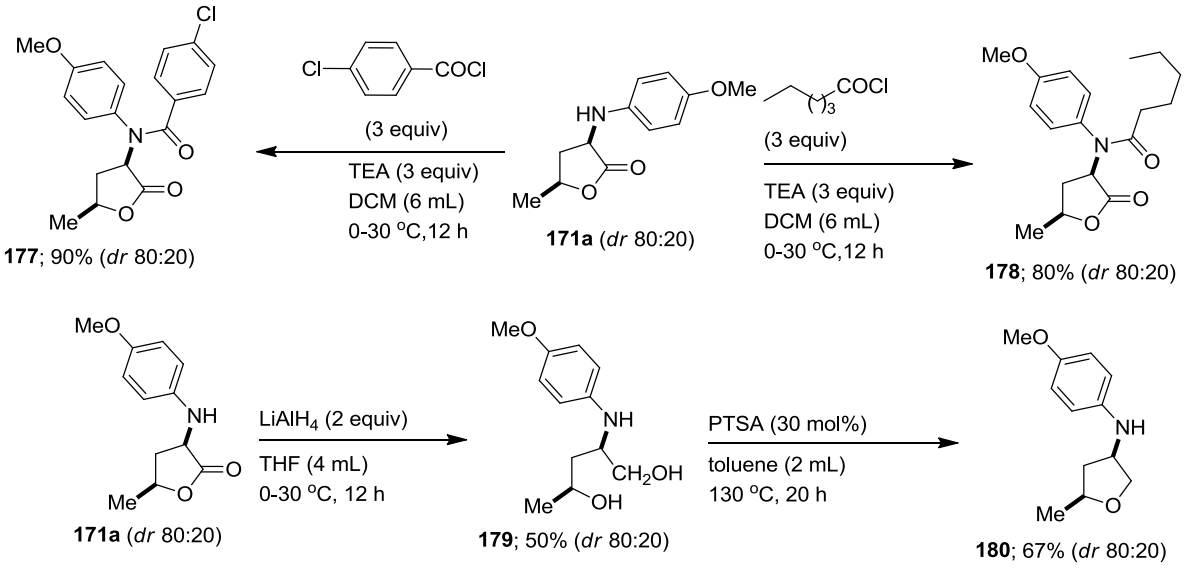
(Table 32). It is a limitation that the product **175i** could not be obtained from the diester **132a** and in this case, the presence of a second ester group might be hindering the lactonization reaction (Table 32).



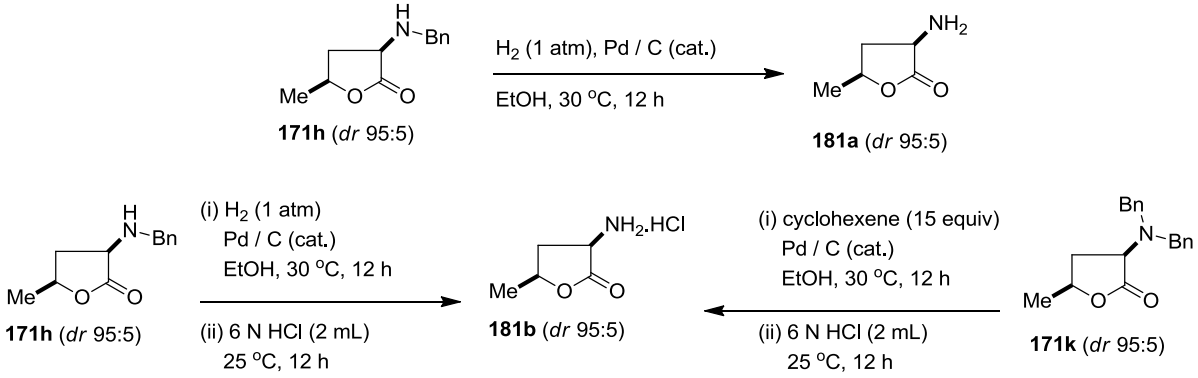

**Scheme 81.** Enantioselective synthesis of α-amino γ-butyrolactones **176a-d**.

Subsequently, it was envisaged to prepare the enantiomerically enriched homoserine lactones and in this regard, at first the enantiomerically enriched α-amino γ,δ-unsaturated acid esters substrates **119a**,**b** and **122a**,**b** were assembled (Scheme 45). Then, the enantiomerically enriched substrates **119a**,**b** and **122a**,**b** were subjected to the direct lactonization in the presence of triflic acid, which led to the assembling of the corresponding enantiomerically enriched homoserine lactones **176a-d** in good yields (65-81%) with high stereoselectivity (*dr* 85:15, *ee* up to 96%; Scheme 81). After assembling various homoserine lactones from the direct lactonization of various γ,δ-unsaturated α-amino esters, it was envisioned to explore the utility of the homoserine lactones by performing the synthetic transformations by using representative homoserine lactones. The reaction of the homoserine lactone **171a** with

hexanoyl chloride or 4-chlorobenzoyl chloride afforded the corresponding homoserine lactone analogs **177** and **178** having two different protecting groups at the amino group (Scheme 82).




**Scheme 82.** Synthetic transformations of homoserine lactone **171a**.




**Scheme 83.** Deprotection of benzyl protecting group of homoserine lactones (**171h** and **171k**).

Then, the homoserine lactone **171a** was subjected to the $LiAlH_4$-mediated reduction to afford the compound **179**, which was then treated with *p*-toluenesulfonic acid to afford the substituted THF derivative **180** having two stereogenic centers (Scheme 82). The deprotection of the benzyl group of the compounds **171h** and **171k** was performed under the

standard hydrogenolysis procedures to afford the α-amino-γ-butyrolactone **181a** and α-amino-γ-butyrolactone hydrochloride **181b** (Scheme 83). A fraction with *dr* 95:5 from column purification of **171h** and **171k** was used for the hydrogenolysis reactions.

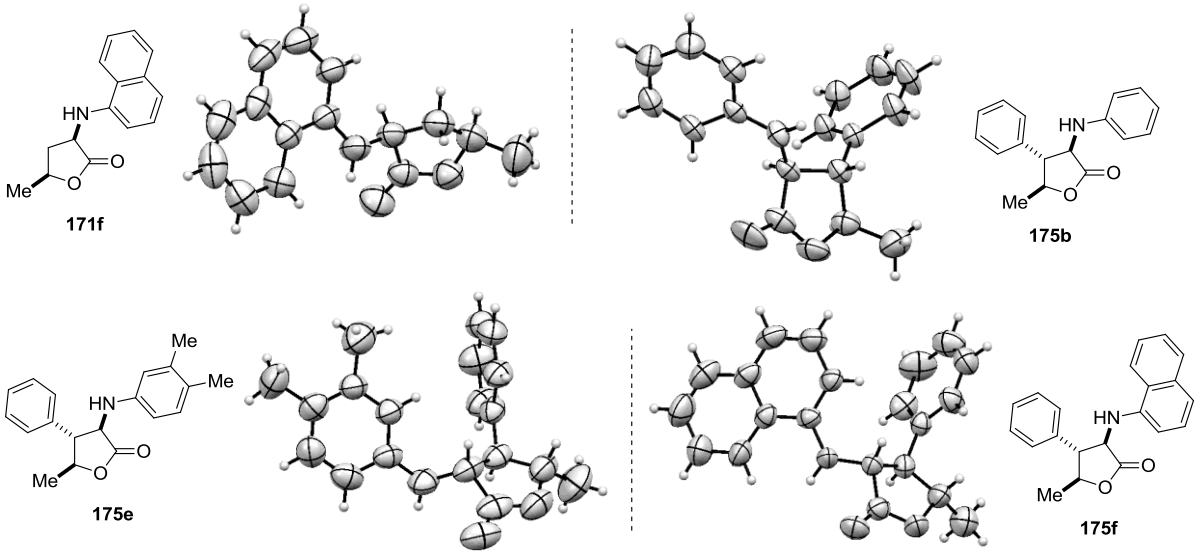
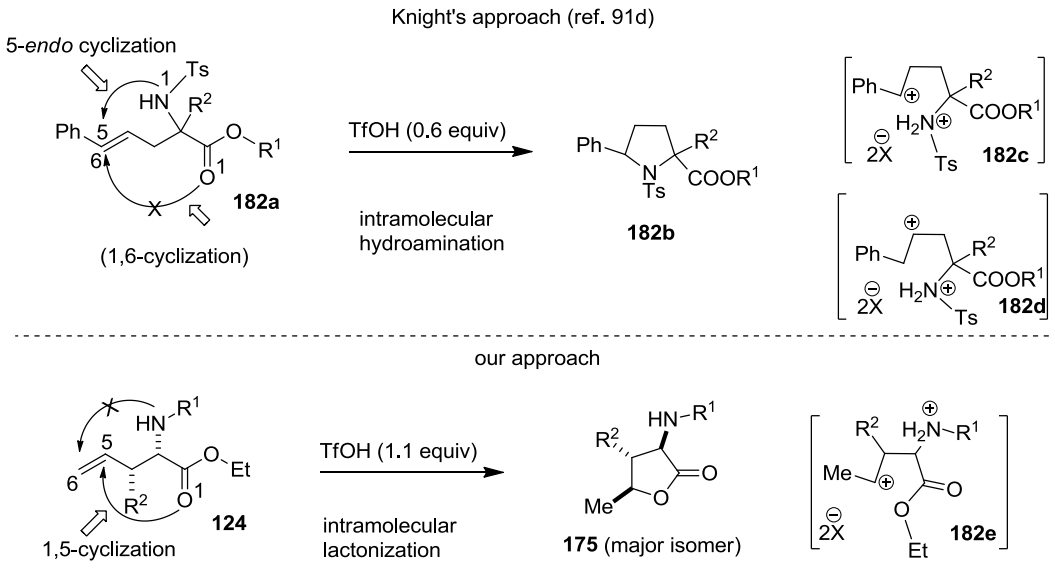
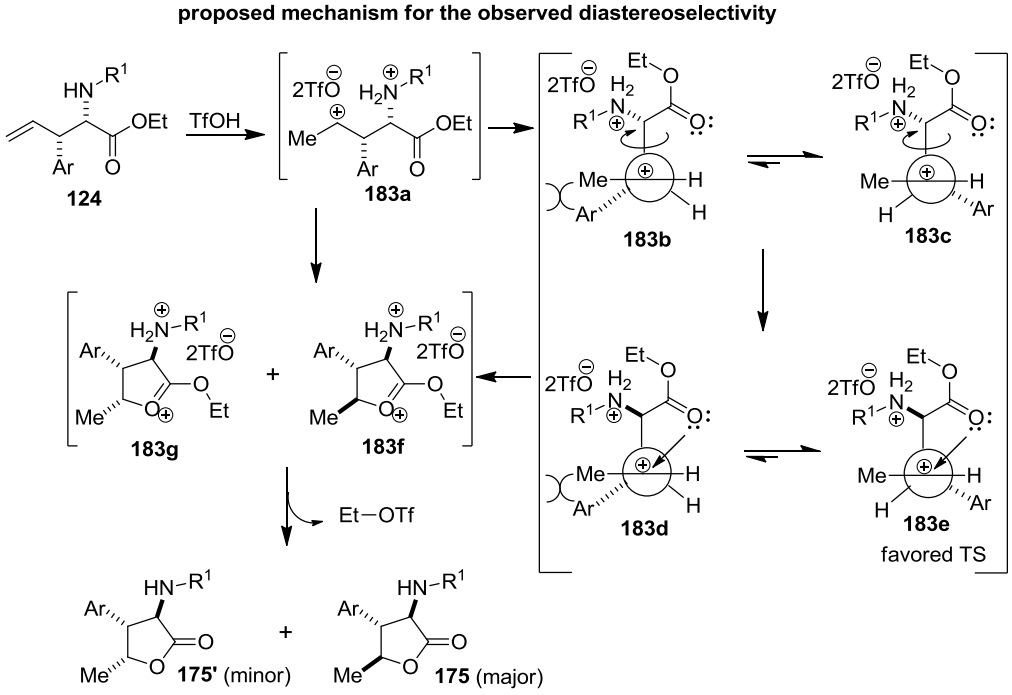



**Figure 17.** X-ray structures of major isomers of **171f**, **175b**, **175e** and **175f**.




**Scheme 84.** Plausible mechanism for the formation of homoserine lactones.

The stereochemistry of the major isomers of **171f**, **175b**, **175e** and **175f** was unambiguously established from the he X-ray structure analysis. Notably, the relative stereochemistry of the α- and γ stereocenters is found to be *syn* in all the major isomers of **171f**, **175b**, **175e** and **175f** (Figure 17). Consequently, the stereochemistry of the major isomers of the products of the respective series **171**, **173**, **174** and **175** was assigned on the basis of the X-ray structures of the major isomers of **171f**, **175b**, **175e** and **175f** and the similarity in the NMR spectral pattern of the products of the respective series **171**, **173**, **174** and **175**. The diastereomeric ratio of the products were determined from the NMR spectra of the corresponding crude reaction mixtures.




**Scheme 85.** Plausible mechanism for the formation of homoserine lactones.

Knight's group[91d] revealed the triflic acid-based reaction of δ-substituted α-amino γ,δ-unsaturated carboxylic acid esters (**182a**) selectively produced pyrrolidines (**182b**). In this case, pyrrolidines are formed from the 5-*endo* cyclization and intramolecular hydroamination[91d-91h] *via* the plausible intermediate **182c** involving a more stable benzylic (2°) carbocation (Scheme 84). Contrastingly, in the present case, the α-amino γ,δ-unsaturated carboxylic acid esters (e.g. **124**) having no substituent at the δ-position underwent

lactonization instead of hydroamination to give the homoserine γ-lactone scaffolds **175** with contiguous stereocenters *via* the 1,5-cyclization. Excess triflic acid is needed for the lactonization of α-amino γ,δ-unsaturated carboxylic acid esters, because, perhaps, amine group is protonated under the experimental condition. Since the amine group is protonated, the regioselective lactonization is predominant than hydroamination. Furthermore, on the basis of the observed very good diastereoselectivity in the lactonization reactions and the unambiguous assignment of the stereochemistry of the major isomers **171f**, **175a**, **175b** and **175d** based on the single crystal X-ray structure analysis of the major isomers **171f**, **175a**, **175b** and **175d**, a plausible mechanism is proposed *via* the TS **183e** comprising a more stable $2^{o}$ carbocation and favorable conformers **183c**/**183e** in which the Ar- and Me groups are *pseudo anti* to each other, thereby, leading to the formation of the major isomer **175** from **124** (Scheme 85).

**General:** Melting points are uncorrected. IR spectra were recorded as neat or thin films or KBr pellets. $^{1}H$ and $^{13}C$ NMR spectra were recorded with 400 and 100 MHz spectrometers, respectively, with TMS as an internal or external standard. Column chromatography was carried out on silica gel (100–200 mesh) or neutral $Al_2O_3$. Reactions were conducted in anhydrous solvent under nitrogen atmosphere where required. Solutions were dried using anhydrous sodium sulfate. Reagents were added to the reaction flask by using a syringe. Thin layer chromatography (TLC) was performed on silica plates or neutral $Al_2O_3$ and components were visualized by observation under iodine. Isolated yields of all the products are reported (yields were not optimized). Ratios of diastereomers were determined from the $^{1}H$ spectra of either crude reaction mixtures or after isolation, in all the reactions, only the major diastereomer was isolated in pure form. The ratio of diastereoselectivity (*dr* 98:2) refers to the predominant presence of the major diastereomer and rarely, traces of the corresponding minor isomer was detected in the NMR spectrum of the crude reaction mixture. The stereochemistry of major isomers was assigned based on the X-ray structure analysis of representative compounds. Good quality single crystals were grown by using a combination of dichloromethane or hexanes or methanol or ethyl acetate by slow solvent evaporation technique at 25 °C and the single crystal X-ray diffraction data for all the compounds was collected using four circle CCD diffractometer (monochromatic Mo Kα radiation). Data collection and unit cell refinement for the data sets were done using APEX-II suit. The crystal structures were solved using Olex2 or WinGx packages using SHELXS97, and the structures were refined using SHELXL97. All the hydrogen atoms have been fixed at their geometrically ideal positions and refined using the riding model available within SHELXS97. All figures have been generated using Mercury. Chiral compounds were analyzed by HPLC using AD-H (0.46 cm IDR25 cm length) as a chiral column.

**General procedure for the synthesis of α-imino esters 100a–q:**[42a,98] α-Imino esters **100a–q** were synthesized by using the standard literature procedures and used without further purification (see Table 1).

**General procedure for the synthesis of α-imino esters 100r-u and 102d:**[98,100,101] α-Imino esters **100r-u** and **102d** were synthesized by using the standard literature procedures and used without further purification (see Scheme 41).

**General procedure for the synthesis of α-imino esters 102a–c:**[99] α-Imino esters **102a–c** were synthesized by using the standard literature procedures and used without further purification (see Scheme 41).

**General procedure for the synthesis of isatin ketimines 105a–k:**[102-105] Isatin ketimines **105a**–**k** are known in the literature and were synthesized by using the standard literature procedures and product was used without further purification (see Table 2).

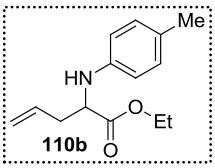
**General procedure for the synthesis of isatin hydrazones 106 and 107:**[103] Isatin hydrazones **106** and **107** were known in the literature and were synthesized by using standard literature procedures and product was used without further purification (see Scheme 42).

**General procedure for the synthesis of isatin ketimines 108a and 108b:**[104] Isatin ketimines **108a** and **108b** were known in the literature and synthesized by using the standard literature procedures (see Scheme 43).

**General procedure for the preparation of *N*-protected allyl glycine esters 110a-i, 112a-e and 115a-d:**[42a] Compounds **110a-i**, **112a-e** and **115a-d** were prepared using the reported/standard procedures. To a mixture of the respective α-imino ester (0.5 mmol) and indium powder (0.75 mmol) in DMF (0.5 mL), acetic acid (3 mmol) was added at room temperature. While stirring the mixture allyl bromide (1 mmol) was added slowly. The mixture was stirred for 12 h at room temperature, then transferred to a separating funnel and extracted with EtOAc (3x15 mL). The combined organic layers were dried with anhydrous $Na_2SO_4$, then, the solvent was evaporated under vacuum. Purification of the resulting crude reaction mixture by column chromatography on silica gel (EtOAc/hexane) gave the product **110a-i**, **112a-e** and **115a-d** (see Tables 3-5).

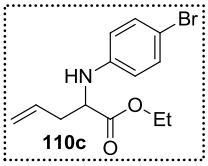
Compounds **110a**, **112a** are known in the literature[42a] and its characterization data matches with that of reported data.

**Ethyl 2-(*p*-tolylamino)pent-4-enoate (110b)**: Following the general procedure described above, **110b** was obtained after purification by silica gel column chromatography



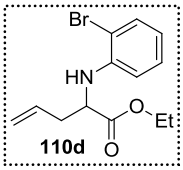

(EtOAc/hexane, 15:85) as a colorless oil (93 mg, 80%); $R_f$ = 0.75 (15% EtOAc/hexane). IR (neat): $\tilde{\upsilon}$ = 3389, 2982, 1732, 1520, 1184 $cm^{-1}$. $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ = 7.04 (d, $J$ = 8.1 Hz, 2 H), 6.61 (d, $J$ = 8.1 Hz, 2 H), 5.91-5.81 (m, 1 H), 5.24-5.19 (m, 2 H), 4.24 (q, $J$ = 7.1 Hz, 2 H), 4.17 (t, $J$ = 6.1 Hz, 1 H), 4.00 (br. s, 1 H), 2.68-2.59 (m, 2 H), 2.29 (s, 3 H), 1.30 (t, $J$ = 7.1 Hz, 3 H). $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta$ = 173.5, 144.4, 133.0, 129.9, 127.6, 118.8, 113.8, 61.1, 56.5, 37.1, 20.5, 14.3. HRMS (ESI): calcd. for $C_{14}H_{20}NO_2$ $[M + H]^+$ 234.1494; found 234.1508.

**Ethyl 2-(4-bromophenylamino)pent-4-enoate (110c):** Following the general procedure described above, **110c** was obtained after purification by silica gel column chromatography



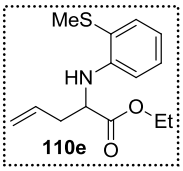

(EtOAc/hexane, 15:85) as a colorless oil (124 mg, 84%); $R_f$ = 0.73 (15% EtOAc/hexane). IR (neat): $\tilde{\upsilon}$ = 3386, 2981, 1738, 1505, 1190 $cm^{-1}$. $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ = 7.26 (d, $J$ = 8.8 Hz, 2 H), 6.51 (d, $J$ = 8.8 Hz, 2 H), 5.83-5.73 (m, 1 H), 5.20-5.16 (m, 2 H), 4.25 (br. s, 1 H), 4.21 (q, $J$ = 7.1 Hz, 2 H), 4.10 (t, $J$ = 5.9 Hz, 1 H), 2.62-2.57 (m, 2 H), 1.27 (t, $J$ = 7.1 Hz, 3 H). $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta$ = 173.0, 145.6, 132.5, 132.0, 119.2, 115.1, 110.0, 61.3, 55.9, 36.8, 14.3. HRMS (ESI): calcd. for $C_{13}H_{17}BrNO_2$ $[M + H]^+$ 298.0443; found 298.0435.

**Ethyl 2-(2-bromophenylamino)pent-4-enoate (110d):** Following the general procedure described above, **110d** was obtained after purification by silica gel column chromatography



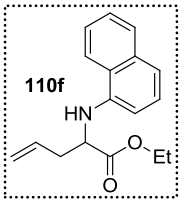

(EtOAc/hexane, 15:85) as a colorless oil (96 mg, 65%); $R_f$ = 0.73 (15% EtOAc/hexane). IR (neat): $\tilde{\upsilon}$ = 3388, 2981, 1738, 1510, 1189 $cm^{-1}$. $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ = 7.46 (d, $J$ = 7.5 Hz, 1 H), 7.18 (t, $J$ = 7.5 Hz, 1 H), 6.65-6.57 (m, 2 H), 5.89-5.78 (m, 1 H), 5.26-5.21 (m, 2 H), 4.91 (d, $J$ = 7.8 Hz, 1 H), 4.26-4.16 (m, 3 H), 2.70-2.65 (m, 2 H), 1.29 (t, $J$ = 7.1 Hz, 3 H). $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta$ = 172.6, 143.6, 132.7, 132.4, 128.5, 119.4, 118.7, 111.8, 110.4, 61.3, 56.0, 36.9, 14.3. HRMS (ESI): calcd. for $C_{13}H_{17}BrNO_2$ $[M + H]^+$ 298.0443; found 298.0435.

**Ethyl 2-(2-(methylthio)phenylamino)pent-4-enoate (110e):** Following the general procedure described above, **110e** was obtained after purification by silica gel column chromatography (EtOAc/hexane, 15:85) as a colorless oil (104 mg, 79%); $R_f$ = 0.73 (15% EtOAc/hexane). IR (neat): $\tilde{\upsilon}$ = 3369, 2982, 1738, 1504, 1187 $cm^{-1}$. $^1H$ NMR (400 MHz,

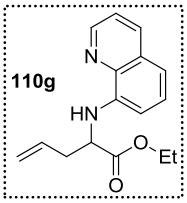



$CDCl_3$): $\delta$ = 7.44 (d, $J$ = 7.5 Hz, 1 H), 7.18 (t, $J$ = 8.0 Hz, 1 H), 6.70 (t, $J$ = 7.5 Hz, 1 H), 6.55 (d, $J$ = 8.0 Hz, 1 H), 5.90-5.79 (m, 1 H), 5.51 (d, $J$ = 8.1 Hz, 1 H), 5.26-5.19 (m, 2 H), 4.24-4.18 (m, 3 H), 2.72-2.63 (m, 2 H), 2.35 (s, 3 H), 1.27 (t, $J$ = 7.2 Hz, 3 H). $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ = 173.0, 146.9, 134.7, 132.8, 129.5, 120.6, 119.1, 117.9, 110.5, 61.2, 55.8, 37.0, 18.3, 14.3. HRMS (ESI): calcd. for $C_{14}H_{20}NO_2S$ $[M + H]^+$ 266.1215; found 266.1215.

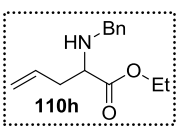
**Ethyl 2-(naphthalen-1-ylamino)pent-4-enoate (110f):** Following the general procedure described above, **110f** was obtained after purification by silica gel column chromatography (EtOAc/hexane, 15:85) as a colorless oil (74 mg, 55%); $R_f$ = 0.74 (15% EtOAc/hexane). IR (neat): $\tilde{\upsilon}$ = 3422, 2923, 1732, 1583, 1194 $cm^{-1}$. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 7.94-7.82 (m, 2 H), 7.51-7.49 (m, 2 H), 7.38-7.30 (m, 2 H), 6.59 (d, $J$ = 7.2 Hz, 1 H), 5.97-5.87 (m, 1 H), 5.31-5.24 (m, 2 H), 5.03 (br. s, 1 H), 4.36 (t, $J$ = 5.9 Hz, 1 H), 4.27 (q, $J$ = 7.1 Hz, 2 H), 2.83-2.74 (m, 2 H), 1.31 (t, $J$ = 7.1 Hz, 3 H). $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ = 173.4, 141.8, 134.4, 133.0, 128.7, 126.4, 125.9, 125.0, 123.7, 120.1, 119.2, 118.4, 105.2, 61.3, 56.0, 36.9, 14.3. HRMS (ESI): calcd. for $C_{17}H_{20}NO_2$ $[M + H]^+$ 270.1494; found 270.1501.




**Ethyl 2-(quinolin-8-ylamino)pent-4-enoate (110g):** Following the general procedure described above, **110g** was obtained after purification by silica gel column chromatography (EtOAc/hexane, 25:75) as a colorless oil (81 mg, 60%); $R_f$ = 0.45 (25% EtOAc/hexane). IR (neat): $\tilde{\upsilon}$ = 3390, 2981, 1738, 1519, 1181 $cm^{-1}$. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 8.77 (dd, $J$ = 4.2, 1.7 Hz, 1 H), 8.07 (dd, $J$ = 8.2, 1.7 Hz, 1 H), 7.41-7.35 (m, 2 H), 7.12 (dd, $J$ = 8.2, 1.0 Hz, 1 H), 6.70 (d, $J$ = 8.2 Hz, 1 H), 6.66 (d, $J$ = 7.6 Hz, 1 H), 5.98-5.88 (m, 1 H), 5.29-5.19 (m, 2 H), 4.34 (q, $J$ = 6.4 Hz, 1 H), 4.23 (q, $J$ = 7.1 Hz, 2 H), 2.81-2.76 (m, 2 H), 1.26 (t, $J$ = 7.1 Hz, 3 H). $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ = 173.1, 147.3, 143.3, 138.3, 135.9, 133.0, 128.6, 127.5, 121.5, 118.8, 115.1, 105.4, 61.1, 56.0, 37.0, 14.3. HRMS (ESI): calcd. for $C_{16}H_{19}N_2O_2$ $[M + H]^+$ 271.1447; found 271.1453.

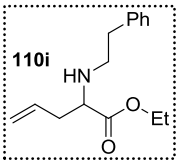



**Ethyl 2-(benzylamino)pent-4-enoate (110h):** Following the general procedure described above, **110h** was obtained after purification by silica gel column chromatography (EtOAc/hexane, 15:85) as a colorless oil (69 mg, 59%); $R_f$ = 0.75 (15% EtOAc/hexane). IR (neat): $\tilde{\upsilon}$ = 3335, 2981, 1731, 1454, 1184 $cm^{-}$



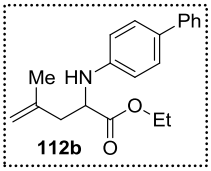
[1]. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 7.36-7.26 (m, 5 H), 5.84-5.74 (m, 1 H), 5.15-5.09 (m, 2 H), 4.24-4.18 (m, 2 H), 3.86 (d, $J$ = 12.9 Hz, 1 H), 3.69 (d, $J$ = 12.9 Hz, 1 H), 3.37 (t, $J$ = 6.4 Hz, 1 H), 2.45 (t, $J$ = 6.9 Hz, 2 H), 1.93 (br. s, 1 H), 1.30 (t, $J$ = 7.1 Hz, 3 H). $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ = 174.6, 139.7, 133.6, 128.4, 128.3, 127.1, 118.0, 60.7, 60.2, 52.0, 37.7, 14.4. HRMS (ESI): calcd. for $C_{14}H_{20}NO_2$ $[M + H]^+$ 234.1494; found 234.1501.

**Ethyl 2-(phenethylamino)pent-4-enoate (110i):** Following the general procedure described above, **110i** was obtained after purification by silica gel column chromatography



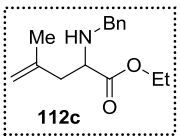

(EtOAc/hexane, 15:85) as a colorless oil (89 mg, 72%); $R_f$ = 0.76 (15% EtOAc/hexane). IR (neat): $\tilde{\upsilon}$ = 3331, 2977, 1732, 1454, 1185 cm$^{-1}$. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 7.33-7.28 (m, 2 H), 7.24-7.21 (m, 3 H), 5.77-5.67 (m, 1 H), 5.13-5.08 (m, 2 H), 4.21-4.14 (m, 2 H), 3.73 (br. s, 1 H), 3.28 (t, $J$ = 6.4 Hz, 1 H), 2.92-2.78 (m, 4 H), 2.43 (t, $J$ = 6.8 Hz, 2 H), 1.26 (t, $J$ = 7.2 Hz, 3 H). $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ = 174.2, 139.5, 133.2, 128.7, 128.5,126.2,118.3, 60.8, 60.7, 49.2, 37.4, 36.2,14.3. HRMS (ESI): calcd. for $C_{15}H_{22}NO_2$ $[M + H]^+$ 248.1651; found 248.1663.

**Ethyl 2-(4-biphenylamino)-4-methylpent-4-enoate (112b):** Following the general procedure described above, **112b** was obtained after purification by silica gel column




chromatography (EtOAc/hexane, 15:85) as a colorless oil (116 mg, 75%); $R_f$ = 0.69 (15% EtOAc/hexane). IR (neat): $\tilde{\upsilon}$ = 3388, 2980, 1732, 1526, 1191 cm$^{-1}$. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 7.58 (d, $J$ = 7.9 Hz, 2 H), 7.48 (d, $J$ = 7.9 Hz, 2 H), 7.43 (t, $J$ = 7.1 Hz, 2 H), 7.30 (t, $J$ = 7.1 Hz, 1 H), 3.73 (d, $J$ = 8.3 Hz, 2 H), 4.95 (s, 1 H), 4.90 (s, 1 H), 4.25 (q, $J$ = 7.2 Hz, 4 H), 2.68-2.54 (m, 2 H), 1.84 (s, 3 H), 1.31 (t, $J$ = 7.2 Hz, 3 H). $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ = 173.9, 146.2, 141.1, 140.8, 131.3, 128.7, 128.0, 126.4, 126.2, 114.6, 113.6, 61.2, 55.0, 41.3, 21.9, 14.3. HRMS (ESI): calcd. for $C_{20}H_{24}NO_2$ $[M + H]^+$ 310.1807; found 310.1800.

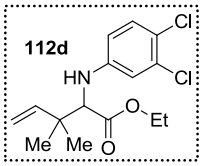
**Ethyl 2-(benzylamino)-4-methylpent-4-enoate (112c):** Following the general procedure described above, **112c** was obtained after purification by silica gel column chromatography




(EtOAc/hexane, 20:80) as a colorless oil (93mg, 75%); $R_f$ = 0.72 (20% EtOAc/hexane). IR (neat): $\tilde{\upsilon}$ = 3331, 2980, 1731, 1454, 1184 cm$^{-1}$. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 7.34-7.26 (m, 5 H), 4.83 (s, 1 H), 4.77 (s, 1 H), 4.20 (q, $J$ = 7.1 Hz, 2 H), 3.87 (d, $J$ = 13.0 Hz, 1 H), 3.69 (d, $J$ = 13.0 Hz, 1 H), 3.45 (t, $J$ = 7.4 Hz, 1 H), 2.40 (d, $J$ = 7.4 Hz, 2 H),1.99 (br. s, 1 H),1.71 (s, 3 H),1.30 (t, $J$ = 7.1 Hz, 3 H). $^{13}$C

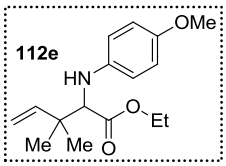
NMR (100 MHz, $CDCl_3$): $\delta$ = 174.8, 141.4, 139.5, 128.4, 128.3, 127.1, 113.7, 60.7, 59.0, 52.1, 41.9, 22.0, 14.3. HRMS (ESI): calcd. for $C_{15}H_{22}NO_2$ $[M + H]^+$ 248.1651; found 248.1659.

**Ethyl 2-(3,4-dichlorophenylamino)-3,3-dimethylpent-4-enoate (112d):** Following the general procedure described above, **112d** was obtained after purification by silica gel column



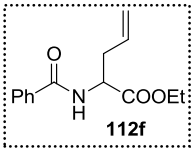

chromatography (EtOAc/hexane, 15:85) as a colorless oil (88 mg, 56%); $R_f$ = 0.75 (15% EtOAc/hexane). IR (neat): $\tilde{\upsilon}$ = 3390, 2976, 1731, 1494, 1133 $cm^{-1}$. $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ = 7.18 (d, $J$ = 8.7 Hz, 1 H), 6.71 (d, $J$ = 2.8 Hz, 1 H), 6.47 (dd, $J$ = 8.7, 2.8 Hz, 1 H), 5.93 (dd, $J$ = 17.4, 10.7 Hz, 1 H), 5.22-5.12 (m, 2 H), 5.24-5.15 (m, 3 H), 3.75 (d, $J$ = 9.7 Hz, 1 H), 1.27 (t, $J$ = 7.1 Hz, 3 H), 1.20 (s, 3 H), 1.17 (s, 3 H). $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta$ = 172.2, 146.8, 142.7, 132.9, 130.7, 120.8, 114.8, 114.8, 113.3, 64.4, 61.0, 40.2, 24.9, 23.7, 14.3. HRMS (ESI): calcd. for $C_{15}H_{20}Cl_2NO_2$ $[M + H]^+$ 316.0871; found 316.0866.

**Ethyl 2-(4-methoxyphenylamino)-3,3-dimethylpent-4-enoate (112e):** Following the general procedure described above, **112e** was obtained after purification by silica gel column




chromatography (EtOAc/hexane, 15:85) as a colorless oil (80 mg, 58%); $R_f$ = 0.73 (15% EtOAc/hexane). IR (neat): $\tilde{\upsilon}$ = 3380, 2970, 1731, 1514, 1240 $cm^{-1}$. $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ = 6.77 (d, $J$ = 8.9 Hz, 2 H), 6.62 (d, $J$ = 8.9 Hz, 2 H), 5.97 (dd, $J$ = 17.4, 10.7 Hz, 1 H), 5.19-5.11 (m, 2 H), 4.16 (q, $J$ = 7.2 Hz, 2 H), 3.75 (br. s, 1 H), 3.75 (s, 3 H), 1.24 (t, $J$ = 7.2 Hz, 3 H), 1.22 (s, 3 H), 1.18 (s, 3 H). $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta$ = 173.1, 152.7, 143.5, 141.4, 115.3, 114.8, 114.0, 66.0, 60.6, 55.7, 40.1, 24.9, 23.7, 14.3. HRMS (ESI): calcd. for $C_{16}H_{24}NO_3$ $[M + H]^+$ 278.1756; found 278.1748.

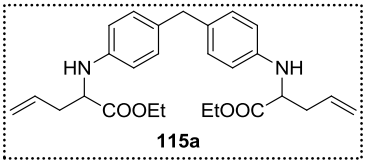
**Ethyl 2-benzamidopent-4-enoate (112f):**[105c,105d] Glycine ethyl ester hydrochloride (4 mmol) in DCM (10 mL) was cooled using an ice bath. To the cold mixture was added $NEt_3$ (4.4




mmol) with stirring. After 10 min, benzoyl chloride (4 mmol) was introduced. Then, the mixture was allowed to stir at 0 $^oC$ for 2 h and then allowed to attain the room temperature and stirring was continued for 24 h. The solvent was removed under reduced pressure and the residue was taken up in saturated aqueous $NaHCO_3$ (100 mL) with stirring. After 30 min of stirring, *N*-benzoylglycine ethyl ester precipitated. After filtration and drying, *N*-benzoylglycine ethyl ester (**113b**) was

obtained as a crystalline white powder. The compound monoallylated *N*-benzoylglycine ethyl ester (**112f**) can easily be obtained by the double deprotonation of the *N*-benzoylglycine ethyl ester (**113b**; 1 mmol) with LiHMDS (1.4 mL) in THF (5 mL) at -78 $^{o}$C, followed by treatment with allyl bromide (1.5 mmol) to selectively produce the C-alkylated product **112f**. After the completion of reaction as revealed by TLC, saturated ammonium chloride solution (2 mL) was added to the reaction mixture. Then, the reaction mixture was transferred in to a separating funnel and extracted with EtOAc (3x15 mL). The combined organic layers were dried with anhydrous $Na_2SO_4$, the solvent was evaporated under vacuum. Purification of the resulting crude reaction mixture by column chromatography on silica gel (EtOAc/hexane, 20:80) gave the product ethyl 2-(benzamido)pent-4-enoate (**112f**) as a colorless liquid (222 mg, 90%); $R_f$ = 0.46 (20% EtOAc/hexane). IR (neat): $\tilde{\upsilon}$ = 3335, 2931, 1750, 1655, 1190 cm$^{-1}$. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 7.80 (d, $J$ = 7.08 Hz, 2 H), 7.51 (t, $J$ = 7.36 Hz, 1 H), 7.44 (t, $J$ = 7.8 Hz, 2 H), 6.78 (d, $J$ = 7.0 Hz, 1 H), 5.82-5.71 (m, 1 H), 5.19-5.14 (m, 2 H), 4.88 (q, $J$ = 5.96 Hz, 1 H), 4.29-4.21 (m, 2 H), 2.77-2.71 (m, 1 H), 2.67-2.60 (m, 1 H), 1.31 (t, $J$ = 7.12 Hz, 3 H). $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ = 171.8,166.9, 134.0, 132.3, 131.7, 128.6, 127.0, 119.3, 61.6, 52.0, 36.6, 14.2. HRMS (ESI): calcd. for $C_{14}H_{18}NO_3$ $[M + H]^+$ 248.1287; found 248.1285.

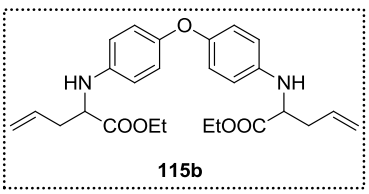
**Compound 115a:** Following the general procedure described above, **115a** was obtained after purification by silica gel column chromatography (EtOAc/hexane, 20:80) as a colorless oil



**115a**

(184 mg, 82%); $R_f$ = 0.67 (20% EtOAc/hexane). IR (neat): $\tilde{\upsilon}$ = 3387, 2982, 1738, 1518, 1216 cm$^{-1}$. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 6.99 (d, $J$ = 8.4 Hz, 4 H), 6.56 (d, $J$ = 8.4 Hz, 4 H), 5.86-5.76 (m, 2 H), 5.21-5.16 (m, 4 H), 4.21 (q, $J$ = 7.2 Hz, 4 H), 4.12 (t, $J$ = 6.0 Hz, 4 H), 3.78 (s, 2 H), 2.64-2.55 (m, 4 H), 1.27 (t, $J$ = 7.2 Hz, 6H). $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ = 173.5, 144.7, 132.9, 131.7, 129.7, 118.9, 113.7, 61.1, 56.3, 40.1, 37.1, 14.3. HRMS (ESI): calcd. for $C_{27}H_{35}N_2O_4$ $[M + H]^+$ 451.2597; found 451.2611.

**Compound 115b:** Following the general procedure described above, **115b** was obtained

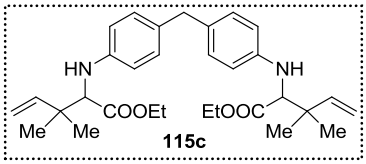


**115b**

after purification by silica gel column chromatography (EtOAc/hexane, 20:80) as a colorless oil (169 mg, 75%); $R_f$ = 0.66 (20% EtOAc/hexane). IR (neat): $\tilde{\upsilon}$ = 3383, 2981, 1731, 1504, 1230 cm$^{-1}$. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 6.83 (d, $J$ =

8.9 Hz, 4 H), 6.58 (d, *J* = 8.9 Hz, 4 H), 5.86-5.76 (m, 2 H), 5.21-5.16 (m, 4 H), 4.21 (q, *J* = 7.1 Hz, 4 H), 4.08 (t, *J* = 6.2 Hz, 2 H), 2.62-2.55 (m, 4 H), 1.27 (t, *J* = 7.1 Hz, 6H). $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ = 173.5, 150.4, 142.3, 132.8, 119.6, 118.9, 114.7, 61.1, 56.8, 37.1, 14.3. HRMS (ESI): calcd. for $C_{26}H_{33}N_2O_5$ $[M + H]^+$ 453.2389; found 453.2398.

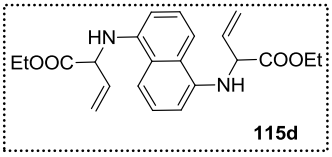
**Compound 115c:** Following the general procedure described above, **115c** was obtained after purification by silica gel column chromatography (EtOAc/hexane, 20:80) as a colorless oil



**115c**

(114mg, 45%); $R_f$ = 0.68 (20% EtOAc/hexane). IR (neat): $\tilde{\upsilon}$ = 3391, 2969,1737,1518, 1202 cm$^{-1}$. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 6.98 (d, *J* = 8.2 Hz, 4 H), 6.58 (d, *J* = 8.2 Hz, 4 H), 6.02-6.94 (m, 2 H), 5.24-5.06 (m, 4 H), 4.16 (q, *J* = 7.0 Hz, 4 H), 3.82 (s, 2 H), 1.72 (d, *J* = 12.0 Hz, 4 H), 1.26 (t, *J* = 7.0 Hz, 6H), 1.22 (s, 6H), 1.19 (s, 6H). $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ = 173.0, 145.4, 143.4, 131.7, 129.6, 114.1, 113.8, 64.9, 60.7, 40.2, 25.0, 23.7, 17.9, 14.3. HRMS (ESI): calcd. for $C_{31}H_{43}N_2O_4$ $[M + H]^+$ 507.3223; found 507.3240.

**Compound 115d:** Following the general procedure described above, **115d** was obtained after purification by silica gel column chromatography (EtOAc/hexane, 20:80) as a colorless



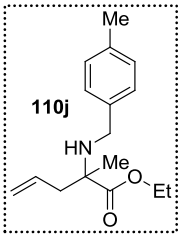
**115d**

oil (160 mg, 78%); $R_f$ = 0.69 (20% EtOAc/hexane). IR (neat): $\tilde{\upsilon}$ = 3403, 2979, 1731, 1434, 1203 cm$^{-1}$. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 7.32-7.30 (m, 6H), 6.57 (dd, *J* = 5.5, 2.7 Hz, 2 H), 5.92-5.83 (m, 2 H), 5.28-5.15 (m, 4 H), 4.99 (br. s, 2 H), 4.33-4.21 (m, 6H), 2.77-2.70 (m, 4 H), 1.28 (t, *J* = 7.1 Hz, 6H). $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ = 173.4, 142.3, 132.9, 125.4, 119.1, 110.1, 105.4, 70.0, 61.3, 56.0, 36.9, 14.3. HRMS (ESI): calcd. for $C_{24}H_{31}N_2O_4$ $[M + H]^+$ 411.2284; found 411.2304.

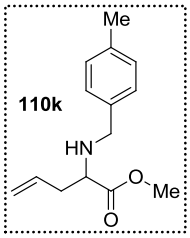
**General procedure for the preparation of *N*-protected allyl glycine esters 110j-n:**[106] To a suspension of the corresponding amino acid ester hydrochloride (1.2 mmol) and anhydrous $Na_2SO_4$ (1.3 mmol) in DCM (1.5 mL) was added $Et_3N$ (1.2 mmol). The mixture was stirred at room temperature for 1 h, then, the *p*-tolualdehyde (1.0 mmol) was added. The reaction was stirred at room temperature overnight, and then the resulting precipitate was removed by filtration. The filtrate was washed with water (2 mL), the aqueous phase was extracted with DCM (2x5 mL), and the combined organic phases were washed with brine, dried over anhydrous $Na_2SO_4$ and concentrated under reduced pressure. The resulting pure imino esters **100AA** (Table 6) were directly used in next step.

The imino ester **100AA** was dissolved in DCM (5 mL) and 10% aqueous NaOH solution (5 mL), allyl bromide (1.5 equiv), and $TBAHSO_4$ (0.1 equiv) were added to the solution. The reaction mixture was stirred at 25 $^oC$ for 5-10 h (check TLC), then transferred to a separating funnel and extracted with DCM (3x5 mL). The combined organic layers were dried with anhydrous $Na_2SO_4$, then, the solvent was evaporated under vacuum. The resulting crude product **100BB** was dissolved in respective anhydrous alcohol (10 mL) at 30 $^oC$, cooled to -30 $^oC$ and sodium borohydride (1.1 equiv) was added. The mixture was stirred for 3 h at -30 $^oC$ and then for 10 h at room temperature. To the resulting mixture, glacial acetic acid (1.1 equiv) was added drop-wise; the mixture was stirred for 1 h and filtered. The solvent was removed under reduced pressure. Purification of the resulting crude reaction mixture by column chromatography on silica gel (EtOAc/hexane) gave the product **110j-n** (see Table 6).

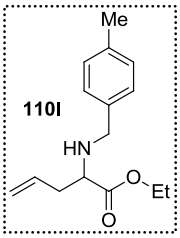
**Ethyl 2-methyl-2-((4-methylbenzyl)amino)pent-4-enoate (110j):** Following the general procedure described above, **110j** was obtained after purification by silica gel column chromatography (EtOAc/hexane, 20:80) as a colorless oil (130 mg, 50%); $R_f$ = 0.65 (20% EtOAc/hexane). IR (neat): $\tilde{\upsilon}$ = 3333, 2980, 1731, 1462, 1209 $cm^{-1}$. $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ = 7.25 (d, $J$ = 7.9 Hz, 2 H), 7.15 (d, $J$ = 7.9 Hz, 2 H), 5.86-5.76 (m, 1 H), 5.16-5.12 (m, 2 H), 4.23 (q, $J$ = 7.1 Hz, 2 H), 3.66 (d, $J$ = 11.5 Hz, 1 H), 3.59 (d, $J$ = 11.5 Hz, 1 H), 2.53-2.40 (m, 2 H), 2.35 (s, 3 H), 1.82 (br. s, 1 H), 1.38 (s, 3 H), 1.33 (t, $J$ = 7.1 Hz, 3 H). $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta$ = 176.0, 137.3, 136.6, 133.0, 129.1, 128.3, 118.7, 62.0, 60.7, 48.2, 43.5, 21.9, 21.1, 14.4. HRMS (ESI): calcd. for $C_{16}H_{24}NO_2$ $[M + H]^+$ 262.1807; found 262.1812.




**Methyl 2-( (4-methylbenzyl)amino)pent-4-enoate (110k):** Following the general procedure described above, **110k** was obtained after purification by silica gel column chromatography (EtOAc/hexane, 20:80) as a colorless oil (105 mg, 45%); $R_f$ = 0.64 (20% EtOAc/hexane). IR (neat): $\tilde{\upsilon}$ = 3331, 2951, 1738, 1435, 1197 $cm^{-1}$. $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ = 7.22 (d, $J$ = 8.0 Hz, 2 H), 7.15 (d, $J$ = 8.0 Hz, 2 H), 5.80-5.70 (m, 1 H), 5.19 (br. s, 1 H), 5.15-5.10 (m, 2 H), 3.81 (d, $J$ = 12.8 Hz, 1 H), 3.74 (s, 3 H), 3.69 (d, $J$ = 12.8 Hz, 1 H), 3.45 (t, $J$ = 6.6 Hz, 1 H), 2.47 (t, $J$ = 6.6 Hz, 2 H), 2.35 (s, 3 H). $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta$ = 174.6,136.9,135.7,133.2,129.1,128.5,118.4, 59.8, 51.8, 51.4, 37.3, 21.1. HRMS (ESI): calcd. for $C_{14}H_{20}NO_2$ $[M + H]^+$ 234.1494; found 234.1496.

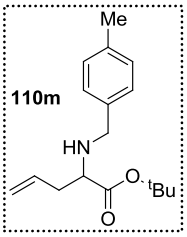


**Ethyl 2-((4-methylbenzyl )amino)pent-4-enoate (110l):** Following the general procedure described above, **110l** was obtained after purification by silica gel column chromatography



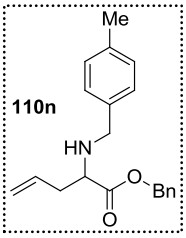

(EtOAc/hexane, 20:80) as a colorless oil (135 mg, 55%); $R_f$ = 0.64 (20% EtOAc/hexane). IR (neat): $\tilde{\upsilon}$ = 3335, 2981, 1732, 1463, 1183 $cm^{-1}$. $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ = 7.23 (d, $J$ = 8.0 Hz, 2 H), 7.15 (d, $J$ = 8.0 Hz, 2 H), 5.84-5.73 (m, 1 H), 5.15-5.08 (m, 2 H), 4.21 (q, $J$ = 7.1 Hz, 2 H), 3.82 (d, $J$ = 12.8 Hz, 1 H), 3.65 (d, $J$ = 12.8 Hz, 1 H), 3.37 (t, $J$ = 6.8 Hz, 1 H), 2.45 (t, $J$ = 6.8 Hz, 2 H), 2.36 (s, 3 H), 1.88 (br. s, 1 H),1.30 (t, $J$ = 7.1 Hz, 3 H). $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta$ = 174.6, 136.7, 136.6, 133.7, 129.1, 128.2, 118.0, 60.6, 60.1, 51.7, 37.7, 21.1, 14.4. HRMS (ESI): calcd. for $C_{15}H_{22}NO_2$ $[M + H]^+$ 248.1651; found 248.1644.

***tert*-Butyl 2-((4-methylbenzyl)amino)pent-4-enoate (110m):** Following the general procedure described above, **110m** was obtained after purification by silica gel column




chromatography (EtOAc/hexane, 20:80) as a colorless oil (105 mg, 38%); $R_f$ = 0.68 (20% EtOAc/hexane). IR (neat): $\tilde{\upsilon}$ = 3335, 2978, 1730, 1456, 1154 $cm^{-1}$. $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ = 7.24 (d, $J$ = 8.0 Hz, 2 H), 7.15 (d, $J$ = 8.0 Hz, 2 H), 5.84-5.73 (m, 1 H), 5.15-5.07 (m, 2 H), 3.81 (d, $J$ = 12.7 Hz, 1 H), 3.65 (d, $J$ = 12.7 Hz, 1 H), 3.25 (t, $J$ = 6.4 Hz, 1 H), 2.42 (t, $J$ = 6.4 Hz, 2 H), 2.35 (s, 3 H), 2.30 (br. s, 1 H), 1.50 (s, 9H). $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta$ = 173.8, 136.7, 136.6, 133.8, 129.1, 128.3, 117.8, 81.2, 60.6, 51.6, 37.8, 28.2, 21.1. HRMS (ESI): calcd. for $C_{17}H_{26}NO_2$ $[M + H]^+$ 276.1964; found 276.1963.

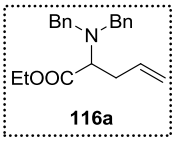
**Benzyl 2-((4-methylbenzyl)amino)pent-4-enoate (110n):** Following the general procedure described above, **110n** was obtained after purification by silica gel column chromatography




(EtOAc/hexane, 20:80) as a colorless oil (127 mg, 41%); $R_f$ = 0.70 (20% EtOAc/hexane). IR (neat): $\tilde{\upsilon}$ = 3335, 2923, 1732, 1455, 1172 $cm^{-1}$. $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ = 7.41-7.38 (m, 5 H), 7.20 (d, $J$ = 7.9 Hz, 2 H), 7.14 (d, $J$ = 7.9 Hz, 2 H), 5.81-5.70 (m, 1 H), 5.19 (d, $J$ = 1.6 Hz, 2 H), 5.12-5.06 (m, 2 H), 3.81 (d, $J$ = 12.8 Hz, 1 H), 3.64 (d, $J$ = 12.8 Hz, 1 H), 3.44 (t, $J$ = 6.5 Hz, 1 H), 2.47 (t, $J$ = 6.5 Hz, 2 H), 2.35 (s, 3 H), 1.92 (br. s, 1 H). $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta$ = 174.4, 136.7, 136.5, 135.8, 133.5, 129.1, 128.6, 128.4, 128.4, 128.3, 118.1, 66.5, 60.2, 51.6, 37.6, 21.1. HRMS (ESI): calcd. for $C_{20}H_{24}NO_2$ $[M + H]^+$ 310.1807; found 310.1813.

**General procedure for the synthesis of *N*,*N*-dibenzylated allyl glycine ethyl esters 116a and 116b:** To the amino ester **110h/112c** (0.5 mmol, 1 equiv) in MeCN (5 mL) was added benzyl bromide (3 equiv) and activated $K_2CO_3$ (3 equiv). The resulting reaction mixture was heated to reflux for 12 h. After completion of the reaction as indicated by the TLC, the reaction mixture was cooled to room temperature, water (5-6 mL) was added, and the resulting reaction mixture was transferred to a separating flask and extracted with EtOAc (3x15 mL). The combined organic layers were dried with anhydrous $Na_2SO_4$ and the solvent was evaporated under vacuum. Purification of the resulting crude reaction mixture by column chromatography on silica gel gave the respective product **116a**/**116b** (see Scheme 45).

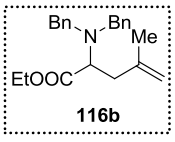
**Ethyl 2-(dibenzylamino)pent-4-enoate (116a):** Following the general procedure described above, **116a** was obtained after purification by silica gel column chromatography



**116a**

(EtOAc/hexane, 05:95) as colorless oil (129 mg, 80%); $R_f$ = 0.88 (5% EtOAc/hexane). IR (neat): $\tilde{\upsilon}$ = 2980, 1731, 1454, 1182, 746 $cm^{-1}$. $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ = 7.42 (d, $J$ = 7.4 Hz, 4 H), 7.35 (t, $J$ = 7.4 Hz, 4 H), 7.24 (t, $J$ = 7.4 Hz, 2 H), 5.82-5.72 (m, 1 H), 5.11-5.07 (m, 2 H), 4.33-4.21 (m, 2 H), 3.97 (d, $J$ = 13.8 Hz, 2 H), 3.59 (d, $J$ = 13.8 Hz, 2 H), 3.46 (t, $J$ = 7.6 Hz, 1 H), 2.56 (t, $J$ = 7.6 Hz, 2 H),1.38 (t, $J$ = 7.1 Hz, 3 H). $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta$ = 172.4, 139.6, 135.1, 128.9, 128.2, 127.0, 116.9, 60.7, 60.2, 54.5, 34.1, 14.6. HRMS (ESI): calcd. for $C_{21}H_{26}NO_2$ $[M + H]^+$ 324.1964; found 324.1963.

**Ethyl 2-(dibenzylamino)-4-methylpent-4-enoate (116b):** Following the general procedure described above, **116b** was obtained after purification by silica gel column chromatography



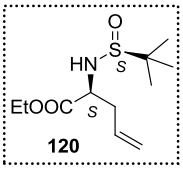
**116b**

(EtOAc/hexane, 05:95) as a colorless oil (143 mg, 85%); $R_f$ = 0.90 (5% EtOAc/hexane). IR (neat): $\tilde{\upsilon}$ = 2979, 1731, 1454, 1172, 747 $cm^{-1}$. $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ = 7.40 (d, $J$ = 7.2 Hz, 4 H), 7.33 (t, $J$ = 7.2 Hz, 4 H), 7.26 (t, $J$ = 7.2 Hz, 2 H), 4.81 (s, 1 H), 4.71 (s, 1 H), 4.32-4.20 (m, 2 H), 3.96 (d, $J$ = 13.7 Hz, 2 H), 3.56-3.52 (m, 3 H), 2.51 (d, $J$ = 7.6 Hz, 2 H), 1.52 (s, 3 H), 1.38 (t, $J$ = 7.1 Hz, 3 H). $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta$ = 172.6, 141.9, 139.6, 129.0, 128.1, 127.0, 113.0, 60.1, 58.9, 54.4, 38.1, 21.7, 14.6. HRMS (ESI): calcd. for $C_{22}H_{28}NO_2$ $[M + H]^+$ 338.2120; found 338.2125.

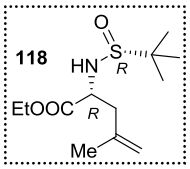
**General procedure for the preparation of *N*-protected allyl glycine esters 117, 118, 120 and 121:**[41b] To a suspension of indium powder (115 mg, 1 mmol) and (*R*)-*N*-*tert*-butanesulfinyl imine or (*S*)-*N*-*tert*-butanesulfinyl imine (**100t** or **100u**) (0.25 mmol) in saturated aqueous NaBr solution (5 mL) was added allyl bromide/2-methyl allyl bromide (1 mmol) at room temperature. The resultant mixture was then stirred at room temperature for 12 h. The reaction was quenched with 10-20 mL of saturated aqueous $NaHCO_3$, extracted with ethyl acetate, dried over anhydrous $Na_2SO_4$. After concentration, the residue was purified by flash column chromatography to afford the desired allylation products **117**, **118**, **120** and **121** (see Scheme 45).

Compound **117** is known in the literature[41b] and its characterization data matches with that of reported data.

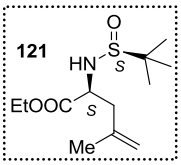
**(*S*)-Ethyl 2-((*S*)-1,1-dimethylethylsulfinamido)pent-4-enoate (120):** Following the general procedure described above, **120** was obtained after purification by silica gel column chromatography (EtOAc/hexane, 40:60) as a colorless oil (34 mg, 55%); $R_f$ = 0.35 (40% EtOAc/hexane). IR (neat): $\tilde{\upsilon}$ = 3284, 2982, 1738, 1366, 1216 $cm^{-1}$. $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ = 5.78-5.68 (m, 1 H), 5.15-5.10 (m, 2 H), 4.23 (q, $J$ = 7.2 Hz, 2 H), 4.16 (d, $J$ = 6.6 Hz, 1 H), 4.04 (q, $J$ = 6.6 Hz, 1 H), 2.57-2.50 (m, 2 H), 1.30 (t, $J$ = 7.2 Hz, 3 H), 1.25 (s, 9H). $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta$ = 172.5, 132.4, 118.8, 61.8, 56.9, 56.1, 38.1, 22.6, 14.2. HRMS (ESI): calcd. for $C_{11}H_{22}NO_3S$ $[M + H]^+$ 248.1320; found 248.1317.




**(*R*)-Ethyl 2-((*R*)-1,1-dimethylethylsulfinamido)-4-methylpent-4-enoate (118):** Following the general procedure described above, **118** was obtained after purification by silica gel column chromatography (EtOAc/hexane, 40:60) as a colorless oil (40 mg, 61%); $R_f$ = 0.37 (40% EtOAc/hexane). IR (neat): $\tilde{\upsilon}$ = 3281, 2969, 1738, 1367, 1205 $cm^{-1}$. $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ = 4.85 (br. s, 1 H), 4.76 (br. s, 1 H), 4.23 (q, $J$ = 7.2 Hz, 2 H), 4.10-4.03 (m, 2 H), 2.51 (dd, $J$ = 14.3, 5.4 Hz, 1 H), 2.40 (dd, $J$ = 14.3, 7.6 Hz, 1 H), 1.76 (s, 3 H), 1.30 (t, $J$ = 7.2 Hz, 3 H), 1.24 (s, 9H). $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta$ = 173.2, 140.3, 114.6, 61.7, 56.2, 42.5, 22.6, 22.1, 14.1. HRMS (ESI): calcd. for $C_{12}H_{24}NO_3S$ $[M + H]^+$ 262.1477; found 262.1479.

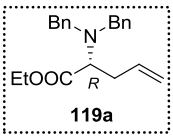


**(*S*)-Ethyl 2-((*S*)-1,1-dimethylethylsulfinamido)-4-methylpent-4-enoate (121):** Following the general procedure described above, **121** was obtained after purification by silica gel column chromatography (EtOAc/hexane, 40:60) as a colorless oil (36 mg, 55%); $R_f$ = 0.37 (40% EtOAc/hexane). IR (neat): $\tilde{\upsilon}$ = 3280, 2969, 1738, 1366, 1216 $cm^{-1}$. $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ = 4.85 (br. s, 1 H), 4.77 (br. s, 1 H), 4.24 (q, *J* = 7.1 Hz, 2 H), 4.11-4.04 (m, 2 H), 2.51 (dd, *J* = 14.3, 5.4 Hz, 1 H), 2.40 (dd, *J* = 14.3, 7.2 Hz, 1 H), 1.77 (s, 3 H), 1.31 (t, *J* = 7.1 Hz, 3 H), 1.25 (s, 9H). $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta$ = 173.2, 140.3, 114.6, 61.7, 56.2, 42.5, 22.7, 22.6, 14.1. HRMS (ESI): calcd. for $C_{12}H_{24}NO_3S$ $[M + H]^+$ 262.1477; found 262.1473.



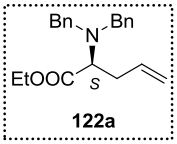

**General procedure for the synthesis of chiral *N*,*N*-dibenzylated allyl glycine ethyl esters 119a, 119b, 122a and 122b:** The corresponding compound **118a**/**118b**/**121a**/**121b** (0.5 mmol) was dissolved in EtOH (5 mL) and dry HCl was bubbled into the solution for 5 h. Then the solvent was removed under vacuum to afford the free amine hydrochloride salt (0.5 mmol, 1 equiv) to which MeCN (5 mL) was added followed by benzyl bromide (3 equiv) and activated $K_2CO_3$ (3 equiv). The resulting reaction mixture was heated to reflux for 12 h. After completion of the reaction as indicated by the TLC, the reaction mixture was cooled to room temperature, water (5-6 mL) was added, and the resulting reaction mixture was transferred to a separating flask and extracted with EtOAc (3x15 mL). The combined organic layers were dried with anhydrous $Na_2SO_4$ and the solvent was evaporated under vacuum. Purification of the resulting crude reaction mixture by column chromatography on silica gel gave the products **119a**, **119b**, **122a** and **122b**, respectively (see Scheme 45).

**(*R*)-Ethyl 2-(dibenzylamino)pent-4-enoate (119a):** Following the general procedure described above, **119a** was obtained after purification by silica gel column chromatography (EtOAc/hexane, 05:95) as a colorless oil (98 mg, 61%); $R_f$ = 0.88 (5% EtOAc/hexane). $[\alpha]_D^{24}$ = +67.7 (c 0.2, DCM). IR (neat): $\tilde{\upsilon}$ = 2979, 1730, 1369, 1182, 746 $cm^{-1}$. $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ = 7.42 (d, *J* = 7.4 Hz, 4 H), 7.35 (t, *J* = 7.4 Hz, 4 H), 7.27 (t, *J* = 7.4 Hz, 2 H), 5.82-5.72 (m, 1 H), 5.12-5.07 (m, 2 H), 4.33-4.21 (m, 2 H), 3.98 (d, *J* = 13.8 Hz, 2 H), 3.59 (d, *J* = 13.8 Hz, 2 H), 3.46 (t, *J* = 7.6 Hz, 1 H), 2.58-2.54 (m, 2 H), 1.38 (t, *J* = 7.1 Hz, 3 H). $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta$ = 172.3,



139.6, 135.1, 128.9, 128.2, 127.0, 116.9, 60.7, 60.2, 54.5, 34.1, 14.6. HRMS (ESI): calcd. for $C_{21}H_{26}NO_2$ $[M + H]^+$ 324.1964; found 324.1976.

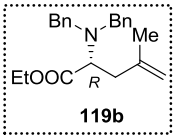
**(*S*)-Ethyl 2-(dibenzylamino)pent-4-enoate (122a):** Following the general procedure described above, **122a** was obtained after purification by silica gel column chromatography



122a

(EtOAc/hexane, 05:95) as a colorless oil (105 mg, 65%); $R_f$ = 0.88 (5% EtOAc/hexane). $[\alpha]_D^{23}$ = –66.2 (c 0.2, DCM). IR (neat): $\tilde{\upsilon}$ = 2979, 1729, 1453, 1182, 746 $cm^{-1}$. $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ = 7.45 (d, $J$ = 7.6 Hz, 4 H), 7.37 (t, $J$ = 7.3 Hz, 4 H), 7.29 (t, $J$ = 7.3 Hz, 2 H), 5.84-5.74 (m, 1 H), 5.14-5.09 (m, 2 H), 4.35-4.23 (m, 2 H), 3.40 (d, $J$ = 13.9 Hz, 2 H), 3.62 (d, $J$ = 13.9 Hz, 2 H), 3.49 (t, $J$ = 7.9 Hz, 1 H), 2.62-2.55 (m, 2 H), 1.40 (t, $J$ = 7.1 Hz, 3 H). $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta$ = 172.3, 139.6, 135.1, 128.9, 128.2, 127.0, 116.9, 60.7, 60.2, 54.5, 34.1, 14.7. HRMS (ESI): calcd. for $C_{21}H_{26}NO_2$ $[M + H]^+$ 324.1964; found 324.1953.

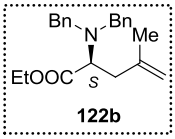
**(*R*)-Ethyl 2-(dibenzylamino)-4-methylpent-4-enoate (119b):** Following the general procedure described above, **119b** was obtained after purification by silica gel column



119b

chromatography (EtOAc/hexane, 04:96) as a colorless oil (145 mg, 86%); $R_f$ = 0.90 (4% EtOAc/hexane). $[\alpha]_D^{24}$ = +65.0 (c 0.2, DCM). IR (neat): $\tilde{\upsilon}$ = 2979, 1731, 1454, 1172, 747 $cm^{-1}$. $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ = 7.43 (d, $J$ = 7.4 Hz, 4 H), 7.36 (t, $J$ = 7.4 Hz, 4 H), 7.28 (t, $J$ = 6.6 Hz, 2 H), 4.84 (s, 1 H), 4.75 (s, 1 H), 4.35-4.23 (m, 2 H), 4.00 (d, $J$ = 13.7 Hz, 2 H), 3.59-3.56 (m, 3 H), 2.54 (d, $J$ = 7.5 Hz, 2 H), 1.55 (s, 3 H), 1.40 (t, $J$ = 7.2 Hz, 3 H). $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta$ = 172.6, 141.9, 139.7, 129.1, 128.2, 127.0, 113.1, 60.1, 58.9, 54.4, 38.1, 21.8, 14.7. HRMS (ESI): calcd. for $C_{22}H_{28}NO_2$ $[M + H]^+$ 338.2120; found 338.2120.

**(*S*)-Ethyl 2-(dibenzylamino)-4-methylpent-4-enoate (122b):** Following the general procedure described above, **122b** was obtained after purification by silica gel column



122b

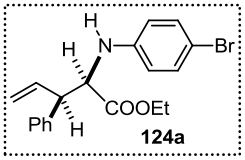
chromatography (EtOAc/hexane, 04:96) as a colorless oil (126 mg, 75%); $R_f$ = 0.90 (4% EtOAc/hexane). $[\alpha]_D^{24}$ = –66.0 (c 0.2, DCM). IR (neat): $\tilde{\upsilon}$ = 2979, 1731, 1454, 1172, 747 $cm^{-1}$. $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ = 7.40 (d, $J$ = 7.1 Hz, 4 H), 7.33 (t, $J$ = 7.1 Hz, 4 H), 7.26 (t, $J$ = 7.1 Hz, 2 H), 4.81 (s, 1 H), 4.72 (s, 1 H), 4.32-4.20 (m, 2 H), 3.96 (d, $J$ = 13.8 Hz, 2 H), 3.58-3.52 (m, 3 H), 2.51 (d, $J$ = 7.6 Hz, 2 H), 1.52 (s, 3 H), 1.38 (t, $J$ = 7.1 Hz, 3 H). $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta$ = 172.6, 141.9,

139.6, 129.0, 128.1, 127.0, 113.0, 60.1, 58.9, 54.4, 38.1, 21.7, 14.6. HRMS (ESI): calcd. for $C_{22}H_{28}NO_2$ $[M + H]^+$ 338.2120; found 338.2121.

**Procedure A. Indium-mediated addition of cinnamyl bromide (123a) to α-imino esters 100:** To a vigorously stirring solution of α-imino ester **100** (0.5 mmol, 1 equiv) and *E*-cinnamyl bromide (**123a**; 1.25 mmol, 2.5 equiv) in THF (3 mL) and $H_2O$ (3 mL), was added indium powder (0.75 mmol, 1.5 equiv). The mixture was stirred vigorously for 12 h at room temperature, then transferred to a separating funnel and extracted with EtOAc (3x15 mL). The combined organic layers were dried with anhydrous $Na_2SO_4$, then the solvent was evaporated under vacuum. Purification of the resulting crude reaction mixture by column chromatography on neutral alumina or silica gel (EtOAc/hexane) gave the product **124** (see Tables 7 and 8 and Scheme 47 for individual entries).

**Procedure B. One-pot synthesis of *N*-aryl α-amino esters (124a**, **124c**, **124e and 124g):** Ethyl glyoxylate **98** (0.6 mmol, 1.2 equiv) and the respective amine **99a**,**c**,**e**,**g** (0.5 mmol, 1 equiv) were dissolved in THF (2 mL) and stirred for 15 min at room temperature. To the resulting solution, *E*-cinnamyl bromide (**123a**; 1.25 mmol, 2.5 equiv), THF (1 mL) and $H_2O$ (3 mL) were added. Indium powder (0.75 mmol, 1.5 equiv) was added while stirring the reaction mixture vigorously, and stirring was continued for 12 h at room temperature. After this period, the reaction mixture was transferred to a separating funnel and extracted with EtOAc (3x15 mL). The combined organic layers were dried with anhydrous $Na_2SO_4$, then the solvent was evaporated under vacuum. Purification of the resulting crude reaction mixture by column chromatography on neutral alumina (EtOAc/hexane) gave the products **124a**, **124c**, **124e** and **124g** (see Scheme 48).

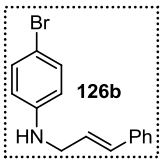
**(2*R**,3*R**)-Ethyl 2-[(4-bromophenyl)amino]-3-phenylpent-4-enoate (124a):** Following the general procedure A as described above, **124a** was obtained after purification by neutral alumina column chromatography (EtOAc/hexane, 2:98) as a colorless solid (123 mg, 66%); mp 89-91 °C (Hexane/EtOAc). $R_f$ = 0.41 (2% EtOAc/hexane). IR (KBr): $\tilde{\upsilon}$ = 3363, 2958, 1725, 1594, 1181, 700 $cm^{-1}$. $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ = 7.32 (t, $J$ = 6.9 Hz, 2 H), 7.26–7.19 (m, 5 H), 6.46 (d, $J$ = 8.8 Hz, 2 H), 6.18–6.09 (m, 1 H), 5.22–5.17 (m, 2 H), 4.29 (t, $J$ = 8.4 Hz, 1 H), 4.14–4.06 (m, 2 H), 4.02 (d, $J$ = 8.4 Hz, 1 H), 3.78 (t, $J$ = 8.4 Hz, 1 H), 1.17 (t, $J$ = 7.1 Hz, 3 H). $^{13}C$



124a

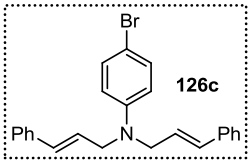
NMR (100 MHz, $CDCl_3$): $\delta$ = 172.4, 145.8, 139.1, 136.6, 132.0, 128.8, 128.0, 127.3, 118.0, 115.4, 110.3, 61.2, 61.1, 53.0, 14.2. HRMS (ESI): calcd. for $C_{19}H_{20}BrNO_2Na$ $[M + Na]^+$ 396.0575; found 396.0570.

**4-Bromo-*N*-cinnamylaniline (126b):**[107c-e] The compound **126b** was obtained after column chromatography (EtOAc/hexane, 1:99) as a colorless solid (17 mg, 12%); mp 75–77 °C. $R_f$ = 0.51 (1% EtOAc/hexane). IR (KBr): $\tilde{\upsilon}$ = 3401, 2926, 1591, 1492, 969, 746 $cm^{-1}$. $^1H$ NMR



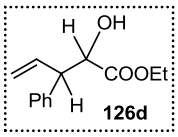

(400 MHz, $CDCl_3$): $\delta$ = 7.36–7.21 (m, 7 H), 6.59 (d, $J$ = 15.9 Hz, 1 H), 6.52 (d, $J$ = 8.8 Hz, 2 H), 6.27 (td, $J$ = 15.9, 4.4 Hz, 1 H), 3.89 (d, $J$ = 4.4 Hz, 3 H). $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta$ = 147.0, 136.7, 132.0, 131.7, 128.6, 127.7, 126.4, 126.3, 114.6, 109.2, 46.1. MS (CI): $m/z$ (%) = 288 (100) $[M + 1]^+$, 286 (90), 210 (10), 208 (13).

**4-Bromo-*N*,*N*-dicinnamylaniline (126c):**[107c] The compound **126c** was obtained after column chromatography (EtOAc/hexane, 0.5:99.5) as a colorless solid (11 mg, 5%); mp 96–




98 °C. $R_f$ = 0.61 (0.5% EtOAc/hexane). IR (KBr): $\tilde{\upsilon}$ = 2923, 1588, 1494, 967, 732 $cm^{-1}$. $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ = 7.34–7.19 (m, 12 H), 6.65 (d, $J$ = 9.0 Hz, 2 H), 6.49 (d, $J$ = 15.9 Hz, 2 H), 6.21 (td, $J$ = 15.9, 5.0 Hz, 2 H), 4.08 (d, $J$ = 5.0 Hz, 4 H). $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta$ = 147.8, 136.7, 131.9, 131.4, 128.6, 127.6, 126.4, 125.2, 114.3, 108.5, 52.4. MS (CI): $m/z$ (%) = 406 (85) $[M + 3]^+$, 404 (100) $[M + 1]^+$.

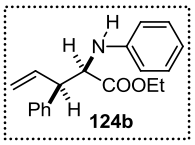
**Ethyl 2-hydroxy-3-phenylpent-4-enoate (126d):**[107f] The compound **126d** was obtained after column chromatography (EtOAc/hexane, 4:96) as a colorless liquid (9 mg, 8%); $R_f$ =




0.31 (4% EtOAc/hexane). IR (neat): $\tilde{\upsilon}$ = 3459, 2979, 1731, 1494, 1257 $cm^{-1}$. $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ = 7.33-7.22 (m, 5 H), 6.26-6.17 (m, 1 H), 5.22 (d, $J$ = 7.5 Hz, 1 H), 5.19 (s, 1 H), 4.50 (d, $J$ = 4.1 Hz, 1 H), 4.13 (q, $J$ = 7.1 Hz, 2 H), 3.77 (dd, $J$ = 7.5, 4.1 Hz, 1 H), 2.69 (s, 1 H), 1.21 (t, $J$ = 7.1 Hz, 3 H). $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta$ = 173.3, 138.3, 137.4, 128.8, 128.4, 127.3, 117.0, 74.0, 61.7, 53.4, 14.2. MS (CI): $m/z$ (%) = 221 (35) $[M + 1]^+$, 203 (60), 175 (35), 157 (37). This compound was isolated as a mixture of diastereomers; the NMR data refer to the major isomer.

**(2*R**,3*R**)-Ethyl 3-phenyl-2-(phenylamino)pent-4-enoate (124b):** Following the general procedure A as described above, **124b** was obtained after purification by neutral alumina column chromatography (EtOAc/hexane, 2:98) as a colorless oil (105 mg, 71%); $R_f$ = 0.45

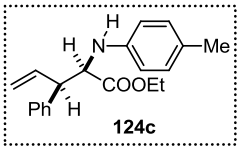
(2% EtOAc/hexane). IR ($CH_2Cl_2$): $\tilde{\upsilon}$ = 3388, 2980, 1734, 1602, 1506, 1181 $cm^{-1}$. $^1H$ NMR



**124b**

(400 MHz, $CDCl_3$): $\delta$ = 7.31 (t, $J$ = 6.5 Hz, 2 H), 7.23 (d, $J$ = 6.5 Hz, 3 H), 7.12 (t, $J$ = 7.5 Hz, 2 H), 6.71 (t, $J$ = 7.5 Hz, 1 H), 6.59 (d, $J$ = 7.5 Hz, 2 H), 6.20–6.11 (m, 1 H), 5.22–5.16 (m, 2 H), 4.34 (t, $J$ = 8.5 Hz, 1 H), 4.14–4.05 (m, 2 H), 4.0 (d, $J$ = 8.5 Hz, 1 H), 3.79 (t, $J$ = 8.5 Hz, 1 H), 1.16 (t, $J$ = 7.1 Hz, 3 H). $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta$ = 172.7, 146.7, 139.4, 136.9, 129.3, 128.8, 128.0, 127.3, 118.6, 117.8, 113.8, 61.3, 61.0, 53.2, 14.2. MS (CI): $m/z$ (%) = 296 (5) $[M + 1]^+$, 223 (20), 222 (100), 180 (20), 178 (22), 104 (80). HRMS (ESI): calcd. for $C_{19}H_{21}NO_2Na$ $[M + Na]^+$ 318.1470; found 318.1460.

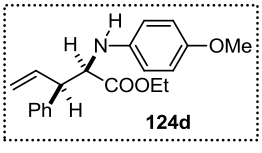
**(2*R**,3*R**)-Ethyl 3-phenyl-2-(*p*-tolylamino)pent-4-enoate (124c):** Following the general procedure A as described above, **124c** was obtained after purification by neutral alumina



**124c**

column chromatography (EtOAc/hexane, 2:98) as a colorless solid (100 mg, 65%); mp 67–69 °C. $R_f$ = 0.47 (2% EtOAc/hexane). IR (KBr): $\tilde{\upsilon}$ = 3359, 2911, 1724, 1619, 1524, 1181 $cm^{-1}$. $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ = 7.30 (t, $J$ = 7.6 Hz, 2 H), 7.23 (d, $J$ = 7.6 Hz, 3 H), 6.93 (d, $J$ = 8.4 Hz, 2 H), 6.51 (d, $J$ = 8.4 Hz, 2 H), 6.19–6.10 (m, 1 H), 5.22–5.15 (m, 2 H), 4.30 (d, $J$ = 7.2 Hz, 1 H), 4.12–4.04 (m, 2 H), 3.88 (s, 1 H), 3.77 (t, $J$ = 7.2 Hz, 1 H), 2.19 (s, 3 H), 1.15 (t, $J$ = 7.1 Hz, 3 H). $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta$ = 173.0, 144.5, 139.5, 137.0, 129.8, 128.8, 128.0, 127.8, 127.2, 117.8, 114.0, 61.7, 60.9, 53.2, 20.4, 14.2. MS (CI): $m/z$ (%) = 310 (5) $[M + 1]^+$, 237 (22), 236 (100), 220 (12), 192 (22), 118 (88). HRMS (ESI): calcd. for $C_{20}H_{23}NO_2Na$ $[M + Na]^+$ 332.1626; found 332.1626.

**(2*R**,3*R**)-Ethyl 2-[(4-methoxyphenyl)amino]-3-phenylpent-4-enoate (124d):** Following the general procedure A as described above, **124d** was obtained after purification by neutral

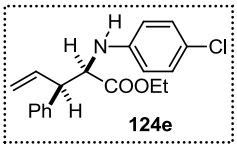


**124d**

alumina column chromatography (EtOAc/hexane, 3:97) as a colorless solid (98 mg, 60%); mp 74–76 °C (Hexane/EtOAc). $R_f$ = 0.46 (3% EtOAc/hexane). IR (KBr): $\tilde{\upsilon}$ = 3361, 2955, 1727, 1520, 1238, 1187 $cm^{-1}$. $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ = 7.29 (t, $J$ = 8.0 Hz, 2 H), 7.22 (d, $J$ = 8.0 Hz, 3 H), 6.70 (d, $J$ = 8.9 Hz, 2 H), 6.54 (d, $J$ = 8.9 Hz, 2 H), 6.16–6.10 (m, 1 H), 5.20–5.14 (m, 2 H), 4.24 (d, $J$ = 7.3 Hz, 1 H), 4.10–4.04 (m, 2 H), 3.77–3.71 (m, 1 H), 3.68 (s, 3 H), 3.38 (s, 1 H), 1.14 (t, $J$ = 7.1 Hz, 3 H). $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta$ = 173.0, 152.9, 140.9, 139.6, 137.0, 128.7, 128.0, 127.2, 117.7, 115.5, 114.8, 62.6, 60.9, 55.7, 53.2, 14.2. MS (CI): $m/z$ (%) = 326

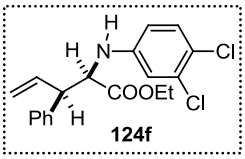
(10) $[M + 1]^+$, 253 (22), 252 (98), 208 (20), 134 (100), 122 (30). HRMS (ESI): calcd. for $C_{20}H_{23}NO_3Na$ $[M + Na]^+$ 348.1576; found 348.1568.

**(2*R**,3*R**)-Ethyl 2-[(4-chlorophenyl)amino]-3-phenylpent-4-enoate (124e):** Following the general procedure A as described above, **124e** was obtained after purification by neutral alumina column chromatography (EtOAc/hexane, 2:98) as a colorless solid (107 mg, 65%); mp 86–87 °C (Hexane/EtOAc). $R_f$ = 0.48 (2% EtOAc/hexane). IR (KBr): $\tilde{\upsilon}$ = 3364, 2960, 1726, 1602, 1516, 1180, 820 $cm^{-1}$. $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ = 7.34–7.31 (m, 2 H), 7.30–7.22 (m, 3 H), 7.07 (d, $J$ = 8.9 Hz, 2 H), 6.51 (d, $J$ = 8.9 Hz, 2 H), 6.18–6.09 (m, 1 H), 5.23–5.18 (m, 2 H), 4.31–4.27 (m, 1 H), 4.14–4.07 (m, 2 H), 4.0 (d, $J$ = 8.5 Hz, 1 H), 3.79 (d, $J$ = 8.5 Hz, 1 H), 1.17 (t, $J$ = 7.1 Hz, 3 H). $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta$ = 172.4, 145.3, 139.1, 136.7, 129.1, 128.8, 128.0, 127.4, 123.2, 118.0, 114.9, 61.4, 61.1, 53.1, 14.2. MS (CI): *m*/*z* (%) = 330 (3) $[M + 1]^+$, 258 (30), 257 (15), 256 (100), 140 (50), 138 (100). HRMS (ESI): calcd. for $C_{19}H_{20}ClNO_2Na$ $[M + Na]^+$ 352.1080; found 352.1072.



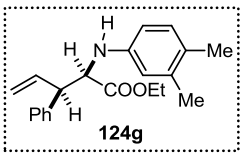
**124e**

**(2*R**,3*R**)-Ethyl 2-[(3,4-dichlorophenyl)amino]-3-phenylpent-4-enoate (124f):** Following the general procedure A as described above, **124f** was obtained after purification by neutral alumina column chromatography (EtOAc/hexane, 2:98) as a colorless solid (104 mg, 57%); mp 70–72 °C. $R_f$ = 0.48 (2% EtOAc/hexane). IR (KBr): $\tilde{\upsilon}$ = 3358, 2909, 1726, 1598, 1476, 1188, 701 $cm^{-1}$. $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ = 7.33–7.26 (m, 2 H), 7.25–7.18 (m, 3 H), 7.12 (d, $J$ = 8.7 Hz, 1 H), 6.64 (d, $J$ = 2.7 Hz, 1 H), 6.39 (dd, $J$ = 8.7, 2.7 Hz, 1 H), 6.15–6.06 (m, 1 H), 5.22–5.17 (m, 2 H), 4.26–4.22 (m, 1 H), 4.15–4.03 (m, 3 H), 3.76 (t, $J$ = 8.3 Hz, 1 H), 1.17 (t, $J$ = 7.1 Hz, 3 H). $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta$ = 172.1, 146.2, 138.8, 136.4, 132.8, 130.6, 129.0, 127.9, 127.5, 121.1, 118.2, 114.9, 113.3, 61.3, 61.0, 53.0, 14.2. MS (CI): *m*/*z* (%) = 366 (65) $[M + 3]^+$, 365 (25) $[M + 2]^+$, 364 (100) $[M + 1]^+$, 292 (45), 290 (70), 246 (15). HRMS (ESI): calcd. for $C_{19}H_{19}Cl_2NO_2Na$ $[M + Na]^+$ 386.0691; found 386.0685.



**124f**

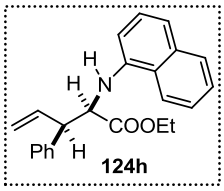
**(2*R**,3*R**)-Ethyl 2-[(3,4-dimethylphenyl)amino]-3-phenylpent-4-enoate (124g):** Following the general procedure A as described above, **124g** was obtained after purification by neutral alumina column chromatography (EtOAc/hexane, 2:98) as a colorless solid (113 mg, 70%); mp 68–70 °C. $R_f$ = 0.49 (2% EtOAc/hexane). IR (KBr): $\tilde{\upsilon}$ = 3353, 2919, 1722, 1617, 1518, 1320,



**124g**

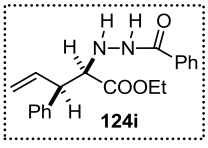
1185 $cm^{-1}$. $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ = 7.30 (t, $J$ = 8.4 Hz, 2 H), 7.24–7.20 (m, 3 H), 6.88 (d, $J$ = 8.0 Hz, 1 H), 6.41 (s, 1 H), 6.36 (d, $J$ = 8.0 Hz, 1 H), 6.19–6.10 (m, 1 H), 5.21–5.15 (m, 2 H), 4.30 (d, $J$ = 8.0 Hz, 1 H), 4.14–4.04 (m, 2 H), 3.84 (s, 1 H), 3.77 (t, $J$ = 8.0 Hz, 1 H), 2.13 (s, 3 H), 2.10 (s, 3 H), 1.16 (t, $J$ = 7.1 Hz, 3 H). $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta$ = 172.9, 144.8, 139.5, 137.3, 137.0, 130.3, 128.7, 128.0, 127.2, 126.6, 117.7, 115.7, 111.1, 61.5, 60.9, 53.2, 20.0, 18.7, 14.2. MS (CI): $m/z$ (%) = 324 (5) $[M + 1]^+$, 323 (5) $[M]^+$, 250 (5), 206 (100), 132 (80), 105 (20). HRMS (ESI): calcd. for $C_{21}H_{25}NO_2Na$ $[M + Na]^+$ 346.1782; found 346.1769.

**(2*R**,3*R**)-Ethyl 2-(naphthalen-1-ylamino)-3-phenylpent-4-enoate (124h):** Following the general procedure A as described above, **124h** was obtained after purification by neutral alumina column chromatography (EtOAc/hexane, 1:99) as a brown solid (86 mg, 50%); mp 77–79 °C. $R_f$ = 0.50 (1% EtOAc/hexane). IR (KBr): $\tilde{\upsilon}$ = 3419, 2979, 1732, 1582, 1528, 1483, 1179 $cm^{-1}$. $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ = 7.74 (d, $J$ = 7.6 Hz, 1 H), 7.64 (d, $J$ = 7.6 Hz, 1 H), 7.43–7.23 (m, 9 H), 6.61 (d, $J$ = 7.6 Hz, 1 H), 6.30–6.21 (m, 1 H), 5.30–5.23 (m, 2 H), 4.75 (d, $J$ = 7.6 Hz, 1 H), 4.50 (t, $J$ = 7.6 Hz, 1 H), 4.19–4.06 (m, 2 H), 3.96 (t, $J$ = 7.6 Hz, 1 H), 1.16 (t, $J$ = 7.1 Hz, 3 H). $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta$ = 172.8, 142.0, 139.4, 136.7, 134.3, 128.9, 128.6, 128.0, 127.4, 126.3, 125.8, 124.9, 123.8, 120.0, 118.6, 118.1, 105.6, 61.1, 61.1, 53.3, 14.2. MS (CI): $m/z$ (%) = 347 (25) $[M + 2]^+$, 346 (100) $[M + 1]^+$, 272 (65), 228 (15), 143 (10). HRMS (ESI): calcd. for $C_{23}H_{23}NO_2Na$ $[M + Na]^+$ 368.1626; found 368.1620.



**124h**

**(2*R**,3*R**)-Ethyl 2-(2-benzoylhydrazinyl)-3-phenylpent-4-enoate (124i):** Following the general procedure A as described above, **124i** (major, *syn* isomer) was obtained after purification by silica column chromatography (EtOAc/hexane, 18:82) as a colorless solid (120 mg, 71%); mp 105–107 °C (Hexane/EtOAc). $R_f$ = 0.48 (18% EtOAc/hexane). IR (KBr): $\tilde{\upsilon}$ = 3362, 2987, 1726, 1664, 1463, 1202 $cm^{-1}$. $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ = 7.81 (d, $J$ = 4.8 Hz, 1 H), 7.67 (d, $J$ = 7.1 Hz, 2 H), 7.50 (t, $J$ = 7.1 Hz, 1 H), 7.42–7.25 (m, 7 H), 6.12–6.03 (m, 1 H), 5.18–5.12 (m, 2 H), 4.89 (s, 1 H), 4.24–4.15 (m, 3 H), 3.74 (t, $J$ = 8.4 Hz, 1 H), 1.22 (t, $J$ = 7.1 Hz, 3 H). $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta$ = 172.0, 167.3, 138.8, 137.2, 132.5, 132.0, 128.9, 128.7, 128.4, 127.5, 126.9, 117.3, 66.8, 61.1, 51.9, 14.2. MS (CI): $m/z$ (%) = 340 (25) $[M + 2]^+$, 339 (100) $[M + 1]^+$, 290 (5), 265 (25). HRMS (ESI): calcd. for $C_{20}H_{22}N_2O_3Na$ $[M + Na]^+$ 361.1528; found

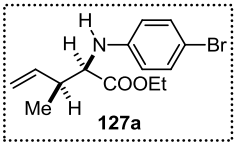


**124i**

361.1532. Only a fraction of the major isomer was obtained in the pure form, **124i** refers to the major (*syn*) isomer, which was characterized by the X-ray structure analysis. The minor isomer could not be separated from the major isomer.

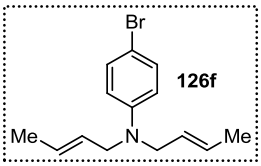
**Procedure C. Indium-mediated addition of crotyl bromide (123b) to α-imino esters 100:** To a vigorously stirring solution of α-imino ester **100** (0.5 mmol, 1 equiv) and *E*-crotyl bromide (**123b**; 1.25 mmol, 2.5 equiv) in THF (3 mL) and $H_2O$ (3 mL) was added indium powder (0.75 mmol, 1.5 equiv). The mixture was stirred vigorously for 12 h at room temperature, then transferred to a separating funnel and extracted with EtOAc (3x15 mL). The combined organic layers were dried with anhydrous $Na_2SO_4$, then the solvent was then evaporated under vacuum. Purification of the resulting crude reaction mixture by column chromatography on neutral alumina or silica gel (EtOAc/hexane) gave the product **127** (see Tables 9 and 10 and Scheme 49 for individual entries).

**(2*R**,3*S**)-Ethyl 2-[(4-bromophenyl)amino]-3-methylpent-4-enoate (127a):** Following the general procedure C as described above, **127a** was obtained after purification by neutral alumina column chromatography (EtOAc/hexane, 2:98) as a colorless liquid (95 mg, 61%); $R_f$ = 0.55 (2% EtOAc/hexane). IR (neat): $\tilde{\upsilon}$ = 3387, 2979, 1731, 1595, 1502, 1193, 674 $cm^{-1}$. $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ = 7.23 (d, $J$ = 8.8 Hz, 2 H), 6.50 (d, $J$ = 8.8 Hz, 2 H), 5.79–5.70 (m, 1 H), 5.15–5.09 (m, 2 H), 4.20–4.13 (m, 3 H), 3.93 (dd, $J$ = 9.5, 5.6 Hz, 1 H), 2.65 (q, $J$ = 6.9 Hz, 1 H), 1.24 (t, $J$ = 7.1 Hz, 3 H), 1.14 (d, $J$ = 6.9 Hz, 3 H). $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta$ = 172.5, 146.0, 138.9, 132.0, 116.7, 115.3, 110.0, 61.1, 61.0, 41.3, 16.4, 14.3. MS (CI): $m/z$ (%) = 313 (10) $[M + 2]^+$, 311 (10) $[M]^+$, 258 (100), 256 (100), 240 (10), 238 (10), 184 (75), 182 (75), 159 (10). HRMS (ESI): calcd. for $C_{14}H_{18}BrNO_2Na$ $[M + Na]^+$ 334.0419; found 334.0410.



**127a**

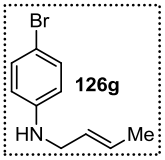
**4-Bromo-*N*,*N*-bis[but-2-en-1-yl]aniline (126f):** The compound **126f** was obtained after purification by chromatography (EtOAc/hexane, 0.5:99.5) as a colorless liquid (15 mg, 11%); $R_f$ = 0.70 (0.5% EtOAc/hexane). IR (neat): $\tilde{\upsilon}$ = 2917, 1593, 1503, 1225, 805 $cm^{-1}$. $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ = 7.24 (d, $J$ = 8.9 Hz, 2 H), 6.55 (d, $J$ = 8.9 Hz, 2 H), 5.60–5.54 (m, 2 H), 5.47–5.41 (m, 2 H), 3.79 (d, $J$ = 3.5 Hz, 4 H), 1.69 (d, $J$ = 6.2 Hz, 6 H). $^{13}C$ NMR (100 MHz,



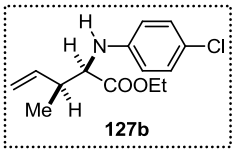
**126f**

$CDCl_3$): $\delta$ = 147.8, 131.6, 127.3, 126.3, 113.9, 107.6, 51.9, 17.7. MS (CI): *m*/*z* (%) = 281 (100) $[M + 2]^+$, 279 (100) $[M]^+$, 266 (20), 264 (20), 227 (80), 225 (80), 145 (40), 130 (50).

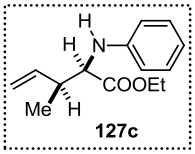
***E*-4-Bromo-*N*-(but-2-en-1-yl)aniline (126g):** The compound **126g** was obtained after purification by chromatography (EtOAc/hexane, 1:99) as a colorless liquid (6 mg, 5%); $R_f$ = 0.71 (1% EtOAc/hexane). IR (neat): $\tilde{\upsilon}$ = 3400, 2925, 1593, 1490, 807 $cm^{-1}$. $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ = 7.23 (d, *J* = 9.0 Hz, 2 H), 6.48 (d, *J* = 9.0 Hz, 2 H), 5.75–5.66 (m, 1 H), 5.59–5.51 (m, 1 H), 3.72 (s, 1 H), 3.64 (d, *J* = 5.8 Hz, 2 H), 1.70 (d, *J* = 6.3 Hz, 3 H). $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta$ = 147.2, 131.9, 128.3, 127.5, 114.5, 108.9, 45.9, 17.8. MS (CI): *m*/*z* (%) = 227 (100) $[M + 2]^+$, 225 (100) $[M]^+$, 211 (45), 209 (45), 173 (55), 171 (55), 130 (80).




**(2*R**,3*S**)-Ethyl 2-[(4-chlorophenyl)amino]-3-methylpent-4-enoate (127b):** Following the general procedure C as described above, **127b** was obtained after purification by neutral alumina column chromatography (EtOAc/hexane, 2:98) as a colorless liquid (80 mg, 60%); $R_f$ = 0.54 (2% EtOAc/hexane). IR (neat): $\tilde{\upsilon}$ = 3388, 2980, 1731, 1600, 1504, 1193, 678 $cm^{-1}$. $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ = 7.10 (d, *J* = 8.9 Hz, 2 H), 6.54 (d, *J* = 8.9 Hz, 2 H), 5.79–5.70 (m, 1 H), 5.15–5.09 (m, 2 H), 4.20–4.14 (m, 3 H), 3.93 (dd, *J* = 9.5, 5.6 Hz, 1 H), 2.65 (q, *J* = 6.9 Hz, 1 H), 1.24 (t, *J* = 7.1 Hz, 3 H), 1.15 (d, *J* = 6.9 Hz, 3 H). $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta$ = 172.6, 145.6, 138.9, 129.1, 123.0, 116.7, 114.8, 61.1, 61.0, 41.3, 16.4, 14.3. MS (CI): *m*/*z* (%) = 269 (12) $[M + 2]^+$, 268 (30) $[M + 1]^+$, 267 (17) $[M]^+$, 214 (35), 212 (100), 194 (15), 140 (25), 138 (85). HRMS (ESI): calcd. for $C_{14}H_{18}ClNO_2Na$ $[M + Na]^+$ 290.0923; found 290.0916.

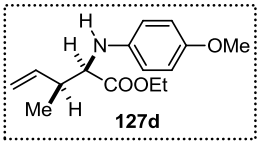



**(2*R**,3*S**)-Ethyl 3-methyl-2-(phenylamino)pent-4-enoate (127c):** Following the general procedure C as described above, **127c** was obtained after purification by neutral alumina column chromatography (EtOAc/hexane, 2:98) as a colorless liquid (63 mg, 54%); $R_f$ = 0.52 (2% EtOAc/hexane). IR ($CH_2Cl_2$): $\tilde{\upsilon}$ = 3387, 2979, 1732, 1603, 1505, 1191 $cm^{-1}$. $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ = 7.17 (t, *J* = 7.3 Hz, 2 H), 6.74 (t, *J* = 7.3 Hz, 1 H), 6.64 (d, *J* = 7.3 Hz, 2 H), 5.84–5.75 (m, 1 H), 5.17–5.10 (m, 2 H), 4.21–4.14 (m, 3 H), 4.0 (s, 1 H), 2.68 (q, *J* = 6.9 Hz, 1 H), 1.25 (t, *J* = 7.1 Hz, 3 H), 1.17 (d, *J* = 6.9 Hz, 3 H). $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta$ = 172.9, 147.0, 139.2, 129.3, 118.4, 116.4, 113.7, 61.1, 60.9, 41.4, 16.5, 14.3. MS (CI): *m*/*z* (%) = 235 (10) $[M + 2]^+$, 234 (65) [M

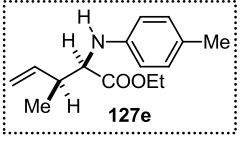


+ 1]$^+$, 178 (30), 161 (12), 160 (100). HRMS (ESI): calcd. for $C_{14}H_{19}NO_2Na$ [M + Na]$^+$ 256.1313; found 256.1301.

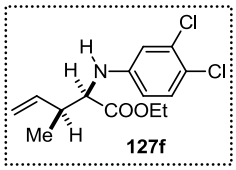
**(2*R**,3*S**)-Ethyl 2-[(4-methoxyphenyl)amino]-3-methylpent-4-enoate (127d):** Following the general procedure C as described above, **127d** was obtained after purification by neutral alumina column chromatography (EtOAc/hexane, 3:97) as a colorless liquid (78 mg, 59%); $R_f$ = 0.53 (3% EtOAc/hexane). IR (neat): $\tilde{\upsilon}$ = 3375, 2979, 1732, 1514, 1240, 1037 cm$^{-1}$. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 6.75 (d, $J$ = 8.9 Hz, 2 H), 6.60 (d, $J$ = 8.9 Hz, 2 H), 5.82–5.73 (m, 1 H), 5.15–5.08 (m, 2 H), 4.17–4.11 (m, 2 H), 3.89 (s, 2 H), 3.73 (s, 3 H), 2.64 (s, 1 H), 1.22 (t, $J$ = 7.1 Hz, 3 H), 1.15 (d, $J$ = 6.9 Hz, 3 H). $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ = 173.2, 152.8, 141.1, 139.3, 116.4, 115.4, 114.8, 62.3, 60.8, 55.7, 41.4, 16.5, 14.3. MS (CI): $m/z$ (%) = 263 (20) [M]$^+$, 208 (70), 134 (100), 77 (10). HRMS (ESI): calcd. for $C_{15}H_{21}NO_3Na$ [M + Na]$^+$ 286.1419; found 286.1410.




**(2*R**,3*S**)-Ethyl 3-methyl-2-(*p*-tolylamino)pent-4-enoate (127e):** Following the general procedure C as described above, **127e** was obtained after purification by neutral alumina column chromatography (EtOAc/hexane, 2:98) as a colorless liquid (73 mg, 59%); $R_f$ = 0.53 (2% EtOAc/hexane). IR (neat): $\tilde{\upsilon}$ = 3376, 2979, 1728, 1514, 1230, 1020 cm$^{-1}$. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 6.95 (d, $J$ = 8.0 Hz, 2 H), 6.53 (d, $J$ = 8.0 Hz, 2 H), 5.80–5.71 (m, 1 H), 5.13–5.06 (m, 2 H), 4.12 (q, $J$ = 7.1 Hz, 2 H), 4.00 (s, 1 H), 3.92 (d, $J$ = 5.4 Hz, 1 H), 2.63 (q, $J$ = 6.9 Hz, 1 H), 2.20 (s, 3 H), 1.21 (t, $J$ = 7.1 Hz, 3 H), 1.13 (d, $J$ = 6.9 Hz, 3 H). $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ = 173.0, 144.7, 139.3, 129.8, 127.6, 116.4, 113.9, 61.5, 60.8, 41.4, 20.4, 16.5, 14.3. MS (CI): $m/z$ (%) = 249 (16) [M + 2]$^+$, 248 (100) [M + 1]$^+$, 216 (55), 192 (10), 174 (6). HRMS (ESI): calcd. for $C_{15}H_{22}NO_2$ [M + H]$^+$ 248.1651; found 248.1656.

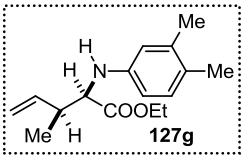



**(2*R**,3*S**)-Ethyl 2-[(3,4-dichlorophenyl)amino]-3-methylpent-4-enoate (127f):** Following the general procedure C as described above, **127f** was obtained after purification by neutral alumina column chromatography (EtOAc/hexane, 2:98) as a colorless liquid (65 mg, 49%); $R_f$ = 0.53 (2% EtOAc/hexane). IR (neat): $\tilde{\upsilon}$ = 3401, 2980, 1731, 1599, 1494, 1133, 675 cm$^{-1}$. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 7.17 (d, $J$ = 8.7 Hz, 1 H), 6.69 (d, $J$ = 2.7 Hz, 1 H), 6.45 (dd, $J$ = 8.7, 2.7 Hz, 1 H), 5.77–5.68 (m, 1 H), 5.15–5.10 (m, 2 H), 4.25 (d, $J$ = 9.4 Hz, 1 H), 4.18 (q, $J$ = 7.1 Hz, 2 H), 3.90



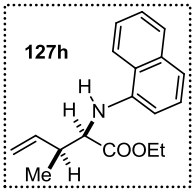
(dd, *J* = 9.4, 5.6 Hz, 1 H), 2.65 (q, *J* = 6.9 Hz, 1 H), 1.25 (t, *J* = 7.1 Hz, 3 H), 1.14 (d, *J* = 6.9 Hz, 3 H). $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ = 172.2, 146.4, 138.6, 132.8, 130.7, 120.8, 116.9, 114.8, 113.3, 61.2, 60.7, 41.2, 16.3, 14.3. MS (CI): *m*/*z* (%) = 304 (60) $[M + 3]^+$, 303 (15) $[M + 2]^+$, 302 (100) $[M + 1]^+$, 248 (15), 246 (25), 230 (30), 230 (30), 228 (45), 174 (7), 172 (11). HRMS (ESI): calcd. for $C_{14}H_{17}Cl_2NO_2Na$ $[M + Na]^+$ 324.0534; found 324.0525.

**(2*R**,3*S**)-Ethyl 2-[(3,4-dimethylphenyl)amino]-3-methylpent-4-enoate (127g):** Following the general procedure C as described above, **127g** was obtained after purification




by neutral alumina column chromatography (EtOAc/hexane, 2:98) as a colorless liquid (63 mg, 48%); $R_f$ = 0.54 (2% EtOAc/hexane). IR (neat): $\tilde{\upsilon}$ = 3384, 2978, 1732, 1619, 1512, 1191 $cm^{-1}$. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 6.90 (d, *J* = 8.0 Hz, 1 H), 6.45 (d, *J* = 2.4 Hz, 1 H), 6.38 (dd, *J* = 8.0, 2.4 Hz, 1 H), 5.81–5.72 (m, 1 H), 5.13–5.06 (m, 2 H), 4.18–4.11 (m, 2 H), 3.99–3.91 (m, 2 H), 2.63 (q, *J* = 6.9 Hz, 1 H), 2.16 (s, 3 H), 2.12 (s, 3 H), 1.23 (t, *J* = 7.1 Hz, 3 H), 1.14 (d, *J* = 6.9 Hz, 3 H). $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ = 173.1, 145.1, 139.3, 137.3, 130.3, 126.4, 116.3, 115.7, 111.1, 61.4, 60.8, 41.4, 20.0, 18.7, 16.5, 14.3. MS (CI): *m*/*z* (%) = 262 (100) $[M + 1]^+$, 206 (15), 188 (40), 132 (5). HRMS (ESI): calcd. for $C_{16}H_{23}NO_2Na$ $[M + Na]^+$ 284.1626; found 284.1618.

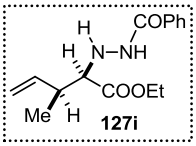
**(2*R**,3*S**)-Ethyl 3-methyl-2-(naphthalen-1-ylamino)pent-4-enoate (127h):** Following the general procedure C as described above, **127h** was obtained after purification by neutral alumina column chromatography (EtOAc/hexane, 2:98) as a brownish red solid (57 mg,




40%); mp 89–91 °C. $R_f$ = 0.61 (2% EtOAc/hexane). IR (KBr): $\tilde{\upsilon}$ = 3369, 2963, 1719, 1581, 1530, 1193 $cm^{-1}$. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 7.86 (dd, *J* = 6.0, 3.3 Hz, 1 H), 7.77 (dd, *J* = 6.0, 3.3 Hz, 1 H), 7.46–7.43 (m, 2 H), 7.31–7.24 (m, 2 H), 6.56 (d, *J* = 7.2 Hz, 1 H), 5.89–5.80 (m, 1 H), 5.24–5.15 (m, 2 H), 4.95 (d, *J* = 8.7 Hz, 1 H), 4.21–4.14 (m, 3 H), 2.82 (q, *J* = 6.9 Hz, 1 H), 1.27–1.24 (m, 6 H). $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ = 172.9, 142.1, 139.2, 134.4, 128.6, 126.4, 125.8, 124.9, 123.8, 120.1, 118.3, 116.7, 105.4, 61.0, 60.8, 41.5, 16.8, 14.3. MS (CI): *m*/*z* (%) = 284 (100) $[M + 1]^+$, 228 (15), 210 (40), 154 (5), 143 (10). HRMS (ESI): calcd. for $C_{18}H_{21}NO_2Na$ $[M + Na]^+$ 306.1470; found 306.1460.

**(2*R**,3*S**)-Ethyl 2-(2-benzoylhydrazinyl)-3-methylpent-4-enoate (127i):** Following the general procedure C as described above, **127i** was obtained after purification by silica gel

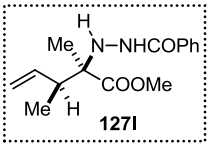
column chromatography (EtOAc/hexane, 12:88) as a colorless oil (90 mg, 65%); $R_f$ = 0.40 (12% EtOAc/hexane). IR (neat): $\tilde{\upsilon}$ = 3289, 2979, 1731, 1643, 1462, 1202 $cm^{-1}$. $^1H$ NMR



**127i**

(400 MHz, $CDCl_3$): $\delta$ = 8.08 (s, 1 H), 7.74 (d, $J$ = 7.4 Hz, 2 H), 7.51 (t, $J$ = 7.4 Hz, 1 H), 7.43 (t, $J$ = 7.4 Hz, 2 H), 6.01–5.80 (m, 1 H), 5.23–5.09 (m, 3 H), 4.29–4.17 (m, 2 H), 3.78 (d, $J$ = 4.0 Hz, 1 H), 2.80 (q, $J$ = 7.0 Hz, 1 H), 1.29 (t, $J$ = 7.1 Hz, 3 H), 1.16 (d, $J$ = 7.0 Hz, 3 H). $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta$ = 172.3, 166.9, 138.9, 132.6, 131.9, 128.7, 126.9, 116.2, 66.7, 61.0, 38.8, 14.5, 14.3. MS (CI): $m/z$ (%) = 278 (15) $[M + 2]^+$, 277 (100) $[M + 1]^+$, 259 (5), 203 (25). HRMS (ESI): calcd. for $C_{15}H_{20}N_2O_3Na$ $[M + Na]^+$ 299.1371; found 299.1365. The product was isolated as a mixture of diastereomers (*dr* 75:25). $^1H$ and $^{13}C$ NMR spectroscopic data given here refer to the major isomer of **127i**.

**(2*R**,3*S**)-Methyl 2-(2-benzoylhydrazinyl)-2,3-dimethylpent-4-enoate (127l):** Following the general procedure as described C above, **127l** was obtained as a mixture of diastereomers



**127l**

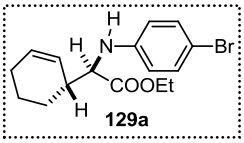
after purification by silica gel column chromatography (EtOAc/hexane, 12:88) as a colorless solid (87 mg, 63%); $R_f$ = 0.41 (12% EtOAc/hexane). IR (KBr): $\tilde{\upsilon}$ = 3283, 2950, 1731, 1644, 1450, 1260, 1130 $cm^{-1}$. $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ = 7.87 (br. s, 1 H), 7.65 (d, $J$ = 7.2 Hz, 2 H), 7.44–7.33 (m, 3 H), 5.81–5.72 (m, 1 H), 5.11–5.03 (m, 2 H), 3.67 (s, 3 H), 2.66–2.57 (m, 1 H), 1.29 (s, 3 H), 1.03 (d, $J$ = 7.0 Hz, 3 H). $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta$ = 175.3, 166.6, 137.7, 132.8, 131.7, 128.7, 126.9, 117.7, 67.8, 52.2, 44.1, 18.7, 14.9. MS (CI): $m/z$ (%) = 277 (100) $[M + 1]^+$, 246 (1). HRMS (ESI): calcd. for $C_{15}H_{20}N_2NaO_3$ $[M + Na]^+$ 299.1372; found 299.1362. $^1H$ and $^{13}C$ NMR spectroscopic data given here refer to the major diastereomer of **127l** (the NMR was recorded for the mixture of diastereomers).

**Procedure D. Indium-mediated addition of cyclohexenyl bromide (123c) to α-imino esters 100:** To a vigorously stirring solution of α-imino ester **100** (0.5 mmol, 1 equiv) and *Z*-cyclohexenyl bromide (**123c**; 1.25 mmol, 2.5 equiv) in THF (3 mL), was added indium powder (0.75 mmol, 1.5 equiv). The mixture was stirred vigorously for 12 h at room temperature under a nitrogen atmosphere. After this period, water (10 mL) was added to the reaction mixture, which was then transferred to a separating funnel and extracted with EtOAc (3x15 mL). The combined organic layers were dried with anhydrous $Na_2SO_4$ and the solvent was then evaporated under vacuum. Purification of the resulting crude reaction mixture by

column chromatography on neutral alumina (EtOAc/hexane) gave the product **129** (see Table 11 for individual entries).

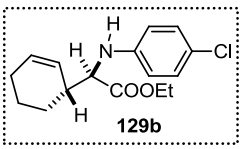
**Procedure E. One-pot synthesis of *N*-aryl α-amino esters (129a):** Ethyl glyoxylate **98** (0.5 mmol, 1.2 equiv) and the respective amine **99a** (0.5 mmol, 1 equiv) were dissolved in THF (2 mL) and stirred for 15 min at room temperature. To the resulting solution, cyclohexenyl bromide (**123c**; 1.25 mmol, 2.5 equiv) and THF (2 mL) were added. Indium powder (0.75 mmol, 1.5 equiv) was added while stirring the reaction mixture vigorously, and stirring was continued for 12 h at room temperature. After this period, the reaction mixture was transferred to a separating funnel and extracted with EtOAc (3x15 mL). The combined organic layers were dried with anhydrous $Na_2SO_4$, then the solvent was evaporated under vacuum. Purification of the resulting crude reaction mixture by column chromatography on neutral alumina (EtOAc/hexane) gave the products **129a** (see Scheme 50).

**(*R**)-Ethyl 2-[(4-bromophenyl)amino]-2-[(*R**)-cyclohex-2-en-1-yl]acetate (129a):** Following the general procedure D as described above, **129a** was obtained after purification




by neutral alumina column chromatography (EtOAc/hexane, 3:97) as a colorless solid (85 mg, 50%); mp 79–81 °C (EtOAc). $R_f$ = 0.39 (3% EtOAc/hexane). IR (KBr): $\tilde{\upsilon}$ = 3350, 2929, 1725, 1594, 1516, 1487, 1184, 677 $cm^{-1}$. $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ = 7.22 (d, $J$ = 8.9 Hz, 2 H), 6.48 (d, $J$ = 8.9 Hz, 2 H), 5.92–5.89 (m, 1 H), 5.63 (dd, $J$ = 10.2, 1.6 Hz, 1 H), 4.20–4.10 (m, 3 H), 3.89 (dd, $J$ = 9.7, 5.2 Hz, 1 H), 2.67 (s, 1 H), 2.02–1.99 (m, 2 H), 1.81–1.78 (m, 2 H), 1.55–1.51 (m, 2 H), 1.24 (t, $J$ = 7.1 Hz, 3 H). $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta$ = 173.1, 146.3, 132.0, 131.4, 125.7, 115.0, 109.8, 61.1, 60.6, 38.7, 26.4, 25.0, 21.6, 14.3. MS (CI): $m/z$ (%) = 340 (98) $[M + 3]^+$, 339 (15) $[M + 2]^+$, 338 (100) $[M + 1]^+$, 266 (50), 264 (52), 258 (10), 182 (5). HRMS (ESI): calcd. for $C_{16}H_{20}BrNO_2Na$ $[M + Na]^+$ 360.0575; found 360.0567.

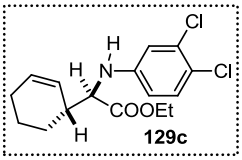
**(*R**)-Ethyl 2-[(4-chlorophenyl)amino]-2-[(*R**)-cyclohex-2-en-1-yl]acetate (129b):** Following the general procedure D as described above, **129b** was obtained after purification




by neutral alumina column chromatography (EtOAc/hexane, 3:97) as a colorless solid (66 mg, 45%); mp 78–80 °C. $R_f$ = 0.38 (3% EtOAc/hexane). IR (KBr): $\tilde{\upsilon}$ = 3384, 2933, 1731, 1600, 1503, 1179, 815 $cm^{-1}$. $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ = 7.11 (d, $J$ = 8.8 Hz, 2 H), 6.53 (d, $J$ = 8.8 Hz, 2 H),

5.93–5.90 (m, 1 H), 5.64 (dd, *J* = 10.1, 1.6 Hz, 1 H), 4.21–4.10 (m, 3 H), 3.90 (dd, *J* = 9.8, 5.2 Hz, 1 H), 2.68 (s, 1 H), 2.03–2.00 (m, 2 H), 1.83–1.79 (m, 2 H), 1.61–1.52 (m, 2 H), 1.25 (t, *J* = 7.1 Hz, 3 H). $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ = 173.1, 145.9, 131.4, 129.1, 125.7, 122.7, 114.6, 61.1, 60.7, 38.7, 26.4, 25.0, 21.6, 14.3. MS (CI): *m*/*z* (%) = 296 (30) $[M + 3]^+$, 295 (15) $[M + 2]^+$, 294 (100) $[M + 1]^+$, 280 (30), 220 (40), 212 (25). HRMS (ESI): calcd. for $C_{16}H_{20}ClNO_2Na$ $[M + Na]^+$ 316.1080; found 316.1084.

**(*R**)-Ethyl 2-[(*R**)-cyclohex-2-en-1-yl]-2-[(3,4-dichlorophenyl)amino]-acetate (129c):** Following the general procedure D as described above, **129c** was obtained after purification

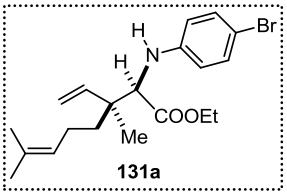


**129c**

by neutral alumina column chromatography (EtOAc/hexane, 3:97) as a colorless solid (74 mg, 45%); mp 73–75 °C. $R_f$ = 0.38 (3% EtOAc/hexane). IR (KBr): $\tilde{\upsilon}$ = 3356, 2932, 1724, 1599, 1476, 1186, 853 $cm^{-1}$. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 7.17 (d, *J* = 8.7 Hz, 1 H), 6.68 (d, *J* = 2.7 Hz, 1 H), 6.44 (dd, *J* = 8.7, 2.7 Hz, 1 H), 5.94–5.91 (m, 1 H), 5.61 (dd, *J* = 10.2, 1.3 Hz, 1 H), 4.20 (q, *J* = 7.1 Hz, 3 H), 3.88 (dd, *J* = 9.6, 5.1 Hz, 1 H), 2.69 (s, 1 H), 2.03–2.00 (m, 2 H), 1.82–1.79 (m, 2 H), 1.56–1.51 (m, 2 H), 1.26 (t, *J* = 7.1 Hz, 3 H). $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ = 172.8, 146.8, 132.8, 131.7, 130.6, 125.3, 120.6, 114.6, 113.0, 61.3, 60.4, 38.6, 26.4, 24.9, 21.5, 14.3. MS (CI): *m*/*z* (%) = 330 (60) $[M + 3]^+$, 329 (15) $[M + 2]^+$, 328 (100) $[M + 1]^+$, 255 (20), 254 (37), 246 (14). HRMS (ESI): calcd. for $C_{16}H_{19}Cl_2NO_2Na$ $[M + Na]^+$ 350.0691; found 350.0679.

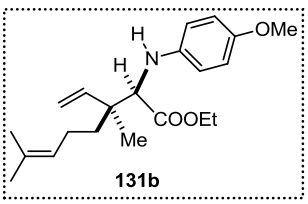
**Procedure F. Indium-mediated addition of geranyl bromide (123d) to α-imino esters 100:** To a vigorously stirring solution of α-imino ester **100** (1 mmol, 1 equiv) in anhydrous DMF (1 mL) was sequentially added indium powder (1.5 mmol, 1.5 equiv), sodium iodide (2 mmol, 2 equiv), and *E*-geranyl bromide (**123d**; 2 mmol, 2 equiv). The mixture was stirred vigorously for 24 h at room temperature under a nitrogen atmosphere, then water (5–10 mL) was added. The resulting reaction mixture was transferred to a separating funnel and extracted with EtOAc (3x15 mL). The combined organic layers were dried with anhydrous $Na_2SO_4$, then the solvent was evaporated under vacuum. Purification of the resulting crude reaction mixture by column chromatography on neutral alumina (EtOAc/hexane as eluent) gave the products **131** (see Scheme 51).

**(2*R**,3*S**)-Ethyl 2-[(4-bromophenyl)amino]-3,7-dimethyl-3-vinyloct-6-enoate (131a):** Following the general procedure F as described above, **131a** was obtained after purification by neutral alumina column chromatography (EtOAc/hexane, 1:99) as a colorless oil (108 mg, 55%); $R_f$ = 0.35 (1% EtOAc/hexane). IR (neat): $\tilde{\upsilon}$ = 3390, 2926, 1731, 1595, 1496, 1180, 813 cm$^{-1}$. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 7.22 (d, $J$ = 8.9 Hz, 2 H), 6.49 (d, $J$ = 8.9 Hz, 2 H), 5.93–5.86 (m, 1 H), 5.27 (dd, $J$ = 10.6, 1.2 Hz, 1 H), 5.12 (dd, $J$ = 16.2, 1.2 Hz, 1 H), 5.08–5.02 (m, 1 H), 4.16–4.10 (m, 3 H), 3.81 (d, $J$ = 10.6 Hz, 1 H), 2.03–1.95 (m, 1 H), 1.91–1.86 (m, 1 H), 1.67 (s, 3 H), 1.58 (s, 3 H), 1.58–1.52 (m, 1 H), 1.39–1.32 (m, 1 H), 1.21 (t, $J$ = 7.1 Hz, 3 H), 1.16 (s, 3 H). $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ = 172.5, 146.3, 141.5, 132.0, 131.7, 124.1, 116.1, 115.3, 109.9, 64.0, 60.8, 43.6, 38.4, 25.7, 22.6, 18.9, 17.6, 14.3. HRMS (ESI): calcd. for $C_{20}H_{28}BrNO_2Na$ $[M + Na]^+$ 416.1201; found 416.1183.



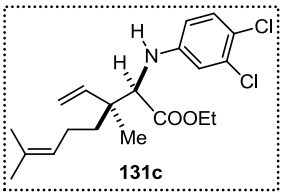
131a

**(2*R**,3*S**)-Ethyl 2-[(4-methoxyphenyl)amino]-3,7-dimethyl-3-vinyloct-6-enoate (131b):** Following the general procedure F as described above, **131b** was obtained after purification by neutral alumina column chromatography (EtOAc/hexane, 1:99) as a colorless oil (105 mg, 61%); $R_f$ = 0.34 (1% EtOAc/hexane). IR (neat): $\tilde{\upsilon}$ = 3397, 2927, 1731, 1514, 1240, 1039 cm$^{-1}$. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 6.74 (d, $J$ = 8.7 Hz, 2 H), 6.59 (d, $J$ = 8.7 Hz, 2 H), 5.95–5.87 (m, 1 H), 5.24 (dd, $J$ = 10.2, 1.2 Hz, 1 H), 5.13–5.05 (m, 2 H), 4.10 (q, $J$ = 7.1 Hz, 2 H), 3.86 (s, 1 H), 3.79 (s, 1 H), 3.72 (s, 3 H), 2.05–1.85 (m, 3 H), 1.67 (s, 3 H), 1.58 (s, 3 H), 1.41–1.32 (m, 1 H), 1.19 (t, $J$ = 7.1 Hz, 6 H). $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ = 173.1, 152.7, 141.9, 141.4, 131.6, 124.3, 115.6, 115.3, 114.8, 65.4, 60.5, 55.7, 43.5, 38.5, 25.7, 22.7, 18.8, 17.6, 14.3. HRMS (ESI): calcd. for $C_{21}H_{32}NO_3$ $[M + H]^+$ 346.2382; found 346.2369.



131b

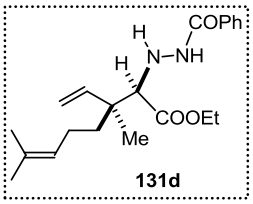
**(2*R**,3*S**)-Ethyl 2-[(3,4-dichlorophenyl)amino]-3,7-dimethyl-3-vinyloct-6-enoate (131c):** Following the general procedure F as described above, **131c** was obtained after purification by neutral alumina column chromatography (EtOAc/hexane, 1:99) as a colorless oil (106 mg, 55%); $R_f$ = 0.34 (1% EtOAc/hexane). IR (neat): $\tilde{\upsilon}$ = 3391, 2926, 1731, 1599, 1494, 1132, 678 cm$^{-1}$. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 7.17 (d, $J$ = 8.7 Hz, 1 H), 6.70 (d, $J$ = 2.7 Hz, 1 H), 6.45 (dd, $J$ = 8.7, 2.7 Hz, 1 H), 5.93–5.86 (m, 1 H), 5.27 (dd, $J$ = 10.5, 1.2 Hz, 1 H), 5.12 (dd, $J$ = 17.4, 1.2 Hz, 1 H), 5.08–5.02 (m, 1 H), 4.16–4.10 (m, 3 H), 3.79 (d, $J$ = 10.5



131c

Hz, 1 H), 2.05–1.87 (m, 2 H), 1.68 (s, 3 H), 1.59 (s, 3 H), 1.58–1.51 (m, 1 H), 1.40–1.33 (m, 1 H), 1.26 (t, $J$ = 7.1 Hz, 3 H), 1.17 (s, 3 H). $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ = 172.2, 146.8, 141.3, 132.8, 131.8, 130.7, 124.0, 120.8, 116.4, 114.8, 113.3, 63.8, 60.9, 43.6, 38.4, 25.7, 22.6, 18.9, 17.6, 14.3. HRMS (ESI): calcd. for $C_{20}H_{27}Cl_2NO_2Na$ $[M + Na]^+$ 406.1317; found 406.1307.

**(2*R**,3*S**)-Ethyl 2-(2-benzoylhydrazinyl)-3,7-dimethyl-3-vinyloct-6-enoate (131d):** Following the general procedure F as described above, **131d** was obtained after purification



**131d**

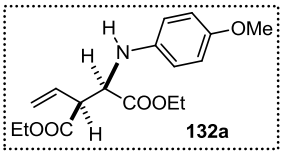
by silica gel column chromatography (EtOAc/hexane, 5:95) as a colorless oil (143 mg, 80%); $R_f$ = 0.40 (5% EtOAc/hexane). IR (neat): $\tilde{\upsilon}$ = 3295, 2975, 1730, 1638, 1447, 1192 $cm^{-1}$. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 7.95 (s, 1 H), 7.71 (d, $J$ = 7.2 Hz, 2 H), 7.49 (t, $J$ = 7.2 Hz, 1 H), 7.40 (t, $J$ = 7.2 Hz, 2 H), 5.94–5.87 (m, 1 H), 5.17–5.04 (m, 4 H), 4.23–4.14 (m, 2 H), 3.60 (s, 1 H), 1.98–1.92 (m, 2 H), 1.66 (s, 3 H), 1.58 (s, 3 H), 1.58–1.46 (m, 2 H), 1.24 (t, $J$ = 7.1 Hz, 3 H), 1.20 (s, 3 H). $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ = 172.2, 167.1, 142.1, 132.7, 131.8, 131.5, 128.6, 126.9, 124.3, 114.6, 71.2, 60.8, 42.9, 37.7, 25.7, 22.5, 19.0, 17.6, 14.2. HRMS (ESI): calcd. for $C_{21}H_{31}N_2O_3$ $[M + H]^+$ 359.2335; found 359.2352.

**Procedure G. In-mediated addition of 4-bromocrotonates (123e or 123f) to α-imino esters 100:** To a vigorously stirring solution of α-imino ester **100** (0.5 mmol, 1 equiv) and ethyl 4-bromocrotonate (**123e**) or methyl-4-bromo crotonate (**123f**; 1.5 mmol, 3 equiv) in EtOH (2 mL) was added indium powder (1 mmol, 2 equiv). The mixture was allowed to stir vigorously for 6 h at 30 $^o$C. After this period, the reaction mixture was quenched with 2 mL of water and transferred to a separating funnel and extracted using ethyl acetate (3x15 mL). The combined organic layers were dried over anhydrous $Na_2SO_4$. Then the solvent was evaporated under vacuum. Purification of the resulting crude reaction mixture by column chromatography on silica gel (EtOAc/hexane as eluent) gave the product **132** (see Tables 12-14 for individual entries).

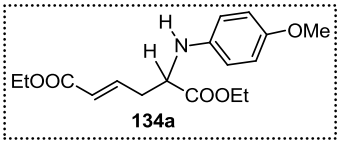
**Procedure H. One-pot synthesis of *N*-aryl α-amino esters (132a, 132d, 132h and 132v):** Ethyl glyoxylate **98** (0.5 mmol, 1 equiv) and the respective amines **99d-f**,**q** (0.5 mmol, 1 equiv) were dissolved in EtOH (2 mL) and stirred for 30 min at room temperature. To the resulting solution, *E*-ethyl-4-bromocrotonate (**123e**, 1.5 mmol, 3 equiv) and indium powder

(1 mmol, 2 equiv) was added successively while stirring the reaction mixture vigorously. The stirring was continued for 6 h at 30 $^{o}$C. After this period, the reaction mixture was quenched with 2 mL of water and transferred to a separating funnel and extracted using ethyl acetate (3x15 mL). The combined organic layers were dried over anhydrous $Na_2SO_4$. The solvent was then evaporated under vacuum. Purification of the resulting crude reaction mixture by column chromatography on silica gel (EtOAc/hexane as eluent) gave the corresponding products **132a**, **132d**, **132h** and **132v** (see Scheme 52).

**(2*R**,3*S**)-Diethyl 2-((4-methoxyphenyl)amino)-3-vinylsuccinate (132a):** Following the general procedure G described above, **132a** was obtained after purification by silica gel column chromatography (EtOAc/hexane, 10:90) as colorless liquid (146 mg, 91%); $R_f$ = 0.43 (10% EtOAc/hexane). IR (thin film): $\tilde{\upsilon}$ = 3365, 2984, 1731, 1515, 1035 cm$^{-1}$. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 6.78 (d, $J$ = 9.0 Hz, 2 H), 6.68 (d, $J$ = 9.0 Hz, 2 H), 5.96–5.86 (m, 1 H), 5.29–5.20 (m, 2 H), 4.42 (d, $J$ = 6.8 Hz, 1 H), 4.23–4.13 (m, 4 H), 3.75 (s, 3 H), 3.49 (dd, $J$ = 9.3, 6.8 Hz, 1 H), 1.29 (t, $J$ = 7.2 Hz, 3 H), 1.24 (t, $J$ = 7.1 Hz, 3 H), 1.30–1.24 (m, 1 H). $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ = 171.7, 171.2, 153.1, 140.2, 131.4, 120.6, 115.9, 114.8, 61.3, 61.2, 60.0, 55.7, 53.1, 14.2, 14.2. HRMS (ESI): calcd. for $C_{17}H_{23}NO_5Na$ $[M + Na]^+$ 344.1474; found 344.1471.

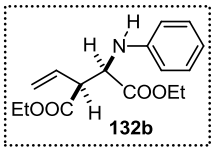



**Diethyl 5-((4-methoxyphenyl)amino)hex-2-enedioate (134a): 134a** was obtained after purification by silica gel column chromatography (EtOAc/hexane, 11:89) as colorless liquid (40 mg, 25%); $R_f$ = 0.42 (11% EtOAc/hexane). IR (thin film): $\tilde{\upsilon}$ = 3364, 2985, 1730, 1518, 1032 cm$^{-1}$. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 6.96–6.88 (m, 1 H), 6.77 (d, $J$ = 8.9 Hz, 2 H), 6.61 (d, $J$ = 8.9 Hz, 2 H), 5.91 (d, $J$ = 15.6 Hz, 1 H), 4.22–4.13 (m, 6 H), 3.74 (s, 3 H), 2.72–2.66 (m, 2 H), 1.30–1.22 (m, 6 H). $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ = 173.0, 165.9, 153.0, 142.9, 140.2, 124.6, 115.4, 114.9, 61.4, 60.4, 56.8, 55.7, 35.5, 14.2, 14.1. MS (CI): $m/z$ (%) = 322 (100) [M + H]. HRMS (ESI): calcd. for $C_{17}H_{24}NO_5$ $[M + H]^+$ 322.1654; found 322.1663.



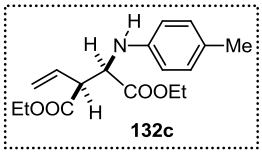

**(2*R**,3*S**)-Diethyl 2-(phenylamino)-3-vinylsuccinate (132b):** Following the general procedure G described above, **132b** was obtained after purification by silica gel column chromatography (EtOAc/hexane, 09:91) as colorless liquid (120 mg, 83%); $R_f$ = 0.45 (9% EtOAc/hexane). IR (thin film): $\tilde{\upsilon}$ = 3386, 2983, 1732, 1604, 1029 cm$^{-1}$. $^1$H NMR (400 MHz,

$CDCl_3$): $\delta$ = 7.18 (dd, $J$ = 8.6, 7.4 Hz, 2 H), 6.76 (t, $J$ = 7.4 Hz, 1 H), 6.69 (d, $J$ = 8.6 Hz, 2 H), 5.94–5.85 (m, 1 H), 5.28–5.18 (m, 2 H), 4.52 (t, $J$ = 6.4 Hz, 1 H), 4.41 (d, $J$ = 7.8 Hz, 1 H), 4.23–4.12 (m, 4 H), 3.52 (dd, $J$ = 9.3, 6.4 Hz, 1 H), 1.27 (t, $J$ = 7.1 Hz, 3 H), 1.23 (t, $J$ = 7.2 Hz, 3 H). $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ = 171.3, 171.1, 146.1, 131.2, 129.4, 120.7, 118.9, 114.1, 61.4, 61.3, 58.6, 52.8, 14.2, 14.2. HRMS (ESI): calcd. for $C_{16}H_{22}NO_4$ $[M + H]^+$ 292.1549; found 292.1539.



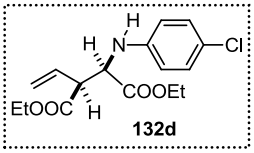
132b

**(2*R**,3*S**)-Diethyl 2-((4-methylphenyl)amino)-3-vinylsuccinate (132c):** Following the general procedure G described above, **132c** was obtained after purification by silica gel column chromatography (EtOAc/hexane, 10:90) as colorless liquid (128 mg, 84%); $R_f$ = 0.45 (10% EtOAc/hexane). IR (thin film): $\tilde{\upsilon}$ = 3376, 2984, 1731, 1519, 1031 cm$^{-1}$. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 7.02 (d, $J$ = 8.4 Hz, 2 H), 6.64 (d, $J$ = 8.4 Hz, 2 H), 5.96–5.87 (m, 1 H), 5.30–5.20 (m, 2 H), 4.51 (br. s, 1 H), 4.29 (br. s, 1 H), 4.24–4.14 (m, 4 H), 3.52 (dd, $J$ = 9.3, 6.8 Hz, 1 H), 2.26 (s, 3 H),1.29 (t, $J$ = 7.2 Hz, 3 H),1.25 (t, $J$ = 7.1 Hz, 3 H). $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ = 171.5, 171.2, 143.8, 131.3, 129.9, 128.2, 120.6, 114.4, 61.3, 61.2, 59.1, 53.0, 20.4, 14.2, 14.2. HRMS (ESI): calcd. for $C_{17}H_{24}NO_4$ $[M + H]^+$ 306.1705; found 306.1698.



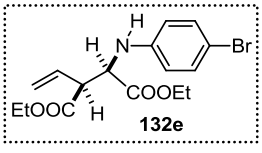
132c

**(2*R**,3*S**)-Diethyl 2-((4-chlorophenyl)amino)-3-vinylsuccinate (132d):** Following the general procedure G described above, **132d** was obtained after purification by silica gel column chromatography (EtOAc/hexane, 10:90) as colorless liquid (153 mg, 94%); $R_f$ = 0.44 (10% EtOAc/hexane). IR (thin film): $\tilde{\upsilon}$ = 3378, 2983, 1731, 1502, 1030 cm$^{-1}$. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 7.26 (d, $J$ = 8.5 Hz, 2 H), 6.56 (d, $J$ = 8.5 Hz, 2 H), 5.91–5.82 (m, 1 H), 5.28–5.18 (m, 2 H), 4.45 (br. s, 2 H), 4.22–4.12 (m, 4 H), 3.49 (dd, $J$ = 9.1, 5.0 Hz, 1 H), 1.28–1.21 (m, 6 H). $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ = 171.0, 145.2, 132.1, 131.0, 120.9, 115.6, 110.6, 61.6, 61.4, 58.6, 52.6, 14.2, 14.2. HRMS (ESI): calcd. for $C_{16}H_{21}ClNO_4$ $[M + H]^+$ 326.1159; found 326.1151.



132d

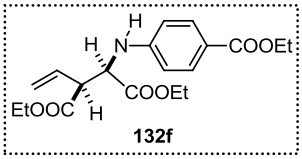
**(2*R**,3*S**)-Diethyl 2-((4-bromophenyl)amino)-3-vinylsuccinate (132e):** Following the general procedure G described above, **132e** was obtained after purification by silica gel column chromatography (EtOAc/hexane, 9:91) as colorless liquid (161 mg, 87%); $R_f$ = 0.45 (9% EtOAc/hexane). IR (thin film): $\tilde{\upsilon}$ = 3374, 2983, 1732, 1477, 1027 cm$^{-1}$. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 7.26 (d, $J$ = 8.9 Hz, 2 H), 6.57 (d, $J$ = 8.9 Hz, 2 H), 5.92–5.83 (m, 1 H), 5.28–5.18 (m, 2 H), 4.46



132e

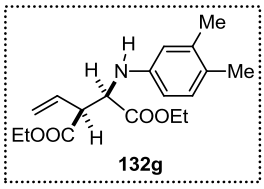
(br. s, 2 H), 4.22–4.13 (m, 4 H), 3.50 (dd, $J$ = 9.2, 5.5 Hz, 1 H), 1.28–1.21 (m, 6 H). $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ = 171.0, 145.2, 132.1, 131.0, 120.9, 115.6, 110.6, 61.6, 61.4, 58.5, 52.6, 14.2, 14.2. HRMS (ESI): calcd. for $C_{16}H_{21}BrNO_4$ $[M + H]^+$ 370.0654; found 370.0658.

**(2*R**,3*S**)-Diethyl 2-((4-(ethoxycarbonyl)phenyl)amino)-3-vinylsuccinate (132f):** Following the general procedure G described above, **132f** was obtained after purification by silica gel column chromatography (EtOAc/hexane, 11:89) as colorless liquid (163 mg, 90%); $R_f$ = 0.40 (11% EtOAc/hexane). IR (thin film): $\tilde{\upsilon}$ = 3371, 2983, 1731, 1526, 1031 cm$^{-1}$. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 7.90 (d, $J$ = 8.9 Hz, 2 H), 6.67 (d, $J$ = 8.9 Hz, 2 H), 5.92–5.83 (m, 1 H), 5.32–5.19 (m, 2 H), 4.93 (d, $J$ = 9.5 Hz, 1 H), 4.59 (dd, $J$ = 9.5, 5.9 Hz, 1 H), 4.32 (q, $J$ = 7.1 Hz, 2 H), 4.25–4.15 (m, 4 H), 3.56 (dd, $J$ = 9.5, 5.9 Hz, 1 H), 1.36 (t, $J$ = 7.1 Hz, 3 H), 1.31–1.23 (m, 6 H). $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ = 171.0, 170.6, 166.6, 149.9, 131.5, 130.8, 121.0, 120.3, 112.6, 61.7, 61.4, 60.3, 57.7, 52.3, 14.4, 14.2, 14.1. HRMS (ESI): calcd. for $C_{19}H_{26}NO_6$ $[M + H]^+$ 364.1760; found 364.1756.



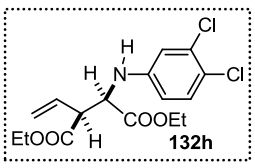
132f

**(2*R**,3*S**)-Diethyl 2-((3,4-dimethylphenyl)amino)-3-vinylsuccinate (132g):** Following the general procedure G described above, **132g** was obtained after purification by silica gel column chromatography (EtOAc/hexane, 10:90) as colorless liquid (112 mg, 70%); $R_f$ = 0.44 (10% EtOAc/hexane). IR (thin film): $\tilde{\upsilon}$ = 3375, 2982,1732,1512, 1030 cm$^{-1}$. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 6.94 (d, $J$ = 8.1 Hz, 1 H), 6.53 (d, $J$ = 2.5 Hz, 1 H), 6.47 (dd, $J$ = 8.1, 2.5 Hz, 1 H), 5.95–5.86 (m, 1 H), 5.28–5.23 (m, 2 H), 4.49 (dd, $J$ = 10.0, 6.6 Hz, 1 H), 4.24–4.13 (m, 5 H), 3.50 (dd, $J$ = 10.0, 6.6 Hz, 1 H), 2.20 (s, 3 H), 2.10 (s, 3 H), 1.28 (t, $J$ = 7.2 Hz, 3 H), 1.24 (t, $J$ = 7.2 Hz, 3 H). $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ = 171.6, 171.2, 144.2, 137.4, 131.4, 130.4, 127.0, 120.5, 116.1, 111.5, 61.3, 61.2, 59.1, 53.1, 20.0, 18.8, 14.2, 14.2. HRMS (ESI): calcd. for $C_{18}H_{26}NO_4$ $[M + H]^+$ 320.1862; found 320.1870.



132g

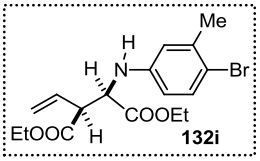
**(2*R**,3*S**)-Diethyl 2-((3,4-dichlorophenyl)amino)-3-vinylsuccinate (132h):** Following the general procedure G described above, **132h** was obtained after purification by silica gel column chromatography (EtOAc/hexane, 10:90) as colorless liquid (173 mg, 96%); $R_f$ = 0.64 (20% EtOAc/hexane). IR (thin film): $\tilde{\upsilon}$ = 3383, 2982,1731,1595, 1028 cm$^{-1}$. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ =



132h

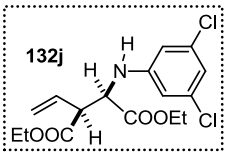
7.18 (d, *J* = 8.7 Hz, 1 H), 6.76 (d, *J* = 2.8 Hz, 1 H), 6.51 (dd, *J* = 8.7, 2.8 Hz, 1 H), 5.90–5.80 (m, 1 H), 5.28–5.19 (m, 2 H), 4.58 (d, *J* = 9.9 Hz, 1 H), 4.39 (dd, *J* = 9.9, 6.1 Hz, 1 H), 4.21–4.13 (m, 4 H), 3.50 (dd, *J* = 9.3, 6.1 Hz, 1 H), 1.28–1.21 (m, 6 H). $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ = 170.9, 170.8, 145.8, 132.9, 130.9, 130.8, 121.4, 121.0, 115.2, 113.5, 61.7, 61.5, 58.4, 52.5, 14.2, 14.1.

**(2*R**,3*S**)-Diethyl 2-((4-bromo-3-methylphenyl)amino)-3-vinylsuccinate (132i):** Following the general procedure G described above, **132i** was obtained after purification by



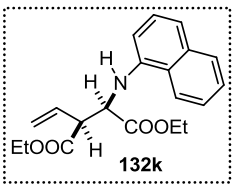

silica gel column chromatography (EtOAc/hexane, 10:90) as colorless liquid (133 mg, 69%); $R_f$ = 0.43 (10% EtOAc/hexane). IR (thin film): $\tilde{\upsilon}$ = 3376, 2983, 1732, 1479, 1027 cm$^{-1}$. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 7.27 (d, *J* = 8.6 Hz, 1 H), 6.57 (d, *J* = 2.8 Hz, 1 H), 6.39 (dd, *J* = 8.6, 2.8 Hz, 1 H), 5.91–5.82 (m, 1 H), 5.27–5.18 (m, 2 H), 4.42 (br. s, 2 H), 4.21–4.12 (m, 4 H), 3.49 (dd, *J* = 9.2, 5.8 Hz, 1 H), 2.29 (s, 3 H), 1.28–1.21 (m, 6 H). $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ = 171.1, 171.0, 145.5, 138.5, 132.8, 131.1, 120.8, 116.5, 113.3, 113.0, 61.5, 61.4, 58.6, 52.7, 23.1, 14.2, 14.2. HRMS (ESI): calcd. for $C_{17}H_{23}BrNO_4$ $[M + H]^+$ 384.0810; found 384.0810.

**(2*R**,3*S**)-Diethyl 2-((3,5-dichlorophenyl)amino)-3-vinylsuccinate (132j):** Following the general procedure G described above, **132j** was obtained after purification by silica gel




column chromatography (EtOAc/hexane, 10:90) as colorless liquid (86 mg, 48%); $R_f$ = 0.43 (10% EtOAc/hexane). IR (thin film): $\tilde{\upsilon}$ = 3375, 2984, 1730, 1594, 1029 cm$^{-1}$. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 6.73 (s, 1 H), 6.56 (s, 2 H), 5.91–5.82 (m, 1 H), 5.31–5.22 (m, 2 H), 4.69 (d, *J* = 9.7 Hz, 1 H), 4.40 (dd, *J* = 9.7, 6.0 Hz, 1 H), 4.23–4.17 (m, 4 H), 3.52 (dd, *J* = 9.1, 6.0 Hz, 1 H), 1.30–1.24 (m, 6 H). $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ = 170.9, 170.6, 148.0, 135.6, 130.8, 121.1, 118.5, 112.1, 61.8, 61.5, 58.1, 52.4, 14.2, 14.1. HRMS (ESI): calcd. for $C_{16}H_{20}Cl_2NO_4$ $[M + H]^+$ 360.0769; found 360.0766.

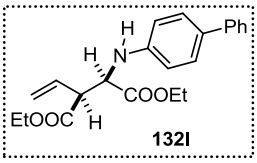
**(2*R**,3*S**)-Diethyl 2-(naphthalen-1-ylamino)-3-vinylsuccinate (132k):** Following the general procedure G described above, **132k** was obtained after purification by silica gel



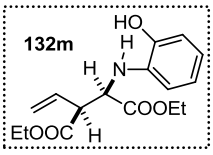

column chromatography (EtOAc/hexane, 10:90) as colorless liquid (99 mg, 58%); $R_f$ = 0.42 (10% EtOAc/hexane). IR (thin film): $\tilde{\upsilon}$ = 3420, 2983, 1734, 1531, 1028 cm$^{-1}$. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 7.89–7.87 (m, 1 H), 7.79–7.76 (m, 1 H), 7.47–7.43 (m, 2 H), 7.34–7.23 (m, 2

H), 6.67 (d, *J* = 7.1 Hz, 1 H), 6.02–5.93 (m, 1 H), 5.28–5.18 (m, 3 H), 4.68 (d, *J* = 6.0 Hz, 1 H), 4.26–4.15 (m, 4 H), 3.66 (dd, *J* = 9.2, 6.0 Hz, 1 H), 1.28 (t, *J* = 7.1 Hz, 3 H), 1.22 (t, *J* = 7.2 Hz, 3 H). $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ = 171.5, 171.3, 141.4, 134.4, 131.2, 128.6, 126.4, 126.0, 125.1, 123.9, 120.8, 120.2, 118.9, 105.8, 61.6, 61.4, 58.6, 52.4,14.2. HRMS (ESI): calcd. for $C_{20}H_{24}NO_4$ $[M + H]^+$ 342.1705; found 342.1693.

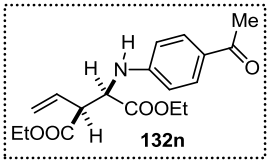
**(2*R**,3*S**)-Diethyl 2-([1,10-biphenyl]-4-ylamino)-3-vinylsuccinate (132l):** Following the general procedure G described above, **132l** was obtained after purification by silica gel column chromatography (EtOAc/hexane, 10:90) as colorless solid (167 mg, 91%); $R_f$ = 0.41 (10% EtOAc/hexane). mp 75–77 °C. IR (KBr): $\tilde{\upsilon}$ = 3349, 2985, 1720, 1527, 1174 cm$^{-1}$. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 7.53 (d, *J* = 7.5 Hz, 2 H), 7.45 (d, *J* = 8.6 Hz, 2 H), 7.39 (t, *J* = 7.5 Hz, 2 H), 7.27 (t, *J* = 7.5 Hz, 1 H), 6.77 (d, *J* = 8.6 Hz, 2 H), 5.96–5.87 (m, 1 H), 5.30–5.21 (m, 2 H), 4.57–4.52 (m, 2 H), 4.24–4.15 (m, 4 H), 3.56 (dd, *J* = 9.2, 5.8 Hz, 1 H), 1.31–1.23 (m, 6 H). $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ = 171.3, 171.1, 145.5, 141.0, 131.8, 131.1, 128.7, 128.1, 126.4, 126.3, 120.8, 114.3, 61.5, 61.4, 58.6, 52.8, 14.2, 14.2. HRMS (ESI): calcd. for $C_{22}H_{26}NO_4$ $[M + H]^+$ 368.1862; found 368.1850.




**(2*R**,3*S**)-Diethyl 2-(2-hydroxyphenylamino)-3-vinylsuccinate (132m):** Following the general procedure G described above, **132m** was obtained after purification by silica gel column chromatography (EtOAc/hexane, 11:89) as colorless liquid (90 mg, 59%); $R_f$ = 0.39 (11% EtOAc/hexane). IR (thin film): $\tilde{\upsilon}$ = 3419, 2983, 1731, 1516, 1195 cm$^{-1}$. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 6.82 (m, 4 H), 6.23 (br. s, 1 H), 5.91–5.82 (m, 1 H), 5.28–5.23 (m, 2 H), 4.26–4.11 (m, 6 H), 3.47 (t, *J* = 8.5 Hz, 1 H), 1.28 (t, *J* = 7.2 Hz, 3 H), 1.20 (t, *J* = 7.1 Hz, 3 H). $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ = 172.3, 172.0, 147.6, 133.8, 131.2, 122.3, 120.8, 120.8, 118.5, 115.6, 60.6, 61.4, 60.8, 53.6, 14.2, 14.1. HRMS (ESI): calcd. for $C_{16}H_{21}NO_5Na$ $[M + Na]^+$ 330.1317; found 330.1300.

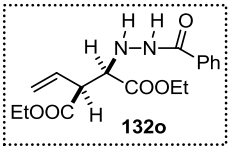



**(2*R**,3*S**)-Diethyl 2-(4-acetylphenylamino)-3-vinylsuccinate (132n):** Following the general procedure G described above, **132n** was obtained after purification by silica gel column chromatography (EtOAc/hexane, 09:91) as colorless liquid (103 mg, 65%); $R_f$ = 0.40 (9% EtOAc/hexane). IR (thin film): $\tilde{\upsilon}$ = 3379, 2985, 1732, 1599, 1035 cm$^{-1}$. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 7.83 (d, *J* = 8.8 Hz, 2 H), 6.67 (d, *J* = 8.8 Hz, 2 H), 5.91–5.82 (m, 1 H), 5.29–5.19 (m, 2 H),

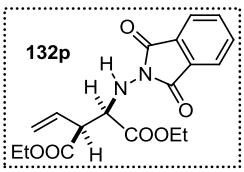


5.05 (d, *J* = 9.4 Hz, 1 H), 4.59 (dd, *J* = 9.4, 5.8 Hz, 1 H), 4.23–4.16 (m, 4 H), 3.56 (dd, *J* = 9.2, 5.8 Hz, 1 H), 2.50 (s, 3 H), 1.29–1.23 (m, 6 H). $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ = 196.4, 170.9, 170.5, 150.2, 130.8, 128.0, 121.0, 112.5, 61.8, 61.5, 57.6, 52.3, 26.1, 14.1, 14.1. HRMS (ESI): calcd. for $C_{18}H_{24}NO_5$ $[M + H]^+$ 334.1654; found 334.1648.

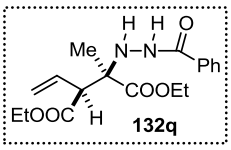
**(2*R**,3*S**)-Diethyl 2-(2-benzoylhydrazinyl)-3-vinylsuccinate (132o):** Following the general procedure G described above, **132o** was obtained after purification by silica gel column chromatography (EtOAc/hexane, 20:80) as colorless solid (134 mg, 81%); $R_f$ = 0.33 (20% EtOAc/hexane). mp 87–89 °C. IR (thin film): $\tilde{\upsilon}$ = 3264, 2981, 1721,1451, 1160 cm$^{-1}$. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 7.96 (s, 1 H), 7.23 (d, *J* = 7.0 Hz, 2 H), 7.51 (t, *J* = 7.0 Hz, 1 H), 7.43 (t, *J* = 7.0 Hz, 2 H), 5.98–5.89 (m, 1 H), 5.39–5.27 (m, 3 H), 4.24–4.16 (m, 4 H), 4.01 (d, *J* = 7.5 Hz, 1 H), 3.61 (t, *J* = 7.5 Hz, 1 H), 1.26 (t, *J* = 7.2 Hz, 6 H). $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ = 171.3, 170.9, 166.9, 132.5, 132.0, 131.3, 128.7, 127.0, 120.4, 64.8, 61.5, 61.4, 51.5, 14.1, 14.1. HRMS (ESI): calcd. for $C_{17}H_{23}N_2O_5$ $[M + H]^+$ 335.1607; found 335.1590.




**(2*R**,3*S**)-Diethyl 2-((1,3-dioxoisoindolin-2-yl)amino)-3-vinylsuccinate (132p):** Following the general procedure G described above, **132p** was obtained after purification by silica gel column chromatography (EtOAc/hexane, 22:78) as colorless oil (90 mg, 50%); $R_f$ = 0.34 (22% EtOAc/hexane). IR (thin film): $\tilde{\upsilon}$ = 3297, 2984, 1730, 1468, 1031 cm$^{-1}$. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 7.85 (dd, *J* = 5.5, 3.1 Hz, 2 H), 7.75 (dd, *J* = 5.5, 3.1 Hz, 2 H), 5.94–5.85 (m, 1 H), 5.41–5.28 (m, 3 H), 4.30–4.14 (m, 5 H), 3.54 (t, *J* = 8.6 Hz, 1 H), 1.32 (t, *J* = 7.1 Hz, 3 H), 1.26 (t, *J* = 7.1 Hz, 3 H). $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ = 171.9,171.1,166.9,135.3, 135.3, 131.8, 131.0,124.5,121.9, 65.3, 62.7, 62.5, 53.4, 15.0, 15.0. HRMS (ESI): calcd. for $C_{18}H_{21}N_2O_6$ $[M + H]^+$ 361.1400; found 361.1393. The compound was isolated with traces of minor isomer and the NMR values given here for the major isomer.

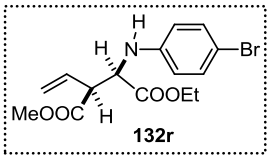



**(2*R**,3*S**)-Diethyl 2-(2-benzoylhydrazinyl)-2-methyl-3-vinylsuccinate (132q):** Following the general procedure G described above, **132q** was obtained after purification by silica gel column chromatography (EtOAc/hexane, 21:79) as colorless oil (80 mg, 46%); $R_f$ = 0.32 (21% EtOAc/hexane). IR (thin film): $\tilde{\upsilon}$ = 3287, 2984, 1731, 1461, 1029 cm$^{-1}$. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 8.39 (s, 1 H), 7.76 (d, *J* = 7.1 Hz, 2 H), 7.53–7.42 (m, 3 H), 6.15–6.06 (m, 1 H), 5.41–5.28 (m, 3 H), 4.22–



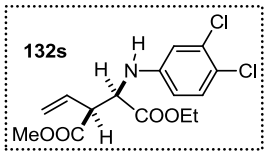
4.09 (m, 4 H), 3.75–3.68 (m, 1 H), 1.41 (s, 3 H), 1.28–1.22 (m, 6 H). $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ = 174.0, 172.2, 166.0, 132.9, 131.7, 130.8, 128.7, 126.9, 121.5, 65.8, 61.7, 61.4, 55.7, 20.1, 14.1, 14.0. HRMS (ESI): calcd. for $C_{18}H_{24}N_2O_5Na$ $[M + Na]^+$ 371.1583; found 371.1578. The compound was isolated with traces of minor isomer and the NMR values given here for the major isomer.

**(2*R**,3*S**)-1-Ethyl 4-methyl 2-((4-bromophenyl)amino)-3-vinylsuccinate (132r):** Following the general procedure G described above, **132r** was obtained after purification by




silica gel column chromatography (EtOAc/hexane, 9:91) as colorless liquid (128 mg, 72%); $R_f$ = 0.41 (9% EtOAc/hexane). IR (thin film): $\tilde{\upsilon}$ = 3374, 2984, 1730, 1497, 1021 $cm^{-1}$. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 7.28 (d, $J$ = 8.9 Hz, 2 H), 6.59 (d, $J$ = 8.9 Hz, 2 H), 5.92–5.83 (m, 1 H), 5.31–5.19 (m, 2 H), 4.47 (d, $J$ = 3.0 Hz, 2 H), 4.22–4.14 (m, 2 H), 3.75 (s, 3 H), 3.54 (td, $J$ = 9.2 Hz, 3.0 Hz, 1 H), 1.25 (t, $J$ = 7.2 Hz, 3 H). $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ = 171.5, 170.9, 145.1, 132.1, 130.8, 121.1, 115.7, 110.7, 61.6, 58.5, 52.4, 14.2. HRMS (ESI): calcd. for $C_{15}H_{19}BrNO_4$ $[M + H]^+$ 356.0497; found 356.0486.

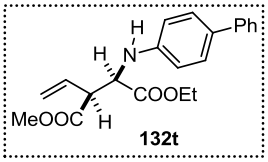
**(2*R**,3*S**)-1-Ethyl 4-methyl 2-((3,4-dichlorophenyl)amino)-3-vinylsuccinate (132s):** Following the general procedure G described above, **132s** was obtained after purification by



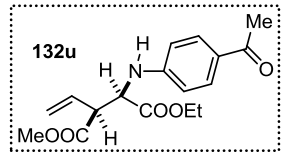

silica gel column chromatography (EtOAc/hexane, 10:90) as colorless liquid (124 mg, 72%); $R_f$ = 0.45 (10% EtOAc/hexane). IR (thin film): $\tilde{\upsilon}$ = 3375, 2985, 1730, 1597, 1020 $cm^{-1}$. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 7.22 (d, $J$ = 8.7 Hz, 1 H), 6.79 (d, $J$ = 2.8 Hz, 1 H), 6.54 (dd, $J$ = 8.7, 2.8 Hz, 1 H), 5.92–5.82 (m, 1 H), 5.32–5.22 (m, 2 H), 4.57 (d, $J$ = 9.9 Hz, 1 H), 4.42 (dd, $J$ = 9.9, 6.0 Hz, 1 H), 4.22–4.16 (m, 2 H), 3.76 (s, 3 H), 3.55 (dd, $J$ = 9.2, 6.0 Hz, 1 H), 1.26 (t, $J$ = 7.2 Hz, 3 H). $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ = 171.4, 170.7, 145.8, 133.0, 130.8, 130.7, 121.5, 121.1, 115.3, 113.6, 61.8, 58.4, 52.4, 52.3, 14.1. HRMS (ESI): calcd. for $C_{15}H_{18}Cl_2NO_4$ $[M + H]^+$ 346.0613; found 346.0600.

**(2*R**,3*S**)-1-Ethyl 4-methyl 2-([1,10-biphenyl]-4-ylamino)-3-vinylsuccinate (132t):** Following the general procedure G described above, **132t** was obtained after purification by silica gel column chromatography (EtOAc/hexane, 10:90) as colorless solid (164 mg, 93%); $R_f$ = 0.43 (10% EtOAc/hexane). mp 72–74 $^o$C. IR (KBr): $\tilde{\upsilon}$ = 3375, 2956, 1723, 1528, 1019 $cm^{-1}$. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 7.49 (d, $J$ = 8.6 Hz, 2 H), 7.42 (d, $J$ = 8.6 Hz, 2 H),

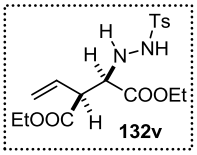
7.35 (t, *J* = 7.4 Hz, 2 H), 7.23 (t, *J* = 7.4 Hz, 1 H), 6.74 (d, *J* = 8.6 Hz, 2 H), 5.92–5.83 (m, 1 H), 5.27–5.17 (m, 2 H), 4.57–4.48 (m, 2 H), 4.19–4.10 (m, 2 H), 3.71 (s, 3 H), 3.55 (dd, *J* = 9.3, 5.9 Hz, 1 H), 1.21 (t, *J* = 7.1 Hz, 3 H). $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ = 171.7, 171.2, 145.5, 141.0, 131.8, 131.0, 128.7, 128.1, 126.4, 126.3, 121.2, 114.3, 61.6, 58.6, 52.6, 52.4, 14.2. HRMS (ESI): calcd. for $C_{21}H_{24}NO_4$ $[M + H]^+$ 354.1705; found 354.1704.




**(2*R**,3*S**)-1-Ethyl 4-methyl 2-(4-acetylphenylamino)-2-methyl-3-vinylsuccinate (132u):** Following the general procedure G described above, **132u** was obtained after purification by silica gel column chromatography (EtOAc/hexane, 09:91) as colorless liquid (91 mg, 57%); $R_f$ = 0.43 (9% EtOAc/hexane). IR (thin film): $\tilde{\upsilon}$ = 3367, 2985, 1731, 1600, 1276 cm$^{-1}$. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 7.80 (d, *J* = 8.8 Hz, 2 H), 6.63 (d, *J* = 8.8 Hz, 2 H), 5.86–5.77 (m, 1 H), 5.27–5.15 (m, 2 H), 4.97 (d, *J* = 9.5 Hz, 1 H), 4.57 (dd, *J* = 9.5, 5.6 Hz, 1 H), 4.20–4.11 (m, 2 H), 3.71 (s, 3 H), 3.56 (dd, *J* = 9.2, 5.6 Hz, 1 H), 2.47 (s, 3 H), 1.21 (t, *J* = 7.1 Hz, 3 H). $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ = 196.5, 171.4, 170.4, 150.1, 130.8, 130.5, 128.1, 121.3, 112.5, 61.9, 57.5, 52.5, 52.1, 26.1, 14.1. HRMS (ESI): calcd. for $C_{17}H_{22}NO_5$ $[M + H]^+$ 320.1498; found 320.1480.



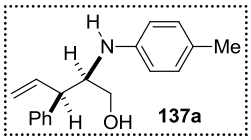

**(2*R**,3*S**)-Diethyl 2-(2-tosylhydrazinyl)-3-vinylsuccinate (132v):** Following the general procedure H described above, **132v** was obtained after purification by silica gel column chromatography (EtOAc/hexane, 19:81) as colorless solid (103 mg, 54%); $R_f$ = 0.33 (19% EtOAc/hexane). mp 107–109 $^o$C. IR (KBr): $\tilde{\upsilon}$ = 3261, 2987, 1722, 1320, 1161 cm$^{-1}$. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 7.76 (d, *J* = 8.3 Hz, 2 H), 7.28 (d, *J* = 8.3 Hz, 2 H), 6.54 (s, 1 H), 5.86–5.77 (m, 1 H), 5.21–5.17 (m, 2 H), 4.35 (dd, *J* = 10.3, 2.9 Hz, 1 H), 4.19–4.13 (m, 2 H), 4.09 (q, *J* = 7.0 Hz, 2 H), 3.78 (dd, *J* = 10.3, 5.5 Hz, 1 H), 3.45 (dd, *J* = 8.8, 5.5 Hz, 1 H), 2.41 (s, 3 H), 1.25–1.19 (m, 6 H). $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ = 172.1, 170.9, 144.0, 134.9, 131.4, 129.5, 128.3, 119.9, 65.1, 61.7, 61.4, 51.2, 21.6, 14.1, 14.0. HRMS (ESI): calcd. for $C_{17}H_{25}N_2O_6S$ $[M + H]^+$ 385.1433; found 385.1410.



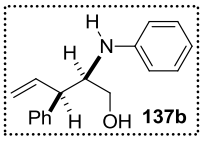

**Procedure I. Reduction of *N*-aryl α-amino esters (124, 131 and 132) to *N*-aryl β-amino alcohols 137:** A dry flask was charged with anhydrous THF (4 mL) and the respective *N*-aryl α-amino ester (**124** or **131** or **132**; 0.5 mmol) under a nitrogen atmosphere, at 0 °C. To this

solution was added $LiAlH_4$ (1 mmol in case of **124**/**131** or 2 mmol in case of **132**) in portions and the mixture was stirred overnight at room temperature. EtOH (few drops) and 5% aq. NaOH solution (1–2 mL) were then added sequentially and the resulting white suspension was filtered through a Celite pad and rinsed with THF (20 mL). The filtrate was dried with anhydrous $Na_2SO_4$, the solvent was removed by rotary evaporation, and the product was purified by column chromatography on silica gel (EtOAc/hexane) to afford the respective *N*-aryl β-amino alcohols **137** (see Scheme 58).

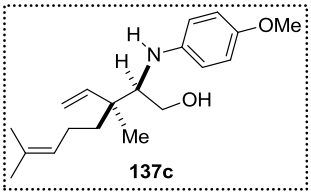
**(2*R**,3*R**)-3-Phenyl-2-(*p*-tolylamino)pent-4-en-1-ol (137a):** Following the general procedure I as described above, **137a** was obtained after purification by silica gel column chromatography (EtOAc/hexane, 6:94) as a colorless liquid (87 mg, 65%); $R_f$ = 0.30 (6% EtOAc/hexane). IR (neat): $\tilde{\upsilon}$ = 3399, 2922, 1616, 1519, 1039 $cm^{-1}$. $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ = 7.34 (t, *J* = 7.6 Hz, 2 H), 7.26 (m, 3 H), 7.01 (d, *J* = 8.2 Hz, 2 H), 6.59 (d, *J* = 8.2 Hz, 2 H), 6.18–6.09 (m, 1 H), 5.23–5.19 (m, 2 H), 3.82–3.77 (m, 2 H), 3.72–3.68 (m, 1 H), 3.64–3.60 (m, 1 H), 2.27 (s, 3 H). $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta$ = 145.1, 140.6, 137.5, 129.9, 128.7, 128.0, 127.8, 126.9, 117.8, 114.6, 61.8, 59.5, 52.0, 20.4. MS (CI): *m*/*z* (%) = 269 (20) $[M + 2]^+$, 268 (100) $[M + 1]^+$, 250 (4), 236 (5), 150 (9). HRMS (ESI): calcd. for $C_{18}H_{21}NONa$ $[M + Na]^+$ 290.1521; found 290.1534.




**(2*R**,3*R**)-3-Phenyl-2-(phenylamino)pent-4-en-1-ol (137b):** Following the general procedure I as described above, **137b** was obtained after purification by silica gel column chromatography (EtOAc/hexane, 6:94) as a colorless liquid (76 mg, 60%); $R_f$ = 0.29 (6% EtOAc/hexane). IR (neat): $\tilde{\upsilon}$ = 3400, 2926, 1600, 1503, 1316, 1040 $cm^{-1}$. $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ = 7.33 (t, *J* = 7.2 Hz, 2 H), 7.28–7.24 (m, 3 H), 7.18 (t, *J* = 8.2 Hz, 2 H), 6.76 (t, *J* = 7.2 Hz, 1 H), 6.14 (d, *J* = 7.2 Hz, 2 H), 6.18–6.09 (m, 1 H), 5.23–5.19 (m, 2 H), 3.86–3.79 (m, 2 H), 3.72–3.68 (m, 1 H), 3.64 (dd, *J* = 10.9, 5.2 Hz, 1 H). $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta$ = 147.5, 140.5, 137.6, 129.4, 128.8, 128.0, 126.9, 118.4, 117.7, 114.3, 62.0, 59.1, 52.1. MS (CI): *m*/*z* (%) = 255 (20) $[M + 2]^+$, 254 (100) $[M + 1]^+$, 236 (4), 222 (5). HRMS (ESI): calcd. for $C_{17}H_{19}NONa$ $[M + Na]^+$ 276.1364; found 276.1371.

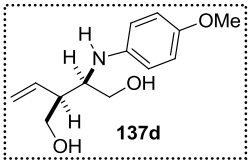



**(2*R**,3*S**)-2-[(4-Methoxyphenyl)amino]-3,7-dimethyl-3-vinyloct-6-en-1-ol (137c):** Following the general procedure I as described above, **137c** was obtained after purification

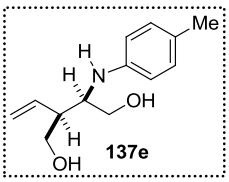



by silica gel column chromatography (EtOAc/hexane, 5:95) as a colorless liquid (121 mg, 80%); $R_f$ = 0.30 (5% EtOAc/hexane). IR (neat): $\tilde{\upsilon}$ = 3399, 2925, 1620, 1513, 1239, 1041 $cm^{-1}$. $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ = 6.75 (d, $J$ = 9.0 Hz, 2 H), 6.65 (d, $J$ = 9.0 Hz, 2 H), 5.84–5.77 (m, 1 H), 5.24 (dd, $J$ = 9.5, 1.3 Hz, 1 H), 5.08 (dd, $J$ = 16.2, 1.3 Hz, 1 H), 5.05–4.95 (m, 1 H), 3.82–3.78 (m, 1 H), 3.74 (s, 3 H), 3.40 (t, $J$ = 9.0 Hz, 1 H), 3.31–3.27 (m, 1 H), 1.93–1.81 (m, 2 H), 1.65 (s, 3 H), 1.55 (s, 3 H), 1.48–1.33 (m, 2 H), 0.94 (s, 3 H). $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta$ = 152.3, 143.7, 143.0, 131.6, 124.3, 115.6, 115.2, 115.0, 64.2, 62.0, 55.8, 45.0, 38.8, 25.7, 22.6, 19.4, 17.6. HRMS (ESI): calcd. for $C_{19}H_{29}NO_2Na$ $[M + Na]^+$ 326.2096; found 326.2101.

**(2*R**,3*S**)-2-((4-Methoxyphenyl)amino)-3-vinylbutane-1,4-diol (137d):** Following the general procedure I described above, **137d** was obtained after purification by silica gel column chromatography (EtOAc/hexane, 30:70) as colorless oil (59 mg, 50%); $R_f$ = 0.35 (30% EtOAc/hexane). IR (thin film): $\tilde{\upsilon}$ = 3377, 2930, 1513, 1241, 1038 $cm^{-1}$. $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ = 6.78 (d, $J$ = 9.0 Hz, 2 H), 6.69 (d, $J$ = 9.0 Hz, 2 H), 5.75–5.66 (m, 1 H), 5.23–5.18 (m, 2 H), 3.81–3.74 (m, 2 H), 3.74 (s, 3 H), 3.68 (dd, $J$ = 11.0, 5.0 Hz, 2 H), 3.56 (dd, $J$ = 11.0, 5.0 Hz, 1 H), 3.48–3.44 (m, 1 H), 2.60–2.52 (m, 1 H). $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta$ = 153.2, 141.0, 136.0, 119.0, 116.8, 115.0, 64.8, 61.8, 59.1, 55.7, 48.5. HRMS (ESI): calcd. for $C_{13}H_{20}NO_3$ $[M + H]^+$ 238.1443; found 238.1449. (OH protons could not be detected perhaps due to the rapid exchange among each other).

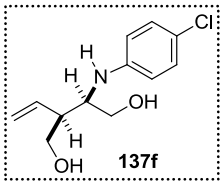



**(2*R**,3*S**)-2-(*p*-Tolylamino)-3-vinylbutane-1,4-diol (137e):** Following the general procedure I described above, **137e** was obtained after purification by silica gel column chromatography (EtOAc/hexane, 29:71) as colorless oil (78 mg, 71%); $R_f$ = 0.34 (29% EtOAc/hexane). IR (thin film): $\tilde{\upsilon}$ = 3369, 2923, 1617, 1518, 1256 $cm^{-1}$. $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ = 6.98 (d, $J$ = 8.0 Hz, 2 H), 6.62 (d, $J$ = 8.0 Hz, 2 H), 5.75–5.66 (m, 1 H), 5.22–5.17 (m, 2 H), 3.75 (dd, $J$ = 10.9, 6.8 Hz, 1 H), 3.71–3.65 (m, 2 H), 3.58–3.51 (m, 2 H), 2.57–2.50 (m, 1 H), 2.23 (s, 3 H). $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta$ = 144.9, 136.0, 130.0, 128.2, 119.0, 115.0, 64.5, 62.0, 57.7, 48.8, 20.4. HRMS (ESI): calcd. for $C_{13}H_{20}NO_2$ $[M + H]^+$ 222.1494; found

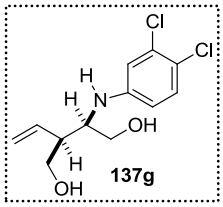


222.1498. (OH protons could not be detected perhaps due to the rapid exchange among each other).

**(2*R**,3*S**)-2-(4-Chlorophenylamino)-3-vinylbutane-1,4-diol (137f):** Following the general procedure I described above, **137f** was obtained after purification by silica gel column chromatography (EtOAc/hexane, 31:69) as colorless oil (54 mg, 45%); $R_f$ = 0.33 (31% EtOAc/hexane). IR (thin film): $\tilde{\upsilon}$ = 3373, 2926, 1599, 1496, 1048 $cm^{-1}$. $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ = 7.08 (d, $J$ = 8.8 Hz, 2 H), 6.57 (d, $J$ = 8.8 Hz, 2 H), 5.74–5.65 (m, 1 H), 5.21–5.14 (m, 2 H), 3.75–3.63 (m, 3 H), 3.58–3.50 (m, 2 H), 2.85 (br. s, 1 H), 2.55–2.48 (m, 1 H). $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta$ = 146.0, 135.8, 129.3, 122.9, 119.2, 115.4, 63.9, 62.1, 56.8, 48.8. HRMS (ESI): calcd. for $C_{12}H_{17}ClNO_2$ $[M + H]^+$ 242.0948; found 242.0951. (OH protons could not be detected perhaps due to the rapid exchange among each other).



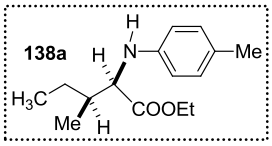

**(2*R**,3*S**)-2-((3,4-Dichlorophenyl)amino)-3-vinylbutane-1,4-diol (137g):** Following the general procedure I described above, **137g** was obtained after purification by silica gel column chromatography (EtOAc/hexane, 30:70) as colorless oil (81 mg, 59%); $R_f$ = 0.33 (30% EtOAc/hexane). IR (thin film): $\tilde{\upsilon}$ = 3379, 2923, 1596, 1511, 1038 $cm^{-1}$. $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ = 7.16 (d, $J$ = 8.7 Hz, 1 H), 6.74 (d, $J$ = 2.8 Hz, 1 H), 6.51 (dd, $J$ = 8.7, 2.8 Hz, 1 H), 5.78–5.69 (m, 1 H), 5.25–5.18 (m, 2 H), 3.77–3.67 (m, 3 H), 3.62–3.52 (m, 2 H), 2.82 (br. s, 1 H), 2.56–2.49 (m, 1 H). $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta$ = 147.1, 135.7, 132.9, 130.8, 120.4, 119.3, 115.0, 113.7, 63.6, 62.1, 56.3, 48.7. HRMS (ESI): calcd. for $C_{12}H_{16}NO_2Cl_2$ $[M + H]^+$ 276.0558; found 276.0548. (OH protons could not be detected perhaps due to the rapid exchange among each other).



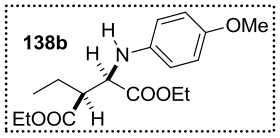

**Procedure J. Hydrogenation of *N*-aryl α-amino esters 127e and 132 to *N*-aryl alloisolucine derivative 138a and β-ethyl aspartates 138b-d:** A dry flask containing *N*-aryl α-amino ester **127e/132** (0.5 mmol, 1 equiv) in anhydrous THF (4 mL) was charged with Pd-C (10 mol-%) and the contents were stirred under $H_2$ (1 atm) at room temperature. After disappearance of starting material (reaction monitored by TLC) the reaction mixture was filtered through a Celite pad and rinsed with EtOAc (20 mL). The solvent was removed by rotary evaporation and the product was purified by column chromatography on silica gel

(EtOAc/hexane) to afford the *N*-aryl alloisolucine derivative **138a** and β-ethyl aspartates **138b-d** (see Scheme 59).

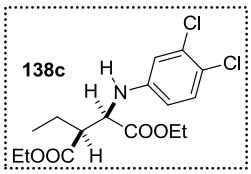
**(2*R**,3*S**)-Ethyl 3-methyl-2-(*p*-tolylamino)pentanoate (138a):** Following the general procedure J as described above, **138a** was obtained after purification by silica gel column chromatography (EtOAc/hexane, 2:98) as a colorless liquid (100 mg, 80%); $R_f$ = 0.43 (2% EtOAc/hexane). IR (neat): $\tilde{\upsilon}$ = 3376, 2979, 1728, 1514, 1230, 1020 cm$^{-1}$. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 6.95 (d, $J$ = 8.4 Hz, 2 H), 6.55 (d, $J$ = 8.4 Hz, 2 H), 4.14 (q, $J$ = 7.1 Hz, 2 H), 3.95 (s, 2 H), 2.21 (s, 3 H), 1.90–1.87 (m, 1 H), 1.57–1.50 (m, 1 H), 1.31–1.26 (m, 1 H), 1.22 (t, $J$ = 7.1 Hz, 3 H), 0.98 (d, $J$ = 6.9 Hz, 3 H), 0.94 (t, $J$ = 7.4 Hz, 3 H). $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ = 174.1, 145.3, 129.8, 127.4, 113.9, 61.2, 60.8, 38.0, 26.2, 20.4, 15.0, 14.3, 11.8. MS (CI): *m*/*z* (%) = 251 (16) $[M + 2]^+$, 250 (100) $[M + 1]^+$, 176 (10). HRMS (ESI): calcd. for $C_{15}H_{24}NO_2$ $[M + H]^+$ 250. 1807; found 250.1791.




**(2*S**,3*R**)-Diethyl 2-ethyl-3-((4-methoxyphenyl)amino)succinate (138b):** Following the general procedure J described above, **138b** was obtained after purification by silica gel column chromatography (EtOAc/hexane, 9:91) as colorless liquid (142 mg, 88%); $R_f$ = 0.43 (9% EtOAc/hexane). IR (thin film): $\tilde{\upsilon}$ = 3379, 2976, 1731, 1515, 1034 cm$^{-1}$. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 6.69 (d, $J$ = 9.0 Hz, 2 H), 6.56 (d, $J$ = 9.0 Hz, 2 H), 4.17–4.01 (m, 6 H), 3.66 (s, 3 H), 2.77–2.66 (m, 1 H), 1.75–1.66 (m, 1 H), 1.57–1.47 (m, 1 H), 1.19 (t, $J$ = 7.1 Hz, 3 H), 1.14 (t, $J$ = 7.1 Hz, 3 H), 0.88 (t, $J$ = 7.4 Hz, 3 H). $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ = 173.2, 172.8, 152.9, 140.7, 115.5, 114.8, 61.2, 60.8, 59.6, 55.7, 49.9, 22.0, 14.3, 14.2, 12.0. HRMS (ESI): calcd. for $C_{17}H_{26}NO_5$ $[M + H]^+$ 324.1811; found 324.1809.

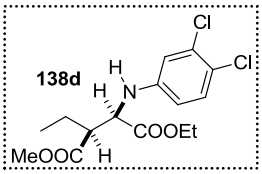



**(2*R**,3*S**)-Diethyl 2-(3,4-dichlorophenylamino)-3-ethylsuccinate (138c):** Following the general procedure J described above, **138c** was obtained after purification by silica gel column chromatography (EtOAc/hexane, 10:90) as colorless liquid (117 mg, 65%); $R_f$ = 0.44 (10% EtOAc/hexane). IR (thin film): $\tilde{\upsilon}$ = 3380, 2978, 1731, 1599, 1193 cm$^{-1}$. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 7.20 (d, $J$ = 8.7 Hz, 1 H), 6.75 (d, $J$ = 2.8 Hz, 1 H), 6.51 (dd, $J$ = 8.7, 2.8 Hz, 1 H), 4.73 (d, $J$ = 9.8 Hz, 1 H), 4.22–4.16 (m, 5 H), 2.85–2.79 (m, 1 H), 1.86–1.75 (m, 1 H), 1.65–1.55 (m, 1 H), 1.29–1.23 (m, 6 H), 0.97 (t, $J$ = 7.3 Hz, 3 H). $^{13}$C NMR (100



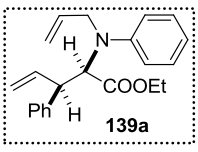
MHz, $CDCl_3$): $\delta$ = 173.1, 171.8, 146.3, 132.9, 130.7, 121.0, 114.8, 113.3, 61.6, 61.0, 57.8, 49.2, 22.1, 14.2, 14.2, 12.0. HRMS (ESI): calcd. for $C_{16}H_{21}NO_4Cl_2Na$ $[M + Na]^+$ 384.0745; found 384.0728.

**(2*R**,3*S**)-1-Ethyl 4-methyl 2-(3,4-dichlorophenylamino)-3-ethylsuccinate (138d):** Following the general procedure J described above, **138d** was obtained after purification by silica gel column chromatography (EtOAc/hexane, 10:90) as colorless liquid (166 mg, 96%); $R_f$ = 0.45 (10% EtOAc/hexane). IR (thin film): $\tilde{\upsilon}$ = 3382, 2970, 1735, 1599, 1201 $cm^{-1}$. $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ = 7.11 (d, $J$ = 8.7 Hz, 1 H), 6.66 (d, $J$ = 2.8 Hz, 1 H), 6.42 (dd, $J$ = 8.7, 2.8 Hz, 1 H), 4.61 (d, $J$ = 8.2 Hz, 1 H), 4.14–4.07 (m, 3 H), 3.64 (s, 3 H), 2.78–2.73 (m, 1 H), 1.75–1.66 (m, 1 H), 1.56–1.46 (m, 1 H), 1.16 (t, $J$ = 7.1 Hz, 3 H), 0.87 (t, $J$ = 7.4 Hz, 3 H). $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta$ = 173.6, 171.7, 146.3, 132.9, 130.7, 121.1, 114.9, 113.3, 61.7, 57.8, 52.1, 49.1, 22.0, 14.2, 12.0. HRMS (ESI): calcd. for $C_{15}H_{19}NO_4Cl_2Na$ $[M + Na]^+$ 370.0589; found 370.0570.



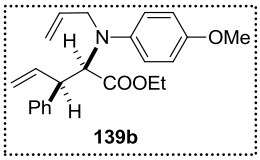

**Procedure K. *N*-allylation of γ,δ-unsaturated β,β'-disubstituted *N*-aryl α-amino acid derivatives 124/127/132:** To the respective *N*-aryl α-amino ester **124**/**127**/**132** (1 mmol, 1 equiv) in MeCN (5 mL) was added allyl bromide (6 equiv), NaI (0.1 equiv), and activated $K_2CO_3$ (3 equiv). The resulting reaction mixture was heated to reflux for 24–48 h. After completion of the reaction as indicated by the TLC, the reaction mixture was cooled to room temperature, water (5–6 mL) was added, and the resulting reaction was transferred to a separating flask and extracted with EtOAc (3x15 mL). The combined organic layers were dried with anhydrous $Na_2SO_4$ and the solvent was evaporated under vacuum. Purification of the resulting crude reaction mixture by column chromatography on silica gel (EtOAc/hexane) gave the products **139a-g** (see Scheme 60).

**(2*R**,3*R**)-Ethyl 2-[allyl(phenyl)amino]-3-phenylpent-4-enoate (139a):** Following the general procedure K as described above, **139a** was obtained after purification by silica gel column chromatography (EtOAc/hexane, 1.5:98.5) as a colorless liquid (214 mg, 64%); $R_f$ = 0.35 (1.5% EtOAc/hexane). IR (neat): $\tilde{\upsilon}$ = 2981, 1732, 1598, 1504, 1163, 1026 $cm^{-1}$. $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ = 7.23–7.10 (m, 7 H), 6.76–6.70 (m, 3 H), 5.97–5.88 (m, 1 H), 5.42–5.34 (m, 1 H), 5.16–5.06 (m, 2 H), 4.94–



4.89 (m, 2 H), 4.74 (d, *J* = 11.1 Hz, 1 H), 4.16 (q, *J* = 7.1 Hz, 2 H), 4.07 (dd, *J* = 11.1, 8.3 Hz, 1 H), 3.92–3.89 (m, 2 H), 1.24 (t, *J* = 7.1 Hz, 3 H). $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ = 171.3, 148.6, 139.7, 138.2, 135.6, 128.7, 128.5, 128.2, 126.8, 118.3, 117.0, 116.0, 115.4, 65.3, 60.7, 50.9, 48.3, 14.3. MS (CI): *m*/*z* (%) = 336 (100) $[M + 1]^+$, 262 (5), 246 (5). HRMS (ESI): calcd. for $C_{22}H_{26}NO_2$ $[M + H]^+$ 336.1964; found 336.1969.

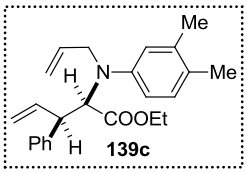
**(2*R**,3*R**)-Ethyl 2-[allyl(4-methoxyphenyl)amino]-3-phenylpent-4-enoate (139b):** Following the general procedure K as described above, **139b** was obtained after purification



**139b**

by silica gel column chromatography (EtOAc/hexane, 2.5:97.5) as a colorless oil (139 mg, 65%); $R_f$ = 0.41 (2.5% EtOAc/hexane). IR (neat): $\tilde{\upsilon}$ = 2929, 1731, 1680, 1513, 1244, 1039 $cm^{-1}$. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 7.24–7.20 (m, 2 H), 7.17–7.12 (m, 3 H), 6.68 (d, *J* = 1.1 Hz, 4 H), 5.94–5.86 (m, 1 H), 5.39–5.29 (m, 1 H), 5.12–5.02 (m, 2 H), 4.91–4.85 (m, 2 H), 4.50 (d, *J* = 11.2 Hz, 1 H), 4.14 (q, *J* = 7.1 Hz, 2 H), 3.99 (dd, *J* = 11.2, 8.2 Hz, 1 H), 3.81 (d, *J* = 5.4 Hz, 2 H), 3.70 (s, 3 H), 1.21 (t, *J* = 7.1 Hz, 3 H). $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ = 171.3, 153.1, 142.7, 140.0, 138.2, 135.9, 128.4, 128.3, 126.7, 118.9, 116.9, 116.1, 114.0, 67.5, 60.5, 55.5, 50.8, 49.0, 14.3. MS (CI): *m*/*z* (%) = 366 (100) $[M + 1]^+$, 208 (15), 163 (5). HRMS (ESI): calcd. for $C_{23}H_{28}NO_3$ $[M + H]^+$ 366.2069; found 366.2079.

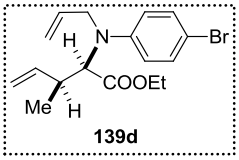
**(2*R**,3*R**)-Ethyl-2-[allyl(3,4-dimethylphenyl)amino]-3-phenylpent-4-enoate (139c):** Following the general procedure K as described above, **139c** was obtained after purification



**139c**

by silica gel column chromatography (EtOAc/hexane, 1.5:98.5) as a colorless liquid (294 mg, 81%); $R_f$ = 0.40 (1.5% EtOAc/hexane). IR (neat): $\tilde{\upsilon}$ = 2922, 1732, 1614, 1505, 1154, 1029 $cm^{-1}$. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 7.23–7.19 (m, 2 H), 7.16–7.12 (m, 3 H), 6.88 (d, *J* = 8.3 Hz, 1 H), 6.55 (d, *J* = 2.6 Hz, 1 H), 6.50 (dd, *J* = 8.3, 2.6 Hz, 1 H), 5.96–5.87 (m, 1 H), 5.39–5.30 (m, 1 H), 5.13–5.03 (m, 2 H), 4.91–4.85 (m, 2 H), 4.66 (d, *J* = 11.0 Hz, 1 H), 4.13 (q, *J* = 7.1 Hz, 2 H), 4.02 (dd, *J* = 11.0, 8.4 Hz, 1 H), 3.87–3.85 (m, 2 H), 2.15 (s, 3 H), 2.11 (s, 3 H), 1.23 (t, *J* = 7.1 Hz, 3 H). $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ = 171.5, 146.8, 139.9, 138.4, 136.7, 136.1, 129.8, 128.4, 128.3, 126.7, 126.5, 117.4, 116.9, 115.8, 113.3, 65.6, 60.6, 51.0, 48.4, 20.3, 18.7, 14.3. MS (CI): *m*/*z* (%) = 364 (100) $[M + 1]^+$, 336 (5), 206 (5). HRMS (ESI): calcd. for $C_{24}H_{30}NO_2$ $[M + H]^+$ 364.2277; found 364.2269.

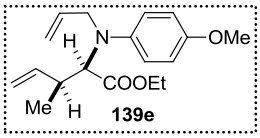
**(2*R**,3*S**)-Ethyl 2-[allyl(4-bromophenyl)amino]-3-methylpent-4-enoate (139d):** Following the general procedure K as described above, **139d** was obtained after purification



**139d**

by silica gel column chromatography (EtOAc/hexane, 1.5:98.5) as a colorless liquid (243 mg, 69%); $R_f$ = 0.45 (1.5% EtOAc/hexane). IR (neat): $\tilde{\upsilon}$ = 2979, 1732, 1589, 1495, 1242, 1027, 670 $cm^{-1}$. $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ = 7.27 (d, $J$ = 9.1 Hz, 2 H), 6.74 (d, $J$ = 9.1 Hz, 2 H), 5.77–5.67 (m, 2 H), 5.16–5.03 (m, 4 H), 4.11–4.00 (m, 5 H), 2.94–2.84 (m, 1 H), 1.19 (t, $J$ = 7.1 Hz, 3 H), 1.00 (d, $J$ = 6.8 Hz, 3 H). $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta$ = 170.9, 147.9, 139.4, 134.8, 131.7, 116.5, 116.4, 116.3, 110.0, 66.6, 60.6, 48.5, 38.6, 17.2, 14.2. MS (CI): *m*/*z* (%) = 353 (95) $[M + 2]^+$, 352 (100) $[M + 1]^+$, 274 (10), 246 (15), 172 (5). HRMS (ESI): calcd. for $C_{17}H_{23}BrNO_2$ $[M + H]^+$ 352.0912; found 352.0910.

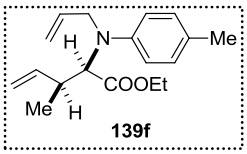
**(2*R**,3*S**)-Ethyl 2-[allyl(4-methoxyphenyl)amino]-3-methylpent-4-enoate (139e):** Following the general procedure K as described above, **139e** was obtained after purification



**139e**

by silica gel column chromatography (EtOAc/hexane, 2.5:97.5) as a colorless liquid (227 mg, 75%); $R_f$ = 0.43 (2.5% EtOAc/hexane). IR (neat): $\tilde{\upsilon}$ = 2980, 1731, 1513, 1243, 1039 $cm^{-1}$. $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ = 6.86 (d, $J$ = 9.2 Hz, 2 H), 6.79 (d, $J$ = 9.2 Hz, 2 H), 5.78–5.67 (m, 2 H), 5.18–5.01 (m, 4 H), 4.07 (q, $J$ = 7.1 Hz, 2 H), 4.00–3.88 (m, 3 H), 3.74 (s, 3 H), 2.91–2.81 (m, 1 H), 1.18 (t, $J$ = 7.1 Hz, 3 H), 1.08 (d, $J$ = 6.7 Hz, 3 H). $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta$ = 171.4, 152.9, 143.2, 139.9, 136.0, 118.2, 116.2, 116.0, 114.3, 68.6, 60.2, 55.5, 49.1, 38.6, 17.3, 14.3. MS (CI): *m*/*z* (%) = 304 (100) $[M + 1]^+$, 262 (4), 208 (6). HRMS (ESI): calcd. for $C_{18}H_{26}NO_3$ $[M + H]^+$ 304.1913; found 304.1909.

**(2*R**,3*S**)-Ethyl 2-[allyl(*p-tolyl*)amino]-3-methylpent-4-enoate (139f):** Following the general procedure K as described above, **139f** was obtained after purification by silica gel

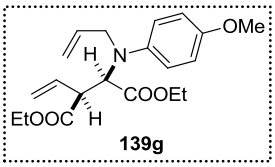


**139f**

column chromatography (EtOAc/hexane, 1.5:98.5) as a colorless liquid (258 mg, 90%); $R_f$ = 0.42 (1.5% EtOAc/hexane). IR (neat): $\tilde{\upsilon}$ = 2980, 1731, 1513, 1243, 1039 $cm^{-1}$. $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ = 7.01 (d, $J$ = 8.4 Hz, 2 H), 6.79 (d, $J$ = 8.4 Hz, 2 H), 5.79–5.68 (m, 2 H), 5.17–5.01 (m, 4 H), 4.09–3.94 (m, 5 H), 2.91–2.85 (m, 1 H), 2.23 (s, 3 H), 1.18 (t, $J$ = 7.1 Hz, 3 H), 1.03 (d, $J$ = 6.7 Hz, 3 H). $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta$ = 171.4, 146.8, 139.8, 135.7, 129.5, 127.4, 116.1, 116.0, 115.3, 67.0, 60.4, 48.5, 38.8, 20.3, 17.3, 14.3. MS (CI): *m*/*z* (%) = 289 (20) $[M + 2]^+$,

288 (100) $[M + 1]^+$. HRMS (ESI): calcd. for $C_{18}H_{26}NO_2$ $[M + H]^+$ 288.1964; found 288.1971.

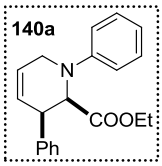
**(2*R**,3*S**)-Diethyl 2-(allyl(4-methoxyphenyl)amino)-3-vinylsuccinate (139g):** Following the general procedure K described above, **139g** was obtained after purification by silica gel column chromatography (EtOAc/hexane, 08:92) as colorless liquid (90 mg, 50%); $R_f$ = 0.40 (8% EtOAc/hexane). IR (thin film): $\tilde{\upsilon}$ = 2983, 1730, 1513, 1154, 1036 $cm^{-1}$. $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ = 6.91 (d, *J* = 9.0 Hz, 2 H), 6.75 (d, *J* = 9.0 Hz, 2 H), 5.84–5.75 (m, 1 H), 5.66–5.57 (m, 1 H), 5.27 (d, *J* = 17.1 Hz, 1 H), 5.18 (d, *J* = 10.2 Hz, 1 H), 5.07 (d, *J* = 17.1 Hz, 1 H), 5.00 (d, *J* = 10.2 Hz, 1 H), 4.46 (d, *J* = 11.2 Hz, 1 H), 4.09–3.91 (m, 5 H), 3.83–3.73 (m, 2 H), 3.71 (s, 3 H), 1.17–1.12 (m, 6 H). $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta$ = 171.4, 169.3, 154.0, 142.1, 135.6, 131.9, 120.4, 120.3, 116.5, 114.0, 66.9, 61.0, 60.6, 55.4, 51.7, 49.5, 14.3, 14.1. HRMS (ESI): calcd. for $C_{20}H_{28}NO_5$ $[M + H]^+$ 362.1967; found 362.1959.



**139g**

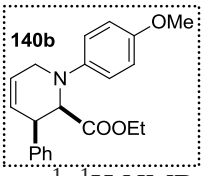
**Procedure L. Synthesis of 140a-g by RCM of Compounds 139a-g:** To the respective compounds **139a-g** (0.5 mmol, 1 equiv) in anhydrous $CH_2Cl_2$ (2 mL) was added Grubbs' 2nd generation catalyst (0.05-0.1 equiv) and the resulting reaction mixture was stirred overnight at room temperature. After completion of the reaction as indicated by the TLC, the reaction mixture was subjected to rotary evaporation. Purification of the resulting crude reaction mixture by column chromatography on silica gel (EtOAc/hexane) gave the products **140a-g** (see Scheme 60).

**(2*R**,3*R**)-Ethyl 1,3-diphenyl-1,2,3,6-tetrahydropyridine-2-carboxylate (140a):** Following the general procedure L as described above, **140a** was obtained after purification by silica gel column chromatography (EtOAc/hexane, 2:98) as a colorless solid (146 mg, 95%); mp 83–84 °C. $R_f$ = 0.56 (10% EtOAc/hexane). IR (KBr): $\tilde{\upsilon}$ = 2977, 1734, 1599, 1502, 1292, 1026 $cm^{-1}$. $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ = 7.35–7.23 (m, 7 H), 6.94 (d, *J* = 8.1 Hz, 2 H), 6.81 (t, *J* = 8.1 Hz, 1 H), 6.16 (dd, *J* = 10.1, 2.8 Hz, 1 H), 5.97 (dd, *J* = 10.1, 2.1 Hz, 1 H), 4.79 (d, *J* = 6.9 Hz, 1 H), 4.13–4.02 (m, 3 H), 3.73–3.66 (m, 1 H), 3.57–3.49 (m, 1 H), 0.74 (t, *J* = 7.1 Hz, 3 H). $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta$ = 171.0, 149.0, 140.0, 129.3, 128.5, 128.4, 127.2, 126.3, 124.0, 119.0, 114.1, 60.2,



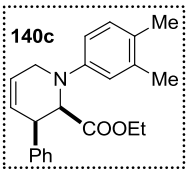
59.9, 45.3, 43.5, 13.6. HRMS (ESI): calcd. for $C_{20}H_{22}NO_2$ $[M + H]^+$ 308.1651; found 308.1663.

**(2*R**,3*R**)-Ethyl 1-(4-methoxyphenyl)-3-phenyl-1,2,3,6-tetrahydropyridine-2-carboxylate (140b):** Following the general procedure L as described above, **140b** was




obtained after purification by silica gel column chromatography (EtOAc/hexane, 3:97) as a colorless solid (126 mg, 75%); mp 67–69 °C. $R_f$ = 0.42 (3% EtOAc/hexane). IR (KBr): $\tilde{\upsilon}$ = 2983, 1723, 1514, 1184, 1040 $cm^{-1}$. $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ = 7.36–7.31 (m, 2 H), 7.29–7.25 (m, 3 H), 6.93 (d, $J$ = 9.2 Hz, 2 H), 6.84 (d, $J$ = 9.2 Hz, 2 H), 6.16 (dd, $J$ = 10.3, 3.7 Hz, 1 H), 5.96 (dd, $J$ = 10.3, 2.2 Hz, 1 H), 4.68 (d, $J$ = 6.9 Hz, 1 H), 4.18–3.94 (m, 3 H), 3.76 (s, 3 H), 3.73–3.65 (m, 1 H), 3.58–3.50 (m, 1 H), 0.73 (t, $J$ = 7.1 Hz, 3 H). $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta$ = 170.9, 153.2, 143.4, 140.1, 128.5, 128.4, 127.2, 126.4, 124.2, 116.4, 114.7, 61.6, 59.7, 55.6, 46.0, 43.7, 13.6. MS (CI): $m/z$ (%) = 338 (100) $[M + 1]^+$, 278 (7), 208 (10), 246 (10). HRMS (ESI): calcd. for $C_{21}H_{24}NO_3$ $[M + H]^+$ 338.1756; found 338.1773.

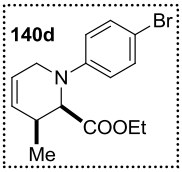
**(2*R**,3*R**)-Ethyl 1-(3,4-dimethylphenyl)-3-phenyl-1,2,3,6-tetrahydropyridine-2-carboxylate (140c):** Following the general procedure L as described above, **140c** was



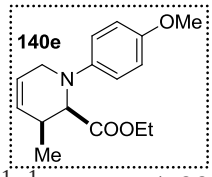

obtained after purification by silica gel column chromatography (EtOAc/hexane, 2:98) as a yellow semisolid (152 mg, 91%); $R_f$ = 0.45 (2% EtOAc/hexane). IR (neat): $\tilde{\upsilon}$ = 2922, 1732, 1615, 1512, 1024 $cm^{-1}$. $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ = 7.34–7.22 (m, 5 H), 7.00 (d, $J$ = 8.3 Hz, 1 H), 6.75 (s, 1 H), 6.70 (d, $J$ = 8.3 Hz, 1 H), 6.14 (dd, $J$ = 10.3, 2.8 Hz, 1 H), 5.94 (dd, $J$ = 10.3, 1.7 Hz, 1 H), 4.74 (d, $J$ = 6.9 Hz, 1 H), 4.13 (br. s, 1 H), 4.05 (br. s, 2 H), 3.73–3.69 (m, 1 H), 3.54–3.49 (m, 1 H), 2.21 (s, 3 H), 2.15 (s, 3 H), 0.74 (t, $J$ = 7.1 Hz, 3 H). $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta$ = 171.1, 147.3, 140.2, 137.3, 130.4, 128.5, 128.4, 127.2, 127.1, 126.5, 124.1, 116.0, 111.9, 60.6, 59.8, 45.6, 43.6, 20.4, 18.7, 13.7. HRMS (ESI): calcd. for $C_{22}H_{26}NO_2$ $[M + H]^+$ 336.1964; found 336.1968.

**(2*R**,3*S**)-Ethyl 1-(4-bromophenyl)-3-methyl-1,2,3,6-tetrahydropyridine-2-carboxylate (140d):** Following the general procedure L as described above, **140d** was obtained after purification by silica gel column chromatography (EtOAc/hexane, 2:98) as an orange oil (136 mg, 84%); $R_f$ = 0.49 (2% EtOAc/hexane). IR (neat): $\tilde{\upsilon}$ = 2977, 1732, 1590, 1494, 1022, 692 $cm^{-1}$. $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ = 7.33 (d, $J$ = 9.2 Hz, 2 H), 6.76 (d, $J$ = 9.2 Hz, 2

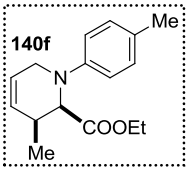
H), 5.88 (dd, *J* = 10.2, 3.1 Hz, 1 H), 5.58 (dd, *J* = 10.2, 2.2 Hz, 1 H), 4.51 (d, *J* = 6.6 Hz, 1 H), 4.08 (q, *J* = 7.1 Hz, 2 H), 3.95–3.79 (m, 2 H), 2.91–2.86 (m, 1 H), 1.91–1.14 (m, 6 H). $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ = 171.3, 148.1, 131.9, 126.8, 123.9, 115.2, 110.6, 60.4, 59.0, 45.4, 32.0, 17.4, 14.4. MS (CI): *m*/*z* (%) = 325 (95) $[M + 2]^+$, 324 (100) $[M + 1]^+$, 246 (30), 172 (10). HRMS (ESI): calcd. for $C_{15}H_{19}NO_2Br$ $[M + H]^+$ 324.0599; found 324.0594.




**(2*R**,3*S**)-Ethyl 1-(4-methoxyphenyl)-3-methyl-1,2,3,6-tetrahydropyridine-2-carboxylate (140e):** Following the general procedure L as described above, **140e** was obtained after purification by silica gel column chromatography (EtOAc/hexane, 3:97) as a brown solid (104 mg, 76%); mp 55–57 °C. $R_f$ = 0.50 (3% EtOAc/hexane). IR (KBr): $\tilde{\upsilon}$ = 2961, 1727, 1514, 1171, 1032 $cm^{-1}$. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 6.88–6.81 (m, 4 H), 5.88 (dd, *J* = 10.1, 3.1 Hz, 1 H), 5.56 (dd, *J* = 10.1, 2.1 Hz, 1 H), 4.45 (d, *J* = 6.6 Hz, 1 H), 4.05 (q, *J* = 7.1 Hz, 2 H), 3.89–3.85 (m, 2 H), 3.75 (s, 3 H), 2.91 (br. s, 1 H), 1.16 (t, *J* = 7.1 Hz, 3 H), 1.11 (d, *J* = 7.5 Hz, 3 H). $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ = 171.7, 152.9, 143.6, 126.8, 124.4, 115.8, 114.6, 60.3, 60.1, 55.6, 46.0, 32.2, 17.4, 14.4. HRMS (ESI): calcd. for $C_{16}H_{22}NO_3$ $[M + H]^+$ 276.1600; found 276.1613.

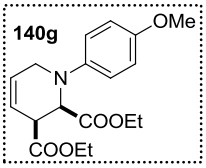



**(2*R**,3*S**)-Ethyl 3-methyl-1-(*p-tolyl*)-1,2,3,6-tetrahydropyridine-2-carboxylate (140f):** Following the general procedure L as described above, **140f** was obtained after purification by silica gel column chromatography (EtOAc/hexane, 2:98) as a colorless oil (78 mg, 60%); $R_f$ = 0.46 (2% EtOAc/hexane). IR (neat): $\tilde{\upsilon}$ = 2976, 1738, 1519, 1450, 1156, 1023 $cm^{-1}$. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 7.05 (d, *J* = 8.6 Hz, 2 H), 6.81 (d, *J* = 8.6 Hz, 2 H), 5.88 (dd, *J* = 10.1, 3.1 Hz, 1 H), 5.56 (dd, *J* = 10.1, 2.1 Hz, 1 H), 4.53 (d, *J* = 6.6 Hz, 1 H), 4.06 (q, *J* = 7.1 Hz, 2 H), 3.97–3.84 (m, 2 H), 2.89 (br. s, 1 H), 2.24 (s, 3 H), 1.16 (t, *J* = 7.1 Hz, 3 H), 1.12 (d, *J* = 7.6 Hz, 3 H). $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ = 171.7, 147.0, 129.8, 127.8, 126.8, 124.4, 113.9, 60.1, 59.4, 45.6, 32.1, 20.3, 17.4, 14.4. HRMS (ESI): calcd. for $C_{16}H_{22}NO_2$ $[M + H]^+$ 260.1651; found 260.1663.



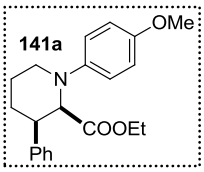

**(2*R**,3*S**)-Diethyl 1-(4-methoxyphenyl)-1,2,3,6-tetrahydropyridine-2,3-dicarboxylate (140g):** Following the general procedure L described above, **140g** was obtained after purification by silica gel column chromatography (EtOAc/hexane, 10:90) as colorless oil (153 mg, 92%); $R_f$ = 0.41 (10% EtOAc/hexane). IR (thin film): $\tilde{\upsilon}$ = 2983, 1736, 1512, 1248,

1032 $cm^{-1}$. $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ = 6.90 (d, $J$ = 9.3 Hz, 2 H), 6.85 (d, $J$ = 9.3 Hz, 2 H), 6.25–6.21 (m, 1 H), 5.92–5.87 (m, 1 H), 5.04 (d, $J$ = 5.0 Hz, 1 H), 4.22 (q, $J$ = 7.1 Hz, 2 H), 4.12–3.95 (m, 2 H), 3.79–3.75 (m, 2 H), 3.77 (s, 3 H), 3.67 (br. s, 1 H), 1.30 (t, $J$ = 7.2 Hz, 3 H), 1.11 (t, $J$ = 7.1 Hz, 3 H). $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta$ = 170.6, 170.0, 153.2, 143.4, 125.8, 122.1, 116.6, 114.5, 61.0, 60.9, 59.0, 55.6, 45.6, 43.7, 14.2, 14.1. HRMS (ESI): calcd. for $C_{18}H_{24}NO_5$ $[M + H]^+$ 334.1654; found 334.1660.



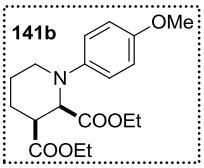

**Procedure J. Hydrogenation of *N*-aryl tetrahydropyridine derivatives (140b and 140g) to *N*-aryl piperidine derivatives (141a and 141b):** A dry flask containing *N*-aryl tetrahydropyridine derivatives **140b/140g** (0.15 mmol, 1 equiv) in anhydrous THF (2 mL) was charged with Pd-C (10 mol-%) and the contents were stirred under $H_2$ (1 atm) at room temperature. After disappearance of starting material (reaction monitored by TLC) the reaction mixture was filtered through a Celite pad and rinsed with EtOAc (20 mL). The solvent was removed by rotary evaporation and the product was purified by column chromatography on silica gel (EtOAc/hexane) to afford the *N*-aryl piperidine derivatives **141a** and **141b** (see Scheme 61).

**(2*R**,3*R**)-Ethyl 1-(4-methoxyphenyl)-3-phenylpiperidine-2-carboxylate (141a):** Following the general procedure J as described above, **141a** was obtained after purification by silica gel column chromatography (EtOAc/hexane, 4:96) as a colorless oil (27 mg, 54%); $R_f$ = 0.45 (4% EtOAc/hexane). IR (neat): $\tilde{\upsilon}$ = 2930, 1727, 1602, 1512, 1148, 1037 $cm^{-1}$. $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ = 7.24–7.13 (m, 5 H), 6.87 (d, $J$ = 9.0 Hz, 2 H), 6.72 (d, $J$ = 9.0 Hz, 2 H), 4.44 (d, $J$ = 5.6 Hz, 1 H), 3.66 (s, 3 H), 3.64–3.52 (m, 3 H), 3.26–3.23 (m, 2 H), 2.30–2.19 (m, 1 H), 2.01–1.97 (m, 1 H), 1.79–1.73 (m, 1 H), 1.17 (s, 1 H), 0.62 (t, $J$ = 7.1 Hz, 3 H). $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta$ = 171.4, 153.6, 144.5, 141.5, 128.3, 127.8, 126.9, 118.3, 114.3, 65.6, 59.4, 55.5, 44.6, 44.3, 25.6, 23.4, 13.7. MS (CI): $m/z$ (%) = 340 (100) $[M + 1]^+$, 288 (10).



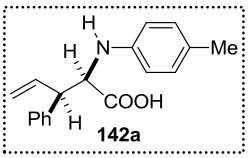

**(2*R**,3*S**)-Diethyl 1-(4-methoxyphenyl)piperidine-2,3-dicarboxylate (141b):** Following the general procedure J described above, **141b** was obtained after purification by silica gel column chromatography (EtOAc/hexane, 10:90) as colorless liquid (33 mg, 65%); $R_f$ = 0.41 (10% EtOAc/hexane). IR (thin film): $\tilde{\upsilon}$ = 2940, 1732, 1512, 1242, 1037 $cm^{-1}$. $^1H$ NMR (400

MHz, $CDCl_3$): $\delta$ = 6.93 (d, $J$ = 9.1 Hz, 2 H), 6.83 (d, $J$ = 9.1 Hz, 2 H), 4.82 (d, $J$ = 5.0 Hz, 1 H), 4.18 (q, $J$ = 7.1 Hz, 2 H), 4.07–3.98 (m, 2 H), 3.76 (s, 3 H), 3.32–3.19 (m, 2 H), 2.93–2.88 (m, 1 H), 2.07–2.02 (m, 1 H), 1.89–1.75 (m, 2 H), 1.72–1.62 (m, 1 H), 1.28 (t, $J$ = 7.1 Hz, 3 H), 1.10 (t, $J$ = 7.1 Hz, 3 H). $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ = 172.3, 170.4, 153.5, 144.7, 118.6, 114.3, 61.7, 60.6, 60.5, 55.6, 44.5, 44.3, 24.5, 22.0, 14.2, 14.1. HRMS (ESI): calcd. for $C_{18}H_{26}NO_5$ $[M + H]^+$ 336.1811; found 336.1807.

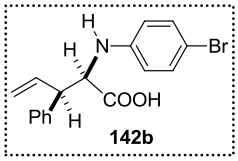



**Procedure M. Hydrolysis of the *N*-aryl α-amino esters 124a**, **124c and 140f for the synthesis of unnatural *N*-aryl α-amino acids 142a-c:** The respective *N*-aryl α-amino ester **124a**/**124c**/**140f** (0.5 mmol, 1 equiv) was hydrolyzed by heating to reflux with 1M aq. potassium hydroxide (3 mL) and methanol (1 mL) for 48 h. After this period the reaction mixture was cooled to room temperature, transferred to a separating flask, and washed with $CH_2Cl_2$ (2x10 mL). To the reaction mixture was added 2 N aq. HCl dropwise and the solid products were filtered to afford the corresponding *N*-aryl α-amino acids **142a-c** (see Scheme 62).

**(2*R**,3*R**)-3-Phenyl-2-(*p*-tolylamino)pent-4-enoic acid (142a):** Following the general procedure M as described above, **142a** was obtained as a yellowish white solid (77 mg, 55%); mp 116–118 °C. IR (KBr): $\tilde{\upsilon}$ = 3247, 3134, 2604–2361, 1709, 1544, 1509, 1246 cm$^{-1}$. $^1$H NMR (400 MHz, $CDCl_3$ + DMSO-$d_6$): $\delta$ = 7.27 (d, $J$ = 4.3 Hz, 4 H), 7.22–7.19 (m, 1 H), 6.99 (d, $J$ = 8.2 Hz, 2 H), 6.84 (d, $J$ = 8.2 Hz, 2 H), 6.22–6.16 (m, 1 H), 5.69 (br. s, 2 H), 5.28–5.19 (m, 2 H), 4.28 (d, $J$ = 7.0 Hz, 1 H), 4.02 (t, $J$ = 7.0 Hz, 1 H), 2.22 (s, 3 H). $^{13}$C NMR (100 MHz, $CDCl_3$ + DMSO-$d_6$): $\delta$ = 177.1, 144.1, 141.1, 134.9, 134.5, 133.4, 132.9, 131.9, 128.1, 123.1, 121.8, 68.7, 56.4, 25.3. MS (CI): $m/z$ (%) = 282 (45) $[M + 1]^+$, 236 (100), 207 (10).

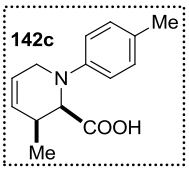



**(2*R**,3*R**)-2-[(4-Bromophenyl)amino]-3-phenylpent-4-enoic acid (142b):** Following the general procedure M as described above, **142b** was obtained as a colorless solid (112 mg, 65%); mp 100–102 °C. IR (KBr): $\tilde{\upsilon}$ = 3571, 3378, 3079–2549, 1713, 1595, 1502, 1273, 702 cm$^{-1}$. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 7.33–7.20 (m, 7 H), 6.46 (d, $J$ = 8.9 Hz, 2 H), 6.16–6.07 (m, 1 H), 5.23–5.18 (m, 2 H), 5.01 (br. s, 2 H), 4.29 (d, $J$ = 7.5 Hz, 1 H), 3.82 (t, $J$ = 7.5 Hz, 1 H). $^{13}$C NMR (100 MHz,

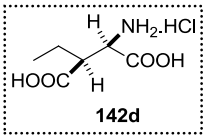


$CDCl_3$): $\delta$ = 177.1, 145.7, 138.7, 136.7, 132.0, 128.9, 128.1, 127.5, 118.0, 115.4, 110.5, 61.3, 52.7. MS (CI): *m*/*z* (%) = 348 (45) $[M + 3]^+$, 346 (50) $[M + 1]^+$, 302 (95), 300 (100), 206 (11). HRMS (ESI): calcd. for $C_{17}H_{17}BrNO_2$ $[M + H]^+$ 346.0443; found 346.0447.

**(2*R**,3*S**)-3-Methyl-1-(*p*-*tolyl*)-1,2,3,6-tetrahydropyridine-2-carboxylic acid (142c):** Following the general procedure M as described above, **142c** was obtained (as a mixture of diastereomers, *dr* 80:20) as a semisolid (104 mg, 90%); IR ($CDCl_3$): $\tilde{\upsilon}$ = 3543–2852, 1714, 1518, 1215, 1037 $cm^{-1}$. $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ = 9.65 (br. s, 1 H), 7.03 (d, *J* = 8.1 Hz, 2 H), 6.72 (d, *J* = 8.1 Hz, 2 H), 5.82–5.71 (m, 2 H), 4.33 (s, 1 H), 3.87–3.76 (m, 2 H), 2.87 (br. s, 1 H), 2.23 (s, 3 H), 1.20 (d, *J* = 6.9 Hz, 3 H). $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta$ = 178.2, 147.9, 129.8, 127.8, 126.9, 124.0, 113.7, 60.9, 45.1, 33.3, 20.3, 17.4. MS (CI): *m*/*z* (%) = 232 (100) $[M + 1]^+$, 200 (50), 188 (70), 120 (5). NMR spectroscopic data given here refers to the major diastereomer.

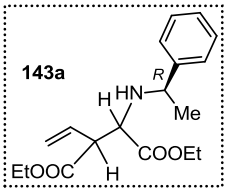



**(2*R**,3*S**)-2-Amino-3-ethylsuccinic acid hydrochloride (142d):** To the *N*-aryl α-amino ester **138b** (0.2 mmol, 1 equiv) in MeCN (2 mL) was added aqueous solution of both $(NH_4)_2S_2O_8$ (2 equiv) and ammonium ceric (III) nitrate (0.1 equiv) at 0 °C. The resulting reaction mixture was stirred for 3 h at 35 °C. After this period, the reaction mixture was washed with DCM (2 mL) and treated with $Na_2CO_3$ to obtain the pH 7. Then, the product was extracted using DCM (5x1 mL). The combined organic layers were dried over anhydrous $Na_2SO_4$. The solvent was evaporated under vacuum, which gave a crude mixture. To this crude reaction mixture 6 N HCl (5 mL) was added and refluxed for 3 h. After completion of the reaction, the reaction mixture was cooled to room temperature and the solvent was removed under vacuum that gave the product **142d** as colorless viscous liquid (20 mg, 50%): IR (thin film): $\tilde{\upsilon}$ = 3562, 3060–2575, 1715, 1273 $cm^{-1}$. $^1H$ NMR (400 MHz, $D_2O$): $\delta$ = 4.17 (d, *J* = 4.0 Hz, 1 H), 3.07–3.02 (m, 1 H), 1.80–1.71 (m, 1 H), 1.59–1.52 (m, 1 H), 0.91 (t, *J* = 8.0 Hz, 3 H). $^{13}C$ NMR (100 MHz, $D_2O$): $\delta$ = 175.7, 53.1, 46.2, 21.1,11.0; MS (CI): *m*/*z* (%) = 162 (100) $[M + 1]^+$, 144 (12), 101 (10). HRMS (ESI): calcd. for $C_6H_{12}NO_4$ $[M + H]^+$ 162.0766; found 162.0777. (OH protons could not be detected perhaps due to the rapid exchange with the $D_2O$ solvent). The NMR values given here for the major isomer and the NMR spectrum were having some traces of minor diastereomer.

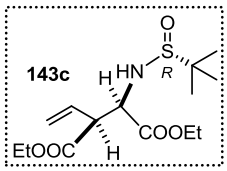


**Procedure G. In-mediated addition of 4-bromocrotonates (123e or 123f) to α-imino esters 100r-u:** To a vigorously stirring solution of α-imino ester **100r-u** (0.5 mmol, 1 equiv) and ethyl 4-bromocrotonate (**123e**) or methyl-4-bromo crotonate (**123f**; 1.5 mmol, 3 equiv) in EtOH (2 mL) was added indium powder (1 mmol, 2 equiv). The mixture was allowed to stir vigorously for 12 h at 30 $^{o}$C. After this period, the reaction mixture was quenched with 2 mL of water and transferred to a separating funnel and extracted using ethyl acetate (3x15 mL). The combined organic layers were dried over anhydrous $Na_2SO_4$. Then the solvent was evaporated under vacuum. Purification of the resulting crude reaction mixture by column chromatography on silica gel (EtOAc/hexane as eluent) gave the product **143a-e** (see Schemes 63 and 64).

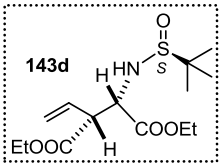
**Diethyl 2-(((*R*)-1-phenylethyl)amino)-3-vinylsuccinate (143a):** Following the general procedure G described above, **143a** was obtained after purification by silica gel column chromatography (EtOAc/hexane, 20:80) as colorless liquid (96 mg, 60%); $R_f$ = 0.75 (20% EtOAc/hexane). $[\alpha]_D^{25}$ = +42.8 (*c* 0.14, DCM). IR (thin film): $\tilde{\upsilon}$ = 3324, 2980, 1734, 1452, 1369, 1305,1158, 1030 cm$^{-1}$. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 7.31–7.24 (m, 5 H), 5.89–5.80 (m, 1 H), 5.21 (d, *J* = 5.6 Hz, 1 H), 5.18 (s, 1 H), 4.24–4.17 (m, 2 H), 4.05–3.94 (m, 2 H), 3.77–3.72 (q, 1 H), 3.69 (d, *J* = 8.8 Hz, 1 H), 3.29–3.25 (t, 1 H), 1.33–1.23 (m, 7 H), 1.19-1.16 (t, 3 H). $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ = 173.05, 171.54, 145.27, 132.02, 128.38, 128.27, 127.16, 127.05, 126.71, 119.80, 61.36, 60.90, 60.70, 56.75, 54.97, 22.81, 14.23, 14.18. HRMS (ESI): calcd. for $C_{18}H_{26}NO_4$ $[M + H]^+$ 320.1862; found 320.1870.



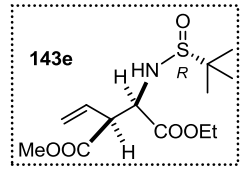

**(2*R*,3*S*)-Diethyl 2-((*R*)-1,1-dimethylethylsulfinamido)-3-vinylsuccinate (143c):** Following the general procedure G as described above, **143c** was obtained after purification by silica gel column chromatography (EtOAc/hexane, 30:70) as colorless liquid (144 mg, 90%); $R_f$ = 0.43 (30% EtOAc/hexane). $[\alpha]_D^{25}$ = –56.4 (*c* 0.20, DCM). IR (neat): $\tilde{\upsilon}$ = 3430, 2983, 1733, 1468, 1084 cm$^{-1}$. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 5.88-5.79 (m, 1 H), 5.28-5.22 (m, 2 H), 4.25-4.11 (m, 6 H), 3.45-3.41 (m, 1 H), 1.30-1.25 (m, 6 H), 1.23 (s, 9 H). $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ = 171.2, 170.5, 131.2, 120.6, 62.0, 61.3, 60.2, 56.4, 54.6, 22.6, 14.1, 14.1. HRMS: (ESI) calcd for $C_{14}H_{26}NO_5S$ $[M + H]^+$ 320.1531; found 320.1534.



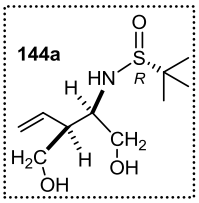
**(2*S*,3*R*)-Diethyl 2-((*S*)-1,1-dimethylethylsulfinamido)-3-vinylsuccinate (143d):** Following the general procedure G as described above, **143d** was obtained after purification by silica gel column chromatography (EtOAc/hexane, 30:70) as colorless liquid (112 mg, 70%); $R_f$ = 0.43 (30% EtOAc/hexane). $[\alpha]_D^{25}$ = +79.9 (*c* 0.20, DCM). IR (neat): $\tilde{\upsilon}$ = 3376, 2982, 1733, 1469, 1368, 1082 $cm^{-1}$. $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ = 5.88-5.78 (m, 1 H), 5.27-5.22 (m, 2 H), 4.25-4.12 (m, 6 H), 3.45-3.41 (m, 1 H), 1.30-1.24 (m, 6 H), 1.22 (s, 9 H). $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta$ = 171.1, 170.4, 131.2, 120.6, 62.0, 61.2, 60.2, 56.4, 54.6, 22.6, 14.1, 14.1. HRMS: (ESI) calcd for $C_{14}H_{25}NNaO_5S$ $[M + Na]^+$ 342.1351; found 342.1351.




**(2*R*,3*S*)-1-Ethyl 4-methyl 2-((*R*)-1,1-dimethylethylsulfinamido)-3-vinylsuccinate (143e):** Following the general procedure G as described above, **143e** was obtained after purification by silica gel column chromatography (EtOAc/hexane, 30:70) as colorless liquid (99 mg, 65%); $R_f$ = 0.42 (30% EtOAc/hexane). $[\alpha]_D^{25}$ = –62.2 (*c* 0.13, $CHCl_3$). IR (neat): $\tilde{\upsilon}$ = 3283, 2983, 1732, 1438, 1078 $cm^{-1}$. $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ = 5.77-5.68 (m, 1 H), 5.18-5.13 (m, 2 H), 4.15-4.10 (m, 4 H), 3.61 (s, 3 H), 3.36 (dd, *J* = 9.0, 7.2 Hz, 1 H), 1.19 (t, *J* = 7.2 Hz, 3 H), 1.13 (s, 9 H). $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta$ = 171.1, 171.0, 131.0, 120.8, 62.0, 56.5, 54.6, 52.3, 22.6, 14.1. HRMS: (ESI) calcd for $C_{13}H_{24}NO_5S$ $[M + H]^+$ 306.1375; found 306.1387.

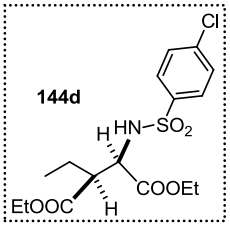



**(*R*)-*N*-((2*R*,3*S*)-1-Hydroxy-3-(hydroxymethyl)pent-4-en-2-yl)-2-methylpropane-2-sulfinamide (144a):** A dry flask was charged with anhydrous THF (4 mL) and the respective *N*-aryl α-amino ester (**143c**; 0.5 mmol) under a nitrogen atmosphere at 0 °C. To this solution was added $LiAlH_4$ (2 mmol) in portions and the mixture was stirred for 12 h at room temperature. EtOH (few drops) and 5% aq. NaOH solution (1–2 mL) were then added sequentially and the resulting white suspension was filtered through a Celite pad and rinsed with THF (20 mL). The filtrate was dried with anhydrous $Na_2SO_4$, the solvent was removed by rotary evaporation, and the product was purified by column chromatography on silica gel (EtOAc/hexane) to afford the respective *N*-aryl β-amino alcohols **144a** (EtOAc/hexane, 50:50) as colorless oil (65 mg, 55%); $R_f$ = 0.38 (50% EtOAc/hexane). $[\alpha]_D^{25}$ = –16.2 (*c* 0.24, DCM). IR (neat): $\tilde{\upsilon}$ = 3290, 2921, 1467, 1011 $cm^{-1}$. $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ = 5.67-5.58 (m, 1 H), 5.13-5.09 (m, 2 H), 4.21 (br. s, 1 H), 3.84 (d, *J* = 9.8 Hz, 1 H), 3.75 (d, *J* = 11.4 Hz, 1 H), 3.66 (dd, *J* = 11.4,



6.2 Hz, 1 H), 3.58-3.50 (m, 2 H), 3.35-3.28 (m, 1 H), 2.90 (br. s, 1 H), 2.42-2.35 (m, 1 H), 1.17 (s, 9 H). $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ = 136.2, 118.7, 64.5, 62.8, 60.9, 56.4, 49.4, 22.8. HRMS: (ESI) calcd for $C_{10}H_{21}NO_3SNa$: $[M + Na]^+$ 258.1134; found 258.1126.

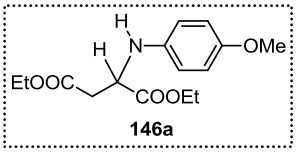
**(2*R*,3*S*)-Diethyl 2-(4-chlorophenylsulfonamido)-3-ethylsuccinate (144d):** HCl gas was bubbled through the ethanolic solution (5 mL) of compound **143c** (0.5 mmol) for 5 h. Then the crude deprotected amine **144b** was subjected to the catalytic olefin hydrogenation in the presence of Pd-carbon (10 mol%) in THF (5 mL). After the completion of reaction as indicated by crude $^1$H-NMR, the reaction mixture was dissolved in DCM (6 mL) and triethyl amine (3 equiv) and *p*-chlorobenzene sulfonyl chloride (3 equiv) was added to it at 0 $^o$C. The resulting reaction mixture was allowed to stir for 2-5 h at 0 $^o$C. After completion of the reaction as indicated by the TLC, saturated aqueous $NaHCO_3$ solution (5-6 mL) was added and the resulting reaction mixture was transferred to a separating flask and extracted using DCM (3x15 mL). The combined organic layers were dried over anhydrous $Na_2SO_4$. Then the solvent was evaporated under vacuum. Purification of the resulting crude reaction mixture by column chromatography on silica gel (EtOAc/hexane, 40:60) gave the product **144d** as a colorless solid (35 mg, 45%); mp 100-102 °C. $R_f$ = 0.56 (40% EtOAc/hexane). $[\alpha]_D^{25}$ = –94.4 (*c* 0.22, DCM). IR (neat): $\tilde{\upsilon}$ = 3380, 2927, 1737, 1586, 1385, 1024 cm$^{-1}$. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 7.81 (d, *J* = 8.6 Hz, 2 H), 7.48 (d, *J* = 8.6 Hz, 2 H), 5.77 (d, *J* = 9.7 Hz, 1 H), 4.16-4.09 (m, 3 H), 3.96 (q, *J* = 7.1 Hz, 2 H), 2.89-2.84 (m, 1 H), 1.88-1.81 (m, 1 H), 1.71-1.64 (m, 1 H), 1.24 (t, *J* = 7.2 Hz, 3 H), 1.08 (t, *J* = 7.1 Hz, 3 H), 1.02 (t, *J* = 7.4 Hz, 3 H). $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ = 173.0, 170.1, 139.2, 138.8, 129.2, 128.7, 62.0, 61.2, 60.0, 49.0, 21.9, 14.1, 13.8, 11.8. HRMS: (ESI) calcd for $C_{16}H_{22}ClNNaO_6S$: $[M + Na]^+$ 414.0754; found 414.0763.




**Procedure N: In-mediated addition of α-halo esters (145a-j) to α-imino esters 100:** To a vigorously stirring solution of α-imino ester **100** (0.25 or 0.5 mmol, 1 equiv) and α-halo ester (**145a-j**; 0.75 or 1.5 mmol, 3 equiv) in THF/DMF (1 mL) was added indium powder (0.5 or 1 mmol, 2 equiv). The mixture was allowed to stir vigorously at 30 $^o$C for given time. After this period, the reaction mixture was quenched with 2 mL of water and transferred to a separating funnel and extracted using ethyl acetate (3x15 mL). The combined organic layers were dried over anhydrous $Na_2SO_4$. Then the solvent was evaporated under vacuum.

Purification of the resulting crude reaction mixture by column chromatography on silica gel (EtOAc/hexane as eluent) gave the product **146**/**147**/**148** (see Tables 15 and 16 and Schemes 67 and 68 for individual entries).

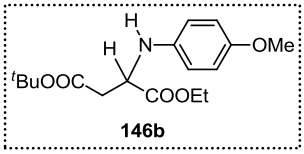
**Diethyl 2-(4-methoxyphenylamino)succinate (146a):** Following the general procedure N described above, **146a** was obtained after purification by silica gel column chromatography



**146a**

(EtOAc/hexane, 10:90) as colorless liquid (48 mg, 65%); $R_f$ = 0.36 (10% EtOAc/hexane). IR (thin film): $\tilde{\upsilon}$ = 3368, 2983, 1730, 1512, 1029 cm$^{-1}$. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 6.77 (d, $J$ = 9.0 Hz, 2 H), 6.65 (d, $J$ = 9.0 Hz, 2 H), 4.34 (t, $J$ = 6.0 Hz, 1 H), 4.22–4.13 (m, 4 H), 3.73 (s, 3 H), 2.82 (d, $J$ = 6.0 Hz, 2 H), 1.27–1.22 (m, 6 H). $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ = 172.7, 170.6, 153.1, 140.4, 115.8, 114.8, 61.5, 61.0, 55.7, 55.0, 37.7, 14.2, 14.1. HRMS: (ESI) calcd. for $C_{15}H_{22}NO_5$ $[M + H]^+$ 296.1498; found 296.1509.

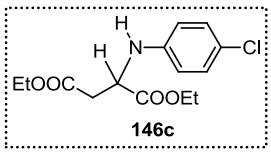
**4-*tert*-Butyl 1-ethyl 2-(4-methoxyphenylamino)succinate (146b):** Following the general procedure N described above, **146b** was obtained after purification by silica gel column



**146b**

chromatography (EtOAc/hexane, 10:90) as colorless liquid (32 mg, 40%); $R_f$ = 0.37 (10% EtOAc/hexane). IR (thin film): $\tilde{\upsilon}$ = 3385, 2979, 1731, 1514, 1155 cm$^{-1}$. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 6.75 (d, $J$ = 8.9 Hz, 2 H), 6.62 (d, $J$ = 8.9 Hz, 2 H), 4.26 (t, $J$ = 5.9 Hz, 1 H), 4.19–4.12 (m, 2 H), 3.71 (s, 3 H), 2.71 (d, $J$ = 5.9 Hz, 2 H), 1.42 (s, 9 H), 1.23–1.20 (m, 4 H). $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ = 172.8, 169.8, 153.0, 140.6, 115.7, 114.9, 114.8, 81.4, 61.4, 55.7, 55.1, 38.8, 28.1, 28.1, 14.2. HRMS: (ESI) calcd. for $C_{17}H_{26}NO_5$ $[M + H]^+$ 324.1811; found 324.1791.

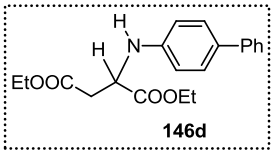
**Diethyl 2-(4-chlorophenylamino)succinate (146c):** Following the general procedure N described above, **146c** was obtained after purification by silica gel column chromatography



**146c**

(EtOAc/hexane, 10:90) as colorless liquid (52 mg, 69%); $R_f$ = 0.38 (10% EtOAc/hexane). IR (thin film): $\tilde{\upsilon}$ = 3382, 2982, 1732, 1498, 1202 cm$^{-1}$. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 7.04 (d, $J$ = 8.8 Hz, 2 H), 6.51 (d, $J$ = 8.8 Hz, 2 H), 4.29 (t, $J$ = 5.8 Hz, 1 H), 4.15–4.04 (m, 4 H), 2.76 (dd, $J$ = 5.8, 3.2 Hz, 2 H), 1.16 (t, $J$ = 7.1 Hz, 6 H). $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ = 172.1, 170.5, 145.0, 129.2, 123.3, 114.9, 61.7, 61.1, 53.6, 37.3, 14.1, 14.1. HRMS: (ESI) calcd. for $C_{14}H_{19}NO_4Cl$ $[M + H]^+$ 300.1003; found 300.0999.

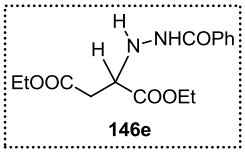
**Diethyl 2-([1,1'-biphenyl]-4-ylamino)succinate (146d):** Following the general procedure N described above, **146d** was obtained after purification by silica gel column chromatography



**146d**

(EtOAc/hexane, 09:91) as yellow color liquid (57 mg, 67%); $R_f$ = 0.39 (9% EtOAc/hexane). IR (thin film): $\tilde{\upsilon}$ = 3395, 2982, 1734, 1609, 1229 $cm^{-1}$. $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ = 7.51–7.49 (m, 2 H), 7.42 (d, $J$ = 8.6 Hz, 2 H), 7.36 (t, $J$ = 7.5 Hz, 2 H), 7.23 (t, $J$ = 7.5 Hz, 1 H), 6.72 (d, $J$ = 8.6 Hz, 2 H), 4.46 (t, $J$ = 5.7 Hz, 1 H), 4.31–4.16 (m, 3 H), 4.14 (q, $J$ = 7.2 Hz, 2 H), 2.86 (dd, $J$ = 5.8, 2.5 Hz, 2 H), 1.24 (dt, $J$ = 7.1 Hz, 2.5 Hz, 6 H). $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta$ = 172.3, 170.6, 145.7, 141.0, 131.6, 128.7, 128.1, 126.4, 126.3, 114.0, 61.7, 61.1, 53.5, 37.5, 14.2. HRMS: (ESI) calcd. for $C_{20}H_{23}NO_4Na$ $[M + Na]^+$ 364.1525; found 364.1525.

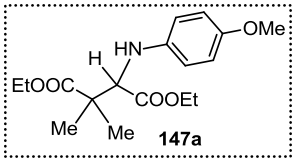
**Diethyl 2-(benzamido)succinate (146e):** Following the general procedure N described above, **146e** was obtained after purification by silica gel column chromatography



**146e**

(EtOAc/hexane, 20:80) as colorless oil (46 mg, 60%); $R_f$ = 0.31 (20% EtOAc/hexane). IR (thin film): $\tilde{\upsilon}$ = 3291, 2928, 1733, 1529, 1028 $cm^{-1}$. $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ = 8.09 (br. s, 1 H), 7.76–7.74 (m, 2 H), 7.54–7.50 (m, 1 H), 7.43 (t, $J$ = 7.7 Hz, 2 H), 5.45 (br. s, 1 H), 4.28–4.14 (m, 4 H), 4.08–4.04 (m, 1 H), 2.87 (d, $J$ = 5.3 Hz, 2 H), 1.30–1.24 (m, 6 H). $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta$ = 171.7, 170.8, 167.1, 132.5, 132.0, 128.7, 127.0, 61.6, 61.1, 59.3, 35.6, 14.1. HRMS: (ESI) calcd. for $C_{15}H_{20}N_2O_5Na$ $[M + Na]^+$ 331.1270; found 331.1266.

**Diethyl 3-((4-methoxyphenyl)amino)-2,2-dimethylsuccinate (147a):** Following the general procedure N described above, **147a** was obtained after purification by silica gel column

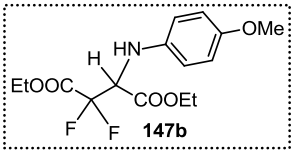


**147a**

chromatography (EtOAc/hexane, 9:91) as colorless liquid (137 mg, 85%); $R_f$ = 0.40 (9% EtOAc/hexane). IR (thin film): $\tilde{\upsilon}$ = 3371, 2982, 1728, 1512, 1238 $cm^{-1}$. $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ = 6.75 (d, $J$ = 9.0 Hz, 2 H), 6.68 (d, $J$ = 9.0 Hz, 2 H), 4.24 (br. s, 1 H), 4.24–4.10 (m, 5 H), 3.72 (s, 3 H), 1.29–1.24 (m, 9 H), 1.20 (t, $J$ = 7.2 Hz, 3 H). $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta$ = 175.6, 172.2, 153.1, 141.4, 116.1, 114.7, 64.7, 61.2, 61.0, 55.7, 45.9, 22.5, 21.6, 14.2, 14.1. HRMS: (ESI) calcd. for $C_{17}H_{26}NO_5$ $[M + H]^+$ 324.1811; found 324.1797.

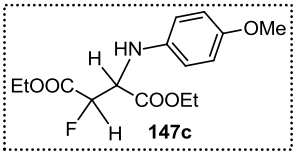
**Diethyl 2,2-difluoro-3-((4-methoxyphenyl)amino)succinate (147b):** Following the general procedure N described above, **147b** was obtained after purification by silica gel column chromatography (EtOAc/hexane, 11:89) as colorless liquid (66 mg, 40%); $R_f$ = 0.36 (11%

EtOAc/hexane). IR (thin film): $\tilde{\upsilon}$ = 3363, 2988, 1745, 1514, 1199 $cm^{-1}$. $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ = 6.77 (d, $J$ = 9.1 Hz, 2 H), 6.71 (d, $J$ = 9.1 Hz, 2 H), 4.64 (dd, $J$ = 15.8, 10.0 Hz, 1 H), 4.63–4.19 (m, 5 H), 3.73 (s, 3 H), 1.32 (t, $J$ = 7.1 Hz, 3 H), 1.26 (t, $J$ = 7.1 Hz, 3 H). $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta$ = 167.5 ($J_{C–F}$ = 3.2 Hz), 162.4 ($J_{C–F}$ = 30.7 Hz), 154.0, 139.6, 116.7, 114.8, 63.4, 62.6, 61.6 ($J_{C–F}$ = 23.2 Hz), 61.3 ($J_{C–F}$ = 23.0 Hz), 55.7, 14.0, 13.9. HRMS: (ESI) calcd. for $C_{15}H_{20}F_2NO_5$ $[M + H]^+$ 332.1310; found 332.1300.



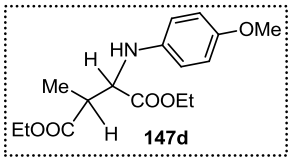
147b

**Diethyl 2-fluoro-3-((4-methoxyphenyl)amino)succinate (147c):** Following the general procedure N described above, **147c** was obtained after purification by silica gel column chromatography (EtOAc/hexane, 11:89) as colorless liquid (92 mg, 59%); $R_f$ = 0.35 (11% EtOAc/hexane). IR (thin film): $\tilde{\upsilon}$ = 3369, 2963, 1746, 1515, 1033 $cm^{-1}$. $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ = 6.75–6.69 (m, 2 H), 6.64–6.60 (m, 2 H), 5.40–5.14 (m, 1 H), 4.57–4.45 (m, 1 H), 4.31–4.14 (m, 4 H), 3.68 (s, 3 H), 1.30–1.18 (m, 6 H). $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta$ = 169.6 ($J_{C–F}$ = 2.3 Hz), 168.4 ($J_{C–F}$ = 6.7 Hz), 167.1 ($J_{C–F}$ = 8.4 Hz), 166.9 ($J_{C–F}$ = 4.2 Hz), 153.7, 153.4, 140.3, 139.6, 116.7, 115.8, 115.0, 114.7, 90.0 ($J_{C–F}$ = 80.0 Hz), 88.1 ($J_{C–F}$ = 81.8 Hz), 62.3, 62.2, 62.1, 62.0, 60.6 ($J_{C–F}$ = 19.7 Hz), 60.2 ($J_{C–F}$ = 21.5 Hz), 55.7, 55.6, 14.1, 14.0. HRMS: (ESI) calcd. for $C_{15}H_{21}FNO_5$ $[M + H]^+$ 314.1404; found 314.1391. $^{13}C$ data given here for the mixture of diastereomers.



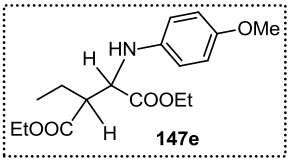
147c

**Diethyl 2-((4-methoxyphenyl)amino)-3-methylsuccinate (147d):** Following the general procedure N described above, **147d** was obtained after purification by silica gel column chromatography (EtOAc/hexane, 9:91) as colorless liquid (98 mg, 66%): $R_f$ = 0.42 (9% EtOAc/hexane); IR (thin film): $\tilde{\upsilon}$ = 3376, 2983, 1731, 1515, 1037 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ = 6.78-6.74 (m, 2 H), 6.69-6.64 (m, 2 H), 4.37-4.03 (m, 6H), 3.73 (s, 3 H), 3.03-2.96 (m, 1 H), 1.29-1.19 (m, 9H). $^{13}C$ NMR (100 MHz, CDCl3): $\delta$ = 173.5, 173.2, 172.5, 172.2, 153.2, 152.9, 140.9, 140.6, 116.2, 115.5, 114.9, 114.7, 61.4, 61.3, 61.0, 60.9, 60.5, 55.7, 55.6, 42.3, 42.2, 14.2, 12.9, 12.2. HRMS: (ESI) calcd. for $C_{16}H_{24}NO_5$ $[M + H]^+$ 310.1654; found 310.1648. The major isomer **147d** could not be separated from the minor isomer. $^{13}C$ data given here for the mixture of diastereomers.

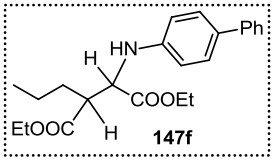


147d

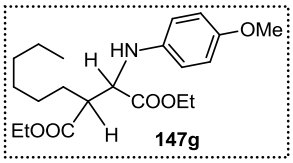
**(2*S**,3*R**)-Diethyl 2-ethyl-3-((4-methoxyphenyl)amino)succinate (147e):** Following the general procedure N described above, **147e** (minor isomer of **138b**) was obtained after purification by silica gel column chromatography (EtOAc/hexane, 9:91) as colorless liquid (100 mg, 62%); $R_f$ = 0.43 (9% EtOAc/hexane). IR (thin film): $\tilde{\upsilon}$ = 3379, 2976, 1731, 1515 1034 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ = 6.69 (d, $J$ = 9.0 Hz, 2 H), 6.56 (d, $J$ = 9.0 Hz, 2 H), 4.17-4.01 (m, 6 H), 3.66 (s, 3 H), 2.77-2.66 (m, 1 H), 1.75-1.66 (m, 1 H), 1.57-1.47 (m, 1 H), 1.19 (t, $J$ = 7.1 Hz, 3 H), 1.14 (t, $J$ = 7.1 Hz, 3 H), 0.88 (t, $J$ = 7.4 Hz, 3 H). $^{13}C$ NMR (100 MHz, CDCl3): $\delta$ = 173.2, 172.8, 152.9, 140.7, 115.5, 114.8, 61.2, 60.8, 59.6, 55.7, 49.9, 22.0, 14.3, 14.2, 12.0. HRMS: (ESI) calcd. for $C_{17}H_{26}NO_5$ $[M + H]^+$ 324.1811; found 324.1809.




**Diethyl 2-([1,1'-biphenyl]-4-ylamino)-3-propylsuccinate (147f):** Following the general procedure N described above, **147f** was obtained after purification by silica gel column chromatography (EtOAc/hexane, 10:90) as colorless liquid (96 mg, 50%); $R_f$ = 0.43 (10% EtOAc/hexane). IR (thin film): $\tilde{\upsilon}$ = 3384, 2962, 1732, 1528, 1027 $cm^{-1}$. $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ = 7.52–7.50 (m, 2 H), 7.42 (d, $J$ = 8.6 Hz, 2 H), 7.37 (t, $J$ = 7.4 Hz, 2 H), 7.25 (t, $J$ = 7.4 Hz, 1 H), 6.71 (d, $J$ = 8.6 Hz, 2 H), 4.39 (br. s, 2 H), 4.21–4.13 (m, 4 H), 2.90–2.85 (m, 1 H), 1.90–1.81 (m, 1 H), 1.65–1.57 (m, 1 H), 1.48–1.30 (m, 2 H), 1.28–1.22 (m, 6 H), 0.92 (t, $J$ = 7.2 Hz, 3 H). $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta$ = 172.9, 172.1, 146.1, 141.0, 131.6, 128.7, 128.0, 126.4, 126.3, 114.1, 61.5, 61.0, 58.4, 48.3, 30.3, 20.9, 14.2, 14.2, 14.0. HRMS: (ESI) calcd. for $C_{23}H_{30}NO_4$ $[M + H]^+$ 384.2175; found 384.2180.

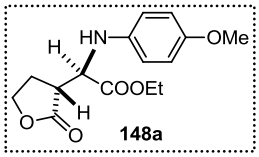



**Diethyl 2-hexyl-3-((4-methoxyphenyl)amino)succinate (147g):** Following the general procedure N described above, **147g** was obtained after purification by silica gel column chromatography (EtOAc/hexane, 9:91) as colorless liquid (65 mg, 35%); $R_f$ = 0.42 (9% EtOAc/hexane). IR (thin film): $\tilde{\upsilon}$ = 3374, 2925, 1732,1515, 1036 $cm^{-1}$. $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ = 6.69 (d, $J$ = 9.0 Hz, 2 H), 6.56 (d, $J$ = 9.0 Hz, 2 H), 4.17 (d, $J$ = 6.1 Hz, 1 H), 4.12–3.87 (m, 5 H), 3.66 (s, 3 H), 2.77–2.72 (m, 1 H), 1.81–1.72 (m, 1 H), 1.58–1.50 (m, 1 H), 1.21–1.12 (m, 14 H), 0.82–0.77 (m, 3 H). $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta$ = 173.0, 172.5, 153.0, 140.8, 115.7, 114.8, 61.3, 60.9, 59.9, 55.7, 48.5, 31.6, 29.1, 28.0, 27.6, 22.6, 14.2, 14.2, 14.1. HRMS:

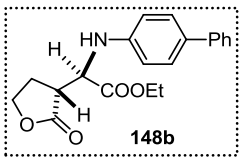


(ESI) calcd. for $C_{21}H_{34}NO_5$ $[M + H]^+$ 380.2437; found 380.2450. The compound was isolated with minor isomer and the NMR values given here for the major isomer.

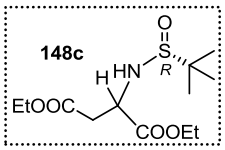
**(*R**)-Ethyl 2-((4-methoxyphenyl)amino)-2-((*R**)-2-oxotetra hydrofuran-3-yl)acetate (148a):** Following the general procedure N described above, **148a** was obtained after purification by silica gel column chromatography (EtOAc/hexane, 20:80) as colorless liquid (98 mg, 67%); $R_f$ = 0.60 (20% EtOAc/hexane). IR (thin film): $\tilde{\upsilon}$ = 3368, 2916, 1739, 1597, 1036 $cm^{-1}$. $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ = 6.76–6.70 (m, 4 H), 4.37–4.31 (m, 2 H), 4.23–4.11 (m, 1 H), 4.21 (t, $J$ = 8.2 Hz, 1 H), 4.14 (q, $J$ = 7.1 Hz, 2 H), 3.68 (s, 3 H), 3.06 (dt, $J$ = 9.6 Hz, 3.5 Hz, 1 H), 2.27–2.21 (m, 2 H), 1.19 (t, $J$ = 7.1 Hz, 3 H). $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta$ = 177.0, 172.4, 153.8, 140.6, 117.3, 114.7, 66.8, 61.9, 59.1, 55.7, 42.7, 23.7, 14.2. HRMS: (ESI) calcd. for $C_{15}H_{20}NO_5$ $[M + H]^+$ 294.1341; found 294.1338. $^1H$ and $^{13}C$ NMR data given here referes to major diastereomer.




**(*R**)-Ethyl 2-([1,1'-biphenyl]-4-ylamino)-2-((*R**)-2-oxotetrahydrofuran-3-yl)acetate (148b):** Following the general procedure N described above, **148b** was obtained after purification by silica gel column chromatography (EtOAc/hexane, 20:80) as yellow solid (122 mg, 72%); $R_f$ = 0.62 (20% EtOAc/hexane). mp 113–115 $^oC$. IR (KBr): $\tilde{\upsilon}$ = 3351, 2984, 1757, 1530, 1025 $cm^{-1}$. $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ = 7.51 (d, $J$ = 8.5 Hz, 2 H), 7.43 (d, $J$ = 8.6 Hz, 2 H), 7.37 (t, $J$ = 7.5 Hz, 2 H), 7.25 (t, $J$ = 7.5 Hz, 1 H), 6.88 (d, $J$ = 8.6 Hz, 2 H), 4.64–4.56 (m, 2 H), 4.42–4.37 (m, 1 H), 4.26 (t, $J$ = 8.3 Hz, 1 H), 4.21 (q, $J$ = 7.1 Hz, 2 H), 3.15 (dt, $J$ = 9.7 Hz, 3.4 Hz, 1 H), 2.35–2.29 (m, 2 H), 1.25 (t, $J$ = 7.1 Hz, 3 H). $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta$ = 176.4, 170.9, 145.9, 140.9, 132.1, 128.7, 128.2, 126.4, 114.0, 66.7, 62.3, 56.4, 42.5, 24.9, 14.1. HRMS: (ESI) calcd. for $C_{20}H_{22}NO_4$ $[M + H]^+$ 340.1549; found 340.1535. $^1H$ and $^{13}C$ NMR data given here referes to major diastereomer.

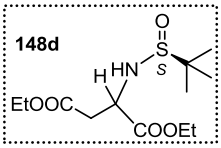



**Diethyl 2-((*R*)-1,1-dimethylethylsulfinamido)succinate (148c):** Following the general procedure N described above, **148c** was obtained after purification by silica gel column chromatography (EtOAc/hexane, 30:70) as colorless liquid (51 mg, 70%); $R_f$ = 0.39 (30% EtOAc/hexane). $[\alpha]_D^{25}$ = –7.1 (*c* 0.26, DCM). IR (neat): $\tilde{\upsilon}$ = 3289, 2983, 1732, 1464, 1031 $cm^{-1}$. $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ = 4.35 (d, $J$ = 5.6 Hz, 1 H), 4.29 (t, $J$ = 5.6 Hz, 1 H), 4.24 (q, $J$ = 7.2 Hz, 2 H), 4.12(q, $J$ = 7.0

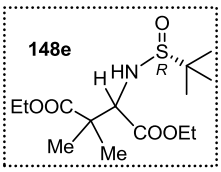


Hz, 2 H), 2.81 (d, *J* = 5.8 Hz, 2 H), 1.28 (t, *J* = 7.2 Hz, 3 H), 1.23 (t, *J* = 7.2 Hz, 3 H), 1.20 (s, 9 H). $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ = 171.5, 169.9, 62.2, 60.9, 56.1, 54.0, 38.5, 22.4, 14.1, 14.0. HRMS: (ESI) calcd. for $C_{12}H_{23}NO_5SNa$ $[M + Na]^+$ 316.1194; found 316.1207. $^1$H and $^{13}$C NMR data given here referes to major diastereomer.

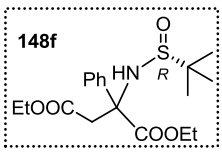
**Diethyl 2-((*S*)-1,1-dimethylethylsulfinamido)succinate (148d):** Following the general procedure N described above, **148d** was obtained after purification by silica gel column chromatography (EtOAc/hexane, 30:70) as colorless liquid (47 mg, 65%); $R_f$ = 0.39 (30% EtOAc/hexane). $[\alpha]_D^{25}$ = +17.3 (*c* 0.24, DCM). IR (neat): $\tilde{\upsilon}$ = 3435, 2983, 1738, 1637, 1371, 1178, 1027 cm$^{-1}$. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 4.38 (d, *J* = 5.6 Hz, 1 H), 4.32 (t, *J* = 5.6 Hz, 1 H), 4.27 (q, *J* = 7.2 Hz, 2 H), 4.15 (q, *J* = 7.2 Hz, 2 H), 2.84 (dd, *J* = 5.6, 1.7 Hz, 1 H), 1.31 (t, *J* = 7.2 Hz, 3 H), 1.26 (t, *J* = 7.2 Hz, 3 H), 1.23 (s, 9 H). $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ = 171.5, 169.9, 62.2, 61.0, 56.1, 54.0, 38.6, 22.5, 14.2, 14.1. HRMS: (ESI) calcd. for $C_{12}H_{23}NO_5SNa$ $[M + Na]^+$ 316.1194; found 316.1204. $^1$H and $^{13}$C NMR data given here referes to major diastereomer.




**Diethyl 3-((*R*)-1,1-dimethylethylsulfinamido)-2,2-dimethylsuccinate (148e):** Following the general procedure N described above, **148e** was obtained after purification by silica gel column chromatography (EtOAc/hexane, 30:70) as colorless liquid (45 mg, 56%); $R_f$ = 0.44 (30% EtOAc/hexane). $[\alpha]_D^{25}$ = –56.3 (*c* 0.11, $CHCl_3$). IR (neat): $\tilde{\upsilon}$ = 3282, 2981, 1732, 1468, 1080 cm$^{-1}$. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 4.31 (d, *J* = 8.5 Hz, 1 H), 4.17-4.04 (m, 5 H), 1.21-1.17 (m, 6 H), 1.17 (s, 9 H), 1.12 (s, 3 H), 1.07 (s, 3 H). $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ = 174.9, 171.4, 63.3, 62.0, 61.0, 56.3, 46.7, 22.7, 21.7, 21.5, 14.1, 14.1. HRMS: (ESI) calcd. for $C_{14}H_{28}NO_5S$ $[M + H]^+$ 322.1682; found 322.1671. The compound was isolated with minor isomer and the NMR values given here for the major isomer.



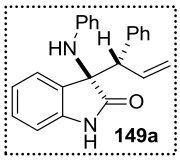

**Diethyl 2-((*R*)-1,1-dimethylethylsulfinamido)-2-phenylsuccinate (148f):** Following the general procedure N described above, **148f** was obtained after purification by silica gel column chromatography (EtOAc/hexane, 30:70) as colorless liquid (37 mg, 40%); $R_f$ = 0.30 (30% EtOAc/hexane). $[\alpha]_D^{25}$ = –15.4 (*c* 0.11, $CHCl_3$). IR (neat): $\tilde{\upsilon}$ = 3383, 2981, 1739, 1448, 1372, 1194, 1077 cm$^{-1}$. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 7.45-7.42 (m, 2 H), 7.37-7.30 (m, 3 H), 5.23 (s, 1 H), 4.24-4.06 (m, 4 H), 3.56 (d, *J* = 16.6 Hz, 1 H), 3.38 (d, *J* = 16.6 Hz, 1 H), 1.23-1.15 (m, 6 H), 1.19



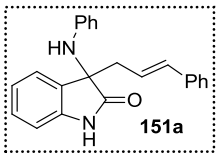
(s, 9 H). $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ = 171.7, 170.2, 139.0, 128.7, 128.6, 126.4, 65.0, 62.4, 60.9, 56.7, 41.5, 22.6, 14.1, 13.8. HRMS: (ESI) calcd. for $C_{18}H_{27}NO_5SNa$ $[M + Na]^+$ 392.1507; found 392.1526. $^1$H and $^{13}$C NMR data given here referes to major diastereomer.

**Procedure O. Indium-mediated addition of cinnamyl bromide (123a) to isatin ketimines 105:** To a vigorously stirring solution of the corresponding isatin ketimine **105** (0.25 mmol, 1 equiv) and *E*-cinnamyl bromide (**123a**; 0.75 mmol, 3 equiv) in THF (0.2 mL) and $H_2O$ (2 mL) was added indium powder (0.5 mmol, 2 equiv) and the mixture was stirred vigorously at 30 $^o$C for 6 h. Then, the reaction mixture was transferred in to a separating funnel and extracted with EtOAc (3x15 mL). The combined organic layers were dried over anhydrous $Na_2SO_4$ and the solvent was evaporated under vacuum. Purification of the resulting crude reaction mixture by column chromatography on silica gel (EtOAc/hexane) gave the corresponding products **149**/**150** (see Tables 17 and 18 and Scheme 70 for individual entries).

**(*R**)-3-((*S**)-1-Phenylallyl)-3-(phenylamino)indolin-2-one (149a):** Following the general procedure O described above, **149a** was obtained after purification by silica gel column chromatography (EtOAc/hexane, 30:70) as a colorless solid (68 mg, 80%); mp 160-162 °C. $R_f$ = 0.60 (30% EtOAc/hexane). IR (thin film): $\tilde{\upsilon}$ = 3307, 3059, 1715, 1602, 1504, 1200 cm$^{-1}$. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 8.12 (s, 1 H), 7.20 (d, $J$ = 7.3 Hz, 1 H), 7.14-7.07 (m, 4 H), 7.01-6.98 (m, 3 H), 6.91 (dd, $J$ = 8.2, 7.8 Hz, 2 H), 6.62-6.48 (m, 3 H), 6.24 (d, $J$ = 7.8 Hz, 2 H), 5.45-5.35 (m, 2 H), 4.70 (s, 1 H), 3.80 (d, $J$ = 10.5 Hz, 1 H). $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ = 178.9, 145.0, 140.1, 136.6, 134.2, 129.1, 129.0, 129.0, 127.9, 127.4, 124.6, 122.7, 120.5, 119.0, 114.8, 110.1, 67.2, 59.6. HRMS (ESI): calcd. for $C_{23}H_{21}N_2O$ $[M + H]^+$ 341.1654; found 341.1653.

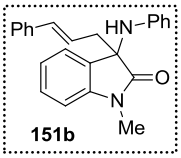



**3-Cinnamyl-3-(phenylamino)indolin-2-one (151a):** The compound **151a** was obtained after purification by silica gel column chromatography (EtOAc/hexane, 30:70) as a colorless solid (55 mg, 65%); mp 196-198 °C. $R_f$ = 0.61 (30% EtOAc/hexane). IR (thin film): $\tilde{\upsilon}$ = 3325, 2935, 1720, 1602, 1468, 1214 cm$^{-1}$. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 8.61 (s, 1 H), 7.25-7.17 (m, 7 H), 7.00 (t, $J$ = 7.5 Hz, 1 H), 6.90 (t, $J$ = 8.0 Hz, 2 H), 6.85 (d, $J$ = 7.5 Hz, 1 H), 6.58 (t, $J$ = 7.5 Hz, 1 H), 6.48 (d, $J$ = 15.7 Hz, 1 H), 6.21 (d, $J$ = 8.0 Hz, 2 H), 6.13-6.05 (m, 1 H), 4.52 (br. s, 1 H), 2.84-2.79 (m, 1 H), 2.69-2.64 (m, 1 H). $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ = 180.1, 145.1, 139.6, 136.7, 135.9,



130.3, 129.1, 128.6, 127.8, 126.4, 124.1, 123.1, 121.4, 119.0, 114.6, 110.7, 64.5, 43.9. HRMS (ESI): calcd. for $C_{23}H_{21}N_2O$ $[M + H]^+$ 341.1654; found 341.1653.

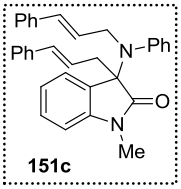
**3-Cinnamyl-1-methyl-3-(phenylamino)indolin-2-one (151b):** The compound **151b** was obtained after purification by silica gel column chromatography (EtOAc/hexane, 20:80) as a



151b

colorless sticky liquid (40 mg, 45%); $R_f$ = 0.47 (20% EtOAc/hexane). IR (thin film): $\tilde{\upsilon}$ = 3356, 2926, 1714, 1602, 1493, 1120, 747 $cm^{-1}$. $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ = 7.40-7.25 (m, 7 H), 7.12 (t, $J$ = 7.5 Hz, 1 H), 7.00-6.94 (m, 3 H), 6.66 (t, $J$ = 7.4 Hz, 1 H), 6.55 (d, $J$ = 15.76 Hz, 1 H), 6.21 (d, $J$ = 8.0 Hz, 2 H), 6.17-6.09 (m, 1 H), 4.48 (s, 1 H), 3.28 (s, 3 H), 2.88 (dd, $J$ = 13.3, 7.0 Hz, 1 H), 2.74 (dd, $J$ = 13.3, 8.2 Hz, 1 H). $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta$ = 177.7, 145.1, 142.6, 136.7, 135.7, 129.9, 129.1, 129.1, 128.6, 127.7, 126.4, 123.8, 123.1, 121.6, 119.0, 114.6, 108.6, 64.2, 44.0, 26.5. HRMS (ESI): calcd. for $C_{24}H_{23}N_2O$ $[M + H]^+$ 355.1810; found 355.1811.

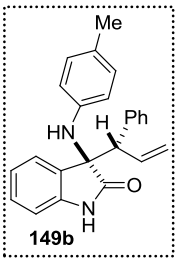
**3-Cinnamyl-3-(cinnamyl(phenyl)amino)-1-methylindolin-2-one (151c):** The compound **151c** was obtained after purification by silica gel column chromatography (EtOAc/hexane,



151c

20:80) as a colorless sticky liquid (27 mg, 23%); $R_f$ = 0.57 (20% EtOAc/hexane). IR (thin film): $\tilde{\upsilon}$ = 3024, 1711, 1611, 1429, 966, 749 $cm^{-1}$. $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ = 7.49 (d, $J$ = 7.8 Hz, 2 H), 7.45 (d, $J$ = 7.3 Hz, 1 H), 7.31-7.10 (m, 13 H), 7.08 (d, $J$ = 7.3 Hz, 2 H), 6.73 (d, $J$ = 7.8 Hz, 1 H), 6.19-6.05 (m, 3 H), 5.64-5.57 (m, 1 H), 3.95 (dd, $J$ = 14.7, 6.9 Hz, 1 H), 3.78 (dd, $J$ = 14.7, 5.3 Hz, 1 H), 3.06 (s, 3 H), 2.84 (dd, $J$ = 13.0, 6.4 Hz, 1 H), 2.69 (dd, $J$ = 13.0, 8.6 Hz, 1 H). $^{13}$CNMR (100 MHz, $CDCl_3$): $\delta$ = 178.3, 147.2, 143.3, 137.3, 137.2, 134.2, 131.3, 130.4, 129.5, 128.8, 128.4, 128.3, 128.0, 127.2, 127.1, 126.3, 126.0, 125.3, 124.6, 123.0, 122.6, 107.9, 70.4, 54.2, 41.1, 25.9. HRMS (ESI): calcd. for $C_{33}H_{31}N_2O$ $[M + H]^+$ 471.2436; found 471.2457.

**(*R**)-3-((*S**)-1-Phenylallyl)-3-(*p*-tolylamino)indolin-2-one (149b):** Following the general procedure O described above, **149b** was obtained after purification by silica

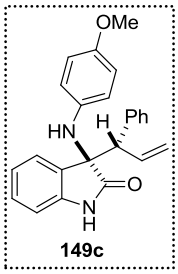


149b

gel column chromatography (EtOAc/hexane, 30:70) as a colorless solid (78 mg, 88%); mp 152-154 °C. $R_f$ = 0.66 (30% EtOAc/hexane). IR (thin film): $\tilde{\upsilon}$ = 3443, 3347, 1712, 1623, 1468, 1155 $cm^{-1}$. $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ = 7.75 (s, 1 H), 7.27 (d, $J$ = 7.8 Hz, 1 H), 7.15-7.12 (m, 4 H), 7.06-7.01 (m, 3 H), 6.76 (d, $J$ = 8.1 Hz, 2 H), 6.64-6.55 (m, 1 H), 6.56 (d, $J$ = 7.9 Hz, 1 H), 6.22 (d, $J$ = 8.1

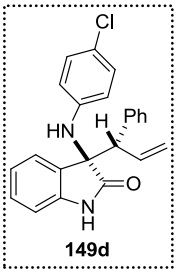
Hz, 2 H), 5.49-5.39 (m, 2 H), 4.61 (br. s, 1 H), 3.83 (d, $J$ = 10.5 Hz, 1 H), 2.12 (s, 3 H). $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ = 178.7, 142.6, 140.0, 136.7, 134.3, 129.6, 129.5, 129.3, 129.0, 128.5, 127.9, 127.3, 124.6, 122.7, 120.5, 115.3, 109.9, 67.4, 59.6, 20.4. HRMS (ESI): calcd. for $C_{24}H_{23}N_2O$ $[M + H]^+$ 355.1810; found 355.1804.

**(*R**)-3-((4-Methoxyphenyl)amino)-3-((*S**)-1-phenylallyl)indolin-2-one (149c):** Following the general procedure O described above, **149c** was obtained after purification by silica gel column chromatography (EtOAc/hexane, 30:70) as a semi solid (88 mg, 95%); $R_f$ = 0.62 (30% EtOAc/hexane). IR (thin film): $\tilde{\upsilon}$ = 3298, 2950, 1712, 1512, 1240, 1031 cm$^{-1}$. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 8.26 (s, 1 H), 7.24 (d, $J$ = 8.0 Hz, 2 H), 7.11-7.06 (m, 4 H), 7.01-6.98 (m, 2 H), 6.57-6.43 (m, 4 H), 6.27 (d, $J$ = 8.0 Hz, 2 H), 5.43-5.33 (m, 2 H), 4.44 (s, 1 H), 3.81 (d, $J$ = 10.5 Hz, 1 H), 3.53 (s, 3 H). $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ = 179.4, 153.5, 140.3, 138.7, 136.9, 134.3, 129.3, 129.0, 127.9, 127.2, 124.8, 122.5, 120.4, 118.0, 114.3, 110.0, 68.4, 59.4, 55.4. HRMS (ESI): calcd. for $C_{24}H_{23}N_2O_2$ $[M + H]^+$ 371.1760; found 371.1764.



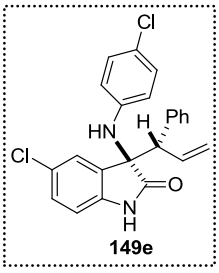
149c

**(*R**)-3-((4-Chlorophenyl)amino)-3-((*S**)-1-phenylallyl)indolin-2-one (149d):** Following the general procedure O described above, **149d** was obtained after purification by silica gel column chromatography (EtOAc/hexane, 30:70) as a colorless solid (67 mg, 71%); mp 134-136 °C. $R_f$ = 0.61 (30% EtOAc/hexane). IR (thin film): $\tilde{\upsilon}$ = 3363, 2963, 1720, 1619, 1453, 1025 cm$^{-1}$. $^1$H NMR (400 MHz, $CDCl_3$+DMSO-$d_6$): $\delta$ = 9.98 (s, 1 H), 7.06-7.02 (m, 5 H), 6.95-6.85 (m, 3 H), 6.81-6.76 (m, 2 H), 6.59-6.55 (m, 1 H), 6.45-6.37 (m, 1 H), 6.13-6.08 (m, 2 H), 5.36-5.25 (m, 2 H), 4.72 (br. s, 1 H), 3.74-3.69 (m, 1 H). $^{13}$C NMR (100 MHz, $CDCl_3$+DMSO-$d_6$): $\delta$ = 177.6, 143.5, 141.0, 136.3, 134.0, 128.7, 128.6, 128.1, 127.8, 127.3, 126.8, 123.8, 122.4, 121.5, 119.6, 115.4, 109.8, 66.4, 58.6. HRMS (ESI): calcd. for $C_{23}H_{19}ClN_2NaO$ $[M + Na]^+$ 397.1084; found 397.1076.



149d

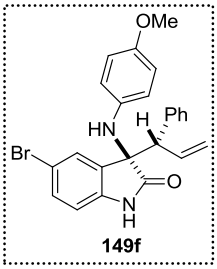
**(*R**)-5-Chloro-3-((4-chlorophenyl)amino)-3-((*S**)-1-phenylallyl)indolin-2-one (149e):** Following the general procedure O described above, **149e** was obtained after purification by silica gel column chromatography (EtOAc/hexane, 30:70) as a colorless solid (85 mg, 83%); mp 150-152 °C. $R_f$ = 0.63 (30% EtOAc/hexane). IR (thin film): $\tilde{\upsilon}$ = 3192, 2846, 1721, 1600, 1495, 1182 cm$^{-1}$. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 7.90 (s, 1 H), 7.33 (d, $J$ = 4.3 Hz, 1



149e

H), 7.25 (d, *J* = 1.6 Hz, 1 H), 7.18-7.14 (m, 3 H), 7.01 (d, *J* = 7.7 Hz, 1 H), 6.94 (d, *J* = 8.7 Hz, 2 H), 6.61-6.55 (m, 1 H), 6.51 (d, *J* = 7.7 Hz, 1 H), 6.20 (d, *J* = 8.7 Hz, 2 H), 5.50-5.43 (m, 2 H), 4.73 (s, 1 H), 3.78 (d, *J* = 10.5 Hz, 1 H). $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ = 177.9, 143.3, 138.4, 135.8, 133.6, 130.7, 129.3, 129.1, 128.9, 128.1, 127.7, 126.5, 124.8, 124.2, 121.1, 116.0, 111.1, 67.3, 59.7. HRMS (ESI): calcd. for $C_{23}H_{19}Cl_2N_2O$ $[M + H]^+$ 409.0874; found 409.0868.

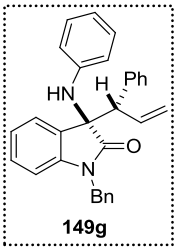
**(*R**)-5-Bromo-3-((4-methoxyphenyl)amino)-3-((*S**)-1-phenylallyl)indolin-2-one (149f):** Following the general procedure O described above, **149f** was obtained after purification by



**149f**

silica gel column chromatography (EtOAc/hexane, 30:70) as a colorless solid (101 mg, 90%); mp 127-129 °C. $R_f$ = 0.63 (30% EtOAc/hexane). IR (thin film): $\tilde{\upsilon}$ = 3405, 2831, 1706, 1617, 1510, 1241 $cm^{-1}$. $^1$H NMR (400 MHz, $CDCl_3$+DMSO-$d_6$): $\delta$ = 9.96 (s, 1 H), 7.33 (d, *J* = 1.6 Hz, 1 H), 7.23 (dd, *J* = 8.2, 1.9 Hz, 1 H), 7.16-7.14 (m, 3 H), 7.05-7.02 (m, 2 H), 6.55-6.48 (m, 4 H), 6.27 (dd, *J* = 8.9, 6.7 Hz, 2 H), 5.44-5.35 (m, 2 H), 4.44 (s, 1 H), 3.78 (d, *J* = 10.5 Hz, 1 H), 3.63 (s, 3 H). $^{13}$C NMR (100 MHz, $CDCl_3$+DMSO-$d_6$): $\delta$ = 178.1, 153.1, 140.5, 138.5, 136.6, 134.1, 131.6, 131.4, 128.8, 127.8, 127.3, 127.1, 120.2, 117.3, 114.3, 114.2, 111.5, 67.9, 59.0, 55.3. HRMS (ESI): calcd. for $C_{24}H_{22}BrN_2O_2$ $[M + H]^+$ 449.0865; found 449.0855.

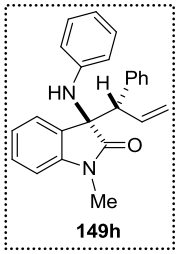
**(*R**)-1-Benzyl-3-((*S**)-1-phenylallyl)-3-(phenylamino)indolin-2-one (149g):** Following the general procedure O described above, **149g** was obtained after purification by silica gel



**149g**

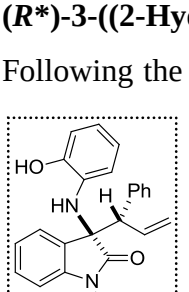
column chromatography (EtOAc/hexane, 30:70) as a colorless solid (54 mg, 50%); mp 158-160 °C. $R_f$ = 0.67 (30% EtOAc/hexane). IR (thin film): $\tilde{\upsilon}$ = 3371, 2920, 1714, 1602, 1497, 1365, 1178 $cm^{-1}$. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 7.36 (d, *J* = 7.2 Hz, 1 H), 7.25-7.24 (m, 3 H), 7.18-7.02 (m, 7 H), 6.97-6.92 (m, 4 H), 6.77-6.67 (m, 2 H), 6.42 (d, *J* = 7.5 Hz, 1 H), 6.24 (d, *J* = 8.4 Hz, 2 H), 5.53-5.44 (m, 2 H), 5.02 (d, *J* = 15.5 Hz, 1 H), 4.77 (br. s, 1 H), 4.22 (d, *J* = 15.5 Hz, 1 H), 3.88 (d, *J* = 10.6 Hz, 1 H). $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ = 176.6, 145.1, 142.4, 136.7, 135.5, 134.5, 129.0, 129.0, 128.9, 128.6, 127.8, 127.7, 127.5, 127.2, 124.1, 122.7, 120.6, 119.3, 115.7, 109.2, 67.0, 59.7, 43.9. HRMS (ESI): calcd. for $C_{30}H_{27}N_2O$ $[M + H]^+$ 431.2123; found 431.2126.

**(*R**)-1-Methyl-3-((*S**)-1-phenylallyl)-3-(phenylamino)indolin-2-one (149h):** Following the general procedure O described above, **149h** was obtained after purification by silica gel column chromatography (EtOAc/hexane, 30:70) as a orange color oil (66 mg, 75%); $R_f$ = 0.65 (30% EtOAc/hexane). IR (thin film): $\tilde{\upsilon}$ = 3385, 2930, 1715, 1602, 1492, 1119 $cm^{-1}$. $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ = 7.31 (d, $J$ = 7.3 Hz, 1 H), 7.23 (t, $J$ = 7.3 Hz, 1 H), 7.13-7.05 (m, 4 H), 6.97 (t, $J$ = 7.5 Hz, 2 H), 6.92 (d, $J$ = 7.5 Hz, 2 H), 6.68-6.63 (m, 2 H), 6.54 (d, $J$ = 7.8 Hz, 1 H), 6.21 (d, $J$ = 7.8 Hz, 2 H), 5.51-5.43 (m, 2 H), 4.75 (s, 1 H), 3.80 (d, $J$ = 10.6 Hz, 1 H), 2.96 (s, 3 H). $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta$ = 176.4, 145.1, 142.9, 136.6, 134.4, 129.1, 129.0, 128.8, 128.7, 127.6, 127.2, 123.8, 122.7, 120.5, 118.9, 114.7, 108.0, 66.9, 60.1, 25.9. HRMS (ESI): calcd. for $C_{24}H_{23}N_2O$ $[M + H]^+$ 355.1810; found 355.1821.



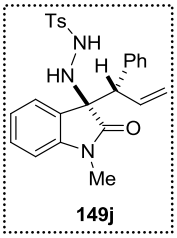
149h

**(*R**)-3-((2-Hydroxyphenyl)amino)-1-methyl-3-((*S**)-1-phenylallyl)indolin-2-one (149i):** Following the general procedure O described above, **149i** was obtained after purification by silica gel column chromatography (EtOAc/hexane, 30:70) as a colorless solid (117 mg, 63%); mp 175-177 °C. $R_f$ = 0.45 (30% EtOAc/hexane). IR (thin film): $\tilde{\upsilon}$ = 3381, 2930, 1702, 1611, 1521, 1372, 1120 $cm^{-1}$. $^1H$ NMR (400 MHz, $CDCl_3$+DMSO-$d_6$): $\delta$ = 8.60 (s, 1 H), 7.27 (dd, $J$ = 7.4, 2.8 Hz, 2 H), 7.18 (t, $J$ = 7.4 Hz, 1 H), 7.08 (dd, $J$ = 7.4, 4.3 Hz, 2 H), 7.02 (t, $J$ = 7.4 Hz, 1 H), 6.89 (d, $J$ = 8.2 Hz, 2 H), 6.69 (d, $J$ = 7.4 Hz, 1 H), 6.64-6.55 (m, 1 H), 6.51 (d, $J$ = 8.2 Hz, 1 H), 6.44 (t, $J$ = 7.4 Hz, 1 H), 6.32 (t, $J$ = 7.4 Hz, 1 H), 5.64 (d, $J$ = 7.4 Hz, 1 H), 5.46 (d, $J$ = 16.3 Hz, 1 H), 5.36 (d, $J$ = 10.3 Hz, 1 H), 5.32 (s, 1 H), 3.86 (d, $J$ = 10.3 Hz, 1 H), 2.93 (s, 3 H). $^{13}C$ NMR (100 MHz, $CDCl_3$+DMSO-$d_6$): $\delta$ = 176.8, 145.4, 142.8, 136.9, 134.3, 134.2, 129.0, 128.8, 128.7, 127.4, 127.0, 123.8, 122.5, 119.9, 119.8, 118.4, 114.3, 112.8, 107.8, 67.0, 59.8, 25.8. HRMS (ESI): calcd. for $C_{24}H_{22}N_2NaO_2$ $[M + Na]^+$ 393.1579; found 393.1593. The OH proton of the compound did not appear clearly in the $^1H$ NMR.



149i

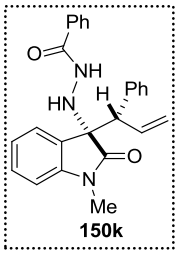
**4-Methyl-*N*'-((*R**)-1-methyl-2-oxo-3-((*S**)-1-phenylallyl)indolin-3-yl) benzenesulfonohydrazide (149j):** Following the general procedure O described above, **149j** was obtained after purification by silica gel column chromatography (EtOAc/hexane, 40:60) as a colorless solid (84 mg, 75%); mp 168-170 °C. $R_f$ = 0.48 (40% EtOAc/hexane). IR (thin film): $\tilde{\upsilon}$ = 3420, 3229, 3059, 1697, 1616, 1471, 1167 $cm^{-1}$. $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ = 7.61 (d, $J$ = 8.3 Hz,



149j

2 H), 7.22 (d, *J* = 8.0 Hz, 2 H), 7.13-7.04 (m, 4 H), 6.88-6.79 (m, 4 H), 6.44 (d, *J* = 7.8 Hz, 1 H), 6.40-6.31 (m, 1 H), 5.84 (d, *J* = 3.9 Hz, 1 H), 5.32-5.21 (m, 2 H), 4.61 (d, *J* = 3.9 Hz, 1 H), 3.64 (d, *J* = 10.4 Hz, 1 H), 2.95 (s, 3 H), 2.46 (s, 3 H). $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ = 176.2, 143.9, 143.5, 137.0, 134.3, 133.7, 129.3, 128.8, 128.5, 127.6, 127.1, 126.6, 125.1, 122.5, 120.1, 107.5, 71.0, 56.5, 25.9, 21.6. HRMS (ESI): calcd. for $C_{25}H_{25}N_3NaO_3S$ [M + Na]$^+$ 470.1514; found 470.1507.

***N*'-((*S**)-1-methyl-2-oxo-3-((*S**)-1-phenylallyl)indolin-3-yl)benzohydrazide (150k):** Following the general procedure O described above, **150k** was obtained after purification by



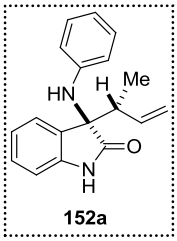
**150k**

silica gel column chromatography (EtOAc/hexane, 40:60) as a colorless solid (50 mg, 50%); mp 186-188 °C. $R_f$ = 0.47 (40% EtOAc/hexane). IR (thin film): $\tilde{\upsilon}$ = 3384, 2925, 1725, 1614, 1378, 1180 cm$^{-1}$. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 8.18 (d, *J* = 5.7 Hz, 1 H), 7.68 (d, *J* = 7.3 Hz, 1 H), 7.64 (d, *J* = 7.7 Hz, 2 H), 7.48-7.44 (m, 1 H), 7.38 (t, *J* = 7.7 Hz, 2 H), 7.29-7.25 (m, 1 H), 7.13-7.06 (m, 2 H), 7.02 (t, *J* = 7.7 Hz, 2 H), 6.69 (d, *J* = 7.7 Hz, 2 H), 6.54 (d, *J* = 7.3 Hz, 1 H), 6.52-6.42 (m, 1 H), 6.08 (d, *J* = 7.3 Hz, 1 H), 5.45 (d, *J* = 10.1 Hz, 1 H), 5.28 (d, *J* = 16.9 Hz, 1 H), 3.95 (d, *J* = 10.1 Hz, 1 H), 2.76 (s, 3 H). $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ = 176.2, 166.7, 144.2, 136.7, 133.9, 132.5, 131.8, 129.6, 128.5, 128.5, 127.6, 127.2, 127.0, 126.0, 125.6, 122.4, 120.8, 107.8, 72.4, 54.9, 25.8. HRMS (ESI): calcd. for $C_{25}H_{23}N_3NaO_2$ [M + Na]$^+$ 420.1688; found 420.1676.

**Procedure P. Indium-mediated addition of crotyl bromide (123b) to isatin ketimines 105:** To a vigorously stirring solution of corresponding isatin ketimine **105** (0.25 mmol, 1 equiv) and *E*-crotyl bromide (**123b**; 0.75 mmol, 3 equiv) in THF (0.2 mL) and $H_2O$ (2 mL) was added indium powder (0.5 mmol, 2 equiv) and the mixture was stirred vigorously at 30 $^o$C for 6-12 h. Then, the reaction mixture was transferred in to a separating funnel and extracted with EtOAc (3x15 mL). The combined organic layers were dried over anhydrous $Na_2SO_4$ and the solvent was evaporated under vacuum. Purification of the resulting crude reaction mixture by column chromatography on silica gel (EtOAc/hexane) gave the corresponding product **152**/**153** (see Table 19 for individual entries).

**(*R**)-3-((*R**)-But-3-en-2-yl)-3-(phenylamino)indolin-2-one (152a):** Following the general procedure P described above, **152a** was obtained after purification by silica gel column

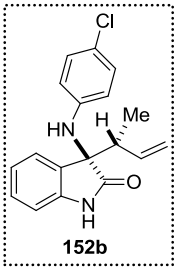
chromatography (EtOAc/hexane, 30:70) as a colorless solid (45 mg, 65%); mp 172-174 °C.



**152a**

$R_f$ = 0.55 (30% EtOAc/hexane). IR (thin film): $\tilde{\upsilon}$ = 3302, 3081, 1706, 1602, 1497, 1199, 914 $cm^{-1}$. $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ = 8.82 (s, 1 H), 7.24 (td, $J$ = 5.8, 1.4 Hz, 2 H), 7.03 (t, $J$ = 7.4 Hz, 1 H), 6.93 (dd, $J$ = 8.6, 7.4 Hz, 2 H), 6.82 (d, $J$ = 7.4 Hz, 1 H), 6.61 (t, $J$ = 7.4 Hz, 1 H), 6.26 (dd, $J$ = 8.6, 1.4 Hz, 2 H), 5.92-5.82 (m, 1 H), 5.31-5.19 (m, 2 H), 4.66 (s, 1 H), 2.74-2.67 (m, 1 H), 0.96 (d, $J$ = 6.9 Hz, 3 H). $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta$ = 179.8, 145.4, 140.6, 137.2, 129.7, 129.1, 124.0, 123.1, 119.0, 118.8, 114.7, 110.4, 67.0, 48.3, 14.3. HRMS (ESI): calcd. for $C_{18}H_{19}N_2O$ $[M + H]^+$ 279.1497; found 279.1488.

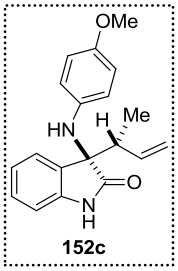
**(*R**)-3-((*R**)-But-3-en-2-yl)-3-((4-chlorophenyl)amino)indolin-2-one (152b):** Following the general procedure P described above, **152b** was obtained after purification by silica gel



**152b**

column chromatography (EtOAc/hexane, 30:70) as a colorless solid (63 mg, 80%); mp 208-210 °C. $R_f$ = 0.57 (30% EtOAc/hexane). IR (thin film): $\tilde{\upsilon}$ = 3127, 2985, 1717, 1600, 1505, 1317, 1196 $cm^{-1}$. $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ = 8.10 (s, 1 H), 7.33-7.27 (m, 2 H), 7.09 (t, $J$ = 7.5 Hz, 1 H), 6.94-6.89 (m, 1 H), 6.92 (d, $J$ = 8.8 Hz, 2 H), 6.21 (d, $J$ = 8.8 Hz, 2 H), 5.97-5.88 (m, 1 H), 5.35-5.25 (m, 2 H), 4.63 (br. s, 1 H), 2.73-2.69 (m, 1 H), 0.97 (d, $J$ = 6.9 Hz, 3 H). $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta$ = 178.6, 144.0, 140.4, 137.0, 129.3, 129.3, 128.9, 124.0, 123.3, 119.1, 116.0, 110.2, 66.8, 48.4, 14.2. HRMS (ESI): calcd. for $C_{18}H_{17}ClN_2NaO$ $[M + Na]^+$ 335.0927; found 335.0927.

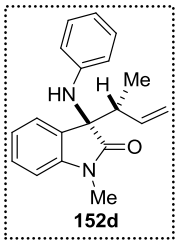
**(*R**)-3-((*R**)-But-3-en-2-yl)-3-((4-methoxyphenyl)amino)indolin-2-one (152c):** Following the general procedure P described above, **152c** was obtained after purification by silica gel



**152c**

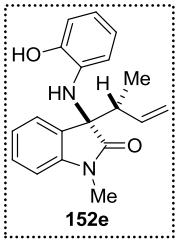
column chromatography (EtOAc/hexane, 30:70) as a colorless solid (38 mg, 50%); mp 139-141 °C. $R_f$ = 0.59 (30% EtOAc/hexane). IR (thin film): $\tilde{\upsilon}$ = 3298, 3031, 1711, 1512, 1239 $cm^{-1}$. $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ = 8.42 (s, 1 H), 7.36 (d, $J$ = 7.4 Hz, 1 H), 7.29-7.25 (m, 1 H), 7.09 (t, $J$ = 7.4 Hz, 1 H), 6.81 (d, $J$ = 7.4 Hz, 1 H), 6.52 (d, $J$ = 9.0 Hz, 2 H), 6.32 (d. $J$ = 9.0 Hz, 2 H), 5.96-5.86 (m, 1 H), 5.33-5.21 (m, 2 H), 4.36 (br. s, 1 H), 3.60 (s, 3 H), 2.78-2.70 (m, 1 H), 0.98 (d, $J$ = 6.9 Hz, 3 H). $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta$ = 179.7, 153.6, 140.8, 139.0, 137.3, 130.0, 129.0, 124.3, 123.0, 118.7, 118.1, 114.3, 110.1, 68.2, 55.4, 48.0, 14.4. HRMS (ESI): calcd. for $C_{19}H_{21}N_2O_2$ $[M + H]^+$ 309.1603; found 309.1593

**(*R**)-3-((*R**)-But-3-en-2-yl)-1-methyl-3-(phenylamino)indolin-2-one (152d):** Following the general procedure P described above, **152d** was obtained after purification by silica gel column chromatography (EtOAc/hexane, 30:70) as a colorless solid (51 mg, 70%); mp 153-155 °C. $R_f$ = 0.67 (30% EtOAc/hexane). IR (thin film): $\tilde{\upsilon}$ = 3365, 2965, 1713, 1604, 1469, 1323 $cm^{-1}$. $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ = 7.38 (t, *J* = 7.7 Hz, 1 H), 7.31 (d, *J* = 7.3 Hz, 1 H), 7.11 (t, *J* = 7.7 Hz, 1 H), 6.98-6.91 (m, 3 H), 6.64 (t, *J* = 7.3 Hz, 1 H), 6.19 (d, *J* = 7.6 Hz, 2 H), 5.93-5.84 (m, 1 H), 5.33-5.21 (m, 2 H), 4.56 (s, 1 H), 3.24 (s, 3 H), 2.77-2.69 (m, 1 H), 0.92 (d, *J* = 6.9 Hz, 3 H). $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta$ = 177.1, 145.4, 143.6, 137.3, 129.2, 129.1, 129.0, 123.7, 123.1, 118.9, 118.6, 114.7, 108.2, 66.5, 48.4, 26.1, 14.3. HRMS (ESI): calcd. for $C_{19}H_{21}N_2O$ $[M + H]^+$ 293.1654; found 293.1660.



152d

**(*R**)-3-((*R**)-But-3-en-2-yl)-3-((2-hydroxyphenyl)amino)-1-methylindolin-2-one (152e):** Following the general procedure P described above, **152e** was obtained after purification by silica gel column chromatography (EtOAc/hexane, 30:70) as a colorless solid (58 mg, 75%); mp 172-174 °C. $R_f$ = 0.50 (30% EtOAc/hexane). IR (thin film): $\tilde{\upsilon}$ = 3382, 2965, 1694, 1609, 1516, 1449, 1236 $cm^{-1}$. $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ = 7.42 (d, *J* = 7.4 Hz, 1 H), 7.35 (td, *J* = 7.4, 1.2 Hz, 1 H), 7.13 (t, *J* = 7.8 Hz, 1 H), 6.87 (d, *J* = 7.4 Hz, 1 H), 6.58-6.50 (m, 2 H), 6.38 (td, *J* = 7.8, 1.7 Hz, 1 H), 5.97 (dd, *J* = 7.8, 1.4 Hz, 1 H), 5.81-5.72 (m, 1 H), 5.32 (dd, *J* = 17.0, 1.4 Hz, 1 H), 5.20 (dd, *J* = 10.0, 1.8 Hz, 1 H), 4.73 (br. s, 1 H), 3.23 (s, 3 H), 2.90-2.82 (m, 1 H), 1.02 (d, *J* = 6.9 Hz, 3 H). $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta$ = 179.5, 147.5, 143.3, 137.0, 133.2, 129.1, 129.1, 124.2, 123.2, 121.3, 120.0, 118.6, 117.2, 115.0, 108.3, 68.4, 47.9, 26.2, 14.5. HRMS (ESI): calcd. for $C_{19}H_{20}N_2NaO_2$ $[M + Na]^+$ 331.1422; found 331.1405. This compound contains traces of the minor isomer and the OH signal was not visible clearly in the $^1H$ NMR spectrum.

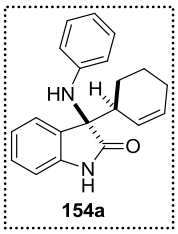


152e

**Procedure Q. Indium-mediated addition of cyclohexenyl bromide (123c) to isatin ketimines 105:** To a vigorously stirring solution of corresponding isatin ketimine **105** (0.25 mmol, 1 equiv) and cyclohexenyl bromide (**123c**; 0.5 mmol, 2 equiv) in DMF (1 mL) was added indium powder (0.37 mmol, 1.5 equiv) and the mixture was stirred vigorously at 30 $^oC$ for 6 h. Then, the reaction mixture was transferred in to a separating funnel and extracted with EtOAc (3x15 mL). The combined organic layers were dried over anhydrous $Na_2SO_4$ and

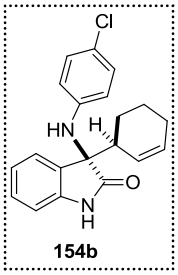
the solvent was evaporated under vacuum. Purification of the resulting crude reaction mixture by column chromatography on silica gel (EtOAc/hexane) gave the corresponding products **154**/**155** (see Tables 20 and 21 for individual entries).

**(*R**)-3-((*S**)-Cyclohex-2-en-1-yl)-3-(phenylamino)indolin-2-one (154a):** Following the general procedure Q described above, **154a** was obtained after purification by silica gel column chromatography (EtOAc/hexane, 30:70) as a colorless solid (68 mg, 90%); mp 199-201 °C. $R_f$ = 0.66 (30% EtOAc/hexane). IR (thin film): $\tilde{\upsilon}$ = 3316, 2928, 1726, 1603, 1468, 1313 $cm^{-1}$. $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ = 8.98 (br. s, 1 H), 7.27 (d, $J$ = 7.0 Hz, 2 H), 7.03-6.95 (m, 3 H), 6.88 (d, $J$ = 7.8 Hz, 1 H), 6.66 (t, $J$ = 7.8 Hz, 1 H), 6.30 (d, $J$ = 7.8 Hz, 2 H), 6.19 (d, $J$ = 10.2 Hz, 1 H), 6.01-5.97 (m, 1 H), 4.51 (br. s, 1 H), 2.77-2.79 (m, 1 H), 1.98 (d, $J$ = 17.5 Hz, 1 H), 1.89-1.77 (m, 2 H), 1.69-1.64 (m, 1 H), 1.52-1.45 (m, 1 H), 1.11-1.02 (m, 1 H). $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta$ = 180.6, 145.7, 140.4, 132.1, 129.1, 128.9, 128.7, 125.6, 124.4, 122.5, 119.0, 115.0, 110.3, 67.7, 44.7, 25.0, 23.4, 21.5. HRMS (ESI): calcd. for $C_{20}H_{21}N_2O$ $[M + H]^+$ 305.1654; found 305.1659. This compound contains traces of the minor isomer.



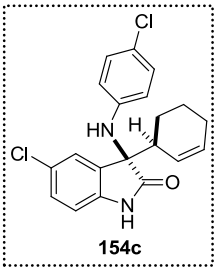
154a

**(*R**)-3-((4-Chlorophenyl)amino)-3-((*S**)-cyclohex-2-en-1-yl)indolin-2-one (154b):** Following the general procedure Q described above, **154b** was obtained after purification by silica gel column chromatography (EtOAc/hexane, 30:70) as a colorless solid (79 mg, 93%); mp 224-226 °C. $R_f$ = 0.67 (30% EtOAc/hexane). IR (thin film): $\tilde{\upsilon}$ = 3333, 2995, 1710, 1601, 1492, 1310 $cm^{-1}$. $^1H$ NMR (400 MHz, DMSO-$d_6$): $\delta$ = 10.71 (s, 1 H), 7.25 (t, $J$ = 7.4 Hz, 1 H), 7.07 (d, $J$ = 7.4 Hz, 1 H), 6.95-6.89 (m, 4 H), 6.50 (s, 1 H), 6.22 (d, $J$ = 8.7 Hz, 2 H), 6.00 (d, $J$ = 10.6 Hz, 1 H), 5.86-5.81 (m, 1 H), 2.76-2.72 (m, 1 H), 1.90-1.81 (m, 1 H), 1.70-1.29 (m, 4 H), 0.81-0.71 (m, 1 H). $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta$ = 179.8, 179.7, 144.3, 144.0, 140.3, 140.0, 132.3, 131.7, 129.2, 129.1, 129.1, 128.9, 128.2, 125.6, 124.9, 124.0, 123.9, 123.8, 123.6, 122.8, 122.7, 116.4, 115.8, 110.6, 110.3, 67.7, 67.7, 44.9, 44.6, 25.0, 25.0, 23.4, 23.3, 21.9, 21.5. HRMS (ESI): calcd. for $C_{20}H_{20}ClN_2O$ $[M + H]^+$ 339.1264; found 339.1276. This compound was isolated as a mixture of diastereomers, The $^1H$ NMR data refers to the major isomer and the $^{13}C$ NMR data given for both the diastereomers.



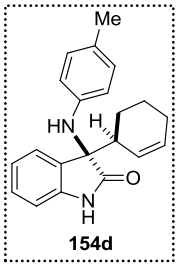
154b

**(*R**)-5-Chloro-3-((4-chlorophenyl)amino)-3-((*S**)-cyclohex-2-en-1-yl)indolin-2-one (154c):** Following the general procedure Q described above, **154c** was obtained after purification by silica gel column chromatography (EtOAc/hexane, 30:70) as a colorless solid (82 mg, 88%); mp 253-255 °C. $R_f$ = 0.68 (30% EtOAc/hexane). IR (thin film): $\tilde{\upsilon}$ = 3388, 2931, 1727, 1498, 1312, 816 $cm^{-1}$. $^1H$ NMR (400 MHz, $CDCl_3$+DMSO-$d_6$): $\delta$ = 10.07 (s, 1 H), 7.10 (dd, $J$ = 8.3, 2.2 Hz, 1 H), 7.04 (t, $J$ = 2.2 Hz, 1 H), 6.79 (d, $J$ = 8.8 Hz, 2 H), 6.77-6.74 (m, 1 H), 6.10 (d, $J$ = 8.8 Hz, 2 H), 5.98-5.93 (m, 1 H), 5.89-5.84 (m, 1 H), 4.61 (s, 1 H), 2.64-2.57 (m, 1 H), 1.88-1.71 (m, 2 H), 1.64-1.50 (m, 2 H), 1.42-1.31 (m, 1 H), 0.92-0.81 (m, 1 H). $^{13}C$ NMR (100 MHz, $CDCl_3$+DMSO-$d_6$): $\delta$ = 178.9, 144.4, 140.1, 132.2, 130.0, 128.9, 128.7, 127.2, 125.3, 123.9, 123.2, 116.0, 111.2, 67.5, 44.3, 24.8, 23.2, 21.4. HRMS (ESI): calcd. for $C_{20}H_{19}Cl_2N_2O$ $[M + H]^+$ 373.0874; found 373.0877. This compound was isolated with traces of minor isomer and the compound has poor solubility in most of the solvents.



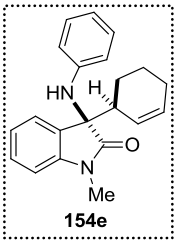
154c

**(*R**)-3-((*S**)-Cyclohex-2-en-1-yl)-3-(*p*-tolylamino)indolin-2-one (154d):** Following the general procedure Q described above, **154d** was obtained after purification by silica gel column chromatography (EtOAc/hexane, 30:70) as a colorless solid (56 mg, 71%); mp 210-212 °C. $R_f$ = 0.67 (30% EtOAc/hexane). IR (thin film): $\tilde{\upsilon}$ = 3344, 2934, 1707, 1618, 1521, 1318 $cm^{-1}$. $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ = 8.58 (s, 1 H), 7.29 (d, $J$ = 8.8 Hz, 1 H), 7.25 (d, $J$ = 8.8 Hz, 1 H), 7.02 (t, $J$ = 7.5 Hz, 1 H), 6.84 (d, $J$ = 7.5 Hz, 1 H), 6.77 (d, $J$ = 8.5 Hz, 2 H), 6.24 (d, $J$ = 8.5 Hz, 2 H), 6.20-6.17 (m, 1 H), 6.00-5.97 (m, 1 H), 4.31 (br. s, 1 H), 2.82-2.74 (m, 1 H), 2.12 (s, 3 H), 2.02-1.94 (m, 1 H), 1.90-1.82 (m, 1 H), 1.79-1.73 (m, 1 H), 1.70-1.62 (m, 1 H), 1.53-1.42 (m, 1 H), 1.11-1.01 (m, 1 H). $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta$ = 180.5, 180.4, 143.3, 143.0, 140.5, 140.2, 131.9, 131.3, 129.5, 128.9, 128.9, 128.8, 128.5, 128.2, 125.7, 124.9, 124.5, 124.2, 122.6, 122.5, 115.7, 115.1, 110.5, 110.2, 68.1, 68.0, 44.9, 44.6, 25.1, 25.0, 23.5, 23.3, 22.0, 21.6, 20.4, 20.4. HRMS (ESI): calcd. for $C_{21}H_{23}N_2O$ $[M + H]^+$ 319.1810; found 319.1812. This compound was isolated as a mixture of diastereomers, The $^1H$ NMR data refers to the major isomer and the $^{13}C$ NMR data given for both the diastereomers.



154d

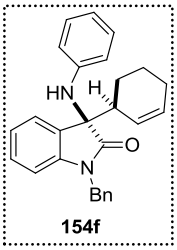
**(*R**)-3-((*S**)-Cyclohex-2-en-1-yl)-1-methyl-3-(phenylamino)indolin-2-one (154e):** Following the general procedure Q described above, **154e** was obtained after purification by



**154e**

silica gel column chromatography (EtOAc/hexane, 30:70) as a colorless solid (40 mg, 50%); mp 197-199 °C. $R_f$ = 0.66 (30% EtOAc/hexane). IR (thin film): $\tilde{\upsilon}$ = 3312, 2942, 1701, 1613, 1468, 1121 $cm^{-1}$. $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ = 7.37 (t, $J$ = 7.4 Hz, 1 H), 7.31 (d, $J$ = 7.4 Hz, 1 H), 7.06 (t, $J$ = 7.4 Hz, 1 H), 6.98-6.91 (m, 3 H), 6.66 (t, $J$ = 7.4 Hz, 1 H), 6.21 (d, $J$ = 7.7 Hz, 2 H), 6.20-6.16 (m, 1 H), 6.00-5.95 (m, 1 H), 4.33 (s, 1 H), 3.25 (s, 3 H), 2.79-2.73 (m, 1 H), 2.00-1.93 (m, 1 H), 1.89-1.80 (m, 1 H), 1.68-1.62 (m, 2 H), 1.51-1.41 (m, 1 H), 1.00-0.87 (m, 1 H). $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta$ = 177.9, 145.8, 143.4, 131.9, 129.0, 128.2, 125.3, 124.5, 122.6, 119.1, 115.1, 108.1, 67.2, 44.9, 26.2, 25.0, 23.4, 21.5. HRMS (ESI): calcd. for $C_{21}H_{23}N_2O$ $[M + H]^+$ 319.1810; found 319.1812. The NH signal was not visible clearly in the $^1H$ NMR spectrum.

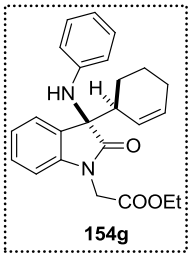
**(*R**)-1-Benzyl-3-((*S**)-cyclohex-2-en-1-yl)-3-(phenylamino)indolin-2-one (154f):** Following the general procedure Q described above, **154f** was obtained after purification by



**154f**

silica gel column chromatography (EtOAc/hexane, 30:70) as a colorless solid (89 mg, 90%); mp 157-159 °C. $R_f$ = 0.68 (30% EtOAc/hexane). IR (thin film): $\tilde{\upsilon}$ = 3331, 2930, 1702, 1602, 1498, 1343 $cm^{-1}$. $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ = 7.37 (d, $J$ = 7.4 Hz, 1 H), 7.28-7.26 (m, 4 H), 7.22-7.19 (m, 2 H), 7.03 (t, $J$ = 7.4 Hz, 1 H), 6.95 (t, $J$ = 8.0 Hz, 2 H), 6.78-6.71 (m, 2 H), 6.28 (d, $J$ = 8.0 Hz, 2 H), 6.24-6.21 (m, 1 H), 6.02-5.98 (m, 1 H), 5.10 (d, $J$ = 15.5 Hz, 1 H), 4.75 (d, $J$ = 15.5 Hz, 1 H), 2.85-2.81 (m, 1 H), 2.01-1.95 (m, 1 H), 1.91-1.83 (m, 1 H), 1.74-1.63 (m, 2 H), 1.54-1.44 (m, 1 H), 1.07-1.00 (m, 1 H). $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta$ = 177.8, 145.7, 142.7, 135.6, 131.9, 129.0, 128.7, 128.3, 127.9, 127.7, 127.6, 125.4, 124.7, 122.5, 119.7, 116.5, 109.3, 67.6, 44.9, 44.0, 25.0, 23.5, 21.6. HRMS (ESI): calcd. for $C_{27}H_{27}N_2O$ $[M + H]^+$ 395.2123; found 395.2124. This compound was isolated with traces of minor isomer.

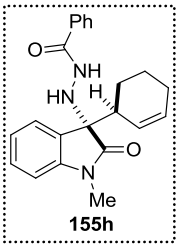
**Ethyl 2-((*R**)-3-((*S**)-cyclohex-2-en-1-yl)-2-oxo-3-(phenylamino)indolin-1-yl)acetate (154g):** Following the general procedure Q described above, **154g** was obtained after purification by silica gel column chromatography (EtOAc/hexane, 30:70) as a colorless solid (87 mg, 89%); mp 169-171 °C. $R_f$ = 0.62 (30% EtOAc/hexane). IR (thin film): $\tilde{\upsilon}$ = 3329, 2933, 1724, 1600, 1465, 1260, 1021 $cm^{-1}$. $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ = 7.36-7.30



154g

(m, 2 H), 7.07 (t, *J* = 7.5 Hz, 1 H), 6.98 (dd, *J* = 8.6, 7.5 Hz, 2 H), 6.80 (d, *J* = 7.5 Hz, 1 H), 6.67 (t, *J* = 7.5 Hz, 1 H), 6.31 (d, *J* = 8.6 Hz, 2 H), 6.22 (d, *J* = 10.4 Hz, 1 H), 6.03-5.98 (m, 1 H), 4.60 (d, *J* = 17.5 Hz, 1 H), 4.44 (d, *J* = 17.5 Hz, 1 H), 4.38 (br. s, 1 H), 4.28-4.20 (m, 2 H), 2.82-2.77 (m, 1 H), 2.01-1.95 (m, 1 H), 1.92-1.83 (m, 1 H), 1.78-1.73 (m, 1 H), 1.70-1.64 (m, 1 H), 1.52-1.42 (m, 1 H), 1.27 (t, *J* = 7.1 Hz, 3 H), 1.12-1.02 (m, 1 H). $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ = 177.8, 167.6, 145.5, 142.0, 132.2, 129.0, 127.9, 125.5, 124.4, 122.8, 119.0, 115.2, 108.2, 67.0, 61.7, 45.0, 41.3, 25.0, 23.6, 21.6, 14.2. HRMS (ESI): calcd. for $C_{24}H_{27}N_2O_3$ $[M + H]^+$ 391.2022; found 391.2018. This compound contains trace of minor isomer and the NMR data refers to the major isomer.

***N*'-((*R**)-3-((*R**)-Cyclohex-2-en-1-yl)-1-methyl-2-oxoindolin-3-yl)benzohydrazide (155h):** Following the general procedure Q described above, **155h** was obtained after



155h

purification by silica gel column chromatography (EtOAc/hexane, 40:60) as a colorless solid (45 mg, 50%); mp 148-150 °C. $R_f$ = 0.40 (40% EtOAc/ hexane). IR (thin film): $\tilde{\upsilon}$ = 3440, 2926, 1706, 1612, 1469, 1120 $cm^{-1}$. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 8.09 (br. s, 1 H), 7.58 (d, *J* = 7.4 Hz, 2 H), 7.52 (d, *J* = 7.4 Hz, 1 H), 7.45 (t, *J* = 7.4 Hz, 1 H), 7.38-7.30 (m, 3 H), 7.07 (t, *J* = 8.0 Hz, 1 H), 6.84 (d, *J* = 8.0 Hz, 1 H), 5.74 (d, *J* = 5.7 Hz, 1 H), 5.64-5.59 (m, 1 H), 5.34 (d, *J* = 10.4 Hz, 1 H), 3.26 (s, 3 H), 2.98-2.93 (m, 1 H), 1.97-1.87 (m, 3 H), 1.82-1.75 (m, 1 H), 1.60-1.42 (m, 2 H). $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ = 177.2, 166.5, 144.0, 132.7, 131.7, 130.2, 129.3, 128.5, 127.4, 127.0, 125.3, 124.6, 122.7, 108.0, 71.3, 41.2, 26.3, 25.0, 23.4, 21.9. HRMS (ESI): calcd. for $C_{22}H_{24}N_3O_2$ $[M + H]^+$ 362.1869; found 362.1858.

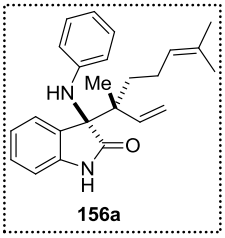
**Procedure R. Indium-mediated addition of geranyl bromide (123d) to isatin ketimines 105:** To a vigorously stirring solution of corresponding isatin ketimine **105** (0.25 mmol, 1 equiv) and geranyl bromide (**123d**; 0.75 mmol, 3 equiv) in EtOH (2 mL) was added sodium iodide (0.75 mmol, 3 equiv) and indium powder (0.5 mmol, 3 equiv) and the mixture was stirred vigorously at 30 $^o$C for 24 h. Then, the reaction mixture was transferred in to a separating funnel and extracted with EtOAc (3x15 mL). The combined organic layers were dried over anhydrous $Na_2SO_4$ and then the solvent was evaporated under vacuum. Purification of the resulting crude reaction mixture by column chromatography on silica gel

(EtOAc/hexane) gave the corresponding product **156**/**157** (see Table 22 for individual entries).

**Procedure S. Indium-mediated addition of neryl bromide (123g) to isatin ketimines 105:** THF solution of (*Z*)-3,7-dimethylocta-2,6-dien-1-ol (nerol) (1 mmol, 1 equiv) was allowed to cool at −10 $^{o}$C. To this cooled solution was added phosphorus tribromide (0.5 equiv) dropwise. Then, the reaction mixture was allowed to stir at 0 $^{o}$C for 3-5 h. After disappearance of the starting material (as shown by TLC), $Et_2O$ (10 mL) was added to the reaction mixture. After that it was washed with 5% $NaHCO_3$ solution (2 mL) and water (2 mL) successively. Drying of organic layers with anhydrous $Na_2SO_4$ and the evaporation of solvent under vacuum gave the crude (*Z*)-1-bromo-3,7-dimethylocta-2,6-diene (*E*-neryl bromide; **123g**) which was used as such for further reaction with isatin ketimines.

To a stirring solution of isatine ketimine **105** (0.25 mmol, 1 equiv) in EtOH (2 mL), was added neryl bromide (**123g**; 0.75 mmol, 3 equiv), sodium iodide (0.75 mmol, 3 equiv) and indium powder (0.5 mmol, 3 equiv) and the reaction mixture was stirred vigorously at 30 $^{o}$C for 24 h. Then, the reaction mixture was transferred in to a separating funnel and extracted with EtOAc (3x15 mL). The combined organic layers were dried with anhydrous $Na_2SO_4$ and the solvent was evaporated under vacuum. Purification of the resulting crude reaction mixture by column chromatography on silica gel (EtOAc/hexane) gave the corresponding product **157**/**156** (see Table 22 for individual entries).

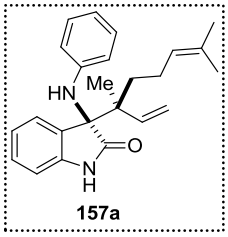
**(*R**)-3-((*R**)-3,7-Dimethylocta-1,6-dien-3-yl)-3-(phenylamino)indolin-2-one (156a):** Following the general procedure R described above, **156a** was obtained after purification by silica gel column chromatography (EtOAc/hexane, 30:70) as a colorless solid (57 mg, 63%); mp 137-139 °C. $R_f$ = 0.65 (30% EtOAc/hexane). IR (thin film): $\tilde{\upsilon}$ = 3376, 2923, 1715, 1602, 1470, 1123 cm$^{-1}$. $^{1}$H NMR (400 MHz, $CDCl_3$): $\delta$ = 8.53 (br. s, 1 H), 7.29-7.24 (m, 2 H), 7.01 (t, *J* = 7.4 Hz, 1 H), 6.92 (t, *J* = 8.0 Hz, 2 H), 6.77 (t, *J* = 7.4 Hz, 1 H), 6.61 (t, *J* = 7.4 Hz, 1 H), 6.43 (dd, *J* = 17.1, 10.9 Hz, 1 H), 6.19 (d, *J* = 8.0 Hz, 2 H), 5.56 (d, *J* = 10.9 Hz, 1 H), 5.39 (d, *J* = 17.1 Hz, 1 H), 4.92 (t, *J* = 6.6 Hz, 1 H), 4.61 (s, 1 H), 1.79-1.72 (m, 2 H), 1.68-1.60 (m, 1 H), 1.61 (s, 3 H), 1.56-1.52 (m, 1 H), 1.50 (s, 3 H), 1.33 (s, 3 H). $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ = 180.3, 145.8, 141.3, 140.4, 131.6, 129.1, 129.0, 128.7, 126.7,



**156a**

124.1, 122.2, 118.8, 118.1, 114.6, 110.3, 69.8, 48.0, 33.8, 25.6, 22.7, 17.6, 16.2. HRMS (ESI): calcd. for $C_{24}H_{29}N_2O$ $[M + H]^+$ 361.2280; found 361.2267.

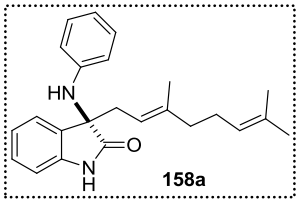
**(*R**)-3-((*S**)-3,7-Dimethylocta-1,6-dien-3-yl)-3-(phenylamino)indolin-2-one (157a):** Following the general procedure S described above, **157a** was obtained after purification by



157a

silica gel column chromatography (EtOAc/hexane, 30:70) as a colorless solid (52 mg, 58%); mp 136-138 °C. $R_f$ = 0.66 (30% EtOAc/hexane). IR (thin film): $\tilde{\upsilon}$ = 3388, 2924, 1722, 1602, 1470, 1115 $cm^{-1}$. $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ = 8.40 (s, 1 H), 7.22 (t, *J* = 7.7 Hz, 1 H), 7.11 (d, *J* = 7.4 Hz, 1 H), 6.98-6.90 (m, 3 H), 6.84 (d, *J* = 7.7 Hz, 1 H), 6.59 (t, *J* = 7.4 Hz, 1 H), 6.23 (d, *J* = 8.6 Hz, 2 H), 6.04 (dd, *J* = 17.7, 11.0 Hz, 1 H), 5.50 (d, *J* = 11.0 Hz, 1 H), 5.35 (d, *J* = 17.7 Hz, 1 H), 4.95 (t, *J* = 6.8 Hz, 1 H), 4.42 (s, 1 H), 1.90-1.82 (m, 1 H), 1.77-1.69 (m, 1 H), 1.64-1.54 (m, 2 H), 1.63 (s, 3 H), 1.52 (s, 3 H), 1.37 (s, 3 H). $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta$ = 179.4, 145.2, 141.2, 140.5, 131.6, 129.0, 128.9, 128.7, 126.0, 124.2, 122.2, 118.5, 117.7, 114.4, 110.0, 69.3, 47.5, 33.1, 25.7, 23.0, 17.7, 15.4. HRMS (ESI): calcd. for $C_{24}H_{29}N_2O$ $[M + H]^+$ 361.2280; found 361.2283.

**3-(3,7-Dimethylocta-2,6-dien-1-yl)-3-(phenylamino)indolin-2-one (158a):** The compound **158a** was obtained after purification by silica gel column chromatography (EtOAc/hexane,

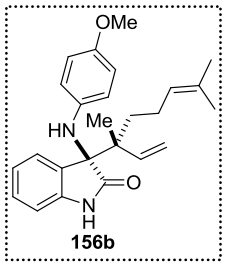


158a

30:70) as a colorless solid (9 mg, 10%); mp 120-122 °C. $R_f$ = 0.61 (30% EtOAc/hexane). IR (thin film): $\tilde{\upsilon}$ = 3310, 2925, 1707, 1603, 1470 $cm^{-1}$. $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ = 8.68 (s, 1 H), 7.22-7.18 (m, 2 H), 7.00-6.85 (m, 3 H), 6.86 (d, *J* = 7.4 Hz, 1 H), 6.60 (t, *J* = 7.4 Hz, 1 H), 6.23 (d, *J* = 7.7 Hz, 2 H), 5.13 (t, *J* = 8.4 Hz, 1 H), 5.03-5.01 (m, 1 H), 4.48 (br. s, 1 H), 2.71 (dd, *J* = 13.8, 8.4 Hz, 1 H), 2.57 (dd, *J* = 13.8, 7.7 Hz, 1 H), 2.01-1.94 (m, 1 H), 1.97 (s, 3 H), 1.67-1.63 (m, 1 H), 1.64 (s, 3 H), 1.57-1.53 (m, 2 H), 1.56 (s, 3 H). $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta$ = 180.5, 145.2, 141.7, 139.7, 131.7, 130.5, 129.1, 128.8, 124.1, 123.9, 122.8, 118.7, 115.4, 114.4, 110.4, 64.7, 40.0, 38.9, 26.6, 25.7, 17.7, 16.4. HRMS (ESI): calcd. for $C_{24}H_{29}N_2O$ $[M + H]^+$ 361.2280; found 361.2267. This compound was isolated in only 9 mg and the NMR spectra shows the presence of traces of some impurity.

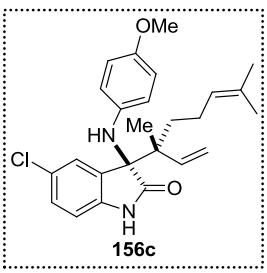
**(*R**)-3-((*R**)-3,7-Dimethylocta-1,6-dien-3-yl)-3-((4-methoxyphenyl)amino)indolin-2-one (156b):** Following the general procedure R described above, **156b** was obtained after purification by silica gel column chromatography (EtOAc/hexane, 30:70) as a colorless

solid (58 mg, 59%); mp 152-154 °C. $R_f$ = 0.64 (30% EtOAc/hexane). IR (thin film): $\tilde{\upsilon}$ = 3294, 2927, 1710, 1511, 1243, 1038 $cm^{-1}$. $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ = 8.34 (s, 1 H), 7.35 (d, $J$ = 7.6 Hz,1 H), 7.25 (t, $J$ = 7.7 Hz, 1 H), 7.03 (t, $J$ = 7.6 Hz, 1 H), 6.73 (d, $J$ = 7.7 Hz, 1 H), 6.46 (d, $J$ = 9.0 Hz, 2 H), 6.44-6.36 (m, 1 H), 6.22 (d, $J$ = 9.0 Hz, 2 H), 5.53 (d, $J$ = 10.7 Hz, 1 H), 5.36 (d, $J$ = 17.6 Hz, 1 H), 4.92 (t, $J$ = 6.8 Hz, 1 H), 3.56 (s, 3 H), 1.79-1.71 (m, 3 H), 1.61 (s, 3 H), 1.53-1.46 (m, 1 H), 1.50 (s, 3 H), 1.34 (s, 3 H). $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta$ = 180.5, 153.3, 141.4, 140.6, 139.4, 131.6, 129.0, 129.0, 127.0, 124.2, 122.1, 118.0, 117.8, 114.3, 110.1, 71.1, 55.3, 47.8, 34.1, 25.6, 22.7, 17.6, 16.2. HRMS (ESI): calcd. for $C_{25}H_{31}N_2O_2$ $[M + H]^+$ 391.2386; found 391.2377.



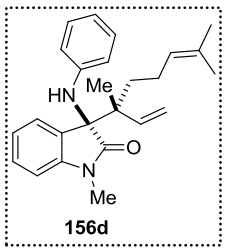
156b

**(*R**)-5-Chloro-3-((*R**)-3,7-dimethylocta-1,6-dien-3-yl)-3-((4-methoxyphenyl)amino) indolin-2-one (156c):** Following the general procedure R described above, **156c** was obtained after purification by silica gel column chromatography (EtOAc/hexane, 30:70) as a colorless solid (66 mg, 62%); mp 152-154 °C. $R_f$ = 0.65 (30% EtOAc/hexane). IR (thin film): $\tilde{\upsilon}$ = 3290, 2926, 1706, 1510, 1248, 1037 $cm^{-1}$. $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ = 8.11 (s, 1 H), 7.34 (d, $J$ = 2.2 Hz, 1 H), 7.25 (dd, $J$ = 8.5, 2.2 Hz, 1 H), 6.67 (d, $J$ = 8.5 Hz, 1 H), 6.50 (d, $J$ = 9.0 Hz, 2 H), 6.38 (dd, $J$ = 17.6, 10.7 Hz, 1 H), 6.22 (d, $J$ = 9.0 Hz, 2 H), 5.55 (d, $J$ = 10.7 Hz, 1 H), 5.37 (d, $J$ = 17.6 Hz, 1 H), 4.92 (t, $J$ = 6.9 Hz, 1 H), 4.32 (br. s, 1 H), 3.60 (s, 3 H), 1.79-1.72 (m, 2 H), 1.63-1.62 (m, 1 H), 1.62 (s, 3 H), 1.51 (s, 3 H), 1.49-1.43 (m, 1 H), 1.33 (s, 3 H). $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta$ = 179.9, 153.6, 140.1, 139.9, 139.0, 131.7, 130.9, 129.1, 127.6, 127.2, 124.0, 118.3, 117.9, 114.4, 110.9, 71.3, 55.4, 47.9, 34.1, 25.6, 22.6, 17.6, 16.2. HRMS (ESI): calcd. for $C_{25}H_{30}ClN_2O_2$ $[M + H]^+$ 425.1996; found 425.1981.



156c

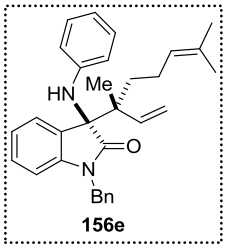
**(*R**)-3-((*R**)-3,7-Dimethylocta-1,6-dien-3-yl)-1-methyl-3-(phenylamino)indolin-2-one (156d):** Following the general procedure R described above, **156d** was obtained after purification by silica gel column chromatography (EtOAc/hexane, 30:70) as a colorless solid (37 mg, 40%); mp 123-125 °C. $R_f$ = 0.68 (30% EtOAc/hexane). IR (thin film): $\tilde{\upsilon}$ = 3388, 2921, 1708, 1608, 1469, 1346, 1116 $cm^{-1}$. $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ = 7.38 (t, $J$ = 7.8 Hz, 1 H), 7.32 (d, $J$ = 7.3 Hz, 1 H), 7.06 (t, $J$ = 7.8 Hz, 1 H), 6.94-6.90 (m, 3 H),



156d

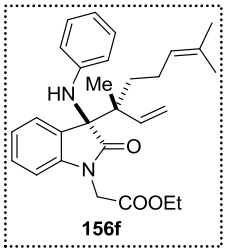
6.61 (t, *J* = 7.3 Hz, 1 H), 6.44-6.42 (m, 1 H), 6.09 (d, *J* = 7.8 Hz, 2 H), 5.53 (d, *J* = 11.0 Hz, 1 H), 5.36 (d, *J* = 17.6 Hz, 1 H), 4.91 (t, *J* = 6.8 Hz, 1 H), 4.61 (br. s, 1 H), 3.24 (s, 3 H), 1.78-1.72 (m, 2 H), 1.67-1.60 (m, 1 H), 1.63 (s, 3 H), 1.50 (s, 3 H), 1.39-1.30 (m, 1 H), 1.33 (s, 3 H). $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ = 177.8, 145.8, 144.3, 140.6, 131.5, 129.2, 129.0, 128.2, 126.4, 124.2, 122.2, 118.7, 117.9, 114.6, 108.1, 69.4, 48.1, 33.7, 26.1, 25.7, 22.7, 17.7, 16.4. HRMS (ESI): calcd. for $C_{25}H_{31}N_2O$ $[M + H]^+$ 375.2436; found 375.2438.

**(*R**)-1-Benzyl-3-((*R**)-3,7-dimethylocta-1,6-dien-3-yl)-3-(phenylamino)indolin-2-one (156e):** Following the general procedure R described above, **156e** was obtained after purification by silica gel column chromatography (EtOAc/hexane, 30:70) as a colorless solid (85 mg, 70%); mp 113-115 °C. $R_f$ = 0.69 (30% EtOAc/hexane). IR (thin film): $\tilde{\upsilon}$ = 3371, 2928, 1708, 1605, 1509, 1322, 1177 cm$^{-1}$. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 7.36-7.24 (m, 7 H), 7.02 (t, *J* = 7.4 Hz, 1 H), 6.90 (t, *J* = 7.8 Hz, 2 H), 6.81 (d, *J* = 7.8 Hz, 1 H), 6.65 (t, *J* = 7.4 Hz, 1 H), 6.53-6.47 (m, 1 H), 6.13 (d, *J* = 7.8 Hz, 2 H), 5.55 (d, *J* = 10.8 Hz, 1 H), 5.39 (d, *J* = 17.6 Hz, 1 H), 4.99-4.86 (m, 3 H), 4.63 (br. s, 1 H), 1.77-1.69 (m, 2 H), 1.65 (s, 3 H), 1.50 (s, 3 H), 1.45-1.34 (m, 2 H), 1.35 (s, 3 H). $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ = 177.8, 145.7, 143.7, 140.7, 135.8, 131.5, 129.1, 128.9, 128.6, 128.2, 127.9, 127.6, 126.6, 124.1, 122.1, 119.0, 118.0, 115.5, 109.2, 69.6, 48.3, 44.1, 34.3, 25.7, 22.6, 17.6, 16.4. HRMS (ESI): calcd. for $C_{31}H_{35}N_2O$ $[M + H]^+$ 451.2749; found 451.2738.



**156e**

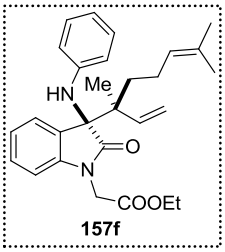
**Ethyl 2-((*R**)-3-((*R**)-3,7-dimethylocta-1,6-dien-3-yl)-2-oxo-3-(phenylamino)indolin-1-yl)acetate (156f):** Following the general procedure R described above, **156f** was obtained after purification by silica gel column chromatography (EtOAc/hexane, 30:70) as a colorless solid (67 mg, 60%); mp 100-102 °C. $R_f$ = 0.65 (30% EtOAc/hexane). IR (thin film): $\tilde{\upsilon}$ = 3353, 2984, 1732, 1601, 1502, 1264, 1183 cm$^{-1}$. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 7.37-7.32 (m, 2 H), 7.07 (t, *J* = 7.6 Hz, 1 H), 6.95 (t, *J* = 7.4 Hz, 2 H), 6.79 (d, *J* = 7.6 Hz, 1 H), 6.62 (t, *J* = 7.4 Hz, 1 H), 6.42 (dd, *J* = 17.5, 11.0 Hz, 1 H), 6.19 (d, *J* = 7.4 Hz, 2 H), 5.54 (d, *J* = 10.9 Hz, 1 H), 5.37 (d, *J* = 17.6 Hz, 1 H), 4.95 (t, *J* = 6.7 Hz, 1 H), 4.60 (br. s, 1 H), 4.61 (d, *J* = 17.4 Hz, 1 H), 4.41 (d, *J* = 17.4 Hz, 1 H), 4.28-4.20 (m, 2 H), 1.79-1.72 (m, 2 H), 1.65-1.62 (m, 1 H), 1.62 (s, 3 H), 1.59 (s, 3 H), 1.59-1.44 (m, 1 H), 1.33 (s, 3 H), 1.26 (t, *J* = 7.1 Hz, 3 H). $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ = 177.6, 167.5, 145.4, 143.1, 140.5, 131.4, 129.1, 128.9,



**156f**

127.7, 126.6, 124.3, 122.5, 118.7, 118.0, 114.8, 108.3, 69.2, 61.6, 48.4, 41.4, 33.7, 25.6, 22.8, 17.7, 16.3, 14.2. HRMS (ESI): calcd. for $C_{28}H_{35}N_2O_3$ $[M + H]^+$ 447.2648; found 447.2638.

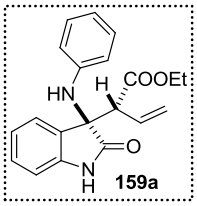
**Ethyl 2-((*R**)-3-((*S**)-3,7-dimethylocta-1,6-dien-3-yl)-2-oxo-3-(phenylamino)indolin-1-yl)acetate (157f):** Following the general procedure S described above, **157f** was obtained after purification by silica gel column chromatography (EtOAc/hexane, 30:70) as a colorless solid (46 mg, 42%); mp 104-106 °C. $R_f$ = 0.65 (30% EtOAc/hexane). IR (thin film): $\tilde{\upsilon}$ = 3411, 2922, 1726, 1602, 1466, 1203 $cm^{-1}$. $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ = 7.30 (t, *J* = 7.7 Hz, 1 H), 7.16 (d, *J* = 7.4 Hz, 1 H), 7.01 (t, *J* = 7.7 Hz, 1 H), 6.95 (t, *J* = 8.6 Hz, 2 H), 6.77 (d, *J* = 7.7 Hz, 1 H), 6.60 (t, *J* = 7.4 Hz, 1 H), 6.23 (d, *J* = 8.6 Hz, 2 H), 6.04 (dd, *J* = 17.5, 10.7 Hz, 1 H), 5.49 (d, *J* = 10.7 Hz, 1 H), 5.34 (d, *J* = 17.5 Hz, 1 H), 4.95 (t, *J* = 6.8 Hz, 1 H), 4.64 (d, *J* = 17.4 Hz, 1 H), 4.47 (d, *J* = 17.4 Hz, 1 H), 4.44 (s, 1 H), 4.27 (q, *J* = 7.1 Hz, 2 H), 1.89-1.80 (m, 1 H), 1.76-1.67 (m, 1 H), 1.64-1.61 (m, 1 H), 1.63 (s, 3 H), 1.56-1.48 (m, 1 H), 1.52 (s, 3 H), 1.35 (s, 3 H), 1.29 (t, *J* = 7.1 Hz, 3 H). $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta$ = 176.9, 167.6, 145.0, 143.0, 140.6, 131.5, 128.9, 128.9, 127.9, 125.8, 124.3, 122.5, 118.5, 117.7, 114.6, 108.0, 68.8, 61.7, 47.9, 41.5, 33.1, 25.7, 23.0, 17.7, 15.6, 14.2. HRMS (ESI): calcd. for $C_{28}H_{34}N_2NaO_3$ $[M + Na]^+$ 469.2467; found 469.2473.



157f

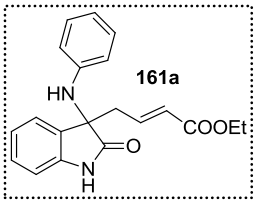
**Procedure T. Indium-mediated addition of ethyl 4-bromocrotonate (123e) to isatin ketimines 105:** To a vigorously stirring solution of corresponding isatin ketimine **105** (0.25 mmol, 1 equiv) and ethyl 4-bromocrotonate (**123e**; 0.75 mmol, 3 equiv) in EtOH (1 mL) was added indium powder (0.5 mmol, 2 equiv) and the reaction mixture was stirred vigorously at 30 $^oC$ for 3 h. Then, the reaction mixture was transferred in to a separating funnel and extracted with EtOAc (3x15 mL). The combined organic layers were dried over anhydrous $Na_2SO_4$ and the solvent was evaporated under vacuum. Purification of the resulting crude reaction mixture by column chromatography on silica gel (EtOAc/hexane) gave the corresponding product **159**/**160** (see Tables 23 and 24 for individual entries).

**(*R**)-Ethyl 2-((*R**)-2-oxo-3-(phenylamino)indolin-3-yl)but-3-enoate (159a):** Following the general procedure T described above, **159a** was obtained after purification by silica gel column chromatography (EtOAc/hexane, 30:70) as a colorless solid (78 mg, 93%); mp 142-144 °C. $R_f$ = 0.58 (30% EtOAc/hexane). IR (thin film): $\tilde{\upsilon}$ = 3288, 2975, 1715, 1605, 1470,



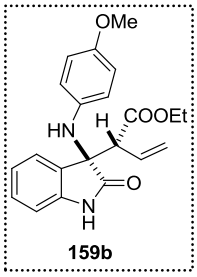

1242 $cm^{-1}$. $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ = 8.99 (s, 1 H), 7.33-7.25 (m, 2 H), 7.04 (t, *J* = 7.6 Hz, 1 H), 6.98 (dd, *J* = 8.5, 7.6 Hz, 2 H), 6.85 (d, *J* = 7.6 Hz, 1 H), 6.69 (t, *J* = 7.6 Hz, 1 H), 6.33 (d, *J* = 8.5 Hz, 2 H), 5.95-5.86 (m, 1 H), 5.31-5.26 (m, 2 H), 4.23-4.13 (m, 2 H), 3.50 (d, *J* = 9.8 Hz, 1 H), 1.22 (t, *J* = 7.1 Hz, 3 H). $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta$ = 178.4, 170.3, 144.9, 140.3, 129.7, 129.7, 129.1, 127.4, 125.8, 122.7, 122.2, 119.6, 115.6, 110.6, 66.1, 61.5, 57.6, 14.0. HRMS (ESI): calcd. for $C_{20}H_{20}N_2NaO_3$ $[M + Na]^+$ 359.1372; found 359.1369.

**Ethyl 4-(2-oxo-3-(phenylamino)indolin-3-yl)but-2-enoate (161a):** The compound **161a** was obtained after purification by silica gel column chromatography (EtOAc/hexane, 30:70)



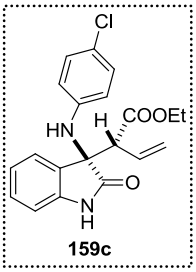

as a colorless solid (33 mg, 40%); mp 182-184 °C. $R_f$ = 0.55 (30% EtOAc/hexane). IR (thin film): $\tilde{\upsilon}$ = 3333, 2980, 1725, 1604, 1467, 1201 $cm^{-1}$. $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ = 8.91 (s, 1 H), 7.20 (t, *J* = 7.5 Hz, 2 H), 6.99 (t, *J* = 7.5 Hz, 1 H), 6.90 (t, *J* = 7.9 Hz, 2 H), 6.86-6.78 (m, 2 H), 6.60 (t, *J* = 7.4 Hz, 1 H), 6.21 (d, *J* = 7.9 Hz, 2 H), 5.87 (d, *J* = 15.6 Hz, 1 H), 4.48 (s, 1 H), 4.11 (q, *J* = 7.1 Hz, 2 H), 2.83 (dd, *J* = 13.7, 7.4 Hz, 1 H), 2.64 (dd, *J* = 13.7, 8.0 Hz, 1 H), 1.21 (t, *J* = 7.1 Hz, 3 H). $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta$ = 179.8, 165.7, 144.9, 140.0, 139.6, 129.4, 129.4, 129.1, 126.6, 124.2, 123.3, 119.4, 114.8, 111.0, 64.3, 60.6, 42.6, 14.2. HRMS (ESI): calcd. for $C_{20}H_{21}N_2O_3$ $[M + H]^+$ 337.1552; found 337.1550.

**(*R**)-Ethyl 2-((*R**)-3-((4-methoxyphenyl)amino)-2-oxoindolin-3-yl)but-3-enoate (159b):** Following the general procedure T described above, **159b** was obtained after purification by




silica gel column chromatography (EtOAc/hexane, 30:70) as a colorless solid (87 mg, 95%); mp 106-108 °C. $R_f$ = 0.59 (30% EtOAc/hexane). IR (thin film): $\tilde{\upsilon}$ = 3265, 2980, 1720, 1511, 1242, 1034 $cm^{-1}$. $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ = 8.42 (br. s, 1 H), 7.45 (d, *J* = 7.4 Hz, 1 H), 7.26 (t, *J* = 7.7 Hz, 1 H), 7.07 (t, *J* = 7.4 Hz, 1 H), 6.78 (d, *J* = 7.7 Hz, 1 H), 6.52 (d, *J* = 8.9 Hz, 2 H), 6.39 (d, *J* = 8.9 Hz, 2 H), 6.01-5.92 (m, 1 H), 5.33-5.29 (m, 2 H), 4.18-4.09 (m, 2 H), 3.61 (s, 3 H), 3.56 (d, *J* = 9.9 Hz, 1 H), 1.18 (t, *J* = 7.1 Hz, 3 H). $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta$ = 178.1, 170.4, 154.3, 140.7, 137.9, 129.9, 129.6, 127.6, 126.1, 122.6, 122.1, 120.0, 114.2, 110.2, 67.2, 61.3, 57.7, 55.3, 14.0. HRMS (ESI): calcd. for $C_{21}H_{22}N_2NaO_4$ $[M + Na]^+$ 389.1477; found 389.1468. The NH signal was not clearly visible in the $^1H$ NMR spectrum.

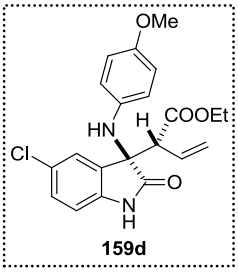
**(*R**)-Ethyl 2-((*R**)-3-((4-chlorophenyl)amino)-2-oxoindolin-3-yl)but-3-enoate (159c):** Following the general procedure T described above, **159c** was obtained after purification by



**159c**

silica gel column chromatography (EtOAc/hexane, 30:70) as a colorless solid (89 mg, 96%); mp 122-124 °C. $R_f$ = 0.59 (30% EtOAc/hexane). IR (thin film): $\tilde{\upsilon}$ = 3275, 2985, 1731, 1492, 1325, 1178 $cm^{-1}$. $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ = 8.75 (s, 1 H), 7.32-7.27 (m, 2 H), 7.05 (t, $J$ = 7.6 Hz, 1 H), 6.92 (d, $J$ = 8.9 Hz, 2 H), 6.86 (d, $J$ = 8.3 Hz, 1 H), 6.25 (d, $J$ = 8.9 Hz, 2 H), 5.96-5.86 (m, 1 H), 5.33-5.26 (m, 3 H), 4.22-4.12 (m, 2 H), 3.47 (d, $J$ = 9.8 Hz, 1 H), 1.21 (t, $J$ = 7.2 Hz, 3 H). $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta$ = 177.9, 170.3, 143.5, 140.2, 129.9, 129.5, 128.9, 127.0, 125.7, 124.5, 122.9, 122.4, 117.0, 110.6, 66.1, 61.6, 57.5, 14.0. HRMS (ESI): calcd. for $C_{20}H_{19}ClN_2NaO_3$ $[M + Na]^+$ 393.0982; found 393.0975.

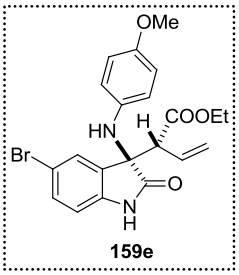
**(*R**)-Ethyl 2-((*R**)-5-chloro-3-((4-methoxyphenyl)amino)-2-oxoindolin-3-yl)but-3-enoate (159d):** Following the general procedure T described above, **159d** was obtained after



**159d**

purification by silica gel column chromatography (EtOAc/hexane, 30:70) as a colorless solid (95 mg, 95%); mp 140-142 °C. $R_f$ = 0.60 (30% EtOAc/hexane). IR (thin film): $\tilde{\upsilon}$ = 3388, 2982, 1728, 1511, 1241, 1035 $cm^{-1}$. $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ = 8.55 (br. s, 1 H), 7.45 (d, $J$ = 1.7 Hz, 1 H), 7.24 (dd, $J$ = 8.3, 1.7 Hz, 1 H), 6.71 (d, $J$ = 8.3 Hz, 1 H), 6.55 (d, $J$ = 8.8 Hz, 2 H), 6.39 (d, $J$ = 8.8 Hz, 2 H), 5.95-5.86 (m, 1 H), 5.32-5.28 (m, 2 H), 4.75 (br. s, 1 H), 4.19-4.13 (m, 2 H), 3.63 (s, 3 H), 3.53 (d, $J$ = 9.8 Hz, 1 H), 1.22 (t, $J$ = 7.1 Hz, 3 H). $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta$ = 178.0, 170.2, 154.4, 139.2, 137.7, 129.6, 129.5, 129.5, 128.1, 126.5, 122.5, 119.9, 114.3, 111.3, 67.4, 61.5, 57.6, 55.3, 14.0. HRMS (ESI): calcd. for $C_{21}H_{21}ClN_2NaO_4$ $[M + Na]^+$ 423.1088; found 423.1069.

**(*R**)-Ethyl 2-((*R**)-5-bromo-3-((4-methoxyphenyl)amino)-2-oxoindolin-3-yl)but-3-enoate (159e):** Following the general procedure T described above, **159e** was obtained after

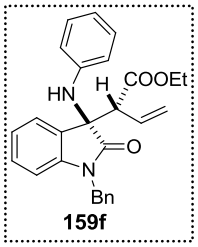


**159e**

purification by silica gel column chromatography (EtOAc/hexane, 30:70) as a colorless solid (109 mg, 98%); mp 116-118 °C. $R_f$ = 0.62 (30% EtOAc/hexane). IR (thin film): $\tilde{\upsilon}$ = 3193, 1734, 1510, 1244, 1179, 1035 $cm^{-1}$. $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ = 8.69 (s, 1 H), 7.57 (d, $J$ = 2.0 Hz, 1 H), 7.39 (dd, $J$ = 8.2, 2.0 Hz, 1 H), 6.65 (d, $J$ = 8.2 Hz, 1 H), 6.54 (d, $J$ = 9.0 Hz, 2 H), 6.38 (d, $J$ = 9.0 Hz, 2 H), 5.95-5.85 (m, 1 H), 5.32-5.28 (m, 2 H),

4.76 (br. s, 1 H), 4.19-4.13 (m, 2 H), 3.62 (s, 3 H), 3.52 (d, *J* = 9.8 Hz, 1 H), 1.21 (t, *J* = 7.1 Hz, 3 H). $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ = 178.0, 170.2, 154.4, 139.7, 137.7, 132.5, 129.9, 129.4, 129.2, 122.5, 119.8, 115.4, 114.3, 111.8, 67.4, 61.5, 57.6, 55.3, 14.0. HRMS (ESI): calcd. for $C_{21}H_{22}BrN_2O_4$ $[M + H]^+$ 445.0763; found 445.0760.

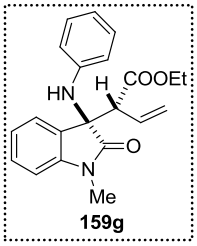
**(*R**)-Ethyl 2-((*R**)-1-benzyl-2-oxo-3-(phenylamino)indolin-3-yl)but-3-enoate (159f):** Following the general procedure T described above, **159f** was obtained after purification by



**159f**

silica gel column chromatography (EtOAc/hexane, 30:70) as a colorless solid (97 mg, 91%); mp 86-88 °C. $R_f$ = 0.65 (30% EtOAc/hexane). IR (thin film): $\tilde{\upsilon}$ = 3351, 2980, 1718, 1602, 1497, 1306, 1182 $cm^{-1}$. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 7.43(d, *J* = 7.5 Hz, 1 H), 7.28-7.23 (m, 4 H), 7.19-7.17 (m, 2 H), 7.06 (t, *J* = 7.5 Hz, 1 H), 6.96 (t, *J* = 8.2 Hz, 2 H), 6.76 (t, *J* = 7.5 Hz, 2 H), 6.31 (d, *J* = 8.2 Hz, 2 H), 6.00-5.91 (m, 1 H), 5.33-5.29 (m, 2 H), 5.14 (s, 1 H), 5.09 (d, *J* = 15.5 Hz, 1 H), 4.69 (d, *J* = 15.5 Hz, 1 H), 4.24-4.13 (m, 2 H), 3.57 (d, *J* = 9.8 Hz, 1 H), 1.23 (t, *J* = 7.2 Hz, 3 H). $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ = 175.8, 170.3, 144.8, 142.6, 135.5, 130.0, 129.6, 129.0, 128.6, 127.7, 127.6, 127.0, 125.7, 122.7, 122.1, 120.3, 117.1, 109.5, 66.0, 61.4, 57.8, 44.1, 14.1. HRMS (ESI): calcd. for $C_{27}H_{27}N_2O_3$ $[M + H]^+$ 427.2022; found 427.2008.

**(*R**)-Ethyl 2-((*R**)-1-methyl-2-oxo-3-(phenylamino)indolin-3-yl)but-3-enoate (159g):** Following the general procedure T described above, **159g** was obtained after purification by

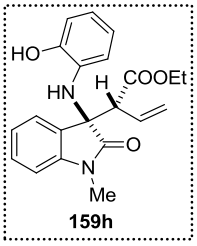


**159g**

silica gel column chromatography (EtOAc/hexane, 30:70) as a colorless liquid (70 mg, 80%); $R_f$ = 0.61 (30% EtOAc/hexane). IR (thin film): $\tilde{\upsilon}$ = 3373, 2930, 1725, 1603, 1470, 1031 $cm^{-1}$. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 7.40-7.35 (m, 2 H), 7.09 (t, *J* = 7.4 Hz, 1 H), 6.97 (dd, *J* = 8.6, 7.4 Hz, 2 H), 6.89 (d, *J* = 7.4 Hz, 1 H), 6.68 (t, *J* = 7.4 Hz, 1 H), 6.24 (d, *J* = 8.6 Hz, 2 H), 5.88-5.79 (m, 1 H), 5.31-5.26 (m, 2 H), 5.14 (br. s, 1 H), 4.21-4.11 (m, 2 H), 3.54 (d, *J* = 9.9 Hz, 1 H), 3.21 (s, 3 H), 1.22 (t, *J* = 7.2 Hz, 3 H). $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ = 175.7, 170.2, 144.9, 143.4, 129.9, 129.7, 129.0, 127.0, 125.4, 122.8, 121.9, 119.6, 115.8, 108.4, 65.6, 61.4, 57.8, 26.3, 14.1. HRMS (ESI): calcd. for $C_{21}H_{23}N_2O_3$ $[M + H]^+$ 351.1709; found 351.1696.

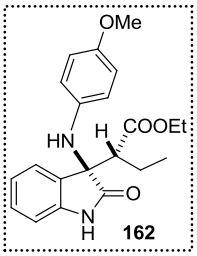
**(*R**)-Ethyl 2-((*R**)-3-((2-hydroxyphenyl)amino)-1-methyl-2-oxoindolin-3-yl)but-3-enoate (159h):** Following the general procedure T described above, **159h** was obtained after

purification by silica gel column chromatography (EtOAc/hexane, 30:70) as a colorless solid (70 mg, 76%); mp 164-166 °C. $R_f$ = 0.52 (30% EtOAc/hexane). IR (thin film): $\tilde{\upsilon}$ = 3316, 1733, 1696, 1610, 1469, 1317, 1176 $cm^{-1}$. $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ = 7.58 (d, $J$ = 7.5 Hz, 1 H), 7.31 (t, $J$ = 7.7 Hz, 1 H), 7.09 (t, $J$ = 7.5 Hz, 1 H), 6.78 (d, $J$ = 7.7 Hz, 1 H), 6.70-6.64 (m, 2 H), 6.45-6.41 (m, 1 H), 6.24 (d, $J$ = 7.7 Hz, 1 H), 5.87-5.78 (m, 1 H), 5.36-5.26 (m, 2 H), 4.75 (br. s, 1 H), 4.20-4.10 (m, 2 H), 3.70 (d, $J$ = 9.7 Hz, 1 H), 3.18 (s, 3 H), 1.21 (t, $J$ = 7.1 Hz, 3 H). $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta$ = 177.6, 170.6, 149.8, 143.5, 131.3, 129.9, 129.8, 126.4, 125.9, 124.0, 122.9, 122.0, 121.4, 120.0, 115.3, 108.3, 67.5, 61.4, 57.8, 26.3, 14.0. HRMS (ESI): calcd. for $C_{21}H_{23}N_2O_4$ $[M + H]^+$ 367.1658; found 367.1649.



159h

**(*R**)-Ethyl 2-((*R**)-3-((4-methoxyphenyl)amino)-2-oxoindolin-3-yl)butanoate (162):** A dry flask containing **159b** (0.5 mmol, 1 equiv) in anhydrous THF (4 mL) was charged with Pd/C (20 mol%) and the reaction mixture was stirred under a hydrogen atmosphere (1 atm) at room temperature. After the disappearance of the starting material (the reaction was monitored by TLC), the reaction mixture was filtered through a Celite pad and rinsed with EtOAc (20 mL). The solvent was evaporated and purification by column chromatography on silica gel (EtOAc/hexane, 30:70) gave the compound **162** as a colorless solid (166 mg, 90%); mp 143-145 °C. $R_f$ = 0.59 (30% EtOAc/hexane). IR (thin film): $\tilde{\upsilon}$ = 3262, 2969, 1722, 1511, 1470, 1240 $cm^{-1}$. $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ = 8.52 (s, 1 H), 7.51 (d, $J$ = 7.4 Hz, 1 H), 7.28 (t, $J$ = 7.4 Hz, 1 H), 7.08 (t, $J$ = 7.4 Hz, 1 H), 6.81 (d, $J$ = 7.4 Hz, 1 H), 6.51 (d, $J$ = 8.0 Hz, 2 H), 6.33 (d, $J$ = 8.0 Hz, 2 H), 4.78 (s, 1 H), 4.29 (q, $J$ = 7.0 Hz, 2 H), 3.60 (s, 3 H), 2.83-2.79 (m, 1 H), 1.67-1.59 (m, 1 H), 1.52-1.47 (m, 1 H), 1.33 (t, $J$ = 7.0 Hz, 3 H), 0.85 (t, $J$ = 7.1 Hz, 3 H). $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta$ = 179.5, 172.6, 154.0, 140.5, 138.4, 129.4, 128.0, 126.7, 122.7, 119.3, 114.2, 110.4, 67.7, 61.0, 55.3, 54.0, 20.0, 14.3, 11.9. HRMS (ESI): calcd. for $C_{21}H_{25}N_2O_4$ $[M + H]^+$ 369.1814; found 369.1811.

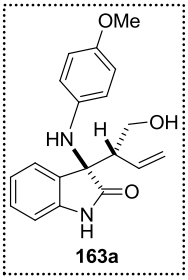


162

**Procedure U. Reduction of 3-substituted-3-aminooxindoles to *N*-aryl-*γ*-amino alcohols 163:** A dry flask was charged with anhydrous THF (4 mL) and the corresponding oxindole derivative **159b** or **162** (0.2 mmol) under a nitrogen atmosphere and the reaction mixture was cooled to 0 °C. Then, $LiAlH_4$ (0.8 mmol) was added in portions and the mixture was stirred 6-12 h at room temperature. After the disappearance of the starting material as shown by

TLC, EtOH (few drops) and water (1–2 mL) were then added sequentially and the resulting white suspension was filtered through a Celite pad and rinsed with EtOAc (20 mL). The filtrate was dried over anhydrous $Na_2SO_4$ and the solvent was removed by rotary evaporation. Then, purification of the crude reaction mixture by column chromatography on silica gel (EtOAc/hexane) gave the respective *N*-aryl-γ-amino alcohols **163** (see Scheme 71).

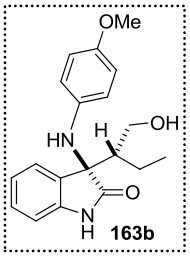
**(*R**)-3-((*R**)-1-Hydroxybut-3-en-2-yl)-3-((4-methoxyphenyl)amino)indolin-2-one (163a):** Following the general procedure U described above, **163a** was obtained after purification by



**163a**

silica gel column chromatography (EtOAc/hexane, 50:50) as a colorless solid (44 mg, 68%); mp 183-185 °C. $R_f$ = 0.41 (50% EtOAc/hexane). IR (thin film): $\tilde{\upsilon}$ = 3458, 2916, 1716, 1511, 1392, 1239 $cm^{-1}$. $^1H$ NMR (400 MHz, DMSO-$d_6$+$CDCl_3$): $\delta$ = 10.5 (s, 1 H), 7.24-7.19 (m, 2 H), 6.95 (t, *J* = 7.4 Hz, 1 H), 6.84 (d, *J* = 7.4 Hz, 1 H), 6.51 (d, *J* = 8.9 Hz, 2 H), 6.15 (d, *J* = 8.9 Hz, 2 H), 5.84 (s, 1 H), 5.26-5.17 (m, 1 H), 5.09-5.04 (m, 2 H), 4.84 (t, *J* = 5.2 Hz, 1 H), 3.89-3.84 (m, 1 H), 3.54 (s, 3 H), 3.51-3.45 (m, 1 H), 2.71-2.65 (m, 1 H), 2.51-2.49 (m, 1 H). $^{13}C$ NMR (100 MHz, DMSO-$d_6$+$CDCl_3$): $\delta$ = 183.4, 156.8, 147.1, 145.3, 139.4, 134.0, 133.9, 129.9, 126.7, 124.8, 120.7, 119.3, 114.9, 72.0, 65.4, 60.3, 58.4. HRMS (ESI): calcd. for $C_{19}H_{21}N_2NaO_3$ $[M + Na]^+$ 347.1372; found 347.1364.

**(*R**)-3-((*R**)-1-Hydroxybutan-2-yl)-3-((4-methoxyphenyl)amino)indolin-2-one (163b):** Following the general procedure U described above, **163b** was obtained after purification by

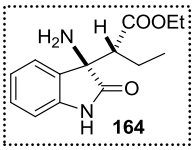


**163b**

silica gel column chromatography (EtOAc/hexane, 50:50) as a sticky solid (45 mg, 70%); $R_f$ = 0.42 (50% EtOAc/hexane). IR (thin film): $\tilde{\upsilon}$ = 3442, 2920, 1714, 1511, 1238, 1037 $cm^{-1}$. $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ = 8.38 (br. s, 1 H), 7.61 (d, *J* = 7.4 Hz, 1 H), 7.24 (t, *J* = 7.4 Hz, 1 H), 7.10 (t, *J* = 7.4 Hz, 1 H), 6.76 (d, *J* = 7.4 Hz, 1 H), 6.54 (d, *J* = 8.5 Hz, 2 H), 6.49 (d, *J* = 8.5 Hz, 2 H), 4.03 (d, *J* = 6.9 Hz, 2 H), 3.60 (s, 3 H), 2.21-2.15 (m, 1 H), 1.34-1.26 (m, 2 H), 0.84 (t, *J* = 7.4 Hz, 3 H), 0.83-0.73 (m, 1 H). $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta$ = 179.6, 155.4, 141.0, 136.6, 129.4, 127.1, 126.6, 122.9, 122.7, 113.9, 110.4, 72.1, 62.7, 55.3, 47.7, 19.4, 12.1. HRMS (ESI): calcd. for $C_{19}H_{23}N_2O_3$ $[M + H]^+$ 327.1709; found 327.1697.

**(*R**)-Ethyl 2-((*R**)-3-amino-2-oxoindolin-3-yl)butanoate (164):** To the *N*-aryl-3-substituted-3-aminooxindole **162** (0.2 mmol, 1 equiv) in MeCN (2 mL) was added aqueous solution of $(NH_4)_2S_2O_8$ (2 equiv) and ammonium ceric (III) nitrate (0.1 equiv) at 0 $^oC$. The

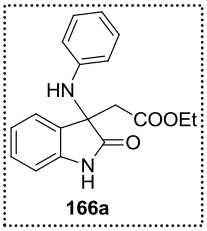
resulting reaction mixture was stirred at 40 $^{o}$C for 12 h. After the complete consumption of starting material as shown by TLC, the reaction mixture was washed with DCM (2 mL) and treated with $Na_2CO_3$ at 0 $^{o}$C to attain the pH 8. Then, the product was extracted using DCM (5 x 1 mL). The combined organic layers were dried over anhydrous $Na_2SO_4$. The solvent was evaporated under vacuum to obtain the product 3-aminooxindole **164** as a colorless solid (32 mg, 60%); mp 134-136 °C. IR (thin film): $\tilde{\upsilon}$ = 3260, 2969, 1722, 1471, 1188, 753 cm$^{-1}$. $^{1}$H NMR (400 MHz, $CDCl_3$): $\delta$ = 9.25 (s, 1 H), 7.57 (d, $J$ = 7.4 Hz, 1 H), 7.24 (t, $J$ = 7.4 Hz, 1 H), 7.05 (t, $J$ = 7.4 Hz, 1 H), 6.91 (d, $J$ = 7.4 Hz, 1 H), 4.19 (q, $J$ = 7.1 Hz, 2 H), 2.85 (dd, $J$ = 11.6, 3.5 Hz, 1 H), 1.91 (br. s, 2 H), 1.59-1.51 (m, 1 H), 1.38-1.32 (m, 1 H), 1.24 (t, $J$ = 7.1 Hz, 3 H), 0.83 (t, $J$ = 7.4 Hz, 3 H). $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ = 181.9, 173.1, 140.8, 130.0, 129.3, 126.2, 122.7, 110.1, 62.6, 60.6, 54.4, 20.5, 14.2, 12.1. HRMS (ESI): calcd. for $C_{14}H_{18}N_2NaO_3$ $[M + Na]^+$ 285.1215; found 285.1211.



164

**Procedure V. Zn-mediated addition of α-halo esters (145) to isatin ketimines 105:** To a vigorously stirring solution of isatin ketimines **105** (0.25 mmol, 1 equiv) and α-halo ester (**145**; 1 mmol, 4 equiv) in DMF (1 mL) was added zinc powder (0.5 mmol, 2 equiv). The mixture was allowed to stir vigorously at 30 $^{o}$C for 12 h. After this period, the reaction mixture was quenched with 2 mL of water and transferred to a separating funnel and extracted using ethyl acetate (3x15 mL). The combined organic layers were dried over anhydrous $Na_2SO_4$. Then the solvent was evaporated under vacuum. Purification of the resulting crude reaction mixture by column chromatography on silica gel (EtOAc/hexane as eluent) gave the product **166** (see Tables 25 and 26 for individual entries).

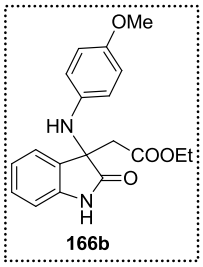
**Ethyl 2-(2-oxo-3-(phenylamino)indolin-3-yl)acetate (166a):** Following the general procedure V described above, **166a** was obtained after purification by silica gel column chromatography (EtOAc/hexane, 30:70) as a colorless solid (72 mg, 93%); mp 166-168 °C. $R_f$ = 0.55 (30% EtOAc/hexane). IR (thin film): $\tilde{\upsilon}$ = 3298, 2978, 1745, 1605, 1500, 1038 cm$^{-1}$. $^{1}$H NMR (400 MHz, $CDCl_3$): $\delta$ = 9.02 (s, 1 H), 7.27 (d, $J$ = 7.4 Hz, 2 H), 7.05-6.98 (m, 3 H), 6.91 (d, $J$ = 7.6 Hz, 1 H), 6.69 (t, $J$ = 7.4 Hz, 1 H), 6.37 (d, $J$ = 7.6 Hz, 2 H), 4.17 (q, $J$ = 7.2 Hz, 2 H), 2.96 (d, $J$ = 14.5 Hz, 1 H), 2.84 (d, $J$ = 14.5 Hz, 1 H), 1.22 (t, $J$ = 7.2 Hz, 3 H). $^{13}$C



166a

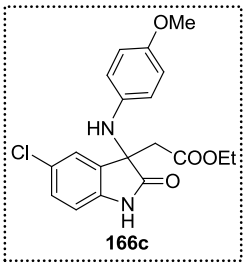
NMR (100 MHz, $CDCl_3$): $\delta$ = 179.0, 169.6, 144.8, 139.9, 129.5, 129.2, 129.1, 124.3, 123.2, 119.5, 115.5, 110.9, 62.9, 61.3, 43.0, 14.1. HRMS (ESI): calcd. for $C_{18}H_{18}N_2NaO_3$ $[M + Na]^+$ 333.1215; found 333.1212.

**Ethyl 2-(3-((4-methoxyphenyl)amino)-2-oxoindolin-3-yl)acetate (166b):** Following the general procedure V described above, **166b** was obtained after purification by silica gel column chromatography (EtOAc/hexane, 30:70) as a colorless solid (62 mg, 73%); mp 164-166 °C. $R_f$ = 0.56 (30% EtOAc/hexane). IR (thin film): $\tilde{\upsilon}$ = 3384, 2985, 1705, 1511, 1195, 1033 $cm^{-1}$. $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ = 8.54 (s, 1 H), 7.34 (d, $J$ = 2.1 Hz, 1 H), 7.23 (dd, $J$ = 8.3, 2.1 Hz, 1 H), 6.76 (d, $J$ = 8.3 Hz, 1 H), 6.58 (d, $J$ = 9.0 Hz, 2 H), 6.43 (d, $J$ = 9.0 Hz, 2 H), 4.93 (br. s, 1 H), 4.18-4.09 (m, 2 H), 3.65 (s, 3 H), 2.99 (d, $J$ = 15.0 Hz, 1 H), 2.89 (d, $J$ = 15.0 Hz, 1 H), 1.21 (t, $J$ = 7.2 Hz, 3 H). $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta$ = 178.6, 169.3, 154.5, 139.0, 137.6, 131.2, 129.5, 128.4, 125.1, 119.9, 114.3, 111.5, 64.2, 61.3, 55.4, 42.5, 14.0. HRMS (ESI): calcd. for $C_{19}H_{20}N_2NaO_4$ $[M + Na]^+$ 363.1321; found 363.1327.



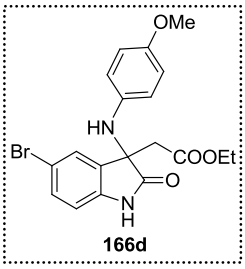
166b

**Ethyl 2-(5-chloro-3-((4-methoxyphenyl)amino)-2-oxoindolin-3-yl)acetate (166c):** Following the general procedure V described above, **166c** was obtained after purification by silica gel column chromatography (EtOAc/hexane, 30:70) as colorless solid (75 mg, 80%); mp 175-177 °C. $R_f$ = 0.57 (30% EtOAc/hexane). IR (thin film): $\tilde{\upsilon}$ = 3331, 2986, 1734, 1510, 1297, 1036 $cm^{-1}$. $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ = 8.38 (s, 1 H), 7.35 (d, $J$ = 2.1 Hz, 1 H), 7.23 (dd, $J$ = 8.3, 2.1 Hz, 1 H), 6.76 (d, $J$ = 8.3 Hz, 1 H), 6.58 (d, $J$ = 8.9 Hz, 2 H), 6.44 (d, $J$ = 8.9 Hz, 2 H), 4.89 (s, 1 H), 4.18-4.10 (s, 2 H), 3.66 (s, 3 H), 2.99 (d, $J$ = 15.0 Hz, 1 H), 2.89 (d, $J$ = 15.0 Hz, 1 H), 1.21 (t, $J$ = 7.2 Hz, 3 H). $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta$ = 178.5, 169.3, 154.5, 138.9, 137.5, 131.2, 129.5, 128.4, 125.1, 120.0, 114.3, 111.5, 64.2, 61.3, 55.4, 42.5, 14.0. HRMS (ESI): calcd. for $C_{19}H_{19}ClN_2NaO_4$ $[M + Na]^+$ 397.0931; found 397.0938.



166c

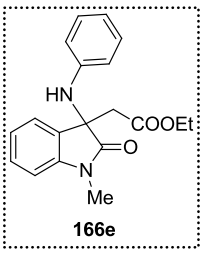
**Ethyl 2-(5-bromo-3-((4-methoxyphenyl)amino)-2-oxoindolin-3-yl)acetate (166d):** Following the general procedure V described above, **166d** was obtained after purification by silica gel column chromatography (EtOAc/hexane, 30:70) as colorless solid (67 mg, 64%); mp 182-184 °C. $R_f$ = 0.58 (30% EtOAc/hexane). IR (thin film): $\tilde{\upsilon}$ = 3406, 2925, 1716, 1651, 1404, 1026 $cm^{-1}$. $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ = 10.73 (s, 1 H), 7.45 (d, $J$ = 2.0 Hz, 1 H),



166d

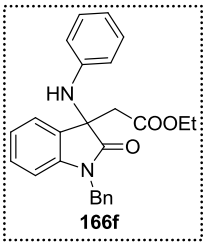
7.39 (dd, *J* = 8.2, 2.0 Hz, 1 H), 6.78 (d, *J* = 8.2 Hz, 1 H), 6.58 (d, *J* = 8.9 Hz, 2 H), 6.28 (d, *J* = 8.9 Hz, 2 H), 5.80 (s, 1 H), 3.86 (q, *J* = 7.1 Hz, 2 H), 3.56 (s, 3 H), 3.05 (d, *J* = 14.8 Hz, 1 H), 3.00 (d, *J* = 14.8 Hz, 1 H), 0.96 (t, *J* = 7.1 Hz, 3 H). $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ = 177.8, 168.6, 152.9, 142.1, 139.6, 132.6, 132.3, 127.4, 117.4, 114.6, 113.9, 112.2, 63.1, 60.5, 55.5, 43.3, 14.1. HRMS (ESI): calcd. for $C_{19}H_{19}BrN_2NaO_4$ $[M + Na]^+$ 441.0426; found 441.0418.

**Ethyl 2-(1-methyl-2-oxo-3-(phenylamino)indolin-3-yl)acetate (166e):** Following the general procedure V described above, **166e** was obtained after purification by silica gel column chromatography (EtOAc/hexane, 30:70) as a colorless solid (64 mg, 79%); mp 144-148 °C. $R_f$ = 0.57 (30% EtOAc/hexane). IR (thin film): $\tilde{\upsilon}$ = 3313, 2981, 1709, 1602, 1196, 1035 cm$^{-1}$. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 7.36 (t, *J* = 7.7 Hz, 1 H), 7.31 (d, *J* = 7.5 Hz, 1 H), 7.07 (t, *J* = 7.5 Hz, 1 H), 6.99 (dd, *J* = 8.5, 7.4 Hz, 2 H), 6.93 (d, *J* = 7.8 Hz, 1 H), 6.69 (t, *J* = 7.4 Hz, 1 H), 6.29 (d, *J* = 7.6 Hz, 2 H), 5.36 (br. s, 1 H), 4.18-4.10 (m, 2 H), 3.29 (s, 3 H), 2.97 (d, *J* = 14.6 Hz, 1 H), 2.81 (d, *J* = 14.6 Hz, 1 H), 1.21 (t, *J* = 7.0 Hz, 3 H). $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ = 176.4, 169.5, 144.8, 143.0, 129.6, 129.0, 128.7, 124.1, 123.1, 119.6, 115.9, 108.7, 62.5, 61.2, 43.0, 26.6, 14.1. HRMS (ESI): calcd. for $C_{19}H_{21}N_2O_3$ $[M + H]^+$ 325.1552; found 325.1553.



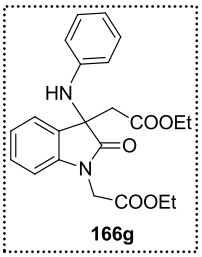
166e

**Ethyl 2-(1-benzyl-2-oxo-3-(phenylamino)indolin-3-yl)acetate (166f):** Following the general procedure V described above, **166f** was obtained after purification by silica gel column chromatography (EtOAc/hexane, 30:70) as colorless solid (85 mg, 85%); mp 106-110 °C. $R_f$ = 0.59 (30% EtOAc/hexane). IR (thin film): $\tilde{\upsilon}$ = 3302, 2983, 1731, 1614, 1494, 1195 cm$^{-1}$. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 7.37 (d, *J* = 7.4 Hz, 1 H), 7.31-7.20 (m, 6 H), 7.05 (t, *J* = 7.4 Hz, 1 H), 6.97 (t, *J* = 7.8 Hz, 2 H), 6.80 (d, *J* = 7.8 Hz, 1 H), 6.76 (t, *J* = 7.4 Hz, 1 H), 6.34 (d, *J* = 7.8 Hz, 2 H), 5.35 (br. s, 1 H), 5.14 (d, *J* = 15.5 Hz, 1 H), 4.76 (d, *J* = 15.5 Hz, 1 H), 4.16 (q, *J* = 7.1 Hz, 2 H), 3.01 (d, *J* = 14.5 Hz, 1 H), 2.91 (d, *J* = 14.5 Hz, 1 H), 1.22 (t, *J* = 7.1 Hz, 3 H). $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ = 176.5, 169.5, 144.7, 142.2, 135.5, 129.5, 129.0, 128.9, 128.8, 127.7, 127.7, 124.1, 123.1, 120.2, 117.0, 109.8, 62.9, 61.2, 44.2, 43.2, 14.1. HRMS (ESI): calcd. for $C_{25}H_{25}N_2O_3$ $[M + H]^+$ 401.1865; found 401.1855.



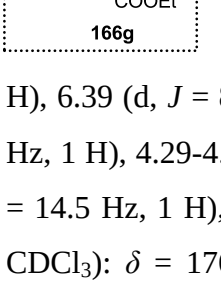
166f

**Diethyl 2,2'-(2-oxo-3-(phenylamino)indoline-1,3-diyl)diacetate (166g):** Following the general procedure V described above, **166g** was obtained after purification by silica gel column chromatography (EtOAc/hexane, 30:70) as a colorless sticky liquid (73 mg, 74%); $R_f$ = 0.58 (30% EtOAc/hexane). IR (thin film): $\tilde{\upsilon}$ = 3375, 2983, 1732, 1605, 1206, 1026 $cm^{-1}$. $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ = 7.32 (t, $J$ = 7.7 Hz, 1 H), 7.29 (d, $J$ = 7.4 Hz, 1 H), 7.06 (t, $J$ = 7.6 Hz, 1 H), 7.01 (dd, $J$ = 8.8, 7.4 Hz, 2 H), 6.82 (d, $J$ = 7.8 Hz, 1 H), 6.68 (t, $J$ = 7.3 Hz, 1 H), 6.39 (d, $J$ = 8.6 Hz, 2 H), 5.63 (br. s, 1 H), 4.62 (d, $J$ = 17.6 Hz, 1 H), 4.50 (d, $J$ = 17.6 Hz, 1 H), 4.29-4.22 (m, 2 H), 4.18 (q, $J$ = 7.2 Hz, 2 H), 2.98 (d, $J$ = 14.5 Hz, 1 H), 2.78 (d, $J$ = 14.5 Hz, 1 H), 1.29 (t, $J$ = 7.2 Hz, 3 H), 1.24 (t, $J$ = 7.1 Hz, 3 H). $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta$ = 176.4, 169.7, 167.4, 144.6, 141.4, 129.5, 129.0, 128.4, 124.2, 123.5, 119.2, 115.3, 108.8, 62.4, 61.9, 61.3, 43.2, 41.5, 14.2, 14.1. HRMS (ESI): calcd. for $C_{22}H_{24}N_2NaO_5$ $[M + Na]^+$ 419.1583; found 419.1586.



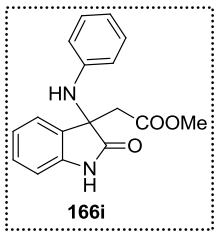
166g

**Ethyl 2-(3-(2-benzoylhydrazinyl)-1-methyl-2-oxoindolin-3-yl)acetate (166h):** Following the general procedure V described above, **166h** was obtained after purification by silica gel column chromatography (EtOAc/hexane, 30:70) as colorless solid (44 mg, 48%); mp 142-144 °C. $R_f$ = 0.49 (30% EtOAc/hexane). IR (thin film): $\tilde{\upsilon}$ = 3280, 2925, 1723, 1614, 1377, 1122 $cm^{-1}$. $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ = 7.84 (d, $J$ = 6.8 Hz, 1 H), 7.68 (d, $J$ = 8.5 Hz, 2 H), 7.54-7.47 (m, 2 H), 7.42 (t, $J$ = 7.7 Hz, 2 H), 7.36 (t, $J$ = 7.7 Hz, 1 H), 7.11 (t, $J$ = 7.8 Hz, 1 H), 6.88 (d, $J$ = 7.8 Hz, 1 H), 5.75 (d, $J$ = 6.8 Hz, 1 H), 4.02-3.93 (m, 2 H), 3.28 (s, 3 H), 3.22 (d, $J$ = 16.0 Hz, 1 H), 3.14 (d, $J$ = 16.0 Hz, 1 H), 1.08 (t, $J$ = 7.1 Hz, 3 H). $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta$ = 175.9, 169.3, 167.0, 144.4, 132.3, 132.0, 130.1, 128.7, 127.2, 127.0, 124.3, 123.0, 108.4, 64.9, 60.8, 38.7, 26.4, 13.9. HRMS (ESI): calcd. for $C_{20}H_{21}N_3NaO_4$ $[M + Na]^+$ 390.1430; found 390.1433.



166h

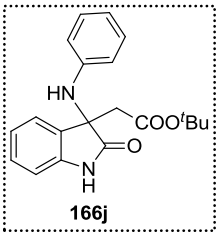
**Methyl 2-(2-oxo-3-(phenylamino)indolin-3-yl)acetate (166i):** Following the general procedure V described above, **166i** was obtained after purification by silica gel column chromatography (EtOAc/hexane, 30:70) as a colorless solid (66 mg, 89%); mp 146-148 °C. $R_f$ = 0.56 (30% EtOAc/hexane). IR (thin film): $\tilde{\upsilon}$ = 3362, 2925, 1731, 1603, 1471, 1045 $cm^{-1}$. $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ = 9.70 (br. s, 1 H), 7.27 (d, $J$ = 8.4 Hz, 2 H), 7.05-6.97



166i

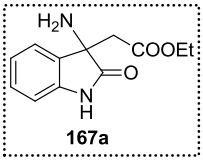
(m, 3 H), 6.90 (d, *J* = 7.9 Hz, 1 H), 6.69 (t, *J* = 7.9 Hz, 1 H), 6.37 (d, *J* = 7.7 Hz, 2 H), 5.55 (s, 1 H), 3.70 (s, 3 H), 2.98 (d, *J* = 14.6 Hz, 1 H), 2.87 (d, *J* = 14.6 Hz, 1 H). $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ = 179.1, 170.2, 144.8, 139.9, 129.6, 129.2, 129.1, 124.2, 123.2, 119.5, 115.5, 110.9, 62.9, 52.2, 42.8. HRMS (ESI): calcd. for $C_{17}H_{16}N_2NaO_3$ $[M + Na]^+$ 319.1059; found 319.1063.

***tert*-Butyl 2-(2-oxo-3-(phenylamino)indolin-3-yl)acetate (166j):** Following the general procedure V described above, **166j** was obtained after purification by silica gel column chromatography (EtOAc/hexane, 30:70) as a colorless solid (66 mg, 78%); mp 207-209 °C. $R_f$ = 0.56 (30% EtOAc/hexane). IR (thin film): $\tilde{\upsilon}$ = 3453, 2927, 1727, 1604, 1471, 1156 cm$^{-1}$. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 8.82 (br. s, 1 H), 7.30 (d, *J* = 7.3 Hz, 1 H), 7.26 (d, *J* = 7.7 Hz, 1 H), 7.05-6.98 (m, 3 H), 6.91 (d, *J* = 7.7 Hz, 1 H), 6.69 (t, *J* = 7.3 Hz, 1 H), 6.37 (d, *J* = 8.3 Hz, 3 H), 5.48 (s, 1 H), 2.88 (d, *J* = 14.2 Hz, 1 H), 2.78 (d, *J* = 14.2 Hz, 1 H), 1.41 (s, 9 H). $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ = 178.9, 168.6, 144.9, 140.0, 129.4, 129.3, 129.0, 124.5, 123.1, 119.4, 115.6, 110.7, 82.3, 63.0, 44.2, 27.9. HRMS (ESI): calcd. for $C_{20}H_{22}N_2NaO_3$ $[M + Na]^+$ 361.1528; found 361.1531.



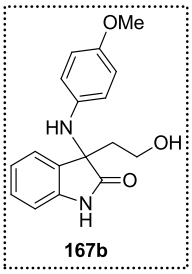
**166j**

**Ethyl 2-(3-amino-2-oxoindolin-3-yl)acetate (167a):** To the Ethyl 2-(3-((4-methoxyphenyl)amino)-2-oxoindolin-3-yl)acetate (**166b**; 0.2 mmol, 1 equiv) in MeCN (2 mL) was added aqueous solution of $(NH_4)_2S_2O_8$ (2 equiv) and ammonium ceric (III) nitrate (0.1 equiv) at 0 $^o$C. The resulting reaction mixture was stirred at 40 $^o$C for 6-12 h. After the complete consumption of starting material as shown by TLC, the reaction mixture was washed with DCM (2 mL) and treated with $Na_2CO_3$ at 0 $^o$C to attain the pH 8. Then, the product was extracted using DCM (5 x 1 mL). The combined organic layers were dried over anhydrous $Na_2SO_4$. The solvent was evaporated under vacuum to obtain the product 3-aminooxindole **167a** as colorless solid (28 mg, 60%); mp 143-145 °C. IR (thin film): $\tilde{\upsilon}$ = 3190, 2984, 1727, 1622, 1473, 1200 cm$^{-1}$. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 9.01 (br. s, 1 H), 7.39 (d, *J* = 7.4 Hz, 1 H), 7.26 (t, *J* = 7.2 Hz, 1 H), 7.04 (t, *J* = 7.5 Hz, 1 H), 6.92 (d, *J* = 7.7 Hz, 1 H), 4.04-3.96 (m, 2 H), 2.96 (s, 2 H), 1.99 (s, 2 H), 1.10 (t, *J* = 7.1 Hz, 3 H). $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ = 181.6, 169.6, 141.0, 131.3, 129.4, 122.8, 110.3, 60.7, 59.0, 42.5, 13.9. HRMS (ESI): calcd. for $C_{12}H_{14}N_2NaO_3$ $[M + Na]^+$ 257.0902; found 257.0909.



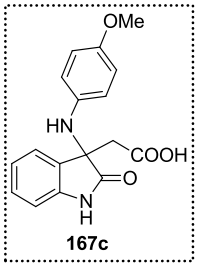
**167a**

**3-(2-Hydroxyethyl)-3-((4-methoxyphenyl)amino)indolin-2-one (167b):** A dry flask was charged with anhydrous THF (4 mL) and the oxindole derivative **166b** (0.2 mmol) under a nitrogen atmosphere and the reaction mixture was cooled to 0 °C. Then, $LiAlH_4$ (0.8 mmol) was added in portions and the mixture was stirred 6-12 h at room temperature. After the disappearance of the starting material as shown by TLC, EtOH (few drops) and water (1–2 mL) were then added sequentially and the resulting white suspension was filtered through a Celite pad and rinsed with EtOAc (20 mL). The filtrate was dried over anhydrous $Na_2SO_4$ and the solvent was removed by rotary evaporation. Then, purification of the crude reaction mixture by column chromatography on silica gel (EtOAc/hexane) gave the respective *N*-aryl-**γ**-amino alcohols **167b** (EtOAc/hexane, 40:60) as a sticky solid (38 mg, 64%); mp 165-167 °C. $R_f$ = 0.20 (40% EtOAc/hexane). IR (thin film): $\tilde{\upsilon}$ = 3301, 2924, 1715, 1512, 1243, 1033 $cm^{-1}$. $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ = 10.55 (s, 1 H), 7.21 (t, *J* = 7.6 Hz, 1 H), 7.17 (d, *J* = 7.2 Hz, 1 H), 6.96 (t, *J* = 7.5 Hz, 1 H), 6.88 (d, *J* = 7.6 Hz, 1 H), 6.52 (d, *J* = 8.9 Hz, 2 H), 6.14 (d, *J* = 8.9 Hz, 2 H), 5.99 (br. s, 1 H), 4.62 (br. s, 1 H), 3.54 (s, 3 H), 3.44-3.40 (m, 1 H), 3.30-3.24 (m, 1 H), 2.07-1.93 (m, 2 H). $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta$ = 179.7, 151.8, 141.6, 140.8, 131.3, 129.0, 124.0, 122.3, 115.3, 114.6, 110.3, 63.9, 56.4, 55.6, 42.2. HRMS (ESI): calcd. for $C_{17}H_{18}N_2NaO_3$ $[M + Na]^+$ 321.1215; found 321.1225.



167b

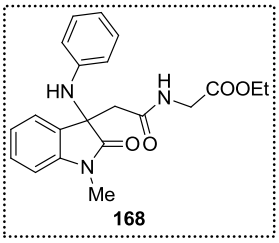
**2-(3-((4-Methoxyphenyl)amino)-2-oxoindolin-3-yl)acetic acid (167c):** The compound **166b** (0.5 mmol) was dissolved in a mixture of THF/MeOH/$H_2O$ = 3/1/1 (5 mL), and LiOH (1.5 mmol) was added at 0 °C. The mixture was allowed to stir for 12 h and then acidified with 1N aqueous HCl to pH = 2 and extracted with EtOAc (3x10 mL). The combined organic layers were dried over anhydrous $Na_2SO_4$. Then the solvent was evaporated under vacuum that gave the product **167c** as colorless solid (140 mg, 90%); mp 199-201 °C. IR (thin film): $\tilde{\upsilon}$ = 3014-2497, 2925, 1715, 1512, 1243, 1033 $cm^{-1}$. $^1H$ NMR (400 MHz, $CD_3OD$): $\delta$ = 7.37 (d, *J* = 7.5 Hz, 1 H), 7.24 (td, *J* = 7.7, 1.0 Hz, 1 H), 7.04 (td, *J* = 7.5 Hz, 1.0 Hz, 1 H), 6.85 (d, *J* = 7.7 Hz, 1 H), 6.56 (d, *J* = 9.1 Hz, 2 H), 6.47 (d, *J* = 9.1 Hz, 2 H), 3.63 (s, 3 H), 3.01 (d, *J* = 1.0 Hz, 2 H). $^{13}C$ NMR (100 MHz, $CD_3OD$): $\delta$ = 179.5, 171.2, 154.7, 142.0, 137.7, 129.4, 129.1, 124.2, 122.2, 120.3, 113.6, 110.0, 64.2, 54.4, 41.7. HRMS (ESI): calcd. for $C_{17}H_{16}N_2NaO_4$ $[M + Na]^+$ 335.1008; found 335.1013.



167c

**Procedure W. Synthesis of oxindole based dipeptides 168 and 169:** The compound **166e** (0.5 mmol) was dissolved in a mixture of THF/MeOH/$H_2O$ = 3/1/1 (5 mL), and LiOH (1.5 mmol) was added at 0 $^oC$. The mixture was allowed to stir for 12 h and then acidified with 1N aqueous HCl to pH = 2 and extracted with EtOAc (3x10 mL). The combined organic layers were dried over anhydrous $Na_2SO_4$. Then the solvent was evaporated under vacuum that gave the corresponding acid which is used further without any purification. Then the acid (0.4 mmol) was dissolved in dry DCM (5 mL) and glycine ethyl ester hydrochloride or phenylalanine methyl ester hydrochloride (0.8 mmol), EDCI (0.8 mmol), HOBt.x$H_2O$ (0.8 mmol), DIPEA (0.8 mmol) were added and the reaction mixture was allowed to stir at room temperature. After 12 h, the reaction mixture was washed with water and the organic layer was dried over anhydrous $Na_2SO_4$. The solvent was evaporated under vacuum and purification of resulting crude reaction mixture by column chromatography on silica gel (EtOAc/hexane) gave the product **168**/**169** (see Scheme 78).

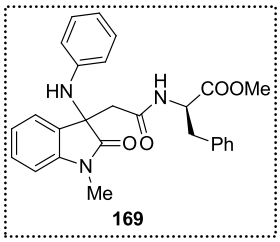
**Ethyl 2-(2-(1-methyl-2-oxo-3-(phenylamino)indolin-3-yl)acetamido)acetate (168):** Following the general procedure W described above, **168** was obtained after purification by



**168**

silica gel column chromatography (EtOAc/hexane, 40:60) as colorless solid (96 mg, 84%); mp 125-127 °C. $R_f$ = 0.30 (40% EtOAc/hexane). IR (thin film): $\tilde{\upsilon}$ = 3330, 3057, 1715, 1661, 1500, 1203, 1021 $cm^{-1}$. $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ = 7.34 (t, $J$ = 7.0 Hz, 2 H), 7.22 (d, $J$ = 7.5 Hz, 1 H), 7.07 (t, $J$ = 7.5 Hz, 1 H), 6.97 (t, $J$ = 8.0 Hz, 2 H), 6.92 (d, $J$ = 7.5 Hz, 1 H), 6.67 (t, $J$ = 7.0 Hz, 1 H), 6.29 (d, $J$ = 8.0 Hz, 2 H), 5.86 (br. s, 1 H), 4.24 (q, $J$ = 7.0 Hz, 2 H), 4.16-4.09 (m, 1 H), 3.98-3.92 (m, 1 H), 3.28 (s, 3 H), 2.90 (d, $J$ = 14.8 Hz, 1 H), 2.67 (d, $J$ = 14.8 Hz, 1 H), 1.30 (t, $J$ = 7.0 Hz, 3 H). $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta$ = 177.5, 169.8, 169.0, 145.0, 142.4, 129.5, 129.1, 128.9, 124.3, 123.6, 119.4, 115.6, 108.7, 62.8, 61.7, 44.5, 41.5, 26.6, 14.2. HRMS (ESI): calcd. for $C_{21}H_{23}N_3NaO_4$ $[M + Na]^+$ 404.1586; found 404.1588.

**(2*R**)-methyl 2-(2-(1-methyl-2-oxo-3-(phenylamino)indolin-3-yl)acetamido)-3-phenylpropanoate (169):** Following the general procedure W described above, **169** was obtained after purification by silica gel column chromatography (EtOAc/hexane, 40:60) as colorless solid (103 mg, 75%); mp 161-163 °C. $R_f$ = 0.31 (40% EtOAc/hexane). IR (thin film): $\tilde{\upsilon}$ = 3322, 3058, 1739, 1613, 1374, 1239 $cm^{-1}$. $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ = 7.42-

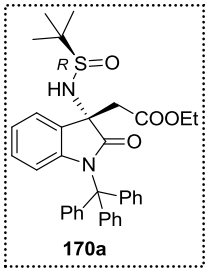


169

6.66 (m, 12 H), 6.22 (d, *J* = 8.0 Hz, 2 H), 5.64 (br. s, 1 H), 5.26 (br. s, 1 H), 4.92-4.85 (m, 1 H), 3.72 (s, 3 H), 3.27 (s, 3 H), 3.19-3.05 (m, 2 H), 2.88 (d, *J* = 15.5 Hz, 1 H), 2.58 (d, *J* = 15.5 Hz, 1 H). $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ = 177.5, 177.0, 172.0, 171.7, 168.8, 168.5, 144.8, 142.5, 142.4, 135.8, 135.7, 129.5, 129.3, 129.2, 128.9, 128.8, 128.6, 128.6, 127.2, 127.1, 126.5, 124.4, 124.3, 123.6, 123.4, 119.6, 119.5, 116.0, 115.8, 108.8, 108.7, 63.0, 53.8, 53.5, 52.5, 52.4, 44.5, 44.2, 37.7, 37.6, 26.6, 26.6. HRMS (ESI): calcd. for $C_{27}H_{28}N_3O_4$ $[M + H]^+$ 458.2080; found 458.2090. $^1$H and $^{13}$C NMR data given here referes to mixture of diastereomers.

**Procedure V. Zn-mediated addition of α-halo esters (145) to isatin ketimines 108:** To a vigorously stirring solution of isatin ketimines **108** (0.25 mmol, 1 equiv) and α-halo ester (**145**, 1 mmol, 4 equiv) in DMF (1 mL) was added zinc powder (0.5 mmol, 2 equiv). The mixture was allowed to stir vigorously at 30 $^o$C for 12 h. After this period, the reaction mixture was quenched with 2 mL of water and transferred to a separating funnel and extracted using ethyl acetate (3x15 mL). The combined organic layers were dried over anhydrous $Na_2SO_4$. Then the solvent was evaporated under vacuum. Purification of the resulting crude reaction mixture by column chromatography on silica gel (EtOAc/hexane as eluent) gave the product **170** (see Scheme 79).

**Ethyl 2-((*S*)-3-((*R*)-1,1-dimethylethylsulfinamido)-2-oxo-1-tritylindolin-3-yl)acetate (170a):** Following the general procedure V described above, **170a** was obtained after

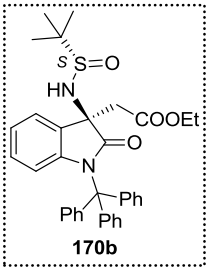


170a

purification by silica gel column chromatography (EtOAc/hexane, 30:70) as colorless solid (130 mg, 90%); mp 192-194 °C. $R_f$ = 0.25 (30% EtOAc/hexane). $[\alpha]_D^{25}$ = –95.91 (*c* 0.20, DCM). IR (thin film): $\tilde{\upsilon}$ = 3414, 2926, 1734, 1465, 1190, 1033 cm$^{-1}$. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 7.59 (d, *J* = 7.9 Hz, 6 H), 7.29-7.18 (m, 10 H), 7.01-6.96 (m, 2 H), 6.44 (d, *J* = 8.7 Hz, 1 H), 4.65 (s, 1 H), 4.02-3.94 (m, 1 H), 3.86-3.78 (m, 1 H), 2.96 (d, *J* = 15.2 Hz, 1 H), 2.83 (d, *J* = 15.2 Hz, 1 H), 1.25 (s, 9 H), 0.96 (t, *J* = 7.1 Hz, 3 H). $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ = 176.5, 168.7, 144.1, 141.8, 129.5, 128.7, 127.6, 126.8, 126.7, 124.7, 122.3, 116.5, 74.6, 61.2, 60.7, 56.5, 42.4, 22.8, 13.8. HRMS (ESI): calcd. for $C_{35}H_{36}N_2NaO_4S$ [M +

Na]$^+$ 603.2293; found 603.2288. $^1$H and $^{13}$C NMR data given here referes to major diastereomer.

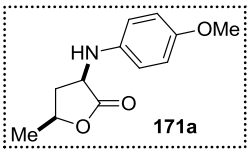
**Ethyl 2-((*R*)-3-((*S*)-1,1-dimethylethylsulfinamido)-2-oxo-1-tritylindolin-3-yl)acetate (170b):** Following the general procedure V described above, **170b** was obtained after purification by silica gel column chromatography (EtOAc/hexane, 30:70) as colorless solid (87 mg, 60%); mp 197-199 °C. $R_f$ = 0.25 (30% EtOAc/hexane). $[\alpha]_D^{25}$ = +91.41 (*c* 0.20, DCM). IR (thin film): $\tilde{\upsilon}$ = 3288, 2925, 1732, 1465, 1192, 1033 cm$^{-1}$. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 7.60 (d, *J* = 8.0 Hz, 6 H), 7.30-7.25 (m, 7 H), 7.22-7.18 (m, 3 H), 7.02-6.96 (m, 2 H), 6.44 (d, *J* = 9.0 Hz, 1 H), 4.60 (s, 1 H), 4.02-3.94 (m, 1 H), 3.86-3.78 (m, 1 H), 2.95 (d, *J* = 15.2 Hz, 1 H), 2.82 (d, *J* = 15.2 Hz, 1 H), 1.26 (s, 9 H), 0.96 (t, *J* = 7.2 Hz, 3 H). $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ = 176.5, 168.7, 144.2, 141.9, 129.5, 128.7, 127.6, 126.8, 124.7, 122.3, 116.5, 74.6, 61.2, 60.7, 56.4, 42.4, 22.8, 13.8. HRMS (ESI): calcd. for $C_{35}H_{36}N_2NaO_4S$ [M + Na]$^+$ 603.2293; found 603.2292. $^1$H and $^{13}$C NMR data given here referes to major diastereomer.



170b

**Procedure X. Reaction of α-amino γ,δ-unsaturated carboxylic acid esters with triflic acid:** To a solution of α-amino γ,δ-unsaturated carboxylic acid esters **110/112/115/116/119/122/124/127/132** (0.3 mmol, 1 equiv) in toluene (2 mL) was added triflic acid (0.33 mmol, 1.1 equiv). The mixture was refluxed for 24 h at 110 $^o$C. After this period, the reaction mixture was cooled to room temperature and quenched with 2 mL of water. Then the reaction mixture was transferred to a separating funnel and extracted using ethyl acetate (3 x 15 mL). The combined organic layers were dried over anhydrous $Na_2SO_4$. Then the solvent was evaporated under vacuum. Purification of the resulting crude reaction mixture by column chromatography on silica gel (EtOAc/hexane as eluent) gave the products **171-176** (see the Tables 27-32 and Scheme 81 for individual entries).

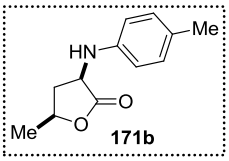
**(3*R**,5*S**)-3-(4-Methoxyphenylamino)-dihydro-5-methylfuran-2(3*H*)-one (171a):** Following the general procedure X as described above, **171a** was obtained after purification by silica gel column chromatography (EtOAc/hexane, 20:80) as a colorless solid (36 mg, 65%); mp 96-98 °C. $R_f$ = 0.45 (20% EtOAc/hexane). IR (thin film): $\tilde{\upsilon}$ = 3368, 2979, 1766, 1512, 1034 cm$^{-1}$.



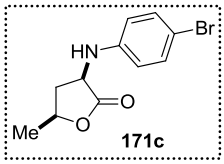
171a

$^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 6.82 (d, $J$ = 8.9 Hz, 2 H), 6.65 (d, $J$ = 8.9 Hz, 2 H), 4.67-4.58 (m, 1 H), 4.13 (dd, $J$ = 11.6, 7.9 Hz, 1 H), 3.77 (s, 3 H), 2.99-2.93 (m, 1 H), 1.78 (q, $J$ = 11.6 Hz, 1 H), 1.50 (d, $J$ = 6.2 Hz, 3 H). $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ = 176.2, 153.2, 140.7, 115.1, 115.0, 74.5, 55.8, 55.7, 40.3, 20.8. HRMS (ESI): calcd. for $C_{12}H_{16}NO_3$ $[M + H]^+$ 222.1130; found 222.1119. This compound was isolated as a mixture of diastereomers and the NMR data refer to the major isomer. NH proton was not detectable.

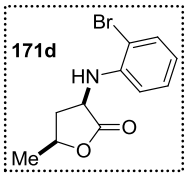
**(3*R**,5*S**)-3-(*p*-Tolylamino)-dihydro-5-methylfuran-2(3*H*)-one (171b):** Following the general procedure X as described above, **171b** was obtained after purification by silica gel column chromatography (EtOAc/hexane, 20:80) as a colorless solid (38 mg, 62%); mp 62-64 °C. $R_f$ = 0.42 (20% EtOAc/hexane). IR (thin film): $\tilde{\upsilon}$ = 3368, 2979, 1768, 1520, 1200 cm$^{-1}$. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 7.01 (d, $J$ = 8.4 Hz, 2 H), 6.57 (d, $J$ = 8.4 Hz, 2 H), 4.63-4.57 (m, 1 H), 4.26 (br. s, 1 H), 4.14 (dd, $J$ = 11.6, 7.9 Hz, 1 H), 2.99-2.92 (m, 1 H), 2.24 (s, 3 H), 1.78-1.69 (m, 1 H), 1.47 (d, $J$ = 6.2 Hz, 3 H). $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ = 176.2, 144.4, 129.9, 128.2, 113.7, 74.6, 55.1, 40.2, 20.8, 20.4. HRMS (ESI): calcd. for $C_{12}H_{16}NO_2$ $[M + H]^+$ 206.1181; found 206.1187. This compound was isolated as a mixture of diastereomers; the NMR data refer to the major isomer.




**(3*R**,5*S**)-3-(4-Bromophenylamino)-dihydro-5-methylfuran-2(3*H*)-one (171c):** Following the general procedure X as described above, **171c** was obtained after purification by silica gel column chromatography (EtOAc/hexane, 20:80) as a colorless solid (65 mg, 81%); mp 100-102 °C. $R_f$ = 0.55 (20% EtOAc/hexane). IR (thin film): $\tilde{\upsilon}$ = 3379, 2980, 1769, 1593, 1200 cm$^{-1}$. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 7.30 (d, $J$ = 8.4 Hz, 2 H), 6.55 (d, $J$ = 8.4 Hz, 2 H), 4.67-4.62 (m, 1 H), 4.41 (br. s, 1 H), 4.24-4.13 (m, 1 H), 3.01-2.94 (m, 1 H), 1.75 (q, $J$ = 11.6 Hz, 1 H), 1.51 (d, $J$ = 6.0 Hz, 3 H). $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ = 175.7, 145.6, 132.1, 115.2, 110.7, 74.6, 54.7, 39.8, 20.7. HRMS (ESI): calcd. for $C_{11}H_{13}BrNO_2$ $[M + H]^+$ 270.0130; found 270.0128. This compound was isolated as a mixture of diastereomers; the NMR data refer to the major isomer.

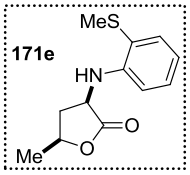



**(3*R**,5*S**)-3-(2-Bromophenylamino)-dihydro-5-methylfuran-2(3*H*)-one (171d):** Following the general procedure X as described above, **171d** was obtained after purification by silica gel column chromatography (EtOAc/hexane, 20:80) as a colorless liquid (53 mg,



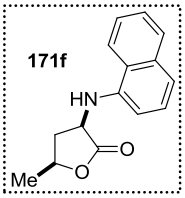

66%); $R_f$ = 0.53 (20% EtOAc/hexane). IR (neat): $\tilde{\upsilon}$ = 3383, 2980, 1770, 1593, 1202 cm$^{-1}$. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 7.48 (d, $J$ = 7.8 Hz, 1 H), 7.21 (t, $J$ = 7.8 Hz, 1 H), 6.67 (t, $J$ = 7.8 Hz, 2 H), 4.97 (br. s, 1 H), 4.69-4.63 (m, 1 H), 4.29-4.23 (m, 1 H), 3.04-2.98 (m, 1 H), 1.81 (q, $J$ = 11.5 Hz, 1 H), 1.53 (d, $J$ = 6.2 Hz, 3 H). $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ = 175.3, 143.6, 132.8, 128.5, 119.4, 111.9, 110.5, 74.5, 54.6, 39.6, 20.8. HRMS (ESI): calcd. for $C_{11}H_{13}BrNO_2$ $[M + H]^+$ 270.0130; found 270.0122. This compound was isolated as a mixture of diastereomers; the NMR data refer to the major isomer.

**(3*R**,5*S**)-3-(2-(Methylthio)phenylamino)-dihydro-5-methylfuran-2(3*H*)-one (171e):** Following the general procedure X as described above, **171e** was obtained after purification



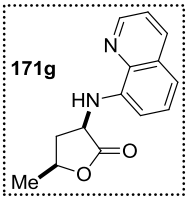

by silica gel column chromatography (EtOAc/hexane, 20:80) as a colorless liquid (46 mg, 65%); $R_f$ = 0.37 (20% EtOAc/hexane). IR (neat): $\tilde{\upsilon}$ = 3354, 2979, 1774, 1588, 1202 cm$^{-1}$. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 7.45 (dd, $J$ = 7.6, 1.5 Hz, 1 H), 7.28-7.19 (m, 1 H), 6.77 (dt, $J$ = 7.6 Hz, 1.2 Hz, 1 H), 6.63 (d, $J$ = 8.1 Hz, 1 H), 5.55 (br. s, 1 H), 4.70-4.61 (m, 1 H), 4.30-4.24 (m, 1 H), 3.04-2.98 (m, 1 H), 2.37 (s, 3 H), 1.86-1.77 (m, 1 H), 1.53 (d, $J$ = 6.2 Hz, 3 H). $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ = 175.6, 146.8, 134.1, 129.3, 121.3, 118.7, 110.7, 74.7, 54.7, 39.8, 20.8, 18.2. HRMS (ESI): calcd. for $C_{12}H_{16}NO_2S$ $[M + H]^+$ 238.0902; found 238.0918. This compound was isolated as a mixture of diastereomers; the NMR data refer to the major isomer.

**(3*R**,5*S**)-Dihydro-5-methyl-3-(naphthalen-1-ylamino)furan-2(3*H*)-one (171f):** Following the general procedure X as described above, **171f** was obtained after purification

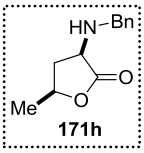



by silica gel column chromatography (EtOAc/hexane, 20:80) as a black solid (48 mg, 67%); mp 149-151 °C. $R_f$ = 0.50 (20% EtOAc/hexane). IR (thin film): $\tilde{\upsilon}$ = 3402, 2979, 1771, 1582, 1203 cm$^{-1}$. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 7.95-7.93 (m, 1 H), 7.85-7.83 (m, 1 H), 7.53-7.50 (m, 2 H), 7.37 (d, $J$ = 4.5 Hz, 2 H), 6.60 (t, $J$ = 4.5 Hz, 1 H), 5.13 (br. s, 1 H), 4.74-4.69 (m, 1 H), 4.38-4.33 (m, 1 H), 3.17-3.10 (m, 1 H), 1.83 (q, $J$ = 11.4 Hz, 1 H), 1.54 (d, $J$ = 6.2 Hz, 3 H). $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ = 176.2, 141.9, 134.3, 128.6, 126.2, 126.1, 125.4, 123.9, 120.2, 119.3, 105.4, 74.9, 54.7, 39.9, 20.8. HRMS (ESI): calcd. for $C_{15}H_{16}NO_2$ $[M + H]^+$ 242.1181; found 242.1173. This compound was isolated as a mixture of diastereomers; the NMR data refer to the major isomer.

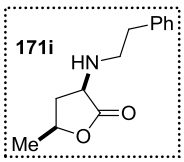
**(3*R**,5*S**)-Dihydro-5-methyl-3-(quinolin-8-ylamino)furan-2(3*H*)-one** (**171g):** Following the general procedure X as described above, **171g** was obtained after purification by silica gel column chromatography (EtOAc/hexane, 20:80) as a colorless solid (31 mg, 42%); mp 115-117 °C. $R_f$ = 0.30 (20% EtOAc/hexane). IR (thin film): $\tilde{\upsilon}$ = 3381, 2979, 1771, 1518, 1198 $cm^{-1}$. $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ = 8.77 (dd, *J* = 4.2, 1.7 Hz, 1 H), 8.09 (dd, *J* = 8.2, 1.7 Hz, 1 H), 7.43-7.38 (m, 2 H), 7.18 (dd, *J* = 8.2, 1.0 Hz, 1 H), 6.74 (d, *J* = 7.4 Hz, 2 H), 4.73-4.67 (m, 1 H), 4.50-4.44 (m, 1 H), 3.10-3.04 (m, 1 H), 1.94 (q, *J* = 11.9 Hz, 1 H), 1.54 (d, *J* = 6.1 Hz, 3 H). $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta$ = 175.6, 147.5, 143.3, 138.3, 136.0, 128.6, 127.3, 121.7, 115.9, 105.7, 74.3, 54.3, 39.3, 20.9. HRMS (ESI): calcd. for $C_{14}H_{15}N_2O_2$ $[M + H]^+$ 243.1134; found 243.1126. Major diastereomer was isolated with traces of minor; the NMR data refer to the major isomer. NH proton could not be detected.




**(3*R**,5*S**)-3-(Benzylamino)-dihydro-5-methylfuran-2(3*H*)-one** (**171h):** Following the general procedure X as described above, **171h** was obtained after purification by silica gel column chromatography (EtOAc/hexane, 20:80) as a colorless liquid (40 mg, 65%); $R_f$ = 0.41 (20% EtOAc/hexane). IR (neat): $\tilde{\upsilon}$ = 3335, 2975, 1764, 1454, 1253 $cm^{-1}$. $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ = 7.36-7.29 (m, 5 H), 4.50-4.44 (m, 1 H), 3.92 (d, *J* = 3.0 Hz, 2 H), 3.65 (1 dd, *J* = 13.9, 8.1 Hz, 1 H), 2.58-2.52 (m, 1 H), 1.71 (q, *J* = 11.8 Hz, 1 H), 1.45 (d, *J* = 6.2 Hz, 3 H). $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta$ = 177.0, 139.0, 128.6, 128.3, 127.5, 74.3, 57.4, 52.0, 38.5, 20.8. HRMS (ESI): calcd. for $C_{12}H_{16}NO_2$ $[M + H]^+$ 206.1181; found 206.1179. This compound was isolated as a mixture of diastereomers; the NMR data refer to the major isomer. NH proton could not be detected.

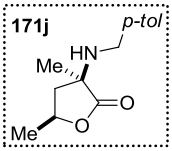



**(3*R**,5*S**)-Dihydro-5-methyl-3-(phenethylamino)furan-2(3*H*)-one** (**171i):** Following the general procedure X as described above, **171i** was obtained after purification by silica gel column chromatography (EtOAc/hexane, 20:80) as a colorless oil (49 mg, 75%); $R_f$ = 0.46 (20% EtOAc/hexane). IR (neat): $\tilde{\upsilon}$ = 3314, 2931, 1771, 1454, 1197 $cm^{-1}$. $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ = 7.32 (t, *J* = 7.5 Hz, 2 H), 7.25 (d, *J* = 7.5 Hz, 3 H), 4.87 (br. s, 2 H), 4.68-4.63 (m, 1 H), 4.32 (dd, *J* = 12.1, 8.4 Hz, 1 H), 3.41-3.34 (m, 1 H), 3.21-3.14 (m, 1 H), 3.08-3.01 (m, 2 H), 2.76-2.70 (m, 1 H), 1.48 (d, *J* = 6.2 Hz, 3 H). $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta$ = 172.8, 136.5, 128.9, 128.8, 127.2, 75.6, 57.2, 48.8, 34.3, 33.3, 20.2. HRMS (ESI): calcd. for $C_{13}H_{18}NO_2$ $[M + H]^+$ 220.1338; found



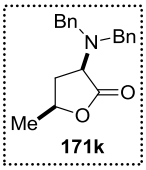
220.1340. Major diastereomer was isolated with traces of minor; the NMR data refer to the major isomer.

**(3*R**,5*S**)-3,5-Dimethyl-3-((4-methylbenzyl)amino)dihydrofuran-2(3*H*)-one (171j):** Following the general procedure X described above, **171j** was obtained after purification by



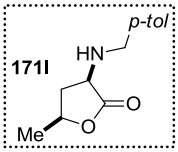

silica gel column chromatography (EtOAc/hexane, 30:70) as a colorless semi solid (59 mg, 85%); $R_f$ = 0.40 (30% EtOAc/hexane). IR (thin film): $\tilde{\upsilon}$ = 2923, 1778, 1633, 1258, 1034 cm$^{-1}$. $^1$H NMR (400 MHz, $CD_3OD$): $\delta$ = 7.40 (d, $J$ = 8.0 Hz, 2 H), 7.32 (d, $J$ = 8.0 Hz, 2 H), 4.88-4.82 (m, 1 H), 4.44 (d, $J$ = 12.6 Hz, 1 H), 4.10 (d, $J$ = 12.6 Hz, 1 H), 2.67 (dd, $J$ = 12.8, 5.3 Hz, 1 H), 2.39 (s, 3 H), 2.26 (dd, $J$ = 12.8, 10.3 Hz, 1 H), 1.75 (s, 3 H), 1.53 (d, $J$ = 6.1 Hz, 3 H). $^{13}$C NMR (100 MHz, $CD_3OD$): $\delta$ = 173.6, 139.8, 129.6, 127.8, 75.0, 62.9, 46.6, 39.4, 19.8, 19.1, 17.5. HRMS (ESI): calcd. for $C_{14}H_{20}NO_2$ $[M + H]^+$ 234.1494; found 234.1491.

**(3*R**,5*S**)-3-(Dibenzylamino)-dihydro-5-methylfuran-2(3*H*)-one (171k):** Following the general procedure X as described above, **171k** was obtained after purification by silica gel




column chromatography (EtOAc/hexane, 20:80) as a colorless oil (79 mg, 89%); $R_f$ = 0.48 (20% EtOAc/hexane). IR (neat): $\tilde{\upsilon}$ = 2977, 1769, 1453, 1184, 741 cm$^{-1}$. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 7.46 (d, $J$ = 7.5 Hz, 4 H), 7.35 (t, $J$ = 7.5 Hz, 4 H), 7.27 (d, $J$ = 7.5 Hz, 2 H), 4.39-4.34 (m, 1 H), 3.96 (d, $J$ = 13.7 Hz, 2 H), 3.86 (dd, $J$ = 12.0, 8.6 Hz, 2 H), 3.69 (d, $J$ = 13.7 Hz, 2 H), 2.43-2.36 (m, 1 H), 1.92-1.83 (m, 1 H), 1.43 (d, $J$ = 6.1 Hz, 3 H). $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ = 175.9, 139.0, 128.7, 128.4, 127.3, 73.5, 59.9, 54.8, 33.1, 21.1. HRMS (ESI): calcd. for $C_{19}H_{23}NO_2$ $[M + H]^+$ 296.1651; found 296.1644. This compound was isolated as a mixture of diastereomers; the NMR data refer to the major isomer.

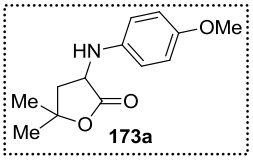
**(3*R**,5*S**)-5-Methyl-3-((4-methylbenzyl)amino)dihydrofuran-2(3*H*)-one (171l):** Following the general procedure X described above, **171l** was obtained after purification by



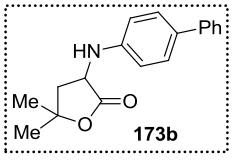

silica gel column chromatography (EtOAc/hexane, 30:70) as a colorless semi solid (54 mg, 82%); $R_f$ = 0.40 (30% EtOAc/hexane). IR (thin film): $\tilde{\upsilon}$ = 2967, 1621, 1258, 1174, 1039 cm$^{-1}$. $^1$H NMR (400 MHz, $CDCl_3$+DMSO-$d_6$): $\delta$ = 7.32 (d, $J$ = 7.8 Hz, 2 H), 7.22 (d, $J$ = 7.8 Hz, 2 H), 4.67-4.61 (m, 1 H), 4.45 (d, $J$ = 12.7 Hz, 1 H), 4.28-4.18 (m, 2 H), 2.84-2.77 (m, 1 H), 2.34 (s, 3 H), 2.07-1.90 (m, 2 H), 1.46 (d, $J$ = 6.1 Hz, 3 H). $^{13}$C NMR (100 MHz, $CDCl_3$+DMSO-$d_6$): $\delta$ = 171.4, 140.1, 130.0, 129.7,

127.0, 75.5, 55.0, 50.0, 34.2, 21.0, 20.0. HRMS (ESI): calcd. for $C_{13}H_{18}NO_2$ $[M + H]^+$ 220.1338; found 220.1333.

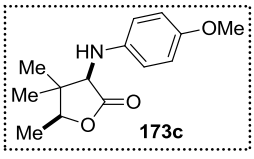
**3-(4-Methoxyphenylamino)-dihydro-5,5-dimethylfuran-2(3*H*)-one** (**173a):** Following the general procedure X as described above, **173a** was obtained after purification by silica gel column chromatography (EtOAc/hexane, 20:80) as a brown solid (40 mg, 57%); mp 79-81 °C. $R_f$ = 0.46 (20% EtOAc/hexane). IR (thin film): $\tilde{\upsilon}$ = 3360, 2977, 1759, 1513, 1237 $cm^{-1}$. $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ = 6.82 (d, $J$ = 8.9 Hz, 2 H), 6.65 (d, $J$ = 8.9 Hz, 2 H), 4.27-4.22 (m, 1 H), 4.11 (br. s, 1 H), 3.77 (s, 3 H), 2.77-2.72 (m, 1 H), 2.00 (q, $J$ = 11.0 Hz, 1 H), 1.54 (s, 3 H), 1.51 (s, 3 H). $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta$ = 175.8, 153.2, 140.7, 115.3, 114.9, 82.6, 55.8, 55.2, 44.3, 29.2, 27.4. HRMS (ESI): calcd. for $C_{13}H_{18}NO_3$ $[M + H]^+$ 236.1287; found 236.1280.




**3-(4-Biphenylamino)-dihydro-5,5-dimethylfuran-2(3*H*)-one** (**173b):** Following the general procedure X as described above, **173b** was obtained after purification by silica gel column chromatography (EtOAc/hexane, 20:80) as a pale yellow solid (42 mg, 50%); mp 74-76 °C. $R_f$ = 0.48 (20% EtOAc/hexane). IR (thin film): $\tilde{\upsilon}$ = 3364, 2973, 1764, 1612, 1300 $cm^{-1}$. $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ = 7.57-7.55 (m, 2 H), 7.50 (d, $J$ = 8.6 Hz, 2 H), 7.43 (t, $J$ = 7.4 Hz, 2 H), 7.30 (t, $J$ = 7.4 Hz, 1 H), 6.75 (d, $J$ = 8.6 Hz, 2 H), 4.44 (br. s, 1 H), 4.38 (dd, $J$ = 11.0, 8.3 Hz, 1 H), 2.83 (dd, $J$ = 12.6, 8.3 Hz, 1 H), 2.03 (dd, $J$ = 12.6, 11.0 Hz, 1 H), 1.57 (s, 3 H), 1.55 (s, 3 H). $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta$ = 175.5, 146.1, 140.9, 132.0, 128.7, 128.1, 126.5, 126.4, 113.9, 82.8, 54.3, 44.2, 29.2, 27.4. HRMS (ESI): calcd. for $C_{18}H_{20}NO_2$ $[M + H]^+$ 282.1494; found 282.1484.

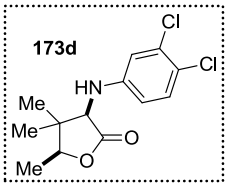



**(3*R**,5*S**)-3-(4-Methoxyphenylamino)-dihydro-4,4,5-trimethylfuran-2(3*H*)-one** (**173c):** Following the general procedure X as described above, **173c** was obtained after purification by silica gel column chromatography (EtOAc/hexane, 20:80) as a colorless oil (46 mg, 62%); $R_f$ = 0.48 (20% EtOAc/hexane). IR (neat): $\tilde{\upsilon}$ = 3381, 2965, 1770, 1513, 1237 $cm^{-1}$. $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ = 6.80 (d, $J$ = 8.9 Hz, 2 H), 6.71 (d, $J$ = 8.9 Hz, 2 H), 4.32-4.27 (m, 1 H), 3.97 (s, 1 H), 3.76 (s, 3 H), 1.35 (d, $J$ = 6.4 Hz, 3 H), 1.25 (s, 3 H), 0.90 (s, 3 H). $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta$ = 176.3, 153.0, 141.4, 115.2, 114.9, 81.6, 65.6, 55.8, 44.8, 23.2, 14.7, 13.3. HRMS (ESI):

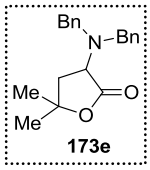


calcd. for $C_{14}H_{20}NO_3$ $[M + H]^+$ 250.1443; found 250.1435. This compound was isolated as a mixture of diastereomers; the NMR data refer to the major isomer.

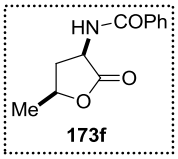
**(3*R**,5*S**)-3-(3,4-Dichlorophenylamino)-dihydro-4,4,5-trimethylfuran-2(3*H*)-one** (**173d):** Following the general procedure X as described above, **173d** was obtained after purification by silica gel column chromatography (EtOAc/hexane, 20:80) as a colorless solid (71 mg, 82%); mp 102-104 °C. $R_f$ = 0.49 (20% EtOAc/hexane). IR (thin film): $\tilde{\upsilon}$ = 3370, 2973, 1766, 1596, 1134 $cm^{-1}$. $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ = 7.20 (dd, $J$ = 8.7, 1.0 Hz, 1 H), 6.79 (d, $J$ = 2.8 Hz, 1 H), 6.56 (dd, $J$ = 8.7, 2.8 Hz, 1 H), 4.34 (q, $J$ = 6.4 Hz, 1 H), 4.24 (br. s, 1 H), 4.04 (d, $J$ = 7.3 Hz, 1 H), 1.34 (d, $J$ = 6.4 Hz, 3 H), 1.25 (s, 3 H), 0.89 (s, 3 H). $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta$ = 175.4, 146.7, 132.9, 130.7, 121.3, 114.7, 113.2, 81.8, 64.1, 45.0, 23.2, 14.7, 13.2. HRMS (ESI): calcd. for $C_{13}H_{16}Cl_2NO_2$ $[M + H]^+$ 288.0558; found 288.0554. Major diastereomer was isolated with traces of minor; the NMR data refer to the major isomer.




**3-(Dibenzylamino)-5,5-dimethyldihydrofuran-2(3*H*)-one (173e):** Following the general procedure X described above, **173e** was obtained after purification by silica gel column chromatography (EtOAc/hexane, 15:85) as a colorless semi solid (64 mg, 69%); $R_f$ = 0.51 (15% EtOAc/hexane). IR (thin film): $\tilde{\upsilon}$ = 2924, 1770, 1454, 1260, 1144 $cm^{-1}$. $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ = 7.45 (d, $J$ = 7.4 Hz, 4 H), 7.36 (t, $J$ = 7.4 Hz, 4 H), 7.28 (t, $J$ = 5.6 Hz, 2 H), 4.00-3.94 (m, 3 H), 3.70 (d, $J$ = 13.8 Hz, 2 H), 2.21 (dd, $J$ = 13.8, 10.0 Hz, 1 H), 2.09 (t, $J$ = 10.0 Hz, 1 H), 1.48 (s, 3 H), 1.30 (s, 3 H). $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta$ = 175.5, 139.0, 128.6, 128.4, 127.3, 81.1, 59.3, 54.7, 37.5, 29.3, 27.7. HRMS (ESI): calcd. for $C_{20}H_{24}NO_2$ $[M + H]^+$ 310.1807; found 310.1801.

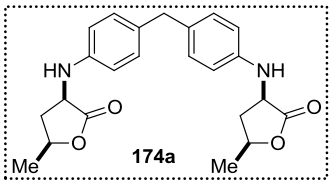



***N*-((3*R**,5*S**)-Tetrahydro-5-methyl-2-oxofuran-3-yl)benzamide** (**173f):** Following the general procedure X as described above, **173f** was obtained after purification by silica gel column chromatography (EtOAc/hexane, 30:70) as a semi solid (19 mg, 35%); $R_f$ = 0.32 (30% EtOAc/hexane). IR (thin film): $\tilde{\upsilon}$ = 3332, 2928, 1774, 1651, 1202 $cm^{-1}$. $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ = 7.83-7.80 (m, 2 H), 7.55-7.50 (m, 1 H), 7.46-7.40 (m, 2 H), 4.94-4.84 (m, 1 H), 4.69-4.62 (m, 1 H), 3.09-2.97 (m, 1 H), 1.93-1.83 (m, 1 H), 1.52 (d, $J$ = 6.2 Hz, 3 H). $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta$ = 175.5, 167.7, 133.0, 132.1, 128.6, 127.2, 51.3, 38.4. 20.6; MS (ESI): $m/z$ (%): 220 $[M+1]^+$ (50),

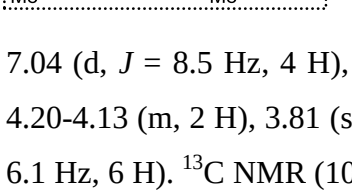


156 (100). This compound was isolated as a mixture of diastereomers and the NMR values given here refer to the major isomer.

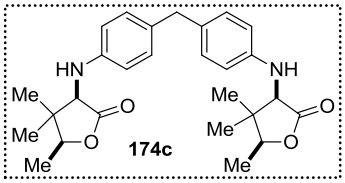
**(3*R**,3'*R**,5*S**,5'*S**)-3,3'-((Methylenebis(4,1-phenylene))bis(azanediyl))bis(5-methyldihydrofuran-2(3*H*)-one)** (**174a):** Following the general procedure X as described above, **174a** was obtained after purification by silica gel column chromatography (EtOAc/hexane, 20:80) as a semi solid (100 mg, 85%); $R_f$ = 0.37 (20% EtOAc/hexane). IR (thin film): $\tilde{\upsilon}$ = 3370, 2979, 1766, 1518, 1199 $cm^{-1}$. $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ = 7.04 (d, $J$ = 8.5 Hz, 4 H), 6.61 (d, $J$ = 8.5 Hz, 4 H), 4.66-4.61 (m, 2 H), 4.32 (br. s, 2 H), 4.20-4.13 (m, 2 H), 3.81 (s, 2 H), 3.01-2.95 (m, 2 H), 1.76 (q, $J$ = 11.7 Hz, 2 H), 1.51 (d, $J$ = 6.1 Hz, 6 H). $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta$ = 176.1, 144.8, 132.3, 129.7, 113.7, 74.5, 55.0, 40.3, 40.1, 20.7. HRMS (ESI): calcd. for $C_{23}H_{27}N_2O_4$ $[M + H]^+$ 395.1971; found 395.1968. Major diastereomer was isolated with traces of minor; the NMR data refer to the major isomer.




**((3*R**,3'*R**,5*S**,5'*S**)-3,3'-((Oxybis(4,1-phenylene))bis(azanediyl))bis(5-methyldihydrofuran-2(3*H*)-one)** (**174b):** Following the general procedure X as described above, **174b** was obtained after purification by silica gel column chromatography (EtOAc/hexane, 20:80) as a semi solid (61 mg, 51%); $R_f$ = 0.39 (20% EtOAc/hexane). IR (thin film): $\tilde{\upsilon}$ = 3369, 2979, 1768, 1498, 1225 $cm^{-1}$. $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ = 6.87 (d, $J$ = 8.8 Hz, 4 H), 6.64 (d, $J$ = 8.8 Hz, 4 H), 4.67-4.61 (m, 2 H), 4.28-4.14 (m, 4 H), 3.01-2.95 (m, 2 H), 1.80 (q, $J$ = 11.6 Hz, 2 H), 1.52 (d, $J$ = 6.3 Hz, 6 H). $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta$ = 176.0, 150.8, 142.4, 119.7, 114.7, 74.5, 55.4, 40.2, 20.8. HRMS (ESI): calcd. for $C_{22}H_{25}N_2O_5$ $[M + H]^+$ 397.1763; found 397.1768. This compound was isolated as a mixture of diastereomers; the NMR data refer to the major isomer and the NH proton could not be detected.

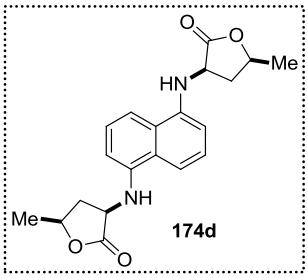



**(3*R**,3'*R**,5*S**,5'*S**)-3,3'-((Methylenebis(4,1-phenylene))bis(azanediyl))bis(4,4,5-trimethyldihydrofuran-2(3*H*)-one)** (**174c):** Following the general procedure X as described above, **174c** was obtained after purification by silica gel column chromatography (EtOAc/hexane, 20:80) as a colorless oil (59 mg, 44%); $R_f$ =

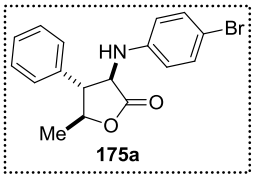


0.40 (20% EtOAc/hexane). IR (neat): $\tilde{\upsilon}$ = 3383, 2966, 1769, 1517, 1277 $cm^{-1}$. $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ = 7.01 (d, $J$ = 8.5 Hz, 4 H), 6.66 (d, $J$ = 8.5 Hz, 4 H), 4.35-4.28 (m, 2 H), 4.04-3.95 (m, 2 H), 3.79 (s, 2 H), 1.35 (d, $J$ = 6.4 Hz, 6 H), 1.25 (s, 6 H), 0.89 (s, 6 H). $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta$ = 176.1, 145.5, 132.1, 129.7, 113.6, 81.6, 64.7, 44.9, 23.2, 14.8, 13.3. HRMS (ESI): calcd. for $C_{27}H_{35}N_2O_4$ $[M + H]^+$ 451.2597; found 451.2598. This compound was isolated as a mixture of diastereomers; the NMR data refer to the major isomer.

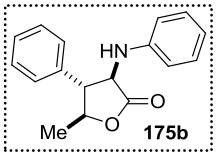
**(3*R**,3'*R**,5*S**,5'*S**)-3,3'-(Naphthalene-1,5-diylbis(azanediyl))bis(5-methyldihydrofuran-2(3*H*)-one)** (**174d):** Following the general procedure X as described above, **174d** was obtained after purification by silica gel column chromatography (EtOAc/hexane, 20:80) as a black color solid (42 mg, 40%); mp 173-175 °C. $R_f$ = 0.39 (20% EtOAc/hexane). IR (thin film): $\tilde{\upsilon}$ = 3403, 2976, 1769, 1537, 1202 $cm^{-1}$. $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ = 7.41-7.34 (m, 4 H), 6.63 (d, $J$ = 7.0 Hz, 2 H), 5.10 (br. s, 2 H), 4.76-4.71 (m, 2 H), 4.37-4.32 (m, 2 H), 3.18-3.12 (m, 2 H), 1.84 (q, $J$ = 11.4 Hz, 2 H), 1.55 (d, $J$ = 6.2 Hz, 6 H). $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta$ = 176.2, 142.4, 125.6, 124.5, 111.3, 105.9, 74.9, 54.7, 39.9, 20.8. HRMS (ESI): calcd. for $C_{20}H_{23}N_2O_4$ $[M + H]^+$ 355.1658; found 355.1664. Major diastereomer was isolated with traces of minor; the NMR data refer to the major isomer.



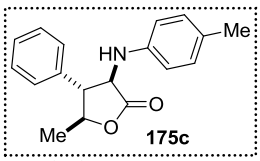

**(3*R**,4*R**,5*S**)-3-(4-Bromophenylamino)-dihydro-5-methyl-4-phenylfuran-2(3*H*)-one** (**175a):** Following the general procedure X as described above, **175a** (major isomer) was obtained after purification by silica gel column chromatography (EtOAc/hexane, 20:80) as a colorless solid (72 mg, 70%); mp 130-132 °C. $R_f$ = 0.44 (20% EtOAc/hexane). IR (thin film): $\tilde{\upsilon}$ = 3381, 2979, 1766, 1488, 1179 $cm^{-1}$. $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ = 7.42-7.37 (m, 3 H), 7.33-7.31 (m, 2 H), 7.09 (d, $J$ = 8.8 Hz, 2 H), 6.21 (d, $J$ = 8.8 Hz, 2 H), 4.73-4.69 (m, 1 H), 4.39 (dd, $J$ = 11.4, 5.0 Hz, 1 H), 4.29 (d, $J$ = 5.0 Hz, 1 H), 3.15 (t, $J$ = 11.4 Hz, 1 H), 1.45 (d, $J$ = 6.1 Hz, 3 H). $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta$ = 174.7, 145.6, 135.7, 131.8, 129.5,128.5, 127.8, 115.6, 110.7, 79.2, 62.2, 58.4, 18.8. HRMS (ESI): calcd. for $C_{17}H_{17}BrNO_2$ $[M + H]^+$ 346.0443; found 346.0441.



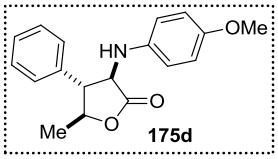
**(3*R**,4*R**,5*S**)-Dihydro-5-methyl-4-phenyl-3-(phenylamino)furan-2(3*H*)-one (175b):** Following the general procedure X as described above, **175b** (major isomer) was obtained after purification by silica gel column chromatography (EtOAc/hexane, 20:80) as a colorless solid (67 mg, 84%); mp 147-149 °C. $R_f$ = 0.41 (20% EtOAc/hexane). IR (thin film): $\tilde{\upsilon}$ = 3381, 3031, 1768, 1602, 1161 $cm^{-1}$. $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ = 7.44-7.33 (m, 5 H), 7.04 (t, $J$ = 7.8 Hz, 2 H), 6.71 (t, $J$ = 7.8 Hz, 1 H), 6.38 (d, $J$ = 7.8 Hz, 2 H), 4.75-7.68 (m, 1 H), 4.44 (dd, $J$ = 11.3, 3.1 Hz, 1 H), 4.24 (br. s, 1 H), 3.18 (t, $J$ = 11.3 Hz, 1 H), 1.47 (d, $J$ = 6.1 Hz, 3 H). $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta$ = 175.0, 146.5, 136.0, 129.4, 129.1, 128.4, 127.9, 119.0, 114.1, 79.2, 62.4, 58.3, 18.9. HRMS (ESI): calcd. for $C_{17}H_{18}NO_2$ $[M + H]^+$ 268.1338; found 268.1347.



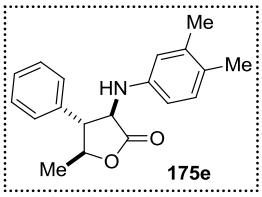

**(3*R**,4*R**,5*S**)-3-(*p*-Tolylamino)-dihydro-5-methyl-4-phenylfuran-2(3*H*)-one (175c):** Following the general procedure X as described above, **175c** (major isomer) was obtained after purification by silica gel column chromatography (EtOAc/hexane, 20:80) as a colorless solid (75 mg, 89%); mp 133-135 °C. $R_f$ = 0.43 (20% EtOAc/hexane). IR (thin film): $\tilde{\upsilon}$ = 3389, 2979, 1769, 1521, 1183 $cm^{-1}$. $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ = 7.44-7.32 (m, 5 H), 6.85 (d, $J$ = 8.1 Hz, 2 H), 6.29 (d, $J$ = 8.1 Hz, 2 H), 4.69 (q, $J$ = 6.1 Hz, 1 H), 4.38 (d, $J$ = 11.0 Hz, 1 H), 3.17 (t, $J$ = 11.0 Hz, 1 H), 2.19 (s, 3 H), 1.46 (d, $J$ = 6.1 Hz, 3 H). $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta$ = 175.1, 144.2, 136.1, 129.6, 129.4, 128.3, 127.9, 114.3, 79.2, 62.8, 58.3, 20.4, 18.9. HRMS (ESI): calcd. for $C_{18}H_{20}NO_2$ $[M + H]^+$ 282.1494; found 282.1492. NH proton could not be detected.



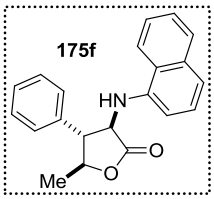

**(3*R**,4*R**,5*S**)-3-(4-Methoxyphenylamino)-dihydro-5-methyl-4-phenylfuran-2(3*H*)-one (175d):** Following the general procedure X as described above, **175d** (major isomer) was obtained after purification by silica gel column chromatography (EtOAc/hexane, 20:80) as a colorless liquid (60 mg, 67%); $R_f$ = 0.40 (20% EtOAc/hexane). IR (neat): $\tilde{\upsilon}$ = 3376, 2980, 1772, 1513, 1230 $cm^{-1}$. $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ = 7.44-7.37 (m, 3 H), 7.34-7.28 (m, 2 H), 6.62 (d, $J$ = 8.9 Hz, 2 H), 6.35 (d, $J$ = 8.9 Hz, 2 H), 4.68 (dd, $J$ = 10.1, 6.1 Hz, 1 H), 4.34 (d, $J$ = 11.5 Hz, 1 H), 3.70 (s, 3 H), 3.16 (t, $J$ = 10.1 Hz, 1 H), 1.45 (d, $J$ = 6.1 Hz, 3 H). $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta$ = 175.2, 153.2, 140.5, 136.1, 129.4, 128.3, 127.9, 116.1, 114.6, 79.2, 63.5, 58.2, 55.6, 18.9. HRMS (ESI): calcd. for $C_{18}H_{20}NO_3$ $[M + H]^+$ 298.1443; found 298.1434. NH proton could not be detected.



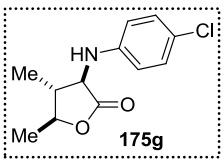
**(3*R**,4*R**,5*S**)-3-(3,4-Dimethylphenylamino)-dihydro-5-methyl-4-phenylfuran-2(3*H*)-one** (**175e):** Following the general procedure X as described above, **175e** (major isomer) was obtained after purification by silica gel column chromatography (EtOAc/hexane, 20:80) as a colorless solid (41 mg, 46%); mp 95-97 °C. $R_f$ = 0.39 (20% EtOAc/hexane). IR (thin film): $\tilde{\upsilon}$ = 3382, 2930, 1771, 1617, 1178 $cm^{-1}$. $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ = 7.43-7.32 (m, 5 H), 6.78 (d, $J$ = 8.1 Hz, 1 H), 6.15 (dd, $J$ = 8.1, 2.6 Hz, 1 H), 6.05 (d, $J$ = 2.6 Hz, 1 H), 4.70 (dd, $J$ = 10.1, 6.1 Hz, 1 H), 4.33 (dd, $J$ = 11.3, 4.2 Hz, 1 H), 4.10 (d, $J$ = 3.5 Hz, 1 H), 3.14 (t, $J$ = 11.3 Hz, 1 H), 2.07 (s, 3 H), 1.98 (s, 3 H), 1.45 (d, $J$ = 6.1 Hz, 3 H). $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta$ = 175.1, 144.7, 137.2, 136.3, 130.1, 129.4, 128.3, 128.0, 127.0, 115.9, 111.8, 79.2, 63.0, 58.9, 19.8, 18.9, 18.6. HRMS (ESI): calcd. for $C_{19}H_{22}NO_2$ $[M + H]^+$ 296.1651; found 296.1642.




**(3*R**,4*R**,5*S**)-Dihydro-5-methyl-3-(naphthalen-1-ylamino)-4-phenylfuran-2(3*H*)-one** (**175f):** Following the general procedure X as described above, **175f** (major isomer) was obtained after purification by silica gel column chromatography (EtOAc/hexane, 20:80) as a Black color solid (65 mg, 69%); mp 135-137 °C. $R_f$ = 0.41 (20% EtOAc/hexane). IR (thin film): $\tilde{\upsilon}$ = 3410, 3059, 1769, 1582, 1152 $cm^{-1}$. $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ = 7.87-7.85 (m, 1 H), 7.78-7.76 (m, 1 H), 7.46-7.34 (m, 7 H), 7.24 (d, $J$ = 8.0 Hz, 1 H), 7.02 (t, $J$ = 8.0 Hz, 1 H), 6.09 (d, $J$ = 8.0 Hz, 1 H), 4.98 (br. s, 1 H), 4.79 (dd, $J$ = 10.0, 6.1 Hz, 1 H), 4.63 (d, $J$ = 11.0 Hz, 1 H), 3.30 (t, $J$ = 11.0 Hz, 1 H), 1.51 (d, $J$ = 6.1 Hz, 3 H). $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta$ = 175.1, 141.6, 136.3, 134.2, 129.4, 128.6, 128.4, 127.8, 125.9, 125.9, 125.2, 123.9, 120.1, 119.3, 107.0, 79.5, 62.2, 58.8, 19.0. HRMS (ESI): calcd. for $C_{21}H_{20}NO_2$ $[M + H]^+$ 318.1494; found 318.1485.

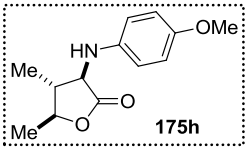



**(3*R**,4*R**,5*S**)-3-(4-Chlorophenylamino)-dihydro-4,5-dimethylfuran-2(3*H*)-one** (**175g):** Following the general procedure X as described above, **175g** was obtained after purification by silica gel column chromatography (EtOAc/hexane, 20:80) as a colorless solid (36 mg, 50%); 114-115 °C. $R_f$ = 0.51 (20% EtOAc/hexane). IR (thin film): $\tilde{\upsilon}$ = 3377, 2976, 1770, 1600, 1179 $cm^{-1}$. $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ = 7.14 (d, $J$ = 8.8 Hz, 2 H), 6.63 (d, $J$ = 8.8 Hz, 2 H), 4.22-4.14 (m, 1 H), 4.08 (br. s, 1 H), 3.91 (d, $J$ = 11.0 Hz, 1 H), 2.08-2.01 (m, 1 H), 1.46 (d, $J$ = 6.1 Hz,

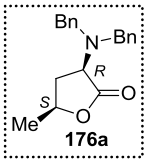


3 H), 1.26 (d, *J* = 6.1 Hz, 3 H). $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ = 175.5, 145.5, 129.2, 123.5, 114.8, 79.7, 60.9, 46.7, 18.5, 14.5. HRMS (ESI): calcd. for $C_{12}H_{15}ClNO_2$ $[M + H]^+$ 240.0791; found 240.0785. This compound was isolated as a mixture of diastereomers; the NMR data refer to the major isomer.

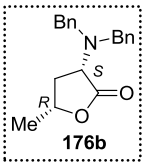
**(3*R**,4*R**,5*S**)-3-(4-Methoxyphenylamino)-dihydro-4,5-dimethylfuran-2(3*H*)-one** (**175h):** Following the general procedure X as described above, **175h** was obtained after purification by silica gel column chromatography (EtOAc/hexane, 20:80) as a semi solid (21 mg, 30%); $R_f$ = 0.49 (20% EtOAc/hexane). IR (thin film): $\tilde{\upsilon}$ = 3375, 2975, 1769, 1513, 1239 cm$^{-1}$. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 6.81 (d, *J* = 8.9 Hz, 2 H), 6.71 (d, *J* = 8.9 Hz, 2 H), 4.78-4.71 (m, 1 H), 3.85 (d, *J* = 10.4 Hz, 1 H), 3.77 (s, 3 H), 2.59-2.53 (m, 1 H), 1.36 (d, *J* = 6.8 Hz, 3 H), 1.22 (d, *J* = 6.8 Hz, 3 H). $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ = 176.3, 153.3, 140.8, 115.8, 114.8, 79.6, 59.6, 55.7, 40.9, 15.9, 13.0. HRMS (ESI): calcd. for $C_{13}H_{18}NO_3$ $[M + H]^+$ 236.1287; found 236.1279. This compound was isolated as a mixture of diastereomers; the NMR data refer to the major isomer and the NH proton could not be detected.




**(3*R*,5*S*)-3-(Dibenzylamino)-dihydro-5-methylfuran-2(3*H*)-one** (**176a):** Following the general procedure X as described above, **176a** was obtained after purification by silica gel column chromatography (EtOAc/hexane, 20:80) as a colorless oil (63 mg, 80%); $R_f$ = 0.48 (20% EtOAc/hexane). $[\alpha]_D^{23}$ = +7.6 (*c* 0.2, DCM). IR (neat): $\tilde{\upsilon}$ = 2977, 1769, 1454, 1184, 741 cm$^{-1}$. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 7.44 (d, *J* = 7.5 Hz, 4 H), 7.34 (t, *J* = 7.5 Hz, 4 H), 7.28 (d, *J* = 7.5 Hz, 2 H), 4.41-4.32 (m, 1 H), 3.95 (d, *J* = 13.7 Hz, 2 H), 3.86 (dd, *J* = 12.0, 8.6 Hz, 1 H), 3.68 (d, *J* = 13.7 Hz, 2 H), 2.42-2.35 (m, 1 H), 1.87 (q, *J* = 12.0 Hz, 1 H), 1.42 (d, *J* = 6.1 Hz, 3 H). $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ = 175.8, 139.0, 128.7, 128.4, 127.3, 73.5, 59.9, 54.8, 33.2, 21.1. HRMS (ESI): calcd. for $C_{19}H_{22}NO_2$ $[M + H]^+$ 296.1651; found 296.1663. The reaction afforded a mixture of diastereomers major diastereomer **176a** was isolated with traces of minor diastereomer and the NMR data refers to the major isomer **176a**. HPLC analysis revealed the enantioselectivity of major isomer (**176a**, *ee* = 96%).

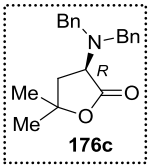



**(3*S*,5*R*)-3-(Dibenzylamino)-5-methyldihydrofuran-2(3*H*)-one (176b):** Following the general procedure described X above, **176b** was obtained after purification by silica gel column chromatography (EtOAc/hexane, 20:80) as a colorless Semi solid (72 mg, 81%); $R_f$ =

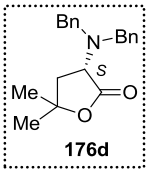



0.48 (20% EtOAc/hexane). $[\alpha]_D^{24}$ = -11.7 (*c* 0.2, DCM). IR (neat): $\tilde{\upsilon}$ = 2927, 1771, 1453, 1184, 742 $cm^{-1}$. $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ = 7.47 (d, *J* = 7.2 Hz, 4 H), 7.36 (t, *J* = 7.2 Hz, 4 H), 7.29 (t, *J* = 7.3 Hz, 2 H), 4.39-4.34 (m, 1 H), 3.98 (d, *J* = 13.7 Hz, 2 H), 3.87 (dd, *J* = 11.7, 8.9 Hz, 1 H), 3.71 (d, *J* = 13.7 Hz, 2 H), 2.44-2.37 (m, 1 H), 1.89 (dd, *J* = 22.9, 12.2 Hz, 1 H), 1.43 (d, *J* = 6.1 Hz, 3 H). $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta$ = 175.8, 139.0, 128.7, 128.4, 127.3, 73.6, 59.9, 54.8, 33.1, 21.1. HRMS (ESI): calcd. for $C_{19}H_{22}NO_2$ $[M + H]^+$ 296.1651; found 296.1651. Isolated as a mixture of diastereomers and the NMR data corresponds to the major isomer. HPLC analysis revealed the enantioselectivity of major isomer (**176b**, *ee* = 84%).

**(*R*)-3-(Dibenzylamino)-5,5-dimethyldihydrofuran-2(3*H*)-one (176c):** Following the general procedure X described above, **176c** was obtained after purification by silica gel column chromatography (EtOAc/hexane, 15:85) as a colorless semi solid (64 mg, 69%); $R_f$ = 0.51 (15% EtOAc/hexane). $[\alpha]_D^{25}$ = +15.3 (*c* 0.1, DCM). IR (neat): $\tilde{\upsilon}$ = 2975, 1769, 1454, 1271, 742 $cm^{-1}$. $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ = 7.45 (d, *J* = 7.5 Hz, 4 H), 7.36 (t, *J* = 7.5 Hz, 4 H), 7.28 (t, *J* = 6.7 Hz, 2 H), 4.00-3.94 (m, 3 H), 3.71 (d, *J* = 13.8 Hz, 2 H), 2.22 (dd, *J* = 12.8, 9.2 Hz, 1 H), 2.09 (t, *J* = 12.8 Hz, 1 H), 1.48 (s, 3 H), 1.30 (s, 3 H). $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta$ = 175.5, 139.0, 128.7, 128.4, 127.3, 81.1, 59.3, 54.7, 37.5, 29.3, 27.7. HRMS (ESI): calcd. for $C_{20}H_{24}NO_2$ $[M + H]^+$ 310.1807; found 310.1802. HPLC analysis revealed the enantioselectivity (**176c**, *ee* = 86%)



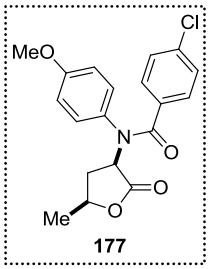

**(*S*)-3-(Dibenzylamino)-5,5-dimethyldihydrofuran-2(3*H*)-one (176d):** Following the general procedure X described above, **176d** was obtained after purification by silica gel column chromatography (EtOAc/hexane, 15:85) as a colorless semi solid (60 mg, 65%); $R_f$ = 0.51 (15% EtOAc/hexane). $[\alpha]_D^{24}$ = –16.1 (*c* 0.1, DCM). IR (neat): $\tilde{\upsilon}$ = 2928, 1769, 1454, 1260, 739 $cm^{-1}$. $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ = 7.44 (d, *J* = 7.2 Hz, 4 H), 7.35 (t, *J* = 7.2 Hz, 4 H), 7.28 (t, *J* = 7.2 Hz, 2 H), 4.00-3.94 (3 H, m), 3.70 (d, *J* = 13.8 Hz, 2 H), 2.21 (dd, *J* = 12.8, 9.2 Hz, 1 H), 2.09 (t, *J* = 12.8 Hz, 1 H), 1.48 (3 H, s), 1.29 (3 H, s). $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta$ = 175.5, 139.0, 128.6, 128.4, 127.3, 81.1, 59.3, 54.7, 37.5, 29.3, 27.7. HRMS (ESI): calcd. for $C_{20}H_{24}NO_2$ $[M + H]^+$ 310.1807; found 310.1810. HPLC analysis revealed the enantioselectivity (**176d**, *ee* = 86%).



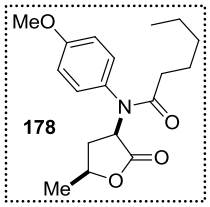

**Procedure Y. *N*-Acylation of homoserine lactone 171a:** To α-amino homoserine lactone **171a** (0.2 mmol, 1 equiv) in DCM (6 mL) was added triethyl amine (3 equiv) and

corresponding acid chloride (3 equiv) at 0 $^{o}$C. The resulting reaction mixture was allowed to stir for 2 h at 0 $^{o}$C and then for 12 h at 30$^{o}$C. After completion of the reaction as indicated by the TLC, saturated aqueous $NaHCO_3$ solution (5-6 mL) was added and the resulting reaction mixture was transferred to a separating flask and extracted using ethyl acetate (3x15 mL). The combined organic layers were dried over anhydrous $Na_2SO_4$. Then the solvent was evaporated under vacuum. Purification of the resulting crude reaction mixture by column chromatography on silica gel (EtOAc/hexane as eluent) gave the products **177** and **178** (see Scheme 82).

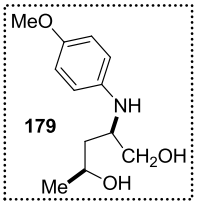
**4-Chloro-*N*-((3*R**,5*S**)-tetrahydro-5-methyl-2-oxofuran-3-yl)-*N*-(4-methoxyphenyl) benzamide** (**177):** Following the general procedure Y as described above, **177** (major isomer) was obtained after purification by silica gel column chromatography (EtOAc/hexane, 10:90) as a colorless solid (64 mg, 90%); mp 146-148 °C. $R_f$ = 0.60 (10% EtOAc/hexane). IR (thin film): $\tilde{\upsilon}$ = 2976, 1774, 1644, 1509, 1245 cm$^{-1}$. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 7.29 (d, $J$ = 8.0 Hz, 2 H), 7.16 (d, $J$ = 8.0 Hz, 2 H), 7.07 (d, $J$ = 8.8 Hz, 2 H), 6.78 (d, $J$ = 8.8 Hz, 2 H), 5.21 (t, $J$ = 9.9 Hz, 1 H), 4.63-4.57 (m, 1 H), 3.77 (s, 3 H), 2.66-2.59 (m, 1 H), 2.23 (q, $J$ = 11.2 Hz, 1 H), 1.47 (d, $J$ = 6.1 Hz, 3 H). $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ = 173.3, 158.9, 136.0, 134.2, 133.4, 130.2, 130.0, 128.1, 114.7, 74.0, 60.1, 55.4, 33.4, 21.0. HRMS (ESI): calcd. for $C_{19}H_{19}ClNO_4$ $[M + H]^+$ 360.1003; found 360.1006.



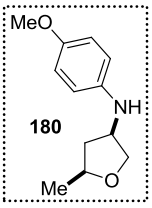

***N*-((3*R**,5*S**)-Tetrahydro-5-methyl-2-oxofuran-3-yl)-*N*-(4-methoxyphenyl)hexanamide** (**178):** Following the general procedure Y as described above, **178** was obtained after purification by silica gel column chromatography (EtOAc/hexane, 10:90) as a colorless oil (51 mg, 80%); $R_f$ = 0.62 (10% EtOAc/hexane). IR (neat): $\tilde{\upsilon}$ = 2955, 1775, 1658, 1510, 1244 cm$^{-1}$. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 7.17 (d, $J$ = 8.0 Hz, 2 H), 6.90 (d, $J$ = 8.0 Hz, 2 H), 5.07 (t, $J$ = 8.8 Hz, 1 H), 4.51-4.46 (m, 1 H), 3.81 (s, 3 H), 2.51-2.44 (m, 1 H), 2.01 (t, $J$ = 8.8 Hz, 3 H), 1.52 (t, $J$ = 6.5 Hz, 2 H), 1.37 (d, $J$ = 6.5 Hz, 3 H), 1.18-1.13 (m, 4 H), 0.79 (t, $J$ = 5.5 Hz, 3 H). $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ = 173.7, 159.5, 133.3, 130.2, 114.9, 73.9, 58.7, 55.5, 34.2, 33.7, 31.3, 24.8, 22.3, 20.9, 13.9. HRMS (ESI): calcd. for $C_{18}H_{26}NO_4$ $[M + H]^+$ 320.1862; found 320.1868. This compound was isolated as a mixture of diastereomers; the NMR data refer to the major isomer.



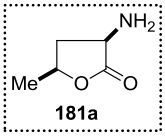
**(2*R**,4*S**)-2-(4-Methoxyphenylamino)pentane-1,4-diol (179):** A dry flask was charged with dry THF (4 mL) and the respective α-Amino Homoserine lactone **171a** (0.5 mmol) under nitrogen atmosphere at 0 $^{o}$C. To this solution was added $LiAlH_4$ (2 mmol) in portions and allowed to stir for 12 h at 30$^{o}$C. EtOH (few drops) and 5% aq. NaOH solution (1-2 mL) were then added sequentially. The resulting white suspension was filtered through Celite pad and rinsed with THF (20 mL). Filtrate was dried over anhydrous $Na_2SO_4$ and the solvent was removed by rotary evaporation and *N*-aryl β-amino pentane 1,4-diol **179** was obtained after purification by silica gel column chromatography (EtOAc/hexane, 40:60) as a semi solid (56 mg, 50%); $R_f$ = 0.18 (40% EtOAc/hexane). IR (thin film): $\tilde{\upsilon}$ = 3368, 2964, 1511, 1237, 1036 cm$^{-1}$. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 6.79 (d, $J$ = 8.9 Hz, 2 H), 6.69 (d, $J$ = 8.9 Hz, 2 H), 4.08-4.03 (m, 1 H), 3.76 (s, 3 H), 3.74-3.61 (m, 4 H), 2.62 (br. s, 2 H), 1.74-1.67 (m, 2 H), 1.25 (d, $J$ = 6.2 Hz, 3 H). $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ = 152.7, 141.4, 115.8, 115.0, 65.7, 64.6, 55.8, 54.3, 41.1, 24.3. HRMS (ESI): calcd. for $C_{12}H_{20}NO_3$ $[M + H]^+$ 226.1443; found 226.1439. This compound was isolated as a mixture of diastereomers; the NMR data refer to the major isomer.




**(3*R**,5*S**)-Tetrahydro-*N*-(4-methoxyphenyl)-5-methylfuran-3-amine (180):** *N*-aryl β-amino pentane 1,4-diol **179** (0.13 mmol) was taken in a round-bottomed flask in toluene (15 ml) and *p*-toluene sulfonic acid (30 mol%) was added. The reaction was heated at reflux for 20 h. With the help of a Dean–Stark apparatus, water was removed azeotropically. The reaction mixture was quenched in water, extracted with ethyl acetate. The combined organic layers were dried over anhydrous $Na_2SO_4$. Then the solvent was evaporated under vacuum. **180** was obtained after purification of the resulting crude reaction mixture by silica gel column chromatography (EtOAc/hexane, 20:80) as a colorless liquid (18 mg, 67%); $R_f$ = 0.39 (20% EtOAc/hexane). IR (neat): $\tilde{\upsilon}$ = 3366, 2930, 1512, 1238, 1038 cm$^{-1}$. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 6.81 (d, $J$ = 8.9 Hz, 2 H), 6.58 (d, $J$ = 8.9 Hz, 2 H), 4.25-4.16 (m, 2 H), 4.07 (br. s, 1 H), 3.77 (s, 3 H), 3.61 (dd, $J$ = 9.2, 3.8 Hz, 1 H), 2.04-1.99 (m, 1 H), 1.82-1.74 (m, 1 H), 1.29 (d, $J$ = 6.1 Hz, 3 H). $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ = 152.4, 141.2, 114.9, 114.8, 74.4, 73.6, 55.8, 55.3, 40.8, 20.8. HRMS (ESI): calcd. for $C_{12}H_{18}NO_2$ $[M + H]^+$ 208.1338; found 208.1332. This compound was isolated as a mixture of diastereomers; the NMR data refer to the major isomer.



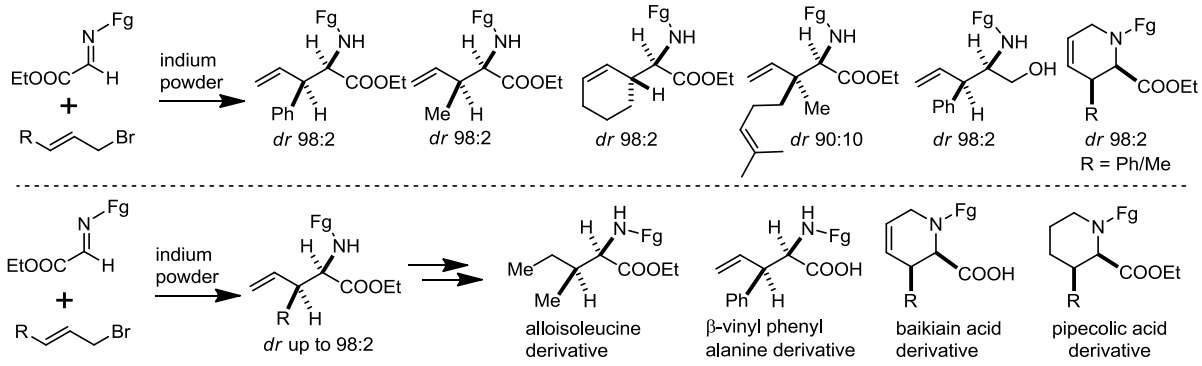
**(3*R**,5*S**)-3-Amino-5-methyldihydrofuran-2(3*H*)-one (181a):** A dry flask containing *N*-benzyl homoserine lactone **171h** (0.5 mmol, 1 equiv) in dry EtOH (4 mL) was charged with Pd/C (10 mol %) and the contents are allowed to stir under $H_2$ (1 atm) at 30 $^oC$. After disappearance of starting material (check by TLC), reaction mixture was filtered through Celite pad and the Celite pad was washed with EtOAc (20 mL). Removal of the solvent by rotary evaporation gave the crude product **181a**. After this the product **181a** can also be converted into **181b** by stirring the product **181a** in 6N HCl for 12 h at 25 $^oC$. Compound **180a** is known in the literature.[97b] Our attempts to purify the compound **180** by silica gel column chromatography was not successful however, the crude product was almost pure and its characterization data matches with that of reported one **180a**.



**181a**

The work presented in this thesis was performed with the view to explore the synthesis of a library of new classes of unnatural amino acid derivatives *via* the metal-mediated Barbier- or Reformatsky-type C-C bond forming reactions involving simple starting materials. The results obtained in the present work are summarized as given below.

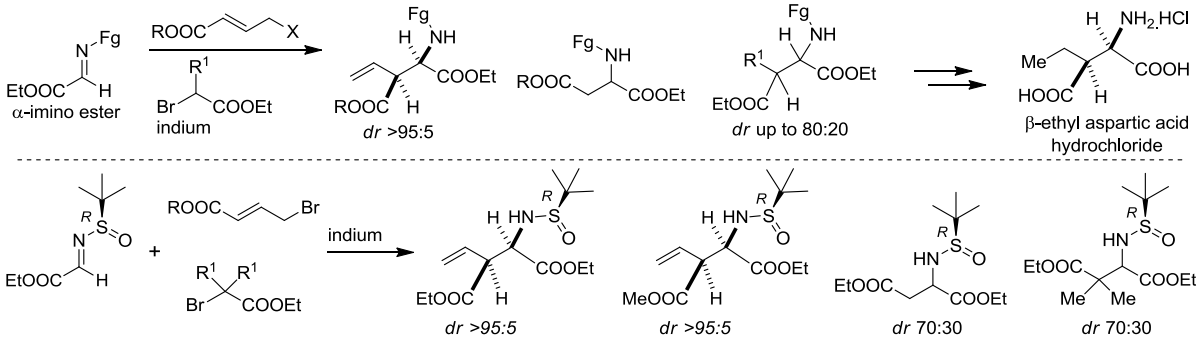
1. A highly diastereoselective C–C bond forming synthetic protocol involving the indium-mediated Barbier-type reaction and the reactivity pattern of the addition variety of γ-substituted allyl halides such as *E*-cinnamyl bromide, *E*-crotyl bromide, cyclohexenyl bromide and geranyl bromide to α-imino ester systems were studied. The indium-mediated addition of a variety of γ-substituted allyl halides to α-imino ester systems led to the assembling of several γ,δ-unsaturated β,β'-disubstituted *N*-protected α-amino acid derivatives bearing two contiguous stereocenters with remarkable diastereoselectivity. Furthermore, the synthetic utility of the γ,δ-unsaturated β,β'-disubstituted *N*-protected α-amino acid derivatives obtained from the indium-mediated Barbier-type reaction was demonstrated by efficiently constructing various 2,3-disubstituted *N*-aryltetrahydropyridine, 2,3-disubstituted *N*-aryl piperidine and *N*-aryl baikiain acid derivatives bearing two contiguous stereocenters.




**Scheme 86.** Diastereoselective synthesis of β-substituted unnatural amino acid derivatives.

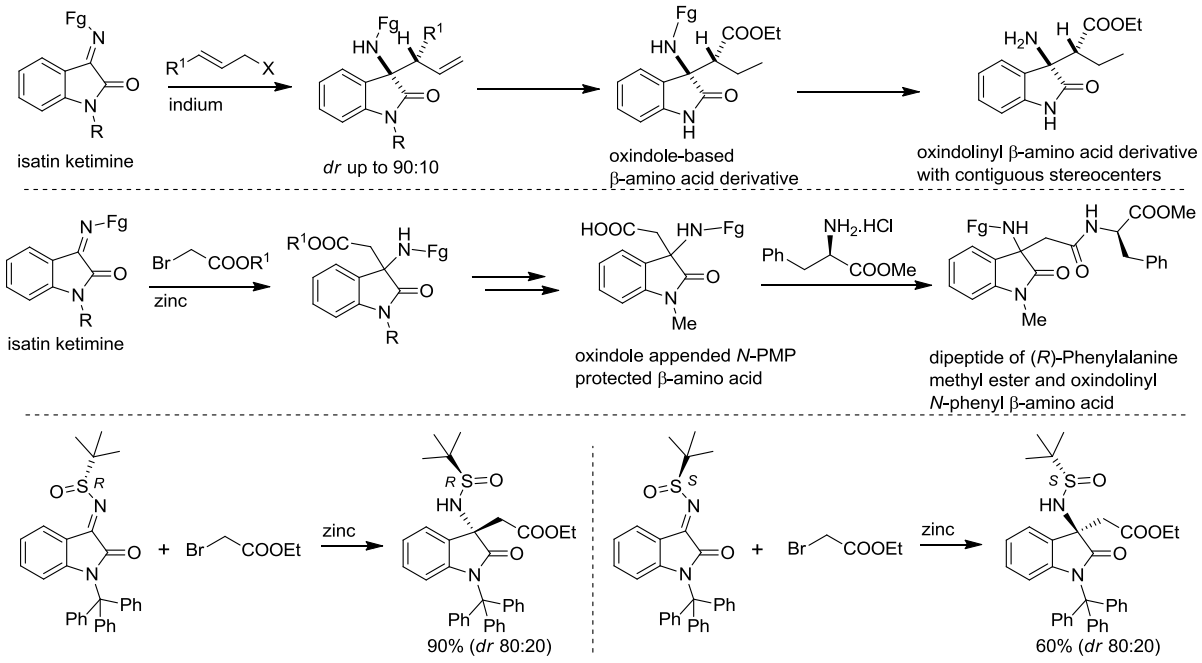
2. Next, the indium-mediated Barbier-type reaction and the reactivity pattern of the addition of *E*-alkyl 4-bromocrotonate and α-halo esters to α-imino ester systems were investigated, which led to the assembling of a variety of *N*-protected β-vinyl aspartate and β-alkyl aspartate derivatives possessing two vicinal stereocenters with high degree of stereocontrol.

Furthermore, the Reformatsky-type reactions of α-halo ester with enantiomerically pure α-imino ester (prepared using enantiopure 2-methylpropane-2-sulfinamide chiral auxiliary) were demonstrated and the synthesis of enantiomerically enriched aspartate derivatives was achieved successfully. Then, the synthesis of functionalized 1,4-diols, *cis*-piperidine-2,3-dicarboxylate derivative and β-ethyl aspartic acid hydrochloride was accomplished by using the *N*-aryl β-vinyl aspartates obtained from the indium-mediated Barbier-type reaction.



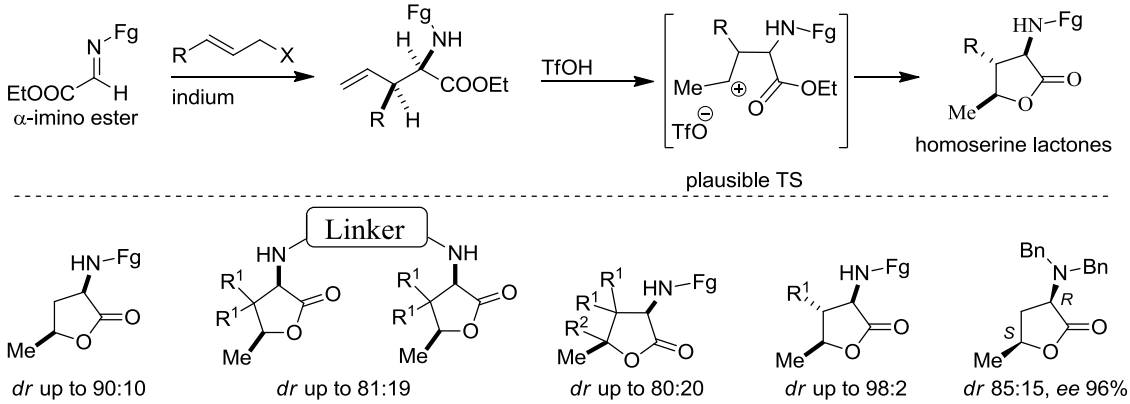

**Scheme 87.** Stereoselective construction of β-substituted aspartic acid derivatives.

3. Successively, the indium-mediated Barbier-type reaction and the reactivity pattern of the addition of a variety of γ-substituted allyl halides such as *E*-cinnamyl bromide, *E*-crotyl bromide, cyclohexenyl bromide and geranyl bromide to isatin ketimines were studied. The diastereoselective construction of new classes of 3-allyl-3-aminooxindole systems (oxindole-based homoallylic amines) having two adjacent stereocenters was accomplished. Especially, the Barbier-type addition reactions of *E*-alkyl 4-bromocrotonate and Reformatsky-type reactions of α-halo esters to isatin ketimines led to the assembling of new classes of 3-allyl-3-aminooxindole-based β-amino acid derivatives possessing two vicinal stereocenters and oxindole-based β-amino acid scaffolds. After obtaining the oxindolinyl β-amino acid derivatives from the Reformatsky-type reactions, further synthetic transformations furnished various oxindole moiety-appended amino alcohols, dipeptide derivatives and other valuable synthetic intermediates. Furthermore, the Reformatsky-type reactions of α-halo ester with enantiomerically pure isatin ketimines (prepared using enantiopure 2-methylpropane-2-sulfinamide chiral auxiliary and istain) were demonstrated and the synthesis of enantiomerically enriched oxindolinyl β-amino ester scaffolds was successfully achieved.




**Scheme 88.** Diastereoselective construction of oxindole-based β-amino acid derivatives.

4. A valuable synthetic protocol dealing with the construction of new classes of γ-butyrolactone structural motifs was developed. The γ,δ-unsaturated α-amino esters which were synthesized from the indium-mediated Barbier-type allylation of α-imino esters, were subjected to the intramolecular direct lactonization reaction in the presence of triflic acid.




**Scheme 89.** Stereoselective construction of homoserine lactones.

Several γ,δ-unsaturated α-amino esters smoothly underwent stereo- and regioselective 1,5-cyclization and furnished various new classes of highly substituted homoserine lactone

derivatives possessing multiple stereogenic centers with high degree of regio- and stereocontrol. Given the importance of naturally occurring homoserine lactones and other homoserine lactones reported in the literature, the present lactonization method and the molecules synthesized are expected to receive considerable attention.

5. Extensive screening of the reaction conditions were carried out to obtain the corresponding products with high stereoselectivity for the respective series involving the Barbier-type or Reformatksy-type reactions. The stereochemistry of the synthesized products was unambiguously established from the X-ray structures of representative compounds obtained from the respective series involving the Barbier-type or Reformatksy-type reactions. The mechanism and observed high diastereoselectivities in the reactions involving the metal-mediated addition of γ-substituted allylic halides or α-halo esters with *N*-protected α-imino esters or isatin ketimines were accounted by using the plausible chelation-controlled TS in concurrence with the literature reports.

6. The present work has demonstrated the diastereoselective construction of a library of new unnatural amino acid derivatives, such as γ,δ-unsaturated β,β′-disubstituted α-amino acid derivatives, aspartate derivatives, oxindole-based β-amino acid derivatives and homoserine lactones, each possessing vicinal stereocenters in an efficient manner by using simple starting materials under ambient reaction conditions. Notably, the Barbier-type reactions are performed in aqueous or alcohol media and the Reformatsky-type reactions in an anhydrous solvent. Given the importance of unnatural amino acids in the fields of chemical biology, medicinal and organic chemistry the unnatural amino acid derivatives synthesized in this work are expected to serve as valuable building blocks.

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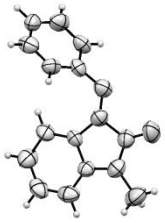
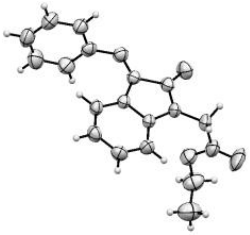
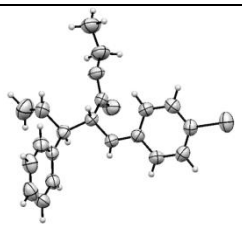
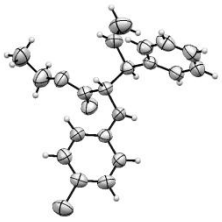
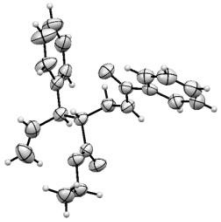
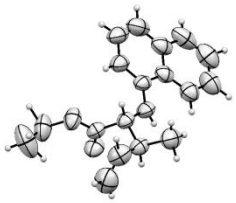
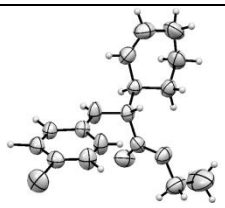
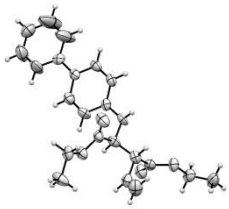
## Crystal Data and Structure Refinement for the Compounds 105i and 105k.

| X-ray Structures |  |  |
|---|---|---|
| Compound | **105i** | **105k** |
| CCDC No. | CCDC 1053607 | 1053608 |
| Empirical formula | $C_{15}H_{12}N_2O$ | $C_{18}H_{16}N_2O_3$ |
| Formula weight | 236.27 | 308.33 |
| Temperature/K | 298 | 298 |
| Crystal system | monoclinic | triclinic |
| Space group | $P2_1/c$ | P-1 |
| a/Å | 13.788(2) | 9.028(3) |
| b/Å | 12.1042(14) | 9.976(4) |
| c/Å | 22.185(3) | 10.522(4) |
| α/° | 90 | 107.503(8) |
| β/° | 101.907(7) | 99.572(6) |
| γ/° | 90 | 113.858(8) |
| Volume/$Å^3$ | 3623.0(9) | 780.2(5) |
| Z | 12 | 2 |
| $\rho_{calc}mg/mm^3$ | 1.299 | 1.312 |
| $m/mm^{-1}$ | 0.083 | 0.091 |
| F(000) | 1488.0 | 324.0 |
| Crystal size/$mm^3$ | 0.2 × 0.2 × 0.2 | 0.3 × 0.3 × 0.3 |
| 2Θ range for data collection | 6.04 to 48.814° | 6.536 to 50.048° |
| Index ranges | $-16 \le h \le 16$,<br>$-12 \le k \le 14$,<br>$-25 \le l \le 25$ | $-10 \le h \le 10$,<br>$-11 \le k \le 11$,<br>$-12 \le l \le 12$ |
| Reflections collected | 19538 | 6771 |
| Independent reflections | 5941[R(int) = 0.037] | 2740[R(int) = 0.104] |
| Data/restraints/ parameters | 5941/0/490 | 2740/0/209 |
| Goodness-of-fit on $F^2$ | 1.014 | 1.062 |
| Final R indexes [I>=2σ (I)] | $R_1$ = 0.0616,<br>$wR_2$ = 0.1660 | $R_1$ = 0.0609,<br>$wR_2$ = 0.1721 |
| Final R indexes [all data] | $R_1$ = 0.1482,<br>$wR_2$ = 0.2281 | $R_1$ = 0.0656,<br>$wR_2$ = 0.1782 |
| Largest diff. peak/hole/e $Å^{-3}$ | 0.21/-0.14 | 0.53/-0.35 |

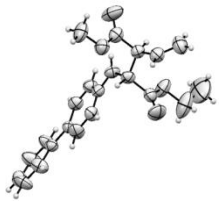
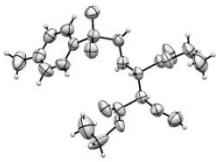
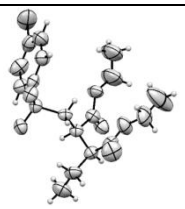
**Crystal Data and Structure Refinement for the Compounds 124a, 124e and 124i.**

| X-ray structure |  |  |  |
|---|---|---|---|
| Compound No. | **124a** | **124e** | **124i** |
| CCDC No. | CCDC 859352 | CCDC 859350 | CCDC 859355 |
| Empirical formula | $C_{19}H_{20}BrNO_2$ | $C_{19}H_{20}ClNO_2$ | $C_{20}H_{22}N_2O_3$ |
| Formula weight | 374.27 | 329.81 | 338.40 |
| Temperature/K | 298 | 298 | 298 |
| Crystal system | triclinic | triclinic | triclinic |
| Space group | P-1 | P-1 | P-1 |
| a/Å | 9.321(5) | 9.3802(4) | 9.771(5) |
| b/Å | 10.060(5) | 9.9245(5) | 10.175(6) |
| c/Å | 10.998(5) | 11.0116(5) | 11.361(10) |
| α/° | 66.96(2) | 66.3210(10) | 107.25(4) |
| β/° | 83.52(2) | 83.0700(10) | 112.37(4) |
| γ/° | 71.87(3) | 71.8310(10) | 102.12(3) |
| Volume/Å$^3$ | 902.0(8) | 891.99(7) | 928.5(11) |
| Z | 2 | 2 | 2 |
| $\rho_{calc}$mg/mm$^3$ | 1.378 | 1.228 | 1.210 |
| m/mm$^{-1}$ | 2.287 | 0.223 | 0.082 |
| F(000) | 384.0 | 348.0 | 360.0 |
| Crystal size/mm$^3$ | 0.2 × 0.2 × 0.15 | 0.2 × 0.1 × 0.1 | 0.2 × 0.2 × 0.2 |
| 2Θ range for data collection | 4.02 to 49.42° | 4.58 to 48.8° | 4.26 to 48.22° |
| Index ranges | -10 ≤ h ≤ 10,<br>-11 ≤ k ≤ 11,<br>-12 ≤ l ≤ 12 | -10 ≤ h ≤ 10,<br>-11 ≤ k ≤ 11,<br>-12 ≤ l ≤ 12 | -11 ≤ h ≤ 9,<br>-11 ≤ k ≤ 10,<br>-12 ≤ l ≤ 13 |
| Reflections collected | 5709 | 7311 | 6176 |
| Independent reflections | 3038<br>[R(int) = 0.0277] | 2912<br>[R(int) = 0.0180] | 2921<br>[R(int) = 0.0297] |
| Data/restraints/ parameters | 3038/0/288 | 2912/0/288 | 2921/0/314 |
| Goodness-of-fit on F$^2$ | 1.024 | 1.012 | 1.046 |
| Final R indexes [I>=2σ (I)] | $R_1$ = 0.0331,<br>$wR_2$ = 0.0719 | $R_1$ = 0.0410,<br>$wR_2$ = 0.1036 | $R_1$ = 0.0385,<br>$wR_2$ = 0.1026 |
| Final R indexes [all data] | $R_1$ = 0.0477,<br>$wR_2$ = 0.0777 | $R_1$ = 0.0577,<br>$wR_2$ = 0.1151 | $R_1$ = 0.0468,<br>$wR_2$ = 0.1094 |
| Largest diff. peak/hole/eÅ$^{-3}$ | 0.31/-0.26 | 0.14/-0.24 | 0.11/-0.16 |

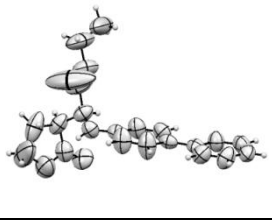
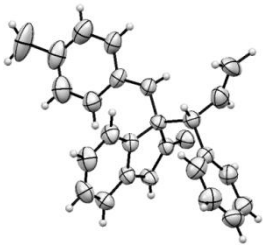
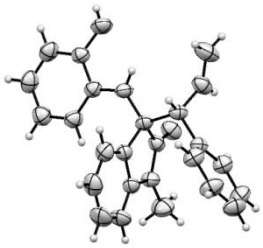
**Crystal Data and Structure Refinement for the Compounds 127h, 129a and 132l.**

| X-ray structure |  |  |  |
|---|---|---|---|
| Compound | **127h** | **129a** | **132l** |
| CCDC No. | CCDC 859354 | CCDC 859353 | CCDC 921500 |
| Empirical formula | $C_{18}H_{22}NO_2$ | $C_{16}H_{20}BrNO_2$ | $C_{22}H_{25}NO_4$ |
| Formula weight | 284.37 | 338.24 | 367.43 |
| Temperature/K | 298 | 298 | 298 |
| Crystal system | monoclinic | triclinic | monoclinic |
| Space group | C2/c | P-1 | $P2_1$ |
| a/Å | 22.809(5) | 9.352(5) | 9.7696(8) |
| b/Å | 7.8791(17) | 9.508(4) | 5.2297(4) |
| c/Å | 18.337(4) | 9.765(4) | 19.0192(17) |
| α/° | 90.00 | 105.04(3) | 90 |
| β/° | 92.432(13) | 96.68(3) | 96.090(4) |
| γ/° | 90.00 | 98.27(4) | 90 |
| Volume/$Å^3$ | 3292.6(12) | 819.0(7) | 966.25(14) |
| Z | 8 | 2 | 2 |
| $\rho_{calc}mg/mm^3$ | 1.147 | 1.372 | 1.263 |
| $m/mm^{-1}$ | 0.074 | 2.511 | 0.087 |
| F(000) | 1224.0 | 348.0 | 392.0 |
| Crystal size/$mm^3$ | 0.2 × 0.1 × 0.1 | 0.2 × 0.2 × 0.1 | 0.3 × 0.2 × 0.1 |
| 2Θ range for data collection | 4.44 to 54.2° | 4.38 to 57.06° | 2.16 to 50.12° |
| Index ranges | $-26 \le h \le 29$,<br>$-10 \le k \le 8$,<br>$-23 \le l \le 18$ | $-12 \le h \le 12$,<br>$-11 \le k \le 11$,<br>$-11 \le l \le 12$ | $-11 \le h \le 11$,<br>$-6 \le k \le 4$,<br>$-19 \le l \le 22$ |
| Reflections collected | 13211 | 5811 | 5316 |
| Independent reflections | 3623<br>[R(int)= 0.0845] | 3512<br>[R(int) = 0.0235] | 2989<br>[R(int) = 0.0456] |
| Data/restraints/ parameters | 3623/0/275 | 3512/0/242 | 2989/1/250 |
| Goodness-of-fit on $F^2$ | 0.992 | 1.019 | 1.002 |
| Final R indexes [I>=2σ (I)] | $R_1$ = 0.0677,<br>$wR_2$ = 0.1657 | $R_1$ = 0.0450,<br>$wR_2$ = 0.1204 | $R_1$ = 0.0584,<br>$wR_2$ = 0.1253 |
| Final R indexes [all data] | $R_1$ = 0.1349,<br>$wR_2$ = 0.2111 | $R_1$ = 0.0898,<br>$wR_2$ = 0.1377 | $R_1$ = 0.0946,<br>$wR_2$ = 0.1439 |
| Largest diff. peak/hole/ e $Å^{-3}$ | 0.20/-0.18 | 0.41/-0.46 | 0.25/-0.29 |

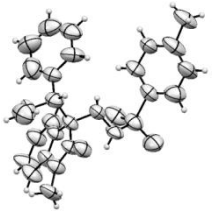
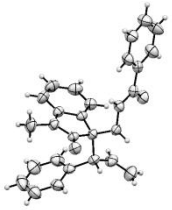
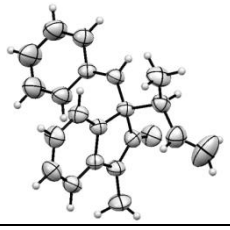
**Crystal Data and Structure Refinement for the Compounds 132t, 132v and 144d.**

| X-ray structure |  |  |  |
|---|---|---|---|
| Compound | **132t** | **132v** | **144d** |
| CCDC No. | CCDC 921501 | CCDC 921498 | CCDC 1428974 |
| Empirical formula | $C_{21}H_{23}NO_4$ | $C_{16.95}H_{23.96}N_2O_6S$ | $C_{16}H_{23}ClNO_6S$ |
| Formula weight | 353.4 | 383.77 | 392.86 |
| Temperature/K | 298 | 298 | 298 |
| Crystal system | monoclinic | orthorhombic | orthorhombic |
| Space group | $P2_1$ | $P2_12_12_1$ | $P2_12_12_1$ |
| a/Å | 8.8514(9) | 16.759(6) | 5.4500(5) |
| b/Å | 5.9553(6) | 5.1692(17) | 17.326(2) |
| c/Å | 18.3976(17) | 23.304(8) | 20.314(2) |
| α/° | 90 | 90 | 90 |
| β/° | 97.931(5) | 90 | 90 |
| γ/° | 90 | 90 | 90 |
| Volume/$Å^3$ | 960.51(16) | 2018.8(12) | 1918.1(3) |
| Z | 2 | 4 | 4 |
| $\rho_{calc}mg/mm^3$ | 1.222 | 1.263 | 1.36 |
| $m/mm^{-1}$ | 0.084 | 0.193 | 0.338 |
| F(000) | 376.0 | 815.0 | 828.0 |
| Crystal size/$mm^3$ | 0.3 × 0.2 × 0.2 | 0.3 × 0.2 × 0.2 | 0.2 × 0.2 × 0.2 |
| 2Θ range for data collection | 2.24 to 50.04° | 4.26 to 54.2° | 6.182 to 50.054° |
| Index ranges | $-10 \le h \le 10$, $-7 \le k \le 7$, $-18 \le l \le 21$ | $-21 \le h \le 21$, $-2 \le k \le 6$, $-29 \le l \le 29$ | $-6 \le h \le 6$, $-20 \le k \le 20$, $-24 \le l \le 23$ |
| Reflections collected | 5261 | 10497 | 11480 |
| Independent reflections | 3096 [R(int) = 0.0462] | 4436 [R(int) = 0.0786] | 3406 [R(int) = 0.0669] |
| Data/restraints/ parameters | 3096/1/238 | 4436/0/271 | 3406/0/223 |
| Goodness-of-fit on $F^2$ | 0.977 | 0.989 | 1.052 |
| Final R indexes [I>=2σ (I)] | $R_1$ = 0.0602, $wR_2$ = 0.1222 | $R_1$ = 0.0580, $wR_2$ = 0.1275 | $R_1$ = 0.0655, $wR_2$ = 0.1782 |
| Final R indexes [all data] | $R_1$ = 0.1642, $wR_2$ = 0.1746 | $R_1$ = 0.1233, $wR_2$ = 0.1557 | $R_1$ = 0.0881, $wR_2$ = 0.2027 |
| Largest diff. peak/ hole/ e $Å^{-3}$ | 0.20/-0.16 | 0.23/-0.25 | 0.47/-0.41 |

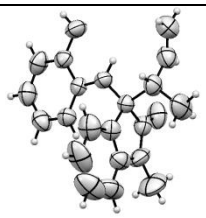
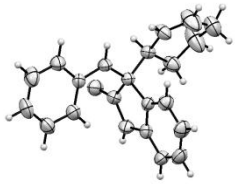
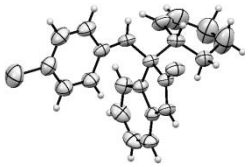
**Crystal Data and Structure Refinement for the Compounds 148b, 149b and 149i.**

| X-ray Structure |  |  |  |
|---|---|---|---|
| Compound | **148b** | **149b** | **149i** |
| CCDC No. | CCDC 921499 | CCDC 1042716 | CCDC 1042717 |
| Empirical formula | $C_{20}H_{21}NO_4$ | $C_{48}H_{44}N_4O_2$ | $C_{24}H_{22}N_2O_2$ |
| Formula weight | 339.38 | 708.87 | 370.45 |
| Temperature/K | 298 | 298 | 298 |
| Crystal system | orthorhombic | monoclinic | monoclinic |
| Space group | $P2_12_12_1$ | $P2_1/n$ | $P2_1/c$ |
| a/Å | 5.6127(11) | 23.7627(10) | 13.609(3) |
| b/Å | 16.985(3) | 7.7869(4) | 9.0259(11) |
| c/Å | 18.795(4) | 24.2216(11) | 16.365(2) |
| α/° | 90 | 90 | 90 |
| β/° | 90 | 116.300(3) | 105.074(7) |
| γ/° | 90 | 90 | 90 |
| Volume/$Å^3$ | 1791.7(6) | 4018.0(3) | 1941.0(5) |
| Z | 4 | 4 | 4 |
| $\rho_{calc}mg/mm^3$ | 1.258 | 1.172 | 1.271 |
| $m/mm^{-1}$ | 0.088 | 0.072 | 0.081 |
| F(000) | 720.0 | 1504.0 | 788.0 |
| Crystal size/$mm^3$ | 0.3 × 0.2 × 0.2 | 0.3 × 0.2 × 0.15 | 0.19 × 0.11 × 0.08 |
| 2Θ range for data collection | 3.24 to 50.14° | 3.218 to 50.054° | 6.202 to 55.016° |
| Index ranges | $-6 \le h \le 5$,<br>$-20 \le k \le 19$,<br>$-22 \le l \le 22$ | $-28 \le h \le 28$,<br>$-9 \le k \le 8$,<br>$-28 \le l \le 28$ | $-17 \le h \le 17$,<br>$-11 \le k \le 11$,<br>$-17 \le l \le 21$ |
| Reflections collected | 8771 | 25620 | 13042 |
| Independent reflections | 3136<br>[R(int) = 0.09] | 7080<br>[R(int) = 0.1334] | 4443<br>[R(int) = 0.0784] |
| Data/restraints/ parameters | 3136/0/227 | 7080/0/506 | 4443/0/255 |
| Goodness-of-fit on $F^2$ | 0.948 | 0.905 | 1.082 |
| Final R indexes [I>=2σ (I)] | $R_1$ = 0.0737,<br>$wR_2$ = 0.1794 | $R_1$ = 0.0641,<br>$wR_2$ = 0.1123 | $R_1$ = 0.0787,<br>$wR_2$ = 0.1337 |
| Final R indexes [all data] | $R_1$ = 0.2050,<br>$wR_2$ = 0.2479 | $R_1$ = 0.2239,<br>$wR_2$ = 0.1613 | $R_1$ = 0.1699,<br>$wR_2$ = 0.1733 |
| Largest diff. peak/hole/ e $Å^{-3}$ | 0.20/-0.19 | 0.21/-0.21 | 0.25/-0.25 |

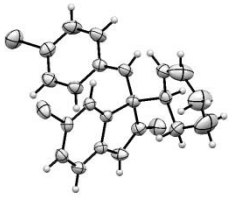
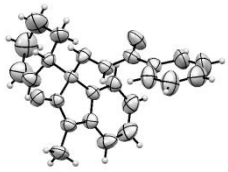
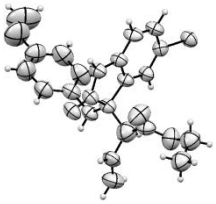
**Crystal Data and Structure Refinement for the Compounds 149j, 150k and 152d.**

| X-ray Structure |  |  |  |
|---|---|---|---|
| Compound | **149j** | **150k** | **152d** |
| CCDC No. | CCDC 1042718 | CCDC 1042726 | CCDC 1042727 |
| Empirical formula | $C_{25}H_{25}N_3O_3S$ | $C_{25}H_{23}N_3O_2$ | $C_{19}H_{20}N_2O$ |
| Formula weight | 447.54 | 397.46 | 292.37 |
| Temperature/K | 298 | 298 | 298 |
| Crystal system | monoclinic | monoclinic | monoclinic |
| Space group | $P2_1$ | $P2_1/c$ | $P2_1/n$ |
| a/Å | 9.407(5) | 9.1113(6) | 8.9983(12) |
| b/Å | 19.749(9) | 15.4212(11) | 9.5729(12) |
| c/Å | 12.882(7) | 14.8792(10) | 19.648(2) |
| α/° | 90 | 90 | 90 |
| β/° | 98.90(3) | 92.064(4) | 101.647(8) |
| γ/° | 90 | 90 | 90 |
| Volume/Å$^3$ | 2365(2) | 2089.3(2) | 1657.6(4) |
| Z | 4 | 4 | 4 |
| $\rho_{calc}$mg/mm$^3$ | 1.257 | 1.264 | 1.172 |
| m/mm$^{-1}$ | 0.168 | 0.081 | 0.073 |
| F(000) | 944.0 | 840.0 | 624.0 |
| Crystal size/mm$^3$ | 0.2 × 0.2 × 0.2 | 0.2 × 0.2 × 0.2 | 0.3 × 0.2 × 0.15 |
| 2Θ range for data collection | 6.02 to 50.048° | 6.084 to 50.046° | 4.234 to 50.146° |
| Index ranges | $-11 \le h \le 11$,<br>$-23 \le k \le 22$,<br>$-15 \le l \le 15$ | $-10 \le h \le 10$,<br>$-16 \le k \le 18$,<br>$-17 \le l \le 17$ | $-10 \le h \le 5$,<br>$-11 \le k \le 11$,<br>$-22 \le l \le 23$ |
| Reflections collected | 11711 | 11528 | 9213 |
| Independent reflections | 6401<br>[R(int) = 0.1122] | 3672<br>[R(int) = 0.0512] | 2895<br>[R(int) = 0.0465] |
| Data/restraints/ parameters | 6401/1/557 | 3672/0/272 | 2895/0/202 |
| Goodness-of-fit on $F^2$ | 0.873 | 1.075 | 1.002 |
| Final R indexes [I>=2σ (I)] | $R_1$ = 0.0882,<br>$wR_2$ = 0.2232 | $R_1$ = 0.0567,<br>$wR_2$ = 0.1589 | $R_1$ = 0.0518,<br>$wR_2$ = 0.1201 |
| Final R indexes [all data] | $R_1$ = 0.1223,<br>$wR_2$ = 0.2564 | $R_1$ = 0.0667,<br>$wR_2$ = 0.1721 | $R_1$ = 0.1114,<br>$wR_2$ = 0.1457 |
| Largest diff. peak/hole / e Å$^{-3}$ | 0.31/-0.35 | 0.46/-0.54 | 0.15/-0.18 |

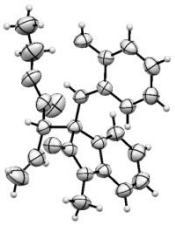
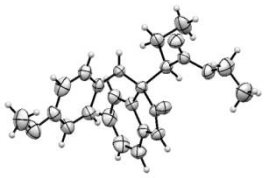
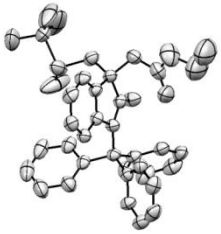
**Crystal Data and Structure Refinement for the Compounds 152e, 154a and 154b.**

| X-ray Structure |  |  |  |
|---|---|---|---|
| Compound | **152e** | **154a** | **154b** |
| CCDC No. | CCDC 1042728 | CCDC 1042729 | CCDC 1042730 |
| Empirical formula | $C_{19}H_{20}N_2O_2$ | $C_{20}H_{20}N_2O$ | $C_{20}H_{19}ClN_2O$ |
| Formula weight | 308.37 | 304.38 | 338.82 |
| Temperature/K | 298 | 298 | 298 |
| Crystal system | orthorhombic | monoclinic | monoclinic |
| Space group | $Pca2_1$ | $P2_1/n$ | $P2_1/c$ |
| a/Å | 13.902(2) | 11.7393(12) | 11.062(13) |
| b/Å | 9.2459(16) | 6.3886(6) | 18.99(2) |
| c/Å | 13.220(3) | 21.318(2) | 8.506(10) |
| α/° | 90 | 90 | 90 |
| β/° | 90 | 90.765(8) | 109.327(19) |
| γ/° | 90 | 90 | 90 |
| Volume/$Å^3$ | 1699.3(5) | 1598.7(3) | 1686(3) |
| Z | 4 | 4 | 4 |
| $\rho_{calc}mg/mm^3$ | 1.205 | 1.265 | 1.335 |
| $m/mm^{-1}$ | 0.079 | 0.079 | 0.235 |
| F(000) | 656.0 | 648.0 | 712.0 |
| Crystal size/$mm^3$ | 0.2 × 0.2 × 0.2 | 0.3 × 0.2 × 0.2 | 0.2 × 0.2 × 0.2 |
| 2Θ range for data collection | 6.124 to 54.966° | 3.82 to 50.04° | 4.3 to 50.06° |
| Index ranges | $-18 \le h \le 18$,<br>$-10 \le k \le 12$,<br>$-17 \le l \le 16$ | $-13 \le h \le 13$,<br>$-6 \le k \le 7$,<br>$-25 \le l \le 25$ | $-13 \le h \le 13$,<br>$-21 \le k \le 22$,<br>$-8 \le l \le 10$ |
| Reflections collected | 11026 | 10154 | 7582 |
| Independent reflections | 3760<br>[R(int) = 0.1039] | 2822<br>[R(int) = 0.0555] | 2971<br>[R(int) = 0.0326] |
| Data/restraints/ parameters | 3760/1/214 | 2822/0/209 | 2971/0/221 |
| Goodness-of-fit on $F^2$ | 1.004 | 0.984 | 1.033 |
| Final R indexes [I>=2σ (I)] | $R_1 = 0.0709$,<br>$wR_2 = 0.1648$ | $R_1 = 0.0666$,<br>$wR_2 = 0.1645$ | $R_1 = 0.0572$,<br>$wR_2 = 0.1629$ |
| Final R indexes [all data] | $R_1 = 0.1378$,<br>$wR_2 = 0.2072$ | $R_1 = 0.1426$,<br>$wR_2 = 0.2033$ | $R_1 = 0.0743$,<br>$wR_2 = 0.1775$ |
| Largest diff. peak/hole / e $Å^{-3}$ | 0.16/-0.15 | 0.39/-0.27 | 0.66/-0.42 |

**Crystal Data and Structure Refinement for the Compounds 154c, 155h and 159e.**

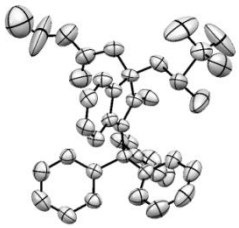
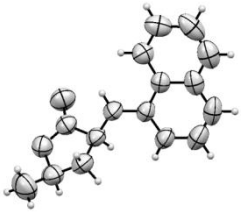
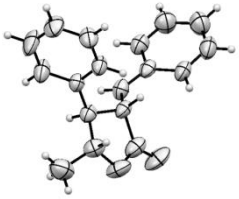
| X-ray Structure |  |  |  |
|---|---|---|---|
| Compound | **154c** | **155h** | **159e** |
| CCDC No. | CCDC 1042731 | CCDC 1042732 | CCDC 1042733 |
| Empirical formula | $C_{20}H_{18}Cl_2N_2O$ | $C_{22}H_{23}N_3O_2$ | $C_{21}H_{21}BrN_2O_4$ |
| Formula weight | 373.26 | 361.43 | 445.31 |
| Temperature/K | 298 | 298 | 298 |
| Crystal system | monoclinic | monoclinic | monoclinic |
| Space group | $P2_1/c$ | $P2_1/c$ | $P2_1/n$ |
| a/Å | 10.5567(2) | 8.764(2) | 22.814(3) |
| b/Å | 18.6081(4) | 21.249(3) | 7.8259(8) |
| c/Å | 9.1981(2) | 10.403(3) | 25.231(4) |
| α/° | 90 | 90 | 90 |
| β/° | 106.4410(10) | 95.030(10) | 104.749(6) |
| γ/° | 90 | 90 | 90 |
| Volume/$Å^3$ | 1733.00(6) | 1929.7(8) | 4356.3(10) |
| Z | 4 | 4 | 8 |
| $\rho_{calc}mg/mm^3$ | 1.431 | 1.244 | 1.358 |
| $m/mm^{-1}$ | 0.385 | 0.081 | 1.914 |
| F(000) | 776.0 | 768.0 | 1824.0 |
| Crystal size/$mm^3$ | 0.3 × 0.3 × 0.2 | 0.2 × 0.2 × 0.2 | 0.2 × 0.2 × 0.2 |
| 2Θ range for data collection | 4.02 to 50.06° | 6.04 to 50.052° | 6.18 to 54.968° |
| Index ranges | $-12 \le h \le 12$,<br>$-18 \le k \le 22$,<br>$-10 \le l \le 10$ | $-10 \le h \le 10$,<br>$-25 \le k \le 25$,<br>$-12 \le l \le 12$ | $-29 \le h \le 23$,<br>$-9 \le k \le 10$,<br>$-32 \le l \le 32$ |
| Reflections collected | 17751 | 15938 | 28314 |
| Independent reflections | 3064<br>[R(int) = 0.0255] | 3412<br>[R(int) = 0.1034] | 9932<br>[R(int) = 0.0804] |
| Data/restraints/ parameters | 3064/0/230 | 3412/0/245 | 9932/1/485 |
| Goodness-of-fit on $F^2$ | 1.044 | 1.112 | 1.094 |
| Final R indexes [I>=2σ (I)] | $R_1$ = 0.0429,<br>$wR_2$ = 0.1122 | $R_1$ = 0.0930,<br>$wR_2$ = 0.1905 | $R_1$ = 0.0921,<br>$wR_2$ = 0.2866 |
| Final R indexes [all data] | $R_1$ = 0.0507,<br>$wR_2$ = 0.1185 | $R_1$ = 0.1691,<br>$wR_2$ = 0.2312 | $R_1$ = 0.1276,<br>$wR_2$ = 0.3256 |
| Largest diff. peak/hole / e $Å^{-3}$ | 0.75/-0.41 | 0.30/-0.26 | 2.11/-1.64 |

**Crystal Data and Structure Refinement for the Compounds 159h, 162 and 170a.**

| X-ray Structure |  |  |  |
|---|---|---|---|
| Compound | **159h** | **162** | **170a** |
| CCDC No. | CCDC 1042734 | CCDC 1042735 | CCDC 1428975 |
| Empirical formula | $C_{21}H_{22}N_2O_4$ | $C_{21}H_{24}N_2O_4$ | $C_{35}H_{36}N_2O_4S$ |
| Formula weight | 366.41 | 368.42 | 580.72 |
| Temperature/K | 298 | 298 | 298 |
| Crystal system | monoclinic | monoclinic | monoclinic |
| Space group | C2/c | C2/c | $P2_1$ |
| a/Å | 19.218(2) | 24.733(2) | 10.2651(10) |
| b/Å | 10.3371(10) | 8.7639(5) | 25.435(2) |
| c/Å | 20.295(3) | 20.2777(17) | 12.0617(12) |
| α/° | 90 | 90 | 90 |
| β/° | 104.906(5) | 118.402(3) | 93.943(4) |
| γ/° | 90 | 90 | 90 |
| Volume/$Å^3$ | 3896.1(8) | 3866.3(5) | 3141.8(5) |
| Z | 8 | 8 | 4 |
| $\rho_{calc}mg/mm^3$ | 1.249 | 1.266 | 1.228 |
| $m/mm^{-1}$ | 0.087 | 0.088 | 0.143 |
| F(000) | 1552.0 | 1568.0 | 1232.0 |
| Crystal size/$mm^3$ | 0.3 × 0.2 × 0.2 | 0.4 × 0.2 × 0.2 | 0.2 × 0.2 × 0.2 |
| 2Θ range for data collection | 6.5 to 50.04° | 6.666 to 50.04° | 6.238 to 50.052° |
| Index ranges | $-22 \le h \le 22$,<br>$-12 \le k \le 12$,<br>$-24 \le l \le 24$ | $-11 \le h \le 11$,<br>$-23 \le k \le 22$,<br>$-15 \le l \le 15$ | $-12 \le h \le 12$,<br>$-30 \le k \le 30$,<br>$-14 \le l \le 14$ |
| Reflections collected | 15961 | 11711 | 23471 |
| Independent reflections | 3424<br>[R(int) = 0.041] | 3355<br>[R(int) = 0.1122] | 10852<br>[R(int) = 0.0566] |
| Data/restraints/ parameters | 3424/0/251 | 3355/0/254 | 10852/3/755 |
| Goodness-of-fit on $F^2$ | 1.039 | 1.152 | 1.048 |
| Final R indexes [I>=2σ (I)] | $R_1$ = 0.0497,<br>$wR_2$ = 0.1416 | $R_1$ = 0.0780,<br>$wR_2$ = 0.2377 | $R_1$ = 0.0596,<br>$wR_2$ = 0.1643 |
| Final R indexes [all data] | $R_1$ = 0.0606,<br>$wR_2$ = 0.1531 | $R_1$ = 0.0987,<br>$wR_2$ = 0.2928 | $R_1$ = 0.0689,<br>$wR_2$ = 0.1782 |
| Largest diff. peak/hole /e $Å^{-3}$ | 0.23/-0.19 | 0.69/-0.42 | 0.44/-0.34 |

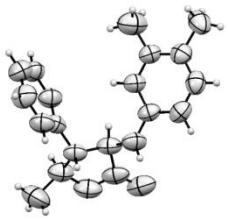
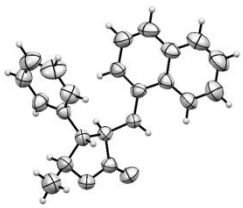
Hydrogens are omitted in case of **170a** for better visualization.

**Crystal Data and Structure Refinement for the Compounds 170b, 171f and 175b.**

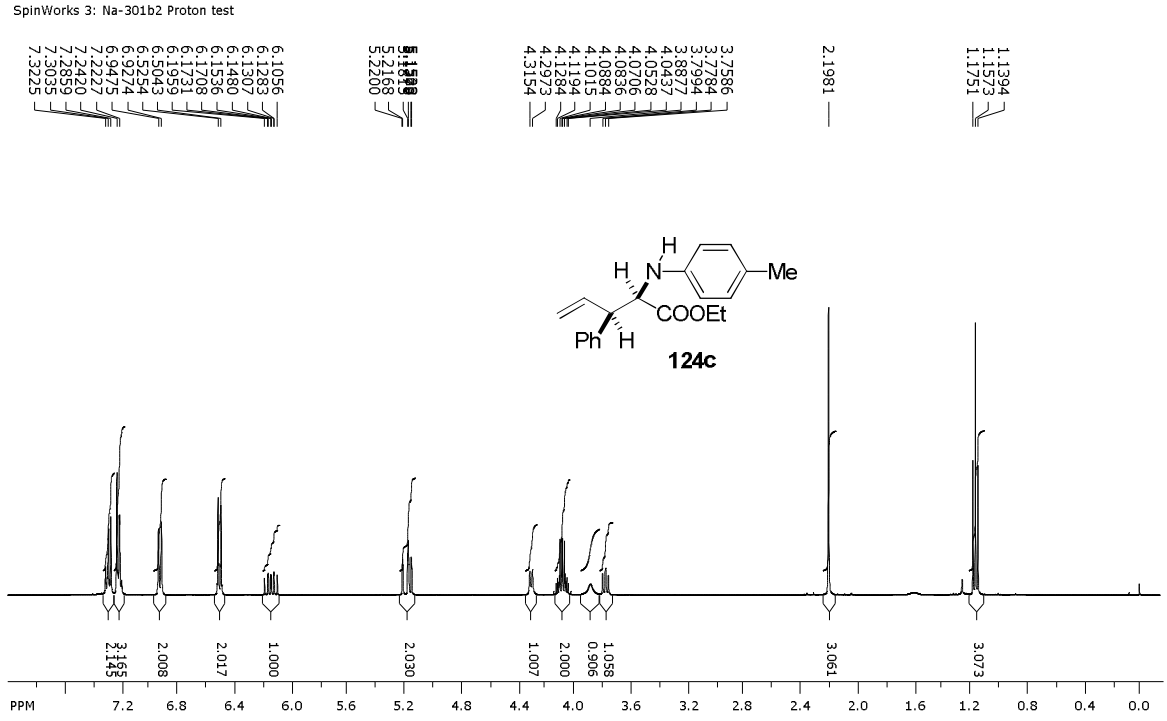
| X-ray Structure |  |  |  |
|---|---|---|---|
| Compound | **170b** | **171f** | **175b** |
| CCDC No. | CCDC 1428976 | CCDC 972901 | CCDC 972904 |
| Empirical formula | $C_{35}H_{36}N_2O_4S$ | $C_{15}H_{15}NO_2$ | $C_{17}H_{17}NO_2$ |
| Formula weight | 580.72 | 241.28 | 267.32 |
| Temperature/K | 298 | 298 | 298 |
| Crystal system | monoclinic | orthorhombic | monoclinic |
| Space group | $P2_1$ | Pbca | C2/c |
| a/Å | 10.2506(18) | 8.7494(5) | 15.6829(10) |
| b/Å | 25.453(4) | 12.1548(8) | 9.9179(6) |
| c/Å | 12.0646(19) | 24.0326(16) | 19.1554(13) |
| α/° | 90 | 90 | 90 |
| β/° | 93.691(9) | 90 | 101.064(3) |
| γ/° | 90 | 90 | 90 |
| Volume/$Å^3$ | 3141.2(9) | 2555.8(3) | 2924.1(3) |
| Z | 4 | 8 | 8 |
| $\rho_{calc}mg/mm^3$ | 1.228 | 1.254 | 1.214 |
| $m/mm^{-1}$ | 0.143 | 0.083 | 0.08 |
| F(000) | 1232.0 | 1024.0 | 1136.0 |
| Crystal size/$mm^3$ | 0.2 × 0.2 × 0.2 | 0.3 × 0.2 × 0.1 | 0.3 × 0.2 × 0.2 |
| 2Θ range for data collection | 6.238 to 50.054° | 3.38 to 50.06° | 4.34 to 50.04° |
| Index ranges | $-12 \le h \le 12$,<br>$-30 \le k \le 30$,<br>$-14 \le l \le 14$ | $-8 \le h \le 10$,<br>$-10 \le k \le 14$,<br>$-28 \le l \le 23$ | $-18 \le h \le 18$,<br>$-11 \le k \le 5$,<br>$-22 \le l \le 22$ |
| Reflections collected | 27897 | 11089 | 6081 |
| Independent reflections | 11065<br>[R(int) = 0.0693] | 2268<br>[R(int) = 0.0311] | 2567<br>[R(int) = 0.0425] |
| Data/restraints/ parameters | 11065/1/772 | 2268/0/164 | 2567/0/182 |
| Goodness-of-fit on $F^2$ | 0.968 | 1.036 | 0.953 |
| Final R indexes [I>=2σ (I)] | $R_1$ = 0.0603,<br>$wR_2$ = 0.1449 | $R_1$ = 0.0463,<br>$wR_2$ = 0.1281 | $R_1$ = 0.0578,<br>$wR_2$ = 0.1304 |
| Final R indexes [all data] | $R_1$ = 0.0889,<br>$wR_2$ = 0.1668 | $R_1$ = 0.1061,<br>$wR_2$ = 0.1588 | $R_1$ = 0.1230,<br>$wR_2$ = 0.1619 |
| Largest diff. peak/hole / e $Å^{-3}$ | 0.32/-0.25 | 0.15/-0.13 | 0.17/-0.19 |

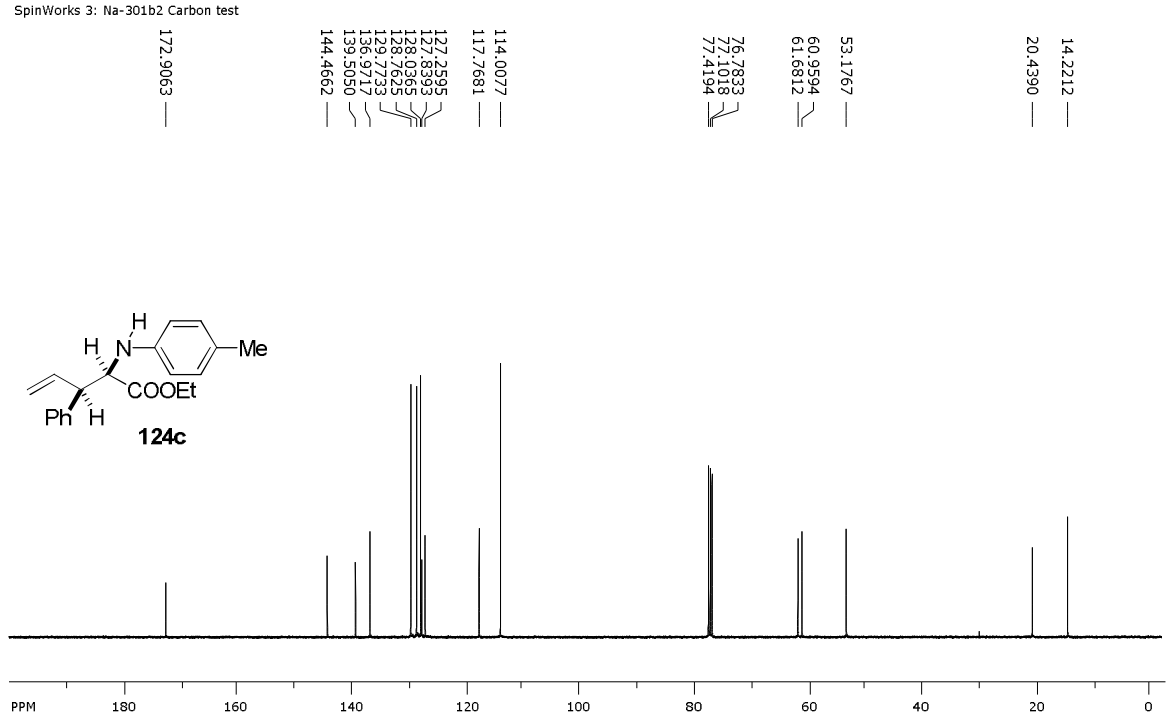
Hydrogens are omitted in case of **170b** for better visualization.

**Crystal Data and Structure Refinement for the Compounds 175e and 175f.**

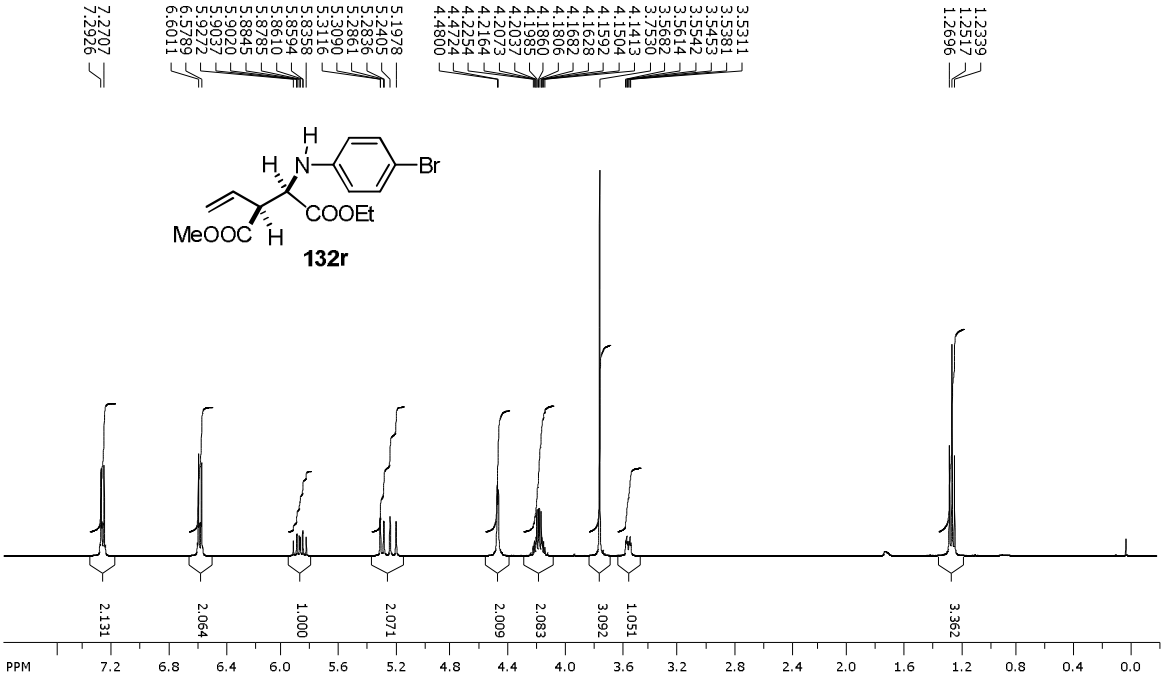
| X-ray Structures |  |  |
|---|---|---|
| Compound | **175e** | **175f** |
| CCDC No. | CCDC 972902 | CCDC 972903 |
| Empirical formula | $C_{19}H_{21}NO_2$ | $C_{21}H_{19}NO_2$ |
| Formula weight | 295.37 | 317.37 |
| Temperature/K | 298 | 298 |
| Crystal system | monoclinic | monoclinic |
| Space group | $P2_1/c$ | $P2_1/n$ |
| a/Å | 10.3789(18) | 18.906(4) |
| b/Å | 17.058(3) | 12.012(2) |
| c/Å | 10.3222(18) | 15.896(3) |
| α/° | 90 | 90 |
| β/° | 114.189(3) | 108.704(3) |
| γ/° | 90 | 90 |
| Volume/$Å^3$ | 1667.1(5) | 3419.5(12) |
| Z | 4 | 8 |
| $\rho_{calc}mg/mm^3$ | 1.177 | 1.233 |
| $m/mm^{-1}$ | 0.076 | 0.079 |
| F(000) | 632.0 | 1344.0 |
| Crystal size/$mm^3$ | 0.3 × 0.2 × 0.2 | 0.3 × 0.2 × 0.1 |
| 2Θ range for data collection | 4.3 to 50.14° | 2.92 to 50.04° |
| Index ranges | $-12 \le h \le 10$, $-16 \le k \le 20$, $-5 \le l \le 12$ | $-21 \le h \le 21$, $-12 \le k \le 13$, $-17 \le l \le 18$ |
| Reflections collected | 6632 | 16577 |
| Independent reflections | 2953[R(int) = 0.0601] | 5141[R(int) = 0.0614] |
| Data/restraints/ parameters | 2953/0/203 | 5141/0/430 |
| Goodness-of-fit on $F^2$ | 0.911 | 0.966 |
| Final R indexes [I>=2σ (I)] | $R_1$ = 0.0668, $wR_2$ = 0.1655 | $R_1$ = 0.0658, $wR_2$ = 0.1580 |
| Final R indexes [all data] | $R_1$ = 0.1876, $wR_2$ = 0.2302 | $R_1$ = 0.1602, $wR_2$ = 0.2118 |
| Largest diff. peak/hole/e $Å^{-3}$ | 0.45/-0.16 | 0.42/-0.35 |

## Representative NMR-spectra.

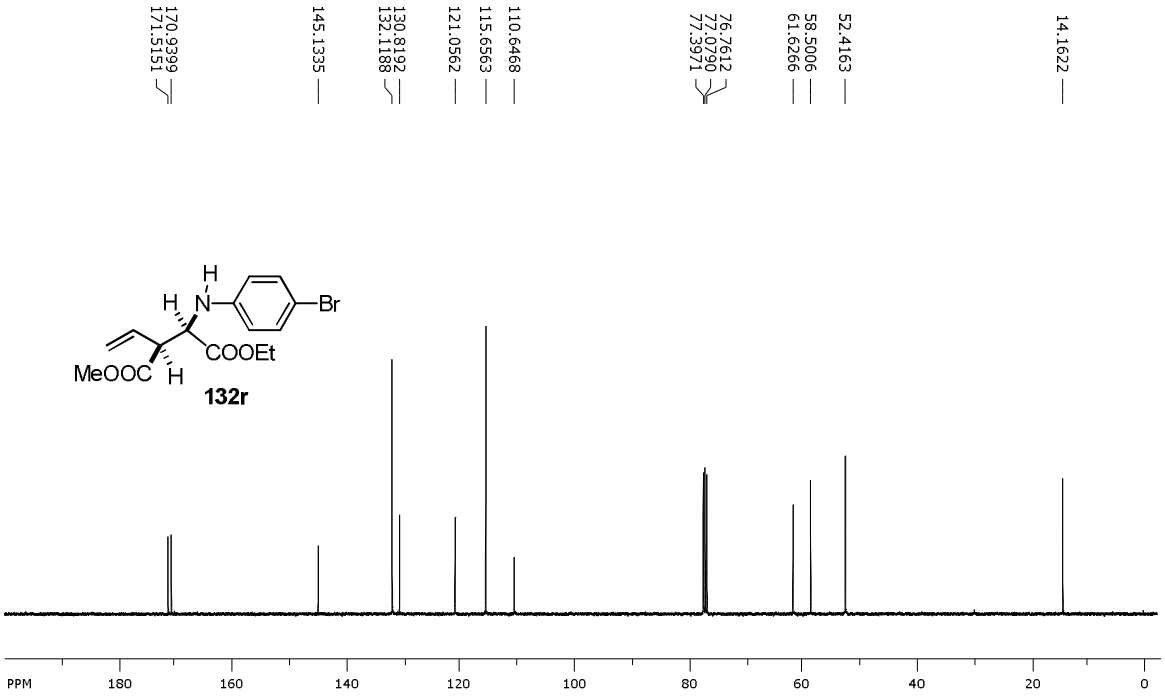


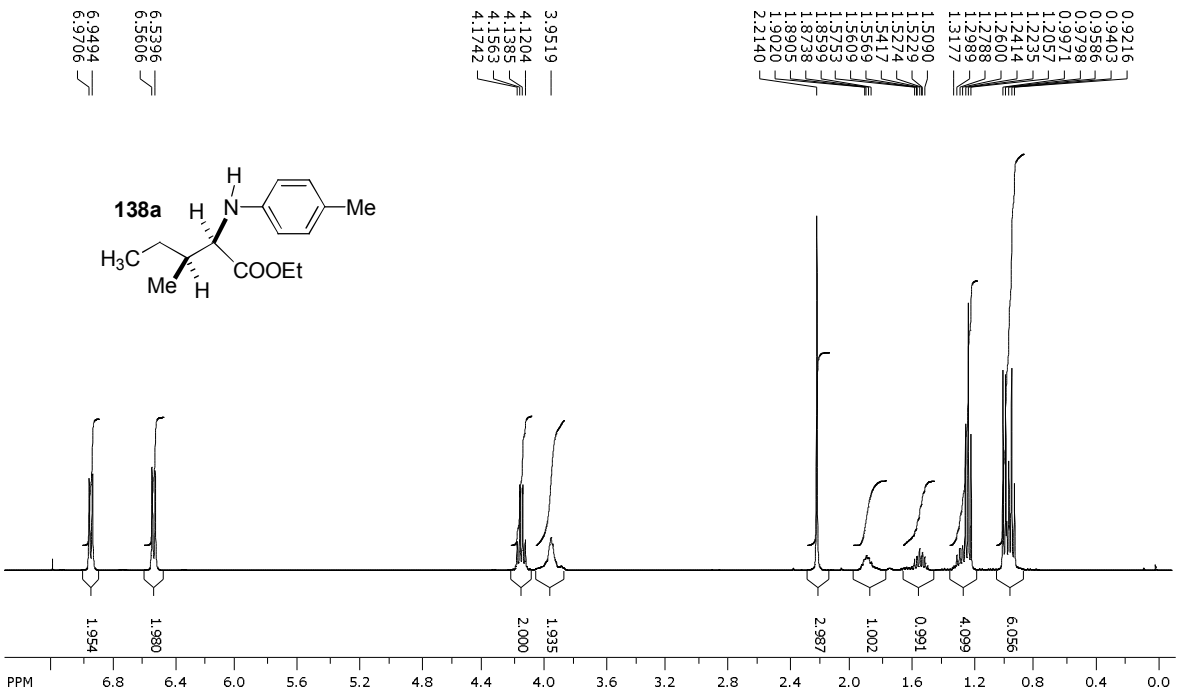
SpinWorks 3: NA-702-A Proton test



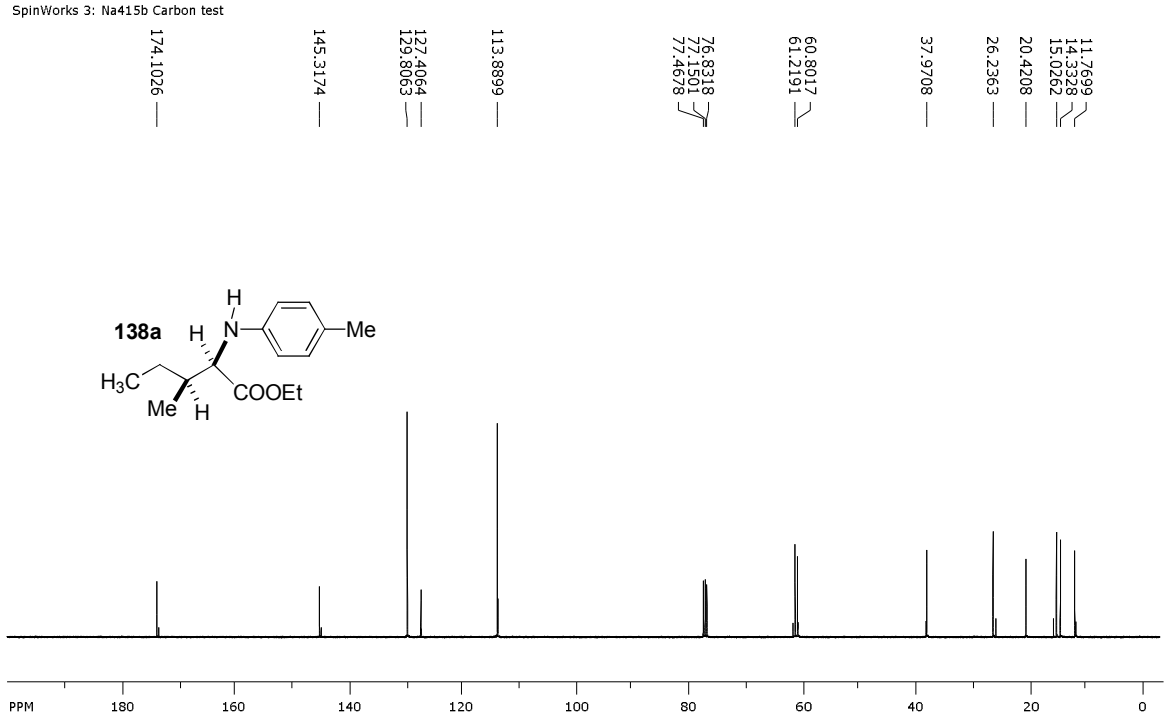

SpinWorks 3: NA-702-A Carbon test



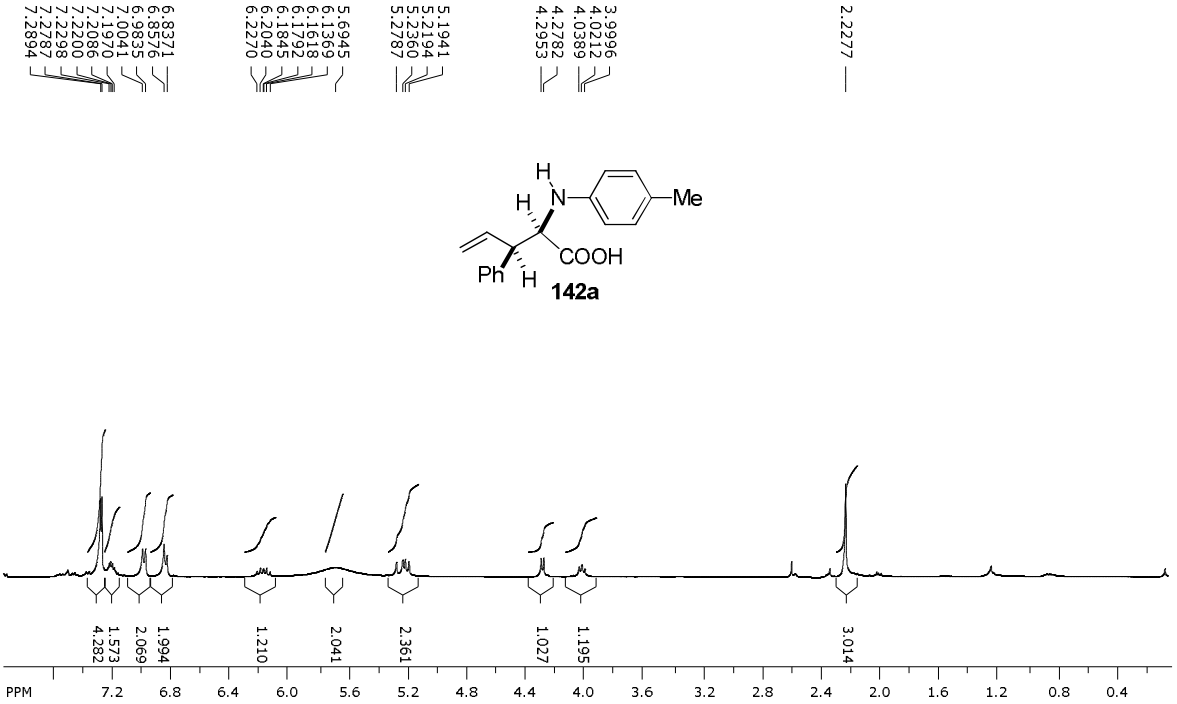
SpinWorks 3: Na415b Proton test



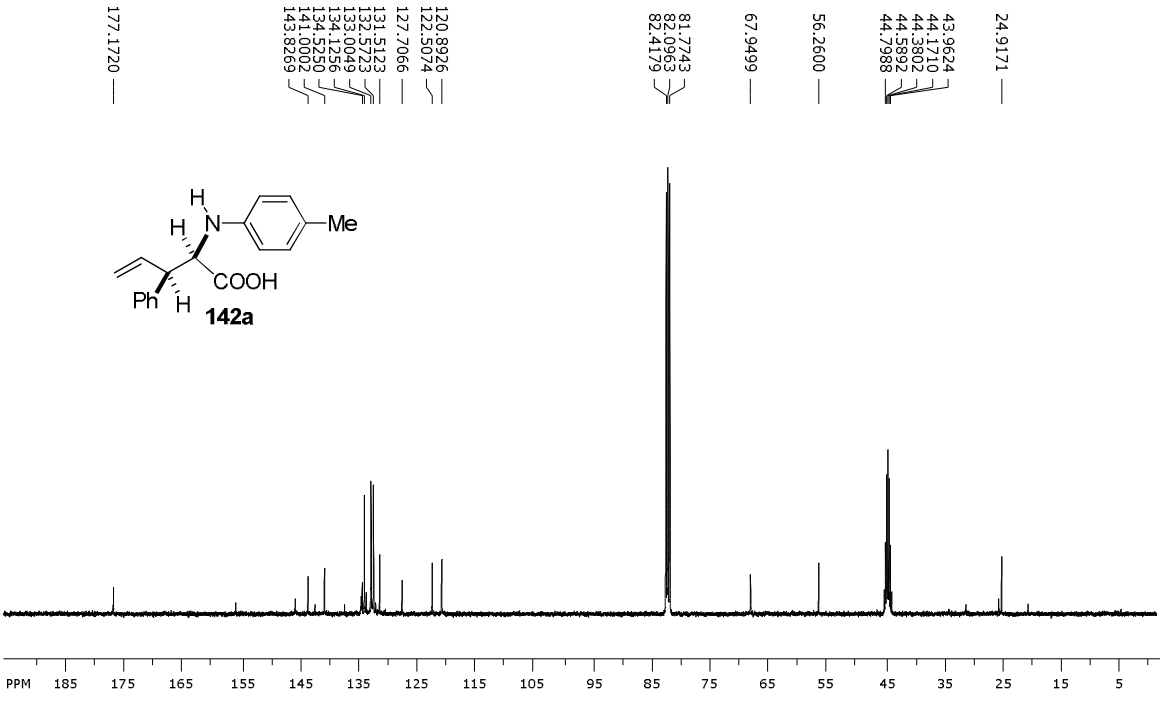

SpinWorks 3: Na415b Carbon test



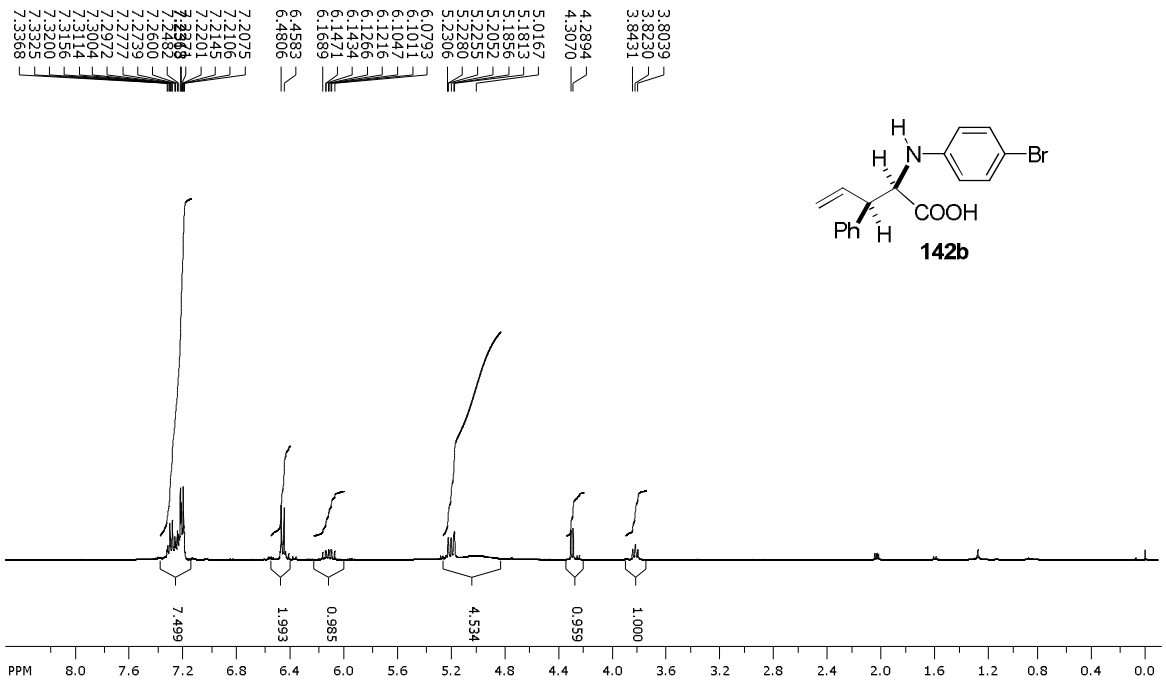
SpinWorks 3: Na-327b Proton test




SpinWorks 3: Na327b Carbon test



SpinWorks 3: Na-322r2b Proton test

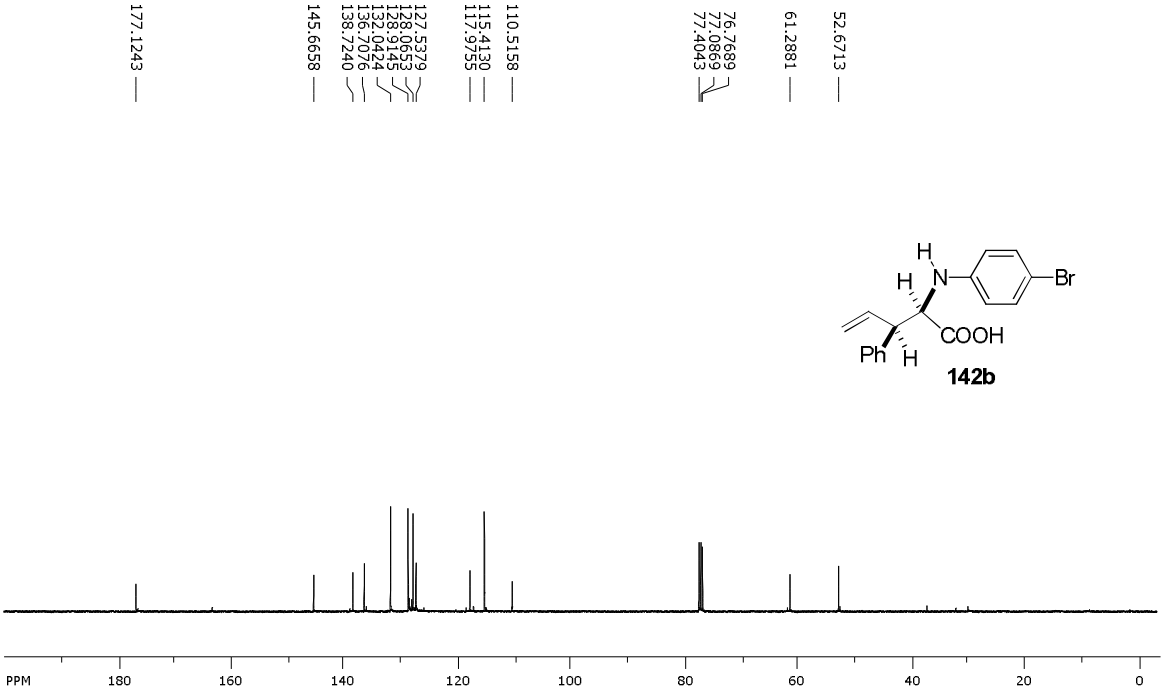






**142b**

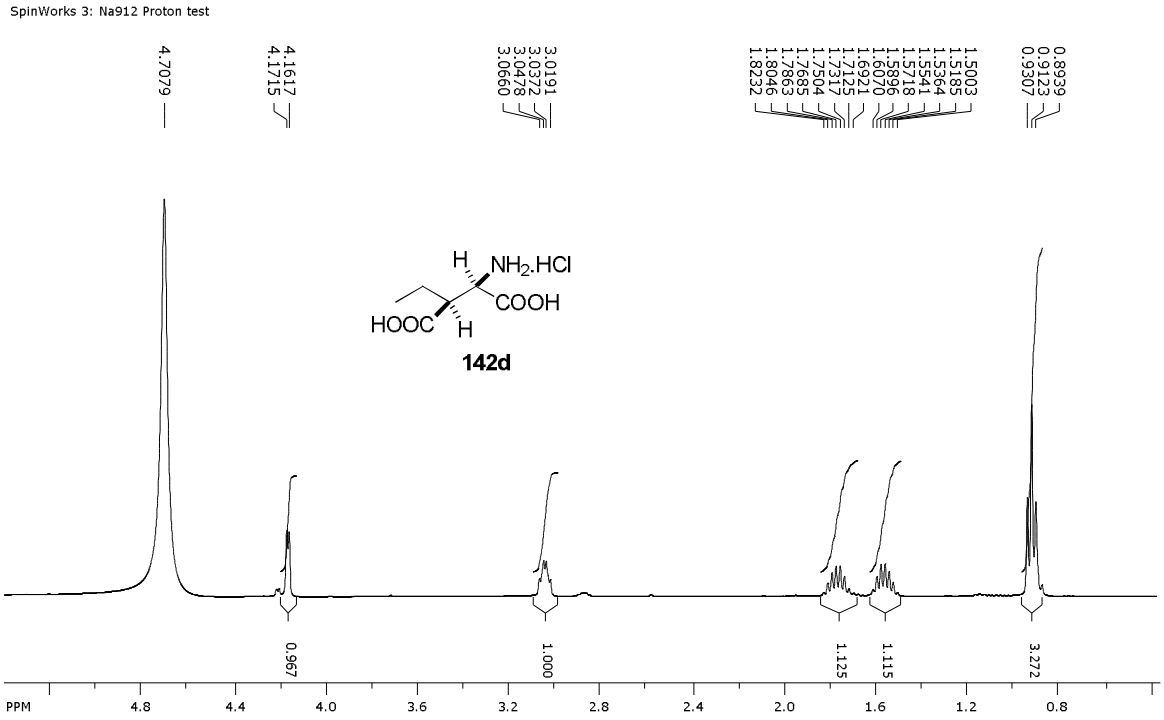
SpinWorks 3: Na-322b Carbon test

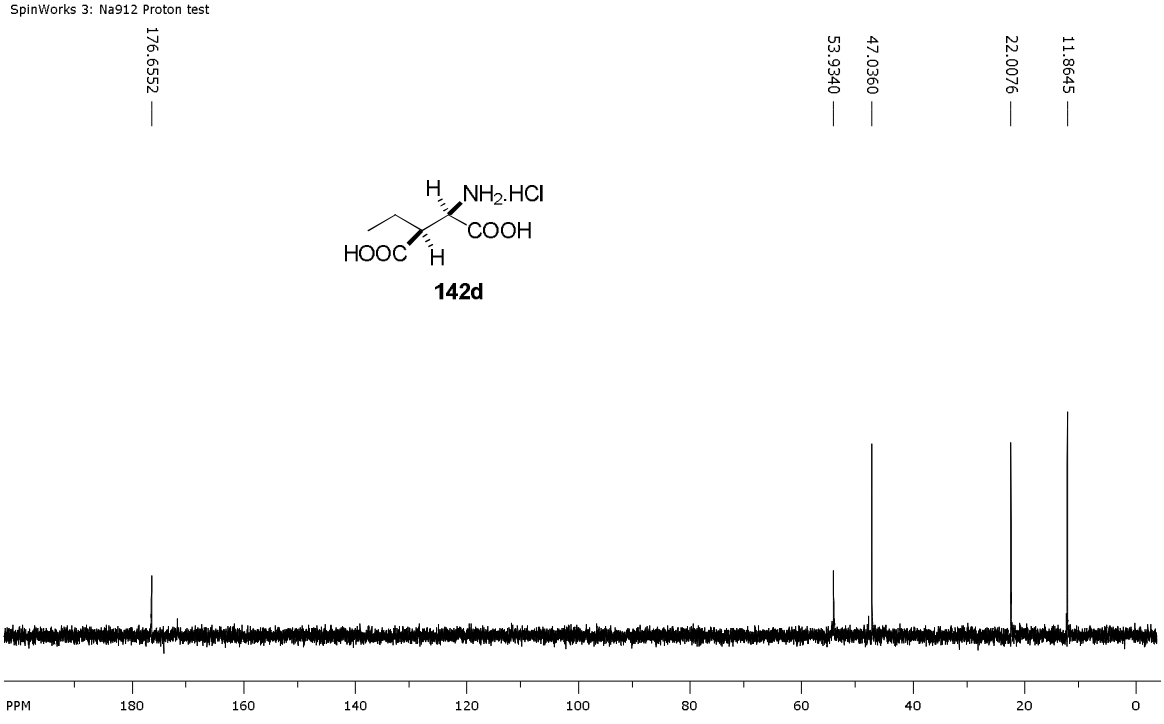


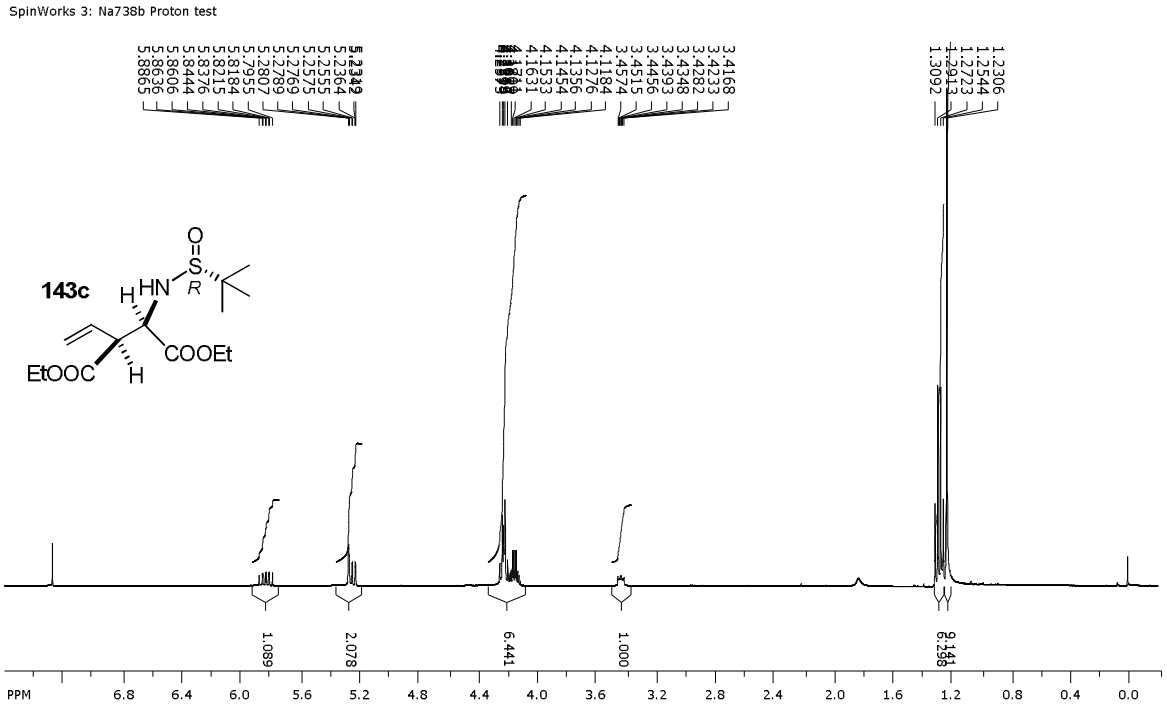


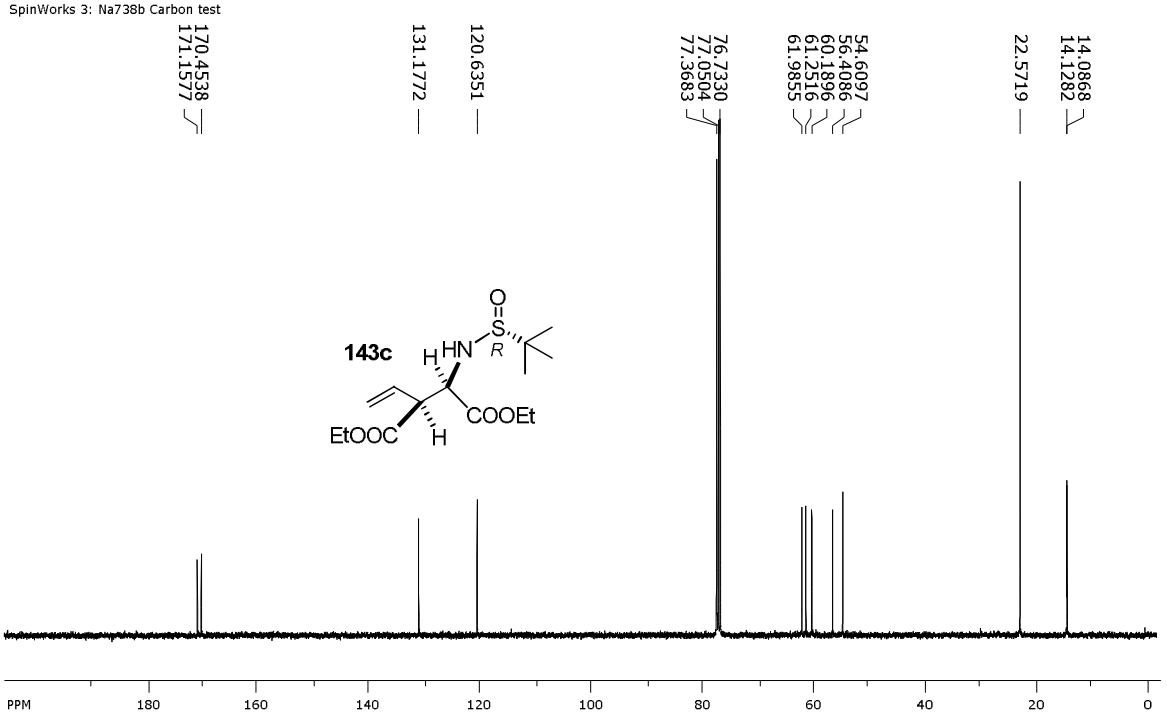


**142b**

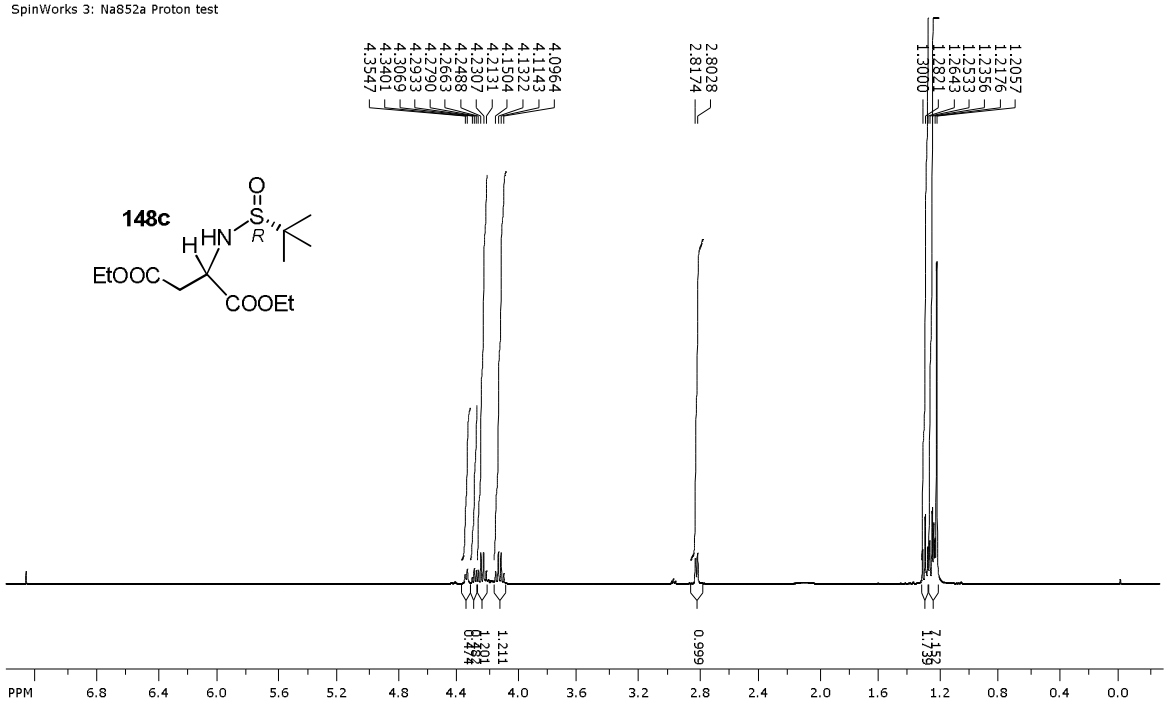

SpinWorks 3: Na912 Proton test
4.7079
4.1617
4.1715
3.0191
3.0372
3.0478
3.0660
1.8232
1.8046
1.7863
1.7685
1.7504
1.7317
1.7125
1.6921
1.6070
1.5896
1.5718
1.5541
1.5364
1.5185
1.5003
0.9307
0.9123
0.8939
H
NH2.HCl
COOH
HOOC
H
142d
0.967
1.000
1.125
1.115
3.272
PPM
4.8
4.4
4.0
3.6
3.2
2.8
2.4
2.0
1.6
1.2
0.8


SpinWorks 3: Na912 Proton test
176.6552
53.9340
47.0360
22.0076
11.8645
H
NH2.HCl
COOH
HOOC
H
142d
PPM
180
160
140
120
100
80
60
40
20
0

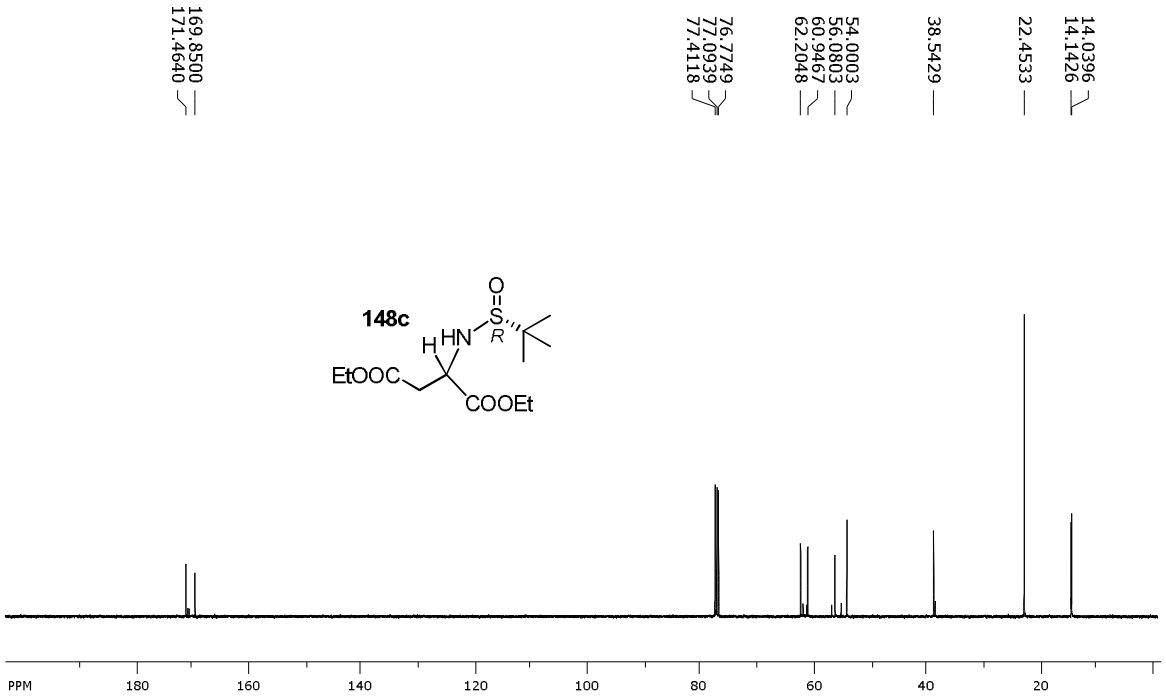

SpinWorks 3: Na738b Proton test
143c
EtOOC
COOEt
PPM

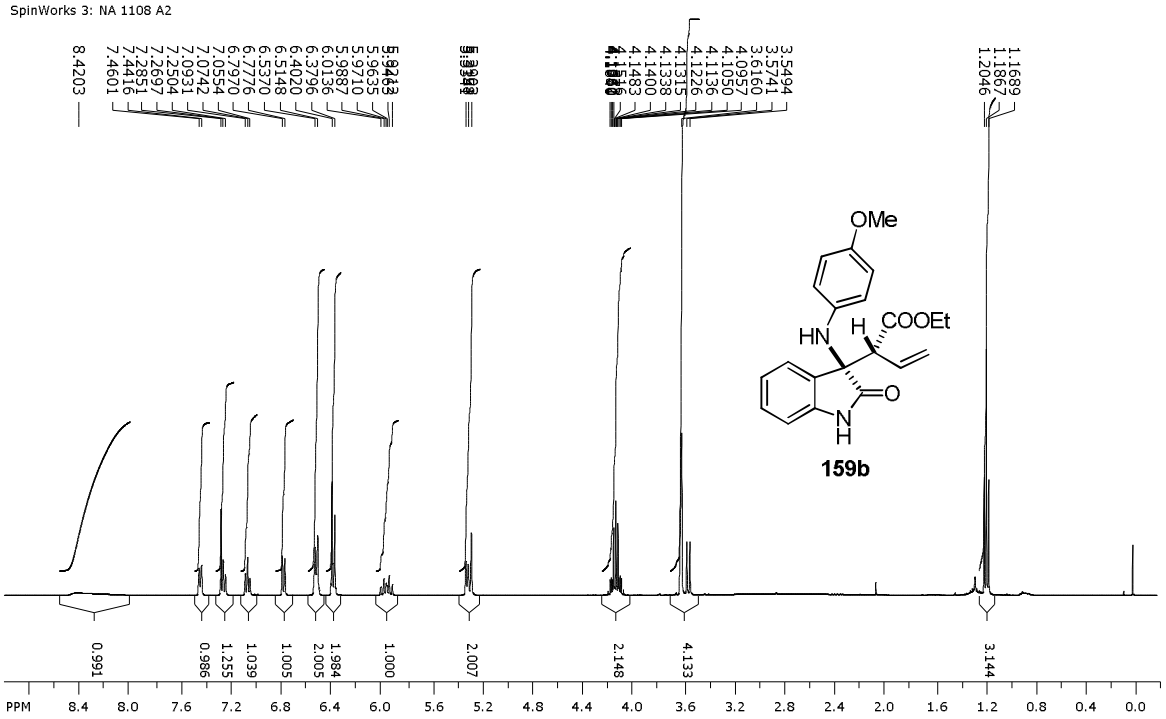

SpinWorks 3: Na738b Carbon test
143c
EtOOC
COOEt
PPM

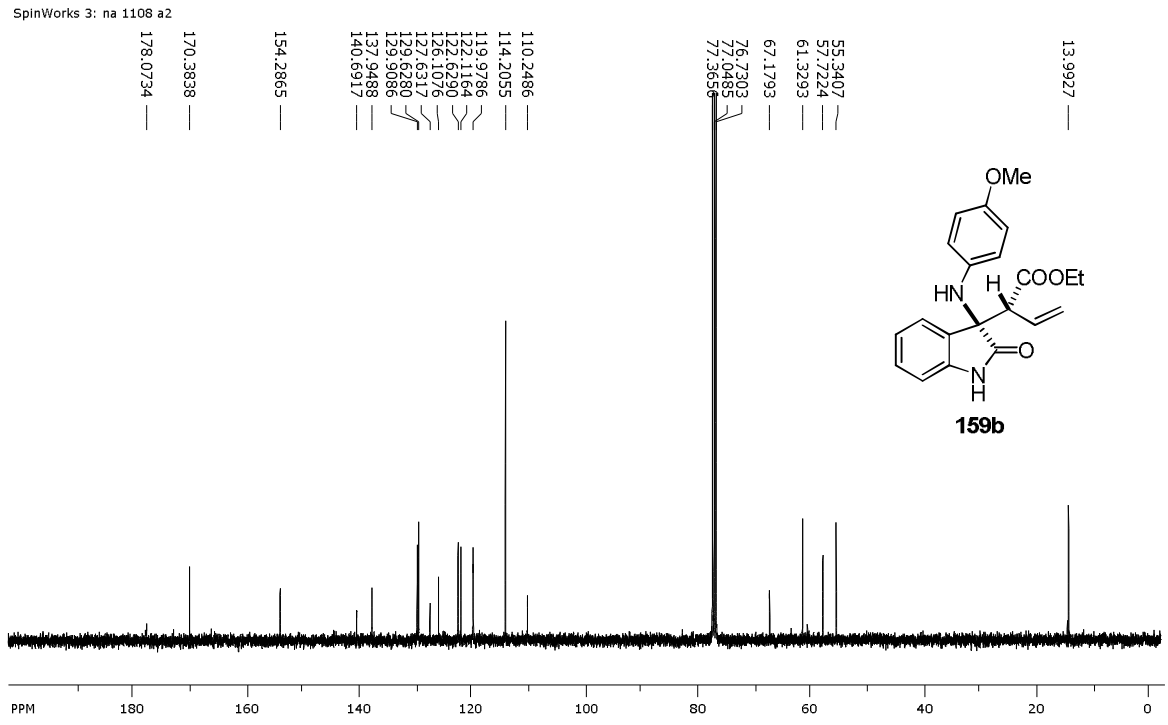
SpinWorks 3: Na852a Proton test

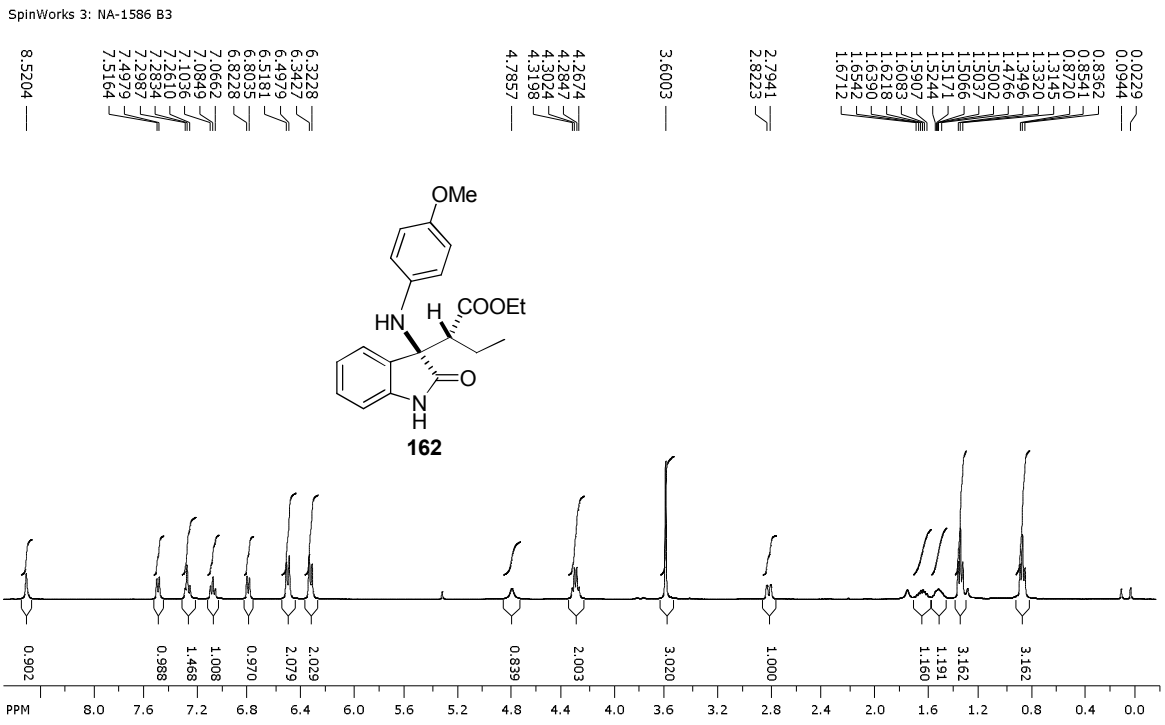



SpinWorks 3: Na852a Carbon test




SpinWorks 3: NA 1108 A2
8.4203
7.4601
7.4416
7.2851
7.2697
7.2504
7.0931
7.0742
7.0554
6.7970
6.7776
6.5370
6.5148
6.4020
6.3796
6.0136
5.9887
5.9710
5.9635
4.1315
4.1226
4.1136
4.1050
4.0957
3.5741
3.5494
3.6160
1.2046
1.1867
1.1689
0.991
0.986
1.255
1.039
1.005
2.005
1.984
1.000
2.007
2.148
4.133
3.144
PPM
OMe
HN
H
COOEt
O
N
H
159b


SpinWorks 3: na 1108 a2
178.0734
170.3838
154.2865
140.6917
137.9488
129.9086
129.6280
127.6317
126.1076
122.6290
122.1164
119.9786
114.2055
110.2486
77.3656
77.0485
76.7303
67.1793
61.3293
57.7224
55.3407
13.9927
PPM
OMe
HN
H
COOEt
O
N
H
159b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7.1036
7.0849
7.0662
6.8228
6.8035
6.5181
6.4979
6.3427
6.3228
4.7857
4.3198
4.3024
4.2847
4.2674
3.6003
2.8223
2.7941
1.6712
1.6542
1.6390
1.6218
1.6083
1.5907
1.5244
1.5171
1.5066
1.5037
1.5002
1.4766
1.3496
1.3320
1.3145
0.8720
0.8541
0.8362
0.0944
0.0229
OMe
HN
H
COOEt
O
N
H
162
0.902
0.988
1.468
1.008
0.970
2.079
2.029
0.839
2.003
3.020
1.000
1.160
1.191
3.162
3.162
PPM
8.0
7.6
7.2
6.8
6.4
6.0
5.6
5.2
4.8
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1.6
1.2
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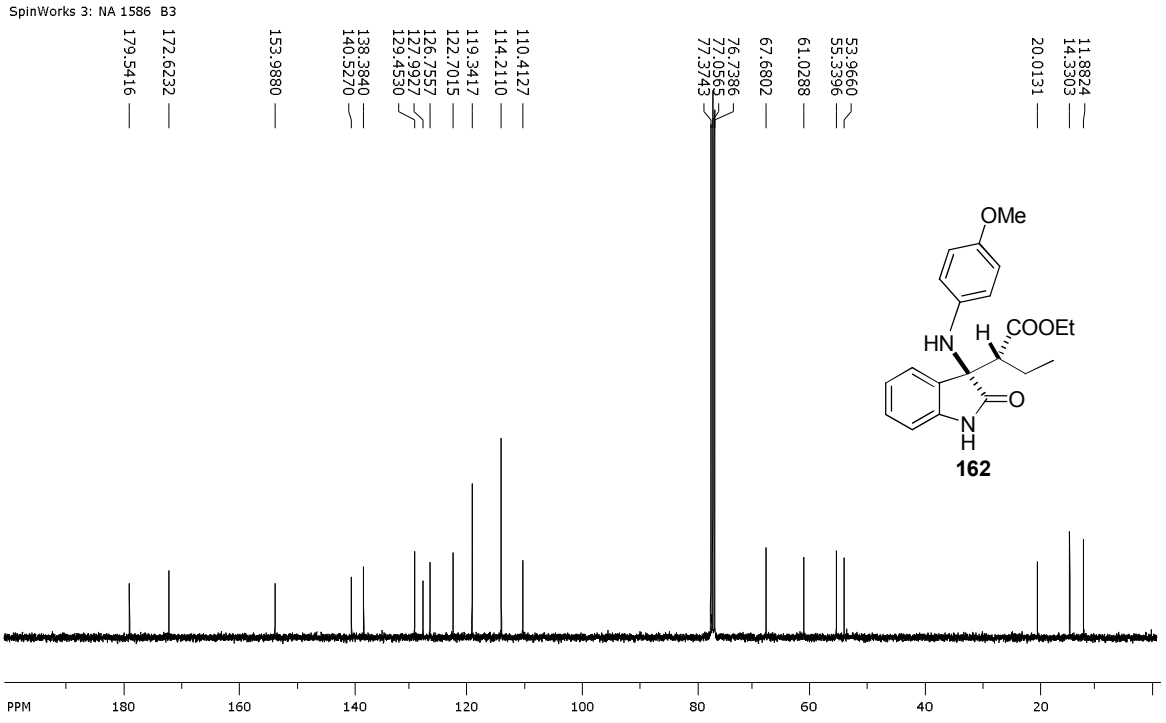
0.4
0.0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153.9880
140.5270
138.3840
129.4530
127.9927
126.7557
122.7015
119.3417
114.2110
110.4127
77.3743
77.0565
76.7386
67.6802
61.0288
55.3396
53.9660
20.0131
14.3303
11.8824
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HN
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COOEt
O
N
H
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PPM
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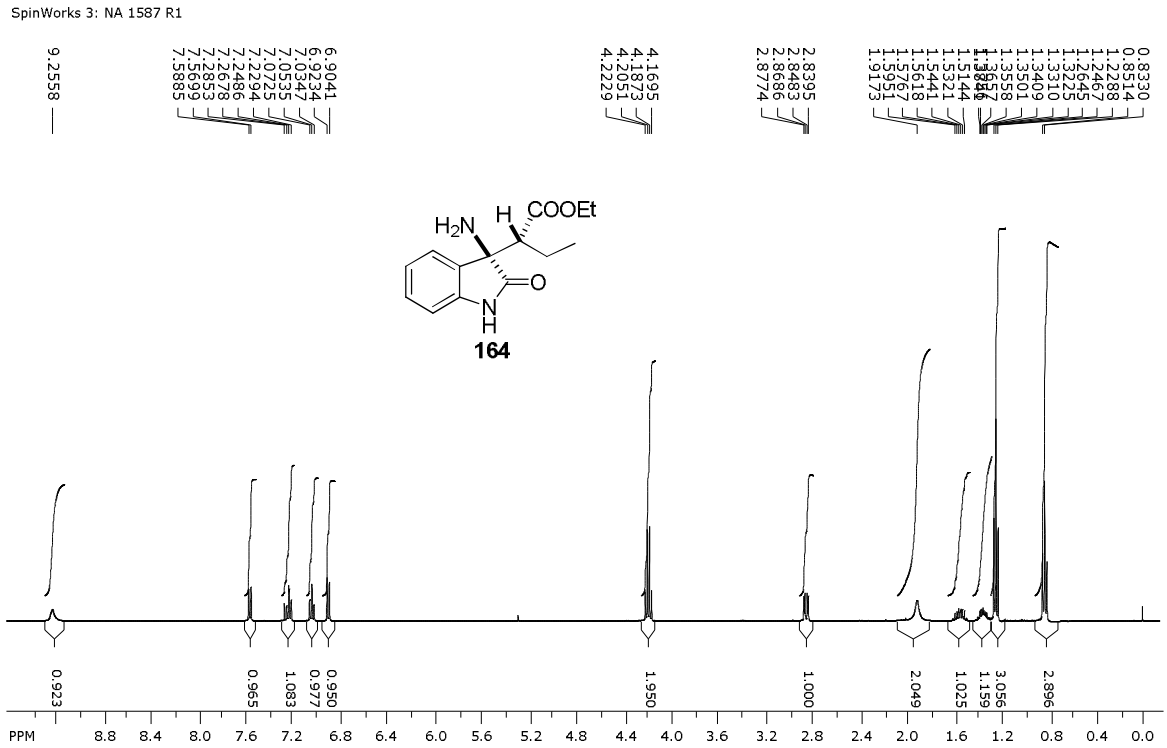
160
140
120
100
80
60
40
20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7.2853
7.2678
7.2486
7.2294
7.0725
7.0535
7.0347
6.9234
6.9041
4.2229
4.2051
4.1873
4.1695
2.8774
2.8686
2.8483
2.8395
1.9173
1.5951
1.5767
1.5618
1.5441
1.5321
1.5144
1.3558
1.3501
1.3409
1.3310
1.3225
1.2645
1.2467
1.2288
0.8514
0.8330
H2N
H
COOEt
O
N
H
164
0.923
0.965
1.083
0.977
0.950
1.950
1.000
2.049
1.025
1.159
3.056
2.896
PPM
8.8
8.4
8.0
7.6
7.2
6.8
6.4
6.0
5.6
5.2
4.8
4.4
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3.6
3.2
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2.4
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1.6
1.2
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0.4
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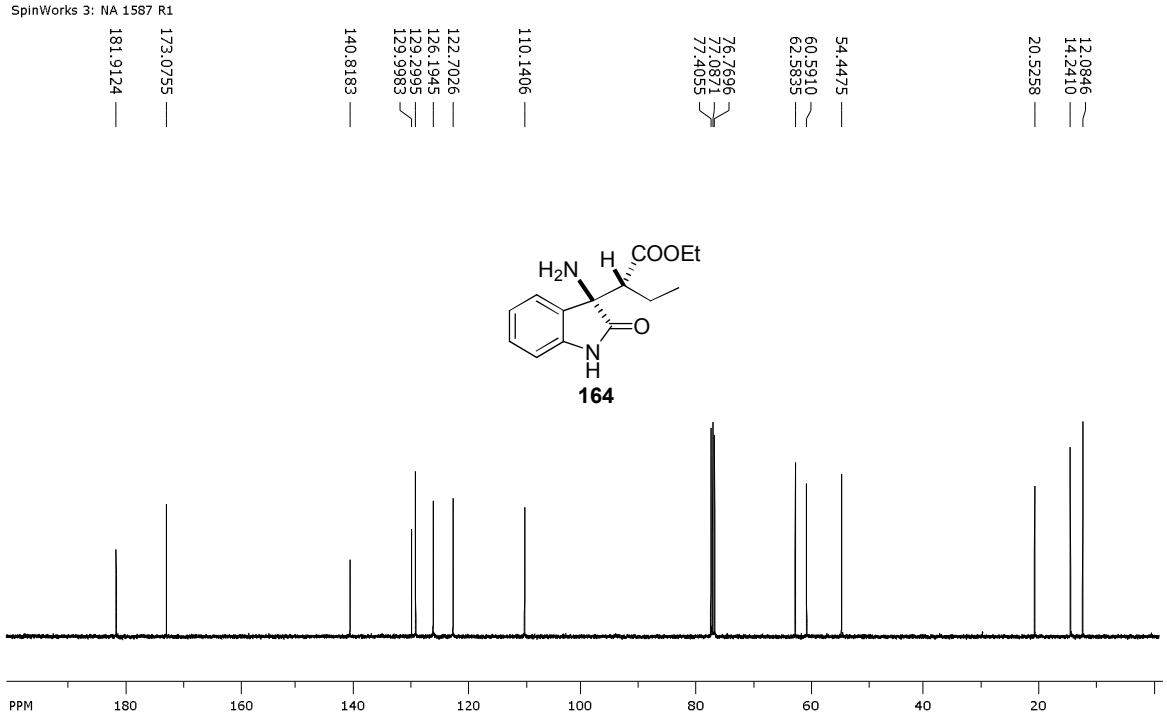
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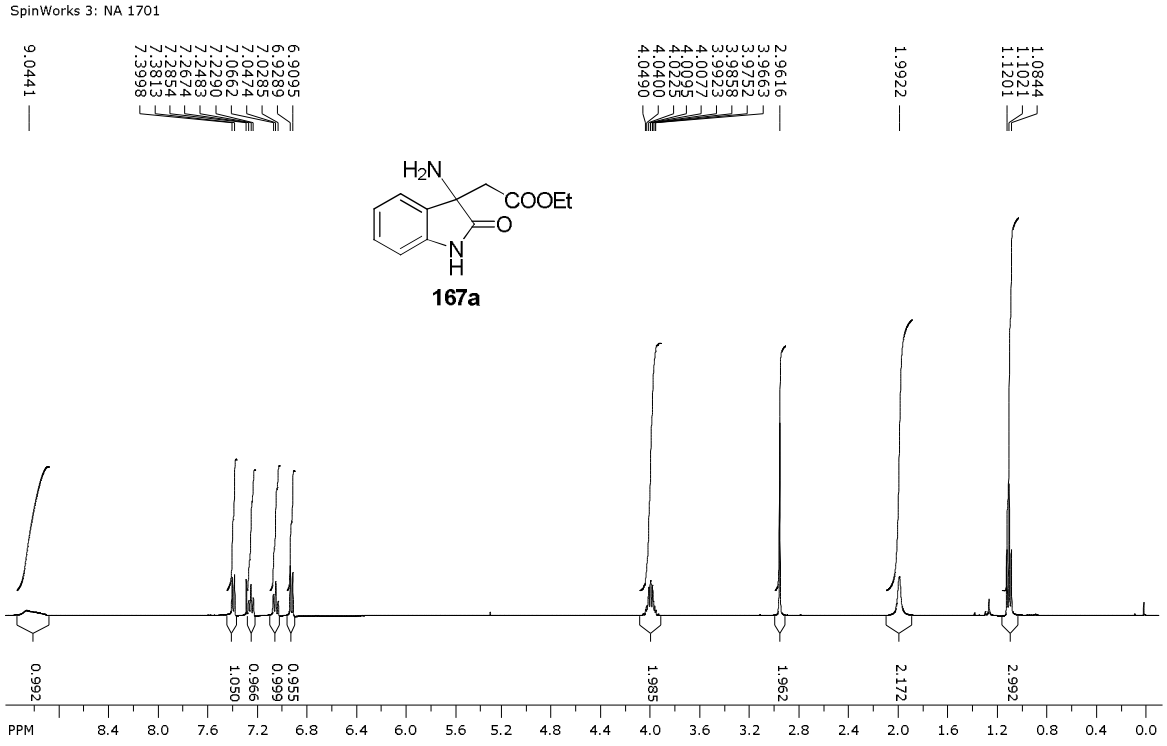
77.4055
77.0871
76.7696
62.5835
60.5910
54.4475
20.5258
14.2410
12.0846
H2N
H
COOEt
O
N
H
164
PPM
180
160
140
120
100
80
60
40
20


SpinWorks 3: NA 1701
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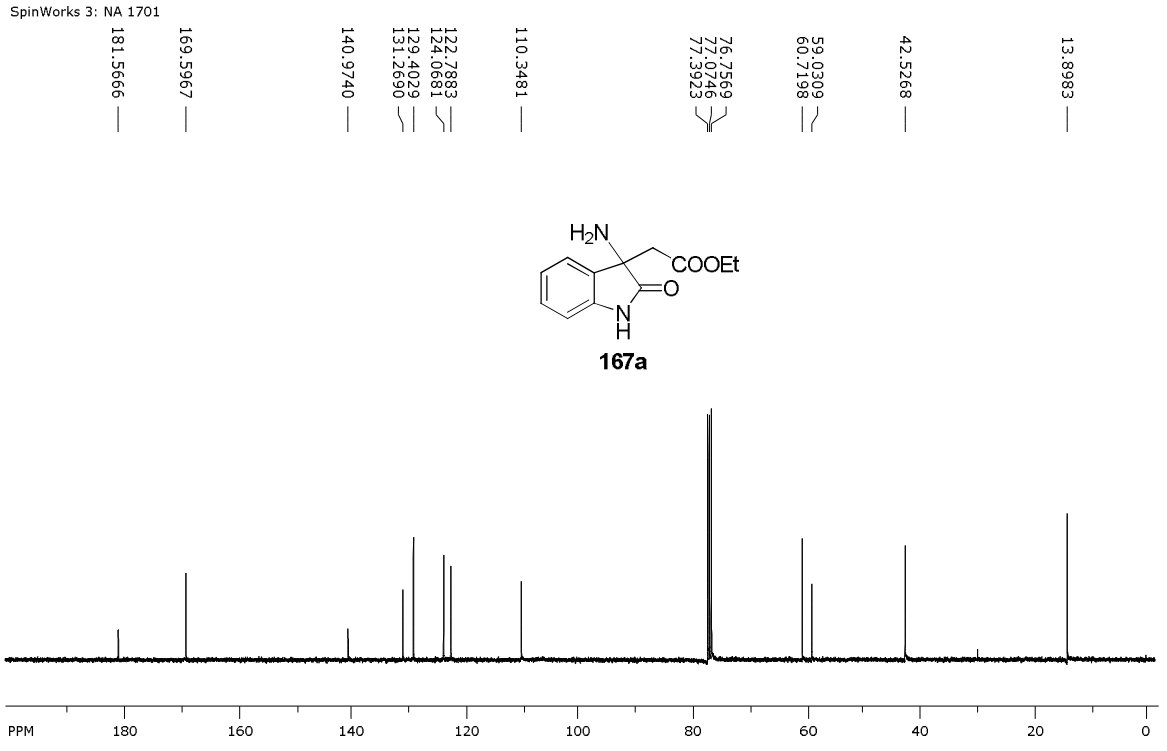
7.3813
7.2854
7.2674
7.2483
7.2290
7.0662
7.0474
7.0285
6.9289
6.9095
4.0490
4.0400
4.0225
4.0077
3.9923
3.9858
3.9752
3.9663
2.9616
1.9922
1.1201
1.1021
1.0844
H2N
COOEt
O
N
H
167a
0.992
1.050
0.966
0.999
0.955
1.985
1.962
2.172
2.992
PPM
8.4
8.0
7.6
7.2
6.8
6.4
6.0
5.6
5.2
4.8
4.4
4.0
3.6
3.2
2.8
2.4
2.0
1.6
1.2
0.8
0.4
0.0


SpinWorks 3: NA 1701
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129.4029
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77.3923
77.0746
76.7569
60.7198
59.0309
42.5268
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COOEt
O
N
H
167a
PPM
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140
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20
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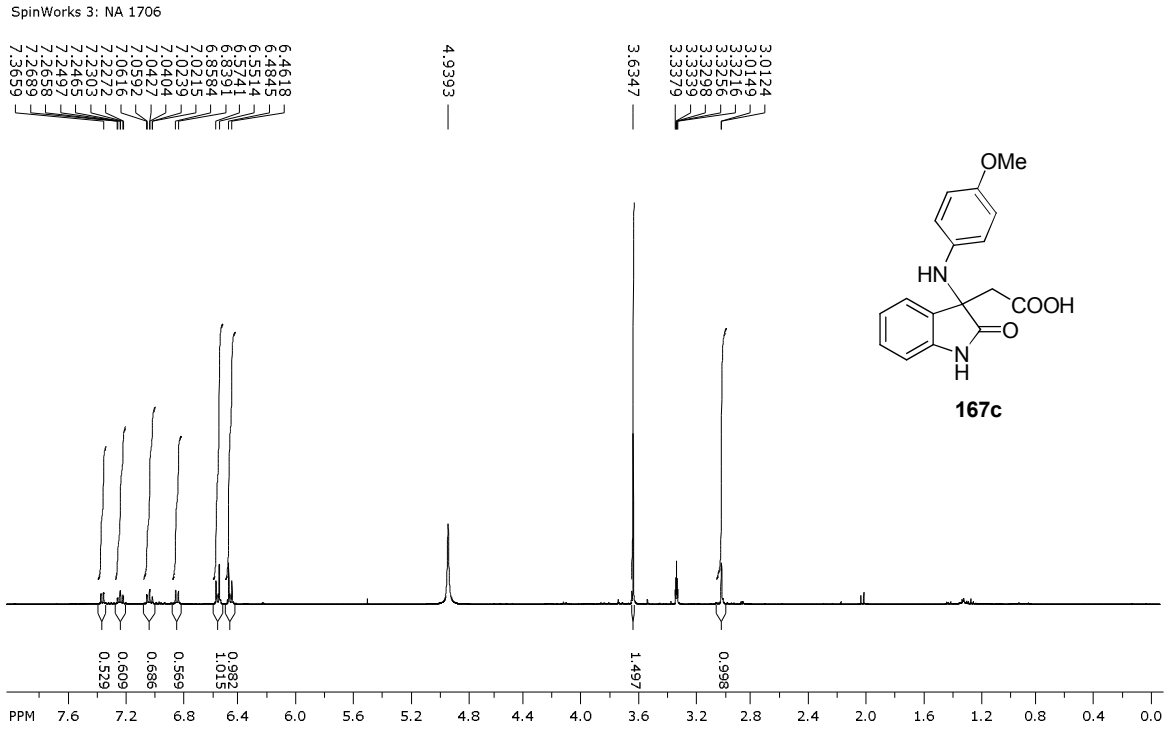
SpinWorks 3: NA 1706
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7.2689
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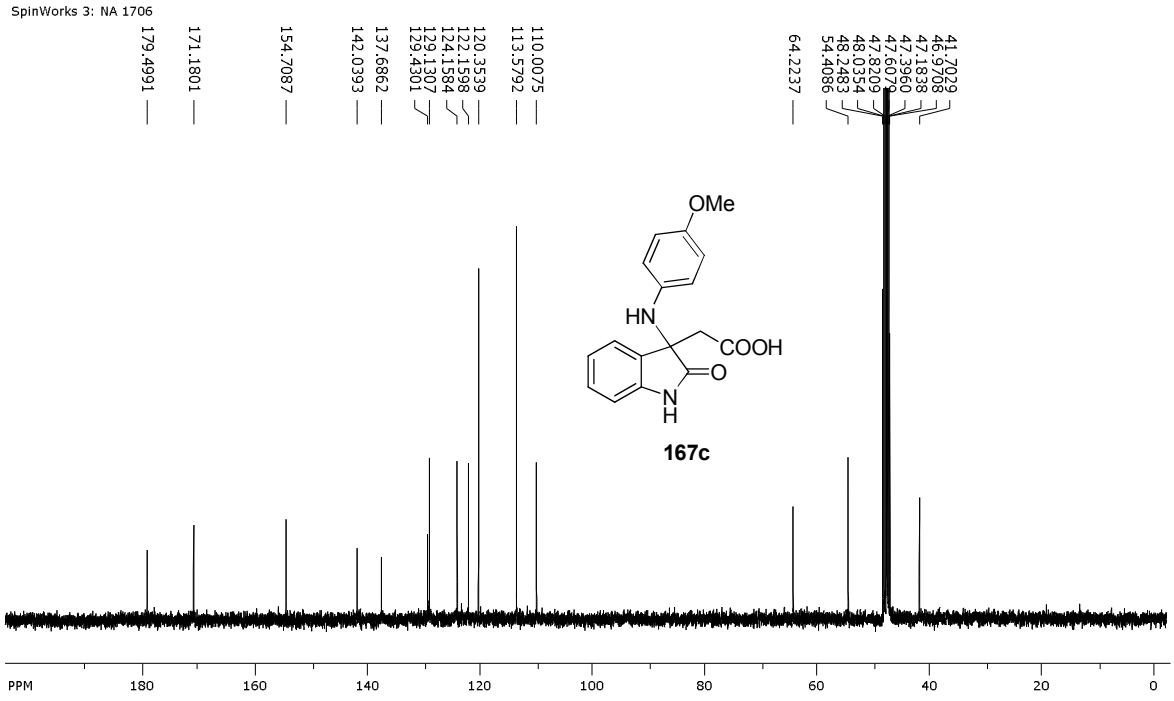
7.2497
7.2465
7.2303
7.2272
7.0616
7.0592
7.0427
7.0404
7.0239
7.0215
6.8584
6.8391
6.5741
6.5514
6.4845
6.4618
4.9393
3.6347
3.3379
3.3339
3.3298
3.3256
3.3216
3.0149
3.0124
OMe
HN
COOH
O
N
H
167c
0.529
0.609
0.686
0.569
0.982
1.015
1.497
0.998
PPM 7.6 7.2 6.8 6.4 6.0 5.6 5.2 4.8 4.4 4.0 3.6 3.2 2.8 2.4 2.0 1.6 1.2 0.8 0.4 0.0


SpinWorks 3: NA 1706
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122.1598
120.3539
113.5792
110.0075
64.2237
54.4086
48.2483
48.0354
47.8209
47.6079
47.3960
47.1838
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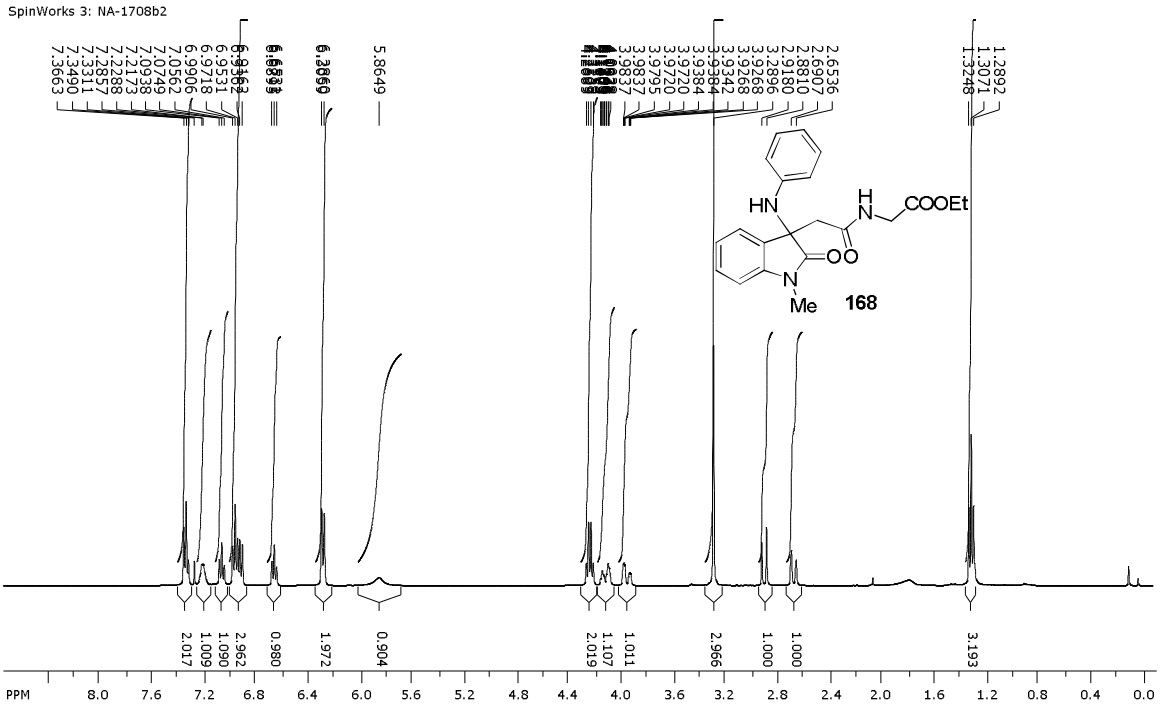
41.7029
OMe
HN
COOH
O
N
H
167c
PPM 180 160 140 120 100 80 60 40 20 0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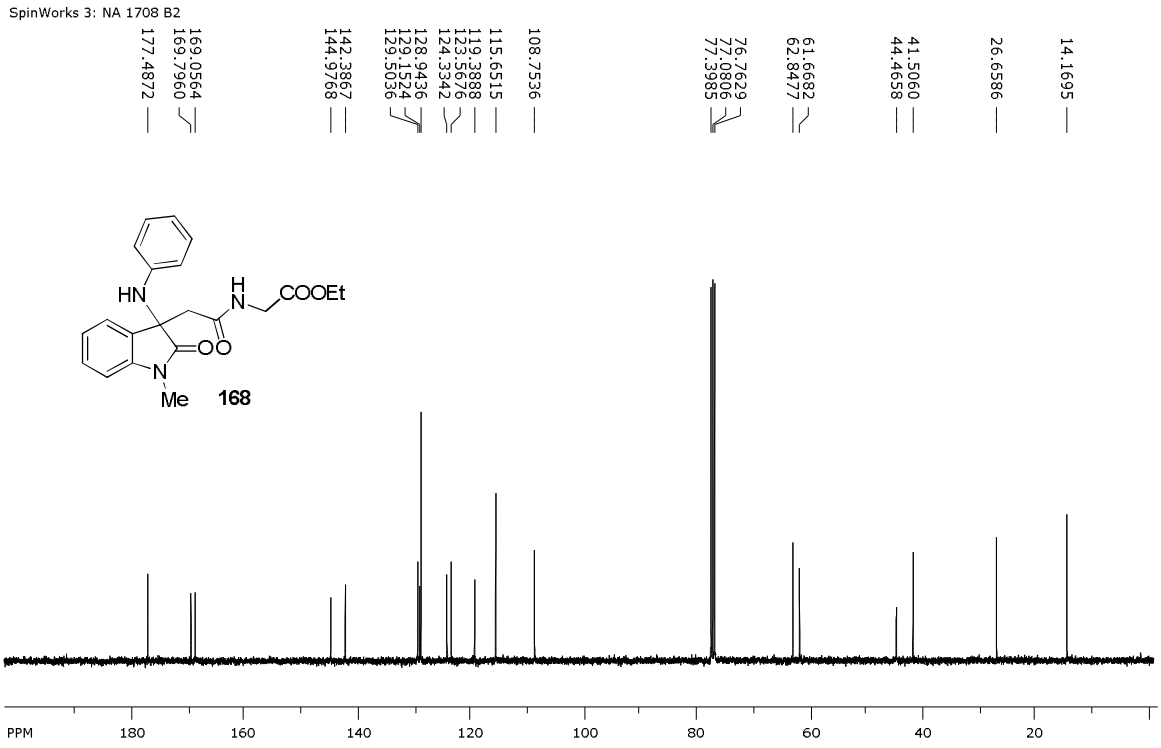
H
N
COOEt
O
O
N
Me
168
PPM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N
COOEt
O
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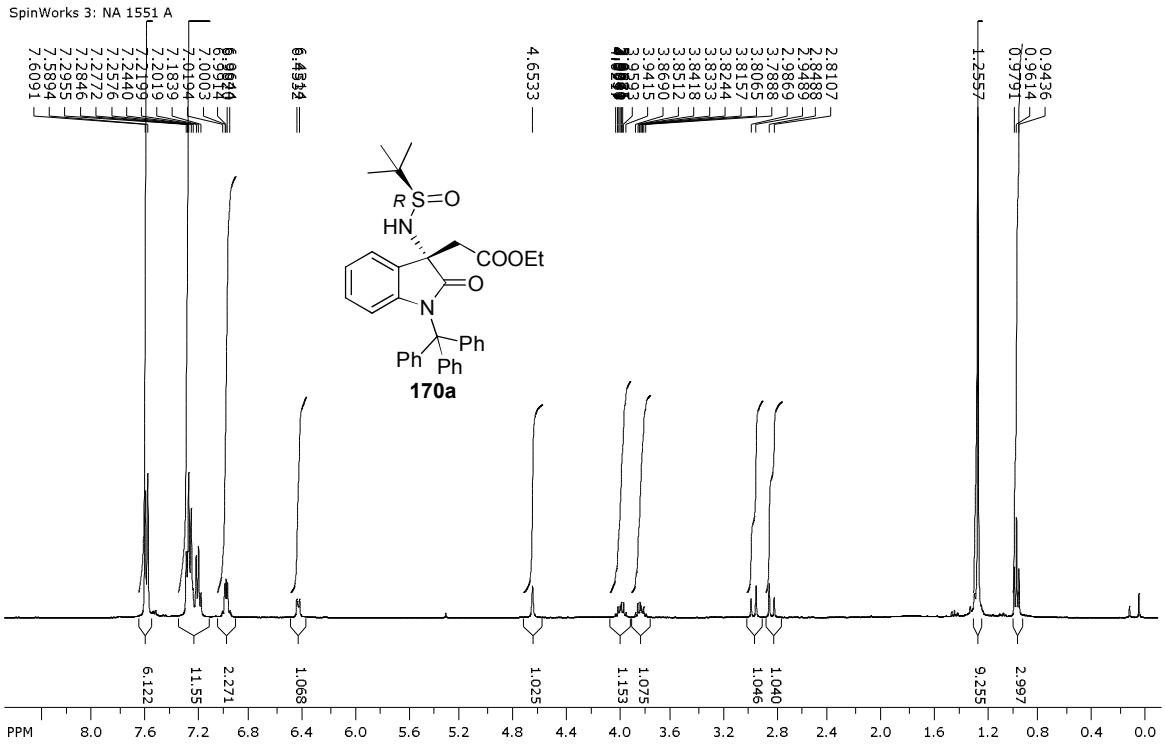
Me
168
PPM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COOEt
O
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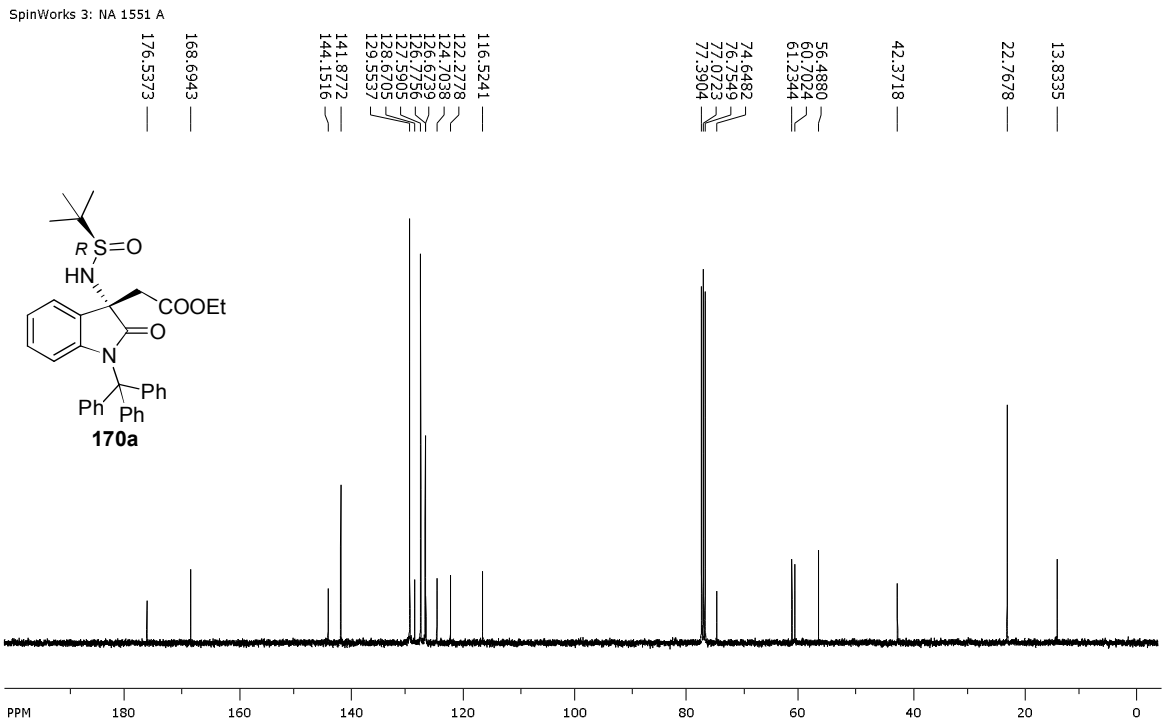
Ph
Ph
Ph
170a
PPM


SpinWorks 3: NA 1551 A
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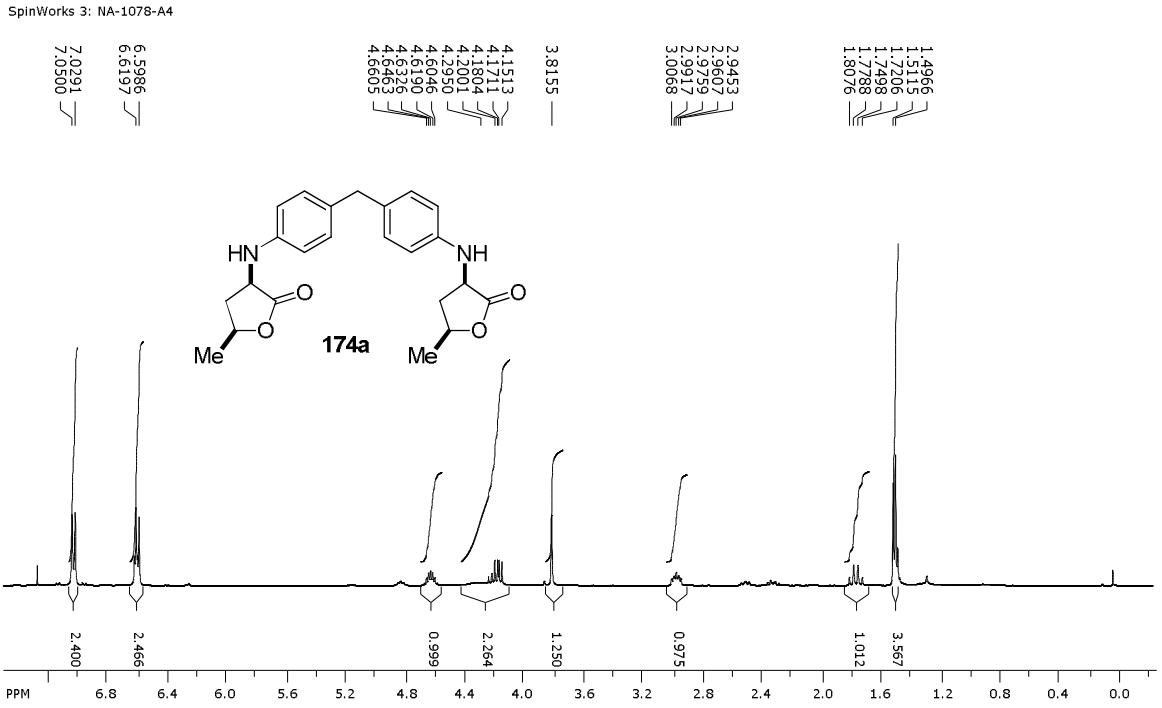
COOEt
O
N
Ph
Ph
Ph
170a
PPM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4.6463
4.6326
4.6190
4.6046
4.2950
4.2001
4.1804
4.1711
4.1513
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3.0068
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2.9607
2.9453
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1.7206
1.5115
1.4966
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O
O
O
O
Me
Me
174a
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PPM
6.8
6.4
6.0
5.6
5.2
4.8
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1.6
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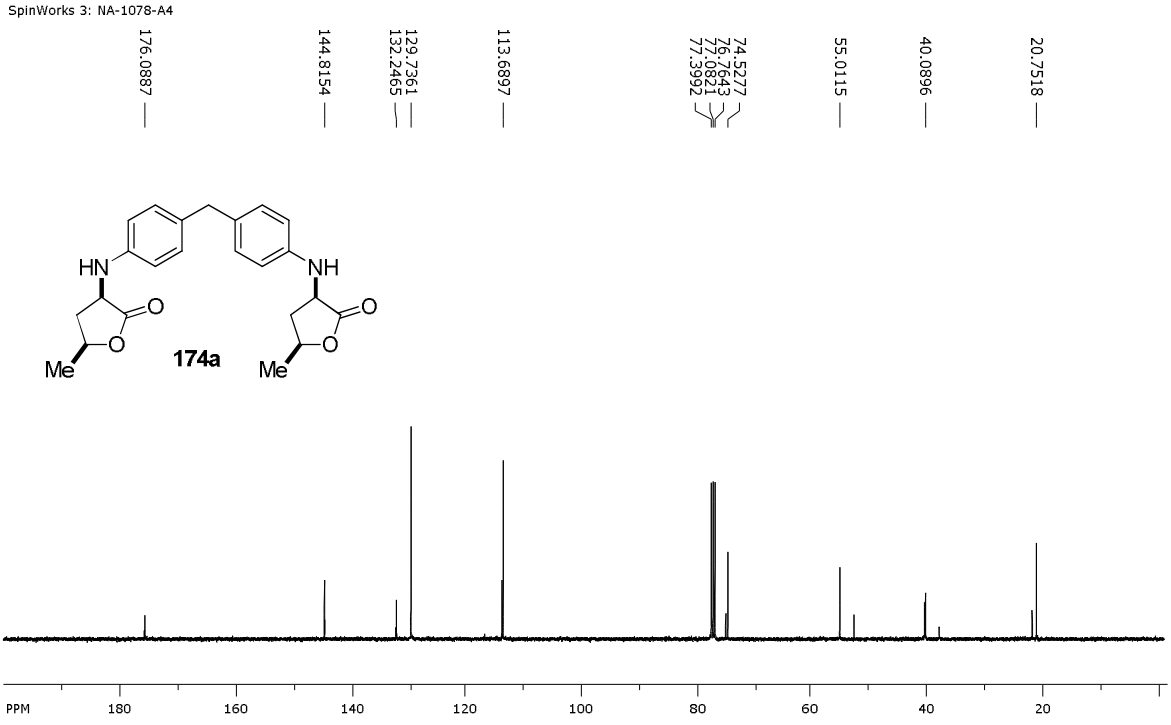
0.0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O
O
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Me
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80
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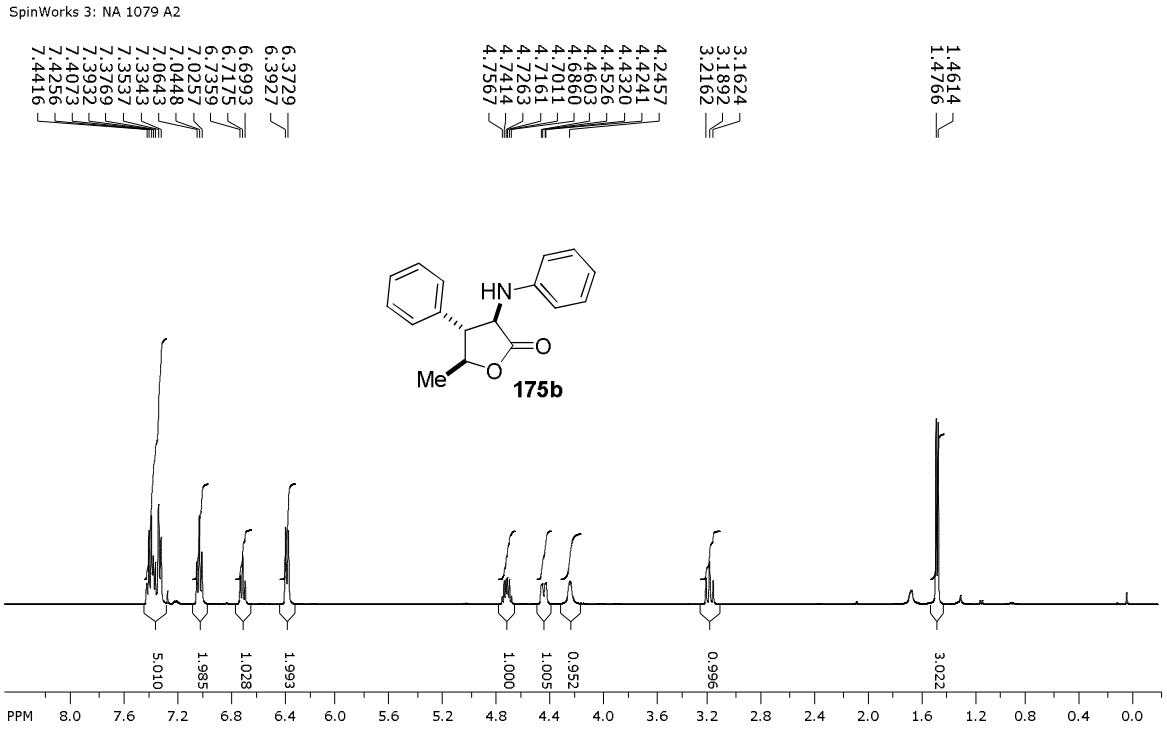
40
20


SpinWorks 3: NA 1079 A2
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7.3769
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7.3343
7.0643
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7.0257
6.7359
6.7175
6.6993
6.3927
6.3729
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4.7414
4.7263
4.7161
4.7011
4.6860
4.4603
4.4526
4.4320
4.4241
4.2457
3.2162
3.1892
3.1624
1.4766
1.4614
HN
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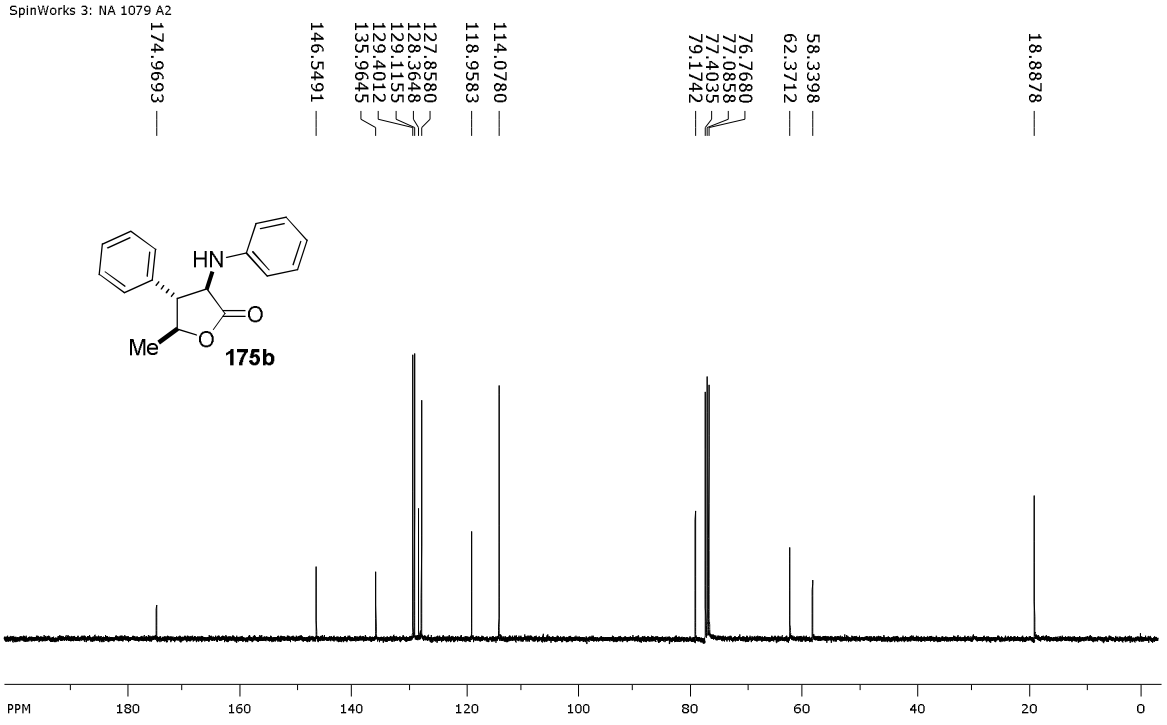
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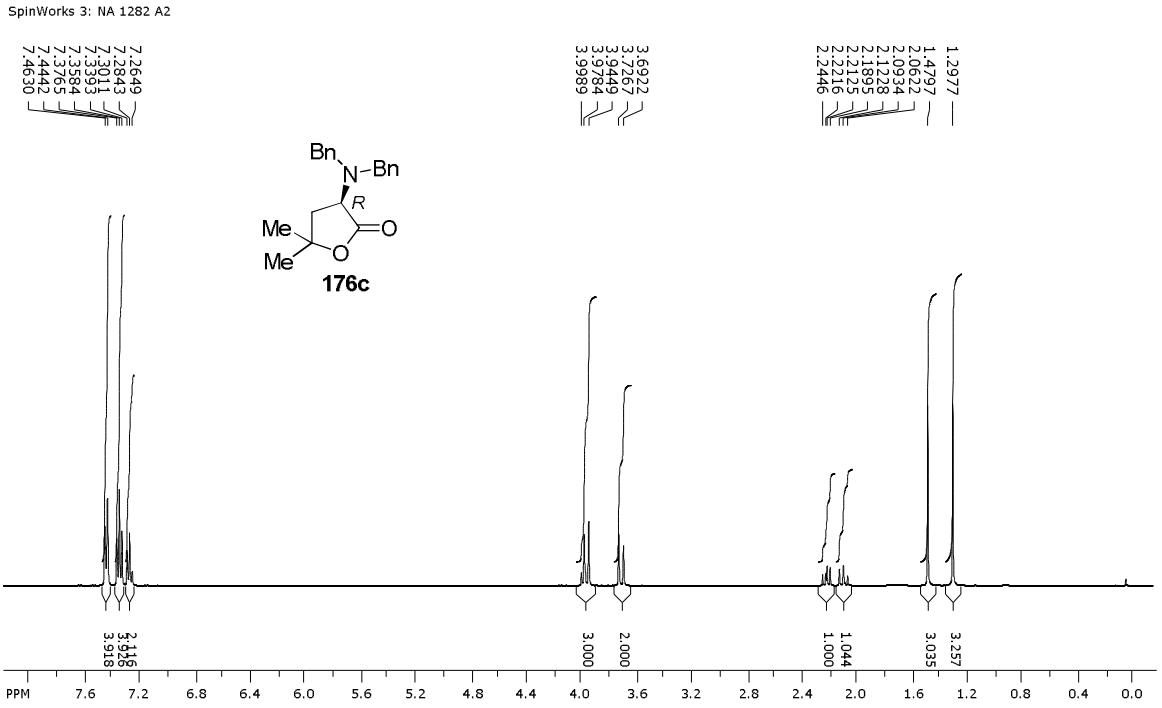
PPM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3.9449
3.7267
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2.1228
2.0934
2.0622
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1.2977
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Bn
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2.000
1.000
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5.2
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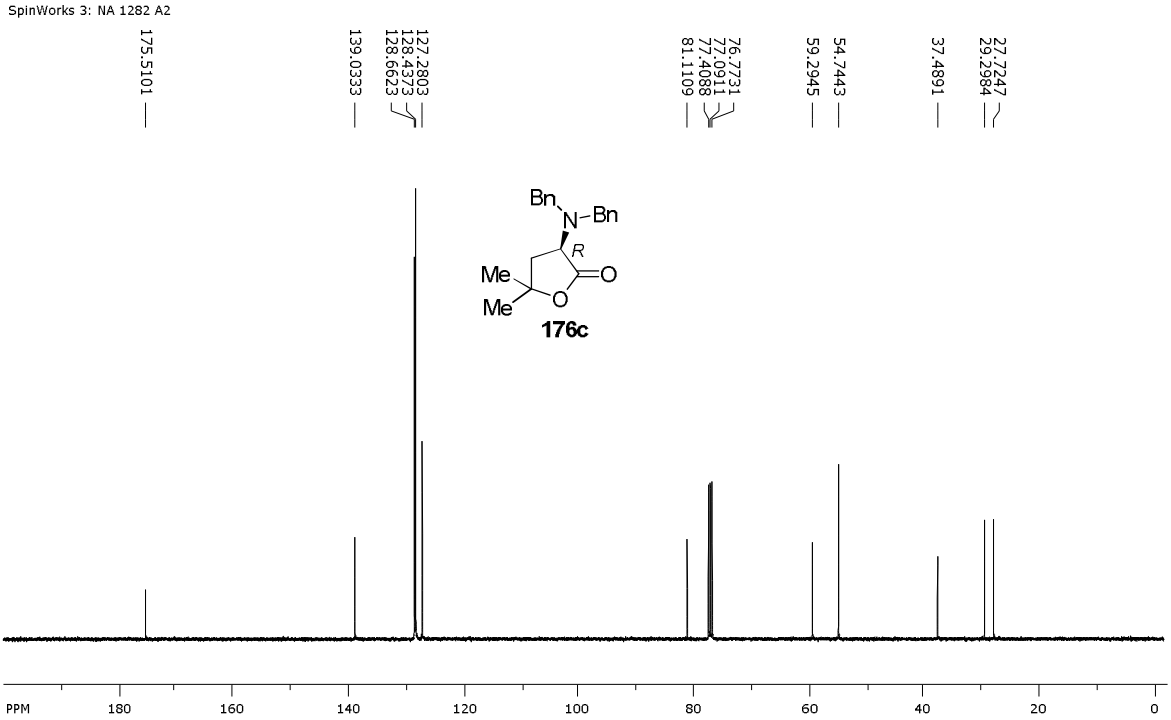
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77.0911
76.7731
59.2945
54.7443
37.4891
29.2984
27.7247
Bn
N
Bn
R
Me
Me
O
O
176c
PPM
180
160
140
120
100
80
60
40
20
0