Transfer Hydrogenation of imines using pentacarbomethoxycyclopentadiene(PCCP) as a catalyst and Hantzsch ester as a Hydrogen source

Vinod Gour

MS16078

A dissertation submitted for the partial fulfillment of

the degree of BS-MS degree in Science

Department of Chemical Sciences

Indian Institute of Science Education and Research Mohali

May 2021

Transfer Hydrogenation of imines using pentacarbomethoxycyclopentadiene(PCCP) as a catalyst and Hantzsch ester as a Hydrogen source

Vinod Gour

MS16078

A dissertation submitted for the partial fulfillment of

the degree of BS-MS degree in Science

Department of Chemical Sciences

Indian Institute of Science Education and Research Mohali

May 2021

Dedicated

To

My Beloved Parents and Friends

For their love, support, and encouragement

Certificate of Examination

This is to certify that the dissertation titled “**Transfer hydrogenation of imines using pentacarbomethoxycyclopentadiene as a catalyst and hantzsch ester as a hydrogen source**” submitted by Mr. Vinod gour (Reg. No. MS16078) for the partial fulfillment of the BS-MS degree program of the Institute, has been examined by the thesis committee duly appointed by the Institute. The committee finds the work done by the candidate satisfactory and recommends that the report be accepted.

25/5/2021

Dr. Sugumar Venkataramani
Assoc. Professor
IISER Mohali

Dr. S. S. V. Rama Sastry
Assoc. Professor
IISER Mohali

Dr. R Vijaya anand
Assoc. Professor
IISER Mohali
(Supervisor)

Date:

Declaration

The work presented in this dissertation has been carried out by me under the guidance of Dr. R. Vijaya Anand at the Department of Chemical Sciences, Indian Institute of Science Education and Research Mohali.

This work has not been submitted in part or in full for a degree, a diploma, or a fellowship to any other university or institute. Whenever contributions of others are involved, every effort is made to indicate this clearly, with due acknowledgment of collaborative research and discussions. This thesis is a bonafide record of original work done by me, and all sources listed within have been detailed in the bibliography.

Vinod Gour

Date:

Place:

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

25/5/2021

Dr. R. Vijaya Anand

Associate professor

Department of chemical science

Indian Institute of Science Education and Research, Mohali

Date:

Place:

Acknowledgement

First and foremost, I would like to express my sincere gratitude to my thesis supervisor Dr. R. Vijaya Anand for his constant support and encouragement throughout my MS thesis. On many occasions, he had given me valuable suggestions that directed me towards the right path and motivated me to learn a new entity. I am feeling blessed and grateful for submitting my master thesis under his guidance.

I would especially want to thank my committee members Dr. Sugumar Venkataramani and Dr. S. S. V. Rama Sastry for their invaluable discussions and suggestions and for evaluating my research improvement yearly by spending their valuable time.

Furthermore, I would like to express my heartful thanks to my brilliant labmates, Dr. Akshi Tyagi, Mr. Yogesh Pankhade, Mr. Feroz Ahmed, Mr. Pavit Kumar, Mr. Rajat Pandey, Mr. Gurdeep Singh, Ms. Sonam Sharma, Mrs. Rekha Yadav, Ms. Shaeen Fatma, Mr. Arjun and Mr. Adarsh for their valuable discussions, cooperation and also for creating a healthy environment around me. I am grateful to Mr. Rajat Pandey and Mr. Gurdeep Singh for their help and guidance during my stay.

I am also thankful to Mr. Balbir and Mr. Triveni, and the chemistry teaching lab assistants for their cooperation during my research period for their help.

I want to express my gratitude towards all my beloved friends, especially Ijaz (Giddu), Abhimanyu, Mayank, Anshul, Shikhar, Kusha, Kimaya, Srinivas, Satendar, Abhijeet, Sasank and Mohak. They stood by me even when I lost my hopes, and they shared all my ups and downs on many occasions.

Last but most significant, it gives me immense pleasure to express my gratitude to **my beloved parents, brothers, and sisters**. They have always believed in me and supported me with unconditional love throughout my life.

Contents

List of Figures

List of Schemes

List of Tables

Notation and Abbreviations

cm	Centimeter
δ	Chemical shift
CDCl3	Chloroform-D
J	Coupling constant
DCM	Dichloromethane
$CHCl_3$	Chloroform
THF	Tetrahydrofuran
KOAc	Potassium acetate
PhMe	Toluene
d	Doublet
dd	Doublet of doublet
ddd	Doublet of doublet of doublet
dt	Doublet of triplets
EWG	Electron withdrawing group
EDG	Electron donating group
°C	Degree celsius
dr	Diastereomeric ratio
EtOAc	Ethylacetate
equiv	Equivalents
FT-IR	Fourier transform infrared spectroscopy
HEH	hantzsch ester
Hz	Hertz
H	Hours

m.p	melting point
mg	Milligram(s)
NMR	Nuclear Magnetic Resonance
PCCP	Penta-carbomethoxycyclopentadiene
q	Quartet
R_f	Retention factor
rt	room temperature
s	singlet
TLC	Thin Layer Chromatography
t	Triplet
td	Triplet of doublets
tt	Triplet of triplet

Abstract

Transfer hydrogenation of imines catalysed by Pentacarbomethoxycyclopentadiene (PCCP) using Hantzsch ester as a Hydrogen source has been achieved. A wide range of secondary amines could be obtained in moderate to good yield.

Chapter 1

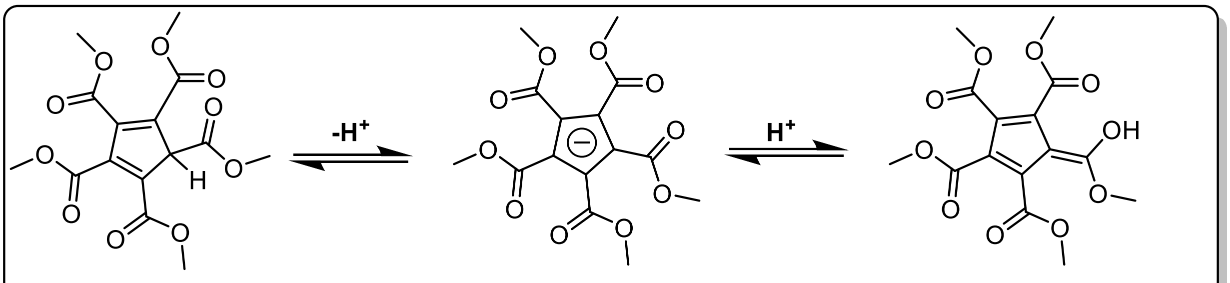
1. Introduction

1.1 Brønsted-Lowry acid-base theory

In 1923, Johannes Nicolaus Brønsted and Thomas Martin Lowry independently proposed the Brønsted-Lowry acid-base theory. According to the theory, Brønsted-Lowry acids are proton donors, and Brønsted-Lowry bases are proton acceptors. On losing the proton, the acid is converted into a corresponding conjugate base while accepting the proton forms the conjugate acid. The mechanism of Brønsted acid catalysis involves the activation of the electrophile via the initial transfer of protons from the Brønsted acid making the electrophile more susceptible towards a nucleophile. The field of Brønsted acid catalysis in the literature is boundless however, mainly dominated by the BINOL-derived phosphoric acids and their derivatives. Initially, these BINOL-derived phosphoric acids were used as resolving agents for chiral amines[1] but, later on in 1992, this Brønsted acid promotes enantioselective cyclization of rhodium carbenes generated from diazo-compounds. Chiral BINOL derived phosphoric acids are very much valued for their ability to catalyse asymmetric transformations. In 2004 Akiyama was one of the first person to be credited for his discovery of the role of phosphoric acids used as organocatalysts in the chiral Mannich reaction of 2-hydroxyphenylimines with silyl ketene acetals.[2,3] Since then, chiral BINOL-derived phosphoric acids catalyse many reactions and allow the formation of new C−C, C−H, and a range of C−X bonds in a highly enantioselective manner.

1.2. Comparison of BINOL derived phosphoric acids with PCCP

The phosphoryl oxygen present on the BINOL derived phosphoric acids act as a Lewis base, which helps in the coordination during bifunctional catalytic methods. Brønsted acid lowers the LUMO of electrophile via protonation and triggers the electrophile towards the nucleophiles.[4] However there are some downsides and one of the major downsides was its extended synthetic route, laborious, and high-cost protocol required, which restricted the optimisation and their application on scale. Hence an alternative to such phosphoric acid catalysts if available is an important need of the hour. Then chemists characterise Carbon acid platform for enantioselective Brønsted acid catalysis that uses aromaticity as its central acidifying component. Cyclopentadiene is a hydrocarbon with high acidity which results from aromatic stabilization of its conjugate base. The acidity can be increased by the substitution of different electron-withdrawing groups at every carbon of the conjugated system. The cyclopentadienes and their derivatives are highly interesting scaffolds in this regard as the cyclopentadiene anion formed are exceptionally stable (Figure 1). The stability can further be increased by the introduction of electron-withdrawing groups at each of the five carbons of the conjugated system.[5] According to this the highly electron-deficient pentacarbomethoxycyclopentadienes (PCCP) first reported by Otto Diels in 1942 are very crucial scaffolds in this condition.[6] The main reason for the stability and acidity of PCCP are: after the liberation of a proton the PCCP gain the aromaticity due to the presence of 6π electrons and the planar structure, due to inductive effect of electron-withdrawing groups, and the presence of resonance.



1

2
Conjugate base

3
PCCP adopting the Hydroxyfulvene structure

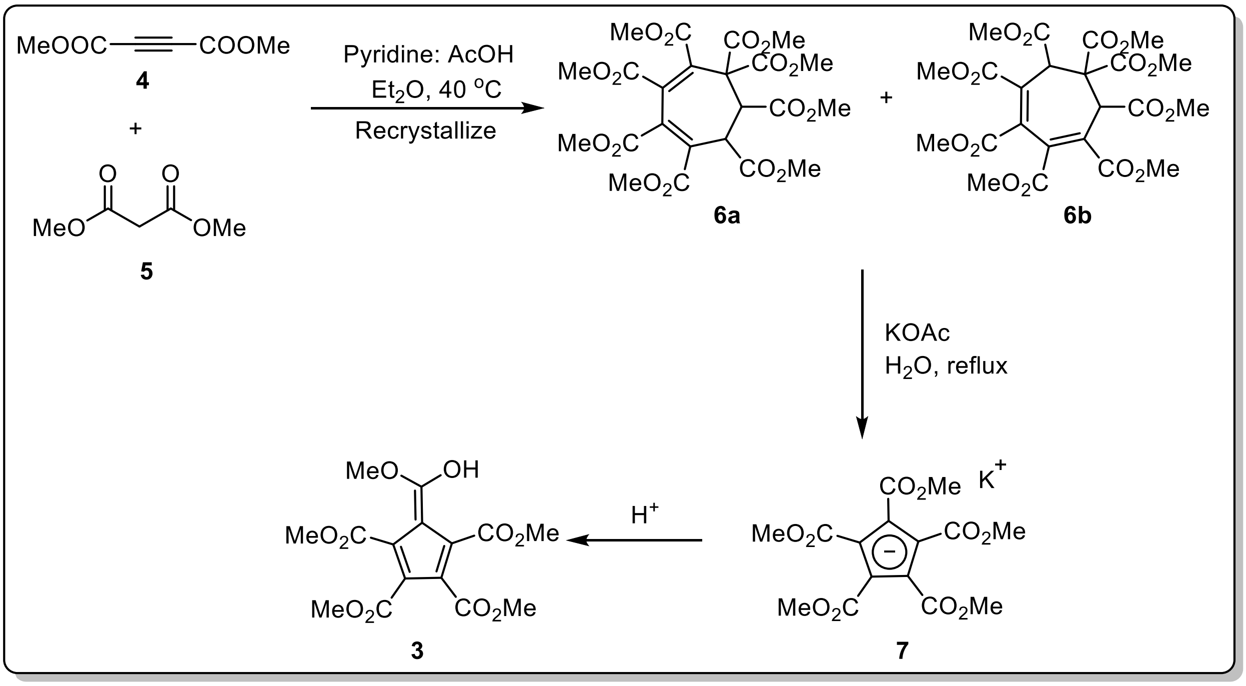
Figure 1: Schematic representation of PCCP

1.3. Synthesis of PCCP

1.3.1. Synthesis of PCCP by Otto Diels

Otto Diels was the first one, who reported the synthesis of PCCP in 1942.[6] The synthetic route mainly consists of two steps. In the first step, one equivalent of dimethyl malonate (DMM) (**4**) was reacted with three equivalents of dimethyl acetylene-dicarboxylate (DMAD) (**5**), which results in an isomeric mixture of two octacarbomethoxy cycloheptadienes **6a** and

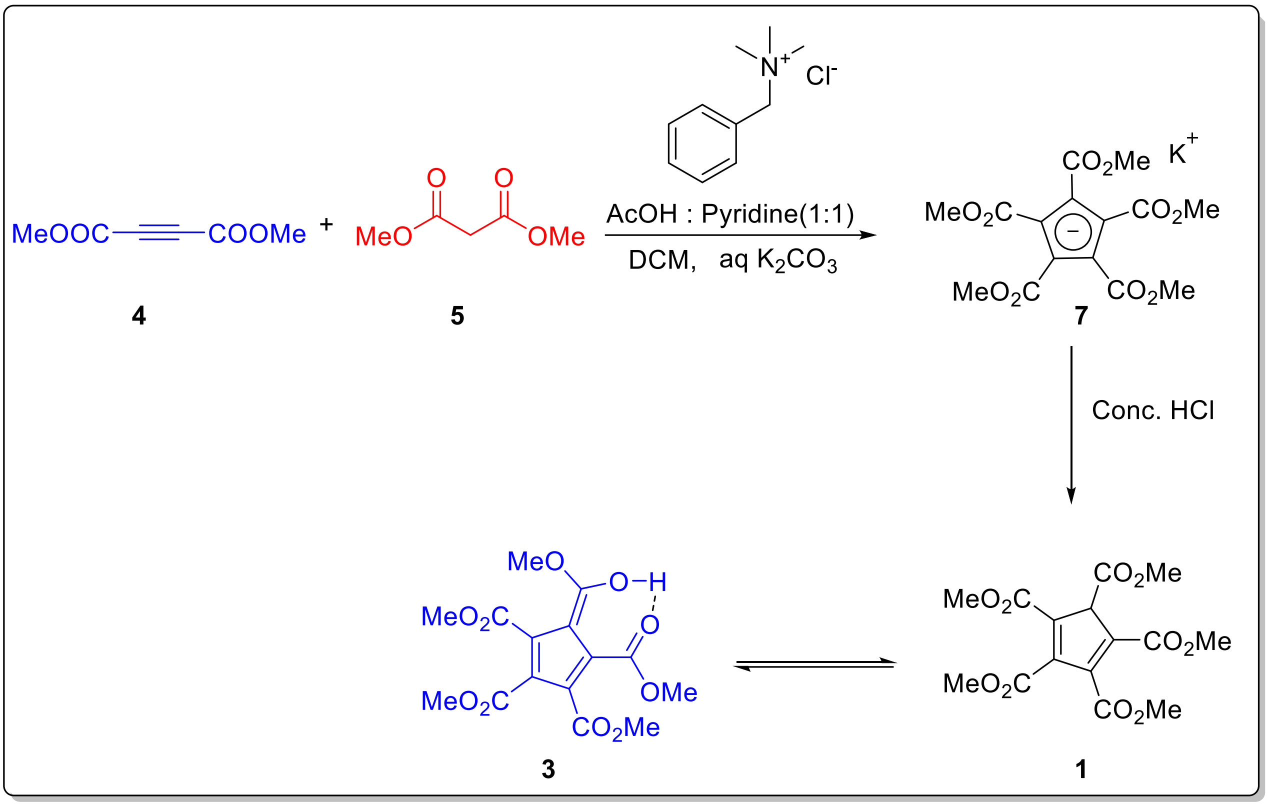
6b. In the next step, these two isomeric mixtures **6a** and **6b** underwent a base (KOAc) mediated ring contraction to gives the potassium salt of PCCP (**7**), which would get precipitated on protonation to give PCCP (**3**)**.** However, the first step of the reaction is highly exothermic and requires constant attention due to the rapid precipitation of the intermediates. There is an additional danger of violent eruption if not the mixture is being continuously cooled. Before the second step, there is an additional requirement of recrystallization without which there would be a significant reduction in the yield formed. Finally, the product formed is highly intractable and would produce additional problems in purification (Scheme 1).



Scheme 1: Synthesis of PCCP as reported by Otto Diels in 1942

1.3.2. One-pot synthesis of PCCP as reported by Lambert

The key requirement for the Lambert group was to develop a synthetic route that was scalable and high-yielding compared to the reported synthesis. Lambert's group managed to overcome these issues by introducing a new scalable one-pot synthesis, which was more user-friendly and less time-consuming (Scheme 2).[7] Moreover, the extreme disadvantage of the uncompromising product formed could be excluded and the product could be collected as a crystalline solid. In this procedure, one equivalent of DMM (**4a**) was reacted with one equivalent of DMAD (**5a**) and the final PCCP (**3a**) was delivered in 48% yield, an improvement of 13% over on unoptimized Diels Synthesis run on a similar scale.

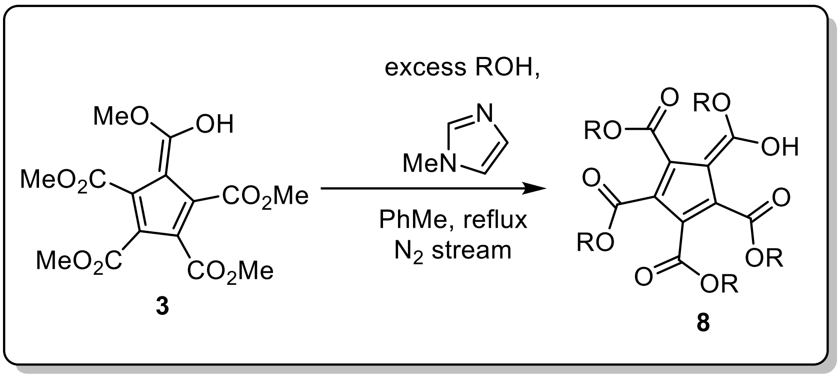


Scheme 2: One-pot synthesis of PCCP as reported by Lambert

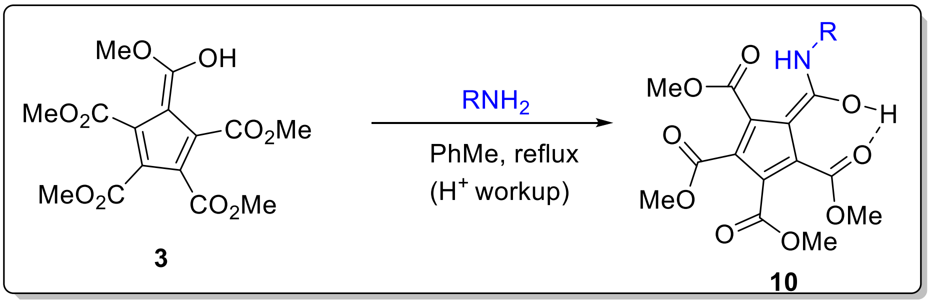
1.3.3 Functionalisation of PCCP

Further, advancing the ability of PCCPs Lambert and co-worker conducted functionalised PCCPs by substituting different EWG via transesterification and transamination reactions. In their report, they mention that they could functionalised PCCP using a variety of alcohols and amines. For the synthesis of different pentacarboxycyclopentadienes, they started from readily available pentacarbomethoxycyclopentadiene (**3**) and transesterification leads to single-step access to aliphatic ester derivatives (**8**) as shown in Scheme 3 also treatment with amines gives mono or diamides as shown in Scheme 4.[8] Among various substituted PCCP

Menthol derived PCCP (**9**) has proved to be quite effective for carrying out enantioselective transformations.



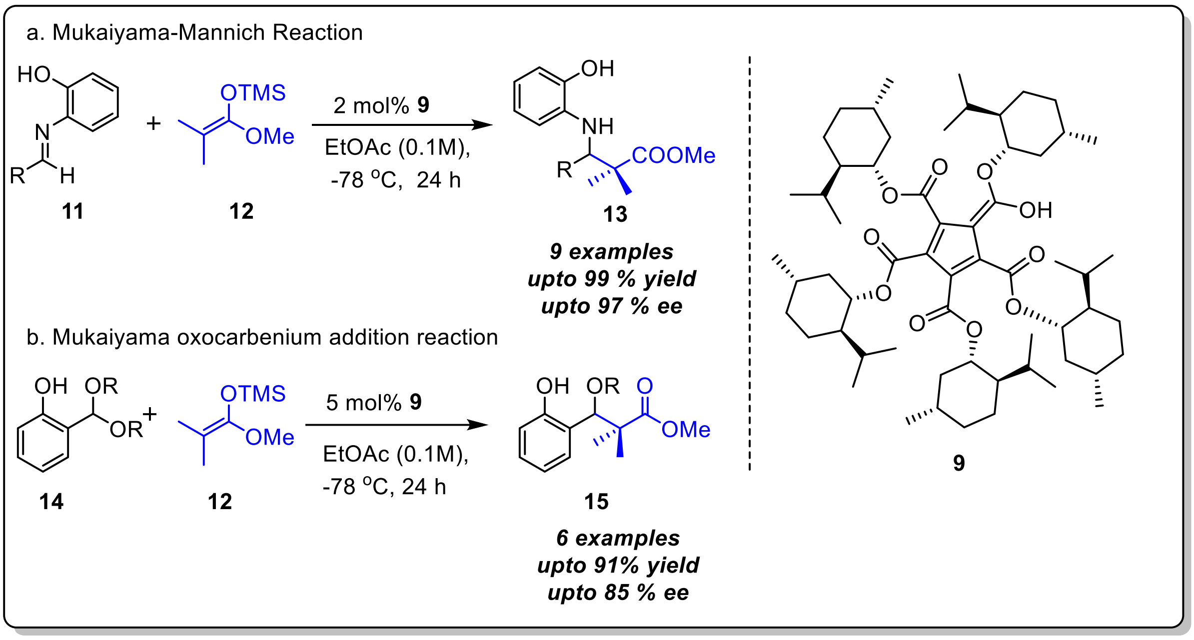
Scheme 3: Synthesis of different PCCPs via transesterification.



Scheme 4: Synthesis of monoamide derivatives.

1.4 Literature reports on chiral Brønsted acids (PCCPs) catalysed transformations

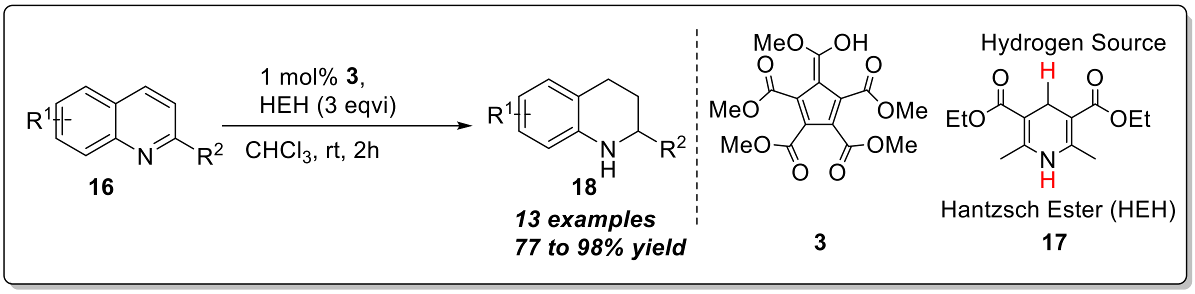
Since PCCPs are newer catalysts, the kind of reactions and substrates that it can catalyse are relatively unknown. Lambert and his group showed that the menthol functionalised PCCP (**9**) was able to catalyse the Mukaiyama Mannich and the Mukaiyama Aldol reactions as shown in Scheme 6.[9]



Scheme 6: a. Menthol based PCCP catalyse Mukaiyama Mannich reaction.

b. Menthol based PCCP catalyse Mukaiyama Aldol reactions.

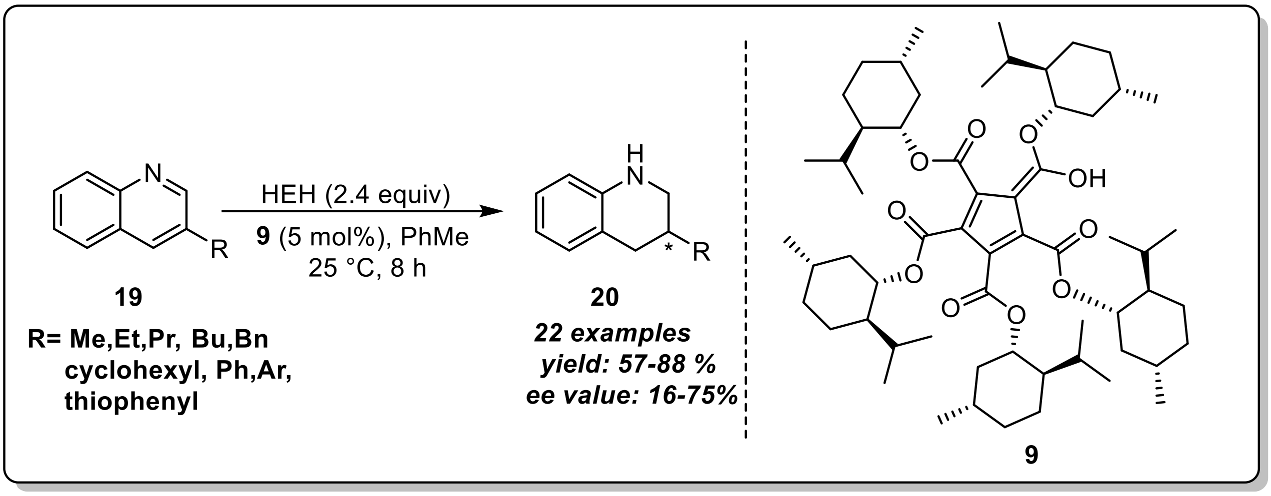
In 2017, X. Qiao and co-workers used Cyclopentadiene-based Brønsted acid (**3**) to catalyse the transfer hydrogenation of 2-substituted quinolones (**16**) using Hantzsch ester (**17**) as the hydrogen source[10]. Initially, the transformation of quinolones to tetrahydroquinolones (**18**) was carried out by transition metal catalyst and Hydrogen gas as a reducing agent.[11] This process is highly reactive and selective. But, there are many disadvantages, such as population and toxicity of transition metal and the risk of handling the high pressure of hydrogen gas. But, here X. Qiao and co-workers, in their protocol, used the Brønsted acid (**3**) as the catalyst and Hantzsch ester (**17**) as the hydrogen source (Scheme 7). The first report, where Brønsted acid catalyse transfer hydrogenation of quinolones, was reported by Rueping and co-worker in 2006[12], using diphenyl phosphate as the catalyst and hantzsch ester as the hydrogen source.



Scheme 7: the transfer hydrogenation of 2-substituted quinolines by X. Qiao

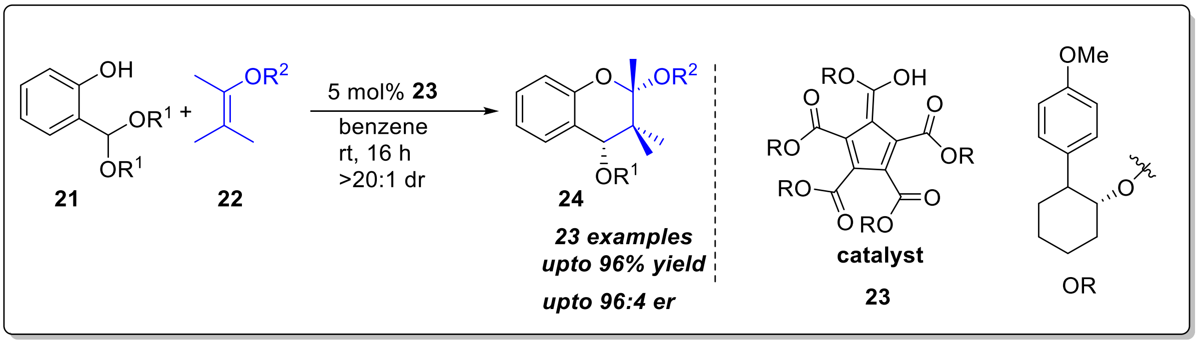
---

In the same year, 2017, an enantioselective reduction of 3-substituted quinolones (**19**) has been reported by Xiaofang Zhao and co-workers.[13] They used cyclopentadiene-based chiral Brønsted acid (**9**) as a catalyst and Hantzsch ester (**17**) as hydrogen donor, which results in corresponding tetrahydroquinolines (**20**) in good yield (Scheme 8**).**



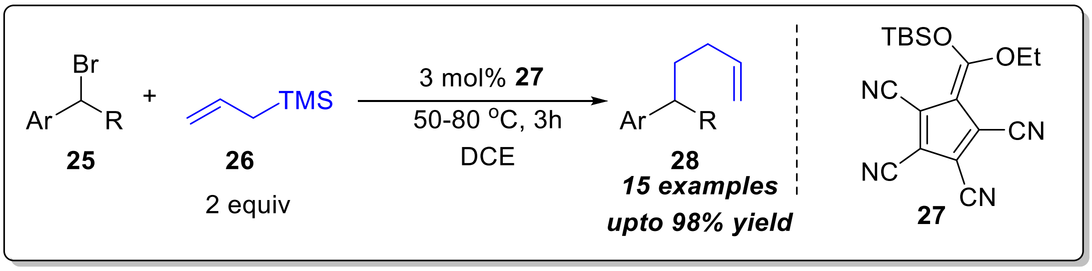
Scheme 8: Enantioselective Reduction of 3-Substituted Quinolines.

In 2018**,** Lambert and co-worker used a chiral Pentacarboxycyclopentadiene acid (**23**) for an enantioselective inverse-electron-demand Diels-Alder reaction[14] between salicylaldehyde acetal (**21**)-derived oxocarbenium ions and vinyl ethers (**23**) to give 2,4-dioxychromances(**24**).



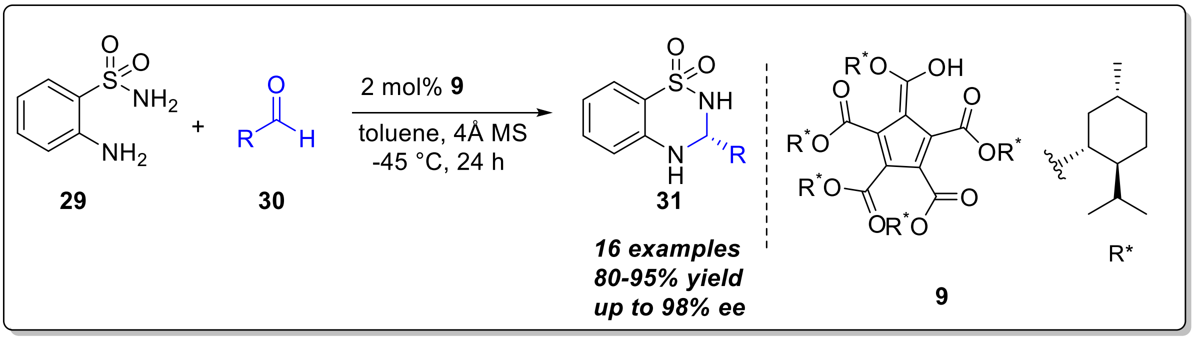
Scheme 9: Inverse-electron-demand Diels−Alder reaction of salicylaldehyde acetals and vinyl ethers to yield 2,4-dioxychromanes

In the same year, Lambert and co-workers also reported the synthesis of CP-based (cyclopentadiene) silicon Lewis acid. The CP-based silicon Lewis acid (**27**) catalysed the halide abstraction from **25** followed by the addition of allylsilanes moiety (**26**) which result in the formation of a C-C bond product (**28**)[Scheme 10].[15]



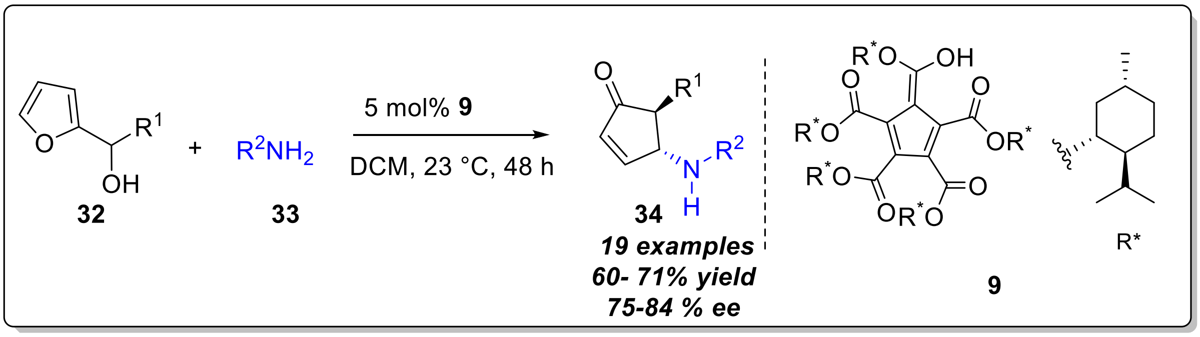
Scheme 10: Benzylic allylation catalysed by CP-based silicon Lewis acid.

In 2018, Haifeng Zhou and co-worker reported an enantioselective aminalization of 2-aminobenzrnesulfonamides (**29**) and aldehydes (**30**) catalysed by a chiral Brønsted acid (**9**) to generate benzothiadiazine (**31**) with up to 98% *ee* as shown in Scheme 11.[16]



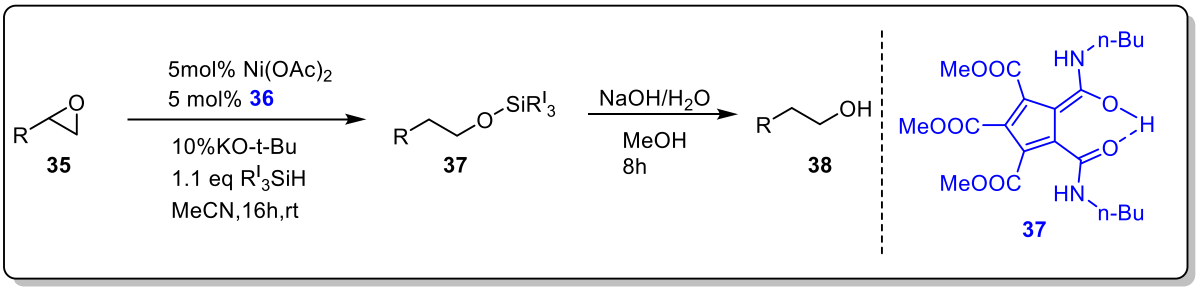
Scheme 11: Synthesis of Cyclic Aminals with a chiral Brønsted acid.

In 2019, Alaniz and co-workers used a (-)-Menthol based pentacarboxycyclopentadiene (PCCP) chiral Brønsted acid (**9**) to catalyse an enantioselective aza-Piancatelli rearrangement to generate a chiral 4-amino-2-cyclopentenone (**34**) from readily available starting material which are Furylcarbinol (**32**) and anilines (**33**) as shown in **(**Scheme 12**).**[17]



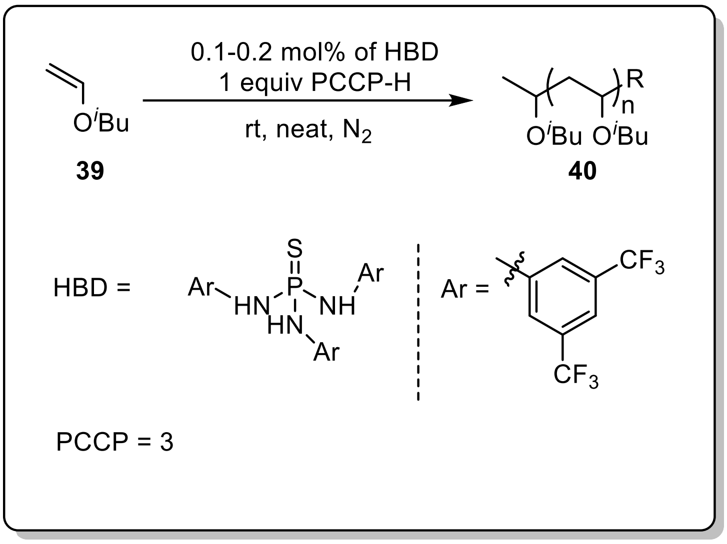
Scheme 12: Enantioselective PCCP Brønsted acid-catalysed aza-Piancatelli rearrangement.

In 2019, Lambert and co-workers reported the first PCCP derivative (**36**) used as a ligand in a transition metal catalysis.[18] In this method the terminal, monosubstituted epoxides (**35**) undergoes the reductive opening to give unbranched, primary alcohol (**38**).



Scheme 13: hydrosilylation of mono-substituted terminal epoxides.

Very recently, Lambert and co-workers reported the synthesis of cationic polymerization reaction of vinyl ethers **(39)** in ambient conditions using a pair of a novel hydrogen bond donor (HBD) and organic acid. They used thiophosphoramide as a hydrogen bond donor (HBD) and pentacarbomethoxycyclopentadiene (**3**) as an organic acid.[19]

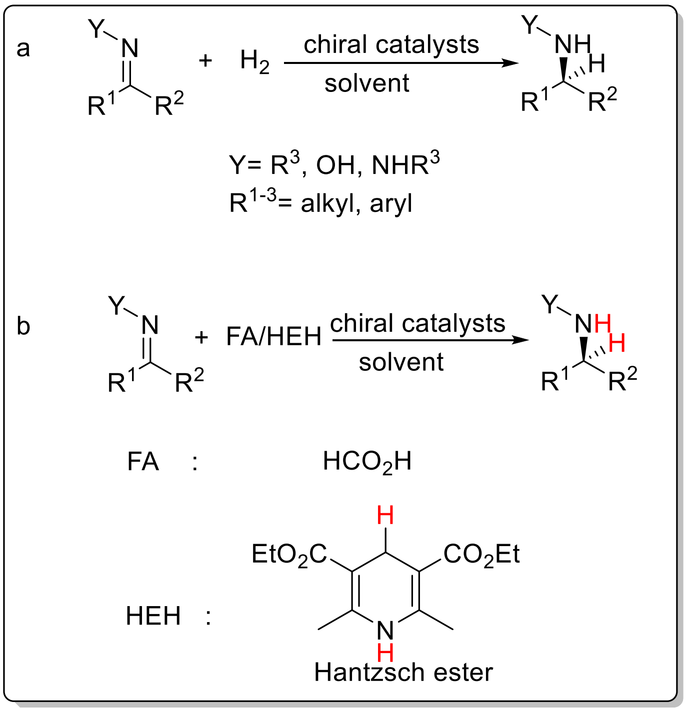


Scheme 14: Cationic polymerization reaction of vinyl ethers.

Chapter 2

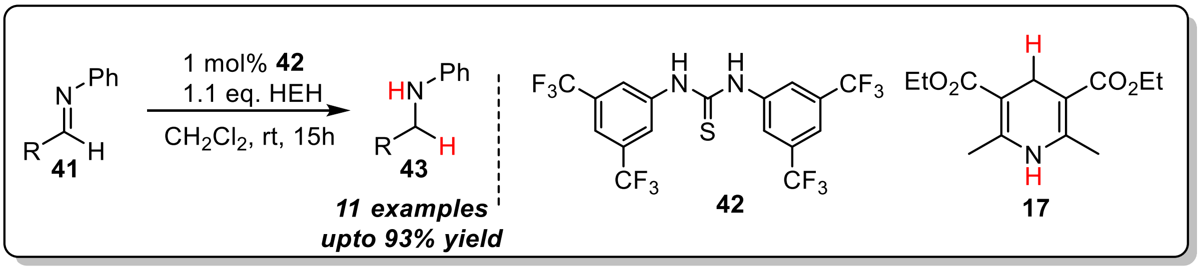
2.1 Literature overview on the synthesis of Amines by transfer hydrogenation.

There are many enantioselective catalysts for the asymmetric hydrogenation of alkenes and ketones bearing various functional groups, but only fewer catalysts are effective for the hydrogenation of substrates with a C=N function. There are two methods for the reduction of C=N (imines). Scheme 15 shows the comparison between the hydrogenation (15a) and transfer hydrogenation (15b).



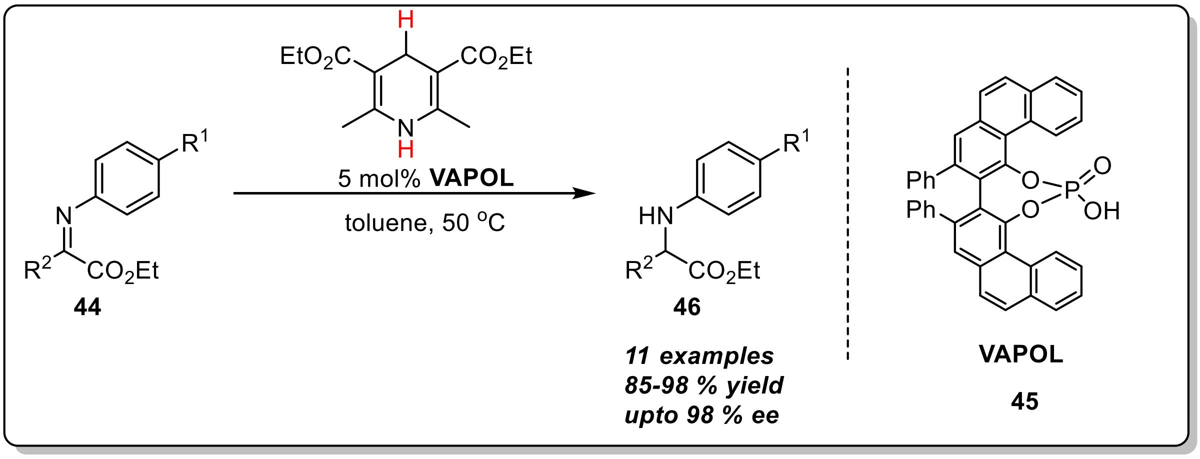
Scheme 15: A comparison between the hydrogenation (a) and transfer hydrogenation (b).

In 2007, Zhang and co-workers used a thiourea based catalyst for transfer hydrogenation of various imines (through hydrogen-bonding activation) and hantzsch ester as the hydrogen source; which gave the respective amines in good yields under acid and metal-free reaction conditions as shown in Scheme 16.[20]



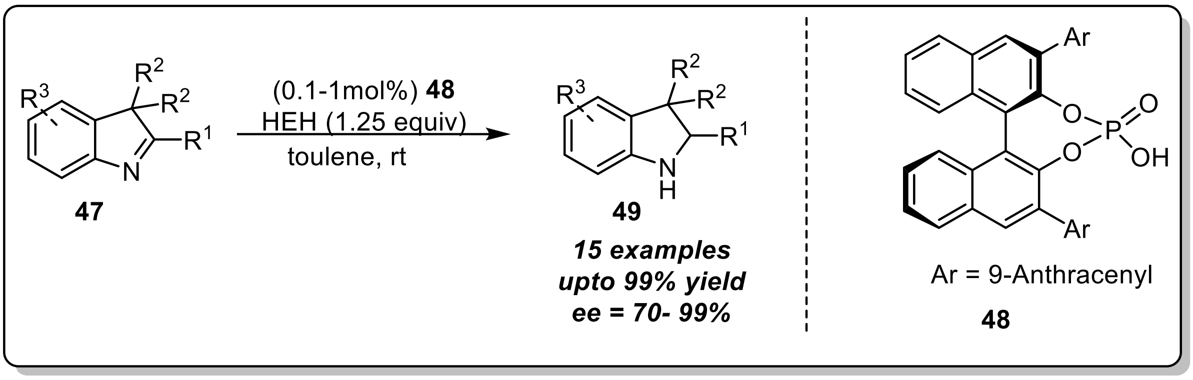
Scheme 16: Thiourea-catalysed transfer hydrogenation of various imines.

In 2007, Antilla and co-worker reported the reduction of C=N groups of α-imino esters using a chiral VAPOL[21] derived phosphoric acid as Brønsted acid and hantzsch ester as a hydrogen source to synthesis chiral α-amino acid derivatives(Scheme 17).[22]



Scheme 17: Reduction of α-Imino Esters catalysed by VAPOL Phosphoric Acid.

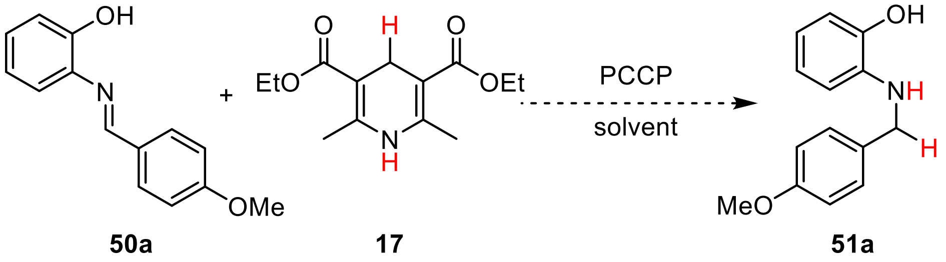
In 2010, Rueping and co-workers reported the enantioselective reduction of 3*H*-indoles (**47**).[23] In this synthetic route they used phosphoric acid derivative (**48**) as chiral Brønsted acid that catalysed the transfer hydrogenation (Scheme 18).



Scheme 18: Enantioselective reduction of 3*H*-indoles.

2.2 Our Hypothesis

Based on the literature reports, it is clear that Brønsted acid could employed for the reduction of C=N, C=C, and C=O bonds.[24, 25] In this context, we envisioned that the PCCP (**3**) could be utilized as a Brønsted acid for the reduction of 2-(benzylideneamino)phenol derivatives moiety with hantzsch ester (**17**) as shown in the Scheme 19. At this point, we assumed that the PCCP could activate the imine through hydrogen bonding between one of the carbonyl oxygen and the OH group present on imine moiety. While the hantzsch ester could be activated by the interaction of the OH group of PCCP and the carbonyl oxygen of hantzsch ester.

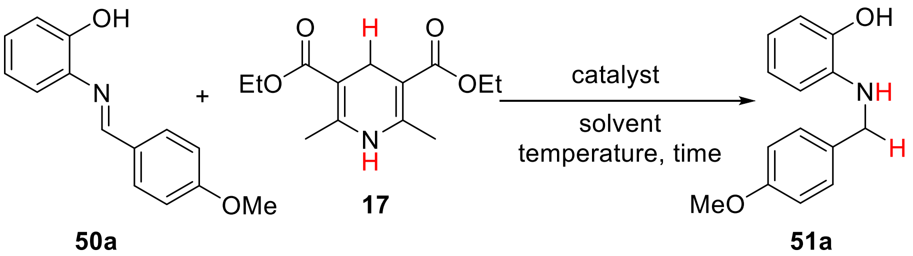


Scheme 19: Our proposed strategy for the reduction of the imines

2.3 Results and Discussion

The optimization studies were accomplished using 2-{(4-methoxybenzylidene)amino}phenol (**50a**), PCCP (**3**), and the hantzsch ester (**17**) as hydrogen source, under different conditions, and the results are shown in Table 1. Initially, when the reaction was carried out in $CHCl_3$, and as expected product **51a** was obtained in 70% yield (entry 1). Inspired by this result, solvent screening was carried out (entry 2-5). In THF the required product was formed in trace amount even after 36 hours (entry 2), when acetone was used as a solvent, the expected product was obtained in 59% yield (entry 3). When the reaction was carried out in acetonitrile and ethyl acetate the expected product was obtained in 60% and 72% respectively. Surprisingly, in toluene, the product was obtained in 87 % yield (entry 6). Further, a few reactions were carried out in 20 mol% and 5 mol% of catalyst in toluene, and product was obtained in 85% and 72% of yields, respectively (entry 7-8). When the reaction was performed without catalyst, no product formation was observed (entry 9), which implies the PCCP was required for the above transformation.

Table 1: Optimization Study^a

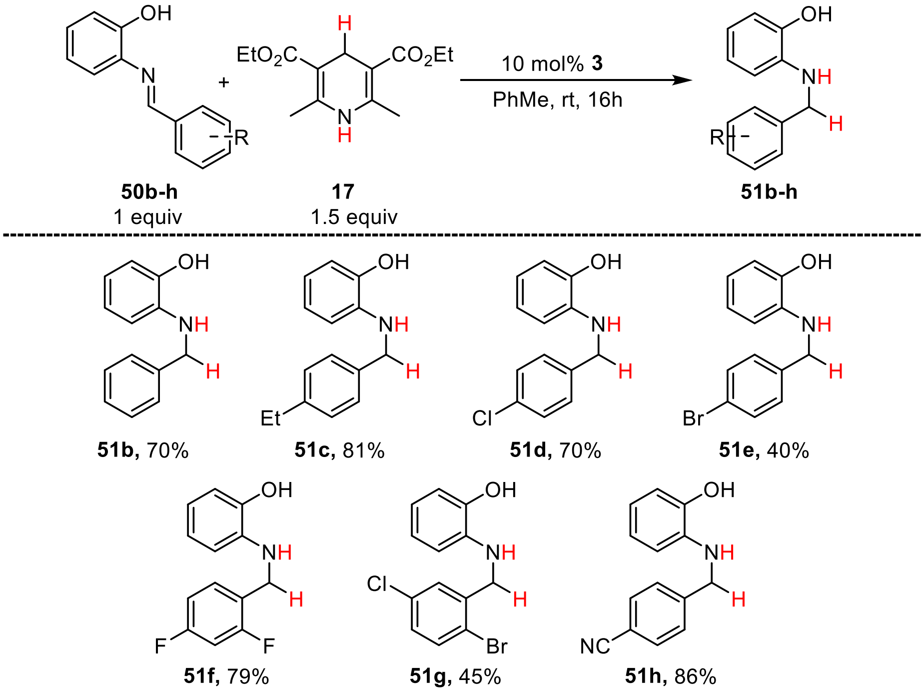


Entry	Catalyst (mol %)	solvent	Time (h)	Yield (%)
1	10	$CHCl_3$	16	70
2	10	THF	36	trace
3	10	Acetone	16	59
4	10	MeCN	16	60
5	10	EtOAc	16	72
6	**10**	**PhMe**	**16**	**87**
7	20	PhMe	16	85
8	5	PhMe	16	72
9	-	PhMe	36	nr

^{a}Reaction condition: All the reactions were carried out in 0.174 mmol of **50a** and 0.262 mmol of (**17**) in 1.5mL of solvent at room temperature. Yields reported are isolated yield.

After getting the optimal conditions in hand (entry 6, Table 1). We explored the scope of transfer hydrogenation of different imines (Table 2). As shown in the table 2, imines (**50b & 50c**) with electron-rich substitution in the aryl ring, gave the corresponding products **51b & 51c** in 70% & 81% of yield, respectively, halo-substituted imines (**50d-g**) also underwent reduction to provide the respective amines derivatives (**51d-g**) in moderate to good yields (40%-79%). Electron-deficient imines **50h** was also screened under standard reaction conditions and the corresponding product (**51h**) was obtained in 86% of yield.

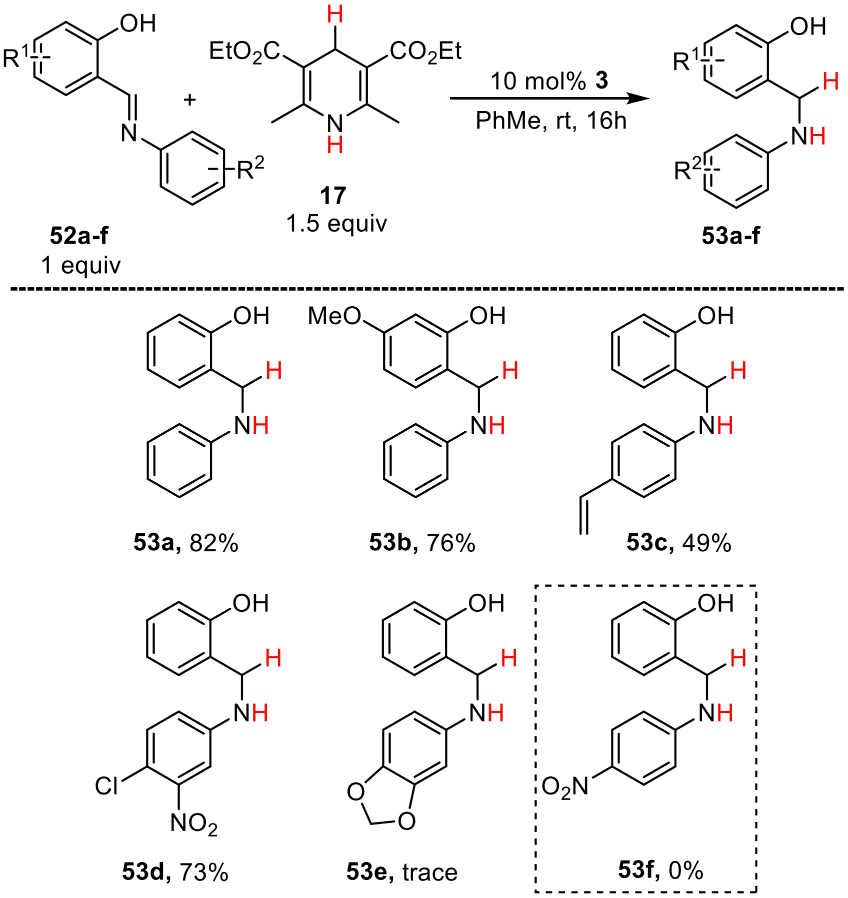
Table 2: Substrate scope of imines derived from 2-aminophenol[a]



[a]Reaction conditions: All the reactions were carried out on 40 mg scale in 1.5mL of solvent, yields reported are isolated yields.

To extend the substrate scope of our methodology, many other imine derivatives have been screened. As can be seen, when the reduction reaction was carried with imines (substitution on the aryl rings with electron-rich groups), the products **53a & 53c** were isolated in moderate to good yield (82 and 76% respectively). The halo-substituted amine (**53d**) was obtained in 73% of yield. Surprisingly, the imines, derived from **52e** and **52f** failed to undergo reduction reaction under standard conditions.

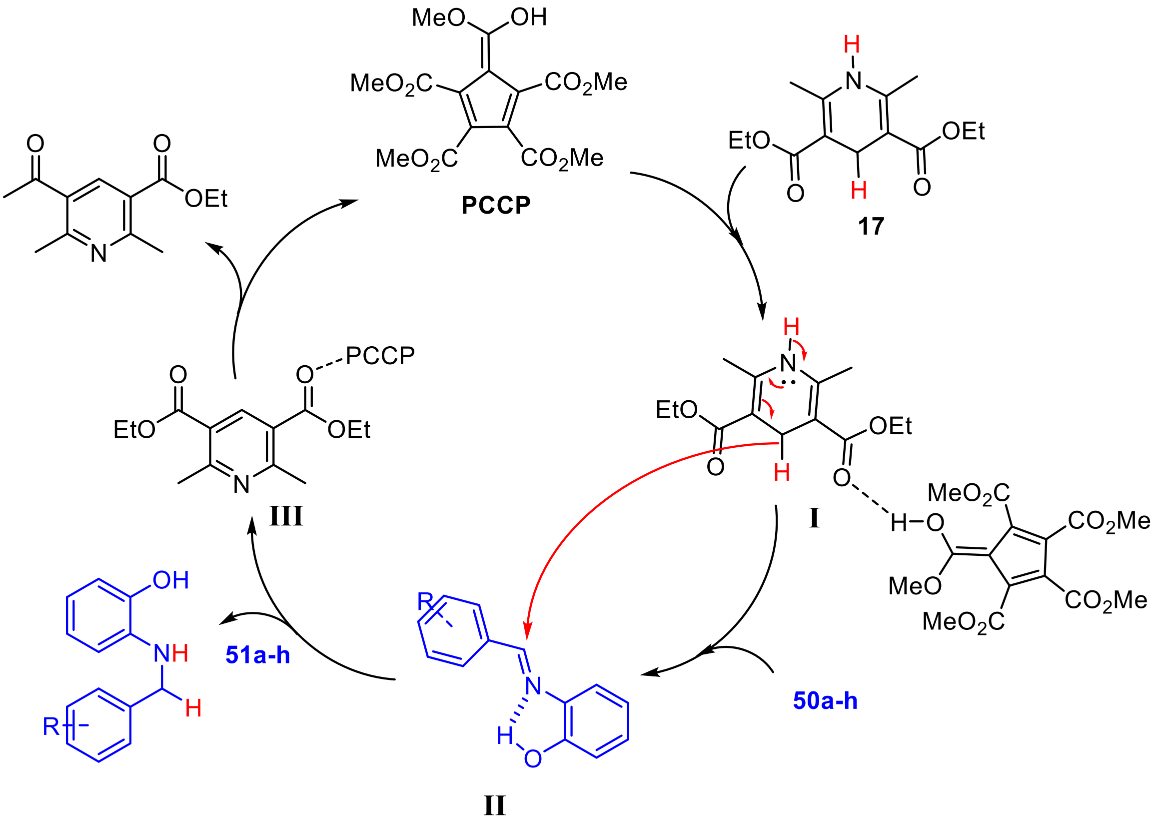
Table 3: Substrate scope imines derived from salicylaldehyde.[a]



[a]Reaction conditions: All the reactions were carried out on 40 mg scale in 1.5mL of solvent, yields reported are isolated yields.

2.4. Plausible Mechanism

Based on the previous literature reports and outcome of reaction, a plausible mechanism is proposed. The catalytic cycle begins with the activation of **17** with PCCP to form an intermediate **I**, which then transfer the hydride to **50a**, which itself is getting activated by PCCP through hydrogen bonding as shown in Scheme 21. Intermediate **II**, upon proton transfer from the hantzsch ester to imine generates the required product **51a** along with complex **III**, which liberates the diethyl 2,6-dimethylpyridine-3,5-dicarboxylate as a by-product and regenerates the catalyst.



Scheme 21: Plausible Mechanism of transfer hydrogenation of imine.

2.5: Conclusion

In summary, we have described the transfer hydrogenation of imine, catalysed by penta-carbomethoxy-cyclopentadiene (PCCP) as a Brønsted acid catalyst and hantzsch ester as a hydrogen source. A wide range of imines, containing electron-rich, electron-deficient, and halo substituted groups, were screened under reaction condition and, corresponding products were obtained in moderate to good yields.

Chapter 3

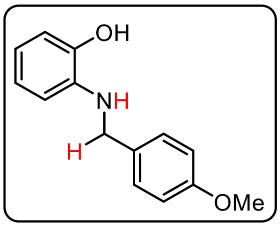
3.1: Experimental Section:

General Information. All reactions were carried out under an argon atmosphere in an oven-dried round bottom flask. All the solvents were distilled before use and stored under an argon atmosphere. Most of the reagents, starting materials were purchased from commercial sources and used as such. The respective imine moieties, which are derived from 2-Aminophenol and corresponding aldehyde (**50a-h**) and salicylaldehyde and anilines (**52a-f**).[26] Melting points were recorded on SMP20 melting point apparatus and are uncorrected. ^{1}H, ^{13}C, and ^{19}F spectra were recorded in $CDCl_3$ (400, 100, and 376 MHz respectively) on Bruker FT–NMR spectrometer. Chemical shift (d) values are reported in parts per million relatives to TMS and the coupling constants (*J*) are reported in Hz. High-resolution mass spectra were recorded on Waters Q–TOF Premier–HAB213 spectrometer. FT-IR spectra were recorded on a Perkin-Elmer FTIR spectrometer. Thin-layer chromatography was performed on Merck silica gel 60 F_{254} precoated TLC plates and visualised by UV irradiation. Column chromatography was carried out through silica gel (100–200 mesh) using EtOAc/hexane as eluent.

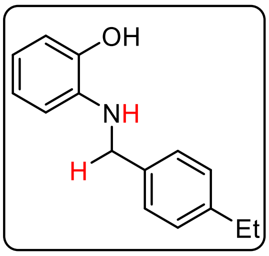
3.2: General procedure for the reduction of imines (51a-h & 53a-f).

Toluene (1.5 mL) was added to a mixture of imines (**50a-h & 52a-f**, 40mg, 1 equiv), hantzsch ester (**17,** 1.5 equiv) and PCCP (**3**, 10 mol%). The reaction mixture was allowed to stir at room temperature for 16 hours. The reaction mixture was concentrated under reduced pressure and the residue was then purified through a silica gel column or neutral alumina, using EtOAc/Hexane mixture as an eluent, to get the pure product (**51a-h & 53a-f**).

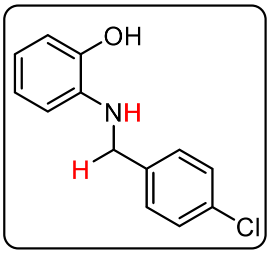
3.3: Characterization data of compounds



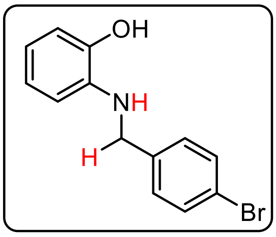
*2-{(4-methoxybenzyl)amino}phenol (**51a**).* The reaction was performed at 0.174 mmol scale of **50a**; R$_f$ = 0.3 (20% EtOAc in hexane); Black solid (35.2 mg, 87% yield); m. p. = 85–88 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31 (d, J = 8.6 Hz, 2H), 6.89 (d, J = 8.6 Hz, 2H), 6.84 (t, J = 7.4 Hz, 1H), 6.7 (t, J = 9.8 Hz, 2H), 6.63 (t, J = 7.5 Hz, 1H), 4.27 (s, 2H), 3.81 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.9, 143.6, 137.1, 131.6, 129.0, 121.8, 117.9, 114.4, 114.1, 112.6, 55.4, 48.2; FT-IR (thin film, neat): 3536, 3410, 2926, 1608, 743 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{14}H_{14}NO_2$ $[M-H]^+$: 228.1025; found : 228.1027.



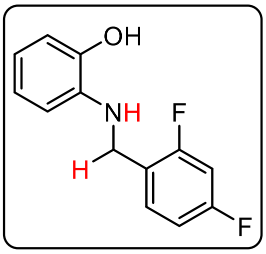
*2-{(4-ethylbenzyl)amino}phenol (**51c**).* The reaction was performed at 0.177 mmol scale of **50c**; R$_f$ = 0.2 (20% EtOAc in hexane); Black gummy solid (32.8, 81% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32 (d, J = 7.9 Hz, 2H), 7.19 (d, J = 8.0 Hz, 2H), 6.84 (t, J = 7.4 Hz, 1H), 6.71 (t, J = 8.8 Hz, 2H), 6.64 (t, J = 7.4 Hz, 1H), 4.31 (s, 2H), 2.68 – 2.63 (m, 2H), 1.25 (t, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.6, 143.3, 137.0, 136.5, 128.1, 127.7, 121.6, 117.8, 114.4, 112.5, 48.4, 28.6, 15.7; FT-IR (thin film, neat): 3675, 3383, 2929, 1605, 750 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{15}H_{16}NO$ $[M-H]^+$: 226.1232; found : 226.1227.



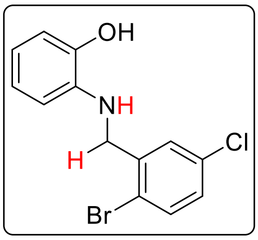
*2-{(4-chlorobenzyl)amino}phenol (**51d**).* The reaction was performed at 0.172 mmol scale of **50d**; R$_f$ = 0.2 (20% EtOAc in hexane); Black solid (28.4 mg, 70% yield); m. p. = 75–78 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31 (s, 4H), 6.81 (t, J = 7.5 Hz, 1H), 6.72 (d, J = 7.5 Hz, 1H), 6.64 – 6.58 (m, 2H), 4.33 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.3, 138.0, 136.7, 132.8, 128.8, 128.7, 121.7, 117.8, 114.3, 112.2, 47.8; FT-IR (thin film, neat): 3627, 3348, 2925, 1606, 761 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{13}H_{13}ClNO$ $[M+H]^+$: 234.0686; found : 234.0671.



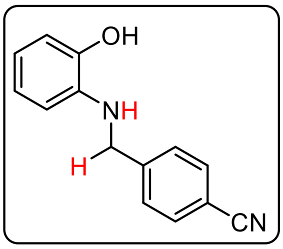
*2-{(4-bromobenzyl)amino}phenol (**51e**).* The reaction was performed at 0.145 mmol scale of **50e**; R_f = 0.3 (20% EtOAc in hexane); Black solid (16 mg, 40% yield); m. p. = 113–115 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45 (d, J = 8.4 Hz, 2H), 7.26 (d, J = 8.2 Hz, 2H), 6.81 (t, J = 7.5 Hz, 1H), 6.73 (d, J = 7.5 Hz, 1H), 6.64 – 6.57 (m, 2H), 4.31 (s, 2H); FT-IR (thin film, neat): 3542, 3217, 3008, 1608, 750 cm^{-1}.



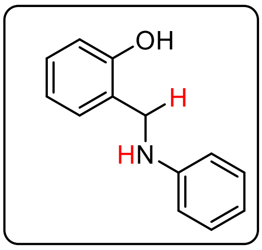
*2-{(2,4-difluorobenzyl)amino}phenol (**51f**).* The reaction was performed at 0.172 mmol scale of **50f**; R_f = 0.2 (20% EtOAc in hexane); Black solid (32 mg, 79% yield); m. p. = 60–62 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 – 7.30 (m, 1H), 6.85 – 6.80 (m, 3H), 6.70 – 6.64 (m, 3H), 4.37 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.8, 147.2, 129.4, 129.3, 128.7, 122.9, 120.9, 120.1, 116.7, 115.9, 48.8; ^{19}F NMR (376 MHz, $CDCl_3$) δ -111.07 (d, J = 7.2 Hz), -111.86 (d, J = 7.0 Hz), -113.81 (d, J = 7.3 Hz), -114.89 (d, J = 7.0 Hz); FT-IR (thin film, neat): 3627, 3334, 2955, 1615, 756 cm^{-1}; HRMS (ESI): m/z calcd for $C_{13}H_{12}F_2NO$ $[M+H]^+$: 236.0887; found : 236.0884.



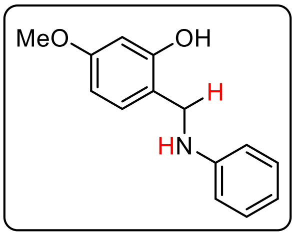
*2-{(2-bromo-5-chlorobenzyl)amino}phenol (**51g**).* The reaction was performed at 0.129 mmol scale of **50g**; R_f = 0.3 (20% EtOAc in hexane); Black solid (18 mg, 45% yield); m. p. = 80–83 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 (t, J = 7.2 Hz, 2H), 7.34 (d, J = 7.6 Hz, 1H), 7.28 (t, J = 7.1 Hz, 1H), 6.83 (t, J = 6.7 Hz, 1H), 6.72 – 6.63 (m, 2H), 4.35 (s, 2H); FT-IR (thin film, neat): 3598, 3418, 2927, 1607, 749 cm^{-1}; HRMS (ESI): m/z calcd for $C_{13}H_{12}F_2NO$ $[M+H]^+$: 236.0887; found : 236.0884.



*4-[{(2-hydroxyphenyl)amino}methyl]benzonitrile (**51h**).* The reaction was performed at 0.18 mmol scale of 50h; R_f = 0.1 (20% EtOAc in hexane); Black solid (35 mg, 86% yield); m. p. = 105–107 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61 (d, J = 8.2 Hz, 2H), 7.48 (d, J = 8.1 Hz, 2H), 6.78 – 6.75 (m, 2H), 6.62 (t, J = 7.2 Hz, 1H), 6.47 (d, J = 7.8 Hz, 1H), 4.45 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.7, 143.4, 136.5, 132.5, 127.9, 121.6, 119, 118, 114.4, 111.8, 110.7, 47.9; FT-IR (thin film, neat): 3672, 3327, 2986, 2230, 1596, 750 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{14}H_{13}N_2O$ $[M+H]^+$: 225.1028; found : 225.1023.

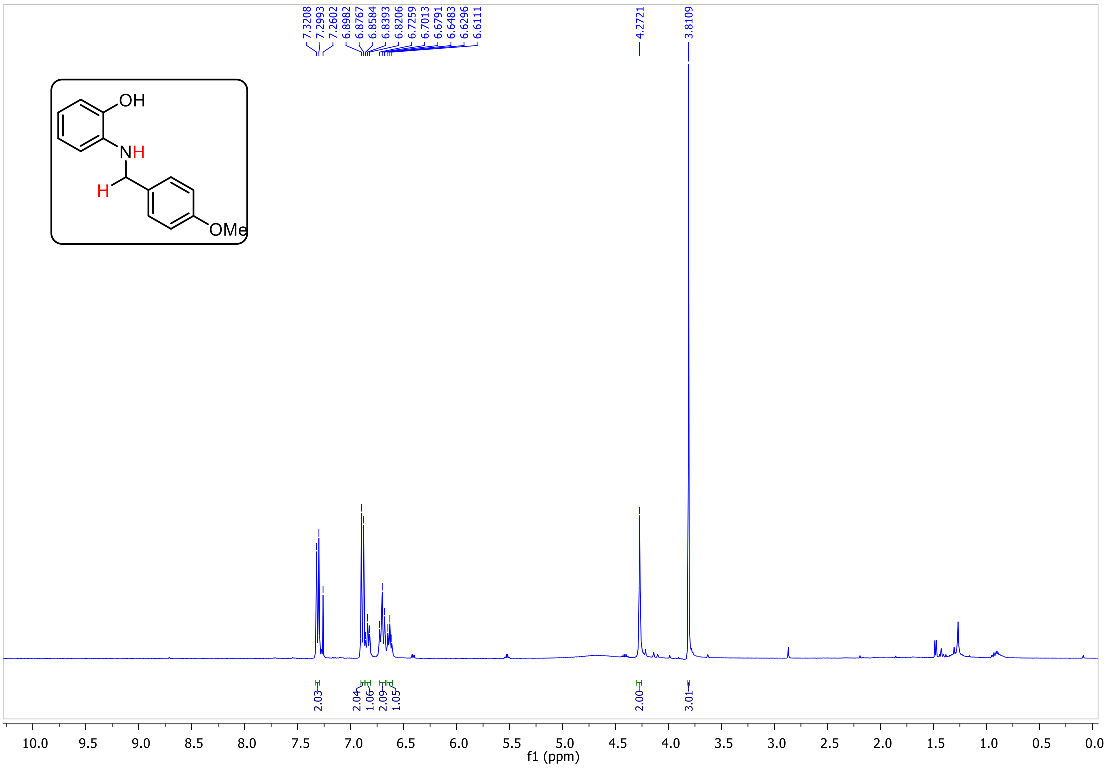


*2-{(phenylamino)methyl}phenol (**53a**).* The reaction was performed at 0.203 mmol scale of **52a**; R_f = 0.4 (20% EtOAc in hexane); Brown solid (33 mg, 82% yield); m. p. = 120–123 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31 (d, J = 8.6 Hz, 2H), 6.89 (d, J = 8.6 Hz, 2H), 6.84 (t, J = 7.4 Hz, 1H), 6.7 (t, J = 9.8 Hz, 2H), 6.63 (t, J = 7.5 Hz, 1H), 4.27 (s, 2H), 3.81 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.8, 147.2, 129.4, 129.3, 128.7, 122.9, 120.9, 120.1, 116.7, 115.9, 48.8; FT-IR (thin film, neat): 3474, 3264, 2986, 1592, 751 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{13}H_{14}NO$ $[M+H]^+$: 200.1075; found : 200.1069.

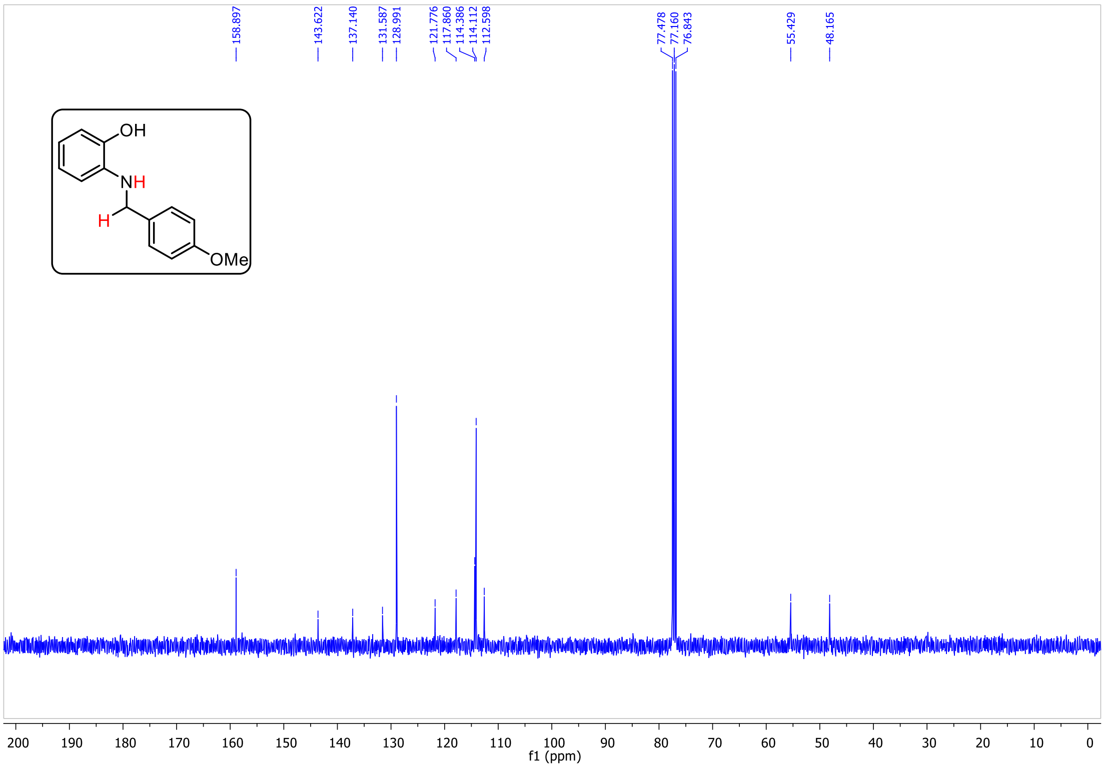


*5-methoxy-2-{(phenylamino)methyl}phenol (**53b**).* The reaction was performed at 0.176 mmol scale of **52b**; R_f = 0.4 (20% EtOAc in hexane); Brown solid (31 mg, 76% yield); m. p. = 118–121 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26 (d, J = 7.6 Hz, 2H), 7.05 (d J = 7.6 Hz, 1H), 6.93 (d, J = 7.4 Hz, 1H), 6.85 (d, J = 7.8 Hz, 2H), 6.72 (t, J = 6.7 Hz, 2H), 4.38 (s, 2H), 3.33 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.6, 147.4, 139.5, 129.5, 128.6, 120.9, 120.8, 120.0, 117.4, 116.0, 48.5, 21.34; FT-IR (thin film, neat): 3516, 3263, 2986, 1584, 751 cm^{-1}.

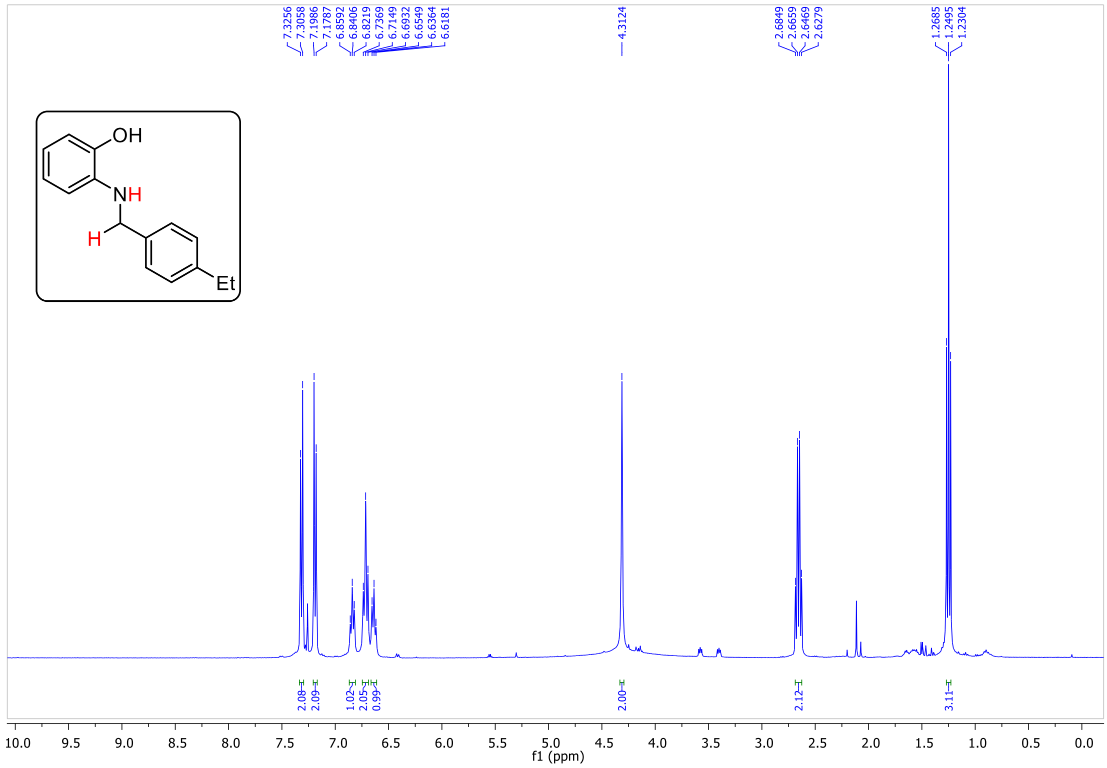
^{1}H NMR Spectrum for **51a**



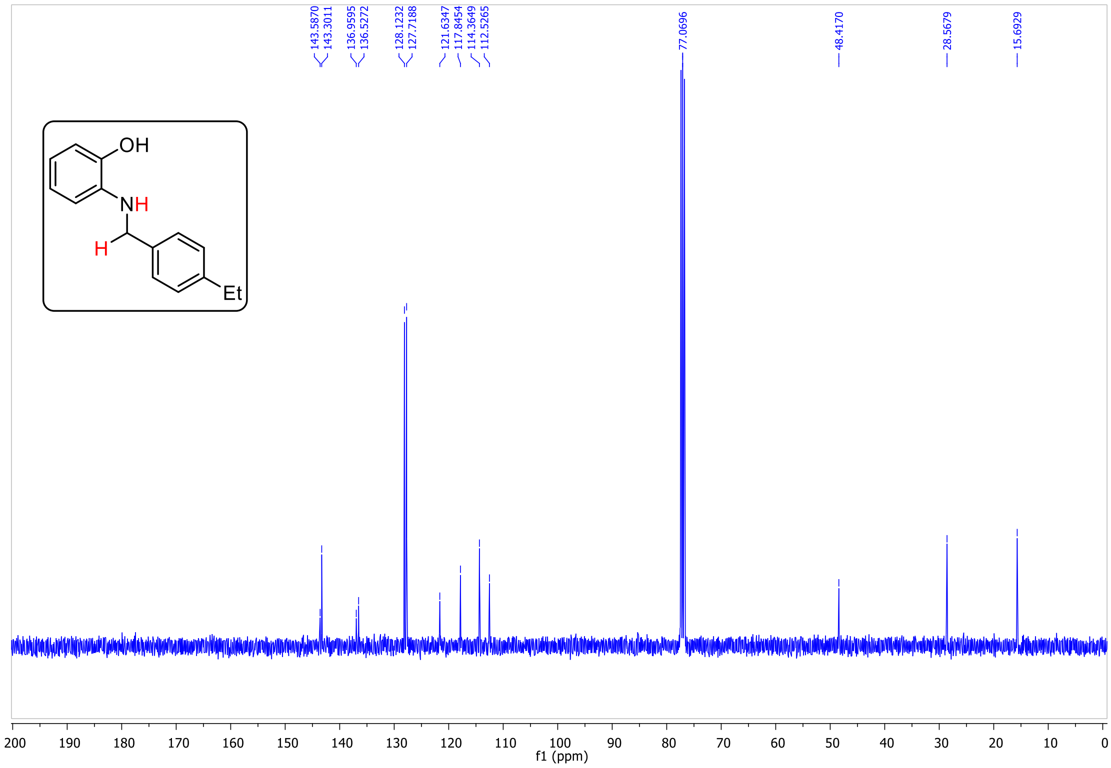
^{13}C NMR Spectrum for **51a**



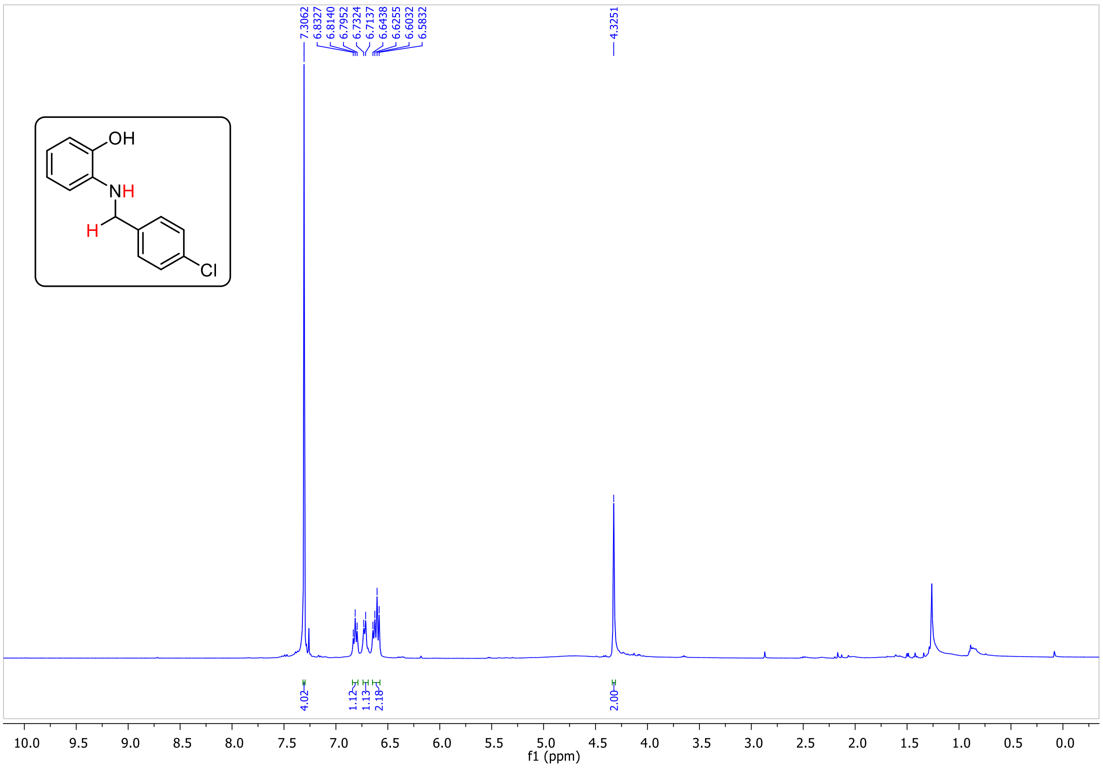
^{1}H NMR Spectrum for **51c**



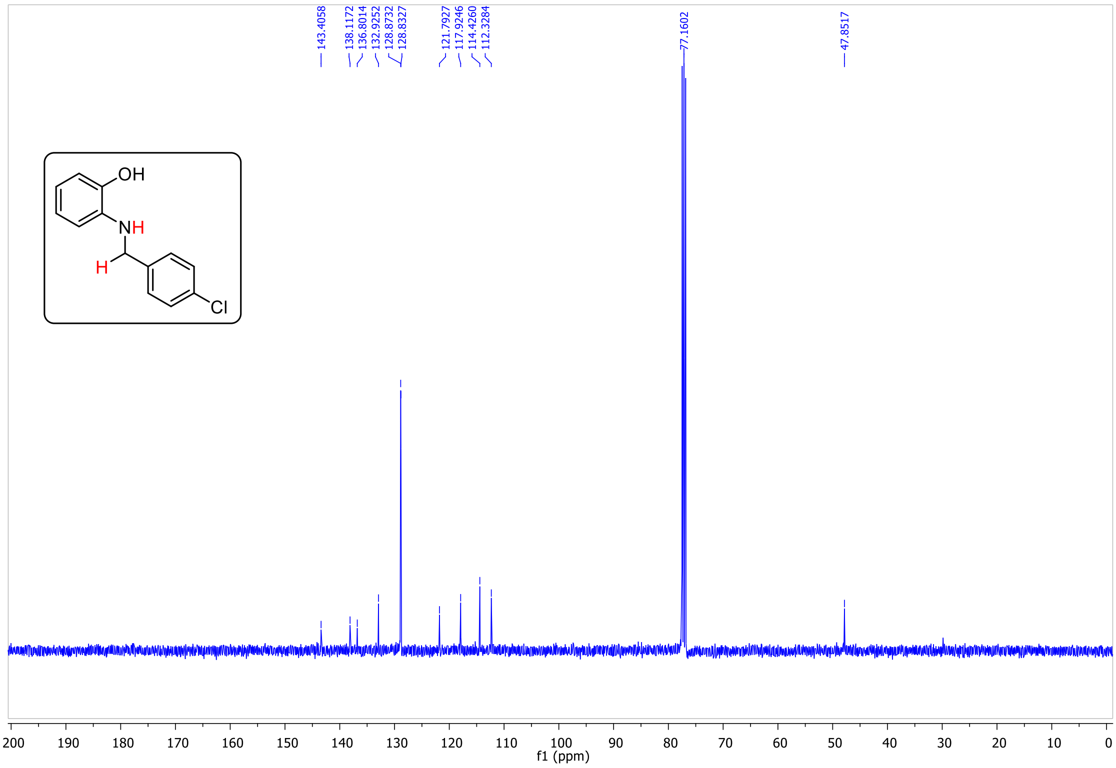
^{13}C NMR Spectrum for **51c**



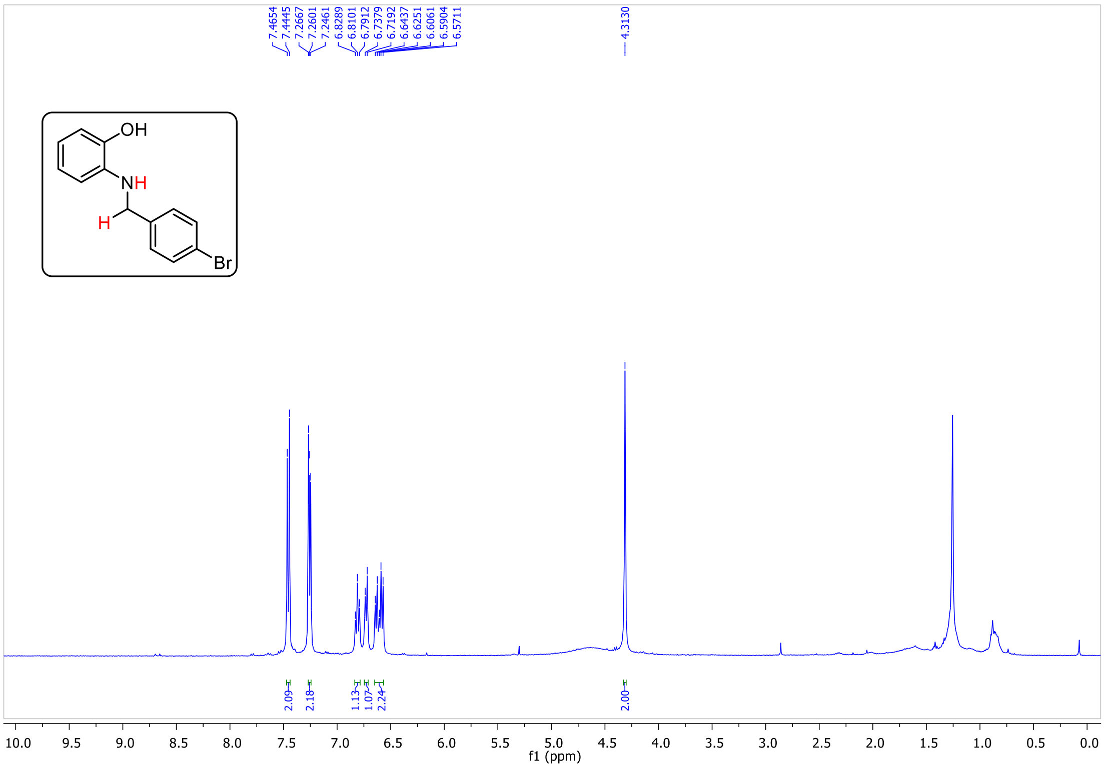
^{1}H NMR Spectrum for **51d**



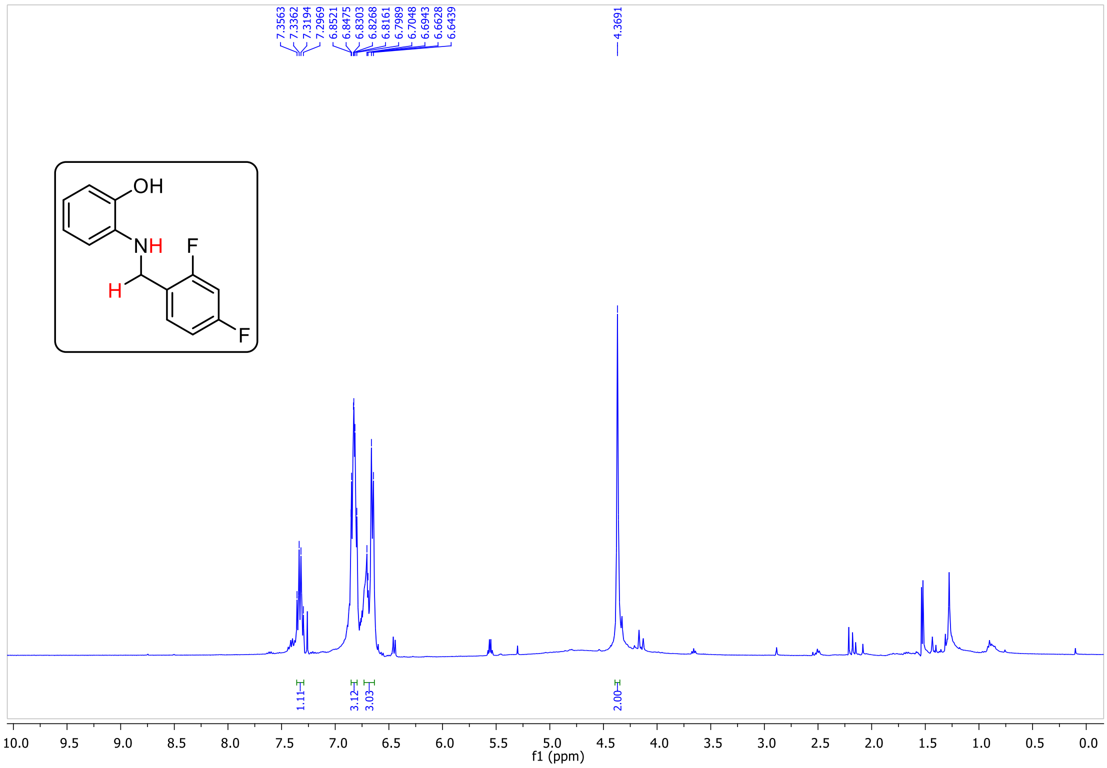
^{13}C NMR Spectrum for **51d**



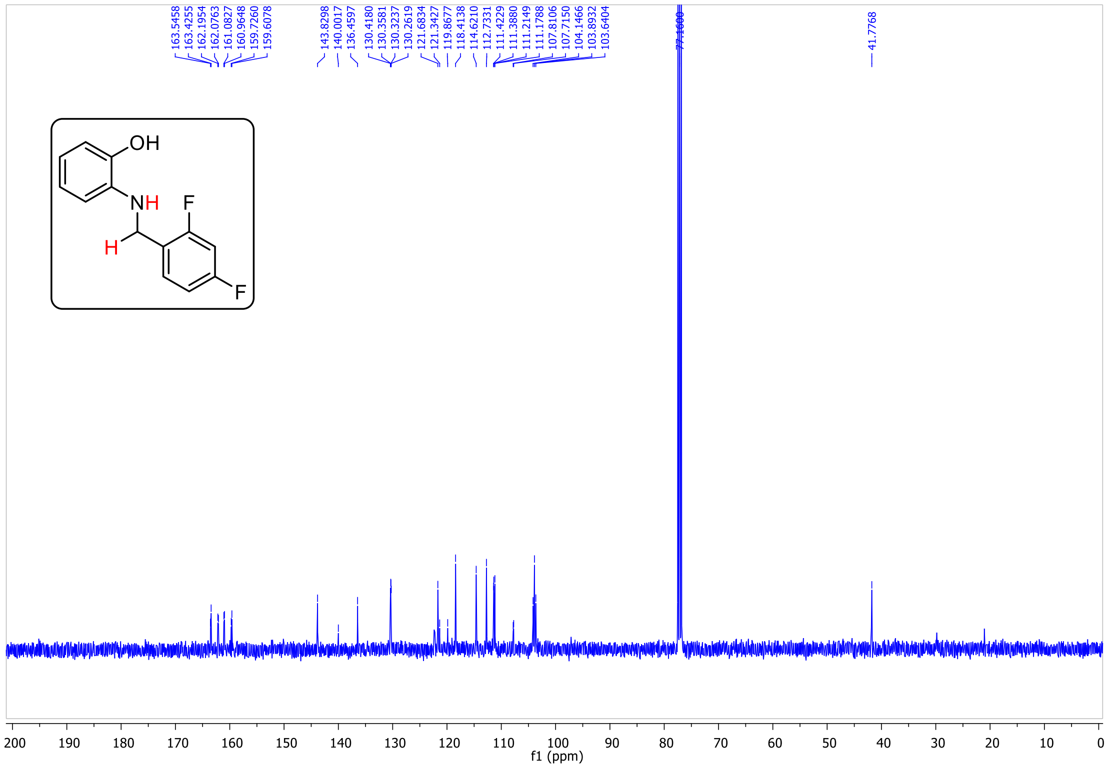
^{1}H NMR Spectrum for **51e**



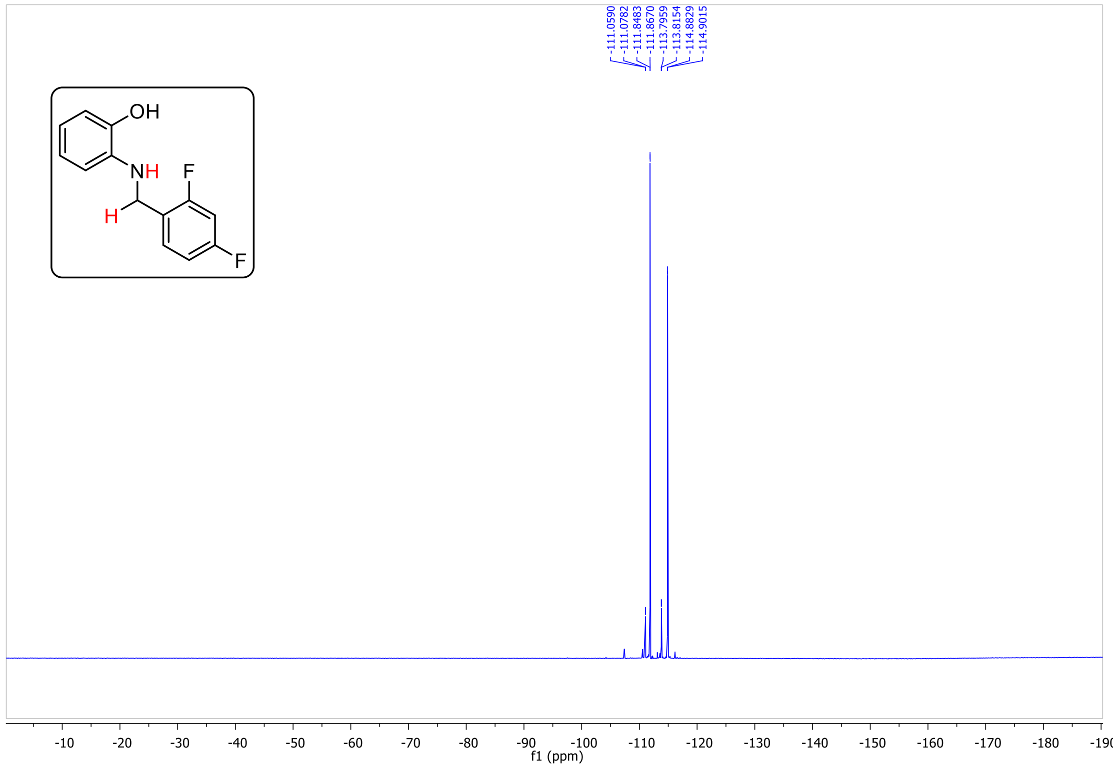
^{1}H NMR Spectrum for **51f**



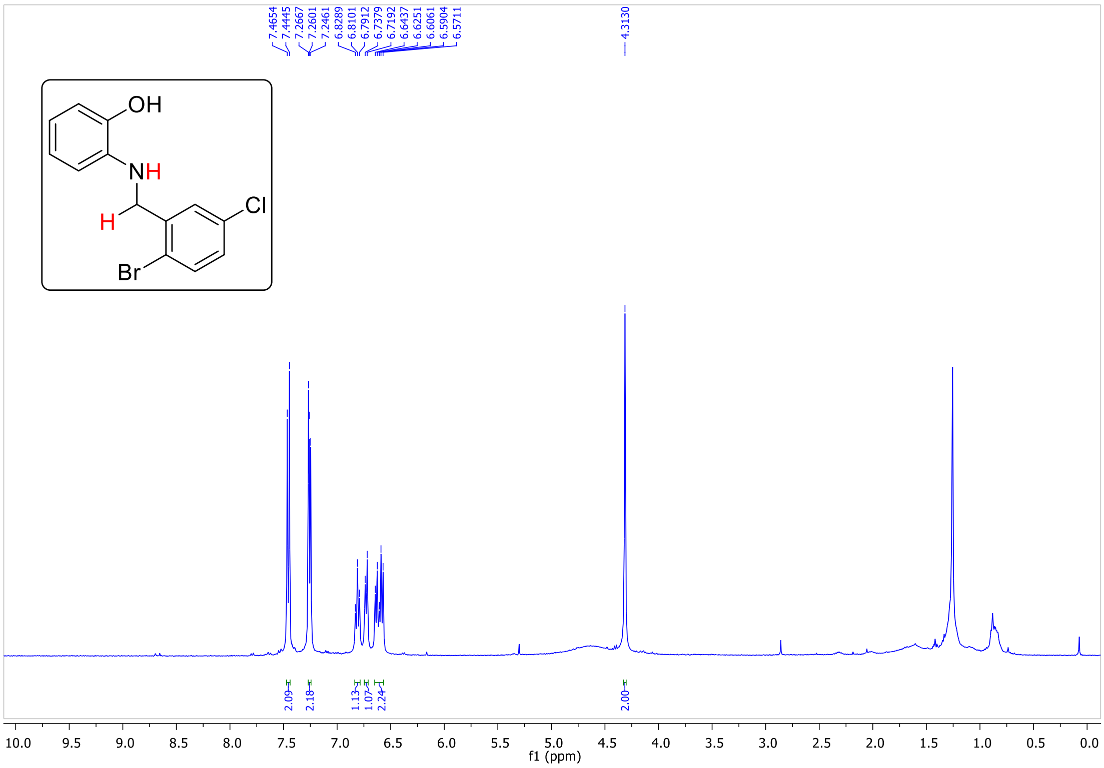
^{13}C NMR Spectrum for **51f**



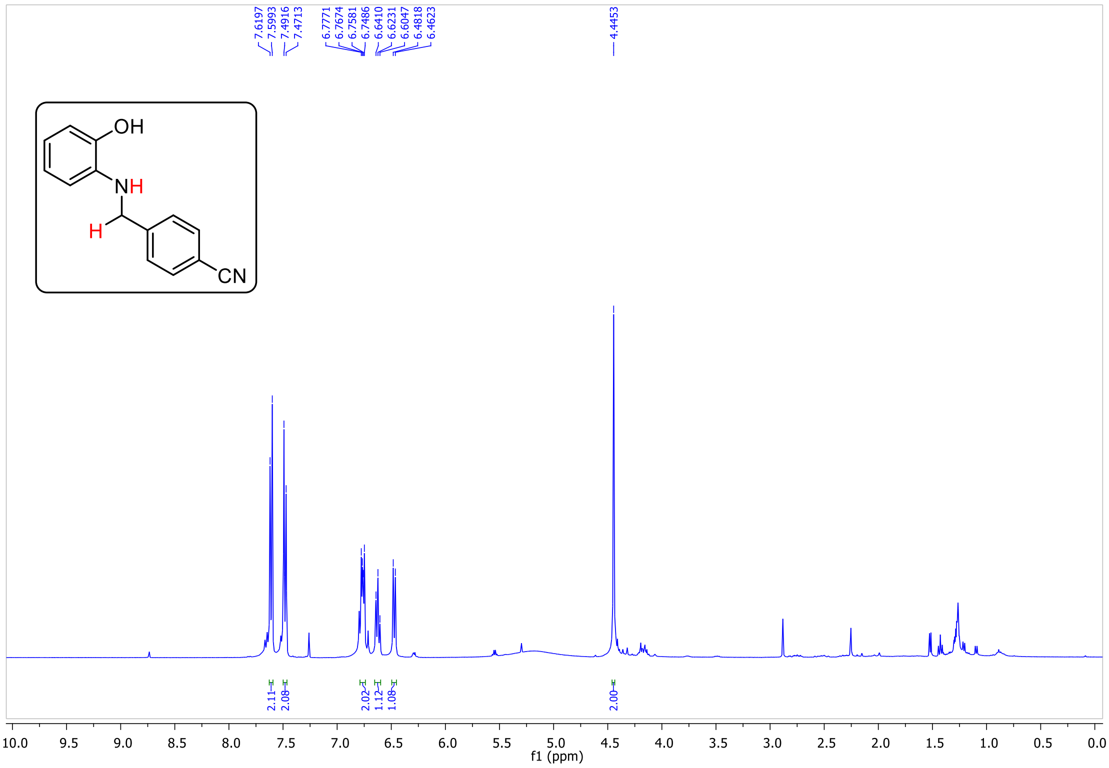
^{19}F NMR Spectrum for **51f**



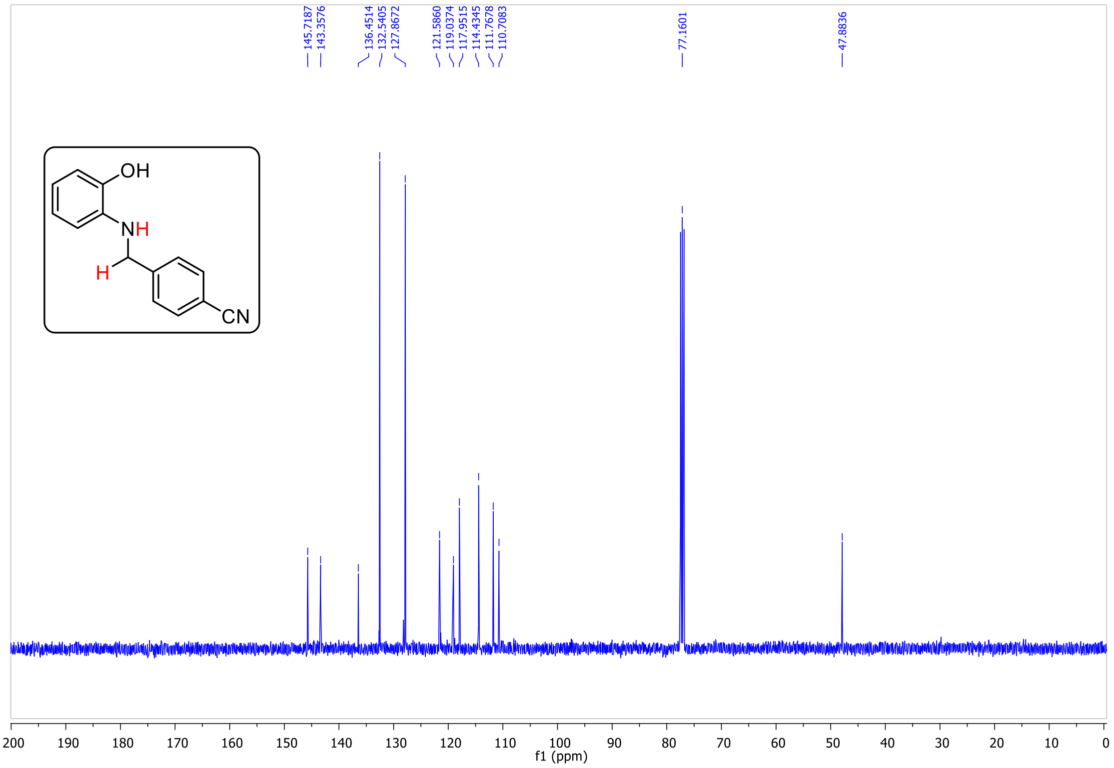
^{1}H NMR Spectrum for **51g**



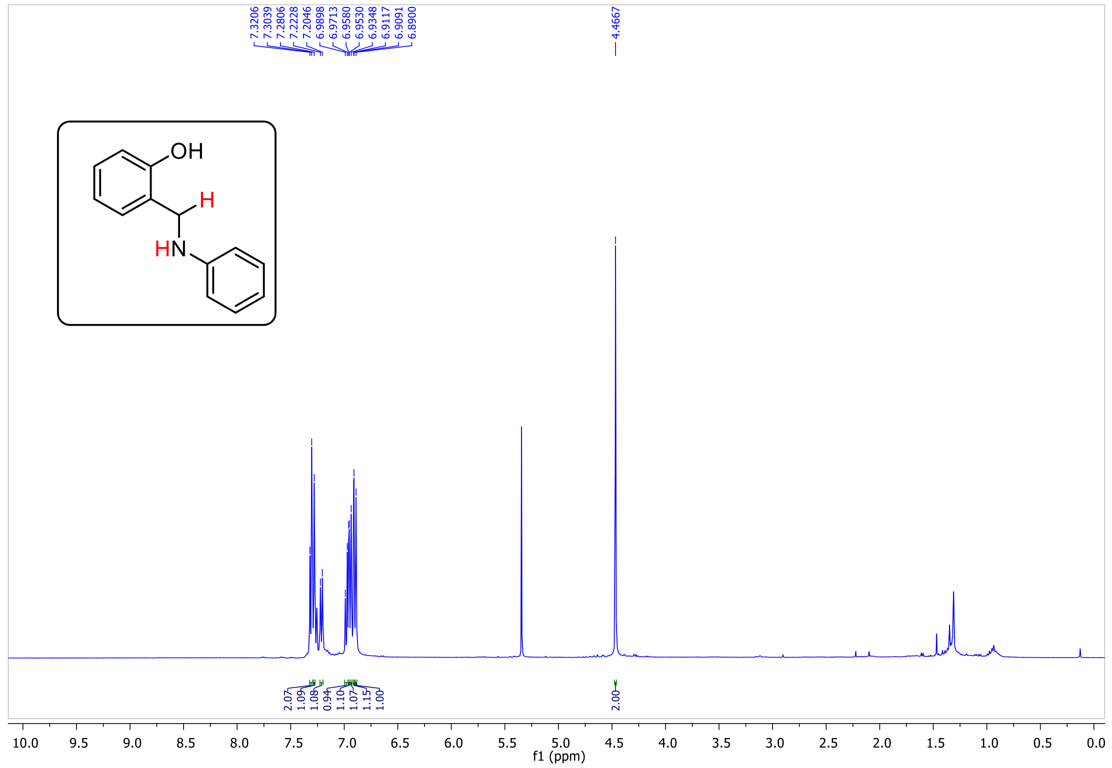
^{1}H NMR Spectrum for **51h**



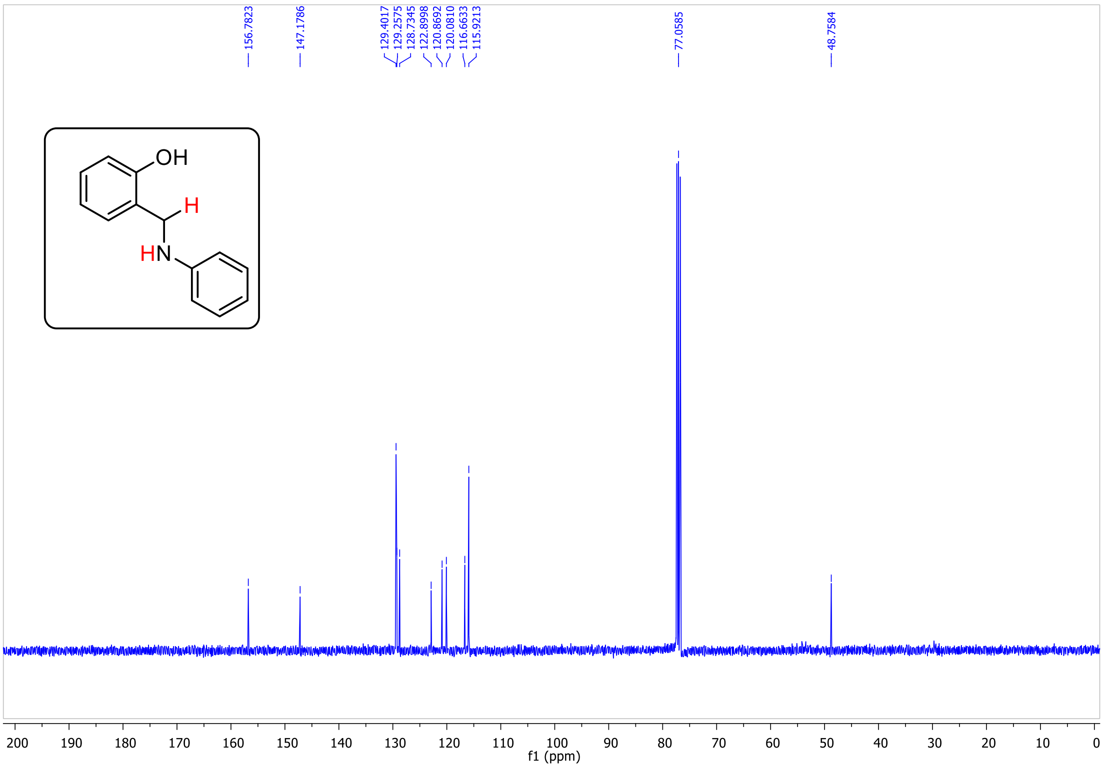
^{13}C NMR Spectrum for **51h**



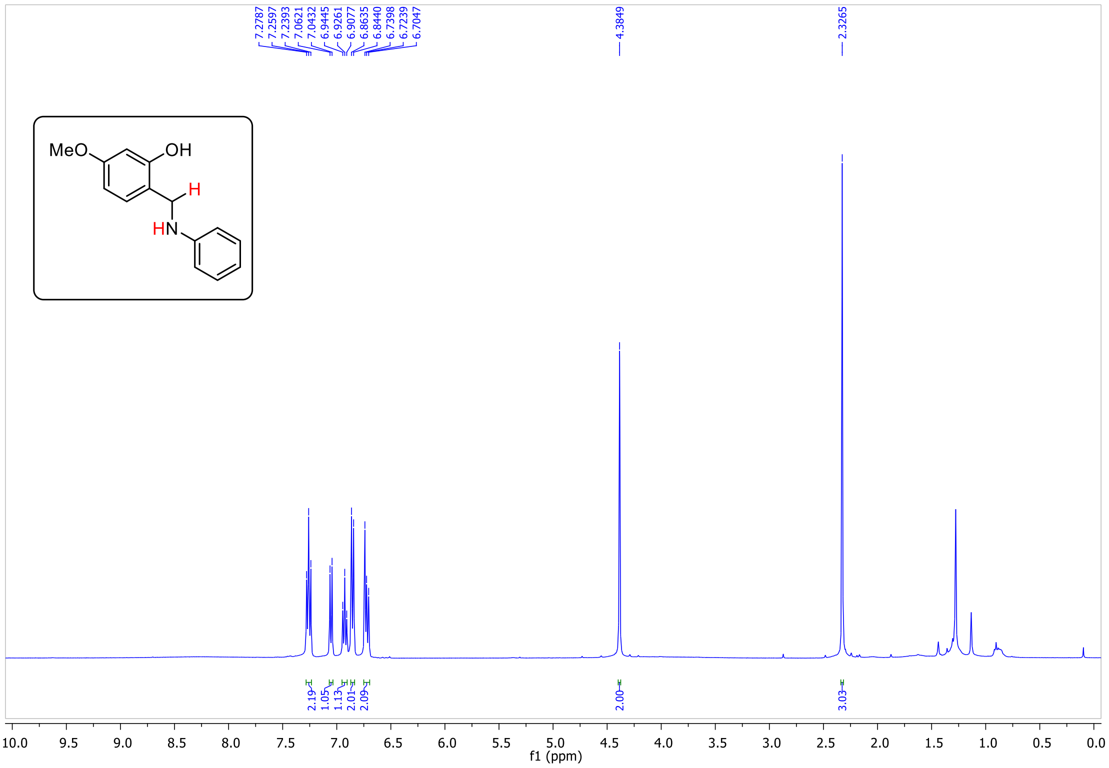
^{1}H NMR Spectrum for **53a**



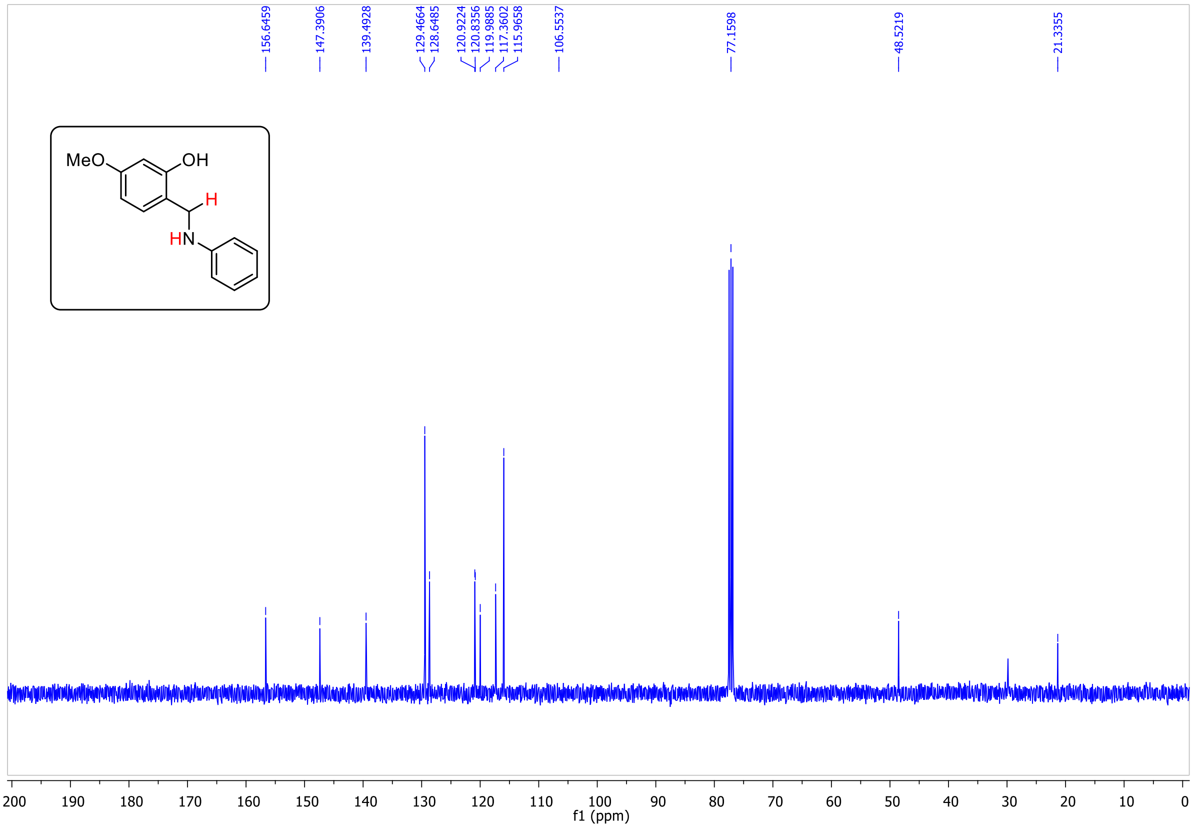
^{13}C NMR Spectrum for **53a**



^{1}H NMR Spectrum for **53b**



^{13}C NMR Spectrum for **53b**



References

(1) Castro, P. P.; Diederich, F. Optically Active Mono and Bis(1,1′-Binaphthyl)-Cyclophanes: Large Differences in the Complexation of Naproxen Derivatives in Aqueous Solution. *Tetrahedron Lett.* **1991**, *32* (44), 6277–6280. https://doi.org/10.1016/0040-4039(91)80146-W.

(2) Akiyama, T.; Itoh, J.; Yokota, K.; Fuchibe, K. Enantioselective Mannich-Type Reaction Catalyzed by a Chiral Brønsted Acid. *Angew. Chemie - Int. Ed.* **2004**, *43* (12), 1566–1568. https://doi.org/10.1002/anie.200353240.

(3) Uraguchi, D.; Terada, M. Chiral Brønsted Acid-Catalyzed Direct Mannich Reactions via Electrophilic Activation. *J. Am. Chem. Soc.* **2004**, *126* (17), 5356–5357. https://doi.org/10.1021/ja0491533.

(4) Parmar, D.; Sugiono, E.; Raja, S.; Rueping, M. Complete Field Guide to Asymmetric BINOL-Phosphate Derived Brønsted Acid and Metal Catalysis: History and Classification by Mode of Activation; Brønsted Acidity, Hydrogen Bonding, Ion Pairing, and Metal Phosphates. *Chem. Rev.* **2014**, *114* (18), 9047–9153. https://doi.org/10.1021/cr5001496.

(5) Richardson, C.; Reed, C. A. Exploration of the Pentacyano-Cyclo-Pentadienide Ion, C5(CN)5−, as a Weakly Coordinating Anion and Potential Superacid Conjugate Base. Silylation and Protonation. *Chem. Commun.* **2004**, *4* (6), 706–707. https://doi.org/10.1039/b316122f.

(6) O. Diels. No Titl. *Ber. Dtsch. Chem. Ges.* **1942**, *75*, 1452–1467.

(7) Radtke, M. A.; Dudley, C. C.; O’Leary, J. M.; Lambert, T. H. A Scalable, One-Pot Synthesis of 1,2,3,4,5-Pentacarbomethoxycyclopentadiene. *Synth.* **2019**, *51* (5), 1135–1138. https://doi.org/10.1055/s-0037-1611650.

(8) Gheewala, C. D.; Radtke, M. A.; Hui, J.; Hon, A. B.; Lambert, T. H. Methods for the Synthesis of Functionalized Pentacarboxycyclopentadienes. *Org. Lett.* **2017**, *19* (16), 4227–4230. https://doi.org/10.1021/acs.orglett.7b01867.

(9) Chirag D. Gheewala, Bridget E. Collins, T. H. L. *Anaromatic Ionplatform for EnantioselectiveBrønsted Acid Catalysis*; 2016; Vol. 351.

(10) Qiao, X.; El-Shahat, M.; Ullah, B.; Bao, Z.; Xing, H.; Xiao, L.; Ren, Q.; Zhang, Z.

Cyclopentadiene-Based Brønsted Acid as a New Generation of Organocatalyst for Transfer Hydrogenation of 2-Substituted Quinoline Derivatives. *Tetrahedron Lett.* **2017**, *58* (21), 2050–2053. https://doi.org/10.1016/j.tetlet.2017.04.038.

(11) Wang, D.; Wang, X.; Wang, D.; Lu, S.; Zhou, Y.; Li, Y. Highly Enantioselective Iridium-Catalyzed Hydrogenation of 2-Benzylquinolines and 2-Functionalized and 2 , 3-Disubstituted Quinolines. **2009**, No. 6, 2780–2787.

(12) Rueping, M.; Theissmann, T.; Antonchick, A. P. Metal-Free Brønsted Acid Catalyzed Transfer Hydrogenation - New Organocatalytic Reduction of Quinolines. *Synlett* **2006**, *2* (7), 1071–1074. https://doi.org/10.1055/s-2006-939706.

(13) Zhao, X.; Xiao, J.; Tang, W. Enantioselective Reduction of 3-Substituted Quinolines with a Cyclopentadiene-Based Chiral Brønsted Acid. *Synth.* **2017**, *49* (14), 3157–3164. https://doi.org/10.1055/s-0036-1589012.

(14) Gheewala, C. D.; Hirschi, J. S.; Lee, W. H.; Paley, D. W.; Vetticatt, M. J.; Lambert, T. H. Asymmetric Induction via a Helically Chiral Anion: Enantioselective Pentacarboxycyclopentadiene Brønsted Acid-Catalyzed Inverse-Electron-Demand Diels-Alder Cycloaddition of Oxocarbenium Ions. *J. Am. Chem. Soc.* **2018**, *140* (10), 3523–3527. https://doi.org/10.1021/jacs.8b00260.

(15) Radtke, M. A.; Lambert, T. H. Silylated Cyclopentadienes as Competent Silicon Lewis Acid Catalysts. *Chem. Sci.* **2018**, *9* (30), 6406–6410. https://doi.org/10.1039/c8sc02279h.

(16) Sui, Y.; Cui, P.; Liu, S.; Zhou, Y.; Du, P.; Zhou, H. Highly Enantioselective Synthesis of Cyclic Aminals with a Cyclopentadiene-Based Chiral Carboxylic Acid. *European J. Org. Chem.* **2018**, *2018* (2), 215–218. https://doi.org/10.1002/ejoc.201701561.

(17) Hammersley, G. R.; Nichol, M. F.; Steffens, H. C.; Delgado, J. M.; Veits, G. K.; Read de Alaniz, J. Enantioselective PCCP Brønsted Acid-Catalyzed Aza-Piancatelli Rearrangement. *Beilstein J. Org. Chem.* **2019**, *15*, 1569–1574. https://doi.org/10.3762/bjoc.15.160.

(18) Steiniger, K. A.; Lambert, T. H. Primary Alcohols via Nickel Pentacarboxycyclopentadienyl Diamide–Catalyzed Hydrosilylation of Terminal Epoxides. *ChemRxiv* **2019**, No. 1. https://doi.org/10.26434/chemrxiv.9936389.v1.

(19) Kottisch, V.; Jermaks, J.; Mak, J. Y.; Woltornist, R. A.; Lambert, T. H.; Fors, B. P. Hydrogen Bond Donor Catalyzed Cationic Polymerization of Vinyl Ethers. *Angew. Chemie - Int. Ed.* **2021**, *60* (9), 4535–4539. https://doi.org/10.1002/anie.202013419.

(20) Zhang, Z.; Schreiner, P. R. Thiourea-Catalyzed Transfer Hydrogenation of Aldimines. *Synlett* **2007**, *3* (9), 1455–1457. https://doi.org/10.1055/s-2007-980349.

(21) Bao, J.; Wulff, W. D.; Dominy, J. B.; Fumo, M. J.; Grant, E. B.; Rob, A. C.; Whitcomb, M. C.; Yeung, S. M.; Ostrander, R. L.; Rheingold, A. L. Synthesis, Resolution, and Determination of Absolute Configuration of a Vaulted 2,2′-Binaphthol and a Vaulted 3,3′-Biphenanthrol (VAPOL). *J. Am. Chem. Soc.* **1996**, *118* (14), 3392–3405. https://doi.org/10.1021/ja952018t.

(22) Li, G.; Liang, Y.; Antilla, J. C. A Vaulted Biaryl Phosphoric Acid-Catalyzed Reduction of α-Imino Esters: The Highly Enantioselective Preparation of α-Amino Esters. *J. Am. Chem. Soc.* **2007**, *129* (18), 5830–5831. https://doi.org/10.1021/ja070519w.

(23) Rueping, M.; Brinkmann, C.; Antonchick, A. P.; Atodiresei, I. Asymmetric Synthesis of Indolines by Catalytic Enantioselective Reduction of 3H-Indoles. *Org. Lett.* **2010**, *12* (20), 4604–4607. https://doi.org/10.1021/ol1019234.

(24) Šterk, D.; Stephan, M.; Mohar, B. Highly Enantioselective Transfer Hydrogenation of Fluoroalkyl Ketones. *Org. Lett.* **2006**, *8* (26), 5935–5938. https://doi.org/10.1021/ol062358r.

(25) Nguyen, Q. P. B.; Kim, T. H. S-Benzyl Isothiouronium Chloride as a Recoverable Organocatalyst for the Direct Reductive Amination of Ketones with Hantzsch Ester. *Synth.* **2012**, *44* (13), 1977–1982. https://doi.org/10.1055/s-0031-1291125.

(26) Morales, S.; Guijarro, F. G.; García Ruano, J. L.; Cid, M. B. A General Aminocatalytic Method for the Synthesis of Aldimines. *J. Am. Chem. Soc.* **2014**, *136* (3), 1082–1089. https://doi.org/10.1021/ja4111418.