Palladium–Catalyzed Allylic Etherification Using Organoboron Salts under mild Conditions

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MS09038

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BS-MS dual degree in science

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Certificate of Examination

This is to certify that the dissertation titled "Palladium–Catalyzed Allylic Etherification Using Organoboron Salts under mild Conditions" submitted by Mr. Chaman Lal Mahawar (Reg. No. MS09038) for the partial ful-filment of BS-MS dual degree programme 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.

Dr. S. A. Babu   Dr. Sugumar Venkataramani   Dr. R Vijaya Anand

                                                                                        (Supervisor)

                                                                Dated: April 25, 2014

Declaration

The work presented in this dissertation has been carried out by me under the guidance of Dr. R Vijaya Anand at the 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 acknowledgement 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.

<div align="right">

Chaman Lal Mahawar (MS09038)

(Candidate)

Dated: April 25, 2014

</div>

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.

<div align="right">

Dr. R Vijaya Anand

(Supervisor)

</div>

Acknowledgement

List of Tables

Abbreviations

|	
TMS-CF3	Trimethyl(trifluoromethyl)silane
DMF	Dimethyl formamide
THF	Tetrahydrofuran
DCM	Dichloromethane
DCE	Dichloroethane
IL	Ionic liquid
PTS	Polyoxyethanyl α-tocopheryl sebacate
MS	Molecular sieves
DMAc	Dimethylacetamide
TMS	Trimethylsilane
NMR	Nuclear magnetic resonance
FT-NMR	Fourier transform nuclear magnetic resonance
$NaBH_4$	Sodium borohydride
EtOAc	Ethyl acetate
TLC	Thin layer chromatography

Contents

Abstract

An efficient and base free palladium catalyzed allylic etherification method was developed for the synthesis of allyl aryl ethers, which are useful synthons of pharmaceutically interesting chroman derivatives, using organoboron salts as a coupling partner under mild conditions. Using this protocol a wide range of allyl aryl ethers were obtained in good to excellent yields using a variety of allyl acetates and organoboron salts.

CHAPTER 1

Introduction:

1.1 Overview:

Tsuji and co-workers, in 1965, developed the Pd-catalyzed methodology for the α-allylation of the carbonyl compounds with allyl acetate. In this protocol the formation of the product takes place via π-allylpalladium complex as an intermediate species (Scheme 1).[1]

$$X = CO_2C_2H_5, COCH_3$$
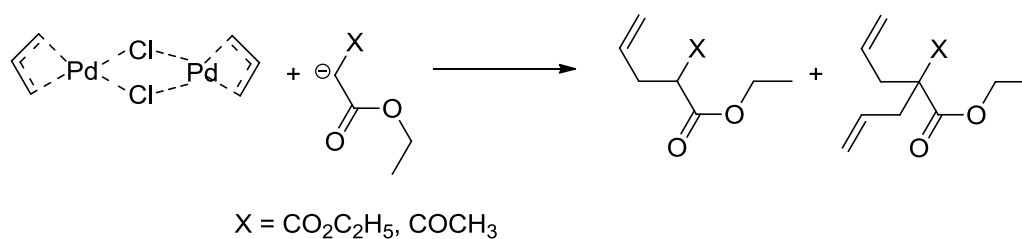
Scheme 1

Later in 1973, Trost and co-workers developed a methodology, where the activation of the allylic position of the olefins was achieved by Palladium (Scheme 2).[2]
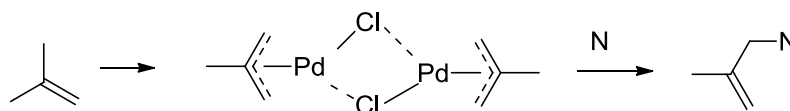

Where N is nucleophile.

Scheme 2

In 1985 Ehud Keinan, Abraham Nudelman and co-workers have developed the methodology for the palladium catalyzed allylic etherification of the allyl acetates in good to excellent yields at room temperature under mild conditions using tin alkoxides as nucleophiles. This methodology has been applied for the protection of the hydroxyl groups of carbohydrates and for selectively glycosidation of the allylic glycons as discussed authors in their work (Scheme 3).[3]
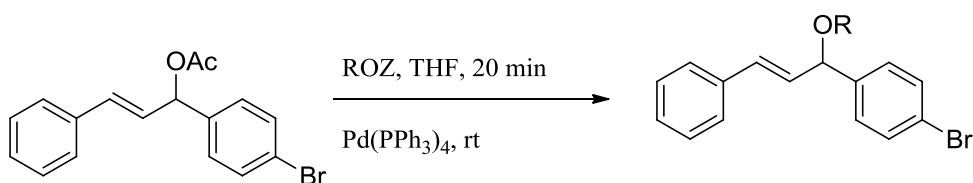
| Z = H | 0% (30 % after 24 h) |
Z = Na	6% (+ 85% of the corresponding allylic alcohol)
Z = SnBu$_3$	90%
Z = SnBu$_3$ [without Pd(0)]	0%
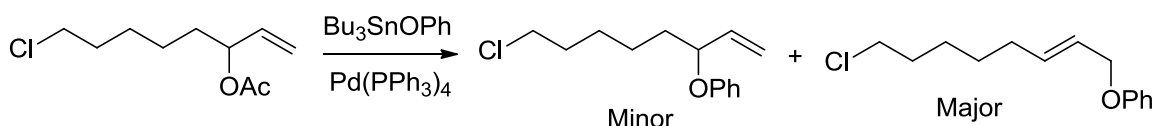
Scheme 3

Later in 1999 Hamada and co-workers reported the Pd catalyzed asymmetric allylic substitution of the allyl acetates with oxygen and nitrogen nucleophiles using chiral monodentate phosphine (9-PBN) as a ligand. Their main focus was on the asymmetric allylic amination of the allyl acetates using Pd(0) and chiral phosphine ligand, further elaboration was done by using the oxygen based nucleophiles. When they used methanol as a nucleophile the product ether was obtained at 60 ^{o}C in good yields but with poor enantiomeric excess. The same strategy was carried out by using trimethyl borate as nucleophile instead of the methanol, in this case the excess of the trimethyl borate (10 eq.) gave moderate to high enantioselectivity but with poor yield (Scheme 4).[4]
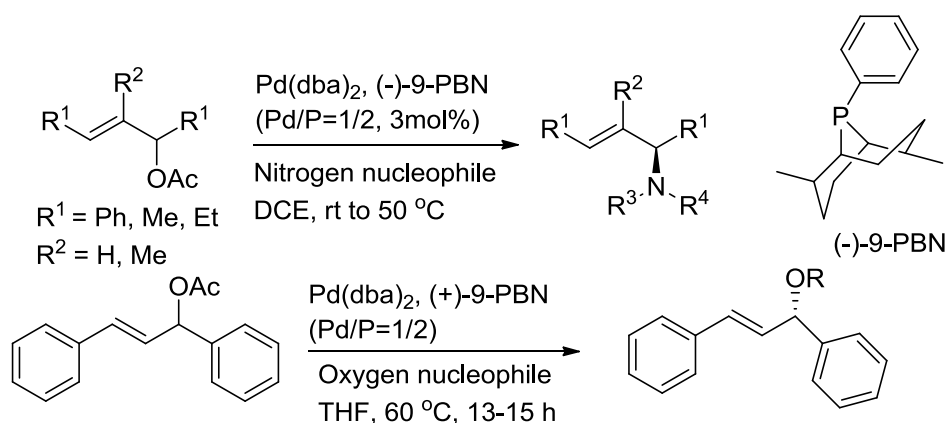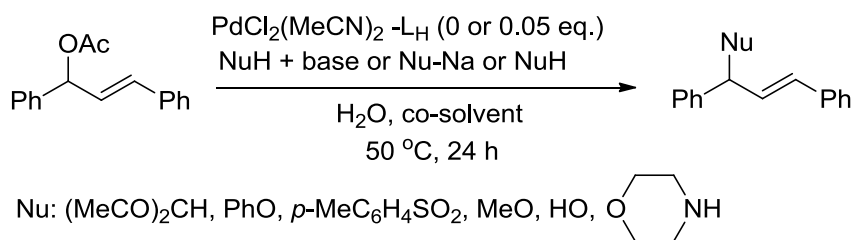

Scheme 4

Lee and co-workers reported Zn(II) alkoxides mediated palladium catalyzed allylic etherification as a mild and efficient method for the stereoselective formation of C-O bonds.

Zn(II) alkoxides promotes the addition of the oxygen nucleophiles (which is basically derived from the aliphatic alcohols) to η^3-allylpalladium complexes (Scheme 5).[5]
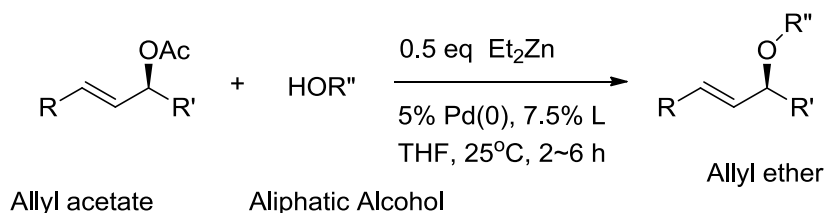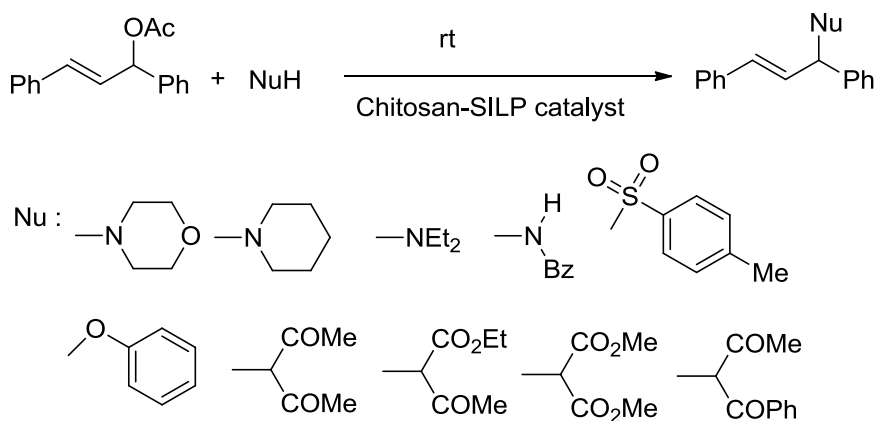

Scheme 5

Muzart and co-workers reported the transition metal free Tsuji-Trost type of the reaction in presence of water as a solvent. In this work the authors has used acetylacetone, phenol, morpholine as nucleophiles. First reaction was carried out using palladium catalyst, but later it was found that reaction can be preceded in absence of the palladium catalyst (Scheme 6).[6]

Nu: $(MeCO)_2CH$, PhO, $p\text{-}MeC_6H_4SO_2$, MeO, HO, $\underset{O}{\overset{}{\bigcirc}}NH$

Scheme 6

Recently Gaumont and co-workers reported the allylic substitution reaction using new SILP (supported ionic liquid phase) catalyst based on chitosan-supported ionic liquid. In the case of the amine as nucleophile the recyclability and reusability of the catalyst was shown, but in the case of phenol as a nucleophile, the product was obtained only in 68% yield. Chitosan is enantiopure biopolymer which has strong affinity towards the transition metals. Due to high absorption capacities towards the transition metals such as Pd and Pt on the surface of chitosan makes it more advantageous for the catalytic support (Scheme 7).[7]
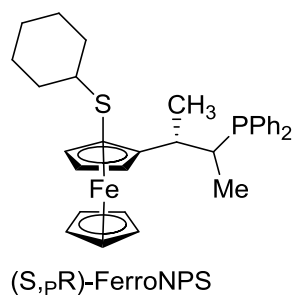
Scheme 7

Chan and co-workers have done the asymmetric allylic etherification using palladium–(S,pR)-ferro NPS-Catalyst. Ferro NPS ligand was synthesized from the Ugi's amine. The application of this ligand with palladium was discussed in their work. It was found that in presence of the ligand (L5) the ether product was isolated in good to excellent enantiomeric excess as well as in excellent yields (Scheme 8).[8]
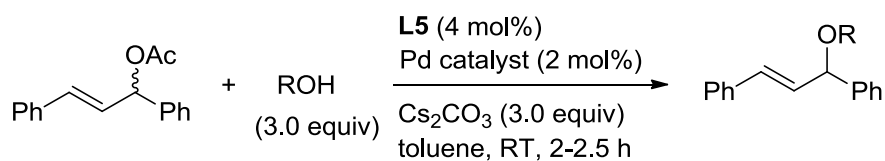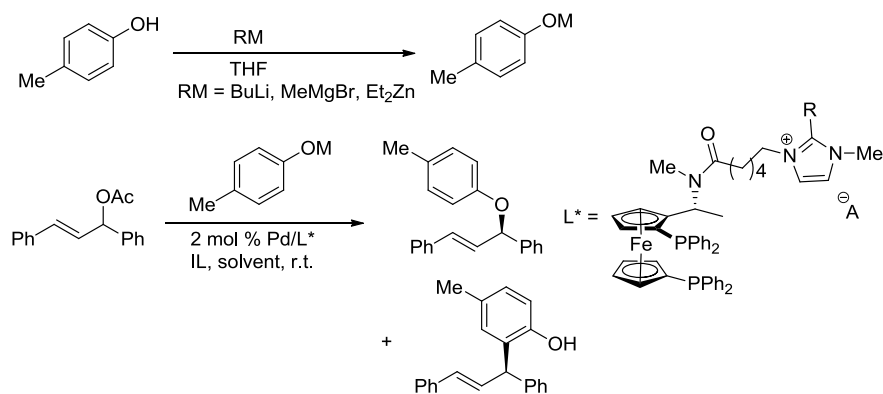

Where $[\{Pd(\eta^3\text{-}C_3H_5)Cl\}_2]$ was used as catalyst.

(S,pR)-FerroNPS

Scheme 8

Sebesta and co-workers reported the allylic substitution with heteroatom nucleophiles. Imidazolium-tagged ferrocenyl diphosphanes was used as ligand along with palladium catalyst. In their work phthalimide and phenol were used as nucleophiles (Scheme 9).[9]

Scheme 9

Very recently, Varma and co-workers reported the synthesis of allyl ethers in water using magnetically recoverable heterogeneous Pd catalyst under ambient conditions. They have prepared the catalyst by sonication of nano-ferrite with dopamine in aqueous suspension, then this dopamine functionalized nano-ferrite was treated with $PdCl_2$ under basic medium to get the Pd(II) catalyst which is basically supported on amine functionalized magnetic Fe_3O_4 nanoparticles (Scheme 10).[10]


Fe_3O_4-dopamine-Pd catalyst
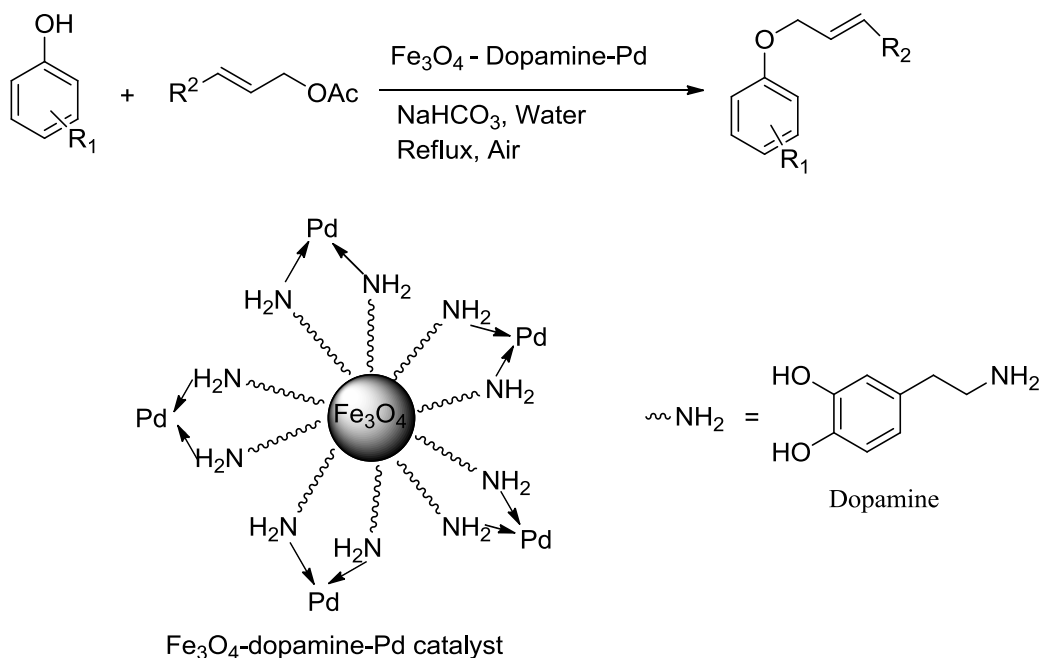
Scheme 10

1.2 Synthetic applications of allyl ethers:

There are many reports known where allyl ethers have been used as synthetic building blocks for the synthesis of the important molecules.

Barluenga and co-workers developed the metal free methodology for the synthesis of chromans and tetrahydroquinoline derivatives via intramolecular arylation reactions of alkenes promoted by iodonium ion (Scheme 11).[11]
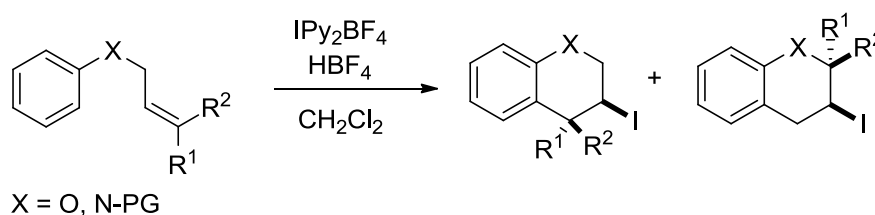
Scheme 11

In 2009 Lipshutz and co-workers reported the aminations of allyl ethers applying micellar catalysis under solvent free conditions. Methyl formate was used as an additive. PTS was used to form nanomicelle and reaction was performed in water (Scheme 12).[12]
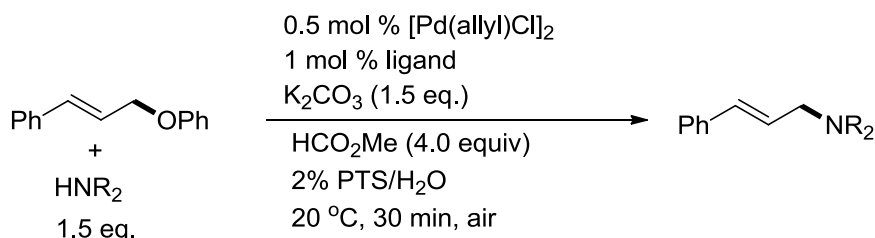
Scheme 12

In the same year 2009 the same authors published the palladium catalyzed Suzuki-Mayaura coupling reaction in water as solvent at room temperature using allyl ethers and boronic acids (Scheme 13).[13]
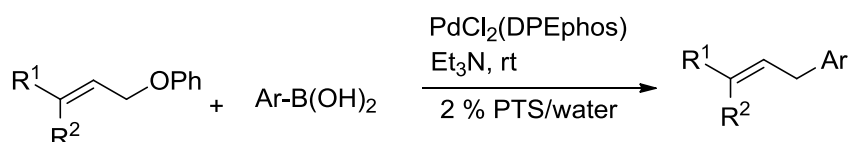
Scheme 13

Recently, Hajra and co-workers reported the copper catalyzed enantioselective aziridoarylation of allyl ethers for synthesis of *trans*-3-Amino-4-aryl chromans. The combination of copper catalyst and chiral bis-oxazoline ligand gave chroman derivatives in moderate yields and good to excellent enantiomeric excess (Scheme 14).[14]


i) PhINNs (1.0 equiv)
Cu-catalyst (0.10 equiv)
Ligand
MS 4A°, CHCl$_3$, 30 °C

ii) Cu(OTf)$_2$ (0.10 equiv)

Yield = 25-55 %, dr > 99:1
ee: up to 95 %

Cu-catalyst = Cu(OTf)$_2$
& Cu(ClO$_4$)$_2$.6H$_2$O

Ligand =
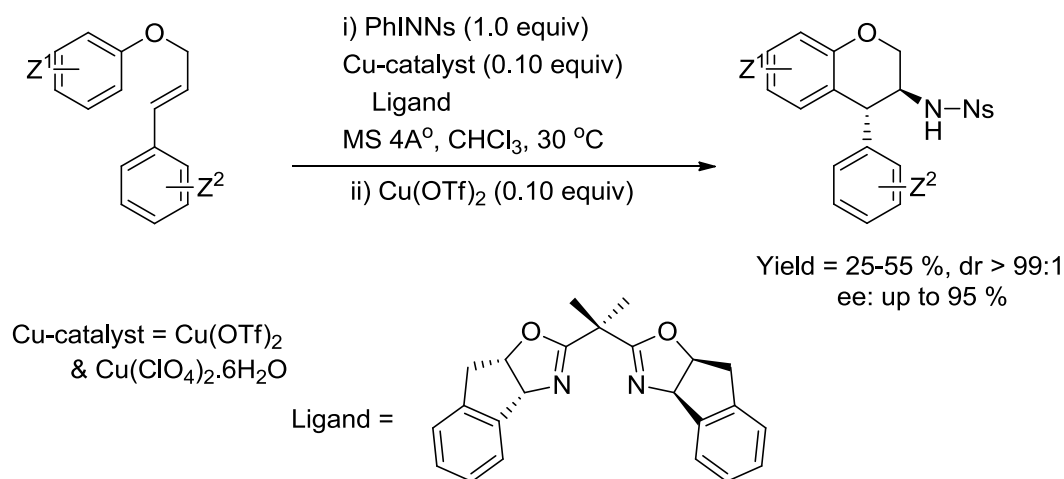
Scheme 14

1.3 Synthetic application of CF$_3$ containing borate salts and copper reagents:

In 2011 Dilman and co-workers reported a new methodology for the nucleophilic trifluoromethylation of the aldehydes and *N*-tosylimines using an organoboron reagent (acts as source of the nucleophilic trifluoromethyl group). They have synthesized the organoboron reagent by the reaction of TMS-CF$_3$ with trialkoxyborates in presence of the KF at room temperature (Scheme 15).[15]

1.2 eq. CF$_3$-B$^-$(OMe)$_3$ K$^+$

DMF, 50 °C, 1 h

1.2 eq. CF$_3$-B$^-$(OMe)$_3$ K$^+$

DMF, 50 °C, 1 h
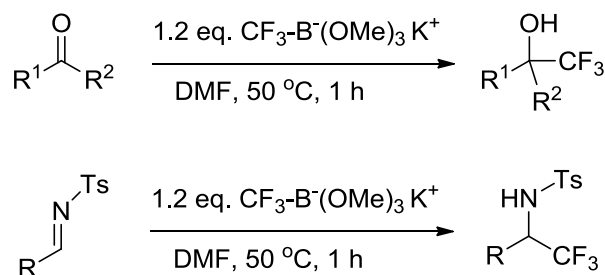
Scheme 15

Later in 2013 the same group reported the nucleophilic fluoroalkylation of (bromomethyl) pinacolboranes using fluoroalkyl silicon reagents. Then the intermediate organoboron salt was converted to boronic acids containing fluoroalkyl group at elevated temperatures (Scheme 16).[16]

7
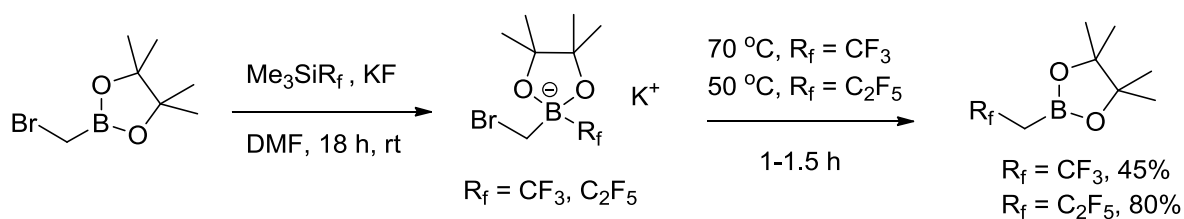
Scheme 16

In 2012 Szabo's group has reported the trifluoromethylation of the propargyl halides and propargyl trifluoroacetates using CF_3 anion transfer copper reagent, which basically provides CF_3 anion as a nucleophile, which leads to formation of allenyl or propargyl trifuoromethyl derivatives (Scheme 17).[17]
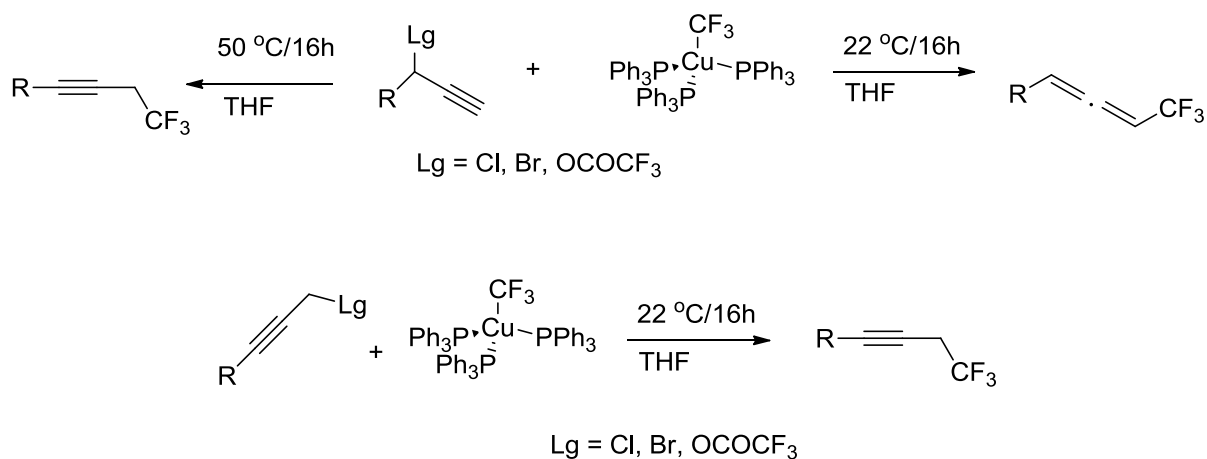

Scheme 17

CHAPTER 2

Experimental Section:

2.1 General Methods: All reactions were performed under inert atmosphere. All the reagents used were purchased from the commercially available sources and used as such. ^{1}H, ^{13}C, ^{19}F and ^{11}B NMR spectra were analyzed in deuterated solvents using 400 MHz, 100 MHz, 376 MHz, 128 MHz Bruker FT-NMR spectrometers. Chemical shift values were analyzed in parts per million keeping TMS and $BF_3.OEt_2$ as background reference. Merck silica gel 60 F_{254} TLC plates were used to perform the thin layer chromatography using EtOAc/Hexane mixture as an eluent. Neutral alumina and acidic silica gel columns were used for the chromatographic separation.

2.2 General procedure for the synthesis of borate salts: A solution of $NaBH_4$ (1 mmol) in THF was stirred with aromatic alcohols (3.8 mmol) at room temperature for 15-80 h. The solvent THF was removed under high vacuum, giving quantitative yields of tetraaryloxyborates.

Sodium Tetraphenoxyborate (1):
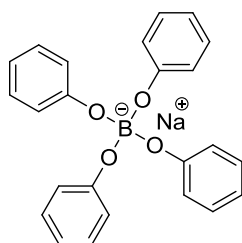
Quantitative yield, ^{1}H NMR (400 MHz, CD$_3$OD): δ 7.19-7.15 (m, 8H), 6.82-6.79 (m, 12H); ^{13}C NMR (100 MHz, CD$_3$OD): δ 159.4, 131.22, 121.1, 117.1; ^{11}B NMR (128 MHz, CD$_3$OD): δ 3.71.

Sodium Tetrakis(2,5-dimethylphenoxy)borate (2):
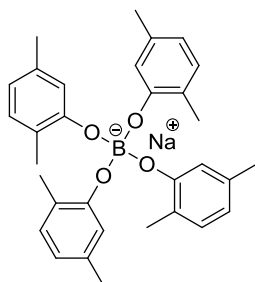
Quantitative yield, ^{1}H NMR (400 MHz, CD$_3$OD): δ 6.93-6.91 (m, 4H), 6.58-6.53 (m, 8H), 2.23 (s, 12H), 2.14 (s, 12H); ^{13}C NMR (100 MHz, CD$_3$OD): δ 157.1, 138.2, 132.3, 123.1, 121.9, 117.1, 21.9, 16.6; ^{11}B NMR (128 MHz, CD$_3$OD): δ 3.14.

Sodium Tetrakis(4-bromophenoxy)borate (3):
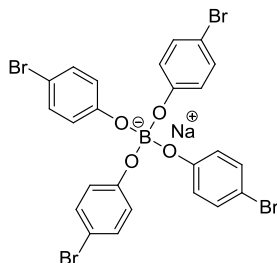
Quantitative yield, ^{1}H NMR (400 MHz, CD$_3$OD): δ 7.28 (d, J = 9.0 Hz, 8H), 6.72 (d, J = 9.0 Hz, 8H); ^{13}C NMR (100 MHz, CD$_3$OD): δ 159.2, 134.0, 119.2, 112.5; ^{11}B NMR (128 MHz, CD$_3$OD): δ 4.21.

Sodium Tetrakis([1,1'-biphenyl]-4-yloxy)borate (4):
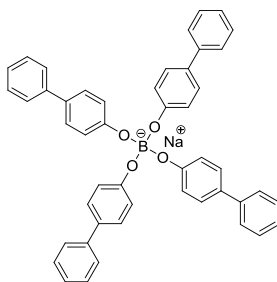
Quantitative yield, ^{1}H NMR (400 MHz, CD$_3$OD): δ 7.55-7.52 (m, 8H), 7.45 (d, J = 8.8 Hz, 8H), 7.40-7.36 (m, 8H), 7.28-7.23 (m, 4H), 6.88 (d, J = 8.8 Hz, 8H); ^{13}C NMR (100 MHz, CD$_3$OD): δ 159.3, 143.3, 134.4, 130.5, 129.8, 128.2, 128.1, 117.6; ^{11}B NMR (128 MHz, CD$_3$OD): δ 3.91.

Sodium Tetrakis(4-(tert-butyl)phenoxy)borate (5):
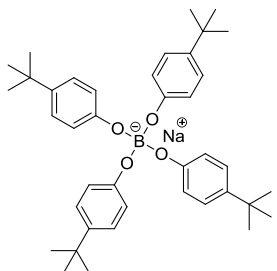
Quantitative yield, ^{1}H NMR (400 MHz, CD$_3$OD): δ 7.23-7.20 (m, 8H), 6.73-6.71 (m, 8H), 1.29 (s, 36H); ^{13}C NMR (100 MHz, CD$_3$OD): δ 156.8, 143.9, 127.9, 116.5, 35.6, 32.8; ^{11}B NMR (128 MHz, CD$_3$OD): δ 3.06.

2.3 General procedure for the synthesis of allyl alcohols:

To a stirred solution of aldehyde (1 mmol) in Et$_2$O (5 ml) was added vinyl magnesium bromide (1.3 mmol) over a period of 15 minutes at 0 ^{o}C. The mixture was stirred over night at room temperature and a saturated solution of NH$_4$Cl was poured into the resulting reaction mixture. It was extracted with Et$_2$O, dried over MgSO$_4$ and concentrated in *vacuo*. The crude product was purified by column chromatography.

1-phenylprop-2-en-1-ol (6):
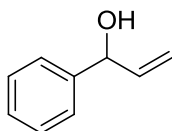
1.17 g, 92.76% yield, ^{1}H NMR (400 MHz, CDCl$_3$): δ 7.39-7.27 (m, 5H), 6.09-6.01 (m, 1H), 5.38-5.33 (m, J = 17.1 Hz, 1H), 5.22-5.18 (m, 2H), 2.11 (s, 1H); ^{13}C NMR (100 MHz, CDCl$_3$): δ 142.6, 140.3, 128.6, 127.8, 126.4, 115.2, 75.4.

1-(4-chlorophenyl)prop-2-en-1-ol (7):
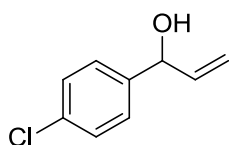
168 mg, 70.35% yield, ^{1}H NMR (400 MHz, CDCl$_3$): δ 7.34-7.29 (m, 4H), 6.00 (ddd, J = 17.1, 10.3, 6.1 Hz, 1H), 5.34 (td, J = 17.1 Hz, 1.32, 1H), 5.22-5.17 (m, 2H), 2.01 (s, 1H); ^{13}C NMR (100 MHz, CDCl$_3$): δ 141.0, 140.0, 133.5, 128.8, 127.8, 115.8, 74.8.

1-(4-methoxyphenyl)prop-2-en-1-ol (8):
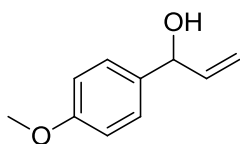
155.5 mg, 86.02% yield, ^{1}H NMR (400 MHz, CDCl$_3$): δ 7.31-7.27 (m, 2H), 6.90-6.87 (m, 2H), 6.08-6.00 (m, 1H), 5.36-5.31 (m, 1H), 55.20-5.15 (m, 2H), 3.80 (s, 3H), 1.96 (s, 1H); ^{13}C NMR (100 MHz, CDCl$_3$): δ 159.4, 140.5, 135.0, 127.9, 115.0, 114.1, 75.1, 55.5.

1-(m-tolyl)prop-2-en-1-ol (9):
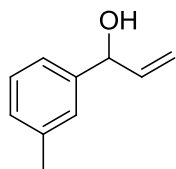
166.2 mg, 67.42% yield, ^{1}H NMR (400 MHz, CDCl$_3$): δ 7.25-7.15 (m, 3H), 7.11 (d, J = 7.4, 1H), 6.05 (ddd, J = 17.1, 16.3, 6.00 Hz, 1H), 5.38-5.34 (m, J = 17.1 Hz, 1H), 5.22-5.17 (m, 2H), 2.36 (s, 3H), 1.9 (s, 1H); ^{13}C NMR (100 MHz, CDCl$_3$): δ 142.6, 140.3, 138.4, 128.6, 127.1, 123.5, 115.1, 75.5, 21.5.

1-(4-nitrophenyl)prop-2-en-1-ol (10):
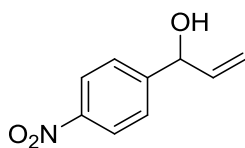
194.3 mg, 54.37% yield, ^{1}H NMR (400 MHz, CDCl$_3$): δ 8.23-8.19 (m, 2H), 7.57-7.54 (m, 2H), 5.99 (ddd, J = 17.0, 10.4, 6.5 Hz, 1H), 5.42-5.37 (m, 1H), 5.31 (d, J = 6.5 Hz, 1H), 5.29-5.26 (m, 1H), 2.14 (s, 1H); ^{13}C NMR (100 MHz, CDCl$_3$): δ 149.6, 139..3, 127.0, 123.8, 117.0, 74.7.

1-(2-fluorophenyl)prop-2-en-1-ol (11):
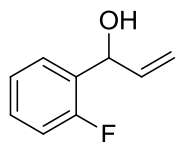
315.7 mg, 85.84% yield, ^{1}H NMR (400 MHz, CDCl$_3$): δ 7.47-7.42 (m, 1H), 7.29-7.24 (m, 1H), 7.17-7.13 (m, 1H), 7.06-7.10 (m, 1H), 6.11-6.03 (m, 1H), 5.52 (d, J = 5.6 Hz, 1H), 5.38-5.33 (m, 1H), 5.22-5.19 (m, 1H), 2.06 (s, 1H); ^{13}C NMR (100 MHz, CDCl$_3$): δ 160.1 (d, $J_{C\text{-}F}$ = 244.9 Hz), 138.9, 129.7 (d, $J_{C\text{-}F}$ = 13.1 Hz), 129.3 (d, $J_{C\text{-}F}$ = 8.5 Hz), 127.7 (d, $J_{C\text{-}F}$ = 4.0 Hz), 124.4 (d, $J_{C\text{-}F}$ = 3.6 Hz), 115.6, 115.4 (d, $J_{C\text{-}F}$ = 3.3 Hz), 69.3 (d, $J_{C\text{-}F}$ = 2.9 Hz); ^{19}F NMR (376 MHz, CDCl$_3$): δ -119.2.

2.4 General procedure for the synthesis of allyl acetates:

To a solution of allyl alcohol (1.0 mmol) in DCM (5 ml) was added Et$_3$N (3.0 mmol) at 0 $^{\circ}$C slowly under dry conditions. After stirring for 15 minutes at 0 $^{\circ}$C, acetic anhydride (3.0 mmol) was added slowly and resulting solution was stirred over-night. Water was added to the reaction mixture and it was extracted with DCM, dried over MgSO$_4$ and concentrated in *vacuo*. The crude product was purified by column chromatography.

1-phenylallyl acetate (12):
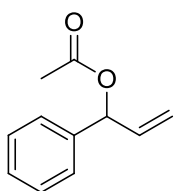
378.8 mg, 96.22% yield, ^{1}H NMR (400 MHz, CDCl$_3$): δ 7.38-7.28 (m, 5H), 6.27 (td, J = 5.9, 1.4 Hz, 1H), 6.01 (ddd, J = 17.1, 16.3, 5.9 Hz, 1H), 5.29 (td, J = 17.1, 1.3 Hz, 1H), 5.25 (td, J = 10.5, 1.3 Hz, 1H), 2.1 (s, 3H); ^{13}C NMR (100 MHz, CDCl$_3$): δ 170.1, 138.9, 136.3, 128.6, 128.2, 127.2, 117.0, 76.3, 21.3.

1-(4-chlorophenyl)allyl acetate (13):
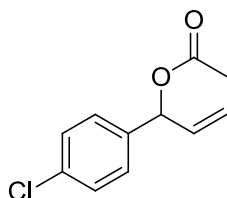
168 mg, 86.97% yield, ^{1}H NMR (400 MHz, CDCl$_3$): δ 7.34-7.27 (m, 4H), 6.21 (d, J = 5.8 Hz, 1H), 5.96 (ddd, J = 17.1, 16.3, 5.9 Hz, 1H), 5.30-5.24 (m, 2H), 2.10 (s, 3H); ^{13}C NMR (100 MHz, CDCl$_3$): δ 170.0, 137.5, 135.9, 134.1, 128.8, 128.7, 117.4, 75.5, 21.3.

1-(4-methoxyphenyl)allyl acetate (14):
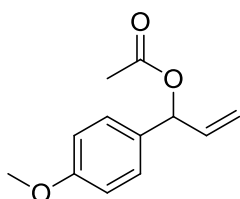
159.7 mg, 78.88% yield, ^{1}H NMR (400 MHz, CDCl$_3$): δ 7.34-7.30 (m, 2H), 6.87-6.83 (m, 2H), 6.59 (d, J = 15.8 Hz, 1H), 6.15 (td, J = 15.8, 6.6 Hz, 1H), 4.7 (d, J = 1.2 Hz, 2H), 3.80 (s, 3H), 2.09 (s, 3H); ^{13}C NMR (100 MHz, CDCl$_3$): δ 171.0, 159.7, 134.1, 129.0, 127.9, 120.9, 114.1, 65.4, 55.3, 21.1.

1-(m-tolyl)allyl acetate (15):
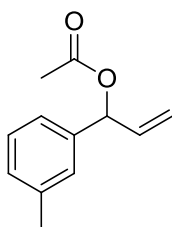
100.3 mg, 68.32% yield, ^{1}H NMR (400 MHz, CDCl$_3$): δ 7.27-7.23 (m, 1H), 7.16-7.11 (m, 3H), 6.22 (d, J = 5.9 Hz, 1H), 6.00 (ddd, J = 17.1, 16.3, 5.9 Hz, 1H), 5.31-5.22 (m, 2H), 2.35 (s, 3H), 2.11 (s, 3H); ^{13}C NMR (100 MHz, CDCl$_3$): δ 170.1, 138.9, 138.3, 136.4, 129.0, 128.6, 127.9, 124.3, 116.8, 76.3, 21.5, 21.4.

1-(4-nitrophenyl)allyl acetate (16):
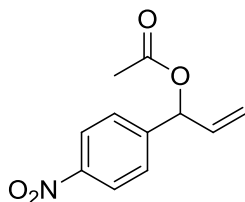
183.5 mg, 76.90% yield, ^{1}H NMR (400 MHz, CDCl$_3$): δ 8.24-8.20 (m, 2H), 7.53-7.50 (m, 2H), 6.30 (d, J = 6.2 Hz, 1H), 6.00-5.91 (m, 1H), 5.36-5.30 (m, 2H), 2.15 (s, 3H); ^{13}C NMR (100 MHz, CDCl$_3$): δ 169.8, 146.1, 135.1, 127.9, 123.9, 118.6, 75.3, 21.2.

1-(2-fluorophenyl)allyl acetate (17):
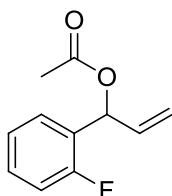
334.8 mg, 83.09% yield, ^{1}H NMR (400 MHz, CDCl$_3$): δ 7.38 (dt, J = 1.8 Hz, 1H), 7.32-7.26 (m, 1H), 7.14 (dt, J = 1.2 Hz, 1H), 7.07-7.03 (m, 1H), 6.53 (d, J = 5.9 Hz, 1H), 6.07-5.99 (m, 1H), 5.31-5.24 (m, 2H), 2.12 (s, 3H); ^{13}C NMR (100 MHz, CDCl$_3$): δ 169.8, 160.1 (d, $J_{C\text{-}F}$ =

247.0 Hz), 135.1, 129.9 (d, J_{C-F} = 8.1 Hz), 128.4 (d, J_{C-F} = 3.7 Hz), 126.3 (d, J_{C-F} = 13.5 Hz), 124.3 (d, J_{C-F} = 3.6 Hz), 117.4, 115.7 (d, J_{C-F} = 21.3 Hz), 70.5 (d, J_{C-F} = 3.0 Hz), 21.2; ^{19}F NMR (376 MHz, CDCl$_3$): δ -117.5.

1-(pyren-4-yl)allyl acetate (18):
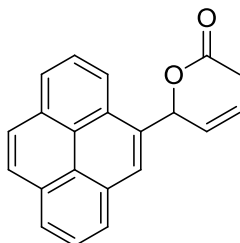
305.2 mg, 58.10% yield, ^{1}H NMR (400 MHz, CDCl$_3$): δ 8.34 (d, J = 9.3 Hz, 1H), 8.18-8.10 (m, 5H), 8.03-7.98 (m, 3H), 7.70 (d, J = 15.7 Hz, 1H), 6.50 (td, J = 15.7, 6.4 Hz, 1H), 4.93 (dd, J = 6.4, 1.4 Hz, 2H), 2.18 (s, 3H); ^{13}C NMR (100 MHz, CDCl$_3$): δ 171.0, 131.5, 131.2, 130.9, 130.8, 128.3, 127.8, 127.5, 127.5, 126.5, 126.1, 125.4, 125.2, 125.1, 124.9, 124.9, 124.1, 122.4, 65.5, 21.2.

2.5 General procedure for the synthesis of allyl ethers:

To a solution of allyl acetate (1.0 mmol) in dry DCM (2 ml) was added sodium tetra-aryloxyborate (1.5 mmol) and Pd(PPh$_3$)$_4$ (5 mol%) at room temperature under dry conditions. Resulting solution was stirred for 12-78 h. After completion of the reaction, reaction mixture was concentrated in *vacuo*. The crude product was purified by column chromatography.

(cinnamyloxy)benzene (19):
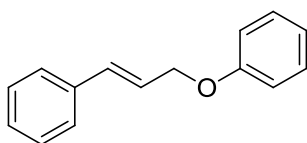
25.4 mg, 99.02% yield, ^{1}H NMR (400 MHz, CDCl$_3$): δ 7.44-7.41 (m, 2H), 7.36-7.25 (m, 5H), 7.00-6.96 (m, 3H), 6.75 (d, J = 15.9 Hz, 1H), 6.44 (td, J = 15.9, 5.8 Hz, 1H), 4.71 (d, J = 5.8 Hz, 2H); ^{13}C NMR (100 MHz, CDCl$_3$): δ 158.7, 130.5, 133.09, 129.6, 128.7, 128.0, 126.7, 124.6, 121.0, 114.9, 68.6.

(E)-1-methyl-2-(3-phenoxyprop-1-en-1-yl)benzene (20):
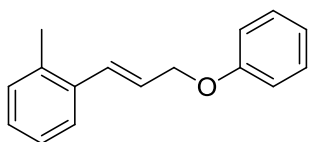
23.4 mg, 91.46% yield, ^{1}H NMR (400 MHz, CDCl$_3$): δ 7.33-7.28 (m, 2H), 7.25-7.22 (m, 3H), 7.09-7.07 (m, 1H), 6.99-6.95 (m, 3H), 6.71 (td, J = 16.0, 1.4 Hz, 1H), 6.42 (td, J = 16.0, 5.8 Hz, 1H), 4.70 (d, J = 5.8 Hz, 2H), 2.35 (s, 3H); ^{13}C NMR (100 MHz, CDCl$_3$): δ 158.7, 138.2, 136.4, 133.2, 129.6, 128.8, 128.6, 127.4, 124.0, 123.8, 120.9, 114.8, 68.7, 21.5.

(E)-1-chloro-4-(3-phenoxyprop-1-en-1-yl)benzene (21):
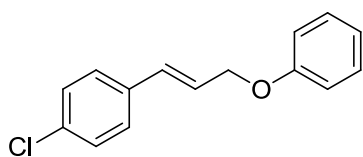
26.41 mg, 96.32% yield, ^{1}H NMR (400 MHz, CDCl$_3$): δ 7.36-7.28 (m, 6H), 7.00-6.94 (m, 3H), 6.69 (td, J = 16.0, 1.5 Hz, 1H), 6.40 (td, J = 16.0, 5.7 Hz, 1H), 4.69 (d, J = 5.7 Hz, 2H); ^{13}C NMR (100 MHz, CDCl$_3$): δ 158.6, 135.0, 133.6, 131.7, 129.6, 128.8, 127.9, 125.3, 121.1, 114.8, 68.44.

(E)-1-methoxy-4-(3-phenoxyprop-1-en-1-yl)benzene (22):
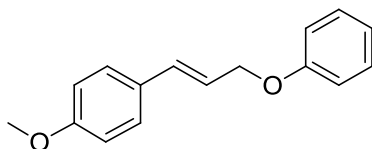
20.4 mg, 94.24% yield, ^{1}H NMR (400 MHz, CDCl$_3$): δ 7.37-7.33 (m, 2H), 7.32-7.27 (m, 2H), 6.98-6.94 (m, 3H), 6.88-6.84 (m, 2H), 6.68 (d, J = 15.9 Hz, 1H), 6.29 (td, J = 15.9, 6.0 Hz, 1H), 4.68 (d, J = 6.0 Hz, 2H), 3.81 (s, 3H); ^{13}C NMR (100 MHz, CDCl$_3$): δ 159.5, 158.7, 132.9, 129.6, 129.3, 127.9, 122.2, 120.9, 114.9, 114.1, 68.9, 55.4.

(E)-1-nitro-4-(3-phenoxyprop-1-en-1-yl)benzene (23):
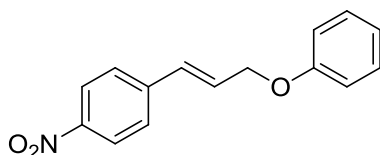
28.02 mg, 93% yield, ^{1}H NMR (400 MHz, CDCl$_3$): δ 8.21-8.17 (m, 2H), 7.55-7.52 (m, 2H), 7.34-7.29 (m, 2H), 7.01-6.94 (m, 3H), 6.82 (d, J = 16.0 Hz, 1H), 6.60 (td, J = 16.0, 5.2 Hz, 1H), 4.75 (d, J = 5.2 Hz, 2H); ^{13}C NMR (100 MHz, CDCl$_3$): δ 158.4, 147.2, 143.0, 130.2, 129.7, 127.2, 127.1, 121.3, 114.8, 67.9.

(E)-4-(3-phenoxyprop-1-en-1-yl)pyrene (24):
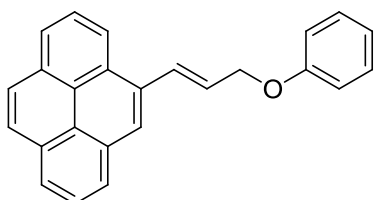
18.3 mg, 77.22% yield, ^{1}H NMR (400 MHz, CDCl$_3$): δ 8.35 (d, J = 9.3 Hz, 1H), 8.21-8.09 (m, 5H), 8.05-7.98 (m, 3H), 7.80 (d, J = 15.8 Hz, 1H), 7.38-7.33 (m, 2H), 7.08-7.06 (m, 2H), 7.03-6.99 (m, 1H), 6.65 (td, J = 15.8, 5.7 Hz, 1H), 4.90 (d, J = 5.7 Hz, 2H); ^{13}C NMR (100 MHz, CDCl$_3$): δ 158.8, 131.5, 131.2, 131.1, 131.0, 130.2, 129.7, 128.3, 127.9, 127.7, 127.5, 127.5, 126.1, 125.4, 125.2, 125.1, 125.0, 125.0, 124.2, 123.1, 121.1, 115.0, 69.0.

(E)-1-fluoro-2-(3-phenoxyprop-1-en-1-yl)benzene (25):
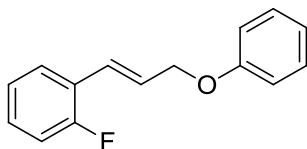
34.69 mg, 90.0% yield, ^{1}H NMR (400 MHz, CDCl$_3$): δ 7.49 (dt, J = 1.8 Hz, 1H), 7.34-7.29 (m, 2H), 7.25-7.20 (m, 1H), 7.13-7.02 (m, 2H), 7.00-6.96 (m, 3H), 6.91 (td, J = 16.1, 1.4 Hz, 1H), 6.52 (td, J = 16.1, 5.7 Hz, 1H), 4.73 (d, J = 5.7 Hz, 2H); ^{13}C NMR (100 MHz, CDCl$_3$): δ 160.4 (d, $J_{C\text{-}F}$ = 248.4 Hz), 158.6, 129.6, 129.3 (d, $J_{C\text{-}F}$ = 8.7 Hz), 127.7 (d, $J_{C\text{-}F}$ = 3.8 Hz), 127.3 (d, $J_{C\text{-}F}$ = 5.1 Hz), 125.4 (d, $J_{C\text{-}F}$ = 3.7 Hz), 124.3 (d, $J_{C\text{-}F}$ = 11.7 Hz), 124.2 (d, $J_{C\text{-}F}$ = 3.7 Hz), 121.0, 115.9 (d, $J_{C\text{-}F}$ = 21.9 Hz), 114.8, 68.7; ^{19}F NMR (376 MHz, CDCl$_3$): δ -117.8.

1-bromo-4-(cinnamyloxy)benzene (26):
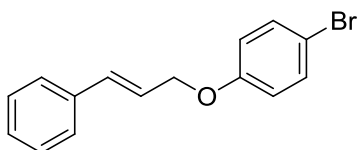
22.7 mg, 84.06% yield, ^{1}H NMR (400 MHz, CDCl$_3$): δ 7.42-7.33 (m, 3H), 7.32-7.25 (m, 4H), 6.86-6.82 (m, 2H), 6.72 (d, J = 15.9 Hz, 1H), 6.39 (td, J = 15.9, 5.8 Hz, 1H), 4.67 (d, J = 5.8 Hz, 2H); ^{13}C NMR (100 MHz, CDCl$_3$): δ 157.8, 136.3, 133.4, 132.4, 128.7, 128.1, 126.7, 124.0, 116.7, 113.1, 68.9.

1-(tert-butyl)-4-(cinnamyloxy)benzene (27):
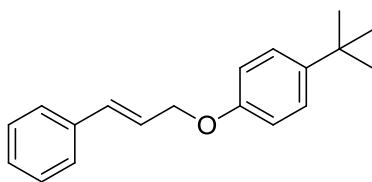
27.5 mg, 91% yield, ^{1}H NMR (400 MHz, CDCl$_3$): δ 7.43-7.40 (m, 2H), 7.35-7.24 (m, 5H), 6.93-6.89 (m, 2H), 6.74 (d, J = 16.0 Hz, 1H), 6.43 (td, J = 16.0, 5.8 Hz, 1H), 4.69 (d, J = 5.8 Hz, 2H), 1.31 (s, 9H); ^{13}C NMR (100 MHz, CDCl$_3$): δ 156.5, 143.6, 136.6, 132.9, 128.7, 127.9, 126.7, 126.4, 124.8, 114.3, 68.7, 34.2, 31.6.

4-(cinnamyloxy)-1,1'-biphenyl (28):
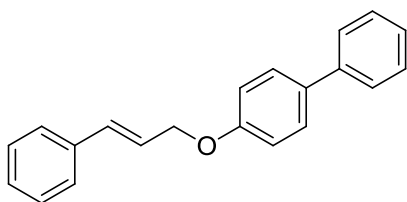
30.6 mg, 94.62% yield, ^{1}H NMR (400 MHz, CDCl$_3$): δ 7.58-7.52 (m, 4H), 7.45-7.40 (m, 4H), 7.36-7.25 (m, 4H), 7.06-7.02 (m, 2H), 6.77 (d, J = 16.0 Hz, 1H), 6.45 (td, J = 16.0, 6.0 Hz, 1H), 4.78 (d, J = 6.0 Hz, 2H); ^{13}C NMR (100 MHz, CDCl$_3$): δ 158.3, 140.9, 136.5, 134.1, 133.2, 128.8, 128.7, 128.3, 128.0, 126.8, 126.8, 126.7, 124.5, 115.1, 68.8.

2-(cinnamyloxy)-1,4-dimethylbenzene (29):
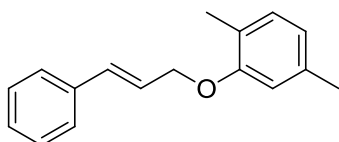
21.6 mg, 85.97% yield, ^{1}H NMR (400 MHz, CDCl$_3$): δ 7.45-7.43 (m, 2H), 7.37-7.33 (m, 2H), 7.29-7.25 (m, 1H), 7.05 (d, J = 7.8 Hz, 1H), 6.78-6.72 (m, 3H), 6.49-6.42 (m, 1H), 4.73 (d, J = 5.9 Hz, 2H), 2.34 (s, 3H), 2.26 (s, 3H); ^{13}C NMR (100 MHz, CDCl$_3$): δ 156.8, 136.7, 136.6, 132.2, 130.5, 128.7, 127.9, 126.6, 125.2, 123.9, 121.1, 112.5, 68.7, 21.5, 16.0.

CHAPTER 3

Results and Discussions:

Since our group is interested in nucleophilic and electrophilic trifluoromethylation reactions, we thought of developing trifluoromethylation of allyl acetates under Tsuji-Trost conditions using $CF_3B(OMe)_3K$ salt as a nucleophilic trifluoromethylating agent (Scheme 18). We tried this reaction under various reaction conditions with different Pd catalysts using cinnamyl acetate as s starting material. Although the starting material was consumed under the reaction conditions, the expected trifluoromethylated product was not obtained; instead methyl migration was observed (Scheme 18, Table 1).
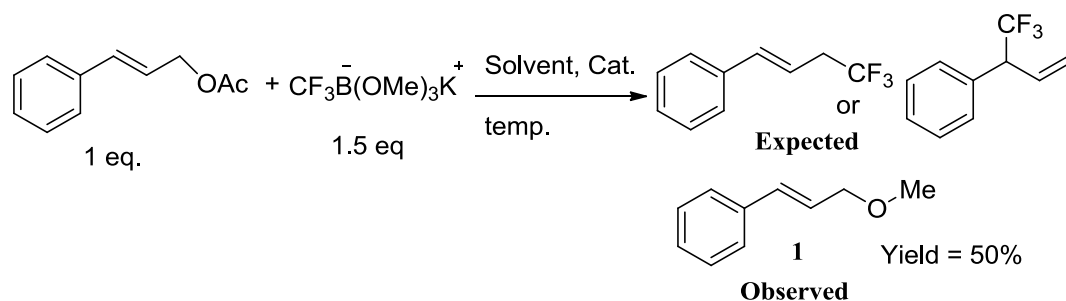
Scheme 18

Table: 1. Optimization Table.

S.N.	Catalyst	Solvent	Temp.	Result
1	Pd(OAc)$_2$	THF	RT, 50 °C, 100 °C	No reaction
2	Pd(PPh$_3$)$_4$	THF	R.T.	Observed 1
3	Pd(PPh$_3$)$_4$	THF	80 °C or 100 °C	No CF$_3$ incorporation and no improvement in the Yield of 1

Encouraged by this preliminary result, we thought of developing the allylic etherification reactions using tetraaryloxyborate salt instead of trifluoromethyl

trialkoxyborate salt (Scheme 19). It was observed that when tetraaryloxyborate salts were used as a source of aryloxy nucleophile, the expected aryloxylated products were obtained in good to excellent yields. Another important thing is that the reaction proceeded smoothly at room temperature. Few reports are already known for the synthesis of the allyl ethers using Tsuji-Trost protocol but involve higher temperatures and bases.
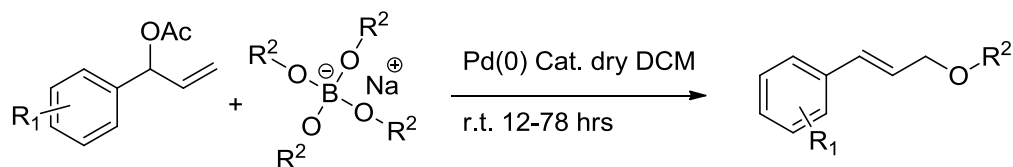
Scheme 19

Before going for the optimization, a variety of sodium tetraaryloxy borate salts were synthesized by reaction of phenols with $NaBH_4$ according to the literature procedure (Table 2).[18] In all the cases borate salts were obtained in the quantitative yields. Depending up on the phenols the reaction time varied from 15-80 h. As $NaBH_4$ is not soluble in THF, on the basis of this completion of the reaction was estimated when the $NaBH_4$ was completely dissolved in the solvent THF. As borate salts are not soluble in Et_2O, small impurities of the phenols were removed by washing the salts with Et_2O under dry conditions. Characterization of the borate salts were done by NMR spectroscopy.

All the allyl alcohols used were synthesized from the reaction of the respective aldehydes with the vinyl magnesium bromide by following the literature procedure (Table 3).[19] These alcohols were used for the synthesis of respective acetates.

Allyl acetates were synthesized by the acetylation of allyl alcohols using literature procedure (Table 4).[20] Pyrene allyl acetate was prepared without isolating the respective allyl alcohol, which was basically prepared by the reaction of pyrene carboxaldehyde with vinyl magnesium bromide, after the workup the next step (acetylation) was carried out.

Table: 2. Synthesis of tetraaryloxy borate salts.
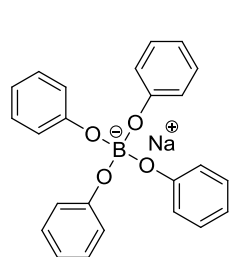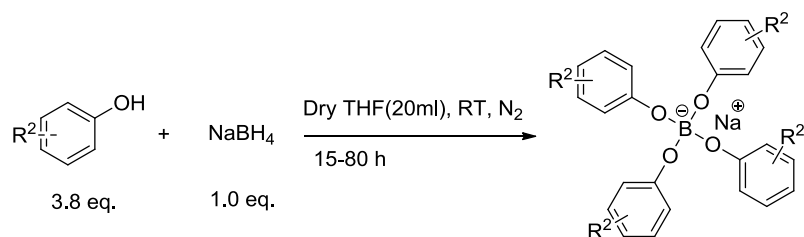
1, 15 h, quantitative yield	**2**, 80 h, quantitative yield	**3**, 28 h, quantitative yield
4, 19 h, quantitative yield	**5**, 26 h, quantitative yield	
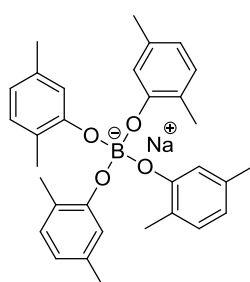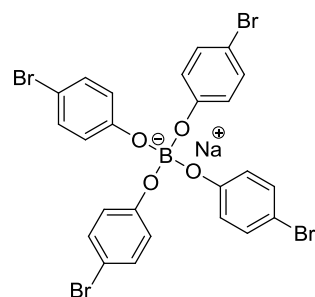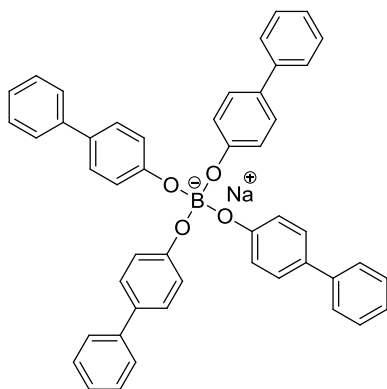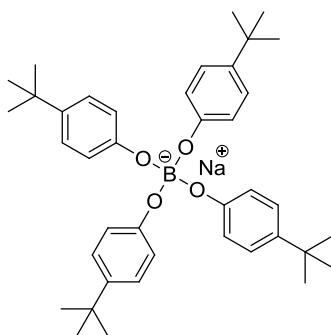
Table: 3. Synthesis of allyl alcohols.

6, 12 h, 93%

7, 12 h, 70%

8, 12 h, 86%

9, 12 h, 67%

10, 12 h, 54%

11, 12 h, 86%
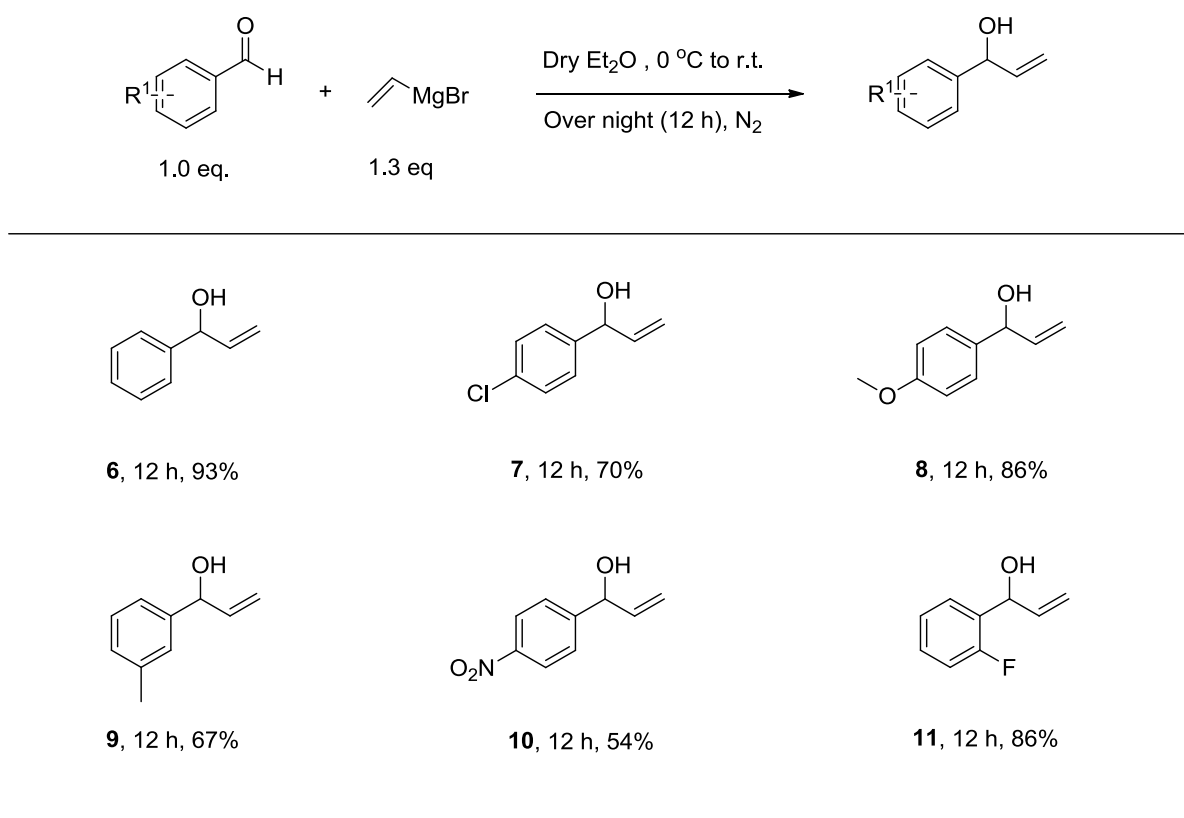
Table: 4. Synthesis of allyl acetates.

12, 12 h, 96%

13, 12 h, 87%

14, 12 h, 79%

15, 12 h, 68%

16, 12 h, 77%

17, 12 h, 83%

18, 12 h, 58%
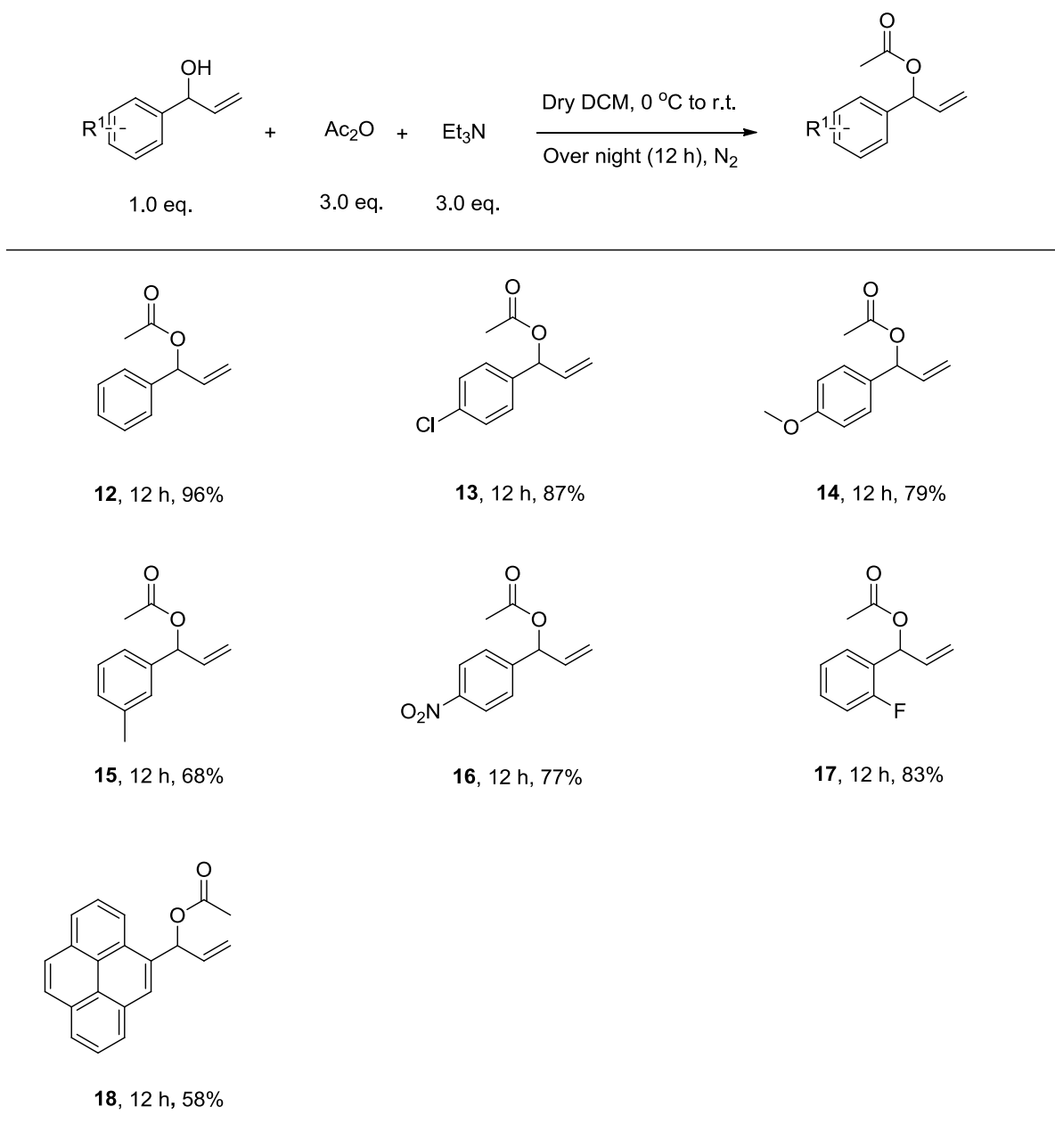
The optimization studies were carried out using allyl acetate derived from benzaldehyde and tetraphenyloxy borate salt (Table 5).

Table: 5. Optimization studies.

Table: 5.1. Solvent screening.
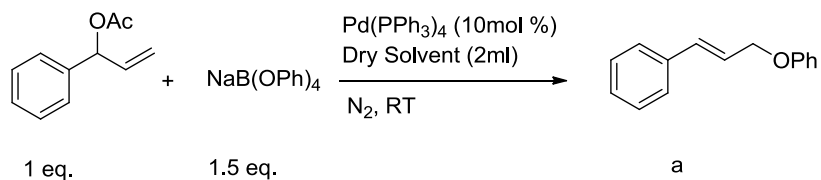
S.No.	Catalyst	Solvent	Time (h)	Yield^a (%)
1	Pd(PPh$_3$)$_4$	THF	4	89
2	"	DMF	3	61
3	"	CH$_3$CN	2	95
4	**Pd(PPh$_3$)$_4$**	**DCM**	**4**	**99**
5	"	DCE	3	95
6	"	MeOH	3	94

It is evident from Table 5.1 that the product was obtained in the maximum yield (99%, entry 4) when DCM was used as a solvent.

Table: 5.2. Screening of number of eq. of borate salt (b) and Pd catalyst.
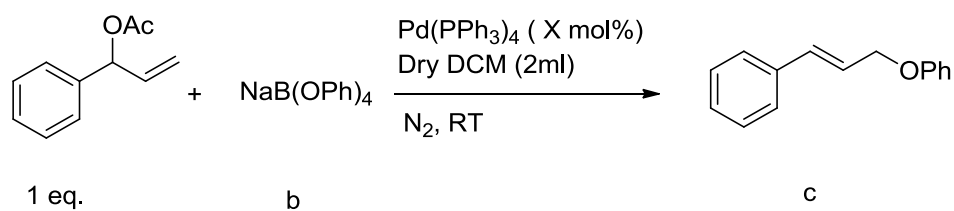
S.No.	(X mol %)	b (equiv.)	Time (h)	Yield^c (%)
1	10	1.5	4	99
2	10	1.2	4	98
3	**5**	**1.5**	**13**	**99**
4	1	1.2	11	96
5	1	1.5	11	93

The above Table (Table 5.2) clearly shows that the yield of the product was maximum when 1.5 equivalent of borate salt was used (Entry 3) and the reaction worked pretty well with 5 mol% of the catalyst.

Table: 5.3. Pd catalyst screening.
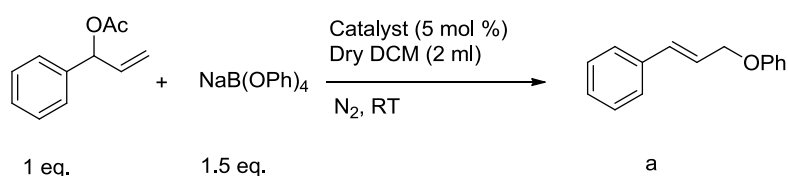
S.No.	Catalyst	Time (h)	Yield^a (%)
1	**Pd(PPh$_3$)$_4$**	**13**	**99**
2	Pd(PPh$_3$)Cl$_2$	40	94
3	Pd(OCOCF$_3$)$_2$	72	87
4	PdCl$_2$	80	77
5	Pd(OAc)$_2$	40	79
6	Pd(dba)$_2$	40	80
7	PEPSI	80	79

Among all the Pd catalysts used for the optimization, Pd(PPh$_3$)$_4$ was found to be superior when compared to the other catalysts in terms of yield of the product as well as the reaction time. So, Entry 1 in the above table was chosen as the best condition. By using Entry 1 as a standard condition, a variety of allyl acates and borate salts were used for substrate scope and the results are summarized in Table 6. Also, this reaction was found to be regioselective as only one product was isolated in all the cases.

Table: 6. Substrate scope for the allyl etherification.

Varying allyl acetates
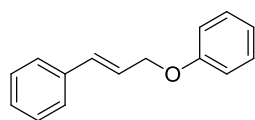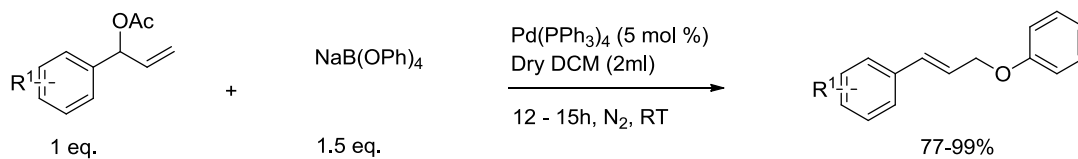
19, 13 h, 99%
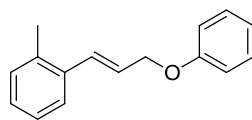
20, 15 h, 91%
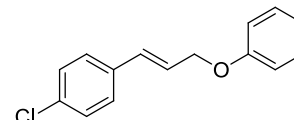
21, 12 h, 96%
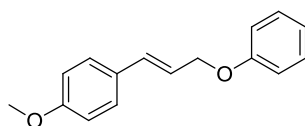
22, 14 h, 94%
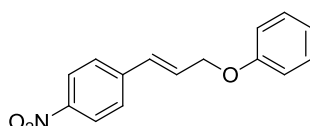
23, 15 h, 93%
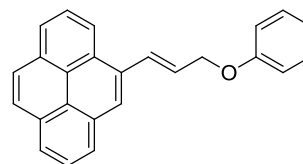
24, 15 h, 77%
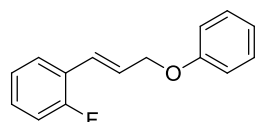
25, 12h, 90%

Varying sodium tetraaryloxy borate salts
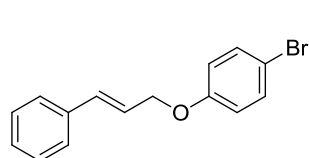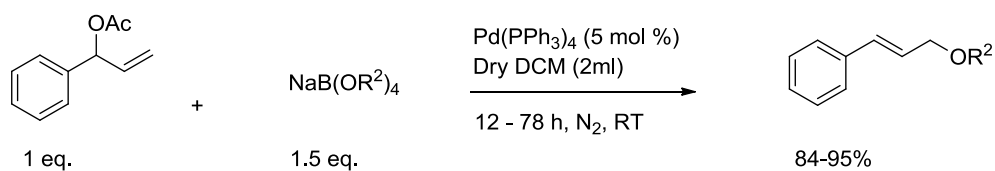
26, 32 h, 84%
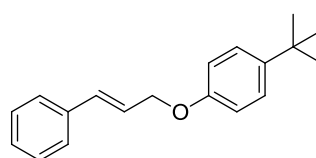
27, 12 h, 91%
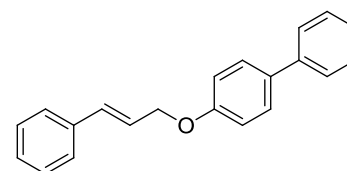
28, 28 h, 95%
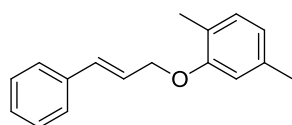
29, 78 h, 86%

Mechanistic Investigation:

Since the mechanism of Tsuji-Trost reaction is well explored in the literature, we proposed the possible mechanism of our methodology which is depicted in Scheme 20. During the experiment, we observed that the secondary allyl acetate was converted in to the primary acetate. Although the nucleophilic attack of the borate salt would happen from both the terminals of the Pd-π-allyl complex, we observed only the terminal attack of the borate salts leading to internal alkenes. Since the borate salt is sterically bulky, we feel the internal attack of the salt towards the Pd-π-allyl complex didn't happen in this particular case.
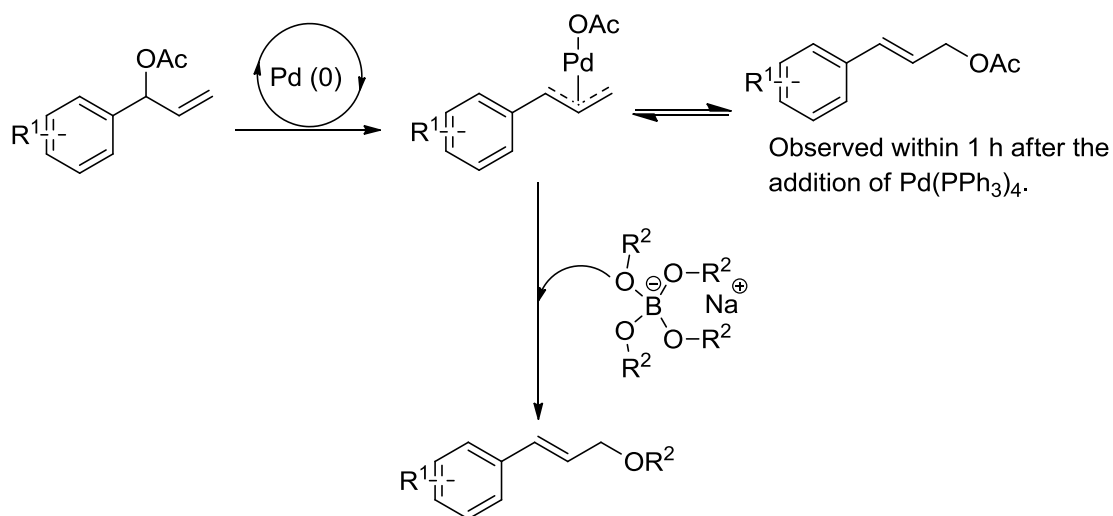
Scheme 20

3.1 Conclusion:

A palladium catalyzed base free method has been developed for the synthesis of allyl ethers from allyl acetates using organo-boron salts as nucleophiles at room temperature. A variety of allyl ethers of phenol have been prepared using a wide range of organoboron salts as well as allyl acetates. The reaction of propargyl acetates under the standard reaction conditions is currently under investigation.

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CHAPTER 4

Spectral Data

IICHA 1
PROTON CDC13 /opt/topspin nmrsu 2

7.20
7.18
7.16
6.83
6.79
5.01
3.34

2.00   3.00
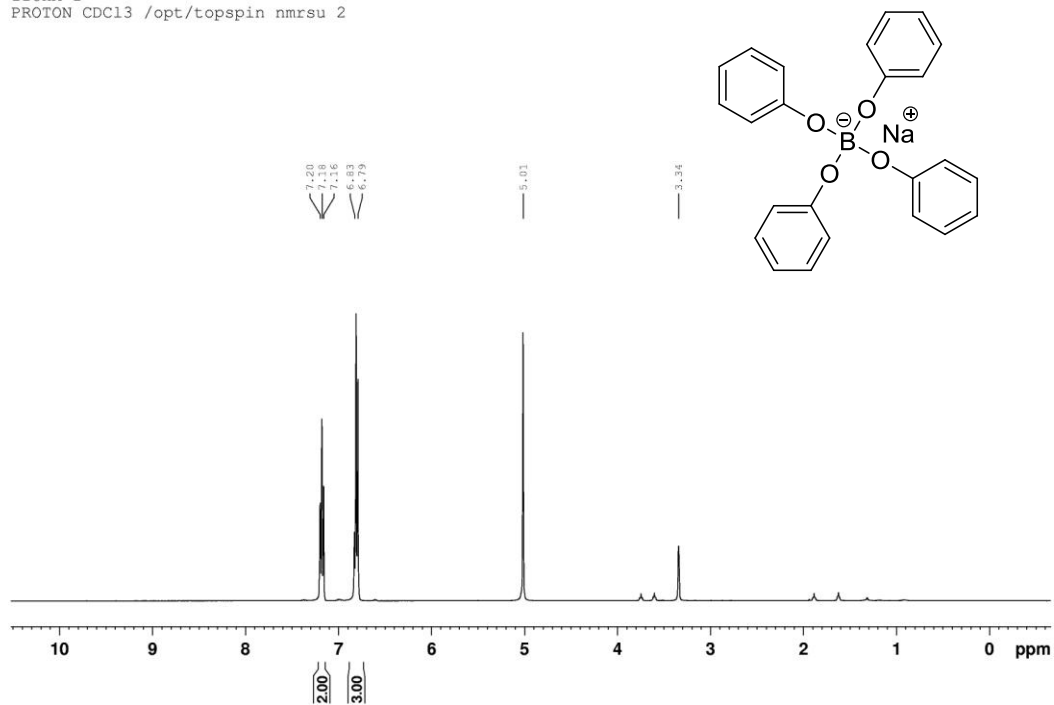
IICHA 1
C13CPD CDC13 /opt/topspin nmrsu 56

159.45
131.22
121.19
117.13
50.50
50.29
50.07
49.86
49.65
49.44
49.22

—3.71
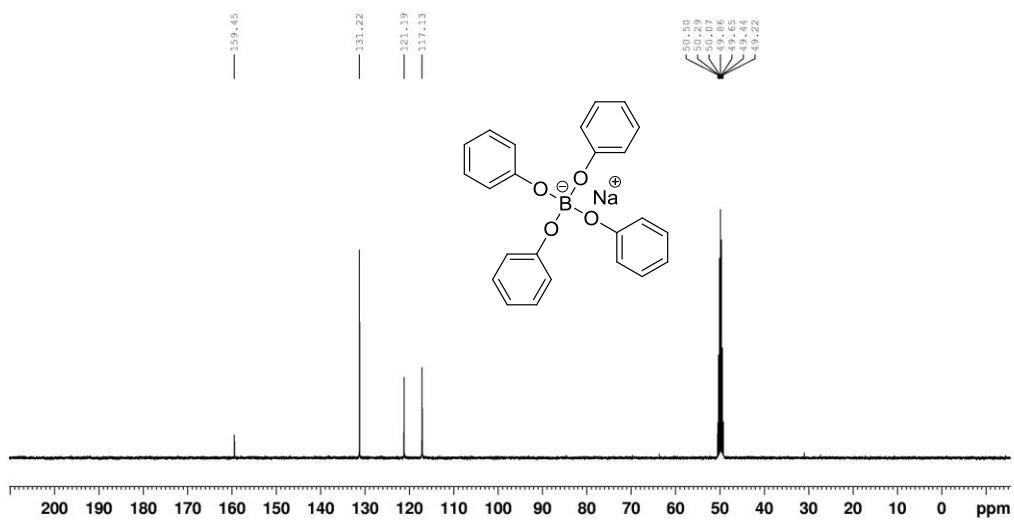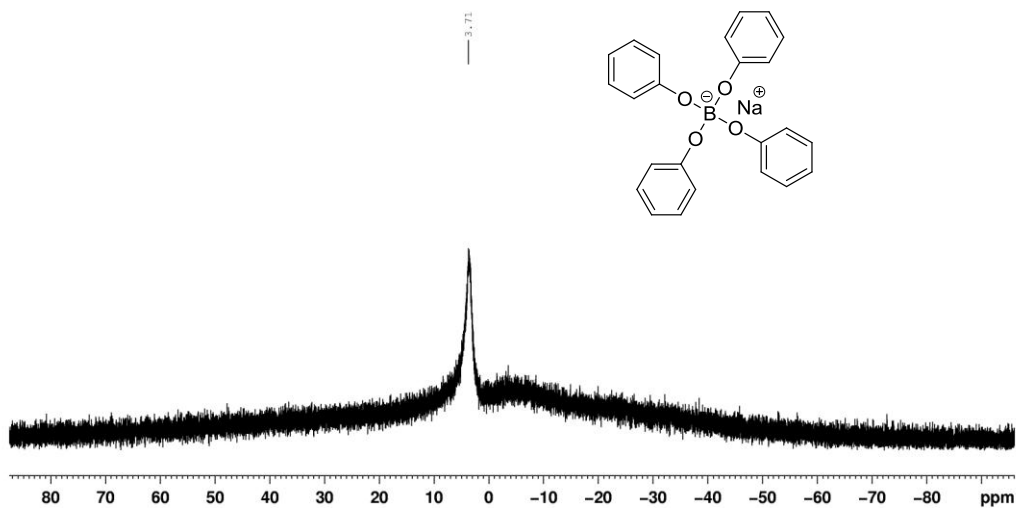
^{1}H, ^{13}C and ^{11}B NMR spectra for **2**

III CHA 37
C13CPD MeOD /opt/topspin nmrsu 32

157.10
138.27
132.32
123.10
121.93
117.14
50.50
50.28
50.15
50.07
49.93
49.86
49.65
49.43
49.22
21.97
16.66

III CHA 37
B11

3.14
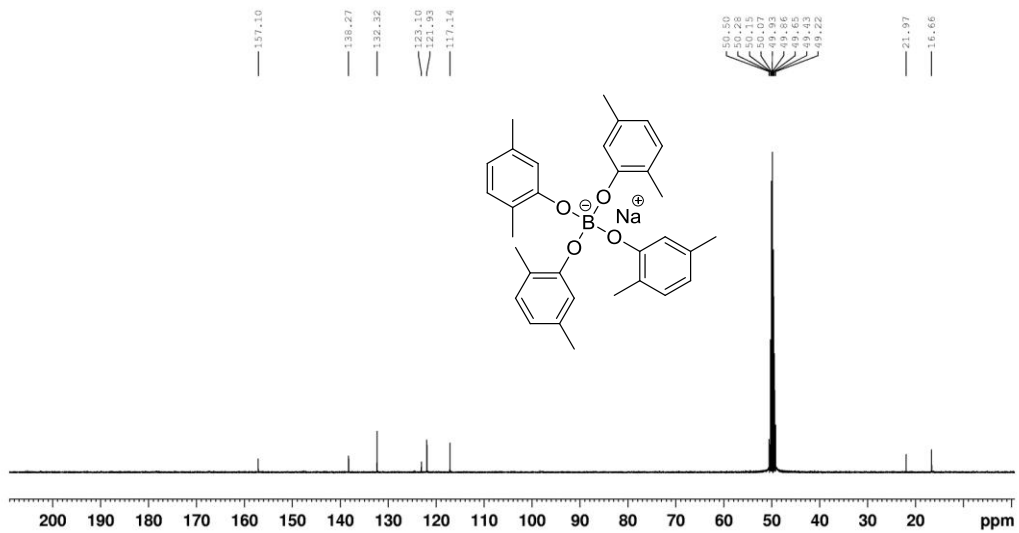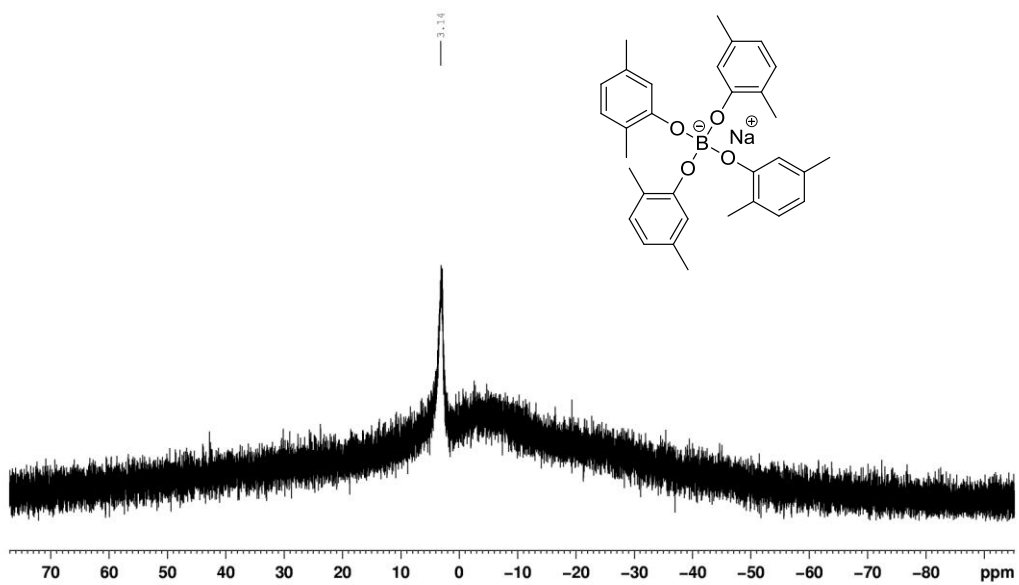
III CHA 38
PROTON MeOD /opt/topspin nmrsu 27
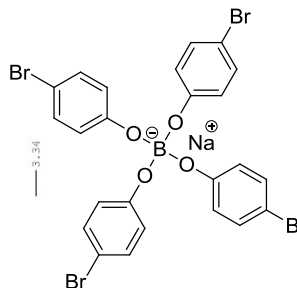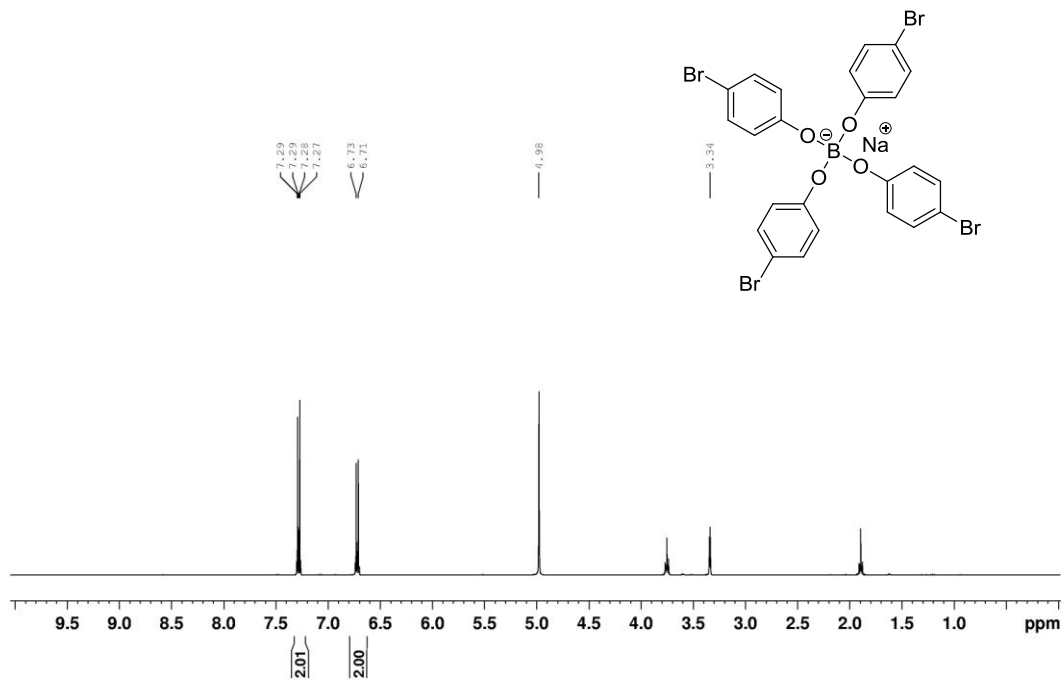
III CHA 38
C13CPD MeOD /opt/topspin nmrsu 27

4.21

^{1}H, ^{13}C and ^{11}B NMR spectra for **4**

159.36
143.32
134.47
130.52
129.82
128.23
128.16
117.61
50.50
50.28
50.07
49.86
49.65
49.43
49.22

200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 ppm

3.91

70 60 50 40 30 20 10 0 −10 −20 −30 −40 −50 −60 −70 −80 −90 ppm

37
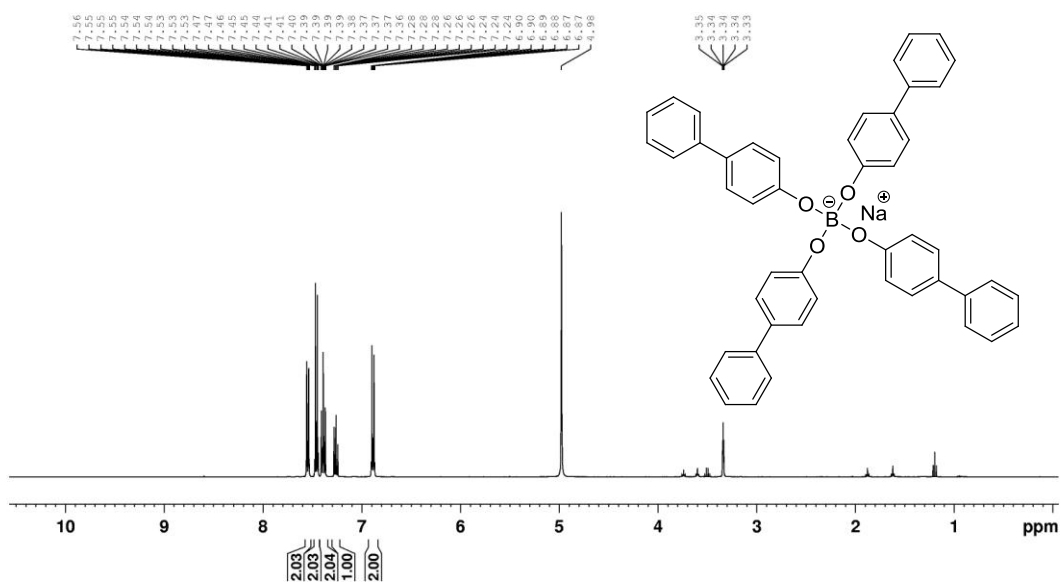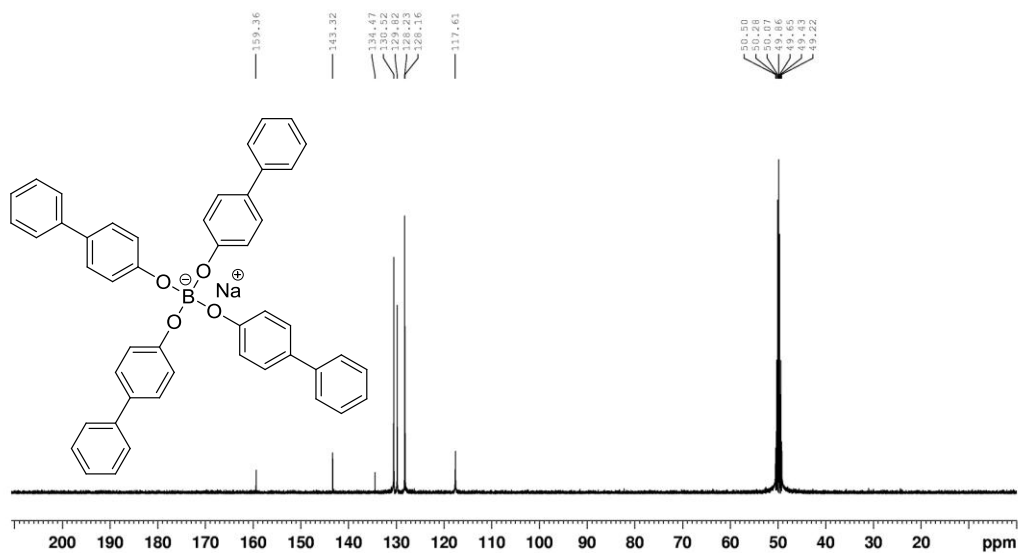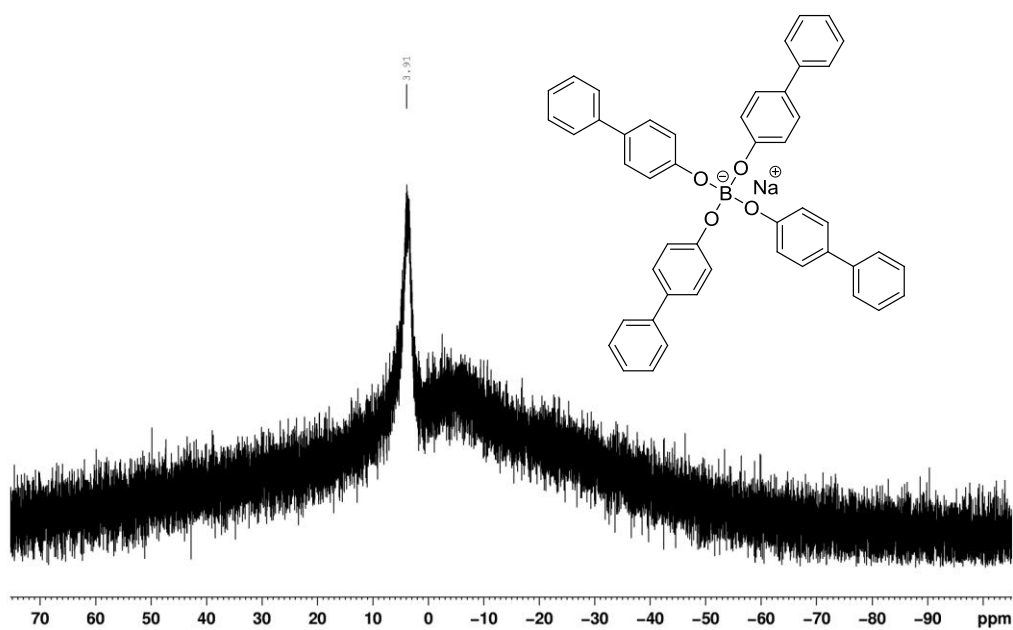
^{1}H, ^{13}C and ^{11}B spectra for 5

3.06

80   60   40   20   0   −20   −40   −60   −80   ppm

^{1}H and ^{13}C spectra for **6**

^{1}H and ^{13}C spectra for **7**

41
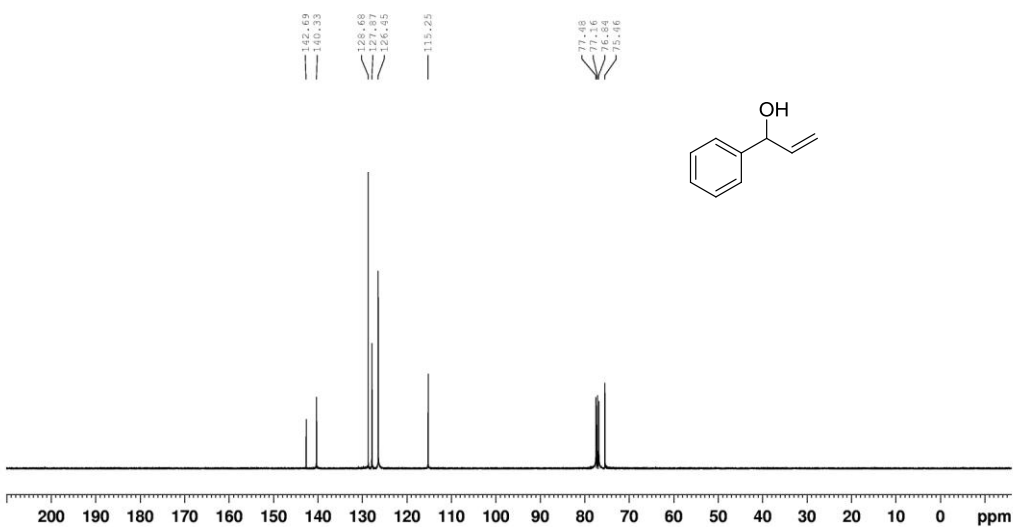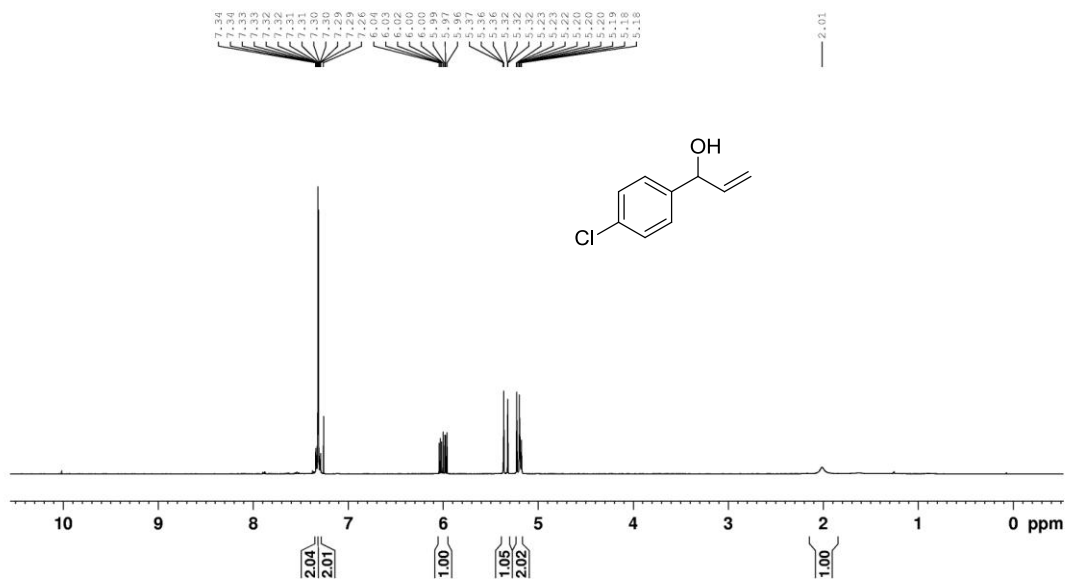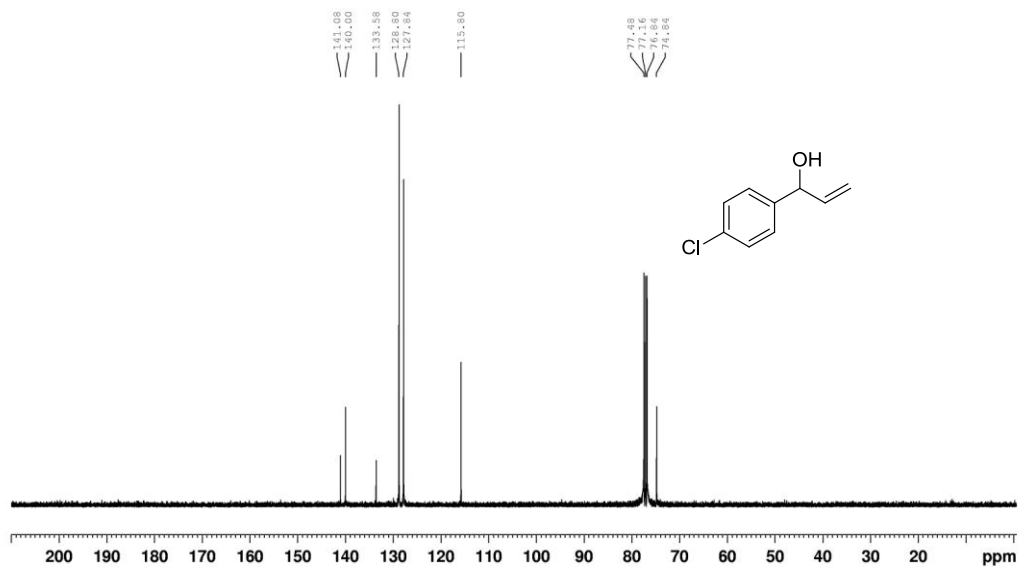
^{1}H and ^{13}C spectra for **8**

^{1}H and ^{13}C spectra for **9**

^{1}H and ^{13}C spectra for **10**

III CHA 46
PROTON CDCl3 /opt/topspin nmrsu 9

8.23
8.22
8.22
8.21
8.20
8.20
7.58
7.57
7.57
7.57
7.56
7.55
7.55
7.55
7.54
7.54
7.26
6.03
6.01
6.01
5.99
5.97
5.95
5.43
5.42
5.42
5.38
5.38
5.33
5.31
5.29
5.29
5.27
5.26
5.26

2.15

2.00
2.03
1.00
1.03
1.02
1.02
1.02
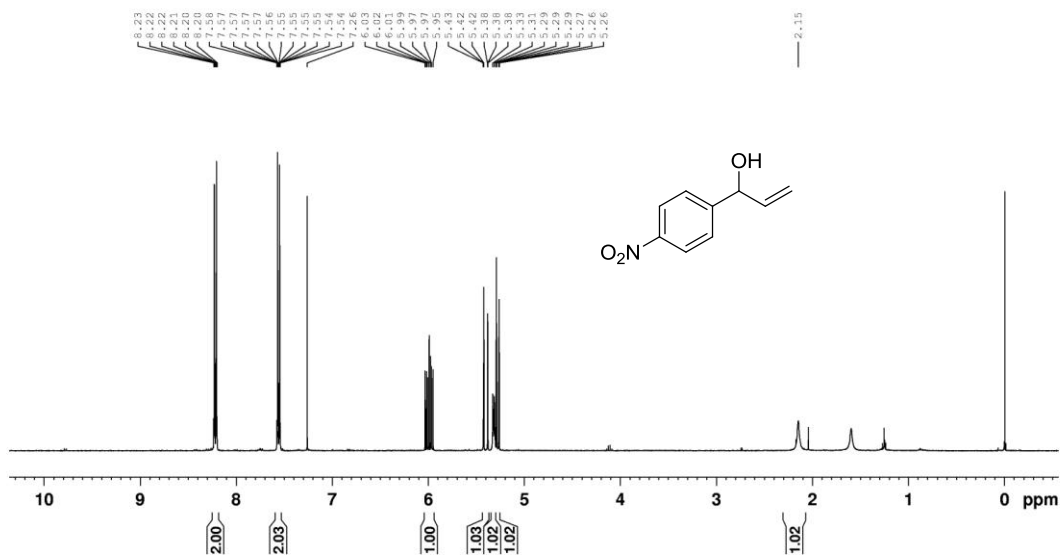
III CHA 46
C13CPD CDCl3 /opt/topspin nmrsu 9

149.65
139.30
127.10
123.89
117.03

77.48
77.16
76.84
74.75

^{1}H, ^{13}C and ^{19}F spectra for 11

-119.25

^{1}H and ^{13}C spectra for **12**

^{1}H and ^{13}C spectra for **13**

ICHA 011
PROTON CDCl3 /opt/topspin nmrsu 8

7.35 7.34 7.34 7.33 7.32 7.30 7.29 7.28 7.27 7.26
6.23 6.22 6.22 6.21 6.01 5.99 5.98 5.97 5.95 5.94 5.93
5.31 5.30 5.30 5.28 5.27 5.26 5.26 5.25 5.25 5.24

2.11

2.04 2.00   1.01 1.00   2.05   3.01

ICHA 011
C13CPD CDCl3 /opt/topspin nmrsu 8

170.02   137.54 135.98 134.16 128.88 128.71   117.49   77.48 77.16 76.84 75.58   21.34

^{1}H and ^{13}C spectra for **14**

^{1}H and ^{13}C spectra for **15**

^{1}H and ^{13}C spectra for 16

^{1}H, ^{13}C and ^{19}F spectra for **17**

—117.52

^{1}H

and ^{13}C spectra for **18**

^{1}H and ^{13}C spectra for **19**

^{1}H and ^{13}C spectra for 20

^{1}H and ^{13}C spectra for 21

^{1}H and ^{13}C NMR spectra for **22**
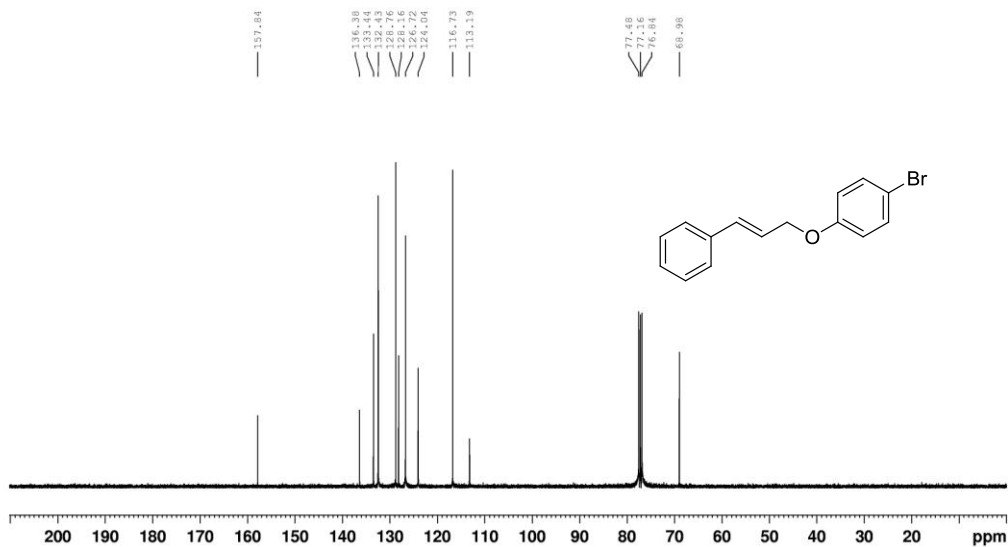
^{1}H and ^{13}C NMR spectra for 23
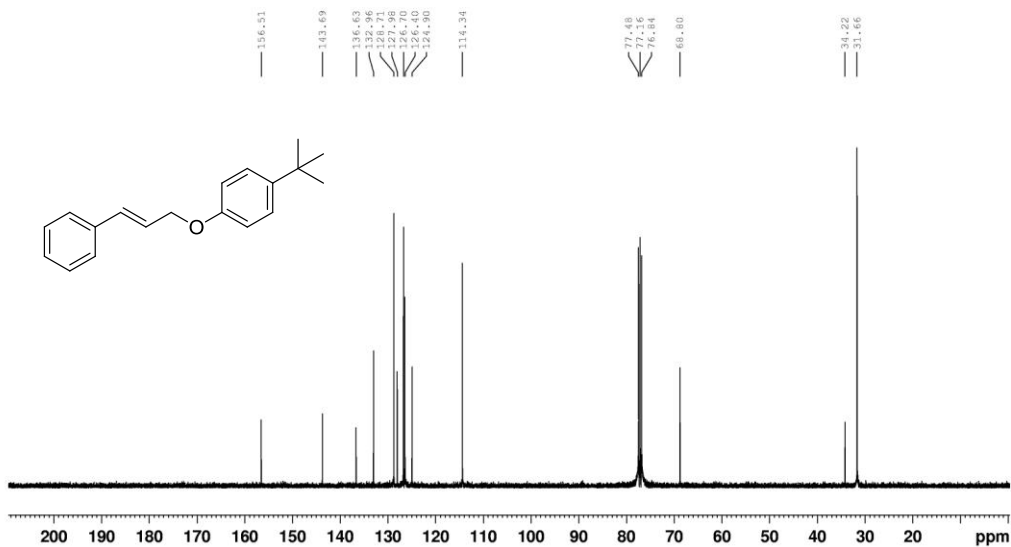
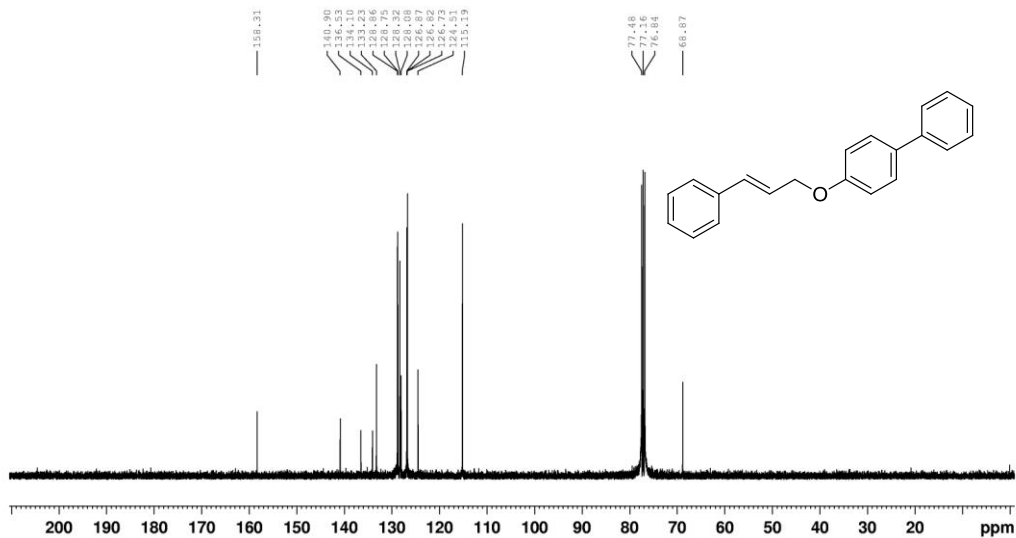# ^{1}H and ^{13}C NMR spectra for **24**

III CHA 95
PROTON CDCl3 /opt/topspin nmrsu 52
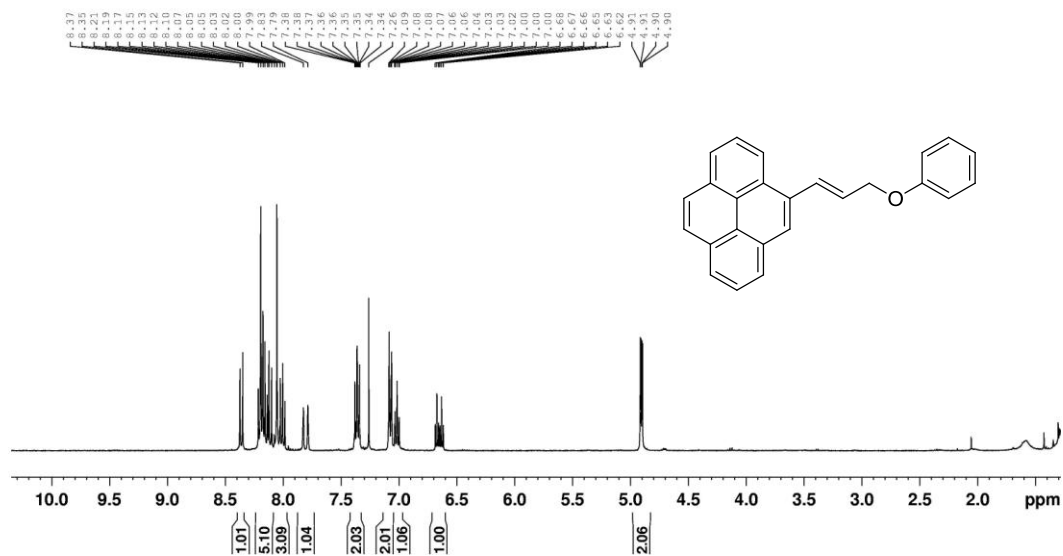
III CHA 95
C13CPD CDCl3 /opt/topspin nmrsu 52
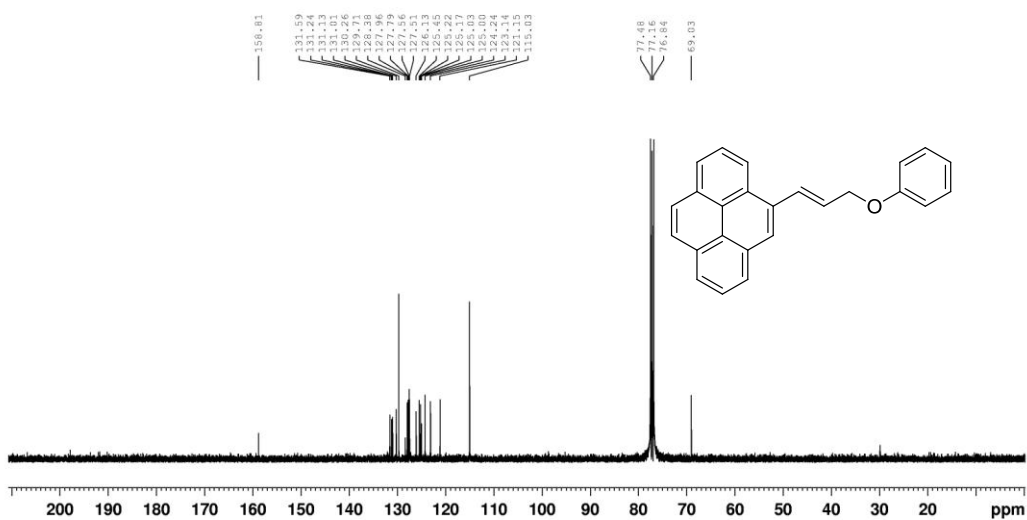
^{1}H, ^{13}C and ^{19}F NMR spectra for 25

−117.83

^{1}H and ^{13}C NMR spectra for 26

¹H and ¹³C NMR spectra for **27**

¹H and ¹³C NMR spectra for **28**

¹H and ¹³C NMR spectra for **29**

156.80
136.76
136.66
132.28
130.58
128.72
127.91
126.67
125.22
123.95
121.20
112.56
77.48
77.16
76.84
68.72
21.58
16.08

200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 ppm

66