5
Asymmetric Allylation Reaction

5.1 INTRODUCTION

Several attempts have been made concerning the synthesis of chiral homoallylic alcohols and amines by asymmetric allylation of aldehydes and imine (Figure 5.1). Yamamoto and co-workers reported the enantioselective allylation of aldehydes for the first time, by using a Lewis acid with a chiral acyloxy borane (CAB) catalyst, in 1991 [Furuta and Mouri *et al,* 1991]. Further studies were directed towards improvement in catalysts and allylic reagents [Marshall and Tang 1992, Cozzi *et al,* 1994]. It has been reported that aldehydes are more active than imines for allylation reactions [Sharma and Samuelson 2006]. The allylation of aldehydes or imines can be promoted by Lewis acids or transition metal complexes with allyltributyltin [Loh and Zhou *et al,* 1999, Shibata *et al,* 2001, Yadav and Reddy *et al,* 2003, Bartoli *et al,* 2004]. However, the traditional methods used with Lewis acids in organic synthesis must be carried out under strictly anhydrous a condition, which causes inconveniences in handling and processing. Other efficient Lewis acids like metal triflates have been developed to overcome the above problems [Kobayashi 1999, Kobayashi and Anwander 1999]**.** Loh *et al*. developed a new method of addition of allyltributyltin to aldehydes using trifluoromethane sulfonic [Loh *et al,* 2000] acid as a promoter in water. Mikami was the first to propose the application of BINOL/Ti(IV) complexes in enantioselective allylation using allylic silanes and stannanes [Aoki *et al,* 1993]. Further various BINOL and BINAP metal complexes were screened for the allylation reaction [Bedeschi and Casolan *et al,* 1995, Yanagisawa and Ishiba *et al,* 1997]. Chiral rhodium and zinc complexes were studied as catalysts for allylation reactions by numerous research groups [Nuss and Rennels 1993, Cozzi and Orioli *et al,* 1997, Motoyama and Okano *et al,* 2001]. Allylindium mediated allylation reaction of imines and aldehydes are carried out [Denmark *et al,* 1994, Ishitani *et al,* 1997] in presence of cinchona alkaloids [Loh and Zhou *et al,* 1999]. Palladium mediated allylation reaction was also performed [Tsuji 1969, Trost and Verhoeven 1976, Maitlis *et al,* 1982, Tsuji 1986, Consiglio and Waymouth 1989]. Sharma *et al*. synthesised a series of new bisphosphinite complexes of Pd (II) and Pt (II) derived from optically pure natural sources, which were tested for allylation of imines and aldehydes [Sharma and Samuelson 2006, Sharma and Samuelson 2007, Sharma and Nethaji *et al,* 2008].

The most common allylic reagents are allylic boron/silicon and tin. These reagents have a good character to transfer allylic group to imines and aldehydes. Among various allylic reagents, allylstannanes are very useful because of their modest reactivity, which can become moderate by using additives such as F^-, RO^- and TBAF. The allylation of aldehydes and imines is a very important synthetic method for the formation of homoallylic alcohols and imines by using allylstannanes as allylic reagents [Yamamoto and Asao 1993, Marshall 1996, Davies 2004, Hisashi and Koichiro 2004].

The mechanism of addition of allylic reagents to carbonyl compounds was proposed by Denmark and Weber in 1983 [Denmark and Weber 1983]. According to literature, the addition mechanism is classified into two types. In type 1, allylic reagents activate substrate and form closed six membered chiral transition states, e.g., allylic boron [Kennedy and Hall 2003]. In contrast, type 2 involves the external Lewis acid (BF_4, $TiCl_4$) to activate substrate and form an open transition state in the presence of allylic reagents, like allyl trialkylsilanes and allyl trialkylstannanes [Yamamoto 2007]. Type 1 and type 2 related allylation reactions have been intensively studied in literature. The reactions usually proceed via Pt-allyl intermediate, resulting from allyltributyltin and a catalyst. Mechanistic studies on the Lewis acid promoted

allylation reaction was studied by Zhao [Li and Zhao 2005], Greeves [Aspinall *et al,* 2002] and Denmark [Denmark *et al,* 2006].

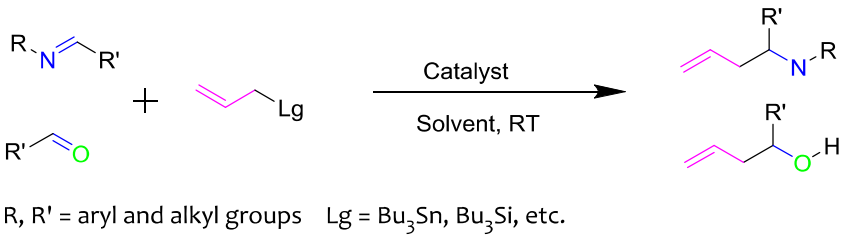


Figure 5.1 Typical nucleophilic allylation reactions of imine and aldehydes

Despite these studies, reaction under ambient conditions, without inert atmosphere, is still a challenge. In this chapter, the main focus is the development of new homogeneous and heterogeneous catalysis systems for allylation of imines. These systems have both Lewis acidity and chiral modifier characteristics that are needed to generate chiral amines.

5.2 ALLYLATION OF IMINES

5.2.1 Earlier work

There are several methods described in the literature to perform the synthesis of chiral amines (Figure 5.2) [Denmark *et al,* 1987, Denmark *et al,* 1993]. Two of them, are well studied. One method is the catalytic reduction of the imine [Langlois *et al,* 1973] and the second is the addition of the allylic and alkyl fragments to the imine by making a C-C bond [Langlois and Dang *et al,* 1973]. The second method is comparatively less studied. Asymmetric allylation and alkylation of imines have been reported in the literature by numerous research groups [Tomioka *et al,* 1990, Inoue *et al,* 1993, Denmark and Nakajima *et al,* 1994, Nakamura *et al,* 1998, Kobayashi and Ishitani 1999, Shibata *et al,* 2004, Shimizu and Kimura *et al,* 2005].

In most studies, allylation of imines was carried out in the presence of Lewis or bronsted acids [Puentes and Kouznetsov 2002], metal triflates [Bloch 1998] and chiral metal complexes [Fang *et al,* 1999]. In case of Lewis acids, the regioselectivity of the reaction is low, due to the existence of a geometric isomer present during the coordination of the Lewis acid to the nitrogen of the imine [McCarty and Patai 1970] and the basic nitrogen of the product trapped by the Lewis acid. For enantioselectivity approach in achiral imines, a chiral source is needed.

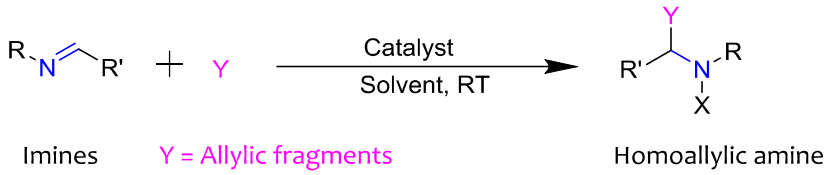


Figure 5.2 Allylation reactions of imines

These studies are encouraging towards the design of new catalytic systems that have chiral centers with acidic character, with the ability to increase the rate of the allylation reaction.

5.2.2 Our work

Imines were synthesized from aldehydes and aniline, as reported in the literature [Touchette 2006, Silverberg *et al,* 2016]. The allylation of imines was carried out in the presence of Selectfluor (16a), F-CD-BF_4 (16b), F-CD-BF_4/MWCNT (16c) and F-CD-BF_4/Pt/MWCNT (16d) (Table 5.4). Allyltributyltin was used as an allylic reagent. Fluorinated cinchonidine (F-CD-BF_4) was synthesized from Selectfluor and F-CD-BF_4 was loaded on MWCNT and Pt/MWCNT (Chapter 3). Product conversion and enantioselectivity were determined by different analytical techniques.

5.2.3 Experimental

General Remarks

The imines were synthesized by an earlier reported method [Rauniyar and Hall 2006]. Aldehydes and amines are purchased commercially (Table 5.1). Synthesis of F-CD-BF_4, F-CD-BF_4/MWCNT, F-CD-BF_4/Pt/MWCNT (Figure 5.3) and characterization are described in Chapter 3**.** New compounds are analyzed by different analytical techniques that are described in Chapter 3**.**

Table 5.1 Detailed information on the used reagents: to sample code, supplier and other specifications

Samples	**CAS No./Product number**	**Specification**	**Supplier**
Benzaldehyde	100-52-7	106.12g/mol	Merck
Aniline	62-53-3	93.13 g/mol	Merck
Allytributyltin	24850-33-7	97%, 1.068 g/mL at 25 °C (lit.). 331.12g/mol	Sigma Aldrich
Selectfluor	140681-55-6/101488580	354.26, >95% in F+ active, mp 260 °C (lit.)	Sigma Aldrich
Acetonitrile	75-05-8	Anhydrous, 99.8%	Sigma Aldrich
Tetrahydrofurane	109-99-9	Anhydrous	Sigma Aldrich

Imines synthesis

All reactions and manipulations were performed under a dry nitrogen atmosphere, by using standard Schlenk techniques. Imines were synthesized (Table 5.2) by dean stark method [Touchette 2006, Silverberg and Coyle *et al,* 2016].

Characterization of imines

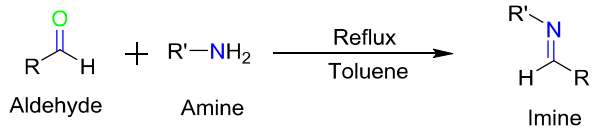
(E)-N, 1-diphenylmethanimine (VII)

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.36-7.07 (m, 5H), 7.22 (m, J = 7.2 Hz, 4H), 7.07 (t, 2H, J = 8.0 Hz, Ph), 6.64 (t, J = 7.2 Hz, 1H), 6.49 (d, J = 8.0 Hz, 2H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 160.0, 152.0, 136.4, 131.0, 130.0, 129.2, 128.2, 127.2, 122.3.

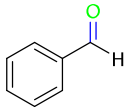
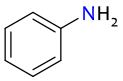
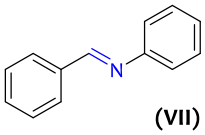
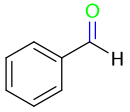
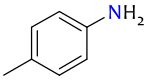
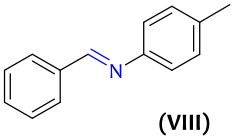
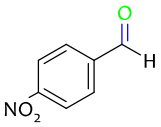
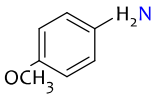
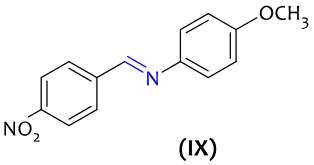
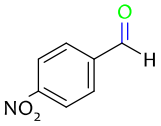
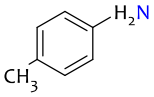
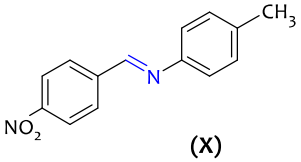
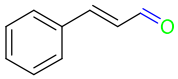
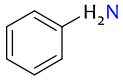
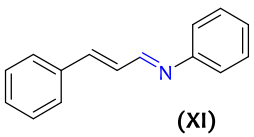
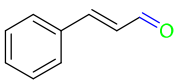
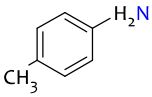
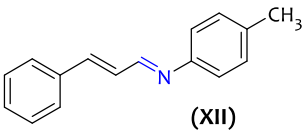
(E)-1-phenyl-N-(p-tolyl) methanimine (VIII)

^{1}H NMR (500 MHz, $CDCl_3$): δ 8.65 (s, 1H, CH), 7.76 (d, J = 7.2 Hz, 2H, Ph), 7.55 (t, J = 8.00 Hz, 2H), 7.58 (t, J = 8.00 Hz, 1H), 7.35-7.20 (m, 4H), 2.34 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 160.0, 149.0, 136.9, 136.4, 131.0, 130.3, 129.2, 128.8, 122.2, 21.3.

Table 5.2 Different types of synthesized Imines [a]



R = -C_6H_5, C_8H_7, $C_6H_4NO_2$ R' = -C_6H_5,- C_7H_7, C_7H_7O

Entry	Substrate 1	Substrate 2	Product	Conversion[b] %	MP (°C)
1			 **(VII)** (E)-N,1-diphenylmethanimine	100	52.4
2			 **(VIII)** (E)-1-phenyl-N-(p-tolyl)methanimine	99	26-62
3			 **(IX)** (E)-N-(4-methoxyphenyl)-1-(4-nitrophenyl)methanimine	99.9	122.5
4			 **(X)** (E)-1-(4-nitrophenyl)-N-(p-tolyl)methanimine	99.5	121.2
5			 **(XI)** (1E,2E)-N,3-diphenylprop-2-en-1-imine	98	109.7
6			 **(XII)** (1E,2E)-3-phenyl-N-(p-tolyl)prop-2-en-1-imine	96.5	77.6

[a]Reaction conditions: Aldehyde/ Aniline/Solvent/time/temperature: 10 mL/10 mL/60 mL/24 h/RT. [b]Determined by HPLC and NM

(E)-N-(4-methoxyphenyl)-1-(4-nitrophenyl) methanimine (IX)

^{1}H NMR (500 MHz, $CDCl_3$): δ 8.58 (s, 1H), 8.31 (d, 2H, J = 7.95 Hz), 8.05 (d, J = 9.08 Hz, 2H), 7.30 (d, J = 9.08 Hz, 2H), 6.95 (d, J = 8.89 Hz, 2H), 3.85 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 159.2, 154.7, 148.9, 143.5, 141.9, 129.0, 124.0, 114.5, 55.5.

(E)-1-(4-nitrophenyl)-N-(p-tolyl) methanimine (X)

^{1}H NMR (500 MHz, $CDCl_3$): δ 8.57 (s, 1H), 8.31 (d, J = 8.58 Hz, 2H), 8.06 (d, J = 8.58 Hz 2H), 7.20 (m, 4H), 2.39 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 156.3, 149.1, 148.2, 141.7, 137.1, 129.9, 129.2, 124.0, 121.0, 21.1.

(1E, 2E)-N, 3-diphenylprop-2-en-1-imine (XI)

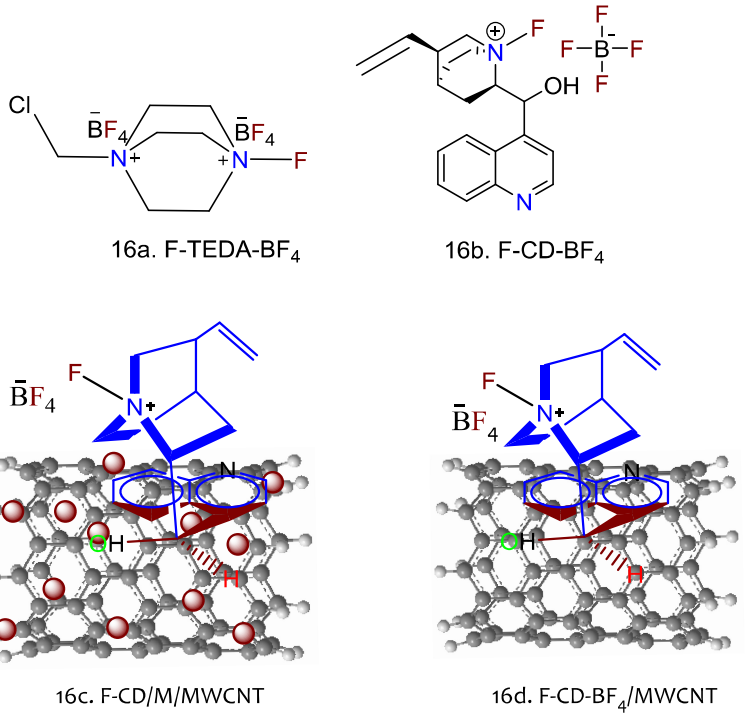
^{1}H NMR (500 MHz, $CDCl_3$): δ 8.50 (m, 1H, CH), 7.54 (d, J = 7.8 Hz, 2H), 7.38 (d, 2H), 7.34 (t, J = 7.2 Hz, 2H), 7.33 (t, J = 7.5 Hz, 1H), 7.22 (d, J = 8.0 Hz, 1H), 7.07 (t, J = 7.2 Hz, 1H), 6.93 (d, J = 8.0 Hz, 2H), 6.85 (t, J = 7.2 Hz, 2H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 163.7, 152.5, 135.2, 133.3 130.0, 128.6, 128.5, 127.9, 127.2, 122.3, 119.9.

(1E, 2E)-3-phenyl-N-(p-tolyl) prop-2-en-1-imine (XII)

^{1}H NMR (500 MHz, $CDCl_3$): δ 8.50 (m, 1H, CH), 7.54 (d, J= 7.26 Hz, 2H), 7.38 (t, J= 7.45 Hz 2H), 7.33 (t, J= 7.45 Hz, 1H), 7.22(m, 1H, CH), 7.20 (d, J= 8.75 Hz, 2H), 7.17 (d, J= 8.75 Hz, 2H), 6.95 (m, 1H, CH), 2.34 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 163.7, 149.5, 136.9, 135.2, 133.3, 130.3, 129.1, 128.6, 128.5, 127.9, 122.2, 119.9, 21.3.

Nucleophilic addition of allyltributylstannane to imines

Initial reactions were carried on the allylation of 1-diphenylmethanimine using allyltributylstannane and Selectfluor catalyst. The reactions performed in CH_3CN, under ambient conditions. Maximum conversion was found with 1.0 mol % of Selectfluor (16a), in 2.5 h (Table 5.3). After that, no attempt was carried out for the optimization.



16a. F-TEDA-BF_4 16b. F-CD-BF_4

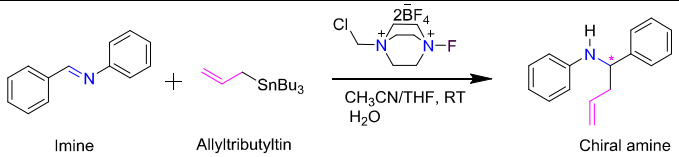
16c. F-CD/M/MWCNT 16d. F-CD-BF_4/MWCNT

Figure 5.3. Homogeneous and heterogeneous catalysts used the reaction

During the optimization process; 1.0 mol % Selectfluor was dissolved in 5 ml of acetonitrile and sonicated for 10 min. After 5 min, 0.072 g imine VII (Entry 1, Table 5.2) was

added and properly mixed. After 15 min 0.25 mL allyltributyltin was added to the above solution and stirred for 12 h. As the reaction proceeded to completion, H_2O (2 mL) is added and the mixture was extracted with CH_2Cl_2 (5 mL×2). The organic layers were combined, dried (Na_2SO_4) and concentrated in vacuum. On completion, the reaction mixture was passed through a silica gel column and elution was carried using 10% ethyl acetate in petroleum ether. Further, the product was analyzed by NMR and HPLC. A racemic product was obtained with 98 % conversion. No product was found in absence of Selectfluor, under similar reaction condition (Table 5.3, Entry 1). The obtained results were extremely encouraging for further studies.

Table 5.3 Allylation of imines with tributylallyltin using Selectfluor[a]



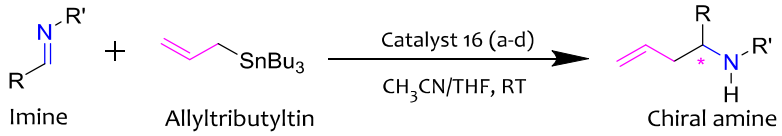
Entry	Selectfluor 16a (mol %)	Reaction time (h)	Isolated yield (%)[b]
1	0.0	1	0
2	0.1	1	40
3	0.5	1.5	55
4	1.0	2.0	77
5	1.0	2.5	98
6	1.5	3.0	97

Standard reaction conditions: [a]To a solution of imine **VII** (0.4 mmol, Entry 1, Table 5.2) in dry CH_3CN (5 ml), and allyltributylstannane (0.8 mmol) was added and stirred for 10 min at RT. Catalyst 16a was added and the reaction mixture was stirred for the given time. [b]The product was separated by column chromatography.

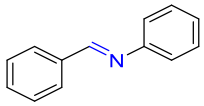
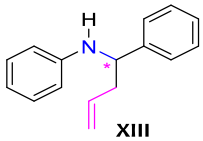
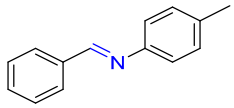
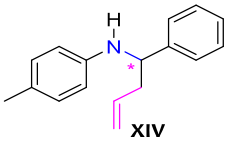
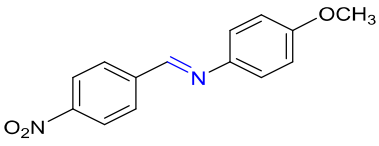
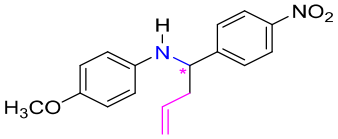
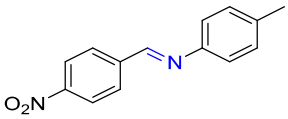
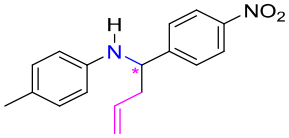
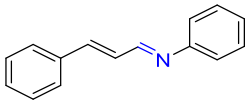
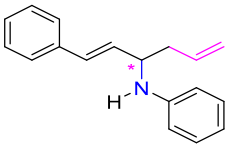
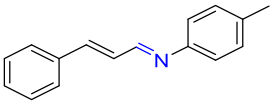
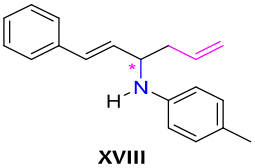
To make the reaction stereoselective, a chiral moiety needs to be introduced. A natural chiral source was used for chiral induction. Cinchonidine was added to the reaction mixture as a chiral source, at optimized conditions. Interesting results were found with good enantioselectivity. With this result, further progress is taken by making a moiety with both characters. Thus, F-CD-BF_4 was prepared and tested for the allylation reaction. Excellent conversion (99 %) and enantioselectivity (94 %) was found. Further, a new strategy was carried out to make the heterogeneous catalyst 16d, described in Chapter 3. The Allylation reaction of imine VII (Entry 1, Table 5.2) was carried out in the presence of F-CD-BF_4 /MWCNT (10 wt % loading) and as a result of which, low conversion and enantioselectivity were obtained. The low activity of the catalyst was due to less loading of F-CD-BF_4 on the surface of MWCNT. It was found that there was no strong interaction between F-CD-BF_4 and MWCNT. To enhance interaction, a connector was used. Transition metals like Pt and Pd acted like connectors. The possible interaction between F-CD-BF_4 and metal (Pt & Pd) was similar to cinchonidine-Pt that was discussed in Chapter 3. Interaction between Pt and functionalized MWNT is also explained in literature [Sharma and Sharma 2015]. Thus, F-CD-BF_4 /Pt/MWCNT (10 wt % loading) was screened and was found to be more active than F-CD-BF_4/MWCNT. These heterogeneous catalysts were applied for allylation of other imines. Product XIII was separated by HPLC and

~94 % enantioselectivity was found. Attempts to separate other homoallylic products are underway. Results are tabulated in Table 5.4.

Table 5.4 Allylation of imines with different catalysts[a]



R' = -C_6H_5,- C_7H_7, C_7H_7O R = -C_6H_5, C_8H_7, $C_6H_4NO_2$

Entry	Imine	Product	Catalysts	Conversion %[b]	Optical activity
1	 VII	 XIII	16a 16b 16c 16d	98 96 92 32	+15
2	 VIII	 XIV	16a 16b 16c 16d	96 95 97 36	+21
3	 IX	 XV	16a 16b 16c 16d	97 96 98 32	+13
4	 X	 XVI	16a 16b 16c 16d	91 86 93 36	+8
5	 XI	 XVII	16a 16b 16c 16d	99 96 91 44	+19
6	 XII	 XVIII	16a 16b 16c 16d	98 95 94 15	+11

[a]Reaction conditions were similar to Table 5.3. [b]The product was separated by column chromatography.

N-(1-phenylbut-3-en-1-yl) aniline (XIII)

Conversion (98 %) and ee (94 %) of product were determined on a normal phase CHIRALPAK ID type chiral column under isocratic and isothermal (at 35˚C) conditions, using a mixture of n-hexane/iso-propanol as the mobile phase. Retention time: 7.8 min for (R)-(+)-N-(1-phenylbut-3-en-1-yl) aniline, 9.5 min for (S)-(-)-N-(1-phenylbut-3-en-1-yl) aniline. Polarimeter measurement revealed that R enantiomer was first eluted (A18). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.36-7.27 (m, 5H), 7.08 (t, J = 7.2 Hz, 1H), 6.83 (d, J = 8.0 Hz, 2H), 6.67 (t, J = 7.2 Hz, 1H), 5.82 (m, 1H), 5.13 (m, 1H), 4.88 (m, 1H), 3.94 (dd, J = 8.0, 5.2 Hz, 1H), 2.63-2.36 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 147.6, 140.6, 134.3, 129.5, 128.5, 126.9, 126.7, 120.8, 116.4, 113.5, 63.4, 44.4.

4-methyl-N-(1-phenylbut-3-en-1-yl) aniline (XIV)

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.36-7.27 (m, 5H), 7.09 (d, J = 7.2 Hz, 2H), 6.47 (d, J = 7.2 Hz, 1H), 5.82 (m, 1H), 5.13 (m, 1H), 4.88 (m, 1H), 3.94 (dd, J = 8.0, 5.2 Hz, 1H), 2.63-2.36 (m, 2H), 2.32 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 144.6, 140.6, 134.3, 129.8, 129.6, 128.5, 126.9, 126.7, 116.4, 113.4, 63.4, 44.4, 21.3.

4-methoxy-N-(1-(4-nitrophenyl) but-3-en-1-yl) aniline (XV)

^{1}H NMR (500 MHz, $CDCl_3$): δ 8.18-7.58 (m, 5H), 6.77 (d, J = 7.2 Hz, 2H), 6.70 (d, J = 7.2 Hz, 2H), 5.82 (m, 1H), 5.13 (m, 1H), 4.88 (m, 1H), 3.94 (dd, J = 8.0, 5.2 Hz, 1H), 2.63-2.36 (m, 2H), 3.81 (s, 3H, CH_3). ^{13}C NMR (125 MHz, $CDCl_3$): δ 151.7, 146.7, 145.7, 139.3, 134.3, 123.4, 123.7, 116.4, 115.8, 115.1, 63.4, 55.8, 44.4.

4-methyl-N-(1-(4-nitrophenyl) but-3-en-1-yl) aniline (XVI)

^{1}H NMR (500 MHz, $CDCl_3$): δ 8.18-7.58 (m, 5H), 7.09 (d, J = 7.2 Hz, 2H), 6.77 (d, J = 7.2 Hz, 2H), 5.82 (m, 1H), 5.13 (m, 1H), 4.88 (m, 1H), 3.94 (dd, J = 8.0, 5.2 Hz, 1H), 2.63-2.36 (m, 2H), 2.32 (s, 3H, CH_3). ^{13}C NMR (125 MHz, $CDCl_3$): δ 146.7, 145.9, 144.6, 134.3, 129.8, 129.6 123.7, 123.4, 116.4, 113.4, 63.4, 44.4, 21.3.

(E)-N-(1-phenylhexa-1,5-dien-3-yl)aniline (XVII)

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.33-7.24 (m, 5H), 7.08 (t, J = 7.2 Hz. 2H), 6.83 (d, J = 8.0 Hz, 2H), 6.67 (t, J = 7.2 Hz, 1H), 6.56 (d, J = 10.3 Hz, 1H), 6.19 (d, J = 17.0 Hz, 1H), 5.82 (m, 1H), 5.13 (m, 1H), 4.88 (m, 1H), 3.34 (dd, J = 8.0, 5.2 Hz, 1H, CHNH), 2.31-2.06 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 147.6, 136.4, 134.4, 132.7, 129.5, 128.6, 128.5, 127.9, 119.7, 116.4, 62.8, 41.2.

(E)-4-mrthyl-N-(1-phenylhexa-1,5-dien-3-yl)aniline (XVIII)

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.33-7.24 (m, 5H), 7.09 (d, J = 7.2 Hz, 2H), 6.47 (d, J = 8.0 Hz, 2H), 6.56 (d, J = 7.2 Hz, 1H), 6.19 (d, J = 17.0 Hz, 1H), 5.82 (m, 2H), 5.13 (m, 1H), 4.88 (m, 1H), 3.34 (dd, J = 8.0, 5.2 Hz, 1H), 2.31-2.06 (m, 2H), 2.32 (s, 3H, CH_3). ^{13}C NMR (125 MHz, $CDCl_3$): δ 144.6, 136.4, 134.4, 132.7, 129.8, 129.6, 128.6, 128.5, 127.9, 116.4, 62.8, 41.2, 21.3.

5.3 CONCLUSION

In summary, new homogeneous and heterogeneous catalysts were developed for the allylation reaction of imines. Selectfluor, F-CD-BF_4, F-CD-BF_4/MWCNT and F-CD-BF_4 /Pt/MWCNT catalyzed the allylation reaction of imines and the results encouraged to perform further in this case. Further, homogeneous F-CD-BF_4 (10 wt %) is immobilized on carbon nanotubes. Heterogeneous catalysis of imines was carried out with allyltributyltin and it is observed that the reaction was much less sensitive towards air and moisture. Products are analyzed using NMR, polarimeter and HPLC. Only N-(1-phenylbut-3-en-1-yl) aniline could be separated by HPLC and other products separation are underway. Further investigation on the mechanism and scope of the utility of F-CD-BF_4 will be carried out in future work.