ORGANIC CHEMICAL TRANSFORMATIONS USING A) PALLADIUM AND B) CLAY AS CATALYSTS

A THESIS

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IN

CHEMISTRY

BY

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CERTIFICATE

This is to certify that the work presented in the thesis entitled **"ORGANIC CHEMICAL TRANSFORMATIONS USING A) PALLADIUM AND B) CLAY AS CATALYSTS,"** submitted by **Nadim S. Shaikh** was carried out by the candidate at the National Chemical Laboratory, Pune, under my supervision. Such materials as obtained from other sources have been duly acknowledged in the thesis.

(Dr. V. H. Deshpande) **Date:**

Research Supervisor

DECLARATION

I hereby declare that the thesis entitled **"ORGANIC CHEMICAL TRANSFORMATIONS USING A) PALLADIUM AND B) CLAY AS CATALYSTS,"** submitted for Ph.D. degree to the University of Pune has been carried out at National Chemical Laboratory (Pune), under the supervision of Dr. V. H. Deshpande . The work is original and has not been submitted in part or full by me for any degree or diploma to this or any other University.

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DEDICATED TO MY PARENTS

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Title	**Organic Chemical Transformations Using A) Palladium and B) Clay as Catalysts**
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ABSTRACT OF THE THESIS

Title of the thesis:

"Organic Chemical Transformations Using A) Palladium and B) Clay as Catalysts."

Thesis is divided into three chapters.
Chapter 1: Palladium Catalyzed Alkyl/ Aryl chloride Activation.
Chapter 2: New Catalytic Applications of Solid Lewis Acid Catalyst.
Chapter 3: Clay Catalyzed Protection and Deprotection of Functional Groups

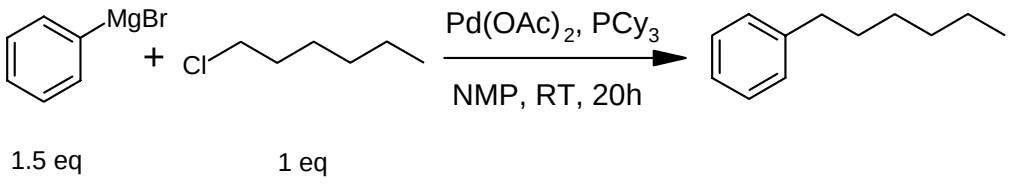
Chapter 1: Palladium Catalyzed Alkyl/ Aryl Chloride Activation.

Palladium based catalysts have provided a plethora of new methodologies for synthetic organic chemistry. Palladium-catalyzed cross-coupling of aryl halides with nucleophiles is firmly established as one of the most important method available for C-C and C-N bond formation[1]. In this regard palladium complexes containing phosphine ligands are among the most successful and widely used catalyst precursors for coupling of sp^2 or sp^3 carbons. It will be interesting to use the aryl chlorides because of the economical viability and ease of availability, for transition metal mediated cross coupling reactions. But the inertness of these substrates needs harsher conditions as compare to aryl bromides and iodides.

This chapter summarizes the efforts towards the investigation of new catalytic system for alkyl and aryl chloride activation for cross-coupling reactions. It is further divided into three sections.

Section A: Palladium Catalyzed Cross-Coupling of Alkyl Chlorides with Aryl-Grignard Reagents.

While catalytic nucleophilic substitution of $(sp^2)C—Cl$ bonds is nowadays well established, the palladium-catalyzed refinement of alkyl chlorides has been largely neglected so far. The difficulty of catalytic nucleophilic substitution at $(sp^3)C—Cl$ has been attributed to the ease of β-hydride elimination reactions of the corresponding palladium alkyl complexes[2]. Therefore, in the present work, Grignard coupling of alkyl chlorides (Kumada coupling) in the presence of various metal catalysts was studied[3]. Reaction conditions are optimized using different catalyst system and solvents for the model reaction as shown below.



Scheme 1

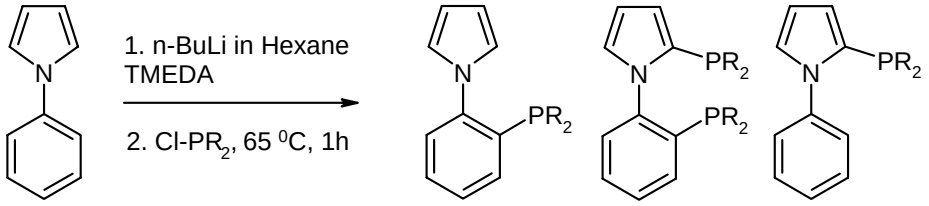
Optimizing the best condition for the reaction of phenylmagnesium bromide with n-chlorohexane i.e. 4 mol% $Pd(OAc)_2$, 4 mol % PCy_3 in NMP as a solvent at room temp. for 20 h. Under the same reaction conditions alkyl chlorides could be coupled to aryl Grignard reagents in good to excellent yields to desired coupling products. Scope of the reaction was studied for the substrate having different functional groups such as ethers, esters, acetals, fluorides, aryl and benzyl to obtain good to excellent yields of the coupling products.

Section B: Synthesis of New Phosphine Ligands by Selective Lithiation of *N*-Phenyl pyrrole.

Tertiary Phosphine ligands, PR3 behave as both σ-donors and π-acceptors. The nature of the R group (R = alkyl or aryl) determines the properties of the ligands and the strength of the phosphine donor/ acceptor properties can be modified through the change in R group.

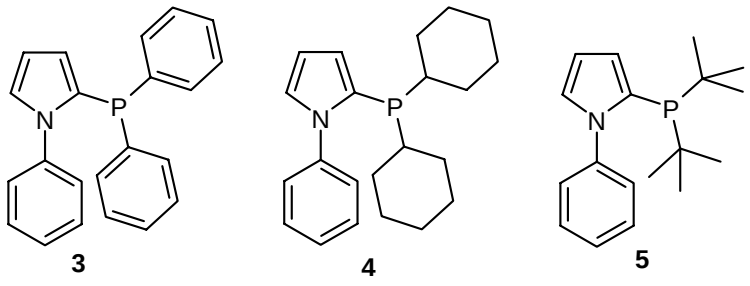
Use of phosphine ligands in palladium catalyzed C-C and C-N bond forming reactions is demonstrated in the literature[4,5], indicating that, electron rich and bulky, basic phosphine ligands can be used for aryl chloride activation.[4]

In present work, new phosphine ligands were prepared by selective lithiation of commercially available *N*-phenyl pyrrole as shown in scheme below.



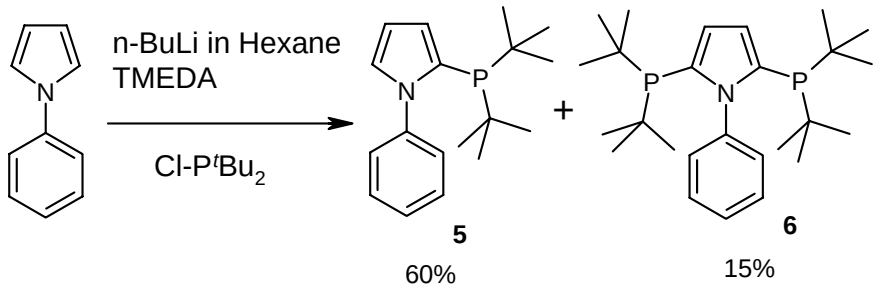
Scheme 2

Formation of trace amount of bis-phosphine **(1)** was observed in the crude reaction mixture whereas monophosphine derivative **(2)** was obtained as a major product. By using Cl-PPh_2, Cl-PCy_2 and Cl-P^tBu_2 as an electrophile three new ligands **(3-5)** were synthesized in moderate to good yields as shown below.



3 **80%** **4** **75%** **5** **45%**

In case of Cl-P^{t}Bu$_2$ as an electrophile two products **5** and **6** were observed and isolated in the pure form as shown below.



Scheme 3

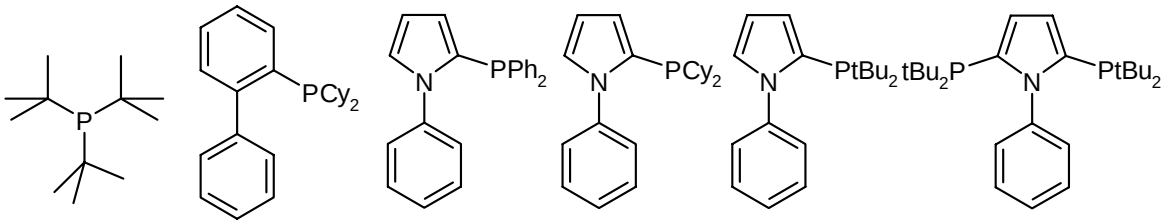
It was believed that binuclear monodentate ligand (**6**) might also work as an efficient ligand for the palladium catalyzed reactions. Those 4-new monodentate phosphine ligands were used for the palladium catalyzed activation of aryl chlorides for amination reactions (in **section C**)

Section C: Palladium Catalyzed Amination of Aryl Chlorides:

(A Comparative study of *insitu* generated palladium(0)carbene complexes with pre-defined Pd(0)carbene complexes and new monodentate phosphine ligands)

Aromatic amines constitute important substructures in natural products as well as in industrially bulk and fine chemicals. Hence interest in palladium-catalyzed C–N coupling reaction has grown constantly during the last years[6].

It has been proved that bulky basic phosphines act as efficient ligands for chloroarene activation reactions. Hence, tricyclohexylphosphine and tri-*tert*-butylphosphine proved to be successful for the coupling of activated and non-activated aryl chlorides with amines. In the present section the catalytic ability of new phosphine ligands fig. **3-6** (preparation as described in **section B**) was studied in comparison with previously known best ligands ^{t}Bu$_3$P and *o*-biphen-PCy$_2$[4] for amination reactions (**reactions 1-5**).



3 **4** **5** **6**

P^{t}Bu$_3$ ***o*-Biphenyl-Cy$_2$** **N-Phos-Ph$_2$** **N-Phos-Cy$_2$** **N-Phos-tBu$_2$** **N-Phos-bis-^{t}Bu$_2$**

Recently alternatives to phosphine have been sought owing to certain of their '*user unfriendly*' properties specifically air and moisture sensitivity and thermal instability, which means that excess ligand is often required to stabilize low valent metal centers during the catalytic cycle. These carbenes[7] are neutral two electron σ-donors, generally bearing electron donationg *N*-substituents.

In the present work, a comparison of *insitu* generated palladium(0)carbene complexes (Fig. **7** and **8**) with pre-defined Pd(0)carbene complexes (Fig. **9-11**) for the amination of aryl chlorides with amines was studied.

CHAPTER 1

Palladium Catalyzed Alkyl/ Aryl Chloride Activation

Section A

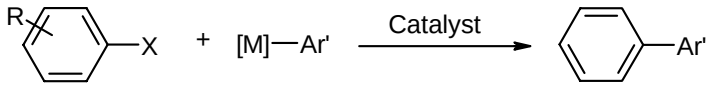
Palladium Catalyzed Cross-Coupling of Alkyl Chlorides with

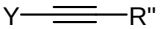
1.1.1 Introduction

During the last several decades, palladium catalyzed carbon-carbon bond formation has been extensively studied for organic synthesis.[1] The cross coupling reaction between an organometallic reagent R^1M and an organic halide R^2X is one of the most important methods for forming a new carbon-carbon bond.[2, 3] (**Scheme 1**)

These cross-coupling reactions employ a range of transmetallating agents as shown below.

Scheme 1



Reaction	Reagent [M]-Ar'
Suzuki-Miyaura	Ar'-$B(OH)_2$
Kumada	Ar'-MgX
Negishi	Ar'-ZnX
Stille	Ar'-SnR''_3
Hiyama	Ar'-$Si(OR'')_3$
Heck	
Sonogashira	
Hartwig-Buchwald Amination	HNR''R'''

Coupling partners for cross-coupling with aryl halides

Palladium or nickel complexes containing phosphine ligands are among the most successful and widely used catalyst precursors for coupling of sp^2 carbons and bulky electron rich tertiary alkyl phosphines are particularly effective.[4] Significant advances have been made in using economically viable aryl chlorides as cross-coupling partners, with a number of

processes mediated by palladium bulky phosphine systems.[4-6] Their success is explained by the catalytic cycle depicted in **Fig. 1**.

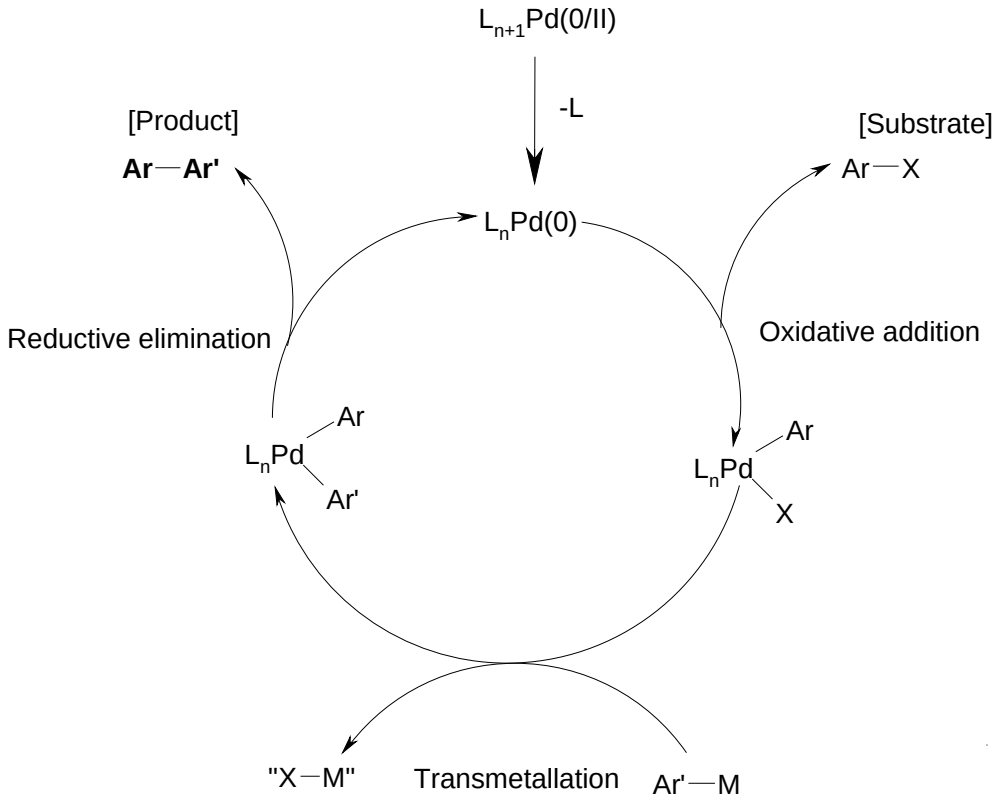
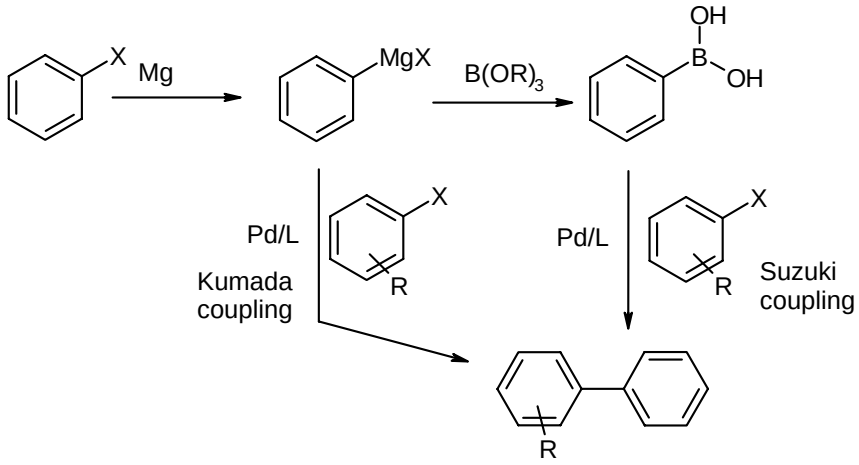


Fig. 1: Catalytic cycle for palladium complex mediated cross-coupling reactions

The increased electron richness imparted to the metal centre by the electron donating phosphine assists in the cleavage of Ar-X bond in the first oxidative addition step, while the steric bulk of the ligand promotes the reductive elimination of the Ar-Ar' coupling product following transmetallation with [M]-Ar' (while Heck and Amination reactions do not involve transmetallation step). Among the most commonly used transition metal mediated C-C bond forming reactions Kumada reaction[7] i.e. reaction of aryl halide with Grignard reagent is of particular importance because of; 1) the easy availability of the substrate/Grignard reagent, 2) most of the aryl boronic acids are synthesized from the corresponding Grignard reagents, the Kumada coupling reaction offers a more direct access to the desired coupling product than the Suzuki reaction. (**Scheme 2**)



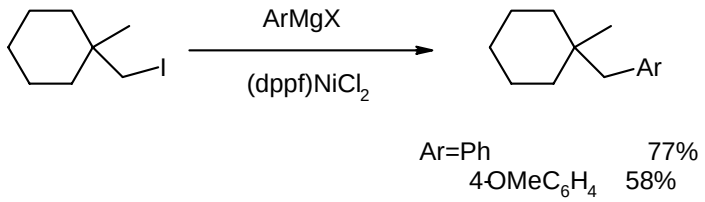
Scheme 2: Direct access to coupling product via Kumada reaction

In 1972 Kumada[8] and Corriu[9] reported that the cross coupling of Grignard reagents with aryl and alkenyl halides could be catalyzed by nickel-phosphine complexes, a wide variety of such coupling reactions have been developed and some of them have achieved great success in synthetic organic chemistry.[10] However, most coupling reactions reported involve at least one sp or sp^2 hybridized carbon. In general, most of the cross-coupling reactions require a good leaving group which is directly attached at or immediately adjacent to a carbon atom with sp^2 (allylic or benzylic) or sp (propargylic) hybridization. Presumably, coordination at these unsaturated centers may facilitate the cleavage of the corresponding C-X bond. Also, either the conjugative stabilization of the π-allyl or π-propargylic organometallic products or the interaction of the π-electrons of the σ-vinylic or alkynyl ligands with *d*-orbitals of the metal may account for the facile formation of these organometallic complexes.

While in case of transition metal catalyzed activation of C-X bonds the oxidative insertion of Pd(0) specie to alkyl-X bond is slow, leading to unstabilised σ-alkyl complexes. Due to the kinetic instability of this σ-alkyl complexes, formation of side products e.g. alkane, alkene (olefin), reductive dehalogenation product, homocoupling is found to be common problem in such type of cross-coupling reactions (**Scheme 10**). Several approaches have been employed to solve this problem.[11, 12] A change of the nucleophilicity at the metal center by modification of the ligands will facilitate the first oxidative addition step across the C-X bond. Variation of electronic or steric features at the catalytic centre will minimize *β*-hydride elimination and favor reductive elimination yielding the corresponding cross-coupling products.

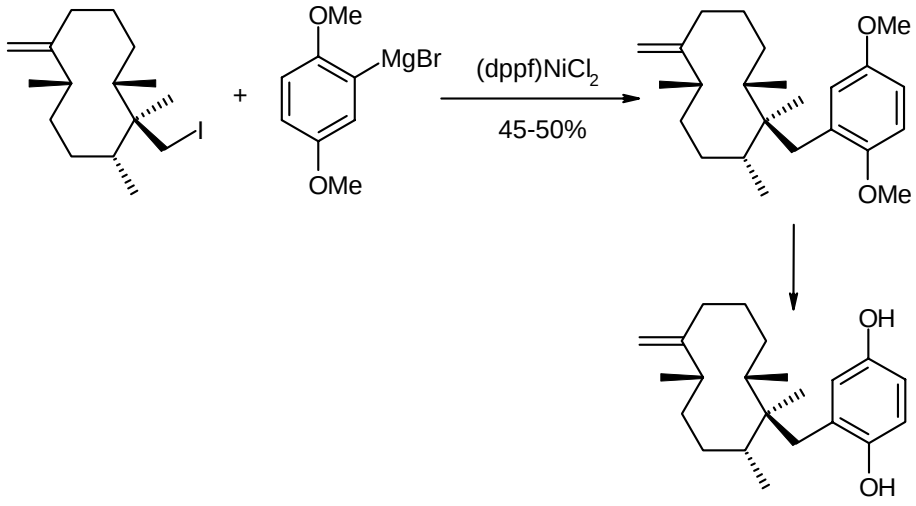
1.1.2 Literature

The first cross-coupling reactions of simple aliphatic iodides with a variety of Grignard reagents in the presence of an *insitu* generated (dppf)Pd(0), [dppf= 1,1'-bis-(diphenylphosphino)ferrocene] catalyst was reported in 1986[13], however a mixture of alkane and alkene is occasionally obtained under these conditions.[14] A more detailed study indicated that neopentyl iodides are the only substrates which give the corresponding coupling products in satisfactory yields. The best results are obtained when aromatic Grignard reagents are employed and $(dppf)NiCl_2$ is used as the catalyst (**Scheme 3**)



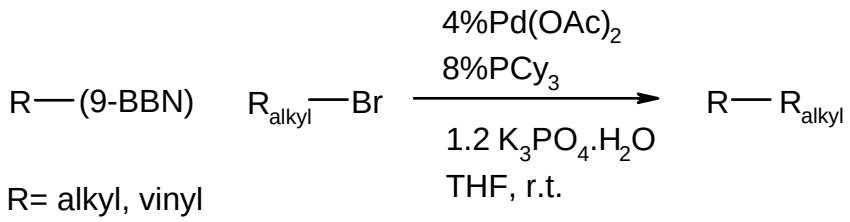
Scheme 3: Cross-coupling of alkyl iodide with aryl Grignard reagent

Even so, homocoupling dimmers are sporadically obtained as side products. Vinyl Grignard reagents do not couple under these conditions. This methodology has been successfully employed as a key step in the synthesis of the marine natural product arenarol[15] (**Scheme 4**)



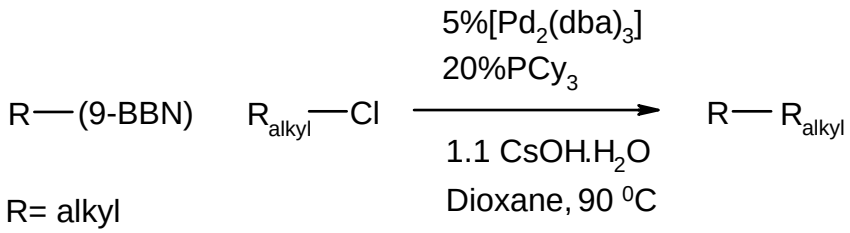
Scheme 4: Synthesis of arenarol via cross-coupling of alkyl iodide

In a pioneering investigation in 1992, Suzuki et al.[16] discovered that $[Pd(PPh_3)_4]$ can catalyze couplings of alkyl iodides with alkyl boranes at 60 °C in yields as high as 71%. Further, very recently Fu et al.[17] established that $Pd(OAc)_2/PCy_3$ effects Suzuki reactions of alkyl bromides that possess β hydrogens. (**Scheme 5**)



Scheme 5: Suzuki cross-coupling of alkyl bromides.

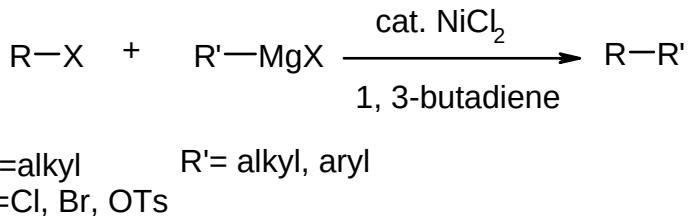
In series of reports, Knochel et al.[18] have demonstrated that a nickel-based catalyst can promote-cross couplings of alkyl bromides and iodides with organozinc reagents. Afterwards it was realized that, it will be more beneficent and interesting to use alkyl chlorides in contrast to iodides or bromides, but they represent a particularly significant challenge. Lower reactivity[19] for alkyl chlorides, as compare to iodides or bromides originates from the decreased leaving group ability of the chlorides ion and/or the higher strength of C-Cl bond (C-Cl: ≈79; C-Br: ≈66; C-I: ≈52 Kcal mol^{-1})[20]. Until, the limited progress that had been achieved in coupling alkyl halides had been restricted to iodides and bromides. But recent investigation by Fu et al.[21] described the first catalyst that is effective for reactions of alkyl chlorides (**Scheme 6**)



Scheme 6: Suzuki cross-coupling of alkyl chlorides.

$[Pd_2(dba)_3]/PCy_3]$ catalyzes the Suzuki cross-coupling of alkyl chlorides using 5% Pd source and 20% PCy_3 as ligand at 90 °C in presence of base to yield required coupling product ranging from 65 to 83%.

Meanwhile a method for the cross coupling reaction of Grignard reagent with alkyl chlorides, bromides and tosylates has been developed with the aid of Ni catalyst and 10 mol% 1,3-butadiene (**Scheme 7**)

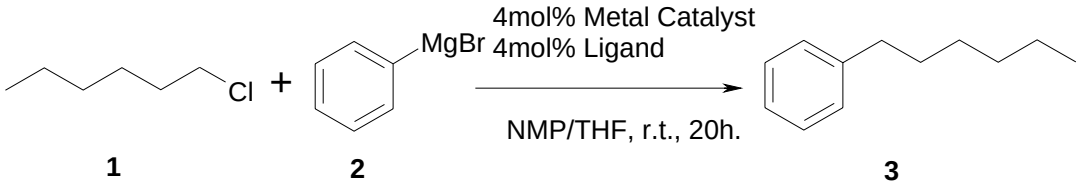


Scheme 7: Nickel-catalyzed cross-coupling of Grignard reagent with alkyl halides and tosylates

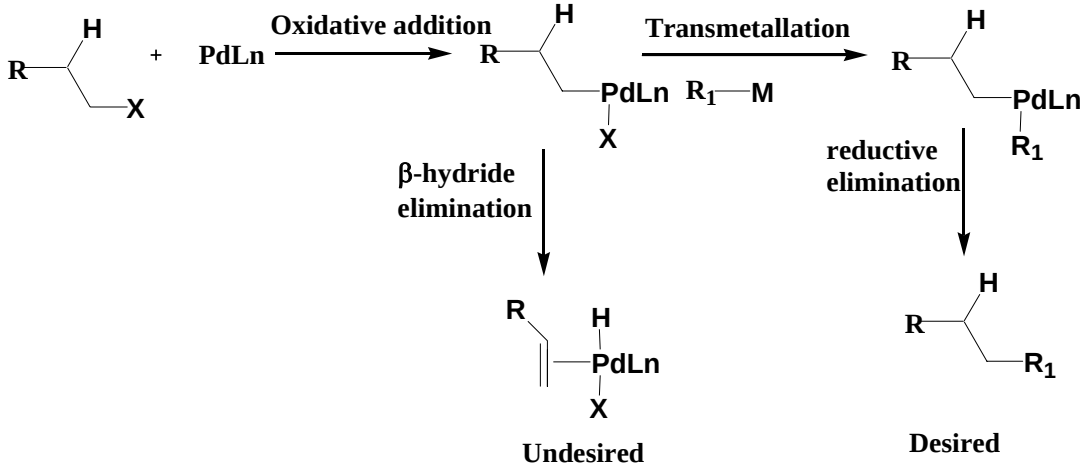
This reaction proceeds efficiently by the use of primary and secondary alkyl or aryl magnesium halide at low temperature.[22] Although each of these studies represents an important development, even collectively they provide a solution to only a small subset of the coupling processes of interest.

1.1.3 Present work

Since there has been essentially limited success to date in palladium or nickel-catalyzed coupling of simple alkyl chlorides, in contrast to iodides or bromides, they represent a particularly significant challenge. As most arylboronic acids are synthesized via the corresponding Grignard reagents, the Kumada coupling offers a more direct access to the desired products compared to the Suzuki reaction. Therefore, we have studied the Grignard coupling of alkyl chlorides (Kumada coupling) in the presence of various metal catalysts (**Scheme 8**).



Scheme 8: Cross-coupling reaction of 1-chloro hexane and phenylmagnesium bromide



Scheme 9: General mechanism for coupling of alkyl halides

General mechanism proposed for this class of reactions is as shown in **scheme 8**. The formation of required coupling product proceeds via oxidative addition, transmetallation and reductive elimination to get desired compound.

1.1.4 Results and discussion:

Initially, we performed the coupling of 1-chlorohexane (**1**) and phenylmagnesium bromide (**2**) as a model reaction **(scheme 8)** in the presence of different metal catalysts. The results are shown in **Table 1**.

Table 1: Coupling of 1-chorohexane and phenylmagnesium bromide

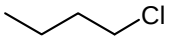
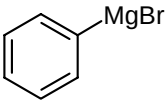
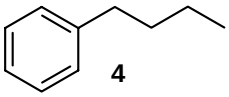
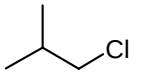
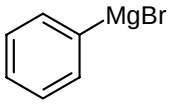
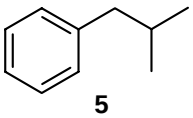
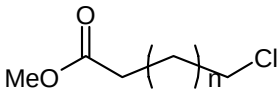
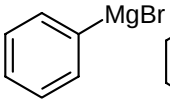
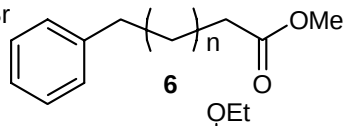
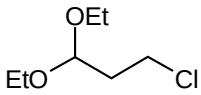
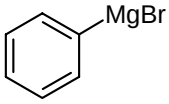
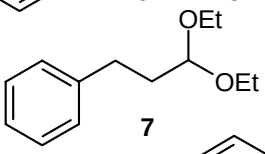
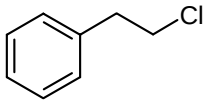
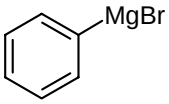
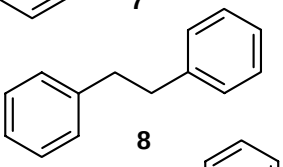
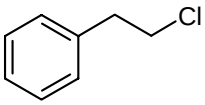
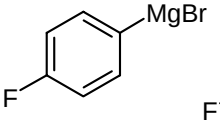
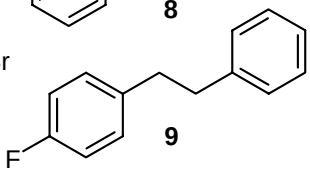
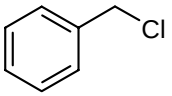
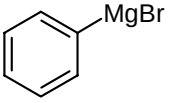
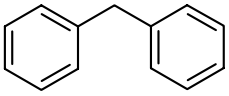
Entry	Solvent	PhMgBr Eq.	Metal compound	Ligand	Conversion %	Yield %
1	NMP	1.2	$CuCl_2$	-	27	3
2	NMP	1.2	$[Fe(acac)_3]$	-	44	7
3	NMP	1.2	$[Ni(acac)_2]$	-	45	2
4	NMP	1.2	$Pd(OAc)_2$	PPh_3	88	9
5	NMP	1.2	$Pd(OAc)_2$	P(*o*-tol)$_3$	92	11
6	NMP	1.2	$Pd(OAc)_2$	P*t*Bu$_3$	70	27
7	**NMP**	**1.2**	**$Pd(OAc)_2$**	**PCy_3**	**99**	**68**
8[a]	NMP	1.2	$Pd(OAc)_2$	PCy_3	99	70
9[a, b]	NMP	1.2	$Pd(OAc)_2$	PCy_3	76	34
10	THF	1.2	$Pd(OAc)_2$	PCy_3	1	1
11	Dioxane	1.2	$Pd(OAc)_2$	PCy_3	1	2
12	DMF	1.2	$Pd(OAc)_2$	PCy_3	70	3
13	NMP	1.0	$Pd(OAc)_2$	PCy_3	91	61
14	NMP	2.0	$Pd(OAc)_2$	PCy_3	99	71
15	NMP	3.0	$Pd(OAc)_2$	PCy_3	99	72
16	DMAc	1.5	$Pd(OAc)_2$	PCy_3	95	84
17	**NMP[c]**	**1.5**	**$Pd(OAc)_2$**	**PCy_3**	**99**	**96**

Reaction conditions: 2 mmol 1-chlorohexane, 4 mol% metal complex, 4 mol% ligand, 5 mL solvent, 20 h, room temperature. a: 40°C; b: 1 mol% $Pd(OAc)_2/PCy_3$, 1/1; c: NMP from Aldrich water-free 99.5%, used as received.

In general, all reactions were run with 4 mol% of metal catalyst at room temperature. A commercially available solution of phenylmagnesium bromide (in THF) **2** was added to a solution of **1** and catalyst in such a way, that the reaction temperature does not exceed 40 °C. No conversion was observed in the absence of catalyst. Simple salts of Cu,[23a, b] Ni or Fe, which have been shown to be active in Grignard coupling reactions of alkyl bromides or aryl chlorides, did not catalyze the desired reaction to an appreciable amount (**Table 1**, entries **1-3**). Upon application of palladium as catalyst, the effect of different phosphine ligands, solvents, and substrate concentration were studied. Although a high conversion was observed in the presence of $Pd(OAc)_2$ and triarylphosphines, the selectivity of the reaction was low (entries **4-5**). Side products were hexene and hexane. In agreement with the results reported by Fu et al. for Suzuki reactions[21], tricyclohexylphosphine (PCy_3) proved to be the best ligand for the Grignard coupling of 1-chlorohexane (entries **7-9**). However, the ligand effect was not pronounced, as Pd/P*t*Bu_3 also gave a significant amount of product. Further optimization of the amount of Grignard reagent (entries **13-18**) led to excellent yield (96 %) of 1-phenylhexane in the presence of 1.5 equiv. of PhMgBr. Apart from the influence of the ligand, the efficiency of the reaction was found to be largely dependent on the solvent (entries **10-12**). So far, only *N*-methylpyrrolidinone (NMP) and dimethylacetamide (DMAc) gave good yields of the coupling product. After having optimized the model reaction, the scope of the coupling reaction was extended as shown in **Table 2**.

Isobutyl chloride led to a slightly lower yield (**Table 2**, entry **2**, 72 %) as compare to n-butyl chloride (entry **1**, 89 %). Unfortunately, reactions with *sec*-butyl, and *tert*-butyl chloride showed no conversion. On the other hand, the method was applicable to functionalized alkyl chlorides. Methyl 6-chlorohexanoate, and 3-chloropropionaldehyde diethyl acetal gave the corresponding products (58 and 74 %; **Table 2**, entries **3** and **4**). Even coupling reactions with 2-phenylethyl chloride, which is amenable to elimination to styrene, proceeded with significant yields (76 and 43 %; **Table 2**, entries **5** and **6**). The reaction time has not been optimized (in general 20 h), except for the model reaction (**Scheme 8**) which exhibited complete conversion after 30 minutes.

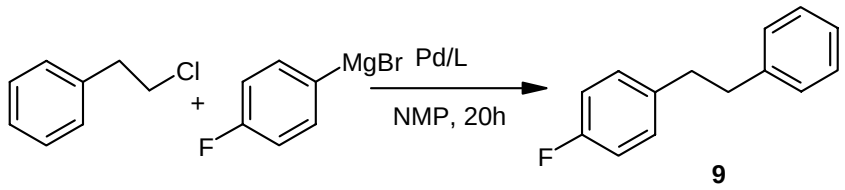
Table 2: Palladium-catalyzed cross-coupling of alkyl chlorides with aryl Grignard reagents

Entry	Alkyl chloride	Grignard reagent	Product	Conversion[a] %	Yield[a] %
1			 **4**	nd	89
2			 **5**	100	72
3			 **6**	80	58
4			 **7**	85	74
5			 **8**	90	76
6			 **9**	96	43
7			 **10**	100	84

n= 3, nd= not determined.; a : Calculated by GC analysis

Among the range of alkyl chlorides studied phenyl ethyl chloride with 4-fluoro phenyl magnesium bromide gave poor yield even though the excellent conversion is observed (**Table 2, entry 6**). This reaction was separately undertaken for the optimization by varying the reaction parameters (as shown in **Table 3**).

Table 3: Optimization to improve the selectivity of coupling product 9



9

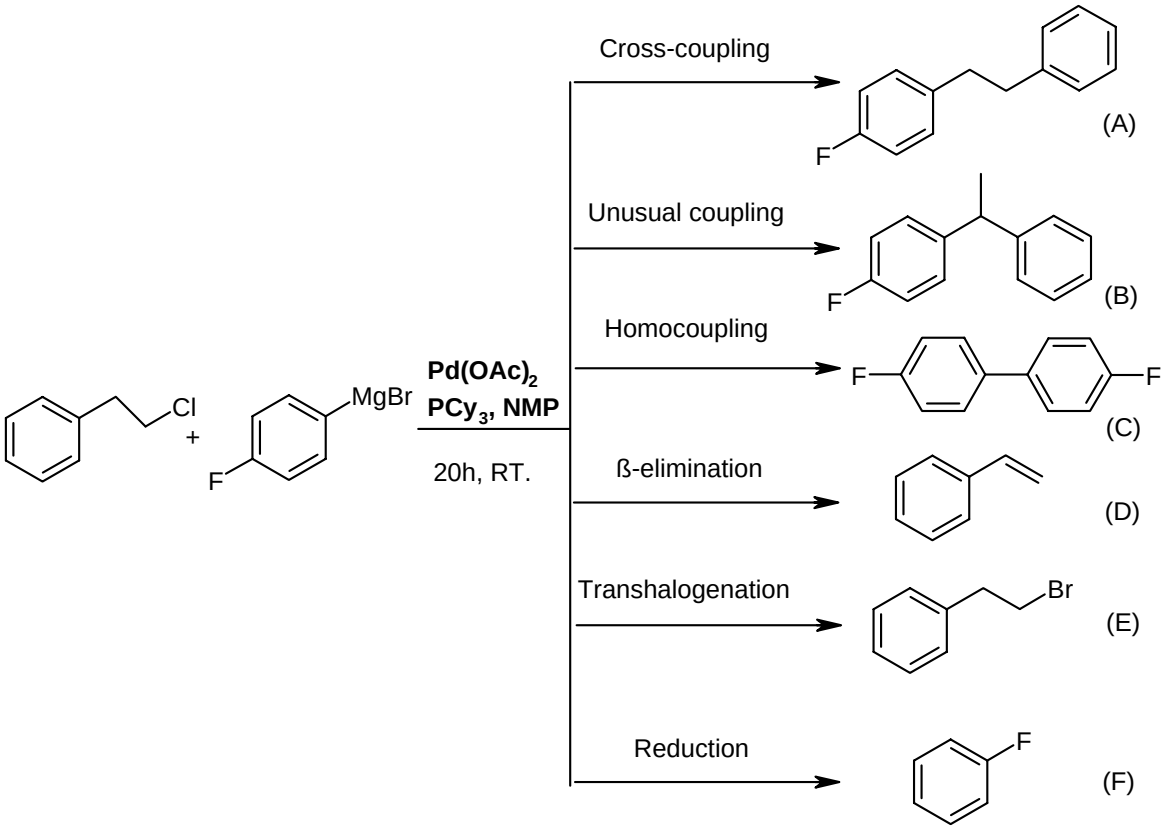
Entry	Chloride	Grignard	Pd:L	Temp. (°C)	Conv. (%)	Yield (%)
1	1	1.5	1:1	r.t.	96	43
2	1	2	1:1	r.t.	88	38
3	2	1	1:1	r.t.	20	15/29[a]
4	1	1.5	1:1	0-5	07	03
5	1	1.5	1:1	40	95	41
6	1	1.5	1:1	60	88	19
7	1	1.5	1:2	r.t.	59	24
8	1	1.5	1:4	r.t.	31	06
9	1	1.5	1:0.5	r.t.	58	25
10	1	1.5	1:1	r.t.	91	40[b]
11	1	1.5	none	r.t.	08	00
12	1	1.5	1:1	r.t.	71	30[c]
13	1	1.5	1:1	r.t.	50	30[d]

Reactions on 2mmol scale, a: Corresponds to Grignard reagent, b: Slow addition of Grignard reagent, c: In presence of 10 mol% TBAB, d: Using $Pd_2(dba)_3$ instead of $Pd(OAc)_2$

Using excess of Grignard reagent from 1.5 to 2 equivalents dropped down the conversion as well as yield (**Table 3**, entry **2**). Half equivalent of the same gave poor results (entry **3**). Variation in temperature did not give any improvement in the yield (entry **4**, **5**, **6**). Decrease in yield of required product was observed by changing the palladium ligand ratio from 1:1 to 1:2 (entry **7**), 1:4 (entry **8**) and 1:0.5 (entry **9**). Although there was 8 % conversion of substrate in absence of catalyst (entry **11**), no required coupling product was detected. Use of catalytic amount of TBAB or change of palladium salt from $Pd(OAc)_2$ to $Pd_2(dba)_3$ gave poor yields (**Table 3**, entries **12** and **13** respectively).

Careful GCMS analysis of the crude reaction mixture (**Table 2**, entry **5**) showed the formation of different side products along with the required coupling reaction product. Unusual cross-coupling product (B) with similar molecular weight as the coupling product (A)

was eluted little earlier than the required product (A). Homocoupling product (C) which is very often formed in such kind of coupling reactions was found to be in considerable amount in this reaction.



Scheme 10: Side products detected by GC-MS analysis of crude reaction mixture

As expected, styrene (D) was also found to be one of the side products due to the *β*-hydride elimination. Further the formation of trans-halogenated product (E) and reduced product (F) from Grignard reagent has also been observed. Further optimization was found to be not possible using the similar catalyst system.

1.1.5 Conclusion:

A novel method for the cross coupling of alkyl chlorides and Grignard reagents in the presence of palladium catalysts have been developed. Good to excellent yields of the coupling products were obtained at room temperature and functional groups such as ethers, esters, acetals, fluorides, aryl and benzyl were tolerated by the procedure. 4 mol% of palladium and 4 mol% PCy_3 is required for the efficient conversion.

Secondary and tertiary alkyl chlorides do not undergo coupling reaction with Grignard reagent using the similar catalyst system.

1.1.6 Experimental:

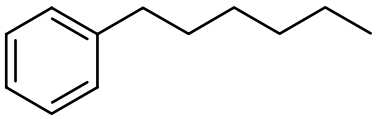
All the substrates i.e. alkyl chlorides, Grignard reagents (1 molar solution in THF), PCy_3, NMP were purchased from Aldrich Chemical co. The conversions and yields were determined by GC-FID using diethyleneglycol di-*n*-butyl ether as an internal standard. The temperature program used for the GC monitoring was 50 °C, 2 min; 15 K / min; 210 °C, 5 min (Hew. Pack. Instrument; HP 5 column).
(All reactions were performed according to the following procedure)

Coupling of alkyl chlorides with aryl Grignard reagents: [23c]

A 25 mL Schlenk flask was charged with $Pd(OAc)_2$ (0.0180 g, 0.080 mmol) and PCy_3 (0.0224 g, 0.080 mmol), sealed with a septum, and purged with argon for 15 min. NMP (5 mL) and 1-chlorohexane (0.27 mL, 2 mmol) were added by syringe. Then, PhMgBr (3 mL, 3 mmol, 1 M in THF) was added dropwise over 1 minute to the stirred mixture. After 20 h at r.t., the reaction was quenched with MeOH (1 mL) and water (1 mL). The reaction was concentrated to appr. 6 mL by rotary evaporation, and subjected to silica gel column chromatography (heptane) to give a colorless liquid (0.276 g, 1.7 mmol, 85 % yield).
(For GC analysis, after quenching the reaction with MeOH and water, known amount of standard (diethylene glycol di-*n*-butyl ether) was added to reaction mixture, followed by dilution with diethyl ether and stirred well. Organic layer of the reaction mixture was filtered through $MgSO_4$ and subjected for GC analysis to calculate the conversion (%) and yield (%).

The compound **5** (iso-Butyl benzene) is commercially obtained and used for GC standardization. Compounds **3**, **4**, **10** are commercially available from Aldrich Chemical Co. and spectral data obtained for those are corresponds with the data obtained from isolated compounds.

Hexylbenzene (3):[24]



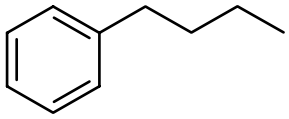
Appearance Colorless liquid.

^{1}H NMR (400MHz, $CDCl_3$): δ 7.25-7.00 (m, 5H), 2.51 (t, *J* = 7.7 Hz, 2H), 1.58-1.47 (m, 2H), 1.30-1.15 (m, 6H), 0.80 (t, *J* = 6.4 Hz, 3H)

^{13}C NMR (100MHz, $CDCl_3$): δ 143.4, 128.9, 128.7, 126.0, 36.5, 32.2, 32.0, 29.5, 23.1, 14.6.

MS (EI, 70 eV): *m*/*z* (%) 162 (33, M^+), 105 (11), 91 (100), 77 (4), 43 (16).

N-Butyl benzene (4):[24]



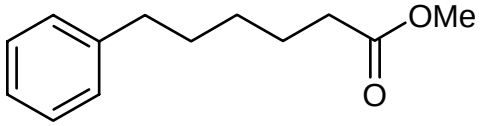
Appearance Colorless liquid

B. p. 180-183 °C

^{1}H NMR (400MHz, $CDCl_3$): δ 7.34-7.12 (m, 5H), 2.61 (t, *J* = 7.5 Hz, 2H), 1.60 (m, 2H), 1.36 (m, 2H), 0.95 (t, *J* = 6.3 Hz, 3H)

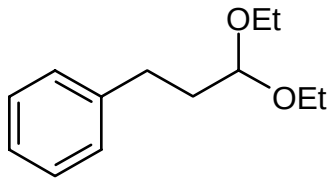
^{13}C NMR (100MHz, $CDCl_3$): δ 142.86, 128.37, 128.18, 125.54, 35.73, 33.69, 22.40, 13.97

6-Phenyl-hexanoic acid methyl ester (6):[25a]



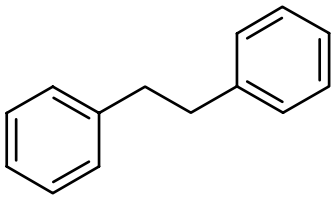
Appearance	Colorless liquid
B. p.	72-74 °C/0.2 Torr
IR (KBr)	2935, 2858, 1740, 1240, 1044, 700 cm^{-1}
^{1}H NMR (400MHz, $CDCl_3$):	δ 7.30-7.26 (m, 2H), 7.20-7.0 (m, 3H), 3.65 (s, 3H), 2.55 (t, J= 7.6 Hz, 2H), 2.31 (t, J= 7.5 Hz, 2H), 1.71-1.56 (m, 4H), 1.42-1.35 (m, 2H).
^{13}C NMR (100MHz, $CDCl_3$):	δ 173.8, 142.8, 128.5, 128.7, 125.1, 51.4, 35.2, 33.7, 31.3, 28.9, 24.4.
MS (EI, 70 eV): *m*/*z* (%):	206 (1, M^+), 146 (98), 117 (92), 104 (98), 91 (100), 77 (10), 65 (24), 43 (80)

3-Phenyl-propionaldehyde diethyl acetal (7): [25b]



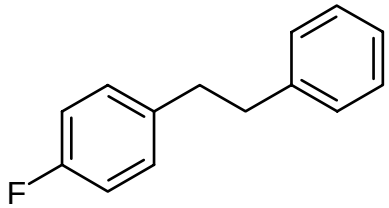
Appearance	Colorless liquid
B. p.	90-91/ 1.5 Torr
IR (KBr)	2975, 2877, 1455, 1374, 1129, 1063, 748, 698 cm^{-1}
^{1}H NMR (400MHz, $CDCl_3$):	δ 7.23-7.06 (m, 5H), 4.41 (t, J = 6 Hz, 1H), 3.62-3.36 (m, 4H), 2.63-2.59 (m, 2H), 1.89-1.84 (m, 2H), 1.13 (t, J = 10.8 Hz, 6H)
^{13}C NMR (100MHz, $CDCl_3$):	δ 142.2, 128.8, 128.7, 126.2, 102.6, 61.4, 35.5, 31.4, 15.8
MS (EI, 70 eV): *m*/*z* (%):	208 (1, M^+), 162 (21), 117 (35), 103 (49), 91 (100), 75 (59), 47 (60).
HRMS:	calculated for $C_{13}H_{20}O_2$ 208.14633; found 208.14460

1, 2-Diphenyl-ethane (8):[27]



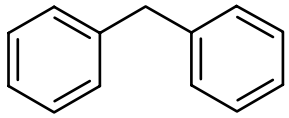
Appearance	White solid
M. p.	50-52 °C; ethanol
IR (KBr)	3026, 2925, 2856, 1946, 1601, 1452, 1180, 1065, 753, 697, 518 cm^{-1}
^{1}H NMR (400MHz, $CDCl_3$):	δ 7.32-7.12-(m, 10H), 2.88 (s, 4H)
^{13}C NMR (100MHz, $CDCl_3$):	δ 142.1, 128.5, 128.4, 126.2, 37.81

4-Fluoro-bibenzyl (9):[28]



Appearance	White solid
M. p.	61-63 °C, ethanol
IR (KBr)	3075, 2860, 2000, 1580, 1450, 1140, 1064, 1020, 753, 696 cm^{-1}
^{1}H NMR (400MHz, $CDCl_3$):	δ 7.28-7.18 (m, 2H), 7.14-7.0 (m, 5H), 6.92-6.82 (m, 2H), 2.85 (s, 4H)
^{13}C NMR (100MHz, $CDCl_3$):	δ 141.8, 130.3, 130.2, 128.9, 128.8, 126.4, 115.5, 115.3, 38.4, 37.5
MS (EI, 70 eV): *m*/*z* (%):	200 (58, M^+), 109 (100), 92 (82), 65 (15).
HRMS:	Calculated for $C_{14}H_{13}F$: 200.10013; found 200.09800.

Diphenylmethan (10):[24]



Appearance	White solid
M. p.	25-27 °C
^{1}H NMR (400MHz, $CDCl_3$):	δ 7.63-7.41 (m, 10H), 4.27 (s, 2H)
^{13}C NMR (100MHz, $CDCl_3$):	δ 141.7, 129.6, 129.1, 126.7, 42.6
Elemental analysis:	Calculated for $C_{13}H_{12}$, C: 92.57, H: 7.36 %
	Found C: 92.81, H: 7.19 %

1.1.7 References

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CHAPTER 1

Section B

Synthesis of New Phosphine Ligands by Selective Lithiation of *N*-Phenyl Pyrrole

1.2.1 Introduction

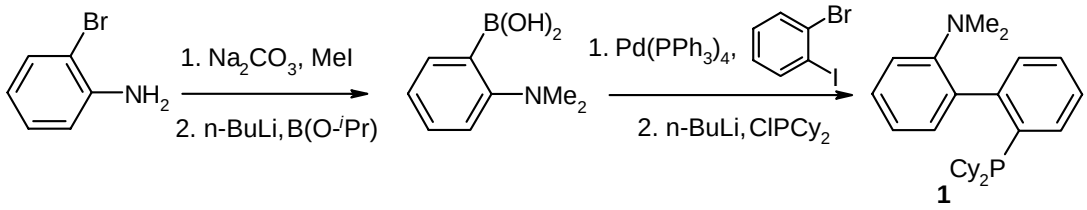
In coordination chemistry, a ligand is generally understood as a complexing group that can either donate or accept electrons. The metal atoms in organometal complexes often are in low-positive, zero or negative formal oxidation states, and π-bonding ligands typically stabilize these low oxidation states by delocalizing the high electron density of the metal atom onto the ligand.[1]

Work towards the synthesis of organophosphorous compounds began early in the 19th century. A major driving force was the recognition of their biochemical activity[2]. Tertiary phosphine ligands, PR_3 (R = alkyl and/or aryl) behave as both σ-donors and π-acceptors. The nature of the R groups determines the properties of the ligands and the strength of the phosphine donor/acceptor properties can be modified through change in the R groups. Steric and electronic properties provide the basis for the selection of a particular ligand for catalytic purposes. Catalytic properties of phosphines depend among other factors, on their basicity. Organophosphine compounds[3] are usually prepared by one of three routes: 1) via organometallic reagents and appropriate halogenophosphines, 2) from metal phosphides or 3) by hydride reduction. In the first route Grignard and organolithium reagents are the commonly used organometallic reagents. Occasionally also other organometallic compounds, such as organozinc and organocadmium, have been used.[4] The first route is the most useful for the synthesis of tertiary phosphines of the type PR_3, PR_2R_1 and PRR_1R_2.[3] The second route can be used for the preparation of primary and secondary phosphines. The required phosphide and organophosphide anions can be obtained by metallating the phoshines with strong base, by halogen metal or metal metal exchange or by reductive metallation.[3] In the third route, two types of reduction are involved in the preparation of phosphorus compounds: reduction that do not involve the formation of a new P-H bond and those where new P-H bonds are formed. Typically, the first type is used for the preparation of tertiary phosphines and the second for the preparation of secondary and primary phosphines. Phosphines are widely used as ligands for transition metals. They promote the solubility of metal complexes in a wide range of organic media. The majority of phosphines are insoluble in water, though water soluble phosphines are found among the sulfonated phenylphosphines and pyridylphosphines.[5-8]

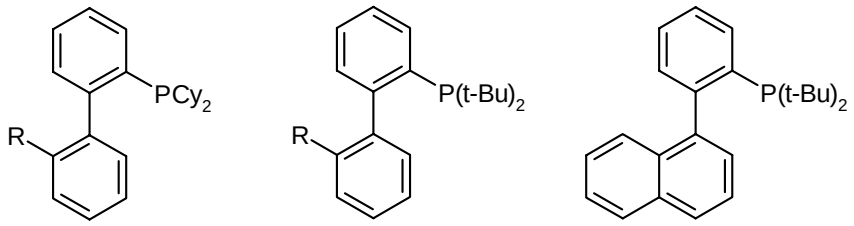
1.2.2 Literature

The property of phosphines to stabilize low oxidation states of metal atoms provides compounds that are useful in homogeneous catalysis.

Concerning the use of phosphines in cross-coupling reactions; it has been proved[10-15] that, monodentate tertiary alkyl phosphines (PR_3) play unique role as catalyst precursor in C-C, C-O and C-N bond forming reactions. Owing the importance of such phosphine ligands, biphenyl based phosphine ligands were synthesized (**scheme 1**)[16] and studied very recently for cross-coupling reactions.



Scheme 1: Synthesis of Biphenyl based Phosphine ligands



1: R=NMe_2
3: R=H
5: R=Me
7: R=*i*-Pr

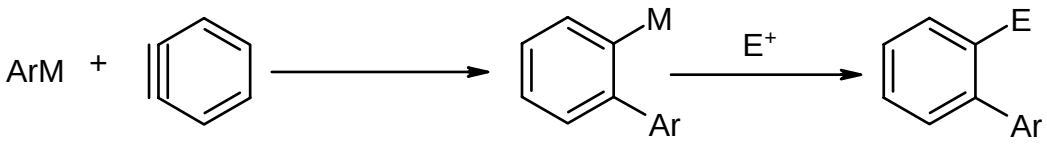
2: R=NMe_2
4: R=H
6: R=Me
8: R=*i*-Pr

9

According to recent reports aminophosphine **1**, when combined with a source of Pd, gives an exceptional catalyst for the amination[12] and Suzuki coupling[13] reactions of aryl chlorides and bromides.[12 i), 13] The catalyst based on **1** could transform aryl bromides or an activated aryl chloride to arylamines at room temperature, and it was the first catalyst that was useful for the amination reactions of electron-rich aryl chlorides. The activity of the catalyst for Suzuki coupling reactions was also unprecedented: even electron-rich aryl chlorides and

aryl bromides could be coupled with arylboronic acid derivatives at room temperature.[12, 13] Although the Pd-catalyst derived from **1** was, the most active catalyst for amination and Suzuki reactions, its usefulness was limited because four steps were required to prepare it (**Scheme 1**).[16 a)]

Further improvement in the synthetic method (**scheme 2**) resulted in desired phosphine ligands (18-59%) in one step using aryl magnesium halide with *insitu* generated bezyne.[16b]



Scheme 2: Improved synthesis of biphenyl based phosphine ligands

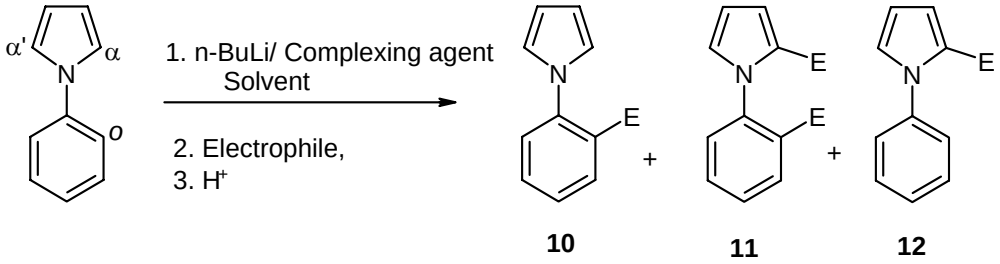
Benzyne in the presence of an aryl magnesium halide or an aryllithum; *cine*-addition[16b] of the organometallic species to benzyne produces an *ortho*-metalated biphenyl derivative, which can subsequently react with an electrophile (**scheme 2**).

Thus, the discovery that Pd-catalysts based on ligands **3** and **4** are also highly active in Suzuki[13] and amination[12] reactions was of considerable importance, since these can be prepared in one step from 2-bromobiphenyl and are now commercially available.[17] The scope of substrates that can be coupled by Pd-catalysts that employ **3** and **4** is large, and in many instances, the utility of these ligands is equals or superior to that of **1**. For example, in amination and Suzuki coupling reactions that are conducted at room temperature, catalysts from ligand **4** are more active than those based on **1**.

The interesting results and importance of this class of ligands[16, 17] in the cross-coupling reactions as well as difficulties encountered in the preparation of such type of ligands encouraged us to design more simple and efficient ligands which will be useful for the cross-coupling reactions.

1.2.3 Present work

The present study is part of a project targeted at developing new, selective catalysts for cross-coupling reactions. The primary focus of the study was the preparation and characterization of new tertiary phosphine ligands from *N*-phenyl pyrrole. The study of the phosphine ligands had two specific objectives: 1) to synthesize and characterize new monodentate ligands for catalytic purposes and 2) to find trends in their behavior as ligands.
Mono and di-lithiation of *N*-phenyl pyrrole has been studied in the literature[18] to make carboxylic ester derivatives.



Scheme 3: Lithiation of*N*-phenyl pyrrole using different complexing agents and solvents

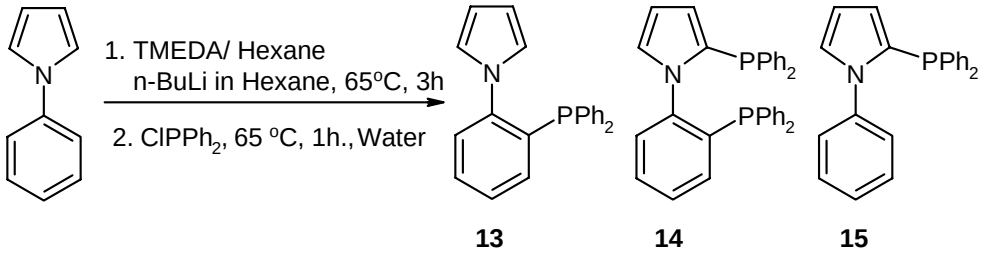
Under appropriate condition the clean preparation of either the α-mono lithiated or the *o*-α dilithiated derivative of *N*-Phenyl pyrrole is possible.
(Where electrophile is solid CO_2 and E is COOMe)

Table 1: Optimization for selective Lithiation of N-Phenyl pyrrole (Literature study)[18]

Complex	Solvent	Temp. (°C)	Time (h)	10 (%)	11(%)	12 (%)
TMEDA	DEE/HEX	0	10	2	13	32
TMEDA	**HEX**	**65**	**3.0**	**-**	**2**	**86**
$KOC(CH_3)_3$	THF	-75	2.5	-	3	75
$KOC(CH_3)_3$	HEX	25	5.0	-	11	24

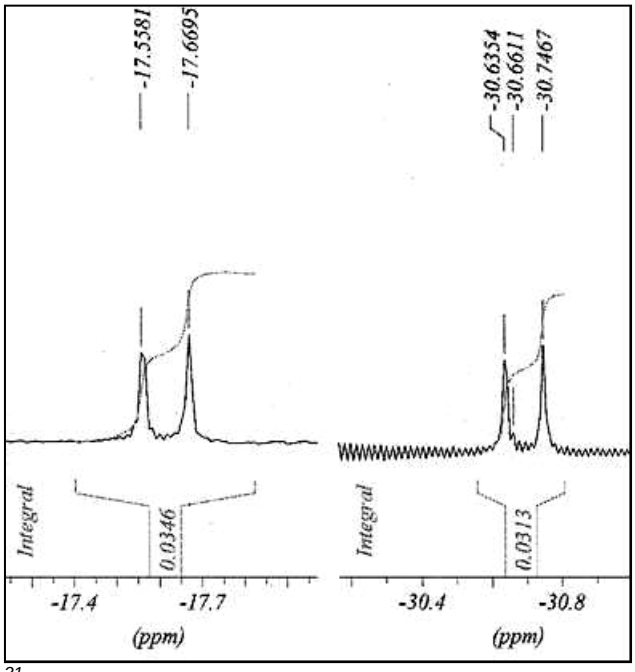
1.2.4 Results and discussion

As shown in table 1 the optimized condition for selectively α-lithiation of *N*-phenyl pyrrole is TMEDA as complexing agent in hexane at 65 ^{0}C for 3h. to give 86% of mono-α-substituted ester derivative (**12**) of *N*-phenyl pyrrole when CO_2 was used as an electrophile followed by esterification with CH_2N_2. 2% of *o*- α-bis-ester (**11**) has also been observed whereas none of the mono-*o*-ester (**10**) was detected. Taking advantage of this study we planned to use diaryl and dialkyl chlorophosphine as an electrophile. Keeping the expectations to achieve selective mono- α-substituted phosphine derivatives of *N*-phenyl pyrrole, chloro-diphenylphosphine was used as an electrophile for the first model reaction. (**Scheme 4**)



Scheme 4: Preparation of N-Phos-Ph

It was observed that low temperature (less than 65 ^{o}C) favors the formation of bis phosphine (**14**). Exclusively bis-phosphine **14** can be obtained at room temperature in diethyl ether[19]. Without using complexing agent sluggish reaction mixture containing phosphine oxide, n-butyl-diphenylphosphine, Ph_2P-PPh_2 and corresponding phosphine mono-oxide has been observed (according to GC-MS analysis of the crude reaction mixture). When 1 eq. of TMEDA was used, 2-diphenylphosphanyl-1-phenyl-1*H*-pyrrole (**15**) was obtained in the form of white solid with 56% yield. Little improvement in yield (64 %) and purity of the desired product (**15**) was obtained when 1.5 eq. of TMEDA was used. 64% of mono phosphine (**15**) and approximately 15 % of bis-phosphine (**14**) was obtained when THF was used as a solvent. The ratio of mono and bis-phosphine is determined by peak integration of ^{31}P-NMR signals with high relaxation time of 5 seconds. Formation of bis-phosphine (**14**) was confirmed by P-P coupling to get two doublets at δ -17.5 (d, $J_{P\text{-}P}$ = 18 Hz) and -30.7 (d, $J_{P\text{-}P}$ = 18 Hz).

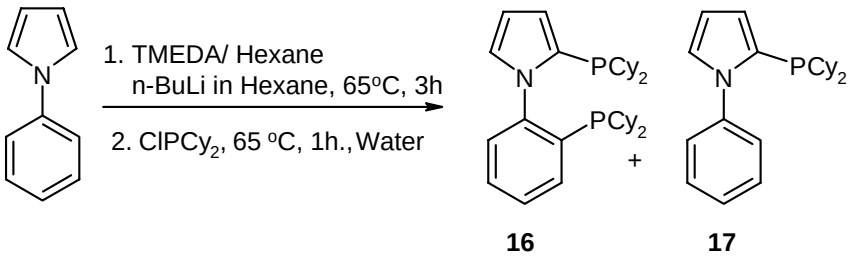


^{31}*P-NMR: P-P coupling of bis-phosphine* ***14***

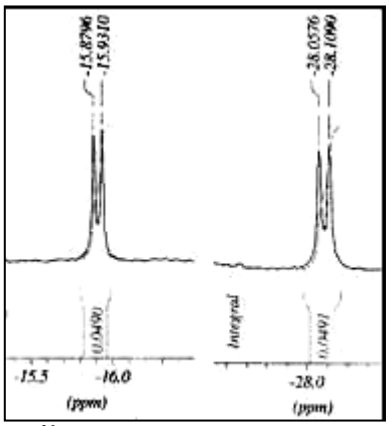
After attempting several experiments a suitable condition was established to make monophosphine (**15**) in 80% yield with 1.5 eq TMEDA, 1 eq. n-BuLi (in hexane) and hexane as solvent at 65 ^{o}C for 3h. Further quenching of the reaction with chlorophosphine solution in hexane and heating it again for 1h. gave bis phosphine (**14**) in 5 % yield along with the desired product **(15)** which can be removed by recrystallization of desired compound (**15**) from methanol.

Mono-*o*-phosphine (**13**) could not be detected during standardization of the reaction conditions.

Having optimum conditions in hand, chloro-dicyclohexyl phosphine was used instead of chloro-diphenyl phosphine as an electrophile (**Scheme 5**) to obtain 2-dicyclohexylphosphanyl-1-phenyl-1*H*-pyrrole (**17**) as a major product (65%) along with small amount (4%) of bis-phosphine (**16**) i.e. 2-Dicyclohexylphosphanyl-1-(2-dicyclohexylphosphanyl-phenyl)-1H-pyrrole.



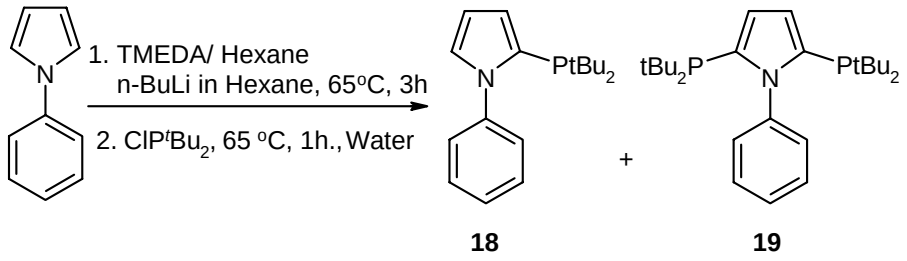
Scheme 5: Preparation of N-Phos-Cy



^{31}*P-NMR: P-P coupling of* ***16***

Formation of bis-phosphine **16** was confirmed by P-P coupling to get two doublets at δ -15.9 (d, $J_{P\text{-}P}$, 8.3 Hz) and -28.1 (d, $J_{P\text{-}P}$, 8.3 Hz).

The more interesting *t*-Butyl analogue was attempted under the similar reaction conditions by making use of chloro-di-^{t}butyl phosphine. (**Scheme 6**)



18 **19**

Scheme 6: Preparation of N-Phos-^{t}Bu

Surprisingly, in case of chloro-di-*t*-butyl phosphine as an electrophile; *α*-di-*t*-butyl phosphine derivative of *N*-phenyl pyrrole (**18**) was obtained with 45% yield along with α, α'-bis-di-*t*-butylphosphine derivative of *N*-phenyl pyrrole i.e. 2,5-Bis-(di-*tert*-butylphosphanyl)-1-phenyl-1*H*-pyrrole (**19)** with 15% isolated yield. Such substitution has not been observed in case of $ClPPh_2$ and $ClPCy_2$. The possibility of such substitution is not mentioned in the literature.[18] Formation of **19** was realized as there was no P-P coupling but MS shows [431] as M^+ peak which belongs to bis-phosphine. It was believed that this new compound **19** may also work as an efficient ligand, as both the P-groups are at opposite sides, it may act as monodentate ligand in transition metal catalyzed reactions. Separation of these two ligands (**18** and **19**) is also found to be easy. First recrystallization from methanol gave bis-phosphine (**19**) as a white solid within a day. Methanolic filtrate was kept at 0 ^{o}C for two days to obtain mono-phosphine **18** in the form of white solid.

1.2.5 Conclusion

The synthesis of four new monodentate phosphine ligands in one pot from commercially available *N*-phenyl pyrrole has been achieved. All those ligands are stable at room temperature and crystalline solids. Ease of isolation, purification and handling while using for the catalytic reactions are main features of these ligands. Also low cost and patent free applications made them attractive for the evaluation in different types of transition metal catalyzed reactions involving use of phosphine as ligands. Preliminary applications are summarized in the **section 3**.

1.2.6 Experimental

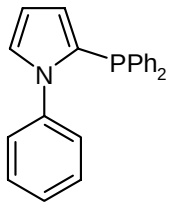
All the operations were carried out under strict exclusion of air. Hexane was distilled over sodium metal under nitrogen. All the chemicals were purchased from Aldrich chemical co. Chlorophosphines were purchased from strem chemical co. and used as received.

Representative procedure for the synthesis of monophosphine:

To a vacuum dried three nacked 100ml round bottom flask with reflux condenser, was placed *N*-phenyl pyrrole (1.43gm, 10 mmol) and dissolved in 20ml of freshly distilled n-hexane (dry). TMEDA was added (15mmol) followed by *n*-BuLi (10 mmol, 1.6 M in Hexane) at r.t. The reaction mixture was refluxed for 3 h. Reaction mixture was allowed to cool at r.t. for 15min. and added diaryl or dialkyl-chlorophosphine (10mmol in 6ml hexane) via syringe (slow addition). The reaction mixture was further refluxed for 1 h. It was cooled to r.t. and degassed water (15ml) was added, to get a clear solution. The organic layer was transferred to an addition funnel via cannula. Aqueous layer was washed with hexane (twice 15 ml each) and organic layer was transferred to addition funnel under argon. The organic layer was washed with degassed water (15ml). The organic layer was collected into a flask containing degassed Na_2SO_4 (anhydrous) then it was filtered and concentrated at below 45°C to get yellow viscous liquid. Methanol added and refluxed for 5 min to dissolve the viscous liquid and allowed to cool at r.t. This solution was kept at r.t. for 24h. and then at 0°C for 3-4 h. to get white crystals. It was filtered and dried under vacuum. The filtrate was stored below 0 °C under argon to obtain second crop within 48 h.

2-Diphenylphosphanyl-1-phenyl-1*H*-pyrrole (15):

This reaction was carried out as per representative procedure on 10 mmol scale.

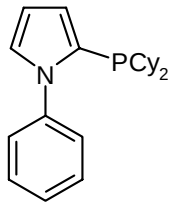


***N*-Phos-Ph (15)**

Appearance	White solid
Yield (%)	80 %
M. p.	100-102°C, MeOH
IR (KBr)	3068, 3050, 3013, 1595, 1493, 1434, 1320, 1203, 1086, 772, 750, 725, 691, 515, 500 cm^{-1}
^{31}P NMR (162MHz, $CDCl_3$):	δ -29.8
^{1}H NMR (400MHz, $CDCl_3$):	δ 7.25-7.20 (m, 13H), 7.17-7.12 (m, 2H), 7.02-6.98 (m, 1H), 6.2 (dd, J_1 = 2.6 Hz, J_2 = 3.6 Hz, 1H), 5.98 (dd, J_1 = 1.7 Hz, J_2 = 3.6 Hz, 1H)
^{13}C NMR (100MHz, $CDCl_3$)	δ 140.90, 138.02, 137.95, 136.14, 133.89 (d, J_{c-p} = 20 Hz), 129.32, 129.20, 128.95, 128.79, 128.72, 127.81, 127.12, 127.09, 126.71, 126.68, 120.40, 110.23
MS (EI, 70 eV): *m*/*z* (%):	327 (100, M^+); 250(12); 219(11); 183(8); 172(53); 145(5); 115(7); 77(14); 51(10); 39(3)
HRMS:	Calculated for $C_{22}H_{18}NP$: 327.11768, found: 327.11698 %.

2-Dicyclohexylphosphanyl-1-phenyl-1*H*-pyrrole (17):

This reaction was carried out as per representative procedure on 10 mmol scale.



***N*-Phos-Cy (17)**

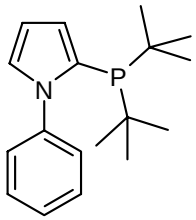
Appearance	White solid
Yield (%)	72%
M. p.	91-93°C, MeOH
^{31}P NMR (162MHz, $CDCl_3$):	δ -27.05
^{1}H NMR (400MHz, C_6D_6):	δ 7.45-7.15 (m, 5H), 6.90-6.81 (m, 1H), 6.47-6.43 (m, 1H), 6.38-6.18 (m, 1H), 1.85-1.45 (m, 15H), 1.22-0.82 (m, 7H).

^{13}C NMR (100MHz, C_6D_6)	δ 141.9, 128.8, 127.4, 126.46, 117.97 (d, $J_{c\text{-}p}$ = 3.81 Hz), 110.2, 35.1, 35.05, 31.1 (d, $J_{c\text{-}p}$ = 17 Hz), 29.6, 29.7, 27.8, 27.7, 27.6, 27.1
MS (EI, 70 eV): *m*/*z* (%):	339 (30, M^+), 257 (38), 174 (100), 143 (6), 77 (7), 55 (15), 41 (14).

2-Di-*t*-butylphosphanyl-1-phenyl-1*H*-pyrrole (18):

This reaction was carried out as per representative procedure on 10 mmol scale with little modified workup procedure (as follows) in order to separate bis-phosphine from mono phosphine.

After concentration of organic layer, 10ml degassed MeOH was added and refluxed for 5 min. Mixture was allowed to cool at room temperature till next day to observe white crystalline material which was filtered and washed with cold MeOH and characterized as bis-phosphine (**19).** The MeOH layer (filtrate) was kept in cold (0 °C) for 2-days to get white soild which was filtered and washed with MeOH, dried under vacuum to get mono-phosphine **18**.



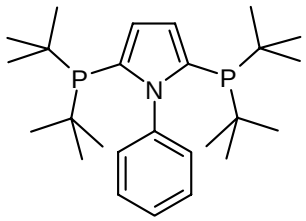
***N*-Phos-^{t}Bu (18)**

Appearance	White solid
Yield (%)	45%
M. p.	51-53°C, MeOH
IR (KBr)	2881, 1599, 1514, 1497, 1457, 1419, 1377, 1362, 1319, 1202, 1176, 1091, 762, 722, 694, 511 **cm^{-1}**
^{31}P NMR (162MHz, $CDCl_3$):	δ 3.64
^{1}H NMR (400MHz, $CDCl_3$):	δ 7.44-7.36 (m, 3H), 7.29-7.26 (m, 2H), 7.00-6.97 (m, 1H), 6.77 (dd, J= 3.8 Hz and 1.6 Hz, 1H), 6.37 (ddd, J_1 = 3.8 Hz, J_2 = 2.7 Hz, J_3 = 0.4 Hz, 1H), 1.14 (d, J = 12.1 Hz, 18H).

^{13}C NMR (100MHz, $CDCl_3$)	δ 142.02, 129.26 (d, J_{c-p} = 12.4 Hz), 128.74, 128.70, 127.77, 126.35 (d, J_{c-p} = 1.9 Hz), 118.76 (d, J_{c-p} = 4.8 Hz), 118.74, 108.92, 33.43 (d, J_{c-p} = 17.16 Hz), 30.72 (d, J_{c-p} = 14.4 Hz)
MS (EI, 70 eV): *m*/*z* (%):	287 (22, M^+), 230 (18), 174 (100), 77 (8), 57 (20), 41 (20).
HRMS:	Calculated for $C_{18}H_{26}NP$: 287.17908, found: 287.18030

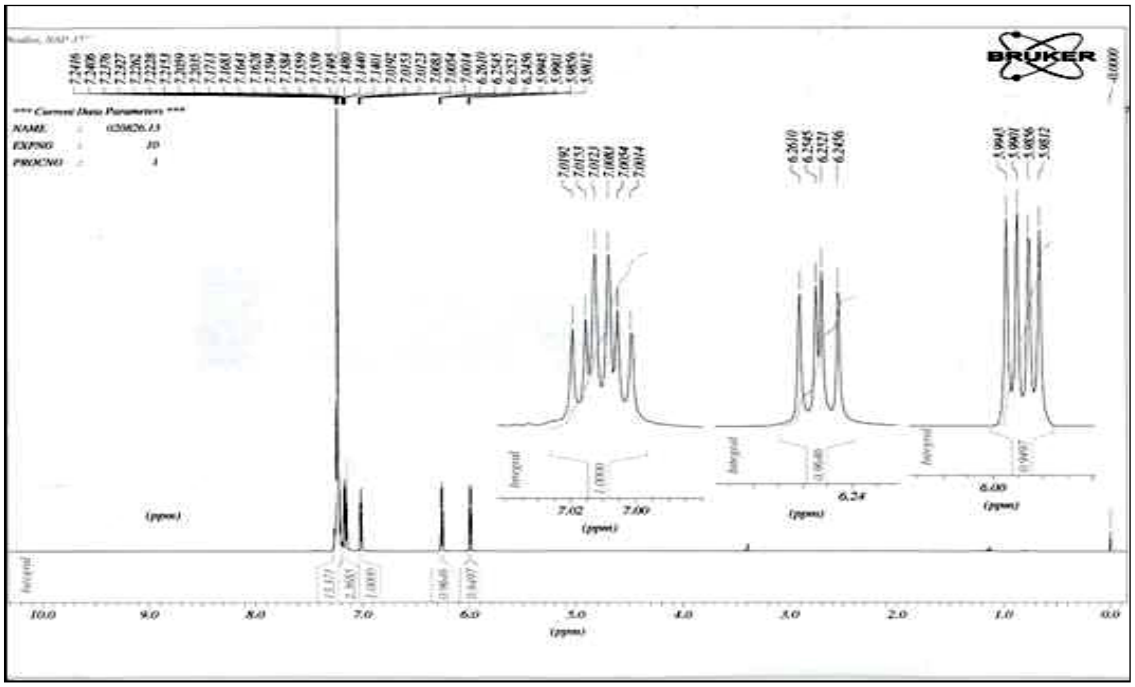
2,5-Bis-(di-*tert*-butylphosphanyl)-1-phenyl-1*H*-pyrrole (19):

This compound is obtained from the reaction mixture of **18** (isolation described as above).

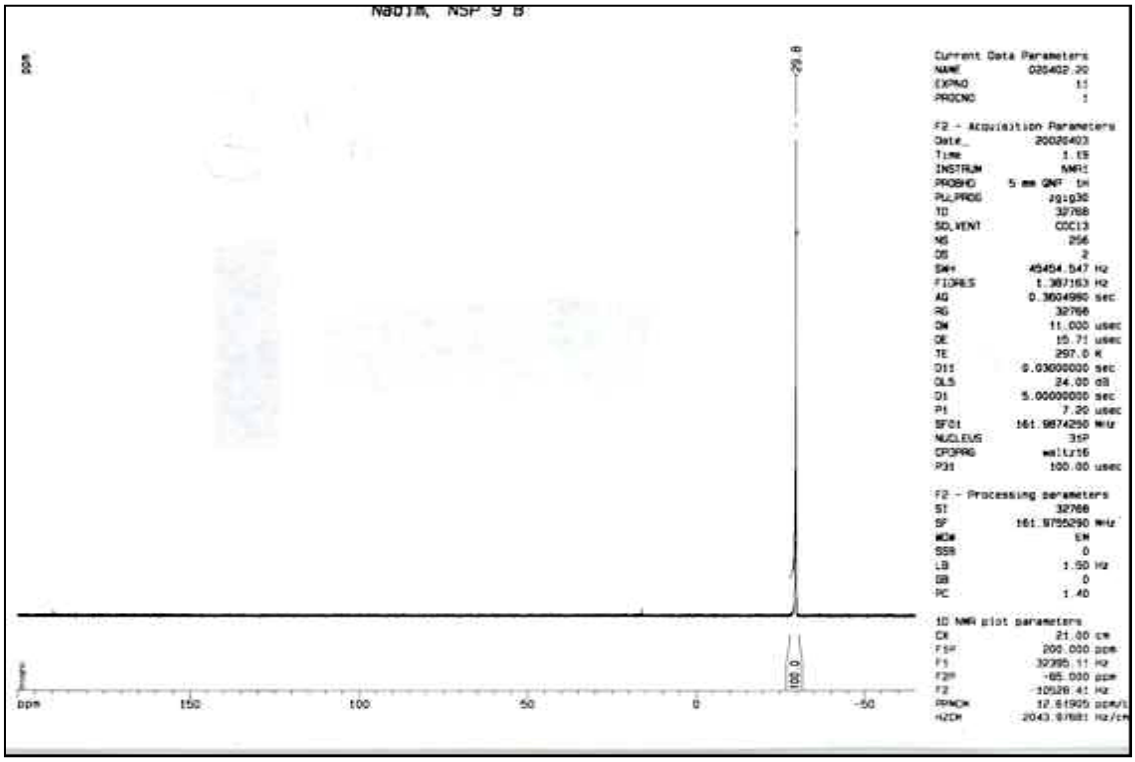


***N*-Phos-bis-^{t}Bu$_2$ (19)**

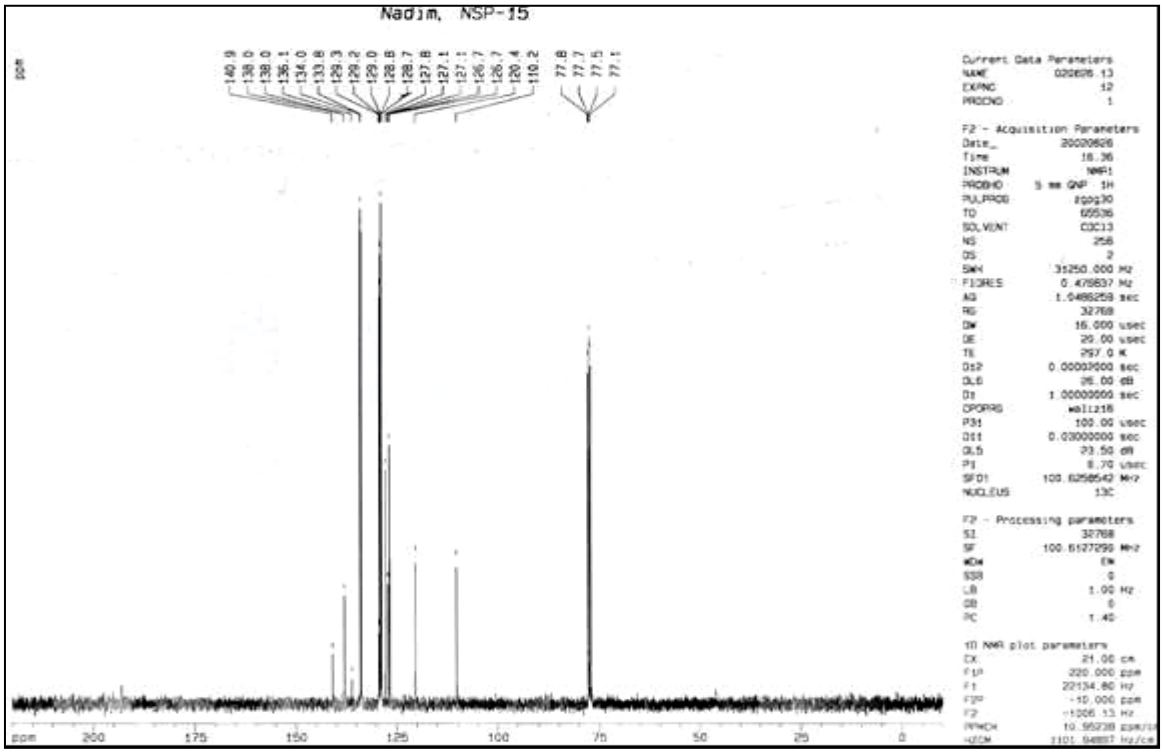
Appearance	White solid
Yield (%)	15%
M. p.	47-49°C, MeOH
IR (KBr)	2900, 1590, 1550, 1495, 1425, 1385, 1352, 1300, 1210, 1180, 1080, 760, 720, 699, 520 **cm^{-1}**
^{31}P NMR (162MHz, $CDCl_3$):	δ 5.21
^{1}H NMR (400MHz, $CDCl_3$):	δ 7.40-7.32 (m, 3H), 7.05-7.00 (m, 2H), 6.79 (s, 2H), 1.12 (d, J = 11.9 Hz, 36H).
^{13}C NMR (100MHz, $CDCl_3$)	δ 140.6, 132.3, 132.2, 130.1, 126.9, 126.4, 116.2, 32.1, 32.0, 31.9, 31.8, 29.5, 29.4, 29.3, 29.2
MS (EI, 70 eV): *m*/*z* (%):	431 (44, M^+), 374 (50), 318 (100), 262 (64), 206 (44), 172 (49), 77 (5), 57 (47), 41 (22).
HRMS:	Calculated for $C_{26}H_{43}NP_2$: 431.28708, found: 431.28773.



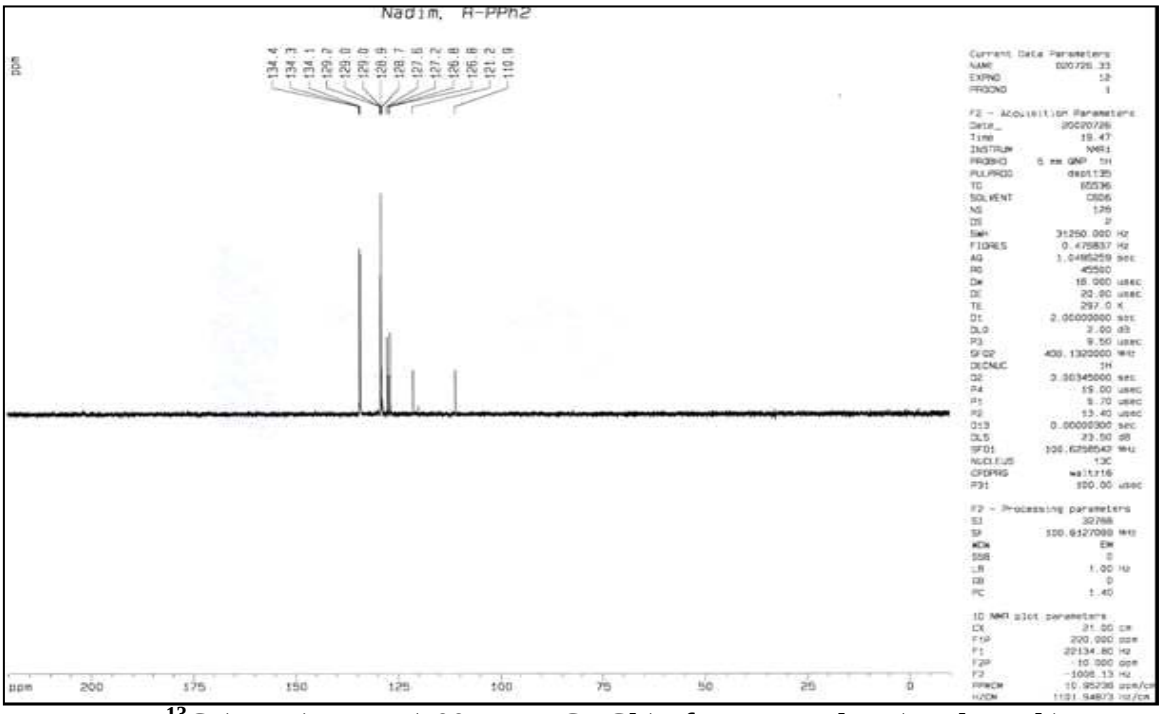
^{1}H-NMR (400 MHz, $CDCl_3$) of compound 15 (*N*-Phos-Ph)



^{31}P-NMR (162 MHz, CDCl3) of compound 15 (*N*-Phos-Ph)



^{13}C-NMR (100 MHz, $CDCl_3$) of compound 15 (*N*-Phos-Ph)



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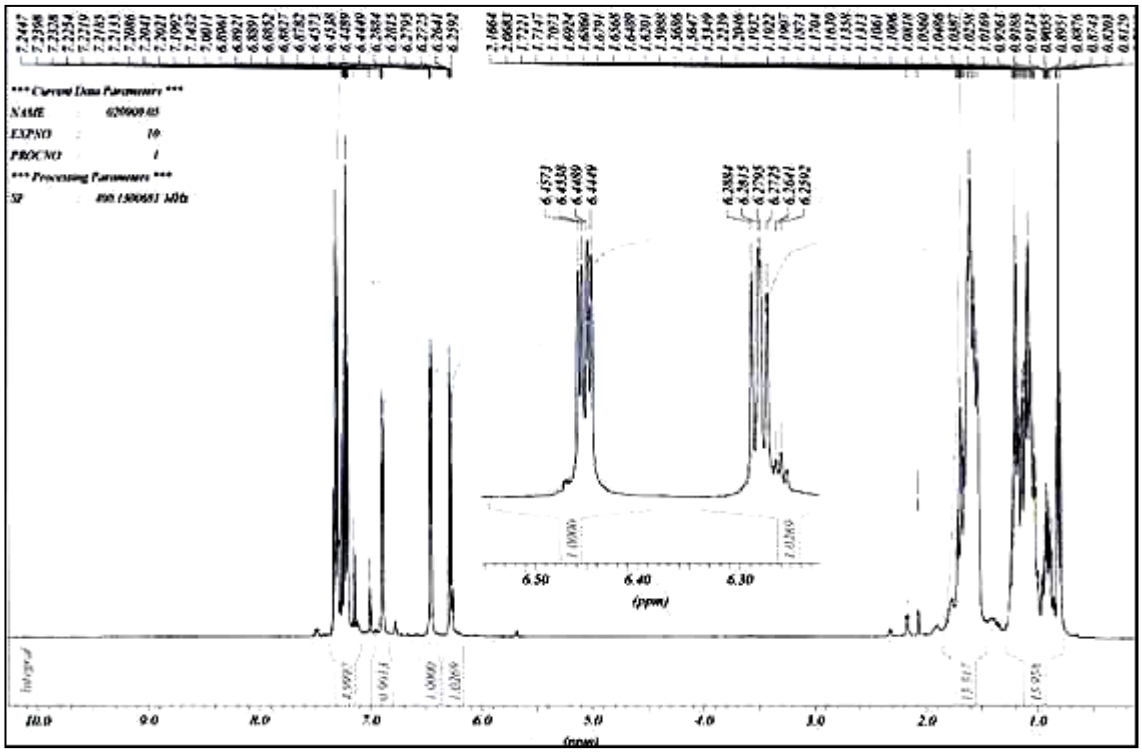
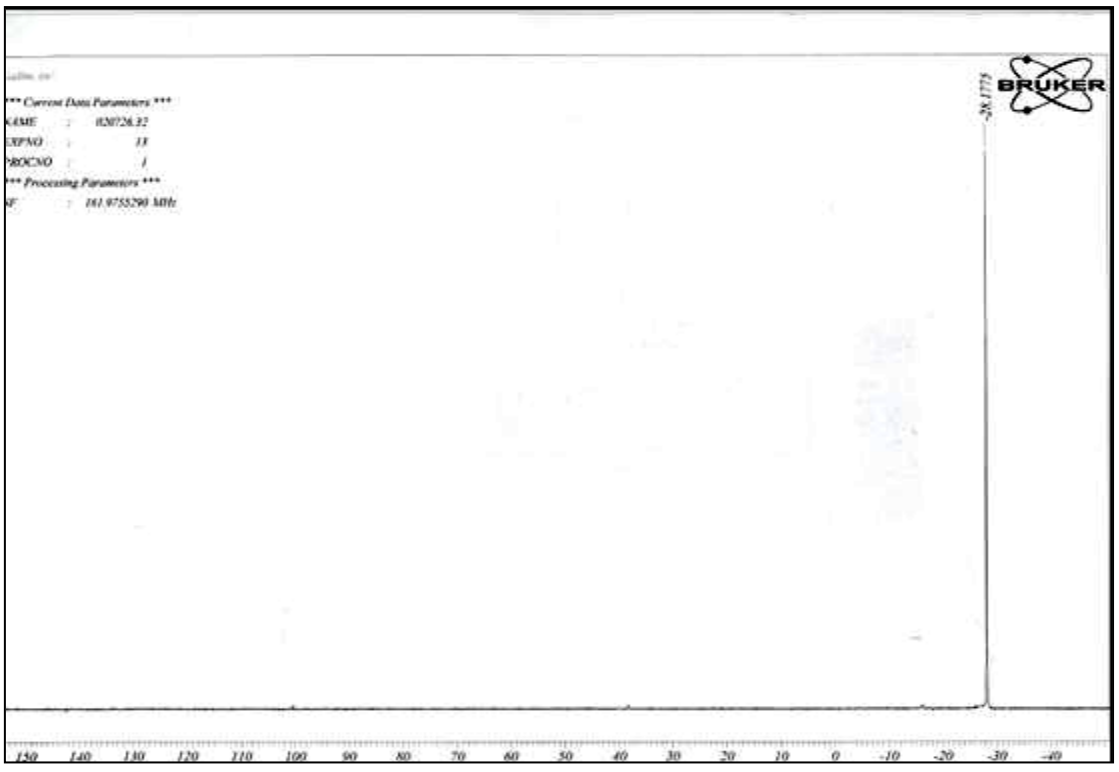
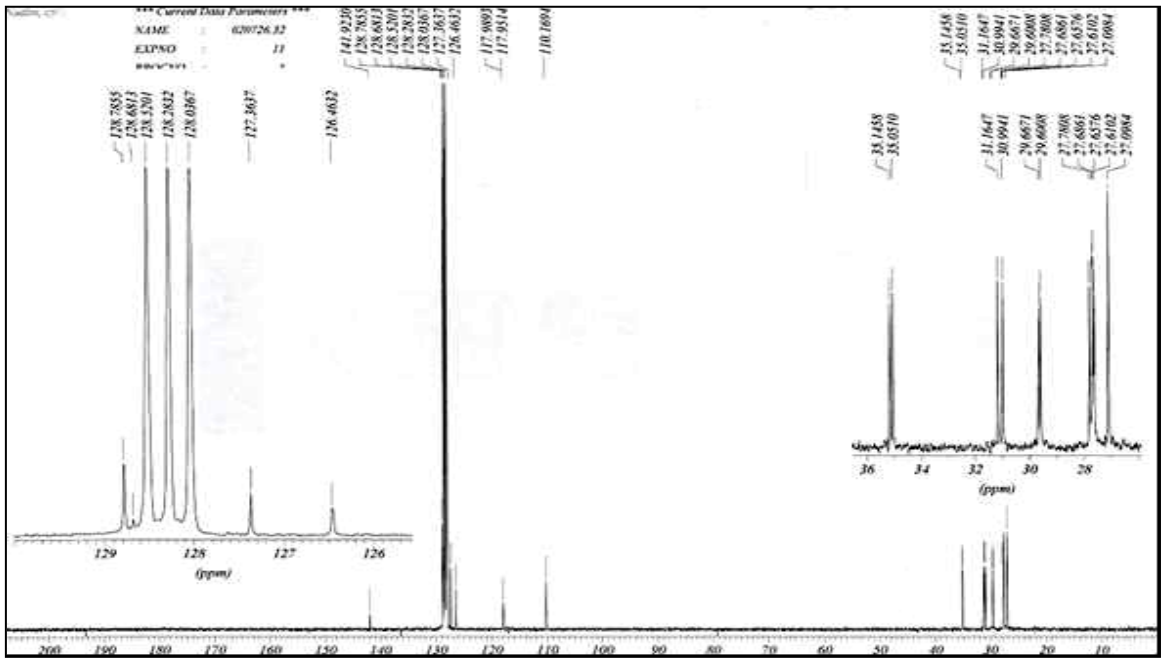


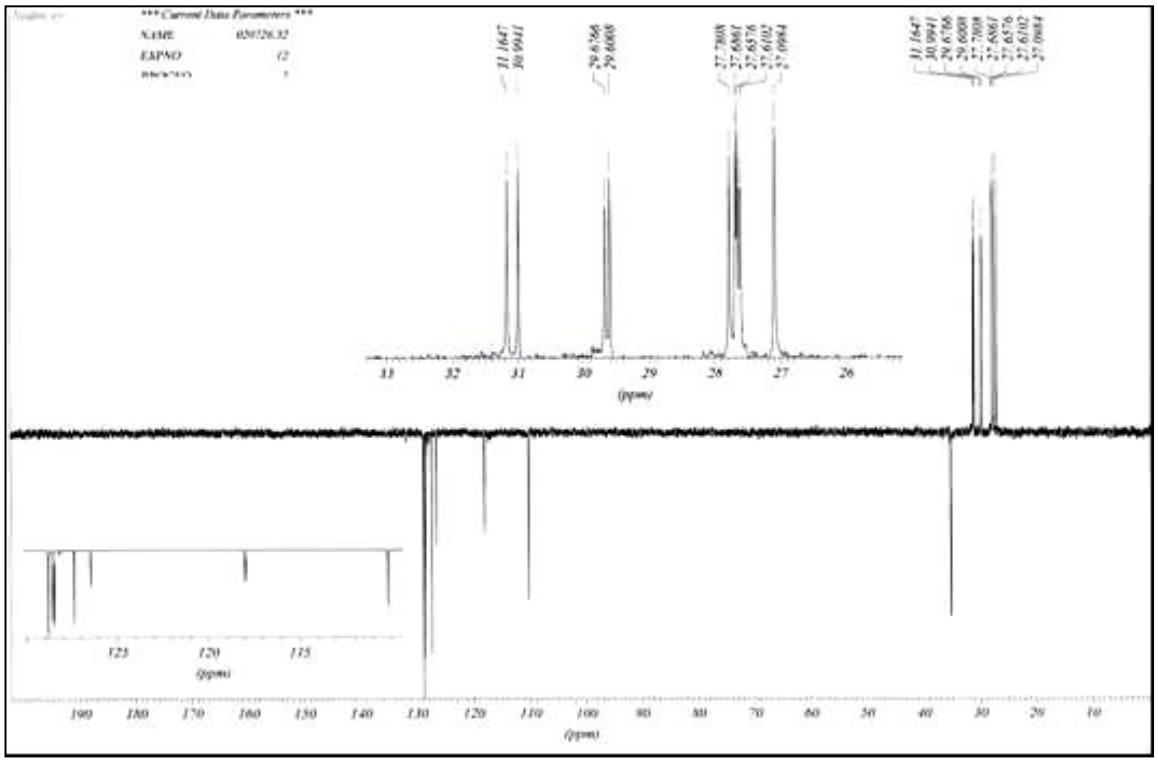
^{1}H-NMR (400 MHz, C_6D_6) of compound 17 (*N*-Phos-Cy)



^{31}P-NMR (162 MHz, $CDCl_3$) of compound 17 (*N*-Phos-Cy_2)



^{13}C-NMR (100 MHz, C_6D_6) of compound 17 (*N*-Phos-Cy)



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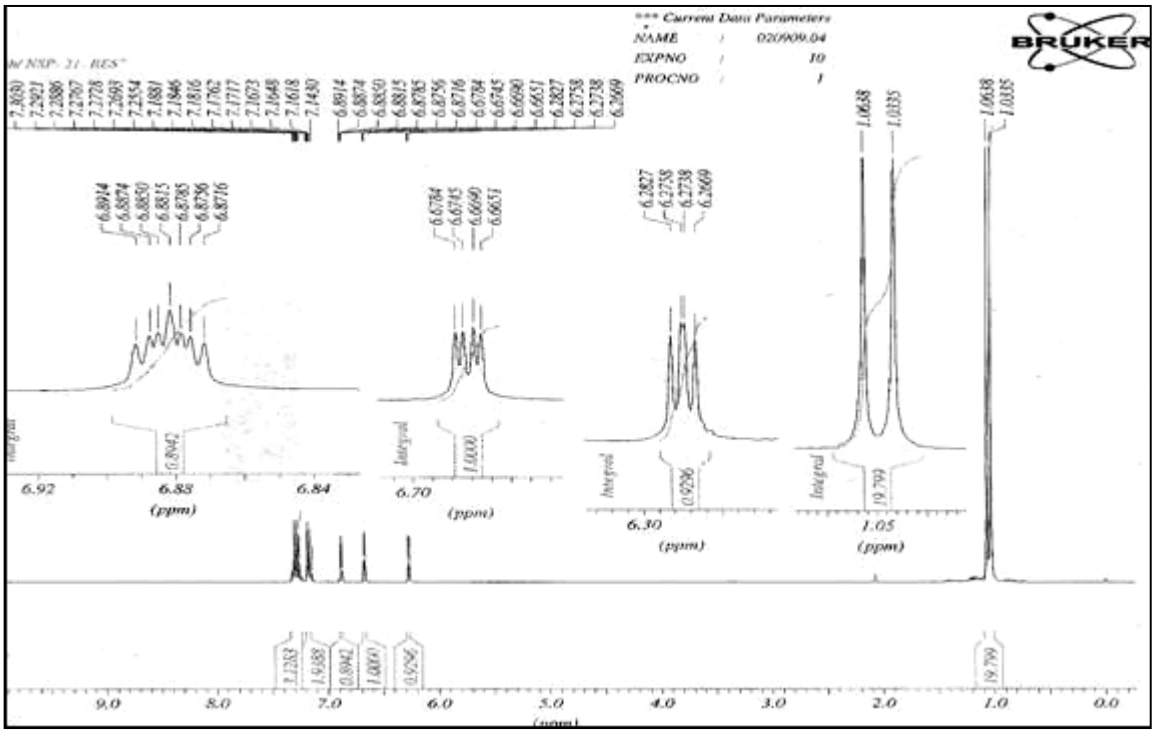

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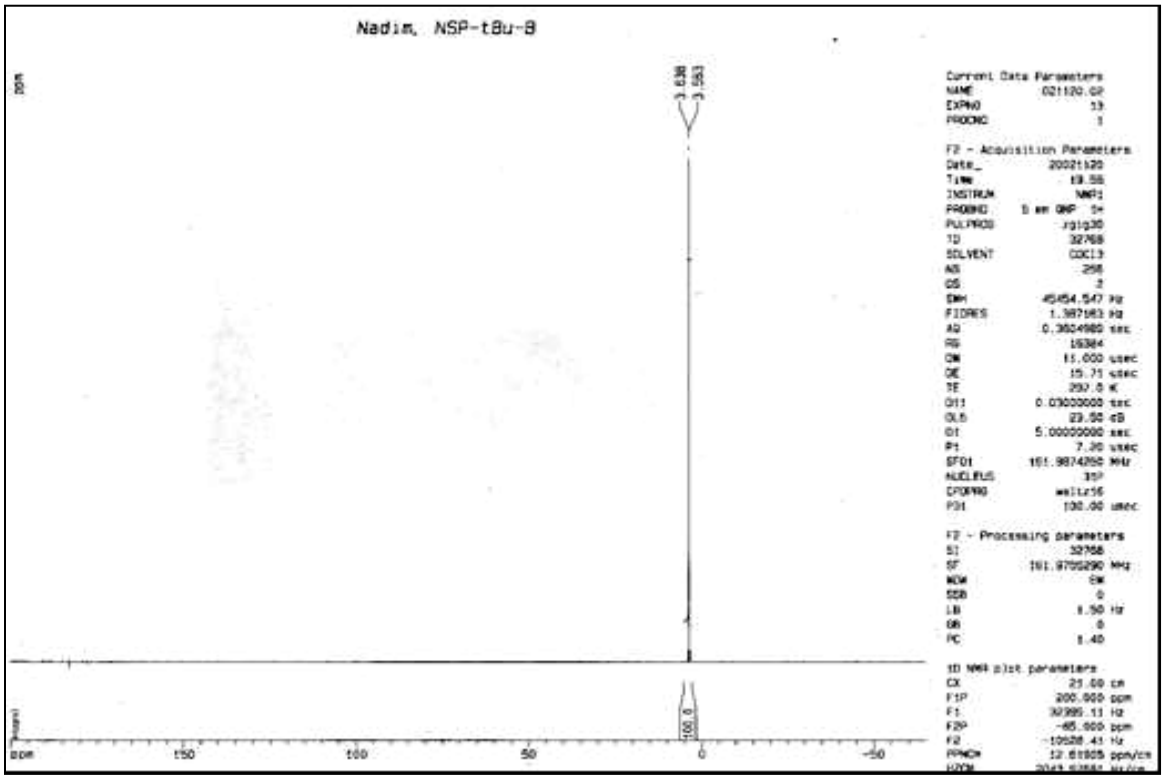
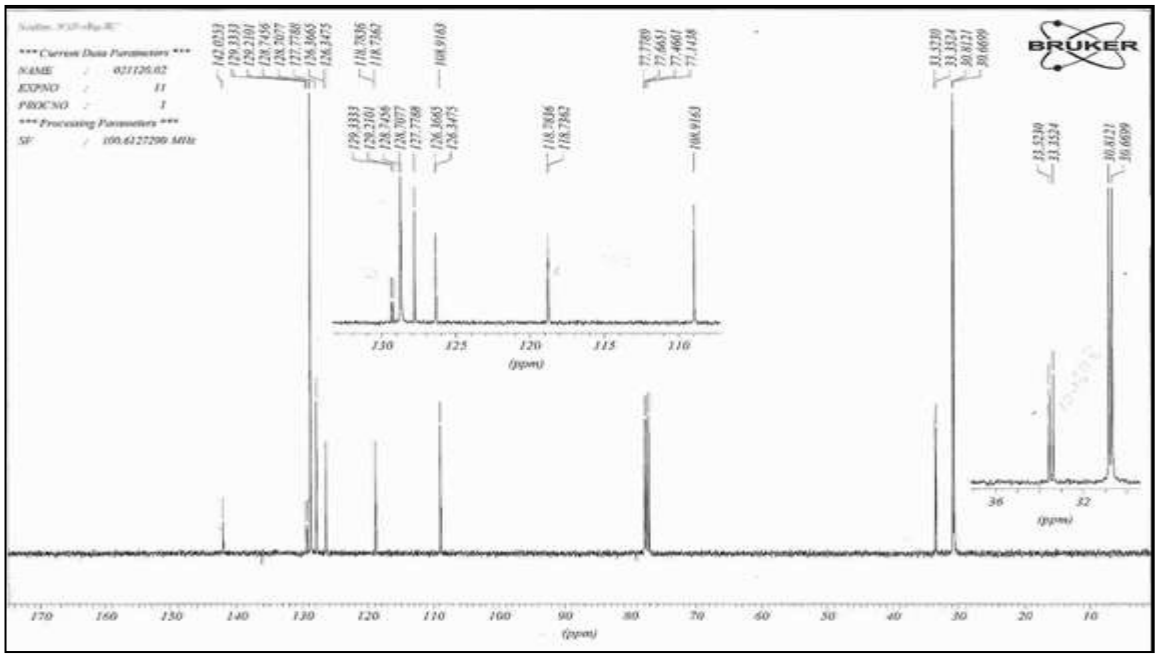


^{31}P-NMR (162 MHz, $CDCl_3$) of compound 18 (*N*-Phos-^{t}Bu)



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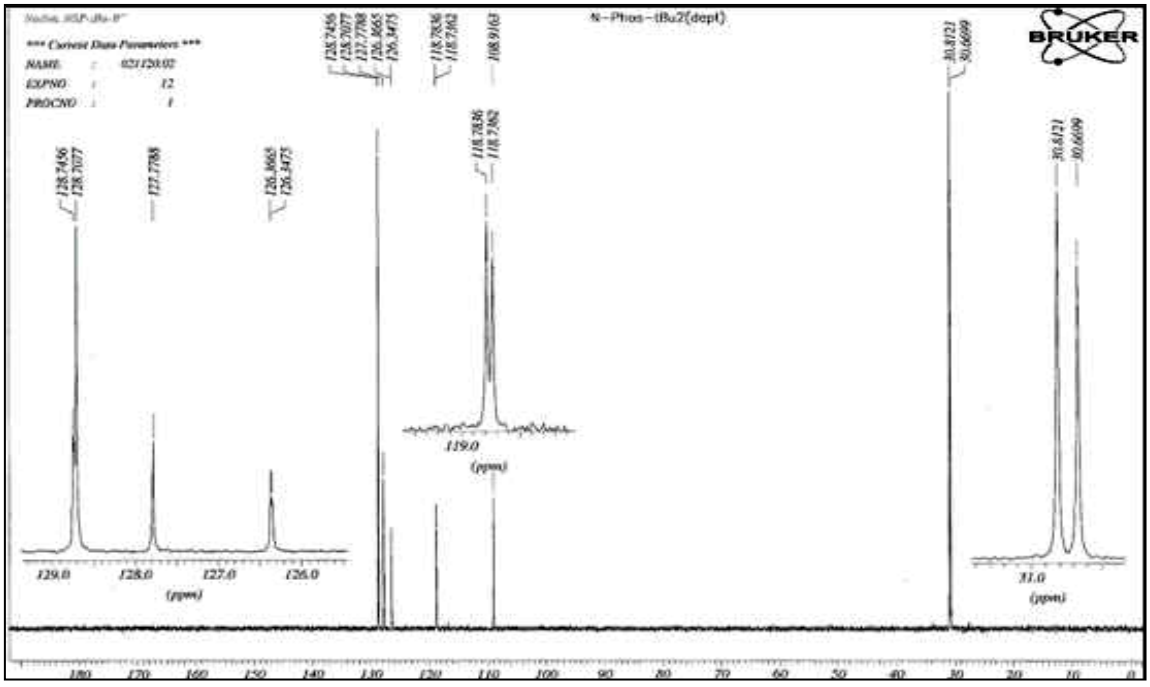

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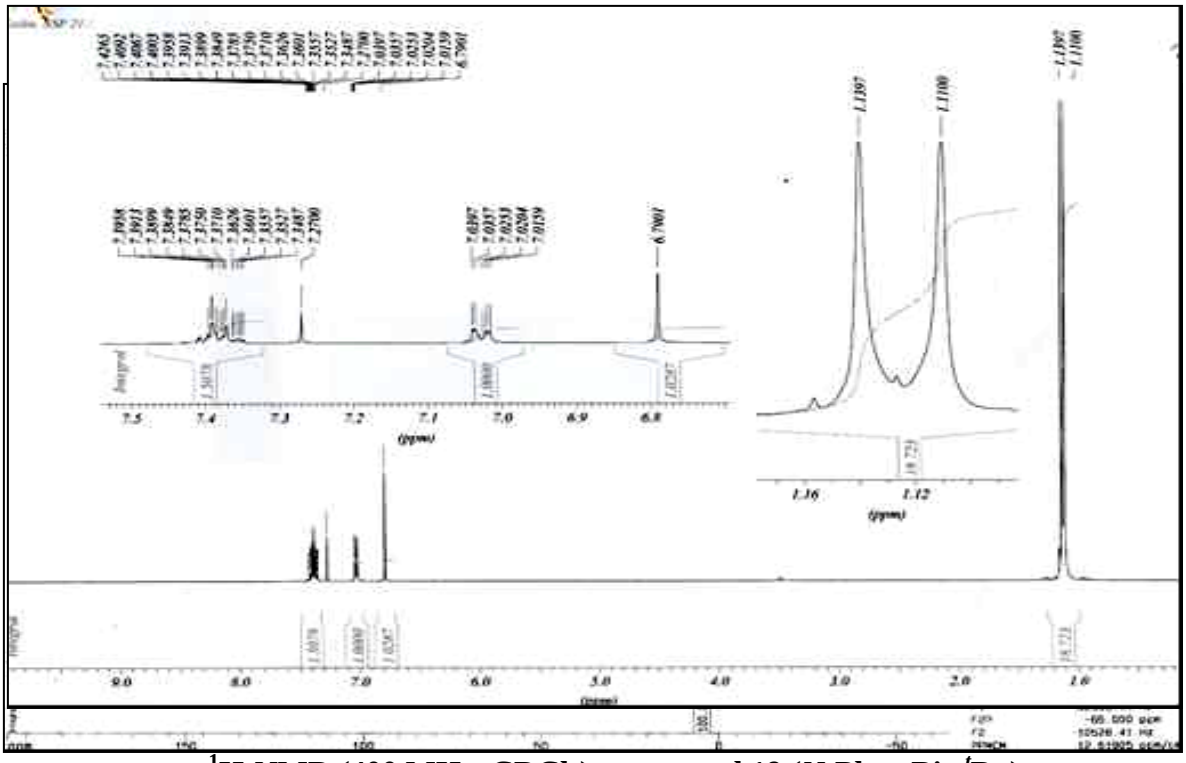
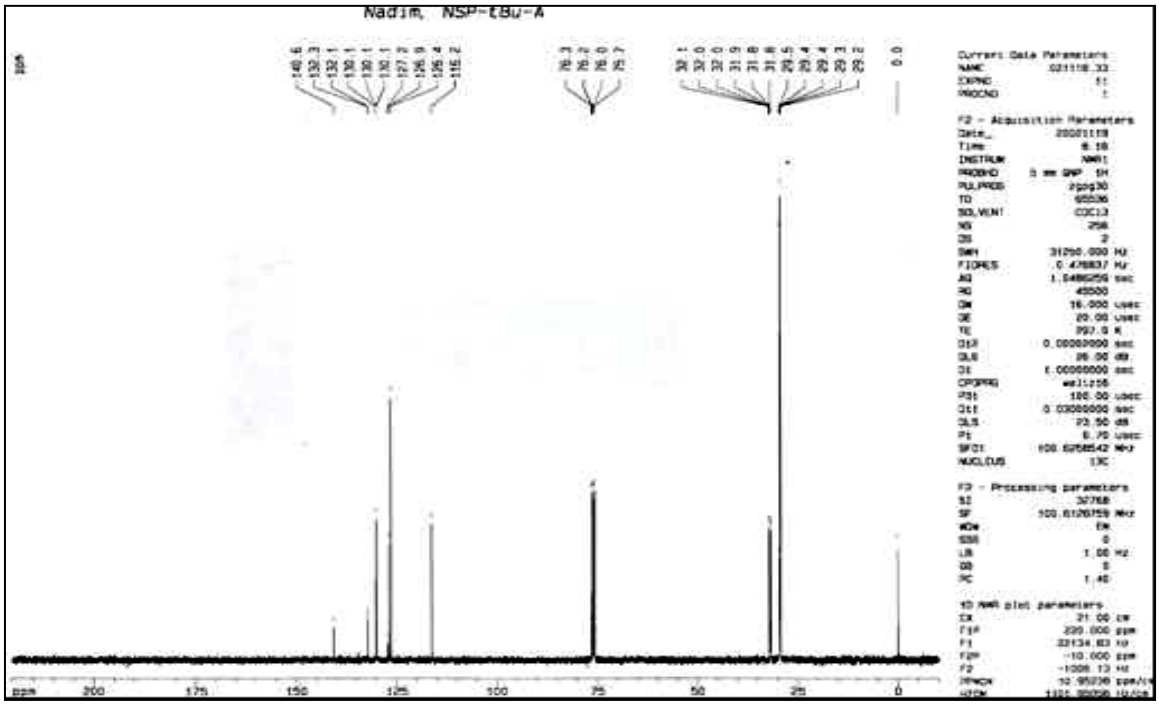
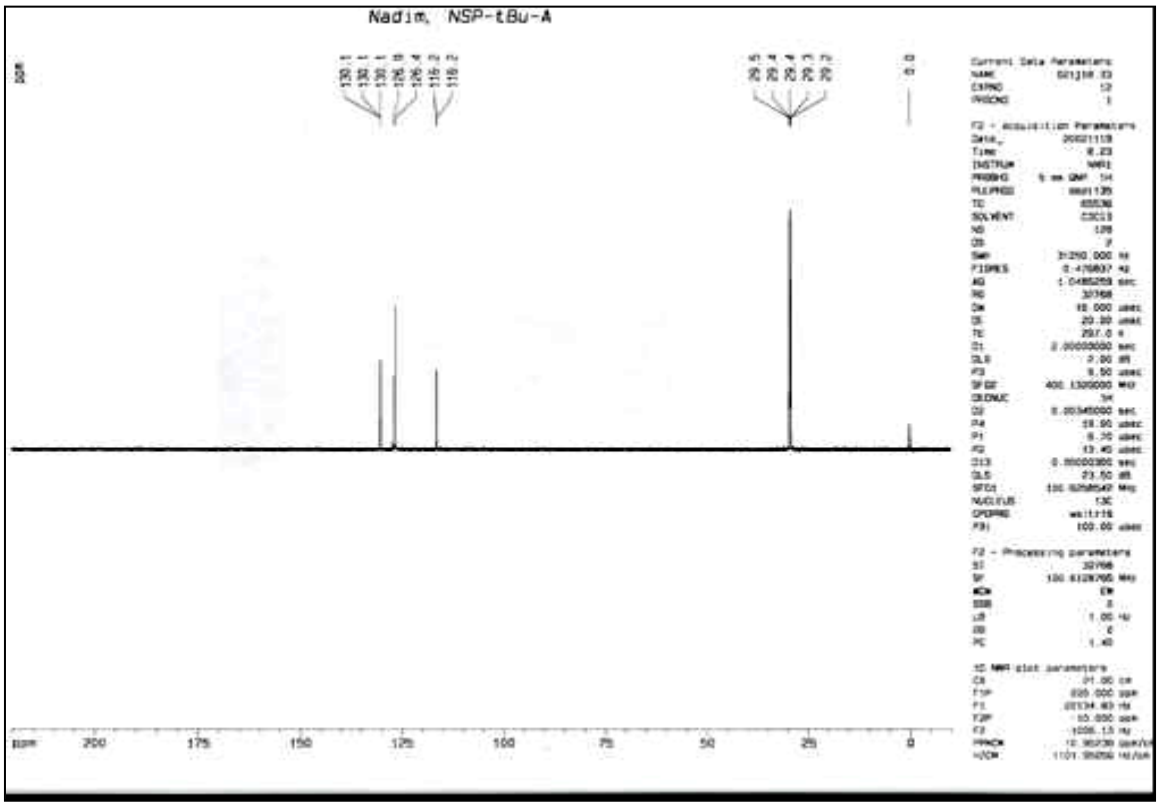


^{1}H-NMR (400 MHz, $CDCl_3$) compound 19 (*N*-Phos-Bis-^{t}Bu)

^{31}P-NMR (162 MHz, $CDCl_3$) of compound 19 (*N*-Phos-Bis-^{t}Bu$_2$)



^{13}C-NMR (100 MHz, $CDCl_3$) of compound 19 (*N*-Phos-Bis-tBu_2)



^{13}C (Dept.)-NMR (100 MHz, $CDCl_3$) of compound 19 (*N*-Phos-Bis-^{t}Bu_2)

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CHAPTER 1

Section C

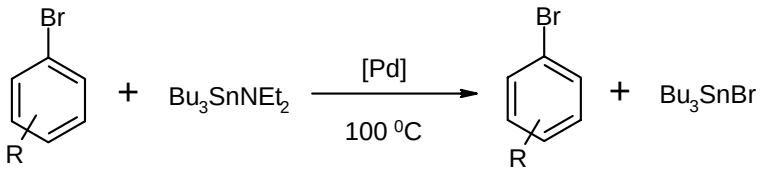
Palladium Catalyzed Amination of Aryl Chlorides

(A comparative study of *insitu* generated palladium(0)carbene complexes with pre-defined Pd(0)carbene complexes and new monodentate phosphine ligands).

1.3.1 Introduction

Palladium-catalyzed cross-coupling reactions of aryl halides or halide equivalents with nucleophiles have been shown to be highly effective and practical methods for the formation of C-C bonds.[1] In a closely related area, palladium or nickel mediated coupling of aryl halides with amines has attracted significant interest because of the use of this methodology in organic synthesis and material science.[2] Until the mid 90´s the preparation of *N*-substituted anilines in general involved nitration of arenes with subsequent reduction of the nitro group. Here, the directing influence of functional groups attached to the arene had to be considered, so often auxiliary groups had to be implemented in the overall procedure. In addition the subsequent monoalkylation of anilines is often a severe problem because of favored further alkylation resulting in large amounts of tertiary amines and ammonium salts. The copper-mediated Ullmann substitution[3] is one way to circumvent these restrictions, but high temperatures have to be applied for this coupling reaction. The methodology has been improved by developing a copper-mediated coupling of *N*-nucleophiles with arylboronic acids instead of aryl halides.[4] Reaction condition is much milder in this case. However, an additional step of the preparation of arylboronic acid from an aryl halide is required.

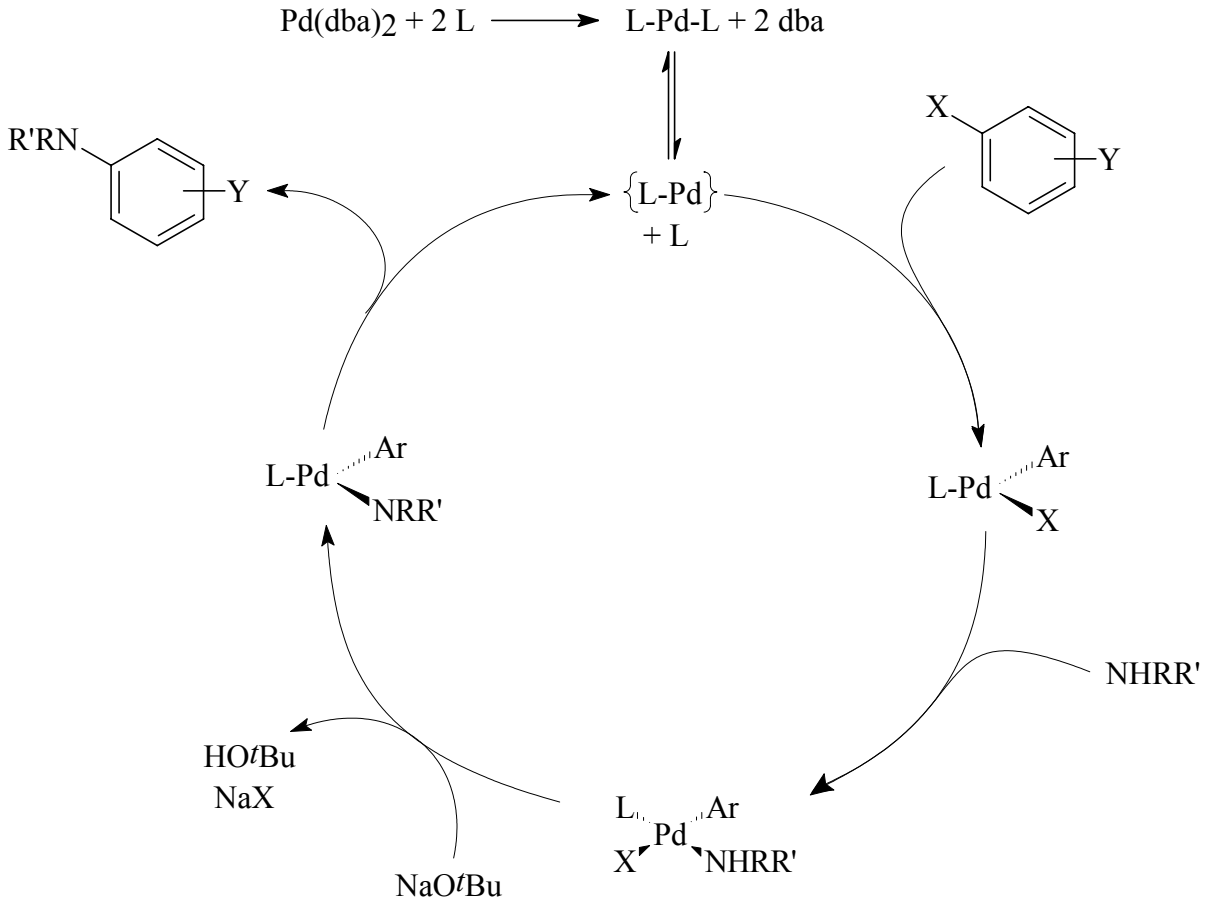
Palladium catalyzed C-N bond forming coupling process was first reported by Migita and co-workers[5] **(Scheme 1).** However the procedure involves the use of toxic and air sensitive tributyl-*N*, *N*-diethyl amminostannane as transamination agent.



Scheme 1: [Pd] = $PdCl_2[P(o\text{-}tolyl)_3]_2$, R = H, 2-$CH_3$, 3-$CH_3$, 4-$CH_3$, 4-$OCH_3$, 4-$COCH_3$, 4-$NO_2$, 4-$N(CH_3)_2$.

This method was improved further by the groups of Buchwald and Hartwig (Buchwald-Hartwig amination)[6] and a variety of primary and secondary amines were used as substrates for the palladium-catalyzed coupling of different aryl halides in the presence of stoichiometric amounts of a strong base.

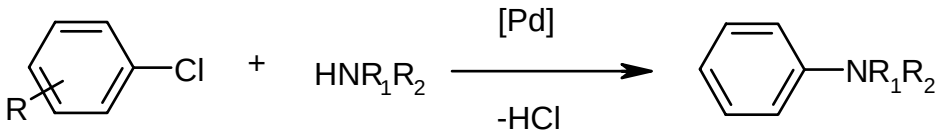
Originally, tri-*o*-tolylphosphine was used as ligand in these protocols. However, this phosphine has the drawback of concomitant reductive dehalogenation of the aryl halide. As an improvement, chelating bisphosphine ligands BINAP[7] and DPPF[8] have been introduced for second generation catalysts. For amination reactions using acyclic secondary amines ferrocenyl phosphines were especially successful.[9]



Scheme 2. Proposed mechanism of aryl–X amination.

The general mechanism of the palladium-catalyzed amination of aryl halides is believed to follow a classical cross coupling route involving oxidative addition of the aryl halide to Pd(0), coordination and deprotonation of the amine, followed by reductive elimination **(Scheme 2)**. Instead of reductive elimination, β-hydride elimination from the palladium amide complex under liberation of the corresponding imine may occur as a side

reaction especially in the case of electron rich arenes, resulting in reductive dehalogenation of the aryl halide.[10] Investigations by Hartwig suggest that anionic palladium *tert.*-butoxide species may be active intermediates in the catalytic cycle.[11]



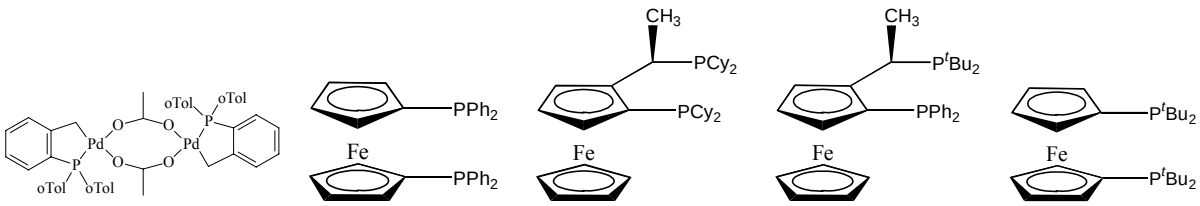
Scheme 3: Catalytic amination of aryl chlorides

Using economically attractive aryl chlorides as substrates **(Scheme 3)** the oxidative addition to the palladium catalyst requires much harsher reaction conditions compared to reactions of the corresponding aryl bromides or iodides.[12] This is a consequence of the experimental bond dissociation energies found to be 402, 339, and 272 kJmol^{-1} (298 K) for chloro, bromo and iodobenzene, respectively[13] and this trend is seen again in the grading of temperatures needed for catalysis. **Table 1** summarizes the efforts which have been made to activate the relatively inert aryl chlorides.

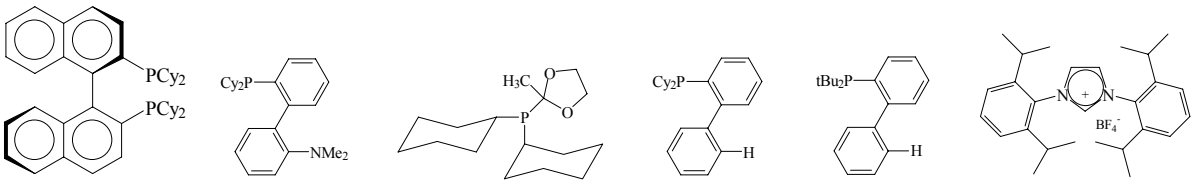
Initially palladacycle **1** was used[14] at higher temperatures, while the group of Buchwald developed a nickel catalyst systems based on DPPF (**2**) or 1,10-phenanthroline as ligand.[15] As reviewed by Grushin and Alper bulky basic phosphines act as efficient ligands for chloroarene activation[16] reactions. Hence, tricyclohexylphosphine[17] and especially tri-*tert.*-butylphosphine[18] proved to be successful for the coupling of activated and non-activated aryl chlorides and amines. Later on, both Hartwig and Buchwald applied chelating bulky basic phosphines in the amination of deactivated chloroarenes successfully. While Hartwig used the ferrocenyl ligands[19] **3**, **4**, and **5**, Buchwald applied the BINAP analog **6** and the aminophosphine **7** as ligands.[20] A similar, non-chelating aryldicyclohexylphosphine ligand, **8**[21], and the non-chelating ligands **9** and **10**[22] have been applied successfully, too. Very recently, a carbene ligand generated *in situ* from imidazolium salt[23] **11** was also shown to be suitable for aryl chloride amination. These latter results are partly in contradiction to the former opinion[24] that chelating ligands are crucial for the success of aryl amination reactions.

Table 1: Overview of palladium-catalyzed amination of aryl chlorides

Entry	Author	R	R_1 / R_2 (Amine)	Catalyst system and additives	Yield [%]
1	Beller (1997)	4-CF_3	Me, Ph	**1**, LiBr	60
2	Beller (1997)	4-CF_3	piperidine	**1**, LiBr	98
3	Buchwald (1997)	4-Me	Me, Ph	$Ni(COD)_2$, 2 **2**	80
4	Buchwald (1997)	4-CN	morpholine	$Ni(COD)_2$, 2 **2**	86
5	Buchwald (1997)	4-CN	morpholine	$Ni(COD)_2$, 1,10-phen	82
6	Reddy/Tanaka (1997)	4-CN	Me, Ph	$Pd(PCy_3)_2Cl_2$	82
7	Reddy/Tanaka (1997)	4-CN	hexyl, hexyl	$Pd(PCy_3)_2Cl_2$	23
8	Yamamoto (1998)	H	Ph, *p*-tolyl	$Pd(OAc)_2$ / 4 P^tBu_3	99
9	Hartwig (1998)	4-Me	Bu, H	$Pd_2(dba)_3$ / 1.5 **3**	87
10	Hartwig (1998)	4-Me	Bu, H	$Pd_2(dba)_3$ / 1.5 **4**	89
11	Hartwig (1998)	4-Me	Ph, H	$Pd(dba)_2$ / 1.5 **4**	92
12	Hartwig (1998)	3-MeO	morpholine	$Pd(OAc)_2$ / 1.5 **5**	81
13	Buchwald (1998)	4-CO_2Me	hexyl, H	$Pd(dba)_2$/ 1.5 **6**	83
14	Buchwald (1998)	4-MeO	Bu, Bu	$Pd(dba)_2$/ 1.5 **7**	90
15	Buchwald (1998)	4-MeO	Me, Ph	$Pd(dba)_2$/ 1.5 **7**	95
16	Guram (1999)	3,5-Me_2	morpholine	$Pd(OAc)_2$ / 3 **8**	92
17	Guram (1999)	2-MeO	octyl	$Pd(OAc)_2$ / 3 **8**	83
18	Buchwald (1999)	4-Me	morpholine	$Pd(OAc)_2$ / 2 **9**	89
19	Buchwald (1999)	4-MeO	morpholine	$Pd(OAc)_2$ / 2 **10**	90
20	Hartwig (2000)	4-Me	hexyl, H	$Pd(dba)_2$ / **11**	40
21	Hartwig (2000)	4-MeO	morpholine	$Pd(dba)_2$ / **11**	96

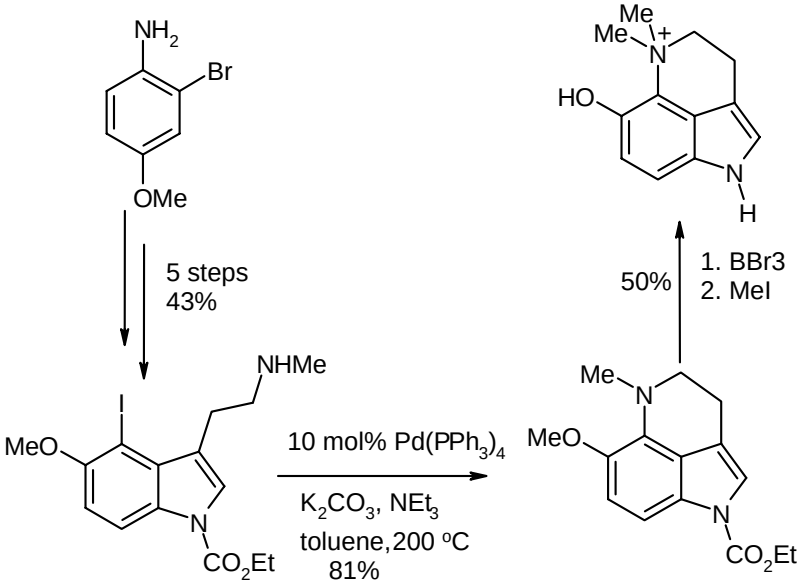


1 **2** **3** **4** **5**



6 **7** **8** **9** **10** **11**

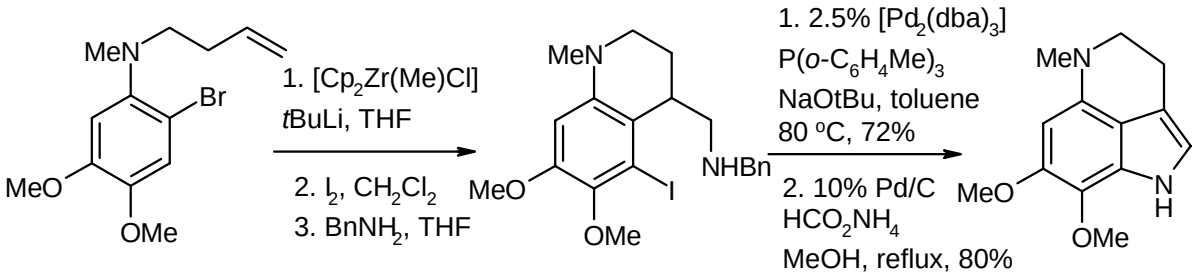
Apart from the aforementioned results the usefulness of palladium-catalyzed aryl amination is shown by applications in natural product synthesis **(Scheme 4)**[25].



Scheme 4: Total synthesis of dehydrobufotenine by Buchwald et al.[25]

In this regard the total synthesis of the toad poison dehydrobufetenine is of particular interest. Here the key step of the synthesis is the intramolecular amination of an aryl iodide.[25]

In another approach **(Scheme 5)**[25] involved formation of the indole five membered ring by



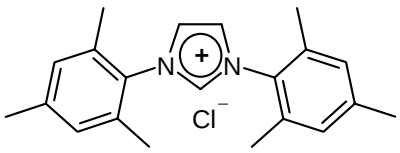
Scheme 5: Formal total synthesis of makaluvamine C and damirones A and B via palladium-catalyzed amination

amination chemistry and the six membered ring by Zr-benzyne chemistry. The product of the cyclization is an intermediate in total synthesis of makaluvamine C and of damirone A and B. Apart from the total synthesis of natural products the amination chemistry has been applied in material science for the synthesis of oligomeric or polymeric arylamines.[26, 27]

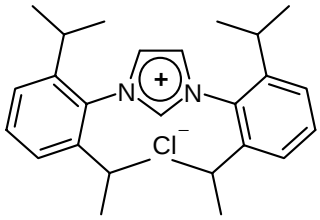
1.3.2 Present work

Several reports have recently appeared dealing with phosphine modified palladium or nickel mediated[2] coupling reactions which employ inexpensive aryl chlorides as substrates.[16, 28] But the multistep preparation[29] of phosphine ligands or highly air sensitive nature of commercially available ligands such as $^{t}Bu_3P$ limits their use in cross- coupling reactions; prompted us to search for a new ligand or catalyst system. Nucleophilic *N*-heterocyclic carbenes,[30] or so called "phosphine mimics", are found to be possible alternative to phosphine ligands.[30] The primary advantage of these ligands appears to be that they do not easily dissociate from the metal centre, hence excess of ligand is not required in order to prevent the aggregation of the catalyst.

Hence palladium carbene complexes were increasingly used as catalysts for Heck, Suzuki and Sonogashira reactions, copolymerization and amination of aryl halides.[31] In general imidazolium salts and palladium salts have been used as precatalysts for these reactions **(table 1, entry 20 and 21)**. Nolan and his co-workers have focused on the application of *N*-heterocyclic carbenes **(12 & 13)** as catalyst precursors for C-C and C-N bond forming reactions.[31, 32] We believe that it is advantageous to use defined palladium(0) carbene complexes, which directly lead to the active palladium(0) complexes without side reactions. This will allow a more efficient use of the actual catalyst.

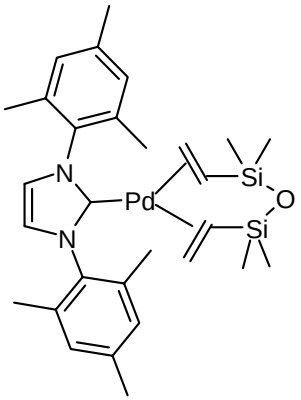


12: IMes

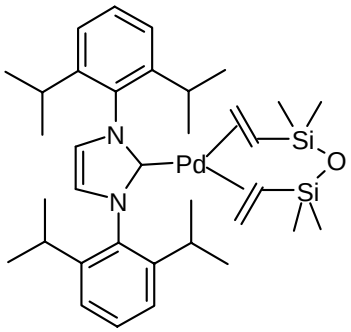


13: IPr

The recent success[33, 34] of defined monocarbenepalladium complexes **{14: IMes-Pd(0)-dvds** and **16: [IMes-Pd(0)-BQ]$_2$ }** as highly stable and active catalyst in Heck and Suzuki coupling reactions with different aryl diazonium salts encouraged us to study the activity of complexes **14**, analogous more hindered complex **15** and benzoquinone complex **16** in amination reactions. It was also decided to compare the relative activity with in situ generated palladium(0) carbene complexes generated from hydrochloride salts of **12** and **13**.

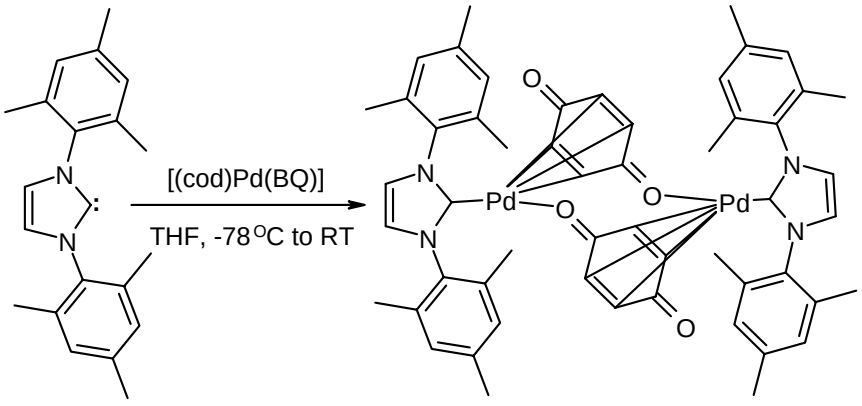


14:IMes-Pd(0)-dvds



15: IPr-Pd(0)-dvds

Monocarbenepalladium(0) complex, 1,3-dimesitylimidazole-2-ylidenepalladium(0)-η^2, η^2-1,1,3,3-tetramethyl-1,3-divinyldisiloxane **(14: IMes-Pd(0)-dvds)** has been synthesized[35] by reacting the palladium(0) diallyl ether complex [($Pd_2(dae)_3$] with 1,3-dimesitylimidazole-2-ylidine carbene (IMes) in the presence of 1,1,3,3-tetramethyl-1,3-divinyldisiloxane (dvds) at −30 °C. Complex **15: IPr-Pd(0)-dvds** i.e. [1,3-(2,6-diisopropylphenyl) imidazole-2-ylidene-palladium(0)-(η^2,η^2)-1,1,3,3-tetramethyl-1,3-divinyldisiloxane] was also prepared by similar procedure using [1,3-(2,6-diisopropylphenyl) imidazole-2-ylidene (IPr) as a carbene precursor. Another benzoquinone complex **(16)** i.e. [1,3- dimesitylimidazol-2-ylidene (benzoquinone) palladium(0)]$_2$ was synthesized[33] by selective exchange of a cyclooctadine ligand (COD) from known [(cod)Pd(benzoquinone)] complex **(Scheme 6)**.



16: [IMes-Pd(0)-BQ]$_2$

Scheme 6: Synthesis of complex 16: [1,3- dimesitylimidazol-2-ylidene (benzoquinone) palladium(0)$_2$]

The electron rich aryl chloride, bromide and sterically hindered aryl chloride as model substrates for the comparative study of those complexes with previously known[32] *insitu* generated carbene complexes for the amination reaction were selected. Hindered aromatic amine (mesitylamine), cyclic aliphatic amine (morpholine) and primary aliphatic amine are considered as representatives of different classes of amines as substrates. Parallel experiments were carried out with predefined carbene palladium complexes and in situ generated carbene complexes under similar reaction conditions. The general reaction conditions were 3 mol% ligand (carbene) and 3 mol% palladium source or 3 mol% complex with 1.5 equiv. base (NaO^tBu) in dioxane at 60 °C up to 18h. The results are summarized in tables 1- 5.

1.3.3 Results and discussion

1.

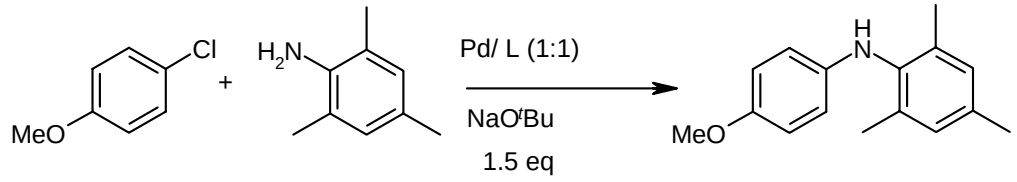


Table 2: Amination of aryl chloride catalyzed by palladium carbene complexes

Entry	Catalyst	Ligand	Complex	Conversion [%]	Yield [%]
1	$Pd_2(dba)_3$	Imes.HCl **(12)**	--	4	0
2	**$Pd_2(dba)_3$**	**IPr.HCl (13)**	--	**35**	**33**
3	--	--	Imes-Pd-dvds **(14)**	6	0
4	--	--	Ipr-Pd-dvds **(15)**	7	6
5	--	--	$(Imes\text{-}Pd\text{-}BQ)_2$ **(16)**	10	5

In the first model reaction of 4-chloroanisole with mesitylamine it was observed that only in situ generated palladium complex using 2,6-di-iso-propylphenylimidazolium hydrochloride salt (Ipr.HCl) gave desired product but in low conversion (35%) and yield (33%) **(Table 2, entry 2)**. The results obtained from isolated complexes carbene(Pd)dvds and also $[Imes(Pd)BQ]_2$ were found to be unexpectedly very poor.

2.

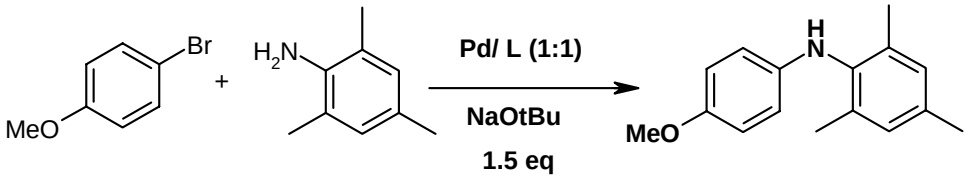


Table 3: Amination of aryl bromide catalyzed by palladium carbene complexes

Entry	Catalyst	Ligand	Complex	Conv. (%)	Yield (%)
1	$Pd_2(dba)_3$	Imes.HCl **(12)**	--	11	02
2	**$Pd_2(dba)_3$**	**IPr.HCl (13)**	--	100	89
3	--	--	Imes-Pd-dvds **(14)**	4	1
4	--	--	Ipr-Pd-dvds **(15)**	53	41
5	--	--	$(Imes\text{-}Pd\text{-}BQ)_2$ **(16)**	7	2

For model reaction **2**, 4-bromoanisole with mesitylamine, among all the carbene complexes (in situ generated and isolated) Ipr.HCl was found to be the most efficient **(Table 3 entry 2)** for this reaction showing complete conversion of the substrate.

3.

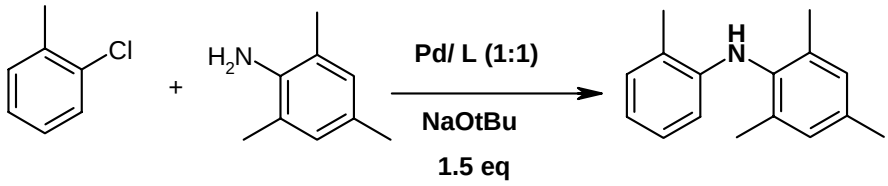


Table 4: Amination of aryl chloride catalyzed by palladium carbene complexes

Entry	Catalyst	Ligand	Complex	Conversion [%]	Yield [%]
1	$Pd_2(dba)_3$	Imes.HCl **(12)**	--	5	0
2	**$Pd_2(dba)_3$**	**IPr.HCl (13)**	**--**	**100**	**96**
3	--	--	Imes-Pd-dvds **(14)**	7	1
4	--	--	Ipr-Pd-dvds **(15)**	6	2
5	--	--	$(Imes\text{-}Pd\text{-}BQ)_2$ **(16)**	76	71

For model reaction **3**, 2-chlorotoluene with sterically hindered 2,4,6-trimethylaniline, among all the carbene complexes tested for this reaction, in situ generated palladium complex with Ipr.HCl **(Table 4, entry 2)** is found to be highly active as demonstrated in the literature. It is worthwhile to mention that the isolated complex **16**: $[Imes(Pd)BQ]_2$ also worked well **(Table 4, entry 5)** for this reaction.

4.

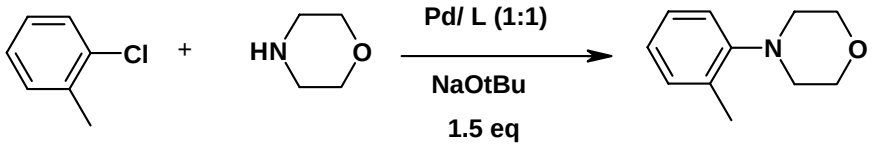


Table 5: Amination of aryl chloride catalyzed by palladium carbene complexes

Entry	Catalyst	Ligand	Complex	Conversion [%]	Yield [%]
1	$Pd_2(dba)_3$	Imes.HCl **(12)**	--	2	0
2	$Pd_2(dba)_3$	IPr.HCl **(13)**	--	56	46
3	--	--	Imes-Pd-dvds **(14)**	3	0

4	--	--	Ipr-Pd-dvds **(15)**	30	23
5	--	--	(Imes-Pd-BQ)$_2$ **(16)**	90	30

In the model reaction **4**, 2-chlorotoluene with morpholine, Interestingly, excellent conversion of the substrate using [Imes(Pd)BQ]$_2$ **(16)** but poor selectivity (toluene as a side product formed by reductive dehalogenation of chlorotoluene) was observed as compared to in situ generated complex using Ipr.HCl. As usual **12** and **14** show almost no conversion.

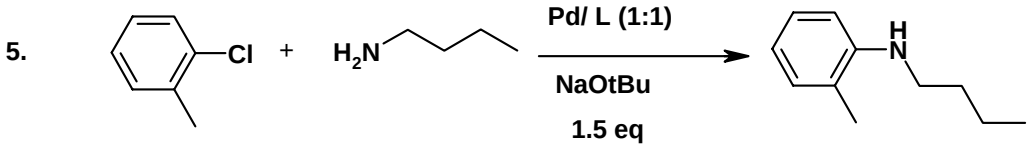


Table 6: Amination of aryl chloride catalyzed by palladium carbene complexes

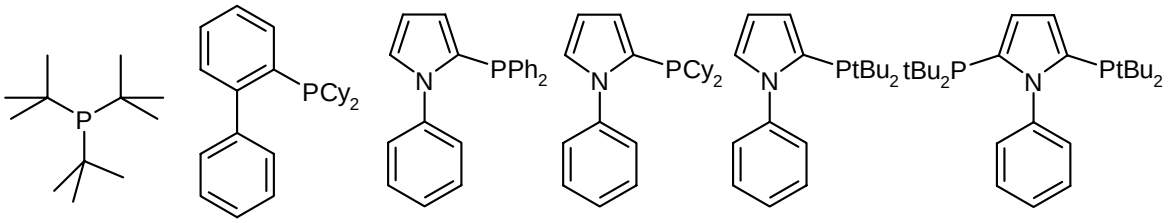
Entry	Catalyst	Ligand	Complex	Conversion [%]	Yield [%]
1	$Pd_2(dba)_3$	Imes.HCl **(12)**	--	2	0
2	$Pd_2(dba)_3$	IPr.HCl **(13)**	--	10	6
3	--	--	Imes-Pd-dvds **(14)**	3	0
4	--	--	Ipr-Pd-dvds **(15)**	7	2
5	--	--	(Imes-Pd-BQ)$_2$ **(16)**	7	5

In the model reaction **5**, 2-chlorotoluene with n-butylamine, very little or no conversion has been observed in all of the cases where IPr.HCl gave very poor results **(table 6)**.

In this way the preliminary study of 5 different carbene palladium (in situ and isolated) complexes was carried out and it was found that in situ generation of Pd(0) complex from Ipr.HCl is the best except in the model reaction 5. One of the isolated complexes [Imes(Pd)BQ]$_2$ attracted our attention by showing good conversions in the model reactions **3** and **4**.

After this, we turned our attention towards the study of catalytic activity of monodentate phosphine ligands for the above mentioned 5-model reactions. As reviewed in **Table 1**, monodentate phosphine ligands **7, 8, 9** and **10** show remarkable activity in amination reactions.[36] We were interested in studying the catalytic ability of our newly synthesized monodentate phosphine ligands *N*-Phos-Cy$_2$ (**19**), *N*-Phos-^{t}Bu$_2$ (**20**) and *N*-Phos-Bis-^{t}Bu$_2$ (**21**)

prepared from commercially available *N*-phenyl pyrrole in one step (as described in **Chapter 1, Section B**) and compare their activity with previously known best ligands P^{t}Bu$_3$[18 (b)] and *o*-biphen-PCy$_2$[37] (**17** and **9**) for the amination reaction.



17 **9** **18** **19** **20** **21**

P^{t}Bu$_2$ ***o*-Biphenyl-Cy$_2$** **N-Phos-Ph$_2$** **N-Phos-Cy$_2$** **N-Phos-tBu$_2$** **N-Phos-bis-^{t}Bu$_2$**

The reaction conditions used are similar to those for by using carbene complexes. Considerable influence of solvent has been observed when toluene was used **(Table 7, entry 1 and 2)**.

1.

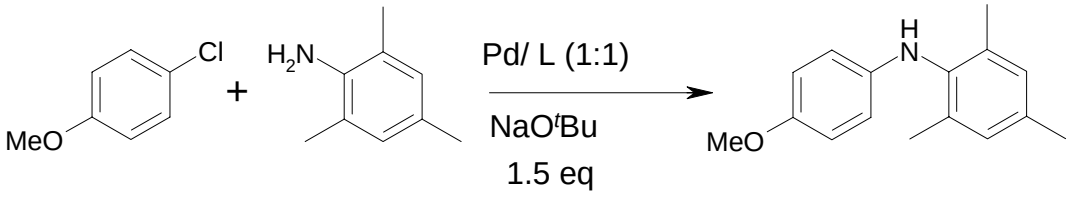


Table 7: Amination of aryl chloride catalyzed by palladium and phosphine ligand

Entry	Catalyst	Ligand	Solvent	Conversion [%]	Yield [%]
1	Pd(dba)$_2$	^{t}PBu$_3$ (17)	Toluene	65	64
2	Pd(dba)$_2$	^{t}PBu$_3$ (17)	Dioxane	100	93
3	Pd(dba)$_2$	*N*-Phos-Cy$_2$ (19)	Dioxane	96	84
4	Pd$_2$(dba)$_3$	*O*-Biphen-Cy$_2$ (9)	Dioxane	97	80
5	Pd$_2$(dba)$_3$	*N*-Phos-^{t}Bu$_2$ (20)	Dioxane	100	92
6	Pd$_2$(dba)$_3$	*N*-Phos-Bis-^{t}Bu$_2$ (21)	Dioxane	97	90

In the first model reaction of 4-chloroanisole with mesitylamine it was observed that P*t*Bu$_3$ and *o*-biphen-PCy$_2$ gave complete conversion and very good yields **(Table 7, entry 2** and **4)** which is in good agreement with the literature reports. Our new ligands worked equally well and reproducible results were obtained in all the cases.

2.

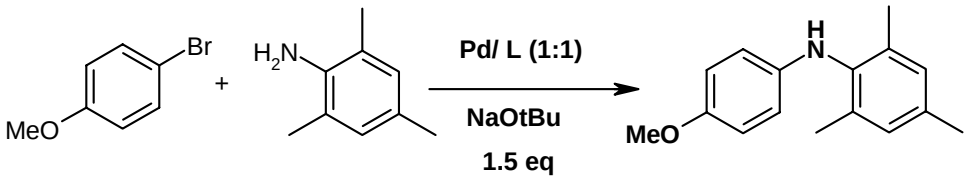


Table 8: Amination of aryl chloride catalyzed by palladium and phosphine ligand

Entry	Catalyst	Ligand	Solvent	Conversion [%]	Yield [%]
1	$Pd(dba)_2$	$^tBu_3P$ (17)	Toluene	100	94
2	$Pd(dba)_2$	$^tBu_3P$ (17)	Dioxane	100	91
3	$Pd(dba)_2$	*N*-Phos-Cy_2 (19)	Dioxane	100	93
4	$Pd_2(dba)_3$	*O*-Biphenyl-Cy_2 (9)	Dioxane	100	82
5	$Pd_2(dba)_3$	*N*-Phos-$^tBu_2$ (20)	Dioxane	100	90
6	$Pd_2(dba)_3$	*N*-Phos-Bis-$^tBu_2$ (21)	Dioxane	100	89

For model reaction **2**, 4-bromoanisole with mesitylamine, our ligands **(19, 20** and **21)** as well as commercially available ligands **(17** and **9)** worked equally well. No influence of solvent was observed unlike in model **reaction 1 (table 8, entry 1 and 2)**.

3.

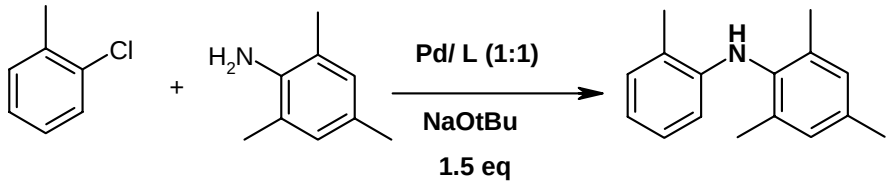


Table 9: Amination of aryl chloride catalyzed by palladium and phosphine ligand

Entry	Catalyst	Ligand	Solvent	Conversion [%]	Yield [%]
1	$Pd(dba)_2$	$^tBu_3P$ (17)	Dioxane	100	94
2	$Pd(dba)_2$	*N*-Phos-Ph_2 (18)	Dioxane	7	0
3	$Pd(dba)_2$	*N*-Phos-Cy_2 (19)	Dioxane	60	54
4	$Pd_2(dba)_3$	*O*-Biphenyl-Cy_2 (9)	Dioxane	69	65
5	$Pd_2(dba)_3$	*N*-Phos-$^tBu_2$ (20)	Dioxane	100	89

For model reaction **3**, 2-chlorotoluene with sterically hindered 2,4,6-trimethylaniline, ligand **21** (*N*-Phos-Bis-tBu_2) was found to be the most efficient as compared to ligand **19** and **20**. The model ligand *N*-Phos-Ph_2 (**18**) was also examined and found to be not useful for such reactions as expected.

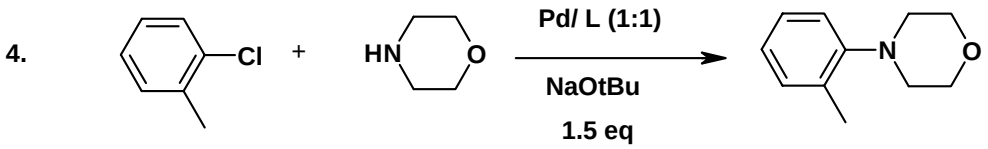


Table 10: Amination of aryl chloride catalyzed by palladium and phosphine ligand

Entry	Catalyst	Ligand	Solvent	Conversion [%]	Yield [%]
1	$Pd(dba)_2$	$^tBu_3P$ (17)	Toluene	85	83
2	$Pd(dba)_2$	$^tBu_3P$ (17)	Dioxane	95	92
3	$Pd(dba)_2$	*N*-Phos-Cy_2 (19)	Dioxane	100	83
4	$Pd_2(dba)_3$	*O*-Biphenyl-Cy_2 (9)	Dioxane	100	71
5	$Pd_2(dba)_3$	*N*-Phos-$^tBu_2$ (20)	Dioxane	100	76
6	$Pd_2(dba)_3$	*N*-Phos-Bis-$^tBu_2$ (21)	Dioxane	100	82

In the model reaction **4**, 2-chlorotoluene with morpholine, ligands N-Phos-Cy_2 **(19)** and *N*-Phos-Bis-$^tBu_2$ **(21)** are found to be highly active as $^tBu_3P$ **(17)**. Dioxane shows improved results than toluene **(Table 10, entry 1** and **2)**. However, the commercially available *o*-biphen-PCy_2 **(9)** and new ligand *N*-Phos-Cy_2 **(19)** gave complete conversion with a little less selectivity. Toluene is observed as a side product in both the cases.

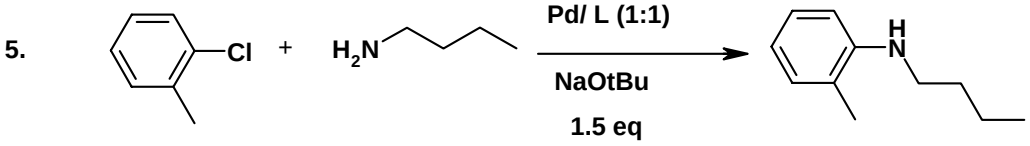


Table 11: Amination of aryl chloride catalyzed by palladium and phosphine ligand

Entry	Catalyst	Ligand	Solvent	Conversion [%]	Yield [%]
1	$Pd(dba)_2$	$^tBu_3P$ (17)	Dioxane	100	94
2	$Pd(dba)_2$	*N*-Phos-Cy_2 (19)	Dioxane	52	48
3	$Pd_2(dba)_3$	*O*-Biphenyl-Cy_2 (9)	Dioxane	93	86
4	$Pd_2(dba)_3$	*N*-Phos-$^tBu_2$ (20)	Dioxane	100	94
5	$Pd_2(dba)_3$	*N*-Phos-Bis-$^tBu_2$ (21)	Dioxane	100	94

In the model reaction **5**, 2-chlorotoluene with n-butylamine (which often leads to side reactions - oxidation to imine and isomers with concomitant formation of Pd hydride species), the bulky ligands *N*-Phos-$^{t}Bu_2$ **(20)** and *N*-Phos-Bis-$^{t}Bu_2$ **(21)** were found to be as efficient as $^{t}Bu_3P$.

Obviously, no desired coupling product was observed in absence of either ligand or palladium catalyst tested in each reaction. But trace amount of isomers of amination product were observed in absence of catalyst/ligand when reaction mixture (reaction **1**) was heated up to 120 °C. for 20h. in sealed tube; indicating the formation of amine via benzyne formation of chloroarene at high temperature in presence of 1.5 eq. base ($NaO^{t}Bu$).

1.3.4 Conclusion

A preliminary study of 5 different carbene palladium (*insitu* and isolated) complexes suggest that *in situ* generation of Pd(0) complex from Ipr.HCl (**13**) is the best except in the model reaction **5**. One of the isolated complexes $[Imes(Pd)BQ]_2$ (**16**) gave good conversion but low selectivity in the model reactions **3** and **4**.

The comparative study of newly synthesized phosphine ligands with two commercially available best ligands for the amination of 5-different model reactions under similar reaction conditions was carried out and it was observed that our new ligands *N*-Phos-Cy_2 **(19)**, *N*-Phos-$^tBu_2$ **(20)** and *N*-Phos-Bis-$^tBu_2$ **(21)** are among the most efficient ligands and comparable with previously known best ligands *o*-biphen-PCy_2 **(17)** and $^tBu_3P$ **(9)**. These ligands are stable solids, hence easy to handle. One step preparation in good yield made them economical and more attractive for such type of coupling reactions. Further optimization of catalyst loading and substrate scope of P-ligands **(19, 20 and 21)** for amination as well as their applications in other cross-coupling reactions is underway in the group.

1.3.5 Experimental

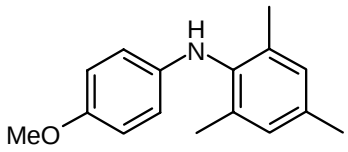
The reactions were carried out under argon atmosphere in oven dried glassware (either Schlenk tube or 12 place Carousel Reaction station with Teflon made reflux head- by Radleys). Dry dioxane stored over molecular sieves was purchased from Fluka with sure seal. The conversions and yields were determined by GC-FID using diethyleneglycol dibutyl ether as an internal standard. The temperature program used for the GC monitoring is **50 °C, 2 min; 15 K / min; 260 °C, 6 min** (Hew. Pack. Instrument; HP 5 column). The reactions using carbene complexes and P-ligands were repeated minimum twice and found to be reproducible. All the amination products were isolated once and characterized by usual spectral analysis (GC-MS, NMR, IR and HRMS). Ligands **17** and **9** are commercially obtained from Strem chemical co. Catalysts **12** to **16** were already prepared in the group.[33, 34, 35] [Phosphine ligands **18, 19, 20** and **21** are prepared according to the procedure described in **chapter 1; section B**]

General Procedure for amination reaction using phosphine/carbene ligands:

An oven dried Schlenk flask was evacuated and backfilled with argon. The flask was charged with $Pd_2(dba)_3$ (15 mg, 0.015 mmol, 3 mol% Pd), phosphine ligand (0.03 mmol, 3 mol%) or imidazolium salt (3 mol %) and NaO^tBu (144 mg, 1.5 mmol). The flask was evacuated and back filled with argon three times successively and then capped with rubber septum. Dioxane (1 ml), aryl chloride/bromide (1.0 mmol), the amine (1.2 mmol) and additional dioxane (1 ml) were added. The septum was replaced with a glass stopper and the reaction mixture was stirred at 60 °C (oil bath temp. 63-66 °C) for 18 h. The reaction mixture was cooled to room temp. and quenched with water (1ml). The GC standard (diethyleneglycol-di-n-butylether as a reference 100 μL.) was added followed by diethyl ether (8 ml). The mixture was stirred for 10 min. The organic layer was filtered from a bed of magnesium sulphate and monitored by GC-FID.

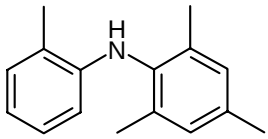
In case of isolation, the aqueous layer was extracted (without addition of GC standard) three times and the organic layer was washed with water, brine and dried over sodium sulphate, filtered and concentrated at 45-60 °C under reduced pressure to obtain colored liquid which was purified by column chromatography over neutral alumina using hexane and ethyl acetate as the eluant.

Reaction 1/2: (4-methoxyphenyl)-(2,4,6-trimethylphenyl)-amine:[38]



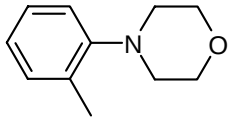
Appearance	Red solid
M. p.	94-96 °C
IR (KBr):	3352, 3002, 2918, 1621, 1507, 1308, 1230, 1174, 1031, 824, 640, 501 cm^{-1}
^{1}H NMR (400MHz, C_6D_6):	δ 6.80 (s, 2H), 6.72 (d, *J* = 8.9 Hz, 2H), 6.37 (d, J = 8.9 Hz, 2H), 4.43 (br, s, 1H), 3.34 (s, 3H), 2.18 (s, 3H), 2.1 (s, 6H).
MS (EI, 70 eV):	241 (100, M^+), 226 (95), 208 (9), 133 (5), 91 (5), 77 (5).
HRMS:	Calculated for $C_{16}H_{19}NO$: 241.14667, found: 241.14550.

Reaction 3: N-(*o*-tolyl)-2,4,6-trimethylanilin:



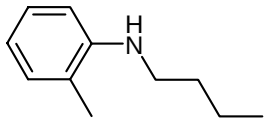
Appearance	White needles
M. p.	74 – 76°C, hexane
IR (KBr):	3406, 2916, 1602, 1506, 1495, 1312, 1257, 1047, 860, 745, 442 cm^{-1}
^{1}H NMR (400MHz, $CDCl_3$):	δ 7.17-7.12 (m, 1H), 7.02-6.95 (m, 3H), 7.74-6.88 (m, 1H), 6.18-6.14 (m, 1H), 2.34 (s, 3H), 2.33 (s, 3H), 2.17 (s, 6H).
^{13}C NMR (100 MHz, C_6D_6):	144.8, 136.4, 136.0 (2C), 135.6, 130.6, 129.6, 127.4, 122.6 (2C), 118.2, 111.9, 21.3, 18.6 (2C), 18.1
MS (EI, 70 eV): *m*/*z* (%)	225 (100, M^+), 210 (25), 208 (18), 195 (15), 134 (10), 121 (19), 106 (8), 91(8), 77(5).
HRMS:	Calculated for $C_{16}H_{19}N$: 225.15175, found: 225.15064

Reaction 4: N-(*o*-tolyl)-morpholine:



Appearance	Colorless liquid.
IR (KBr):	3020.1, 2958, 2851.9, 2815.8, 1492.9, 1224.6, 1117.7, 762.1 cm^{-1}
^{1}H NMR (400MHz, C_6D_6):	δ 7.05-7.1 (m, 2H), 6.92-6.99 (m, 1H), 6.81-6.85 (m, 1H), 3.50-3.69 (m, 4H), 2.51-2.61 (m, 4H), 2.18 (s, 3H)
^{13}C NMR (100 MHz, C_6D_6):	δ 152.1, 133.0, 131.65, 127.3, 132.97, 119.58, 67.6 (2C), 52.8 (2C), 18.19
MS (EI, 70 eV): *m*/*z* (%)	177 (81, M^+), 118 (100), 91 (20), 77 (5), 65 (10).

Reaction 5: N-butyl-*o*-toluidine:



Appearance	Colorless liquid.
IR (KBr):	3430.6, 2957, 2928, 2871, 1606, 1513, 1472, 1317, 1050, 745. cm^{-1}
^{1}H NMR (400MHz, $CDCl_3$):	δ 7.20-7.11 (m, 1H), 7.10-7.05 (m, 1H), 6.75-6.60 (m, 2H), 3.82 (bs, 1H), 3.18 (t, *J* = 7.1 Hz, 2H), 2.17 (s, 3H), 1.68 (m, 2H), 1.47 (m, 2H), 0.99 (t, *J* = 7.3 Hz, 3H).
^{13}C NMR (100MHz, $CDCl_3$):	δ 136.1, 130.5, 127.5, 122.4, 117.4, 110.41, 44.3, 32.0, 20.8, 17.9, 14.4
MS (EI, 70 eV): *m*/*z* (%)	163 (22, M^+), 120 (100), 91 (10), 77(8).
HRMS:	Calculated for $C_{11}H_{17}N$: 163.13610, found: 163.13587.

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CHAPTER 2

Section A

Clay Catalyzed Conversion of Isatoic Anhydride to 2-(*o*-Aminophenyl)oxazolines and its Polymer Supported Analogues

2.0.1 Introduction

Catalysis in General

The term, "Catalysis" is defined as, physiological and chemical reactions proceeded in the presence of a substance which does not itself get altered during the course of the reaction. According to Berzelius[1] (in 1835), catalyst is the substance which by its mere presence evokes chemical actions which could not take place in its absence; e.g. i) oxidation of ethyl alcohol to acetic acid, ii) combustion of hydrogen in presence of platinum at room temperature, etc.
According to Ostwald[2], based on the knowledge of chemical equilibrium, that all chemical reactions proceed via a number of more or less stable intermediates A more precise and perhaps better definition states that, "a catalyst is a substance which increases the rate of attainment of equilibrium of a reacting system without causing any great alteration in the free energy change involved."

Another important aspect of the catalysts behavior is that, it determines the path of reaction. e. g. the decomposition of ethanol over alumina catalysts yields ethylene and water. While over copper or silver catalysts, acetaldehyde and hydrogen are the products.

Classification:

The catalysts are classified into two main types 1) Homogeneous catalysts and 2) Heterogeneous catalysts.

Homogeneous catalysis: In more recent years the term has become to be applied more specifically to the use of a solution of certain organometallic compounds in which central metal atom is surrounded by a regular pattern of atoms or molecules, known as ligands, with which it is coordinated. Depending on the nature of the ligands, the metal atom may be in a low positive, zero or low negative state.

Special feature of homogeneous catalytic transition metal complex reactions is the enhanced selectivity compared with heterogeneous catalytic reactions.

In homogeneous catalytic reactions the catalysts and reactants are present in one phase and from an engineering point of view, a major disadvantage of this arises from the difficulty in separating the product from the catalysts; this is a peculiar problem in large scale conversions with open reaction systems. The reactions of industrial importance are hydroformylation (oxo synthesis), carbonylation, hydrocyanation and olefin polymerization.

Heterogeneous catalysis:

In heterogeneous catalysis the reaction takes place at the interface between the catalysts and the less dense phase. In other words heterogeneous catalysis describes the enhancement in the rate of a chemical reaction brought about by the presence of an interface between two phases. In general much higher temperatures are used in heterogeneous catalytic reactions than in homogeneous catalytic ones.

Heterogeneous catalysts may be divided naturally into two distinct groups, 1) metals and 2) non-metals.

The former group comprised largely of the metals of groups VIII and IB, the latter of metal oxides and sulfides, salts and acids; the first mentioned are the most important. The non-metal catalysts may be further subdivided according to their electrical conductivity into a) semiconductors and b) insulators. Thus metals are in general, good catalysts for reactions involving hydrogen atom addition or removal of oxygen atoms. Conversely, semiconductor catalysts are poor hydrogenation catalysts. Insulators, of which alumina and silica are most important, are good dehydration catalysts, but they possess very little ability to catalyze hydrogenation or oxidation.

Clays as heterogeneous catalyst:

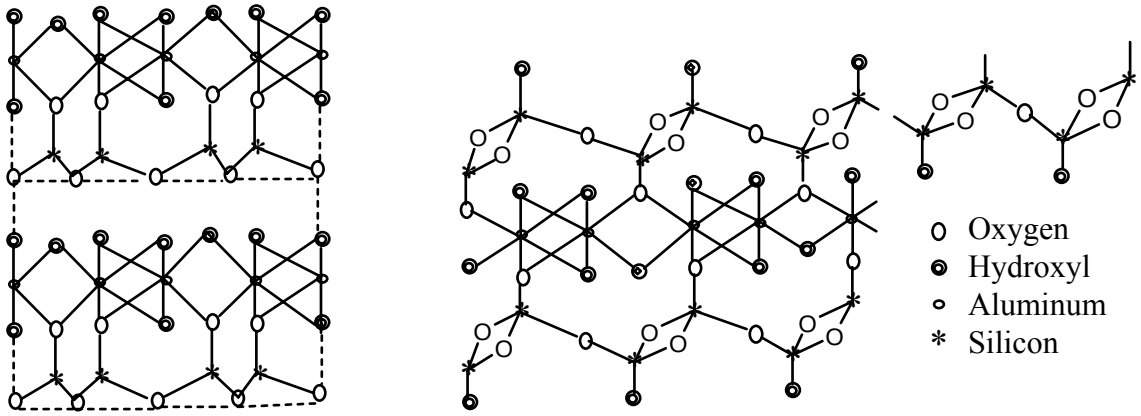
Clays are predominantly composed of hydrous phyllosilicates[3] referred to as "clay minerals".[3, 4] These are hydrous silicates of aluminum, magnesium, potassium and iron. Clay minerals are extremely fine crystals or particles, often colloidal in size and usually plate like in shape. Many clay mineral crystals carry an excess negative electric charge owing to internal substitution by lower valent cations which increase the internal reactivity in chemical combination and ion-exchange.

Heterogeneous catalytic organic transformations using clay have been reviewed recently by Cornelis and Laszlo.[4] A few monographs on clay catalysis have also appeared recently.[5-9]

The Al^{3+}-cations in clays are bonded to an octahedral arrangement of oxygen anions. Repetition of these AlO_6 units in two dimensions forms an octahedral layer.

Likewise, a tetrahedral layer is formed from SiO_4 units. The resulting sheets are planar. These planar clay platelets stack on top of one another.

The least complicated clay minerals are the 1:1 clay minerals composed of one tetrahedral (T) layer and one octahedral (O) layer. The 1:1 clay minerals are referred to as TO



(a) Kaolinite (b) Montmorillonite

Fig. 1

minerals. The TO package has a basal spacing of 0.7 nm (7Å). For example, kaolinite (Fig. 1a), refer to the dioctahedral (1:1)-mineral, it has Al^{3+} filling two of three octahedral sites (Fig. 1). Clay minerals that are composed of two tetrahedral layers and one octahedral layer are referring to as (2:1)-clay mineral or TOT mineral. The apical oxygens of the two tetrahedral sheets project into the octahedral sheets. The (2:1)-clay mineral structure has a basal spacing of 1.5nm (15Å). For example, a montmorillonite (Fig. 1b)[6b] is a clay mineral in which one octahedral aluminate layer is sandwiched between two tetrahedral silicate layers (Fig. 1).

Clay particles generally give well defined X–ray diffraction patterns from which the mineral composition and the basal distances are determined. They are so finely divided that clay properties are often controlled by the surface properties of the minerals rather than by bulk chemical composition. Particle size, shape, nature and the distribution of amount of both mineral and organic impurities, nature and amount of exchangeable ions and degree of crystal perfection are all known to affect the properties of clays profoundly. Clays are classified according to the relative number of tetrahedral and octahedral layers.

Along with the high Bronsted acidic surfaces, the catalytic sites are edge sites where the platelets break off, offering coordinately-unsaturated Al^{3+}-sites; Fe^{2+} and Fe^{3+}-centers

arising often from substitution of Al^{3+} in the octahedral layer. Furthermore, dehydrative activation of clay through heating in an oven at 150-300°C results in generation of surface radical sites of the O_3SiO silyloxy type. Due to planar topology and the geometrical constraint of insertion between the parallel plates of two adjacent clay layers, substrate molecules are restricted in their orientation as they chemisorb on to catalytic sites.

The Bronsted acidity stems from the terminal hydroxyl groups and from the bridging oxygens. High acidity especially due to the latter. It is measured using a standard set of dye indicators by Hammett H_o acidity function. These surface acidity for natural clays with Na^+ or NH_4^+ as interstitial cations range from +1.5 to -3. Simple washing of the clay with mineral acid exchanging the interlamellar Na^+, K^+, NH_4^+-cations with proton brings their surface acidity to H_o values between -5.6 to -8 which is between that for conc. nitric acid (H_o= -5) and that for conc. sulfuric acid (H_o= -12).

Most commonly, the modification of clays is carried out either by exchanging the cations present in the clay with any other suitable cations like Fe, Zn, Pd, Cu, Ru, Rh, Ce, *etc*. or by increasing the interlameller space by pillaring.[5] Cation-exchanged clays were prepared by stirring a mixture of the clay and a metal salt in aqueous medium or aqueous acetone at room temperature or above. Pillared layered structures (PLS) are ultra large pore materials consisting of layered structures with pillars in the interlamellar region. Smectite is one of the families of minerals that can be used as pillared material.[3] Montmorillonite is most widely used smectites for the preparation of PLS. The general procedure for preparing these clays consists of exchanging the cations in the interlamellar position with larger inorganic hydroxymetal cations. These hydroxy species are polymeric or oligomeric hydroxyl metal cations formed by the hydrolysis of metal salts of Al, Zr, Ga, Cr, Si, Ti, Fe, *etc*. and mixtures of them. When the exchanged samples are subjected to a thermal treatment, dehydration and dehydroxylation occur, forming stable metal oxide clusters which serve to separate the layers, creating a two dimensional opening (space length > 1.0 nm). Among the advantages of pillared smectic clays over faujasite-zeolites is that their pore size can be made larger and under controlled pillaring condition, the pore size can be adjusted to suit a particular application.

Advantages of using Clay in Organic Reactions:

Clays have many advantages over conventional homogeneous catalyst. They offer;

a) Remarkable ease of handling and use. A simple filtration suffices to remove the contaminated by-products. The evaporation of solvent from the filtrate is often sufficient to provide the product in pure form.
b) Reduced product contamination by having the reagent fully bound to the solid support (in case of supported reagent).
c) It is non-corrosive; relatively safe handling owing to the full chemisorptions of the toxic chemicals.
d) Reduced environmental problems upon workup. Many inorganic species are powerful oxidants and sometimes can cause explosions. However, they can be restrained by prior adsorption onto the solid support.
e) Good thermal and mechanical stability, allowing higher stirring rates, if necessary.
f) Good dispersion of active sites of reagent, which leads to significant improvement in the reactivity.
g) Improvement in reaction selectivity due to the constraints of the pores and the characteristics of surface adsorption.
h) Clay can be recycled and reused without loss in the activity in most of the cases, making them economically viable.

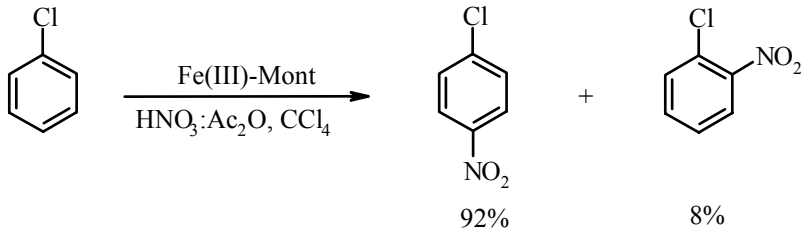
2.0.2 Clay in Organic Synthesis: (Literature)

Due to the Bronsted and Lewis acidities, clays in its natural as well as cation-exchanged (montmorillonites) form possess the ability to catalyze various organic transformations. Our group recently reported the catalytic property of natural kaolinitic clay for transdithioacetalization of acetals, ketals, oximes, enamines and tosylhydrazones[10], tetrahydropyranylation[11], selective regeneration of carboxylic acids from their corresponding allyl or cinnamyl esters[12] and for the preparation of oxazolines from nitriles[13]. Apart from this there are several reports on the success of organic reactions using clay as catalyst e.g.

Nitration

Nitration of aromatics is a fundamental reaction in synthetic organic chemistry; normally carried out in a mixture of nitric acid and sulfuric acid. Aromatic substrates (*e. g.* benzene, toluene, anisole *etc*.) are nitrated by an activated mixture of a silicate (*e. g.* montmorillonite clay, aluminosilicates *etc*.) optionally modified with metal nitrates (*e. g.* $Al(NO_3)_3$, $Bi(NO_3)_3$, $Cd(NO_3)_2$, *etc*.) and acid anhydride (*e. g.* Ac_2O, propionic anhydride, trifluoroacetic anhydride *etc*.) and an organic solvent (*e. g.* $CHCl_3$, CCl_4, DCM, EDC *etc*.). Thus, addition of HNO_3 to the above reaction mixture results in the formation of the nitrated product (*e. g.* 1,3-dinitrobenzene, 2,4-dinitrotoluene *etc*.).[14] This process can produce either mono or polynitrated aromatic compounds depending upon the condition selected and with respect to the aromatic substrate. Thus, it is an industrially advantageous process due to high yield, cost effective and safer than previously used nitration methods.

The Fe(III)-exchanged montmorillonite clay was employed to achieve the high *para*-selective nitration of chlorobenzene.[15] The nitration is carried out using fuming nitric acid and acetic anhydride in CCl_4 in the presence of Fe(III)-exchanged montmorillonite as the catalyst. It is possible to achieve the *para*-selectivity up to 92% and the yield of the product is about 90% (Scheme 1). The porous nature of the montmorillonite results in the shape selective nitration. Similar report of nitration of toluene and chlorobenzene with *para*-selectivity has been reported by Peng *et al*.[16]



Scheme 1: Clay catalyzed nitration of chlorobenzene

A facile solvent-free synthesis of β-nitrostyrenes from styrene and its substituted derivatives used inexpensive "doped" clay reagents, clayfen and clayan.[17] A one-pot nitration of aromatic compounds by clay-cop, a reagent consisting of an acidic montmorillonite clay impregnated with anhydrous cupric nitrate has been reported.[18] By simple variation of the

conditions, it is possible to drive the reaction towards mononitration or polynitration. Both the yield and selectivities are superior to those obtained under homogeneous conditions. Nitration of phenol was carried out using ferric nitrate and fluoridated clay (tonsil) and also using cupric nitrate and fluoridated clay.[19]

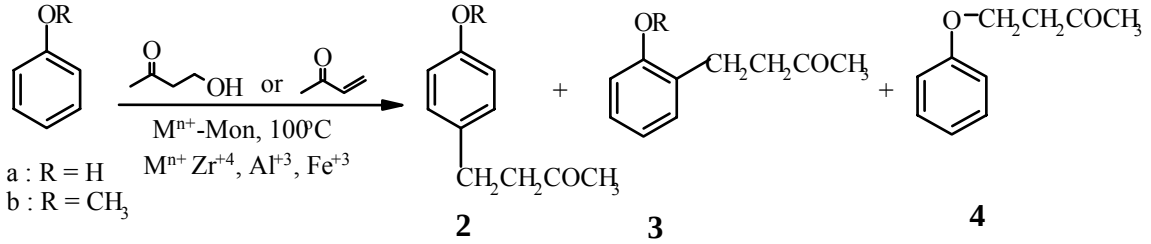
Alkylation

Friedel-Crafts reactions are of great interest due to their importance and common use in synthetic and industrial chemistry. The major disadvantages encountered in the use of anhydrous $AlCl_3$ include corrosion, unfriendliness to the environment, and stoichiometric requirement of reagent thereby generating large amount of waste.

The acid-treated $FeCl_3$-montmorillonite catalyst has been found to promote both acylation as well as alkylation.[20] The alkylation of toluene with ethyl bromide has been investigated over a series of Thuan Hai clays obtained by exchanging the original Na^+ cations with Fe^{3+}, Zn^{2+}-cations.[21]

Vanadia-montmorillinite is found to be useful for the monoalkylation of aniline.[22] The propene alkylation of biphenyl has been studied at 250°C and 140psi using two mesoporous clays *viz*. acid-treated montmorillonite K10 and aluminas-dealuminated-laponite.[23] A series of 3-β-arylcholestenes were synthesized by Friedel-Crafts alkylation of cholesterol with arenes catalyzed by montmorillonite K-10.[24] The mesoporous clays exhibit reactivities and selectivities towards monoalkylated product that are substantially different from those exhibited by microporous alumina pillared clays. Alkylation of phenol with C16-C18 olefins was also reported in the presence of activated clay and monohydric alcohols in 94% yield.[25] Synthesis of alkylamines such as tertiary butylamines over montmorillonite clay or other catalysts is carried out using NH_3 and isobutylene as the olefin.[26] This constitutes the commercialized way to synthesize tertiary amines which are difficult to obtain by normal alkyl halogen substitution method.

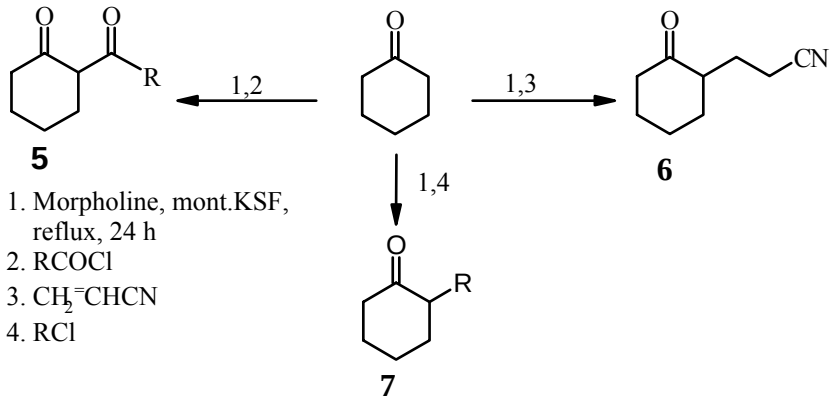
Alkylation of phenol, anisole and methoxynaphthalene with 4-hydroxybutan-2-one or



Scheme 2

methyl vinyl ketone in the presence of Zr^{+4}, Al^{+3} or Fe^{+3}-montmorillonite clay produces raspberry ketone (**2**) and pharmaceutically active compounds (**3-4**) in low yield (**Scheme 2**).[27]

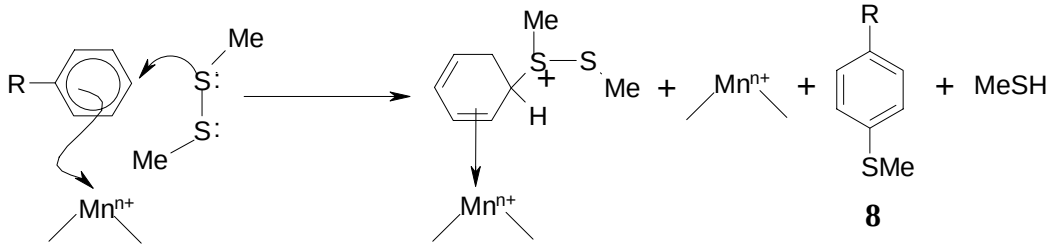
The alkylation of benzene with olefins using pillared clays to give detergent range low molecular weight alkylbenzene has been reported.[28] A single step Stork's alkylation and acylation of cylclohexanone without isolation of enamine in the presence of montmorillonite



Scheme 3

KSF (KSF) clay as catalyst has been studied to give alkylated products (**6**) and (**7**) and acylated product **5** (**Scheme 3**). [29]

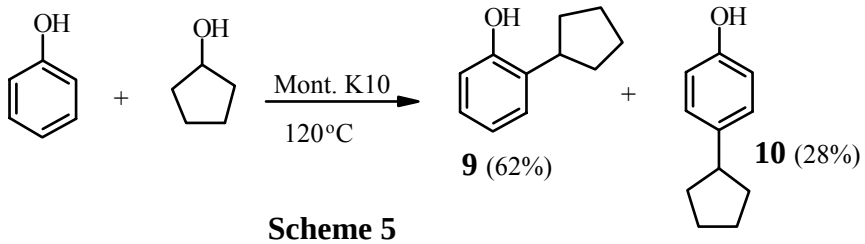
Iron-pillared-clays (FePILCs) were found to be most efficient catalysts for the benzylation of aromatic compounds producing quantitative conversion of benzylated derivatives in short reaction times.[30] A method for the direct thioalkylation of thiophenol and benzothiophene by reaction with an alkyl disulfide using $ZnCl_2$-modified montmorillonite clay



Scheme 4

has been reported.[31] The direct introduction of $-SCH_3$ group into activated aromatic and heteroaromatic compounds producing S-alkylated products (**8**) has been achieved by reaction with dimethyl disulfide over a $MnCl_2$ promoted montmorillonite K10 clay.[32] The Mn-promoted clay appears to promote the reaction by coordination of the aromatic substrate at the active site followed by the attack of the disulfide at the activated aromatics (**Scheme 4**).

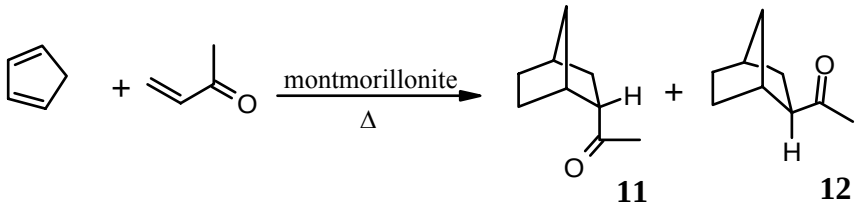
Another interesting observation of clay alkylation was found in our laboratory for the synthesis of cyclopentylphenol.[33] Alkylation of phenol was carried out with cyclopentanol using montmorillonite K10 clay as catalyst without the use of solvent. Interestingly, *o*-substituted product (**9**) was found to be predominant, the *ortho*/*para* ratio being 2:1 (**Scheme 5**).



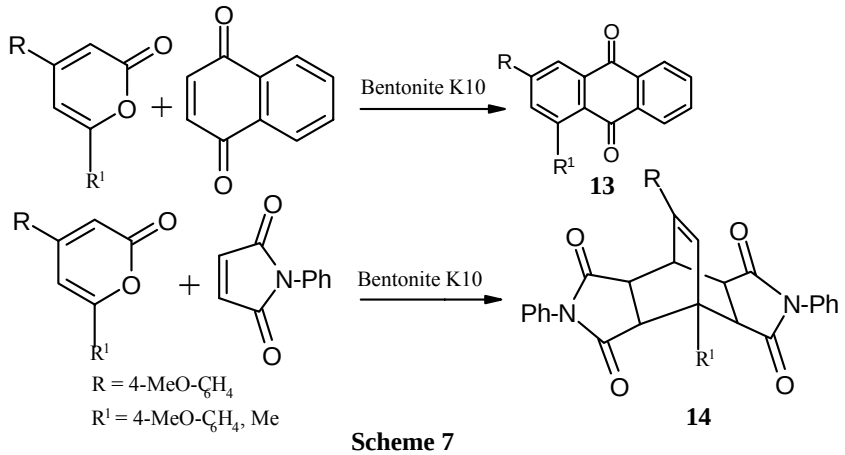
Scheme 5

Diels-Alder Reaction

A wide range of transition metal-exchanged Tonsil (a German montmorillonite) clays were used for Diels-Alder reactions which involves the use of α, β-unsaturated carbonyl compounds, such as methyl vinyl ketone and methyl acrylate as dienophiles (**Scheme 6**).[34]



Scheme 6

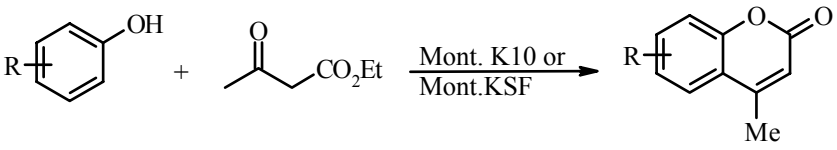


Scheme 7

The Diels-Alder reaction of 4,6-*bis*-(4-methoxyphenyl) and 4-(4-methoxyphenyl)-6-methyl-2H-pyran-2-one with 1,4-napthoquinone and N-phenylmaleimide have been carried

out by adsorbing the reactant on silica gel, ν-silica or bentonite K10 clay in the absence of solvent (**Scheme 7**).[35]

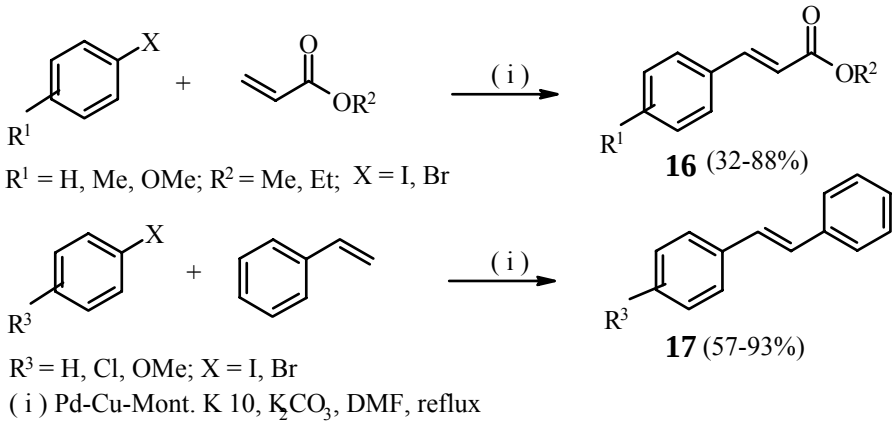
A simple and rapid method for the synthesis of flavones was described *via* a solid-state dehydrative cyclization of *o*-hydroxydibenzoylmethanes on a clay surface using microwave.[36] Montmorillonite clay is used to synthesize coumarins (**15**) *via* Pechmann condensation of phenol and ethyl acetoacetate (**Scheme 8**).[37]



15

Scheme 8

Vinylation of aryl halides (Heck reaction) catalyzed very efficiently by Pd(II) and Cu(II)-exchanged montmorillonite clays to provide unsaturated compounds (**16**) and (**17**).[38] Various Cu-exchanged as well as Pd-exchanged montmorillonite were examined for the Heck reaction and found that best result was obtained if both palladium and copper are present in the same catalyst system (**Scheme 9**).



Scheme 9

Palladium acetate immobilized on montmorillonite acts as an efficient catalyst for the alkoxyformylation of olefins with CO and methanol in the presence of PPh_3 and an acid promoter affording branched chain esters.[39]

Also the synthesis of diaryl carbonates from the reaction of phenols with phosgene or phenyl chloroformate in presence of montmorillonite clay catalyst has been patented.[40] A new method or production of 2-phenylbenzoxazole *via* cyclocondensation of 2-aminophenol with benzoic acid in the presence of montmorillonite clay has been reported.[41] Condensation of indoles with carbonyl compounds in the presence of montmorillonite clay produces *bis*(indol-3-yl)methanes in good yield; an extension of this procedure, involving nucleophilic ring opening of oxiranes, produces 1,2-*bis*(indol-3-yl)ethanes.[42]

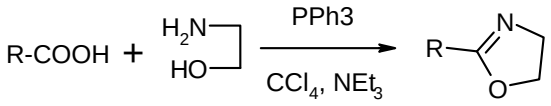
Clays are widely available in nature and find wide applications[6b] as solid catalysts. They can be modified easily by exchanging or pillaring with various transition metal-cations. Their properties can be suitably molded for a specific catalytic activity. A large number of organic reactions catalyzed by clays are being reported every year.[6c] These clays both in the natural as well as modified forms exhibit high regioselectivity, enhanced rate, excellent yields and unusual reactivity pattern in various organic reactions. Clays being inexpensive, readily available and reusable solid catalyst,[6d] show tremendous potential for many industrial reactions such as nitrations, alkylations, acylations, oxidations, reductions, *etc* asymmetric catalysis using clays as catalysts holds promise in the future work.

2.1.1 Introduction

Oxazoline is an important functionality as a protecting group[43] in organic synthesis. Oxazolines exist in a variety of natural products[44] and biologically active compounds[45] and they can be easily converted into optically active β-amino alcohols which are useful synthetic intermediates. The optically active aromatic oxazolines are used extensively to control the stereochemistry in many asymmetric transformations.[46] Hence oxazolines have gained paramount importance as ligands in recent years.[47] They can be readily synthesized from easily available chiral amino alcohols. The stereogenic center is quite close to the reactive site of the catalyst, causing efficient chiral induction. In particular, the oxazoline ligands with C_2 symmetry have achieved high enantioselectivities in various catalytic processes.[48] Several methods are known to prepare oxazolines from carboxylic acid[49a], carboxylic ester[49b], nitriles[49c], aldehyde[49d] and amido alcohols.[49e] Most of the methods utilize complex reagent, strongly acidic conditions and stringent reaction parameters with occasionally low yields of the reaction products. Some of the recent methods are briefly presented here.

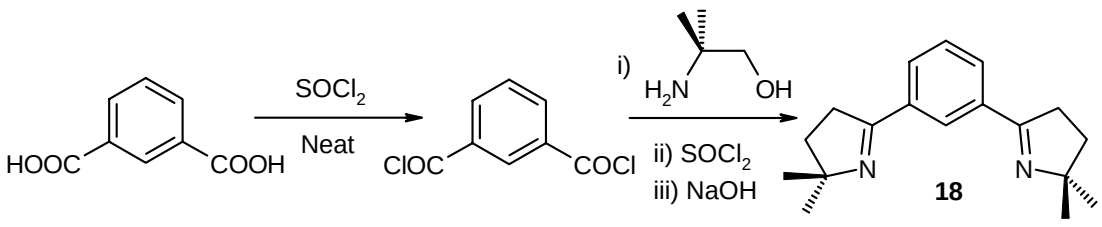
1. From carboxylic acids

   As shown in **scheme 10**, traditional and modified reaction conditions[49f] are effective in preparation of oxazolines.



Scheme 10: Oxazolines from carboxylic acid

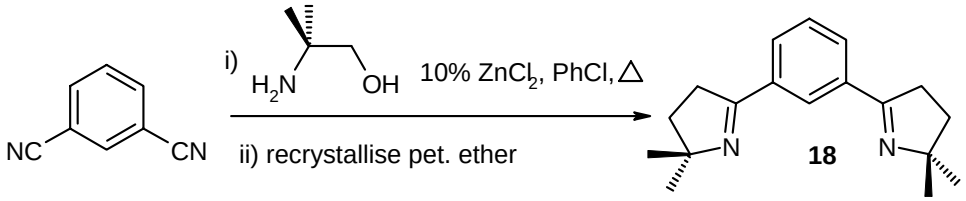
Earlier synthetic protocol for construction of oxazoline moiety from carboxylic acid involve use of excess thionyl chloride (**Scheme 11**) which makes isolation of final compound difficult; probably due to the resulting oil retaining some $SOCl_2$ following the



Scheme 11: Oxazolines via acid chloride

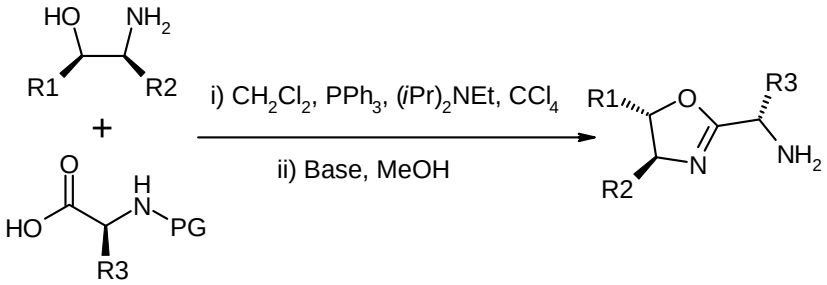
cyclization step.[49g]

This method was further modified by making use of $ZnCl_2$ (10 mol %) as a Lewis acid catalyst for the large scale production of bis-oxazoline (**Scheme 12**) starting from commercially available 1, 3-dicyanobenzene and 2-methyl-2-amino-1-propanol.[49h]



Scheme 12: Lewis-acid catalysed large scale preparation of bis-oxazoline

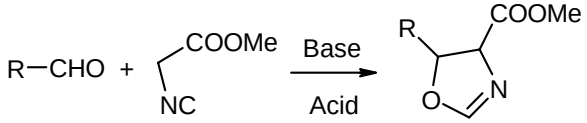
2. Amine functionalized oxazolines have been prepared from β-amino alcohols and protected α-amino-acid.[49i]



Scheme 13: Synthesis of amine fuctionalized oxazoline

3. Schollkpf method[49f]

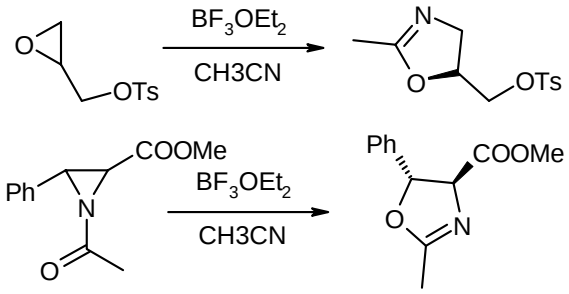
Aldehydes on condensation with isocyanides produce oxazolines in presence of basic as well as acidic catalyst in high yield.



Scheme 14: Oxazolines from aldehydes

4. Epoxide/ aziridine ring opening[49f]

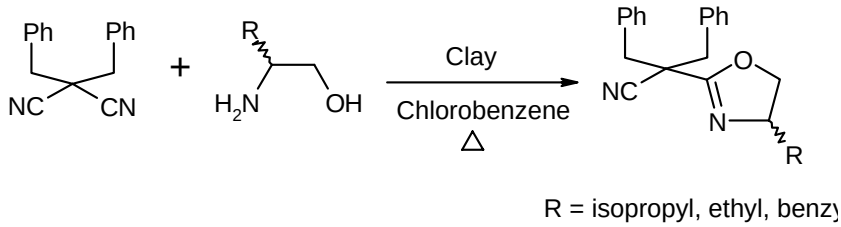
Epoxide or aziridine ring opening reaction is a useful method for the preparation of racemic and non racemic oxazolines.



Scheme 15: Oxazolines from epoxide/ aziridine ring opening

In general, the synthesis of chiral oxazolines from natural amino acids involves several steps.[47] Although natural amino acids are readily available chiral sources; their use causes limitations in absolute configuration and the diversity of substituents on the formed oxazoline ring. The majority of syntheses of bis-oxazoline (BOX) ligands followed a general synthetic route in which oxalic acid or the substituted malonic acids were first condensed with the corresponding optically active 1, 2-amino alcohol to form the bis(hydroxyl)amide derivatives. The hydroxyl groups were then activated and the resulting intermediate was cyclized to provide the bis-oxazoline ligands. Activating agents such as $SOCl_2$, methanesulfonic acid for certain tertiary alcohols, Me_2SnCl_2, ZnCl2, diethylamino-sulfurtrifluoride (DAST) reagent, triflic acid and $BF_3.OEt_2$ were employed.[48]

However there are a few reports of catalysts with unsymmetrical oxazoline ligands which also have two coordinating nitrogen atoms. Our group has demonstrated the use of natural kaolinitic clay as efficient catalyst for the preparation of 2-oxazolines from nitriles.[13, 50]

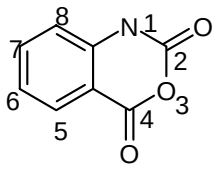


Scheme 16: Clay catalyzed conversion of nitriles to oxazolines

The R substituent can be varied by varying the starting optically pure amino alcohol. The ligands were synthesized in simple steps from dibenzyl malononitrile and used successfully for asymmetric transfer hydrogenation reactions using rhodium as catalyst.[51]

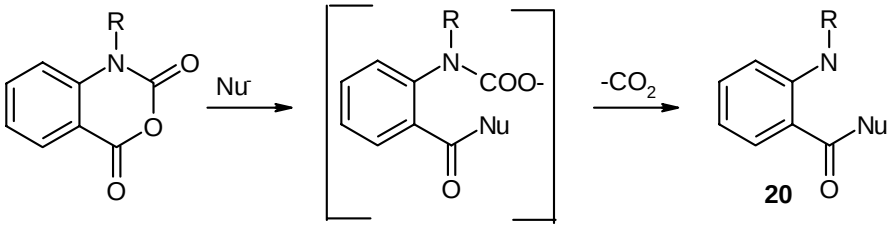
2.1.2 Present work

Isatoic anhydride i.e. (2*H*)-3,1-benzoxazine-2,4(1*H*)-dione **(Fig. 19)** is an extremely versatile compound due to its reactivity towards electrophile and nuclophiles, its analogs and derivatives have found wide application in the manufacture of agricultural chemicals, dyes, pigments, flavors, pharmaceuticals, etc. The chemistry of isatoic anhydride is reviewed at length by Coppola[52] the example of the preparation of benzothiazoline from **19** and 2-aminothiophenol[53] is mentioned therein. Coppola has also recently reported preparation of polymer-supported isatoic anhydride and its use as a scavenger of amines.[54]



Isatoic anhydride (19)

Isatoic anhydride is an internally protected and activated form of 2-aminobenzoic acid. The C-4 carbonyl of the heterocyclic ring is highly susceptible to attack by a variety of nucleophiles to give **20** along with carbon dioxide as the only by-product **(Scheme 17)**. The nitrogen of **19** (R= H) can be readily alkylated by deprotonation with sodium hydride followed by reaction with an alkyl halide to give an N-substituted isatoic anhydride.



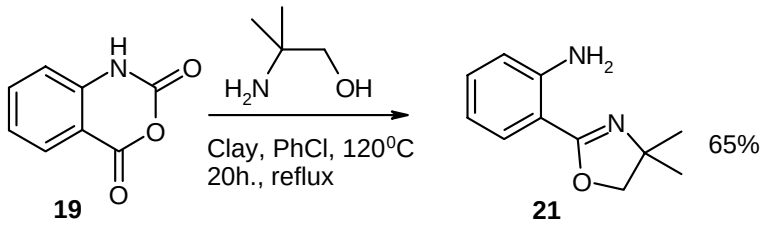
Scheme 17: Reaction of nucleophile with Isatoic anhydride

Since oxazoline formation is catalyzed by Lewis and Brönsted acids, we thought that clay might be an efficient and mild catalyst for the activation of isatoic anhydride for nucleophilic reaction of amine. If commercially available 2-amino alcohol is used as a nucleophile, possibly one can obtain oxazoline moiety after *insitu* cyclization.

2.1.3 Results and Discussions

Initial reaction of isatoic anhydride with 2-amino-2-methylpropanol was carried out in dry chlorobenzene at 120 °C in the presence of acidic kaolinitic clay[8] as the catalyst to furnish 2-(*o*-aminophenyl)oxazoline **(Scheme 18)** with 65% isolated yield **(Table 1, entry 1)**. We presume the Lewis acidic sites of the catalyst assist the nucleophilic attack of amino group on C-4 of **19** followed by cyclization to give the oxazoline. The final product is formed by the loss of carbon dioxide to give free amine. The work up and isolation of final product was found to be easy with column chromatography because of the larger difference between R_f values of substrate and the final product.

As shown in **Table 1 (entry 2)** none of the desired product has been obtained in absence of catalyst. Starting amino alcohol is found to be unreacted in the reaction.



Scheme 18: Clay catalyzed conversion of isatoic anhydride to oxazoline

Table 1: Catalytic conversion of isatoic anhydride (19) to *o*-amino-oxazoline 21

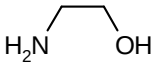
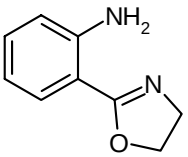
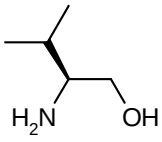
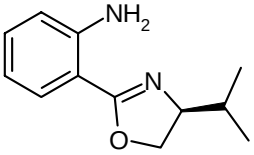
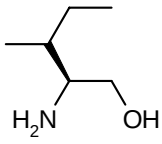
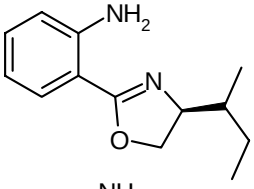
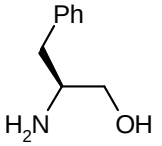
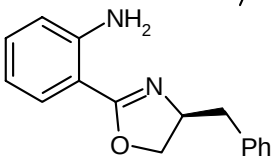
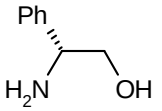
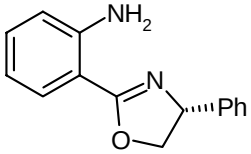
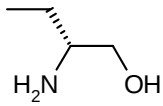
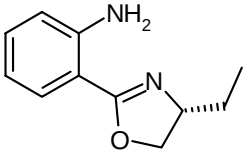
Entry	Catalyst (% w/w)	Conditions	Substrate ratio (equivalent) 19 : amino alcohol	Isolated yield (%) (21)
1	Kaolinitic clay (20)	120 ^{0}C, 20h.	1 : 2.5	65
2	None	120 ^{0}C, 48h.	1 : 2.5	0
3	$ZnCl_2$	120 ^{0}C, 20h.	1 : 2.5	45
4	Mont K10 (20)	120 ^{0}C, 20h.	1 : 2.5	55
5	Kaolinitic clay (20)	Microwave, 20min.	1 : 2.5	70
6	Kaolinitic clay (20)	120 ^{0}C, 20h.	2 : 1	70
7	Kaolinitic clay (40)	120 ^{0}C, 20h.	2 : 1	68

However, experiment with $ZnCl_2$ (10 mol %) gave slightly lower yield **(entry-3)** for this reaction. Commercially available montmorillonite K10 was also found efficient as catalyst to produce slightly lower yield of the desired product **21 (entry 4)**. Reaction was found to

proceed with considerable acceleration when carried out under the microwave conditions **(entry-5)**. Slightly modified reactions with excess of **19** (2 equivalent of **19**) showed some improvement in the conversion as evident from entry **6**. No further improvement in reaction has been observed by using excess of catalyst **(entry 7)**. As we were interested in chiral derivatives of this type of compounds different optically pure 2-aminoalcohols were used for this reaction to furnish desired products with low to moderate yields. A series of derivatives of 2-(*o*-aminophenyl)oxazolines were synthesized with different 2-aminoalcohols and results summarized in **Table-2**.

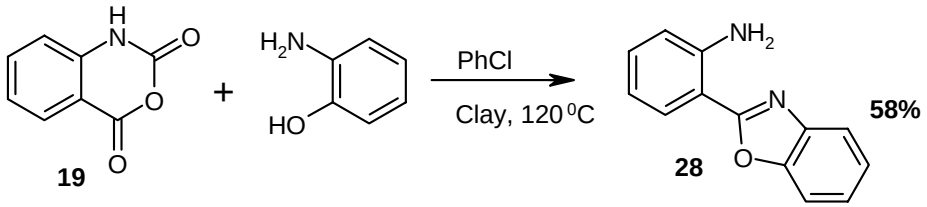
Poor yield of oxazoline **22** has been obtained when ethanolamine was used as a substrate **(entry 1)**. Yield enhanced to little extent when the reaction was carried out in an open vessel under microwave irradiation for 20 min. Yield has not been improved even after 1 hour when irradiated in microwave. A similar result has been observed in case of L-Valinol to get oxazoline **23**. L-isoleucinol gave 55% yield of **24** when 2:1 ratio of isatoic anhydride **(entry 3)** with aminoalcohol was used. Detectable amount of unreacted aminoalcohol was observed. L-phenylalaniol which was prepared by reduction of L-phenylalanine gave 58% of oxazoline **25.** Reaction was reproduced three times to get almost similar results. Use of commercially obtained montmorillonite K10 slightly lowers the yield by 5% in this case (entry **4**). As shown in entry **5**, R(-)2-phenylglycinol gave oxazoline **26** with 62% yield, which was further converted to its NHTs derivative. The optical rotation of which was found to be $[\alpha]_D$ -48.2 (C 0.75, $CHCl_3$) at 25 ^{0}C in accordance with the reported value[55] indicating no loss of optical purity during the reaction. D-2-amino-1-butanol **(entry 6)** gave oxazoline **27** with 70% yield by using 2 equivalent of isatoic anhydride.

Table 2: Catalytic conversion of isatoic anhydride to 2-(o-aminophenyl)oxazolines[a]

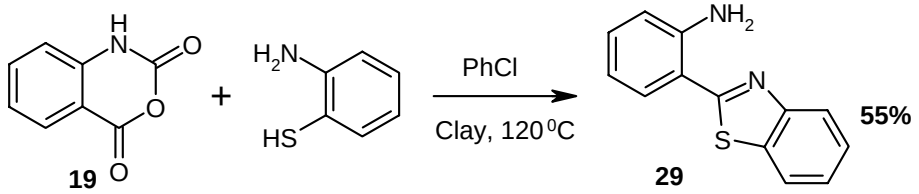
Entry	aminoalcohol	Product		Yield (%)[b]
1			**22**	40 45[c]
2			**23**	41[d]
3			**24**	50 55[d]
4			**25**	58[d]
5			**26**	35 62[d]
6			**27**	70[d]

a: Isatoic anhydride was heated in dry chlorobenzene under argon with 2-aminoalcohol (2.5 eq.), catalyst (20% w/w) for 20h., b: Isolated yield. All the compounds were characterised by usual spectral methods. c: With microwave irradiation in a domestic oven for 20 min., d: With 2 eq. isatoic anhydried

The catalytic conversion of **19** also works with 2-aminophenol[52] **(Scheme 19)** and 2-aminothiophenol with the formation of oxazoline **28** and thiazoline **29** respectively and only a little amount of disulfide was formed in latter case **(Scheme 20)**.

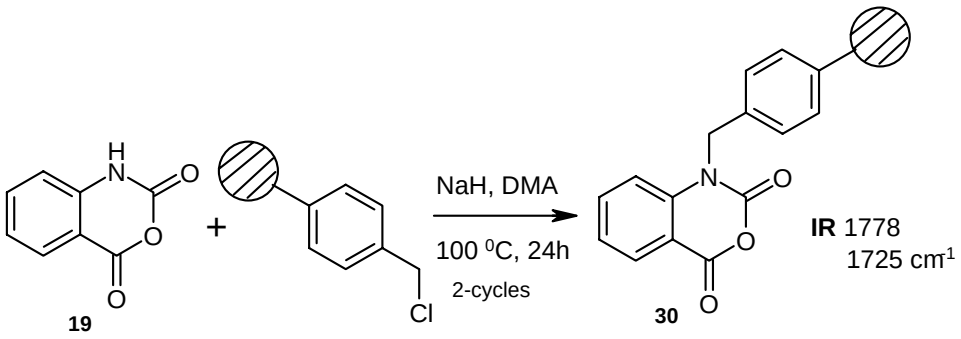


Scheme 19: Clay catalyzed reaction of isatoic anhydride with *o*-aminophenol



Scheme 20: Clay catalyzed reaction of isatoic anhydride with *o*-aminothiophenol

It was further decided to prepare polymer-supported oxazolinyl ligands for heterogeneous asymmetric catalysis. The polymer-supported isatoic anhydride **30** was prepared **(Scheme 21)** from chloromethylated styrene-DVB polymer (4.8 equiv. Cl^- /g) by the procedure described by Coppola.[53]

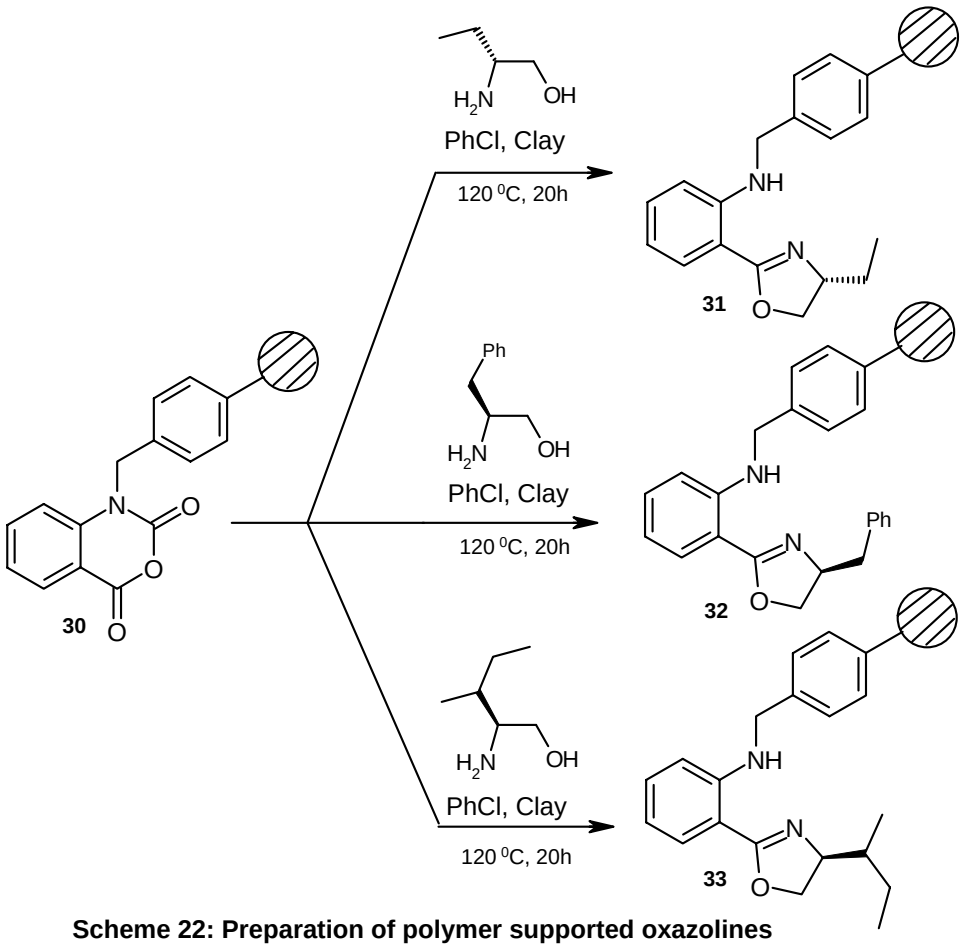


Scheme 21: Preparation of polymer supported isatoic anhydride

Treatment of **19** with DVB-polymer in presence of sodium hydride gives resin **30**. Two strong IR absorptions at 1778 and 1725 cm^{-1} for resin beads **30** are observed, indicative of polymer bound anhydride. Loading of **19** was determined by Cl content of resin **30**. The product **30** was subjected for the same reaction (second cycle) to achieve a maximum amount of loading. Also increase in polymer weight of **30** after each cycle proved successful anchoring

of isatoic anhydride onto chloromethylated DVB-polymer. Cl content of starting DVB-polymer was 22.5 %, after the 1st reaction (**Scheme 21**), it was found to be 12 % and after 2nd cycle of **30** it was found to be 11.41 %.

A sample of **30** was exposed to 2.5 equivalent of D-2-aminobutanol and catalytic amount of kaolinitic clay (20 % w/w) in chlorobenzene to afford polymer-anchored amino oxazoline **31 (Scheme 22)**.



Scheme 22: Preparation of polymer supported oxazolines

FT-IR analysis of polymer beads **31** showed a peak at 3419 cm^{-1} and absence of the two carbonyl peaks at 1778 and 1725 cm^{-1} indicated successful conversion. Two more chiral polymer supported amino oxazolines **32** and **33** were prepared by the same method using L-phenylalaniol and L-isoleucinol as the aminoalcohols. Degree of functionalizaton, i.e. mmol ligand/g resin; calculated by elemental analysis of nitrogen with the known formula.[56]

2.1.4 Conclusion

A simple one pot procedure for the preparation of 2-(*o*-aminophenyl)oxazolines from isatoic anhydride has been developed using clay as a catalyst.[57] Also preparation of polymer supported title compound has been investigated which will be helpful for the catalytic asymmetric transformations as heterogeneous catalyst.

(*Application of those polymer supported ligands is demonstrated in asymmetric ethylation of aldehydes in* ***section B***).

2.1.5 Experimental

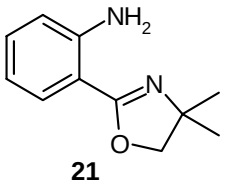
Optically pure amino alcohols were prepared from chiral amino acids by the known procedure.[58] Chlorobenzene was distilled over CaH_2 and stored over activated molecular sieves. Merrifield resin, the co-polymer of chloromethylpolystyrene cross-linked with 1% divinylbenzene, with loading of 4.8 equivalent Cl^- g^{-1} resin was obtained from Ion Exchange (India) Ltd. and it was washed with water, water-ethanol mixture (1:1) and finally with ethanol. Any adsorbed material was removed by extracting the polymer in a soxhlet using ethanol-benzene mixture for 10 h. Chlorine content of the polymer beads was estimated using standard method and found to be 22.5 %. Montmorillonite K10 and isatoic anhydride were purchased from Aldrich Chemicals.

Purification of Natural Kaolinitic Clay[10c, 59]

The kaolinitic clay was procured from the Padappakara mine of Quilon District, Kerala, India and it was subsequently purified by separating coarser mineral impurities from clay particles, followed by drying and calcinations. The 550 ^{0}C calcined clay samples (1 part by wt) were boiled with 2M HCl (4 parts by wt) for 45 min. The leached samples were then washed free of chloride ions and dried at 110 ^{0}C for 12 hr.

It was characterized by FT IR, XRD, UV, ESR, SEM, EDX and chemical analysis by AAS. The composition of the clay was determined by wet chemical analysis (in %):
SiO_2= 67.45, $Al2O_3$= 22.2, Fe_2O_3= 6.1, TiO_2= 3.45, K= 0.8

2-(4,4-Dimethyl-4,5-dihydro-1,3-oxazol-2-yl)aniline 21 (Table-1):



21

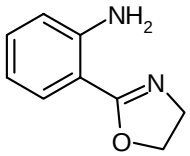
A mixture of **19** (0.50 g; 3.06 mmol), 2-amino-2-methyl-1-propanol (0.68 g; 7.64 mmol) and kaolinitic clay (0.10 g) was stirred in chlorobenzene (5 mL) at ca. 120 °C for 20 h. After completion of the reaction, the catalyst was filtered and the product was purified by

column chromatography on neutral alumina to afford compound **21** as white solid (0.38 g; 65 %).

M.P.	103.6 – 106.0 °C.
IR	3439, 3187, 3151, 1401, 1329, 1185, 752 $cm.^{-1}$
^{1}H NMR (200MHz, $CDCl_3$)	δ 7.70 – 7.65 (m, 1H), 7.25 – 7.15 (m, 2H), 6.65 (m, 1H), 6.35 (br s, 2H), 4.05 (s, 2H), 1.35 (s, 6H).
Mass m/z (%)	190 (M^+, 91), 175 (100), 145 (51), 130 (65), 118 (76), 92 (20), 65 (13).
Microanalysis:	Cal. for $C_{11}H_{14}N_20$ C:69.47, H:7.37, N:14.74; Found C:69.58, H:7.31, N:14.89 %.

{The same procedure was followed for preparation of all the 2-(*o*-aminophenyl)oxazolines listed in **Table-2**, as well as oxazolines **28** and **29**}.

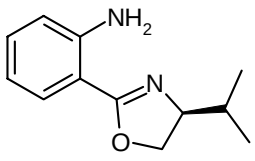
2-(4,5-Dihydro-1,3-oxazol-2-yl)aniline 22 (Entry-1; Table-2):



22

Appearance:	Light yellow oil.
IR:	3379, 3187, 3120, 1625, 1390, 1260, 747 $cm.^{-1}$
^{1}H NMR (200MHz, $CDCl_3$)**:**	δ 7.70 (m, 1H), 7.15 (m, 1H), 6.85 – 6.55 (m 2H), 6.05 (br s, 2H), 4.25 - 4.12 (m, 2H), 4.12 – 4.00 (m, 2H).
Mass m/z (%)**:**	162 (M^+, 100), 130 (48), 118 (70), 106 (55), 92 (20), 65 (20).
Microanalysis:	Cal. for $C_9H_{10}N_20$ C:66.66, H:6.17, N:17.28; Found C:66.45, H:6.28, N:17.42 %.

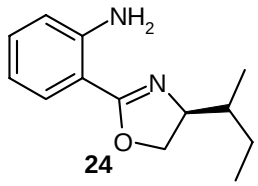
2-(4-Iso-Propyl-4,5-dihydro-1,3-oxazol-2-yl)aniline 23 (Entry-2; Table-2):



23

Appearance:	Yellow oil.
IR:	3395, 3288, 2955, 1686, 1633, 1598, 1456, 1047, 746 $cm.^{-1}$
^{1}H NMR (200MHz, $CDCl_3$)**:**	δ 7.72 – 7.60 (m, 1H), 7.30 – 7.10 (m, 1H), 6.80 – 6.55 (m 2H), 6.50 (br s, 2H), 4.40 - 4.22 (m, 1H), 4.20 – 3.95 (m, 2H), 1.90 – 1.65 (m, 1H), 1.10 - 0.90 (two d, J = 7.8 Hz, 6H).
Mass m/z (%)**:**	204 (M^+, 50), 193 (10), 161 (100), 133 (32), 119 (25), 106 (10), 92 (15).
Microanalysis:	Cal. for $C_{12}H_{16}N_20$ C:70.59, H:7.84, N:13.72; Found C:70.91, H:7.82, N:13.64 %.
$[\alpha]_D^{24}$	– 1.35 (0.85, $CHCl_3$).

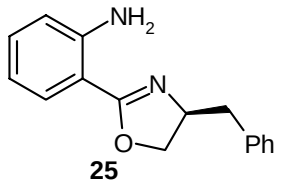
2-(4-sec-Butyl-4,5-dihydro-1,3-oxazol-2-yl)aniline 24 (Entry-3; Table-2):



24

Appearance:	Yellow oil.
IR:	3462, 3283, 2960, 1634, 1599, 1491, 1046, 969, 748 $cm.^{-1}$
^{1}H NMR (200MHz, $CDCl_3$)**:**	δ 7.75 – 7.65 (d, J = 8.0 Hz, 1H), 7.30 – 7.10 (m, 1H), 6.55 – 6.52 (m 2H), 6.15 (br s, 2H), 4.40 - 4.15 (m, 2H), 4.00 (m, 1H), 1.80 – 1.50 (m, 2H), 1.40 – 1.15 (m, 1H), 0.93 (t, J = 6.0 Hz, 3H), 0.88 (d, J = 6.0 Hz, 3H).
Mass m/z (%)**:**	218 (M^+, 45), 187 (10), 161 (100), 133 (40), 118 (18), 106 (10), 92 (8).
Microanalysis:	Cal. for $C_{13}H_{18}N_20$ C:71.56, H:8.27, N:12.84; Found C:71.10, H:8.71, N:12.20 %.
$[\alpha]_D^{24}$	+ 7.94 (1.26, $CHCl_3$)

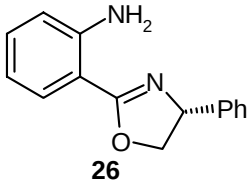
2-(4-Benzyl-4,5-dihydro-1,3-oxazol-2-yl)aniline 25 (Entry-4; Table-2):



25

Appearance:	Yellow oil.
IR:	3448, 3320, 3042, 2901, 1629, 1480, 1200, 1150, 769 $cm.^{-1}$
^{1}H NMR (200MHz, $CDCl_3$)**:**	δ 7.65 (m, 1H), 7.45 – 7.15 (m, 5H), 6.75 – 6.60 (m, 3H), 6.15 (br s, 2H), 4.70 - 4.50 (m, 1H), 4.30 (m, 1H), 4.05 (m, 1H), 3.15 (dd, J = 14.0 & 6.0 Hz, 1H), 2.75 (dd, J = 14.0 & 8.0 Hz, 1H)
Mass m/z (%)**:**	252 (M^+, 80), 224 (2), 160 (40), 131 (40), 118 (90), 91 (50), 83 (100), 71 (2).
Microanalysis:	Cal. for $C_{16}H_{16}N_20$ C:76.19, H:6.35, N:11.11; Found C:76.22, H:6.39, N:11.52 %.
$[\alpha]_D^{24}$	+ 26.54 (1.04, $CHCl_3$)

2-(4-Phenyl-4,5-dihydro-1,3-oxazol-2-yl)aniline 26 (Entry-5; Table-2):



26

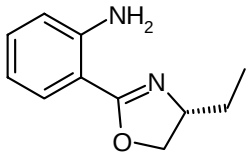
Appearance:	Yellow oil.
IR:	3463, 3365, 2955, 1685, 1630, 1590, 1495, 1037, 753, 697 $cm.^{-1}$
^{1}H NMR (200MHz, $CDCl_3$)**:**	δ 7.80 (d, J = 8.0 Hz, 1H), 7.35 (m, 6H), 6.70 (m 2H), 6.15 (br s, 2H), 5.45 (m, 1H), 4.68 (m, 1H), 4.15 (m, 1H).
Mass m/z (%)**:**	238 (M^+, 94), 218 (8), 207 (48), 193 (3), 180 (10), 160 (25),

147 (18), 131 (28), 118 (96), 91 (55), 83 (100), 77 (37).

Microanalysis: Cal. for $C_{15}H_{14}N_20$ C:75.63, H:5.88, N:11.76; Found C:75.17, H:5.91, N:11.20 %.

$[\alpha]_D^{24}$ + 5.66 (1.06, $CHCl_3$)

2-(4-Ethyl-4,5-dihydro-1,3-oxazol-2-yl)aniline 27 (Entry-6; Table-2):



27

Appearance: Yellow oil.

IR: 3440, 3290, 2948, 1660, 1450, 1052, 748 $cm.^{-1}$

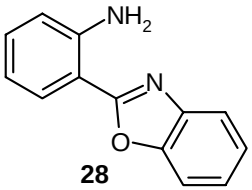
^{1}H NMR (200MHz, $CDCl_3$)**:** δ 7.74 (d, J = 8.0 Hz, 1H), 7.22 (t, J = 8.0 Hz, 1H), 6.80 – 6.60 (m 2H), 6.20 (br s, 2H), 4.45 – 4.20 (m, 2H), 4.00 - 3.85 (m, 1H), 1.85 – 1.55 (m, 2H), 1.05 (t, J = 8.0 Hz, 3H).

Mass m/z (%)**:** 190 (M^+, 91), 175 (100), 161 (45), 133 (40), 118 (76), 106 (60), 92 (20), 65 (13).

Microanalysis: Cal. for $C_{11}H_{14}N_20$ C:69.53, H:7.97, N:13.99; Found C:69.47, H:7.37, N:14.73 %.

$[\alpha]_D^{24}$ –7.45 (1.45, $CHCl_3$)

2-(Benzo[d][1,3]oxazol-2-yl)aniline 28 (Scheme 19):



28

Appearance: Dark viscous oil.

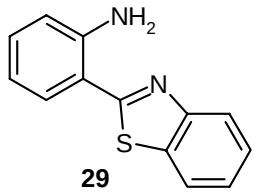
IR: 3481, 3370, 3013, 2942, 1686, 1482, 1293, 1243, 1156, 1100, 750 $cm.^{-1}$

^{1}H NMR (200MHz, $CDCl_3$)**:** δ 7.95 – 7.80 (m, 2H), 7.72 – 7.62 (m, 4H), 7.35 – 7.20 (m, 2H), 5.75 (br s, 2H).

Mass m/z (%)**:** 210 (M^+, 3), 151 (81), 119 (100), 92 (55), 75 (2), 65 (12).

Microanalysis: Cal. for $C_{13}H_{10}N_20$ C:74.28, H:4.76, N:13.33; Found C:74.48, H:4.26, N:13.61 %.

2-(Benzo[d][1,3]thiazol-2-yl)aniline 29 (Scheme 20):



29

Appearance: Brown solid.

M. P. 164– 166 °C.

IR: 3377, 3057, 3011, 2955, 2921, 2855, 1685, 1580, 1297, 1210, 759, 741, 665 $cm.^{-1}$

^{1}H NMR (200MHz, $CDCl_3$)**:** δ 7.80 – 8.10 (m, 2H), 7.60 – 7.30 (m, 4H), 6.90 – 7.15 (m, 2H), 5.85 (br s, 2H).

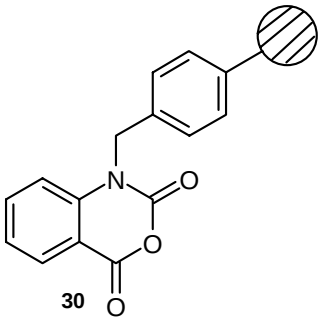
Mass m/z (%)**:** 226 (M^+, 65), 211 (5), 198 (38), 177 (12), 149 (95), 135 (100), 119 (75), 92 (25), 69 (15).

Microanalysis: Cal. for $C_{13}H_{10}N_2S$ C:69.03, H:4.42, N:12.39; S:14.16, Found C:68.70, H:4.21, N:12.00, S:14.60 %.

Polymer supported isatoic anhydride 30:

Merrifield resin (chloromethylated divinyl benzene polymer) purified by soxhlet extraction with benzene ethanol mixture and was dried under vacuum (1 mmHg, at 50 ^{0}C for 6 h.) and kept under argon. The resin (1.0 g, 6.338 mmol of Cl/g) evacuated and flushed with argon, was swelled with 8 ml of DMA (anhydrous). In a separate flask was dissolved 10 g (63 mmol) of isatoic anhydride **(19)** in 50 mL of DMA. To this solution was added 1.5 g of

sodium hydride in portions. After the evolution of hydrogen ceased, the mixture was stirred at room temperature for one hour then this solution was added to the preswelled resin and the mixture was shaken for 48 h. The solvent was drained and the resin was sequentially washed with DMF (3 X 10 ml), CH_2Cl_2 (4 X 10 ml), THF (1 X 10 ml) and then was dried under vacuum to give 1.50 g of **30**. The resin **30** (1.43 g) was recycled using 30 mmol of isatoic anhydride and sodium hydride to get polymer supported isatoic anhydride (1.61 g) in the form of pale yellow beads.



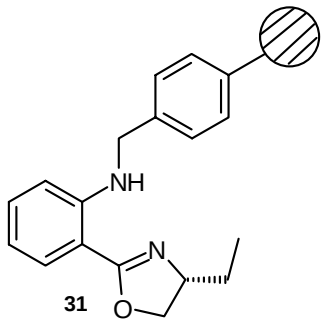
30

IR (nujol): 2922, 2854, 1778, 1725, 1603, 1458, 1374, 1319, 1255 cm^{-1}

Microanalysis: (1 st cycle) Found C 66.97, H 4.86, N 3.33, Cl 12.00 %

(II nd Cycle) Found C 65.33, H 5.50, N 3.98, Cl 11.41 %

Polymer supported amino oxazoline 31: (Scheme 22)



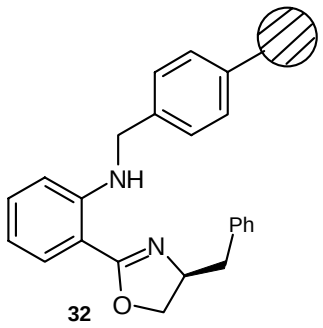
31

A mixture of **30** (0.50 g.; with about 1.6 mmol of isatoic anhydride), D-2-aminobutanol (0.36 g. 4.00 mmol) and kaolinitic clay (0.10 g.; 20 % w/w) was agitated in dry chlorobenzene (3 mL) at 100 ºC for 24 h. The resin beads were isolated and washed with organic solvents [water in THF (50 %, 25 %, 10 % and 0 %) acetone, methanol, dichoromethane] and dried under vacuum. The polymer **31** was characterized by FT-IR and microanalysis.

IR (nujol): 3419, 3212, 2918, 2852, 1621, 1570, 1425, 1322, 1213, 769 cm.$^{-1}$

Microanalysis: Found C 65.12, H 6.50, N 4.50, Cl 8.94 %

Polymer supported amino oxazoline 32:



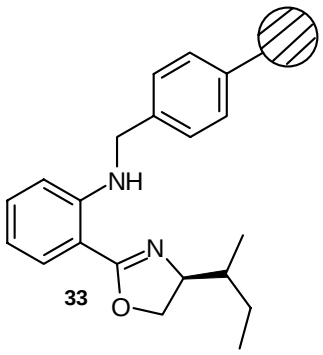
32

Prepared by the same process as for **31** but with L-phenylalaniol as 2-aminoalcohol.

IR (nujol): 3460, 3309, 2955, 2867, 1590, 1495, 1037, 753, 697 cm.$^{-1}$

Microanalysis: Found C 65.31, H 6.78, N 4.47, Cl 9.30 %

Polymer supported amino oxazoline 33:



33

Prepared by the same process as for **31** but with L-isoleucinol as 2-aminoalcohol.

IR (nujol): 3388, 3282, 2918, 2853, 1616, 1500, 1456, 1369, 1218, 742 cm.$^{-1}$

Microanalysis: Found C 69.86, H 7.44, N 5.02, Cl 10.78 %

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CHAPTER 2

Section B

New Polymer Anchored Chiral Amino Oxazolines as Effective Catalysts for Enantioselective Addition of Diethylzinc to Aldehydes

2.2.1 Introduction

Chirality is a major phenomenon in nature and molecular asymmetry in particular is playing a crucial role in science and technology.[1] A variety of biological processes emerging through molecular recognition requires strict matching of chirality. The growing awareness of the importance of chirality in conjunction with biological activity has resulted in a steadily increasing effort being devoted to the development of methods for the synthesis of optically active compounds. Discovery of truly efficient method for obtaining chiral substances is a challenge for the synthetic organic chemist.

Carbon-Carbon bond forming reaction is the backbone of organic synthesis. Important advances that have occurred in recent years are for the formation of C-C bond stereoselectively.[2] The chemists approach involving the use of small amount of catalyst to produce naturally occurring and non-natural optically active compounds in large holds great promise in this area. Over the past decade there has been virtually an explosive growth in the discovery of organic reactions that exert perfect control over bond construction. A multitude of chiral reagents and catalysts are now available that can differentiate the enantiotopic atom, group or face in the achiral molecule and are capable of exercising precise control over stereoselection, once thought to be impossible to achieve *via* non-enzymatic methods.

One of the research directions that hold great influence in this area is the stereoselective addition of nucleophiles to a carbonyl group. It would be a major accomplishment to be able to dictate the direction of the attack of any nucleophile (Nu) to a predefined enantioface exclusively through the agency of a chiral catalyst (**Fig. 1**).

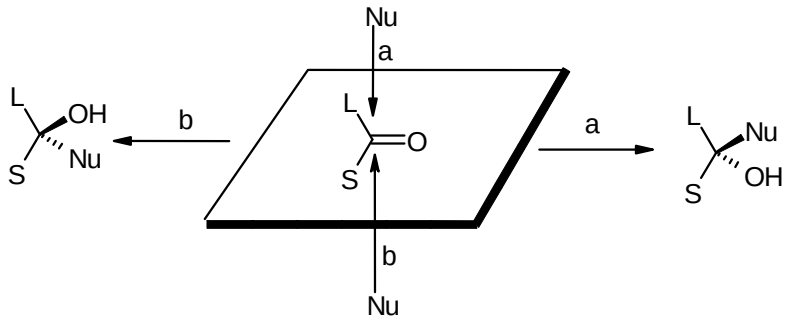


Fig. 1

In these reactions, defined stereochemical outcome can be controlled through the proper chiral auxiliary (stoichiometric) or a chiral catalyst (catalytic). Such reactions whether designed by

keen insight or discovered by serendipity, have provided a new dimension to the art and science of molecular building. Amongst these stereoselective reactions, the addition of organometallic reagents to the aldehydes constitute the most reliable method for the synthesis of hydroxy compounds.[3] The optically active secondary alcohols are components of many naturally occurring compounds, biologically active compounds and materials such as liquid crystals. They are also important as synthetic intermediates of various functionalities such as halide, amine, ester, ether, etc.[4] Two major methods for the enantioselective synthesis of optically active secondary alcohols are the enantioselective alkylation of aldehydes (i.e. addition of organometallic reagents to aldehydes) and enantioselective reduction of ketones. The former reaction can achieve at the same time the formation of optically active alcohols and the construction of carbon skeleton of the alcohol (carbon-carbon bond formation). Even though there have been successful examples of alkylation by organomagnesium or lithium compounds using a stoichiometric or even excess amount of chiral auxiliary; do not meet kinetic requirements of the reaction. In this context, dialkylzinc reagents act as a perfect donor of alkyl group for the catalytic asymmetric synthesis, generating a novel domain of asymmetric catalysis.

As such, diorganozinc compounds are less reactive and do not react with aldehyde to give addition product. This can be attributed to the fact that Zn-Carbon bond can be regarded as occupying two equivalent Sp- hybridized molecular orbitals, resulting in a linear geometry of the molecule **(Fig. 2)**.

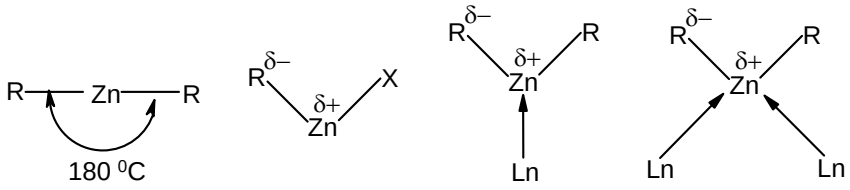
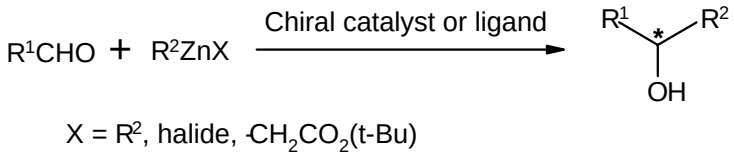


Fig. 2: Reactivity of dialkylzinc reagent

If one of the organic group in a diorganozinc compound is replaced by an electronegative substituent like a halogen atom or by a group bound to zinc via an electronegative atom like oxygen/ nitrogen, both the acceptor character of zinc and the donor character of the zinc bound nucleophiles are enhanced. This formation of coordinatively bent

structure[5] enhances the reactivity of alkyl group towards carbonyl compounds. Initially, the addition of dialkylzinc to aldehydes has rarely been utilized in organic synthesis, because the reaction is extremely sluggish and a side reaction such as reduction usually occurs.

Recently many methods are investigated and further developed for the enhancement of the nucleophilicity of dialkylzinc and related organozinc reagents. Many important optically active compounds have been synthesized using various kinds of chiral compounds as chiral catalysts for enentioselective addition of organozinc reagents to aldehydes (**Scheme 1**).

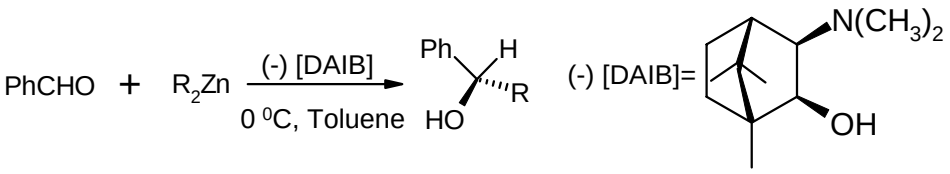


Scheme 1: Enantioselective addition of organozinc to aldehyde

2.2.2 Literature

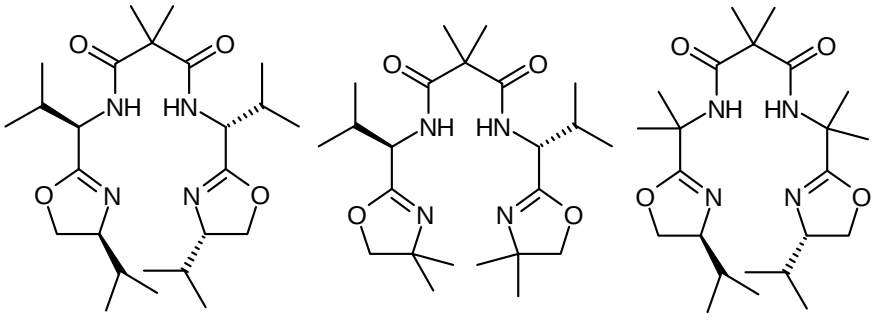
The major finding in the alkylation of aldehydes with diethylzinc was made by Oguni and Omi, who demonstrated[6] the use of 20 mol % *S*-(-) leucinol gave product with 49 % ee and 96 % yield for the reaction with benzaldehyde.

The first highly enantioselective catalytic addition of dialkylzincs to aromatic aldehydes was reported by Noyori et al.[7] (-)-3-exo-(Dimethylamino)isoborneol [**DAIB**] catalyzes the addition reaction of diethylzinc to benzaldehyde to afford (***S***)-1-phenylpropanol with 99% ee in 98% yield **(Scheme 2)**.



Scheme 2: (-)[DAIB] catalyzed enantioselective addition of diethylzinc to aldehyde

This reaction has been extended to a range of alkylating agents and aldehydes. Extensive investigation by Noyori's group[8] led to the elucidation of exact mechanism of the amino alcohol catalyzed alkylation of aldehydes; indicating that, the sterically demanding DAIB auxiliary plays a pivotal role in the effective and selective creation of chiral Zn chelate complexes. Several amino alcohol based chiral ligands were investigated and studied for this reaction thereafter, and reviewed recently.[9a] In most of the cases, the results of the catalysts



3a **3b** **3c**

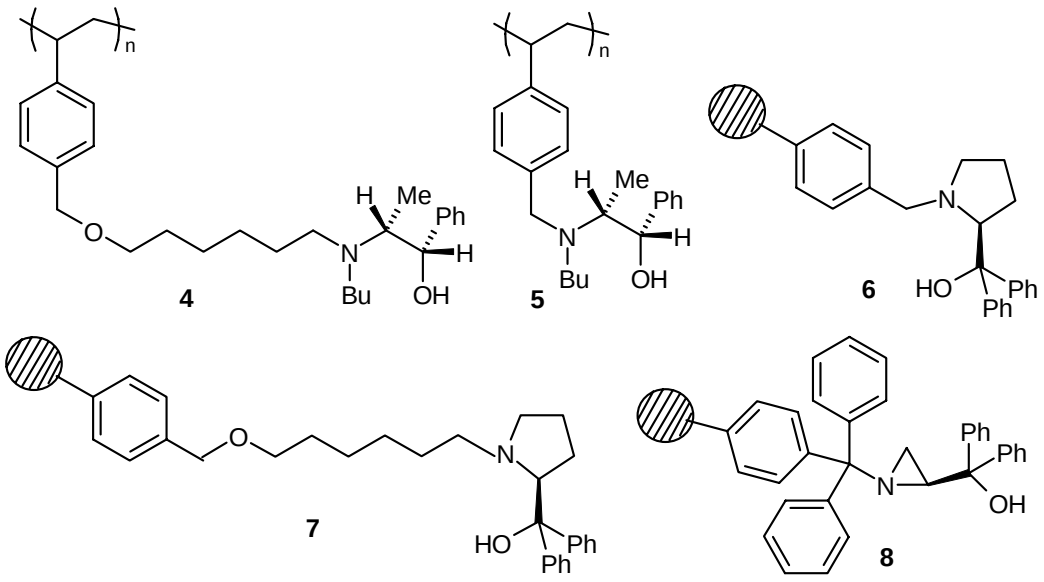
with enantioselectivity over 90% ee are obtained. The catalytic asymmetric reactions of various zinc reagents including alkyl-, alkenyl-, and alkynylzincs with carbonyls, mostly aldehydes are studied.

The oxazoline ligands **3a**, **3b** and **3c** were employed[9b] in the titanium-catalyzed addition of diethylzinc to benzaldehyde, and depending on conditions used, moderate to high enantioselectivities (73, 89, 25 % ee and 93, 83, 18 % yield respectively) of the formed 1-phenylpropanol were obtained.

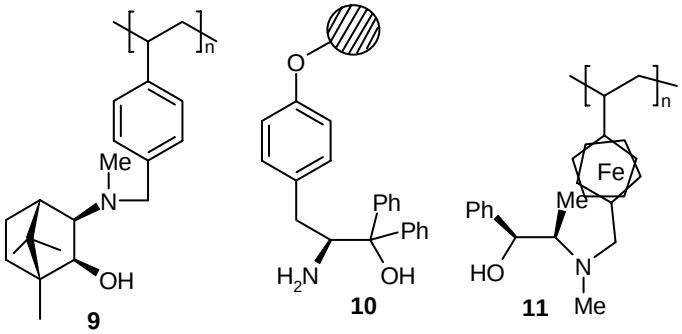
Macromolecule-based chiral catalysts and catalysis on inorganic supports are also investigated. Tedious preparation and high expenses of chiral ligands limit their use on large scale especially for the reactions to be carried out in reactors.[9c] In order to solve problems associated with the separation of the catalyst from the reaction products and to allow recovery and reuse of the expensive ligands or metal complexes, a wide range of methods to anchor the homogeneous ligands to various supports have been explored.[10]

Pioneering work in this field was done by Merrifield[11] on 'solid phase' peptide synthesis, which induced the study of a wide range of synthetic organic reactions. These reactions exhibit well-documented advantages over the homogeneous systems.[12] They are found to be very attractive because not every site needs to react, low loadings are often acceptable, they do not contaminate the product solution, they are odorless, amenable to large scale synthesis, are non-toxic and the crosslinked polymeric species is often available for immediate reuse.[13] At the same time such methods facilitate more efficient reaction design, including use of combinatorial methods and high-throughput screening.

Fréchet, Itsuno and Soai pioneered the use of polymer-anchored chiral catalysts for the asymmetric organozinc addition to aldehydes.[4, 14, 15] In most cases the enantioselectivity of the polymer supported catalysts was lower than the corresponding monomer catalyst. Recently, Watanabe and Soai[14] studied the use of the polystyrene-supported ligands **(fig. 4-7)** for the reaction of diethylzinc with aldehydes. These polymers (**4, 5 and 7**) showed 82%, 89% and 61% ee, respectively for the reaction of diethylzinc with benzaldehyde. For the reaction of aliphatic aldehydes (e.g. nonyl aldehyde), polymer **4** gave the highest enantioselectivity (71% ee) among the amino-alcohol based polymers. Comparatively, polymer **5** gave much lower selectivity (17% ee). The reactions using these polymers were carried out in hexane, which allowed the polymer ligands to be easily recycled by simple filtration, and the recovered polymers showed the same enantioselectivity as the original polymers.



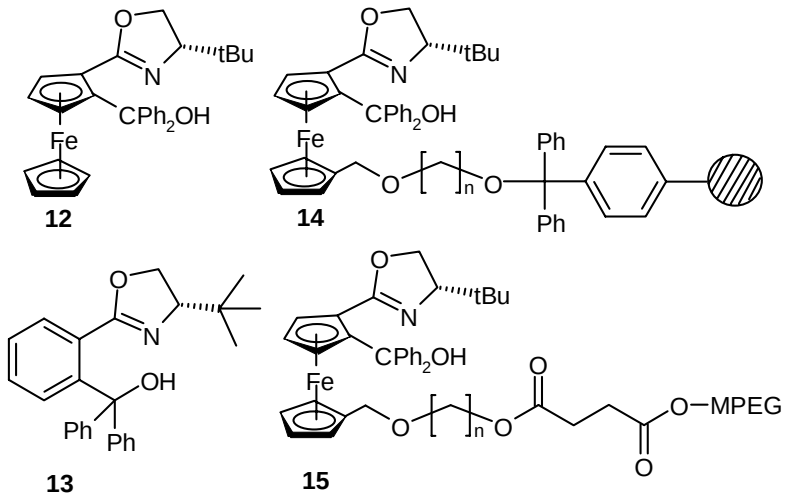
The comparative study of ligands with methylene spacer (**7**) i.e. hexyl group and without methylene spacer (**6**) has been carried out for this reaction. Enantioselectivity obtained by polymer **7** was much higher than that of polymer **6** (61% ee using **7** and 24% ee using **6** for benzaldehyde). The polymer supported *N*-tritylaziridinyldiphenylmethanol **8** was used by Zwanenburg and co-workers[14e] to catalyze the reaction of diethylzinc with aldehydes. The enantioselectivity obtained for benzaldehyde was very high i.e. 96% ee and for cyclohexanecarboxaldehyde is 97% ee at room temperature; whereas the corresponding monomer of **8** gave 99% ee for both the substrates.



Itsuno and Fréchet reported[16] very high enantioselectivity in the addition of diethylzinc to arylaldehydes (up to 99% ee) by utilizing a polymer supported DAIB (**9**) catalyst. The same group has reported that cross linked polymers binding an amino alcohol (**10**)[15a] affords the

products in up to 99% ee. It was proposed that primary amino group of the chiral amino alcohol reacts with the aldehyde to form Schiff base which accelerates the ethylation of aldehydes. Watanabe et al.[17] reported 72% ee for the ethylation of benzaldehyde with diethylzinc catalyzed by a chiral polymer anchored *N*-ferrocenylephedrine (**11**).

Bolm and co-workers[18] demonstrated the use of chiral ferrocenyl oxazoline ligand **12** for diethylzinc addition to benzaldehyde to get 93% ee whereas hydroxy phenyloxazoline **13** gave 92% ee for benzaldehyde under similar conditions for **12** and **13**.

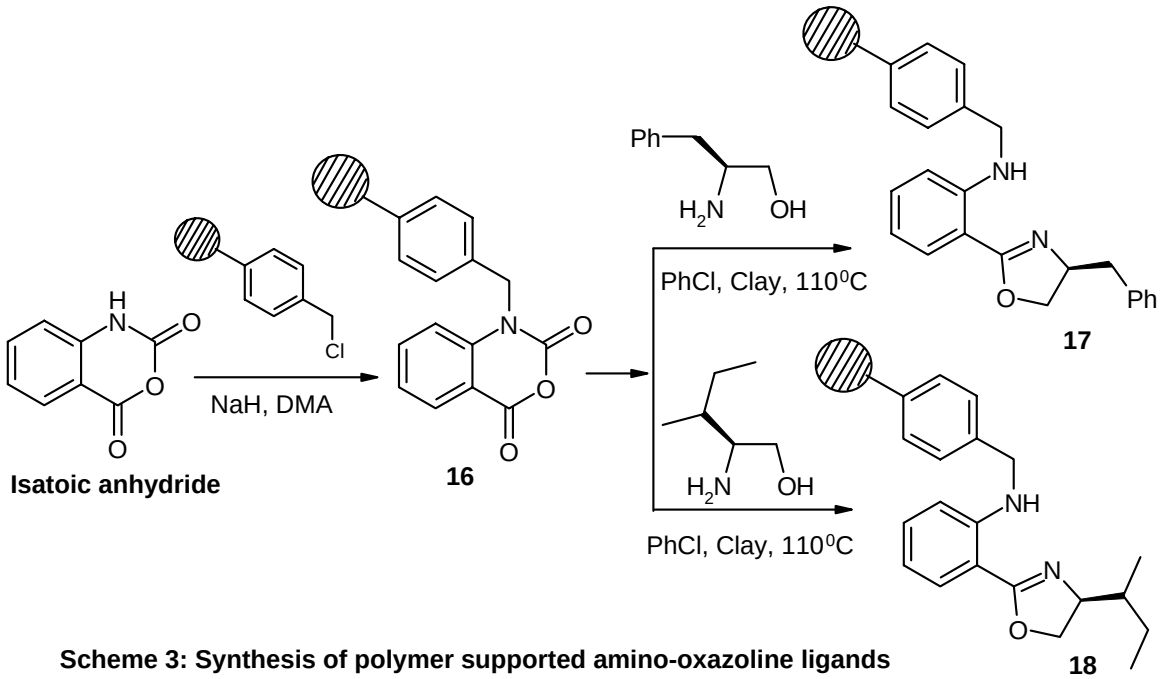


This indicates identical structural organization of **13** as that of **12** during the catalysis. After the successful utilization of these homogeneous oxazoline ligands the same group prepared supported ferrocenyl oxazoline for enantioselective phenyl transfer to aldehyde. For including both soluble and insoluble supports, applying commercially available polyethyleneglycol monomethyl ether [MeO-PEG-OH (MPEG); MW= 5000] and a trityl chloride resin, respectively. For phenyl transfer reaction racemic product was obtained using resin **14**; however soluble polymer **15** gave 97% ee for the similar reaction. For diethylzinc addition to *p*-chlorobenzaldehyde **14** gave 87% ee and **15** gave 86% ee. The homogeneous counterpart **12** gave 93% ee for the same reaction.

2.2.3 Present work

Several types of oxazoline-containing ligands have proven to serve as highly versatile ligands in asymmetric metal catalysis.[19, 20] The oxazoline containing ligands are characterized by their ability to coordinate to a large number of metal ions in different oxidation states, yielding rigid metal complexes with well defined conformational spaces.

The chelation of diethylzinc with ligands is crucial to increase its nucleophilicity and, hence, reactivity towards aldehydes. The chiral environment of ligand is responsible for determining the stereochemical outcome of the addition reaction. Few examples of chiral hydroxy oxazolines have been used as ligands in this reaction but we believe that amino oxazolines could be better chelates due to higher nucleophilicity of amino group compared to alcohols. This enhanced chelation ability may help overcome the problem of low reactivity of heterogeneous polymer-supported chiral ligands. With this concept we have prepared a new type of polymer-anchored oxazolines starting from commercially available isatoic anhydride. The polymer supported isatoic anhydride **16** was exposed to chiral amino alcohol in the presence of acidic clay to furnish polymer anchored amino oxazolines.[21] We have prepared two catalysts, (**Scheme 3**) **17** with (*S*)-(-)-2-amino-3-phenyl-1-propanol and **18** with (*S*)-(+)-isoleucinol as amino alcohol .(*As described in chapter 2 section A*)



Scheme 3: Synthesis of polymer supported amino-oxazoline ligands

2.2.4 Results and discussion

The catalytic activity of these polymer-supported amino oxazolines was first studied using standard reaction of diethylzinc with benzaldehyde. It is well documented in the literature that solvent and temperature has major influence on the yield as well as enantioselectivity. This reaction was tested in toluene-dichloromethane/ hexane mixture at different temperatures and results are summarized in **Table 1**.

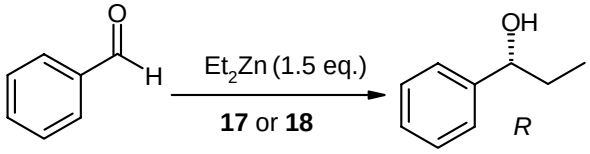


Table 1: Effect of Solvent and temperature on addition of diethylzinc to benzaldehyde employing catalyst **17** or **18**.

Entry	Ligand	Solvent [Temp in ^{o}C]	Isolated yield in %	% ee (Config.)[a]
1	**17**	Toluene-Hexane (1:1) [-78]	46	21 (R)
2	**18**	Toluene-Hexane (1:1) [-78]	52	36 (R)
3	**17**	Toluene-Hexane (1:1) [-10]	60	34 (R)
4	**18**	Toluene-Hexane (1:1) [0]	72	38 (R)
5	**17**	20 % CH_2Cl_2 in Toluene [0]	80	84 (R)
6	**18**	**20 % CH_2Cl_2 in Toluene [0]**	**90**	**89 (R)**
7	**17**	20 % CH_2Cl_2 in Toluene [30]	74	24 (R)
8	**18**	20 % CH_2Cl_2 in Toluene [30]	75	50 (R)
9	**18**	Toluene [0]	81	84 (R)

a: The optical purity and configuration was determined by comparison of specific rotation with reported values and HPLC analysis using *R,R*-Whelk-*O*1 column.

Toluene and hexane (1:1) mixture at -78 ^{0}C gave poor yields and low enantioselectivity of 1-phenyl propanol as a product (entry **1**) with *R* configuration. Further increase in temperature shows improvement in yield as well as enantioselectivity for both the ligands **17** and **18**. The catalyst **18** was marginally more selective compared to **17** in each set of reaction. When the hexane was replaced by dichloromethane under similar reaction conditions yield

enhanced from 72 to 90% and ee from 38 to 89% (entry **4** and **6**) indicating the great influence of solvent. The presence of dichloromethane helps the swelling of polymer essential for the satisfactory accessibility of ligand by substrate.[9b] The yield and enantioselectivity decreased when reaction temperature was increased to 30 ^{0}C (entry **7** and **8**). THF was found to be unsuitable for this reaction giving very sluggish reaction mixture, while mixture of 20 % dichloromethane in toluene at 0 ^{0}C was found optimum; however reaction time was not optimized (24 h.).

The reaction was then extended to a variety of substituted aldehydes which were smoothly alkylated in moderate to high enantioselectivity (43-90%) as shown in **table 2**.

Table 2: Enantioselective addition of diethylzinc to aromatic aldehydes using polymer supported catalyst 18.

Entry	Aldehyde	Isolated yield in %	% ee[a] (config.)[b]
1	*p*-chlorobenzaldehyde	92	83 (R)[c, 11a]
2	*p*-methoxybenzaldehyde	86	68 (R)[11a]
3	*o*-methoxybenzaldehyde	70	43 (R)[11b]
4	*trans*-cinnamaldehyde	75	53 (R)[11c]
5	*p*-*N*,*N*-dimethylaminobenzaldehyde	87	76 (R)[11d]
6	9-anthraldehyde	90	84 (R)[d, 11e]
7	**3,4,5-trimethoxybenzaldehyde**	**86**	**90 (R)**[d,11e]
8	nonyl aldehyde	68	52 (R)[a, 11f]

a: The optical purity determined by comparison of specific rotation with reported values. b: Literature reference for optical rotation. c: HPLC analysis using *R*,*R*-Whelk-*O*1 column. d: HPLC analysis using chiralcel OD column.

Both *p*-chloro and *p*-methoxy benzaldehyde were ethylated using 1.5 eq. diethylzinc to give 83 % and 68 % ee with high yield (92 and 86% respectively). Unlike in other cases *o*-methoxybenzaldehyde gave good yield (70 %) but low ee (43%). The secondary alcohols were obtained with *R* configuration at the newly formed chiral center in each case. It is worthwhile to note that the other types of aldehydes such as allylic and aliphatic ones were also

successfully ethylated using **18** as catalyst. Each class is represented by example of *trans*-cinnamaldehyde (**entry 4, table 2**) and nonyl aldehyde (**entry 8, table 2**) which gave products in moderate yield and enantioselectivity (53 and 52% ee respectively). Electron rich arene i.e. 3,4,5-trimethoxy benzaldehyde gave highest ee of 90% with 86% yield (**entry 7**) among all the aldehydes studied for this reaction using polymer **18**.

Polymeric ligand was separated by filtration. The recovered catalyst was washed with different solvents (THF, methanol, acetone, and dichroromethane) dried at 45 ^{0}C under vacuum (at 0.5 mm) for 4 h. and recycled for successive reactions with very little loss of activity (**Table 3**).

Table 3: Enantioselective addition of diethylzinc to benzaldehyde using recycled polymer-supported catalyst **18**.

Cycle	Isolated yield in %	% ee[a]
1	90	89
2	86	84
3	87	85

a: The reactions were performed with conditions similar to **entry-6**, **Table-1**. The optical purity was determined by HPLC analysis using *R*,*R*-Whelk-O column.

The catalytic activity of new polymer anchored ligand **18** in successive reactions was investigated by performing the three cycles of reaction of addition of diethylzinc to benzaldehyde. It can be confirmed from results in **table 3** that the catalyst **18** survives the reaction condition, work-up procedure and retains its activity. The FT-IR spectra recorded for ligand **18** after third cycle is identical to those obtained for freshly prepared ligand **18** indicating no change in the anchored moiety.

2.2.5 Conclusion

Thus the applications[22] of a new type of polymer-supported chiral amino oxazoline for catalytic asymmetric addition of diethylzinc to aromatic aldehydes has been demonstrated, without any additive, which work fairly well with aliphatic and allylic ones. This easily accessible catalyst was effectively recycled for successive set of reactions, which is prerequisite for usefulness of this type of heterogeneous asymmetric catalysis.

2.2.6 Experimental:

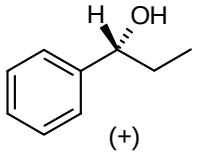
Enanatiomeric excess was determined either by Chiralcel OD or (*R*, *R*)-Whelk-O1: Lichrocart® 250-4 chiral column with bonded chiral selector (3R, 4R)-4-(3,5-dinitrobenzamido)-1,2,3,4-tetrahydrophenanthrene (5μm); sample eluted with hexane/ 2-propanol= 9.7: 0.3, with flow rate 0.9mL/min. unless otherwise stated. HPLC analysis was performed on a *Shimadzu LC-10A* equipped with SPD-10A UV-VIS detector using special grade solvents. Optical rotations were measured on a Jasco DIP-181 digital polarimeter. Absolute configuration was assigned by comparison with the sign of reported value.

(*Ligands **17** and **18** are prepared by the procedure described in **chapter 2, section A***)

Enantioselective addition of diethylzinc to benzaldehyde using polymer-supported catalyst 18.

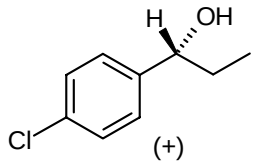
A suspension of polymer **18** (110 mg; 0.175 mmol/g) in a mixture of dry toluene (12 mL) and dichoromethane (3 mL) was allowed to stir slowly at ambient temperature for 4 h to allow the polymer to swell. This mixture was cooled to 0 °C and diethylzinc (15 mL of 1 M solution in hexane, 15 mmol) was slowly added over 15 minutes. This was followed by addition of benzaldehyde (1.06 g, 10.0 mmol) and stirred for 24 h at 0 °C. The reaction mixture was quenched with water and the resin was removed by filtration. The resin was washed with dichloromethane (3X10 mL) while the aqueous layer was extracted with same solvent (3X25 mL). The combined organic layer was dried over dry sodium sulphate, concentrated and products were purified by column chromatography to get colorless liquid. Alcohol was further purified by bulb-to-bulb distillation for optical rotation. Isolated alcohols were characterized by usual spectral analysis while the optical purity was determined by chiral phase HPLC analysis and recording specific rotation. The recovered catalyst was washed with different solvents (THF, methanol, acetone, and dichroromethane) dried and recycled for successive reactions with negligible loss of activity.

(*R*)-1-Phenyl-propanol: (Table 1)



Appearance:	Colorless liquid
B. p.:	94-96 °C/ 8 mm, [Lit 150 °C/ 20 mm]
IR (neat)	3372, 3028, 2965, 2874, 1453, 1330, 1095, 974, 764 cm^{-1}
^{1}H NMR (200MHz, $CDCl_3$)**:**	δ 7.60-7.24 (m, 5H), 4.57 (t, J= 6.5Hz, 1H), 2.23 (br, s, 1H), 1.90-1.65 (m, 2H), 0.92 (t, J= 7.4Hz, 3H)
^{13}C NMR (75MHz, $CDCl_3$)	δ 144.57, 128.21, 127.3, 125.89, 75.81, 31.71, 9.92
Mass m/z (%)**:**	136 (M^+, 90), 107(100), 91 (10), 79 (90), 57 (10).
Microanalysis:	Calculated for $C_9H_{12}O$: C, 79.41; H, 8.82; Found: C, 79.23; H, 8.57.
Optical rotation $[\alpha]_D^{24}$	+40.56 (4.65, $CHCl_3$); [Lit. +32.1(4.6, $CHCl_3$)[23] in 71%ee for *R*-isomer].
Retention time (t_R min)	10.25 min for *S* isomer (minor) and 11.30 min for *R* isomer (major) with ee 89.1%
Enantiomeric excess (ee%)	89.1

(*R*)-1-(4-Chlorophenyl)-1-propanol: (Table 2, entry 1)

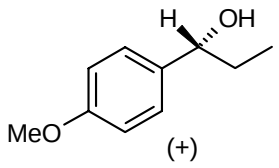


Appearance:	Colorless liquid
^{1}H NMR (200MHz, $CDCl_3$)**:**	δ 7.30 (d, J= 8.3Hz, 2H), 7.25 (d, J= 8.3Hz, 2H), 4.55 (t, J= 6.4Hz, 1H), 2.41 (br, s, 1H), 1.81-1.65 (m, 2H), 0.89 (t, J= 7.4Hz, 3H)
Microanalysis:	Calculated for $C_9H_{11}ClO$: C, 63.36; H, 6.45; Cl, 20.80; Found: C, 63.57; H, 6.78; Cl, 20.54.
Optical rotation $[\alpha]_D^{24}$	+20.2 (5, benzene); [Lit. -25.00(5, benzene)[24a] in 100%ee for *S*-isomer].
Retention time (t_R min)	14.13 min for *S*-isomer (minor) and 18.17 min for *R*-isomer

(major) with ee 82.7%.

Enantiomeric excess (ee%) 82.7

1-(4-methoxyphenyl)propan-1-ol: (Table 2, entry 2)



Appearance: Colorless oil

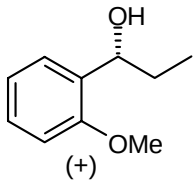
^{1}H NMR (200MHz, $CDCl_3$)**:** δ 7.33-7.18 (m, 2H), 6.98-6.67 (m, 2H), 4.53 (t, J= 6.6Hz, 1H), 3.80 (s, 3H), 1.98-1.62 (m, 3H), 0.92 (t, J= 7.3 Hz, 3H).

Microanalysis: Calculated for $C_{10}H_{14}O_2$: C, 72.29; H, 8.43;
Found: C, 72.47; H, 8.72.

Optical rotation $[\alpha]_D^{24}$ +22.37 (3, benzene); [Lit. -32.25(3, benzene)[24a] in 98%ee for *S*-isomer.].

Enantiomeric excess (ee%) 67.97

1-(2-methoxyphenyl)propan-1-ol: (Table 2, entry 3)



Appearance: Colorless oil

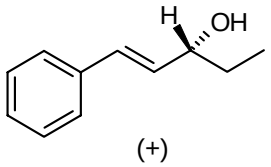
^{1}H NMR (200MHz, $CDCl_3$)**:** δ 7.35-7.21 (m, 2H), 7.00-6.85 (m, 2H), 4.80 (m, 1H), 3.85 (s, 3H), 2.52 (br, s, 1H), 1.79-1.82 (m, 2H), 0.93 (t, J= 7.6 Hz, 3H).

Microanalysis: Calculated for $C_{10}H_{14}O_2$: C, 72.29; H, 8.43;
Found: C, 72.39; H, 8.65.

Optical rotation $[\alpha]_D^{24}$: +23.5 (1.2, toluene); [Lit. +47.0(1.2, toluene)[24b] in 87%ee for *R*-isomer.].

Enantiomeric excess (ee%) 43.5

1-Phenyl-1-penten-3-ol: (Table 2, entry 4)



(+)

Appearance: Colorless oil

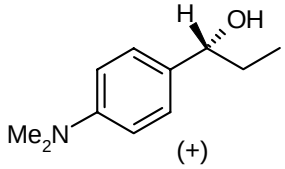
^{1}H NMR (200MHz, $CDCl_3$)**:** δ 7.61-7.17 (m, 5H), 6.80 (d, J= 16 Hz, 1H), 6.25 (dd, J= 6.9 Hz, 1H), 4.23 (m, 2H), 1.85-1.22 (m, 3H), 1.00 (t, J= 7.4 Hz, 3H).

Microanalysis: Calculated for $C_{11}H_{14}O$: C, 81.48; H, 8.64;
Found: C, 81.71; H, 8.38.

Optical rotation $[\alpha]_D^{24}$: +4.66 (3.10, $CHCl_3$); [Lit. -6.6 (3.18, $CHCl_3$)[24c] in 75%ee for *S*-isomer].

Enantiomeric excess (ee%) 52.95

1-(4-*N*,*N*-dimethylaminophenyl)propan-1-ol: (Table 2, entry 5)



(+)

Appearance: Yellow oil

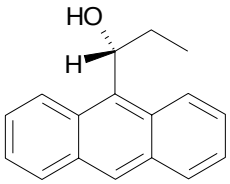
^{1}H NMR (200MHz, $CDCl_3$)**:** δ 7.27 (d, J= 8.6 Hz, 2H), 6.72 (d, J= 8.6 Hz, 2H), 4.51 (t, 6.6 Hz, 1H), 2.93 (s, 6H), 1.97-1.60 (m, 2H), 0.94 (t, J= 7.4 Hz, 3H)

Microanalysis: Calculated for $C_{11}H_{17}NO$: C, 73.74; H, 9.56; N, 7.82 %
Found: C, 73.45; H, 9.38; N, 7.56 %

Optical rotation $[\alpha]_D^{24}$: +25.2 (2, benzene); [Lit. +31.3 (2.2, benzene)[24d] in 94.9%ee for *R*-isomer].

Enantiomeric excess (ee%) 76.4

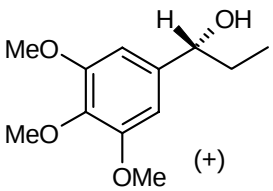
(R)-(+)-1-(9-phenanthryl)propan-1-ol: (Table 2, entry 6)



(+)

Appearance:	White solid
M. p.:	82-84 °C
IR (nujol)	3439, 3052, 3014, 2970, 2875, 1672, 1215, 1017, 966, 763, 668 cm^{-1}
^{1}H NMR (200MHz, $CDCl_3$)**:**	δ 8.75-8.25 (m, 3H), 8.11-7.76 (m, 2H), 7.6-7.21 (m, 4H), 5.97 (t, J= 7.3Hz, 1H), 2.89 (br, s, 1H), 2.45-2.05 (m, 2H), 0.93 (t, J= 7.3Hz, 3H).
^{13}C NMR (75MHz, $CDCl_3$)	δ 134.76, 131.45, 129.1, 129.06, 127.7, 125.16, 124.82, 124.50, 72.16, 30.48, 11.07.
Mass m/z (%) 70eV**:**	236 (M^+, 5), 207 (10), 178 (12), 152 (4), 83 (100), 57 (8).
Microanalysis:	Calculated for $C_{17}H_{16}O$: C, 86.40; H, 6.82; found: C, 86.74; H, 6.98.
Optical rotation $[\alpha]_D^{24}$:	+7.94 (1.63, $CHCl_3$); [Lit. -7.46(1.6, $CHCl_3$)[24e] in 78%ee for *S*-isomer].
Retention time (t_R min):	12.37 min for *R*-isomer (major) and 15.27 min for *S*-isomer (minor).
Enantiomeric excess (ee%)	84.

1-(3,4,5-Trimethoxyphenyl)propan-1-ol: (Table 2, entry 7)



(+)

Appearance:	Colorless liquid
IR (nujol)	3439, 3052, 3014, 2970, 2875, 1672, 1215, 1017, 966, 763,

668 cm^{-1}

^{1}H NMR (200MHz, $CDCl_3$)**:** δ 6.57 (s, 2H), 4.53 (t, J= 6.5Hz, 1H), 3.86 (s, 6H), 3.84 (s, 3H), 2.08 (br, s, 1H), 1.60-1.90 (m, 2H), 0.94 (t, J= 7.4Hz, 3H)

^{13}C NMR (75MHz, $CDCl_3$) δ

Mass m/z (%)**:** 226 (M^+, 80), 197 (100), 181 (5), 169 (70), 138 (40), 95 (25), 84 (50), 77 (15), 66 (18).

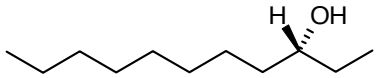
Microanalysis: Calculated for $C_{17}H_{18}O_4$: C, 63.70; H, 8.02; found: C, 63.44; H, 8.28.

Optical rotation $[\alpha]_D^{24}$: +18.98 (1.7, benzene); [Lit. -18.55(1.7, benzene)[24e] in 86%ee for *S*-isomer].

Retention time (t_R min): 15.19 min for *R*-isomer (major) and 16.93 min for *S*-isomer (minor).

Enantiomeric excess (ee%) 89.7

(*R*)-Undecan-3-ol: (Table 2, entry 8)



(+)

Appearance: Colorless liquid

IR (nujol) 3359, 2925, 2855, 2357, 1459 cm^{-1}

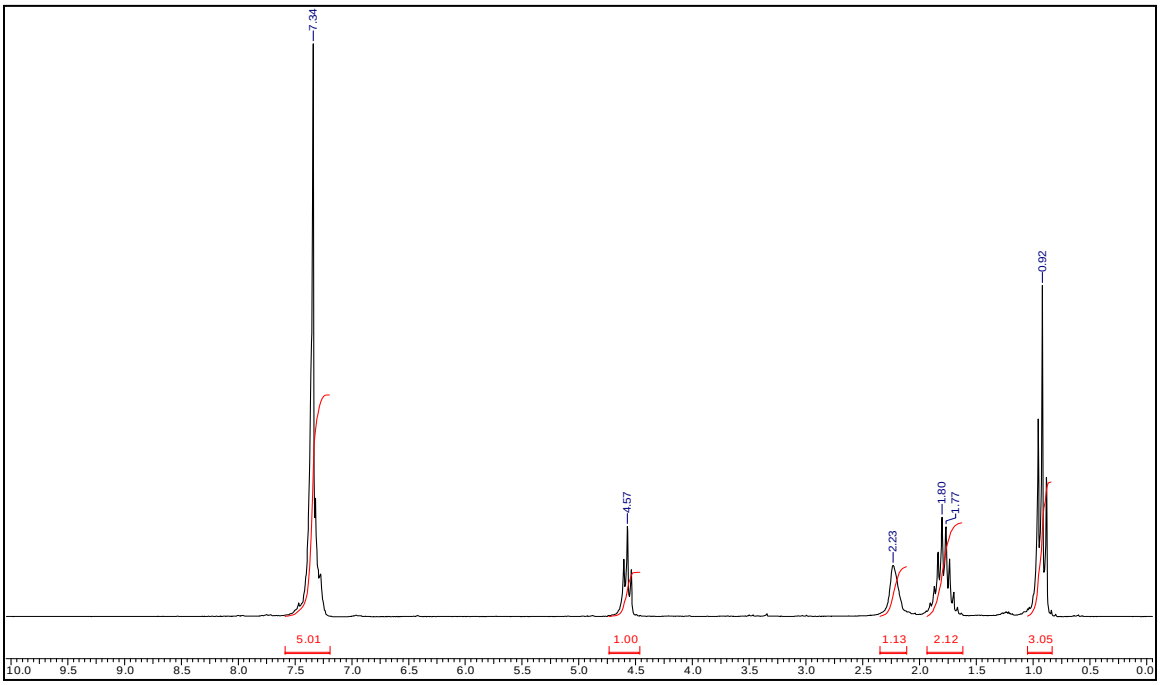
^{1}H NMR (200MHz, $CDCl_3$)**:** δ 2.38 (br, s, 1H). 3.56 (m, 1H), 1.60-1.16 (m, 16H), 0.94 (t, J= , 3H), 0.88 (t, J= , 3H),

Mass m/z (%)**:** 171 (M^+ -1, 5), 154 (7), 143 (10), 97 (5), 83 (15), 69 (50), 59 (100), 55 (60).

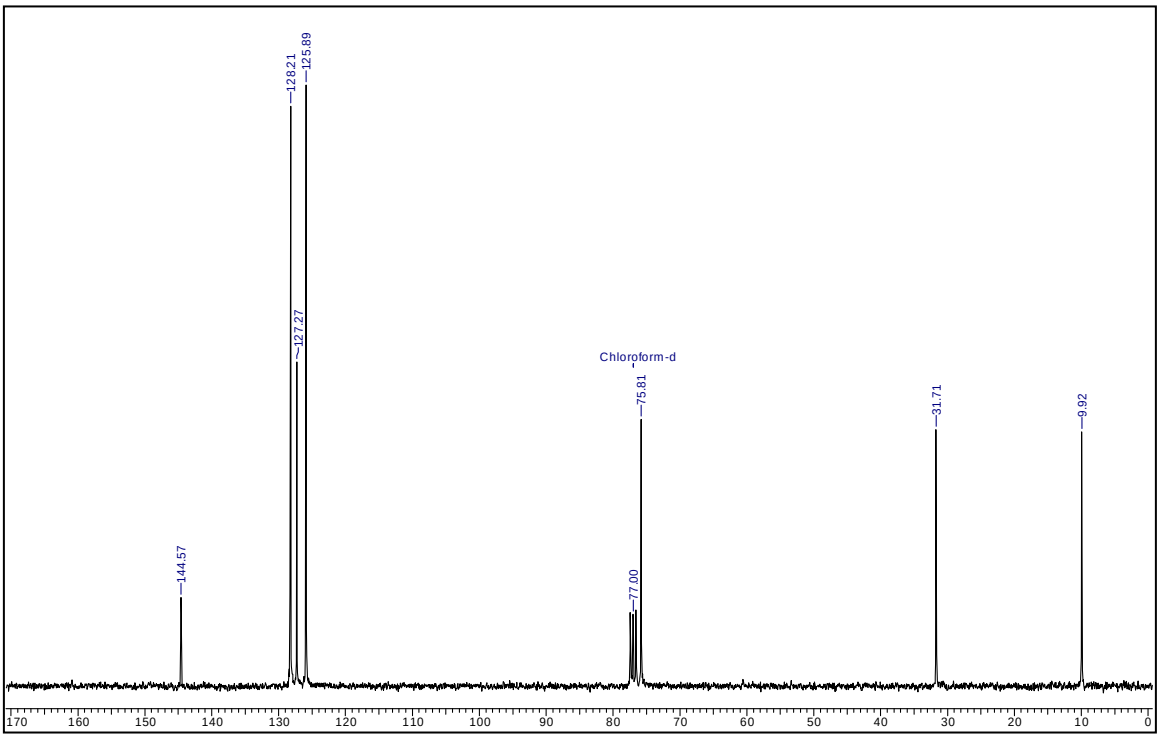
Microanalysis: Calculated for $C_{17}H_{18}O_4$: C, 63.70; H, 8.02; found: C, 63.44; H, 8.28.

Optical rotation $[\alpha]_D^{24}$: - 4.76 (6.13, ethanol); [Lit. +6.22(6.15, ethanol)[24f] in 69 %ee for *S*-isomer].

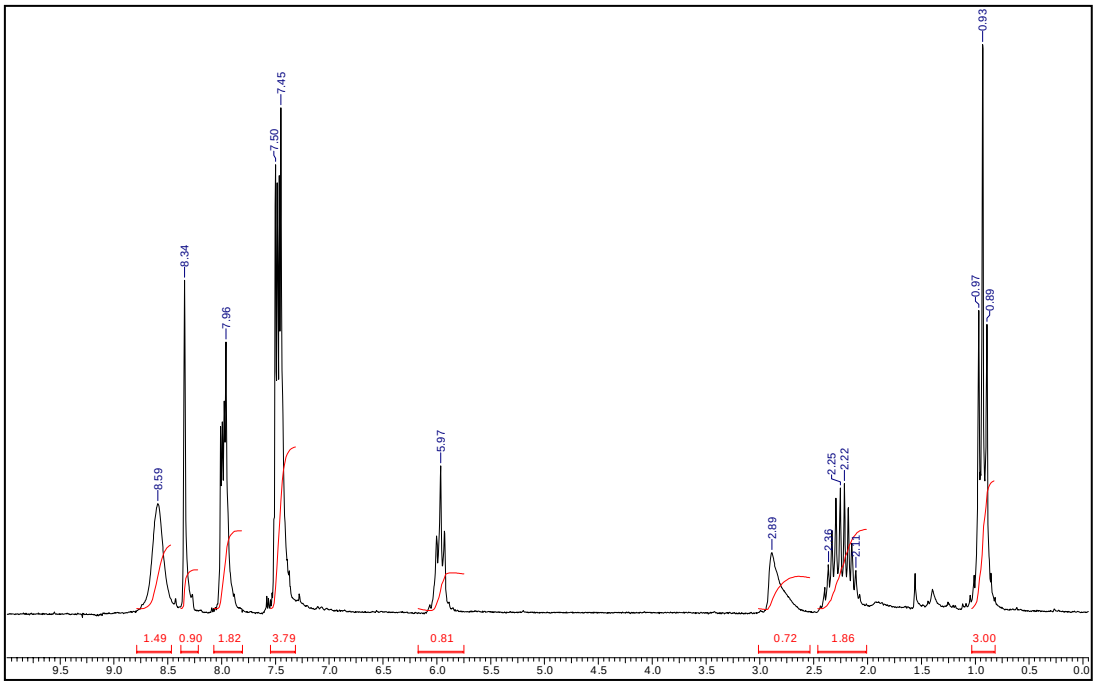
Enantiomeric excess (ee%) 52.



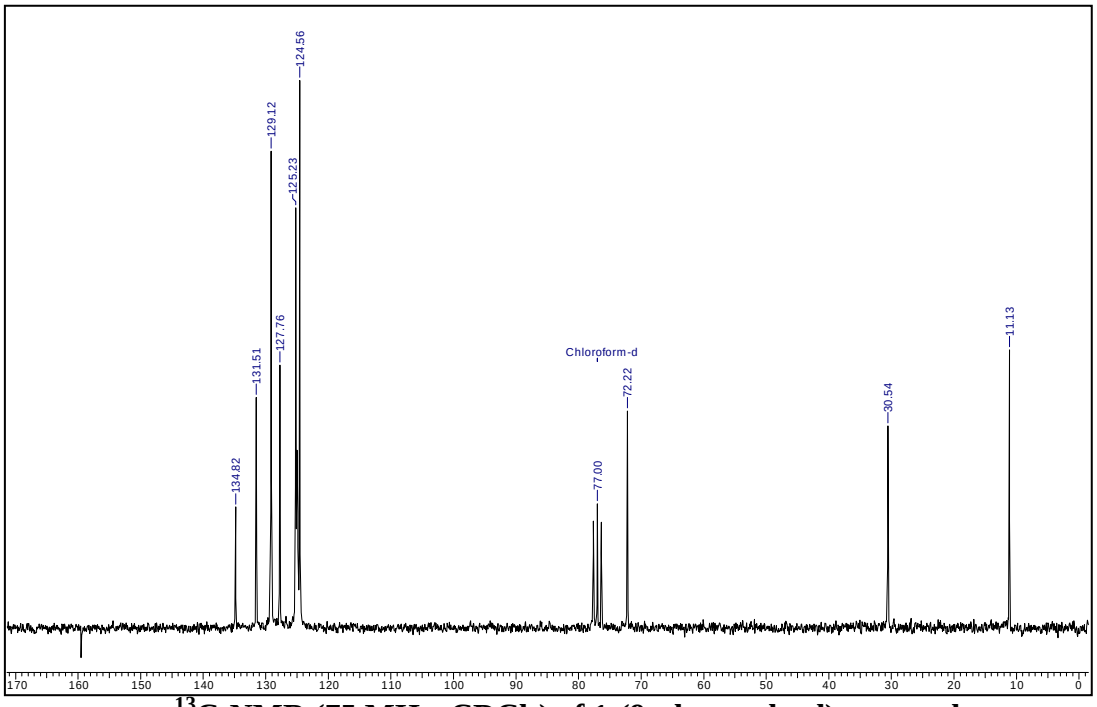
^{1}H-NMR (200 MHz, $CDCl_3$) of 1-Phenyl-propanol



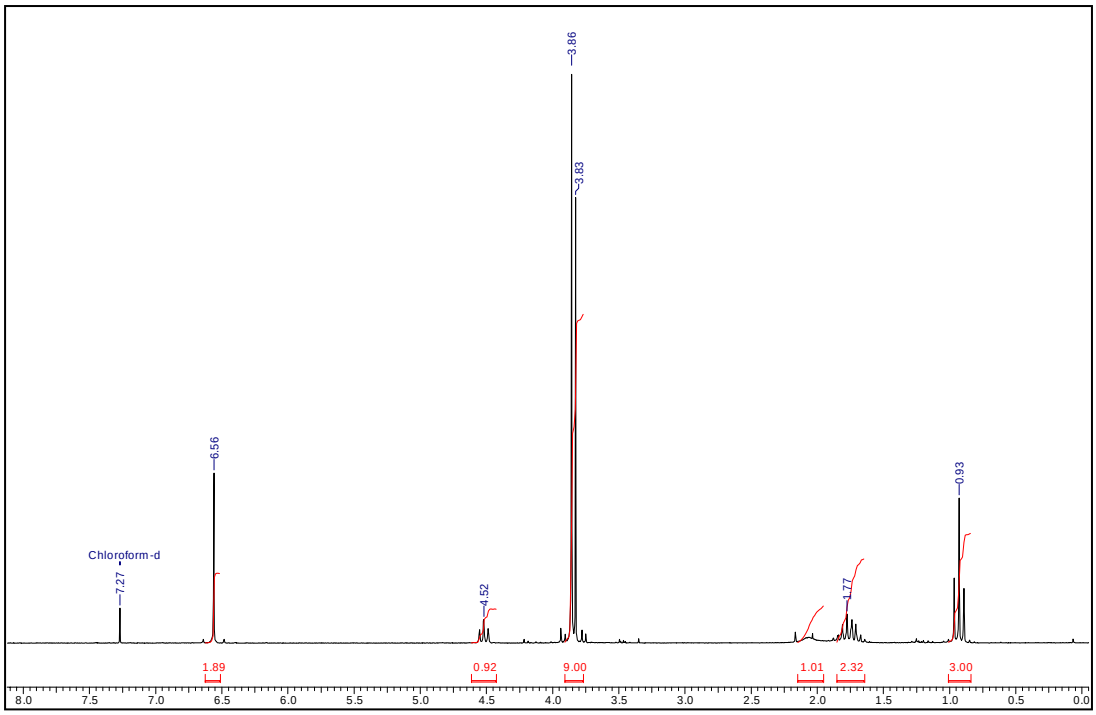
^{13}C-NMR (75 MHz, $CDCl_3$) of 1-Phenyl-propanol



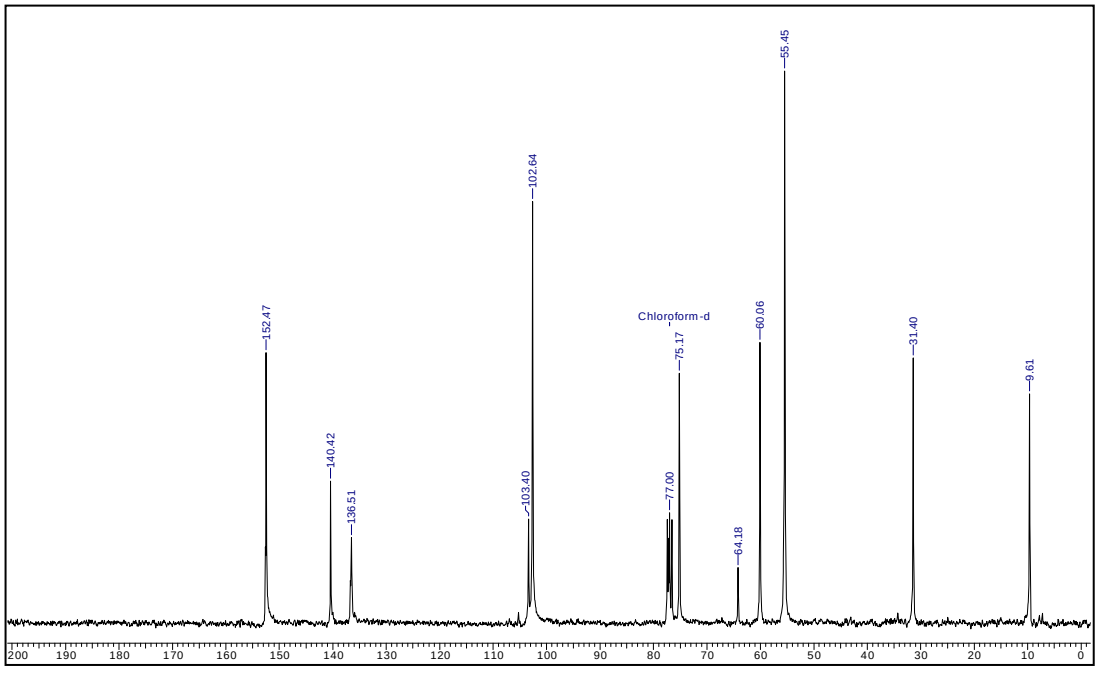
^{1}H-NMR (200 MHz, $CDCl_3$) of 1-(9-phenanthryl)propanol



^{13}C-NMR (75 MHz, $CDCl_3$) of 1-(9-phenanthryl)propanol



^{1}H-NMR (200 MHz, $CDCl_3$) of 1-(3,4,5-Trimethoxyphenyl)propanol



^{13}C-NMR (75 MHz, $CDCl_3$) of 1-(3,4,5-Trimethoxyphenyl)propanol

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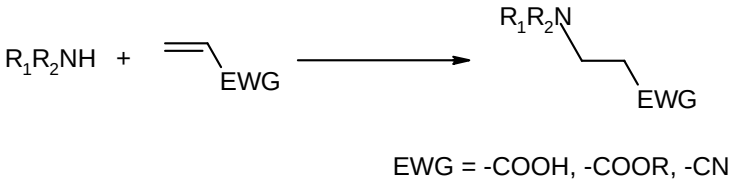
CHAPTER 2

Section C

Michael Type Addition of Aliphatic Amines to *α, β*-Ethylenic Compounds

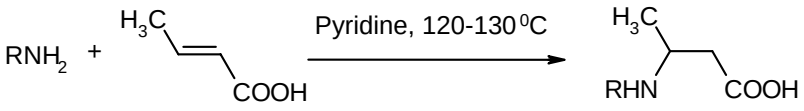
2.3.1 Introduction and literature

Michael additions are inherently atom economic and have therefore been the subject of considerable attention. *β*-Amino acids or esters have achieved premier importance as substructures of numerous biologically active natural products[1] as well as building blocks for *β*-lactum antibiotics.[2] One of the simple approaches (**Scheme 1**) towards *β*-amino derivatives such as *β*-aminoesters is via the Lewis acid- mediated addition of amines to *α,β*-ethylenic compounds.[3] However only simple primary non bulky amines can react with simple unsubstituted acrylic compounds without special activation,[4] in others stronger reaction conditions are required.[5]



Scheme 1: 1, 4-addition of amines to acrylates and nitrile

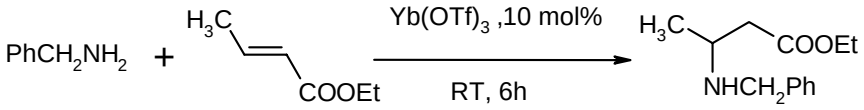
Initially *N*-alkyl derivatives of β-aminobutyric acid were usually prepared in low yield by reduction of the intermediate imino derivative obtained by the reaction of the appropriate amine with ethyl acetoacetate.[6] Some esters of these compounds were prepared by the reaction between amines and ethyl crotonate, which requires a long reaction time and usually gives low yields.[7]



Scheme 2: Synthesis of DL-*β*-Aminobutyric acid and its *N*-alkyl derivative

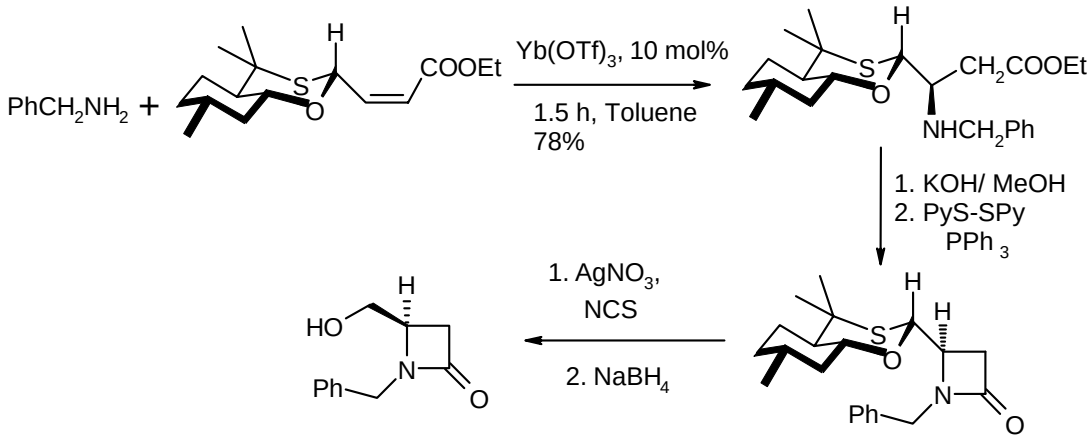
The reaction of amines with crotonic acid in pyridine at 120-130 ^{0}C proceeded according to the **scheme 2**, to give required addition products[8] ranging from 65 to 95 % yield depending upon the amines used (R-group). Less reactive aromatic amines and secondary amines did not interact with double bond. Lewis acid such as $BF_3.OEt_2$ or $TiCl_4$ could not catalyze the conjugate addition of amines to *α,β*-unsaturated esters by preferential complex

formation of amines.[9] It is demonstrated that lanthanoid triflate can catalyze conjugate addition of amines to 2-alkenoic acid esters to give *β*-amino esters (**Scheme 3**).



Scheme 3: Yb(OTf)$_3$ catalyzed addition of amines to *α*,*β*-unsaturated esters

The scope of this reaction was extended for the synthesis of optically active *β*-lactum (**Scheme 4**).[9]

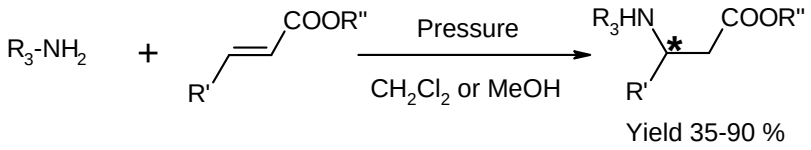


Scheme 4: Yb(OTf)$_3$ Catalyzed conjugate addition of benzylamine for optically active*β*-lactum precursors

The reaction of benzylamine with *α,β*-unsaturated esters containing a stereogenic centre at γ-position proceeded diastereoselectively to yield active *β*-lactum precursor with 78% yield and 76% de.

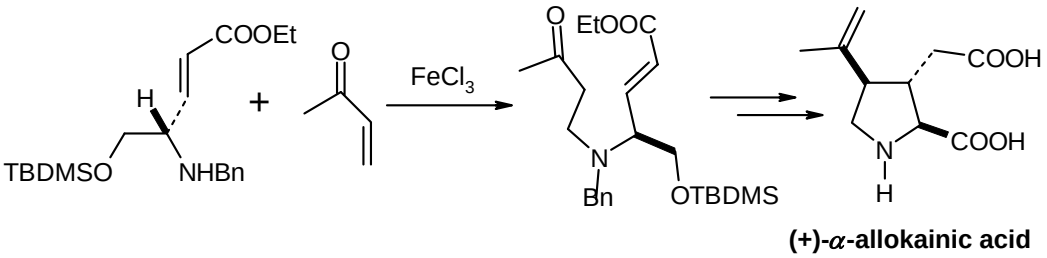
Asymmetric syntheses of *β*-amino acids were achieved by conjugate addition of chiral amines, *R*(+)- and *S*(-)-α-methylbenzylamines to crotonitrile, methyl crotonate, l-methyl crotonate, ethyl cinnamate and methyacrylonitirle. Amines were refluxed in ethanol with crotonates up to 6 hrs. to get the addition products which was further hydrolyzed to acid and deprotected to get free amine with low yields (ranging from 9 to 47 % isolated yields).[10]

Enantioselective synthesis of β-aminoesters through high pressure induced addition of amines to α,β-ethylenic esters has been investigated by Angelo and Maddaluno (**Scheme 5**).[5b] The addition reaction was found to be sluggish under thermal conditions. Use of high pressure i.e. 5-15 Kbar is found to be essential for the activation of double bond for addition of amines.



Scheme 5: High pressure induced addition of amines to α,β -ethylenic esters

A convergent, one pot conversion of functionalized pyrrolidine ring system has been investigated via conjugate addition of a nitrogen nuclophile to an electrophilic olefin during the synthesis of (+)-α-allokainic acid and (-)-kainic acid (**Scheme 6**). It has been observed that, the reaction of methyl vinyl ketone (MVK) with the Michael donor-acceptor γ-amino-α,β-unsaturated ester in ethanol solution proceeded rather slowly (15 days), however $FeCl_3$ enhances the rate of reaction.[11]



Scheme 6: $FeCl_3$ catalyzed Intermolecular Michael addition of amine

Hindered β-aminoesters are obtained in fair to high yields by the conjugate addition of amines to α,β-unsaturated esters, under high pressure in the presence of catalytic amount of ytterbium triflate.[12]

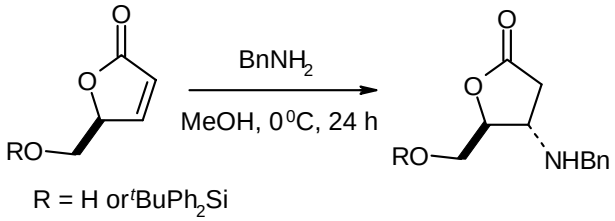
Table 1: High pressure synthesis of β-aminoesters using $Yb(OTf)_3$ as a catalyst (5 mol%)[a]

Entry	Methyl ester	Amine	Temp. (^{0}C)	Pressure (bar)	Yield (%)[b]
1	Acrylate	iPr_2NH	50	3000	80
2	Methacrylate	$tBuNH_2$	30	3000	47
3	Methacrylate	Ph_2CHNH_2	50	9500	100
4	Methacrylate	iPr(Me)NH	50	3000	50
5	Crotonate	iPr(Me)NH	50	3000	61
6	Crotonate	iBuNH	50	3000	47
7	Crotonate	iPr_2NH	50	9500	10
8	3,3-dimethyl acrylate	$iPrNH_2$	50	9500	78
9	3,3-dimethyl acrylate	$tBuNH_2$	50	9500	13

a: Reaction was carried out in acetonitrile for 24 hr., b: Isolated yields

At atmospheric pressure, no or very little reaction takes place in the absence of the ytterbium compound. It has been observed that high pressure is the determining parameter (compare the yields in the catalyzed versus uncatalyzed reactions when pressure is increased from atmospheric to 3 kb).[12] Reaction was found to be unsuccessful when carried out in water at atmospheric pressure using water soluble $Yb(OTf)_3$.

Another important application of the C-N bond forming strategy i.e. conjugate addition of amines has been demonstrated by the addition of benzylamine to (*S*)-5-hydroxymethyl-2(5*H*)-furanone to obtain new aminolactone (**Scheme 7**).[13]

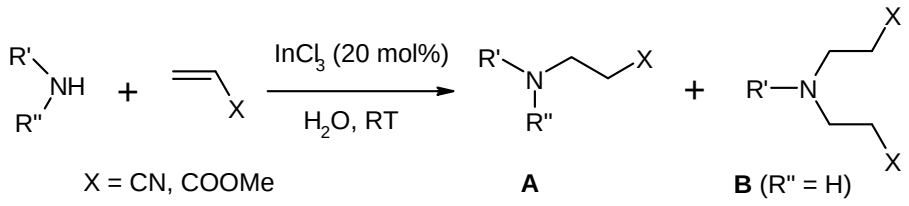


Scheme 7: Diastereoselective synthesis of aminolactone

Reaction of benzylamine with lactone at 0 ^{0}C resulted in poor yield (26%) of required aminolactone, which was further hydrolysed to β-aminoester as a direct precursor of β-lactum.

During the total synthesis of medicinally important alkaloid Manzamine A and D involved the Michael addition of secondary amines to acrolein to get the desired β-amino aldehyde in quantitative yield. The reaction was carried out in THF at -15 ^{0}C using DBU as a catalyst.[14]

The important finding in this area has been done recently by Loh and Wei[15] by using 20 mol% indium (III) trichloride ($InCl_3$) as a Lewis acid catalyst for conjugate addition of amines to α,β-ethylenic compounds in water (**Scheme 8**). A wide variety of primary and secondary amines were reacted with acrylate and acrylnitrile to yield the addition product in moderate to good yields.



Scheme 8: $InCl_3$ catalyzed conjugate addition of amines to α,β -unsaturated compounds

However in case of primary amines additional alkylation is found to be difficult to control hence giving the mixture of products **A** and **B** (**Scheme 8**).

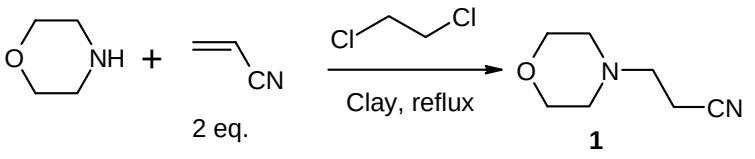
To the best of our knowledge the report by Laszlo[16] with transition metal doped catalysts is the only reference available in the literature for the heterogeneous version of this reaction.

2.3.2 Present work

Scope for the heterogeneous catalytic organic transformations is rapidly growing due to their well documented, advantages over the homogeneous catalytic systems. Clays have emerged as ideal acidic heterogeneous catalysts as they are abundantly available in nature making them inexpensive. These clays have Bronsted as well as Lewis acidic sites and thus increase their utility in both kinds of catalytic applications.

As discussed in the introduction the importance of conjugate addition of amines to activated double bonds for C-N bond formation in synthetic organic chemistry suggested us to develop a mild and efficient protocol. Clay catalyzed nucleophilic addition of amines to carbonyl has been demonstrated in previous section (Chapter 2, section A) for the preparation of oxazolines. Success of Lewis acid catalyzed organic reactions using clay encouraged us to apply clay as a catalyst in this transformation.

Hence effectiveness of clays to catalyze this conversion was tested for the reaction of morpholine and acrylonitrile (**Scheme 9**).



Scheme 9

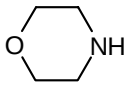
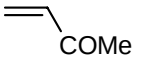
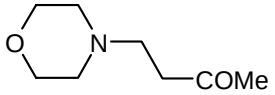
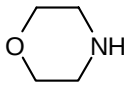
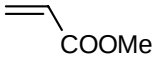
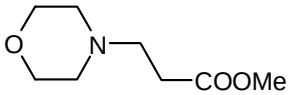
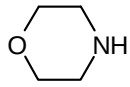
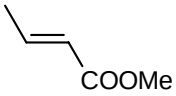
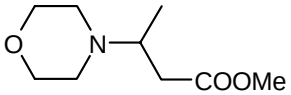
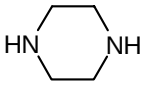
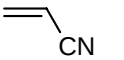
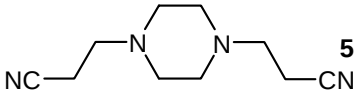
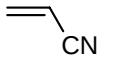
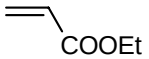
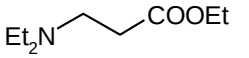
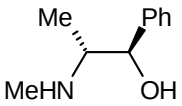
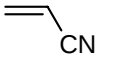
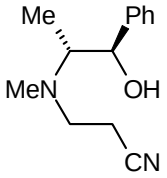
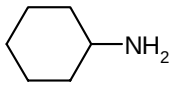
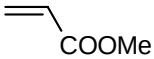
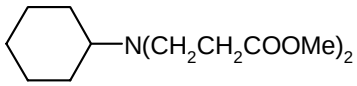
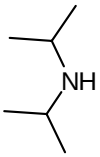
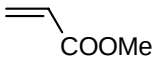
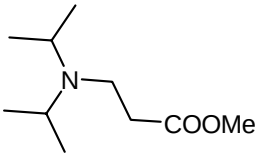
Catalyst	Yield
Natural KC	82
Mont K10	80
No Catalyst	20

To our satisfaction the addition product was obtained in high yield in very short reaction time (3 h.). Initially morpholine was treated with 1.3 equivalent of acrylonitrile in dichloroethane in presence of 20% (w/w) natural kaolinitic clay to obtain 62 % of 1, 4 addition product after purification. By using 2 equivalent of acrylonitrile gave improved result (82 %). Similar effect of commercially available Montmorillonite K10 clay has been observed. Reaction gave very poor yield (20 %) even after longer duration (12 h) without catalyst. The clay was recovered after the reaction and reused three times for the same reaction (**Scheme 9**) to obtain similar results.

2.3.3 Results and discussion

Different aliphatic amines and α,β-ethylenic compounds were studied as substrates for this transformation which were catalyzed equally well with either kaolinitic clay or commercially available Montmorillonite K10 and the results are presented in **Table 2**.

Table 2: Clay Catalyzed Michael Addition of Amines toα,β -Ethylenic Compounds

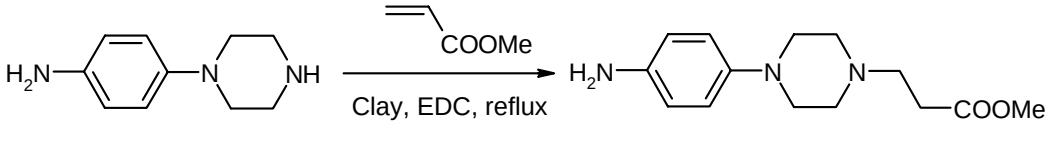
Entry	Amines	Michael acceptor	Time (h.)	Product		Yield (%)[a]
1			3		**2**	88
2			3		**3**	91
3			3		**4**	90 38[b]
4			6		**5**	76
5	$HO(CH_2)_3NH_2$		3	$HO(CH_2)_3N(CH_2CH_2CN)_2$	**6**	85
6	Et_2NH		3		**7**	83
7			6		**8**	86
8			6		**9**	68 25[b]
9			6		**10**	80 15[b]

a: Isolated yields, All the reactions were carried out in refluxing 1,2-dichloroethan using clay catalyst (20 % w/w) with 2 eq. (entry 1-3,6 and 7) and 3.5 eq. ethylenic component (entry 4,5 and 8). b: Reaction was carried out without catalyst.

Different Michael acceptors such as acrylonitrile, MVK (methyl vinyl ketone), methyl crotonate, methyl acrylate and ethyl acrylate were used for the addition of primary and secondary amines to get good to excellent yields. Morpholine with MVK reacted within 3 h. to give required addition product in excellent yield (88%) whereas the same reaction needs 42 h. to give similar results when $FeCl_3$ is used as a catalyst.[16] Morpholine with methylacrylate undergo conjugate addition to get complete conversion within 3 h. However without catalyst reaction needs three days to obtain the similar results.[17] β-substituted acrylate (**entry 3**) gave 90 % yield whereas only 38 % of required product was obtained when the reaction was carried out without catalyst. Primary amines (**entry 5 and 8**) with excess of Michael reagent gave bis addition product in 85 and 68 % yields respectively. Less reactive[9] diethyl amine and hindered di-isopropylamine gave the desired product in 83 and 80% yields respectively (**entry 6 and 9**); comparable with the reaction carried out under high pressure (3000 bar)[12] (**Table 1, entry 1**).

No –OH or –SH addition product was detected when mercaptoethanol was subjected for clay catalyzed addition with acrylonitrile. Several aromatic amines such as aniline, *p*-chloroaniline, *p*-nitroaniline, *p*-anisidine, *p*-toluidine, *o*-aminophenol and *o*-aminothiophenol were subjected for this reaction with clay as catalyst and methylacrylate or acrylonitrile as the Michael acceptors. In most of the cases, aromatic amine remained unchanged or in some cases only a small amount of product of single addition was detected.

This was further established by following two experiments (**scheme 10**). A diamine **11** with aromatic and aliphatic amino groups incorporated in the same molecule was exposed to excess of methylacrylate in refluxing dichoroethane. Careful analysis of the single product **12** revealed the inertness of aromatic amino group while the aliphatic one underwent the addition reaction.

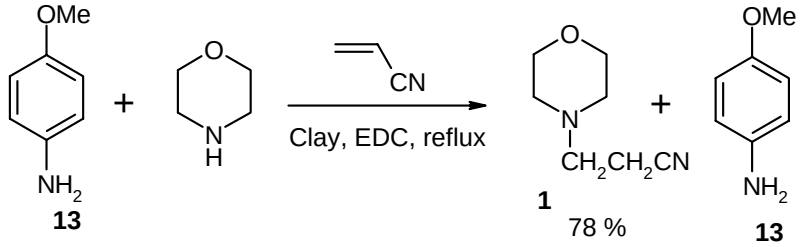


11 **12**

Scheme 10: Selective 1,4 addition of amine to α,β -unsaturated ester

When the similar reaction was carried out without catalyst < 10 % of **12** was obtained whereas major amount of substrate **11** was isolated, indicating the influence of catalyst.

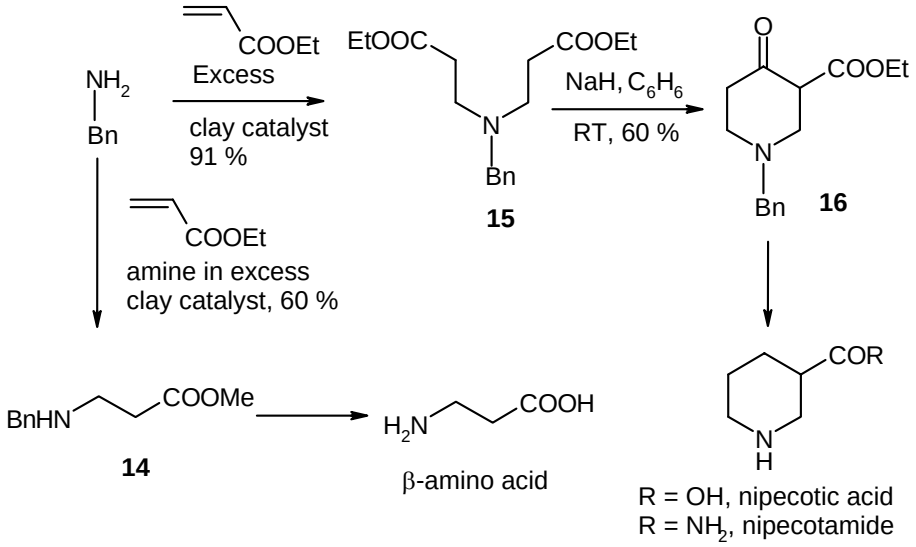
Another controlled experiment was performed with equal mixture of *p*-anisidine (**13)** and morpholine with excess of acrylonitrile under same catalytic conditions (**scheme 11**). As expected the former (**13**) remained unaffected while latter furnished the addition product **1** in high yield. These experiments clearly show that the Lewis acidity of clays is suitable only to activate aliphatic amines for the addition towards α,β-ethylenic compounds and failed for less nucleophilic aromatic amines.



Scheme 11: Comparision of reactivity of amines

We feel that this selectivity could be useful to discriminate the two types of amines for synthetic applications.

Reaction of benzylamine and acrylates was separately investigated to establish conditions for selective preparation of mono and bis-addition products. Reaction of methylacrylate with excess of benzylamine in presence of clay furnished **14** as a single product due to mono addition reaction, albeit in moderate yield (**Scheme 12**).



Scheme 12: Synthetic application of conjugate addition of benzylamine

The reaction of benzylamine with excess of ethylacrylate in presence of clay gave product **15** of bis-addition in excellent yield. However the uncatalyzed reaction, i.e. benylamine and acrylate (2 equivalent) when refluxed without solvent for 20 h. is known[18] to give 65 % of desired addition product **15**, indicating influence of clay as a catalyst on rate of reaction. Compound **15** was subjected to Dieckmann cyclization with sodium hydride to give ethyl-*N*-benzyl-4-oxo-3-piperidinecarboxylate (**16)** in moderate yield, while compound **14** is direct precursor of *β*-aminoacids. The **16** was used as starting material for the synthesis of numerous heterocyclic compounds[19] and derivatives of nipecotic acids. Nipecotic acid derivatives have received importance as they are *γ*–aminobutyric acid (GABA) uptake inhibitors[20] and many new analogues are being prepared recently.[21] Also the members of these series of compounds (**6**) are very potent local anesthetic, possessing about seven times the anesthetic power of cocaine and considerably less toxicity.[22]

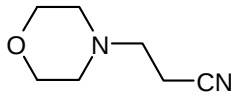
2.3.4 Conclusion

The application of clay as heterogeneous catalyst for the 1,4-addition of aliphatic amines to α,β–unsaturated ketone, esters and nitrile has been successfully carried out. It is observed that only aliphatic amines undergo addition reaction, while aromatic amines remain unreacted. Range of primary and secondary amines were studied including cyclic, acyclic and hindered amines with different Michael acceptors. Good to excellent yields of desired product was obtained with controlled mono or bis addition in case of primary amines. It was also observed that the catalyst can be recycled and reused without loss in activity. Reaction is found to be very slow when no catalyst was used, proving the influence of catalyst.

2.3.5 Experimental

3-Morpholin-4-yl-propionitrile[23] (scheme 9):

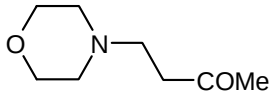
A mixture of morpholine (200 mg, 2.3 mmol), acrylonitrile (244 mg, 4.6 mmol) and kaolinetic clay (20 mg, 10 % w/w) in dry 1,2-dichloroethane was refluxed for 3 hr under argon. After the completion of reaction (tlc); the catalyst was filtered and the crude product was purified by column chromatography on silica gel to get pure product as yellow oil (264 mg, 82 %). Similar experimental procedure is followed for other examples and the chemical yields of isolated products are indicated in **Table 2**.



1

Appearance:	Yellow oil.
IR ($CHCl_3$)	3446, 2814, 2243, 1356, 1278, 1113, 751 cm^{-1}.
^1H NMR (200MHz, $CDCl_3$)**:**	δ 3.70 (m, 4H), 2.70-2.60 (t, J = 6.6 Hz, 2H), 2.55-2.40 (m, 6H).
Mass m/z (%)**:**	140 (M^+, 10), 109 (5), 100 (100), 82 (5), 70 (10).
Microanalysis:	Calculated for $C_7H_{12}N_2O$: C 60.00; H: 8.57; N: 20.00, Found: C: 60.22; H: 8.37; N: 20.10 %.

4-Morpholin-4-yl-butan-2-one (Table 2, entry 1):



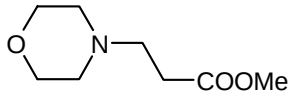
2

Appearance:	Colorless liquid
IR (neat)	2914, 1698, 1260, 1107 cm^{-1}.
^1H NMR (200MHz, $CDCl_3$)**:**	δ 3.64 (t, J = 7.25, 4H), 2.70-2.56 (m, 4H), 2.44 (t, J = 7.21, 4H), 2.12 (s, 3H).
Mass m/z (%)**:**	157 (M^+, 10), 135 (10), 114 (10), 100 (100), 91 (15), 84 (10),

70 (20), 60 (20), 56 (50).

Microanalysis: Calculated for $C_8H_{15}NO_2$: C: 61.14; H: 9.55; N: 8.92
Found: C: 61.70; H: 9.82; N: 8.75 %.

Methyl(3-morpholin-4-yl)-propionate (Table 2, entry 2):[17]



3

Appearance: Yellow oil.

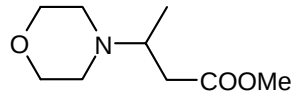
IR (neat) 3536, 2980, 1741, 1385, 1280, 1153, 887 cm^{-1}.

^{1}H NMR (200MHz, $CDCl_3$)**:** δ 3.80-3.50 (m, 7H), 2.70-2.40 (m, 8H)

Mass m/z (%)**:** 173 (M^+, 30), 142 (10), 115 (10), 100 (96), 84 (30), 70 (35), 56 (100).

Microanalysis: Calculated for $C_8H_{15}NO_3$: C: 55.49; H: 8.67; N: 8.09
Found: C: 55.80; H: 8.85; N: 8.35 %

Methyl(3-morpholin-4-yl)-butylate (Table 2, entry 3):



4

Appearance: Colorless oil.

IR (neat) 3467, 2955, 1740, 1450, 1360, 1283, 1133, 1020, 870, cm^{-1}.

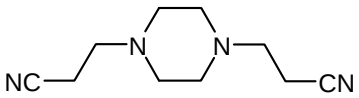
^{1}H NMR (200MHz, $CDCl_3$)**:** δ 3.60-3.40 (m; including a singlet, 7H), 3.07 (m, 1H), 2.60-2.40 (m, 4H), 2.20-2.10 (dd, J = 8.30 & 7.80 Hz, 2H), 1.03 (d, J = 8.84 Hz, 3H).

Mass m/z (%)**:** 187 (M^+, 10), 172 (12), 130 (5), 114 (100), 98 (6), 70 (15), 56 (20).

Microanalysis: Calculated for $C_9H_{17}NO_3$: C 57.75; H: 9.09; N: 7.49

Found: C: 57.44; H: 9.33; N: 7.35 %.

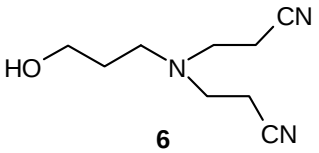
3-[4-(2-Cyanoethyl)-piperazine-1-yl]-propionitrile (Table 2, entry 4):



5

Appearance:	White solid.
M. p.:	187 °C
IR (neat)	3373, 2937, 2816, 2241 cm^{-1}.
^{1}H NMR (200MHz, $CDCl_3$)**:**	δ 2.69 (m, 4H), 2.55-2.45 (m, 12H).
Mass m/z (%)**:**	192 (M^+, 25), 152 (100), 138 (10), 109 (80), 97 (30), 83 (40), 70 (75), 56 (60).
Microanalysis:	Calculated for $C_{10}H_{16}N_4$: C 62.50; H: 8.30; N: 29.16 Found: C: 62.27; H: 8.59; N: 29.43 %.

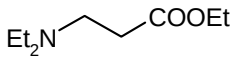
3-[(2-Cyanoethyl)-(3-hydroxypropyl)-amino]-propionitrile (Table 2, entry 5):



6

Appearance:	Yellow oil.
IR (neat)	3425, 3260, 2928, 2853, 2249, 1638, 1400, 1051 cm^{-1}.
^{1}H NMR (200MHz, $CDCl_3$)**:**	δ 3.73 (t, J= 6.92, 2H), 2.84 (t, J=7.3, 4H), 2.66 (t, J=7.25, 2H), 2.49 (t, J=7.1, 4H), 1.68 (m, 2H)
Mass m/z (%)**:**	181 (M^+, 10), 141 (30), 136 (50), 117 (60), 97 (100), 90 (25), 83 (30), 71 (15), 54 (40).
Microanalysis:	Calculated for $C_9H_{15}N_3O$: C 59.66; H: 8.28; N: 23.20 Found: C: 59.50; H: 8.50; N: 23.40 %.

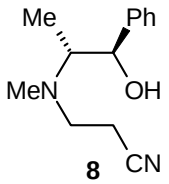
Ethyl(3-diethylamino)-propionate (Table 2,entry 6):[24]



7

Appearance:	White semisolid
IR (neat)	3405, 2912, 2833, 1732, 1425, 1265, 1110 cm^{-1}.
^{1}H NMR (200MHz, $CDCl_3$)**:**	δ 4.059(q, J=7.52, 2H), 2.76(t, J=7.33, 2H), 2.53-2.37(m, 6H), 1.21(t, J=7.81, 3H), 0.99(t, J=7.33, 6H)
Mass m/z (%)**:**	173 (M^+, 8), 158(16), 144(10), 106(10), 86(100), 72(20), 57(50).
Microanalysis:	Calculated for $C_9H_{19}NO_2$: C 62.43; H: 10.98; N: 8.09, Found: C: 62.10; H: 11.00; N: 8.11 %.

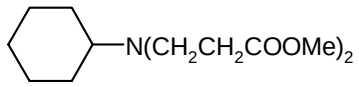
3-[(2-Hydroxy-1(*R*)-methyl-2(*R*)-phenyl-ethyl)-methylamino]-propionitrile (Table 2, entry 7):



8

Appearance:	Colorless thick oil.
IR (neat)	3401, 2963, 2920, 2802, 2238, 1374, 1038, 696 cm^{-1}.
^{1}H NMR (200MHz, $CDCl_3$)**:**	δ 7.40-7.20 (m, 5H), 4.81 (d, J=4.39, 1H), 2.90-2.71 (m, 4H), 2.42 (t, J=6.84, 2H), 2.33 (s, 3H), 0.95 (d, J=6.84, 3H),
Mass m/z (%)**:**	218 (M^+, 8), 148 (2), 117 (10), 111 (100), 105 (10), 77 (15), 68 (25).
Microanalysis:	Calculated for $C_{13}H_{18}N_2O$: C 71.56; H: 8.26; N: 12.84, Found: C: 71.48; H: 7.90; N: 12.92 %.

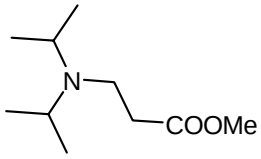
Methyl-3-[cyclohexyl-(2-methoxycarbonyl-ethyl)-amino]-propionate (Table 2, entry 8):[4a]



9

Appearance:	Yellow oil.
IR (neat)	1745, 1150, 880 cm^{-1}.
^{1}H NMR (200MHz, $CDCl_3$)**:**	δ 3.68 (s, 6H), 2.90 (t, J=6.84, 4H), 2.60-2.40 (m, 5H), 1.90-1.60 (m, 8H), 1.30-1.10 (m, 2H)
Mass m/z (%)**:**	271 (M^+, 5), 250 (10), 228 (25), 207 (20), 198 (40), 171 (15), 142 (30), 128 (100), 98 (50).
Microanalysis:	Calculated for $C_{14}H_{25}NO_4$, C 61.99; H: 9.22; N: 5.16, Found: C: 62.11; H: 9.50; N: 5.40 %.

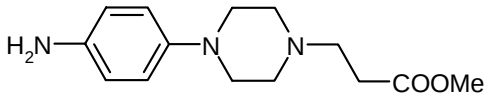
Methyl-(3-diisopropylamino)-propionate (Table 2, entry 9):



10

Appearance:	White semisolid
IR (neat)	2935, 2810, 1725, 1345, 1181, 980, 847, cm^{-1}.
^{1}H NMR (200MHz, $CDCl_3$)**:**	δ 3.49 (s, 3H), 2.68 (m, 2H), 2.63 (t, J = 5.87, 2H), 2.28 (t, J = 7.52H), 0.86 (d, J = 6.35, 12H).
Mass m/z (%)**:**	187 (M^+, 10), 172 (50), 158 (8), 130 (12), 114 (60), 98 (70), 70 (72), 56 (100).
Microanalysis:	Calculated for $C_{10}H_{21}NO_2$, C 64.17; H: 11.23; N: 7.48, Found: C: 64.30; H: 11.50; N: 7.80 %.

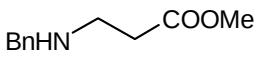
Methyl-{3-[4-(4-aminophenyl)piperazine-1yl]-propionate (2): Scheme 10



12

Appearance:	Red oil.
IR (neat)	3373, 3017, 2950, 2824, 1731, 1513, 1261, 1215, 666, cm^{-1}.
^{1}H NMR (200MHz, $CDCl_3$)**:**	δ 6.77(d, J=8.79, 2H), 6.61(d, J=8.79, 2H), 3.69(s, 3H), 3.31(bs, 2H), 3.04(t, J=5.12, 4H), 2.74(t, 7.33, 2H), 2.62(t, J=5.13, 4H), 2.53(t, J=7.3, 2H).
^{13}C NMR (75MHz, $CDCl_3$)	δ 172.10, 143.93, 139.69, 118.11, 115.58, 53.04, 52.58, 51.05, 50.36, 31.59.
Mass m/z (%)**:**	263 (M^+, 100), 248 (10), 190 (25), 176 (12), 147 (15), 120 (90), 106 (20), 70 (80), 56 (85).
Microanalysis:	Calculated for $C_{14}H_{21}N_3O_2$, C 63.88; H: 7.98; N: 15.96, Found: C: 64.00; H: 7.91; N: 15.85 %.

Methly-(3-benzylamino)-propionate (4): Scheme 12

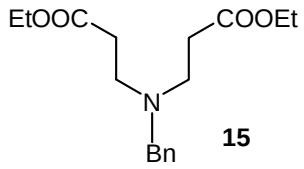


14

Appearance:	Pale yellow oil.
IR (neat)	3217, 2921, 2861, 1742, 1550, 1417, 1325, 1260, 1207, 649, cm^{-1}.
^{1}H NMR (200MHz, $CDCl_3$)**:**	δ 7.2-7.4 (m, 5H), 3.88 (s, 2H), 3.7 (s, 3H), 3.40 (bs, 1H), 2.95 (t, J = 6.84, 2H), 2.64 (t, J = 6.34, 2H).
Mass m/z (%)**:**	193 (M^+, 7), 175 (12), 160 (5), 120 (10), 91 (100), 77 (5), 65 (20), 56 (5).
Microanalysis:	Calculated for $C_{11}H_{15}NO_2$, C: 68.39, H: 7.77; N: 7.25,

Found: C: 68.45; H: 7.95; N: 7.43%.

Ethyl-{3-[benzyl-(2-ethoxycarbonyl-ethyl)-amino]-propionate (5):

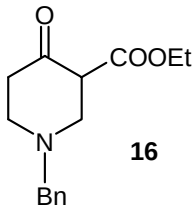


15

Appearance:	Colorless oil.
IR (neat)	3020, 2922, 2860, 1738, 1510, 1403, 1308, 1243, 1207, 1107, 752, cm^{-1}.
^{1}H NMR (200MHz, $CDCl_3$)**:**	δ 7.1-7.4 (m, 5H), 4.13 (quart, J=7.33, 4H), 3.60 (2H, s), 2.82 (t, J = 7.32, 4H), 2.47 (t, J = 7.33, 4H), 1.24 (t, J= 7.32, 6H).
Mass m/z (%)**:**	307 (M^+, 8), 278 (7), 230 (5), 220 (100), 206 (30), 190 (5), 170 (6), 146 (7), 132 (7), 118 (10), 105 (6), 91 (75), 77 (4), 65 (5).
Microanalysis:	Calculated for $C_{17}H_{25}NO_4$, C 66.45; H: 8.14; N: 4.56, Found: C: 66.20; H: 8.41; N: 4.66 %.

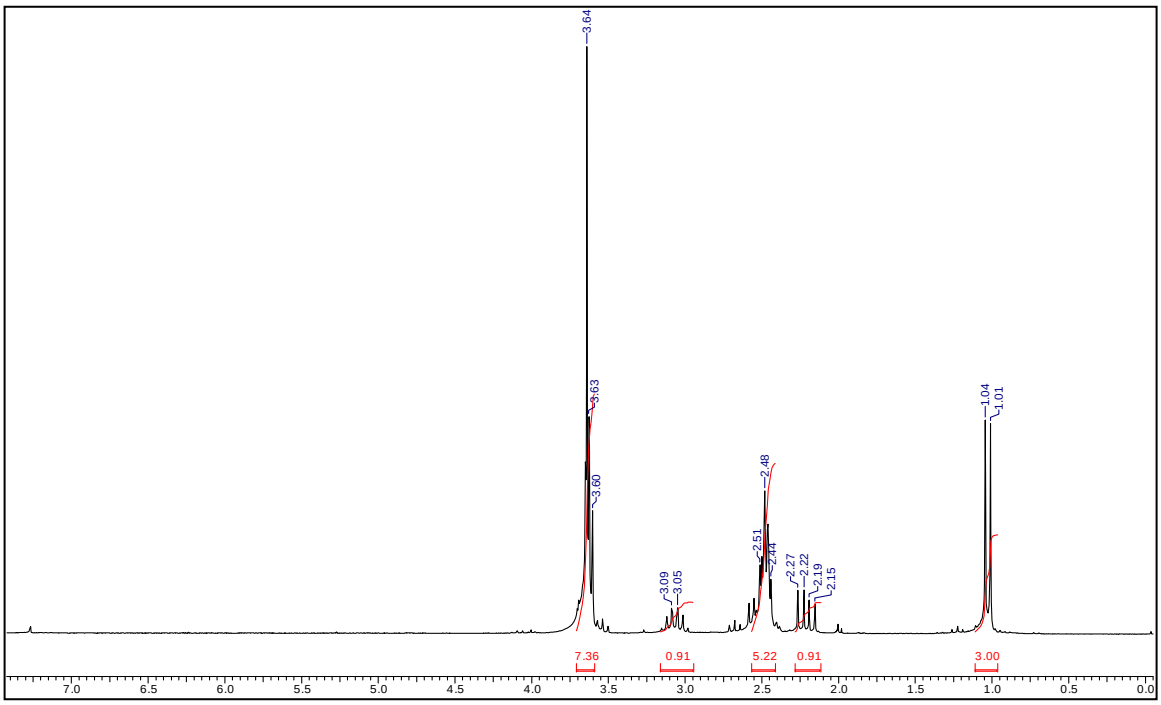
Ethyl-(1-benzyl-4-oxo-3-piperidinecarboxylate (6):[22]

A solution of 1 g. (3.26mmol) of diester 5 in 7ml of anhydrous benzene was slowly added, under nitrogen atmosphere, over a suspension of 0.194g. (8.14mmol) of paraffin free sodium hydride in 9 ml of anhydrous benzene. Few drops of absolute ethanol were added and when the reaction starts (exothermic), the reaction mixture was refluxed for 3.5 h. After completion of the reaction (monitored by tlc), it was cooled, 1ml. of glacial acetic acid was added followed by 3 ml of water at room temperature. The reaction mixture was stirred for 30 min. The organic layer was separated and dried over K_2CO_3 and concentrated in vacuo to get 0.507g. (60%) of red oil as a compound **6**.

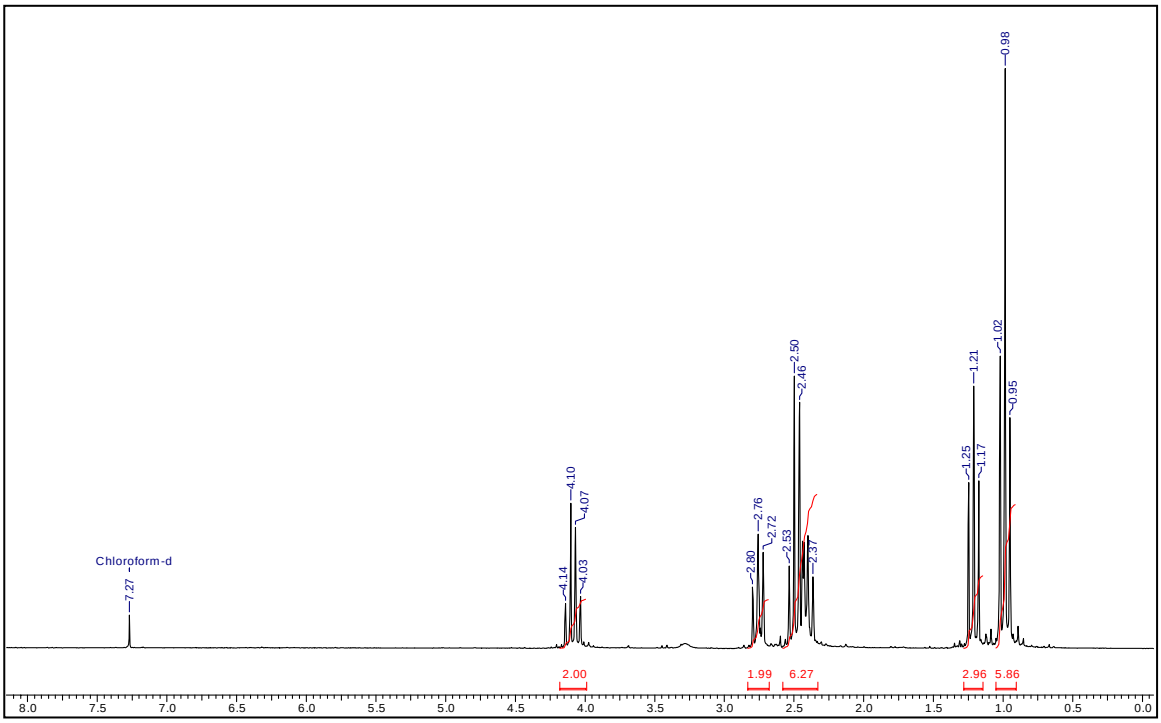


16

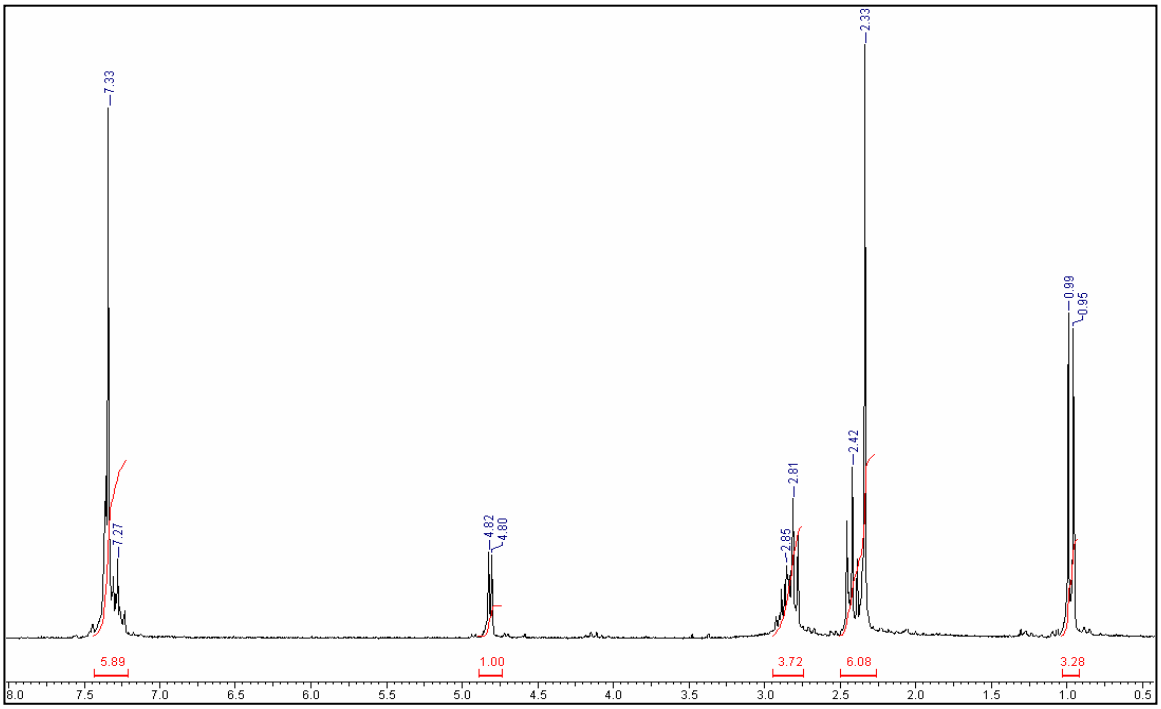
Appearance:	Red oil.
IR (neat)	2914, 1730, 1694, 1637, 1326, 1520, 1217, 1113, 740, cm^{-1}.
^{1}H NMR (200MHz, $CDCl_3$)**:**	δ 7.31 (br, s, 5H), 4.20 (quartet, J =7.2, 2H), 3.66 (s, 2H), 3.1(d, J = 7.33, 2H), 2.81 (m, 1H), 2.62 (m, 2H), 2.41 (t, J = 7.32, 2H), 1.29 (t, J = 7.33, 3H).
Mass m/z (%)**:**	261 (M^+, 20), 232 (10), 214 (60), 188 (50), 170 (10), 14 6(5), 132 (5), 124 (35), 96 (7), 91 (100), 77 (5), 65 (7).
Microanalysis:	Calculated for $C_{15}H_{19}NO_3$, C 68.96; H: 7.28; N: 5.36, Found: C: 69.11; H: 7.34; N: 5.56 %.



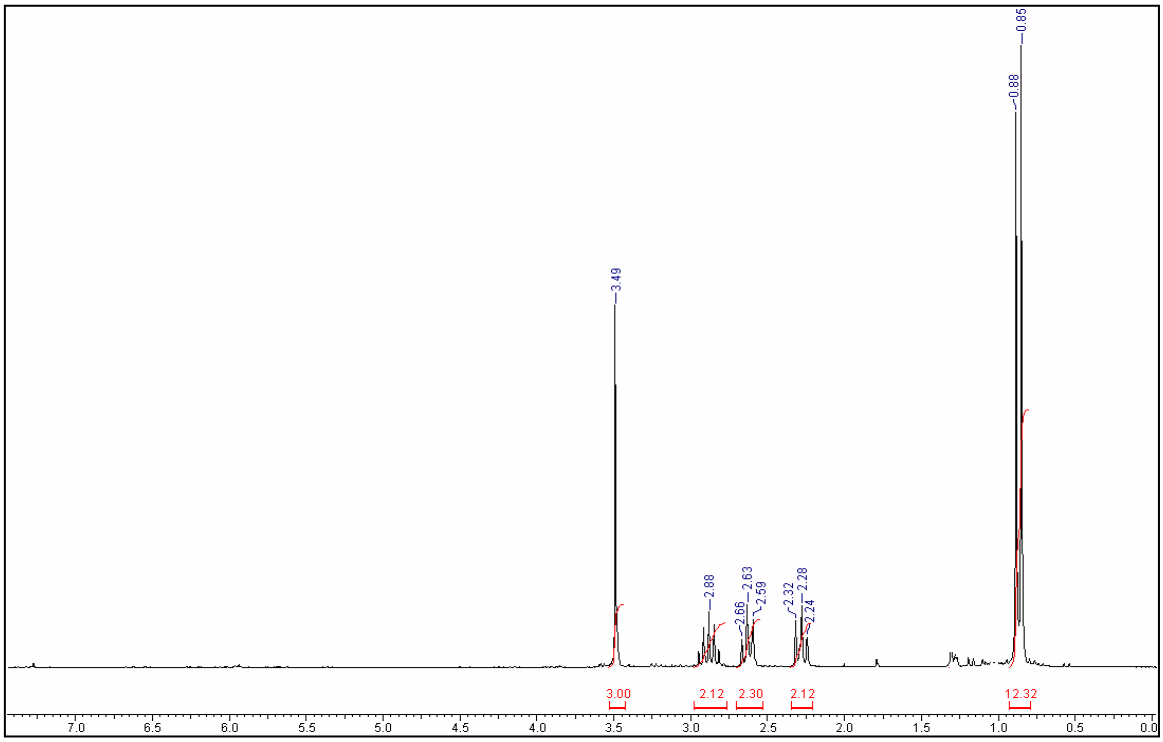
^{1}H-NMR (200 MHz, $CDCl_3$) of compound 4



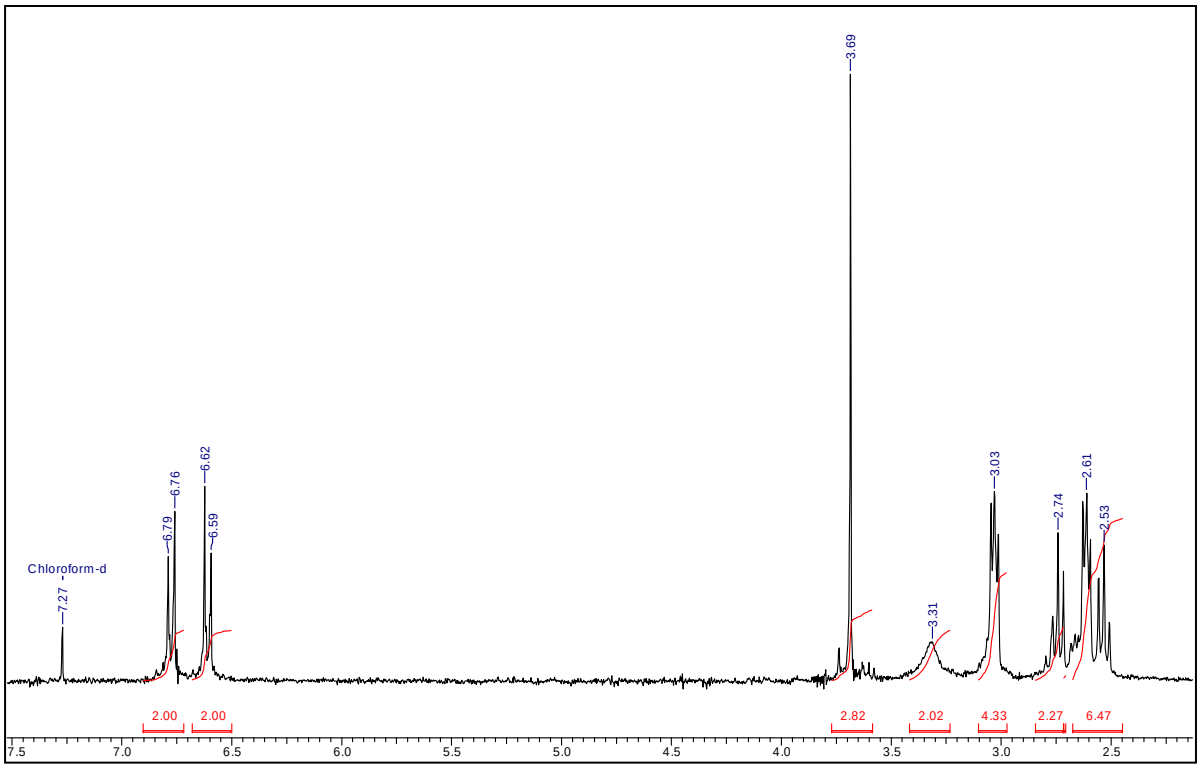
^{1}H-NMR (200 MHz, $CDCl_3$) of compound 7



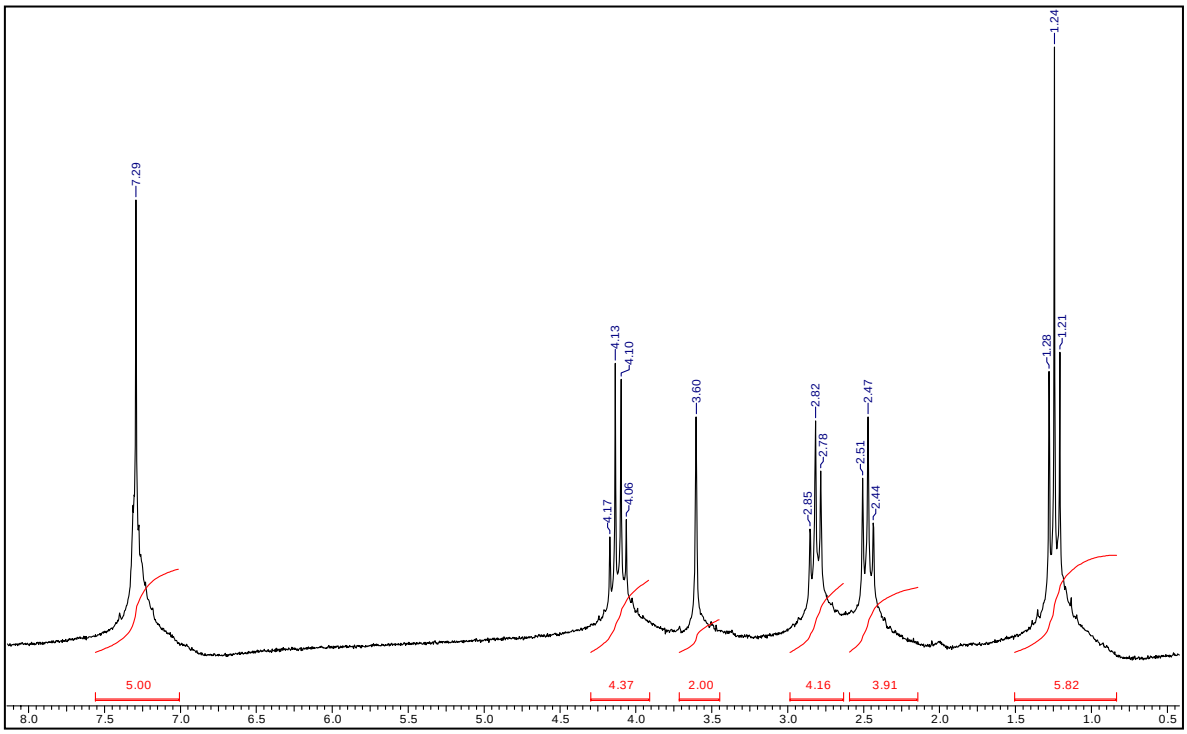
^{1}H-NMR (200 MHz, $CDCl_3$) of compound 8



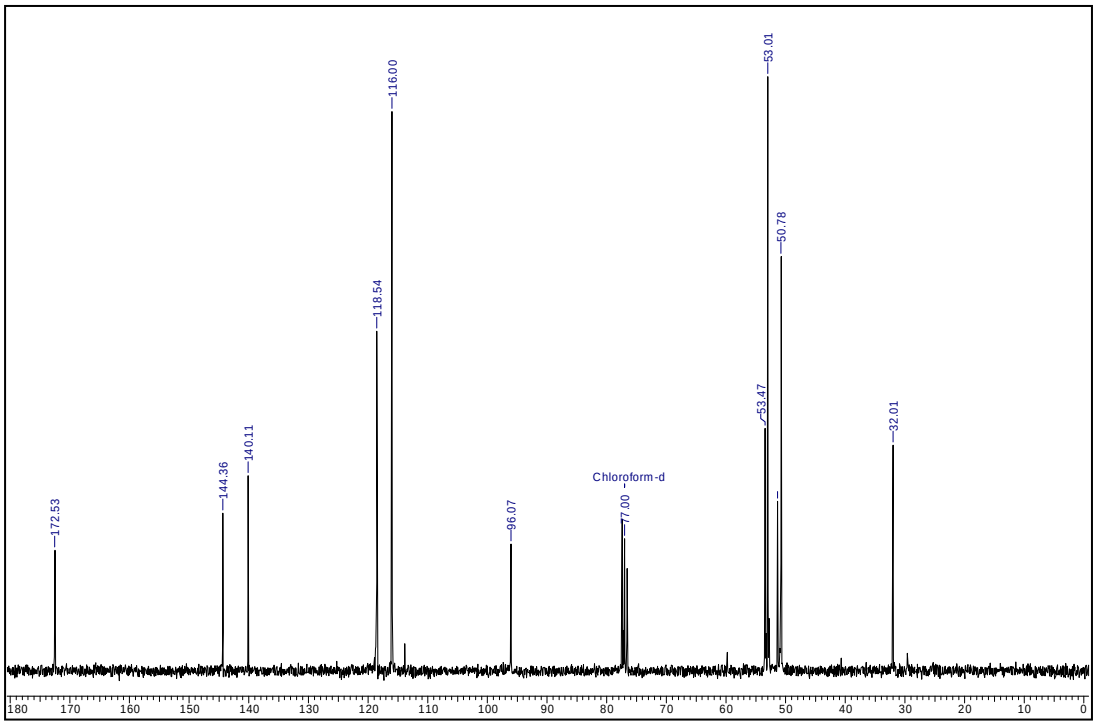
^{1}H-NMR (200 MHz, $CDCl_3$) of compound 10



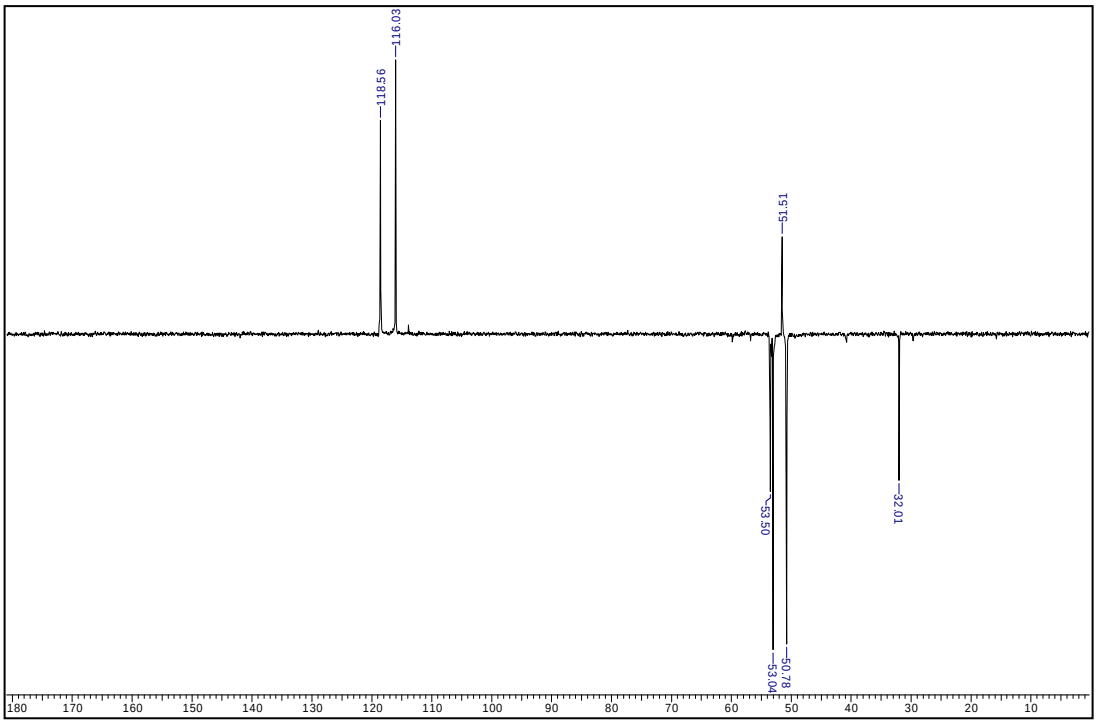
^{1}H-NMR (200 MHz, $CDCl_3$) of compound 10



^{1}H-NMR (200 MHz, $CDCl_3$) of compound 15



^{13}C-NMR (75 MHz, $CDCl_3$) of compound 10



^{13}C (Dept.)-NMR (75 MHz, $CDCl_3$) of compound 10

2.3.6 References

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CHAPTER 3

Clay Catalyzed Protection and Deprotection of Functional Groups

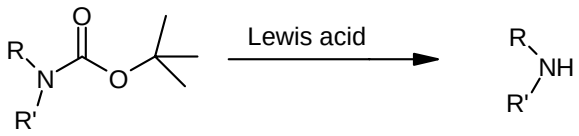
Section A

Selective Removal of *N-tert*-Butoxy Carbonyl Protecting Group from Aromatic Amines.

3.1.1 Introduction and literature

Developing mild and selective methods for the protection of functional groups and the deprotection of the protected derivatives continues to be a significant aspect in the synthetic chemistry of polyfunctional molecules including the total synthesis of natural products. Thus a large variety of protective groups have been developed along with numerous methods for their removal.

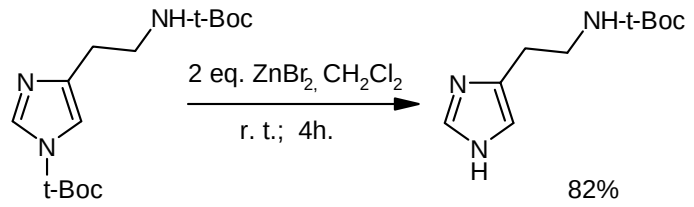
The *tert*-butoxycarbonyl group (t-Boc) is frequently used as a protecting group for primary and secondary amines[1] and amino acids in peptide chemistry[2] due to its stability to mildly acidic as well as basic conditions. The utility of the t-Boc group has been primarily due to the ease of introduction by the controlled pH technique,[3] the properties of t-Boc peptide derivatives and the relatively mild conditions required for removal of the group. There are several deprotecting conditions, adjustable to different chemical environments, but generally protic media or strong Lewis acids[4] are recommended (**Scheme 1**).



Scheme 1: Deprotection of BOC-group from amines

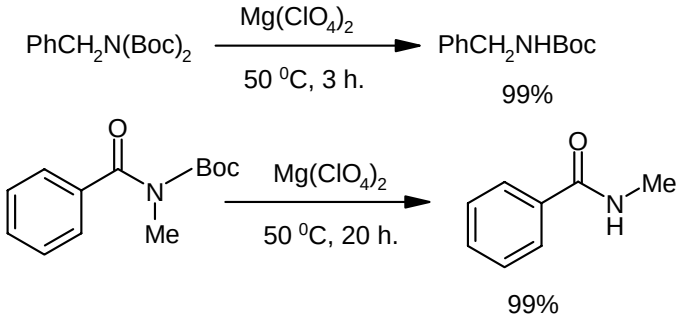
Reagents such as trifuloroacetic acid,[5] hydrochloric acid in ethyl acetate,[6] ceric ammonium nitrate,[7] tin tetrachloride[8] are generally used for deprotection of Boc group from amines.

t-Boc removal in case of water- insoluble peptide derivatives has been carried out using boron trifluoride etherate (three fold excess) along with 10% glacial acetic acid under anhydrous conditions.[9] While in case of water soluble peptides the similar reagent can cause formation of boric acid salt. In another report, 2 equivalent of anhydrous $ZnBr_2$ was found to be selective reagent which can discriminate between primary and secondary protected amines (**Scheme 2**).



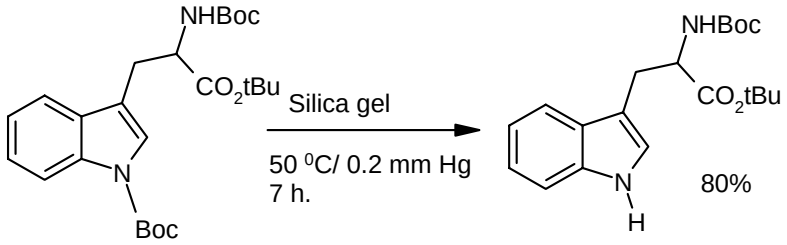
Scheme 2: $ZnBr_2$ mediated removal of BOC group

Using similar reagent no reaction has been observed in case of Boc protected primary aliphatic amines. Stafford et al. have reported the use of catalytic $Mg(ClO_4)_2$ in acetonitrile for Boc deprotection from amide (or carbamate). In case of diprotected (di-Boc) amines only mono deprotection has been observed.[10] (**Scheme 3**). However the duration of reaction varies from 3 to 72 h. depending upon the substrate to obtain good to excellent yields.



Scheme 3: $Mg(ClO_4)_2$- catalyzed deprotection of Boc-amides and carbamates.

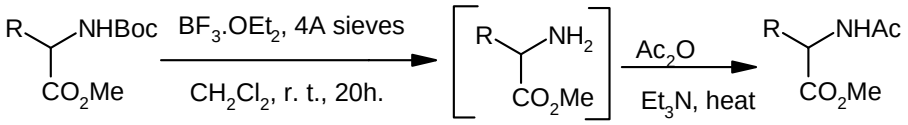
Selective removal of Boc group from nitrogen atoms in conjugation with an aromatic or carbonyl group, employing silica gel, was described by Wensbo and Apelqvist.[11]



Scheme 4: Selective removal of the N-Boc group using silica gel at low pressure

N-Boc protected amine was adsorbed on silica gel and heated under reduced pressure (0.2 mm Hg). (**Scheme 4**) Simple aliphatic Boc protected amines did not show any conversion whereas simple aromatic substrates need prolonged duration to obtain satisfactory results; e. g. *p*-anisidine and *p*-nitro aniline were obtained in 83 and 92% yields after 144 and 48 h. respectively from corresponding Boc protected compounds.

Boron trifluoride etherate in presence of 4A molecular sieves[12] was found to be good substitute for the glacial acetic acid as a modification of earlier protocol.[9]



Scheme 5: Boc-deprotection using $BF_3.OEt_2$, 4A sieves

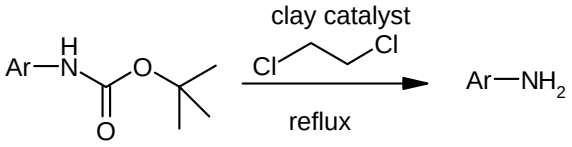
Five equivalent boron reagent and prolonged duration of the reaction limits the application of this procedure even for simple aromatic amines.

During the studies on β-lactum antibiotics, Tsuji and coworkers[13] reported that concurrent deprotection of the carboxyl ester (benzyl) and amino protecting group (t-Boc) was observed by using aluminium chloride (3.0 eq.) and anisole (3.0 eq.) in $CH_2Cl_2/MeNO_2$ at room temperature. This was further generalized by Bose et al.[14] Equivalent amount of aluminium chloride in dichloromethane at room temperature resulted the cleavage of Boc group from aromatic as well as aliphatic protected amines in satisfactory yields within 3 h.

3.1.2 Present work

A number of reagents have been known[4] to effect clean removal of t-Boc protecting group, mostly under homogeneous conditions. The only example known of this cleavage using solid reagents is the use of silica gel under reduced pressure[11]. Developing new applications for heterogeneous catalysts for organic transformations has been a subject of interest. Recently there has been an upsurge in new applications of clays as catalysts for several organic reactions. The use clay as efficient catalyst for selective removal of t-Boc group from aromatic amines has been demonstrated in this section.

A mixture of the *N*-Boc aromatic amine and kaolinitic clay (KC) or commercial montmorillonite K10 (20 % w/w) was refluxed in dichloroethane to afford the deprotected amine in excellent yield.

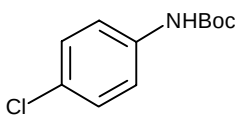
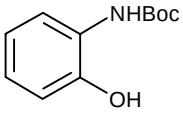
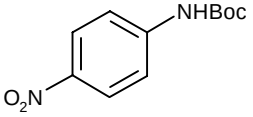
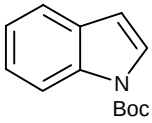
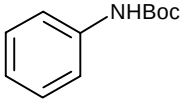
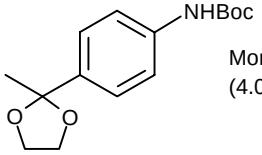
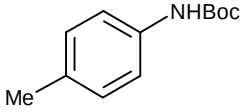
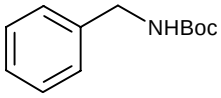
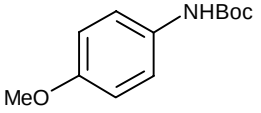
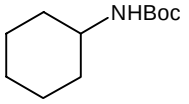


Scheme 6: Clay catalyzed t-Boc-deprotection of aromatic amines

A series of *N*-Boc amines were subjected to the deprotection reactions with different solid catalysts and the results are presented in **Table 1**. The recoverability and reusability of catalyst was tested by the experiment recorded in **entry 3** of **Table 1**.

Different substituted t-butoxycarbonyl aromatic amines were subjected for the deprotection to obtain parent amine using clay in dichloroethane. Natural kaolinitic clay, commercially available Montmorillonite K10 clay and EPZG® were tested for this transformation and found to be equally effective. (Envirocat a new family of supported reagents: Envirocat EPZG® composition is iron trichloride (19.6%) and inert carrier(s) (80.4%).[15] EPZG® is a solid supported acid catalyst which exhibits both Bronsted and Lewis acids characteristics). After removal of t-Boc group, amines are obtained in good to quantitative yields. Substrates including electron rich as well as electron poor arenas are effectively underwent this transformation. Mere filtration of the reaction mixture as a workup itself is sufficient to explain the importance of using heterogeneous catalyst.

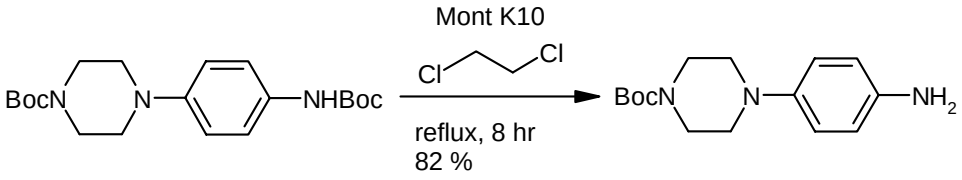
Table-1: Catalytic deprotection of *N*-Boc amines.

Entry	Substrate	Catalyst (time in h)	% Yield[a]	Entry	Substrate	Catalyst (time in h)	% Yield[a]
1.		none (15) KC (2.0) Mont K10 (1.5)	no reaction 98 98	6.		Mont K10 (2.25)	86
2.		EPZG[R] (1.5) Mont K10 (2.5)	99 94	7.		Mont K10 (4.0)	94
3.		Mont K10 (2.5)	77 72[b]	8.		Mont K10 (4.0)	64
4.		Mont K10 (2.0)	97	9.		Mont K10 (15)	no reaction
5.		KC (1.5)	97	10		Mont K10 (15)	no reaction

a: Isolated yields. Amines characterized by usual spectral analyses. b: With recovered catalyst from the 1st cycle.

Reaction failed to undergo deprotection without catalyst (**entry 1**). When reaction was carried out at room temperature in presence of 20 % (w/w) of kaolinitic clay, none of the desired product has been observed. But when the reaction was refluxed for 2 h. complete conversion of substrate has been observed (by tlc), only parent amine was detected as the only product in almost quantitative yield. Another acid sensitive group such as acetal (entry 8) remains intact removing t-Boc group to give free amine in moderate yield.

To our surprise aliphatic t-Boc protected amines does not show any deprotection reaction under the reaction conditions studied as evidenced by **entry 9** and **10**. This selective nature of the catalyst was confirmed by the following example.



Scheme 7: Selective removal of t-Boc group from aromatic amine

The substrate having both aromatic and aliphatic amines (*t*-Boc protected) was subjected for the deprotection reaction using Mont K10 clay under reflux for 8 hr. The aromatic amine was found to be selectively deprotected rather than both. Parallel experiment without catalyst did not show any deprotection reaction.

3.1.3 Conclusion

In summary, it has been shown that naturally occurring kaolinitic clay, EPZG® as well as commercially available Montmorillonite K10 clay could efficiently remove the t-butoxy carbonyl protecting group from aromatic amines. Variety of substituted aromatic amines were studied to obtain parent amines in good to excellent yields within short period of time. However aliphatic amines failed to undergo this transformation using clay as catalyst. Simple workup procedure allows separating the catalyst from the product. The catalyst is found to be reusable without loss in activity.

High chemoselectivity exhibited by the clay-catalyzed reaction should be useful for selective deprotection of aromatic amines in presence of aliphatic amines or other acid sensitive group. Beside the high selectivity and reactivity exhibited by the clay, the method has other environmentally benign features i.e. no inorganic wastes are produced.

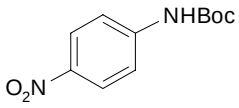
3.1.4 Experimental

t-Boc derivatives of amines were prepared by stirring together a solution of the amine (1 eq.) and di-*tert*-butyl dicarbonate (1.2 eq.) in acetonitrile in the presence of DMAP (0.1 eq.) at room temperature for 6 to 10 h. and used as a substrate after purification by column chromatography. The compounds obtained after deprotection were compared (tlc) with authentic samples as a preliminary analysis of the product. All *N*-Boc-protected amines and products (free-amines) gave satisfactory analytical and spectroscopic data.

General procedure for deprotection of amines:

t-Boc protected amine was dissolved in dichloroethane, was added clay catalyst (20 % w/w). Reaction mixture was refluxed for specified period of time (**Table 1**), which was monitored by tlc. After complete disappearance of starting material, reaction was cooled at room temperature and filtered to remove the catalyst. Catalyst was washed with dichloroethane and organic layer collected was evaporated using rotary evaporator. Residue was purified using column chromatography over neutral alumina or silica gel to obtain pure amine.

(4-Nitrophenyl)carbamic acid *tert*-butyl ester:

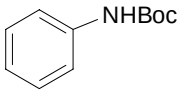


Pale yellow solid

IR ν_{max} /cm^{-1} ($CHCl_3$): 3430, 3020, 1731, 1215, 1159.

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.5 (s, 9H), 6.5 (bs, 1H), 7.8 (d, J = 8.9, 2H), 8.2 (d, J = 8.9, 2H).

Phenylcarbamic acid *tert*-butyl ester:



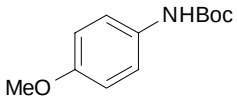
White solid: M.P. 64^{o}C

IR ν_{max} /cm^{-1} ($CHCl_3$): 3437, 3019, 1723, 1518, 1215, 1159.

^{1}H NMR (200 MHz, $CDCl_3$) δ 1.5 (s, 9H), 6.5 (bs, 1H), 7.15-7.65 (m, 5H).

MS (m/z, rel. int %): M^+ 193 (9), 137 (67), 93 (100), 65 (56), 57 (95).

(4-Methoxyphenyl)carbamic acid *tert*-butyl ester:

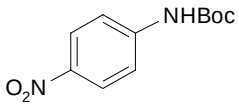


White solid: M.P. 105-110^{o}C

IR ν_{max} /cm^{-1} ($CHCl_3$): 3440, 2981, 1717, 1520, 1368, 1242.

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.5 (s, 9H), 3.77 (s, 3H), 6.36 (bs, 1H), 6.88 (d, J = 7.5, 2H), 7.26 (d, J = 7.5, 2H).

(4-Nitrophenyl)carbamic acid *tert*-butyl ester:



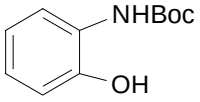
Pale yellow solid

IR ν_{max} /cm^{-1} ($CHCl_3$): 3430, 3020, 1731, 1215, 1159.

^{1}H NMR (200 MHz, $CDCl_3$) : δ 1.5 (s, 9H), 6.5 (bs, 1H), 7.8 (d, J = 8.9, 2H), 8.2 (d, J = 8.9, 2H).

MS: m/z (%) 238 (M^+, 5), 182 (8), 138 (40), 108 (35), 92 (20), 65 (45), 57 (100).

(2-Hydroxyphenyl)carbamic acid *tert*-butyl ester:



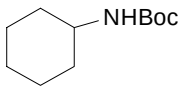
White solid: M.P. 170^{o}C

IR ν_{max} /cm^{-1} ($CHCl_3$): 3224, 2921, 1705, 1455, 1231.

^{1}H NMR (200 MHz, $CDCl_3$) δ 1.5 (s, 9H), 5.5 (br, s, 1H), 6.5 (br, s, 1H), 6.90-7.25 (m, 4H).

MS: m/z (%) 209 (M^+, 7), 153 (80), 135 (10), 109 (100), 80 (20), 57 (10)

Cyclohexylcarbamic acid *tert*-butyl ester:

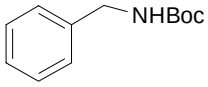


White solid: M.P. 45°C

IR ν_{max} /cm^{-1} ($CHCl_3$): 3345, 2979, 1705, 1504, 1393, 1169.

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.00-2.00 (m, 11H), 1.5 (s, 9H), 3.15 (m, 1H).

Benzylcarbamic acid *tert*-butyl ester:

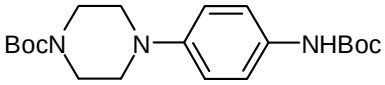


White solid: M.P. 75°C

IR ν_{max} /cm^{-1} ($CHCl_3$): 3348, 2978, 1712, 1525, 1368, 1169.

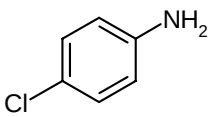
^{1}H NMR (200 MHz, $CDCl_3$): δ 1.5 (s, 9H), 4.5 (s, 2H), 5.5 (s, 1H), 7.2-7.5 (m 5H).

4-(4-*tert*-butoxycarbonylamino-phenyl)-piperazine-1-carboxylic acid-*tert*-butyl-ester:



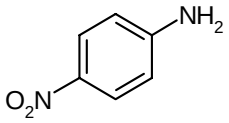
Yield	58 %
Appearance	Yellow viscous liquid
IR ($CHCl_3$)	3431, 3326, 3009, 2973, 2922, 2820, 1677, 1514, 1416, 1215, 1158, 1046, 909, 752, 662 cm^{-1}
^{1}H NMR (200MHz, $CDCl_3$)	7.24 (d, J = 8.1 Hz, 2H), 6.88 (d, J = 8.1 Hz, 2H), 3.56 (t, J = 5.3 Hz, 4H), 3.03 (t, J = 5.2 Hz, 4H), 1.50 (s, 9H), 1.47 (s, 9H)
MS: m/z (%)	377 (M^+, 10), 321 (40), 277 (5), 265 (100), 220 (12), 191 (5), 179 (15), 135 (16), 119 (14), 92 (5)

4-Chloroaniline: (Table 1 entry 1)



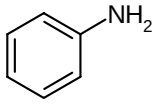
Yield	98 %
Appearance	White solid
M. p.	69-71 °C (Lit.[16] m.p. 70 °C)
IR ($CHCl_3$)	3612, 3510, 3320, 1570, 1420, 1280, 1120, 1000, 820 cm^{-1}
^1H NMR (200MHz, $CDCl_3$)	7.08 (d, J = 8.6 Hz, 2H), 6.56 (d, J = 8.6 Hz, 2H), 3.62 (br, s, 2H).

4-nitroaniline (Table 1, entry 2):



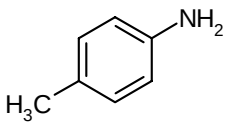
Yield	94 %
Appearance	Yellow solid
M. p.	147-149 °C (Lit.[16] m.p. 150 °C)
IR ($CHCl_3$)	3510, 3500, 2830, 1625, 1490, 1170, 835, 760 cm-1
^1H NMR (200MHz, $CDCl_3$)	7.92 (d, J = 8.9 Hz, 2H), 6.63 (d, J = 8.9 Hz, 2H), 6.42 (br, s, 2H)

Aniline (Table 1, entry 3):



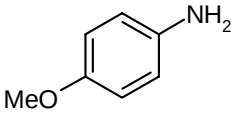
Yield	77 %
Appearance	Colorless liquid
IR ($CHCl_3$)	3515, 3500, 3100, 1640, 1480, 1290, 1000, 890, 760 cm^{-1}
^1H NMR (200MHz, $CDCl_3$)	7.20-7.08 (m, 2H), 6.73 (m, 1H), 6.62 (m, 2H), 3.57 (br, s, 2H)

4-Tolylamine (Table 1, entry 4):



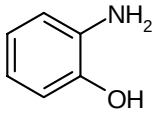
Yield	97 %
Appearance	Solid
M. p.	43-45 °C (Lit.[16] m.p. 45 °C)
IR ($CHCl_3$)	3460, 3182, 2850, 1635, 1470, 1420, 1270, 1110, 820 cm^{-1}
^{1}H NMR (200MHz, $CDCl_3$)	6.92 (d, J = 8.3 Hz, 2H), 6.53 (d, J = 8.3 Hz, 2H), 3.48 (br, s, 2H), 2.18 (s, 3H)

4-Anisidine (Table 1, entry 5):



Yield	97 %
Appearance	Red solid
M. p.	58-60 °C (Lit.[16] m.p. 57-60 °C)
IR ($CHCl_3$)	3520, 3500, 2910, 1575, 1460, 1280, 1050, 820 cm^{-1}

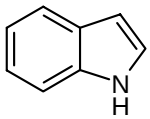
2-Aminophenol (table 1, entry 6):



Yield	86 %
Appearance	Red solid
M. p.	173-175 °C (Lit.[16] m.p. 176 °C)
IR (Nujol)	3505, 3200, 2700, 1620, 1500, 1360, 1120, 900, 780,

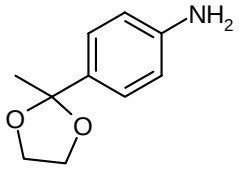
	670 cm^{-1}
^{1}H NMR ($CDCl_3$)	8.91 (br, s, 1H), 6.71-6.52 (m, 3H), 6.46-6.32 (m, 1H), 4.43 (br, s, 2H)

1*H*-Indole (Table 1, entry 7):



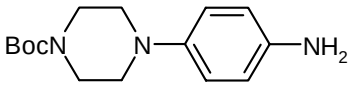
Yield	94 %
Appearance	White solid
M. p.	51-53 °C (Lit.[16] m.p. 53 °C)
IR (Nujol)	3460, 3000, 1500, 1420, 1320, 1255, 1080, 870, 740 cm^{-1}
^{1}H NMR ($CDCl_3$)	7.76 (br, s, 1H), 7.64 (m, 1H), 7.30-6.92 (m, 4H), 6.48 (m, 1H).

4-(2-Methyl-[1,3]dioxolan-2-yl)-aniline (table 1, entry 8):



Yield	64 %
Appearance	Viscous liquid
IR (Neat)	3500, 3363, 2967, 1589, 1043, 860 cm^{-1}
^{1}H NMR (200 MHz, $CDCl_3$)	7.19 (d, J = 8.9 Hz, 2H), 6.74 (d, J = 8.9 Hz, 2H), 4.1 (m, 2H), 3.83 (m, 2H), 3.21 (br, s, 2H), 1.67 (s, 3H)

4-(4-Amino-phenyl)-piperazine-1-carboxylic acid *tert*-butyl ester (Scheme 7):



Yield	82 %
Appearance	Yellow oil
IR ($CHCl_3$)	3610, 3426. 3015, 2397, 1676, 1511, 1420, 1211, 919, 759, 666 cm^{-1}
^{1}H NMR (200MHz, $CDCl_3$):	6.82 (d, J = 8.9 Hz, 2H), 6.67 (d, J = 8.9 Hz, 2H), 3.31-2.86 (m, 10H including NH_2), 1.48 (s, 9H).
Mass m/z (%):	277 (M^+, 52), 257 (30), 221 (50), 204 (25), 149 (48), 135 (100), 120 (65), 106 (20), 99 (24), 91 (30), 77 (15).
Microanalysis:	Calculated for $C_{15}H_{23}N_3O_2$; C 64.95; H: 8.36; N: 15.15, Found: C: 64.74; H: 8.47; N: 15.07 %.

3.1.5 References

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Envirocat EPZG® was supplied by Contract Chemicals, Penrhyn Road, Knowsley, Industrial Park south, Prescot Merseyside, England. Information about Envirocat EPZG® was obtained from Envirocats -Supported Reagents: *Product Information of Contract Chemicals , England*.

®: Registered trade mark of contract chemicals, England.

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CHAPTER 3

Section B

Microwave Accelerated Deprotection of Allyl Esters Catalyzed by Montmorillonite K 10

3.2.1 Introduction

Microwave technology:

The rapid heating of foodstuffs in microwave ovens is routinely used by a significant proportion of mankind. However people have recognized other potential applications for this method of heating and scientists engaged in a number of disciplines have applied the rapid heating associated with microwave technology to a number of useful processes. These include the preparation of samples for analysis[1]; application to waste treatment[2]; polymer technology[3]; drug release/targeting[4]; ceramics[5] and alkane decomposition.[6] The technique has also found use in a range of decomposition processes including hydrolysis of proteins and peptides.[7]

General principles:

The microwave region of the electromagnetic spectrum lies between 1cm and 1m and in order to avoid interfering with radar and telecommunication activities which operate within this range, most domestic and commercial microwave instruments operate at 2.45GHz.

When a substance or molecule is irradiated with microwaves it rotates to align itself with the applied field. The frequency of molecular rotation is similar to the frequency of microwave radiation and consequently the molecule continually attempts to realign itself with the changing field and energy is absorbed.[8a]

Microwave and Chemistry:

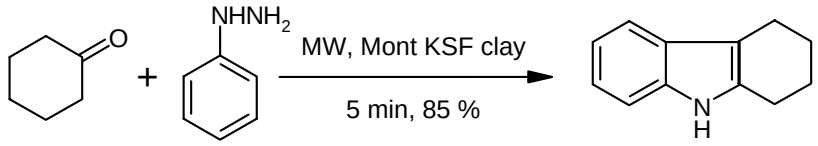
In liquid systems, microwave primarily heat a material by inducing rotation of polar molecules to align and relax at a given frequency, in the field of the electromagnetic radiation. It is the energy dissipated during such collisions that leads to the heating effect. So when a solvent is heated using microwaves, the heat is generated within the reaction medium rather than being transferred from an external source such as heating mantle. This leads to a situation where the reaction medium is hotter than the walls of the vessel, resulting in non-nucleated super heating of the reaction medium.

Under such conditions, the reaction can exist at temperatures above its boiling point without physical boiling, even in an open system. As the temperature increases, the rate of reaction increases and it is this effect, coupled with the efficient heating processes induced by microwaves, that leads to the many observed enhancements in reduced reaction times, increased yield and improved extraction efficiency.

Microwave assisted organic reactions:

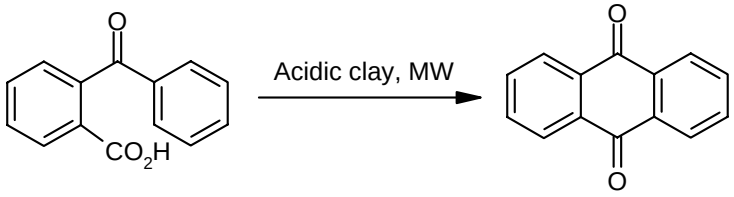
Microwave assisted heterogeneous reactions[8] with the various solid inorganic support have attracted the researchers because of the simplicity, greater stability and rapid synthesis of variety of organic compounds. Enhanced reaction rates, formation of pure products in high yields and the ease of operation are the salient features of the microwave approach along with the use of mineral supported reagents or catalysts. Recently solvent free microwave assisted reactions[9] are gaining more popularity as they provide an opportunity to work with open vessels. This avoids the risk of development of high pressure and with a possibility of upscaling the reaction on preparative scale and helps the induction of reaction under 'dry conditions'.[10] Among the number of reports;[8] few of the successful applications are mentioned below.

Montmorillonite KSF clay has been shown to catalyze microwave assisted Fischer indole synthesis[11] in high yield.



Scheme 1: Microwave assisted Indole synthesis using clay catalyst

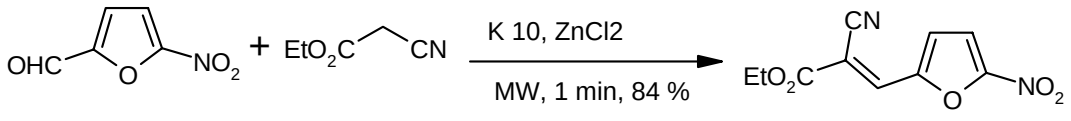
The application of microwaves to the industrially important raw material anthraquinone has been investigated.[12]



Scheme 2: Microwave assisted preparation of anthraquinone using clay

As shown in **scheme 2**, clay catalyzed cyclodehydration was carried out under microwave conditions. Similar reaction under thermal condition is found to be low yielding. In

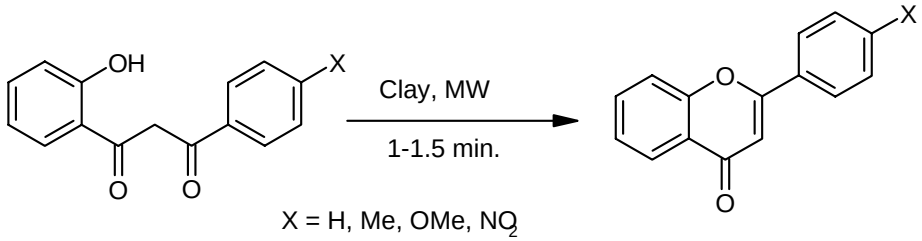
another report, clay catalyst has been used to aid microwave assisted condensation of "active methylenes" with aldehydes (**Scheme 3**).



Scheme 3: Microwave assisted condensation of aldehyde with active methylene

Condensation of 5-nitro-2-furaldehyde with active methylene was achieved in high yields by adsorbing the reagents on the Lewis acid K 10 clay, $ZnCl_2$ and irradiation with microwaves.[13]

In yet another report, the most prevalent approach, however, involves the Baker-Venkatraman rearrangement, wherein *o*-hydroxyacetopheneone is benzoylated to form the benzoyl ester followed by the treatment with base (pyridine/KOH) to effect an acyl group migration, forming a 1,3-diketone. The resulting diketone is then cyclized under strongly acidic conditions with sulfuric acid and acetic acid to deliver the flavone.



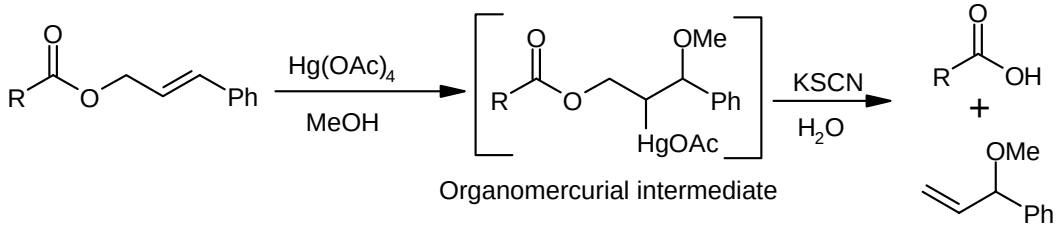
Scheme 4: Microwave assisted synthesis of flavones using Mont K 10

A solvent free synthesis of flavones has been achieved[14a] which simply involves the microwave irradiation of *o*-hydroxydibenzoylmethanes adsorbed on montmorillonite K 10 clay. A rapid and exclusive formation of cyclized flavones occurs in good yields (**Scheme 4**). Recently, microwave assisted facile synthesis of elvirol, curcuphenol and sesquichamaenol using Montmorillonite K 10 clay in dry media has been carried out.[14b] All these and other related reports[14c] demonstrate the application of microwave in synthetic organic chemistry.

3.2.2 Literature

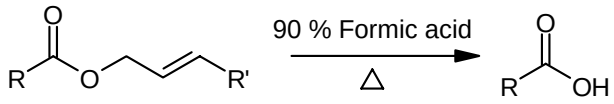
Functional group protection and deprotection strategies are essential to target oriented synthesis in organic chemistry.[15] Carboxylic acids can be protected as anhydrides,[16] amides[17] or esters.[18] Unsaturated esters are particularly useful as protecting groups because of their stability, the ease with which they can be obtained by reaction of the corresponding alcohol with acid chloride or alkylation of the acid with the corresponding allyl halide under base catalyzed conditions.[19] Deprotection of allyl ester can be done by using methodologies like $Pd(OAc)_2$,[20a] $PdCl_2(Ph_3P)_2$,[20b] $(Ph_3P)_3RhCl$,[20c] Me_2CuLi,[20d] formic acid[21] and sulphated SnO_2.[22] Reports also show few carboxylic acids which were protected as 3-buten-1-yl ester have been deprotected *via*. Ozonolysis[23a] and β-elimination.[23b] Recently our group reported the use of natural kaolinitic clay and EPZG® for selective allyl ester deprotection.[24]

Earlier, two step protocol for deprotection of cinnamyl esters has been described by E. J. Corey[25] (**scheme 5**). Even though yields were good, it is limited for cinnamyl ester and also expensive and toxic mercuric acetate (1.15 eq.) was used.



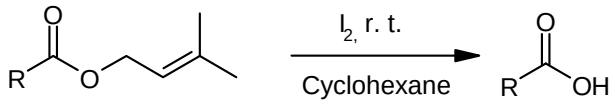
Scheme 5: Regeneration of carboxylic acid from cinnamyl ester via mercuration-demercuration

In another report substituted allylic esters were cleaved in refluxing 90% formic acid to afford carboxylic acids[21] (**scheme 6**). Allyl, crotyl and cinnamyl esters were also completely removed under these conditions.



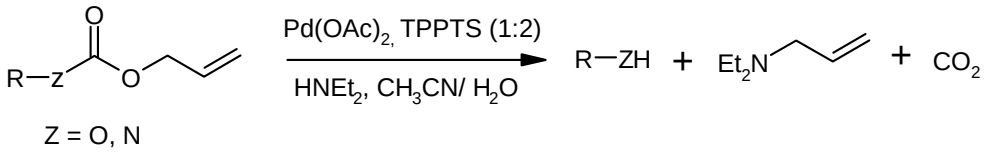
Scheme 6

Another recent publication[26] utilizes excess iodine for the deprotection of allyl esters (**scheme 7**) in mild and neutral conditions.



Scheme 7

Allyloxycarbonyl and allylcarboxy groups can be removed without affecting dimethyl allyl carboxy and cinnamylcarboxy groups in the same molecule, using Pd (O) water soluble catalyst prepared *in situ* from palladium(II)acetate and TPPTS (m-sulphonated triphenyl phosphine) with diethylamine as allyl scavenger[27] (**scheme 8**)



Scheme 8: Selective deprotective method using Pd-water soluble catalysts

Recent publication describes the deprotection of allyl esters using solid super acid sulphated SnO_2 in presence of nucleophile such as anisol to obtain corresponding acid in good yields.[22]

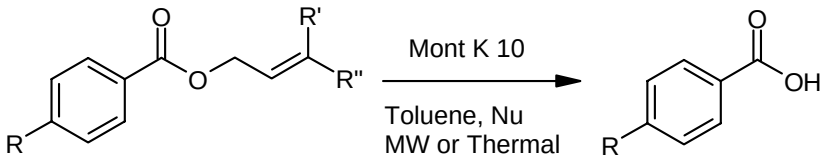
However all these methods for deprotection of allyl esters employ harsh conditions, use of excess oxidizing agents, or employ expensive reagents like Pd, mercuric acetate.

As there is a need of 'clean technology revolution', the use of solid, inorganic catalyst promises to go a long way where a current technology is very inefficient or leads to unacceptable levels of waste.[28] Clays can be used as an efficient and versatile catalyst for various organic reactions. This clay is non-toxic, non-corrosive, and can be recycled. Montmorillonite clay shows availability of both Brϕnsted and Lewis acidic catalytic sites (discussed in **chapter 3, section A**).

3.2.3 Present work

Previous protocol[24] for the deprotection of allyl esters using Kaolinitic clay or EPZG® which was unsuccessful in case of *p*-substituted allyl esters; encouraged us to re-examine the reaction in microwave using commercially available Montmorillonite K 10 clay.

Table lists a variety of allyl esters which were converted to their parent acid in the presence of nucleophile, catalyst montmorillonite K 10 by both thermal and microwave accelerated solvent free conditions (**Scheme 9**). The time required for completion of reaction by microwave method is appreciably reduced than in the thermal conditions with mild reaction conditions. It was assumed[22] that during the course of reaction, the allyl cation formed reacts with the aromatic nucleus (Nu) toluene, 1,4-dimethoxy benzene or anisole via alkylation.



R = H, Me, OMe, NO_2, Cl

R', R" = H, Me; H, Ph
R', R" ≠ H

Scheme 9: Mont K 10 clay catalyzed allyl ester derotection

Different para substituted allyl and cinnamyl esters were studied for their deprotection using Mont. K 10 clay (20 % w/w) in presence or absence of solvent. The results are summarized in table. It has been observed that (**Table; entries 2, 4, 5, 6 and 18**) allyl esters are easily hydrolyzed where as cinnamyl ester requires the presence of more nucleophilic aromatic species as anisole. It is also important to note that aryl or alkyl esters (**entries 19 and 20**) remain unaffected under these reaction conditions.

Table

Deprotection of allyl esters catalyzed by montmorillonite K-10

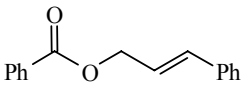
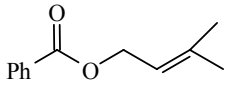
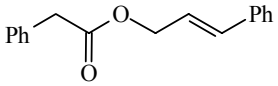
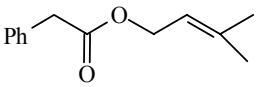
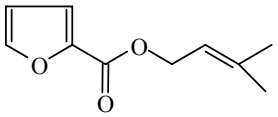
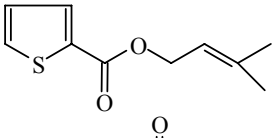
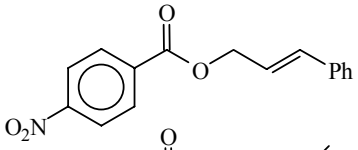
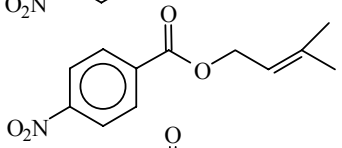
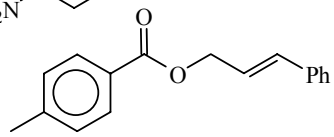
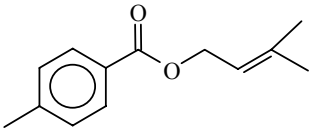
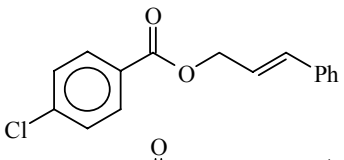
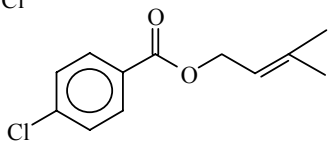
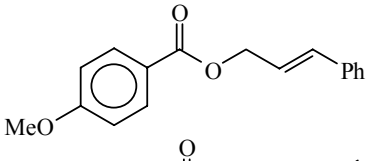
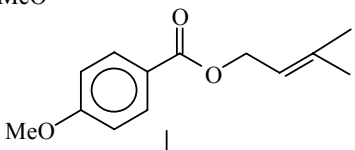
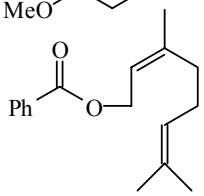
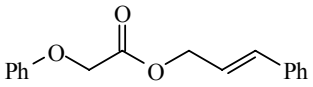
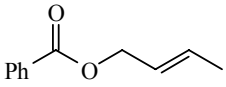
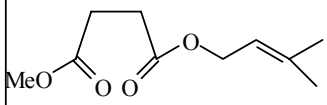
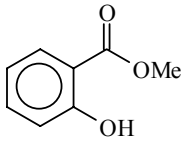
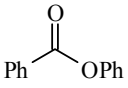
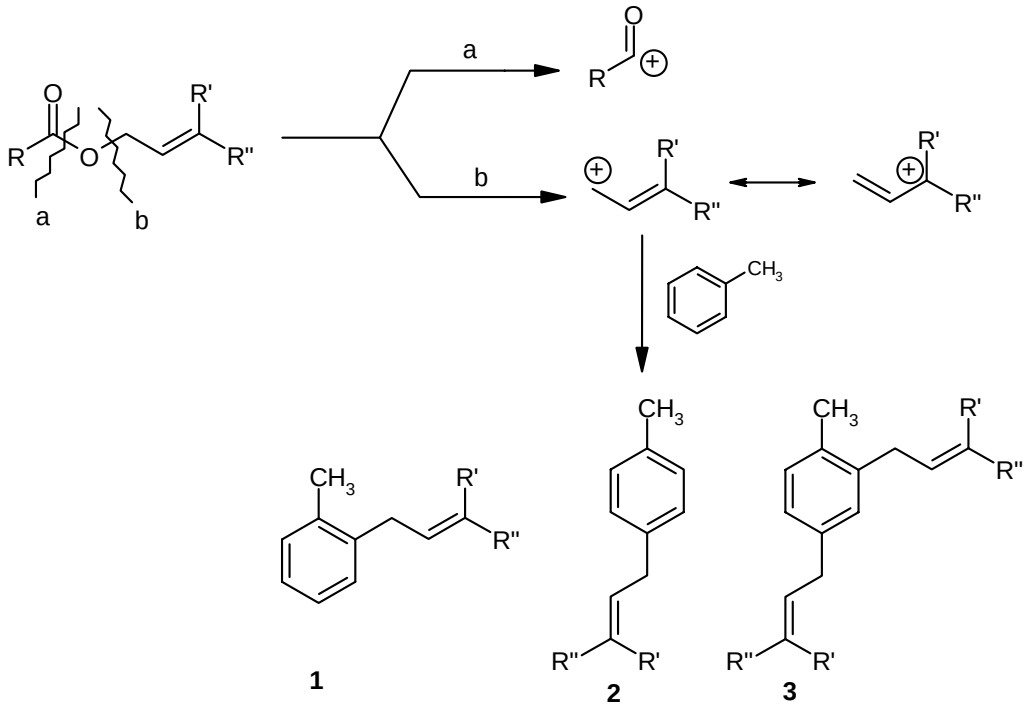
Entry	Allyl esters	Thermal		Microwave	
		Time (hrs.)	%Yield[a]	Time (min.)	%Yield[a]
1		6	94	20	96
2		5	94[b]	20	98
3		8.5	80	20	85
4		8.5	90[b]	20	97
5		14	60[b, c]	20	70[c]
6		14	62[b, c]	10	70[c]
7		10	87	10	92
8		10	85	10	90
9		8	92	20	97
10		8.5	90	20	95

Table (Continued)……

Entry	Allyl esters	Thermal		Microwave	
		Time (hrs.)	% Yield[a]	Time (min.)	% Yield[a]
11		8.5	92	20	95
12		8	90	20	97
13		10	85	10	90
14		10	87	10	92
15		15	87	20	97
16		9	80	20	85
17		10	47	20	60[c]
18		20	67[b, c]	20	72[c]
19		20	00	20	00
20		20	00	20	00

a) Isolated yield characterized by M.P., IR and ^{1}H NMR; b) Without addition of nucleophile, yields. c) Remaining was essentially the starting material.

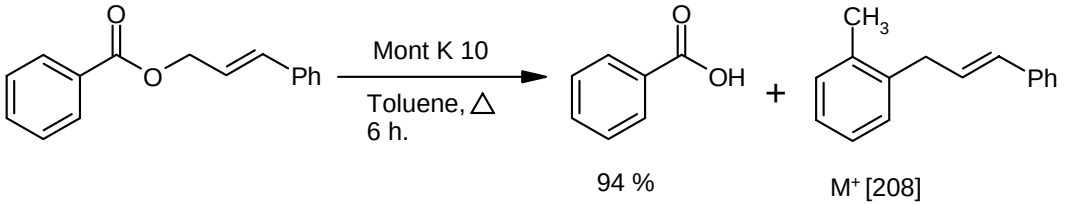
Allyl esters were deprotected with catalyst clay in refluxing toluene as well as under microwave conditions to give carboxylic acid in good to high yield. Although exact mechanism is not known, there can be two possibilities of cleavage of allyl ester (**scheme 10**) considering the pattern of reactivity of various allylic esters dimethyl allyl cinnamyl esters, path 'b' seems to be operative.



Scheme 10: Possible pathway for cleavage of allyl ester and proposed alkylated species

The propensity of reaction of substituted allylic systems over simple allyl can be explained by the increased allylic cation stability provided by alkyl substitution or conjugation. Allyl cation formed after the cleavage via path b, seems to be trapped by nucleophile used such as 1,4-dimethoxybenzene or anisole or solvent used toluene itself to form possible isomers such as **1**, **2** and **3**.

In a representative example (**Table 1, entry 1**) when cinnamyl benzoate was heated in presence of toluene and Mont K 10 clay (20 % w/w) the benzoic acid was isolated in 94 % yield. Where as the organic layer of the same reaction shows a mixture of products. Purification and isolation of single product showed as a molecular ion peak M^+[208], which suggested the formation of mono alkylated product (either **1** or **2**, **scheme 10**).



Scheme 11: Mont K 10 catalyzed allyl ester deprotection via alkylation of toluene

While ^{1}H NMR spectra showed peak at δ 7.61 to 7.23 as a multiplate for 9 protons in aromatic region and none of the *p*-substitution pattern was observed. A typical singlet at δ 2.46 for methyl protons suggests the formation of mono alkylated toluene (with 21 % yield) rather than para or di-alkylation.

Acid chlorides of the substituted benzoic acids such as *p*-nitrobenzoic acid, *p*-methoxy benzoic acid, *p*-methyl benzoic acid, *p*-chloro benzoic acid, phenylacetic acid, furon-2-carboxlic acid, thiophene-2-carboxylic acid were treated with dimethyl allyl alcohol and cinnamyl alcohol to give the corresponding substituted allyl esters. Succinic anhydride when treated with allyl alcohol in basic media gave monoester which on treatment with dimethyl sulphate and K_2CO_3 in refluxing acetone gave diester (**entry 18**, **Table 1**). The allyl esters thus prepared were characterized by IR, ^{1}H NMR and were in agreement with the reported values.[29]

3.2.4 Conclusion

A catalytic efficient deprotection of allyl ester has been achieved in presence of commercially obtained Montmorillonite K 10 clay under microwave conditions.[30] This is in contrast with the earlier reported procedure, which employ harsh conditions, excess oxidizing agents or expensive reagents. The present method is non-oxidative, catalytic and practically irreversible. Since the ease of formation of allyl cation governs the ease of deprotection of allyl esters, normal esters are resistant to the above conditions.

Being a heterogeneous reaction condition the catalyst can be reused and nonpolluting. The present method provides a useful alternative for deprotection of allyl esters. The notable advantages of this methodology are mild and solvent free conditions, short reaction time (10 to 20 min.), chemoselective and its environmental friendly conditions.

3.2.5 Experimental

General procedure for preparation of allyl esters:

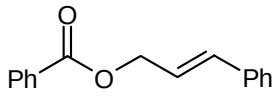
To a stirred solution of allyl alcohol (10 m mol) in dichloromethane (15 ml) at 0°C was added triethylamine (10 m mol) dropwise and stirred for 10-15 min. Acid chloride(10 m mol) was added slowly with vigorous stirring at low temperature for 10 min. The reaction mixture was stirred at 0°C for 2 hrs. and the reaction mixture was allowed to stir at room temperature for another 2 hrs. After completion of the reaction (TLC), dil. HCl was added and the aqueous layer was extracted with dichloromethane. The organic layer was washed with water (10 ml) and brine (2 x 10 ml) and dried over anhydrous sodium sulphate. Evaporation of the solvent was carried out under reduced pressure to give the crude allyl ester, which was further purified by flash chromatography using petroleum ether acetone as eluant. All the allyl esters gave satisfactory spectroscopic and analytic data and are consistent with the reported values.[29]

General procedure for the deprotection of allyl esters: (Thermal or microwave)

To a mixture of the allyl ester (10 mmol.), 1,4-dimethoxybenzene or anisole (15 mmol.) and/or toluene (15 ml, in case of thermal reactions) and catalyst montmorillonite K-10 clay (10% w/w) was added in a glass test tube or in round bottom flask and admixed thoroughly and irradiated in a microwave oven or heated with stirring under reflux condition in oil bath. (Toluene 15 ml as solvent). The reaction was monitored by TLC. After the completion of the reaction, this mixture was cooled to room temperature and the catalyst was separated by filtration. The reaction mixture was concentrated to remove excess of toluene under vacuum. The reaction mixture was diluted with chloroform and washed with 1N NaOH (3-4 times). The aqueous layer was separated and acidified with dil HCl. The acidified aqueous layer was extracted with organic solvent to get the corresponding acid in pure form. The chloroform layer was washed with brine, dried and concentrated to get crude alkylated product, which was purified by column chromatography over silica gel. Pure monoalkylated product can be obtained as one of the products in poor yield.

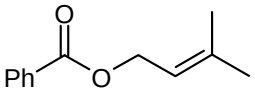
The acids prepared were compared with the authentic samples.

Cinnamyl benzoate:



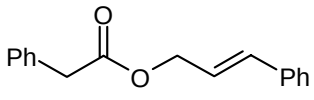
Yield	80%
Appearance	Pale yellow viscous liquid
Mol formula	$C_{16}H_{14}O_2$
IR (Neat)	3020, 2350, 1800, 1720, 1600, 1500, 1450, 1380, 1280, 1180, 980, 580 cm^{-1}
^{1}H NMR (90MHz, $CDCl_3$)	δ 8.00-7.50 (m, 10H), 6.8 (d, J = 16Hz, 1H); 6.50 (dt, J = 6.5, 16.1Hz, 1H); 4.80 (d, J = 6.5Hz, 2H).
Mass m/z (%)**:**	238 (M^+, 5), 133(8), 122 (6), 115(35), 105(100), 91 (12), 77 (55).

Dimethyl allyl benzoate:



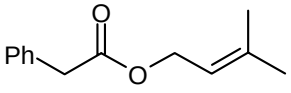
Yield	75%
Appearance	Viscous liquid
Mol formula	$C_{12}H_{14}O_2$
IR (Neat)	3000, 2350, 1720, 1620, 1600, 1450, 1380, 1200, 1080, 920, 580, 450 cm^{-1}
^{1}H NMR (90MHz, $CDCl_3$)	δ 8.10 (m, 2H), 7.50 (m, 3H), 5.50 (t, J = 9.7 Hz, 1H); 4.80 (d, J = 9.7 Hz, 2H); 1.50 (s, 6H).

Cinnamyl phenylacetate



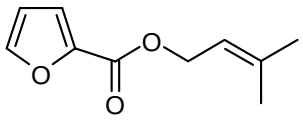
Yield	83%
Appearance	Yellow viscous liquid
Mol formula	$C_{17}H_{16}O_2$
IR (Neat)	3010, 2850, 1740, 1600, 1500, 1450, 1350, 1250, 1150, 980, 750, 550 cm^{-1}
^{1}H NMR (90MHz, $CDCl_3$)	δ 7.40 (m, 10H). 6.70 (d, J = 16.1Hz, 1H); 6.30 (dt, J = 9.7 and 16.3Hz, 1H); 4.80 (d, J=9.7 Hz, 2H); 3.80 (s, 2H)

Dimethyl allyl phenyl acetate



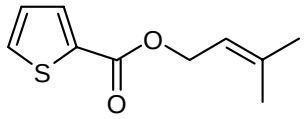
Yield	80%
Appearance	Colorless liquid
Mol formula	$C_{13}H_{16}O_2$
IR (Neat)	2950, 1730, 1600, 1500, 1450, 1380, 1250, 1150, 980, 750, 720, 550 cm^{-1}
^{1}H NMR (90MHz, $CDCl_3$)	δ 7.40 (m, 5H), 5.40 (t, J = 9.7 Hz, 1H); 4.70 (d, J = 9.7 Hz, 2H); 3.70 (s, 2H); 1.80 (s, 6H).

Dimethyl allyl 2-furyl ester



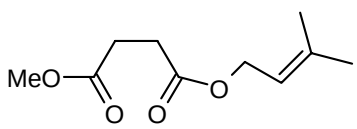
Yield	88%
Appearance	Yellow viscous liquid
Mol formula	$C_{13}H_{16}O_2$
IR (Neat)	2950, 1730, 1600, 1500, 1450, 1380, 1250, 1150, 980, 750, 720, 550 cm^{-1}
^{1}H NMR (90MHz, $CDCl_3$)	δ 7.80 (m, 1H), 7.30 (d, J = 3.6 Hz, 1H), 6.60 (dd, J_1 = 3.6 Hz and J_2 = 2.8 Hz, 1H,), 5.52 (t, J = 9.7 Hz, 1H); 4.95 (d, J = 6.8 Hz, 2H); 2.10 (s, 6H)

Dimethyl allyl 2-thineyl ester



Yield	88%
Appearance	Yellow viscous liquid
Mol formula	$C_{10}H_{12}O_2S$
IR (Neat)	3020, 1720, 1600, 1520, 1480, 1300, 1140, 750, 720, 540 cm^{-1}
^{1}H NMR (90MHz, $CDCl_3$)	δ 8.0 (m, 1H), 7.80 (dd, J = 3.5 Hz and 5.1 Hz, 1H); 7.30 (dd, , J = 3.5 Hz and 2.8 Hz, 1H); 5.55 (t, J = 9.7 Hz, 1H), 4.0 (d, J = 6.6 Hz, 2H), 2.09 (s, 6H).

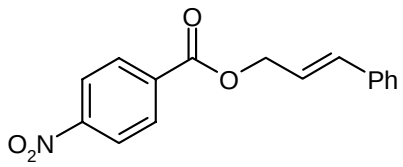
Dimethyl allyl methyl succinate



Yield	62%

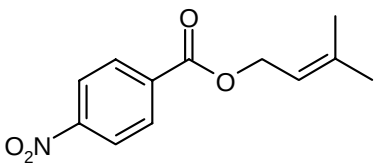
Appearance	Colorless liquid
Mol formula	$C_{10}H_{16}O_4$
IR (Neat)	2950, 1750, 1720, 1450, 1380, 1350, 1250, 1120, 1020, 850, 720, 580 cm^{-1}
^{1}H NMR (90MHz, $CDCl_3$)	δ 5.30 (t, J = 8.1Hz, 1H), 4.50 (d, J = 8.1Hz, 2H), 3.70 (s, 3H); 2.65 (bs, 4H); 1.70 (s, 6H);

Cinnamyl-4-nitro-benzoate: (4-Nitrobenzoic acid-3-phenyl-allyl ester)



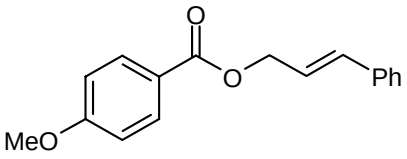
Yield	78%
Appearance	Pale yellow solid
M. p.	113 °C
Mol formula	$C_{16}H_{13}NO_4$
IR (nujol)	3050, 2960, 1725, 1624, 1575, 1402, 1285, 1020, 910, 788, 640, 580 cm^{-1}
^{1}H NMR (90MHz, $CDCl_3$)	δ 8.00-7.50 (m, 9H), 6.8 (d, J = 16.1 Hz, 1H), 6.48 (dt, J = 16.1 and 9.1 Hz, 1H), 4.80 (d, J = 9.1 Hz, 2H)
Mass m/z (%)**:**	283 (M^+, 10), 254 (5), 241 (8), 150 (75), 133 (40), 155 (100), 105 (38), 91 (30), 76 (25).

Dimethyl allyl *p*-nitro-benzoate:



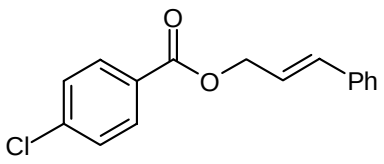
Yield	86%
Appearance	Pale yellow solid
M. p.	63 °C
Mol formula	$C_{12}H_{13}NO_4$
IR (nujol)	3020, 2950, 1720, 1620, 1550, 1410, 1280, 1020, 920, 760, 680, 580 cm^{-1}
^{1}H NMR (90MHz, $CDCl_3$)	δ 8.40-8.12 (m, 4H), 5.50 (t, J = 9.7 Hz, 1H), 4.8 (d, J = 9.7 Hz, 2H), 1.80 (s, 6H)

Cinnamyl 4-methoxy benzoate:



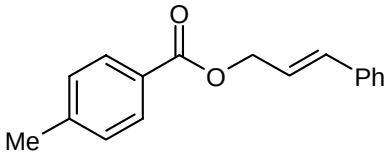
Yield	70%
Appearance	Light yellow viscous liquid
Mol formula	$C_{17}H_{16}O_3$
IR (Neat)	3050, 1720, 1640, 1280, 1020, 550 cm^{-1}
^{1}H NMR (90MHz, $CDCl_3$)	δ 7.30 - 8.00 (m, 9H), 6.90 (d, J = 16 Hz, 1H), 6.45 (dt, J = 16 Hz and 9.7 Hz, 1H), 4.80 (d, J = 9.7 Hz, 2H), 3.85 (s, 3H).

Cinnamyl 4-chloro benzoate:



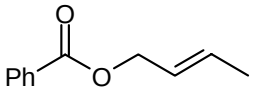
Yield	76%
Appearance	Colourless viscous liquid
Mol formula	$C_{16}H_{13}ClO_2$
IR (Neat)	3030, 1720, 1640,1500, 1450, 1050, 540 cm^{-1}
^{1}H NMR (90MHz, $CDCl_3$)	δ 7.10-8.00 (m, 9H), 6.65 (d, J = 15.8 Hz, 1H), 6.40 (dt, J = 15.8 Hz and 6.5 Hz, 1H), 4.85 (d, J = 6.5 Hz, 2H).

Cinnamal 4-methyl benzoate:



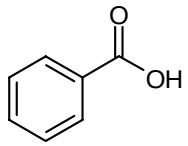
Yield	80%
Appearance	Light yellow viscous liquid
Mol formula	$C_{17}H_{16}O_2$
IR (Neat)	3020, 2350, 1800, 1720, 1600, 1520, 1450, 1300, 1280, 965, 585 cm^{-1}
^{1}H NMR (90MHz, $CDCl_3$)	δ 7.00-8.00 (m, 9H), 6.75 (d, J = 16 Hz, 1H), 6.40 (dt, J = 16 Hz and 6.5 Hz, 1H,), 4.90 (d, J = 6.5 Hz, 2H,), 2.20 (s, 3H,).

Crotyl benzoate:



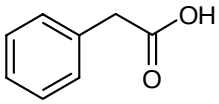
Yield	80%
Appearance	Yellow viscous liquid
Mol formula	$C_{11}H_{12}O_2$
IR (Neat)	3020, 2350, 1800, 1720, 1600, 1500, 1450, 1280, 1150, 1080, 920, 750, 680 cm^{-1}
^{1}H NMR (2000MHz, $CDCl_3$)	δ 8.20-7.41 (m, 5H), 5.9 (m, 1H), 5.8 (dt, J = 7.3 Hz and 12 Hz, 1H), 4.8 (d, J = 7.3 Hz, 2H), 1.8 (d, J = 5.4 Hz, 3H).

Benzoic acid



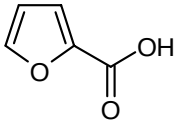
Yield	78%
Appearance	White soild
M. p.	122 °C (lit 122-123 °C)
Mol formula	$C_7H_6O_2$
IR (nujol)	2950, 2800, 1710, 1700, 1600, 1480, 1450, 1380, 1200, 1150, 1300, 1080, 950, 820, 720 cm^{-1}
^{1}H NMR (90MHz, $CDCl_3$)	δ 7.50 (m, 5H), 3.20 (bs, OH, exchangeable proton).

Phenyl acetic acid



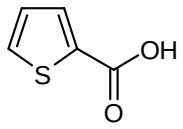
Appearance	White soild
M. p.	77°C (lit 77-78°C).
Mol formula	$C_8H_8O_2$
IR (nujol)	3020, 2980, 2850, 1710, 1600, 1480, 1420, 1250, 850, 780, 710, 550 cm^{-1}
^{1}H NMR (90MHz, $CDCl_3$)	δ 7.4 (m, 5H), 4.2 (bs, 1H, exchangeable proton), 3.60 (s, 2H).

Furon-2-carboxylic acid



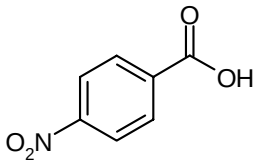
Appearance	White soild
M. p.	129°C (lit 129-130°C).
Mol formula	$C_5H_4O_3$
IR (nujol)	3112, 3010, 2860, 1715, 1660, 1450, 1120, 780 cm^{-1}
^{1}H NMR (90MHz, $CDCl_3$)	δ 7.82 (m, 1H), 7.35 (m, 1H), 6.70 (m, 1H).

Thiophene-2-carboxylic acid



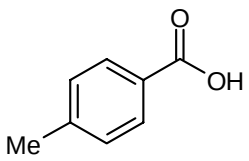
Appearance	Light yellow powder
M. p.	128°C (lit 128-130°C).
Mol formula	$C_5H_4O_2S$
IR (nujol)	3212, 3016, 2860, 1715, 1660, 1370, 1150, 751 cm^{-1}
^{1}H NMR (90MHz, $CDCl_3$+DMSO-D_6)	δ 7.91 (m, 1H), 7.70 (m, 1H), 7.30 (m, 1H).

***p*-Nitro benzoic acid:**



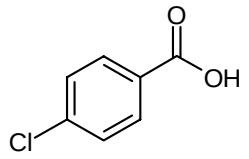
Appearance	Yellow powder
M. p.	240°C (lit 239-241°C).
Mol formula	$C_7H_5NO_4$
IR (nujol)	3000, 2980, 2920, 1710, 1620, 1600, 1500, 1450, 1320, 1280, 1020, 920, 880, 820, 720, 550 cm^{-1}
^{1}H NMR (90MHz, $CDCl_3$)	δ 8.60 (br, s, 1H), 7.63 (m, 4H).

***p*-Toluic acid:**



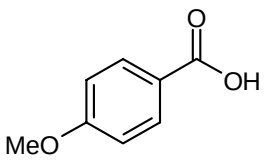
Appearance	White solid
M. p.	182°C (lit 180-182°C).
Mol formula	$C_8H_8O_2$
IR (nujol)	3000, 2980, 2920, 1710, 1620, 1600, 1450, 1320, 1280, 1020, 920, 720, 550 cm^{-1}
^{1}H NMR (90MHz, DMSO-d_6+$CDCl_3$)	δ 8.50 (br, s, 1H), 7.95 (d, J = 8.3 Hz, 2H), 7.30 (d, J = 8.3 Hz, 2H), 2.39 (s, 3H).

***p*-Chloro benzoic acid:**



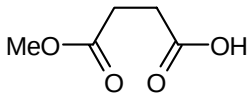
Appearance	White solid
M. p.	240°C (lit 239-241°C).
Mol formula	$C_7H_5ClO_2$
IR (nujol)	3010, 2975, 2920, 1730, 1640, 1610, 1500, 1450, 1280, 910, 858, 550 cm^{-1}
^{1}H NMR (90MHz, DMSO-d_6+$CDCl_3$)	δ 7.95 (d, J = 8.3 Hz, 2H), 7.50 (br, s, 1H), 7.35 (d, J = 8.3 Hz, 2H).

_p_-Methoxy benzoic acid:



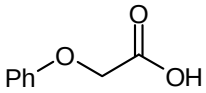
Appearance	White solid
M. p.	184°C (lit 182-185°C).
Mol formula	$C_8H_8O_3$
IR (nujol)	3030, 2960, 2875, 1710, 1622, 1605, 1500, 1460, 1550, 910, , 540 cm^{-1}
^{1}H NMR (90MHz, $CDCl_3$)	δ 9.30 (br, s, 1H), 7.91 (d, J = 8.3 Hz, 2H), 6.95 (d, J = 8.3 Hz, 2H).

Monomethyl succinate



Appearance	Viscous liquid
Mol formula	$C_5H_8O_4$
IR (nujol)	3400, 3000, 2850, 1720, 1450, 1180, 920, 750 cm^{-1}
^{1}H NMR (90MHz, $CDCl_3$)	δ 4.20 (bs, 1H exchangeable proton), 3.70 (s, 3H); 2.60 (s, 4H).

Phenoxy acetic acid:



Appearance	Red solid
M. p.	98°C (lit 98-100°C).
Mol formula	$C_8H_8O_3$
IR (nujol)	3020, 2900, 2850, 1740, 1710, 1620, 1600, 1490, 1450, 1380, 1250, 1100, 980, 780 cm^{-1}
^{1}H NMR (90MHz, $CDCl_3$)	δ 7.40 (m, 5H), 4.40 (s, 2H).

3.2.6 References

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CHAPTER 3

Section C

Clay Catalyzed Acetonide Protection of *N*(Boc)-Amino Alcohol and 1, 2-Diols

3.3.1 Introduction

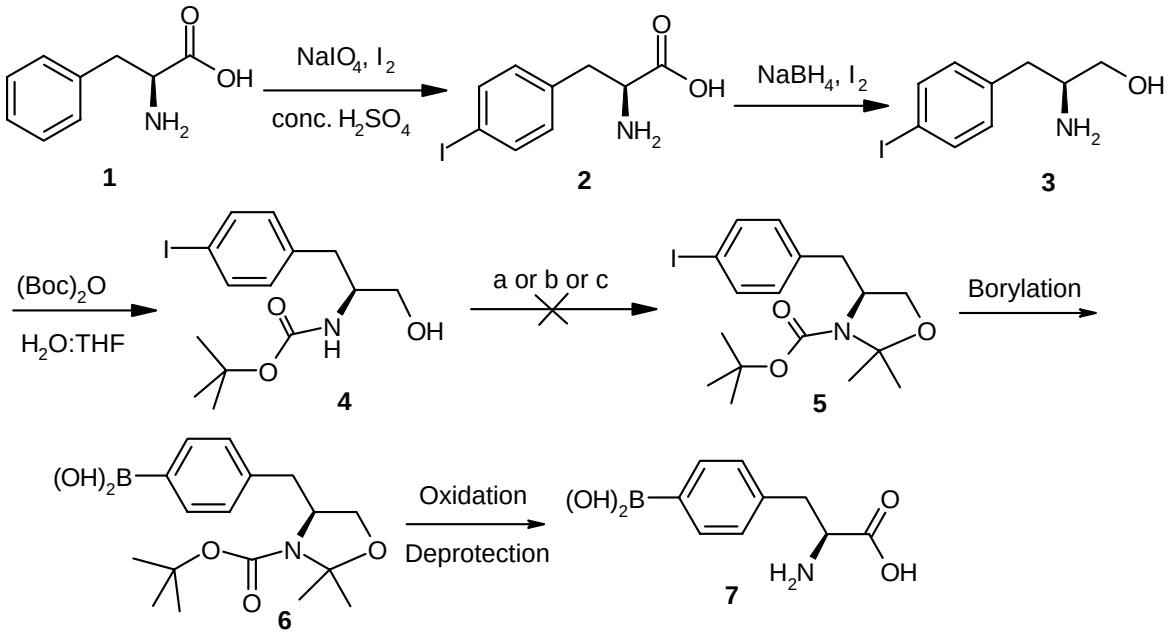
The acetonide functionality is frequently used as a protecting group for 1, 2-amino alcohols and 1,2-diols in carbohydrate and peptide chemistry[1] due to it's stability to mildly acidic as well as basic conditions. During the course of synthetic sequence, most of the times it becomes necessary to protect a free hydroxyl or amino groups present in the substrate or the intermediate. Many syntheses failed just because the protecting groups gave poor results giving low overall yield or protecting groups were unable to cleave at the appropriate step.[2] Hence in effecting an efficient conversion of functional groups present in the side chain of 1, 2-aminoalcohols and 1, 2-diols an appropriate protection of amine and alcohol functionality is highly desirable.

Classical acetonation of diols in carbohydrates have been achieved with acetone with several mineral acids, such as conc. sulphuric acid or fuming HCl or phosphoric acid, in the presence or absence of copper (II) sulfate or zinc chloride.[3] Use of 2,2-dimethoxy propane (DMP), CSA (Camphorsulphonic acid), catalytic amount of *p*-TsOH in combination with appropriate solvent such as DMF is useful for conversion of 1,2-diequatorial hydroxyl groups of carbohydrates into isopropylidene derivatives.[4,5] However 1,2-amino(Boc) alcohol can be protected to oxazolidene using DMP and PPTS (pyridinium p-toluenesulphonate) at ambient temperature.[6] While dil. HCl, TFA (trifluoro acetic acid) and methanolic *p*-TsOH[2] are the reagents generally used for the deprotection of acetonide to obtain parent diol or amino alcohol.

Although several methods are available for the protection of 1,2 diols to isopropylidene in sugar moiety and for 1,2 amino alcohols to corresponding oxazolidine derivatives.[1] However the development of mild and efficient methods is still entailing. Recently in the course of our studies directed towards the total synthesis of "4-borono-*L*-phenylalanine" (as shown in **scheme 1**) the acetonide protection of N(Boc)-protected amino alcohol **4** to give the protected derivative of phenylalaniol **5** was unsatisfactory with $BF_3.OEt_2$,[7] *p*-TsOH and $CuSO_4$ in presence of acetone and/or DMP; decomposed material was obtained in the first case whereas a mixture of products or low yield of desired compound **5** in later case was observed.

3.3.2 Present Work

During the synthesis of *L*-4-boronophenylalanine; an important compound used in "Boron Neutron Capture Therapy"[8a] it was proposed to prepare the acetonide protection of amino alcohol **4** to obtain protected derivative **5** (**Scheme 1**).



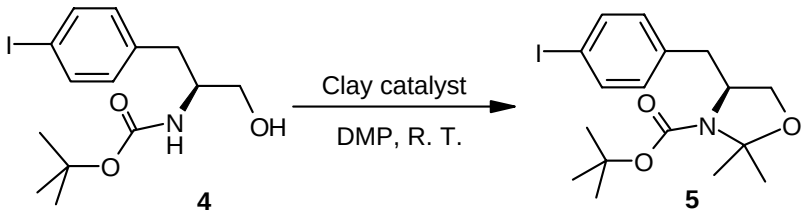
a: p-TsOH, 2, 2-DMP or acetone heat; b:BF_3.OEt_2, acetone or 2, 2-DMP;
c: $CuSO_4$, Acetone, conc. H_2SO_4

Scheme 1: Synthetic sequence for 4-borono-*L*-phenylalanine

The route designed for the synthesis of medicinally important precursor **7** involved[8b] selective iodination of enantiopure *L*-phenylalanine (**1**) to **2**, reduction of amino acid to amino alcohol using $NaBH_4$ in presence of iodine to get **3** followed by N-Boc protection of amine to obtain compound **4**. Further it was decided to protect both the β-OH and the α-carbamate -NH functionalities simultaneously through oxazolidine formation. 2,2-DMP with catalytic p-TSOH gave only 10 % of required protected compound **5**. While rest of the material got decomposed. Use of BF_3.OEt_2 along with acetone or 2,2-DMP gave a complex mixture and no desired comp. **5** could be isolated. Using $CuSO_4$ in dry acetone in presence of catalytic amount of conc. H_2SO_4 resulted in a mixture of compounds including 26 % of desired protected derivative **5**.

3.3.3 Results and discussion

Recently, clay minerals have become available for organic syntheses as heterogeneous acid catalysts. Commercially available Montmorillonite K 10 clay has been used successfully in many important organic transformations (as mentioned in **Chapter 2, Section A**). The experimental procedure using clay is simple with regard to treatment and removal of the catalyst because of the non hygroscopic and insoluble property of clay mineral.

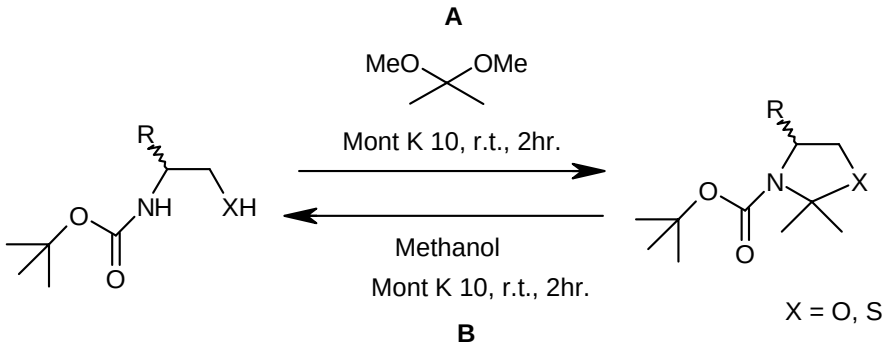


4 **5**

Scheme 2: Clay catalysed protection of amino alcohol

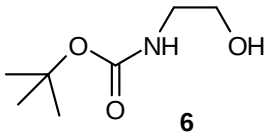
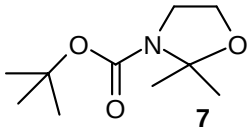
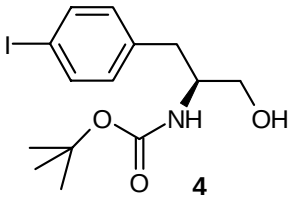
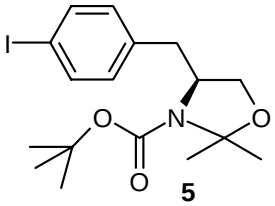
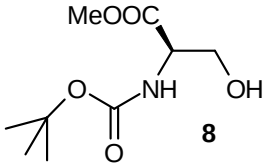
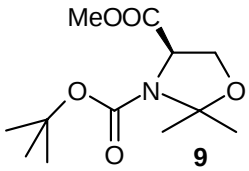
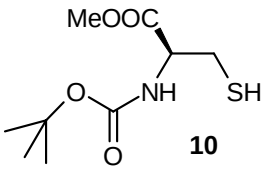
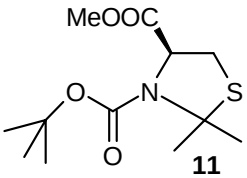
As application of clay in Lewis acid catalyzed reactions is ongoing interest for us, we applied Mont K 10 clay in acetone under reflux temperature to convert **4** into **5**. Only negligible amount of required comp. **5** was isolated. But when acetone was replaced with 2,2-DMP in excess, complete conversion of starting **4** was observed. Comp. **5** was isolated as the only product in excellent yield. . In a typical experiment when derivative **4** was stirred in the mixture of dry acetone and DMP (3 equivalents) in presence of Mont K 10 clay (20 %) 75 % of desired product **5** was isolated (3 h.)

Selective removal of isopropylidene protection was attempted using methanolic *p*-TsOH at room temperature; was incomplete after 14 h. Furthermore when reaction was refluxed for 1 h. in methanolic solution of *p*-TsOH, partial deprotection of Boc was observed. The clay catalyst was examined for the selective cleavage of acetonide **5** to obtain **4**. Methanol when used as a solvent; reaction preceded and completed within 2 h. to obtain comp. **4** in quantitative yield without affecting Boc group. These results prompted us to develop a simple catalytic system for different substrates for protection and deprotection as shown in **scheme 3**. The results for both the reactions (A and B) are summarized in **table 1**.



Scheme 3: Clay catalyzed protection (A) and deprotection (B) of N(Boc)-amino alcohol

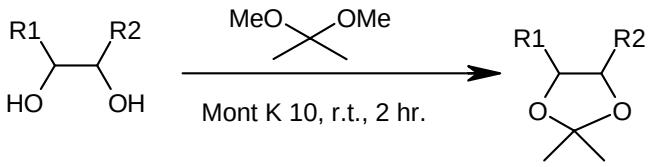
Table 1: Clay catalyzed acetonide protection (A) and deprotection (B) of 1,2-amino alcohol

Entry	Substrate	Product	Yield (%) **A**	Yield (%) **B**
1	 **6**	 **7**	95 91[a] 93[b] 15[c]	98 95[a] 97[b] 20[c]
2	 **4**	 **5**	94 0[c] 92[d]	95 10[c] 98[d]
3	 **8**	 **9**	85	82
4	 **10**	 **11**	82	81

a: Using EPZG[R], b: using Natural kaolinitic clay, c: without catalyst for 24 h.,
d: with recycled catalyst

Model substrate N(Boc) protected ethanolamine underwent acetonation reaction using Montmorillonite K 10 clay in presence of DMP to get 95 % of protected compound within 2 h. Natural kaolinitic clay and EPZG® also showed comparable results in both protection and deprotection of acetonide. While in blank experiment (without catalyst), it took 24 h. and obtained poor yield (**table 1, entry 1**) of desired protected compound (15 % and 20 %). Another substrate, methyl ester of N(Boc) protected *L*-serine gave almost identical yield for protection and good yield after deprotection reaction (**table 1**, **entry 3**). Such fully protected serine derivative has many synthetic applications including preparation of valuable unnatural α-amino acids.[9a] Optical rotation for this compound is in good agreement with reported value indicating no loss in optical purity during the transformation. Similar observation was made in case of methyl ester of N(Boc) *L*-cystein to obtain thiazolidine[9b] (**entry 4**). In all the cases studied during protection and deprotection underwent smoothly keeping N-Boc group intact. However reaction failed to undergo protection of free 1,2-amino alcohol such as *L*-phenylalaniol and ethanolamine without Boc protection of amine.

Similar strategy was applied for the acetonide protection of 1, 2-diols to convert them into corresponding isopropylidene ketal (**Scheme 4**).



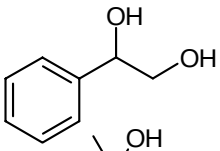
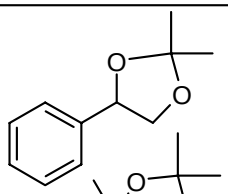
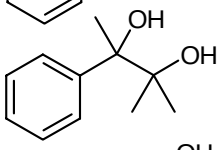
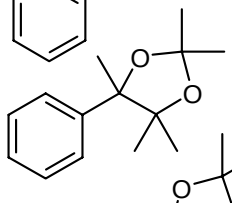
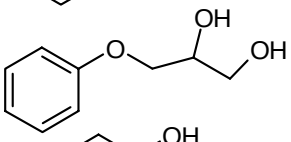
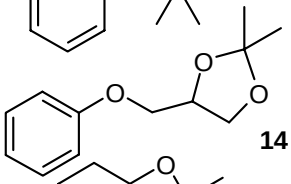
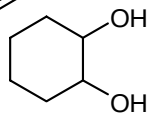
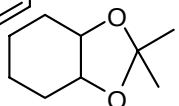
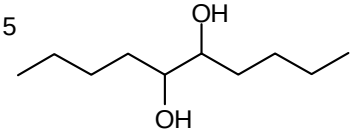
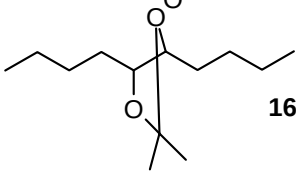
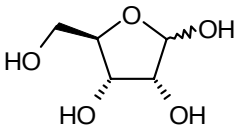
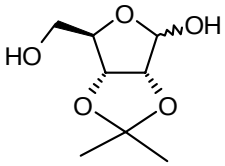
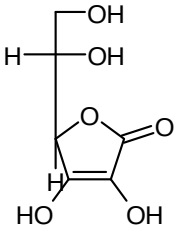
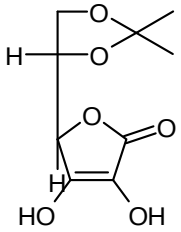
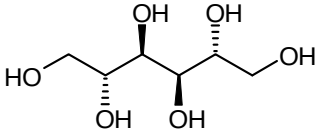
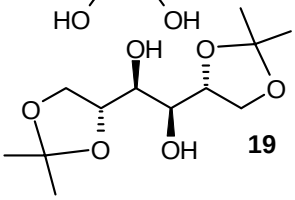
Scheme 4: Mont K 10 catalyzed acetonide protection of 1,2-diols

Different 1, 2-diols were studied for this transformation and the results are summarized in **table 2**. 1,2-Diol of styrene when stirred with 2,2-DMP in presence of clay catalyst (40 % w/w), corresponding isopropylidene derivative (**table 2, entry 1**) was obtained with 87 % isolated yield. As shown in **table 2**, satisfactory yields were obtained in all the cases including cyclic, linear aliphatic and sugar diols. In case of D-mannitol alongwith diacetonide (**table 2, entry 8**) triacetonide formation was observed with 25% isolated yield.

Unfortunately reaction does not work for D-glucose even after heating for 12 h. Also, reaction failed to undergo acetonation in case of *o*-hydroxy phenol.

As in the case of N(Boc)amino alcohols, deprotection of acetonide of 1,2-diols was studied. When deprotection was carried out using MeOH and clay catalyst, reaction does not occur even at reflux temperature.

Table 2: Mont K 10 catalyzed acetonide protection of 1, 2-diols

Entry	Substrate	Product[a]	Yield (%)[b]
1		 **12**	87
2		 **13**	80
3		 **14**	84
4		 **15**	92
5		 **16**	74
6		 **17**	90
7		 **18**	52[c]
8		 **19**	60[d]

a: All the products are characterised by usual spectral analysis,
b: Isolated yields, c: reaction time 8 h., d: 25 % of triacetonide **(20)** was isolated

Further this type of transformation (acetonide deprotection) is found to be known by "CLAYAN" (ammonium nitrate supported clay)[10a] or $CeCl_3$ in presence of oxalic acid[10b] is effective in deprotection of acetonide in case of diols.

It is assumed that the acidity of the clay catalyst is not sufficient to cleave the acetonide in case of 1, 2-diols.

3.3.4 Conclusion

The application of clay as a catalyst for acetonide protection of *N*(Boc)amino alcohol and 1,2 diols have been successfully carried out. Yields of the acetonide protected derivatives of amino alcohol are good to excellent. Also deprotection of acetonide to obtain parent amino alcohol was carried out using similar catalyst in presence of methanol as a solvent. Reaction takes place at room temperature within 2 h. to give parent amino alcohols in quantitative yields keeping *N*(Boc) group intact. The catalyst is recycled and reused for successive set of reaction without any loss in catalytic activity.

Reaction failed to undergo acetonide protection in case of free amino alcohol such as phenylalaniol, ethanolamine and *L*-serine [i.e. substrate without *N*(Boc) protection]. Also cleavage of acetonide did not take place in case of 1,2-diols using Mont K 10 clay in methanol even at high temperature.

Thus mild and efficient method for the protection and deprotection of N-Boc protected 1,2-amino alcohols, 1,2-amino thiol and acetonide formation of 1, 2-diols have been developed using heterogeneous catalyst. Short reaction time, higher yields of desired products and simple workup procedure are the main features of this method.

3.3.5 Experimental

L-serine and *L*-cystein were converted to corresponding methyl ester and N-Boc-protection by known procedure.[7] 4-Iodo-*L*-phenylalanine **(2)**[11a] and 4-Iodo-L-phenylalaniol **(3)**[11b] were prepared by reported procedure.

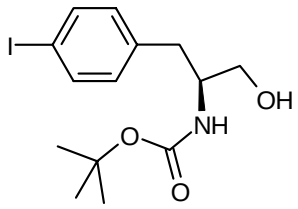
A) Acetonide protection of *N*(Boc)-protected 1, 2-amino alcohol and 1, 2-diols:

General procedure: Substrate (amino alcohol or 1, 2-diol: 5 mmol) was stirred wih 2, 2-DMP (8 ml) in presence of (20 % w/w) clay (40 % in case of diol) under argon atmosphere at room temperature. After complete conversion of substrate (TLC), the reaction mixture was filtered and catalyst was washed with dry acetone. The filtrate was concentrated to get crude product in the form of viscous oil. Further purification by column chromatography over neutral alumina (or preparative TLC) gave desired product in pure form.

B) Acetonide deprotection of *N*(Boc)-protected 1, 2-amino alcohol:

General procedure: Acetonide protected derivative of amino alcohol (2 mmol) was stirred with methanol (10 ml) in presence of clay catalyst (20 % w/w) at room temperature for 2 h. After complete conversion of substrate (monitored by TLC) reaction mixture was filtered and filtrate was concentrated to get crude product. Further column chromatographic purification of the crude product gave desired deprotected compound.

[1-Hydroxymethyl-2-(4-iodo-phenyl)-ethyl]-carbamic acid *tert*-butyl ester: (4)



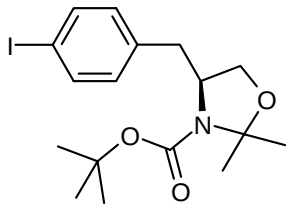
Appearance Colorless viscous oil

IR ($CHCl_3$) 3430, 3380, 3015, 2397, 1700, 1676, 1511, 1420, 1211, 919, 759, 666 cm^{-1}

^{1}H NMR (200MHz, $CDCl_3$): 7.61 (d, J = 8 Hz, 2H), 6.95 (d, J = 8 Hz, 2Hz), 4.75 (br, s, 1H),

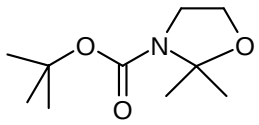
	3.80 (br, s, 1H), 3.60 (dd, J_1 = 3.4 Hz, J_2 = 9.3 Hz, 2H), 2.78 (d, 7.3 Hz, 2H), 2.21 (m, 1H), 1.41 (s, 9H).
^{13}C NMR (75MHz, $CDCl_3$)	155, 137.3, 131.1, 91.5, 79.4, 63.5, 36.5, 28.1
Mass m/z (%):	377 (M^+, 5), 321 (22), 304 (15), 290 (6), 260 (16), 217 (40), 160 (100), 128 (10), 104 (50), 90 (10), 57 (20).
Microanalysis:	Calculated for $C_{14}H_{20}INO_3$; C; 44.58; H: 5.34; N 3.71, I 33.64 Found: C: 44.72; H: 5.67; N: 3.48 I: 33.41 %.

4-(4-Iodo-benzyl)-2,2-dimethyl-oxazolidine-3-carboxylic acid *tert*-butyl ester: (**Scheme 2: 5**)



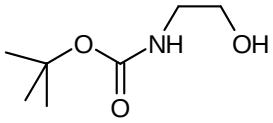
Appearance	Colorless viscous oil
IR ($CHCl_3$)	3015, 2397, 1700, 1676, 1511, 1420, 1211, 919, 759, 666 cm^{-1}
^{1}H NMR (200MHz, $CDCl_3$):	7.60 (d, J = 8.3 Hz, 2H), 6.99 (d, J = 8.3 Hz, 2H), 3.81 (m, 1H), 3.58 (m, 2H), 2.79 (d, J = 7.3 Hz, 2H), 1.52 (s, 6H), 1.40 (s, 9H).
^{13}C NMR (75MHz, $CDCl_3$)	155, 138, 137.3, 131.4, 100, 91.5, 79.1, 61.2, 51.5, 37.6, 28.4, 24.4.
Mass m/z (%):	417 (M^+, 5), 377 (9), 344 (50), 290 (10), 217 (20), 174 (25), 158 (20), 118 (100), 100 (20).
Microanalysis:	Calculated for $C_{17}H_{24}NIO_3$; C 48.93, H 5.80, I 30.41, N 3.36, Found: C: 48.67, H: 6.11; I 30.10, N: 3.61 %.
Optical rotation $[\alpha]_D^{24}$	-34.32 (C = 4, $CHCl_3$).

2,2-Dimethyl-oxazolidine-3-carboxylic acid *tert*-butyl ester: (Table 1, entry 1)



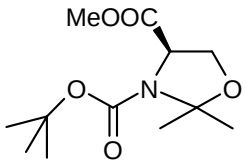
Appearance	Colorless oil
IR ($CHCl_3$)	3035, 2990, 2915, 2300, 1700, 1676, 1541, 1150 cm^{-1}
^1H NMR (200MHz, $CDCl_3$):	4.07-3.81 (m, 2H), 3.71-3.35 (m, 2H), 1.49 (br, s, 3H), 1.45 (br, s, 3H), 1.42 (s, 9H).
Mass m/z (%):	201 (M^+, 1), 186 (25), 130 (100), 86 (75), 70 (30), 57 (55)

(2-Hydroxyethyl)carbamic acid *tert*-butyl ester:



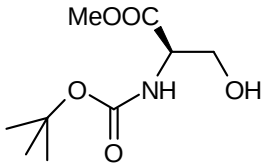
Appearance	Colorless oil
IR (Neat)	3303, 3097, 2935, 1705, 1528, 1430, 1060 cm^{-1}
^1H NMR (200MHz, $CDCl_3$):	δ 5.25 (br, s, 1H), 3.58 (m, 2H), 3.22 (m, 2H), 2.66 (br, s, 1H), 1.41 (s, 9H).
Microanalysis:	Calculated for $C_7H_{15}NO_3$; C; 52.16; H: 9.38; N 8.69 Found: C: 52.42; H: 9.67; N: 8.47 %.

2,2-Dimethyl-oxazolidine-3,4-dicarboxylic acid 3-tert-butyl ester 4-methyl ester: (Table 1, entry 3)



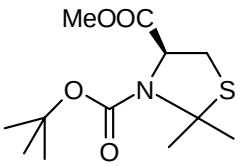
Appearance	Colorless oil
IR (Neat)	3100, 3097, 2935, 1760, 1705, 1528, 1430, 1060 cm^{-1}
^{1}H NMR (200MHz, C_6D_6):	δ 4.26 (m, 1H), 3.81 (dd, J = 8.5 and 3.3 Hz, 1H), 3.75 (m, 1H), 3.37 (s, 3H), 1.78 (br, s, 3H), 1.51 (s, 3H), 1.41 (s, 9H).
Microanalysis:	Calculated for $C_{12}H_{21}NO_5$; C; 55.58; H: 8.16; N 5.40 Found: C: 55.82; H: 8.37; N: 5.58 %.
Optical rotation $[\alpha]_D^{24}$	-45.5 (1, $CHCl_3$) lit.[11] -46.7 (1.30, $CHCl_3$)

2-*tert*-Butoxycarbonylamino-3-hydroxy-propionic acid methyl ester:



Appearance	Colorless oil
IR (Neat)	3400, 3000, 1720 cm^{-1}
^{1}H NMR (200MHz, C_6D_6):	δ 5.56 (br, s, 1H), 4.42 (m, 1H), 3.73 (dd, J = 11 and 4 Hz, 1H), 3.64 (dd, J = 11 and 4 Hz, 1H), 3.28 (s, 3H), 2.52 (br, s 1H), 1.41 (s, 9H).
Microanalysis:	Calculated for $C_9H_{17}NO_5$; C; 49.31; H: 7.82; N 6.39 Found: C: 49.67; H: 8.10; N: 6.48 %.

2,2-Dimethyl-thiazolidine-3,4-dicarboxylic acid 3-tert-butyl ester 4-methyl ester: (table 1, entry 4)



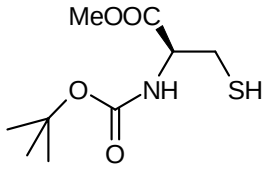
Appearance	Colorless oil
IR (Neat)	3303, 3097, 2935, 1715, 1620, 1528, 1430, 1060 cm^{-1}
^{1}H NMR (200MHz, $CDCl_3$):	δ 3.81 (s, 3H), 3.76 (dd, J = 7.8 and 4.5 Hz, 1H), 3.61-3.35 (m,

2H), 1.73 (s, 3H), 1.62 (br, s, 3H), 1.41 (s, 9H)

Microanalysis: Calculated for $C_{12}H_{21}NO_4S$; C; 52.34; H: 7.69; N 5.09, S: 11.64

Found: C: 52.64; H: 7.80; N: 5.48; S: 11.95 %.

2-*tert*-Butoxycarbonylamino-3-mercapto-propionic acid methyl ester:



Appearance Colorless oil

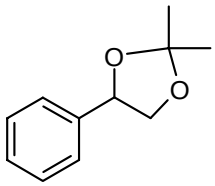
IR (Neat) 3363, 3097, 2945, 1705, 1660, 1528, 1430, 1060, 885 cm^{-1}

^{1}H NMR (200MHz, $CDCl_3$): δ 5.42 (m,1H), 4.61 (m, 1H), 3.78 (s, 3H), 3.35 (m, 1H), 3.18 (m, 2H), 1.42 (s, 9H)

Microanalysis: Calculated for $C_9H_{17}NO_4S$; C; 45.94; H: 7.28; N 5.95, S 13.63

Found: C: 45.76; H: 7.57; N: 5.66, S: 13.41 %.

2,2-Dimethyl-4-phenyl-[1,3]dioxolane: (Table 2, entry 1)



Appearance Colorless oil

IR (KBr) 2986, 2875, 1455, 1380, 1371, 1219, 1156, 1059, 861, 755, 699, 507, cm^{-1}

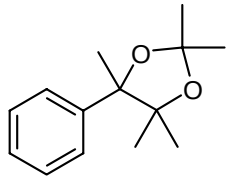
^{1}H NMR (400MHz, $CDCl_3$): δ 7.25 (m, 5H), 4.99 (dd, J = 8.1 and 6.1 Hz, 1H), 4.22 (dd, J = 8.3 and 6.1 Hz, 1H), 3.6 (t, J = 8.1 Hz, 1H), 1.48 (s, 3H), 1.47 (s, 3H).

^{13}C NMR (100MHz, $CDCl_3$): 139.5, 129, 128.5, 126.5, 110.1, 78.4, 72.1, 27, 26.4.

MS m/z (%): 178 (M^+, 10), 163 (65), 120 (50), 103 (15), 91 (40), 77 (15), 72 (80), 43 (100), 39 (10)

Microanalysis: Calculated for $C_{11}H_{14}O_2$; C; 74.13; H: 7.92
Found: C: 74.32; H: 8.27%.

2,2,4,4,5-Pentamethyl-5-phenyl-[1,3]dioxolane: (Table 2, entry 2)



Appearance Colorless oil

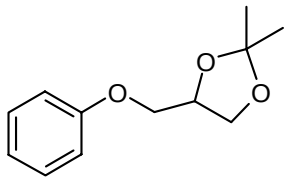
IR (KBr) 3060, 2985, 2938, 1495, 1446, 1371, 1224, 1153, 1062,1008, 925, 843, 763, 702, 565 cm^{-1}

^{1}H NMR (400MHz, $CDCl_3$): δ 7.37-7.35 (m, 2H), 7.26-7.21 (m, 2H), 7.20-7.14 (m, 1H), 1.53 (s, 3H), 1.47 (s, 6H), 1.37 (s, 3H), 0.76 (s, 3H).

^{13}C NMR (100MHz, $CDCl_3$): 144.3, 128.4 (2C), 127.1, 125.1 (2C), 107.2, 86.9, 83.9, 30.6, 30.1, 27.6, 26.6, 24.7

Microanalysis: Calculated for $C_{14}H_{20}O_2$; C; 76.33; H: 9.15
Found: C: 76.52; H: 9.47%.

***) 2,2-Dimethyl-4-phenoxymethyl-[1,3]dioxolane: (Table 2, entry 3)**



Appearance Colorless oil

IR (KBr) 3056, 2993, 2978, 2945, 2889, 1601, 1500, 1250, 1049, 973, 838, 759, 693, 512cm^{-1}

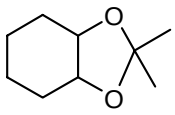
^{1}H NMR (200MHz, $CDCl_3$): δ 7.25-7.15 (m, 2H), 6.93-6.78 (m, 3H), 4.48-4.36 (m, 1H), 4.12 (m, 1H), 4.05 (m, 1H), 3.75 (m 2H), 1.41 (s, 3H), 1.32 (s, 3H)

^{13}C NMR (100MHz, $CDCl_3$): δ 159, 130, 121.5, 114.9, 110.2, 74.5, 69.1, 67.3, 27.2, 25.8

MS m/z (%): 208 (M^+, 60), 193 (90), 133 (70), 101 (100), 77 (30), 43 (50)

Microanalysis: Calculated for $C_{12}H_{16}O_3$; C; 69.21; H: 7.74
Found: C: 69.53; H: 7.97%.

2,2-Dimethyl-hexahydro-benzo[1,3]dioxole: (Table 2, entry 4)



Appearance Colorless oil

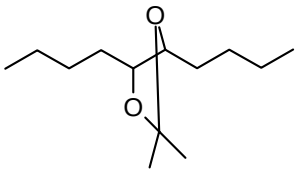
IR (Neat) 2932, 2860, 1375, 1240, 1170, 1100, 920 cm^{-1}

^{1}H NMR (400MHz, $CDCl_3$): δ 4.05 (m, 2H), 1.81-1.35 (m, 4H), 1.34 (s, 3H), 1.30 (s, 3H), 1.31-1.12 (m, 4H).

^{13}C NMR (100MHz, $CDCl_3$): δ 108, 74.1, 28.9, 28.7, 26.8, 21.3

Microanalysis: Calculated for $C_9H_{16}O_2$; C; 69.19; H: 10.32
Found: C: 69.33; H: 10.17%.

4,5-Dibutyl-2,2-dimethyl-[1,3]dioxolane: (Table 2, entry 5)

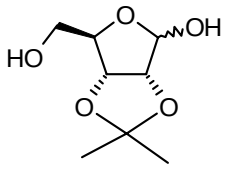


Appearance Colorless oil

IR (Neat) 2958, 2861, 1467, 1377, 1241, 1171, 1104, 1041, 865, 518 cm^{-1}

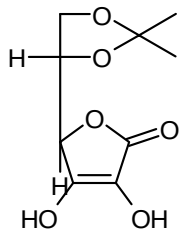
^{1}H NMR (200MHz, $CDCl_3$):	δ 3.52 (m, 2H), 1.42 (m, 6H), 1.31 (s, 6H), 1.27 (m, 6H), 0.84 (t, J = 7.1 Hz, 6H).
^{13}C NMR (100MHz, $CDCl_3$):	δ 108.1, 81.4, 33.1, 28.7, 27.7, 23.3, 14.4
MS m/z (%):	213 (M^+-1; 5), 199 (100), 157 (30), 139 (7), 128 (20), 113 (45), 97 (30), 83 (65), 59 (50), 43 (40), 29 (10).
Microanalysis:	Calculated for $C_{13}H_{26}O_2$; C; 72.84; H: 12.23 Found: C: 72.63; H: 12.55%.

6-Hydroxymethyl-2,2-dimethyl-tetrahydro-furo[3,4-*d*][1,3]dioxol-4-ol:
(or 2,3-*O*-isopropylidene-α-D-lyxofuranose) (Table 2, entry 6)



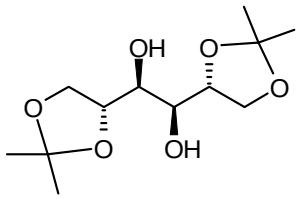
Appearance	Colorless oil
IR (Nujol)	3420, 3100, 1430, 1250, 880 cm^{-1}
^{1}H NMR (200MHz, acetone-D_6):	δ 5.24 (d, J = 3.8 Hz, 1H), 5.21 (d, J = 3.8 Hz, 1H), 4.82 (dd, J = 5.9 and 3.8 Hz, 1H), 4.54 (d, J = 5.9 Hz, 1H), 4.18 (m, 1H), 3.82 (m, 1H), 3.72 (m, 1H), 3.61 (dd, J = 6.5 and 5.5 Hz, 1H), 1.36 (s, 3H), 1.28 (s, 3H).
Microanalysis:	Calculated for $C_8H_{14}O_5$; C; 50.52; H: 7.42 Found: C: 50.68; H: 7.75%.

5-(2,2-Dimethyl-[1,3]dioxolan-4-yl)-3,4-dihydroxy-5*H*-furan-2-one:
or **(O5,O6-isopropylidene-*L*-ascorbic acid) (Table 2, entry 7)**



Appearance	White solid
M. p.	221 °C (lit., 214-218 °C)[12a]
IR (Nujol)	3250, 3110, 2840, 1754, 1660, 1450, 1330, 1150, 1050, 885, 820, 620 cm^{-1}
^{1}H NMR (200MHz, DMSO-D_6 + $CDCl_3$):	δ 10.8 (br, s, 1H), 8.4 (br, s, 1H), 4.4 (d, J = 3 Hz, 1H), 3.82-4.50 (m, 3H), 1.34 (s, 6H).
MS m/z (%):	216 (M^+, 10), 201 (30), 141 (28), 129 (12), 113 (18), 101 (100), 85 (35), 73 (15), 59 (10).
Microanalysis:	Calculated for $C_9H_{12}O_6$; C; 50.00; H: 5.59 Found: C: 50.38; H: 5.73%.
Optical rotation $[\alpha]_D^{24}$	+13.4 (1, methanol); [Lit. +15 (1, ethanol)][12b]

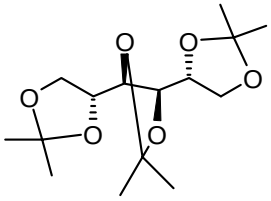
1,2-Bis-(2,2-dimethyl-[1,3]dioxolan-4-yl)-ethane-1,2-diol:
(or 1,2:5,6-Di-O-isopropylidene-D-mannitol) (Table 2, entry 8)



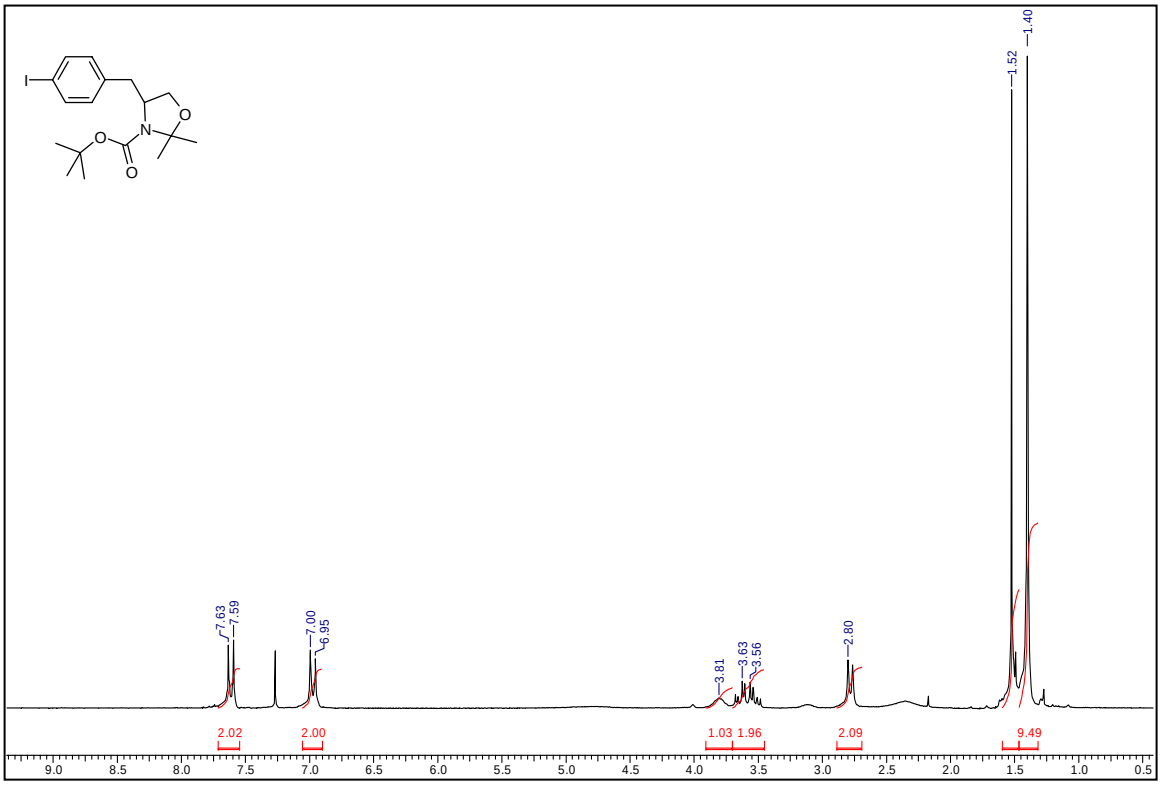
Appearance	White solid
M. p.	125 °C (lit., 123-124 °C)
IR (nujol)	3390, 3280, 2970, 1370, 1250, 1075, 945, 850, 665 cm^{-1}
^{1}H NMR (200MHz, $CDCl_3$):	δ 4.18-4.07 (m, 4H), 4.03-3.81 (m, 2H), 3.70 (t, J = 6 Hz, 2H), 2.81 and 2.79 (br, d, 2H for 2 ×-OH), 1.40 (s, 6H), 1.35 (s, 6H).
^{13}C NMR (50MHz, $CDCl_3$):	δ 109.2 (2C), 75.8 (2C), 70.9 (2C), 66.7 (2C), 26.7 (2C), 25.2

	(2C)
Mass m/z (%):	247 (M^+-15), 189 (18), 147 (5), 131 (15), 111 (21), 101 (90), 83 (25), 73 (50), 59 (100).
Microanalysis:	Calculated for $C_{12}H_{22}O_6$; C; 54.95; H: 8.45 Found: C: 55.18; H: 8.52%.
Optical rotation $[\alpha]_D^{24}$	+2.4 (2.2, methanol); [Lit. +1.9 (2, methanol)][12b]

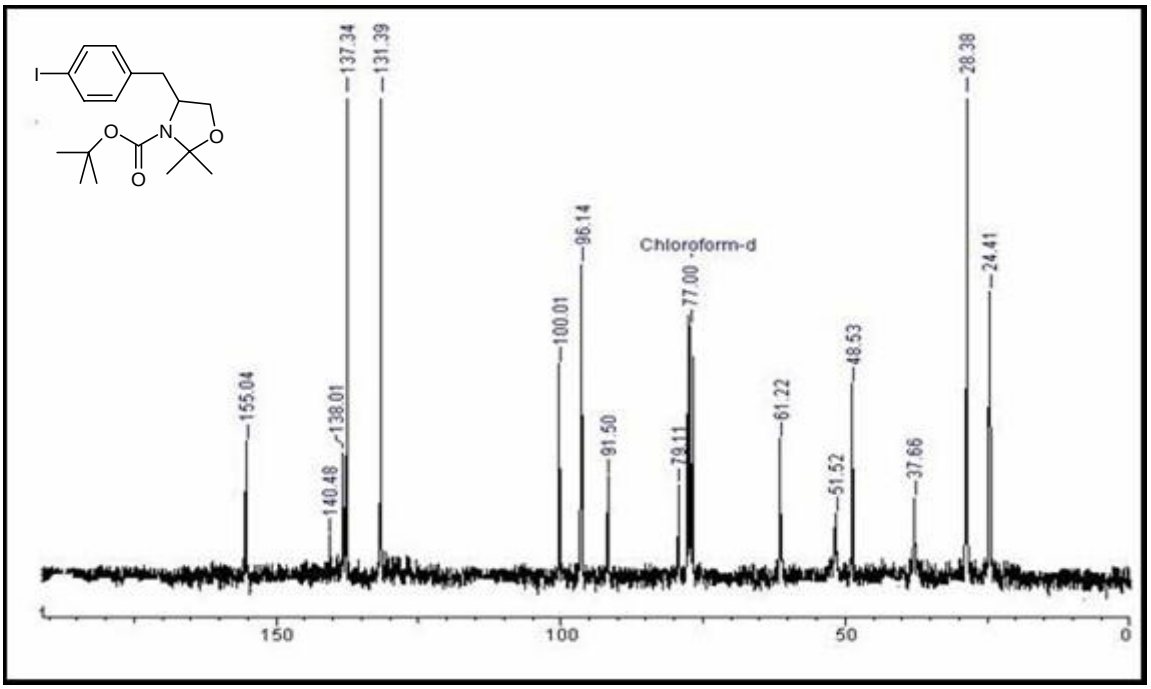
2,2,2',2',2",2"-Hexamethyl-[4,4',5',4"]ter{[1,3]dioxolane}



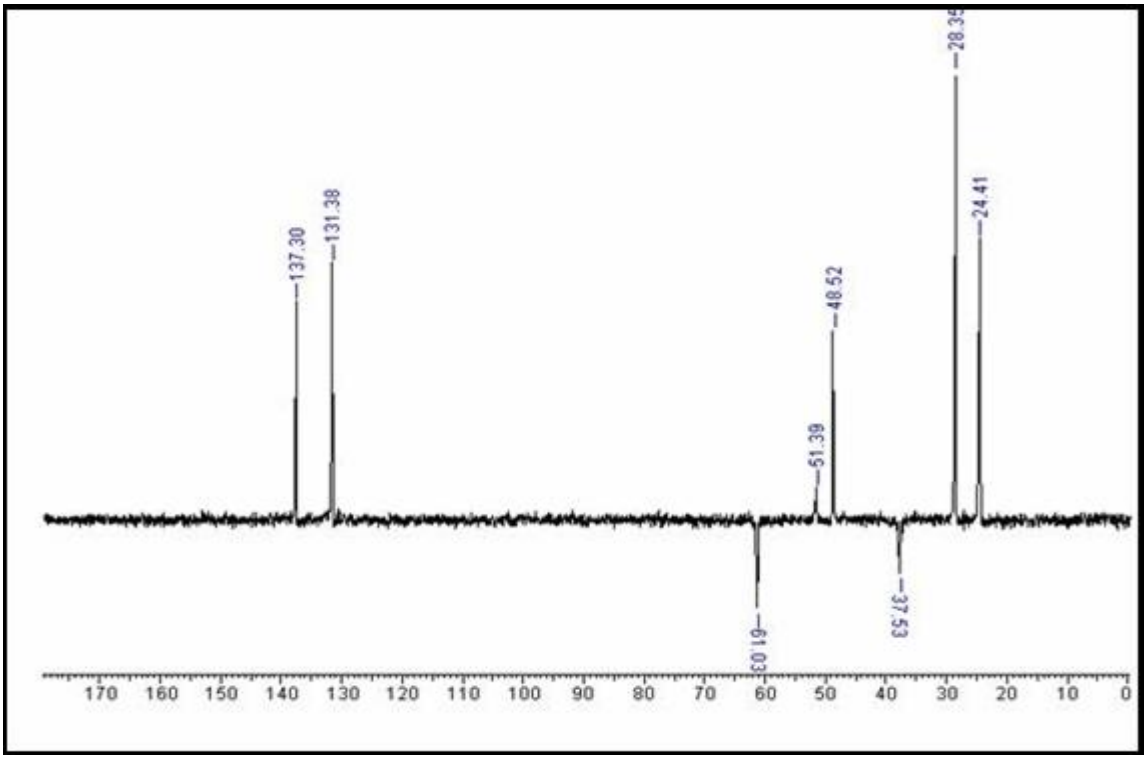
Yield	25 %
Appearance	White solid
IR (nujol)	3190, 3250, 2910, 1270, 1250, 1055, 870, 660 cm^{-1}
^{1}H NMR (200MHz, $CDCl_3$):	δ 4.24-3.75 (m, 8H), 1.40 (s, 6H), 1.37 (s, 6H), 1.33 (s, 6H).
^{13}C NMR (50MHz, $CDCl_3$):	δ 109.9, 109.4 (2C), 79.4 (2C), 76.3 (2C), 66.2 (2C), 27.5 (2C), 26.4 (2C), 25.3 (2C).
Mass m/z (%):	287 (M^+-15), 229 (5), 169 (12), 143 (95), 111 (20), 101 (100), 85 (50), 73 (45), 59 (95)
Microanalysis:	Calculated for $C_{15}H_{26}O_6$; C; 59.58; H: 8.67 Found: C: 59.76; H: 8.51%.



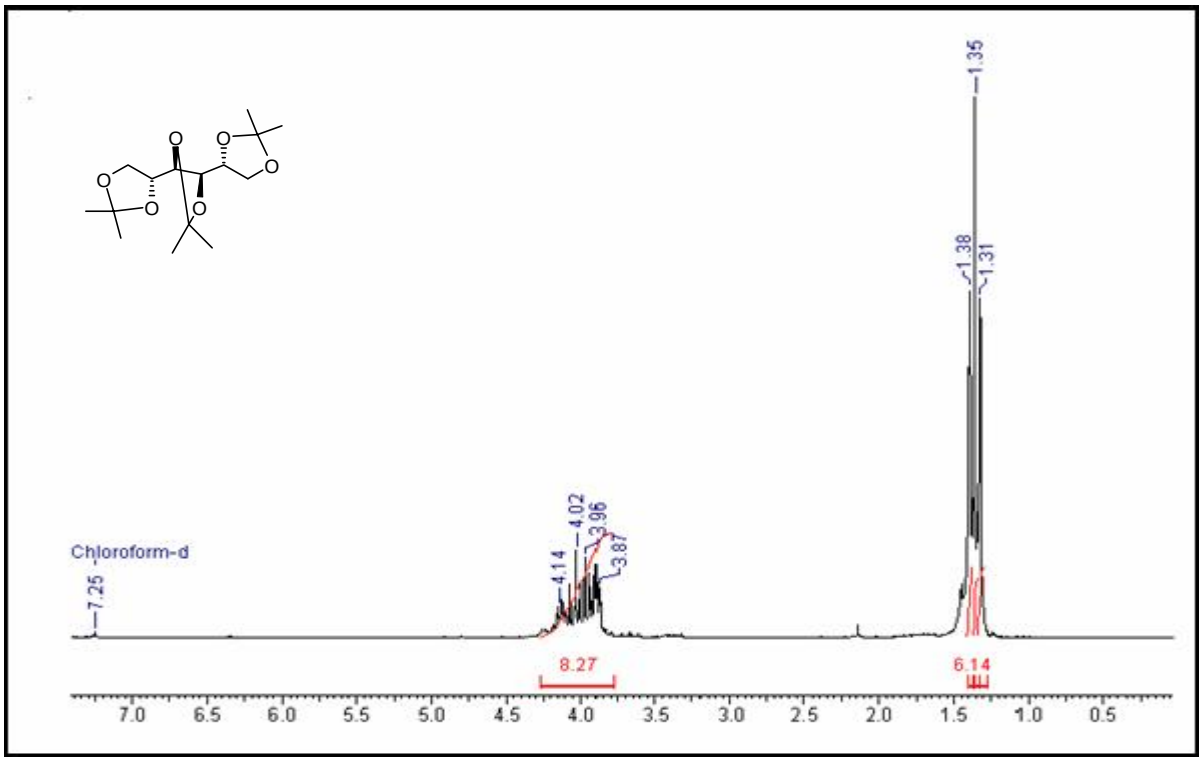
^{1}H NMR spectra of compound 5 (200 MHz, $CDCl_3$)



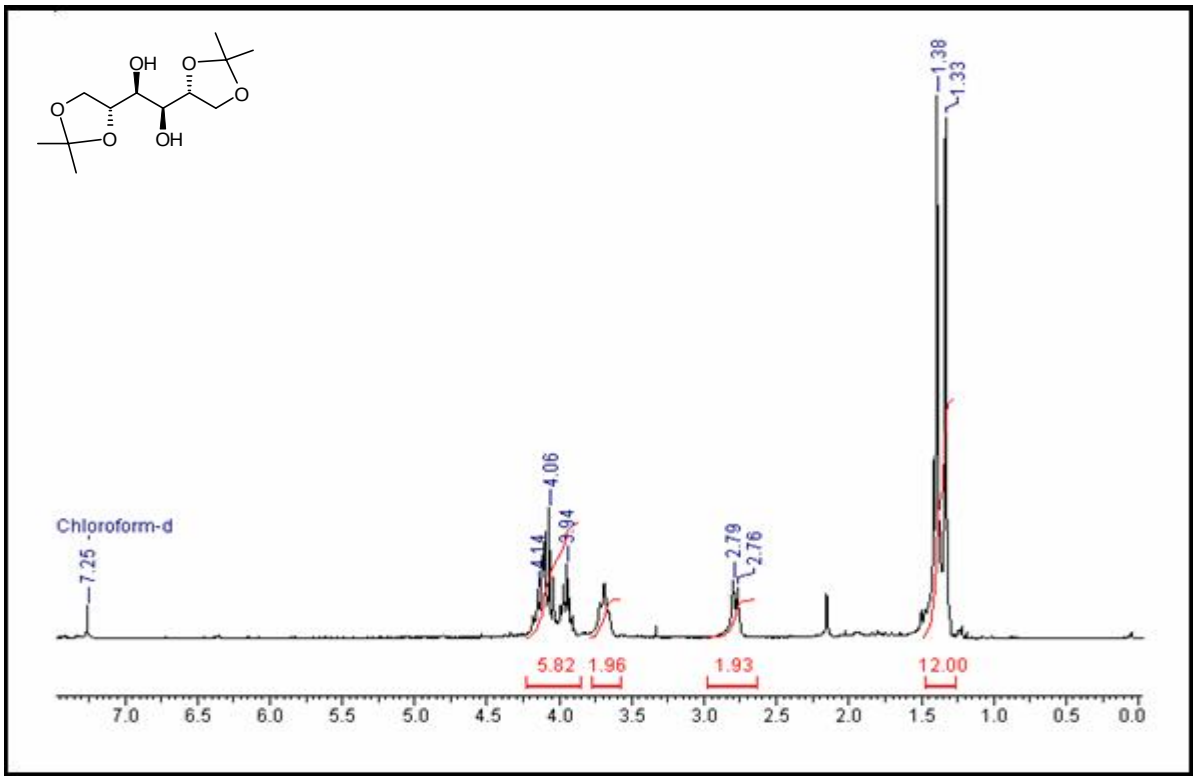
^{13}C-NMR of compound 5 (200 MHz, $CDCl_3$)



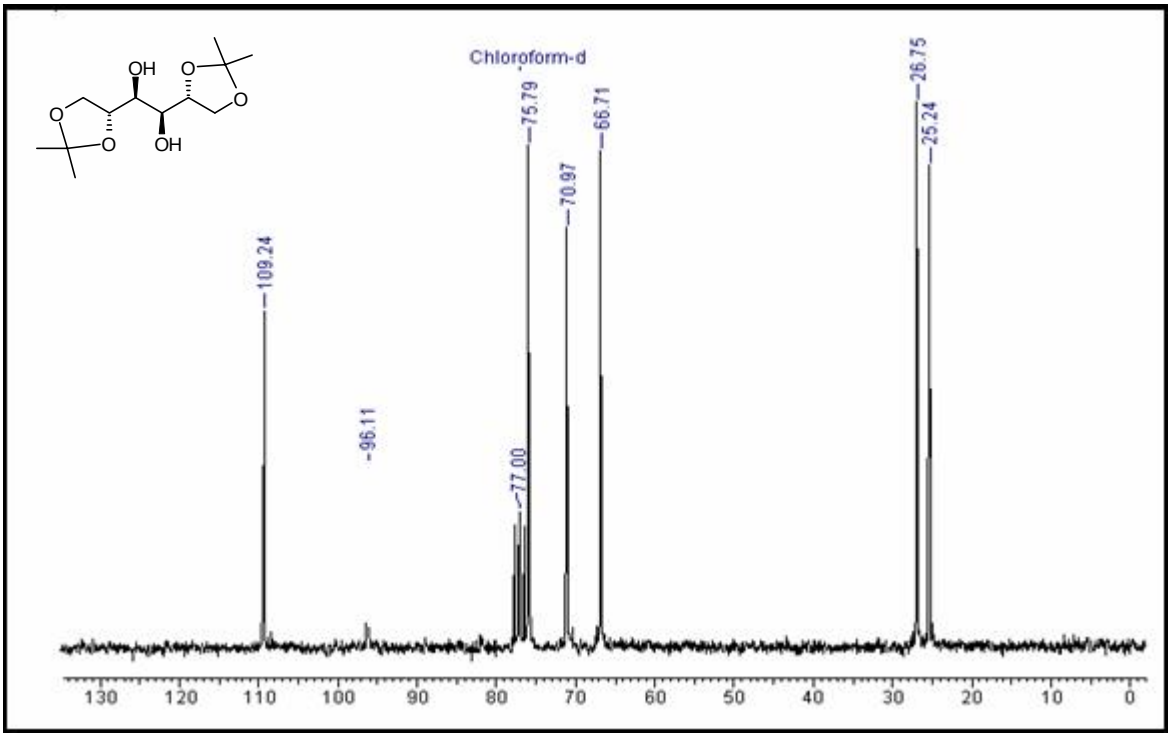
^{13}C-Dept. NMR of compound 5 (200 MHz, $CDCl_3$)



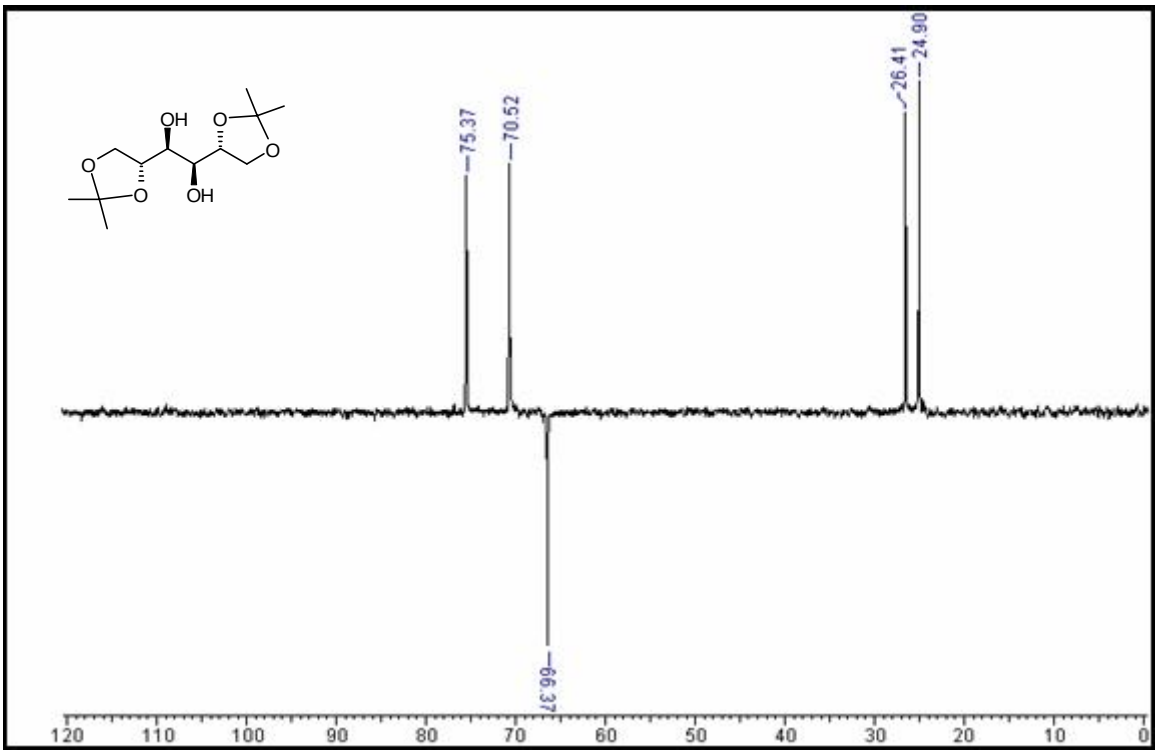
^{1}H NMR spectra of compound … (200 MHz, $CDCl_3$)

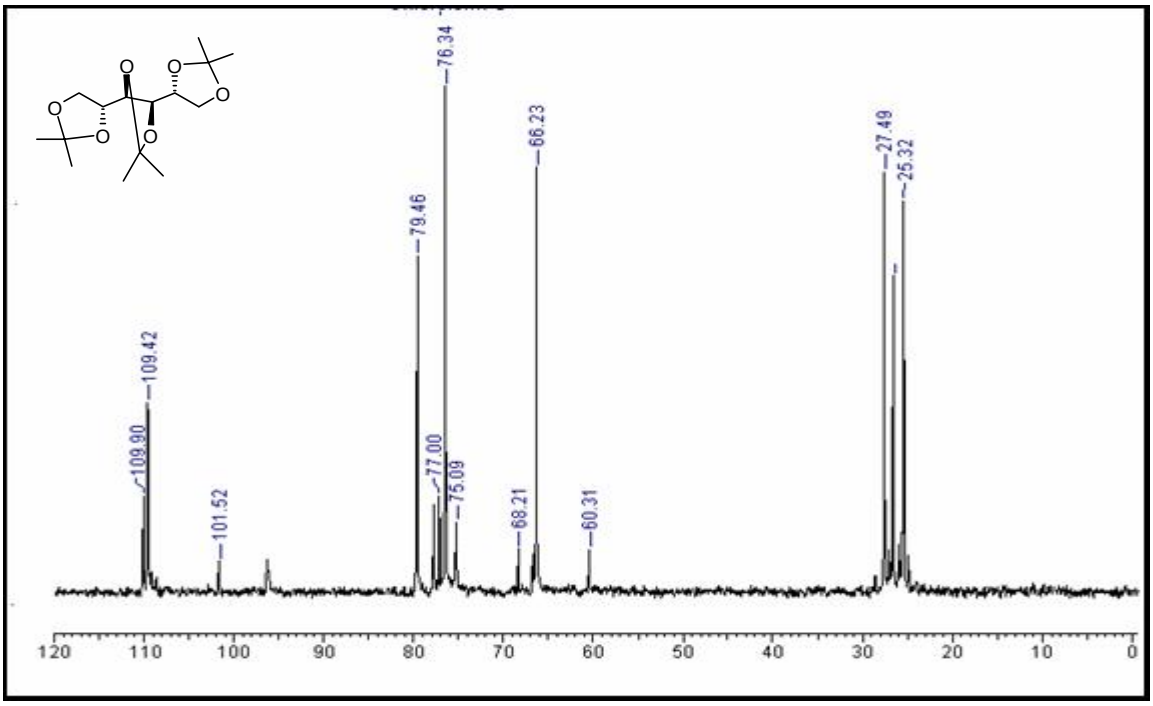


^{1}H NMR spectra of compound … (200 MHz, $CDCl_3$)

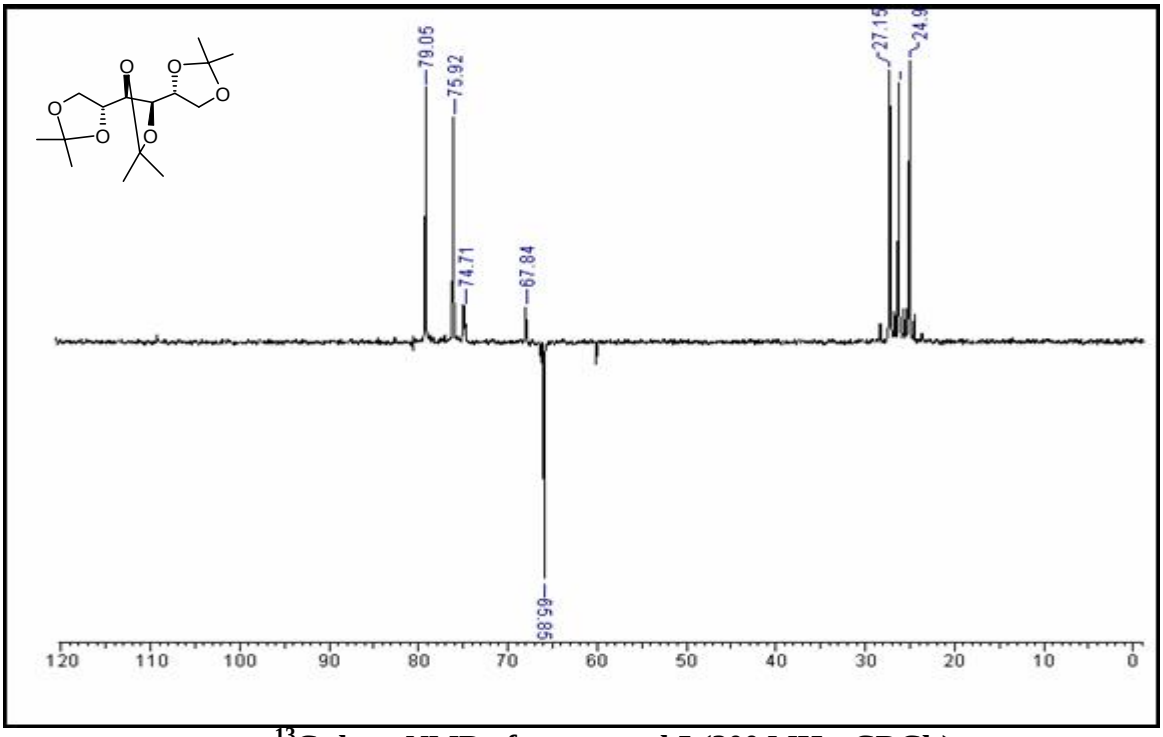


^{13}C-NMR of compound 5 (200 MHz, $CDCl_3$)





^{13}C-NMR of compound 5 (200 MHz, $CDCl_3$)



^{13}C-dept. NMR of compound 5 (200 MHz, $CDCl_3$)

3.3.6 References

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