CHAPTER 3: TRANSITION METAL FREE C-1 ARYLATION OF N-METHYL-1,2,3,4-TETRAHYDROISOQUINOLINES VIA OXIDATIVE COUPLING: C-C BOND FORMATION ADJACENT TO NITROGEN ATOM

3.1 INTRODUCTION:

Nitrogen containing compounds are abundant in nature as they form an important constituent of proteins, nucleic acids and enzymes etc. Also, these are found in large number of alkaloids and drugs and have significant medicinal importance.

In particular, 1,2,3,4-tetrahydroisoquinoline (THIQ) forms the basic framework of many alkaloids and biologically active compounds. This chapter describes our findings on the transition metal free α-arylation of N-methyl THIQ’s with aryl Grignard reagents under oxidative conditions which leads to C-C bond formation adjacent to a nitrogen atom and results in the formation of C-1 arylated products (Figure 3.1).

![Figure 3.1: Basic skeleton of C-1 arylated tetrahydroisoquinoline](image)

C-1 arylated tetrahydroisoquinolines have been demonstrated to have interesting properties such as antibacterial, anti HIV and neuroprotective activities. Various analogs of 1-aryl tetrahydroisoquinolines act as dopamine D1, NMDA and AMPA receptor antagonists (Figure 3.2) which mediates dopamine and glutamate neurotransmission in the central nervous system. Overactivation of these receptors can lead to neuronal damage, psychiatric disorders and cell death. These are also found to be neuroprotective agents for the treatment of neuro-degenerative disorders such as Huntington’s, Epilepsy, Ischemia, Alzheimer and Parkinson’s diseases.
Solifenacin (YM-905) has been investigated as a bladder selective muscarinic M₃ receptor antagonist which reduces the contractions of bladder muscles (Figure 3.3).\textsuperscript{158}

Cryptostyline I, II and III (Figure 3.4) are found in Orchidaceae family and isolated from the plant cryptostylis fulva. These 1-aryl-N-methyl tetrahydroisoquinoline alkaloids show important pharmacological properties and are of considerable biological significance.\textsuperscript{159}
Due to wide applications of such compounds in pharmaceutics and medicinal field, many synthetic methods have been developed for their synthesis. Pictet-Spengler condensation is one of the most commonly employed method. It is a two-step process which involves the condensation of β-phenylethyamines with aromatic aldehydes to generate intermediate imines. These undergo intramolecular cyclization in the presence of acid to form 1-aryl-1,2,3,4-tetrahydroisoquinolines. Eschweiler-Clarke N-methylation of leads to the synthesis of 1-aryl-N-methyl-1,2,3,4-THIQ’s.
Another efficient method is Bischler-Napieralski reaction,\textsuperscript{161} which involves the cyclization of $\beta$-aryl ethyl amides 184 in the presence of a dehydrating agent, generally POCl$_3$, to form 1-aryl-3,4-dihydroisoquinoline imines 185. Methylation of 185 with methyl iodide generates the methiodide salts 186 which on reduction with sodium borohydride furnish 1-aryl-$N$-methyl-1,2,3,4-THIQ’s 183.

![Chemical reaction diagram]

Saitoh et al. demonstrated that modified Pummerer reaction\textsuperscript{162} provides an efficient and convenient method for the synthesis of 1-aryl-$N$-methyl tetrahydroisoquinolines that lacked electron donating groups in the aromatic ring by taking sulfoxides as the starting substrates. Condensation of the ketone 187 and 2-phenylsulfanylethyl amine (188) in presence of titanium (IV) isopropoxide followed by reduction with NaBH$_4$ gave 189 which on subsequent formylation and oxidation furnished $N$-formyl sulfoxide derivative 190. Pummerer reaction of 190 in the presence of trifluoroacetic anhydride (TFAA) and BF$_3$·OEt$_2$ afforded 191 which on further treatment with NiCl$_2$·NaBH$_4$ gave $N$-formyl tetrahydroisoquinoline 192. Reduction of 192 with lithium aluminium hydride (LiAlH$_4$) afforded the desired product 183a.
Gray et al.\textsuperscript{163} reported an alternative synthesis of 1-aryl-\textit{N}-methyl tetrahydroisoquinolines. Reaction of amine 180 with benzoyl chloride 193 in the presence of a base gives the amide 184 which undergoes Bischler-Napieralski cyclization followed by reduction and further methylation with dimethyl sulphate to afford 183 in 54\% yield.
Costa and Radesca reported a one-pot synthesis of 1-aryl-N-methyl tetrahydroisoquinoline 183a by the reaction of N-methyl-1,2,3,4-tetrahydroisoquinoline (24a) with triphenylcarbenium tetrafluoroborate to generate iminium cation 194 which on further reaction with Grignard reagent 195a gave 183a in 78% yield.\(^{164}\)

![Diagram of the synthesis of 1-aryl-N-methyl tetrahydroisoquinoline 183a](image.png)

Another procedure for the synthesis of 1-aryl-N-methyl THIQ’s from \(\alpha\)-siloxy amines has been reported by Tokitoh \textit{et al.}\(^{165}\) \(\alpha\)-Siloxy amine 199 was prepared by Polonovski reaction of tertiary amine \(N\)-oxide 196 with trialkyl silyl trifluoromethane sulfonate 197 to give 198 followed by reaction with a base. Addition of Grignard reagent 195a to 199 in presence of a Lewis acid furnished the desired product 183a in 74% yield.

![Diagram of the synthesis of 1-aryl-N-methyl tetrahydroisoquinoline 183a](image.png)

Asao \textit{et al.} reported the synthesis of (S)-cryptostyline II alkaloid (178) by thermal double cyclization reaction.\(^{166}\) The reaction of \(o\)-vinyl benzaldehyde (201) [prepared from 6-bromo varetraldehyde (200)] with amino alcohol 202 (which acts as a chiral auxillary) gave aldimine 203 which undergoes 6\(\pi\) aza electrocyclization to give tetrahydroisoquinoline 204. The reaction of tetrahydroisoquinoline 204 with Grignard reagent 195d affords 205 in 85% yield and 96% d.e. The auxillary was later removed by
hydrogenation and further N-methylation furnished (S)-cryptostyline II (178) in 57% yield with 96% ee.

Meyers et al.\textsuperscript{167} demonstrated the enantioselective synthesis of (+)-cryptostyline II in five steps. Reaction of the ester 206 with 3,4-dimethoxy benzoic acid (108b) in presence of polyphosphoric acid (PPA) followed by alkaline hydrolysis gave the keto acid 207 in 50% yield. The keto acid 207 reacts with (S)-phenyl glycinol (202) (which acts as a chiral auxillary) in toluene under reflux to give diastereomerically pure bicyclic lactam 208 which undergoes reduction with lithium aluminium hydride (LiAlH\textsubscript{4}) in THF.
to afford isoquinoline 205 as a 14:1 mixture of diastereomers. The removal of chiral auxillary by hydrogenation followed by Eschweiler-Clarke methylation gave (+)-cryptostyline II (178).

Miyaura et al. described the synthesis of enantiopure cryptostyline I (177) and cryptostyline II (178) using N-linked bidentate phosphoramidate ligand (N-Me-BIPAM).159 N-Me-BIPAM 210 was prepared by the treatment of N-Me linked BINOL 209 with P(NMe₂)₃ in toluene. Addition of aryl boronic acids 49 to N nosyl amine 211 in presence of catalytic amount of Rh(acac)(C₂H₄)₂/ N-Me-BIPAM at 80 °C gave 212. This was followed by deprotection of nosyl group in the presence of 4-MeOC₆H₄SH and potassium carbonate (K₂CO₃) at 50 °C in CH₃CN/DMSO to give the lactam 213 in 97% yield. Methylation in presence of methyl iodide and sodium hydride followed by reduction with BH₃·Me₂S in THF gave the desired cryptostyline I (177) and cryptostyline II (178).
Cho et al. reported enantioselective synthesis of cryptostyline I, II and III via asymmetric reduction. The iminium salts 217 were prepared by Bischler-Napieralski cyclization of the amides 215 with POCl₃ followed by quaternization with methyl iodide. These iminium salts were then reduced in presence of chiral reducing agent K-glucoride in THF at -78 °C to give cryptostyline I, II and III in 37% ee, 43% ee and 25.2% ee respectively.

Takano et al. demonstrated the synthesis of racemic cryptostylines I, II and III via aryl radical initiated cyclization. The reaction of 2-bromo-4,5-dimethoxy phenylethylamine (218) with aromatic aldehyde 219 gave the Schiff base 220 which on reaction with tributyl tin hydride (n-Bu₃SnH) and azoisobutyronitrile (AIBN) in toluene forms an aryl radical intermediate 221 which undergoes endo cyclization to give 1-aryl tetrahydroisoquinoline 222 as the major product along with a slight amount of 1-benzyl indoline 223 formed by exo cyclization. Reductive N-methylation of 222 in presence of formalin and sodium borohydride furnished the desired cryptostyline I, II and III alkaloids (177, 178 and 179) in 88.4%, 72.3% and 94.8% yield respectively.
Very recently, Singh et al.\textsuperscript{170} reported a one-pot synthesis of 1-aryl-\(N\)-methyl tetrahydroisoquinoline along with cryptostyline I, II and III by the reaction of Lewis acid complexed \(\alpha\)-amino carbanions with \textit{in situ} generated arynes. The amine-BF\(_3\) complex \textsuperscript{24} (obtained by the reaction of tetrahydroisoquinoline \textsuperscript{24} with BF\(_3\).OEt\(_2\)) was treated with \(s\)-butyl lithium at -78 °C to generate \(\alpha\)-amino carbanion which was followed by addition of aryl halide along with another lot of \(s\)-butyl lithium to generate benzyne. The coupling of \(\alpha\)-amino carbanion and benzyne gave the coupled product \textsuperscript{171} in a good yield.
3.2 RESULTS AND DISCUSSION:

It is evident from the introduction that C-1 arylated tetrahydroisoquinolines are extremely important compounds and many methods have been developed for their synthesis. Direct C-H activation under oxidative conditions has also been realized as a convenient and an efficient route for the synthesis of such biologically active compounds. 50,127,171

Many examples of arylation at C-1 position of N-phenyl protected tetrahydroisoquinoline (16) with indole (32a), 37,40,72a,172 2-naphthol (44) 44 and aryl boronic acids 46 49 using catalytic amount of copper salt have been mentioned in the general introduction. One major drawback of these reported procedures is the removal of phenyl group from the nitrogen atom which is quite difficult and requires harsh reaction conditions. 173 Thus, further functionalization cannot be pursued which limits the synthetic utility. 174 Some metal free procedures for the arylation of N-protected tetrahydroisoquinolines are also known. From the perspective of green chemistry, a transition metal free, simple and efficient approach is highly desirable.

Li et al. reported 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) mediated C(sp^3)-H bond arylation of tetrahydroisoquinoline under metal free conditions. 84 The coupling of N-p-methoxyphenyl (PMP) protected tetrahydroisoquinoline with aryl Grignard reagent 195 in presence of 1.1 equiv. of DDQ as an oxidant furnished the desired C-1 arylated product 227 in 80% yield. The N-PMP protecting group was removed with cerium ammonium nitrate (CAN). 175
Similar coupling to access 227 using hypervalent iodine III \textit{i.e.} [bis (trifluoroacetoxy) iodo] benzene (PIFA) as an oxidant under metal free conditions has also been reported by Li \textit{et al.}^{176}

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\text{Similar reaction has been reported in the presence of sodium persulfate as an oxidant at 80 °C.}^67
\]

Xie \textit{et al.} described a metal free one step arylation of \(N\)-CBz protected tetrahydroisoquinoline in the presence of triphenyl carbenium perchlorate as an oxidant.\textsuperscript{177} Similar reaction has been reported in the presence of sodium persulfate as an oxidant at 80 °C.\textsuperscript{67}

A metal free two step TBHP mediated C-1 arylation of \(N\)-Boc 41, \(N\)-CBz 51 and \(N\)-benzyl 228 protected tetrahydroisoquinoline catalyzed by bronsted acid has been demonstrated by Klussmann \textit{et al.}\textsuperscript{178} In the first step, \(N\)-CBz THIQ (51) was heated with TBHP/decane to synthesize amino \textit{tert}-butyl peroxide 229 which can serve as a precursor to iminium ion intermediate A.
In the second step, the amino tert-butyl peroxide 229 was coupled with the 1,3,5-trimethoxy benzene (230) using a catalytic amount of methane sulfonic acid (10 mol%) in acetic acid at room temperature to furnish C-1 arylated product 231 in 83% yield.

This two-step procedure, however, did not succeed with N-methyl tetrahydroisoquinoline (24a) and only products of over oxidation were detected. Also, in all other procedures reported for arylation of tetrahydroisoquinolines under oxidative conditions, the nitrogen atom is protected. To the best of our knowledge, C-1 arylation of N-alkyl tetrahydroisoquinolines under metal free conditions is not known. In this context, this chapter describes our investigations for the transition metal free arylation of N-alkyl THIQ’s with aryl Grignard reagents in the presence of diethyl azodicarboxylate (DEAD) as an oxidant.

The required N-methyl tetrahydroisoquinoline (24a) was prepared by a known route. Reaction of isoquinoline (232) with methyl iodide in ethanol gave the methiodide salt 233 which on reduction with sodium borohydride (NaBH₄) in methanol afforded the desired amine 24a in 63% yield.

The ¹H NMR spectrum of 24a showed a singlet at δ 3.46 for the two benzylic protons adjacent to nitrogen atom (Ph-CH₂-N-). The two non-benzylic methylene protons adjacent to nitrogen were seen as a triplet at δ 2.82 (Ph-CH₂-CH₂-N-) and other two
benzylic methylene protons away from nitrogen appeared as a triplet at $\delta$ 2.56 (Ph-CH$_2$-CH$_2$-N-). $N$-methyl protons were observed as a singlet at $\delta$ 2.35. A multiplet was seen at $\delta$ 7.00-6.96 for three aromatic protons and a doublet at $\delta$ 6.87 for remaining one proton of the ring.

We initiated our study with the oxidative coupling of $N$-methyl tetrahydroisoquinoline (24a) and aryl magnesium bromide 195a (prepared in THF from bromobenzene) (Scheme 3.1). The reaction was performed by taking amine/Grignard reagent/DEAD in the ratio 1:2:1.1 in THF and the reaction mixture was stirred at room temperature for 2 h under nitrogen atmosphere. Workup and purification by column chromatography afforded the desired coupled product 183a in 20% yield (Table 3.1, entry 1).

**Scheme 3.1:** Oxidative coupling of $N$-methyl THIQ with aryl Grignard reagent

The structure of the product 183a was confirmed by $^1$H and $^{13}$C NMR spectroscopy (Figure 3.5 and 3.6). The $^1$H NMR spectrum of 183a showed a singlet at $\delta$ 4.13 for the benzylic (C-1) proton (Ph-CH-N-). The $N$-methyl protons were seen as a singlet at $\delta$ 2.14. The methylene protons were observed as a multiplet at $\delta$ 3.19-2.52 (Ph-CH$_2$-CH$_2$-N-). The five aromatic protons appeared as a multiplet at $\delta$ 7.23-7.16. A multiplet at $\delta$ 7.01-6.85 was seen for three protons and one aromatic proton appeared as a doublet at $\delta$ 6.53 ($J = 7.8$ Hz).$^{162}$ The $^{13}$C NMR spectrum of 183a showed a peak at $\delta$ 71.6 for the substituted benzylic carbon (C-1). The non-benzylic carbon adjacent to nitrogen appeared at $\delta$ 52.4 and the benzylic carbon away from nitrogen (C-4) was seen at $\delta$ 44.4. The $N$-methyl carbon was observed at $\delta$ 29.6 and the aromatic carbons appeared at $\delta$ 144.0-125.7.$^{162}$
Figure 3.5: $^1$H NMR spectrum of compound 183a

Figure 3.6: $^{13}$C NMR spectrum of compound 183a
The reaction conditions were optimized by using different solvents, oxidants and varying the amount of Grignard reagent. With the use of four and six equiv. of Grignard reagent, a significant increase in the yield of 183a from 20% to 42% and 65% respectively was observed (Table 3.1, entry 2 and 3). However, use of eight equiv. of Grignard reagent did not improve the yield further (Table 3.1, entry 4). Various solvents such as toluene, chloroform and di-ethyl ether were tried and it was found that toluene gave inferior results (Table 3.1, entry 5) while in case of chloroform and ether, the product 183a was obtained in 60-62% yield (Table 3.1, entry 6 and 7). The use of DDQ gave the product 183a in 22% yield (Table 3.1, entry 8) while trace formation of the product was observed with cerium ammonium nitrate (CAN) and m-chloro perbenzoic acid (m-CBPA) (Table 3.1, entry 9 and 10). TBHP/I\textsubscript{2} also did not improve the yield of

<table>
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<th>Entry</th>
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<th>Oxidant</th>
<th>Solvent</th>
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<td>THF</td>
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<td>DEAD</td>
<td>THF</td>
<td>65</td>
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<td>8</td>
<td>DEAD</td>
<td>THF</td>
<td>64</td>
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<td>Toluene</td>
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<td>10</td>
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<td>m-CPBA</td>
<td>THF</td>
<td>Traces</td>
</tr>
<tr>
<td>11</td>
<td>6</td>
<td>TBHP/I\textsubscript{2}</td>
<td>THF</td>
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<td>12\textsuperscript{d}</td>
<td>6</td>
<td>DEAD</td>
<td>THF</td>
<td>64</td>
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13. Reaction conditions: 24a (1 equiv.), oxidant (1.1 equiv.), solvent (2 mL), 2 h, r.t. b Isolated yield. c The Grignard reagent was prepared in THF and iminium cation was generated in DMF, toluene or chloroform. d 3 h. e 1 h. f Refluxing THF. g CuI (5 mol%) was used as a catalyst. h DEAD (0.5 equiv.). i DEAD (2.2 equiv.). j DEAD (3.3 equiv.).

**183a.** Higher reaction temperature and increase in the reaction time did not affect the yield (Table 3.1, entry 14 and 12) but decreasing the reaction time somewhat lowered the yield (Table 3.1, entry 13). No increase in the product yield was observed when CuI (5 mol%) was used as a catalyst (Table 3.1, entry 15). As expected, the use of 0.5 equiv. of DEAD led to decrease in the yield of the product (Table 3.1, entry 16). When 2.2 equiv. of oxidant was used, only a marginal change in the yield of 183a was observed (Table 3.1, entry 17). Surprisingly, further increase in the amount of oxidant depressed the yield of the product (Table 3.1, entry 18). It was concluded that six equiv. of Grignard reagent and 1.1 equiv. of DEAD in THF at room temperature gave the best results.

To investigate the scope and generality of this oxidative arylation, a variety of substituted aryl Grignard reagents were prepared by the reaction of corresponding aryl bromide with magnesium in THF.180

1-Bromo-3-methoxy benzene (234a) was prepared by Sandmeyer reaction of m-anisidine (114b) in presence of Cu(I)Br/HBr in 57% yield. The 1H NMR spectrum of 234a showed a singlet at δ 3.74 corresponding to the three methoxy protons. The protons of phenyl ring were seen as a multiplet at δ 7.12-7.06 for one proton, another multiplet at δ 6.81-6.78 for two protons and a doublet was observed at δ 6.64 (J = 8.4 Hz) for one proton.
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4-Bromo-1,2-dimethoxy benzene (234b) was synthesized by the reaction of 1,2-dimethoxy benzene 54f with N-bromosuccinimide (NBS) in presence of silica gel in DCM at room temperature for 24 h.\textsuperscript{181} The \textsuperscript{1}H NMR spectrum of 234b showed two singlets at δ 3.75 and δ 3.74 which correspond to the six methoxy protons. Two aromatic protons appeared as a multiplet at δ 6.77-6.71 and a doublet was seen at δ 6.61 for one aromatic proton.

Further, 1-bromo-2-methoxynaphthalene (234d) was synthesized from β-naphthol (44) in two steps. Bromination of β-naphthol (44) with bromine in presence of acetic acid gave 1-bromonaphthalen-2-ol (235)\textsuperscript{182} which was methylated with dimethyl sulphate under alkaline conditions to give 1-bromo-2-methoxynaphthalene (234d) in 69% yield.

The aryl magnesium bromides were coupled with amine 24a and the corresponding C-1 arylated tetrahydroisoquinolines 183a-f were obtained in moderate to good yields (Table 3.2). The reaction was tolerant to methoxy/methyl substituents on the phenyl rings of the coupling partners. 1-Naphthyl magnesium bromide (195e) and 2-methoxy-1-naphthyl magnesium bromide (195f) also coupled effectively to give the products in 64% and 67% yield respectively.
Table 3.2: Oxidative coupling of N-methyl THIQ 24a with aryl Grignard reagent

<table>
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</tr>
<tr>
<td>5</td>
<td>1-naphthyl 195e</td>
<td><img src="image5" alt="" /></td>
<td>64</td>
</tr>
</tbody>
</table>
6 2-methoxy naphthyl 195f 67

67

- methoxy naphthyl 195f 183f

Reaction conditions: 24a (1 equiv.), Grignard reagent 195 (6 equiv.), DEAD (1.1 equiv.), THF (2 mL), 2 h, r.t.  Isolated yield.

The structure of products 183a-f was confirmed by $^1$H and $^{13}$C NMR spectroscopy. The $^1$H NMR spectrum of 183b showed a singlet at $\delta$ 4.08, which corresponds to the benzylic C-1 proton (Ph-CH-N-). A singlet at $\delta$ 3.71 was seen for the three methoxy protons and another singlet for the three N-methyl protons appeared at $\delta$ 2.13. The methylene protons were observed as a multiplet at $\delta$ 3.21-2.50 (Ph-CH$_2$-CH$_2$-N-). A multiplet appeared at $\delta$ 7.09-6.71 for the seven aromatic protons and a doublet at $\delta$ 6.54 ($J$ = 7.8 Hz) for one aromatic proton. The $^{13}$C NMR spectrum of 183b showed a peak at $\delta$ 70.9 for the substituted carbon adjacent to nitrogen. The non-benzylic carbon adjacent to nitrogen (C-3) appeared at $\delta$ 52.4 and the benzylic carbon away from nitrogen (C-4) was seen at $\delta$ 44.3. The methoxy carbon appeared at $\delta$ 55.0 and N-methyl carbon was observed at $\delta$ 29.5. The aromatic carbon to which methoxy is attached was observed at $\delta$ 158.8 and other carbons of the phenyl ring were seen at $\delta$ 138.8-113.5.

The $^1$H NMR spectrum of 183c showed a singlet at $\delta$ 4.17 which is attributed to the benzylic C-1 proton (Ph-CH-N-). Two singlets at $\delta$ 2.33 and $\delta$ 2.21 were seen for the N-methyl protons and the protons of methyl group attached to phenyl ring respectively. The non-benzylic methylene protons adjacent to nitrogen appeared as a multiplet at $\delta$ 3.29-3.08 (Ph-CH$_2$-CH$_2$-N-) and the benzylic methylene protons away from nitrogen were also seen as a multiplet at $\delta$ 2.82-2.58 (Ph-CH$_2$-CH$_2$-N-). A multiplet was observed for the seven protons of the phenyl ring at $\delta$ 7.13-6.91 and a doublet for one proton at $\delta$ 6.60 ($J$ = 7.8 Hz). The $^{13}$C NMR spectrum of 183c showed a peak at $\delta$ 71.2 for the substituted carbon adjacent to the nitrogen atom. The non-benzylic carbon adjacent to the nitrogen atom appeared at $\delta$ 52.3 and the benzylic carbon away from nitrogen (C-4) was seen at $\delta$ 44.3. The N-methyl carbon was observed at $\delta$ 29.5 and the carbon of methyl group attached to the phenyl ring was seen at $\delta$ 21.2. The carbons of phenyl ring were seen at $\delta$ 140.8-125.6.
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The $^1$H NMR spectrum of 183d showed a singlet at $\delta$ 4.11 which corresponds to the benzylic C-1 proton (Ph-CH$_2$N-). Two singlets appeared at $\delta$ 3.81 and $\delta$ 3.74 which were attributed to six methoxy protons. The non-benzylic methylene protons adjacent to nitrogen were seen as a multiplet at $\delta$ 3.24-3.06 (Ph-CH$_2$-CH$_2$N-) and the benzylic methylene protons away from nitrogen atom were also seen as a multiplet at $\delta$ 2.77-2.53 (Ph-CH$_2$-CH$_2$N-). The N-methyl protons were observed as a singlet at $\delta$ 2.18. The six aromatic protons were seen as a multiplet at $\delta$ 7.05-6.70 and a doublet at $\delta$ 6.60 ($J = 7.8$ Hz) was observed for one proton. The $^{13}$C NMR spectrum of 183d showed a peak at $\delta$ 71.4 for the substituted benzylic carbon adjacent to the nitrogen atom. The non-benzylic carbon adjacent to nitrogen appeared at $\delta$ 52.5 and the benzylic carbon away from nitrogen (C-4) was seen at $\delta$ 44.3. The methoxy carbons were observed at $\delta$ 55.8 and $\delta$ 55.7. The N-methyl carbon was observed at $\delta$ 29.3. The carbons of di-substituted phenyl ring were seen at $\delta$ 149.0 and $\delta$ 148.2 and the remaining aromatic carbons appeared at $\delta$ 134.0-110.2.

The $^1$H NMR spectrum of 183e showed a singlet at $\delta$ 4.70 corresponding to the benzylic C-1 proton (Ph-CH$_2$N-). The non-benzylic methylene protons adjacent to nitrogen were seen as a multiplet at $\delta$ 3.37-3.12 (Ph-CH$_2$-CH$_2$N-) and the benzylic methylene protons away from nitrogen were also seen as a multiplet at $\delta$ 2.83-2.57 (Ph-CH$_2$-CH$_2$N-). The N-methyl protons were observed as a singlet at $\delta$ 2.09. The aromatic protons showed up as a doublet at $\delta$ 8.17 ($J = 8.5$ Hz) for one proton, a triplet at $\delta$ 7.72 ($J = 8.7$ Hz) for two protons, a multiplet at $\delta$ 7.39-7.21 for four protons, three triplets at $\delta$ 7.09 ($J = 8.8$ Hz), $\delta$ 6.98 ($J = 7.4$ Hz), $\delta$ 6.77 ($J = 7.5$ Hz) for one proton each and a doublet at $\delta$ 6.47 ($J = 7.8$ Hz) for one proton. The $^{13}$C NMR spectrum of 183e showed a peak at $\delta$ 76.6 for the substituted benzylic carbon adjacent to nitrogen. The non-benzylic carbon adjacent to nitrogen appeared at $\delta$ 53.3 and the benzylic carbon away from nitrogen (C-4) was seen at $\delta$ 44.5. The N-methyl carbon was observed at $\delta$ 29.3 and the carbons of the phenyl ring were seen at $\delta$ 139.0-125.0.

The $^1$H NMR spectrum of 183f showed a singlet at $\delta$ 5.37 corresponding to the benzylic C-1 proton (Ph-CH$_2$N-). Another singlet was seen at $\delta$ 3.89 which is attributed to the three methoxy protons. The non-benzylic methylene protons adjacent to nitrogen were seen as a multiplet at $\delta$ 3.45-3.16 (Ph-CH$_2$-CH$_2$N-) and the benzylic methylene
protons away from nitrogen were also seen as a multiplet at δ 2.83-2.60 (Ph-CH₂-CH₂-N-). Three N-methyl protons were seen as a singlet at δ 2.07. A doublet was observed at δ 8.07 (J = 7.3 Hz) corresponding to one aromatic proton, a multiplet was seen at δ 7.72-7.60 for two protons. Another doublet was seen at δ 7.24 (J = 9.1 Hz) for one proton of the phenyl ring and a multiplet at δ 7.13-7.05 for three protons. A triplet was observed at δ 6.96 (J = 7.3 Hz) for one proton, another triplet was seen at δ 6.76 (J = 7.5 Hz) for one proton and a doublet appeared at δ 6.42 (J = 7.8 Hz) for one aromatic proton. The ¹³C NMR spectrum of 183f showed a peak at δ 62.2 for the substituted benzylic carbon adjacent to nitrogen. The methoxy carbon attached to naphthyl ring appeared at δ 57.0. The non-benzylic carbon adjacent to nitrogen appeared at δ 54.4 and the benzylic carbon away from nitrogen (C-4) was seen at δ 44.1. The N-methyl carbon was observed at δ 29.9. The carbon of the phenyl ring to which methoxy is attached appeared at δ 156.4 and the remaining carbons of the ring were observed at δ 139.2-113.1.

We further explored this metal free arylation with differently substituted N-methyl THIQ’s. For this 6,7-dimethoxy-N-methyl-1,2,3,4-tetrahydroisoquinoline (24b) and 7-ethoxy-6-methoxy-N-methyl-1,2,3,4-tetrahydroisoquinoline (24c) were examined.

6,7-Dimethoxy-N-methyl-1,2,3,4-tetrahydroisoquinoline (24b) was prepared by Pictet-Spengler reaction. The reaction of homoveratrylamine (180a) with 37% formaldehyde in refluxing benzene gave the Schiff base 236 which was heated with 20% hydrochloric acid to give the cyclized amine 237a in 60% yield. The structure of 237a was confirmed by ¹H NMR spectroscopy and the spectrum showed two singlets at δ 3.75 and δ 3.73 for the six methoxy protons. The benzylic protons adjacent to nitrogen were seen as a singlet at δ 3.55 (Ph-CH₂-N-). Two triplets were observed at δ 3.15 and δ 2.73, corresponding to the non-benzylic protons adjacent to nitrogen and benzylic proton away from nitrogen. The labile –NH proton was seen as a broad singlet at δ 1.66 and two aromatic protons were observed as singlets at δ 6.46 and δ 6.40. The N-methylation of amine 237a was carried out via Leukart-Wallach reductive amination of carbonyl compounds, using 37% HCHO and 85% formic acid to give 24b in 75% yield.
The $^1$H NMR spectrum of 24b showed a singlet at $\delta$ 3.4 which is attributed to the benzylic protons adjacent to the nitrogen atom. The non-benzylic and the benzylic methylene protons adjacent and away from the nitrogen atom were seen as triplets at $\delta$ 2.78 and $\delta$ 2.62 respectively. Two singlets appeared at $\delta$ 3.76 and $\delta$ 3.75 which correspond to the six methoxy protons. N-methyl protons were seen as a singlet at $\delta$ 2.38 and the two aromatic protons were observed as singlets at $\delta$ 6.49 and $\delta$ 6.40.

Further, 7-ethoxy-6-methoxy-N-methyl-1,2,3,4-tetrahydroisoquinoline (24c) was prepared. Vanillin (238) was treated with diethyl sulphate under alkaline conditions to give 4-ethoxy-3-methoxy benzaldehyde (239) in 63% yield. The reaction of 239 with nitromethane in presence of ammonium acetate and glacial acetic acid furnished the nitrostyrene 240 in 65% yield which was reduced to the corresponding amine 180b.
using NaBH₄ and BF₃·OEt₂ in THF.¹⁸⁷ Amine 180b was then cyclized to the required 7-ethoxy-6-methoxy-1,2,3,4-tetrahydroisoquinoline (237b) in presence of formaldehyde and 20% HCl.¹⁸³ N-methylation of 237b using 37% HCHO and 85% formic acid gave the desired 24c in 59% yield.¹⁸⁴,¹⁸⁵ Amine 24c was characterized by ¹H NMR spectroscopy. The spectrum showed a singlet at δ 3.73 corresponding to the methoxy protons. A multiplet appeared at δ 3.51 which is attributed to the two methylene protons of ethoxy moiety and a triplet was seen at δ 1.33 for the methyl protons. The benzylic protons adjacent to nitrogen were observed as a singlet at δ 3.39. The non-benzylic protons adjacent to nitrogen and the benzylic protons away from nitrogen were seen as triplets at δ 2.70 and δ 2.53. N-methyl protons were seen as a singlet at δ 2.18. The two aromatic protons appeared as singlets at δ 6.46 and δ 6.40.

Both the amines 24b and 24c coupled smoothly with differently substituted Grignard reagents under the standard reaction conditions to give the corresponding products in good yields (Table 3.3).
Table 3.3: Oxidative coupling of substituted $N$-methyl THIQ’s with aryl Grignard reagents \(^a\)

<table>
<thead>
<tr>
<th>Entry</th>
<th>24</th>
<th>195</th>
<th>183</th>
<th>Yield (%)(^b)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>24b</td>
<td>195a</td>
<td></td>
<td>60</td>
</tr>
<tr>
<td>2</td>
<td>24b</td>
<td>195b</td>
<td></td>
<td>58</td>
</tr>
<tr>
<td>3</td>
<td>24b</td>
<td>195c</td>
<td></td>
<td>67</td>
</tr>
<tr>
<td>4</td>
<td>24b</td>
<td>195g</td>
<td></td>
<td>57</td>
</tr>
</tbody>
</table>

\(^a\) R\(^1\) = R\(^2\) = OMe: 24b  
R\(^1\) = OMe, R\(^2\) = OEt: 24c  
R\(^1\) = H, R\(^3\) = H: 195a  
R\(^3\) = OMe, R\(^4\) = H: 195b  
R\(^3\) = Me, R\(^4\) = H: 195c  
R\(^3\) = H, R\(^4\) = OMe: 195g

\(^b\) Yields determined by NMR analysis.
The structure of the products was confirmed by $^1$H and $^{13}$C NMR spectroscopy. The $^1$H NMR spectrum of 183g showed a singlet at δ 4.07, which corresponds to the benzylic C-1 proton (Ph-CH-N). The methoxy protons were seen as two different singlets at δ 3.76 and δ 3.47. The non-benzylic methylene protons adjacent to nitrogen appeared as a multiplet at δ 3.13-2.98 (Ph-CH$_2$-CH$_2$-N) and another multiplet at δ 2.66-2.49 was observed for the benzylic methylene protons away from nitrogen (Ph-CH$_2$-CH$_2$-N). The three N-methyl protons were seen as a singlet at δ 2.14. The five protons of unsubstituted phenyl ring appeared as a multiplet at δ 7.23-7.16 and the two protons of substituted phenyl ring were observed as singlets at δ 6.48 and δ 5.97. The $^{13}$C NMR spectrum of 183g showed a peak at δ 71.2 for the substituted carbon adjacent to nitrogen. The methoxy carbons appeared at δ 55.8 and δ 55.7. The non-benzylic carbon adjacent to nitrogen was seen at δ 52.4 and the benzylic carbon away from nitrogen (C-4) appeared at δ 44.4. The N-methyl carbon was observed at δ 29.1 and the carbons of phenyl ring were seen at δ 147.5-110.9.

The $^1$H NMR spectrum of 183h showed a singlet at δ 4.20 corresponding to the benzylic C-1 proton (Ph-CH-N). The six methoxy protons at C-6 and C-7 position were seen as singlets at δ 3.80 and δ 3.84 respectively and the protons of methoxy attached to
the phenyl ring also appeared as a singlet at $\delta$ 3.58 (Ph-OCH$_3$). The non-benzylic methylene protons adjacent to nitrogen were observed as a multiplet at $\delta$ 3.20-3.08 (Ph-CH$_2$-CH$_2$-N-) and another multiplet was seen at $\delta$ 2.78-2.60 for the benzylic methylene protons away from nitrogen (Ph-CH$_2$-CH$_2$-N-). The $N$-methyl protons were observed as a singlet at $\delta$ 2.25. A doublet was seen at $\delta$ 7.18 ($J = 8.6$ Hz) for the two aromatic protons and another doublet was seen at $\delta$ 6.85 ($J = 8.6$ Hz) for the other two aromatic protons. Two singlets appeared at $\delta$ 6.59 and $\delta$ 6.11 which were attributed to the two aromatic protons of the di-substituted phenyl ring. The $^{13}$C NMR spectrum of 183h showed a peak at $\delta$ 70.0 for the substituted carbon adjacent to nitrogen. The methoxy carbons appeared at $\delta$ 55.7 and $\delta$ 55.1. The non-benzylic carbon adjacent to nitrogen was seen at $\delta$ 51.8 and the benzylic carbon away from nitrogen (C-4) appeared at $\delta$ 43.9. The $N$-methyl carbon was observed at $\delta$ 28.6. The carbon of phenyl ring to which methoxy is attached was seen at $\delta$ 158.8 and the remaining carbons were seen at $\delta$ 147.3-110.5.

The $^1$H NMR spectrum of 183i showed a singlet at $\delta$ 4.20 corresponding to the benzylic C-1 proton (Ph-CH-N-). The methoxy protons were observed as singlets at $\delta$ 3.84 and $\delta$ 3.57. The non-benzylic methylene protons adjacent to nitrogen were seen as a multiplet at $\delta$ 3.17-3.07 (Ph-CH$_2$-CH$_2$-N-) and another multiplet at $\delta$ 2.77-2.60 was observed for the benzylic methylene protons away from nitrogen (Ph-CH$_2$-CH$_2$-N-). The $N$-methyl protons appeared as a singlet at $\delta$ 2.33 and the protons of methyl moiety attached to phenyl ring were seen as a singlet at $\delta$ 2.24 (Ph-CH$_3$). The protons of mono-substituted ring showed a multiplet at $\delta$ 7.15-7.12 and the two protons of di-substituted phenyl ring were observed as two singlets at $\delta$ 6.60 and $\delta$ 6.12. The $^{13}$C NMR spectrum of 183i showed a peak at $\delta$ 70.3 for the substituted carbon adjacent to nitrogen. The carbons of methoxy group were seen at $\delta$ 55.6. The non-benzylic carbon adjacent to nitrogen appeared at $\delta$ 51.7 and the benzylic carbon away from nitrogen (C-4) was seen at $\delta$ 43.9. The $N$-methyl carbon was observed at $\delta$ 28.6 and the carbon of methyl group attached to phenyl ring appeared at $\delta$ 21.0. The carbons of phenyl ring were seen in a range at $\delta$ 147.2-110.5.

The $^1$H NMR spectrum of 183j showed a singlet at $\delta$ 4.16 corresponding to the benzylic C-1 proton (Ph-CH-N-). The methoxy protons of the di-substituted phenyl ring were seen as singlets at $\delta$ 3.78 and $\delta$ 3.71 and the methoxy protons at $m$-position of the
mono-substituted phenyl ring appeared as a singlet at δ 3.51. The non-benzylic methylene protons adjacent to nitrogen were seen as a multiplet at δ 3.09-3.05 (Ph-CH$_2$-CH$_2$-N-) and another multiplet at δ 2.71-2.58 was observed for the benzylic methylene protons away from nitrogen (Ph-CH$_2$-CH$_2$-N-). The N-methyl protons appeared as a singlet at δ 2.21. The mono-substituted phenyl ring showed a multiplet at δ 7.19-7.14 for one aromatic proton and another multiplet at δ 6.80-6.73 for three aromatic protons. The aromatic protons of di-substituted phenyl ring were seen as two singlets at δ 6.53 and δ 6.07. The $^{13}$C NMR spectrum of 183j showed a peak at δ 70.9 for the substituted carbon adjacent to nitrogen. The carbons of methoxy group were seen at δ 55.9, δ 55.8 and δ 55.3. The non-benzylic carbon adjacent to nitrogen appeared at δ 52.0 and the benzylic carbon away from nitrogen (C-4) was seen at δ 44.1. The N-methyl carbon was observed at δ 28.6. The aromatic carbon of the mono-substituted phenyl ring to which methoxy is attached was observed at δ 159.7 and the remaining carbons of the phenyl rings were seen at δ 147.6-110.7.

The $^1$H NMR spectrum of 183k showed a broad singlet at δ 4.70 corresponding to the benzylic C-1 proton (Ph-CH-N-). The methoxy protons of the di-substituted phenyl ring were seen differently as singlets at δ 3.76 and δ 3.30. The non-benzylic methylene protons adjacent to nitrogen appeared as a multiplet at δ 3.27-3.11 (Ph-CH$_2$-CH$_2$-N-) and another multiplet at δ 2.78-2.58 was observed for the benzylic methylene protons away from nitrogen (Ph-CH$_2$-CH$_2$-N-). The N-methyl protons appeared as a singlet at δ 2.14. The protons of naphthyl ring showed up as a doublet at δ 8.22 ($J = 8.4$ Hz) for one proton and a multiplet at δ 7.74-7.69 for two protons. Another multiplet was seen at δ 7.35-7.25 for four protons. The two protons of di-substituted phenyl ring appeared as singlets at δ 6.57 and δ 5.97. The $^{13}$C NMR spectrum of 183k showed a peak at δ 76.6 for the substituted carbon adjacent to nitrogen. The carbons of methoxy group were seen at δ 55.7 and δ 55.6. The non-benzylic carbon adjacent to nitrogen appeared at δ 52.7 and the benzylic carbon away from nitrogen (C-4) was seen at δ 44.3. The N-methyl carbon was observed at δ 28.4 and the aromatic carbons appeared in the range at δ 147.4-110.6.

The $^1$H NMR spectrum of 183l showed a singlet at δ 4.10 which corresponds to the benzylic C-1 proton (Ph-CH-N-). A singlet at δ 3.76 was seen for the methoxy protons. The methylene protons of the ethoxy moiety showed up as a multiplet at δ 3.74-
3.62 (Ph-OCH$_2$-CH$_3$) and the methyl protons were observed as a triplet at $\delta$ 1.19 ($J = 7$ Hz) (Ph-OCH$_2$-CH$_3$). The non-benzylic methylene protons adjacent to nitrogen were seen as a multiplet at $\delta$ 3.05-3.01 (Ph-CH$_2$-CH$_2$-N-) and another multiplet at $\delta$ 2.68-2.54 was observed for the benzylic methylene protons away from nitrogen (Ph-CH$_2$-CH$_2$-N-). The $N$-methyl protons appeared as a singlet at $\delta$ 2.16. The aromatic protons of unsubstituted phenyl ring were observed as a multiplet at $\delta$ 7.25-7.16 and the two protons of di-substituted phenyl ring were seen as singlets at $\delta$ 6.53 and $\delta$ 6.02. The $^{13}$C NMR spectrum of 183l showed a peak at $\delta$ 70.0 for the substituted carbon adjacent to nitrogen. The methylene carbon of the ethoxy group appeared at $\delta$ 63.1 and the methyl carbon was observed at $\delta$ 13.5. The carbon of methoxy group appeared at $\delta$ 54.8. The non-benzylic carbon adjacent to nitrogen was seen at $\delta$ 51.2 and the benzylic carbon away from nitrogen (C-4) appeared at $\delta$ 43.2. The $N$-methyl carbon was observed at $\delta$ 27.9 and the carbons of phenyl ring were seen at $\delta$ 146.7-109.8.

The $^1$H NMR spectrum of 183m showed a singlet at $\delta$ 4.08 corresponding to the benzylic C-1 proton (Ph-CH$_2$-N-). The methoxy protons appeared as singlets at $\delta$ 3.79 and $\delta$ 3.76. The methylene protons of the ethoxy moiety were seen as a multiplet at $\delta$ 3.75-3.64 and the methyl protons as a triplet at $\delta$ 1.21 ($J = 7$ Hz). The non-benzylic methylene protons adjacent to nitrogen were seen as a multiplet at $\delta$ 3.09-2.99 (Ph-CH$_2$-CH$_2$-N-) and another multiplet at $\delta$ 2.69-2.51 was observed for the benzylic methylene protons away from nitrogen (Ph-CH$_2$-CH$_2$-N-). The $N$-methyl protons appeared as a singlet at $\delta$ 2.16. The aromatic protons of unsubstituted phenyl ring were observed as a multiplet at $\delta$ 7.10-7.07 and the two protons of di-substituted phenyl ring were seen as singlets at $\delta$ 6.52 and $\delta$ 6.04. The $^{13}$C NMR spectrum of 183m showed a peak at $\delta$ 70.2 for the substituted carbon adjacent to nitrogen. The methylene carbon of the ethoxy group appeared at $\delta$ 64.2 and methyl carbon was observed at $\delta$ 14.6. The methoxy carbons were seen at $\delta$ 55.8 and $\delta$ 55.2. The non-benzylic carbon adjacent to nitrogen was seen at $\delta$ 52.1 and the benzylic carbon away from nitrogen (C-4) at $\delta$ 44.1. The $N$-methyl carbon was observed at $\delta$ 28.8. The carbon of phenyl ring to which methoxy is attached appeared at $\delta$ 158.8 and the remaining carbons of phenyl ring were seen at $\delta$ 147.7-110.8.

Another $N$-alkyl amine i.e. $N$-ethyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (242) was also evaluated which was prepared by Pictet-Spengler reaction starting from
homoveratrylamine (180a) and formaldehyde followed by cyclization under acidic conditions to give 237a. Treatment of 237a with ethyl iodide in the presence of sodium hydride in DME gave the corresponding N-ethyl THIQ 242 in 53% yield.\textsuperscript{188}

The \textsuperscript{1}H NMR spectrum of 242 showed a singlet at δ 3.39 which is attributed to the two benzylic protons adjacent to nitrogen atom. The non-benzylic and the benzylic methylene protons adjacent and away from nitrogen were seen as triplets at δ 2.60 and δ 2.47 respectively. Two singlets appeared at δ 3.72 and δ 3.69 which correspond to the six methoxy protons. The methylene protons of ethyl moiety were observed as a multiplet at δ 2.72-2.66 and the methyl protons appeared as a triplet at δ 1.09 (J = 7.2 Hz). The two aromatic protons were observed as singlets at δ 6.42 and δ 6.37.

\textit{N}-Ethyl THIQ (242) also coupled efficiently with 195a and 195b under the standard reaction conditions to give the coupled products 243a and 243b in 68% and 65% yield respectively.
The structure of products was confirmed by $^1$H and $^{13}$C NMR spectroscopy. The $^1$H NMR spectrum of 243a showed a singlet at δ 4.46 which corresponds to the benzylic C-1 proton (Ph-CH-N-). The methoxy protons were seen as two different singlets at δ 3.77 and δ 3.51. The methylene protons of the ring (Ph-CH$_2$-CH$_2$-N-) and the methylene protons of ethyl moiety (-N-CH$_2$-CH$_3$) appeared as a multiplet at δ 3.09-2.26. The methyl protons of ethyl moiety were seen as a triplet at δ 0.99 ($J = 7.1$ Hz). The protons of unsubstituted phenyl ring were observed as a multiplet at δ 7.23-7.13 and the two protons of disubstituted phenyl ring appeared as singlets at δ 6.52 and δ 6.09. The $^{13}$C NMR spectrum of 243a showed a peak at δ 67.2 for the substituted carbon adjacent to nitrogen. The methoxy carbons appeared at δ 55.7 and the methylene carbons were seen at δ 48.0 and δ 46.3. The N-methyl carbon was observed at δ 28.1 and methyl carbon of ethyl group was seen at δ 11.6. The carbons of phenyl ring appeared in the range at δ 147.3-110.7.

The $^1$H NMR spectrum of 243b showed a singlet at δ 4.43 which corresponds to the benzylic C-1 proton (Ph-CH-N-). The methoxy protons of disubstituted ring were seen as two different singlets at δ 3.77 and δ 3.72 and the methoxy of mono-substituted ring appeared as a singlet at δ 3.53. The methylene protons of the ring (Ph-CH$_2$-CH$_2$-N-) and the methylene protons of ethyl moiety (-N-CH$_2$-CH$_3$) appeared as a multiplet at δ 3.09-2.28. The methyl protons of ethyl moiety were seen as a triplet at δ 1.00 ($J = 7.1$ Hz). The protons of mono-substituted phenyl ring were observed as multiplets at δ 7.10-7.06 and δ 6.77-6.74 and the two protons of disubstituted phenyl ring appeared as singlets at δ 6.52 and δ 6.10. The $^{13}$C NMR spectrum of 243b showed a peak at δ 66.6 for the substituted carbon adjacent to nitrogen. The methoxy carbons appeared at δ 55.8 and δ 55.2. The methylene carbons adjacent to nitrogen were seen at δ 47.9 and the one away from nitrogen atom appeared at δ 46.2. The N-methyl carbon was observed at δ 28.1 and the methyl carbon of ethyl moiety was seen at δ 11.6. The aromatic carbon of the ring to which methoxy is attached was seen at δ 158.6 and the remaining carbons of phenyl ring appeared at δ 147.4-99.9.
Figure 3.7: $^1$H NMR spectrum of compound 243a

Figure 3.8: $^{13}$C NMR spectrum of compound 243a
Further, $N$-benzyl tetrahydroisoquinoline 228 was evaluated and synthesized by following the literature procedure.\(^{189}\) Treatment of tetrahydroisoquinoline 244 with benzyl bromide in presence of triethyl amine in DCM gave the required $N$-benzyl-1,2,3,4-tetrahydroisoquinoline (228) in 85\% yield.\(^{189}\)

![Chemical Structure](image)

The $^1$H NMR spectrum of 228 showed a singlet at $\delta$ 3.59 for the two C-1 benzylidene protons adjacent to nitrogen atom and another singlet at $\delta$ 3.48 for the benzylidene protons of the benzyl moiety. The non-benzylidene protons adjacent to nitrogen (Ph-CH$_2$-CH$_2$-N-) and the benzylidene protons away from nitrogen at C-4 position (Ph-CH$_2$-CH$_2$-N-) appeared as triplets at $\delta$ 2.79 and $\delta$ 2.65 respectively. The aromatic protons were seen as multiplets at $\delta$ 7.31-7.15 for five protons, $\delta$ 7.01-6.89 for three protons and $\delta$ 6.89-6.87 for one proton.

Under similar conditions, $N$-benzyl-1,2,3,4-tetrahydroisoquinoline (228) coupled with 195a and 195b to furnish the products 245a and 245b in 51\% and 40\% yield respectively.

![Chemical Structure](image)

The $^1$H NMR spectrum of 245a showed a singlet at $\delta$ 4.52 which corresponds to the benzylidene C-1 proton (Ph-CH-N). The benzylidene protons adjacent to nitrogen were observed as a doublet at $\delta$ 3.74 ($J = 13.5$ Hz) and $\delta$ 3.18 ($J = 13.5$ Hz). The
methylene protons of the ring were seen as a multiplet at δ 3.04-2.39. The protons of phenyl ring showed a multiplet at δ 7.30-7.28 for two protons, a multiplet at δ 7.24-7.10 for eight protons, another multiplet at δ 7.03-7.00 for two protons. A triplet was seen at δ 6.92 (J = 7.8 Hz) for one proton and a doublet at δ 6.65 (J = 7.5 Hz) for one proton was observed. The $^{13}$C NMR spectrum of 245a showed a peak at δ 68.9 for the substituted carbon adjacent to nitrogen. The benzylic methylene carbon of the N-benzyl moiety was seen at δ 58.8. The non-benzylic carbon adjacent to nitrogen appeared at δ 47.3 and the benzylic carbon away from nitrogen (C-4) was seen at δ 29.2. The carbons of phenyl ring were observed at δ 144.4-125.7.

The $^1$H NMR spectrum of 245b showed a singlet at δ 4.50, which corresponds to the benzylic C-1 proton (Ph-CH-N). A singlet appeared at δ 3.71 for the methoxy protons. One methylene proton of N-benzyl moiety was seen as a singlet at δ 3.76 and other proton appeared as a multiplet at δ 3.18-3.15. The methylene protons of the ring were seen as a broad singlet at δ 3.00 for two protons, a multiplet at δ 2.71-2.67 for one proton and another broad singlet at δ 2.44 for one proton was observed. The protons of phenyl ring showed a multiplet at δ 7.22-7.13 for seven protons, a multiplet at δ 7.04-6.99 for two protons, a multiplet at δ 6.95-6.87 for one proton and another multiplet at δ 6.80-6.76 for two protons. A doublet was observed at δ 6.66 (J = 7.8 Hz) for one aromatic proton. The $^{13}$C NMR spectrum of 245b showed a peak at δ 67.9 for the substituted carbon adjacent to nitrogen. The carbon of methoxy group appeared at δ 59.5. The benzylic methylene carbon of the N-benzyl moiety was seen at δ 55.2. The non-benzylic carbon adjacent to nitrogen appeared at δ 47.2 and the benzylic carbon away from nitrogen (C-4) was seen at δ 29.7. The carbons of phenyl ring to which methoxy is attached appeared at δ 158.9 and the remaining carbons of phenyl ring were observed at δ 130.8-113.7.
Figure 3.9: $^1$H NMR spectrum of compound 245a

Figure 3.10: $^{13}$C NMR spectrum of compound 245a
With the aim of demonstrating the utility of this procedure for the synthesis of naturally occurring alkaloids, we further applied this metal free reaction sequence for the synthesis of cryptostyline II (178) and cryptostyline III (179). These alkaloids were synthesized by the reaction 6,7-dimethoxy-\(N\)-methyl-1,2,3,4-tetrahydroisoquinoline (24b) with the Grignard reagent of 1,2-dimethoxy bromobenzene 195d and Grignard reagent of 3,4,5-trimethoxy bromobenzene 195h respectively. The required 3,4,5-trimethoxy bromobenzene (234c) was synthesized by following the known procedure.

Treatment of gallic acid (246) with dimethyl sulphate under alkaline conditions gave trimethylgallic acid 108c in 76% yield\(^{190}\) which was then nitrated using nitric acid in acetic acid to give 3,4,5-trimethoxy nitrobenzene (247) in 80% yield\(^ {191}\). The \(^1\)H NMR spectrum of 247 showed two singlets at \(\delta 3.88\) and \(\delta 3.85\), which corresponds to six and three methoxy protons respectively and the two aromatic protons were seen as a singlet at \(\delta 7.42\). Palladium catalyzed reduction of 247 in presence of 85% hydrazine hydrate in ethanol gave 3,4,5-trimethoxy aniline (114d) in 65% yield\(^ {192}\). The \(^1\)H NMR spectrum of 114d showed two singlets at \(\delta 3.71\) and \(\delta 3.66\) which were attributed to six and three methoxy protons respectively. The two aromatic protons were seen as a singlet at \(\delta 5.79\) and the labile -NH\(_2\) protons appeared at \(\delta 3.31\). Sandmeyer reaction of 114d in presence of Cu(I)Br/HBr furnished the desired 3,4,5-trimethoxy bromobenzene (234c) in 50%
yield.\textsuperscript{193} \textsuperscript{1}H NMR spectrum of 234c showed two singlets at \(\delta 3.78\) and \(\delta 3.73\) corresponding to six and three methoxy protons respectively. The two aromatic protons were seen as doublets at \(\delta 7.06\) \((J = 9 \text{ Hz})\) and \(\delta 6.46\) \((J = 9 \text{ Hz})\).

The Grignard reagent of 3,4,5-trimethoxy bromobenzene was then prepared following the usual procedure.\textsuperscript{180}

\[
\begin{align*}
\text{Br} & \quad \text{Mg} \\
\text{HCO} & \quad \text{THF} \\
\text{OCH}_3 & \quad \text{HCO} \\
\text{OCH}_3 & \quad \text{OCH}_3 \\
\end{align*}
\]

The coupling of 6,7-dimethoxy-N-methyl-1,2,3,4-tetrahydroisoquinoline (24b) with 195d and 195h afforded the products 178 and 179 in 58% and 54% yield (Scheme 3.2).

\begin{center}
\begin{figure}
\centering
\includegraphics[width=\textwidth]{Scheme3.2.png}
\caption{Synthesis of cryptostyline alkaloids}
\end{figure}
\end{center}
The structure of the products was confirmed by $^1$H and $^{13}$C NMR spectroscopy. The $^1$H NMR spectrum of 178 showed a singlet at $\delta$ 4.07 which corresponds to the benzylic C-1 proton (Ph-CH$_2$N-). The nine methoxy protons were seen as three different singlets at $\delta$ 3.82, $\delta$ 3.78 and $\delta$ 3.75 and other three methoxy protons appeared slightly upfield as a singlet at $\delta$ 3.51. The non-benzylic methylene protons adjacent to nitrogen were seen as a multiplet at $\delta$ 3.12-3.06 (Ph-CH$_2$-CH$_2$-N-) and another multiplet at $\delta$ 2.69-2.55 was observed for the benzylic methylene protons away from nitrogen (Ph-CH$_2$-CH$_2$-N-). The three N-methyl protons were seen as a singlet at $\delta$ 2.18. The aromatic region showed a multiplet at $\delta$ 6.78-6.69 for the three protons and other two protons of the phenyl ring appeared differently as singlets at $\delta$ 6.53 and $\delta$ 6.06. The $^{13}$C NMR spectrum of 178 showed a peak at $\delta$ 70.9 for the substituted carbon adjacent to nitrogen. The methoxy carbons appeared at $\delta$ 56.0 and $\delta$ 55.8. The non-benzylic carbon adjacent to nitrogen was seen at $\delta$ 52.3 and the benzylic carbon away from nitrogen (C-4) appeared at $\delta$ 44.1. The N-methyl carbon was observed at $\delta$ 29.7 and the carbons of phenyl ring were seen at $\delta$ 149.1-110.3.

The $^1$H NMR spectrum of 179 showed a singlet at $\delta$ 4.11 which corresponds to the benzylic C-1 proton (Ph-CH$_2$N-). The twelve methoxy protons were seen as two different singlets at $\delta$ 3.78 and $\delta$ 3.74 and other three methoxy protons appeared slightly upfield as a singlet at $\delta$ 3.54. The non-benzylic methylene protons adjacent to nitrogen were seen as a broad singlet at $\delta$ 3.11 (Ph-CH$_2$-CH$_2$-N-) and a multiplet at $\delta$ 2.69-2.58 was observed for the benzylic methylene protons away from nitrogen (Ph-CH$_2$-CH$_2$-N-). The three N-methyl protons were seen as a singlet at $\delta$ 2.22. The aromatic region showed a multiplet at $\delta$ 6.53-6.45 for three protons and one proton of the phenyl ring appeared as a singlet at $\delta$ 6.09. The $^{13}$C NMR spectrum of 179 showed a peak at $\delta$ 71.6 for the substituted carbon adjacent to nitrogen. The methoxy carbons appeared at $\delta$ 60.8, $\delta$ 56.1, $\delta$ 55.9 and $\delta$ 55.7. The non-benzylic carbon adjacent to nitrogen was seen at $\delta$ 52.5 and the benzylic carbon away from nitrogen (C-4) appeared at $\delta$ 44.4. The N-methyl carbon was observed at $\delta$ 28.7 and the carbons of phenyl ring were seen at $\delta$ 153.0-106.3.
Chapter 3

Results and Discussion

**Figure 3.11:** $^1$H NMR spectrum of compound 178

**Figure 3.12:** $^{13}$C NMR spectrum of compound 178
Figure 3.13: $^1$H NMR spectrum of compound 179

Figure 3.14: $^{13}$C NMR spectrum of compound 179
A tentative mechanism for the coupling of 24a and 195a as depicted in Scheme 3.3 is proposed in accordance with literature.\textsuperscript{27,30,31} N-alkyl tetrahydroisoquinoline undergoes nucleophilic addition on N=N bond of DEAD and forms 1:1 adduct which on hydrogen abstraction generates iminium cation A. The attack of the nucleophile on iminium cation A furnishes the C-1 arylated product 183a.

Scheme 3.3: Plausible Mechanism

Despite a remarkable progress in the field of oxidative coupling reactions, the majority of them are still focussed on the intermolecular reactions with very few examples reported on intramolecular reactions.\textsuperscript{194} Zhang et al. reported DDQ mediated intramolecular oxidative alkylation of a C($sp^3$)-H bond $\alpha$ to nitrogen atom under metal free conditions to synthesize ring fused tetrahydroisoquinolines 249 in good yield.\textsuperscript{195}
Floreancing et al. disclosed the synthesis of tetrahydropyrene 253 via intramolecular oxidative C-H bond activation using DDQ as an oxidant. It was proposed that a single electron transfer occurs from \( p \)-methoxy benzyl ether (250) to DDQ to form the radical ion pair 251 which is followed by hydrogen atom abstraction and a second electron transfer to give oxocarbenium 252. Subsequent cyclization and acetyl group removal gives the product 253.

The successful synthesis of C-1 arylated tetrahydroisoquinolines via intermolecular oxidative coupling prompted us to investigate their synthesis via intramolecular oxidative coupling methodology. For this, 6,7-dimethoxy-\( N \)-benzyl-\( N \)-methyl tetrahydroisoquinoline (255) was chosen as the substrate. Reduction of the Schiff’s base 181a (prepared from homoveratryl amine (180a) and benzaldehyde
(124a) with NaBH₄ in methanol gave 254. N-methylation of 254 in presence methyl iodide and sodium hydride in THF furnished the required amine 255.

\[
\text{MeO} \quad \text{NH}_2 + \quad \text{CHO} \quad \text{Benzene, p-TSA} \quad \Delta \quad \text{MeO} \quad \text{N} \\
180a \quad 124a \quad 181a \\
\text{MeO} \quad \text{MeO} \quad \text{MeO} \\
\text{N} \quad \text{MeO} \quad \text{NH} \\
255 \quad 254
\]

The amine 255 was characterized by \(^1\text{H}\) NMR spectroscopy. The spectrum showed a singlet at \(\delta 3.70\) for the six methoxy protons. The two benzylic protons \(\alpha\) to nitrogen appeared as a singlet at \(\delta 3.42\). The two methylene protons adjacent to nitrogen and the other two away from nitrogen were observed as multiplets at \(\delta 2.67-2.63\) and \(\delta 2.53-2.50\). The \(N\)-methyl protons were seen as a singlet at \(\delta 2.15\). The three aromatic protons of the substituted phenyl ring appeared as a multiplet at \(\delta 6.65-6.58\) and the five aromatic protons of the unsubstituted ring were observed as a multiplet at \(\delta 7.17-7.10\).

We envisaged that the formation of an iminium cation may occur at the benzylic position \(\alpha\) to the nitrogen atom in presence of an oxidant which can then undergo intramolecular Friedel Craft’s arylation due to strong aromatic ring current and can lead to the synthesis of cyclic amines.
However, reaction of 255 under different reaction conditions shown below did not afford 183g. The reason for the failure of these reactions is not clear.

In summary, a convenient one step procedure for the synthesis of 1-aryl-N-alkyl-1,2,3,4-tetrahydroisoquinolines has been achieved via oxidative coupling of N-alkyl tetrahydroisoquinolines with aryl Grignard reagents using DEAD in the absence of any transition metal catalyst. Various C-1 arylated tetrahydroisoquinolines have been synthesized including naturally occurring alkaloids i.e. cryptostyline II and cryptostyline III.