

FeCl₃-Catalyzed Oxidative Allylation of sp² and sp³ C–H Bond Adjacent to a Nitrogen Atom: Easy Access to Homoallyl Tertiary Amines

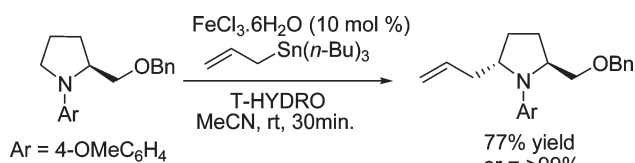
Gullapalli Kumaraswamy,^{*,†} Akula Narayana Murthy,^{†,‡} and Arigala Pitchaiah[†]

[†]Organic Division-III, Indian Institute of Chemical Technology, Hyderabad 500 007, India, and

[‡]An Associate Institution of University of Hyderabad, Hyderabad 500 046, India

gkswamy_iict@yahoo.co.in

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Oxidative allylation to sp²- and sp³-carbon attached to the nitrogen atom was accomplished. The α-allylation of tertiary amines was catalyzed by easily available hydrated iron(III) chloride in combination with air or aqueous ^tBuOOH. Remarkably, *N*-allyl- and *N*-propargyl-tethered tertiary amines were also allylated through this protocol.

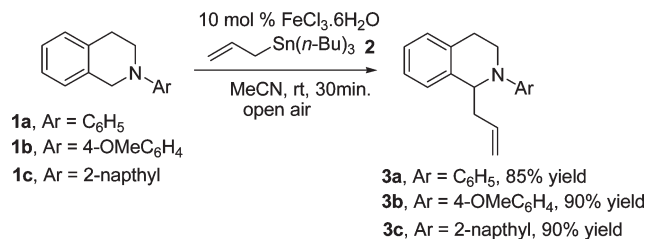
In recent years, there has been a resurgence of interest in the oxidative functionalization of sp³ C–H bonds adjacent to a nitrogen atom.¹ A plethora of methods have been developed to achieve this functionalization with various nucleophiles.² The prominent route appears to be transition-metal catalysis together with either organic peroxides or elemental oxygen to generate iminium cation, which in turn reacts with various nucleophiles. Following the pioneering work of Murahashi et al. on the Ru-catalyzed α-cyanation of tertiary amines,³ many other alternative transition metals

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(3) (a) Murahashi, S.-I.; Komiya, N.; Terai, H.; Nakae, T. *J. Am. Chem. Soc.* **2003**, *125*, 15312. (b) Murahashi, S.-I.; Komiya, N.; Terai, H. *Angew. Chem., Int. Ed.* **2005**, *44*, 6931.

SCHEME 1. FeCl₃-Catalyzed Allylation of Electronically Activated Tetrahydroisoquinoline



have also been explored for this transformation.⁴ Among them, copper salts turned out to be the most efficient catalysts⁵ for the α-functionization to nitrogen. With our continued interest in developing transition-metal-catalyzed novel methodologies,⁶ we focused on oxidative coupling of tertiary amines⁷ with allyl tributyltin using a catalytic amount of FeCl₃ in the presence of air or T-HYDRO (70% ^tBuOOH in H₂O) as terminal oxidant.

After considerable experimentation, *N*-phenyltetrahydroisoquinoline **1a** (3 equiv) reacted with allyl tributyltin (2 equiv) in acetonitrile at room temperature using 10 mol % of FeCl₃·6H₂O. It was observed that the desired reaction proceeded within 30 min under the atmosphere of air to give **3a** in 85% yield (Scheme 1).

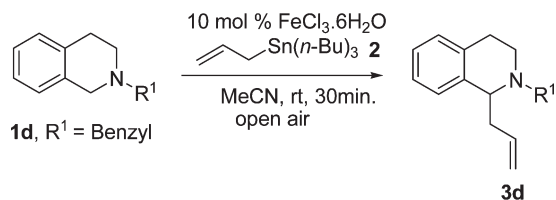
Further, under the same conditions, improvement of yield was observed when the *N*-phenyl moiety was replaced with electron-rich 4-methoxyphenyl **1b** (**3b**, 90% yield) or 2-naphthyl moiety **1c** (**3c**, 90%) (Scheme 1), while *N*-benzyltetrahydroisoquinoline **1d** failed to yield the required product **3d** under similar conditions. On the other hand, using T-HYDRO (70% ^tBuOOH in H₂O) (2 equiv) as terminal oxidant under otherwise identical conditions resulted in **3d** in 85% yield (Table 1, entry 11). The reaction performed under air balloon and oxygen balloon did not proceed. A longer reaction time decreased the product yield.

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TABLE 1. Screening of Catalysts, Oxidants, And Molar Ratios of Substrate^{a,b}

entry	catalyst	1d (equiv)	oxidant	yield (%)
1	RuCl ₃	3	T-HYDRO	NR
2	Pd(OAc) ₂	3	T-HYDRO	NR
3	CuCl ₂	3	T-HYDRO	NR
4	CuCl	3	T-HYDRO	30
5	CuBr	3	T-HYDRO	50
6	CuI	3	T-HYDRO	42
7	FeCl ₂	3	T-HYDRO	NR
8	FeCl ₃ ·6H ₂ O	3	TBHP(anhydrous)	85
9	FeCl ₃ ·6H ₂ O	1	T-HYDRO	30
10	FeCl ₃ ·6H ₂ O	2	T-HYDRO	70
11	FeCl₃·6H₂O	3	T-HYDRO	85
12	FeCl ₃ ·6H ₂ O	3	H ₂ O ₂ (50% aqueous)	50
13	FeCl ₃ ·6H ₂ O	3	BzOOBz	NR
14	FeCl ₃ ·6H ₂ O	3	urea peroxide	NR

^aAll reactions carried out in open air with 10 mol % of catalyst, 2 equiv of oxidant, and 1 equiv of **2**. ^bYield based on **2** but not optimized. NR = no reaction.

Interestingly, experiments were conducted with other metal salts (RuCl₃, CuCl₂, FeCl₂, and Pd(OAc)₂) as catalyst in combination with T-HYDRO for this transformation, but none could catalyze the desired reaction (Table 1, entries 1–3), whereas CuCl, CuBr, and CuI initiated the reaction and the corresponding product **3d** was obtained albeit low yields (Table 1, entries 4–6).

Molar ratios of reactants and solvents have shown influence on product yields. The use of excess tertiary amine substrate (**1d**/**2** is 3:1 molar equiv) improved the desired product **3d** yield (Table 1, entries 9–11). In addition to T-HYDRO, other oxidants, namely 50% aqueous H₂O₂, urea peroxide, and benzoyl peroxide, were also investigated. Only H₂O₂ provided the desired product but with low yields in comparison to T-HYDRO (Table 1, entries 12–14). A brief survey of solvents indicated that the acetonitrile is the only suitable solvent for this reaction. Using anhydrous TBHP as oxidant did not improve the product **3d** yield (Table 1, entry 8). However, in the absence of metal catalyst no reaction was observed. The optimum catalyst loading was found to be 10 mol % (based on **2**), while reducing it to 5 mol % led to a significant drop in the yield of product **3d**. Interestingly, replacing allyltributyltin with allyltrimethylsilane⁸ or allyltrichlorosilane failed to generate allyl-coupled product **3d**. However, allyl dioxaborinane coupled with only sp³-carbon containing tertiary amine **6a** under the standard protocol furnished the expected product **7a** in 70% yield (Table 2, entry 3).

To check the generality of this protocol, the experiment was extended to various tertiary amine substrates under optimized conditions, and the results are summarized in Table 2. Much to our delight, *N*-allyl- and *N*-propargyl-tethered tetrahydroisoquinoline **1e** and **1f** underwent efficiently oxidative coupling

(8) Allylation of cyclic carbamate has been achieved with allyltrimethylsilane by electrochemical methods in moderate yields. See: Horii, D.; Amemiya, F.; Fuchigami, T.; Atobe, M. *Chem.—Eur. J.* **2008**, *14*, 10382.

TABLE 2. FeCl₃·6H₂O-Catalyzed Oxidative Allylation of Various Tertiary Amines with Allyltributyltin **2**^{a,b}

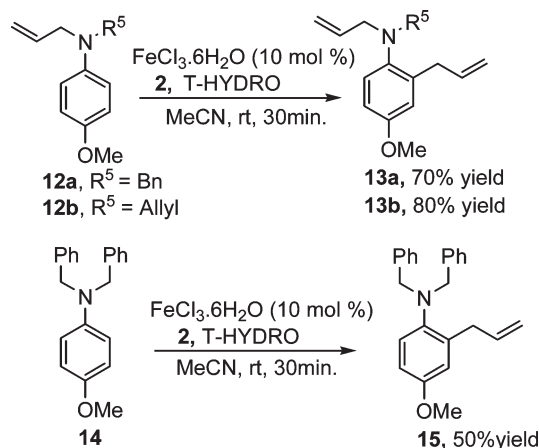
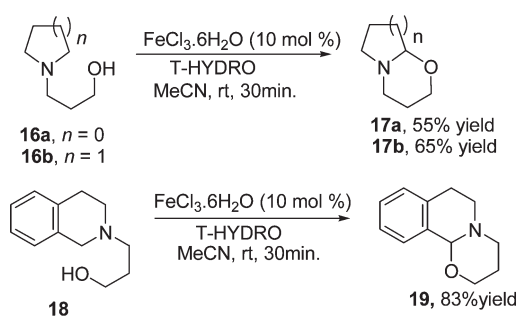
entry	substrate	product	%yield
1			3e , 85 3f , 65
2			5 , 90
3			7a , 75 7b , 80 7c , 70 7d , 75 7e , 65
4			9 , 55
5			11 , 45

^aAll reactions carried out in open air with a molar ratio of 1:3:2 allyltributyltin/tertiary amine/T-HYDRO with 10 mol % of FeCl₃·6H₂O, and reactions were quenched after 30 min. ^bYield based on **2** but not optimized. All products gave satisfactory analytical data.

with **2** to lead to the products **3e** and **3f** in good yields (Table 2, entry 1). Remarkably, the products **3e** and **3f** have an option of being subjected to the RCM reaction followed by one-pot oxidation, which would result in hydroxylated motifs as structural units.^{6a} Similarly, *N*-(4-methoxyphenyl)tetrahydroquinoline **4** and *N*-substituted *N*-methylbenzeneamine **6a–e** with various activating groups on the aromatic nucleus coupled with **2** efficiently furnished the corresponding products **5** and **7a–e**⁹ with moderate to good yields (Table 2, entries 2 and 3). Cyclic amines **8** and **10** were also coupled with allyl moiety to yield the desired product **9** and **11** in moderate yield (Table 2, entries 4 and 5).

When *N*-benzyl-*N*-methyl-4-methoxybenzeneamine **6d** was reacted with **2** under standard protocols, allylation of the methyl group was observed (Table 2, entry 3). This result indicates that oxidation takes place at less hindered sp³ carbon rather than at the benzylic carbon. In a similar vein,

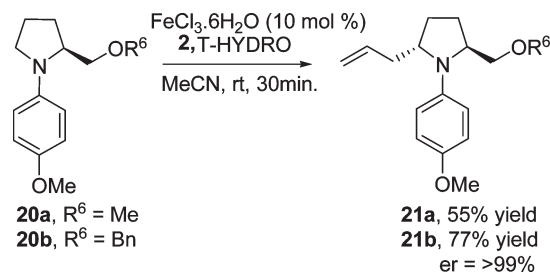
(9) The isolated product **7e** was subjected to RCM and the resulting product 3,4-dihydro *N*-(4-methoxyphenyl)piperidine isolated in 90% yield.

SCHEME 2. $\text{FeCl}_3/\text{T-HYDRO}$ -Catalyzed *ortho*-Allylation of Anisidine DerivativeSCHEME 3. $\text{FeCl}_3/\text{T-HYDRO}$ -Catalyzed Synthesis of 1,3-Oxazolidines

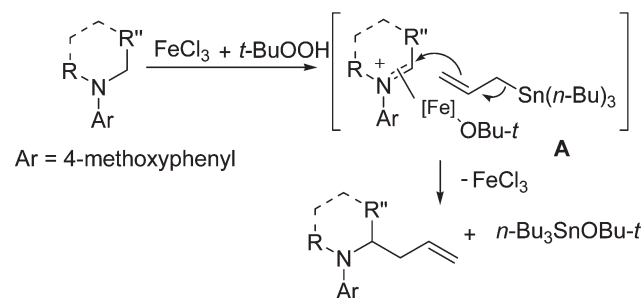
12a, **12b**, and **14** were subjected to oxidation using the above conditions. To our surprise, allylation has occurred in both cases at the *ortho*-position to amine of the aromatic ring, and subsequent products **13a** (70%), **13b** (80%), and **15** (50%)¹⁰ were isolated in good yields (Scheme 2).

As a representative example, $\text{FeCl}_3/\text{T-HYDRO}$ induced the oxidation of cyclic amines tethered with oxynucleophiles **16a**, **16b**, and **18**, which were investigated in the absence of **2**. The expected products 1,3-oxazolidines **17a**, **17b**, and **19** were obtained with 55%, 65%, and 83% yields, respectively.¹¹ This result is significant, as alkyl tertiary amines also undergo oxidation generating iminium ion which in turn reacts with nucleophiles leading to the observed product (Scheme 3).

Finally, we focused on diastereoselective allylation of (*S*)-2-(methoxymethyl)-*N*-(4-methoxyphenyl)pyrrolidine **20a** with **2** using similar conditions. We were pleased to see the corresponding 5-allylated product **21a** in moderate yield (55%). By replacing methyl protection group with benzyl in **20a**, the substrate **20b** led to *trans*-5-allylated product **21b** in good yield (77%) with *er* > 99%. The *er* value was analyzed by HPLC on the chiral stationary phase. The relative stereochemistry was confirmed by NOE studies (Scheme 4). Routine synthetic manipulations on **21b** could lead to

SCHEME 4. $\text{FeCl}_3/\text{T-HYDRO}$ -Induced Enantioselective Allylation

SCHEME 5. Tentative Mechanism for Oxidation of Tertiary Amines



unsymmetrical *trans*-2, 5-dialkylpyrrolidines which are antivenom alkaloids.¹²

A tentative mechanism is proposed in analogy with Cu-catalyzed oxidative reaction of tertiary amines.⁵ Initial activation by $\text{FeCl}_3-t\text{-BuOOH}$ generates metal-coordinated iminium intermediate **A**. Intermolecular nucleophilic addition on iminium ion **A** could lead to the observed product (Scheme 5).

In conclusion, we have demonstrated a rapid oxidative coupling protocol with readily available benchtop chemical hydrated FeCl_3 in combination with T-HYDRO. To the best of our knowledge, this is the first report wherein the allyl functionality is introduced to the sp^2 - and sp^3 -carbon attached to the nitrogen atom by FeCl_3 -mediated catalysis. Remarkably, *N*-allyl- and *N*-propargyl-tethered tertiary amines were also allylated, which can lead the RCM reaction to generate cyclic nitrogen structural units.

Experimental Section

1-Allyl-2-phenyl-1,2,3,4-tetrahydroisoquinoline (3a). A 25 mL round-bottom flask was charged with $\text{FeCl}_3 \cdot 6\text{H}_2\text{O}$ (0.027 g, 10 mol %) and **1a** (0.624 g, 3.0 mmol). To this were added successively acetonitrile (5 mL) and allyltributyltin (0.33 g, 1.0 mmol) via syringe. The resulting reaction mixture was stirred at room temperature for 30 min under open air. Thereafter, the reaction mixture was filtered through a Celite pad and washed with EtOAc (2×5 mL). The combined organic layers were evaporated under reduced pressure. The crude residue was purified by column chromatography (silica gel 100–200 mesh) eluting with hexane–EtOAc (98: 2) to give **3a** as a yellow oil (0.211 g, 85%); $^1\text{H NMR}$ (300 MHz, CDCl_3) δ 7.21–7.06 (m, 6H), 6.83 (d, $J = 7.9$ Hz, 2H), 6.69–6.65 (m, 1H), 5.88–5.74 (m, 1H), 5.05–5.00 (m, 2H), 4.71 (t, $J = 6.7$ Hz, 1H), 3.66–3.52 (m, 2H), 3.05–2.95 (m, 1H), 2.89–2.80 (m, 1H), 2.75–2.66 (m, 1H),

(10) Further, the compound **15** was subjected to hydrogenation (10% Pd/C, EtOH, 20 min, H_2 balloon). The resulting product 2-propyl-4-methoxyaniline was isolated and confirmed by $^1\text{H NMR}$ and MS.

(11) (2-Pyrrolidine)ethanol did not cyclize under these conditions. Only starting material was recovered.

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2.50–2.40 (m, 1H); ^{13}C NMR (75 MHz, CDCl_3); δ 138.9, 135.6, 134.9, 129.2, 127.3, 126.4, 125.6, 117.1, 116.9, 113.8, 59.3, 41.8, 40.8, 27.3; IR (KBr, cm^{-1}) 2917, 2837, 1638, 1597, 1503, 1474, 1391, 1222, 1154, 989, 914, 746, 691; HRMS (ESI) calcd for $\text{C}_{18}\text{H}_{20}\text{N}$ $[\text{M} + \text{H}]^+$ 250.1595, found 250.1588.

2,3,4,6,7,11b-Hexahydro[1,3]oxazino[2,3-*a*]isoquinoline (19). Tertiary aminopropanol **18** (0.191 g, 1.0 mmol) and $\text{FeCl}_3 \cdot 6\text{H}_2\text{O}$ (0.09 g, 10 mol %) were dissolved in acetonitrile (5 mL). To this stirred reaction mixture was added dropwise *tert*-butyl hydroperoxide (0.257 mL, 70% $t\text{BuOOH}$ in H_2O , 2.0 mmol). The resulting reaction mixture was stirred at room temperature for 30 min under open air. Thereafter, the reaction mixture was filtered through a Celite pad and washed with EtOAc (2×5 mL). The combined organic layers were evaporated under reduced pressure. The crude residue was purified by column chromatography on silica gel eluting with chloroform/methanol (8:2) to give **19** as a yellow oil; yield yellow oil; yield 0.156 g (83%); ^1H NMR (300 MHz, CDCl_3) δ 7.28–7.24 (m, 1H), 7.15 (t, $J = 3.5$ Hz, 2H), 7.05–7.02 (m, 1H), 4.83 (s, 1H),

4.20 (dd, $J = 4.9, 11.0$ Hz, 1H), 3.89–3.81 (m, 1H), 3.28–3.20 (m, 1H), 3.13–3.08 (m, 1H), 3.00–2.70 (m, 3H), 2.66 (p, $J = 6.0$ Hz, 1H), 2.23–2.07 (m, 1H), 1.34 (t, $J = 13.4$ Hz, 2H); ^{13}C NMR (75 MHz, CDCl_3) 128.2, 127.7, 127.2, 125.9, 89.7, 68.3, 53.0, 46.0, 28.9, 22.8; IR (KBr, cm^{-1}) 2924, 2850, 1636, 1463, 1267, 1084, 1058, 745, 666, 501; MS (ESIMS) m/z 190 ($\text{M} + \text{H}$) $^+$; HRMS (ESI) calcd for $\text{C}_{12}\text{H}_{16}\text{NO}$ $[\text{M} + \text{H}]^+$ 190.1231, found 190.1241.

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Supporting Information Available: Experimental procedures and characterization data for all new compounds along with copies of ^1H and ^{13}C NMR spectral data. This material is available free of charge via the Internet at <http://pubs.acs.org>.