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Iron-Catalyzed Oxidative C(3)−H Functionalization of Amines

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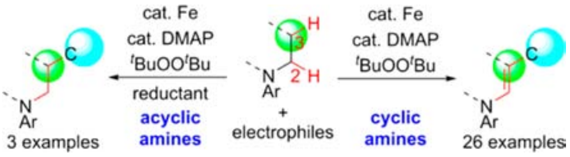
ABSTRACT



Fe-catalyzed direct dehydrogenative C(3)-functionalization of tertiary arylamines was developed via activation of the sp^3 C(3)−H bond. The reaction is applicable to both cyclic and acyclic amines. The key process is the catalytic desaturative enamine formation from tertiary amines and position-selective C−C bond formation (addition to nitro olefins) at the β-carbon. Products can be converted to versatile and unique nitrogen-containing molecules.

Many C(3)-functionalized amines have remarkable biological activities,[1] but access to such molecules generally requires multistep, indirect pathways.[2,3] Direct C(3)-functionalization of amines[4,5] through catalytic conversion of an sp^3 C(3)−H bond has scarcely been developed, other than the recently reported catalyses.[6,7] These potentially useful reactions require further improvement for application to the practical construction of carbon skeletons, however, such as use of ubiquitous metals instead of precious metals, expansion of the limited substrate scope, and development of milder reaction conditions. Here we report an iron-catalyzed C(3)−H functionalization of amines that is applicable to both cyclic and acyclic substrates under mild conditions using nitroalkenes as a coupling partner.

We and others previously reported oxidative C(2)-functionalizations of amines through the oxidation of amines to electrophilic imines or iminium ions, followed by addition of nucleophiles to the thus generated electrophiles (Scheme 1a).[8−11] In this general reaction profile, the oxidatively generated iminium ions possessing a β-hydrogen atom will isomerize to enamines in the absence of

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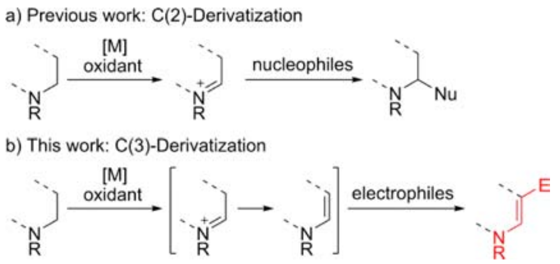
nucleophiles.[6,7,12] The thus-generated enamines act as nucleophiles for C(3)-functionalization in the presence of appropriate electrophiles (Scheme 1b).

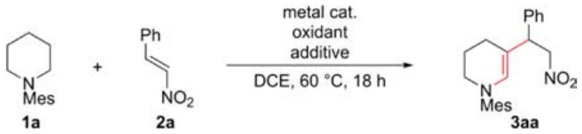
Scheme 1. Oxidative C(2)- and C(3)-Functionalization of Amines via in Situ Generation of Iminium Ions and Enamines, Respectively



Based on such a blueprint, we attempted to optimize the reaction conditions between piperidine derivatives and nitrostyrene (**2a**) by following Liang's report[7a] using various first-row transition-metal catalysts and terminal oxidants. Screening of the *N*-protecting groups revealed that a bulky substituent on the nitrogen atom afforded higher yields than sterically less demanding substituents (such as phenyl and benzyl), and a mesityl (Mes) group was found to be the best (**1a**: 3 equiv).[13]

Investigation of catalytic metal sources using di-*tert*-butyl peroxide (TBP: 2 equiv) as an oxidant revealed that iron halides, especially $FeCl_2$, produced a higher yield than other metal salts (Table 1, entries 1−5). Use of TBHP as an oxidant, instead of TBP, produced many byproducts, and the use of O_2 resulted in significantly lower reactivity (entries 6 and 7). In the absence of an oxidant or iron source, however, the reaction proceeded poorly (entries 8 and 9). The addition of a catalytic amount of *N*,*N*-dimethylaminopyridine (DMAP) aimed at suppressing the product inhibition[11d,13] markedly improved the yield to 55% (entry 10). Decreasing the catalyst loading (5 mol % of $FeCl_2$ and 7.5 mol % of DMAP) produced similar results when the amount of TBP was slightly increased to 2.5 equiv (entry 11). Use of $FeCl_3$, a more soluble iron source in DCE than $FeCl_2$, further increased the yield to 67% (entry 12). The moderate yield was partially due to the overoxidation of product **3aa**;[14] thus, we increased the amount of **1a** (4 equiv) to obtain **3aa** in an optimum yield of 78% (entry 13).

Table 1. Optimization of the Reaction Conditions[a]



entry	metal cat. (mol %)	oxidant (equiv)	additive (mol %)	yield[b] (%)
1	CuCl (20)	TBP (2)	none	2
2	CuBr (20)	TBP (2)	none	1
3	$FeCl_2$ (20)	TBP (2)	none	15
4	$FeBr_2$ (20)	TBP (2)	none	9
5	$Fe(OAc)_2$ (20)	TBP (2)	none	4
6	$FeCl_2$ (20)	TBHP (2)	none	10
7	$FeCl_2$ (20)	O_2 (1 atm)	none	trace
8	$FeCl_2$ (20)	none	none	trace
9	none	TBP (2)	none	NR
10	$FeCl_2$ (20)	TBP (2)	DMAP (30)	55
11	$FeCl_2$ (5)	TBP (2.5)	DMAP (7.5)	62
12	$FeCl_3$ (5)	TBP (2.5)	DMAP (7.5)	67
13[c]	$FeCl_3$ (5)	TBP (2.5)	DMAP (7.5)	78 (70)

[a] Reaction conditions: 3.0 equiv of *N*-mesitylpiperidine **1a** (0.60 mmol), 1.0 equiv of nitrostyrene (0.20 mmol), metal catalyst, oxidant, and solvent (1.0 mL) at 60 °C unless otherwise noted. [b] Determined by ^1H NMR using nitromethane as an internal standard. Number in parentheses is the isolated yield after silica gel column chromatography. [c] Using 4.0 equiv of **1a**. TBP = di-*tert*-butyl peroxide, TBHP = *tert*-butyl hydroperoxide, DCE = 1,2-dichloroethane, Mes = 2,4,6-trimethylphenyl, DMAP = *N*,*N*-dimethylaminopyridine, NR = no reaction.

We next investigated the substrate scope under the optimized conditions. The scope of electrophiles was investigated using **1a** (Table 2). Nitroalkenes possessing substituted aryl groups or a heteroaromatic ring at the β-position efficiently afforded the corresponding products (57−74% yield, entries 1−10). α-Alkyl nitroalkenes, which are susceptible to polymerization, also afforded the products in synthetically useful yields (entries 11 and 12). The reaction using trisubstituted β-methylnitrostyrene (**2m**) as an acceptor also proceeded giving **3am** in 41% yield (entry 13).

We then investigated the scope of amine substrates **1** using **2a** as an electrophile (Scheme 2). Heteroatom-containing cyclic amines **1b**−**d** were suitable and afforded the coupling products **3ba**−**da** in good to moderate yield. Seven- and eight-membered cyclic amines (**1e** and **1f**) produced the corresponding adducts **3ea** and **3fa** in high yield.[15] Reactions of substituted piperidines were also

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(10) Representative examples using oxidative catalysis: (a) Catino, A. J.; Nichols, J. M.; Nettles, B. J.; Doyle, M. P. *J. Am. Chem. Soc.* **2006**, *128*, 5648. (b) Condie, A. G.; González-Gómez, J. C.; Stephenson, C. R. J. *J. Am. Chem. Soc.* **2010**, *132*, 1464. (c) Jiang, G.; Chen, J.; Huang, J.-S.; Che, C.-M. *Org. Lett.* **2009**, *11*, 4568. (d) Alagiri, K.; Prabhu, K. R. *Org. Biomol. Chem.* **2012**, *10*, 835. (e) Hari, D. P.; König, B. *Org. Lett.* **2011**, *13*, 3852. (f) Ohta, M.; Quick, M. P; Yamaguchi, J.; Wünsch, B.; Itami, K. *Chem. Asian J.* **2009**, *4*, 1416. (g) Kumaraswamy, G.; Murthy, A. N.; Pitchaiah, A. *J. Org. Chem.* **2010**, *75*, 3916. (h) Volla, C. M. R.; Vogel, P. *Org. Lett.* **2009**, *11*, 1701. (i) Jia, X.; Peng, F.; Qing, C.; Huo, C.; Wang, X. *Org. Lett.* **2012**, *14*, 4030. (j) Zhang, G.; Zhang, Y.; Wang, R. *Angew. Chem., Int. Ed.* **2011**, *50*, 10429.

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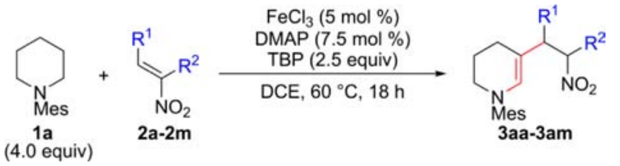
(13) We speculate that catalyst deactivation by strong coordination of the product and/or substrate is problematic. Bulky protecting groups would suppress such catalyst deactivation. See the Supporting Information.

(14) See the Supporting Information.

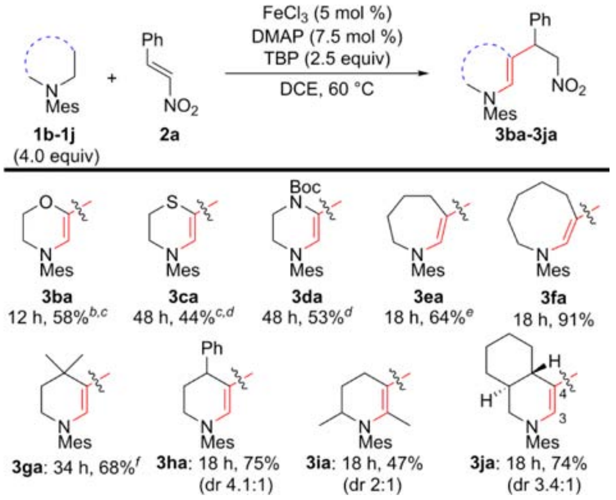
Table 2. Substrate Scope of the C(3)−H Functionalization of *N*-Mesitylpiperidine **1a** with Various Nitroalkenes **2a**−**m**[a]



entry	R^1, R^2	product	yield[b] (%)
1	Ph, H (**2a**)	**3aa**	70
2	4-MeC_6H_4, H (**2b**)	**3ab**	63
3	4-$MeOC_6H_4$, H (**2c**)	**3ac**	57
4[c,d]	4-ClC_6H_4, H (**2d**)	**3ad**	69
5[c,d]	4-BrC_6H_4, H (**2e**)	**3ae**	73
6	3-BrC_6H_4, H (**2f**)	**3af**	66
7[c]	2-BrC_6H_4, H (**2g**)	**3ag**	70
8[c,d]	2-IC_6H_4, H (**2h**)	**3ah**	74
9	2-$CF_3C_6H_4$, H (**2i**)	**3ai**	70
10	2-thienyl, H (**2j**)	**3aj**	59
11	Me, H (**2k**)	**3ak**	52
12	cyclohexyl, H (**2l**)	**3al**	60
13[d]	Ph, Me (**2m**)	**3am**	41[e]

[a] Reactions were carried out by using 4.0 equiv of *N*-mesitylpiperidine (**1a**: 0.80 mmol), 1.0 equiv of nitroalkenes **2** (0.20 mmol), 5 mol % of $FeCl_3$ (0.01 mmol), 7.5 mol % of DMAP (0.015 mmol), and 2.5 equiv of TBP (0.50 mmol) in DCE (0.20 M, 1.0 mL) at 60 °C unless otherwise noted. [b] Isolated yield after silica gel column chromatography. [c] Using 3.0 equiv of TBP at 50 °C. [d] 24 h. [e] Diastereomeric ratio (dr) was determined by ^{1}H NMR to be 1.1:1.

Scheme 2. Substrate Scope of the C(3)−H Functionalization of Various Cyclic Amines **1b**−**j** with Nitrostyrene **2a**[a]



[a] Reactions were carried out by using 4.0 equiv of *N*-mesitylamines **1** (0.80 mmol), 1.0 equiv of nitrostyrene **2a** (0.20 mmol), 5 mol % of $FeCl_3$ (0.01 mmol), 7.5 mol % of DMAP (0.015 mmol), and 2.5 equiv of TBP (0.50 mmol) in DCE (0.20 M, 1.0 mL) unless otherwise noted. Isolated yields after silica gel column chromatography were shown. The dr was determined by ^{1}H NMR analysis. [b] Using 10 equiv of amine. [c] Using 15 mol % of DMAP. [d] Using 5 equiv of amine. [e] 1.0 equiv of 2,6-di-*tert*-butyl-4-hydroxytoluene (BHT) was added. [f] At 80 °C. Boc = *tert*-butoxycarbonyl.

investigated. In the case of *N*-mesityl-4,4-dimethylpiperidine (**1g**), reactivity was low due to the distorted conformation and steric hindrance of the intermediate enamine.[16] Desired product **3ga** was still obtained in 68% yield, however, by increasing the temperature to 80 °C. The reaction with *N*-mesityl-2,6-dimethylpiperidine (**1i**) proceeded regioselectively on the ring carbon to produce *endo*-enamine **3ia** in 47% yield. An unsymmetrical substrate, *N*-mesityl *trans*-decahydroisoquinoline (**1j**), produced C(4)-alkylated-$\Delta^{3,4}$-enamine **3ja** in 74% yield with complete regioselectivity. These findings suggest that the reaction site is determined by the fine balance between electronic (in the case of **3ia**) and steric (in the case of **3ja**) factors.

The current catalytic dehydrogenative C(3)-functionalization proceeded under quite mild conditions and could thus be extended to acyclic amines for the first time (Scheme 3). The product acylic enamines were too unstable to be isolated, and therefore coupling products were isolated as stable, saturated amines after reduction. Addition of 3Å molecular sieves (3AMS) as a desiccant was essential to avoid undesired decomposition of the intermediate and product enamines. When the *β*-substituent of the amine was a hydrogen or a methyl group, the reaction proceeded at 60 °C in good yield. In the case of *β*-phenyl-substituted amine **4c** (3 equiv), the yield of **5c** was moderate even at a higher temperature (80 °C) due to the attenuated nucleophilicity of the intermediate conjugated enamine. Although the diastereoselectivity (1:1−2:1) in the reduction step requires further improvement, this one-pot process offers a unique method to access 1,4-diamine precursors starting from simple alkylamines.[17]

Representative transformations of product **3aa** are shown in Scheme 4. The enamine moiety of **3aa** was selectively reduced with $NaCNBH_3$ in the presence of $ZnCl_2$, producing **6** in 98% yield. Partial hydrogenation of the nitro group using a Pd/C catalyst in the presence of Boc_2O (affording *N*,*O*-di-Boc-protected hydroxylamine) and successive reductive cleavage of the N−O bond afforded selectively protected 1,4-diamine **7** in 61% overall yield. Reduction of **3aa** with Zn in AcOH produced 3,4-disubstituted pyrrolidine[18] **8** in high yield and diastereoselectivity via skeletal reorganization. Reduction of **3aa** with Zn under aqueous conditions in the presence of Boc_2O produced octahydro-2H-pyrido[3,2-e][1,2]oxazine **9** through a partial reduction of the nitro group followed by diastereoselective cyclic aminal formation.[19]

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(15) We speculate that the role of BHT is a proton source to suppress further addition of intermediate nitronate generated by the Michael addition of the enamine to **2a** with the iminium cation derived from **1e**.

(16) An enamine derived from **3g** was isolated, supporting the proposed reaction mechanism. See the Supporting Information.

(17) Catalytic production of enamines from acyclic amines and application to C−C bond formation were recently reported. This method, however, failed to produce C(3)-functionalized amines: Morigaki, A.; Kawamura, M.; Arimitsu, S.; Ishihara, T.; Konno, T. *Asian J. Org. Chem.* **2013**, *2*, 239.

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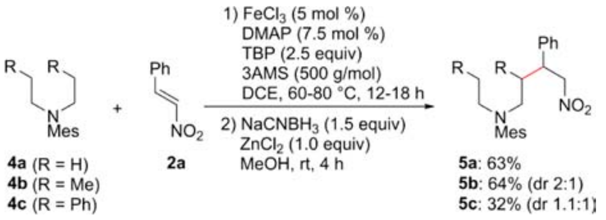
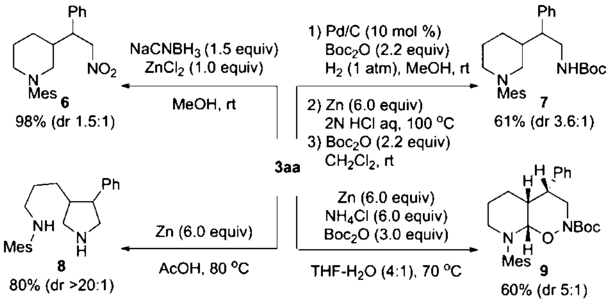
Scheme 3. C(3)−H Functionalization of Acyclic Amines



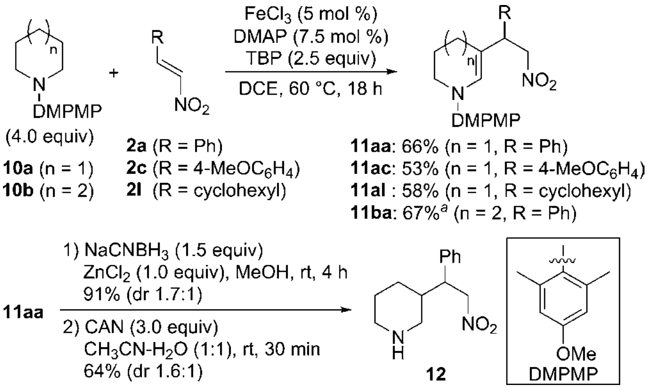
Scheme 4. Representative Transformations of the Coupling Products



We also devised a cleavable 2,6-dimethyl-4- methoxyphenyl (DMPMP) group instead of the mesityl group to enhance the synthetic utility of this catalytic method (Scheme 5). *N*-DMPMP-protected piperidines **10** afforded products **11** in yields comparable to those of **1a** and **1e**. After reduction of the enamine moiety of **11aa**, the DMPMP group was successfully removed with cerium(IV) ammonium nitrate (CAN) to produce free secondary amine **12**.

A plausible catalytic cycle of this dehydrogenative C(3)-functionalization of amines is proposed in Figure 1. First, a Fenton-type reaction[20] between Fe(II) and TBP would produce *tert*-butoxy radical (^{t}BuO$^{\bullet}$) and Fe(III). Fe(III) abstracts one electron from the nitrogen atom of the substrate amine to generate an aminiumyl radical **13**.[21] Then, subsequent abstraction of the α-hydrogen radical by ^{t}BuO$^{\bullet}$ should afford iminium ion intermediate **14**.[11a−c,22] After isomerization from iminium to enamine **15**, nucleophilic addition to nitroalkenes (E^{+}) produces coupling products **3** and **5**.

Scheme 5. Catalytic Oxidative C(3)-Functionalization of *N*-DMPMP-piperidine **10a**−**c** and Deprotection of the Product



^{a} Conducted in the presence of BHT (1.0 equiv).

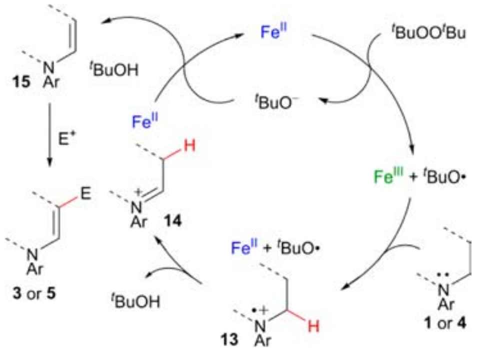


Figure 1. Plausible catalytic cycle.

In conclusion, we developed an iron-catalyzed C(3)-functionalization of tertiary amines via in situ oxidative enamine generation. An unactivated sp^{3} C(3)−H bond of the amines was regioselectively converted to a C−C bond under mild conditions using a ubiquitous metal catalyst. Because enamines are very versatile nucleophiles in organic synthesis,[12h,i] a unique synthetic route for bioacitve amine compounds can be designed based on this catalytic reaction starting from simple amines in combination with various electrophiles. Additional studies to expand the substrate scope and explore enantioselective variants are ongoing.

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Supporting Information Available. Experimental procedures, syntheses and characterization of new products, and supporting data. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.

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(20) Fe(II) can be generated by reduction of Fe(III) by the substrate amine. Detailed mechanism of Fenton reaction is still under debate. For recent discussions, see: Rachmilovich-Calis, S.; Masarwa, A.; Meyerstein, N.; Meyerstein, D.; van Eldik, R. *Chem.*—*Eur. J.* **2009**, *15*, 8303 and references cited therein.

(21) Generation of aminium radical was supported by a radical clock experiment. (a) Lal, D.; Griller, D.; Husband, S.; Ingold, K. U. *J. Am. Chem. Soc.* **1974**, *96*, 6355. (b) Maillard, B.; Forrest, D.; Ingold, K. U. *J. Am. Chem. Soc.* **1976**, *98*, 7024. (c) Maeda, Y.; Ingold, K. U. *J. Am. Chem. Soc.* **1980**, *102*, 328. See the Supporting Information for experimental details.

(22) (a) Boess, E.; Sureshkumar, D.; Sud, A.; Wirtz, C.; Farès, C.; Klussmann, M. *J. Am. Chem. Soc.* **2011**, *133*, 8106. (b) Boess, E.; Schmitz, C.; Klussmann, M. *J. Am. Chem. Soc.* **2012**, *134*, 5317. (c) Ratnikov, M. O.; Doyle, M. P. *J. Am. Chem. Soc.* **2013**, *135*, 1549.