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Efficient Intermolecular Iron-Catalyzed Amidation of C−H Bonds in the Presence of *N*-Bromosuccinimide

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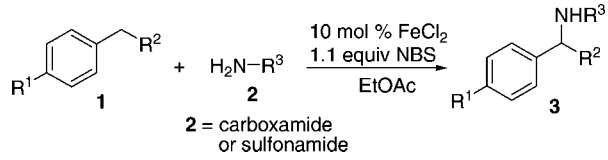
ABSTRACT



We have developed an efficient, inexpensive, and air-stable catalyst/oxidant ($FeCl_2$/NBS) system that could efficiently promote amidation of benzylic sp^3 C−H bonds in ethyl acetate under mild conditions.

The direct functionalization of carbon−hydrogen bonds is receiving increasing attention; however, achieving selectivity among many different C−H bonds remains a challenge.[1] Metal-mediated C−N bond formation via a C−H activation strategy is an important chemical process for synthesis of valuable nitrogen-containing compounds,[2] and most of them use nitrene derivatives as the primary nitrogen source.[3] For example, significant progress on PhI═NTs and related iminoiodane derivatives has been made in amidation of C−H bonds; however, their practical limits include the use of noncommercial and unstable hypervalent iodine reagents and the generation of ArI as the byproducts. Some examples of in situ iminoiodane generation for catalytic nitrene transfer have been reported,[4,5] and alternative nitrene sources such as chloramines-T,[6] bromamines-T,[7] and tosyloxycarbamates[8] were also used as the nitrogen sources. Obviously, direct use of unmodified carboxamides and/or sulfonamides is more convenient and practical for amidation of unactivated C−H bonds in the presence of readily available oxidant. Recently, Powell and co-workers reported $Cu(OTf)_2$/^{t}BuOOAc/1,10-

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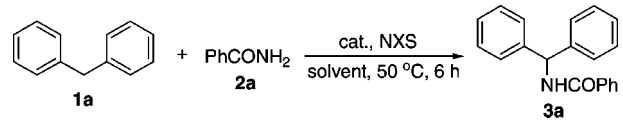
phenanthroline-mediated amidation of benzylic sp^3 C−H bonds in which free sulfonamides were used as the substrates.[9] Very recently, we have developed an inexpensive CuBr/^{t}BuOOH system for the amidation of unactivated sp^3 C−H bonds adjacent to a nitrogen atom via a free-radical mechanism, and unmodified carboxamides and sulfonamides were used as the nitrogen source.[10] In the previous methods for the construction of C−N bonds from C−H bonds, various metal catalysts such as rhodium, ruthenium, manganese, silver, and copper were used.[2−10] Iron is one of the most abundant, inexpensive, and environmentally friendly metals on earth.[11] However, to our knowledge, no example concerning iron-catalyzed amidation of C−H bonds was reported. In this paper, we have developed an inexpensive, readily available, and air-stable $FeCl_2$/NBS catalyst/oxidant system to efficiently catalyze amidation of benzylic sp^3 C−H bonds.

Initially, we investigated the catalysis conditions, including optimization of iron catalysts, oxidants, and solvents. Herein, diphenylmethane and benzamide were chosen as the model substrates, *N*-bromosuccinimide (NBS) or *N*-chlorosuccinimide (NCS) was used as the oxidant[12] and the free radical initiator,[13] and the reaction was performed at 50 °C without exclusion of air as shown in Table 1. Several iron salts, $Fe(acac)_3$, Fe_2O_3, $FeCl_3$, and $FeCl_2$ (10 mol % catalytic amount relative to benzamide), were tested in ethyl acetate in the presence of NBS (see entries 1−4), and $FeCl_2$ was found to be the most effective catalyst. NCS provided a slightly lower yield than NBS when it replaced NBS as the oxidant (see entry 5). It is worth noting that $FeCl_3$ showed weaker activity than $FeCl_2$, and the result displayed that Fe(II) did not change into Fe(III) after amidation process of benzylic reagent. Several solvents (CH_2Cl_2, $CHCl_3$, CCl_4, hexane, 1,2-dichloroethane, THF, and CH_3OH) (without any previous procedure for the commercial available solvents) were investigated (compare entries 4 and 6−12), and ethyl acetate gave the highest yield (entry 4). When the amount of $FeCl_2$ decreased to 5 mol % from 10 mol % relative to benzamide, the yield reduced to 58% (entry 13), but the use of 15 mol % of $FeCl_2$ showed the same yield as entry 4 in Table 1. Only a trace amount of amidation product was observed in the absence of NBS (entry 15) or catalyst (entry 16). The use of a slight excess of diphenylmethane (1.2 equiv) improved amide conversion and increased the yield. After the optimization process of catalysts, oxidants, and solvents, the following amidation was performed under our standard conditions: 10 mol % of $FeCl_2$ as the catalyst, 1.1 equiv of NBS as the oxidant relative to amides, and ethyl acetate as the solvent. The reaction temperature was maintained at 50 or 80 °C without exclusion of air.

Table 1. Iron-Catalyzed Amidation of Benzylic sp^3 C−H Bond: Optimization of Conditions[a]



1a 3a

entry	cat.	NXS	solvent	yield[b] (%)
1	$Fe(acac)_3$ (10%)	NBS	EtOAc	0
2	Fe_2O_3 (10%)	NBS	EtOAc	40
3	$FeCl_3$ (10%)	NBS	EtOAc	58
4	$FeCl_2$ (10%)	NBS	EtOAc	68
5	$FeCl_2$ (10%)	NCS	EtOAc	52
6	$FeCl_2$ (10%)	NBS	CH_2Cl_2	56
7	$FeCl_2$ (10%)	NBS	$CHCl_3$	38
8	$FeCl_2$ (10%)	NBS	CCl_4	16
9	$FeCl_2$ (10%)	NBS	hexane	18
10	$FeCl_2$ (10%)	NBS	ClC_2H_4Cl	50
11	$FeCl_2$ (10%)	NBS	THF	47
12	$FeCl_2$ (10%)	NBS	CH_3OH	trace
13	$FeCl_2$ (5%)	NBS	EtOAc	58
14	$FeCl_2$ (15%)	NBS	EtOAc	68
15	$FeCl_2$ (10%)		EtOAc	trace[c]
16		NBS	EtOAc	trace[d]

[a] Reaction conditions: diphenylmethane (1.2 mmol), benzamide (1.0 mmol), NXS (1.1 mmol, X = B, C), catalyst (0.1 mmol), solvent (2 mL). [b] Isolated yield. [c] No addition of NBS. [d] No addition of catalyst.

We investigated the scope of $FeCl_2$-catalyzed amidation of benzylic sp^3 C−H bonds under our standard conditions. As shown in Table 2, the benzylic reagents examined could be performed smoothly, and the corresponding amidation products were provided in moderate to good yields. The activity order of the benzylic reagents is diphenylmethane > ethylbenzene > 4-bromoethylbenzene. For example, the amidation of diphenylmethane could be carried out at 50 °C (entries 1−6), while the coupling reaction of 4-bromoethylbenzene with amide was not performed until the temperature was raised to 80 °C (entry 14). In general, no significant difference of reactivity was observed for the examined carboxamides and sulfonamides with varied electronic properties.

(5) For representative examples of in situ iminoiodane generation for catalytic nitrene transfers, see: (a) Liang, C.; Robert-Peillard, F.; Fruit, C.; Muller, P.; Dodd, R. H.; Dauban, P. *Angew. Chem., Int. Ed.* **2006**, *45*, 4641. (b) Fiori, K. W.; Du Bois, J. *J. Am. Chem. Soc.* **2007**, *129*, 562. (c) Liang, J.-L.; Yuan, S.-X.; Huang, J.-S.; Yu, W.-Y.; Che, C.-M. *Angew. Chem., Int. Ed.* **2002**, *41*, 3465. (d) Espino, C. G.; Du Bois, J. *Angew. Chem., Int. Ed.* **2001**, *40*, 598. (e) Cui, Y.; He, C. *Angew. Chem., Int. Ed.* **2004**, *43*, 4210. (f) Yu, X.-Q.; Huang, J.-S.; Zhou, X.-G.; Che, C.-M. *Org. Lett.* **2000**, *2*, 2233. (g) Dauban, P.; Saniere, L.; Tarrade, A.; Dodd, R. H. *J. Am. Chem. Soc.* **2001**, *123*, 7707. (h) Li, Z.; Ding, X.; He, C. *J. Org. Chem.* **2006**, *71*, 5876. (i) Reddy, R. P.; Davies, H. M. L. *Org. Lett.* **2006**, *8*, 5013.

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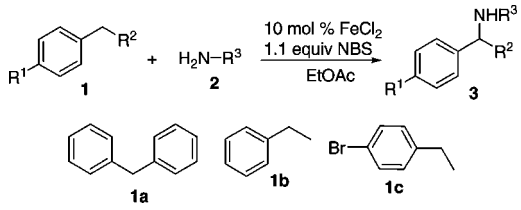
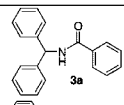
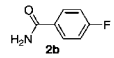
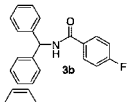
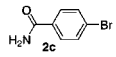
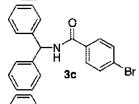
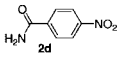
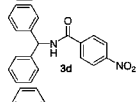
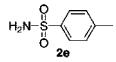
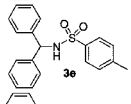
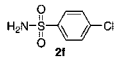
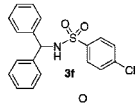
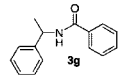
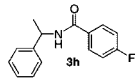
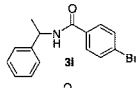
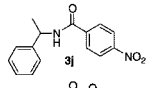
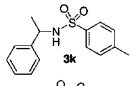
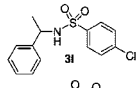
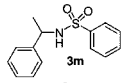
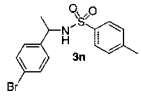
Table 2. $FeCl_2$/Catalyzed Amidation of Benzylic sp^3 C−H Bonds in the Presence of NBS[a]

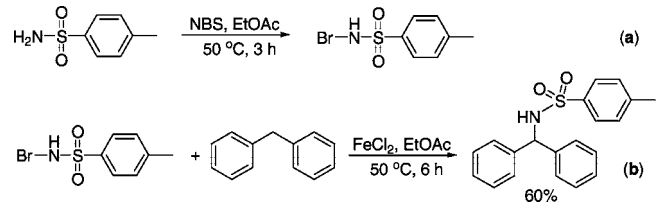


entry	2	temp/time	product	yield (%)[b]
1		50 °C/6 h		68
2		50 °C/6 h		77
3		50 °C/6 h		74
4		50 °C/6 h		81
5		50 °C/6 h		75
6		50 °C/6 h		78
7	**2a**	50 °C/8 h		62
8	**2b**	50 °C/8 h		64
9	**2c**	50 °C/8 h		68
10	**2d**	50 °C/8 h		60
11	**2e**	50 °C/8 h		64
12	**2f**	50 °C/8 h		70
13	**2g**	50 °C/8 h		62
14	**2e**	80 °C/6 h		60

[a] Reaction conditions: benzylic reagent (1.2 mmol), amide/sulfonamide (1.0 mmol), NBS (1.1 mmol), $FeCl_2$ (0.1 mmol). [b] Isolated yield.

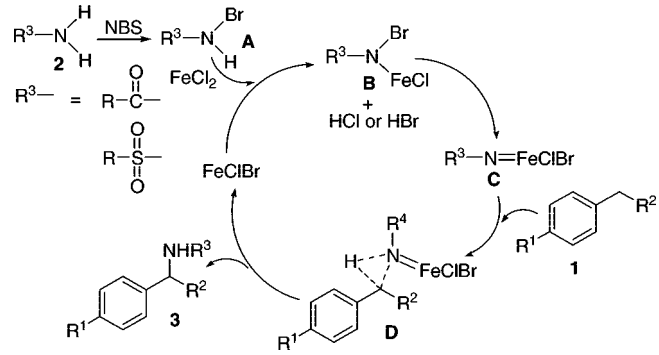
The amidation mechanism of $FeCl_2$-catalyzed benzylic sp^3 C−H bonds was also investigated. Since *N*-bromocarboxamides and *N*-bromosulfonamides can be potential intermediates during the amidation process, the following control experiments were performed. As shown in Scheme 1a, reaction of sulfonylamide with NBS in ethyl acetate produced

Scheme 1. (a) Conversion of Sulfonylamide to *N*-Bromosulfonamide, (B) Reaction of Diphenylmethane with *N*-Bromobenzamide



N-bromosulfonamide, whose similar products were obtained and identified by Sudalai.[14] Diphenylmethane and $FeCl_2$ were added to the resulting solution, and the reaction provided 60% amidation product (Scheme 1b). Therefore, a possible mechanism for the amidation of benzylic sp^3 C−H bonds is proposed in Scheme 2. Reaction of NBS with carboxamide

Scheme 2. Possible Mechanism for Iron-Catalyzed Amidation of Benzylic sp^3 C−H Bonds



or sulfonylamide produces *N*-bromocarboxamide or *N*-bromosulfonamide (**A**),[14] treatment of **A** with iron salt provides **B**, and the exchange of metal ion with proton in sulfonamides was proposed in the previous catalytic cycle.[15] In fact, **B** is similar to chloramines-T,[6] bromamines-T,[7] and tosyloxycarbamates[8] used as the alternative nitrene source, and it can be transferred into iron−nitrene complex **C**. Reaction of **C** with benzylic C−H bonds forms intermediate **D**,[16] and removal of iron salt (catalyst) in **D** provides the target product **3**.

In summary, we have developed an efficient, inexpensive, and air-stable $FeCl_2$/NBS-mediated amidation of benzylic sp^3 C−H bonds; the protocol uses $FeCl_2$ as the catalyst, nonexplosive NBS (compared with the usual oxidants) as the oxidant, and ethyl acetate as the solvent, and the amidation provided the reasonable yields under mild conditions. The reactions are insensitive to atmospheric moisture and oxygen,

(14) (a) Thakur, V. V.; Talluri, S. K.; Sudalai, A. *Org. Lett.* **2003**, *5*, 861. (b) Talluri, S. K.; Sudalai, A. *Org. Lett.* **2005**, *7*, 855.
(15) Taylor, J. G.; Whitall, N.; Hill, K. K. *Org. Lett.* **2006**, *8*, 3561.
(16) He, L.; Yu, J.; Zhang, J.; Yu, X.-Q. *Org. Lett.* **2007**, *9*, 2277.

and neither dried solvent nor an inert atmosphere is required. The inexpensive and readily available catalyst−oxidant ($FeCl_2$/NBS) system is of practical applications for amidation of the unactivated C−H bonds. The scope, further mechanism, and synthetic application of this reaction are under investigation.

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Supporting Information Available: Synthetic procedures, characterization data, and ^1H and ^{13}C NMR spectra of these synthesized compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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