Iron-Catalyzed Direct C(sp^3)–H Amination Reactions of Isochroman Derivatives with Primary Arylamines under Mild Conditions

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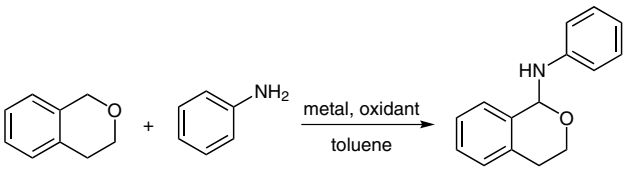
Abstract: A direct C(sp^3)–H amination reaction of isochroman derivatives with arylamines was developed in the presence of iron(II) salt. A variety of isochroman derivatives and primary amines were selectively transformed into the corresponding oxidative coupling products in good to excellent yield under mild conditions

Key words: C(sp^3)–H amination, isochroman, arylamines, iron

In the past decade, C–H functionalization has emerged as one of the most attractive and efficient strategies for the construction of carbon–carbon and carbon–heteroatom bonds in a step- and atom-economical fashion. Among these, various oxidative intermolecular cross-dehydrogenative coupling (CDC) reactions on two different C–H bonds or X–H bonds have also been developed greatly.[1] Regardless of the vast research findings of various CDC reactions, functionalization of C(sp^3)–H bonds is still challenging because of the low reactivity and the lack of an arbitrarily site selectivity. However, a lot of breakthrough achievements have also been made recently, such as C(sp^3)–H bond functionalization of cycloalkanes,[2] C(sp^3)–H bond functionalization with the assistance of a chelating group,[3] and the functionalization of C(sp^3)–H bond adjacent to heteroatoms,[4] double bonds,[5] and phenyl groups.[6] C–H functionalization adjacent to a heteroatom is receiving increasing attention as the product can usually be part of the motifs in biologically active compounds. A number of excellent outcomes about this powerful approach have been obtained, such as the coupling with C(sp^3)–H bond,[7] C(sp^2)–H bond,[8] C(sp)–H bond,[9] and X–H bond (X = O, N).[10]

In seeking step- and atom-economical green processes, reports on direct C–H amination reactions have increased rapidly in the past decade. Compared with using special nitrogen sources such as PhI=NTs (Ts = *p*-toluenesulfonyl) and -N_3, the direct CDC of the C–H bond with the N–H bond has been recognized as a more efficient approach and has already been reported by many groups. However, most of the nitrogen sources were limited to amides, sulfonamides, azoles, or anilines with strong electron-withdrawing groups. It was an ongoing challenge to couple amines without any electron-withdrawing groups with C–H bonds. In recent years, some breakthroughs have been made in this field, for example, the Mori group[11] and the Armstrong group[1a] reported the amination reactions at the 2-position of azoles with the additive of bases; the Wang group reported the synthesis of polysubstituted oxazoles involving an α-position C–H amination reaction of 1,3-dicarbonyl derivatives with the addition of iodine;[12] the Ishii group,[13] the Guo group,[14] the Warren group,[15] and the Bao group[16] reported the benzylic or allylic C–H amination reactions. *N*-Phenylisochroman-1-amine derivatives are fragments of the glucocorticoid-selective benzopyrano[3,4-*f*]quinolines which are anti-

Table 1 Optimization of Reaction Conditions[a]



1a **2a** **3a**

Entry	Metal (0.1 equiv)	Oxidant (equiv)	Time (h)	Temp (°C)	Yield (%)[b]
1	$FeCl_3$	*t*-BuOOH(2.0)	24	50	21
2	$FeCl_3$	*t*-BuOOH(2.0)	24	75	0
3[c]	$FeCl_3$	*t*-BuOOH(2.0)	24	75	0
4	$FeSO_4$	*t*-BuOOH(2.0)	24	75	13
5	$FeCl_2{\cdot}4H_2O$	*t*-BuOOH(2.0)	24	75	32
6	–	*t*-BuOOH(2.0)	24	75	8
7	$FeCl_2{\cdot}4H_2O$	*t*-BuOOH(2.0)	36	75	27
8	$FeCl_2{\cdot}4H_2O$	NBS(1.1)	24	60	0
9	$FeCl_2{\cdot}4H_2O$	DDQ(1.2)	24	75	0
10	$FeCl_2{\cdot}4H_2O$	$(t\text{-BuO})_2$(2.0)	24	75	0
11[d]	$FeCl_2{\cdot}4H_2O$	*t*-BuOOH(2.0)	24	75	11
12[e]	$FeCl_2{\cdot}4H_2O$	*t*-BuOOH(2.0)	24	75	61

[a] Reaction conditions: catalyst (0.05 mmol), oxidant (1.0 mmol), **1a** (0.5 mmol), **2a** (0.5 mmol) for 24 h under the nitrogen atmosphere.
[b] Yield of isolated product.
[c] 1.0 equiv $FeCl_3$.
[d] Compound **1a** was added drop-wise to the system.
[e] Compound **2a** was added drop-wise to the system.

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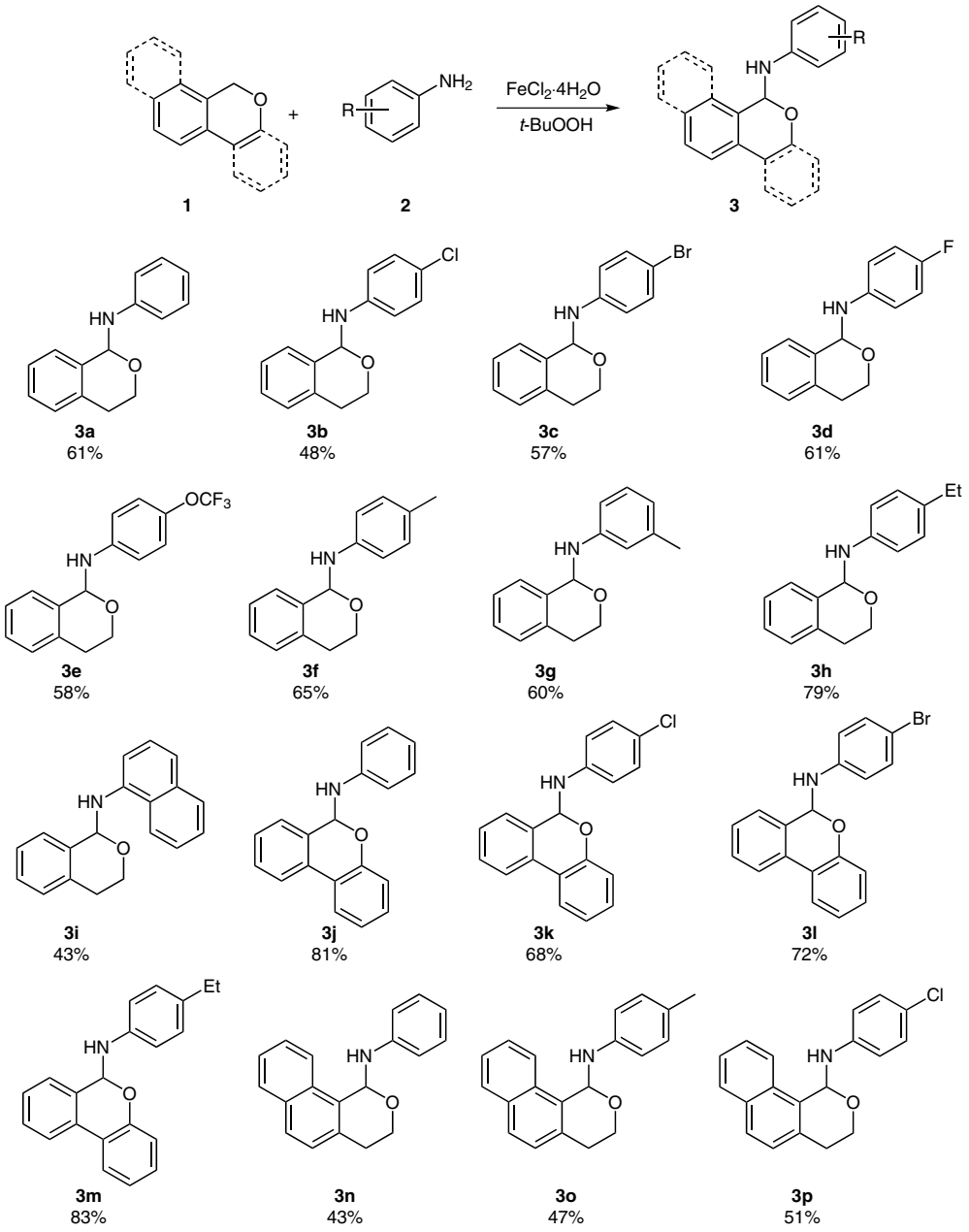
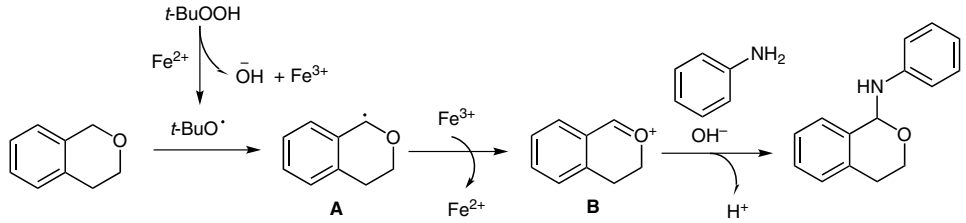
inflammatory agents with low toxicity,[17] while the direct amination reactions of the C(sp^3)–H bond adjacent to an oxygen atom using primary amines are rarely realized. Herein we report the C(sp^3)–H amination reactions of isochroman derivatives with arylamines catalyzed by iron under mild reaction conditions.

As the $FeCl_3$/*t*-BuOOH system has been proven to be very efficient for the functionalization of the C(sp^3)–H bond adjacent to heteroatoms,[18] we initially applied $FeCl_3$/*t*-BuOOH to the reaction of isochroman (**1a**) and aniline (**2a**) under nitrogen atmosphere. However, the desired coupling product **3a** was isolated in only 21% yield after 24 hours at 50 °C (Table 1, entry 1), most of the aniline was oxidized. It was useless to elevate the temperature or change the amount of the catalyst (Table 1, entries 2 and 3). Subsequently, other kinds of iron catalysts were studied to enhance the yield of **3a** on this template reaction (Table 1, entries 4 and 5). Although the yield was better when $FeCl_2{\cdot}4H_2O$ was used, it was still unsatisfying. Removing $FeCl_2{\cdot}4H_2O$, only 8% yield was obtained (Table 1, entry 6). It was unsuitable to increase the reaction time (Table 1, entry 7). Then, different kinds of oxidants were screened, with *t*-BuOOH being the choice (Table 1, entries 8–10). Considering that the raw materials were easy to be oxidized, we changed the addition way of the two standard substrates. It turned out that a satisfying yield was obtained when the amine was added drop-wise into the system through a dropping funnel (Table 1, entries 11 and 12).



Scheme 1 Scope of the CDC. *Reagents and conditions*: catalyst (0.05 mmol), oxidant (1.0 mmol), **1** (0.5 mmol), **2** (0.5 mmol) for 24 h under nitrogen atmosphere.



Scheme 2 Probable mechanistic route

With the optimized reaction conditions in hand (Table 1, entry 12), the generality of the reaction between isochroman derivatives and various amines were explored. Some results are outlined in Scheme 1. Amines with an electron-donating group worked well under the standard reaction conditions (Scheme 1, **3f**,**h**). Amines with a weak electron-withdrawing group also reacted well with isochroman (Scheme 1 **3b**–**d**). Benzopyran – due to its higher stability – gave a satisfying isolated yield when used as reactant (Scheme 1, **3j**–**m**). 3,4-Dihydro-1*H*-benzo[*h*]isochromene also coupled with amines, but the yields were comparatively low (Scheme 1, **3n**–**p**), maybe because of the steric hindrance. Anilines with strong electron-withdrawing groups, such as nitro, difluoro, and dichloro groups, were also applied in this reaction, but no desired product was obtained. This can be attributed to the instability of the isochroman in the weak acidic conditions, that are present when amines with strong electron-withdrawing groups are used. Applying 4-methoxyaniline also did not lead to the desired product, because of its sensitivity to oxidization.

According to the experiments and the literature,[1c] a plausible mechanism was proposed (Scheme 2). TBHP decomposed into the *tert*-butoxyl radical and hydroxyl anion in the presence of the ferrous catalyst. A hydrogen abstraction of the C–H bond adjacent to an oxygen atom afforded intermediate **A**. Then **A** was oxidized to **B** by the ferric ion. Aniline coupled with **B** and, thereafter, deprotonation by the previously released hydroxyl anion gave the desired product.

In summary, we have successfully realized the direct C(sp^3)–H amination reactions of isochroman derivatives with arylamines catalyzed by iron under mild reaction conditions. Further investigations of the application of this kind of iron salt in organic reactions are under way in our laboratory.

General Procedure

$FeCl_2 \cdot 4H_2O$ (0.05 mmol) was placed in a Schlenk tube. Toluene (2 mL), isochroman (**1**, 0.5 mmol), and *t*-BuOOH(1.0 mmol) were then added. The tube was sealed and flushed with nitrogen, and then the contents were stirred at 75 °C. Arylamine (**2**, 0.5 mmol) was slowly added drop-wise into the system through a dropping funnel. The reaction mixture was stirred for 24 h, then cooled to r.t. and flushed through a short column of silica gel with EtOAc. The solvent was removed under vacuum. The product was isolated from the dark purple crude mixture by column chromatography (PE–EtOAc, 20:1).

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Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

Reference and Notes

(1) For selected examples, see: (a) Armstrong, A.; Collins, J. C. *Angew. Chem. Int. Ed.* **2010**, *49*, 2282. (b) Iglesias, Á.; Pérez, E. G.; Muñiz, K. *Angew. Chem. Int. Ed.* **2010**, *49*, 8109. (c) Pan, S.; Liu, J.; Li, H.; Wang, Z.; Guo, X.; Li, Z. *Org. Lett.* **2010**, *12*, 1932. (d) Sibbald, P. A.; Rosewall, C. F.; Swartz, R. D.; Michael, F. E. *J. Am. Chem. Soc.* **2009**, *131*, 15945. (e) Su, Y.; Zhao, M.; Han, K.; Song, G.; Li, X. *Org. Lett.* **2010**, *12*, 5462. (f) Xu, H.; Zhang, Y.; Huang, J.; Chen, W. *Org. Lett.* **2010**, *12*, 3704.

(2) For selected examples, see: (a) Geraghty, N. W.; Hannan, J. J. *Tetrahedron Lett.* **2001**, *42*, 3211. (b) Zhang, B.; Zhu, S.-F.; Zhou, Q.-L. *Tetrahedron* **2012**, *69*, 2033. (c) Zhang, Y.; Li, C. J. *Eur. J. Org. Chem.* **2007**, 4654.

(3) For selected examples, see: (a) Aihara, Y.; Chatani, N. *J. Am. Chem. Soc.* **2013**, *135*, 5308. (b) Lee, J. M.; Chang, S. *Tetrahedron Lett.* **2006**, *47*, 1375. (c) Lou, S.-J.; Xu, D.-Q.; Shen, D.-F.; Wang, Y.-F.; Liu, Y.-K.; Xu, Z.-Y. *Chem. Commun.* **2012**, *48*, 11993. (d) Nakao, Y.; Morita, E.; Idei, H.; Hiyama, T. *J. Am. Chem. Soc.* **2011**, *133*, 3264. (e) Vuppalapati, S. V.; Lee, Y. R. *Tetrahedron* **2012**, *68*, 8286. (f) Wasa, M.; Yu, J.-Q. *Tetrahedron* **2010**, *66*, 4811.

(4) (a) Li, Z.; Li, C.-J. *J. Am. Chem. Soc.* **2005**, *127*, 3672. (b) Li, Z.; Li, H.; Guo, X.; Cao, L.; Yu, R.; Li, H.; Pan, S. *Org. Lett.* **2008**, *10*, 803. (c) McQuaid, K. M.; Sames, D. *J. Am. Chem. Soc.* **2008**, *131*, 402. (d) Richter, H.; García Mancheño, O. *Eur. J. Org. Chem.* **2010**, 4460. (e) Zhou, G.; Liu, F.; Zhang, J. *Chem. Eur. J.* **2011**, *17*, 3101.

(5) (a) Cheng, D.; Bao, W. *Adv. Synth. Catal.* **2008**, *350*, 1263. (b) Li, Z.; Li, C.-J. *J. Am. Chem. Soc.* **2004**, *126*, 11810. (c) Niu, M.; Yin, Z.; Fu, H.; Jiang, Y.; Zhao, Y. *J. Org. Chem.* **2008**, *73*, 3961.

(6) (a) Li, Z.; Cao, L.; Li, C. J. *Angew. Chem. Int. Ed.* **2007**, *46*, 6505. (b) Pelletier, G.; Powell, D. A. *Org. Lett.* **2006**, *8*, 6031. (c) Zhang, Y.; Li, C.-J. *J. Am. Chem. Soc.* **2006**, *128*, 4242.

(7) (a) Baslé, O.; Li, C.-J. *Green Chem.* **2007**, *9*, 1047. (b) Li, Z.; Li, C. J. *Eur. J. Org. Chem.* **2005**, 3173. (c) Zhang, Y.; Li, C. J. *Angew. Chem.* **2006**, *118*, 1983.

(8) (a) Li, Z.; Li, C.-J. *J. Am. Chem. Soc.* **2005**, *127*, 6968. (b) Mo, H.; Bao, W. *Adv. Synth. Catal.* **2009**, *351*, 2845. (c) Pan, S.; Endo, K.; Shibata, T. *Org. Lett.* **2011**, *13*, 4692.

(9) (a) Murahashi, S.-I.; Komiya, N.; Terai, H.; Nakae, T. *J. Am. Chem. Soc.* **2003**, *125*, 15312. (b) Volla, C. M. R.; Vogel, P.

Org. Lett. **2009**, *11*, 1701. (c) Xu, X.; Li, X. *Org. Lett.* **2009**, *11*, 1027.
(10) (a) Messaoudi, S.; Brion, J. D.; Alami, M. *Adv. Synth. Catal.* **2010**, *352*, 1677. (b) Wei, Y.; Ding, H.; Lin, S.; Liang, F. *Org. Lett.* **2011**, *13*, 1674. (c) Xia, Q.; Chen, W. *J. Org. Chem.* **2012**, *77*, 9366. (d) Zhang, Y.; Fu, H.; Jiang, Y.; Zhao, Y. *Org. Lett.* **2007**, *9*, 3813.
(11) Monguchi, D.; Fujiwara, T.; Furukawa, H.; Mori, A. *Org. Lett.* **2009**, *11*, 1607.
(12) Wan, C.; Zhang, J.; Wang, S.; Fan, J.; Wang, Z. *Org. Lett.* **2010**, *12*, 2338.
(13) Shimizu, Y.; Obora, Y.; Ishii, Y. *Org. Lett.* **2010**, *12*, 1372.
(14) Xia, R.; Niu, H.-Y.; Qu, G.-R.; Guo, H.-M. *Org. Lett.* **2012**, *14*, 5546.
(15) Gephart, R. T. III.; Huang, D. L.; Aguila, M. J.; Schmidt, G.; Shahu, A.; Warren, T. H. *Angew. Chem. Int. Ed.* **2012**, *51*, 6488.
(16) Wang, Z.; Mo, H.; Cheng, D.; Bao, W. *Org. Biomol. Chem.* **2012**, *10*, 4249.
(17) Coghlan, M. J.; Edwards, J. P.; Elmore, S. W.; Jones, T. K.; Kort, M. E.; Kym, P. R.; Moore, J. L.; Pratt, J. K.; Wang, A. X. US 6506766 (B1), **2003**.
(18) For selected examples, see: (a) Li, Z.; Yu, R.; Li, H. *Angew. Chem. Int. Ed.* **2008**, *47*, 7497. (b) Guo, X.; Pan, S.; Liu, J.; Li, Z. *J. Org. Chem.* **2009**, *74*, 8848. (c) Liu, W.; Liu, J.; Ogawa, D.; Nishihara, Y.; Guo, X.; Li, Z. *Org. Lett.* **2011**, *13*, 6272. (d) Li, Y.; Jia, F.; Li, Z. *Chem. Eur. J.* **2013**, *19*, 82. (e) Li, Y.; Ma, L.; Jia, F.; Li, Z. *J. Org. Chem.* **2013**, *78*, 5638.

