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An efficient and mild iron-mediated synthesis of alkenyl halides via direct C–C bond formation of benzyl alcohols and aryl alkynes

Zhong-Quan Liu *, Jianguo Wang, Jie Han, Yankai Zhao, Bo Zhou

Institute of Organic Chemistry, Gannan Normal University, Ganzhou, Jiangxi 341000, PR China
State Key Laboratory of Applied Organic Chemistry and Department of Chemistry, Lanzhou University, Lanzhou, Gansu 730000, PR China

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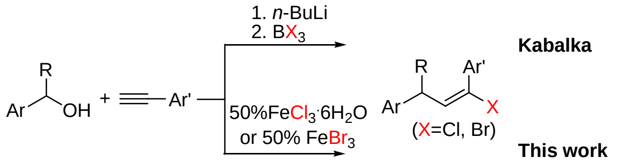
ABSTRACT

This work demonstrated an efficient and mild method for preparing various substituted alkenyl halides via direct C–C bond formation of benzyl alcohols and aryl alkynes in CH_2Cl_2 at 50 °C by using 50 mol % of $FeCl_3{\cdot}6H_2O$ or $FeBr_3$. Compared with the systems using excessive boron trihalides and stoichiometric *n*-BuLi to prepare substituted alkenyl halides, the present procedure would provide an excellent alternative due to the environmentally benign system and atom efficiency.

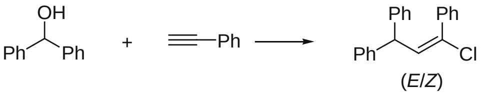
Although few direct C–C bond formations by the utilization of benzyl alcohols have been achieved due to the poor leaving ability of the hydroxide group, it remains very attractive since it would be atom-efficient and environmentally benign as water is the only by-product.[1] Among these interesting transformations, direct C–C bond formation by using benzyl alcohols and alkynes represents more attractive transformation.[2] Recently, some efficient methods for preparing stereodefined alkenyl halides using direct C–C bond formation of benzyl alcohols have been developed by Kabalka et al.[3] However, most of these systems needed stoichiometric *n*-BuLi and boron trihalide (Scheme 1). Therefore, development of novel catalytic procedures to generate alkenyl halides by utilization of benzyl alcohols is attractive. By taking advantage of the high activity of benzyl alcohols to Lewis acid, we successfully accomplished an efficient and mild method for preparing alkenyl halides via direct C–C bond formation of benzyl alcohols and aryl alkynes in CH_2Cl_2 by using 50 mol % of $FeCl_3{\cdot}6H_2O$ or 50 mol % $FeBr_3$ (Scheme 2). To the best of our knowledge, synthesis of alkenyl halides via substitution of benzyl alcohols with alkynes followed by direct abstraction of halogen atom from iron halide has not been reported before.[4]

As the initial research, we select diphenylmethanol **1a** and phenyl ethyne **2a** as standard substrates to optimize suitable conditions for this reaction (Table 1). The desired alkenyl chloride **3a** was obtained in 78% yield using 40 mol % of anhydrous $FeCl_3$ at 50 °C in CH_2Cl_2 (entry 1). Interestingly, the isolated yield of **3a** increased to 82% by using 40 mol % of $FeCl_3{\cdot}6H_2O$ (entry 2). However, other iron salts and copper salts were inactive to this reaction (entries 3–6). Increase of the Lewis acid dosage to 50 mol % and 60 mol % gave 85% and 80% isolated yields of the products, respectively (entries 7 and 8). A very low yield of **3a** was isolated at room



Scheme 1. Synthesis of alkenyl halides using benzyl alcohols and aryl alkynes.

Table 1
Optimization of the typical reaction conditions[a]



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

Entry	Lewis acid (mol %)	Solvent	*T* (°C)	Yield[b] (%)
1	$FeCl_3$ (40)	CH_2Cl_2	50	78
2	$FeCl_3{\cdot}6H_2O$ (40)	CH_2Cl_2	50	82
3	$Fe_2(SO_4)_3$ (40)	CH_2Cl_2	50	0
4	$FeCl_2$ (40)	CH_2Cl_2	50	0
5	$CuBr_2$ (40)	CH_2Cl_2	50	0
6	CuBr (40)	CH_2Cl_2	50	0
7	**$FeCl_3{\cdot}6H_2O$ (50)**	**CH_2Cl_2**	**50**	**85**
8	$FeCl_3{\cdot}6H_2O$ (60)	CH_2Cl_2	50	80
9	$FeCl_3{\cdot}6H_2O$ (50)	CH_2Cl_2	RT	9
10	$FeCl_3{\cdot}6H_2O$ (50)	DCE	50	43
11	$FeCl_3{\cdot}6H_2O$ (50)	$CHCl_3$	50	39
12	$FeCl_3{\cdot}6H_2O$ (50)	Cyclohexane	50	72
13	$FeCl_3{\cdot}6H_2O$ (50)	CH_3NO_2	50	Mix
14	$FeCl_3{\cdot}6H_2O$ (50)	Benzene	50	0
15	$FeCl_3{\cdot}6H_2O$ (50)	THF	50	0
16	$FeCl_3{\cdot}6H_2O$ (50)	CH_3CN	50	0

[a] Reaction conditions: diphenylmethanol **1a** (0.5 mmol), phenyl ethyne **2a** (0.6 mmol), 10 h.
[b] Isolated yield of the *E*/*Z* isomer.

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* Corresponding author. Fax: +86 797 8393536.
E-mail address: lzq@gnnu.cn (Z.-Q. Liu).

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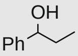
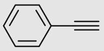
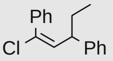
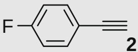
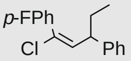
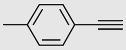
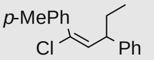
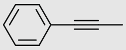
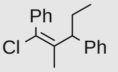
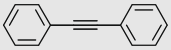
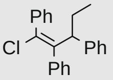
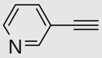
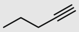
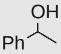
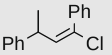
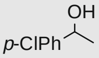
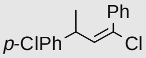
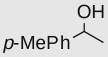
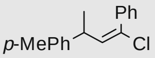
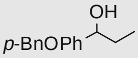
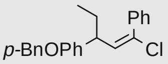
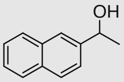
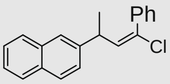
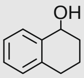
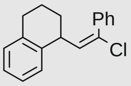
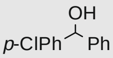
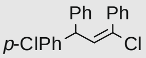
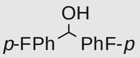
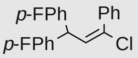
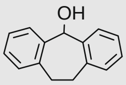
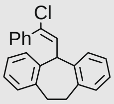
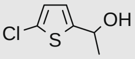
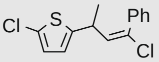
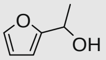
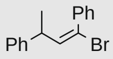
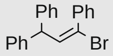
Table 2
Reaction of benzyl alcohols and alkynes[a]

Entry	Alcohols	Alkynes	Major product	Iron salts	Yield (%) *E*/*Z*[b]
1	 **1b**	 **2a**	 **3b**	$FeCl_3{\cdot}6H_2O$	85 (7:1)
2	**1b**	 **2b**	 **3c**	$FeCl_3{\cdot}6H_2O$	74 (8:1)
3	**1b**	 **2c**	 **3d**	$FeCl_3{\cdot}6H_2O$	100 (8:1)
4	**1b**	 **2d**	 **3e**	$FeCl_3{\cdot}6H_2O$	71 (15:1)
5	**1b**	 **2e**	 **3f**	$FeCl_3{\cdot}6H_2O$	53 (1:1)
6	**1b**	 **2f**	–	$FeCl_3{\cdot}6H_2O$	0
7	**1b**	 **2g**	–	$FeCl_3{\cdot}6H_2O$	0
8	 **1c**	**2a**	 **3g**	$FeCl_3{\cdot}6H_2O$	62 (6:1)
9	 **1d**	**2a**	 **3h**	$FeCl_3{\cdot}6H_2O$	98 (6:1)
10	 **1e**	**2a**	 **3i**	$FeCl_3{\cdot}6H_2O$	72 (6:1)
11	 **1f**	**2a**	 **3j**	$FeCl_3{\cdot}6H_2O$	46 (5:1)
12	 **1g**	**2a**	 **3k**	$FeCl_3{\cdot}6H_2O$	42 (5:1)
13	 **1h**	**2a**	 **3l**	$FeCl_3{\cdot}6H_2O$	28 (6:1)
14	 **1i**	**2a**	 **3m**	$FeCl_3{\cdot}6H_2O$	67 (5:1)
15	 **1j**	**2a**	 **3n**	$FeCl_3{\cdot}6H_2O$	80 (5:1)
16	 **1k**	**2a**	 **3o**	$FeCl_3{\cdot}6H_2O$	60 (24:1)
17	 **1l**	**2a**	 **3p**	$FeCl_3{\cdot}6H_2O$	49 (6:1)
18	 **1m**	**2a**	–	$FeCl_3{\cdot}6H_2O$	0

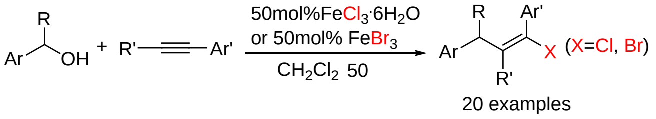
(*continued on next page*)

Table 2 (*continued*)

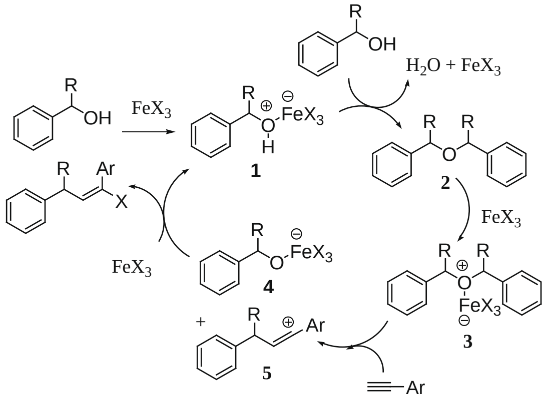
Entry	Alcohols	Alkynes	Major product	Iron salts	Yield (%) *E*/*Z*[b]
19	**1c**	**2a**	 **3q**	$FeBr_3$	96 (3:1)
20	**1a**	**2a**	 **3r**	$FeBr_3$	75 (7:1)

[a] Reaction conditions: benzyl alcohol **1** (0.5 mmol), aryl alkynes **2** (0.6 mmol), $FeCl_3 \cdot 6H_2O$ (0.25 mmol), or $FeBr_3$ (0.25 mmol), 50 °C, 10 h.

[b] Isolated yield of the *E*/*Z* isomer and the ratio were determined by ^1H NMR.



Scheme 2. Reaction of benzyl alcohols and aryl alkynes.



Scheme 3. A plausible mechanism for reaction of benzyl alcohols and aryl alkynes.

temperature (entry 9). Further investigation of solvent effect showed that CH_2Cl_2 is a more effective solvent (entries 10–16).

Various aryl alkynes and benzyl alcohols were investigated as substrates for the reaction under the typical conditions (Table 2). It is seen from Table 2 that aryl alkynes with electron-donating groups gave higher yields of the desired products than those bearing electron-withdrawing groups, such as fluorine (entries 1–3). Middle alkynes such as 1-phenyl-1-propyne **2d** and diphenyl ethyne **2e** also gave moderate to good yields of the corresponding alkenyl chlorides (entries 4 and 5). Heteroaryl alkynes such as 3-ethynyl pyridine and alkyl alkynes were inactive in this reaction (entries 6 and 7). Benzyl alcohols gave moderate to excellent yields of the corresponding chloroalkenes by using $FeCl_3 \cdot 6H_2O$, electronic and steric effects were not obvious (entries 8–12). However, 1-(4-nitro-phenyl)-ethanol gave no products under the conditions. 1,2,3,4-Tetrahydro naphthalen-1-ol **1h** gave low yield of the product (entry 13). Diaryl methanols gave good yields of the desired products (entries 14–16). 1-(5-Chloro-thiophen-2-yl)-ethanol **1l** gave moderate yield of the corresponding product, while 1-furan-2-yl-ethanol **1m** gave a mixture (entries 17 and 18). Benzyl alcohols with carboxyl group and alkyl alcohols remained inactive. It is noteworthy that both benzyl alcohols and diaryl methanols gave good to excellent yields of the corresponding alkenyl bromides by using 50 mol % of $FeBr_3$ at 50 °C (entries 19 and 20). Although only benzyl alcohols are effective under the conditions, synthesis of various substituted alkenyl chlorides and bromides via direct C–C bond formation by benzyl alcohols and alkynes using 50 mol % $FeCl_3 \cdot 6H_2O$ or $FeBr_3$ makes this procedure very attractive.

A plausible mechanism for the iron-mediated C–C bond formation using benzyl alcohols and aryl alkynes is depicted in Scheme 3. Benzyl alcohol is activated by the Lewis acid to form an intermediate **1**, which is substituted by benzyl alcohol to form an ether **2**.[5] The ether can be easily observed and isolated. It combines with the iron salt to generate an intermediate **3**, which attacks the electron-rich aryl alkynes to give intermediate **4** and a vinyl cation **5**. The sp-hybridized vinyl cation can be attacked by halides to give the *E*/*Z* isomer of product and the intermediate **1** which will be run in the next cycle.

In summary, this work demonstrates an efficient and mild iron-mediated method for synthesis of alkenyl halides via direct C–C bond formation of benzyl alcohols and aryl alkynes. Compared with the systems using stoichiometric Lewis acid and strong base to prepare substituted alkenyl halides, the present procedure would provide an excellent alternative due to the environmentally benign system and atom efficiency. Further investigation of this procedure is underway in our laboratory.

Acknowledgment

The authors thank Gannan Normal University for financial support.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.01.013.

References and notes

1. For selected examples, see: (a) Dau-Schmidt, J. P.; Mayr, H. *Chem. Ber.* **1994**, *127*, 205; (b) Iovel, I.; Mertins, K.; Kischel, J.; Zapf, A.; Beller, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 3913; (c) Mertins, K.; Iovel, I.; Kischel, J.; Zapf, A.; Beller, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 238; (d) Zhan, Z.; Yu, J.; Liu, H.; Cui, Y.; Yang, R.; Yang, W.; Li, J. *J. Org. Chem.* **2006**, *71*, 8298; (e) Kischel, J.; Mertins, K.; Michalik, D.; Zapf, A.; Beller, M. *Adv. Synth. Catal.* **2007**, *349*, 865; (f) Jana, U.; Maiti, S.; Biswas, S. *Tetrahedron Lett.* **2007**, *48*, 7160; (g) Jana, U.; Biswas, S.; Maiti, S. *Tetrahedron Lett.* **2007**, *48*, 4065; (h) Jana, U.; Maiti, S.; Biswas, S. *Tetrahedron Lett.* **2008**, *49*, 858; (i) Liu, Y.; Liu, L.; Wang, Y.; Han, Y.; Wang, D.; Chen, Y. *Green Chem.* **2008**, *10*, 635; (j) Pridmore, S. J.; Williams, J. M. J. *Tetrahedron Lett.* **2008**, *49*, 7413.
2. Jana, U.; Biswas, S.; Maiti, S. *Eur. J. Org. Chem.* **2008**, *34*, 5798.
3. (a) Kabalka, G. W.; Yao, M.; Borella, S.; Wu, Z. *Chem. Commun.* **2005**, 2492; (b) Kabalka, G. W.; Yao, M.; Borella, S.; Wu, Z. *Org. Lett.* **2005**, *7*, 2865; (c) Kabalka, G. W.; Yao, M.; Borella, S. *J. Am. Chem. Soc.* **2006**, *128*, 11320.
4. A negative referee pointed out that this work is not urgent. However, we think that it is important and urgent because the work reported here has not been reported before. And we would like to state that after our work was almost finished, we found that a similar work was under study in Jana's group (Ref. 18 cited in *Eur. J. Org. Chem.* **2008**, *34*, 5798).
5. Bisaro, F.; Prestat, G.; Vitale, M.; Poli, G. *Synlett* **2002**, 1823.