$FeCl_2$-Catalyzed Aminobromination of Alkenes Using Amides or Sulfonamides and NBS as the Nitrogen and Bromine Sources

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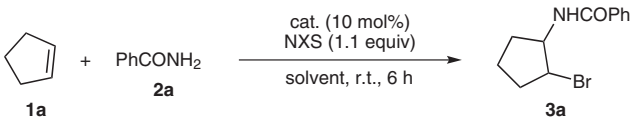
Abstract: We have developed a convenient and efficient iron-catalyzed aminobromination of the alkenes using inexpensive $FeCl_2$ as the catalyst, amides/sulfonamides and NBS as the nitrogen and bromine sources, respectively, under mild conditions.

Key words: iron, alkene, aminobromination, amide, sulfonamide, NBS

The aminohalogenation of alkenes has attracted much attention because the resulting vicinal haloamines are important building blocks in organic and medicinal chemistry.[2–6] Although some synthetic approaches to the vicinal haloamine functionality have been developed in the past few years,[7–9] the study of efficient and highly regioselective and stereoselective aminohalogenation of alkenes still remains important and challenging. The efficiency of the aminohalogenation mainly depends on the types of nitrogen and halogen sources and catalysts, so it has become popular to develop the highly efficient, readily available and stable nitrogen and halogen reagents and catalysts. The reported nitrogen and halogen sources are 4-$TsNCl_2$,[7a,b] 2-NsNNsCl (2-Ns: 2-nitrophenylsulfonyl), a combination of 2-$NsNCl_2$ and 2-NsNHNa,[7c,d] and a combination of NBS and $TsNH_2$.[7e] Although nonmetal-catalyzed procedures for the preparation of 1,2-haloamines by the addition of *N*-halo derivatives to alkenes have been reported,[10] metal-catalyzed 1,2-functionalization of alkenes with amines and halogens represents an important transformation in organic synthesis. Metal catalysts that have been used include $Cu(OTf)_2$, $ZnCl_2$,[7a] CuOTf,[7c,d,8b,c] and dichloro-(1,10-phenanthroline)-palladium(II), CuI, $MnSO_4$, V_2O_5, Mn(III)-salen, $SnCl_4$.[11] Iron is one of the most abundant metals on earth, and consequently one of the most inexpensive and environmentally friendly ones,[12] but iron-catalyzed aminohalogenation is rare.[13] Very recently, we have developed an efficient catalyst/oxidant ($FeCl_2$ and NBS) system to promote the amidation of benzylic sp^3 C–H bonds.[14] Herein, we report a convenient and inexpensive system ($FeCl_2$, NBS, and amides or sulfonylamides) to perform the aminobromination of alkenes.

Initially, cyclopentene and benzamide were chosen as the model substrates to optimize the reaction conditions, including optimization of the iron catalysts, *N*-halosuccinimides [*N*-bromosuccinimide (NBS), *N*-chlorosuccinimide (NCS)] and solvents at room temperature without exclusion of air in aminohalogenation as shown in Table 1. Several iron salts including $FeCl_3$, Fe_2O_3, $Fe(acac)_3$, and $FeCl_2$ (10 mol% catalytic amount relative to benzamide) were tested in EtOAc (entries 1–4), and $FeCl_2$ was found to be the most effective catalyst. The ^1H NMR analysis of product **3a** showed the excellent stereoselectivity (*anti*/*syn* >99:1). The effect of solvents (EtOAc, CH_2Cl_2, $CHCl_3$, CCl_4, hexane, DCE, THF, and

Table 1 Iron-Catalyzed Aminohalogenation of Cyclopentene Using Benzamide and *N*-Halosuccinimide as Nitrogen and Halogen Source: Optimization of the Catalysis Conditions[a]



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

Entry	Catalyst	NXS	Solvent	Yield (%)[b]	*anti*/*syn*[c]
1	$FeCl_3$	NBS	EtOAc	78	>99:1
2	Fe_2O_3	NBS	EtOAc	35	
3	$Fe(acac)_3$	NBS	EtOAc	Trace	
4	**$FeCl_2$**	**NBS**	**EtOAc**	**80**	**>99:1**
5	$FeCl_2$	NBS	CH_2Cl_2	76	
6	$FeCl_2$	NBS	$CHCl_3$	57	
7	$FeCl_2$	NBS	CCl_4	15	
8	$FeCl_2$	NBS	Hexane	21	
9	$FeCl_2$	NBS	DCE	65	
10	$FeCl_2$	NBS	THF	61	
11	$FeCl_2$	NBS	MeOH	34	
12	$FeCl_2$	NCS	EtOAc	52	>99:1
13		NBS	EtOAc	52	4:1

[a] Reaction conditions: cyclopentene (1.2 mmol), benzamide (1.0 mmol), NBS or NCS (1.1 mmol), catalyst (0.1 mmol), solvent (2 mL).
[b] Isolated yield.
[c] Determined by ^1H NMR of product.

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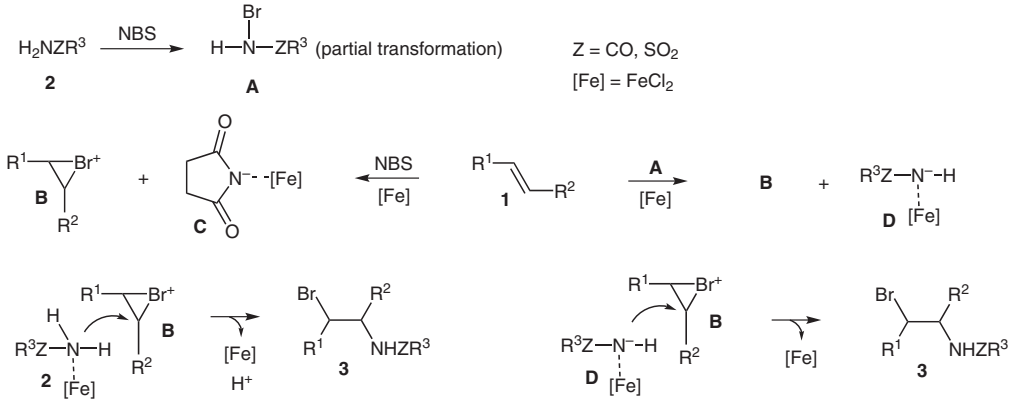


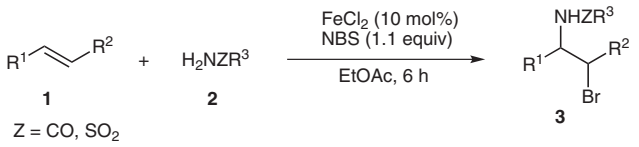
Scheme 1 Possible mechanism for $FeCl_2$-catalyzed reaction of alkene, NBS, and amide or sulfonamide to form vicinal bromoamines

MeOH) was also investigated (compare entries 4–11), and EtOAc provided the highest product yield (see entry 4). A slightly lower yield was obtained when NCS replaced NBS as the halogenating agent (compare entries 4 and 12). A lower yield with poor product stereoselectivity was provided in the absence of catalyst (entry 13).

After the optimization process of catalysts, solvents and *N*-halosuccinimides, the scope of $FeCl_2$-catalyzed aminobromination of alkenes was investigated under our standard conditions (10 mol% $FeCl_2$ as the catalyst, 1.1 equiv of NBS as the halogen source relative to amides and EtOAc as the solvent).[15] As shown in Table 2, the aminobromination could be performed for all the substrates examined, and the desired target products were obtained in moderate to good yields. Cyclopentene, cyclohexene, and 1,2-diphenylethylene showed higher activity, and their aminobromination could be smoothly carried out at room temperature using amides or sulfonamides as the partners (entries 1–10, 13). The reactions of styrene with benzamide or *p*-toluenesulfonamide could not be performed unless the temperature was raised to 50 °C (entries 11 and 12). The aminobromination of alkenes showed the excellent regioselectivity and stereoselectivity. In general, no significant difference of reactivity was observed for the examined amides and sulfonamides with varied electronic properties (electron-rich, electron-poor).

A possible mechanism for the $FeCl_2$-catalyzed aminobromination of alkenes is proposed in Scheme 1. Reaction of amide or sulfonamide with NBS yields *N*-bromocarboxamide or *N*-bromosulfonamide (**A**) which was obtained and identified by Gottardi, Sharpless, and Sudalai before.[16a–d] Reaction of alkene with NBS or **A** produces bromonium cation **B**[7e,16c,d] and anion–iron complexes **C** or **D**. Nucleophilic attack of **2** or **D** to **B** gives the target product **3**.

Table 2 $FeCl_2$-Catalyzed Aminobromination of Alkenes Using Amides or Sulfonamides and NBS as Nitrogen and Bromine Source[a]

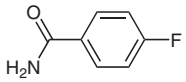
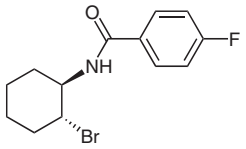
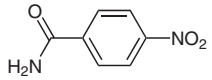
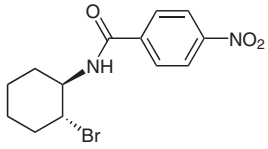
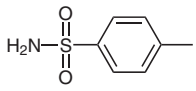
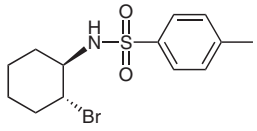
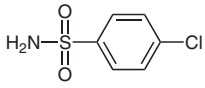
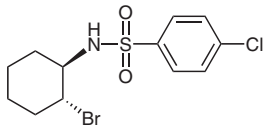
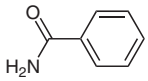
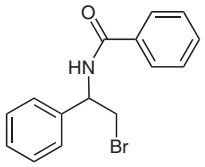
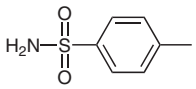
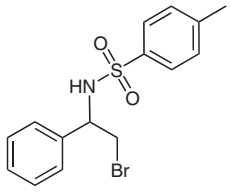
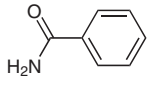
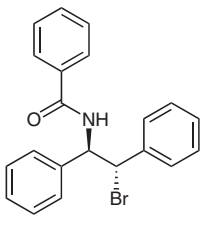


Entry	**2**	Product (±)-**3**	Yield (%)[b]
1	**2a**	**3a**	80
2	**2b**	**3b**	84
3	**2c**	**3c**	78
4	**2d**	**3d**	79
5	**2e**	**3e**	83
6	**2a**	**3f**	75

Table 2 FeCl$_2$-Catalyzed Aminobromination of Alkenes Using Amides or Sulfonamides and NBS as Nitrogen and Bromine Source[a] (continued)

1 2 3

Z = CO, SO$_2$

Entry	2	Product (±)-3	Yield (%)[b]
7	 **2b**	 **3g**	73
8	 **2d**	 **3h**	75
9	 **2e**	 **3i**	76
10	 **2g**	 **3j**	72
11	 **2a**	 **3k**	80
12	 **2e**	 **3l**	75
13	 **2a**	 **3m**	68

[a] Reaction conditions: reaction temperature (r.t. for entries 1–12, 15; 50 °C for entries 11 and 12), alkene (1.2 mmol), amide or sulfonamide (1 mmol), NBS (1.1 mmol), FeCl$_2$ (0.1 mmol), solvent (2 mL).
[b] Isolated yield.

In summary, we have developed an iron-catalyzed method for aminobromination of alkenes. The protocol uses FeCl$_2$ as the catalyst, NBS as the halogen source, ethyl acetate as the solvent, and the aminobrominations were efficiently performed under very mild conditions (r.t. or 50 °C). The direct 1,2-functionalization of alkenes by inexpensive and convenient catalyst–bromine source (FeCl$_2$ and NBS) system is of practical application.

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

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(15) **General Experimental Procedure for Aminohalogenation of Alkenes**
Solid NBS (1.1 mmol, 196 mg) was added to the flask charged with $FeCl_2$ (0.1 mmol, 13 mg), alkene (1.2 mmol), and amide or sulfonamide (1 mmol) in EtOAc (2 mL). The solution was stirred at r.t. (25 °C) or 50 °C for about 6 h. The resulting solution was diluted with EtOAc (8 mL) and washed with H_2O and brine. The organic phase was dried over anhyd Na_2SO_4 and concentrated under rotary evaporation, and the residue was purified by column chromatography on silica gel (EtOAc–PE, v/v, 20:1 to 4:1) to provide the pure aminohalogenation product.
(±)-*trans*-1-(*p*-Fluorobenzamido)-2-bromocyclopentane (3b)
Yellow oil, yield 84%. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.94–7.91 (m, 2 H), 7.09–7.04 (m, 2 H), 5.10 (t, 1 H, *J* = 5.9 Hz), 4.71 (t, 1 H, *J* = 7.2 Hz), 2.11–1.92 (m, 2 H), 1.74–1.45 (m, 4 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 162.9, 130.5, 124.1, 115.3, 85.1, 72.0, 34.8, 34.0, 23.3. HRMS: *m/z* calcd for $C_{12}H_{13}BrFNO$ [M^+]: 285.0165; found: 285.0171.

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