



InX₃-catalyzed haloamidation of vinyl arenes: a facile synthesis of α -bromo- and α -fluoroamides

J. S. Yadav*, B. V. Subba Reddy, D. Narasimha Chary, D. Chandrakanth

Division of Organic Chemistry, Indian Institute of Chemical Technology, Hyderabad 500 007, India

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ABSTRACT

A variety of alkenes are converted into the corresponding α -fluoroamides in high yields by selectfluorTM in the presence of 10 mol % of InF₃ in nitrile solution. α -Bromoamides are obtained with NBS in the presence of 10 mol % InBr₃ under similar conditions. The use of Lewis acid in haloamidation significantly improved the yields and reaction rates.

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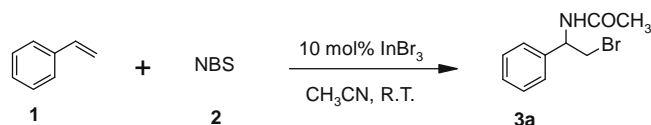
The haloamidation is an important process for the preparation of α -haloamides. They are useful precursors for the synthesis of aziridines and oxazolines, which in turn are used as intermediates for *vic*-amino alcohols (from oxazolines by reduction and hydrolysis) or *trans*- β -substituted amines (via ring opening of *N*-acyl aziridines).¹ SelectfluorTM, [1-chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane-bis-(tetrafluoroborate)], has been the subject of considerable interest as a powerful and user-friendly (non-gaseous, non-explosive, and less toxic) site-selective, electrophilic fluorinating agent.² It has also been used as an oxidant to generate iodonium ions [I⁺] from molecular iodine for the nuclear iodination of arenes^{3a} and for α -iodination of aryl alkyl ketones to produce α -iodoketones.^{3b} Recently, this has been used to generate useful electrophiles such as Cl⁺, Br⁺, SCN⁺, and NO₂⁺ from their respective sodium and potassium salts in acetonitrile, to accomplish aromatic electrophilic substitution and the Markovnikov-type addition reactions of alkenes.^{4,5} There have also been some reports on bromoamidation of alkenes to provide *vic*-bromoamides,^{1,5,6} while only a few examples are reported for *vic*-fluoroamidation of alkenes.⁷ However, many of these uncatalyzed methods involve low conversions and high temperature, and are limited to acetonitrile.⁸

In recent years, indium reagents have received increasing attention as water-tolerant green Lewis acid catalysts for organic synthesis demonstrating highly chemo-, regio-, and stereoselective results.⁹ Compared to conventional Lewis acids, indium halides have advantages of water stability, recyclability, operational

simplicity, low catalyst loading, and strong tolerance to oxygen and nitrogen-containing substrates.

In continuation of our research on the use of indium(III) reagents for various organic transformations,^{10,11} we herein report a simple and efficient protocol for α -haloamidation of alkenes using indium(III) halides. Initially, we attempted the bromoamidation of styrene (**1**) with *N*-bromosuccinimide (**2**) and acetonitrile in the presence of 10 mol % InBr₃. The reaction was complete in 10 min at room temperature, and the desired *N*-(2-bromo-1-phenylethyl)acetamide **3a** was isolated in 85% yield (Scheme 1).


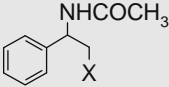
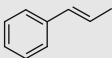
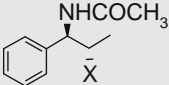

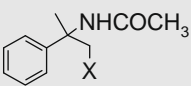
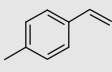
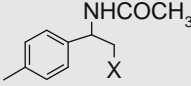

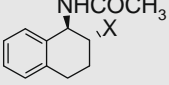

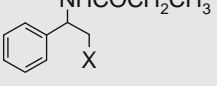
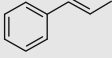
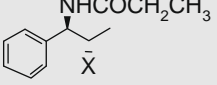

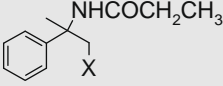
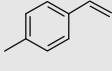
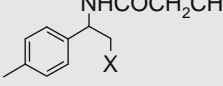

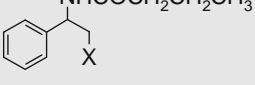
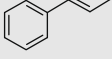
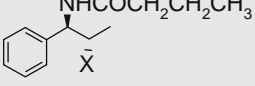

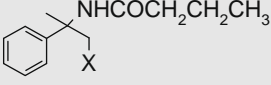
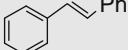
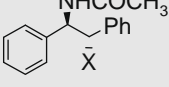
Similarly, various vinyl arenes such as β -methyl styrene, α -methyl styrene, and *p*-methyl styrene reacted smoothly with acetonitrile under these reaction conditions to provide substituted *vic*-bromoamides in good yields (Table 1). Various nitriles such as propionitrile and butyronitrile were also found to react with vinyl arenes to furnish the corresponding bromoamides in good yields. The reactions were carried out in nitrile solution at room temperature using 0.1 equiv of InBr₃ as a catalyst. The previous reports showed the superiority of CH₃CN in bromoamidation and the requirement of a Lewis acid to activate the Br⁺ donor.¹ The bromoamidation proceeds via the nucleophilic attack of nitrile on initially formed bromonium ion, in a fashion analogous to the



Scheme 1.

* Corresponding author. Tel.: +91 40 27193535; fax: +91 40 27160512.
E-mail address: yadavpub@iict.res.in (J.S. Yadav).

Table 1
InX₃-catalyzed *cis*-haloamidation of vinyl arenes

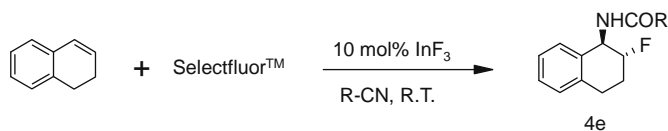
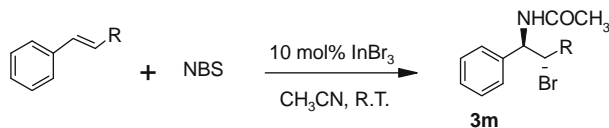
Entry	Alkene	Nitrile	Product ^a		Time (min)	Yield ^b (%)
a		CH ₃ CN		3a : X = Br	10	85
				4a : X = F	25	82
b		CH ₃ CN		3b : X = Br	15	87
				4b : X = F	15	90
c		CH ₃ CN		3c : X = Br	15	84
				4c : X = F	20	82
d		CH ₃ CN		3d : X = Br	10	85
				4d : X = F	20	80
e		CH ₃ CN		3e : X = Br	10	83
				4e : X = F	30	85
f		CH ₃ CH ₂ CN		3f : X = Br	20	78
				4f : X = F	25	87
g		CH ₃ CH ₂ CN		3g : X = Br	20	75
				4g : X = F	30	83
h		CH ₃ CH ₂ CN		3h : X = Br	25	72
				4h : X = F	30	75
i		CH ₃ CH ₂ CN		3i : X = Br	20	75
				4i : X = F	25	78
j		CH ₃ CH ₂ CH ₂ CN		3j : X = Br	25	80
				4j : X = F	25	85
k		CH ₃ CH ₂ CH ₂ CN		3k : X = Br	30	82
				4k : X = F	25	87
l		CH ₃ CH ₂ CH ₂ CN		3l : X = Br	30	80
				4l : X = F	20	75
m		CH ₃ CN		3m : X = Br	35	75
				4m : X = F	25	80

^a All products were characterized by ¹H NMR, IR, and mass spectroscopy.

^b Yield refers to pure products after chromatography.

well-known Ritter reaction.⁸ However, the bromoamidation of cyclic olefins, such as 1,2-dihydronaphthalene, with 1.2 equiv of *N*-

bromosuccinimide and 0.1 equiv of InBr₃ in CH₃CN at room temperature for 10 min gave the *trans*-bromoacetamide stereoselectively in



83% yield (entry e, Table 1). In the case of β -substituted styrenes such as β -methyl styrene and stilbene, the desired bromoamides were obtained with *trans*-stereoselectivity (Scheme 2).

The stereochemistry of products **3m** and **4e** was assigned as *trans* by coupling constants of protons and also by comparison of their spectral data with authentic samples.^{1b} Next, we studied α -fluoroamidation of alkenes with Selectfluor using InF_3 as an activating Lewis acid. Interestingly, various alkenes underwent smooth α -fluoroamidation to give *N*-(2-fluoro-1-alkyl)acetamides in high yields (Scheme 3).

Similarly, β -methyl styrene and stilbene also gave the corresponding *trans*-fluoroamides. The formation of *vic*-fluoroamides can be rationalized by assuming the formation of π -fluoro carbocationic intermediate, which is attacked by the nucleophilic nitrogen of the nitrile like the Ritter-type reaction. Of various indium(III) reagents such as $\text{In}(\text{OTf})_3$, $\text{In}(\text{ClO}_4)_3$, and $\text{In}(\text{NO}_3)_3$ tested, InX_3 was shown to be effective for this conversion. In the absence of catalyst, low conversions (20–35%) were achieved even at 80 °C over 24 h. The use of 10 mol % of InX_3 is essential for the success of the reaction. The scope and generality of this process are illustrated with respect to various vinyl arenes, and the results are presented in Table 1.¹²

In summary, this Letter describes a rapid and an efficient catalytic method for the haloamidation of vinyl arenes using a catalytic amount of indium(III) halides. The use of water-tolerant InX_3 makes this procedure quite simple and convenient. This method offers significant advantages such as low catalyst loading, high conversions, water-tolerant catalyst, and operational simplicity.

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- Typical procedure:** To a stirred solution of β -methyl styrene (118 mg, 1.0 mmol) and Selectfluor or NBS (1.2 mmol) in acetonitrile (4.0 mL) was added InX_3 (0.1 mmol) at room temperature. The resulting solution was stirred for the appropriate time, until the complete consumption of β -methyl styrene as indicated by TLC. Then, reaction mixture was quenched with water (5 mL) and was extracted with ethyl acetate (2×15 mL). The organic layer was separated, dried over anhydrous Na_2SO_4 , and concentrated in vacuo. The crude product was purified by column chromatography on silica gel using hexane/EtOAc (3:1) to afford pure α -haloamide. **Spectral data for selected compounds:** *N*-1-(2-fluoro-1-phenylpropyl)acetamide: **4b**: IR (KBr): ν_{max} 3783, 3697, 3321, 3060, 2989, 2935, 2359, 1883, 1813, 1651, 1543, 1443, 1375, 1302, 1070, 1029, 742, 700 cm^{-1} . ^1H NMR (200 MHz, CDCl_3): δ 7.20–7.44 (m, 5H), 6.3 (d, $J = 8.8$ Hz, 1H), 4.97–5.16 (m, 1H), 4.78–4.91 (m, 1H), 2.02 (d, $J = 10.0$ Hz, 3H), 1.09–1.47 (m, 3H). ^{13}C NMR (75 MHz, CDCl_3): δ 170.1, 169.8, 138.3, 137.2, 128.6, 128.4, 127.6, 127.0, 93.8, 93.6, 91.4, 91.2, 64.0, 63.8, 63.7, 63.7, 23.4, 18.2, 18.1. LC-MS: m/z : 218 (M+Na). HRMS calcd for $\text{C}_{11}\text{H}_{14}\text{FNONa}$: 218.0951; Found, 218.0961. *N*-1-(2-bromo-1-phenylpropyl)acetamide: **3b**: IR (KBr) ν_{max} 3308, 3062, 3031, 2965, 2873, 1736, 1651, 1538, 1454, 1375, 1261, 1184, 1089, 753, 700 cm^{-1} . ^1H NMR (200 MHz, CDCl_3): δ 7.15–7.35 (m, 5H), 4.57 (d, $J = 7.5$ Hz, 1H), 4.29–4.38 (m, 1H), 2.07 (d, $J = 1.5$ Hz, 3H), 1.46 (d, $J = 16.0$ Hz, 3H). LC-MS: m/z : 176 (M+Na) (–HBr). HRMS calcd for $\text{C}_{11}\text{H}_{14}\text{BrNONa}$: 176.1075; Found: 176.1073. *N*-1-(2-fluoro-1,2,3,4-tetrahydro-1-naphthalenyl)acetamide: **4e**: IR (KBr): ν_{max} 3286, 3063, 2921, 2852, 1638, 1544, 1437, 1370, 1057, 744, 701 cm^{-1} . ^1H NMR (200 MHz, CDCl_3): δ 7.03–7.30 (m, 4H), 6.0 (d, $J = 8.3$ Hz, 1H), 4.85–5.41 (m, 2H), 2.96–3.16 (m, 1H), 2.65–2.79 (m, 1H), 2.24–2.41 (m, 1H), 2.12 (s, 3H), 1.79–2.07 (m, 1H). ^{13}C NMR (75 MHz, CDCl_3): δ 170.0, 169.8, 139.2, 137.0, 128.6, 128.6, 128.5, 128.0, 127.0, 93.4, 93.2, 91.0, 90.8, 57.4, 57.2, 56.6, 56.2, 23.0, 19.6, 19.4, 18.6, 18.4. LC-MS: m/z : 208 (M+1). HRMS calcd for $\text{C}_{12}\text{H}_{14}\text{FNONa}$: 230.0957; Found, 230.0953. *N*-1-(2-fluoro-1-methyl-1-phenylethyl)propanamide: **4h**: IR (KBr): ν_{max} 3288, 3068, 2928, 2853, 1654, 1550, 1496, 1456, 1371, 1264, 1015, 697 cm^{-1} . ^1H NMR (300 MHz, CDCl_3): δ 7.22–7.34 (m, 5H), 5.73 (s, 1H), 4.67–4.76 (m, 1H), 4.56 (dd, $J = 9.2$, 18.8 Hz, 1H), 2.23 (dd, $J = 8.3$, 15.8 Hz, 2H), 1.75 (d, $J = 2.2$ Hz, 3H), 1.16 (t, $J = 7.5$ Hz, 3H). LC-MS: m/z : 232 (M+Na). HRMS calcd for $\text{C}_{12}\text{H}_{16}\text{FNONa}$: 232.1113; Found, 232.1122. *N*-1-(2-bromo-1,2-diphenylethyl)acetamide: **3m**: IR (KBr): ν_{max} 3384, 2922, 1643, 1537, 1451, 1377, 1216, 1056, 761, 700 cm^{-1} . ^1H NMR (200 MHz, CDCl_3): δ 7.15–7.44 (m, 10H), 5.15 (d, $J = 7.3$ Hz, 1H), 4.93–5.01 (m, 1H), 2.21 (d, $J = 1.4$ Hz, 3H). LC-MS: m/z : 238 (M+Na) (–HBr). HRMS calcd for $\text{C}_{16}\text{H}_{16}\text{BrNONa}$: 238.1231; Found, 238.1243.