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Ionic liquid media resulted in more efficient regio- and stereoselective aminohalogenation of cinnamic esters

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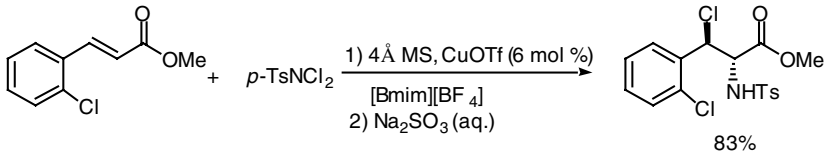
Abstract—The ionic liquid, butylmethylimidazolium tetrafluoroborate ([Bmim][BF4]), was found to be superior to classical organic solvents for the metal catalyzed regio- and stereoselective aminohalogenation of cinnamic esters. The aminohalogenation reaction of cinnamic esters with *p*-$TsNCl_2$ proceeded at a faster rate (within 12 h) in the presence of a reduced amount of catalyst (CuOTf, 6.0 mol%). Good yields (76–82%) and excellent regio- and stereoselectivity (one isomer) were achieved for eight examples.

The vicinal haloamines derived from inexpensive α,β-unsaturated carboxylic esters are important building blocks in organic synthesis.[1–6] They can be readily transformed to other biologically important compounds by replacing the halogen via intramolecular or intermolecular reactions. The aminohalogenation of electron-deficient alkenes remained difficult until we reported several stereo and regioselective routes for the synthesis of these products using transition and main group metal catalysts such as Cu(II)OTf, Cu(I)OTf, $ZnCl_2$, and dichloro-(1,10-phenanthroline)-palladium(II).[7–9] However, for some substrates, the reaction gave poor to modest yields under the known conditions and required relatively long reaction periods. For example, when methyl 2-chlorocinnamate was employed as the substrate, only 52–66% chemical yields were obtained under the above catalytic systems. In this letter, we report by using an ionic liquid (IL), [bmim][BF_4], as the reaction media, the aminohalogenation of cinnamic esters can proceed at a faster rate and give higher yields in the presence of a reduced amount of catalyst. The reaction is represented in Scheme 1 with the results listed in Table 1.

As compared with normal organic solvents, ionic liquids (IL) as reaction media has several attractive properties for chemical transformations.[10–12] These properties include nonvolatility, noncombustibility, and dissolvability of polar compounds. Ionic liquids can be easily recycled, and therefore, are environmentally friendly. In fact, ionic liquid-based organic synthesis has become an active topic in organic chemistry in the past several years. Since the aminohalogenation reaction is believed to go through the formation of aziridinium ion intermediate, ionic liquid can play the important role on the reaction through ionic solvation effect in two possible manners: (1) to help the chlorine atom to leave the nitrogen source (4-$TsNCl_2$), which is supported by the situation the partial negative charge on chlorine is surrounded by positively charged 1,3-dialkyl



Scheme 1.

Keywords: Aminohalogenation; Ionic liquid; Cinnamates; Copper(I)triflate.
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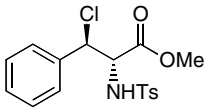
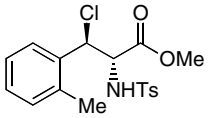
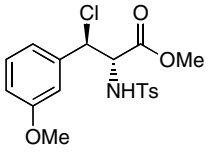
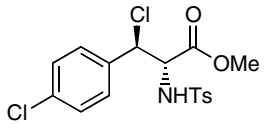
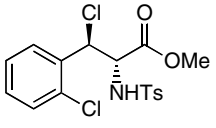
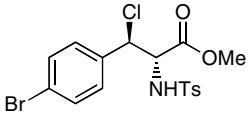
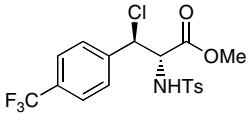
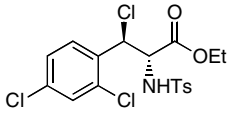
Table 1. Results of aminohalogenation of cinnamates in [bmim][BF_4][13,14]

Entry	R	Product (±)	Yield (%)[a,b]	mp (°C)
1	Me	 **1**	81	142–144
2	Me	 **2**	82	132–135
3	Me	 **3**	81	123–125
4	Me	 **4**	85	92–95
5	Me	 **5**	83	135–138
6	Me	 **6**	77	Oil
7	Me	 **7**	76	136–137
8	Et	 **8**	78	109–111

[a] The yields after column chromatography purification.
[b] No minor isomer was detected for each case as revealed by crude ^{1}H NMR determination.

imidazolium ion of the ionic liquid; (2) to make the resulting key ionic intermediate species, aziridinium ion, more stable. This species should be surrounded by chlorine anion in ionic liquid solution.

The previous aminohalogenation of cinnamates in acetonitrile required 24 h to go to completion. However, the present reaction only needed 12 h to achieve the complete consumption of the starting materials. Moreover, the loading of the catalyst was also reduced from 8 to 6 mol% by using [bmim][BF_4] to give higher chemical yields. To optimize the yields, 4 Å molecular sieves were also added, which is similar to the situation of the former system. Meanwhile, it is necessary to add *N*,*N*-dichloro-*p*-toluenesulfonamide (4-TsNCl_2) into the reaction system in two potions with the second part (0.2 equiv) added 6 h later after the reaction was started.

It should be mentioned methyl 3-methoxycinnamate, methyl 4-triflouromethylcinnamate, and ethyl 2,4-dichlorocinnamate performed poorly in our previous catalytic system. However, the three substrates (entries 3, 7, and 8 in Table 1) afforded good yields (76–81%) and excellent regio- and stereoselectivities under the current ionic liquid condition. For methyl 2-methylcinnamate (entries 2 in Table 1), only 8% improvement on

chemical yield was achieved. Interestingly, for the rest of the substrates (entries 1, 4, and 6 in Table 1), there was no obvious improvement realized.

Ionic liquid employed for this reaction was readily prepared by reacting 1-methyl imidazole with 1-butyl bromide.[10] The anion metathesis was carried out by using sodium tetrafluoroborate in acetone solution. The resulting ionic liquid, [bmim][BF_4], was carefully dried by heating at 60 °C in vacuum.

Similar to our previous aminohalogenation processes, this reaction is very convenient to perform by simply mixing the three reactants, cinnamates, *N*,*N*-dichloro-*p*-toluenesulfonamide, and catalyst together with 4 Å molecular sieves at room temperature in [bmim][BF_4] in any convenient vial of appropriate size. A slight excess amount of 4-$TsNCl_2$ (1.2 equiv) proved to be necessary for the complete consumption of the cinnamate as monitored by TLC.

In conclusion, the ionic liquid, [bmim][BF_4], has been proven to be an effective reaction media for the aminohalogenation of cinnamates. Higher chemical yields, faster reaction rate, and reduced catalyst loading have been achieved. The reaction scope was also extended under the ionic liquid-based catalytic aminohalogenation. The asymmetric aminohalogenation of α,β-unsaturated substrates by using ionic liquid is currently being pursued in our laboratories and will be reported in due course.

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13. Typical experimental procedure: Into a dry vial was loaded methyl cinnamate (81 mg, 0.50 mmol, 1.0 equiv), 4 Å molecular sieves (100 mg), *p*-$TsNCl_2$ (120 mg, 0.5 mmol, 1.0 equiv), [bmim][BF_4] (300 mg) and CuOTf·benzene complex (15 mg, 6.0 mol%) and the mixture was stirred at room temperature for 6 h, and added by another portion of *p*-$TsNCl_2$ (24.0 mg, 0.20 equiv). The reaction mixture was stirred for another 6 h. The reaction was finally quenched with saturated aqueous solution of Na_2SO_3. The product was extracted with ether (10 × 2) and the combined ether extracts were dried over Na_2SO_4. The crude product was subjected to flash chromatography (EtOAc and hexane, v/v = 2/8) to yield 149 mg of product as white solid (81%). The ionic liquid was recovered by extracting the aqueous layer with EtOAc.
14. Analytical data: **1** ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.66–7.63 (m, 2H), 7.32–7.30 (m, 3H), 7.29–7.24 (m, 4H), 5.20 (d, J = 9.5 Hz, 1H), 5.15 (d, J = 6 Hz, 1H), 4.44 (dd, J = 5.5, 4.0 Hz, 1H), 3.50 (s, 3H), 2.41 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.8, 143.8, 136.4, 135.7, 129.6, 129.0, 128.6, 127.5, 127.2, 61.9, 61.8, 52.6, 21.5. **2** ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.63–7.58 (m, 2H), 7.35–7.33 (m, 1H), 7.25–7.23 (m, 2H), 7.21–7.12 (m, 3H), 5.32 (d, J = 6.5 Hz, 2H), 4.41 (dd, J = 7.0, 3.0 Hz, 1H), 3.47 (s, 3H), 2.41 (s, 3H), 2.33 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.1, 143.9, 136.2, 135.4, 134.1, 130.6, 129.6, 128.8, 127.8, 127.6, 127.2, 60.4, 58.6, 52.4, 21.5, 19.1. **3** ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.63 (m, 2H), 7.24–7.20 (m, 4H), 6.99 (d, J = 3 Hz, 1H), 6.78 (dd, J = 3.0, 6.0 Hz, 1H), 5.52 (d, J = 6.5 Hz, 1H), 5.29 (d, J = 10.0 Hz, 1H), 4.46 (dd, J = 6.0, 3.5 Hz, 1H), 3.76 (s, 3H), 3.51 (s, 3H), 2.41 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.7, 158.4, 143.9, 136.3, 134.3, 130.1, 129.5, 127.3, 124.0, 116.4, 114.5, 60.3, 57.7, 55.5, 52.6, 21.5. **4** ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.61–7.60 (m, 2H), 7.27–7.24 (m, 4H), 7.21–7.19 (m, 2H), 5.19 (d, J = 10.0 Hz, 1H), 5.07 (d, J = 6.0 Hz, 1H), 4.39 (dd, J = 6.5, 3.5 Hz, 1H), 3.54 (s, 3H), 2.42 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.8, 144. 0, 136.3, 135.0, 134.5, 129.6, 128.9, 128.7, 127.2, 61.8, 61.0, 52.8, 21.5. **5** ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.76–7.65 (m, 2H), 7.53–7.50 (m, 1H), 7.34–7.31 (m, 1H), 7.25–7.24 (m, 3H), 5.58 (d, J = 6.0 Hz, 1H), 5.33 (d, J = 10 Hz, 1H),

4.51 (dd, J = 6.5, 4.0 Hz, 1H), 3.46 (s, 3H), 2.41 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.6, 143.9, 136.4, 133.5, 132.7, 130.1, 129.7, 129.4, 129.0, 127.3, 127.2, 60.2, 58.0, 52.5, 21.5. **6** ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.61–7.59 (m, 2H), 7.41–7.39 (m, 2H), 7.25–7.24 (m, 2H), 7.15–7.13 (m, 2H), 5.22 (d, J = 9.5 Hz, 1H), 5.05 (d, J = 6.5 Hz, 1H), 4.38 (dd, J = 6.5, 3.5 Hz, 1H), 3.55 (s, 3H), 2.43 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) 168.8, 144.0, 136.2, 135.0, 131.7, 129.6, 129.2, 127.1, 123.2, 61.8, 61.0, 52.8,21.5. **7** ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.63–7.61 (m, 2H), 7.27–7.24 (m, 4H), 7.00–6.96 (m, 2H), 5.21(d, J = 10 Hz, 1H), 5.10 (d, J = 6.5 Hz, 1H), 4.40 (dd, J = 6.0, 4.0 Hz, 1H), 3.52 (s, 3H), 2.41 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) 168.8, 143.9, 136.3, 131.8, 129.6, 129.4, 127.2, 115.7,115.5, 61.9, 61.0, 52.7, 21.5. **8** ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.64–7.61 (m, 2H), 7.44 (d, J = 8.5 Hz, 1H), 7.32 (d, J = 2.0 Hz, 1H), 7.25–7.22 (m, 2H), 7.20 (dd, J = 2, 6.5 Hz, 1H), 5.49 (d, J = 6.5 Hz, 1H), 5.33 (bm, 1H), 4.42 (dd, J = 6.5, 3.5 Hz, 1H), 4.01–3.91 (m, 2H), 2.42 (s, 3H), 1.09 (t, J = 7.0 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.1, 144.0, 136.4, 135.4, 133.5, 132.5, 130.8, 129.6, 129.4, 129.1, 127.4, 127.2, 62.3, 60.3, 57.4, 21.5, 13.7.