ORGANIC LETTERS

2004
Vol. 6, No. 26
4881−4884

# Ionic Liquid Media Resulted in the First Asymmetric Aminohalogenation Reaction of Alkenes

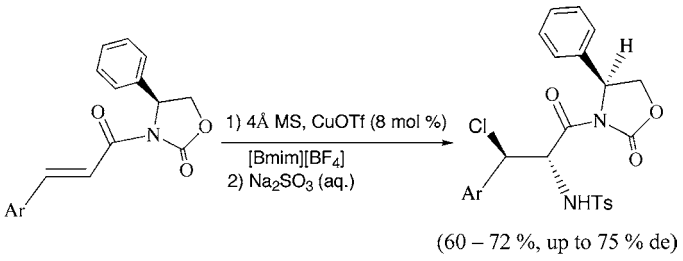
**Xin Xu, S. R. S. Saibabu Kotti, Junying Liu, John F. Cannon,[†] Allan D. Headley,* and Guigen Li***

*Departments of Chemistry and Biochemistry, Texas Tech University, Lubbock, Texas 79409-1061 and Brigham Young University, Provo, Utah 84602-5700*

*guigen.li@ttu.edu*

**Received September 25, 2004**

## ABSTRACT




**The first asymmetric aminohalogenation of functionalized alkenes has been established. The ionic liquid [bmim][$BF_4$] was found to be the only effective media for success as normal organic solvents failed to give any product for this reaction. The reaction is also 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 without special protection from inert gases. Good chemical yields (60–72%) and diastereoselectivities (up to 75% de) have been obtained with a good scope of substrates. The resulting individual diastereomers have been cleanly separated via column chromatography. The absolute stereochemistry of the reaction was unambiguously determined by X-ray structural analysis.**

The aminohalogenation and related reactions of multiple functionalized alkenes and alkynes has become an active topic in organic synthesis because the resulting vicinal haloamines are important building blocks in organic and medicinal chemistry.[1−5] In the past several years we[6−10] and others[11,12] have reported stereo- and regioselective catalytic methods for the synthesis of vicinal haloamine derivatives by using transition and main group metal catalysts, such as Cu(II)OTf, Cu(I)OTf, $ZnCl_2$, and dichloro-(1,10-phenanthroline)-palladium(II). Unfortunately, when chiral α,β-unsaturated *N*-acyl 4-alkyloxazolidinones[13] were subjected to these reactions, the success has been very limited; in fact,

[†] Brigham Young University.

(1) (a) Kemp, J. E. G. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, 1991; Vol. 3, pp 471−513 and references therein. (b) DuBois, J.; Tomooka, C. S.; Hong, J.; Carreira, E. M. *Acc. Chem. Res.* **1997**, *30*, 364−372.

(2) (a) Griffith, D. A.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1991**, *113*, 5863−5870. (b) Barton, D. H. R.; Britten-Kelly, M. R.; Ferreira, D. *J. Chem. Soc., Perkin Trans. 1* **1978**, 1090−1100. (c) Driguez, H.; Vermes, J.-P.; Lessard, J. *Can. J. Chem.* **1978**, *56*, 119−130. (d) Lessard, J.; Driguez, H.; Vermes, J.-P. *Tetrahedron Lett.* **1970**, *11*, 4887−4891.

(3) (a) Daniher, F. A.; Butler, P. E. *J. Org. Chem.* **1968**, *33*, 4336−4340. (b) Daniher, F. A.; Butler, P. E. *J. Org. Chem.* **1968**, *33*, 2637−2642. (c) Daniher, F. A.; Melchior, M. T.; Butler, P. E. *Chem. Commun.* **1968**, 931−932. (d) Seden, T. P.; Tuner, R. W. *J. Chem. Soc. C* **1968**, 876−878.

(4) Orlek, B. S.; Stemp, G. *Tetrahedron Lett.* **1991**, *32*, 4045−4048.

(5) Qui, J.; Silverman, R. B. *J. Med. Chem.* **2000,** *43*, 706−720.

(6) Karur, S.; Kotti, S. R. S. S.; Xu, X.; Cannon, J. F.; Headley, A. D.; Li, G. *J. Am. Chem. Soc.* **2003**, *125*, 13340−13341.

(7) (a) Li, G.; Wei, H.-X.; Kim, S. H.; Neighbors, M. *Org. Lett.* **1999**, *1*, 395−397. (b) Li, G.; Wei, H.-X.; Kim, S. H. *Org. Lett.* **2000**, *2*, 2249−2252.

(8) (a) Wei, H.-X.; Kim, S. H.; Li, G. *Tetrahedron* **2001**, *57*, 3869−3973. (b) Li, G.; Wei, H.-X.; Kim, S. H. *Tetrahedron* **2001**, *57*, 8407−8411.

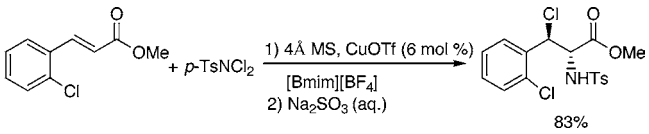
(9) For aminohalogenation of enones see: Chen, D.; Timmons, C.; Chao, S.; Li, G. *Eur. J. Org. Chem.*, **2004**, 3097−3101.

(10) Kotti, S. R. S. S.; Xu, X.; Wang, Y.; Headley, A. D.; Li, G. *Tetrahedron Lett.* **2004**, *45*, 7209−7212.

10.1021/ol048045i CCC: $27.50 
**Published on Web 12/02/2004**

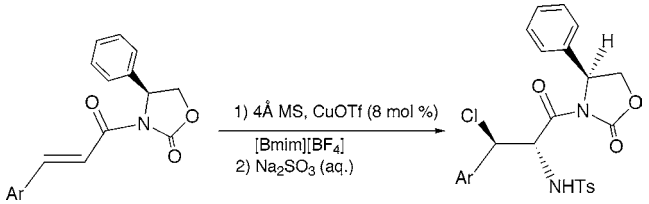
there were no desired products observed at all in all normal organic solvents we examined. Very recently, we reported that when an ionic liquid (IL), [bmim][$BF_4$], was employed as the reaction media,[10] the aminohalogenation reaction of cinnamates proceeded at a faster rate and gave higher chemical yields with extended reaction scope. Meanwhile, the loading of catalyst was also reduced (Scheme 1).

**Scheme 1**




In this Letter, we would like to describe the asymmetric aminohalogenation of $\alpha,\beta$-unsaturated *N*-acyl 4-alkyloxazolidinones, which do not proceed in normal organic solvents but does in ionic liquid (IL) media only. To the best of our knowledge, the work described in this paper not only is the first asymmetric aminohalogenation of alkenes but also is among very rare examples that show only ionic liquids can result in an organic reaction when classic organic solvents cannot (Scheme 2, Table 1).

**Scheme 2**

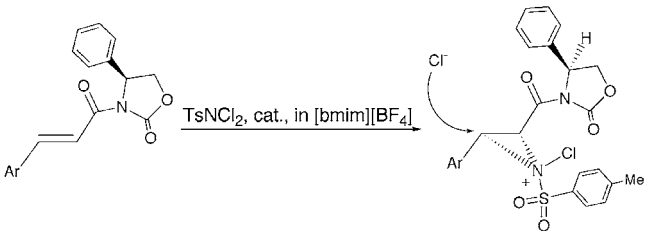



It should be noted that as compared with normal organic solvents, the use of ionic liquids as reaction media has several attractive properties for chemical transformations, including their nonvolatile and noncombustible properties and their enhanced solubility properties for polar compounds.[11−17] Furthermore, ionic liquids can be easily recycled and therefore are environmentally friendly. We believe the success of the present asymmetric aminohalogenation is largely attributed to the high polarity of ionic liquids. The aminohalogenation reaction is believed to go through the formation of an aziridinium ion intermediate at the initial key step.[6−10,18,19] This intermediate is next subjected to regio- and stereoselective ring openings (Scheme 3). The ionic liquid media can accelerate the formation of this polar intermediate by a solvation effect to make this species and the resulting chlorine anion more stable. At the same time, the polar ionic liquid can also help the chlorine atom of 4-$TsNCl_2$ to leave the nitrogen source.

It should be noted that nearly all of the applications of ionic liquids in organic synthesis have been focused on the improvement of reaction efficiencies in terms of yields, stereo-, diastereo-, and enantioselectivity. It is very rare to find an example in which a reaction does not proceed in normal organic solvents but successfully occurs in ionic liquids.

Since there are not Lewis acid species involved during the reaction process, it is impossible to form the coordination complex from the two carbonyl groups of the substrate. The most stable conformation of the substrate is determined by the interactions of dipoles of these two carbonyl groups which are anti parallel (Scheme 3). There-

**Scheme 3**




fore, the diastereochemistry is controlled by a nonchelation model, i.e., the electrophilic species approaches the substrate from the less hindered side of the oxazolidinone ring. The opening of the aziridinium intermediate via $S_N2$ substitution has to proceed through the more bulky side of the phenyl ring of the oxazolidinone ring to give the *anti* stereochemistry.

The absolute stereochemistry was unambiguously confirmed by X-ray structural analysis for product 1 of Table 1


(11) (a) Qi, X.; Lee, S. H.; Kwon, J. Y.; Kim, Y.; Kim, S. J.; Lee, Y. S.; Yoon, J. *J. Org. Chem.* **2003**, *68*, 9140−9143. (b) Thakur, V. V.; Talluri, S. K.; Sudalai, A. *Org. Lett.* **2003**, *5*, 861−864. (c) Volonterio, A.; Bravo, P.; Panzeri, W.; Pesenti, C.; Zanda, M. *Eur. J. Org. Chem.* **2002**, *19*, 3336−3340. (d) Raghavan, S.; Reddy, S. R.; Tony, K. A.; Kumar, C. N.; Nanda, S. *Synlett* **2001**, *6*, 851−853. (e) Nadir, U. K.; Singh, A. *Synth. Commun.* **2004**, *34*, 1337−1347.

(12) (a) Bach, T.; Schlummer, B.; Harms, K. *Chem. Commun.* **2000**, 287−288. (b) Koziara, A.; Zwierzak, A. *Tetrahedron* **1976**, *32*, 1649−1654. (c) Klepacz, A.; Zwierzak, A. *Tetrahedron Lett.* **2001**, *42*, 4539−4540.

(13) (a) Evans, D. A.; Bartrolli, J.; Shih, T. L. *J. Am. Chem. Soc.* **1981**, *103*, 2127−2129. (b) Walker, M. A.; Heathcock, C. H. *J. Org. Chem.* **1991**, *56*, 5747−5750.

(14) (a) Sheldon, R. *Chem. Commun.* **2001**, 2399−2407. (b) Dzyuba, S. V.; Bartsch, R. A. *Angew. Chem., Int. Ed.* **2003**, *42*, 148−150.

(15) (a) Earle, M. J.; McCormac, P. B.; Seddon, K. R. *Green Chem.* **1999**, 23−25. (b) Jaeger, D. A.; Tucker, C. E. *Tetrahedron Lett.* **1989**, *30*, 1785−1788. (c) Howarth, J.; Hanlon, K.; Fayne, D.; McCormac, P. *Tetrahedron Lett.* **1997**, *38*, 3097−3100. (d) Park, S.; Kazlauskas, R. *J. Org. Chem.* **2001**, *66*, 8395−8401. (e) Wu, J. X.; Beck, B.; Ren, R. X. *Tetrahedron Lett.* **2002**, *43*, 387−389.

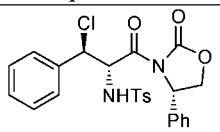
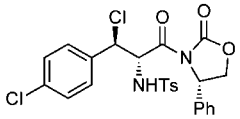
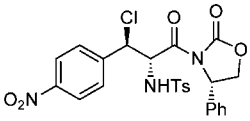
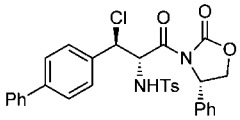
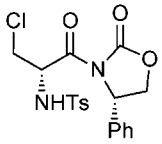
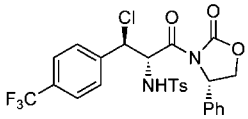
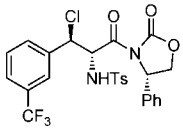
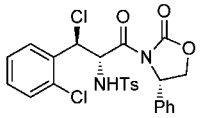
(16) (a) Kabalka, G. W.; Venkataiah, B.; Dong, G. *Tetrahedron Lett.* **2003**, *44*, 4673−4675. (b) Kotti, S. R. S. S.; Xu, X.; Li, G.; Headley, A. *Tetrahedron Lett.* **2004,** *45*, 1427−1431.

(17) (a) Headley, A. D.; Jackson, N. M. *J. Phys. Org. Chem.*, **2002**, *15*, 52−55. (b) Headley, A. D.; Nam, J. *J. Phys. Org. Chem.*, **2002**, *15*, 62−68.

(18) (a) Li, G. Wei, H.-X.; Kim, S. H.; Carducci, M. *Angew. Chem., Int. Ed.* **2001**, *40*, 4277−4280. (b) Pei, W.; Timmons, C.; Xu, X.; Wei, H.-X.; Li, G. *Org. Biomol. Chem.* **2003**, *1*, 2919−2921.

(19) (a) Wei, H.-X.; Kim, S. H.; Li, G. *J. Org. Chem.* **2002**, *67*, 4777−4781. (b) Chen, D.; Timmons, C.; Wei, H.-X.; Li, G. *J. Org. Chem.* **2003**, *68*, 5742−5745.

**Table 1.** Results of Asymmetric Aminohalogenation in [bmim][$BF_4$][20]

| entry | product | dr | % yield | $[\alpha]_D^{25}$ [a] | mp / °C [b] |
|---|---|---|---|---|---|
| 1 |  | 3:1 | 63 | +89.2, c= 0.9<br>(+94.1, c= 0.21) | 81- 83<br>(244, dec) |
| 2 |  | 7: 1 | 70 | +67.5, c= 0.52<br>(+68.0, c= 0.54) | 78- 80<br>(275, dec) |
| 3 |  | 6: 1 | 65 | +65.4, c= 0.42<br>(+17.0, c= 0.21) | 190- 192<br>(263- 265) |
| 4 |  | 3: 1 | 72 | +85.9, c= 0.34<br>(+25.1, c= 0.21) | 92- 94<br>(210- 212) |
| 5 |  | 3: 1 | 65 | +53.9, c= 0.92<br>(+95.5, c= 1.96) | 60- 62<br>(172- 174) |
| 6 |  | 3: 1 | 64 | +81.5, c= 0.46<br>(+73.0, c= 0.14) | 90- 92<br>(249- 251) |
| 7 |  | 4: 1[c] | 60 | +66.3, c= 0.4 | 65- 67 |
| 8 |  | 4: 1 | 65 | +68.8, c= 0.64<br>(+160.0, c=0.08) | 163- 165<br>(245- 247) |

[a] Optical rotations were measured in dichloromethane. [b] Data for the minor isomer are given in parentheses. [c] The minor diastereomer has not been isolated.

as shown in Figure 1. It is interesting that the aromatic ring of the nitrogen source is nearly parallel with the five-membered oxazolidinone ring. This interaction enforces the favored staggered conformation of the main side chain in which $\beta$-chloro and α-amino groups are onto opposite positions.

It is anticipated that the phenyl ring of the chiral auxiliary is relatively far away from the reactive side of the C═C double bond of the substrate; this is responsible for the modest selectivity of the asymmetric induction. However, the resulting two individual diastereoisomers can be readily separated via column chromatography for all of the cases except for entry 7. In this case, **7**, the major diastereoisomer

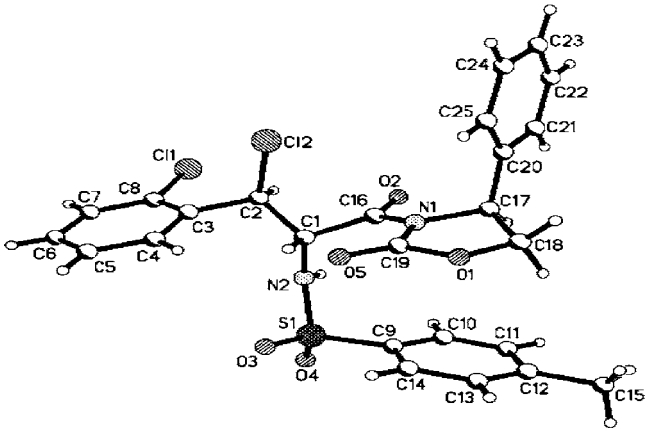



**Figure 1.** X-ray structure of product **1**.

(20) **Typical Experimental Procedure.** Into a dry vial was loaded α,$\beta$-unsaturated *N*-acyl-4-phenyl oxazolidinone (0.15 mmol), 4Å MS (50 mg), copper(I) trifluoromethanesulfonate benzene (0.015 mmol, 10 mol %), and dry ionic liquid BmimBF$_4$ (400 mg). *N*,*N*-Dichloro-*p*-methylbezenesulfonamide (0.17 mmol, 1.1 equiv) was then added into the above mixture. The reaction vial was capped, and the resulting mixture was stirred at room temperature 12 h. The reaction was finally quenched with a saturated aqueous solution of $Na_2SO_3$ (2 mL). The product was extracted with ether (4 × 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 = 1/3) to give product. The ionic liquid was recovered by extracting the aqueous layer with EtOAc.

was obtained, but the minor diastereoisomer was not cleanly separated from the remaining mixture because of the similarity of its polarity to that of the major isomer.

The previous aminohalogenation of cinnmates in acetonitrile required 24 h to go to completion. The present reaction only needed 12 h for the complete consumption of the starting materials, which is similar to the cinnmate-based aminohalogenation we reported very recently.[10] The ionic liquid employed for this reaction was readily prepared by reacting 1-methyl imidazole with 1-butyl bromide. The IL anion exchange 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 a vacuum.[15]

The reaction is also 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 without special protection with inert gases. However, in the present system it is not necessary to add *N*,*N*-dichloro-*p*-toluenesulfonamide (4-$TsNCl_2$) in two potions.

As shown in Table 1, the reaction occurs with a wide variety of substrates, although only one aliphatic substrate was examined. It turned out the reaction is general for α,*β*-unsaturated *N*-acyl-4-phenyl oxazolidinones. Interestingly, the strong electron-withdrawing group attached substrates resulted in chemical yields similar to those from neutral α,*β*-unsaturated *N*-aryl-4-phenyl oxazolidinones. Only two cases (entries 2 and 3, Table 1) gave good diastereoselectivity (75% and 71% de, respectively), whereas the other six substrates resulted in only marginal diastereoselectivity (50−60% de).

In conclusion, the first asymmetric aminohalogenation of functionalized alkenes has been established. The absolute stereochemistry of the reaction was unambiguously determined by X-ray structural analysis. The ionic liquid [bmim][$BF_4$] was found to be the only effective reaction media as normal organic solvents failed to give any product. This work represents a unique example for this area of ionic liquid research. Acceptable chemical yields and diastereoselectivities have been obtained with a good scope of substrates. The resulting individual diastereomers have been cleanly separated via column chromatography.

**Acknowledgment.** We gratefully acknowledge the National Institutes of Health (CA 99995-1) and the Robert A. Welch Foundation (D-1361, D-1460) for the generous support of this work. We thank Dianjun Chen and Cody Timmons for their assistance.

**Supporting Information Available:** Experimental procedures, analytical data, $^1H$ and $^{13}C$ NMR spectra, and crystallographic data in CIF format. This material is available free of charge via the Internet at http://pubs.acs.org.

OL048045I