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Sulfonimidamides: Efficient Chiral Iminoiodane Precursors for Diastereoselective Copper-Catalyzed Aziridination of Olefins

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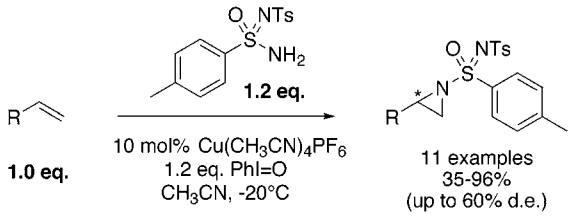
ABSTRACT



***N*-(*p*-Toluenesulfonyl)-*p*-toluenesulfonimidamide reacts with iodosylbenzene to afford in situ a chiral iminoiodane. The latter gives, in the presence of a copper(I) catalyst, a nitrene that is very efficiently transferred under stoichiometric conditions to a variety of alkenes with diastereoselectivities up to 60%.**

The past decade has witnessed a growing interest in carbon−nitrogen bond formation via functionalization of alkanes and alkenes by nitrene insertion or addition.[1] Considering the high number of nitrogen-containing natural and/or biologically active compounds, these methodologies display a promising potential in total synthesis. As a result, several methods are now available for the generation of highly reactive nitrene intermediates starting from *N*-aminoheterocycles,[2] azides,[3] haloamines,[4] or iminoiodanes.[5] Among these nitrene precursors, the latter have gained popularity since their use in copper-catalyzed aziridination of olefins[6] and rhodium-catalyzed C−H amidation[7] has found applications in total synthesis.[5,8] Moreover, enantioselective nitrene transfer[9] has been developed from iminoiodanes in conjunction with chiral transition metal catalysts.

It has been recently demonstrated that iminoiodanes can be efficiently generated in situ using iodosylbenzene[10] or iodosylbenzene(diacetate).[7,11] These processes greatly simplify the troublesome handling of iminoiodanes but more importantly enhance the variety of nitrogenous compounds

(1) (a) Watson, I. D. G.; Yudin, A. K. *Curr. Opin. Drug Discovery Dev.* **2002**, *5*, 906−917. (b) *Modern Amination Methods*; Ricci, A., Ed.; Wiley-VCH: Weinheim, 2000.

(2) (a) Atkinson, R. S. *Tetrahedron* **1999**, *55*, 1519−1559. (b) Siu, T.; Yudin, A. K. *J. Am. Chem. Soc.* **2002**, *124*, 530−531.

(3) (a) Bach, T.; Schlummer, B.; Harms, K. *Chem. Eur. J.* **2001**, *7*, 2581−2594. (b) Omura, K.; Murakami, M.; Uchida, T.; Irie, R.; Katsuki, T. *Chem. Lett.* **2003**, *32*, 354−355.

(4) (a) Jeong, J. U.; Tao, B.; Sagasser, I.; Henniges, H.; Sharpless, K. B. *J. Am. Chem. Soc.* **1998**, *120*, 6844−6845. (b) Chanda, B. M.; Vyas, R.; Bedekar, A. V. *J. Org. Chem.* **2001**, *66*, 30−34.

(5) Dauban, P.; Dodd, R. H. *Synlett* **2003**, 1571−1586.

(6) Evans, D. A.; Faul, M. M.; Bilodeau, M. T. *J. Am. Chem. Soc.* **1994**, *116*, 2742−2753.

(7) (a) Espino, C. G.; Du Bois, J. *Angew. Chem., Int. Ed.* **2001**, *40*, 598−600. (b) Espino, C. G.; Wehn, P. M.; Chow, J.; Du Bois, J. *J. Am. Chem. Soc.* **2001**, *123*, 6935−6936.

(8) For recent examples, see: (a) White, R. D.; Keaney, G. F.; Slown, C. D.; Wood, J. L. *Org. Lett.* **2004**, *6*, 1123−1126. (b) Hinman, A.; Du Bois, J. *J. Am. Chem. Soc.* **2003**, *125*, 11510−11511.

(9) Müller, P.; Fruit, C. *Chem. Rev.* **2003**, *103*, 2905−2919.

(10) Dauban, P.; Sanière, L.; Tarrade, A.; Dodd, R. H. *J. Am. Chem. Soc.* **2001**, *123*, 7707−7708.

(11) (a) Yu, X. Q.; Huang, J. S.; Zhou, X. G.; Che, C. M. *Org. Lett.* **2000**, *2*, 2233−2236.

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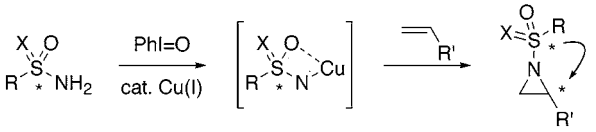
Scheme 1. Diastereoselective Aziridination with a Chiral Sulfur(VI) Reagent



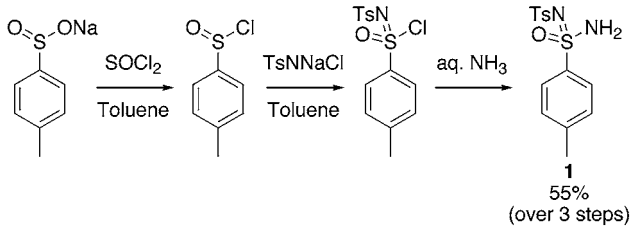
likely to be transformed into these hypervalent iodine(III) reagents. Thus, while formerly, only iminoiodanes derived from sulfonamides were available,[5,12] carbamates[7a,13] and sulfamates[7b,13b,14] can now be used as practical and synthetically useful precursors.

Despite these improvements, the intermolecular copper-catalyzed aziridination of olefins still suffers from low to moderate yields when stoichiometric conditions are employed in the case of simple aliphatic or electron-deficient alkenes. Moreover, although a large number of ligands have been described for asymmetric aziridination,[15] their application remains limited to styrene-type substrates.

It was therefore with the intention of enhancing the scope of this process that we felt it interesting to apply our one-pot methodology to generate chiral iminoiodanes in situ. As has been previously noted,[5] this strategy has not been explored so far. To this end, we aimed to prepare a chiral sulfur(VI) reagent since it was expected that the stereogenic information could be transmitted to the targeted carbon atom of the aziridine (Scheme 1).[16]

We therefore turned our attention to sulfonimidamides first described by Levchenko[17] more than 40 years ago but which have received little attention so far, particularly those with an unsubstituted amido nitrogen.[18] Since initial experiments with *N*-(alkyl)arylsulfonimidamides did not lead to satisfactory results (less than 20% aziridination), we decided to use the more robust *N*-(*p*-toluenesulfonyl)-*p*-toluenesulfonimidamide **1**. The latter is easily prepared in three steps from commercially available sodium *p*-toluenesulfinate (Scheme 2) via the corresponding sulfonimidoyl chloride obtained by action of anhydrous chloramine-T.[19]

Scheme 2. Preparation of *N*-(*p*-Toluenesulfonyl)-*p*-toluenesulfonimidamide **1**



The first investigations of the copper-catalyzed aziridination with **1** were performed on methyl acrylate. It has been previously observed that this olefinic substrate displays poor reactivity with sulfonamide-derived iminoiodanes under these conditions,[20] a frustrating result since the corresponding aziridine-2-carboxylate is a useful precursor of α- or *β*-amino acids.[21] In contrast, we have now found that methyl acrylate is an excellent aziridination substrate for **1**. Thus, after extensive screening of the reaction parameters, treatment of 5 equiv of methyl acrylate with **1** at −20 °C in acetonitrile in the presence of 10 mol % $Cu(MeCN)_4PF_6$ led to compound **2a** in 93% yield and 55% de. However, more interestingly, the sulfonimidamide-derived iminoiodane appeared to be highly reactive since the same procedure gave aziridine **2a** in 81% yield and 50% de using methyl acrylate as the limiting component (Table 1, entry 1). Similar results were obtained with other α,*β*-unsaturated esters. Reactions with methyl methacrylate and tiglate are nearly quantitative (96 and 92%, respectively, entries 2 and 4) but occur with a slightly lower de (41 and 38%, respectively), while the highest diastereoselectivity has been obtained by using 5 equiv of the less reactive methyl crotonate (63% yield, 60% de, entry 3).

Application of these conditions to simple aliphatic alkenes of moderate reactivity[6,22] also demonstrates the high reactivity of sulfonimidamide **1** in the copper-catalyzed aziridination. The monosubstituted terminal olefin 1-heptene was transformed to aziridine **2e** in 60% yield under stoichiometric conditions (entry 5), while cyclic systems such as cyclohex-

(12) (a) Yamada, Y.; Yamamoto, T.; Okawara, M. *Chem. Lett.* **1975**, 361−362. (b) Södergren, M. J.; Alonso, D. A.; Bedekar, A. V.; Andersson, P. G. *Tetrahedron Lett.* **1997**, *38*, 6897−6900.

(13) (a) Levites-Agababa, E.; Menhaji, E.; Perlson, L. N.; Rojas, C. M. *Org. Lett.* **2002**, *4*, 863−865. (b) Cui, Y.; He, C. *Angew. Chem., Int. Ed.* **2004**, *43*, 4210−4212. (c) Padwa, A.; Flick, A. C.; Leverett, C. A.; Stengel, T. *J. Org. Chem.* **2004**, *69*, 6377−6386.

(14) (a) Duran, F.; Leman, L.; Ghini, A.; Burton, G.; Dauban, P.; Dodd, R. H. *Org. Lett.* **2002**, *4*, 2481−2483. (b) Guthikonda, K.; Du Bois, J. *J. Am. Chem. Soc.* **2002**, *124*, 13672−13673. (c) Wehn, P. M.; Lee, J.; Du Bois, J. *Org. Lett.* **2003**, *5*, 4823−4826. (d) Fruit, C.; Müller, P. *Tetrahedron: Asymmetry* **2004**, *15*, 1019−1026. (e) Fruit, C.; Müller, P. *Helv. Chim. Acta* **2004**, *87*, 1607−1615. (f) Liang, J. L.; Yuan, S. X.; Huang, J. S.; Che, C. M. *J. Org. Chem.* **2004**, *69*, 3610−3619.

(15) (a) Evans, D. A.; Faul, M. M.; Bilodeau, M. T.; Anderson, B. A.; Barnes, D. M. (b) Li, Z.; Conser, K. R.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1993**, *115*, 5326−5327. (c) Gillespie, K. M.; Sanders, C. J.; O'Shaughnessy, P.; Westmoreland, I.; Thickitt, C. P.; Scott, P. *J. Org. Chem.* **2002**, *67*, 3450−3458.

(16) Initial experiments with chiral sulfinamides failed since these sulfur-(IV) reagents did not survive the oxidizing conditions of the PhI═O-mediated aziridination. See also: Leca, D.; Song, K.; Amatore, M.; Fensterbank, L.; Lacôte, E.; Malacria, M. *Chem. Eur. J.* **2004**, *10*, 906−916.

(17) Levchenko, E. S.; Derkach, N. Y.; Kirsanov, A. V. *Zh. Obshch. Khim.* **1962**, *32*, 1208−1212.

(18) (a) Takei, H.; Watanabe, I.; Mukaiyama, T. *Bull. Chem. Soc. Jpn.* **1965**, *38*, 1989−1993. (b) Jones, M. R.; Cram, D. J. *J. Am. Chem. Soc.* **1974**, *96*, 2183−2190. (c) Johnson, C. R.; Jonsson, E. U.; Bacon, C. C. *J. Org. Chem.* **1979**, *44*, 2055−2061. (d) Okuma, K.; Koike, T.; Ohta, H. *J. Org. Chem.* **1988**, *53*, 4190−4193. (e) Tsushima, S.; Yamada, Y.; Onami, T.; Oshima, K.; Chaney, M. O.; Jones, N. D.; Swartzendruber, J. K. *Bull. Chem. Soc. Jpn.* **1989**, *62*, 1167−1178. (f) Toth, J. E.; Grindey, G. B.; Ehlhardt, W. J.; Ray, J. E.; Boder, G. B.; Bewley, J. R.; Klingerman, K. K.; Gates, S. B.; Rinzel, S. M.; Schultz, R. M.; Weir, L. C.; Worzalla, J. F. *J. Med. Chem.* **1997**, *40*, 1018−1025. (g) Cathers, B. E.; Schloss, J. V. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 1527−1532.

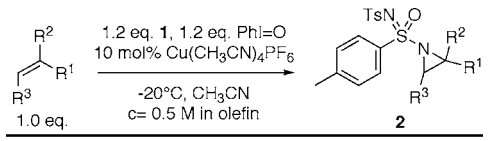
(19) Levchenko, E. S.; Derkach, N. Y.; Kirsanov, A. V. *Zh. Obshch. Khim.* **1960**, *30*, 1971−1975.

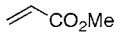
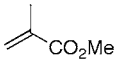
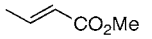
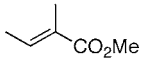
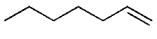
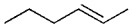
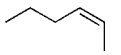
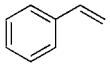
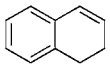
(20) Dauban, P.; Dodd, R. H. *Tetrahedron Lett.* **1998**, *39*, 5739−5742.

(21) (a) McCoull, W.; Davis, F. A. *Synthesis* **2000**, 1347−1365. (b) Tanner, D. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 599−619.

(22) (a) Dauban, P.; Dodd, R. H. *J. Org. Chem.* **1999**, *64*, 5304−5307. (b) Mairena, M. A.; Díaz-Requejo, M. M.; Belderraín, T. R.; Nicasio, M. C.; Trofimenko, S.; Pérez, P. J. *Organometallics* **2004**, *23*, 253−256.

Table 1. Copper-Catalyzed Aziridination of Olefins with Sulfonimidamide **1**



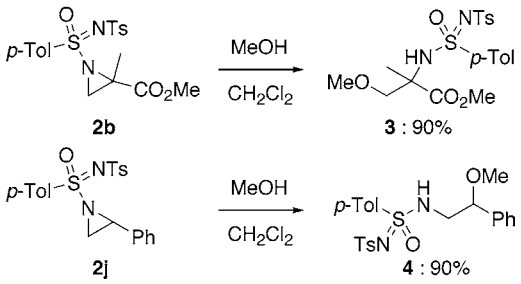
entry	substrate	Yield (%)[a]	d.e. (%)[b]
1		**2a** : 81 (93)	50 (55)
2		**2b** : 96 (97)	41 (38)
3		**2c** : 35 (63)	50 (60)
4		**2d** : 92 (90)	38 (40)
5		**2e** : 60 (78)	10 (10)
6		**2f** : 40 (73)[c]	<10 (<10)
7		**2g** : 57 (79)[d]	<10 (<10)
8		**2h** : 62 (89)	-
9		**2i** : 59 (91)	-
10		**2j** : 63 (96)	20 (<10)
11		**2k** : 63 (88)	25 (22)

[a] Isolated yield after flash chromatography. Diastereoisomers could not be separated on silica gel. Value in parentheses for yield obtained with 5 equiv of olefins. [b] Diastereomeric excess was measured by NMR. Value in parentheses for de was obtained with 5.0 equiv of olefins. [c] *trans*-Aziridine. [d] *cis*-Aziridine

ene or cyclopentene gave 62 and 59% of the corresponding aziridines **2h** and **2i**, respectively (entries 8 and 9). The *trans*- and *cis*-aziridines **2f** and **2g**, respectively, were also obtained stereospecifically in good yield (entries 6 and 7). However, these alkenes did not afford appreciable diastereoselectivities.

In the cases of styrene and of 1,2-dihydronaphthalene, the reaction with an excess of olefin still occurred with very high efficiency (96 and 88%, respectively), while the procedure applied to 1.0 equiv of substrate gave a good yield of 63% for each compound (entries 10 and 11). Surprisingly, only very modest diastereomeric excesses of 20 and 25%, respectively, were observed. These rather disappointing results are, however, likely to be improved by using sulfonimidamides in conjunction with one of the several chiral ligands described for the asymmetric copper-catalyzed aziridination of styrene-type olefins.[9,15] Initial experiments have shown that such higher diastereoselectivities could indeed be observed. Thus, a combination of (−)-**1**[23] with

Scheme 3. Aziridine Ring-Opening



(*S*)-bis((*t*-Bu)oxazoline) ligand affords aziridine **2j** in 77% yield and 60% de under stoichiometric conditions.

The synthetic value of aziridines is directly related to their ability to undergo nucleophilic ring-opening.[24] Such reactions are facilitated by the introduction on the nitrogen atom of the aziridine of an electron-withdrawing group, which is clearly the case of the *N*-(*p*-toluenesulfonyl)-*p*-toluenesulfonimidoyl group. This was indeed confirmed by the efficient and regioselective ring-opening of aziridines **2b** and **2j** with methanol under mild conditions (Scheme 3).

In conclusion, we have demonstrated that use of a chiral sulfur(VI) reagent, i.e., sulfonimidamide **1**, has allowed the generation in situ of the first chiral iminoiodane. The latter is a highly efficient nitrene precursor that reacts with a wide range of olefins in the presence of a catalytic copper(I) salt to afford the corresponding aziridines **2** in good to excellent yields, particularly in the case of the poorly reactive α,β-unsaturated esters.[25] Diastereoselectivities of up to 60% have been obtained, results that pave the way for the development of an efficient methodology for the stereoselective synthesis of amino acids.[26] To this end, screening of sulfonimidamides is in progress in order to optimize their reactivities and diastereoselectivities.

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Supporting Information Available: General experimental procedures and characterization for compounds **2a**−**k**, **3**, and **4**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(23) Both enantiomers of sulfonimidamide **1** are accessible by resolution using (*S*)- or (*R*)-α-methylbenzylamine. See ref 18e.

(24) Hu, X. E. *Tetrahedron* **2004**, *60*, 2701−2743.

(25) During the submission of this manuscript, a paper has appeared where the use of *N*-(benzoyl)sulfonimidamides for copper-mediated nitrene transfer is described. See: Leca, D.; Toussaint, A.; Mareau, C.; Fensterbank, L.; Lacôte, E.; Malacria, M. *Org. Lett.* **2004**, *6*, 3573−3575.

(26) In this context, it should be mentioned that the *N*-(*p*-toluenesulfonyl)-*p*-toluenesulfonimidoyl group may be cleaved under reductive conditions, i.e., by using sodium naphthanelide. See ref 18e.