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Asymmetric Synthesis of Terminal *N*-*tert*-Butylsulfinyl Aziridines from Organoceriums and an α-Chloroimine

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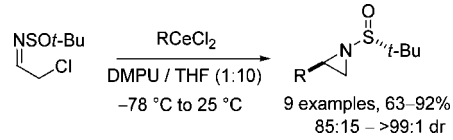
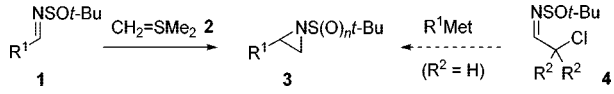
ABSTRACT



Addition of *N*-(2-chloroethylidene)-*tert*-butylsulfinamide to organocerium reagents in DMPU/THF (1:10) at −78 °C followed by warming to 25 °C provides terminal *N*-*tert*-butylsulfinyl aziridines in good yields (63−92%, nine examples) and diastereomeric ratios (85:15−>99:1).

The synthetic value of aziridines conventionally resides in their ability, usually when bearing a suitable activating/electron-withdrawing group on nitrogen, to undergo ring-opening with nucleophiles.[1] Terminal aziridines (e.g., **3**, Scheme 1) are, arguably, the most useful aziridines of all

Scheme 1. Aziridines from Imines



because of the ease, generality, and predictable regioselectivity with which they undergo such ring-openings. Recently, our laboratory has reported several new transformations of terminal aziridines that proceed by α-lithiation, including trapping of electrophiles, dimerization, and intramolecular cyclopropanation of *N*-Bus (Bus = *tert*-butylsulfonyl) terminal aziridines **3** ($n = 2$).[2] However, the use of terminal aziridines in any of the above chemistry in the context of asymmetric synthesis is limited because there is currently no general, straightforward method to access highly enantioenriched 2-substituted (particularly 2-alkyl-substituted) aziridines in an efficient manner.[3−6] Catalytic asymmetric nitrene transfer to terminal alkenes may ultimately provide one solution, but despite significant progress it is not yet a viable route to 2-alkyl-substituted aziridines.[3] Aziridination by formal methylene transfer to imines bearing a chiral *N*-activating group has been achieved using dimethylsulfo-

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(1) (a) Hu, X. E. *Tetrahedron* **2004**, *60*, 2701–2743. (b) *Aziridines and Epoxides in Organic Synthesis*; Yudin, A. K., Ed.; Wiley-VCH: Weinheim, 2006. (c) Padwa, A. *In Comprehensive Heterocyclic Chemistry III*; Katritzky, A. R., Ramsden, C. A., Scriven, E. F. V., Taylor, R. J. K., Eds.; Elsevier: Oxford, 2008, Vol. 1, pp 1−104.

(2) (a) Hodgson, D. M.; Humphreys, P. G.; Ward, J. G. *Org. Lett.* **2005**, *7*, 1153–1156. (b) Hodgson, D. M.; Miles, S. M. *Angew. Chem., Int. Ed.* **2006**, *45*, 935–938. (c) Hodgson, D. M.; Humphreys, P. G.; Ward, J. G. *Org. Lett.* **2006**, *8*, 995–998. (d) Hodgson, D. M.; Humphreys, P. G.; Miles, S. M.; Brierley, C. A. J.; Ward, J. G. *J. Org. Chem.* **2007**, *72*, 10009–10021. For recent reviews, see: (e) Hodgson, D. M.; Bray, C. D.; Humphreys, P. G. *Synlett* **2006**, *1*, 22. (f) Hodgson, D. M.; Humphreys, P. G.; Hughes, S. P. *Pure Appl. Chem.* **2007**, *79*, 269–280.

(3) Kawabata, H.; Omura, K.; Uchida, T.; Katsuki, T. *Chem. Asian J.* **2007**, *2*, 248–256.

(4) (a) Morton, D.; Pearson, D.; Field, R. A.; Stockman, R. A. *Synlett* **2003**, *1985*, 1988. (b) For a recent review on chiral nonracemic sulfinimines, see: Morton, D.; Stockman, R. A. *Tetrahedron* **2006**, *62*, 8869–8905.

(5) For efficient resolution-based approaches to terminal aziridines from epoxides, see: (a) Kim, S. K.; Jacobsen, E. N. *Angew. Chem., Int. Ed.* **2004**, *43*, 3952–3954. (b) Bartoli, G.; Bosco, M.; Carlone, A.; Locatelli, M.; Melchiorre, P.; Sambri, L. *Org. Lett.* **2004**, *6*, 3973–3975.

(6) For a recent approach to terminal aziridines, see: Jamookeeah, C. E.; Beadle, C. D.; Jackson, R. F. W.; Harrity, J. P. A. *J. Org. Chem.* **2008**, *73*, 1128–1130.

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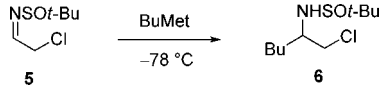
nium methylide (**2**); with *N*-*tert*-butylsulfinyl-substituted aldimines **1**, Stockman and co-workers' observed <97.5:2.5 dr for an α-branched imine **1** (R^1 = cyclohexyl, 63% yield), but dr fell to 90:10 for an unbranched case (**1**, R^1 = pentyl, 65% yield).[4] De Kimpe and co-workers recently reported an asymmetric synthesis of 2,2,3-trisubstituted aziridines by addition of Grignard reagents to nonenolizable α-chloro aldimines **4** (R^2 = alkyl),[7] and in the present work we describe adaptation of this chemistry using imine **4** (R^2 = H), which has resulted in a promising route to terminal aziridines **3**.

Initial application of De Kimpe's conditions (BuMgCl, CH_2Cl_2, −78 °C) with imine **5** (Scheme 2, prepared in

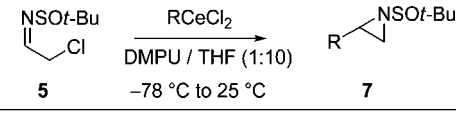
Scheme 2. Organometallic Additions to α-Chloroimine **5**



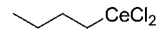
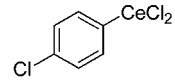
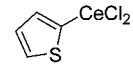
essentially quantitative yield from anhydrous chloroacetaldehyde[8] and commercially available *t*-BuSONH$_2$) led to virtually no diastereoselectivity in the resulting chlorosulfinamide **6**. Variation of the reaction conditions (solvent, Grignard reagent)[7,9,10] did not lead to a significant improvement in diastereoselectivity, whereas reaction with BuLi (THF, −78 °C) gave no discernible products.

Ellman and co-workers, in their seminal studies on additions of organometallics to simple *N*-*tert*-butylsulfinyl-substituted aldimines, noted in a single example (**5**, Me instead of Cl) that MeCeCl$_2$ (THF, −78 °C) was inferior to MeMgBr (CH_2Cl_2, −48 °C) with respect to diastereoselectivity (78:22 compared with 97:3, respectively).[9] However, encouraged by Denmark and co-workers' earlier report on organocerium additions to SAMP-hydrazones,[11] we examined BuCeCl$_2$ with imine **5** in THF or Et_2O at −78 °C and were pleased to observe dramatic rises in diastereoselectivity (93:7 and 87:13, respectively). The diastereoselectivity in THF could be further improved to >99:1 (GC analysis) by addition of DMPU.[12] Allowing a reaction under the latter conditions to warm to room temperature led to ring-closure and isolation of terminal aziridine **7a** (Table 1, entry 1) in 86% yield and unchanged dr.

Table 1. Aziridines **7** from α-Chloroimine **5**



5 **7**

entry	organocerium		yield (%)	dr[a]
1		**7a**	86	>99:1
2	*t*-BuCeCl$_2$	**7b**	76	99:1
3		**7c**	83	99:1
4	PhCeCl$_2$	**7d**	92	92:8
5		**7e**	84	85:15
6		**7f**	81	92:8
7		**7g**	82	85:15

[a] By GC of crude reaction mixtures.

The scope of this reaction was then examined with a range of organocerium reagents (Table 1).[13] The organocerium reagents were prepared from the corresponding organolithiums and $CeCl_3$. Alkyl and allyl cerium reagents added with essentially complete diastereocontrol (entries 1−3).[14] The reaction was less diastereoselective for aryl, heteroaryl and alkynyl cerium reagents (entries 4−7). Entries 3 and 5 illustrate the ability to carry additional functionality into the aziridine **7**. For entry 5, relative stereochemistry of the major diastereomer was determined to be R_s*, *R** by X-ray crystallographic analysis.[15] To demonstrate this reaction in asymmetric synthesis, $C_{10}H_{21}CeCl_2$ was added to imine (R_s)-**5** (prepared as before, but using commercially available (R_s)-*t*-BuSONH$_2$) to give aziridine **7h** in 78% yield and 97:3 dr (Scheme 3). *m*-CPBA has previously been reported to oxidize 2,3-disubstituted *N*-*tert*-butylsulfinyl aziridines to *N*-Bus

(7) Denolf, B.; Mangelinckx, S.; Törnroos, K. W.; De Kimpe, N. *Org. Lett.* **2006**, *8*, 3129–3132.

(8) Prepared in one-step from commercially available 4-chloro-1,3-dioxolan-2-one, see:Gross, H.; Costisella, B. *Org. Prep. Proced. Int.* **1969**, *1*, 97–98.

(9) (a) Cogan, D. A.; Liu, G.; Ellman, J. *Tetrahedron* **1999**, *55*, 8883–8904. (b) Ellman, J. A.; Owens, T. D.; Tang, T. P. *Acc. Chem. Res.* **2002**, *35*, 984–995.

(10) During the course of our work, an isolated example of addition of a Grignard reagent to imine **5** (mesitylMgBr, toluene, −78 °C) was reported to give a single diastereomer of the corresponding chlorosulfinamide; this might be attributable to steric effects with this particular reagent, see: Crimmins, M. T.; Shamszad, M. *Org. Lett.* **2007**, *9*, 149–152.

(11) (a) Denmark, S. E.; Weber, T.; Piotrowski, D. W. *J. Am. Chem. Soc.* **1987**, *109*, 2223–2225. (b) For a review on organocerium reagents, see: Liu, H.-J.; Shia, K.-S.; Shang, X.; Zhu, B.-Y. *Tetrahedron* **1999**, *55*, 3803–3830.

(12) Mukhopadhyay, T.; Seebach, D. *Helv. Chim. Acta* **1982**, *65*, 385–391.

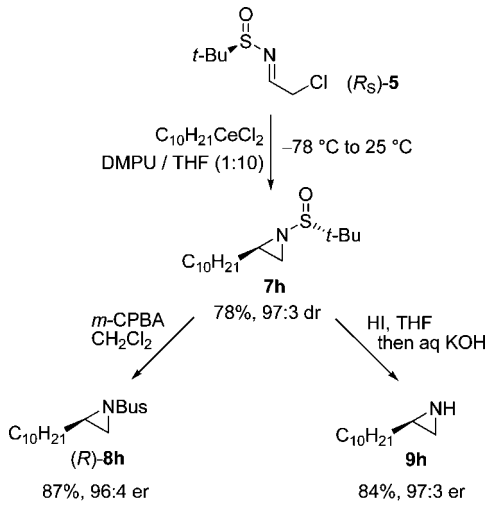
(13) General Procedure. The organolithium (1.2 mmol) in THF (5 mL) was added dropwise to a stirred slurry of $CeCl_3$ (295 mg, 1.2 mmol) in THF (7 mL) at −78 °C under argon. After 45 min DMPU (1.5 mL) was added, followed after 15 min by a solution of imine **5** (181 mg, 1 mmol) in THF (3 mL) and the reaction mixture was then allowed to warm to room temperature overnight. Saturated aq NH_4Cl (10 mL) and Et_2O (5 mL) were added, the reaction mixture filtered through a pad of Celite, and the filter cake washed thoroughly with Et_2O (3 × 10 mL). The combined organic layers were washed with H_2O (2 × 15 mL) and brine (15 mL), dried ($MgSO_4$) and evaporated under reduced pressure. Purification of the residue by column chromatography (SiO_2, petroleum ether/Et_2O) gave the corresponding aziridine **7**.

(14) Use of 10% DMPU in THF also improved the dr reported by Ellman and co-workers in the addition of MeCeCl$_2$ to imine **5** (Me instead of Cl) from 78:22 (89% yield)[9] to 96:4 (75% yield).

(15) For details, see Supporting Information.

(16) (a) Hodgson, D. M.; Stefane, B.; Miles, T. J.; Witherington, J. *Chem. Commun.* **2004**, 2234–2235. (b) Hodgson, D. M.; Stefane, B.; Miles, T. J.; Witherington, J. *J. Org. Chem.* **2006**, *71*, 8510–8515. (c) Hanessian, S.; Del Valle, J. R.; Xue, Y.; Blomberg, N. *J. Am. Chem. Soc.* **2006**, *128*, 10491–10495.

Scheme 3. Asymmetric Synthesis, Oxidation, and Deprotection of Aziridine **7h**

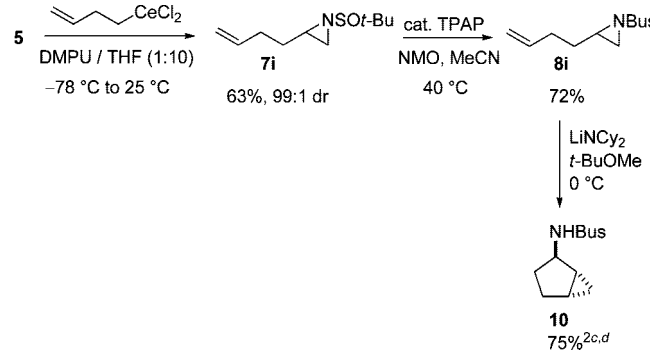


aziridines,[16] and in the present case efficient oxidation of aziridine **7h** to give known sulfonamide (*R*)-**8h**[2d] (87%, 96:4 er by chiral HPLC) illustrates asymmetric access to synthetically valuable terminal *N*-Bus aziridine functionality. The sense of asymmetric induction found using imine **5** with both aryl and alkyl cerium reagents parallels that observed in De Kimpe's study (and in other reports concerning *N*-sulfinyl imines containing α-coordinating groups).[7]

Although deprotection of several *tert*-butylsulfinyl aziridines have been reported, typically using HCl in dioxane,[17] in our hands these methods did not prove viable with terminal aziridines **7**.[18] After extensive screening, it was found that the *tert*-butylsulfinyl group can be rapidly and cleanly removed using aq HI in THF, followed by neutralization with aq KOH (eg, **7h** gave **9h** in 84% yield, and 97:3 er by chiral GC, Scheme 3).

Finally, the chemistry can be extended to illustrate preparation of an unsaturated *N*-Bus terminal aziridine suitable for intramolecular cyclopropanation (Scheme 4). Thus, addition of homoallylcerium dichloride (prepared from homoallylithium)[19] to imine **5** gave *N*-sulfinyl aziridine **7i**

Scheme 4. Synthesis of Unsaturated *N*-Bus Aziridine **8i**



(63% yield, 99:1 dr), and the latter underwent chemoselective oxidation using cat. TPAP/NMO[20] to give unsaturated *N*-Bus aziridine **8i** (72% yield), which has previously been converted into the bicyclic *N*-Bus amine **10**using $LiNCy_2$.[2c,d]

In conclusion, we have developed an efficient and highly diastereoselective access to terminal *N*-*tert*-butylsulfinyl aziridines **7** from readily prepared *t*-$BuSONH_2$-derived *N*-(2-chloroethylidene)*tert*-butylsulfinamide (**5**) and a range of organolithium-derived organoceriums. By using one of the commercially available *t*-$BuSONH_2$ enantiomers we have also demonstrated that the chemistry provides an entry to terminal *N*-Bus aziridine functionality in high er. Deprotection of a terminal *N*-*tert*-butylsulfinyl aziridine, and selective oxidation to *N*-Bus aziridine functionality in the presence of unsaturation are also noteworthy transformations which expand the utility of the methodology.

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Supporting Information Available: Preparation and characterization data for imine **5** and aziridines **7**−**9**, including ^1H and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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(18) The principal authors of refs 17a,c and d have accepted that their published data for material obtained on deprotection are not consistent with that expected for the deprotected aziridines (personal communications with Profs. Stockman, De Kimpe, and Aggarwal).

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(20) Guertin, K. R.; Kende, A. S. *Tetrahedron Lett.* **1993**, *34*, 5369–5372.