Asymmetric Catalysis

General Catalytic Synthesis of Highly Enantiomerically Enriched Terminal Aziridines from Racemic Epoxides**

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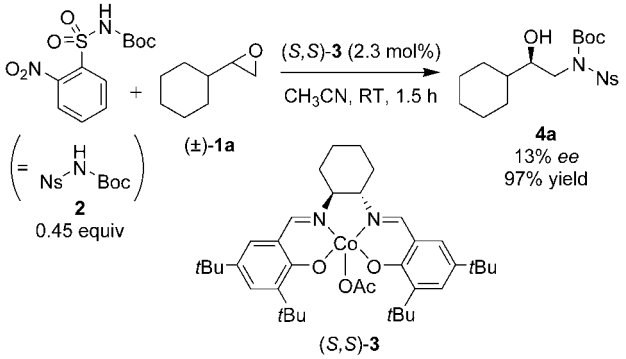
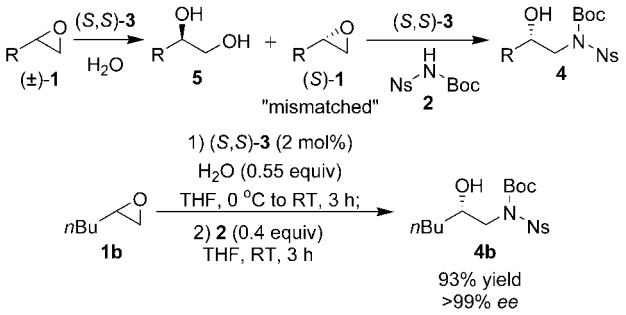
Exploitation of terminal aziridines in organic synthesis has been constrained to a significant extent by the lack of useful methods for their preparation in suitably protected and enantiopure form.[1] Direct enantioselective aziridination of alkene or imine substrates represents a most straightforward approach to these chiral building blocks. However, despite recent advances in the development of effective asymmetric aziridination catalysts,[1a,b,e–j] these have not proven generally useful in the context of terminal aziridine synthesis.[2] At this stage, indirect routes involving preparation and cyclization of 1,2-amino alcohols stand as the most viable alternatives.[1b] We report here a new and practical route to highly enantioenriched (>99% *ee*) 1,2-amino alcohol derivatives from racemic epoxides,[3] and the efficient conversion of these products to terminal aziridines bearing labile *N*-sulfonyl protecting groups. The utility of these aziridines in representative nucleophilic ring-opening reactions is also described.

Enantiomerically enriched 1-azido-2-ols are accessible by the [(salen)Cr]-catalyzed kinetic resolution of terminal epoxides by using trimethylsilyl azide ($TMSN_3$).[4] However, practical concerns associated with the use of azides[5] limit the application of this reaction, and we have sought to identify alternative ammonia equivalents capable of participating in enantioselective epoxide ring-opening reactions. Unfortunately, an extensive screen of nucleophiles led only to modest results in the best cases (e.g. kinetic resolution of vinylcyclohexane oxide (**1a**) with phthalimide is catalyzed by [(salen)Co] complex with $k_{rel}=10$). However, an intriguing result was obtained in attempted kinetic resolutions of terminal epoxides using *N*-Boc-2-nitrobenzenesulfonamide (**2**)[6] as the nucleophilic component (Scheme 1). The reaction of (±)-vinylcyclohexane oxide (**1a**) with 0.45 equivalents of sulfonamide **2** in the presence of [(salen)Co–OAc] complex (*S*,*S*)-**3** provided adduct **4a** in high yield (97% based on **2**) but only 13% *ee*. No reaction was observed in the absence of catalyst, indicating that (*S*,*S*)-**3** promoted addition to both enantiomers of **1a** with very similar rates ($k_{rel}<1.5$). Given that complex **3** is a highly effective catalyst for the hydrolytic kinetic resolution (HKR) of terminal epoxides,[7] this result suggested the possibility of an *indirect* kinetic resolution



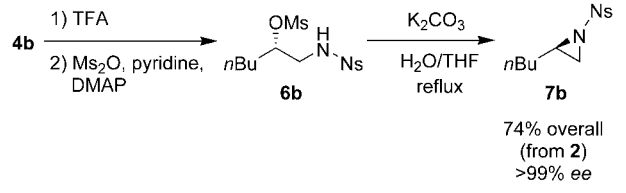
Scheme 1. Kinetic resolution with sulfonamide **2**. Boc = *tert*-butoxycarbonyl, Ns = 2-nitrobenzenesulfonyl.

process with sulfonamide **2**, wherein a highly selective HKR would be followed by ring-opening of the "mismatched", unreacted enantiomer of the epoxide by **2** promoted by the same catalyst (Scheme 2). A one-pot reaction sequence to generate enantiopure adduct **4** could be envisioned, as long as the diol by-product **5** of the HKR did not interfere with the second step. In this manner, the only practical deviation from the original goal of direct kinetic resolution with **2** would be inclusion of water as a co-reagent.



Scheme 2. Indirect kinetic resolution with sulfonamide **2**.

Proof-of-principle was provided through the sequential addition of water (0.55 equiv) and sulfonamide **2** (0.4 equiv) to a solution of (±)-1,2-epoxyhexane (**1b**) and catalyst (*S*,*S*)-**3** in THF, which afforded **4b** in >99% *ee* and 93% yield based on **2** (Scheme 2).[8] Product isolation was effected simply by filtration of the crude reaction mixture through a pad of silica gel. Compound **4b** was then transformed to the corresponding *N*-nosylaziridine by removal of the Boc group, conversion to the *O*-mesylate, and cyclization with K_2CO_3 (Scheme 3).[9]



Scheme 3. Synthesis of *N*-Ns-butylaziridine (**7b**). TFA = trifluoroacetic acid, DMAP = 4-dimethylaminopyridine, Ms = methanesulfonyl.

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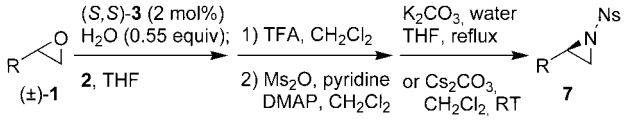
The overall process afforded analytically pure aziridine **7b** in >99% *ee* and 74% yield based on **2** as limiting reagent, with only one chromatographic purification in the sequence.

The scope of the aziridine synthesis is summarized in Table 1. A range of terminal aziridines bearing aliphatic substituents of varying steric demand (**7a**–**7c**) was accessed in high enantiomeruc excess. The synthesis of the methyl glycidate derived aziridine **7d** required a modified procedure (Cs_2CO_3/CH_2Cl_2/room temperature) to prevent ester hydrolysis in the aziridine ring-closure. Successful preparation of highly enantioenriched chloromethylaziridine **7e** also relied on these modified conditions, because elevated reaction temperatures in the cyclization resulted in partial racemization by the reversible formation of the achiral dichloride derivative. The intermediate mesylate **6e** was recrystallized from EtOAc, and **7e** was isolated in pure form simply by filtration through a silica pad. Aziridine **7e** was thus synthesized on an 8.4 mmol (2.3 g) scale without recourse to column chromatography. This constitutes the first synthesis of this very interesting building block in enantiopure form (vide infra).[10]

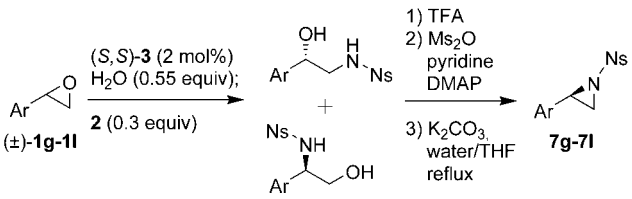
Table 1: Syntheses of nosyl-protected terminal aziridines.[a]



Aziridine	R	Yield [%][b]	*ee* [%][c]	Method[d]
7a	*c*Hex	86	>99	A
7b	*n*Bu	79	>99	A
7c	*t*Bu	67	99.8	A
7d	CO_2Me	69	>99	B
7e	CH_2Cl	75	>99	B
7f	1-butene	58	>99	A
7g	Ph	81	98.9	C
7h	3-ClPh	82	99.9	C
7i	2-ClPh	81	99.8	C
7j	4-ClPh	85	99.5	C
7k	3-MeOPh	80	99.4	C
7l	3-NO_2Ph	72	99.7	C

[a] Reactions were carried out with 2.5 mmol of epoxide. [b] Yield of isolated product based on **2**. [c] The enantioselectivities were determined by HPLC by using a commercially available chiral stationary phase. For details, see Supporting Information. [d] Method A: 0.4 equivalents of **2** and saturated aqueous K_2CO_3/THF (1/9), reflux in the last step. Method B: 0.4 equivalents of **2** and 1.1 equivalents of Cs_2CO_3, CH_2Cl_2, RT in the last step. Method C: 0.3 equivalents of **2** and O_2 atmosphere in the first step, column chromatography performed after the second step and saturated aqueous K_2CO_3/THF (1/9), reflux in the last step.

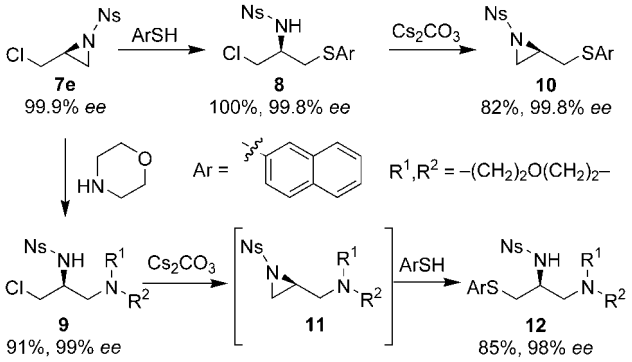
Arylaziridine derivatives (**7g**–**7l**) were also synthesized in high enantiomeric excess, with consistent results obtained for a variety of aryl substituents. Ring-opening of styrene oxide derivatives with sulfonamide **2** occurred with modest regioselectivity to afford mixtures of isomeric amino alcohol adducts. However, separation of these products proved unnecessary, as both isomers were transformed to the same aziridine enantiomer by using the deprotection/mesylation/cyclization protocol (Scheme 4).



Scheme 4. Synthesis of *N*-Ns-arylaziridines.

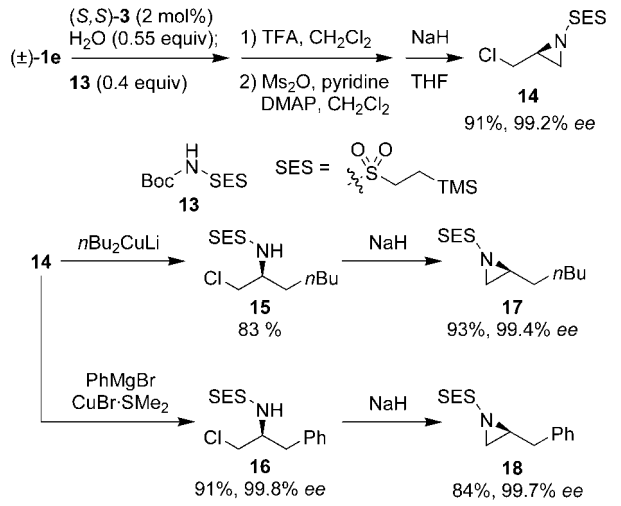
The *N*-nosyl protecting group imparts several useful properties to the terminal aziridine derivatives. For example, nosylaziridines are 50–60 times more reactive toward nucleophilic addition than the corresponding tosylaziridines;[11] in addition, *N*-nosyl amines obtained after aziridine ring-opening are alkylated and/or deprotected selectively under mild conditions.[12]

Compound **7e**, an aziridine analogue of epichlorohydrin, displays a range of useful reactivity reminiscent of its epoxide counterpart.[13] For example, it may be elaborated to other *N*-nosylaziridine derivatives through a simple two-step nucleophilic ring-opening/base-induced cyclization sequence (Scheme 5). This methodology affords convenient access to aziridines in cases in which the corresponding racemic epoxides are either poor substrates for the HKR (due to the presence of strongly Lewis basic functionality) or too precious to be used practically in a resolution process.



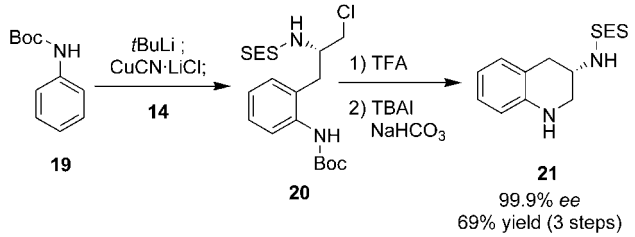
Scheme 5. Representative transformations of *N*-Ns-chloromethylaziridine (**7e**).

Nitro groups are not compatible with strongly basic carbon nucleophiles,[14] and this imposes a significant limitation on the utility of *N*-nosylaziridines in ring-opening reactions. In contrast, the 2-(trimethylsilyl)ethanesulfonyl-(SES-) protecting group is compatible with anionic carbon nucleophiles and is easily removed by treatment with fluoride ion.[15] *N*-SES-protected chloromethylaziridine **14** was synthesized in 91% yield and 99.2% *ee* from **13**[16] by using a method similar to that applied in the synthesis of **7e** (Scheme 6).[17] Aziridine **14** underwent clean reaction with both alkyl and aryl cuprates to afford the corresponding ring-opening products **15** and **16**. These were converted smoothly to the highly enantioenriched aziridines **17** and **18** with NaH. Aziridine **14** was also used in the asymmetric synthesis of 3-



Scheme 6. Synthesis of *N*-SES-chloromethylaziridine (**14**) and its applications. SES = 2-(trimethylsilyl)ethanesulfonyl.

aminotetrahydroquinoline[18] (Scheme 7). The cuprate generated from the dianion of **19** and CuCN·LiCl underwent reaction with **14** to afford the ring-opening product **20**. Deprotection followed by cyclization in the presence of added iodide afforded 3-aminotetrahydroquinoline **21**.



Scheme 7. Synthesis of 3-aminotetrahydroquinoline **21**. TBAI = tetrabutylammonium iodide.

In summary, a general asymmetric catalytic method for the preparation of highly enantiomerically enriched *N*-sulfonylated terminal aziridines has been devised. Enantiopure chloromethylaziridines **7e** and **14** were synthesized for the first time, and the synthetic utility of these difunctional building blocks was demonstrated. Current efforts are directed toward elucidation of the mechanism of the reaction between epoxides and **2** and toward synthetic extensions and applications of this methodology.

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Keywords: asymmetric catalysis · aziridines · nitrogen heterocycles · small ring systems · sulfonamides

[1] For reviews on the preparation and reactions of aziridines, see: a) J. B. Sweeney, *Chem. Soc. Rev.* **2002**, *31*, 247–258; b) V. H. Dahanukar, I. A. Zavialov, *Curr. Opin. Drug Discovery Dev.* **2002**, *5*, 918–927; c) W. McCoull, F. A. Davis, *Synthesis* **2000**, 1347–1365; d) H. Stamm, *J. Prakt. Chem.* **1999**, *341*, 319–331; e) D. Tanner, *Angew. Chem.* **1994**, *106*, 625–646; *Angew. Chem. Int. Ed. Engl.* **1994**, *33*, 599–619; f) P. Müller, C. Fruit, *Chem. Rev.* **2003**, *103*, 2905–2919; g) E. N. Jacobsen in *Comprehensive Asymmetric Catalysis, Vol. 2* (Eds.: E. N. Jacobsen, A. Pfaltz, H. Yamamoto), Springer, Berlin, **1999**, pp. 607–618; h) R. S. Atkinson, *Tetrahedron* **1999**, *55*, 1519–1559; i) H. M. I. Osborn, J. Sweeney, *Tetrahedron: Asymmetry* **1997**, *8*, 1693–1715.

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[8] Simultaneous addition of the two reagents led to inferior results, consistent with the observation that the rates of epoxide hydrolysis and ring-opening with **2** are competitive.

[9] Synthesis of **7b** under Mitsunobu conditions proceeded in low yield (44%) as a result of the instability of the nosylaziridine to the reaction conditions.

[10] For racemic syntheses, see: a) R. S. Atkinson, E. Barker, S. Ulukanli, *J. Chem. Soc. Perkin Trans. 1* **1998**, 583–589; b) R. S. Atkinson, M. P. Coogan, C. L. Cornell, *J. Chem. Soc. Perkin Trans. 1* **1996**, 157–166; c) R. S. Atkinson, B. J. Kelly, *J. Chem. Soc. Perkin Trans. 1* **1989**, 1627–1630.

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[13] Compound **7e** undergoes decomposition upon storage as a neat liquid, but was stored safely for prolonged periods as a frozen 0.78 M solution in benzene at −30 °C.

[14] a) A. Ricci, M. Fochi, *Angew. Chem.* **2003**, *115*, 1482–1484; *Angew. Chem. Int. Ed.* **2003**, *42*, 1444–1446; b) G. Köbrich, P. Buck, *Angew. Chem.* **1966**, *78*, 1062–1063; *Angew. Chem. Int. Ed. Engl.* **1966**, *5*, 1044.

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[17] NaH was employed in the final cyclization step because the corresponding reaction with Cs_2CO_3 proved much slower. Thus, the NaH reaction was completed in 30 min, whereas the Cs_2CO_3 reaction required 23 h.

[18] 3-Aminotetrahydroquinoline is the core structure of sumanirole, a drug candidate for the treatment of Parkinson's disease. a) P. G. M. Wuts, R. L. Gu, J. M. Northuis, T. A. Kwan, D. M. Beck, M. J. White, *Pure Appl. Chem.* **2002**, *74*, 1359–1368; b) P. G. M. Wuts, *Curr. Opin. Drug Discovery Dev.* **1999**, *2*, 557–564.

