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General Access to Chiral *N*-Alkyl Terminal Aziridines via Organocatalysis

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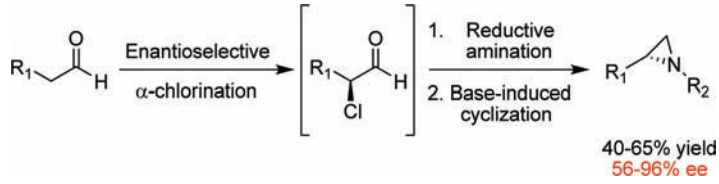
ABSTRACT

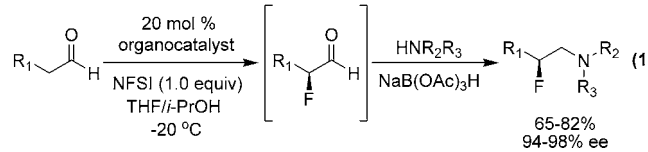


A three step, one-pot protocol involving enantioselective α-chlorination of aldehydes, subsequent reductive amination with a primary amine, and S_N2 displacement to afford chiral *N*-alkyl terminal aziridines in 40−65% yield (74−87%/step) and, in most cases, >90% ee is reported.

Aziridines represent an important class of nitrogen heterocycles with a wide range of synthetic utility and prevalence in natural products.[1] Despite their value, synthetic routes to aziridines are limited in terms of generality and diversity of the *N*-substituent. Classical methods for the synthesis of terminal aziridines include nitrene transfer to olefins,[2] carbene methodology,[3] aza-Darzens approaches,[4] addition/elimination sequences,[5] and ylide-mediated strategies.[6] For many of these tactics, the *N*-substituent is typically a *p*-toluenesulfonyl moiety or other electron-withdrawing group.[1,2] The synthesis of chiral terminal aziridines with diversity at the *N*-substituent is extremely rare.[1] One recent example was reported for the synthesis of terminal diarylaziridines by the enantioselective reductive amination of α-chloroketones.[7] Here, we report a general one-pot protocol for the enantioselective synthesis of *N*-alkyl terminal aziridines via organocatalysis.

We recently reported on a one-pot protocol for the enantioselective α-fluorination of aldehydes, followed by reductive amination to produce pharmaceutically relevant chiral *β*-fluoroamines (Figure 1, eq 1).[8,9] Previously, both MacMillan[11] and Jørgensen[12] disclosed the enantioselective α-chlorination of aldehydes via organocatalysis. Based on this precedent and our chiral *β*-fluoroamine work, we envisioned a three-step, one-pot protocol involving enanti-

Chiral β-Fluoroamines via Organocatalysis



Chiral *N*-Alkyl Terminal Aziridines via Organocatalysis

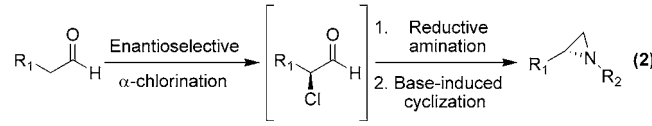


Figure 1. Organocatalytic approach to chiral *β*-fluoroamines and envisioned route to chiral *N*-alkyl terminal aziridines.

(1) For a recent review on the asymmetric synthesis of aziridines, see: Pellissier, H. *Tetrahedron* **2010**, *66*, 1509.
(2) Li, Z.; Cosner, K. R.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1993**, *115*, 5326.
(3) Badea, F.; Condeiu, C.; Gherighiu, M.; Iordache, A.; Simion, C. *Rev. Roum. Chim.* **1992**, *37*, 393.
(4) Davis, F. A.; Wu, Y.; Yan, H.; McCoull, W.; Prasad, K. R. *J. Org. Chem.* **2003**, *68*, 2410.
(5) Barros, M. T.; Matias, P. M.; Maycock, C. D.; Ventura, M. R. *Org. Lett.* **2003**, *5*, 4321.
(6) Davis, F. A.; Zhou, P.; Liang, C.-H.; Reddy, R. E. *Tetrahderon: Asymmetry* **1995**, *6*, 1511.
(7) Malkov, A. V.; Stončius, S.; Kočovský, P. *Angew. Chem.* **2007**, *119*, 3722.

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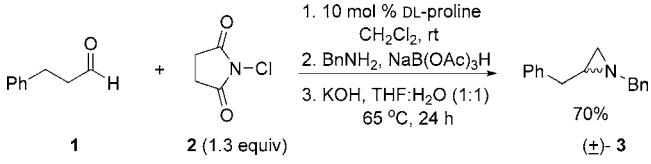
oselective α-chlorination of aldehydes, subsequent reductive amination with a primary amine, and S_N2 displacement to afford previously unattainable chiral terminal aziridines with a wide range of *N*-substituents (Figure 1, eq 2). Overall, this new approach represents the effective addition of a primary amine across an olefin to form aziridines and is a notable extension of the Linchpin SOMO catalysis concept to access chiral epoxides reported by MacMillan.[10]

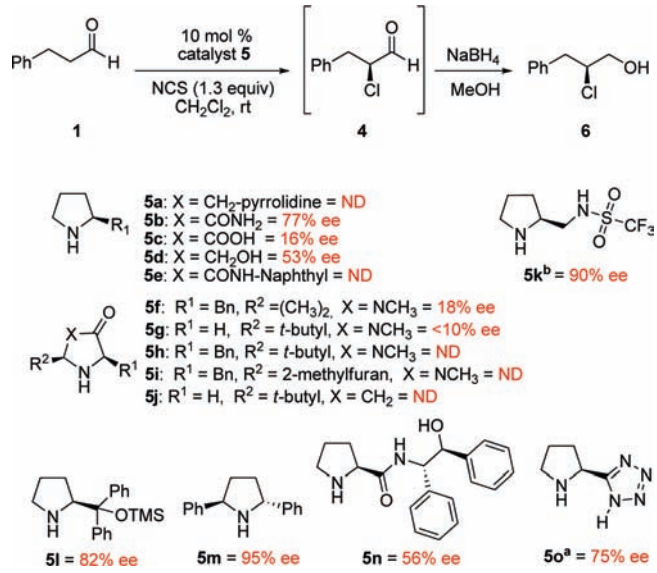
For a one-pot protocol involving a reductive amination step, we could not use the MacMillan α-chlorination chemistry, as that route employed a chloroquinone as the chlorinating agent and acetone as a solvent.[11] The Jørgensen route was attractive, as NCS was the chlorinating agent, and the optimized solvent was DCE.[12] We first set out to determine if this proposal would allow access to racemic *N*-alkyl terminal aziridines. Thus, DL-proline-catalyzed α-chlorination of **1** with NCS **2**, followed by reductive amination with benzylamine and subsequent base-induced S_N2 cyclization with KOH in THF/H_2O at 65 °C, did provide racemic aziridine **3** in 70% yield (Scheme 1) for the three step, one-pot protocol (average of 90% per step). Importantly, KOH was critical for the production of **3**, as a screen of organic (ie., Et_3N, pyridine, DBU, KO-*t*-Bu) and inorganic bases (ie., NaH, K_2CO_3) provided less than 50% conversion to **3**.[13]

Scheme 1. One-Pot Protocol for Racemic *N*-Alkyl Terminal Aziridines



Efforts now focused on developing an enantioselective one-pot protocol. To ensure we had optimal conditions for the enantioselective α-chlorination of **1**, we elected to survey a set of 15 organocatalysts **5a**−**o** employing NCS as the chlorinating agent and DCM as the solvent. This study demonstrated that the Jørgensen[11] catalyst **5m** was indeed optimal, affording **4** in >97% conversion. In order to determine the degree of enantioselectivity by chiral HPLC, **4** was reduced to the corresponding *β*-chloroalcohol **6** and found to possess 95% ee (Scheme 2). Organocatalysts **5k**, **5l**, **5n**, and **5o** never before employed for this transformation

Scheme 2. Enantioselective α-Chlorination of Hydrocinnamaldehyde*

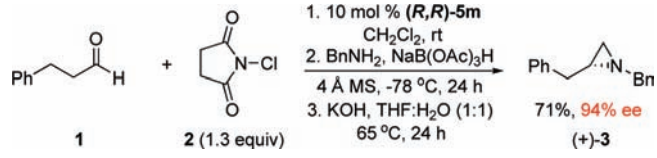


* All reactions were 0.05 mmol scale. Enantiomeric ratios were measured using chiral stationary-phase HPLC. [a] 5 mol % catalyst loading. ND = not determined. [b] Reaction performed at −20 °C for 24 h.

afforded comparable conversion (>95%), but lower enantioselectivity (56−90% ee).

With optimal α-chlorination conditions in hand, we attempted the three step, one-pot protocol to deliver **3** enantioselectively. Utilizing the protocol in Scheme 1, but replacing DL-proline with **5m**, we were disappointed to find that this approach afforded **3** in comparable yield, but in less than 40% ee. Thus, we investigated the most probable source of epimerization in the sequence: the room-temperature reductive amination step. Molecular sieves proved essential, and we found a direct correlation between enantioselectivity and temperature. As shown in Scheme 3, reducing the temperature for the reductive amination step to −78 °C resulted in the enantioselective synthesis of aziridine **3** in 71% yield for the three steps (∼90% per step) and 94% ee. As expected, the (*S*,*S*)-**5m** catalyst afforded the opposite enantiomer of **3** in good yield (74%) and excellent enantioselectivity (95% ee).

Scheme 3. One-Pot Protocol for Chiral *N*-Alkyl Terminal Aziridines



As shown in Scheme 4, the reaction scope is general with respect to both aldehyde and amine, providing chiral terminal

(8) Fadeyi, O. O.; Lindsley, C. W. *Org. Lett.* **2009**, *11*, 943.

(9) For the initial disclosures of organocatalytic α-fluorination of aldehydes, see: (a) Beeson, T. D.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2005**, *127*, 8826. (b) Marigo, M.; Fielenbach, D.; Braunton, A.; Kjaersgaard, A.; Jørgensen, K. A. *Angew Chem., Int. Ed.* **2005**, *44*, 3703. (c) Steiner, D. D.; Mase, N.; Barbas, C. F., III *Angew Chem., Int. Ed.* **2005**, *44*, 3706.

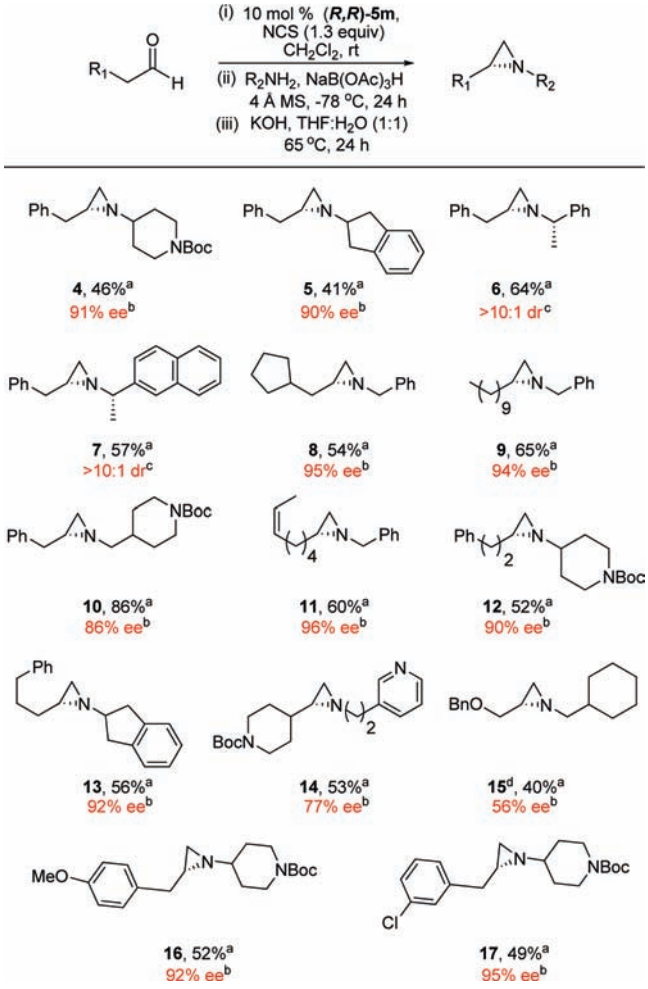
(10) Amatore, M.; Beeson, T. D.; Brown, S. P.; MacMillan, D. W. C. *Angew Chem., Int. Ed.* **2009**, *48*, 5121.

(11) Brochu, M. P.; Brown, S. P.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2004**, *126*, 4108.

(12) (a) Halland, N.; Braunton, A.; Bachmann, S.; Marigo, M.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2004**, *126*, 4790. (b) Marigo, M.; Bachmann, S.; Halland, N.; Braunton, A.; Jørgensen, K. A. *Angew Chem. Int. Ed.* **2004**, *43*, 5507.

(13) See the Supporting Information for full details.

Scheme 4. Substrate Scope of Enantioselective *N*-Alkyl Terminal Aziridines*

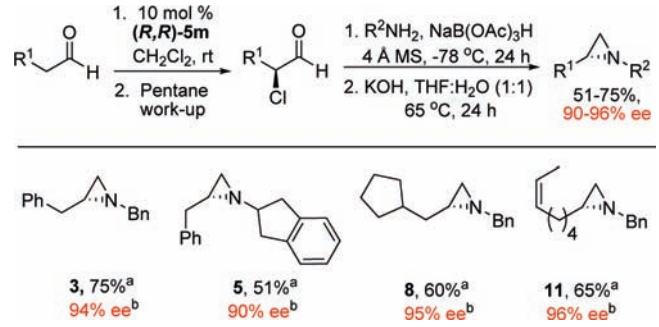


* All reactions were 0.50 M in substrate and proceeded to complete conversion. [a] Yield after chromatography. [b] Enantiomeric excess detremined by chiral HPLC or SFC analysis. [c] Diastereomeric ratio determined via NMR experiments using chiral solvating agents (Pirkle alcohol).[14] [d] Because homoaldol product formation occurred at −20 °C with use of **5m**, catalyst **5o** was used.

N-alkyl aziridines **4**−**17** in overall yields of 40−65% (74−87% per step) and, in most cases, >90% ee for the three step, one-pot protocol. Determining the enantioselectivity required classical reversed-phase chiral HPLC, SFC, or NMR chiral shift reagents.[13]

(14) Pirkle, W. H.; Sikkenga, D. L.; Pavlin, M. S. *J. Org. Chem.* **1977**, *42*, 384.

Scheme 5. Two-Pot Protocol for Chiral *N*-Alkyl Terminal Aziridines*



* All reactions were 0.50 M in substrate and proceeded to complete conversion. [a] Yield after chromatography. [b] Enantiomeric excess determined by chiral HPLC or SFC analysis.

Finally, modest improvements in yield and comparable enantioselectivty were observed if we performed a workup after the α-chlorination step. The addition of pentane to the crude reaction mixture precipitated both the succinimide and organocatalyst **5m**. Removal of the pentane, concentration, resupsension in CH_2Cl_2, and proceeding with the reductive amination and base-induced cyclization steps now provided *N*-alkyl terminal aziridines in 51−75% yield and >90% ee (Scheme 5); however, isolation proved more facile.

In summary, we have developed a three step, one-pot protocol for the *general* enantioselective synthesis of terminal *N*-alkyl aziridines via organocatalysis. This new methodology provides access to aziridines that were previously difficult to prepare, utilizing aldehydes and amines for which thousands are commercially available.

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Supporting Information Available: Complete experimental procedures, compound characterization, chiral HPLC/SFC analysis, and supplemental tables. This material is free of charge via the Internet at http://pubs.acs.org.

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