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 MacMillan11 and Jørgensen12 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 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.

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.
oselective α-chlorination of aldehydes, subsequent reductive amination with a primary amine, and S_{\text{N}}2 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.\(^\text{10}\)

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.\(^\text{11}\) The Jørgensen route was attractive, as NCS was the chlorinating agent, and the optimized solvent was DCE.\(^\text{12}\) 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 was followed by reductive amination with benzylamine and subsequent base-induced S_{\text{N}}2 cyclization with KOH in THF/H\(_2\)O 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\(_3\)N, pyridine, DBU, KO-t-Bu) and inorganic bases (ie., NaH, K\(_2\)CO\(_3\)) provided less than 50% conversion to 3.\(^\text{13}\)

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\(^\text{11}\) 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 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).

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

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

\[
\begin{align*}
1. & \quad 10 \text{ mol } \% \text{ DL-proline} \\
2. & \quad \text{CH}_2\text{Cl}_2, \text{rt} \\
3. & \quad 2 \text{ (1.3 equiv)} \\
4. & \quad \text{BrNH}_2, \text{NaB(OAc)}_2 \text{H} \\
5. & \quad \text{KOH, THF/H}_2\text{O (1:1)} \\
6. & \quad 65 ^\circ \text{C, 24 h} \\
\end{align*}
\]

\(\text{70% yield} \quad (+)\text{-}3\)

(13) See the Supporting Information for full details.
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

Finally, modest improvements in yield and comparable enantioselectivity 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, resuspension in CH₂Cl₂, 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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