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A General, Enantioselective Synthesis of Protected Morpholines and Piperazines

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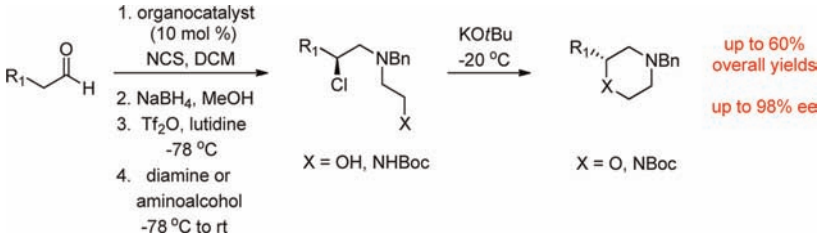
ABSTRACT



A short, high yielding protocol has been developed for the enantioselective and general synthesis of C2-functionalized, benzyl protected morpholines and orthogonally *N,N′*-protected piperazines from a common intermediate.

Morpholines and piperazines are saturated aza-heterocycles commonly employed as bases in organic synthesis.[1] These heterocycles have also become key components of pharmaceutical compositions, typically with chiral *C*-functionalization at C2.[2,3] However, chemistry to access enantiopure C2-functionalized morpholines and piperazines is limited, relying on the chiral pool, stoichiometric auxilaries, or HPLC resolution of racemic mixtures.[1−6] Based on our earlier efforts to access chiral β-fluoroamines and *N*-termial aziridines via organocatalysis,[7−9] we applied this strategy to the enantioselective synthesis of C2-functionalized morpholines and piperazines (Figure 1). Here, an organocatalytic, enantioselective chlorination of aldehyde **1** produced **2**,[10,11] which was used without purification. A subsequent reductive amination step occurred with an amine containing an embedded 'O' or 'N' nucleophile (**3** or **4**), such that, after base-induced cyclization of either **5** or **6**, *N*-benzyl protected morpholines **7** and orthogonally *N*,*N*′-protected piperazines **8**, respectively, were prepared with C2-functionalization.[12] While this result was gratifying, the methodology suffered from two key limitations: (1) the

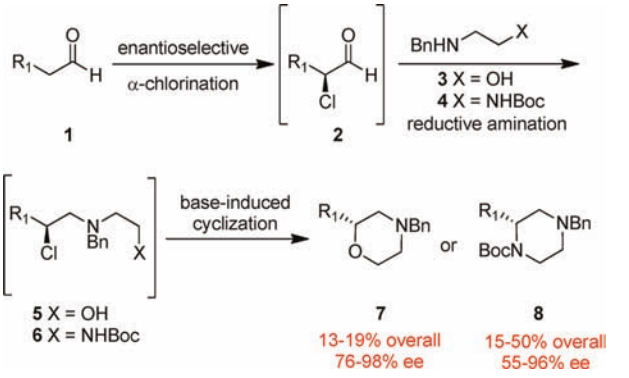


Figure 1. First generation organocatalytic approach for the enantioselective synthesis of C2-functionalized, *N*-protected morpholine and orthogonally *N*,*N*′-protected piperazines.

(1) Wijtmans, R.; Vink, M. K. S.; Schoemaker, H. E.; van Delft, F. L.; Blaauw, R. H. *Synthesis* **2004**, *5*, 641–662 and references therein.
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(3) Stachel, S. J.; Steele, T. G.; Petrocchi, A.; Haugbook, S. J.; McGaughey, G.; Holloway, K. M.; Allison, T.; Munshi, S.; Zuck, P.; Colussi, D.; Tugasheva, K.; Woolfe, A.; Graham, S. L.; Vacca, J. P. *Bioorg. Med. Chem. Lett.* **2012**, *22*, 240–244.
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(8) Schulte, M. L.; Lindsley, C. W. *Org. Lett.* **2011**, *13*, 5684–5687.
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three-step overall yield was low (13−50%) and (2) the % ee was variable (55−98% ee) due to the epimerization prone α-chloroaldehyde **2**. In fact, one trial where the α-chloroaldehyde **2** was left on the bench for hours prior to subsequent reductive amination led to a % ee erosion of greater than 30%. Furthermore, four separate trials of this reaction sequence, with immediate use of the chloroaldehyde, afforded 78−94% ee immediately upon generation. In addition to varying % ee, the incipient imine could also be attacked by the latent oxygen nucleophile to form an undesired hemiaminal that further compromised yields, leading to recovered aldehyde starting material upon workup. Thus, in this Letter, we report a general, high yielding solution for the enantioselective synthesis of these valuable aza-heterocycles that overcomes the limitations of the first generation approach affording good overall yields and high enantioselectivities.

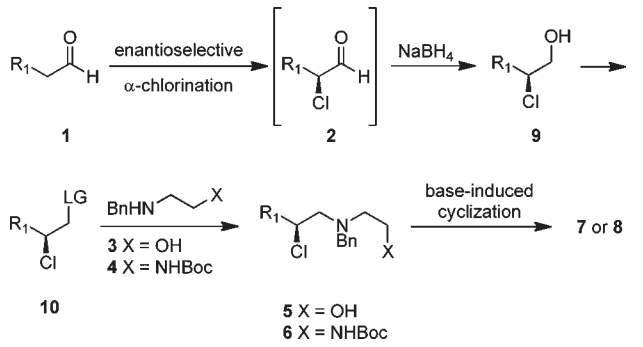
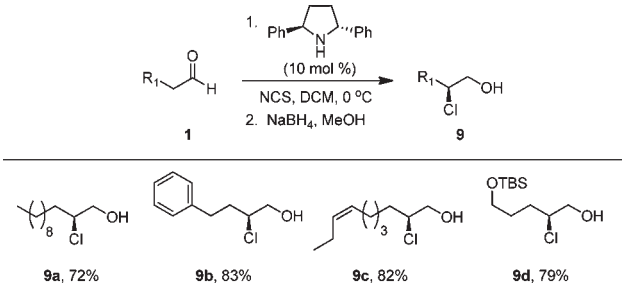


Figure 2. Envisioned second generation organocatalytic approach for the enantioselective synthesis of C2-functionalized, *N*-protected morpholine and orthogonally *N*,*N*′-protected piperazine.

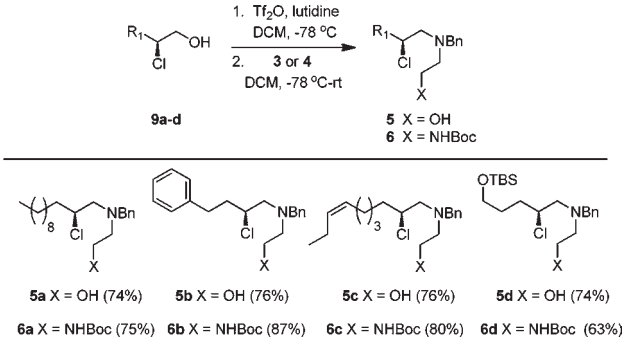
In the original Jørgensen methodology for the organocatalytic α-chlorination of aldehydes,[10,11] the aldehydes could be immediately reduced with $NaBH_4$ to the corresponding 2-chloro alcohols **9** without any loss in enantioselectivity; moreover, the alcohol derivatives were configurationally stable. Thus, if we could convert the hydroxyl moiety of the 2-chloro alcohol into an efficient leaving group **10**, followed by a chemoselective displacement by **3** or **4**, substrates **5** or **6** would result which could be smoothly cyclized to form either **7** or **8** (Figure 2). This envisioned approach was attractive as it would eliminate the variable % ee, avoid the undesired hemiaminal formation, and, thus, improve the overall yields of **7** and **8**.

To test this new approach, we prepared various 2-chloro alcohol substrates **9a**−**d** under standard conditions in high yield (72−83%) over two steps and in high enantioselectivity (80−98% ee) as expected from literature precedent (Scheme 1).[10−12] Now the challenge was to convert **9a**−**d** into the appropriate *bis*-electrophile that would allow for a

Scheme 1. Organocatalytic, Enantioselective Synthesis of 2-Chloro Alcohols **9a**−**d**

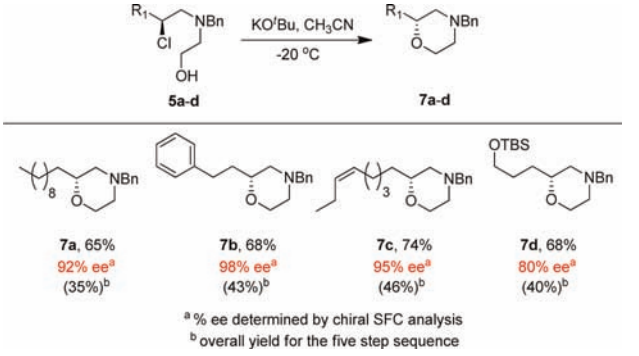


Scheme 2. Synthesis of Cyclization Substrates **5a**−**d** and **6a**−**d**



chemoselective displacement of the primary leaving group, something not yet reported in the literature. After surveying a number of potential primary leaving groups (mesylate, tosylate, and iodide), the triflate emerged as the optimal moiety to deliver congeners of **5** and **6**. Here, treatment of **9a**−**d** with triflic anhydride in DCM with lutidine at −78 °C smoothly generated the corresponding triflates, which were then immediately exposed to either secondary amine **3** or **4** to generate **5a**−**d** and **6a**−**d** (Scheme 2) in good yields (63−87%) for the two-step sequence.

Scheme 3. Enantiospecific Cyclization To Afford Morpholines **7a**−**d**

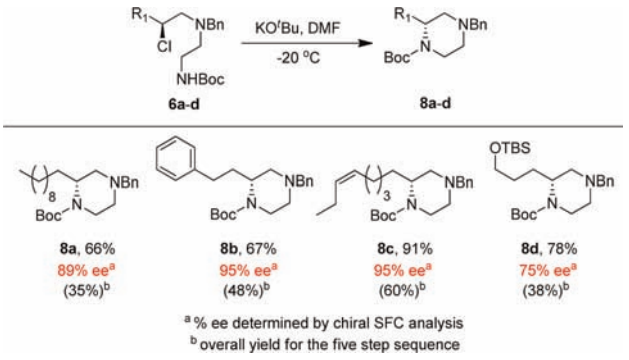


With **5a**−**d** in hand, we employed our optimized cyclization conditions (KO^{t}Bu, CH_3CN, −20 °C) to afford

(10) Halland, N.; Braunton, A.; Bachmann, S.; Marigo, M.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2004**, *126*, 4790–4791.
(11) Marigo, M.; Bachmann, S.; Halland, N.; Braunton, A.; Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2004**, *43*, 5507–5510.
(12) O'Reilly, M. C.; Lindsley, C. W. *Tetrahedron Lett.* **2012**, *53*, 1539–1542.

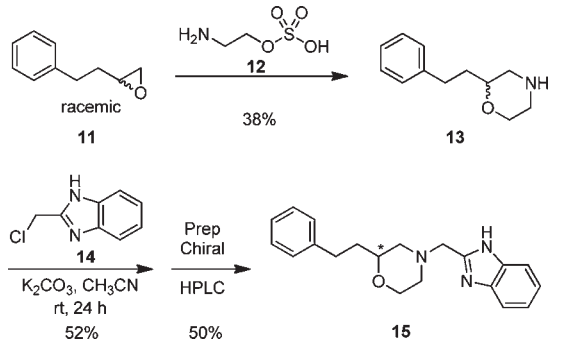
N-benzyl protected morpholines **7a**–**d** (Scheme 3) in good yield (65–74%) and with excellent enantioselectivities (80–98% ee). The only marginal % ee was in the silyl ether substrate **7d**, which resulted from the initial α-chlorination step, and was expected based on literature precedent.[10,11] Overall yields for **7a**–**d** from the commercial aldehydes ranged from 35 to 46% for the new five-step sequence, a notable improvement over the 13–19% overall yields of the first generation, three-step approach as well as improved % ee.[12]

Scheme 4. Enantiospecific Cyclization To Afford Orthogonally *N,N′*-Protected Piperazines **8a**–**d**



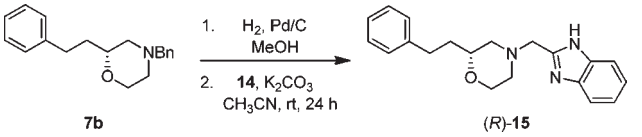
In a similar fashion (Scheme 4), but employing DMF as the solvent, orthogonally *N,N′*-protected piperazines **8a**–**d** were arrived at in good yields (66–91%) and with high enantioselectivities (75–95% ee). As discussed earlier, the one low % ee was due to the substrate. Once again, this new methodology afforded comparable or improved overall yields (35–60%) for the five-step sequence and uniformly high % ee relative to the first generation approach (15–50% overall yields and 55–96% ee). Thus, this new five-step sequence for the enantioselective synthesis of C2-functionalized, *N*-protected morpholines and piperazines affords access to these valuable aza-heterocycles that often cannot be accessed readily.

Scheme 5. Published Synthesis of Morpholine **15**



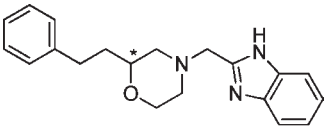
Finally, we applied this new methodolgy to a pharmaceutically relevant morpholine target with antipsychotic activity from the patent literature.[13] Chiral morpholine **15**, reported to be a specific dopamine subtype 4 (D_4) antagonist,[6] was previously prepared in three steps, including a preparative chiral HPLC separation, in 9.9% overall yield (Scheme 5). Though they claim a single enantiomer of **15** to be more preferred, they did not disclose the absolute stereochemistry or the differences in D_4 potency.

Scheme 6. Enantioselective Synthesis of (*R*)-Morpholine **15**



Therefore, we took advantage of already synthesized enantiopure (*R*)-morpholine **7b**, removed the benzyl protecting group via hydrogenation, and alkylated with **14** to deliver (*R*)-**15** (Scheme 6). In contrast to the known route, our methodology provided enantiopure (*R*)-**15** in 98% ee and in 35% overall yield, a significant improvement. In a similar manner, racemic **15** was prepared, according to Figure 2 utilizing D,L-proline as the organocatalyst, as well as (*S*)-**15**, and all three were evaluated against the full dopamine family of receptors, D_1–D_4, in both radioligand binding (K_i) and functional (IC_{50}) assays (Table 1).[14] Racemic (±)-**15** is devoid of activity at D_1 and D_2 (K_i and IC_{50}'s $>100\ \mu M$), and highly selective for D_4 versus D_3 (K_i and IC_{50} $>10\ \mu M$). Upon evaluation of the pure enantiomers (*R*)-**15** and (*S*)-**15**, enantiospecific activity is clearly present. As shown in Table 1, (*S*)-**15** is uniformly inactive against D_1–D_4 (IC_{50}'s $> 25\ \mu M$); however, (*R*)-**15** is twice as potent (D_4 $K_i = 0.07\ \mu M$, $IC_{50} = 0.18\ \mu M$) as racemic (±)-**15**, indicating that all of the activity of the racemate is due to the (*R*)-enantiomer. These data further highlight the utility of our methodology to afford high yielding, enantioenriched access to chiral, C2-functionalized morpholines and piperazines.

Table 1. Biological Activity Data at D_1–D_4 for Racemic and Enantiopure Isomers of Morpholine **15**



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	D_1[a]		D_2[a]		D_3[a]		D_4[a]	
compd	K_i	IC_{50}	K_i	IC_{50}	K_i	IC_{50}	K_i	IC_{50}
(±)-**15**	>100	>100	>100	>100	10.8	31.8	0.14	0.36
(*R*)-**15**	>100	>100	>100	>100	15.7	46.2	0.07	0.18
(*S*)-**15**	>100	>100	>100	>100	25.9	76.4	>100	>100

[a] K_i and IC_{50} values are in μM and represent at least three measurements.

(13) Merck, Sharpe &Dohme: WO95/14690, 1995.

In summary, we have developed an optimized five-step procedure for the enantioselective synthesis of *N*-benzyl protected morpholines and orthogonally *N*,*N*′-protected piperazines with chiral alkyl groups installed at the C2 position of each heterocyclic core via organocatalysis. This methodology allows for the rapid preparation of functionalized, pharmaceutically relevant morpholines and piperazines in 35−60% overall yields and in 75−98% ee. This new methodology addresses the major shortcomings (variable % ee and low overall yields) of our first generation approach. Of major significance, this methodology does not rely on the chiral pool; instead we can employ simple aldehydes and commercial organocatalysts, thereby allowing access to either enantiomer of the corresponding morpholines and piperazines. Application of this new methodology to the synthesis and biological evaluation of a known D_4 antagonist further highlights the power of the methodology and sheds light on the enantioselective inhibition of dopamine receptors. Additional refinements are under development and will be reported in due course.

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Supporting Information Available. Experimental procedures, characterization data, chiral HPLC traces, and ^1H and ^{13}C NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

(14) Biology performed at Ricerca: www.ricerca.com.

The authors declare no competing financial interest.