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Enantioselective synthesis of C2-functionalized, N-protected morpholines and orthogonally N,N′-protected piperazines via organocatalysis

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Abstract

In this Letter, we describe a novel three-step, one-pot 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 morpholines and piperazines that are not readily accessible through any other chemistry in good to excellent % ee (55–98% ee).

Keywords

Morpholine; Piperazine; Enantioselective; Organocatalysis; Cyclization

Both morpholines (**1**) and piperazines (**2**) are widely used azaheterocyclic bases in organic synthesis;[1] furthermore, they are a frequently found component in both natural products and pharmaceutical compositions,[1–3] finding applications as key pharmacophores in antidepressants (**3**),[4] antibiotics (**4**),[5] antipsychotics (**5**),[6] anticancer agents (**6**)[7] and antihypertensive agents (**7**)[8] (Fig. 1). Many of the pharmacologically relevant congeners possess chiral C-functionalization, frequently at C2.[1] Importantly, synthetic chemistry to access enantiomerically pure C2-functionalized morpholines and piperazines is limited.[1] The majority of synthetic efforts rely either on the resolution of racemic mixtures, or employ enantiopure amino alcohols and amino acids accessible from the chiral pool.[1,9] Alas, reliance on the chiral pool limits the structural diversity of C2-functionalized congeners, decreasing the synthetic versatility of these methods.[1] Recently, alternative approaches to these scaffolds are beginning to appear.[10–13] With our NIH sponsored Molecular Probe Center Network (MLPCN) efforts,[14] many screening hits are based on these motifs, and we required new synthetic methods to enable rapid lead optimization campaigns. In this Letter, we describe a novel three-step, one-pot 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.

Our approach for the enantioselective synthesis of C2-functionalized morpholines and piperazines is based upon our recent application of organocatalysis to access chiral β-fluoroamines,[15,16] which in turn, led us to develop a one-pot protocol for the

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enantioselective synthesis of *N*-alkyl terminal aziridines (Scheme 1).[17] Here, commercial aldehydes **8** are subjected to an organocatalytic, enantioselective α-chlorination to produce **9**,[18] which then undergoes a reductive amination reaction with a primary amine, followed by base induced cyclization to deliver *N*-alkyl terminal aziridines **10** in good yields (40–65% for the one-pot, three step sequence) and good to excellent enantioselectivity (55–96% ee).[17]

Based on the precedent, we hypothesized that we should be able to employ an amine in the reductive amination step containing an embedded nucleophile (**11** or **12**), such that after based-induced cyclization of either **13** or **14**, *N*-benzyl protected morpholines **15** and orthogonally N,N′-protected piperazines **16**, respectively, with chiral alkyl groups (with inversion of stereochemistry) at the C2 position could be obtained (Scheme 2). Here, we recount our efforts toward the realization of this hypothesis.

We initially proceeded with a racemic chlorination employing 10 mol % D,L-proline as catalyst to validate the approach, and to provide access to racemic analogs to optimize separation of the enantiomers via chiral supercritical fluid chromatography (SFC) to determine % ee.[15–17] Dodecanal **17** smoothly underwent the desired racemic α-chlorination to provide **18** after a quick pentane work-up. Reductive amination with **11** and $NaB(OAc)_3H$ at −78 °C, followed by KO*t*Bu-induced cyclization in CH_3CN at −10 °C provided racemic C2-functionalized, benzyl-protected morpholine **19** (Scheme 3). While we were thrilled to see the approach successful, the overall yield for the three step, one-pot process was low (11% overall, or ~48% yield per step). Of note, the reductive amination step required low temperature, −78 °C. Above −78 °C, we observed severe racemization of the α-stereocenter, elimination, alkylation and other by-products, while at −78 °C, reductive aminations proceeded smoothly with amines such as **11** and **12**.

Efforts now focused on optimization of the reaction sequence. The racemic α-chlorination was a robust step, affording **18** and related congeners in yields of >90% routinely; thus, the low yields had to be the result of either the reductive amination and/or the base-induced cyclization step. In addition to **19**, the major isolated by-product from the one-pot process was the α-chloroaldehyde **18**; however, by TLC, LCMS, and NMR analysis of the crude reactions, **18** was consumed. This led us to speculate that the incipient iminium ion **20** could either be reduced by the hydride to provide the desired **13**, or the free hydroxyl could attack **20** producing an oxazolidine **21**, which could be hydrolyzed back to **18** upon aqueous work-up and/or chromatography (Scheme 4). To explore this possibility, an NMR study was conducted and confirmed that a stereoisomeric mixture of oxazolidines **21** was being formed, as shown by the shift and coupling of the two characteristic downfield diastereotopic protons indicated below. To improve the yield of the three step, one-pot process, we would need to prevent this undesired oxazolidine pathway.

Two approaches were pursued to prevent the formation of **21**. First, we protected the hydroxyl moiety as a TBDMS ether such that the silyl analog of **13** was generated without the ability to produce **21**. A subsequent TBAF deprotection and cyclization afforded racemic morpholine **19** in 35% overall yield, a notable improvement; however, this route added an additional protection/deprotection sequence. Alternatively, we focused on the reducing agent. Simply replacing $NaB(OAc)_3H$/DCM with $NaCNBH_3$/5% HOAc/THF provided morpholine **19** once again in 35% overall yield for the three steps (~70%/step); therefore, these latter conditions were employed to generate the racemic examples for SFC separation and % ee determination. The enantioselective congeners utilized the same protocol, except the D,L-proline catalyst was replaced with 10 mol % (2*R*,5*R*)-diphenylpyrrolidine.[18,19] This proved to be the optimal catalyst/chlorination system, as it proceeds in DCM; the majority of other organocatalysts/chlorination systems require acetone as solvent, which is not compatible with our one-pot reductive amination sequence, as described in our earlier

aziridine work.[17] Therefore, asymmetric α-chlorination, reductive amination and cyclization afforded enantioenriched C2-functionalized morpholines **19**, **22** and **23** in 76–98% ee (Fig. 2).[20] Interestingly, the one-pot, three step yields for the racemic analogs were higher (35–40% overall or 70–75% per step) than for the enantioenriched congeners (13–19% overall or 50–58% per step).

We next explored the synthesis of orthogonally N,N′-protected piperazines **16**. Here, we did not need to worry about the undesired oxazolidine pathway, so we piloted our initial morpholine conditions. To our surprise, the one-pot protocol afforded **24** in good yield, with very little of the desired **25** (Scheme 5), suggesting the cyclization conditions required optimization. After surveying a number of solvents (THF, CH_3CN and DMF), bases (NaH, KO*t*Bu, KHMDS) and temperatures, we found that simply replacing the CH_3CN with DMF and employing KO*t*Bu at −20 °C enabled the formation of **25** from **24** in 98% conversion. Application of this modification to the one-pot, three step protocol (Scheme 6) delivered racemic **25** in 47% overall yield (78% per step).

As shown in Table 1, the three step, one-pot yields for orthogonally N,N′-protected piperazines were uniformly better (15–50% overall or 53–79% per step) than for the analogous morpholines, and % ee, obtained by chiral SFC analysis, remained good to excellent (55–96% ee).[21]

Finally, since the piperazines worked well, we elected to see if this approach would allow entry into enantioenriched homopiperazines, the seven-membered ring congeners of **16**. Beginning with **17**, racemic organocatalytic α-chlorination, followed by reductive amination with the *N*-benzyl-*N*-Boc protected diaminopropane delivered **29** in 55% overall yield for the two steps. Our standard base-induced cyclization conditions for piperazines (KO*t*Bu, DMF, −20 °C) did deliver the desired C2-functionalized, orthogonally N,N′-protected homopiperazine **30**, but as a 4:1 mixture with the elimination product **31** in 65% yield (Scheme 7). This was not totally unexpected, as the cyclization to produce the seven-membered ring was anticipated to be slow, allowing the competing elimination pathway to the alkene to compete. All attempts to modify the reaction conditions to increase the rate of cyclization leading to **30** and diminish the production of **31** were unsuccessful; therefore we did not produce an enantioselective variant of **30**.

In summary, we have developed a novel three-step, one-pot procedure for the enantioselective synthesis of *N*-benzyl protected morpholines and orthogonally N,N′-protected piperazines with chiral alkly groups installed at the C2 position of each heterocyclic core via organocatalysis. Notably, this methodology does not rely on the chiral pool; instead we can employ simple aldehydes and commercial organocatalysts. Thus, either enantiomer of the corresponding morpholines and piperazines can be arrived at by employing either the (*R*)- or (*S*)-organocatalyst. This methodology allows for the rapid preparation of functionalized, pharmaceutically relevant morpholines and piperazines in 13–50% overall yield (50–79% per step) that are not readily accessible through any other chemistry in good to excellent % ee (55–98% ee). Further refinements and improvements are under development and will be reported in due course.

Acknowledgments

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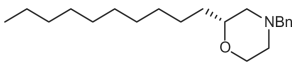
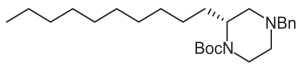
20. Representative experimental for the synthesis of enantioenriched C2-functionalized morpholines: To a solution of aldehyde (1 mmol, 1 equiv) and (2*R*,5*R*)-2,5-diphenylpyrrolidine (22.3 mg, 0.1 mmol, 0.1 equiv) in DCM (2.0 mL) was added *N*-chlorosuccinimide (173 mg, 1.3 mmol, 1.3 equiv) at 0 °C. The reaction was kept at 0 °C for 1 h at which point it was allowed to warm to ambient temperature. It was then stirred until the aldehyde was completely consumed as determined by ^{1}H NMR spectroscopy of the reaction mixture. Pentane was added to the reaction mixture at −78 °C and the precipitated NCS, succinimide, and catalyst were filtered off. After removal of the solvent at 0 °C, the filtration process was repeated one time. The crude oil was redissolved in THF (3 mL) and 4 Å molecular sieves (500 mg) were added. The reaction was cooled to −78 °C and a solution of amine (1.5 mmol, 1.5 equiv) in THF (2 mL) was added followed by the addition of $NaBH_3CN$ (100.5 mg, 1.6 mmol, 1.6 equiv) and acetic acid (120.1 mg, 2 mmol, 2 equiv). The reaction vessel was purged and left to stir at −78 °C for greater than 16 h at which time it was filtered through a pad of celite eluting with ethyl acetate. It was extracted with ethyl acetate and washed with saturated $NaHCO_3$ and brine, and the organic layer was dried over $MgSO_4$ followed by concentration in vacuo resulting in a crude oil, which was then redissolved in acetonitrile (50 mL). The solution was cooled to −20 °C followed by the addition of KO^{t}Bu (560 mg, 5 mmol, 5 equiv). It was then stirred until the β-chloroaminoalcohol was completely consumed as determined by thin layer chromatography. The reaction was extracted with diethyl ether (3×) and washed with brine. The crude oil was concentrated and purified by flash column chromatography (Hexanes/Ethyl Acetate) to afford the product. Enantiomeric Excess was determined via chiral SFC analysis.



(*R*)-4-benzyl-2-decylmorpholine

The product was prepared according to the above description and was purified by silica chromatography (9:1 Hexanes/EtOAc) to afford the product as a clear oil (57 mg, 18%). ^{1}H NMR (400.1 MHz, $CDCl_3$) δ (ppm): ^{1}HNMR (400.1 MHz, $CDCl_3$) δ (ppm): 7.32-7.24 (m, 5H); 3.84 (dq, J_1 = 11.5 Hz, J_2 = 1.8, 1H); 3.65 (td, J_1 = 11.5, J_2 = 2.5, 1H); 3.52-3.45 (m, 3H), 2.74-2.71, (m, 1H), 2.65 (dq, J_1 = 11.4, J_2 = 1.8, 1H), 2.14 (td, J_1 = 11.4, J_2 = 3.3, 1H), 1.87-1.82 (m, 1H), 1.5-1.25 (m, 18H), 0.87 (t, J = 7.1, 3H). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ (ppm): 137.76, 129.11, 128.17, 127.03, 75.76, 66.73, 63.29, 58.80, 53.12, 33.67, 31.83, 29.60, 29.52, 29.51, 29.45, 29.24, 25.33, 22.60, 14.04. Specific rotation $[\alpha]_{D}^{22}$ = + 13.04 ° (*c* 100, MeOH).

21. Representative experimental for the synthesis of enantioenriched C2-functionalized orthogonally N,N′-protected piperazines: To a solution of aldehyde (1 mmol, 1 equiv) and (2*R*,5*R*)-2,5-diphenylpyrrolidine (22.3 mg, 0.1 mmol, 0.1 equiv) in DCM (2.0 mL) was added *N*-chlorosuccinimide (173 mg, 1.3 mmol, 1.3 equiv) at 0 °C. The reaction was kept at 0 °C for 1 h at which point it was allowed to warm to ambient temperature. It was then stirred until the aldehyde was completely consumed as determined by ^{1}H NMR spectroscopy of the reaction mixture. Pentane was added to the reaction mixture at −78 °C and the precipitated NCS, succinimide, and catalyst were filtered off. After removal of the solvent at 0 °C, the filtration process was repeated one time. The crude oil was redissolved in DCM (3 mL) and 4 Å molecular sieves (500 mg) were added. The reaction was cooled to −78 °C and a solution of amine (1.5 mmol, 1.5 equiv) in DCM (2 mL) was added followed by the addition of $NaBH(OAc)_3$ (339 mg, 1.6 mmol, 1.6 equiv). The reaction vessel was purged and left to stir at −78 °C for greater than 16 h at which time it was filtered through a pad of celite eluting with ethyl acetate. It was extracted with ethyl acetate and washed with saturated $NaHCO_3$ and brine, and the organic layer was dried over $MgSO_4$ followed by concentration in vacuo resulting in a crude oil, which was then redissolved in DMF (50 mL). The solution was cooled to −20 °C followed by the addition of KO^{t}Bu (560 mg, 5 mmol, 5 equiv). It was then stirred until the β-chlorodiamine was completely consumed as determined by thin layer chromatography. The reaction was extracted with diethyl ether (3 ×) and washed with brine. The crude oil was concentrated and purified by flash column chromatography (9:1 Hexanes/Ethyl Acetate) to afford the product. Enantiomeric Excess was determined via chiral SFC analysis.



(*R*)-*tert*-butyl4-benzyl-2-decylpiperazine-1-carboxylate

The product was prepared according to the above description and was purified by silica chromatography (9:1 Hexanes/EtOAc) to afford the product as a clear oil (208 mg, 50%). ^{1}H NMR (400.1 MHz, $CDCl_3$) δ (ppm): ^{1}HNMR (400.1 MHz, $CDCl_3$) δ (ppm): 7.32-7.21 (m, 5H); 3.99 (s, br r, 1H); 3.90-3.82 (m, 1H); 3.53 (d, J = 13.2, 1H); 3.37 (d, J = 13.3, 1H); 3.05 (t, J = 12.5, 1H); 2.75-2.65 (m, 2H); 2.06-2.00 (m, 2H); 1.78-1.73 (m, 1H); 1.66-1.61 (m, 1H); 1.45 (s,

9H); 1.30-1.15 (m, 16H); 0.88 (t, J = 7.5, 3H). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ (ppm): 154.81, 138.39, 128.68, 128.12, 126.93, 79.18, 62.80, 55.39, 53.29, 51.37, 39.24, 31.84, 29.74, 29.59, 29.56, 29.53, 29.50, 29.27, 28.38, 26.20, 22.52, 14.04. Specific rotation $[\alpha]_D^{22} = -34.68°$ (c 100, MeOH).

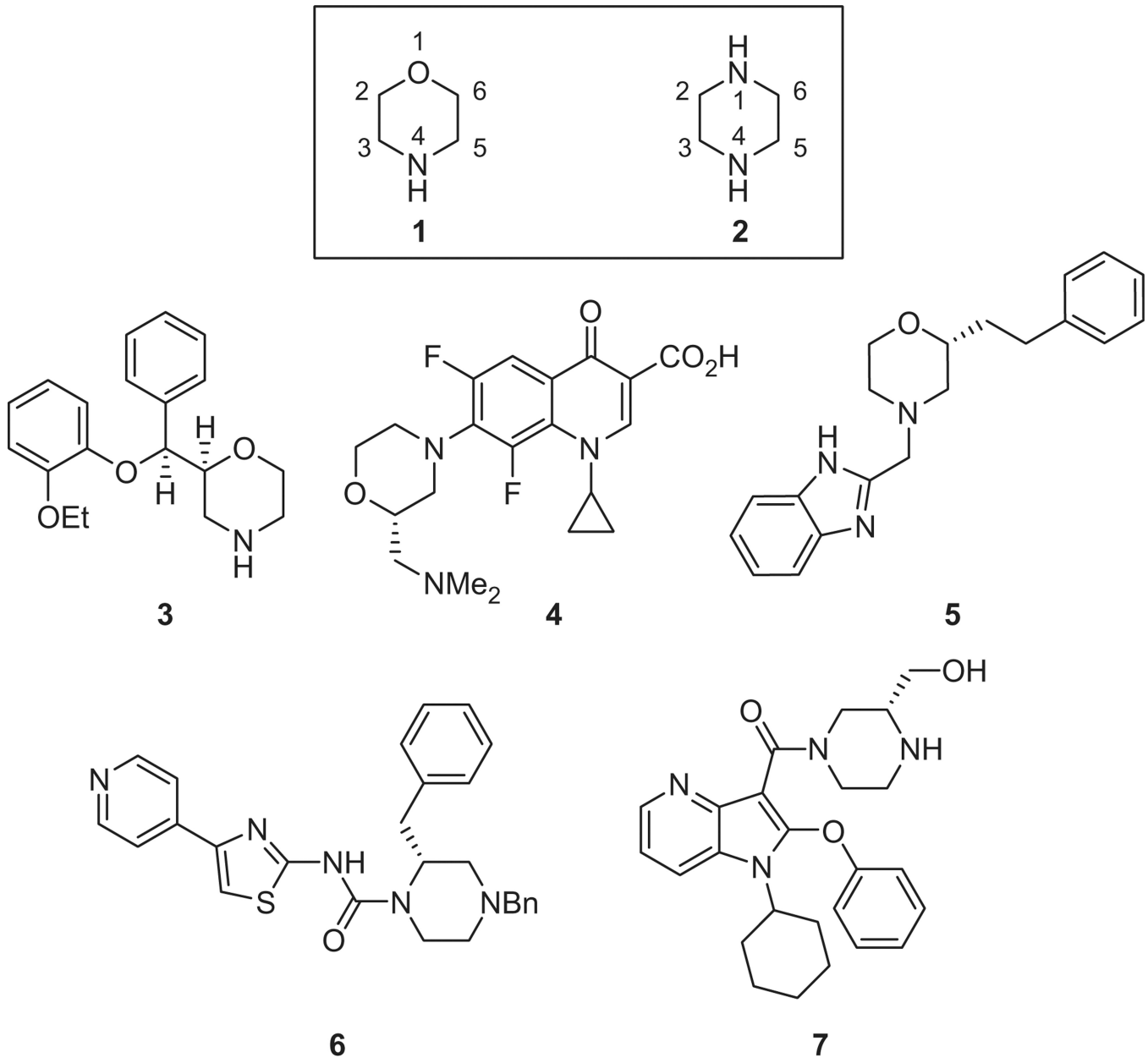


Figure 1.
Structures of morpholine (**1**), piperazine (**2**) and pharmaceutical compositions **3**–**7**, possessing C2-functionalization of these aza-heterocycles.

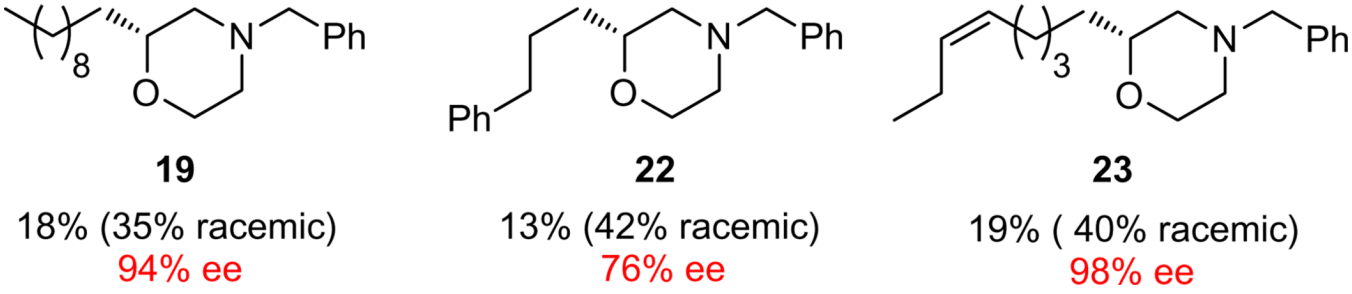
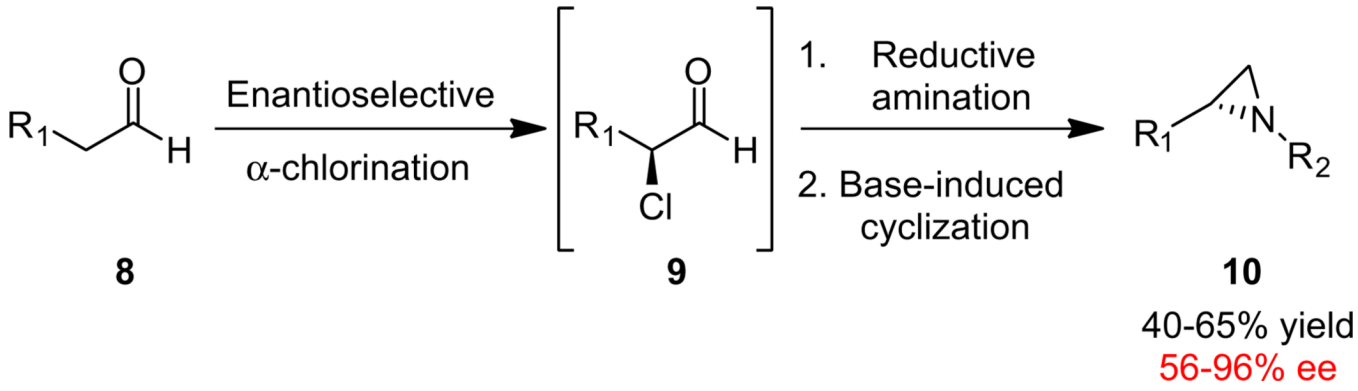
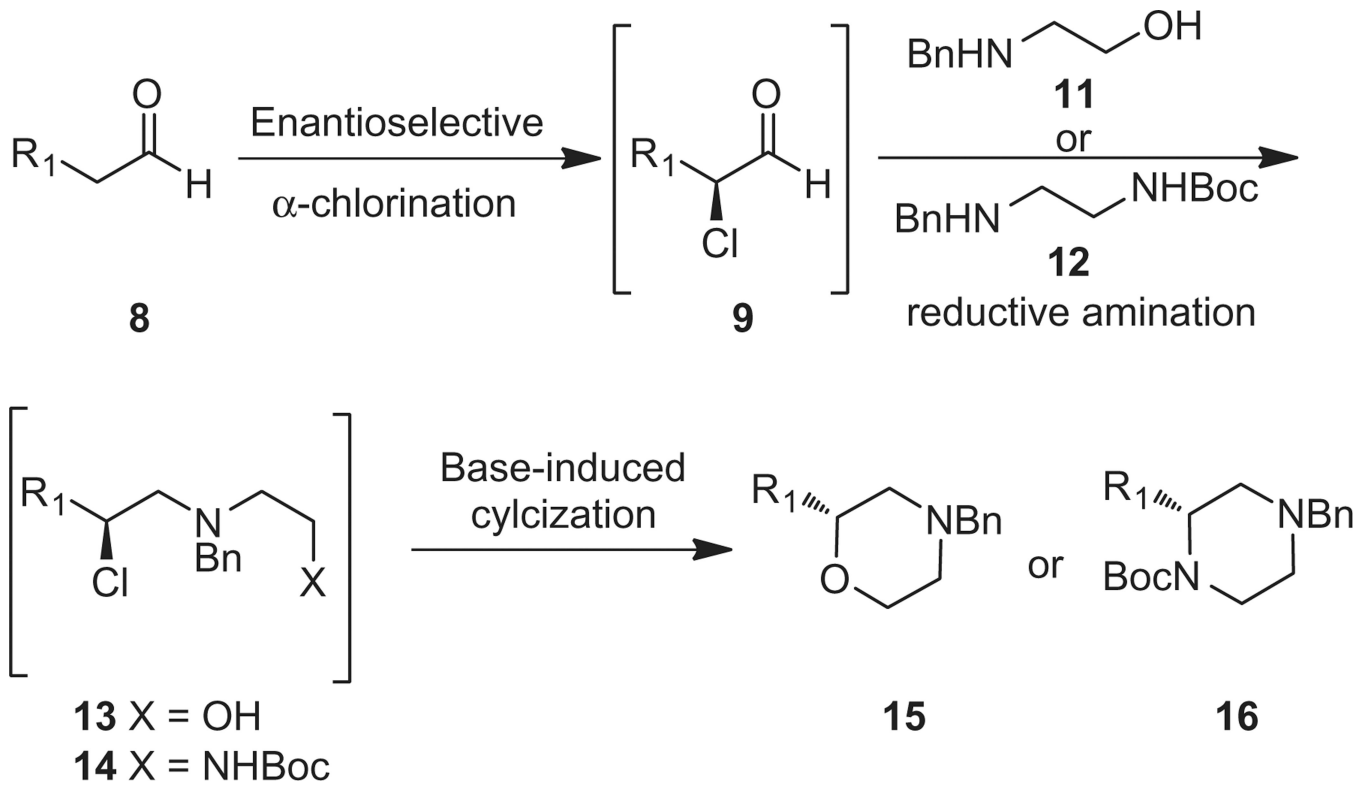


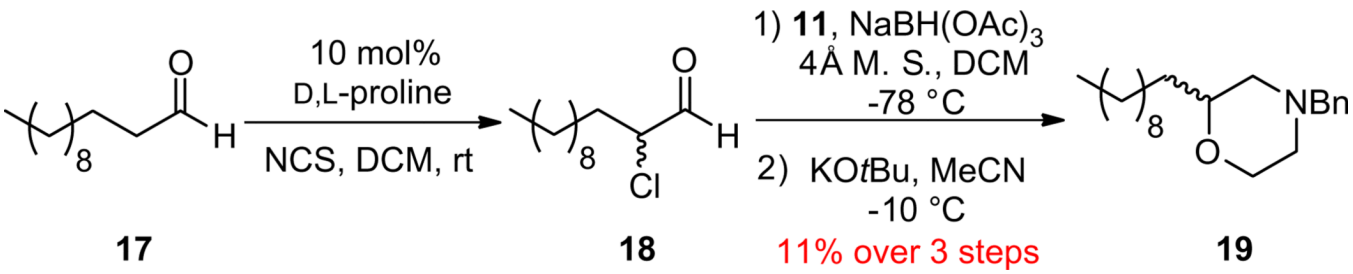
Figure 2.
Structures and yields for the one-pot, three step synthesis of racemic and enantioenriched C2-functionalized, *N*-benzyl protected morpholines.



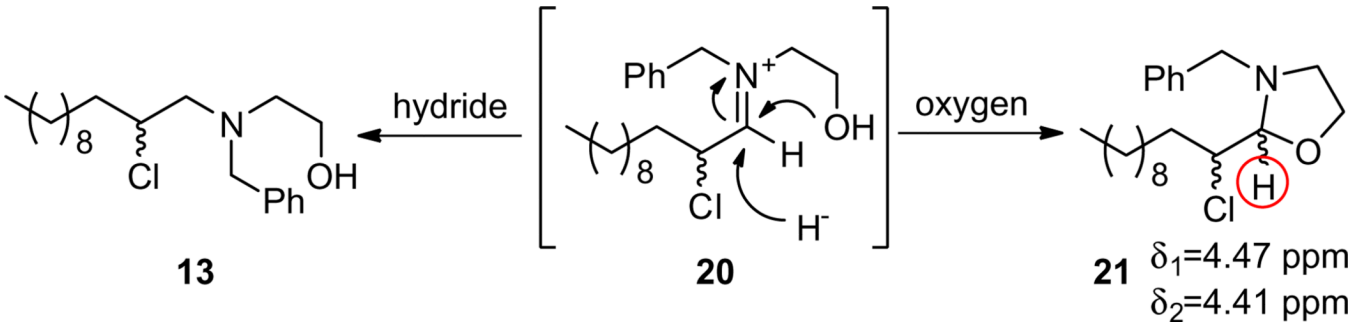
Scheme 1.
Organocatalytic approach to chiral *N*-alkyl terminal aziridines **10**.



Scheme 2.
Proposed organocatalytic approach to C-functionalized, N-protected morpholines **15** and orthogonally N,N′-protected piperazine **16**.

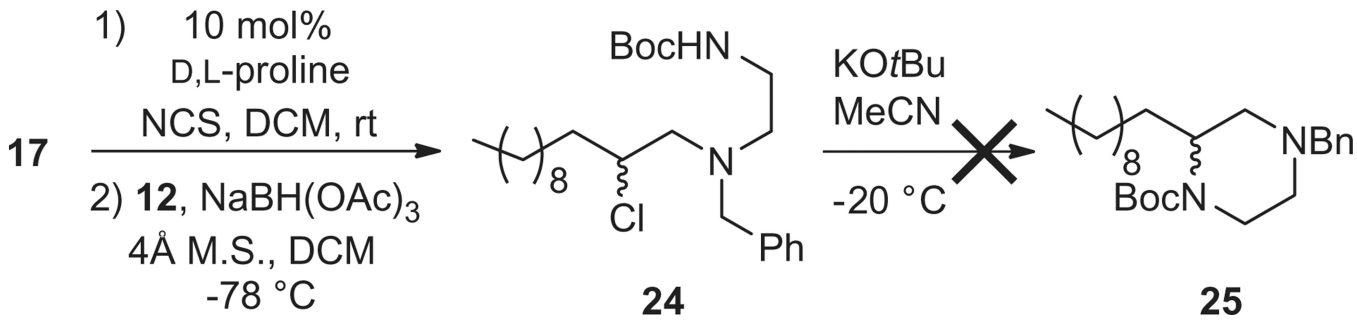


Scheme 3.
Three step, one-pot synthesis of C2-functionalized, *N*-benzyl protected morpholine **19**.

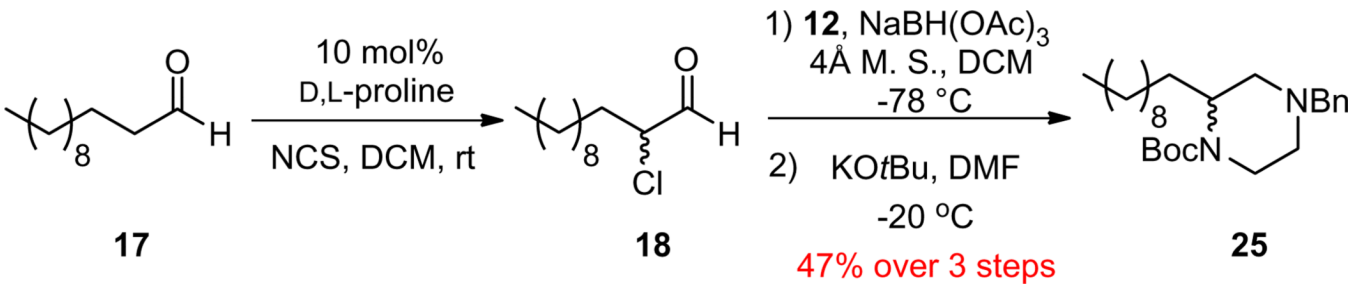


13 20 21

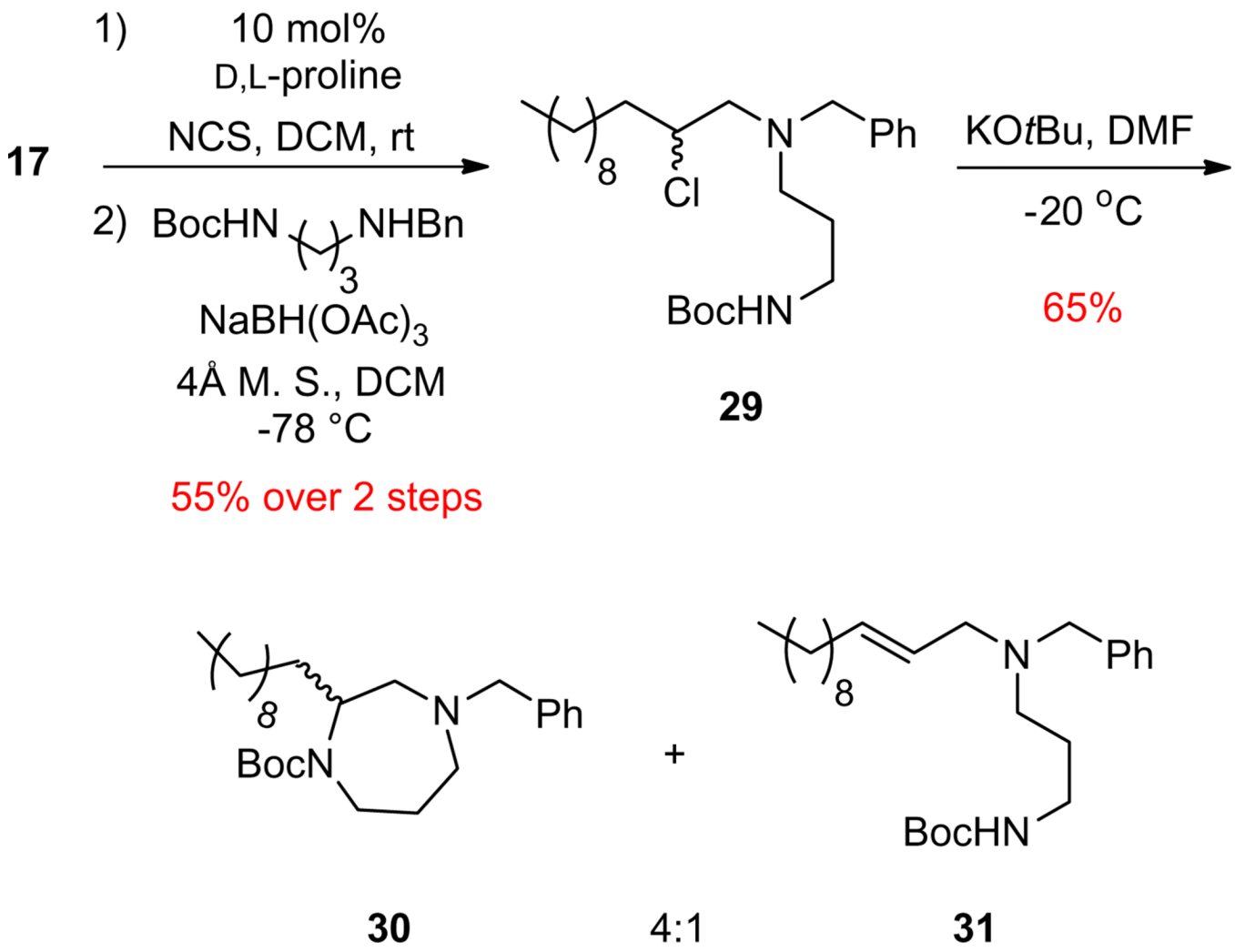
Scheme 4.
Competing pathways: undesired oxazolidine **21** formation.



Scheme 5.
First attempt at a three step, one-pot synthesis of a C2 functionalized, orthogonally N,N′-protected piperazine **25**.



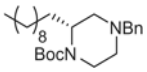
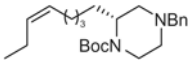
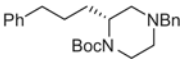
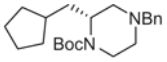
Scheme 6.
Three step, one-pot synthesis of C2-functionalized, orthogonally N,N′-protected piperazine **25**.



Scheme 7.
Three step, one-pot synthesis of C2-functionalized, orthogonally N,N′-protected homopiperazine **30**.

Table 1

Structures and yields for enantioenriched C2-functionalized, orthogonally N,N′-protected piperazines

Compd	Piperazines	3-Step, one-pot yield % (racemic)	% ee[a]
25		50 (47)	96
26		45 (55)	92
27		21 (31)	55
28		15 (21)	70

[a]% ee determined by chiral SFC.