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Synthesis of Enantiopure Substituted Piperidines *via* an Aziridinium Ring Expansion

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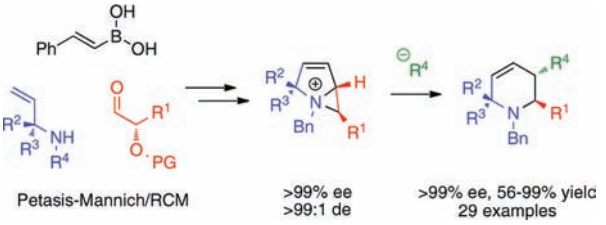
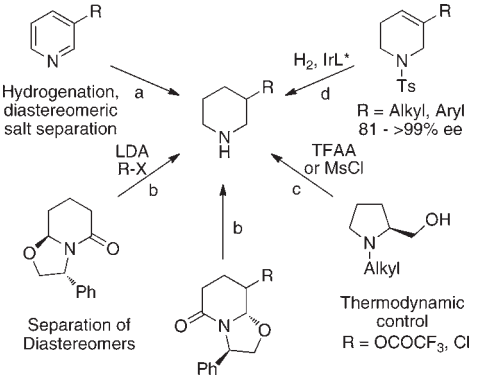
ABSTRACT



Herein we report a novel methodology for the asymmetric synthesis of 3-substituted piperidines from readily available chiral building blocks. This method, which features a novel irreversible dihydropyrole-tetrahydropyridine ring expansion, allows the introduction of a large variety of substituents at the 3-position and permits substitution at the 2- and 6-position giving mono-, di-, or trisubstituted piperidines with high diastereocontrol.

Substituted piperidines are widespread subunits in natural products and pharmaceuticals. Twenty-three of the "Top 200 Brand-Name Drugs by Retail Dollars in 2009" contain piperidine fragments.[1] Consequently, their synthesis has garnered much attention;[2] however, the construction of enantiopure 3-substituted piperidines still remains a significant synthetic challenge (Scheme 1). The most common ways to access these molecules are (a) hydrogenation of pyridines followed by a resolution of the enantiomers by diastereomeric salt separation;[3] (b) alkylation and reduction of oxazolopiperidones;[4] and (c) ring expansion under thermodynamic control via an aziridinium salt from prolinol to yield 3-halo and 3-*O*-acylated piperidines.[5] Another approach involving an iridium-catalyzed enantioselective hydrogenation was recently developed by Andersson (d).[6]

Scheme 1. Methods To Prepare Chiral 3-Substituted Piperidines



These methods, although efficient, suffer from several drawbacks including a dearth of substrate scope, lack of

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(2) (a) Beng, T. K.; Gawley, R. E. *J. Am. Chem. Soc.* **2010**, *132*, 12216. (b) Lovick, H. M.; Michael, F. E. *J. Am. Chem. Soc.* **2010**, *132*, 1249. (c) Lemonnier, G. R.; Charette, A. B. *J. Org. Chem.* **2010**, *75*, 7465. (d) Wurz, R. P.; Fu, G. C. *J. Am. Chem. Soc.* **2005**, *127*, 12234. (e) Barbe, G.; St-Onge, M.; Charette, A. B. *Org. Lett.* **2008**, *10*, 5497. (f) Legault, C. Y.; Charette, A. B. *J. Am. Chem. Soc.* **2005**, *127*, 8966. (g) Pattenden, L. C.; Wybrow, R. A. J.; Smith, S. A.; Harrity, J. P. A. *Org. Lett.* **2006**, *8*, 3089. (h) Kobayashi, T.; Hasegawa, F.; Tanaka, K.; Katsumura, S. *Org. Lett.* **2006**, *8*, 3813. (i) Goodenough, K. M.; Moran, W. J.; Raubo, P.; Harrity, J. P. A. *J. Org. Chem.* **2005**, *70*, 207. (j) Poupon, E.; Francois, D.; Kunesch, N.; Husson, H. P. *J. Org. Chem.* **2004**, *69*, 3836. (k) Goodenough, K. M.; Moran, W. J.; Raubo, P.; Harrity, J. P. A. *J. Org. Chem.* **2004**, *70*, 207. For reviews, see:(l) Buffat, M. G. P. *Tetrahedron* **2004**, *60*, 1701. (m) Escolano, C.; Amat, M.; Bosch, J. *Chem.—Eur. J.* **2006**, *12*, 8198. (n) Cossy, J. *Chem. Rec.* **2005**, *5*, 70.

(3) For an example, see: Grayson, N. A.; Bowen, W. D.; Rice, K. C. *Heterocycles* **1992**, *34*, 2281.

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general conditions, the required separation of diastereomeric mixtures, limited substitution at other points on the piperidine, and/or inability to yield enantiopure products. Therefore, a new method giving access to enantiopure 3-substituted piperidines would be highly desirable.

Herein we report the highly efficient and versatile synthesis of enantiopure 3-substituted piperidines from easily accessible chiral building blocks. The key step involves an unprecedented irreversible regioselective nucleophilic ring opening of an aziridinium salt leading to a ring expansion process.

Cossy described an elegant and related prolinol/piperidine ring expansion process involving halides and trifluoroacetate as nucleophiles (Figure 1A, b).[5] This ring expansion process succeeds only if the nucleophile is also a good leaving group. The piperidine, the major product, derives from the thermodynamic equilibrium between the two constitutional isomers (piperidine vs pyrrolidine) through an aziridinium intermediate.[5,7] When such an aziridinium salt is produced from either an *N*-alkyl-2-halomethylpyrrolidine or an *N*-alkyl-3-halopiperidine and treated with a nucleophile that is a poor leaving group such as an arylcuprate, carbanion, amine, or acetate, then the 2-substituted pyrrolidine is obtained selectively (Figure 1A, a).[8] We envisioned that achieving such a transformation with nonlabile nucleophiles to form a piperidine as the kinetic product selectively would require two important modifications: the use of a leaving group leading to an aziridinium salt irreversibly and the use of a directing group favoring nucleophilic attack at the more hindered electrophilic center (c vs d). Directing groups, such as a carbonyl, enone, or aryl, have been reported to override the steric demands of aziridinium salts so that nucleophiles attack at the more hindered carbon.[9] We envisioned testing the opening of an α,β-unsaturated aziridinium that would be produced from a substituted dihydropyrole, as shown in Figure 1B. This intermediate would then be reacted with nucleophiles in a regioselective manner to yield the desired tetrahydropyridine. We theorized that the S_N2' product should be precluded due to the lack of significant orbital overlap between the π electrons of the alkene and the σ^* of the bridged C−N bond of the aziridinium due to the conformational constraint of the bicyclic system. However, the unsaturation should still be capable of activating the allylic position and of reducing the undesired attack at the least hindered position (d).

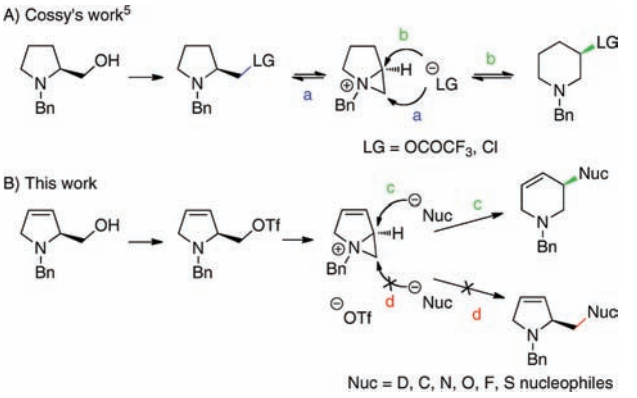

Figure 1. Ring expansion to piperidines via an aziridinium.

To accomplish this ring expansion and to avoid undesired reactive pathways the aziridinium was formed cleanly and irreversibly by treating a hydroxymethylpyrroline with triflic anhydride in the presence of base at −15 °C. The choice of base was vital with the proton sponge furnishing superior results. Temperature was also critical with the aziridinium being unstable above −10 °C.[10] The aziridinium salt was then reacted with sodium dimethyl malonate to produce the desired 3-substituted tetrahydropyridine with a >99:1 ratio of tetrahydropyridine to pyrroline, thus validating our hypothesis.

With the optimized conditions in hand, we submitted the aziridinium intermediate to a variety of nucleophiles and were pleased to find the ring expansion proceeds smoothly to substituted tetrahydropyridines (Table 1). Sodium borodeuteride was an effective nucleophile to afford the isotopically labeled tetrahydropyridine in a 77% yield (entry 1). Carbon nucleophiles such as cyanide (entry 2), malonate (entry 3), an ethyl cuprate (entry 6), and the first reported example of an enamine reacting with an aziridinium (entry 8) all produced the ring expansion product in excellent yields. Variable substitution patterns at the 2-position of the piperidine were well tolerated for the ring expansion (entries 3−5, and product **4**). Nitrogen nucleophiles were well accepted with amide, carbamate, phthalimide, azide, amine, and anilines, giving good to excellent

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(10) See Supporting Information for optimization data.

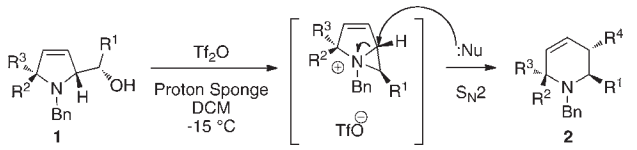
yields (entries 9–17). Also, oxygen nucleophiles, such as an acetate, phenoxide, or alcohol, all gave good to excellent yields (entries 18–21). Sulfur nucleophiles and fluoride gave moderate yields (entries 22–24). Substituting the 5-position of the pyrroline was also compatible with the ring expansion, which could yield the 2,3,6-trisubstituted tetrahydropyridine as a single diastereomer enantiopure with either diastereomer at the 6-position available (entries 25–26).

The limitation in the choice of nucleophile appears to be directly related to its basicity, which has been alluded to in literature.[9b] For example, the sodium enolate of acetophenone furnished poor yields (< 40%) with significant decomposition; however, the enamine of acetophenone gave a good yield to obtain **2h**. Likewise, sodium ethoxide decomposed the aziridinium to unidentifiable products; however, relatively unreactive ethanol afforded the ether **2s** in a good yield.

The stereochemical outcome of the reaction was further investigated by substituting the pyrrolinemethanol moiety with a methyl group (Table 1: $R^1 = CH_3$). The diastereomeric purity and enantiomeric excess of the pyrrolinemethanol was preserved during the ring expansion to the tetrahydropyridine, with the regioselectivity and relative stereochemistry confirmed by NMR. In all cases, only one isomer was observed after the ring expansion except when the nucleophile was an alkyl organocuprate (entries 6 and 7; entry 6: −15 °C, 1:3 *anti* S_N2:*syn* S_N2'). However, decreasing the temperature of the reaction significantly improved the selectivity (−78 °C, 18:1 *anti* S_N2:*syn* S_N2'). When no methyl substituent was present ($R^1 = H$), only one regioisomer was obtained (entries 3, 10, 16, and 22) except for the organocuprate example where a 20:1 ratio was observed (entry 7).

For our approach to be efficient, an expedient synthesis of enantio- and diastereoenriched pyrrolinol derivatives had to be conceived from cheap and commercially available starting materials. *trans*-4-Hydroxyproline is a common precursor for 3,4-dehydroproline,[11] but we found it to be suboptimal due the length of the synthesis and due to partial epimerization occurring during the synthesis which has been noted by others.[11b,12] An enantioselective Birch reduction of a pyrrole to a pyrroline with good enantioselectivity has been reported by Donohoe;[13] however, we sought enantiopure material with the flexibility of substituting other positions with high diastereocontrol. These limitations led us to consider using the Petasis–Mannich (PM) condensation as the key step to assemble the basic core of 2-hydroxymethyldihydropyrrole units.

Table 1. Pyrrolinol Ring Expansion to Piperidines



entry	nucleophile	product	R^1	R^2	R^3	R^4	yield (%)
1	$NaBD_4$	**2a**	CH_3	H	H	D	77
2	TBACN	**2b**	CH_3	H	H	CN	79
3	$NaCH(CO_2CH_3)_2$	**2c**	H	H	H	$CH(CO_2CH_3)_2$	87[a]
4	$NaCH(CO_2CH_3)_2$	**2d**	CH_3	H	H	$CH(CO_2CH_3)_2$	71
5	$NaCH(CO_2CH_3)_2$	**2e**	$CH(CH_3)_2$	H	H	$CH(CO_2CH_3)_2$	73
6	EtCuMgBrCN	**2f**	CH_3	H	H	Et	78[b]
7	EtCuMgBrCN	**2g**	H	H	H	Et	73[c]
8		**2h**	CH_3	H	H		81
9	$NaNHCOCF_3$	**2i**	CH_3	H	H	$NHCOCF_3$	58
10	$NaNHCOCF_3$	**2j**	H	H	H	$NHCOCF_3$	69[a]
11		**2k**	CH_3	H	H		86
12		**2l**	CH_3	H	H		70[d]
13	$TBAN_3$	**2m**	CH_3	H	H	N_3	75
14	NH_2Ph	**2n**	CH_3	H	H	NHPh	80
15	NHMePh	**2o**	CH_3	H	H	NMePh	93
16	NHMePh	**2p**	H	H	H	NMePh	>99[e]
17	$NHEt_2$	**2q**	CH_3	H	H	NEt_2	87
18	NaOAc	**2r**	CH_3	H	H	OAc	65
19	HOEt	**2s**	CH_3	H	H	OEt	73
20	NaOPh	**2t**	CH_3	H	H	OPh	85
21	NaOPh	**2u**	H	H	H	OPh	97[a]
22	TBAF	**2v**	CH_3	H	H	F	57
23	HSEt	**2w**	CH_3	H	H	SEt	56
24	NaSPh	**2x**	CH_3	H	H	SPh	70
25	$NaCH(CO_2CH_3)_2$	**2y**	CH_3	H	Bn	$CH(CO_2CH_3)_2$	81
26	$NaCH(CO_2CH_3)_2$	**2z**	CH_3	Bn	H	$CH(CO_2CH_3)_2$	89

[a] Enantiomeric excess was the same as that of a pyrrolinol precursor prepared from 4-hydroxyproline, 94% ee. [b] Run at −78 °C; obtained a ratio of 18:1 of *anti*-2,3- to *syn*-2,5-disubstituted tetrahydropyridine. [c] Obtained a 20:1 ratio of six- to five-membered ring. [d] Enantiomeric excess was the same as that of the pyrrolinemethanol precursor, > 99% ee. [e] Obtained by analysis of the crude mixture by ^1H NMR using 1,3,5-trimethoxybenzene as an internal standard.

The PM condensation would allow us to prepare 1, 2-amino-alcohols with high enantiomeric purity and diastereocontrol.[14] A previous drawback of this elegant reaction was that it required α-hydroxyaldehydes, which are nontrivial to prepare in enantiopure form even at a moderate scale. *In situ* deprotection of an enantiopure α-siloxyether aldehyde with TBAF in the presence of a vinylboronic acid and an allylic amine led to the PM condensation product with excellent diastereoselectivity (> 99%) and yield. More importantly, the enantiomeric purity of the precursors was maintained (Table 2).[15] This

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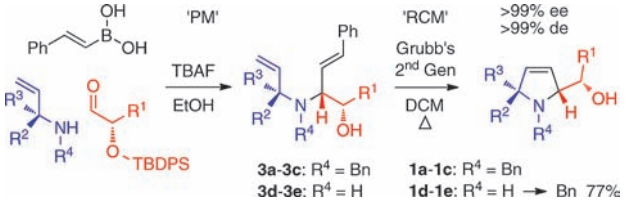
(15) The products in entries 1 and 3 of Table 2 were determined to be > 99% ee (SFC on chiral stationary phase). Entries 4 and 5 combined two enantiopure precursors to obtain the intermediate as a single diastereomer.

greatly simplified the synthesis of the precursors as these enantiopure aldehydes are trivial to prepare in significant amounts. Therefore, this procedure was used to prepare the precursors necessary to access 2,3,6-substituted tetrahydropyridine with high diastereocontrol (entries 4–5 in Table 2 and entries 25–26 in Table 1). The RCM of the PM products proceeded well under typical conditions using Grubb's second generation catalyst to yield the 2-hydroxymethyldihydropyrroles, even when done on the reaction mixture resulting from the PM condensation (entry 5).

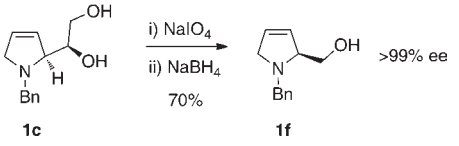
Table 2. Petasis–Mannich and Ring Closing Metathesis Sequence To Prepare Substituted Pyrrolinols



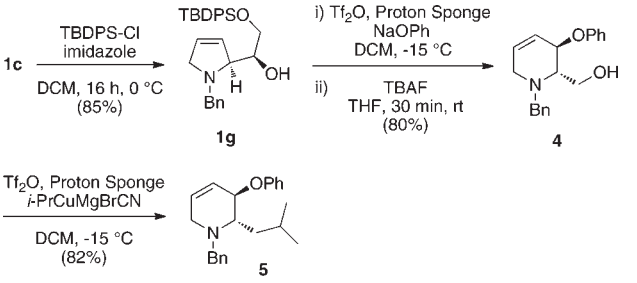
entry	R^1	R^2	R^3	products	yield **3** (%)	yield **1** (%)
1	CH_3	H	H	**3a**, **1a**	83	70
2	$CH(CH_3)_2$	H	H	**3b**, **1b**	61	71
3	CH_2OH[a]	H	H	**3c**, **1c**	77	65
4	CH_3	Bn	H	**3d**, **1d**	76	68
5	CH_3	H	Bn	**1e**	nd	35[b]

[a] Unprotected hydroxyaldehyde was used, and the TBAF treatment was omitted. [b] Combined yield for the two steps, with the RCM done on the mixture from the PM.

Scheme 2. Synthesis of Chiral *N*-Bn-3,4-Dehydroprolinol **1f**



Scheme 3. Preparing Both the 2- and 3-Substituents of a Piperidine from a Common Intermediate



Moreover, to further show the versatility of this method, we prepared **1c** in two steps from commercially available materials (Table 2). **1c** can be easily prepared in either enantiomeric form with enantiopurity. It can be used to prepare **1f** in a one-pot procedure with >99% ee (Scheme 2), or **1c** can be used to synthesize the versatile intermediate **1g** (Scheme 3). From **1g**, both the 2- and 3-substituents of the piperidine can be changed in three steps via aziridinium intermediates to compounds such as **5**. Finally, access to the fully reduced substituted piperidines can be accomplished upon treating tetrahydropyridines with hydrogen gas and PtO_2, or $Pd(OH)_2$ on carbon.[2c,e]

In conclusion, we have developed a concise and flexible asymmetric method to prepare substituted piperidines from easily available enantiopure precursors. This method affords 3-substituted tetrahydropyridines with a large variety of nucleophiles and with excellent regio- and stereocontrol. Application of this methodology to assemble complex piperidine containing natural products will be reported in due course.

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Supporting Information Available. Experimental procedures for the preparation and spectroscopic data. This material is free of charge via the Internet at http://pubs.acs.org.