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Enantioselective Synthesis of Planar Chiral Organonitrogen Cycles

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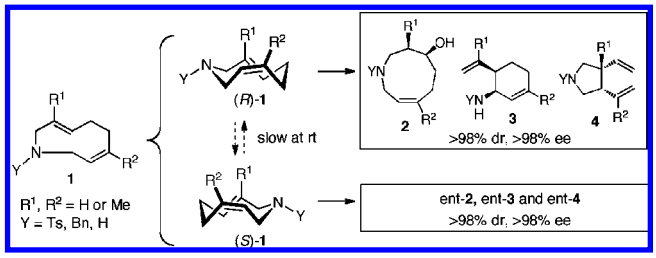
Abstract: Enantioselective synthesis of a planar chiral organonitrogen cycle has been newly developed based on the unprecedented prochiral face-selective cyclization of achiral linear precursors by an appropriate chiral promoter.

A series of nine-membered diallylic organonitrogen cycles **1** display appreciable planar chirality arising from their topological constraint.[1] Notably, the planar chirality in **1** is completely transmittable to central chirality in their chemical transformation into multiply functionalized nitrogen-containing compounds such as **2**−**4** (Scheme 1). Moreover, this class of compounds serve as useful chiral building blocks to provide a number of alkaloids in a highly stereospecific manner.[2] Unfortunately, however, such great synthetic potential of **1** has not been fully developed because the preparative method relied on the optical resolution of (±)-**1**.[3] Therefore, the development of a practical enantioselective synthesis of **1** was desirable for further studies.[4]

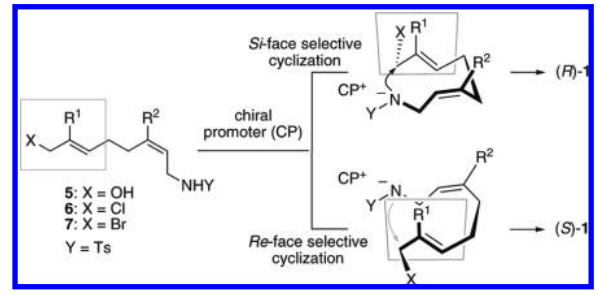
Scheme 1. Planar Chiral **1** and Their Synthetic Elaboration



As illustrated in Scheme 2, we originally prepared (±)-**1** by intramolecular Mitsunobu reaction of achiral amino alcohol **5** (X = OH).[1a] On the other hand, we also found that the similar amino halides **6** (X = Cl) or **7** (X = Br) furnish (±)-**1** upon treatment with an aqueous alkaline base containing TBAI as a phase transfer catalyst (PTC) (see Supporting Information). In either case, prochiral face selection at the designated olefin in **5**, **6**, or **7** should be involved to develop planar chirality in **1**. Accordingly, we began to explore a suitable chiral promoter (CP) in the hope of inducing enantioselectivity in these processes. As a result, we found that not only chiral PTC[5] but also sugar-derived chiral alkoxides effectively promote unprecedented asymmetric cyclization to give **1** in a highly enantioselective manner. Herein, we disclose this novel asymmetric cyclization, whose enantioselectivity is determined as dextral or sinistral by lithium ion-mediated steric interaction between linear substrates and chiral alkoxides.

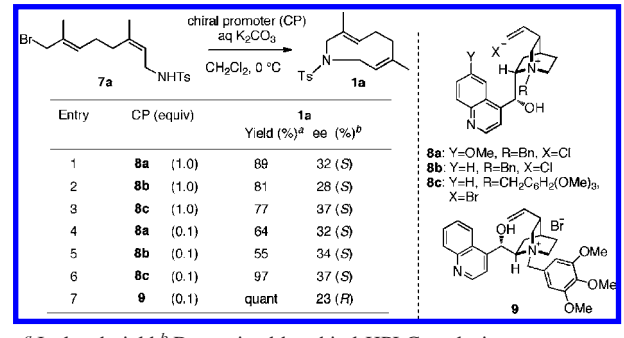
We first examined the impact of several chiral PTCs in the cyclization of **7a** (R^1 = Me, R^2 = Me) as a model reaction to see whether **1a** is obtainable in an enantioenriched form or not. The reaction was carried out in biphasic 40−50 wt % aq K_2CO_3−CH_2Cl_2 containing a chiral PTC (100 mol %) at 0 °C for 24 h,[6] and selected results are summarized in Table 1.

Scheme 2. A Strategy for Enantioselective Synthesis of **1**



Chiral PTCs including the salts of (−)-sparteine/MeI or (*S*,*S*)-*β*-Nap-NAS-Br[7] promoted the cyclization efficiently (81 and 71%, respectively), but (±)-**1a** was obtained in both cases. However, cinchona alkaloid derived **8a**−**c** did furnish enantioenriched (*S*)-**1a** and their ee values were ranging from 28−37% (entries 1−3).[8] It should be noted that the decrease of the amount of **8a**−**c** from 100 to 10 mol % did not cause any deterioration of the stereoselectivity (entries 4−6). Not surprisingly, (*R*)-**1a** with 23% ee was obtained with **9**, which should be one of the readily available surrogates for the antipode of **8** (entry 7).[8c] Unfortunately, however, we were not successful in finding a superior chiral PTC any further in terms of enantioselectivity.[9] Accordingly, we then turned our attention toward structural modification of the anionic part instead of the cationic part in CP.

Table 1. Asymmetric Cyclization of **7a** Using Chiral PTCs



Entry	CP (equiv)		1a Yield (%)[a]	1a ee (%)[b]
1	**8a**	(1.0)	89	32 (*S*)
2	**8b**	(1.0)	81	28 (*S*)
3	**8c**	(1.0)	77	37 (*S*)
4	**8a**	(0.1)	64	32 (*S*)
5	**8b**	(0.1)	55	34 (*S*)
6	**8c**	(0.1)	97	37 (*S*)
7	**9**	(0.1)	quant	23 (*R*)

[a] Isolated yield. [b] Determined by chiral HPLC analysis.

In fact, the stoichiometric use of lithium alkoxides **10** and **11**,[10] which are structurally similar to **8b** and **9**, provided enantioenriched **1a** with moderate stereoselectivities [45% ee (*S*), 40% ee (*R*), respectively], although the reaction rates were lowered (15% yield after 80 h and 30% yield after 60 h, respectively, in CH_2Cl_2 at 0

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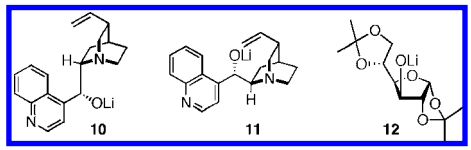
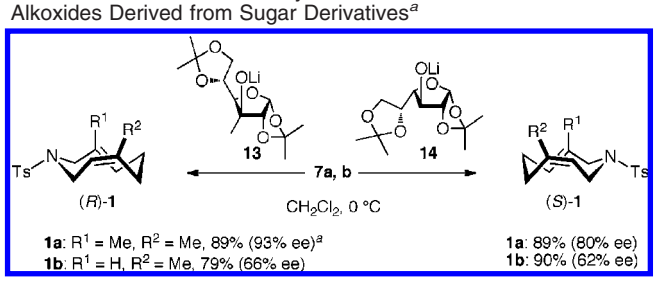
°C). Surprisingly, the lithium salt of diacetone D-glucose **12** having no amino group[11] was also equally effective to give (*R*)-**1a** under otherwise identical conditions with 51% ee in 52% yield after 48 h, and the use of double amounts of **12** greatly improved enantioselectivity as well as chemical yield to give (*R*)-**1a** with 63% ee in 59% yield after 48 h. It was conceivable that the extra amount of **12** possibly serves merely as a base to generate the conjugate base of **7a** (*vide infra*) since the pretreatment of **7a** with *n*-BuLi followed by the cyclization with an equimolar amount of **12** gave almost identical results (66% ee, 55% yield). Notably, lithium was the alkaline metal of choice, because the replacement of lithium with sodium or potassium in **12** gave only disappointing enantioselectivity.



These results encouraged us to explore a variety of sugar-derived lithium alkoxides, among which **13** and **14** have proved to be the most appropriate CPs for the cyclization of **7a** and **7b** (R^1 = H, R^2 = Me) (Scheme 3). For example, the reaction of **7a** with an excess amount of D-glucose derived **13** provided (*R*)-**1a** with 93% ee in 89% yield.[12] Moreover, the similar reaction of **7b** provided (*R*)-**1b** in 66% ee under otherwise identical conditions. In sharp contrast, D-galactose-derived **14** completely reversed the mode of cyclization from dextral to sinistral to give (*S*)-**1a** with 80% ee and (*S*)-**1b** with 62% ee, respectively. It should be noted that **13** and **14** can be prepared from readily available sugar derivatives,[13] recovered easily from the reaction mixture, and used repeatedly to provide both enantiomers of **1**. The usefulness of our present method was demonstrated by the preparation of (*R*)-**1a** with >98% ee in moderate scale after fractional recrystallization as well as by the total synthesis of both enantiomers of kainic acid using (*S*)- or (*R*)-**1b** as a starting material.[2b]

Scheme 3. Enantioselective Synthesis of **1** with Chiral Lithium Alkoxides Derived from Sugar Derivatives[a]



[a] >98% ee: after fractional recrystallization.

To gain further insight into the stereochemistry of this novel asymmetric cyclization, we next performed calculations of possible transition states for the reaction of lithium salt of **7a** and **12** at the HF/3-21G level.[14] As shown in Figure 1, the 1:1 complex of the lithium salt of **7a** and **12** through N--Li--O and O--Li--O=S=O interaction provided the lowest energy geometries **i** and **ii**, which were most suitable for dextral and sinistral cyclizations, respectively (*vide supra*). Although these results might oversimplify the effect of protonated **12** and solvent in the reaction mixture, the calculated energy of **i** was lower than that of **ii** by ΔE = 1.22 kcal/mol, which was consistent with the preferential dextral cyclization mode.

In summary, we have developed the unprecedented asymmetric cyclization of achiral linear amino halides to provide planar chiral organonitrogen cycles, in which chiral lithium alkoxides derived from readily available sugar derivatives play a key role for determining the cyclization mode as dextral or sinistral. These results along with our previous studies should increase the synthetic value of planar chiral heterocycles as new chiral building blocks in asymmetric synthesis.

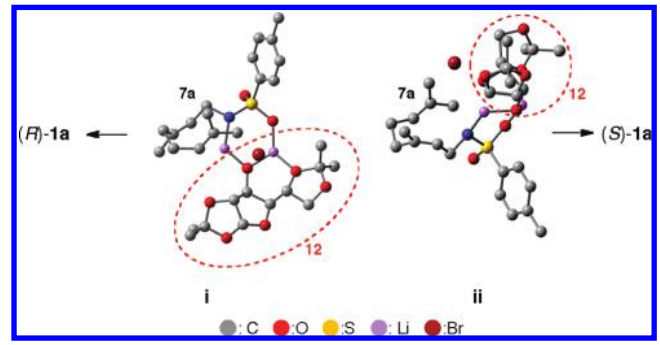


Figure 1. Possible transition states for asymmetric cyclization.

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

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(3) Separation of (±)-**1** is effected by (i) HPLC with a semipreparative chiral stationary phase column, by (ii) kinetic resolution with asymmetric transformations and by (iii) fractional crystallization of ammonium salt prepared from **1** (Y = H) and chiral acids. For details, see ref 1a.
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(9) The replacement of R in **8b** from a Bn group to a Me, $CH_2C_6H_4pCF_3$, $CH_2C_6H_4p$OMe, or 9-anthracenylmethyl group and that of X from Cl to Br or I caused no remarkable improvement in terms of enantioselectivity.
(10) Alkoxides **10** and **11** were prepared from cinchonidine or cinchonine with *n*-BuLi.
(11) We have separately reported that **12** acts as an efficient CP for enantioselective Stevens rearrangement: Tomooka, K.; Sakamaki, J.; Harada, M.; Wada, R. *Synlett* **2008**, 683.
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(14) Performed with Gaussian 03 on a TSUBAME system at Tokyo Institute of Technology.

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