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Planar Chiral Cyclic Amine and Its Derivatives: Synthesis and Stereochemical Behavior

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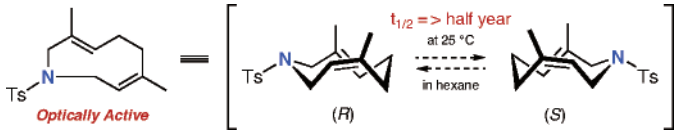
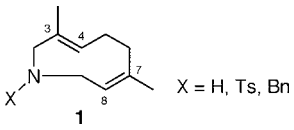
ABSTRACT



Nine-membered diallylic cyclic amines and amides have remarkably stable planar chirality. The transformation of enantiomerically enriched amides provides optically active nitrogen heterocycles containing stereogenic centers in a stereospecific fashion.

The importance of chiral amines and their derivatives in asymmetric synthesis is undisputed. Indeed, a variety of chiral amines are synthesized and utilized as chiral building blocks, chiral reagents, chiral ligands, and so on. Herein, we wish to report a novel chiral amine and amide **1** without any stereogenic carbon.



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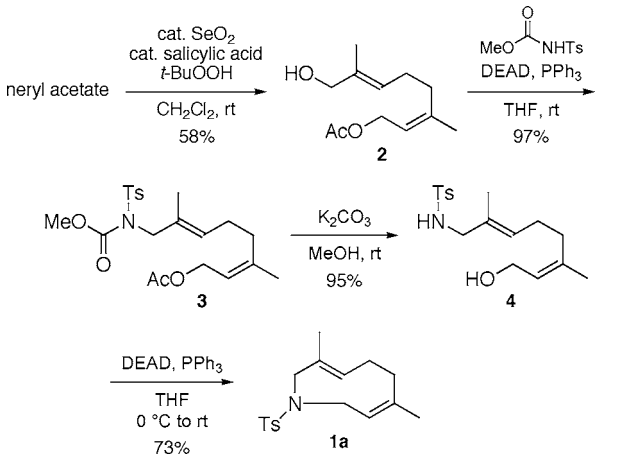
Recently, we have reported planar chirality in nine-membered cyclic ethers.[1,2] Based on this result, we envisioned that the amine analogues should also have planar chirality and so they would constitute a new class of chiral molecules.

To realize this chemistry, we designed *N*-tosyl amide **1a** (X = Ts) as a target molecule and chose the intramolecular Mitsunobu reaction for constructing a nine-membered skeleton. Requisite precursor **4** was readily available from neryl acetate in three steps: allylic oxidation with SeO_2,[3] a Mitsunobu-type reaction with methyl *N*-(*p*-toluenesulfonyl)-carbamate,[4,5] and base-promoted deprotection (Scheme 1).

Scheme 1. Synthesis of Amide **1a**



(1) Tomooka, K.; Komine, N.; Fujiki, D.; Nakai, T.; Yanagitsuru, S. *J. Am. Chem. Soc.* **2005**, *127*, 12182−12183.

(2) Studies on planar chirality of cycloalkenes have several precedents, see: (a) Blomquist, A. T.; Liu, L. H.; Bohrer, J. C. *J. Am. Chem. Soc.* **1952**, *74*, 3643−3647. (b) Cope, A. C.; Howell, C. F.; Knowles, A. *J. Am. Chem. Soc.* **1962**, *84*, 3190−3191. (c) Cope, A. C.; Banholzer, K.; Keller, H.; Pawson, B. A.; Whang, J. J.; Winkler, H. J. S. *J. Am. Chem. Soc.* **1965**, *87*, 3644−3649. (d) Cope, A. C.; Pawson, B. A. *J. Am. Chem. Soc.* **1965**, *87*, 3649−3651. (e) Binsch, G.; Roberts, J. D. *J. Am. Chem. Soc.* **1965**, *87*, 5157−5162. (f) Marshall, J. A.; Konicek, T. R.; Flynn, K. E.; *J. Am. Chem. Soc.* **1980**, *102*, 3287−3288. Recently, chiral sila-cycloheptene has been synthesized: (g) Krebs, A.; Pforr, K.-I.; Raffay, W.; Thölke, B.; König, W. A.; Hardt, I.; Boese, R. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 159−160.

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An intramolecular Mitsunobu reaction of **4** was performed with diethyl azodicarboxylate (DEAD) and PPh_3 under high dilution conditions (0.01 M), providing desired cyclic amide **1a** in good yield (73%). It should be noted that only a negligible amount of dimerized product (<1%) was formed in this reaction.

Fortunately, amide **1a** afforded a crystal suitable for X-ray analysis. As shown in Figure 1, the C3−C4 and C7−C8

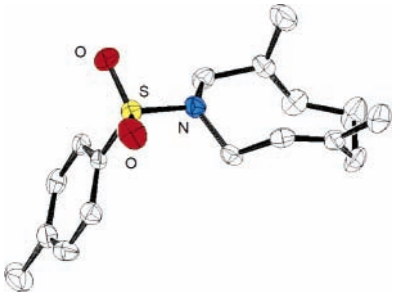


Figure 1. Molecular structure of **1a**.

olefinic moieties form chiral planes in the solid state.[6,7]

Moreover, the ^{1}H NMR analysis of amide **1a** in $CDCl_3$ at ambient temperature shows two sets of nonequivalent α-*N*-allylic geminal protons (at C2 and C9), which suggests that the above-mentioned chiral planes are maintained even in solution.[8] Analytical and semipreparative-scale HPLC using a chiral stationary column equipped with a CD spectropolarimeter successfully separated both enantiomers of **1a** as shown in Figure 2.[9,10]

Enantiopurity of **1a** was *unchanged in the solid state (crystal) at ambient temperature for at least 2 months*. It should be noted that **1a** only racemizes at a very slow rate even in solution: the half-life of optical activity of **1a** in hexane at 25 °C was estimated as 203 days.[11] Encouraged by these results, we next performed several transformation

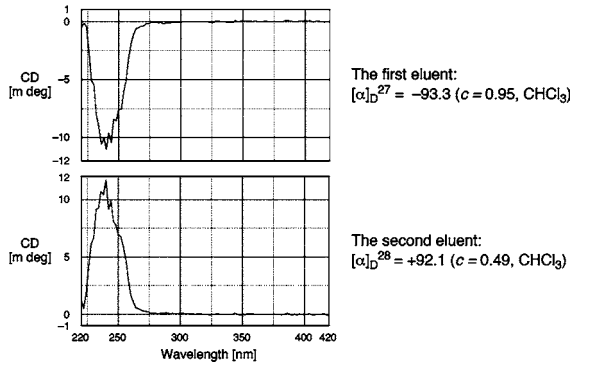
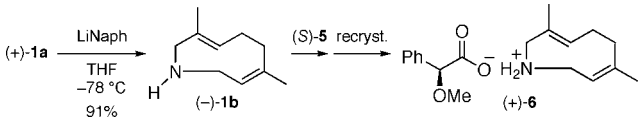


Figure 2. CD spectra and specific rotation of **1a**.

starting from enantioenriched **1a**. At the outset, we examined a reductive detosylation of (+)-**1a** (>98% ee) using lithium naphthalenide (LiNaph). The reaction successfully has provided secondary amine (−)-**1b** in good yield without any racemization.[12] The obtained amine readily gave a variety of ammonium salts upon treatment with carboxylic acids. Ammonium salt (+)-**6** prepared from amine (−)-**1b** and (*S*)-α-methoxyphenylacetic acid [(*S*)-**5**] gave a crystal suitable for X-ray analysis, which has led to the determination of the absolute configuration of (−)-**1b** and its precursor (+)-**1a** as *S* (Scheme 2) (Figure 3).[6,12]

Scheme 2. Synthesis of Amine **1b** and Its Salt **6**



High crystallinity of the salt **6** suggested a possibility for optical resolution of amine **1b** by fractional crystallization. In fact, diastereomerically enriched (+)-**6** (93% dr, 42% yield) deposited preferentially from ether solution of a 1:1 mixture of *rac*-**1b** and (*S*)-**5**, and enantioenriched **1b** (62% ee, *R*)[12] was recovered from mother liquor. Further recrystallization of (+)-**6**, followed by tosylation provided an enantiomerically pure amide (*S*)-**1a** (eq 1).

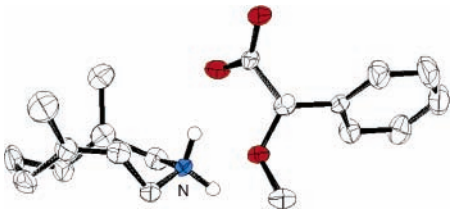


Figure 3. Molecular structure of (+)-**6** derived from (+)-**1a**.

(3) We used a slightly modified procedure of the one described by: Marshall, J. A.; Lebreton, J. *J. Org. Chem.* **1988**, *53*, 4108−4112.

(4) For reviews, see: (a) Mitsunobu, O. *Synthesis*, **1981**, 1−28. (b) Hughes, D. L. *Org. React.* **1992**, *42*, 335−656.

(5) Henry, J. R.; Marcin, L. R.; McIntosh, M. C.; Scola, P. M.; Harris, G. D., Jr.; Weinreb, S. M. *Tetrahedron Lett.* **1989**, *30*, 5709−5712.

(6) The structures of *rac*-**1a**, (+)-**6**, and *rac*-**7** were determined by X-ray crystallography; see the Supporting Information. In Figures 1 and 3, hydrogen atoms have been omitted for clarity, except the hydrogen attached to the nitrogen.

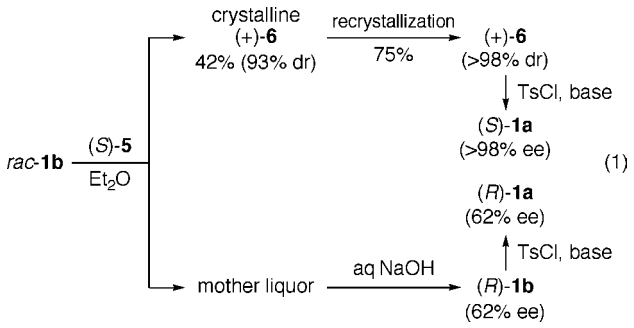
(7) Note that the sum of the nitrogen's bond angles is 348.2°, which means that the nitrogen center of **1a** is chiral in the solid state.

(8) Selected ^{1}H NMR data of **1a** (300 MHz, $CDCl_3$): δ 3.00 (d, J = 10.2 Hz, 1H; C2-H), 3.01 (dd, J = 14.1, 4.2 Hz, 1H; C9-H), 3.86 (dd, J = 14.1, 11.7 Hz, 1H; C9-H), 4.25 (d, J = 10.2 Hz, 1H; C2-H).

(9) Analytical HPLC: CHIRALCEL OD-H (4.6 × 250 mm), hexane/EtOH = 1/1, 0.5 mL/min, UV 254 nm, rt, t_R = 9.9 min for (−)-(*R*)-isomer, 13.1 min for (+)-(*S*)-isomer. Preparative HPLC: CHIRALCEL OD-H (20 × 250 mm), hexane/EtOH = 1/1, 3.0 mL/min, UV 254 nm, rt, t_R = 30.2 min for (−)-(*R*)-isomer, 41.0 min for (+)-(*S*)-isomer.

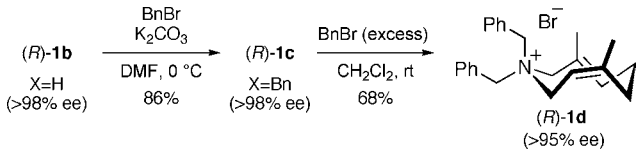
(10) CD spectroscopy was measured by a stopped-flow procedure.

(11) The half-life was calculated by the chiral HPLC measurement of enantiopurity; enantiopurity of **1a** decreased to 93% ee from >98% ee within 21 days in hexane at 25 °C.



Enantioenriched amine **1b** was convertible to corresponding tertiary amine and also quaternary ammonium salt without loss of its planar chirality. For example, a reaction of (*R*)-**1b** (>98% ee) with slightly excess amount of benzyl bromide at 0 °C provides benzylamine **1c** (>98% ee) (Scheme 3). Further benzylation of **1c** gave planar chiral

Scheme 3. Synthesis of Amine **1c** and Ammonium Salt **1d**

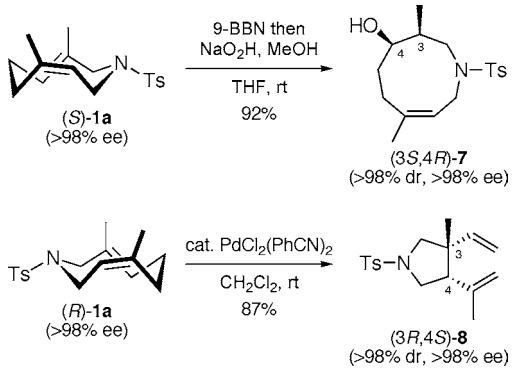


quaternary ammonium salt **1d** (>95% ee)[13] which serves as a potentially useful chiral phase-transfer catalyst.[14]

At this stage, we turned our attention to the transmission of planar chirality in **1a** to central chirality by the transformation of olefinic moieties. Gratifyingly, hydroboration of enantioenriched (*S*)-**1a** (>98% ee) using 9-BBN proceeded stereospecifically to give (3*S*,4*R*)-**7** exclusively in excellent yield (92%) (Scheme 4).[15−17]

Also transannular reaction of (*R*)-**1a** with Pd(II)-catalyzed Cope rearrangement gave pyrrolidine (3*R*,4*S*)-**8** (>98% dr, >98% ee) in 87% yield.[15,18−20] These results clearly show that the planar chiral **1** is a valuable source for nitrogen-containing compounds with central chiralities.

Scheme 4. Chirality Transformation of **1a**



In summary, we have described a synthetic and stereochemical study of a novel class of chiral amine and its derivatives. Incorporation of two double bonds in nitrogen-heterocycles not only contributes to the conformational rigidity relevant to planar chirality, but also provides the unique possibility for their stereospecific transformation. A wide range of their synthetic applications as well as elucidation of origin of their planar chirality are now in progress in our laboratory.

Acknowledgment. This research was supported in part by a Grant-in-Aid for Scientific Research on Priority Areas (A) "Exploitation of Multi-Element Cyclic Molecules" and "Creation of Biologically Functional Molecules", Basic Area (B) No. 14350473 and The 21st Century COE Program "Creation of Molecular Diversity and Development of Functionalities" from the Ministry of Education Culture, Sports, Science and Technology, Japan.

Supporting Information Available: Experimental procedures, characterization data for new compounds, and X-ray crystallographic data (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(12) Stereochemical stability of **1b** under a number of reaction conditions was confirmed by the tosylation (TsCl, Et_3N, DMAP) followed by the measurement of enantiopurity of the resulting **1a**.

(13) Enantiomers of **1d** were barely separable by HPLC using CHIRALCEL OD-RH (4.6 × 150 mm), MeOH/0.1 M aq KPF_6 = 9/1, 0.5 mL/min.

(14) These results will be reported separately.

(15) The absolute stereochemistry of **7** and **8** was deduced from the configuration of **1a** and the steric course of the reactions.

(16) The relative stereochemistry of alcohol **7** was determined by the X-ray analysis of a racemic one, see ref 6.

(17) The high reactivity of C3−C4 olefin compared with that of C7−C8 is explainable by means of its distortion: the C3−C4 bond is twisted by ca. 30°, while the C7−C8 bond is almost flat (ca. 3°) in the X-ray crystallography.

(18) The relative stereochemistry of pyrrolidine **8** was determined by the NOE experiment.

(19) Pd(II)-catalyzed Cope rearrangement, see: Overman, L. E.; Renaldo, A. F. *Tetrahedron Lett.* **1983**, *24*, 3757−3760.

(20) Thermal Cope rearrangement of (*R*)-**1a** in refluxing toluene provides (3*R*,4*S*)-**8** in 98% yield with significant racemization (10% ee). A racemization was probably caused before the rearrangement.