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Stereoselective Multimodal Transformations of Planar Chiral 9-Membered Diallylic Amides

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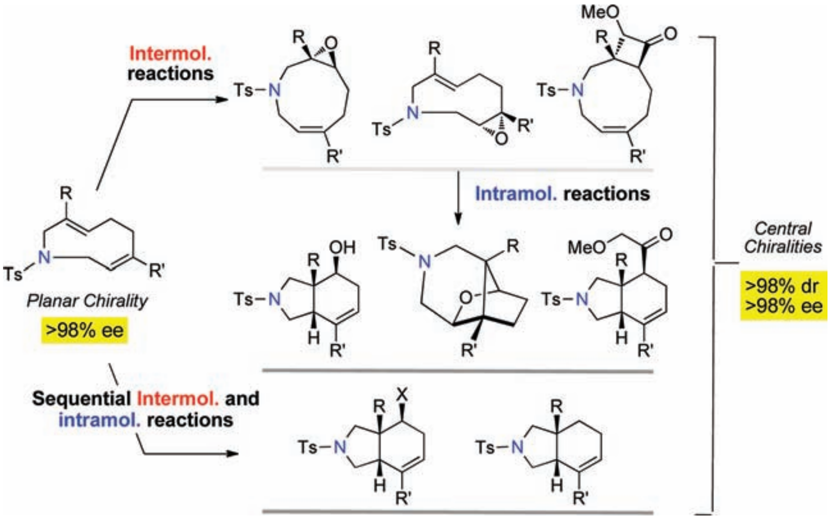
ABSTRACT



Intermolecular reactions of planar chiral 9-membered diallylic amides provide a variety of bicyclic compounds with central chiralities in a stereospecific fashion with high group selectivity. Lewis-acid-promoted intramolecular reactions of the obtained bicyclic compounds provide transannular products in a stereospecific fashion. Furthermore, a direct transannular reaction of diallylic amide involving sequential intermolecular–intramolecular reactions has been developed.

The stereochemical study of macrocyclic alkenes is classical and an important issue in structural organic chemistry and has attracted much attention in connection with stereoselective transformations of conformationally restricted olefins and their application for stereoselective synthetic approaches.[1] It is well-known that the olefinic moiety in medium-sized cyloalkenes is approximately perpendicular to the plane of the ring. Since one face of the olefinic π-system is severely hindered by the position of the allylic moiety and by the transannular ring moiety, it would be expected that an intermolecular reaction would only occur from the outer peripheral face. To the contrary, intramolecular transannular reactions only occur from the

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(1) (a) *Conformational Analysis of Medium-Sized Heterocycles*; Glass, R. S., Ed.; VCH Publishers, Inc.: New York, 1988. (b) *Stereochemistry of Organic Compounds*; Eliel, E. L., Wilen, S. H., Mander, L. N., Eds.; Wiley: New York, 1994.

(2) For a review of transannular reactions in medium-sized rings, see: (a) Cope, A. C.; Martin, M. M.; McKervey, M. A. *Q. Rev., Chem. Soc.* **1966**, *20*, 119–152. For reviews of stereoselective transformation of macrocyclic compounds, see: (b) Still, W. C.; Galynker, I. *Tetrahedron* **1981**, *37*, 3981–3996. (c) Nubbemeyer, U. *Eur. J. Org. Chem.* **2001**, 1801–1816.

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inner peripheral face.[2] On the basis of this stereochemical principle, the stereoselective transformation of alkenes has been accomplished in conformationally restricted macrocylic systems.[3] However, this kind of strategy is often prevented by the number of stable conformers and their easy interconversion by low-energy-barrier pseudorotation.

Recently, we have reported a novel cyclic amide **1** that has only two enantiomeric conformers at ambient temperature and displays stable planar chirality arising from its topological constraint (Figure 1).[4] Both of its two olefins are approximately perpendicular to the ring and, hence, amide **1** will be a superior substrate for the abovementioned stereoselective transformation. Herein, we report the stereo- and group-selective transformation of **1** by a variety of intermolecular reactions and a stereospecific transannular reaction of the resulting products.

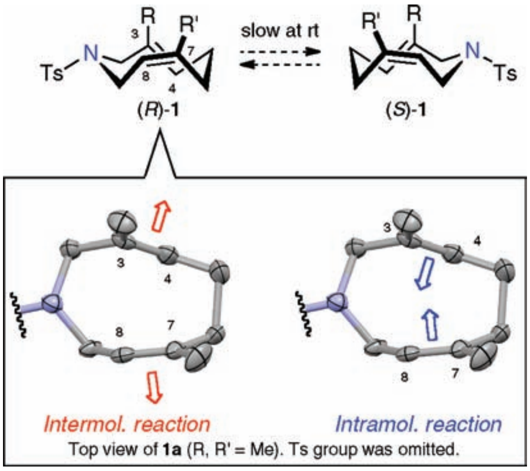
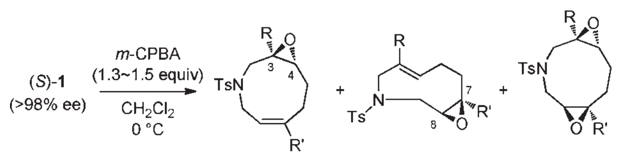


Figure 1. Stable confomers of **1** and their expected reaction sites.

At the outset, we examined the epoxidation reaction of **1** using *m*-CPBA (Scheme 1).[5] A reaction of (*S*)-**1a** (R, R′ = Me) (>98% ee) with 1.3 equiv of *m*-CPBA at 0 °C for 4 h provided C3–C4 epoxide (3*R*, 4*R*)-**2a**, C7–C8 epoxide (7*R*, 8*S*)-**3a**, and diepoxide (3*R*, 4*R*, 7*R*, 8*S*)-**4a** in 64, 10, and 24% yields, respectively.[6,7] The observed group selectivity between the C3–C4 olefin and C7–C8 olefin can be explained by its distortion: the C3–C4 bond is twisted by ca. 30°, while the C7–C8 bond is almost flat (ca. 3°) as per X-ray crystallographic analyses.[4a,8,9] A similar reaction of (*S*)-**1b** (R, R′ = H) (>98% ee) also provides the C3–C4 epoxide (3*R*, 4*R*)-**2b** as the major product in 72% yield, although it requires a much longer reaction time [*m*-CPBA (1.5 equiv) at 0 °C for 22 h]. All of the obtained epoxides **2**–**4** are diastereomerically and enantiomerically pure, and their stereochemistry attests to the fact that the epoxidation reaction only occurs from the outer peripheral faces, as we expected.

Scheme 1. Epoxidation of **1**

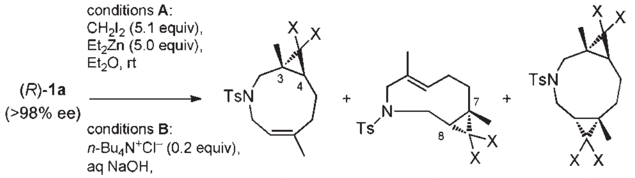


	(3*R*,4*R*)-**2**[a]	(7*R*,8*S*)-**3**[a]	(3*R*,4*R*,7*R*,8*S*)-**4**[a]
from (*S*)-**1a** (R, R' = Me)	64%	10%	24%
from (*S*)-**1b** (R, R' = H)	72%	11%	11%

[a] >98% dr, >98% ee

Similar C3–C4 olefin selectivity and stereoselectivity were observed in cyclopropanation reactions. As shown in Scheme 2, both the Simmons-Smith reaction and dichlorocyclopropanation provide **5** (X = H or Cl) as the major product.

Scheme 2. Cyclopropanation of **1a**



	5[a]	**6**[a]	**7**[a]
condition A (X = H)	69%	2%	16%
condition B (X = Cl)	44%	14%	36%

[a] >98% dr, >98% ee

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(3) For representative examples of natural product synthesis based on stereoselective transformation of macrocyclic compounds, see: (a) Still, W. C. *J. Am. Chem. Soc.* **1979**, *101*, 2493–2495. (b) Larionov, O. V.; Corey, E. J. *J. Am. Chem. Soc.* **2008**, *130*, 2954–2955.

(4) (a) Tomooka, K.; Suzuki, M.; Shimada, M.; Yanagitsuru, S.; Uehara, K. *Org. Lett.* **2006**, *8*, 963. For the ether congeners, see: (b) Tomooka, K.; Komine, N.; Fujiki, D.; Nakai, T.; Yanagitsuru, S. *J. Am. Chem. Soc.* **2005**, *127*, 12182. For the organosulfur congeners, see: (c) Uehara, K.; Tomooka, K. *Chem. Lett.* **2009**, *38*, 1028.

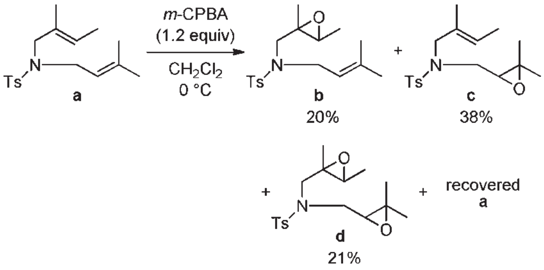
(5) Enantio-enriched **1** can be prepared by the enantioselective cyclization of readily available acyclic precursors, see: Tomooka, K.; Uehara, K.; Nishikawa, R.; Suzuki, M.; Igawa, K. *J. Am. Chem. Soc.* **2010**, *132*, 9232–9233.

(6) All new compounds were fully characterized by ^{1}H-, ^{13}C NMR, IR, and HRMS analysis. The enantiomeric purity of products was determined by a HPLC analysis using a chiral stationary column; see Supporting Information for details.

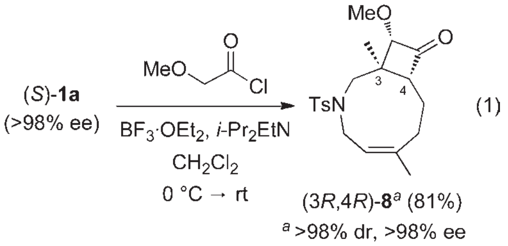
(7) The structures of **4a**, **7b**, **8**, **10a**, **11**, **12a**, **12c**, **13b**, and **14b** were determined by X-ray crystallography; see Supporting Information.

(8) The relationship between alkene strain and reactivity of epoxidation has been investigated, see: Shea, K. J.; Kim, J.-S. *J. Am. Chem. Soc.* **1992**, *114*, 3044–3051.

(9) In contrast, a similar epoxidation of acyclic congener **a** shows low and opposite group selectivity (**b**/**c** = 34: 66).

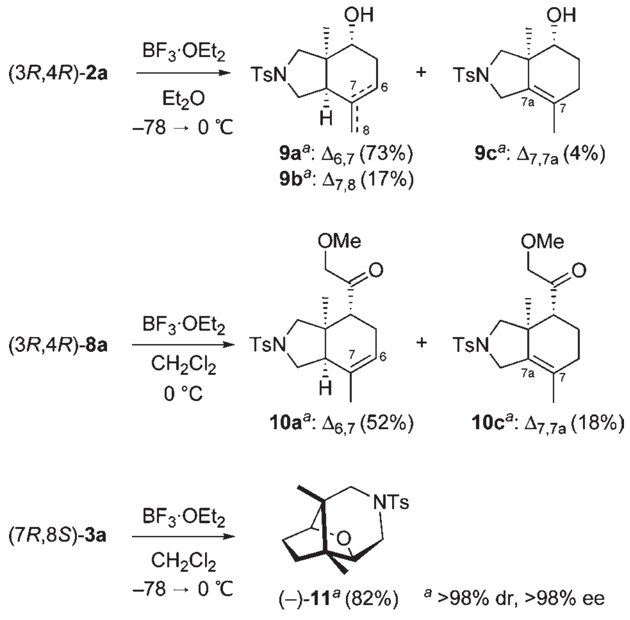


A much higher group selectivity was realized in a [2 + 2]-cycloaddition reaction with alkoxyketene.[10,11] The reaction of (*S*)-**1a** (> 98% ee) with methoxyketene, which was prepared in situ from methoxyacetyl chloride and Hunig's base in the presence of $BF_3 \cdot OEt_2$, yields C3–C4 cyclobutanone **8** as the sole product in 81% yield with > 98% dr and > 98% ee along with recovered (*S*)-**1a** (19%) (eq 1).[12]



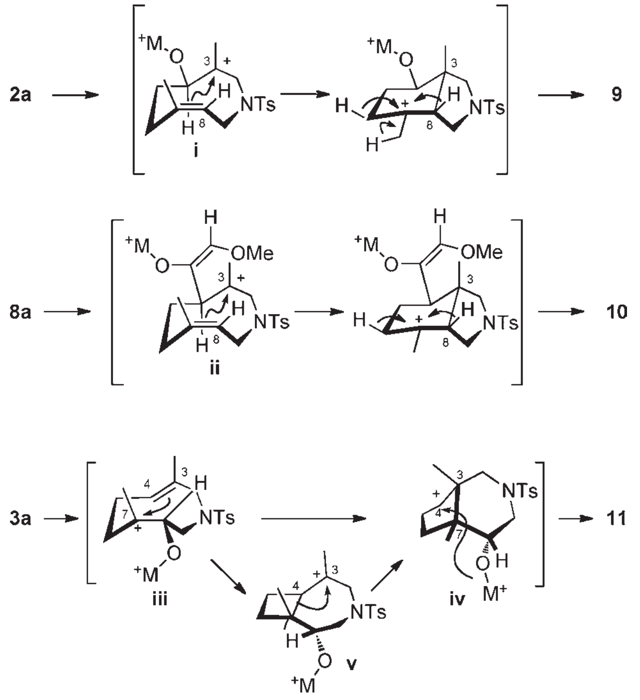
The obtained compounds **2**, **3**, and **8** have strained small rings, which can be activated by Lewis acids, and the C7–C8 or C3–C4 olefin is properly located at the back side of the rings. Therefore, they would be suitable substrates for transannular reactions. As shown in Scheme 3, $BF_3 \cdot OEt_2$-promoted reactions of (3*R*, 4*R*)-**2a** and (3*R*, 4*R*)-**8a** provide octahydroisoindole derivatives **9** and **10**, respectively, as a mixture of the regioisomer of the olefin moiety in good to excellent yields with high stereoselectivity. In contrast, a similar reaction with (7*R*, 8*S*)-**3a** provides a unique oxa- and aza-tricyclo decane **11** as the sole product, which again occurs with high stereoselectivity.

Scheme 3. $BF_3 \cdot OEt_2$-Promoted Transannular Reactions of **2a**, **3a**, and **8a**



Plausible mechanisms for these transannular reactions are shown in Scheme 4. The reactions of **2a** and **8a** should involve C3-cation intermediates **i** or **ii**, which are formed by epoxide or cyclobutanone ring cleavage, respectively. Then, a C–C bond formed between C3 and C8 (i.e., C3 and C7a in **9** and **10**) followed by the elimination of a proton to yield **9** and **10**. In a similar manner, the reaction of **3a** forms a C7-cation intermediate **iii**, which provides the C4-cation intermediate **iv** via direct C3–C7 bond formation or via skeletal rearrangement of the C3-cation intermediate **v**. Then, C4–O bond formation provides **11**.

Scheme 4. Plausible Mechanisms for the Transannular Reactions of **2a**, **3a**, and **8a**



Furthermore, we found a direct transannular reaction of **1a**, as shown in Scheme 5. The reaction of **1a** with NBS or NIS provides the octahydroisoindole derivatives **12** or **13**, respectively, as a mixture of the regioisomer of the olefin moiety in an excellent yield with high stereoselectivity.[13]

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[10] The related [2 + 2] cycloaddition of alkoxyketene has been reported, see: Matsui, S.; Kinbara, K.; Saigo, K. *Tetrahedron Lett.* **1999**, *40*, 899–902.

[11] The reaction was performed by a slightly modified procedure of the one described by: Yoon, T. P.; Dong, V. M.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **1999**, *121*, 9726–9727.

[12] A similar reaction without Lewis acid also provides **8**, albeit in low yield (30%) along with recovered **1a** (67%).

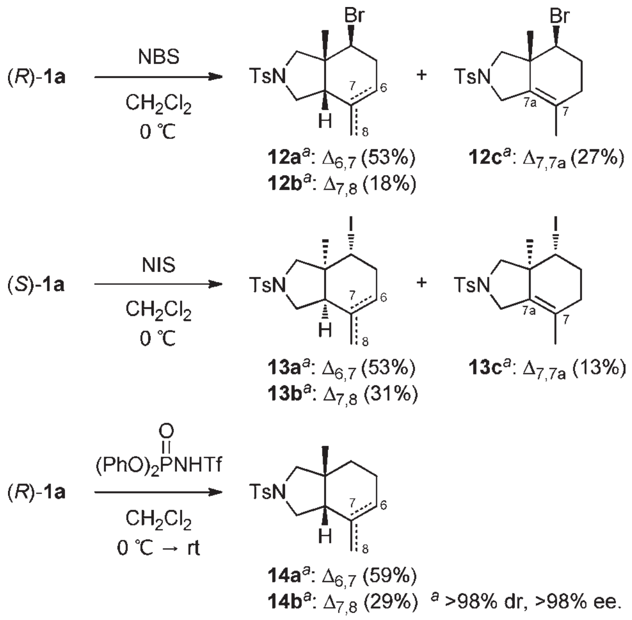
[13] It has been reported that halogenation-induced cyclization of 1-aza-4-cyclooctene provides transannular aminohalogenation product, see: (a) Wilson, S. R.; Sawicki, R. A. *J. Org. Chem.* **1979**, *44*, 287–291. (b) Royzen, M.; Yap, G. P. A.; Fox, J. M. *J. Am. Chem. Soc.* **2008**, *130*, 3760–3761.

[14] For the pioneering work of phosphoramide-promoted reaction, see: Nakashima, D.; Yamamoto, H. *J. Am. Chem. Soc.* **2006**, *128*, 9626–9627.

[15] For recent work of phosphoramide-promoted reaction, see: (a) Rueping, M.; Nachtsheim, B. J.; Moreth, S. A.; Bolte, M. *Angew. Chem., Int. Ed.* **2008**, *47*, 593–596. (b) Schneekloth, J. S., Jr.; Kim, J.; Sorensen, E. J. *Tetrahedron* **2009**, *65*, 3096–3101.

[16] A similar reaction using other acids such as $(PhO)_2POOH$ and CF_3COOH does not provide any transannular product; a substrate **1a** was recovered quantitatively.

Scheme 5. Direct Transannular Reactions of **1a**



In addition, a similar reaction using $(PhO)_2PONHTf$ provides **14** in a good yield.[14−16] These reactions should involve cationic activation at the C3−C4 olefin of **1a** from the outer face and transannular C4−C7 bond (i.e., C3−C7a bond in **14**) formation. Thus, the observed unique reactivity of **1a** is due to the high reactivity of the C3−C4 olefin and the presence of a properly located C7−C8 olefin.

In summary, we described stereoselective multimodal transformations of a planar chiral 9-membered diallylic amide to provide a variety of chiral molecules that are otherwise difficult to obtain. Further work is in progress to strengthen the synthetic utility of the planar chiral heterocycles.

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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.