Communication

Synthesis of trans-Cycloalkenes via Enantioselective Cyclopropanation and Skeletal Rearrangement

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Synthesis of *trans*-Cycloalkenes *via* Enantioselective Cyclopropanation and Skeletal Rearrangement

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Supporting Information Placeholder

ABSTRACT: An efficient one-pot two-step procedure for asymmetric synthesis of piperidine-fused *trans*-cycloalkenes is reported. The method comprises the initial enantioselective installation of another cyclopropane ring onto methylenecyclopropanes and the subsequent thermal skeletal rearrangement in which the installed as well as inherent cyclopropane rings are both opened. A concerted mechanism is proposed for the latter thermal rearrangement reaction together with a closed transition state model.

Both *cis* and *trans* isomers are synthetically accessible for cyclic alkenes consisting of more than 7 carbon atoms. Unlike acyclic alkenes, *trans* isomers of cyclic alkenes from seven- to ten-membered ring are less stable than their *cis* counterparts.[1] Seven-membered *trans*-cycloheptene is too distorted to retain its *trans* geometry at temperatures higher than –78 °C.[2] The torsion strain is alleviated by increment of the ring-size, and eight-membered *trans*-cyclooctene is stable at room temperature. Medium-sized cyclic *trans*-alkenes take twisted forms, and are characterized by planar chirality. The properties inherent to their unique structures have found a wide variety of applications in organic synthesis[3] and chemical biology.[4] Therefore, the development of stereoselective preparative methods of medium-sized cyclic *trans*-alkenes has been a subject of considerable investigation.[5] Yet, synthetic methods available for optically active ones are limited. There are only a few examples of enantioselective syntheses,[6] and the other precedents are based on either resolution of racemates[7] or multi-step derivatization of chiral pool molecules.[8] Now, we report a one-pot two-step procedure for the synthesis of enantioenriched piperidine-fused *trans*-cycloalkenes from achiral methylenecyclopropanes and triazoles. The procedure can be modified even to directly start from terminal alkynes in place of triazoles (Figure 1).

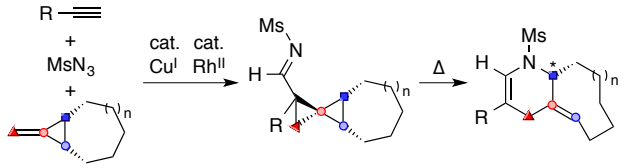
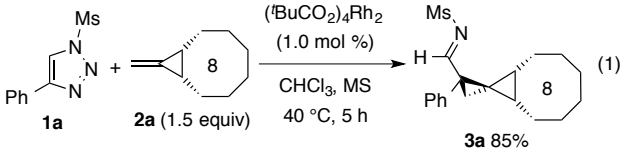
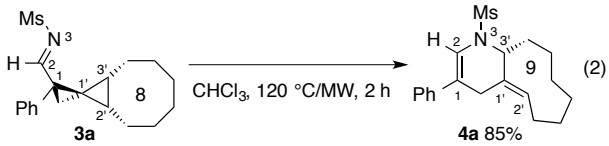


Figure 1. Construction of piperidine-fused *trans*-cycloalkenes from terminal alkynes, mesyl azide, and methylenecyclopropanes.

N-Sulfonyl-1,2,3-triazoles are readily prepared from terminal alkynes and *N*-sulfonyl azides using copper(I) catalyst.[9] Upon treatment with rhodium(II) or nickel(0) complexes, they generate metal complexes of α-imino carbenes, which subsequently react with various electron-rich compounds.[10] Fokin and co-workers reported a rhodium(II)-catalyzed, highly enantioselective cyclopropanation reaction of simple alkenes with *N*-sulfonyl-1,2,3-triazoles.[11] Our previous study[12] on the reaction of spiropentanes led us to examine the use of methylenecyclopropanes, hoping that enantioenriched spiropentanes became accessible.[13,14] Thus, we treated methylenecyclopropane **2a** (1.5 equiv), which was synthesized from *cis*-cyclooctene simply according to a literature procedure,[15] with 1-mesyl-4-phenyl-1,2,3-triazole (**1a**, 1.0 equiv) in the presence of (^{t}BuCO$_2$)$_4$Rh$_2$ (1.0 mol %) and 4 Å molecular sieves (MS) in $CHCl_3$ (0.2 M) at 40 °C (eq 1). The cyclopropanation reaction was complete in 5 h, and after chromatographic purification, α-imino spiropentane **3a** was obtained as a single diastereomer in 85% yield. The stereochemistry is explained by assuming that the carbenoid species has added onto the exocyclic C–C double bond of **2a** from its less-hindered side.



Next, the thermal reactivities[16] of **3a** were investigated, and an unprecedented rearrangement reaction was identified; when **3a** in $CHCl_3$ (0.2 M) was heated at 120 °C under microwave irradiation (MW) in a sealed microwave vial for 2 h, the piperidine-fused cyclononene **4a** was cleanly formed in a stereochemically pure form (85% isolated yield), and its nOe study in ^{1}H-NMR proved the *trans* geometry for its bridgehead double bond (eq 2). The C(1)–C(1') σ-bond, C(2')–C(3') σ-bond, and C(2)–N(3) π-bond of **3a** are cleaved, and instead the N(3)–C(3') σ-bond, C(1)–C(2) π-bond, and C(1')–C(2') π-bond are newly formed with **4a** with installation of a *trans* geometry for the C(1')–C(2') double bond. These bond cleavages and formations result in a structural reorganization of the tricyclic skeleton into the twisted bicyclic skeleton.



This thermal rearrangement reaction is generalized as depicted in Figure 2. If we focus on the cleavage of the C(1)–C(1') σ-bond occurring with **A** and the formation of the N(3)–C(3') σ-bond occurring with **B**, the former σ-bond migrates to the new position between the N(3) and C(3') atoms which are both two atoms removed from the bonded loci. In this sense, the present skeletal rearrangement can be described as a [3,3] sigmatropic rearrangement. In the case of the retro process[17] of the Claisen rearrangement from **C** to **D**, which would serve as a prototype for [3,3] sigmatropic rearrangement, the C(1)–C(1') σ-bond being cleaved with **C** is flanked by two

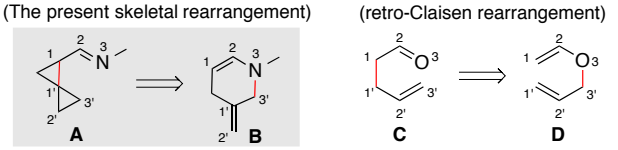
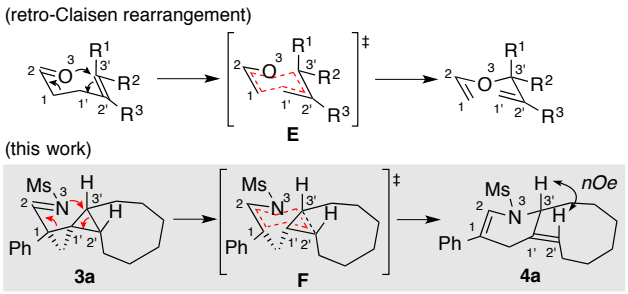


Figure 2. The general diagram of thermal rearrangement.

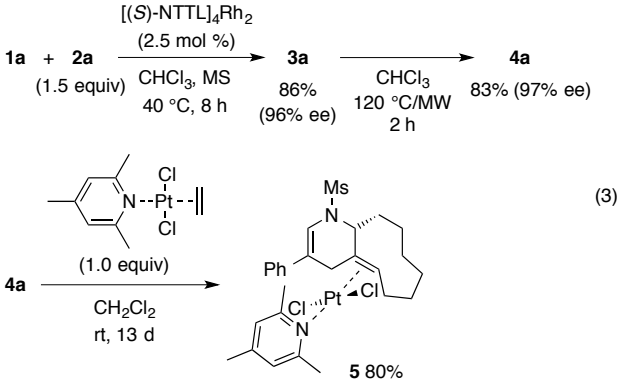
π-electron systems. Terminal sp^2 atoms [O(3) and C(3')] change into sp^3 atoms by losing a π-bond and gaining a new σ-bond between themselves. The structural deviation of **A** from **C** is that a cyclopropane ring replaces one π-electron system of **C**. With **A**, the σ-bond being cleaved is flanked by one π-electron system and one cyclopropane ring. The sp^3 C(3') loses the σ-bond to C(2') gaining a new σ-bond to N(3). The major driving force of the present skeletal rearrangement is presumably attributed to the release of the ring strain of the spirocyclic structure (*ca.* 61 kcal/mol), which is considerably larger than the double of the ring strain of a simple cyclopropane ring (*ca.* 28 kcal/mol).[18]

The transition state model **F** is proposed for the skeletal rearrangement of **3a** in analogy with that of the retro process of the Claisen rearrangement reaction (Scheme 1).[17] The sigmatropic interconversion between γ,δ-unsaturated aldehydes and allyl vinyl ethers is assumed to proceed *via* a closed six-membered chair-like transition state model **E**. The α-imino spiropentane **3a** can be considered as the cyclopropane homolog of γ,δ-unsaturated aldehydes, and therefore, the transition state model **F** which is conformationally analogous to **E** can be expected on the mechanistic pathway from **3a** to **4a**. The transition state model **F** reasonably depicts how the stereochemistry at the C(2') position dictates the geometry of the resulting bridgehead double bond. The substituent at C(2') orients downward in parallel to the methylene bridge of the adjacent cyclopropane ring, and upon skeletal rearrangement, the π-bond develops in between with these orientations retained. Further support was lent to the transition state model **F** by additional experimental results (*vide infra*).

Scheme 1. The Proposed Transition State Model

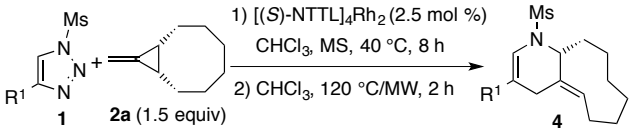


Thus, the piperidine-fused *trans*-cyclononene **4a** was stereoselectively constructed from **2a** through the cyclopropanation with **1a** and subsequent thermal skeletal rearrangement. Next, we challenged the asymmetric synthesis of **4a** by using chiral rhodium(II) catalysts in the first cyclopropanation reaction. As with the case of cyclopropanation of simple alkenes,[11] an excellent enantioselectivity of 96% ee was observed with **3a** when [(*S*)-NTTL]$_4$Rh$_2$ (2.5 mol %, NTTL = *N*-naphthoyl-*tert*-leucinate) was used as the catalyst (eq 3). Of note was that three new chiral centers were stereoselectively installed in a single step. Then, the enantioenriched spiropentane **3a** was subjected to the second skeletal rearrangement reaction. The resulting *trans*-cyclononene **4a** exhibited an enantiopurity of 97% ee to assure the integrity of chirality transfer within an experimental accuracy during the skeletal rearrangement. In order to determine the absolute stereochemistry of **4a**, we followed a procedure in literature[19] to treat it with *trans*-$PtCl_2$(2,4,6-collidine)(η^2-ethylene). The resulting platinum(II) complex **5** was obtained as a crystalline solid and its single-crystal X-ray analysis proved the absolute stereochemistry.[20]



The two-step transformation of **1a** and **2a** into the enantioenriched **4a** was successfully integrated into a one-pot procedure (Table 1).[21] The *trans*-cyclononene **4a** was prepared in 88% yield with 97% ee by applying the two reaction conditions to the mixture of **1a** and **2a** in sequence (entry 1). Various other 4-aryl-substituted triazoles **1b–e** were subjected to the one-pot procedure, and similar results were obtained when a mixed solvent of chloroform/methanol was used; *trans*-cyclononenes **4b–e** were produced in good yield with enantioselectivities ranging from 93% ee to 98% ee (entries 2–5). 4-(1-Cyclohexenyl)triazole **1f** was also a suitable triazole (entry 6). On the other hand, a complex mixture arose from alkyl-substituted triazoles, because the latter thermal skeletal process was more sluggish.

Table 1. One-Pot Transformation of Triazoles 1 and 2a[a]



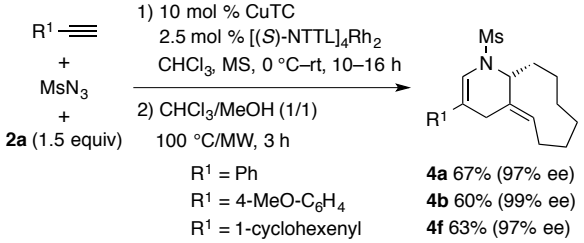
entry	1	R^1	4	yield (%)[b]	ee (%)
1	**1a**	Ph	**4a**	88	97
2	**1b**	4-MeO-C_6H_4	**4b**	82[c]	98
3	**1c**	4-CF_3-C_6H_4	**4c**	91[c]	97
4	**1d**	2-naphthyl	**4d**	88[c]	96
5	**1e**	3-thienyl	**4e**	93[c]	93
6	**1f**	1-cyclohexenyl	**4f**	83	98

[a]A 0.2 mmol scale. [b]Yield of isolated product (average of two runs). [c]The second step [$CHCl_3$/MeOH (1/1), 100 °C/MW, 3 h].

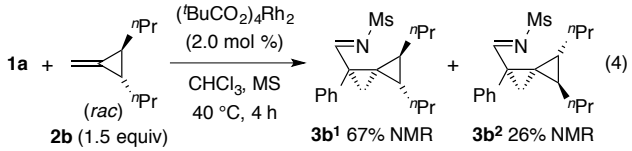
Exemplified in Scheme 2 is an ultimate one-pot procedure starting directly from terminal alkynes. An arylethyne, mesyl azide, **2a**, CuTC, [(*S*)-NTTL]$_4$Rh$_2$, MS, and $CHCl_3$ were all placed in a reaction vessel, and the reaction mixture was stirred from 0 °C to 25 °C for 10–16 h, and subsequently at 100 °C under MW irradiation for additional 3 h. Finally, the cooled reaction mixture was subjected to chromatographic purification. The products **4a**, **4b**, and **4f** were isolated in 60–67 % overall yields with excellent enantioselectivities (97–99% ee)

according to this all-in-one-pot procedure. It is notable that the molecular complexities including the absolute stereochemistry have dramatically increased through this one-pot process, during which a work-up procedure is executed only once.

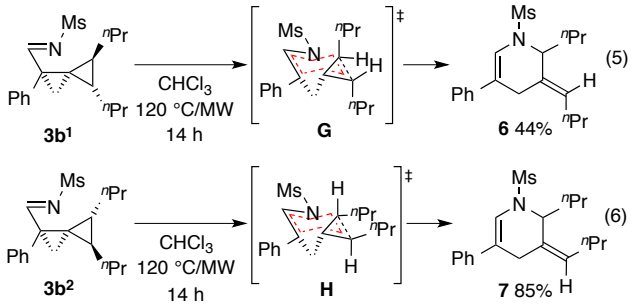
Scheme 2. One-Pot Synthesis Starting from Terminal Alkynes



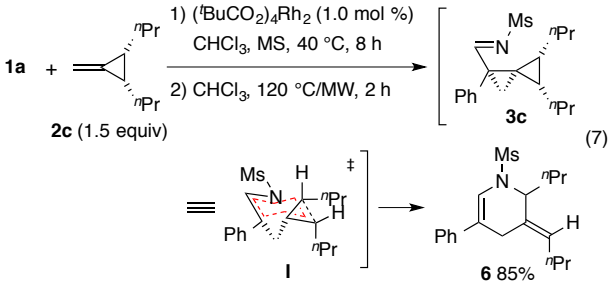
In order to corroborate the transition state model **F** proposed above, the two-step transformation was examined in more detail using a pair of symmetrically disubstituted methylenecyclopropanes **2b** and **2c** prepared from *trans*- and *cis*-oct-4-ene, respectively. The cyclopropanation reaction of the racemic **2b** with the triazole **1a** using $(^t BuCO_2)_4Rh_2$ as the catalyst yielded a 5:2 mixture of diastereomers **3b**[1] and **3b**[2] (eq 4). The diastereomers were separated by HPLC, and their structures were determined by a set of NMR analyses (DEPT, COSY, HMQC, HMBC, and nOe).



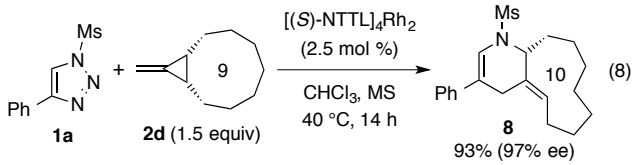
The subsequent skeletal rearrangement of the major diastereomer **3b**[1] under the standard thermal conditions (120 °C/MW) was slower than that of **3a** to afford piperidine derivative **6** in 44% yield after 14 h (eq 5). Noteworthy was the exclusive stereochemistry of the exocyclic double bond; the propyl substituent is oriented away from the other propyl group. In contrast, the rearrangement of the minor diastereomer **3b**[2] was much faster than that of **3b**[1] to selectively produce the geometrical isomer **7** with its propyl substituent oriented in the opposite direction in 85% yield (eq 6). The stereospecificity observed with the reaction using the pair of the diastereomers **3b**[1] and **3b**[2] is well accounted for by assuming the transition state models **G** and **H**, which are similar to the model **F** in Scheme 1. Moreover, the transition state models **G** and **H** explain the slower reaction of **3b**[1]; the transition state model **G** having the two propyl substituents in pseudoaxial positions would be energetically higher than **H** having the two propyl substituents in pseudoequatorial positions.



On the other hand, the one-pot, two-step transformation of **2c**, prepared from *cis*-oct-4-ene, using **1a** and $(^t BuCO_2)_4Rh_2$ yielded the piperidine derivative **6** with the propyl substituent oriented away from the other propyl group (eq 7). The first cyclopropanation reaction would have occurred selectively from the less-hindered side of **2c** to form the intermediary spiropentane **3c** diastereoselectively as with the case of **2a**. Granting this stereoselectivity, the double bond stereochemistry of **6** is in accordance with the proposed transition state model **I** with the two propyl groups oriented downward, one is in a pseudoaxial position and the other is in a pseudoequatorial position, which is also virtually similar to the model **F**.



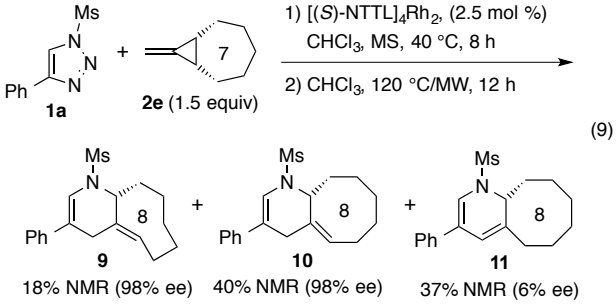
Methylenecyclopropanes derived from cycloalkenes of other ring-sizes than eight were also employed in the sequential transformation. When 10-methylenebicyclo[7.1.0]decene (**2d**), derived from *cis*-cyclononene, was subjected to the cyclopropanation reaction with **1a** using $[(S)\text{-NTTL}]_4Rh_2$ as the catalyst at 40 °C, the second skeletal rearrangement reaction occurred concurrently with the first cyclopropanation to directly furnish *trans*-cyclodecene **8** in 94% yield with 97% ee (eq 8). We suppose that the faster reaction may be ascribed to the conformation of the intermediate spiropentane derived from **2d**; the intermediate spiropentane would be conformationally closer to the transition state of the skeletal rearrangement than in the case of **3a** so that a smaller structural change is required to reach the transition state.



The stability of planar chirality of medium-sized *trans*-cycloalkenes generally decreases with increment in ring size, and *trans*-cyclononene racemizes considerably faster ($t_{1/2}$ = 6 s at 30 °C) than *trans*-cyclooctene ($t_{1/2}$ = ~10^5 years at 30 °C) through swiveling of the twisted double bond.[22] Nonetheless, double bond swiveling was not observed with both **4a** and **8** up to 120 °C. We suppose that the twisted conformation is locked by the central chirality at the bridgehead position,[8a] which has been originally set in the achiral molecules upon the enantioselective cyclopropanation.

On the other hand, the eight-membered *trans*-cyclooctene derivative **9** (eq 9) was expected to be more strained than the cyclononene and cyclodecene counterparts **4a** and **8**.[1] We next tried to synthesize **9** by using 8-methylenebicyclo[5.1.0]octane (**2e**), derived from *cis*-cycloheptene. When the standard conditions of the one-pot two-step transformation (2.5 mol % of $[(S)\text{-NTTL}]_4Rh_2$ at 40 °C for 8 h, then at 120 °C/MW for 2 h) were applied to a mixture of **1a** and **2e**, the major product was the corresponding α-imino spiropentane because the second rearrangement reaction was considerably slower than that of **3a**. Then, the duration of time of heating (120 °C/MW) for the second skeletal rearrangement was extended to 12 h, and a mixture of *trans*-cyclooctene **9** (18% NMR yield, 98% ee), *cis*-cyclooctene **10** (40% NMR yield, 98% ee), and 1,3-diene **11**[23] (37% NMR yield, 6% ee) was generated. Although it was pos-

sible to separate them by HPLC, a mixture of **9** and **10** (5:2)[24] resulted again even when the purified *trans*-cyclooctene **9** was left in vacuo at room temperature for 9 h. Thus, decrease in ring size from nine to eight brought about a significant increase in the structural strain.



In summary, we have developed a new method for the asymmetric synthesis of piperidine-fused *trans*-cycloalkenes, which comprises the enantioselective construction of a cyclopropane ring and the thermal skeletal rearrangement opening the two cyclopropane rings.

ASSOCIATED CONTENT

Supporting Information. Experimental procedures, spectral data for the new compounds, and details of the X-ray analysis. This material is available free of charge via Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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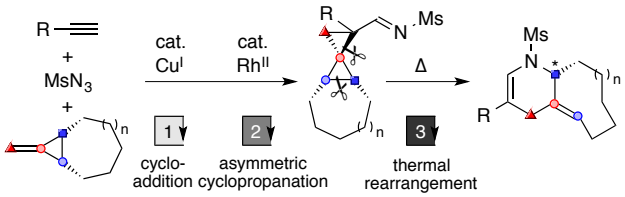
REFERENCES

(1) Barrows, S. E.; Eberlein, T. H. *J. Chem. Educ.* **2005**, *82*, 1334.
(2) Squillacote, M. E.; DeFellipis, J.; Shu, Q. *J. Am. Chem. Soc.* **2005**, *127,* 15983 and references therein.
(3) (a) Dorr, H.; Rawal, V. H. *J. Am. Chem. Soc.* **1999**, *121,* 10229. (b) Lledó, A.; Fuster, A.; Revés, M.; Verdaguer, X.; Riera, A. *Chem. Commun.* **2013**, *49*, 3055.
(4) Selvaraj, R.; Fox, J. M. *Curr. Opin. Chem. Biol.* **2013**, *17*, 753 and references therein.
(5) (a) Nakazaki, M.; Yamamoto, K.; Yanagi, J. *J. Am. Chem. Soc.* **1979**, *101*, 147. (b) Royzen, M.; Yap, G. P. A.; Fox, J. M. *J. Am. Chem. Soc.* **2008**, *130*, 3760. (c) Wang, X.-N.; Krenske, E. H.; Johnston, R. C.; Houk, K. N.; Hsung, R. P. *J. Am. Chem. Soc.* **2014**, *136*, 9802 and references therein.
(6) (a) Deiters, A.; Mück-Lichtenfeld, C.; Fröhlich, R.; Hoppe, D. *Chem. Eur. J.* **2002**, *8*, 1833. (b) Tomooka, K.; Uehara, K.; Nishikawa, R.; Suzuki, M.; Igawa, K. *J. Am. Chem. Soc.* **2010**, *132*, 9232 and references therein.
(7) (a) Tomooka, K.; Komine, N.; Fujiki, D.; Nakai, T.; Yanagitsuru, S. *J. Am. Chem. Soc.* **2005**, *127*, 12182. (b) Tomooka, K.; Suzuki, M.; Shimada, M.; Yanagitsuru, S.; Uehara, K. *Org. Lett.* **2006**, *8*, 963.
(8) (a) Nakazaki, M.; Naemura, K.; Nakahara, S. *J. Org. Chem.* **1979**, *44*, 2438. (b) Sudau, A.; Münch, W.; Nubbemeyer, U.; Bats, J. W. *J. Org. Chem.* **2000**, *65*, 1710. (c) Larionov, O. V.; Corey, E. J. *J. Am. Chem. Soc.* **2008**, *130*, 2954. (d) Prévost, M.; Woerpel, K. A. *J. Am. Chem. Soc.* **2009**, *131*, 14182.
(9) Raushel, J.; Fokin, V. V. *Org. Lett.* **2010**, *12*, 4952.
(10) Davies, H. M. L.; Alford, J. S. *Chem. Soc. Rev.* **2014**, *43*, 5151 and references therein.
(11) Chuprakov, S.; Kwok, S. W.; Zhang, L.; Lercher, L.; Fokin, V. V. *J. Am. Chem. Soc.* **2009**, *131*, 18034.
(12) Matsuda, T.; Tsuboi, T.; Murakami, M. *J. Am. Chem. Soc.* **2007**, *129*, 12596.
(13) For a review: (a) D'yakonov, V. A.; Trapeznikova, O. A.; de Meijere, A.; Dzhemilev, U. M. *Chem. Rev.* **2014**, *114*, 5775. For recent examples: (b) Charette, A. B.; Jolicoeur, E.; Bydlinski, G. A. S. *Org. Lett.* **2001**, *3*, 3293. (c) Yashin, N. V.; Averina, E. B.; Grishin, Y. K.; Kuznetsova, T. S.; Zefirov, N. S. *Synthesis* **2006**, 279.
(14) A singular example of related intramolecular cyclopropanation of a methylenecyclopropane moiety is reported: Chen, K.; Zhu, Z.-Z.; Zhang, Y.-S.; Tang, X.-Y.; Shi, M. *Angew. Chem. Int. Ed.* **2014**, *53*, 6645.
(15) Arora, S.; Binger, P. *Synthesis* **1974**, 801.
(16) For a review: (a) de Meijere, A.; Kozhushkov, S. I. *Chem. Rev.* **2000**, *100*, 93. For selected examples: (b) Gajewski, J. J. *J. Am. Chem. Soc.* **1970**, *92,* 3688. (c) Gajewski, J. J.; Burka, L. T. *J. Am. Chem. Soc.* **1972**, *94,* 8865. (d) Brinker, U. H.; Wilk, G.; Gomann, K. *Angew. Chem. Int. Ed. Engl.* **1983**, *22*, 868. (e) Wiberg, K. B.; Snoonian, J. R. *J. Org. Chem.* **1998**, *63*, 1390. (f) Anichini, B.; Goti, A.; Brandi, A.; Kozhushkov, S. I.; de Meijere, A. *Chem. Commun.* **1997**, 261.
(17) For reviews: (a) Carpenter, N. E.; Overman, L. E. *Org. React.* **2005**, *66*, 1. (b) Majumdar, K. C.; Bhattacharyya, T.; Chattopadhyay, B.; Sinha, B. *Synthesis* **2009**, 2117. For recent examples: (c) Boeckman, R. K.; Genung, N. E.; Chen, K.; Ryder, T. R. *Org. Lett.* **2010**, *12*, 1628. (d) Levin, S.; Nani, R. R.; Reisman, S. E. *J. Am. Chem. Soc.* **2011**, *133,* 774.
(18) Beckhaus, H.-D.; Rüchardt, C.; Kozhushkov, S. I.; Belov, V. N.; Verevkin, S. P.; de Meijere A. *J. Am. Chem. Soc.* **1995**, *117,* 11854.
(19) Tomooka, K.; Shimada, M.; Uehara, K.; Ito, M. *Organometallics* **2010**, *29*, 6632.
(20) The absolute configurations of other products were assigned by analogy.
(21) Jones, A. C.; May, J. A.; Sarpong, R.; Stoltz, B. M. *Angew. Chem. Int. Ed.* **2014**, *53*, 2556.
(22) Cope, A. C.; Banholzer, K.; Keller, H.; Pawson, B. A.; Whang, J. J.; Winkler, H. J. S. *J. Am. Chem. Soc.* **1965**, *87,* 3644.
(23) A further study for the formation of **11** with racemization is under way.
(24) For a possible mechanism of isomerization from **9** to **10**, see reference 2.

TOC Graphic:


R
+
MsN3
+
n
cat.
CuI
cat.
RhII
1
2
cyclo-
addition
asymmetric
cyclopropanation
R
N
Ms
n
Δ
3
thermal
rearrangement
Ms
N
R
n