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Axially Chiral Macrocyclic *E*-Alkene Bearing Bisazole Component Formed by Sequential C–H Homocoupling and Ring-Closing Metathesis

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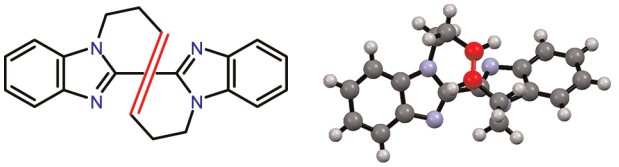
ABSTRACT



Clipping by ring-closing metathesis freezes rotation of a C–C bond to result in forming axial chirality. Treatment of bisbenzimidazole bearing an *N*-(3-butenyl) substituent with a Grubbs' catalyst undergoes ring-closing metathesis, in which the stereochemistry of the thus formed olefin was exclusively *E*-form. Analysis by HPLC with a chiral stationary column confirmed clear baseline separation of each enantiomer.

Medium- to large-membered molecules attract much attention to their stereochemical and conformational characteristics, and it is thus interesting to design functionalities induced by such molecular structures.[1] It is of topochemical interest whether linkage between both ends of a rigid rod takes place in a twisted manner (**A**) or not (**B**) when ring formation is conducted on a rigid molecule such as a biaryl with a long flexible alkyl chain as illustrated in Figure 1. Synthesis of such a molecule by ring formation has not been necessarily easy due to the competition of an intra- vs intermolecular reaction during cyclization. However, the discovery of ring-closing metathesis (RCM) with a ruthenium catalyst allowed extensive studies on a variety

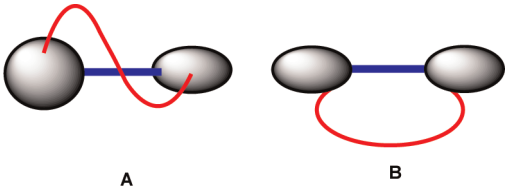


Figure 1. Possible conformation of a rod molecule in forming a large-membered ring.

of macrocyclic compounds.[2] A wide range of macrocycles including natural products and biologically active compounds are synthesized by employing the metathesis strategy. Accordingly, it would also be possible to give a solution to the above issue shown in Figure 1 if ring-closing metathesis is applied to the linkage in the rigid compound. Herein, it was first achieved with a bisazole derivative, which is a class of heteroaromatic compounds. Organic molecules bearing a heteroaromatic moiety are widely employed in materials science and found in various

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(1) (a) Marshall, J. *Acc. Chem. Res.* **1980**, *13*, 213–218. (b) Eliel, E. L.; Wilen, S. H.; Manger, L. N. *Stereochemistry of Organic Compounds*; Wiley: New York, U.S.A., 1994. (c) Tomooka, K.; Ezawa, T.; Inoue, H.; Uehara, K.; Igawa, K. *J. Am. Chem. Soc.* **2011**, *133*, 1754–1756. (d) Sauer, L. O.; Barriault, L. *J. Am. Chem. Soc.* **2004**, *126*, 8569–8575.

(2) (a) Grubbs, R. H.; Cossy, J.; Arseniyadis, S.; Meyer, C. *Metathesis in Natural Product Synthesis: Strategies, Substrates and Catalysts*; Wiley-VCH: Weinheim, Germany, 2010. (b) Fürstner, A. *Angew. Chem., Int. Ed.* **2000**, *39*, 3012–3043.

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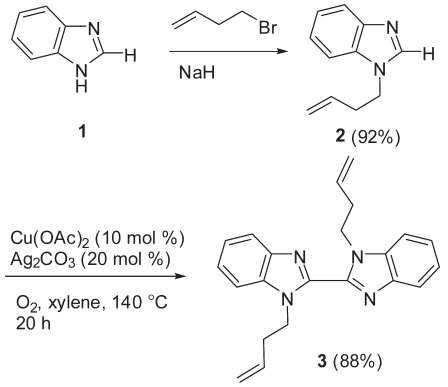
pharmaceutical and agrochemical products showing biological activities. We have been studying transition-metal-catalyzed coupling reactions at the C−H bond of heteroaromatic compounds for the purpose of facile construction of organic frameworks.[3,4] During the course of our studies we have revealed that copper/silver-catalyzed homocoupling of imidazole derivatives at the C−H bond of the heteroaromatic ring takes place under oxidative conditions to afford the corresponding bisimidazole smoothly.[5] We thus envisaged the synthesis of macrocyclic compounds bearing a bisazole moiety by metathesis, in which the difference of spectroscopic properties caused by ring closure is of interest. We report the synthesis of a new class of large-membered cycloalkene bearing a bisazole moiety, whose stereochemistry is *E*-specific, via ring-closing metathesis. In addition, further findings on the thus induced novel axial chirality in the macrocyclic bisazole by the twisted structure along with an axial carbon−carbon bond between azoles are described.

Scheme 1



Preparation of the metathesis precursor was carried out as shown in Scheme 1. The reaction of benzimidazole **1** with 1-bromo-3-butene in the presence of NaH afforded *N*-alkenylated imidazole **2** in 92% yield. Homocoupling of **2** was carried out under similar conditions as described previously to afford bisazole **3** in 88% yield.[5] The reaction was found to take place similarly with a substrate bearing a terminal alkene group as a substituent of the nitrogen atom.

The ring-closing metathesis was examined with thus obtained bisimidazole **3** catalyzed by several Grubbs' catalysts.[6] The results are summarized in Table 1. The attempted reaction with Grubbs' first generation catalyst ($RuCl_2$(=CHPh)(PCy_3)$_2$) was found to be ineffective under standard reaction conditions for general 1,ω-dienes to result in complete recovery of the starting material, while the use of the second generation catalyst ($RuCl_2$(=CHPh)(SIMes)(PCy_3)) afforded the ring-closed product as a single isomer albeit still in a lower yield (32%). The yield of the ring-closed product was found to improve when an additive as a Lewis acid was employed along with the ruthenium catalyst.[7] Addition of 10 mol % of zinc chloride for the reaction of **3** in the presence of 5.0 mol % of the Grubbs' second catalyst resulted in consumption of the starting bisimidazole suggesting that ring-closed large-membered cycloalkene **4** was obtained in 74% yield. The reaction proceeded similarly by decreasing the amount of $ZnCl_2$ to afford the ring-closed product in 64% yield. The use of titanium(IV) tetraisopropoxide (20 mol %) as an additive was also effective to result in giving **4** smoothly. It was found to be necessary to undergo the reaction at a higher temperature; otherwise, no desired product was obtained at room temperature.

Table 1. Ring-Closing Metathesis of **3** with Grubbs' Catalyst[a]

3 —(Ru cat. additive, $(CH_2Cl)_2$, 80 °C)→ Ring-closedproduct **4**

catalyst (mol %)	additive (mol %)	time, temp (h, °C)	yield[b] (%)
Grubbs' 1st (5.0)	none	80, 20	0
Grubbs' 2nd (5.0)	none	80, 23	32
	$ZnCl_2$ (20)	80, 24	74
	$ZnCl_2$ (10)	80, 24	64
	Ti(O^iPr)$_4$ (20)	80, 24	72
	Ti(O^iPr)$_4$ (20)	25, 24	0
	Ti(O^iPr)$_4$ (10)	80, 24	48

[a] The reaction was carried out with 0.1 mmol of **3**, 5.0 mol % of the ruthenium catalyst, and the additive in 1,2-dichloroethane (1 mL) at 80 °C. [b] Isolated yield.

Measurement of the high resolution mass spectrum of **4** indicated that $C_{20}H_{19}N_4$ (M + H: m/z = 315.1610) was afforded, and the ^{1}H NMR spectrum also showed that NCH_2 signals (4H) and an olefinic triplet signal (2H) were observed at 4.32, 4.52, and 4.69 ppm, respectively, supporting that the metathesis reaction took place. However, stereochemistry of the formed internal double bond has been difficult to assign although the reaction was found to afford a single isomer, predominantly. X-ray structure

(3) (a) Tanaka, S.; Tamba, S.; Tanaka, D.; Sugie, A.; Mori, A. *J. Am. Chem. Soc.* **2011**, *133*, 16734–16737. (b) Tamba, S.; Shono, K.; Sugie, A.; Mori, A. *J. Am. Chem. Soc.* **2011**, *133*, 9700–9703. (c) Masui, K.; Ikegami, H.; Mori, A. *J. Am. Chem. Soc.* **2004**, *126*, 5074–5075. (d) Mori, A.; Sekiguchi, A.; Masui, K.; Shimada, T.; Horie, M.; Osakada, K.; Kawamoto, M.; Ikeda, T. *J. Am. Chem. Soc.* **2003**, *125*, 1700–1701.

(4) (a) Mori, A.; Sugie, A. *Bull. Chem. Soc. Jpn.* **2008**, *81*, 548–561. (b) Satoh, T.; Miura, M. *Chem. Lett.* **2007**, *36*, 200–205. (c) Ackermann, L. *Synlett* **2007**, 507–526. (d) Mori, A. *J. Synth. Org. Chem. Jpn.* **2011**, *69*, 1202–1211. (e) Gellina, F.; Rossi, R. *Tetrahedron* **2009**, *65*, 10269–10310.

(5) (a) Monguchi, D.; Yamamura, A.; Fujiwara, T.; Somete, T.; Mori, A. *Tetrahedron Lett.* **2010**, *51*, 850–852. (b) Monguchi, D.; Fujiwara, T.; Furukawa, H.; Mori, A. *Org. Lett.* **2009**, *11*, 1607–1610.

(6) (a) Grubbs, R. H. *Angew. Chem., Int. Ed.* **2006**, *45*, 3760–3765. (b) Schwab, P.; France, M. B.; Ziller, J. W.; Grubbs, R. H. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 2039. (c) Bielawski, C. W.; Grubbs, R. H. *Angew. Chem., Int. Ed.* **2000**, *39*, 2903–2906.

(7) Yang, Q.; Xiao, W.-J.; Yu, Z. *Org. Lett.* **2005**, 871–874.

analysis revealed that the ring-closed product involved a 10-membered cycloalkene with an *E*-configuration as shown in Figure 2a. Although the stereochemistry of the metathesis generally results in giving a mixture of both configurations, the *E*-isomer was exclusively formed in the present case.[8] The double bond was located above the 2,2′ C−C bond of bisazole. Thus, the olefinic proton would be at the deshielded region caused by the ring current of the heteroaromatic structure. Indeed, the chemical shift of the olefinic proton by ^{1}H NMR analysis shifted to the lower frequency compared to that of regular alkene protons. It was also found that the dihedral angle of two azole moieties was 47.8°; thereby, the π-conjugation between the azoles was less extended by ring closure. Figure 2b shows UV−vis absorption spectra of bisimidazoles **3** and **4**. In contrast, the λ_{max} of the metathesis precursor **3** was

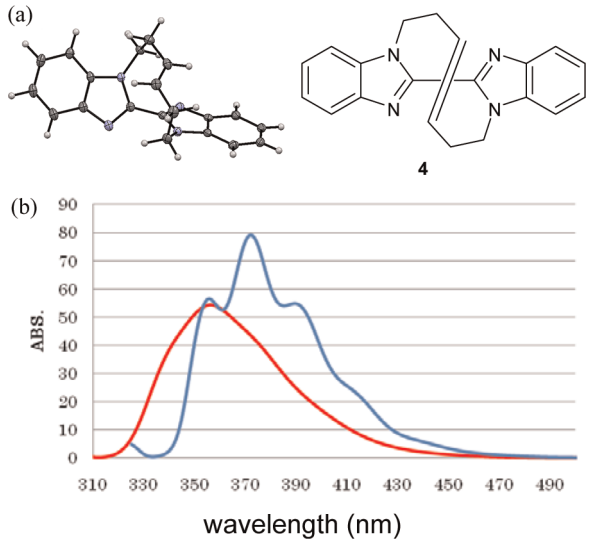
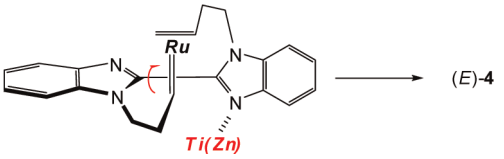


Figure 2. (a) X-ray structure of **4** (b) UV−vis absorption spectra of bisazole of 10-membered ring **4** (red) and metathesis precursor **3** (blue) .

found at 372 nm; the corresponding peak of **4** shifted ca. 20 nm toward a lower wavelength.

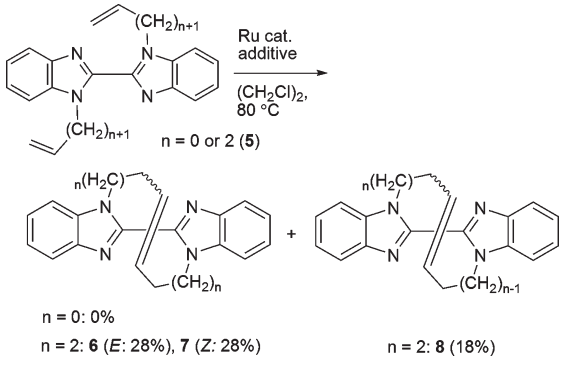
Worthy of note is the formation of the *E*-isomer in the ring closure. There are a few reports concerning the *E*-selective RCM,[8,9] in which structural demand of the substrate would cause a stereochemical preference by employing a usual metathesis catalyst. Addition of a Lewis acid in the ruthenium-catalyzed reaction would favor the twisted conformation of bisimidazole by coordination of a titanium or zinc atom to imino nitrogen and thus lead to the formation of *E*-olefin as well as accelerate the metathesis efficiency by avoiding the interaction of the ruthenium catalyst with the nitrogen atom to result in poisoning (Scheme 2). Although attempted *E*-selective RCM to extend the substrate scope with various biaryl derivatives with/without a heteroaromatic moiety was carried out, such a reaction leading to the formation of a large-membered cyclic *E*-alkene was not observed so far.

Scheme 2



The scope of the formation of a large-membered cycloalkene is another concern; however, attempted metathesis of the *N*-allyl analogue to form the eight-membered ring was found to be unsuccessful. The ring-closed product was not obtained under similar conditions, but afforded a complex mixture of unidentified products probably caused by a competing intermolecular metathesis. On the other hand, the reaction of the homologated analogue *N*-4-penten-1-yl bisimidazole (**5**) afforded the mixture of **6** and **7** in 28% and 28% yields, respectively, accompanied by unexpected side product **8**. The former **6** and **7** showed

Scheme 3



good correspondence in HRMS analyses as the ring-closed 12-membered product ($C_{22}H_{22}N_4$, m/z = 342.1846) suggesting a mixture of *E* and *Z* isomers, whereas HRMS analysis of **8** suggested $C_{21}H_{20}N_4$ (18% yield) to result in CH_2 (14 mass) being lost during the reaction leading to the formation of the 11-membered ring (m/z = 328.1675)[10] as summarized in Scheme 3. Indeed, X-ray structure analysis of **6** and **7** revealed that ring-closing metathesis led to 12-membered *E*- and *Z*-alkenes (Figure 3).

(8) Examples of *E*-specific RCM: (a) Matsui, R.; Seto, K.; Fujita, K.; Suzuki, T.; Nakazaki, A.; Kobayashi, S. *Angew. Chem., Int. Ed.* **2010**, *49*, 10068–10073. (b) Boal, A. K.; Guryanov, I.; Moretto, A.; Crisma, M.; Lanni, E. L.; Toniolo, C.; Grubbs, R. H.; O'Leary, D. J. *J. Am. Chem. Soc.* **2007**, *129*, 6986–6987. (c) Bourgeois, D.; Pancrazi, A.; Ricard, L.; Prunet, J. *Angew. Chem., Int. Ed.* **2000**, *39*, 725–728. (d) Prunet, J. *Angew. Chem., Int. Ed.* **2003**, *42*, 2826–2830.

(9) (a) For a review: Connon, S. J.; Blechert, S. *Angew. Chem., Int. Ed.* **2003**, *42*, 1900–1923. (b) *Z*-Selective olefin metathesis. See also: Keitz, B. K.; Endo, K.; Patel, P. R.; Herbert, M. B.; Grubbs, R. H. *J. Am. Chem. Soc.* **2012**, *134*, 693–699. (c) See also: Meek, S. J.; O'Brien, R. V.; Llaveria, J.; Schrock, R. R.; Hoveyda, A. H. *Nature* **2011**, *471*, 461–466.

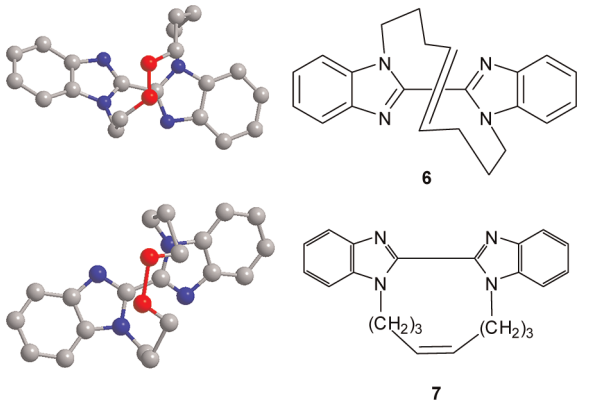


Figure 3. Structures of **6** and **7**. Hydrogen atoms are omitted.

It should also be pointed out that careful analysis of the X-ray structure data of bisimidazole of 10-membered **4** was composed of a pair of enantiomers along the axis of the carbon−carbon bond between two imidazole rings at the 2- and 2′-positions as shown in Figure 4a suggesting axial chirality. HPLC analysis of **4** with a chiral column (Daicel CHIRALPAK IC) revealed two peaks with complete baseline separation as shown in Figure 4b. The peaks were confirmed to show positive (the former) and negative (the latter) signals by measurement with an optical rotation detector (426 nm). Although axial chirality of biaryl derivatives has been generally achieved by introducing sterically bulky groups as substituents on the aromatic ring to avoid racemization via free rotation, *the ring-closed bisazole derivative bearing no such bulky groups induced the molecular asymmetry*.[11] It is thus remarkable that clipping the *N*-substituent through such a simple ring-closing metathesis in a facile manner affords a new class of chirality.[12]

In summary, we have shown that 10-membered cycloalkene **4** involving the bisimidazole structure, which was confirmed by X-ray structure analysis, was synthesized by stereoselective ring-closing metathesis leading to the *E*-form. The product **4** revealed a twisted conformation along the carbon−carbon bond between 2,2′-positions;

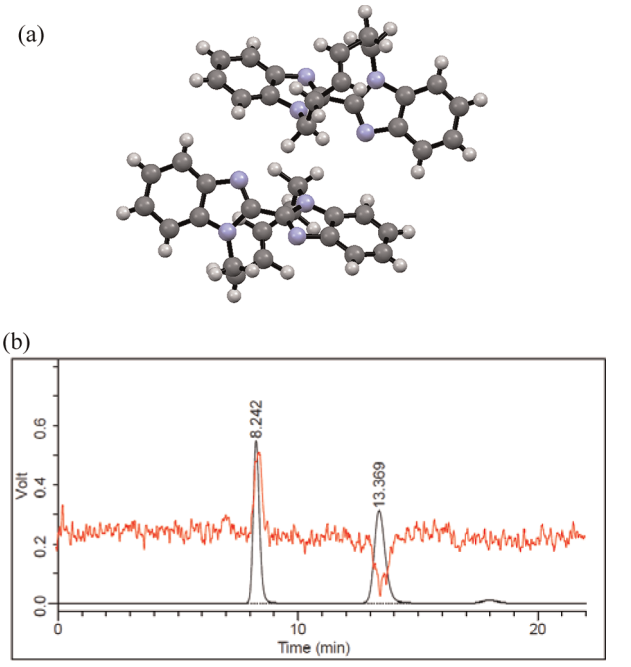


Figure 4. (a) Enantiopaired crystal structure of **4**. (b) HPLC profile of **4** with chiral column and UV(black)/optical rotatory-(red) detectors.

thus **4** induced axial chirality, which was confirmed by HPLC with a chiral stationary phase column. The novel bisazole derivative is potentially available as a chiral auxiliary for asymmetric induction and a liquid crystalline molecule after an appropriate resolution protocol is established.

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Supporting Information Available. Experimental details and characterization of new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

(10) An example of ring-contraction metathesis: Lazarova, T. I.; Binet, S. M.; Vo, N. H.; Chen, J. S.; Phan, L. T.; Or, Y. S. *Org. Lett.* **2003**, *5*, 443–445.

(11) (a) Bringmann, G.; Price Mortimer, A. J.; Keller, P. A.; Gresser, M. J.; Garner, J.; Breuning, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 5384–5427. (b) Mislow, K.; Hyden, S.; Schaefer, H. *J. Am. Chem. Soc.* **1962**, *84*, 1449–1455. (c) Ohmori, K.; Kitamura, M.; Suzuki, K. *Angew. Chem., Int. Ed.* **1999**, *38*, 1226–1228.

(12) Sugimura, T.; Matsushita, N.; Minokami, K.; Kurita, S. *Tetrahedron* **2007**, *63*, 1762–1769.

The authors declare no competing financial interest.