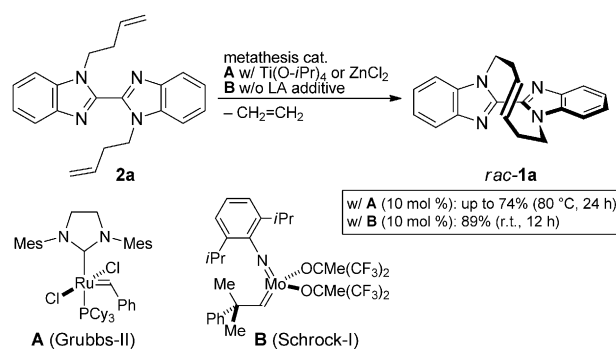


Enantioselective Synthesis of Macrocyclic Heterobiaryl Derivatives of Molecular Asymmetry by Molybdenum-Catalyzed Asymmetric Ring-Closing Metathesis**

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Abstract: Winding vine-shaped molecular asymmetry is induced by enantioselective ring-closing metathesis with a chiral molybdenum catalyst. The reaction proceeds under mild conditions through an *E*-selective ring-closing metathesis leading to macrocyclic bisazoles with enantioselectivities of up to 96 % *ee*.

Chiral molecules devoid of stereogenic centers have attracted considerable attention in organic chemistry. These stereochemical issues, often referred to as molecular asymmetry or non-centrochirality, include axial-, planar-, or helical chirality, etc.^[1] Among them, biaryl axial chirality has been widely utilized in various asymmetric reactions as chiral ligands in metal catalysts^[2] or as key substructures in organocatalysts^[3] showing excellent enantioselection abilities. In general, axial chirality in biaryls is induced by the introduction of sterically demanding substituents at the positions proximal to the carbon–carbon bond between the two aryl moieties, which inhibit free rotation about the single bond. If one could freeze the free rotation of the carbon–carbon single bond by macrocyclic ring formation, analogous axial chirality is induced in a biaryl molecule. We recently reported the synthesis and characterization of bisbenzimidazole derivative **1a**. Compound **1a** was prepared by the ruthenium-catalyzed ring-closing metathesis (RCM)^[4] of acyclic precursor **2a**, which possesses two 3-butenyl substituents at both sp³-nitrogen atoms. The RCM reaction took place predominantly in the *E*-selective fashion, and RCM product **1a** was found to



Scheme 1. Synthesis of macrocyclic bisbenzimidazole **1a** by ring-closing metathesis reaction of acyclic **2a**.

be chiral even without a stereogenic carbon atom as shown in Scheme 1.^[5] The *E*-alkenylene moiety bridging the two benzimidazoles inhibits the free rotation about the carbon–carbon bond in **1a**, and, indeed, two enantiomers of the molecule can be separated by chiral HPLC. Compound **1a**, whose skewed shape resembles a vine winding around a branch, shows unique molecular asymmetry, and this unprecedented chirality can be explained in several other ways in addition to the biaryl axial chirality: 1) helical chirality of the winding alkenylene chain along the rigid axis of the bisimidazole,^[6] 2) planar chirality of the *trans*-cycloalkene^[7] (*trans*-5,8-diazacyclodecene) whose conformational freedom is constrained by the fused imidazoles, or 3) central chirality based on the distorted stereogenic nitrogen atoms^[8] whose inversion is retarded by placement at the bridgeheads.

In this report, we focus our attention on the catalytic enantioselective synthesis of this peculiar chiral molecule, which would be plausible if an appropriate chiral metal-alkylidene complex is employed as a metathesis catalyst.^[9] Although an asymmetric metathesis reaction itself does not form a stereogenic carbon atom directly, it has been demonstrated to control peripheral chirality by kinetic resolution of racemic chiral molecules or desymmetrization of prochiral substrates by the use of a chiral metathesis catalyst. However, less studies have shown how to control noncarbon centrosterogenicities^[10] and non-centrochirality.^[11–13] Although we have shown how to successfully control the planar chirality in ferrocenes^[12] as well as in (π -arene)-chromium complexes by asymmetric metathesis reactions,^[13] we were challenged to apply the metathesis protocol to the enantioselective synthesis of the winding-vine-shaped com-

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pounds. Herein, we report the results of our studies for preparing bisimidazole derivatives **1** in high enantiomeric purity by the molybdenum-catalyzed asymmetric ring-closing metathesis (ARCM).

At the outset, we examined the catalytic activity of achiral molybdenum-alkylidene complex **B** toward the ring-closing metathesis reaction of bisbenzimidazole **2a** and the reaction was shown to proceed smoothly at room temperature affording the metathesis product **1a** in 89 % yield (Scheme 1). The result markedly contrasts with our previous results, in which much higher temperatures 80–140 °C were required to promote the reaction in the presence of the ruthenium-based Grubbs II catalyst (**A**). It was also observed that no Lewis acid additive was required for the molybdenum-catalyzed reaction, whereas the related metathesis reaction with Grubbs II was accelerated by addition of ZnCl₂ or Ti(OR)₄.^[5a,14]

The obtained racemic macrocyclic bisazole **1a** was subjected to preparative HPLC with a chiral stationary phase column (Daicel Chiralpak-IF, 20 mm i.d. × 200 mmL) using hexane/EtOH (50:50) as an eluent to achieve the baseline separation of its two enantiomers. The separated enantiomers exhibited [α]_D values of +136° (the fast-eluting enantiomer: (+)-**1a**) and [α]_D = −145° (the slow-eluting enantiomer: (−)-**1a**), respectively. The racemization behavior of the resolved enantiomer was studied at various temperatures. It was shown that significant racemization hardly occurred in a 1,2-dichloroethane solution of (+)- or (−)-**1a** at and below 80 °C. Whereas less than 5 % diminution of the enantiomeric purity in **1a** was detected at 80 °C for 24 h, nearly complete racemization was observed at 140 °C in chlorobenzene within 3 h. The Gibbs free energy for the racemization in **1a** at 100 °C was thus calculated to be Δ*G*[‡](100 °C) = 130 [kJ mol^{−1}] based on the treatment of (+)-**1a** in chlorobenzene for 24 h (98 % *ee* → 45 % *ee*).^[15,16] Interestingly, the racemization process was greatly accelerated in the presence of a catalytic amount of the Grubbs II complex. For example, a mixture of (+)-**1a** (> 99 % *ee*) and Grubbs II (10 mol %) in 1,2-dichloroethane was stirred at 80 °C, and **1a** racemized completely within 24 h. The ruthenium-catalyzed racemization is proposed to proceed through a ring-opening/recyclization sequence as shown in Scheme 2.

Although molybdenum-alkylidene complex **B** showed the better catalytic activity than ruthenium complex **A** in the RCM reaction of **1a**, the enantioselective synthesis of **1a** was examined using chiral molybdenum-alkylidene species. The

chiral catalysts were generated in situ by mixing molybdenum-pyrrolide **C** and an appropriate chiral bishydroxy ligand.^[17] The structures of the chiral ligands used are listed in Figure 1.

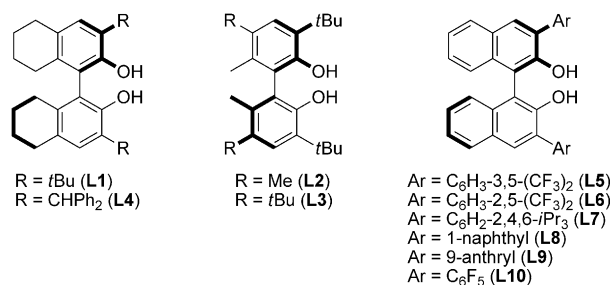


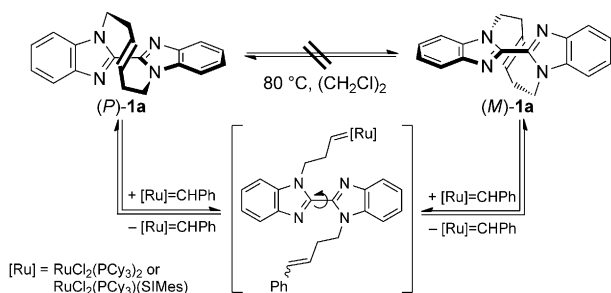
Figure 1. Chiral binaphthol/biphenol ligands for Mo-alkylidene complexes.

The ARCM reaction of **2a** was conducted with the molybdenum catalyst (10 mol %) in benzene and the results are summarized in Table 1. The use of substituted biphenol derivatives (*R*)-**L1–L3** bearing *tert*-butyl groups adjacent to the hydroxy groups resulted in giving (+)-**1a** in 68–85 % *ee* with reasonable high conversions after stirring for 12 h at 40 °C (entries 1–3), whereas the reaction with (*R*)-**L4**, which contains less bulky diphenylmethyl groups, brought about inferior enantioselectivity (37 % *ee*; entry 4). The molybdenum catalysts generated from ligands (*R*)-**L5–(R)-L10**, which are composed of 3,3'-diarylbinaphthyl structures, were found to be less reactive. Little or no reactions took place when **L5** and **L6** were employed at 40 °C (entries 5 and 6). Elevated

Table 1: Enantioselective ring-closing metathesis of **2a** with various chiral Mo catalysts.^[a]

Entry	Ligand	<i>T</i> [°C]	Conv. [%] ^[b]	<i>ee</i> [%] ^[c]
1	(<i>R</i>)- L1	40	86	(<i>P</i>)-85
2	(<i>R</i>)- L2	40	88	(<i>P</i>)-68
3	(<i>R</i>)- L3	40	96	(<i>P</i>)-76
4	(<i>R</i>)- L4	40	44	(<i>P</i>)-37
5	(<i>R</i>)- L5	40	7	< 1
6	(<i>R</i>)- L6	40	NR	—
7	(<i>R</i>)- L7	60	61	< 1
8	(<i>R</i>)- L8	40	37	(<i>P</i>)-27
9	(<i>R</i>)- L9	40	6	—
10	(<i>R</i>)- L1	23	90	(<i>P</i>)-88
11	(<i>R</i>)- L2	23	80	(<i>P</i>)-73
12	(<i>R</i>)- L3	23	86	(<i>P</i>)-96

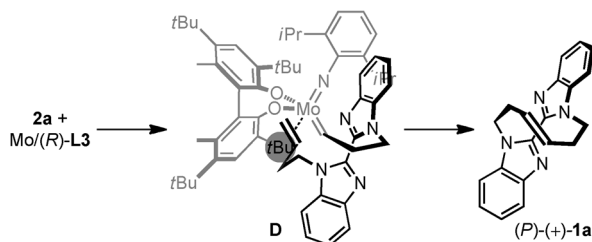
[a] The reaction of **2a** (0.1 mmol) was carried out for 12 h in anhydrous benzene (2 mL) in the presence of 10 mol % molybdenum precursor **C** and 10 mol % chiral ligand. [b] The conversion was determined by ¹H NMR analysis of the crude mixture. [c] The enantiomeric excess was determined by HPLC using a chiral stationary phase column (Daicel Chiralpak IC).



Scheme 2. Proposed pathway for Ru-catalyzed racemization of **1a**.

reaction temperature at 60 °C resulted in virtually no selectivity with **L7** (entry 7). The use of **L8** bearing a 1-naphthyl substituent in the reaction led to moderate conversion and 27 % *ee* (entry 8), whereas the ligand with the 9-anthryl group (**L9**) hardly effected the reaction at 40 °C even at a longer reaction time of 48 h (entry 9). The highest enantioselectivity was finally achieved at lower temperature (23 °C) with **L3** to result in 96 % *ee* (entry 12).

The absolute configuration of the major enantiomer in the ARCM products was determined to be (*P*)^[18] when the (*R*)-isomer of the chiral ligands were employed.^[19] The stereochemistry of the preferential formation of (*P*)-(+)-**1a** can be rationalized as in Scheme 3. The initial metathesis occurs



Scheme 3. Plausible stereochemical pathway of the Mo-catalyzed ARCM of **2a**.

between the Mo-catalyst and **2a** to form bisimidazole-bound Mo-alkylidene intermediate **D**, in which the nonmetalated imidazole moiety takes the opposite position with respect to the Ar-imido ligand to avoid steric congestion. Subsequently, the second alkenyl pendant approaches the molybdenum center from the more open side (the side opposite to the marked *t*Bu group) to furnish (*P*)-**1a** predominantly.

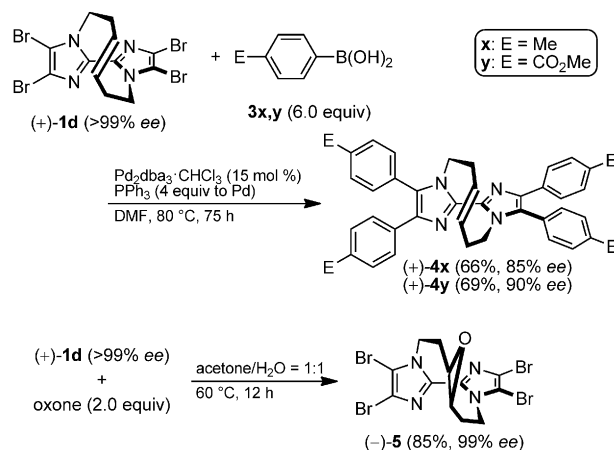
In addition to bisbenzimidazole **1a**, several other bisimidazole derivatives **1b–d**, whose metathesis precursors **2b–d** were synthesized in a similar manner to the preparation of **2a**,^[5a,20] were also subjected to the asymmetric metathesis reaction (Table 2). Although 4,4',5,5'-unsubstituted bisimidazole **2b** also underwent the reaction to afford the ring-closed product **1b**, very low enantioselectivity was observed (4–6 % *ee*) with the molybdenum catalysts coordinated with **L1** or **L3** (entries 1 and 2). The selectivity was slightly improved at a low conversion when **L4** was employed as a chiral ligand, however, the selectivity was still insufficient (30 % *ee*; entry 3). Introduction of bromo substituents in the 5,5'-positions of the bisimidazole (the reaction with **2c**) showed little effect in improving the enantioselectivity using **L1–L3**, although the reaction proceeded smoothly to deliver **1c**. The use of binaphthyl-derived ligand **L8** resulted in 22 % *ee*, while the conversion values were much inferior. It should be pointed out that excellent selectivity was achieved in the reaction of tetrabrominated derivative **2d**. The reaction with chiral ligands **L1–L3** was carried out at 40 °C to 60 °C for 12 h. It is remarkable to observe excellent enantioselectivities of up to 94 % *ee* (entry 13).

The obtained RCM product **1d** possesses modifiable substructures, such as carbon–bromine bonds and an olefinic double bond. Thus, **1d** is potentially transformable into

Table 2: Mo-catalyzed asymmetric ring-closing metathesis of bisimidazole derivatives **2b–d**.^[a]

Entry	Substrate	Ligand	T [°C]	Conv. [%] ^[b]	<i>ee</i> [%] ^[c]
1	2b	L1	60	89	4
2		L3	60	55	6
3		L4	60	19 ^[b]	30
4	2c	L1	60	95	0
5		L2	60	96	0
6		L3	60	95	2
7	2d	L8	60	11	22
8		L1	60	95	86
9		L1	40	95	90
10		L2	60	96	75
11		L2	40	94	90
12		L3	60	86	92
13		L3	40	90	94

[a] The reaction of **2b–d** (0.1 mmol) was carried out for 12 h in anhydrous benzene (2 mL) in the presence of 10 mol % molybdenum precursor **C** and 10 mol % chiral ligand. [b] The conversion was determined by ¹H NMR analysis of the crude mixture. [c] Enantiomeric excess was determined by HPLC using a chiral stationary phase column (Daicel Chiralpak IC).

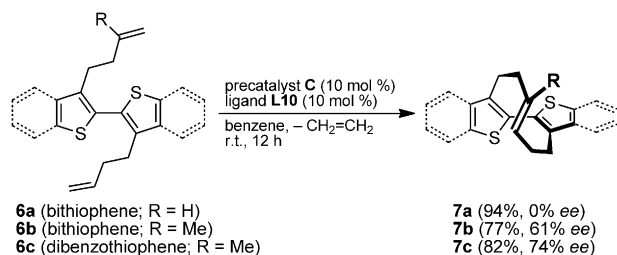


Scheme 4. Transformation reactions of (+)-**1d**.

various functional compounds by standard organic reactions with retention of the helical structure (Scheme 4). For example, **1d** was subjected to the Suzuki–Miyaura coupling.^[21] Treatment of (+)-**1d** (> 99 % *ee*) with *p*-tolylboronic acid **3x** in the presence of a palladium catalyst (15 mol %) smoothly afforded the corresponding tetra(*p*-tolyl)bisimidazole (+)-**4x** (66 %). The mass spectrum (ESI+) showed the formation of **4x** as a sole product^[16] and the enantiopurity of (+)-**4x** was found to be 85 % *ee*. Likewise, the palladium-catalyzed reaction of (+)-**1d** with *p*-methoxycarbonylphenylboronic acid (**3y**) gave the corresponding tetraaryl bisimidazole (+)-**4y** (90 % *ee* in 69 % yield).

It was found that the transformation of the olefinic moiety also took place. The reaction of (+)-**1d** (>99% *ee*) with oxone/acetone at 60 °C for 12 h afforded the corresponding epoxide (–)-**5** in 99% *ee* and 85% yield (Scheme 4).^[22]

The winding-vine-shaped molecular asymmetry is not unique to the bisimidazole derivatives. Bithiophene derivatives **6** underwent ARCM similarly in the presence of the molybdenum catalyst generated in situ from **C** and **L10**, which is bearing pentafluorophenyl groups at the 3- and 3'-positions (Figure 1) and exhibited high selectivity, to afford the corresponding helically chiral ring-closed product **7** (Scheme 5).^[23] Although bithiophene **6a** bearing 3-butenyl



Scheme 5. Enantioselective ARCM of bithiophene derivatives **6**.

substituents at the 3- and 3'-positions afforded **7a** in 94% yield, little enantioselectivity was observed. Improved selectivity was attained when a methyl group was introduced to one of the olefin moieties, which resulted in 61% *ee* in the reaction of **6b**. Use of dibenzothiophene **6c** as a substrate induced higher enantioselectivity to afford **7c** in 82% yield (74% *ee*).

In conclusion, highly enantioselective RCM with a chiral molybdenum–alkylidene complex afforded an axially chiral bisazole of a macrocyclic olefin showing winding-vine-shaped molecular asymmetry. Several binaphthol or biphenol derivatives were found to be effective as a chiral ligand in the molybdenum–alkylidene catalysts. The obtained products were successfully transformed to introduce further functional groups, which could be employed as chiral ligands or chiral components to construct linear and/or cyclic supramolecular compounds.

Keywords: asymmetric catalysis · bisimidazoles · molybdenum catalyst · molecular asymmetry · ring-closing metathesis

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