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

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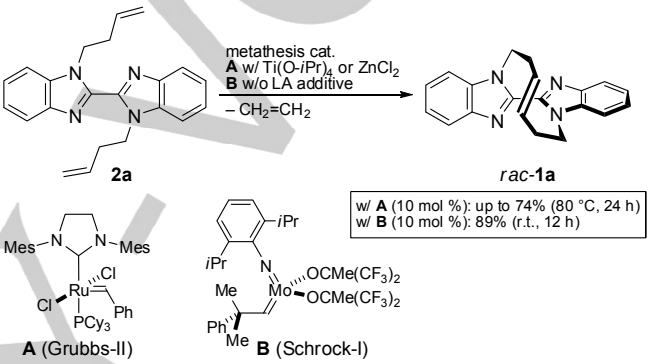
Enantioselective Synthesis of Macrocyclic Heterobiaryl Derivatives of Molecular Asymmetry by Molybdenum-Catalyzed Asymmetric Ring-Closing Metathesis

Yoichi Okayama,[a] Satoru Tsuji,[a] Yuka Toyomori, [a] Atsunori Mori, [a]* Sachie Arae, [b] Wei-Yi Wu, [b] Tamotsu Takahashi, [b] Masamichi Ogasawara[b]*

Abstract: Winding vine-shaped molecular asymmetry is induced by enantioselective ring-closing metathesis with a chiral molybdenum catalyst. The reaction takes place under mild conditions to undergo *E*-selective ring-closing metathesis leading to macrocyclic bisazole with the enantioselectivities 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, biarylic 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 ability. 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 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 sp^3-nitrogen atoms. The RCM reaction took place predominantly in the *E*-selective fashion, and RCM product **1a** was found to be chiral even without a stereogenic carbon atom as shown in Scheme 1.[5] The *E*-alkenylene moiety bridging between the two benzimidazoles inhibits the free rotation about the carbon-carbon bond in **1a**, and, indeed, the molecule can be separated into a pair of enantiomers by the 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 biarylic *axial chirality*: (i) *helical chirality* of the winding alkenylene chain along the rigid axis of the bisimidazole,[6] (ii) *planar-chirality* of the *trans*-cycloalkene[7] (*trans*-5,8-diazacyclodecene) of which conformational freedom is constrained by the fused imidazoles, or (iii) *central chirality* based on the stereogenic nitrogen atoms[8] whose inversion is retarded by placement at the bridgeheads.



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

In this report, we focus our attention to 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 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 been shown to control non-carbon centrostereogenicities[10] and non-centrochirality.[11-13] Whereas we have successful experiences of controlling the planar-chirality in ferrocenes[12] as well as in (π-arene)chromium complexes by the asymmetric metathesis reactions,[13] we have challenged to apply the metathesis protocol for the enantioselective synthesis of the winding vine-shaped compounds. 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 revealed 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 was required to undergo the reaction in the presence of the ruthenium-based Grubbs-II

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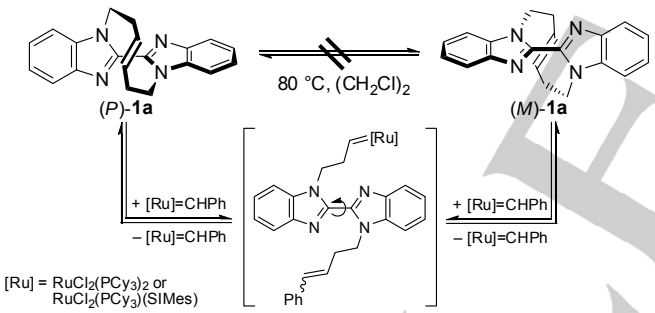
catalyst (**A**). It was also observed that no Lewis acid additive was required for the molybdenum-catalyzed reaction while the related metathesis reaction with Grubbs-II was accelerated by addition of $ZnCl_2$ or $Ti(OR)_4$.[5a,14]

Obtained racemic macrocyclic bisazole **1a** was subjected to the preparative HPLC with a chiral stationary phase column (Daicel Chiralpak-IF, 20 mm i.d. × 200 mm L) using hexane/EtOH (50/50) as an eluent to achieve the baseline separation of its two enantiomers. The separated enantiomers exhibited $[\alpha]_D$ values of +136° (the fast-eluting enantiomer: (+)-**1a**) and $[\alpha]_D$ = –145° (the slow-eluting enantiomer: (–)-**1a**), respectively. Racemization behavior of the resolved enantiomer was studied at various temperatures. It was revealed 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 $\Delta G^{\ddagger}$(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 in 24 h. The ruthenium-catalyzed racemization is proposed to proceed via the ring-opening/recyclization sequence as shown in Scheme 2.



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

Whereas molybdenum-alkylidene complex **B** showed the better catalytic activity than ruthenium complex **A** in the RCM reaction of **1a**, 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 bis-hydroxy ligand.[17] The structures of the chiral ligands used are listed in Chart 1.

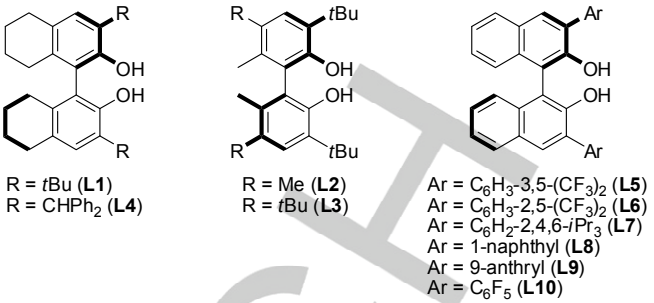
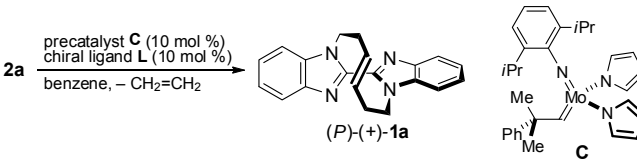


Chart 1. Chiral binaphthol/biphenol ligands for Mo-alkylidene complexes.

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**-**3** bearing *t*-butyl groups adjacent to the hydroxy groups resulted in giving (+)-**1a** in 68-85% ee with reasonably high conversions after stirring for 12 h at 40 °C (entries 1-3), whereas the reaction with (*R*)-**L4** which is with less bulky diphenylmethyl groups brought about inferior enantioselectivity (37% ee; entry 4). The molybdenum catalysts generated from ligands (*R*)-**L5**-**10**, 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 reaction temperature at 60 °C resulted in giving virtually no selectivity with **L7** (entry 7). The use of **L8** bearing 1-naphthyl substituent underwent the reaction in moderate conversion and 27% ee (entry 8), whereas the ligand with 9-anthryl group (**L9)** hardly effected the reaction at 40 °C even for 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).

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

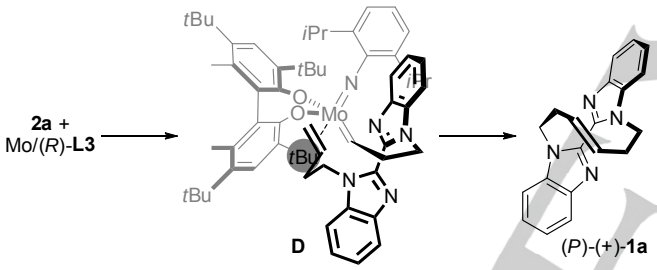


Entry	Ligand	Temp. [°C]	Conv. [%][b]	%ee[c]
1	(*R*)-**L1**	40	86	(*P*)-85
2	(*R*)-**L2**	40	88	(*P*)-68
3	(*R*)-**L3**	40	96	(*P*)-76
4	(*R*)-**L4**	40	44	(*P*)-37
5	(*R*)-**L5**	40	7	<1
6	(*R*)-**L6**	40	NR	--
7	(*R*)-**L7**	60	61	<1
8	(*R*)-**L8**	40	37	(*P*)-27

9	(*R*)-**L9**	40	6	--
10	(*R*)-**L1**	23	90	(*P*)-88
11	(*R*)-**L2**	23	80	(*P*)-73
12	(*R*)-**L3**	23	86	(*P*)-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 ^{1}H NMR analysis of the crude mixture. [c] Enantiomeric excess was determined by HPLC bearing a chiral stationary phase column Daicel Chiralpak IC.

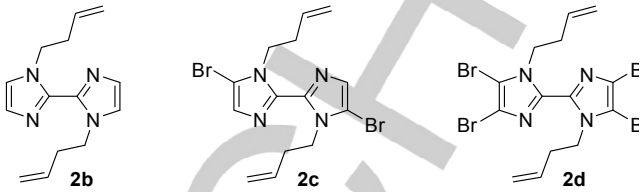
The absolute configuration of the major enantiomer in the ARCM products was determined to be (*P*)[18] when the (*R*)-isomer of the chiral ligands were employed.[19] The stereochemistry of the preferential formation of (*P*)-(+)-**1a** can be rationalized as in Scheme 3. The initial metathesis between the Mo-catalyst and **2a** to form bisimidazole-bound Mo-alkylidene intermediate **D**, in which the non-metalated imidazole moiety takes the opposite position with respect to the Ar-imido ligand to avoid the steric congestion. Subsequently, the second alkenyl pendant approaches to the molybdenum center from the more open side (the side opposite to the marked *t*Bu group) to furnish (*P*)-**1a** predominantly.



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

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. 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** and **L3** (entries 1 and 2). The selectivity was slightly improved in a low conversion when **L4** was employed as a chiral ligand, however, the selectivity was still insufficient (30% ee; entry 3). Introduction of the bromo substituents into the 5,5'-positions of the bisimidazole (the reaction with **2c**) showed little effect to improve the enantioselectivity using **L1**-**L3** although the reaction proceeded smoothly to deliver **1c**. The use of binaphthyl derived ligands **L8** exhibited 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 ligand **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).

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



2b **2c** **2d**

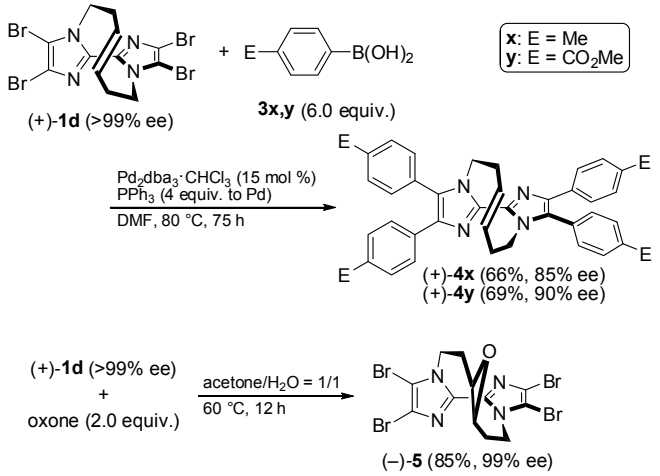
Entry	Substrate	Ligand	Temp. [°C]	Conv. [%][b]	%ee[c]
1	**2b**	**L1**	60	89	4
2		**L3**	60	55	6
3		**L4**	60	19[b]	30
4	**2c**	**L1**	60	95	0
5		**L2**	60	96	0
6		**L3**	60	95	2
7		**L8**	60	11	22
8	**2d**	**L1**	60	95	86
9		**L1**	40	95	90
10		**L2**	60	96	75
11		**L2**	40	94	90
12		**L3**	60	86	92
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 ^{1}H NMR analysis of the crude mixture. [c] Enantiomeric excess was determined by HPLC bearing a chiral stationary phase column Daicel Chiralpak IC.

Obtained RCM product **1d** possesses modifiable substructures, such as carbon-bromine bonds and an olefinic double bond. And thus, **1d** is potentially transformable into 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 %) underwent the smooth coupling reaction affording 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 revealed to be 85% ee. Likewise, the palladium-catalyzed reaction of (+)-**1d** with *p*-methoxycarbonylphenylboronic acid (**3y)** gave the corresponding tetraarylbisimidazole (+)-**4y** (90% ee in 69% yield).

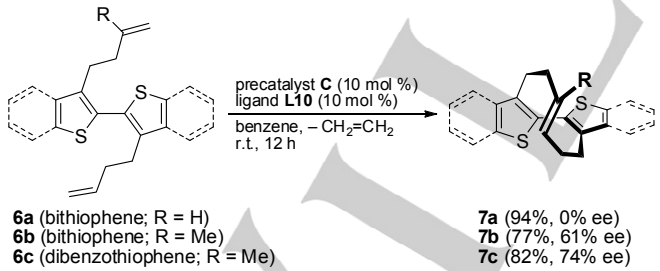
It was found that transformation of the olefinic moiety also took place. The reaction of (+)-**1d** (>99% ee) with oxone/acetone at

60 °C for 12 h afforded the corresponding epoxide (–)-**5** of 99% ee in 85% yield (Scheme 4).[22]



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

The winding vine-shaped molecular asymmetry is not unique to the bisimidazole derivatives. Bithiophene derivatives **6** underwent ARCM similarly in the presence of the molybednum catalyst generated in situ from **C** and **L10**, which is bearing pentafluorophenyl groups at the 3- and 3'-positions (see Chart 1) exhibited high selectivity, to afford the corresponding helically chiral ring-closed product **7** as shown in Scheme 5.[23] Although bithiophene **6a** bearing 3-butenyl substituents at 3- and 3'-positions afforded **7a** in 94% yield, little enantioselectivity was observede. Improved selectivity was attained when a methyl group is introduced to one of the olefin moieties to result in 61% ee in the reaction of **6b**. Use of dibenzothiophene **6c** as a substrate induced the improved enantioselectivity to afford **7c** in 82% yield (74% ee).



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

In conclusion, highly enantioselective RCM with a chiral molybdenum-alkylidene complex afforded axially chiral bisazole of 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 would be potentially employed for chiral ligands or chiral components to construct linear and/or cyclic supramolecular compounds.

Acknowledgements

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Keywords: chiral Mo catalyst • molecular asymmetry • winding vine • ring-closing metathesis • bisimidazole

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[18] The (*P*)-descriptor for (+)-enantiomer of **1a** was assigned based on the helical chirality of the winding alkenylene chain in the molecule.

[19] The absolute configuration of (+)-isomer of **1a** was assigned as *P* form with crystalline sponge method. The details will be described by the Fujita group in due course. See: Y. Inokuma, S. Yoshioka, J. Ariyoshi, T. Arai, Y. Hirota, K. Takada, S. Matsunaga, K. Rissanen, M. Fujita, *Nature* **2013**, *495*, 461-466.

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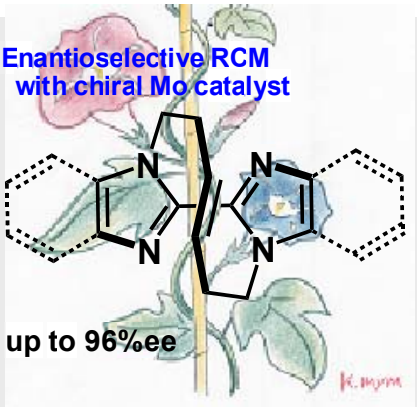
Layout 1:

COMMUNICATION

Winding vine-shaped molecular asymmetry is induced by enantioselective ring-closing metathesis with a chiral molybdenum catalyst. The reaction takes place under mild conditions to undergo *E*-selective ring-closing metathesis leading to macrocyclic bisazole with the enantioselectivities up to 96% ee.



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