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Modular Mo-based catalysts for efficient asymmetric olefin metathesis. Catalytic enantioselective synthesis of cyclic ethers and acetals†

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Abstract

Chiral Mo-based complexes **1**–**3** promote the catalytic enantioselective ring-closing metathesis of various polyenes to afford unsaturated furans, pyrans and siloxanes efficiently and in high ee (70–98% ee). The structural modularity of this class of chiral catalysts plays a critical role in these studies. Modification of the diolate or imido moities of these chiral catalysts gives rise to a range of complexes that can be screened for higher reactivity and/or enantioselectivity.

Keywords: asymmetric catalysis; enantioselective olefin metathesis; modular chiral catalysts.

Catalytic olefin metathesis has emerged as a practical and powerful method in organic synthesis.[1] The use of metal-catalyzed ring-closing metathesis (RCM) in the synthesis of complex target molecules is now considered relatively routine.[2] Nevertheless, in the context of the development of new catalysts for olefin metathesis, several critical issues remain to be addressed. One important objective is the development of *chiral* catalysts that promote ring-closing, ring-opening or cross metathesis reactions to afford optically enriched materials.

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† This paper is fondly dedicated to our mentor, friend and role model Professor Harry H. Wasserman on the occasion of his 80th birthday.

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We recently reported a series of chiral Mo-based catalysts (**1a**–**b**[3] and **2**[4]) that efficiently provide materials of high optical purity by desymmetrization of achiral trienes through asymmetric ring-closing metathesis (ARCM). We also disclosed the first examples of catalytic enantioselective ring-opening metathesis; these transformations may be followed by a Mo-catalyzed cross metathesis process,[5] or by a ring-closing reaction.[6] One of the most attractive attributes of the Mo-based chiral catalysts, represented by those shown in Fig. 1, is that they are easily varied: sterically- and electronically-modified catalysts can be prepared and screened for optimal reactivity and enantioselectivity.[7] Herein we disclose several examples of catalytic ARCM transformations (desymmetrization of acyclic polyenes), where the levels of asymmetric induction and reaction efficiencies are significantly improved by alteration of either the diolate (**1** versus **2**) or imido (**1** versus **3**[8]) segments of the chiral Mo complex. New catalytic ARCM processes effected by catalysts **1** and **2**, and asymmetric reactions for which the halogenated chiral catalyst **3** is particularly well suited, are described below.

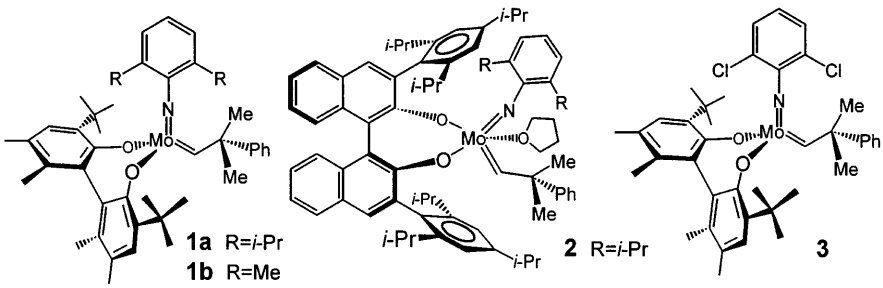
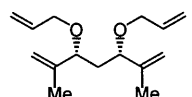
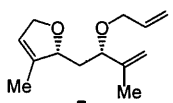
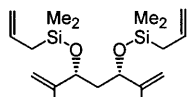
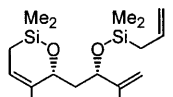


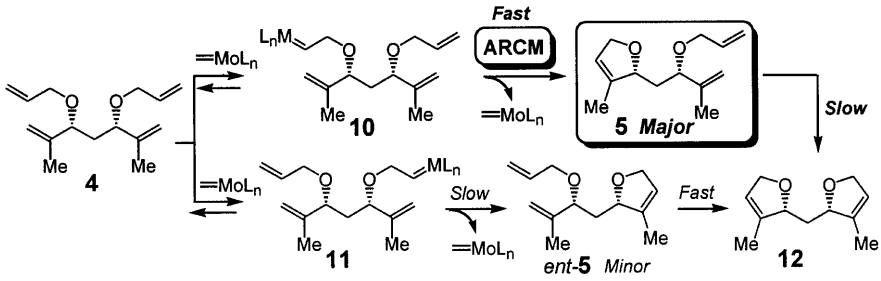
Figure 1.

As illustrated in Table 1 (entry 1), treatment of **4** with 5 mol% **1a** leads to the formation of **5**[9] in >98% ee (72%, 15 min). The unpurified mixture contains 20% of the achiral bicycle (cf. **12**, Scheme 1; easily separable from **5**). With the more reactive **1b** as the catalyst, the derived *meso* bicyclic adduct is formed exclusively within 5 min (22°C). When the binol-based complex **2** is used as the chiral catalyst (entry 3), catalytic ARCM is significantly slower (30% conv. in 1 h) and **5** is isolated with lower enatioselectivity (73% ee).

Table 1
Desymmmetrization of tetraenes by Mo-catalyzed asymmetric ring-closing metathesis[a]

entry	substrate	product	catalyst	time	conv (%);[b] bicycle (%)[c]	yield (%);[d] ee (%)[e]
1			**1a**	15 min	***>99; 20***	***72; >98***
2			**1b**	5 min	100; >98	--
3	**4**	**5**	**2**	1 h	30; 10	ND; 73
4			**1a**	14 h	<20; <2	ND; >98
5			**1b**	14 h	56; <2	ND; >98
6	**6**	**7**	**2**	1 h	***>99; <2***	***76, >98***[f]

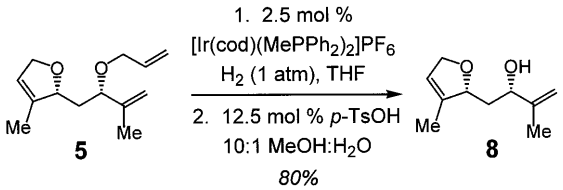
a. Conditions: 5 mol % catalyst, Ar atm, C_6H_6, 22°C. *b.* By GLC (internal standard). *c.* By 400 MHz ^{1}H NMR analysis. *d.* Isolated yield of purified products after silica gel chromatography (**5**) or distillation (**7**). *e.* By chiral GLC analysis (CD-GTA for **5**, BETADEX for **7**). *f.* Reaction carried out at 60°C. ND = not determined.



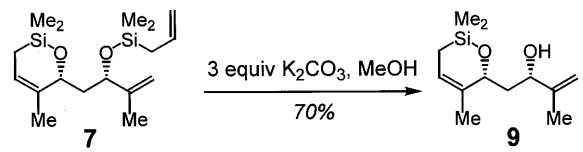
Scheme 1.

Similar ARCM reactions may be carried out with silyl ether tetraene **6**, where the expected product is a six-membered ring. In direct contrast to the reactions with **4**, here it is Mo complex **2**—and not **1a** or **1b**—that proves to be the catalyst of choice (entry 6). Whereas biphen complexes **1a** and **1b** deliver <60% conversion (14 h), with binol-based catalyst **2**, triene **7** is isolated in >98% ee after 1 h (60°C).[10] When **7** is resubjected to the reaction conditions for an additional 2 h, <2% of the derived *meso* bicycle is formed.

As shown in Eqs (1) and (2), the uncyclized ether moieties of the ARCM adducts can be selectively removed so that the derived functionalized optically enriched allylic ethers are obtained. Treatment of **5** with 2.5 mol% $[Ir(cod)(MePPh_2)_2]PF_6$ under 1 atm of H_2[11] and subsequent hydrolysis of the resulting enol ether leads to the formation of **8** (80% overall). When **7** is directly treated with methanolic K_2CO_3, **9** is obtained in 70% yield.



(1)



(2)

The outcome of catalytic asymmetric processes in Table 1 can be rationalised (Scheme 1). Mo–alkylidenes **10** and **11** are probably formed in equal amounts, as it is unlikely that stereogenic centers distal to the terminal olefins promote preferential formation of one isomer. If **10** undergoes RCM faster than **11**, which in turn rapidly reverts back to **4** by methylene transfer with an available terminal olefin (e.g. **4**), monocyclic polyene **5** can be obtained enantioselectively.[12] Facile regeneration of **4** from the slower reacting Mo–alkylidene (**11**) is critical. The non-selective formation of the Mo–alkylidenes would otherwise be stereochemistry-determining. Additional factors that can lead to high enantioselectivity are: (i) upon ring closure (**10**→**5**), Mo–methylidene dissociates from the substrate, reducing the possibility of a second closure. (ii) When selectivity falters and *ent*-**5** is generated, a second expeditious ring closure affords the easily separable **12**.

The model in Fig. 2 provides a plausible rationale for the selective formation of **5**. The intermediacy (higher reactivity) of the *anti* Mo–alkylidene (alkylidene C–C *anti* to C–N) is supported by previous mechanistic studies.[13] The stereochemistry of olefin-transition metal association is based on the position of the LUMO of the chiral complex.[14] It is likely that the 1,1-disubstituted olefin interacts with Mo away from the *t*-Bu group of the diolate and *iso*-Pr groups of the imido ligands. The reason for the inefficiency of **1a** in promoting the asymmetric formation of **7** or the ineffectiveness of **2** in promoting the synthesis of **5** is unclear.

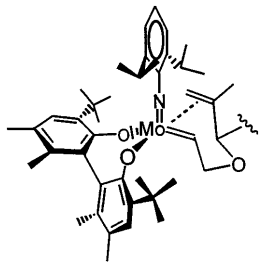
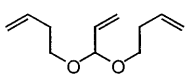
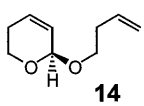
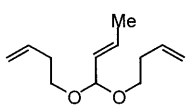
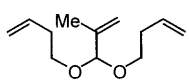
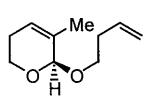
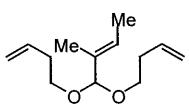


Figure 2.

Table 2
Desymmmetrization of triene acetals by Mo-catalyzed asymmetric ring-closing metathesis[a]

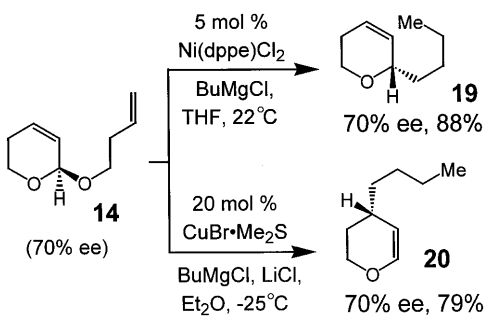
entry	substrate	product	catalyst	conv (%);[b] yield (%)[c]	ee (%)[d]
1			**1a**	>98; ND	<5
2			**1b**	>98; ND	<5
3			**2**	>98; ND	<5
4	**13**	**14**	**3**	>98; ND	10
5			**1a**	>98; 53	40
6			**1b**	>98; ND	43
7			**2**	>98; ND	19
8	**15**		**3**	***>98; 55***	***70***
9			**1a**	>98; 47	22
10			**1b**	>98; ND	21
11			**2**	>98; 49	62
12	**16**	**17**	**3**	***>98; 66***	***82***
13			**1a**	>98; 58	29
14			**1b**	>98; 56	51
15			**2**	>98; ND	13
16	**18**		**3**	***>98; 41***	***83***

a. Conditions: 5 mol % catalyst, Ar atm, 12 h, 22°C in C_6H_6; *iso*-octane was used in entries 8 and 12. *b*. By 400 MHz ^1H NMR analysis. *c*. Isolated yield of purified products after silica gel chromatography. *d*. By chiral GLC analysis (α–DEX). ND = not determined.

The data in Table 2 summarize the results of studies directed towards enantioselective synthesis of unsaturated cyclic acetals by catalytic ARCM.[15] As illustrated in entries 1–4, attempts at enantioselective ring-closure of the all-terminal triene **13** proved unsuccessful (<10% ee). Previous studies[3a] indicate that high levels of stereoinduction in ARCM are achieved when the *second* reacting alkene is adjacent to the stereogenic center (first olefin being that which forms the initial Mo–alkylidene). If the central Mo–alkylidene is generated, which then reacts with a remaining olefin, low enantioselection could result. We thus judged that low enantioselection in reactions of **13** is partly due to indiscriminate formation of Mo–alkylidene intermediates at all olefin sites and subsequent rapid closure on a terminal alkene.

When triene **15**, bearing a less reactive central disubstituted alkene, is subjected to the catalytic desymmetrization conditions (entries 5–8), notably higher levels of enantioselectivity are attained. Importantly, *complex **3** (entry 8) emerges as the most effective chiral catalyst (70% ee, 55%).*[16] Complexes **1a** and **1b**, which only differ from **3** in that they bear *i*-Pr and Me units at the C2 and C6 positions of their imido ligands, deliver significantly lower levels of enantioselectivity. Catalytic desymmetrization of trienes **16** (entries 9–12) and **18** (entries 13–16) affords acetal **17** with the highest enantioselectivity when **3** is used as the chiral catalyst (82 and 83% ee, respectively). Similar mechanistic models as shown in Fig. 2 may be used to rationalize the enantioselective formation of **14** and **17**; it is however difficult to explain why **3** is the superior catalyst in these asymmetric desymmetrizations.

As the examples in Scheme 2 illustrate, chiral non-racemic unsaturated acetals can be used in a variety of metal-catalyzed stereoselective functionalizations. Ni-catalyzed alkylation of **14**[17] in the presence of 5 mol% $Ni(dppe)Cl_2$ and BuMgCl leads to the formation of 2-substituted dihydropyran **19** (88% yield, >98% regioselectivity) without any detectable loss of enantiopurity (chiral GLC). Treatment of **14** with 20 mol% $CuBr{\cdot}Me_2S$ and BuMgCl[18] leads to a highly stereoselective allylic substitution to afford 4-substituted dihydropyran **20** in 79% isolated yield (>98% regioselectivity and <2% loss of optical purity).



Scheme 2.

In summary, we present two methods for the enantioselective synthesis of unsaturated heterocycles by Mo-catalyzed ARCM. *meso* Tetraenes are effectively desymmetrized with excellent enantioselectivity. Whereas biphen-based ligand **1b** is most suitable for the formation of dihydrofuran **5**, it is the binol-based complex **2** that efficiently promotes the asymmetric synthesis of dihydropyran **7**. In studies involving catalytic asymmetric synthesis of cyclic acetals, it is chiral catalyst **3**, containing a 2,6-dichloroimido ligand, that delivers appreciable levels of asymmetric induction. The work described herein provides an additional demonstration of the unique utility of Mo-catalyzed enantioselective olefin metathesis in asymmetric synthesis.

Acknowledgements

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7. For recent examples, where structurally-related substrates have different optimum chiral catalysts, see, (a) Shimizu, K. D.; Cole, B. M.; Krueger, C. A.; Kuntz, K. W.; Snapper, M. L.; Hoveyda, A. H. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 1704–1707. (b) Krueger, C. A.; Kuntz, K. W.; Dzierba, C. D.; Wirschun, W. G.; Gleason, J. D.; Snapper, M. L.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1999**, *121*, 4284–4285.
8. Synthesis and structural details of chiral Mo complex **3** will be disclosed in an upcoming manuscript (unpublished results of Jennifer. Y. Jamieson and Peter J. Bonitatebus).
9. All reaction products have been characterized by ^{1}H NMR, ^{13}C NMR, IR, C,H analysis and/or HRMS.
10. When reaction is performed with **2** at 22°C, 30% conv. is observed after 24 h (product includes ~10% *meso* bicycle).
11. Oltvoort, J. J.; van Boeckel, C. A. A.; De Konong, J. H.; van Boom, J. H. *Synthesis* **1981**, 305–308.
12. The stereochemical identity of **5** and **7** (Table 1) was established by comparison with authentic optically enriched materials. Authentic materials were prepared by Ti-catalyzed kinetic resolution of the mono-TBS ether of the parent diols, subsequent installment of the requisite allyl and silyl ethers, followed by RCM with $Mo(CHCMe_2Ph)(N(2,6\text{-}(i\text{-}Pr)_2C_6H_3))(OCMe(CF_3)_2)_2$. See, Gao, Y.; Hanson, R. M.; Klunder, J. M.; Ko, S. Y.; Masamune, H.; Sharpless, K. B. *J. Am. Chem. Soc.* **1987**, *109*, 5767–5780 and references cited therein.
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15. In certain cases *iso*-octane is used as solvent, since initial solvent screens indicate it to be a superior solvent to C_6H_6.
16. The stereochemical identity of the major enantiomer for desymmetrization of **15** was determined by the comparison of the product of the Ni-catalyzed alkylation of **14** (cf. Scheme 2) with authentic optically pure 2-alkyl substituted dihydropyrans (chiral GLC). This assignment is also based on substantial mechanistic evidence that the Ni-catalyzed alkylation proceeds with net inversion of stereochemistry (Didiuk, M. T.; Morken, J. P.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1995**, *117*, 7273–7274 and references cited therein). The stereochemical assignment for **17** is by inference.

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