Catalytic Enantioselective Ring-Closing Metathesis by a Chiral Biphen−Mo Complex

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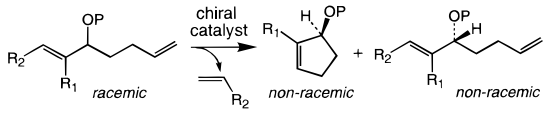
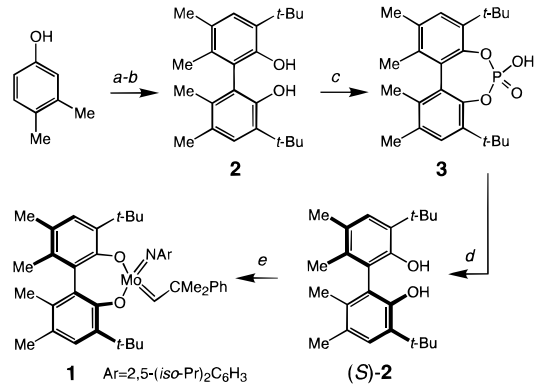
Mo-based[1] and Ru-based[2] complexes are regularly used to catalyze a range of ring-forming or ring-opening processes.[3] Mo-catalyzed reactions that give rise to macrocyclic trisubstituted olefins,[4] and Ru-based catalysts that effect the formation of disubstituted olefins within large rings,[5] have been employed to fabricate an impressive array of complex molecules. In most instances, without catalytic ring-closing metathesis (RCM), such synthesis schemes would have been notably longer and less convergent, if not impossible. The discovery and development of a chiral catalyst that effects efficient asymmetric ring-closing metathesis (ARCM) thus stands as a significant and compelling research objective.[6] Within this context, as outlined in Scheme 1, one possible scenario is where reaction by an optically pure RCM catalyst gives rise to nonracemic cycloalkenes and acyclic dienes. Herein, we report a chiral Mo-based complex that can efficiently catalyze ARCM to effect the kinetic resolution of dienes with excellent levels of enantioselectivity.

Scheme 1



To initiate our studies, we decided to use the chiral biphenol-containing complex **1** as the catalyst. This preference was based on the ability of the related chiral Mo systems that contain the 6,6′-dimethyl-3,3′,5,5′-tetra-*tert*-butyl-1,1′-biphenyl-2,2′-diol unit to control the stereochemistry of ring-opening metathesis polymerization.[7] Synthesis of **1** begins with the commercially available 3,4-dimethylphenol, which after alkylation is subjected to biaryl coupling conditions to afford **2**; this two-step procedure delivers the desired product in 50% yield when performed on a scale of 0.4 mol (∼50 g). Subsequent resolution of **2** (via **3**)[8] affords (*S*)-**2**. Specifically, treatment of **3** with (−)-cinchonidine (in EtOH), followed by recrystallization, leads to the recovery of optically pure (−)-cinchonidine salt of **3**.[9] The methyl ester derivative of the nonracemic phosphoric acid is generated by sequential treatment with 6 N HCl and dimethyl sulfate. Optically pure (>95% enantiomeric excess (ee)) biphen (**2**) is obtained by reduction of the resulting phosphoric acid methyl ester with Red-Al ($[\alpha]_D = -53.0$ ($c = 0.352$, THF)). Chiral complex **1** is accessed enantiomerically pure by the addition of the dipotassium salt of (*S*)-**2** to Mo(CHCMe$_2$Ph)(NAr)(triflate)$_2$(dimethoxyethane) (Ar = 2,6-(*i*-Pr)$_2$C$_6$H$_3$); **1** is purified and isolated as a four-coordinate species through recrystallization from Et$_2$O.[10]

Scheme 2[a]



[a] Key: a. $(CH_3)_2C{=}CH_2$ (20 psi), H_2SO_4, 65 °C, 3 h, quantitative; b. K_2CrO_7, H_2SO_4, H_2O, glacial acetic acid, 60 °C, 1h, 50%; c. NaH, 2 h; $POCl_3$, 1 h; H_2O, Et_3N, reflux, 5 h; HCl, reflux, 5 h, 95% from **3**; d. (−)-cinchonidine, EtOH, reflux, 1 h; EtOAc, acetone (5:1); HCl, EtOH, 70 °C, 1 h, 90%; Me_2SO_4, *N*,*N*-dimethylacetamide, 10 min, $NaHCO_3$, 8 h, 90%; Red-Al, 2h, 89%; e. KH, THF, 8 h; Mo(CHCMe$_2$Ph)(NAr)-(triflate)$_2$(dimethoxyethane), THF, 22 °C, 3 h, 64%.

Analysis of ^{1}H and ^{13}C NMR spectral data suggest that the neophilydene ligand in **1** exists primarily as its syn isomer (alkylidene H; δ 10.98 in ^{1}H NMR and δ 277.1 in ^{13}C NMR; C_6D_6). An X-ray crystal structure unambiguously establishes the stereochemical identity of the transition-metal complex. It is important to note that, in phenoxide complexes of this type, the syn isomer typically is in rapid equilibrium with its derived anti rotamer; both isomers are likely available in the course of the metathesis reaction. Although it is unclear at the present time whether the syn or the anti form is responsible for promoting ARCM, there is evidence that, in the case of Mo(CHCMe$_2$Ph)-(NAr)[(OCMe(CF$_3$)$_2$)]$_2$, the anti rotamer can be as much as 10^5 times more reactive than the alternative syn isomer.[11]

As illustrated in entry 1 of Table 1, when unsaturated TES (triethylsilyl) ether **4a** is subjected to 5 mol % **1** (benzene, 22 °C),[12] after only 10 min, 43% **5a** and 38% of the corresponding dimeric product is formed (by the reaction of terminal olefins). Most importantly, *cyclic product* ***5a*** *is obtained in 93% ee (*k_{rel}

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(1) (a) Schrock, R. R.; Murdzek, J. S.; Bazan, G. C.; Robbins, J.; DiMare, M.; O'Regan, M. *J. Am. Chem. Soc.* **1990**, *112*, 3875−3886. (b) Bazan, G. C.; Schrock, R. R.; Cho, H.-N.; Gibson, V. C. *Macromolecules* **1991**, *24*, 4495−4502.

(2) Wu, Z.; Nguyen, S. T.; Grubbs, R. H.; Ziller, J. W. *J. Am. Chem. Soc.* **1995**, *117*, 5503−5511.

(3) For recent reviews on olefin metathesis in organic synthesis, see: (a) Schuster, M.; Blechert, S. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2036−2056. (b) Armstrong, S. K. *J. Chem. Soc., Perkin Trans. 1* **1998**, 371−388.

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(5) For example, see: Meng, D.; Su, D.-S.; Balog, A.; Bertinato, P.; Sorensen, E. J.; Danishefsky, S. J.; Zheng, Y.-H.; Chou, T.-C.; He, L.; Horwitz, S. B. *J. Am. Chem. Soc.* **1997**, *119*, 2733−2734.

(6) For a recent report on ARCM, see: Fujimura, O.; Grubbs, R. H. *J. Am. Chem. Soc.* **1996**, *118*, 2499−2500. In this study, in all cases, $k_{rel} \leq 2.5$.

(7) Totland, K. M.; Boyd, T. J.; Lavoie, G. G.; Davis, W. M.; Schrock, R. R. *Macromolecules* **1996**, *29*, 6114−6125.

(8) Bao, J.; Wulff, W. D.; Dominy, J. B.; Fumo, M. J.; Grant, E. B.; Rob, A. C.; Whitcomb, M. C.; Yeung, S.-M.; Ostrander, R. L.; Rheingold, A. L. *J. Am. Chem. Soc.* **1996**, *118*, 3392−3405.

(9) The stereochemical purity of the crystalline phosphoric acid-cinchonidine salt is readily established through ^{31}P NMR analysis of the derived (−)-cinchonidine salt. Deprotonation of free phosphonic acid with (−)-cinchonidine affords a mixture of diastereomeric salts with resonances at −0.32 and −0.44 in^{31}P NMR spectrum (5% MeOH:EtOAc; H_3PO_4 reference).

(10) Complex **1** will be commercially available from Strem Chemicals, Inc., Newburyport, Massachusetts.

(11) Oskam, J. H.; Schrock, R. R. *J. Am. Chem. Soc.* **1993**, *115*, 11831−11845.

(12) ARCM can be carried out in toluene with similar levels of efficiency and enantioselection.

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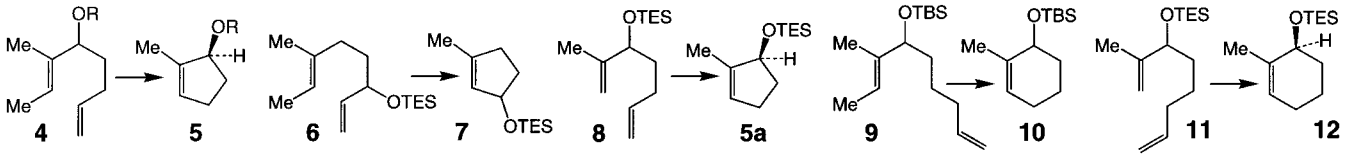
Table 1. Kinetic Resolution of Acyclic Dienes Catalyzed by Mo Complex **1**[a]



entry	substrate	product	R	reaction time (min); conv (%)	percent product[b]	percent dimer[b]	unreacted substrate config, ee (%)[c]	product ee (%)[c]	k_{fast}/k_{slow}
1	**4a**	**5a**	**a**, R = TES	10; 81	43	38	*R*, >99	93	58[d]
2	**4b**	**5b**	**b**, R = TBS	60; 75	42	33	*R*, >99	93	56[d]
3	**4c**	**5c**	**c**, R = TBDPS	120; 83	43	40	*R*, 95	92	52[d]
4	**4d**	**5d**	**d**, R = Bn	180; 76	41	35	*R*, 91	85	22[d]
5	**6**	**7**		120; 50	40	10	<5	<5	
6	**8**	**5a**		5; 59	55	<5	*R*, 97	65	11[e]
7	**9**	**10**		120; 50	<5	50			
8	**11**	**12**		30; 58	47	11	*R*, 57	45	4[e]

[a] Reaction conditions: 5 mol % **1**, C_6H_6, Ar atm, 22 °C. Mass balance >90%. [b] Conversion determined by analysis of 400 MHz ^{1}H NMR of unpurified mixture. [c] Enantioselectivity determined by GLC analysis (CHIRALDEX-GTA by Alltech) of derived acetates in comparison with authentic material. [d] Relative rate calculated based on formation and selectivity of product (see ref 13). [e] Relative rate determined based on the recovered starting material.

= 58)[13] *and the unreacted* ***4a*** *(19%) is isolated in >99% ee* (chiral GLC analysis). Ring closure is slower with reduced catalyst loadings, but resolution remains effective: with 1 mol % **1**, under otherwise identical conditions, after 4 h, 33% **5a** and 33% dimer are formed. Chiral GLC analysis indicates that the RCM product **5a** is generated in 95% ee, whereas **4a** is recovered in 70% ee. Entries 2 and 3 indicate that similarly high levels of enantioselectivity and reaction efficiency are obtained with the bulkier silyl protective groups (**4b** and **4c** as substrates). When the smaller benzyloxy group is used (entry 4), catalytic ARCM proceeds smoothly and resolution efficiency remains high (k_{rel}=22).

As the example in entry 5 depicts (**6** → **7**), when the stereogenic center is positioned α to the terminal alkene, dimer formation is diminished, but efficient catalytic kinetic resolution is not achieved. This finding suggests that formation of Mo−alkylidene of the substrate terminal olefin is reversible and does not occur with significant stereodifferentiation—it is the subsequent formation or the decomposition of the metallabicyclobutane that determines the identity of the faster reacting enantiomer. With substrates such as **4a**−**c**, significant diastereotopic face differentiation is attained in the cyclic transition state for the addition of the terminal metal−carbene to the trisubstituted olefin (en route to metallabicyclobutane).

To minimize dimer formation,[14,15] yet attain high asymmetric induction, we turned our attention to the 1,1-disubstituted alkene substrate **8**. We surmized that cyclization of the less-substituted olefin would compete more effectively with dimerization to lead to a more efficient ARCM. As shown in entry 6, reaction with diene **8** affords 55% of cyclic product **5a** and <5% dimeric product *after only 5 min*. The recovered starting material is obtained in 97% ee (k_{rel} = 11). This result, together with the data in entry 1, indicates that both the starting diene and the product cycloalkene can be isolated in excellent optical purity and good yield, depending on whether the trisubstituted (e.g., **4a**) or the 1,1-disubstituted olefin (e.g., **8**) is utilized as the starting material. In light of the data in entry 5, it is feasible that, with **8** as the substrate, resolution efficiency suffers because the chiral Mo−alkylidene no longer selects the terminal alkene as its initial site of reaction. That product enantioselection is higher in the reaction of **4a** than in ARCM of **8** is intriguing. It is tenable that, in the former instance, concomitant dimerization enhances product enantioselectivity because the slow-reacting enantiomer concentration is simultaneously diminished through this reaction pathway. Since the slower substrate enantiomer is consumed at a higher rate through dimerization as the reaction proceeds, cyclization of this isomer is expected occur less significantly than expected. Catalytic RCM of 1,7-diene **9** (entry 7) results only in the formation of the derived dimer. As before, dimerization is minimized in the ARCM of the lesser substituted **11**. The latter resolution efficiency represents an improvement to previous related results on similar substrates[6] but is lower than that detected for **8**.[16]

Studies in connection to the catalytic kinetic resolution of other classes of chiral substrates, as well as catalytic enantioselective ring-opening metathesis processes and various Mo-catalyzed rearrangements,[15] are in progress.

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Supporting Information Available: Experimental procedures and spectral and analytical data for all recovered starting materials and reaction products, in addition to crystallographic details (52 pages, print/PDF). See any current masthead page for ordering information and Web access instructions.

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(13) The value for k_{rel} is calculated by the equation reported by Kagan: Kagan, H. B.; Fiaud, J. C. *Top. Stereochem.* **1988**, *18*, 249−330. However, this calculation is only an approximation of the relative rates of reactions of enantiomers, as it is based on a first-order equation, where a simultaneous process that consumes both enantiomers (dimer formation) does not occur.

(14) Under an atmosphere of ethylene, the rate of ring closure is reduced. Little or no change in the relative amount of dimeric product or enantioselectivity is observed.

(15) For the use of ethylene atmosphere to minimize dimeric products, see: Harrity, J. P. A.; Visser, M. S.; Gleason, J. D.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1997**, *119*, 1488−1489.

(16) Related resolutions of the derived acetate by a related Mo complex proceeds with significantly lower levels of efficiency (see ref 6).