Mo-Catalyzed Asymmetric Synthesis of Dihydrofurans. Catalytic Kinetic Resolution and Enantioselective Desymmetrization through Ring-Closing Metathesis

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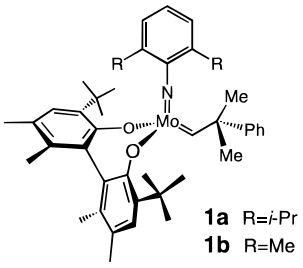
We recently reported that in the presence of chiral catalyst **1a**,

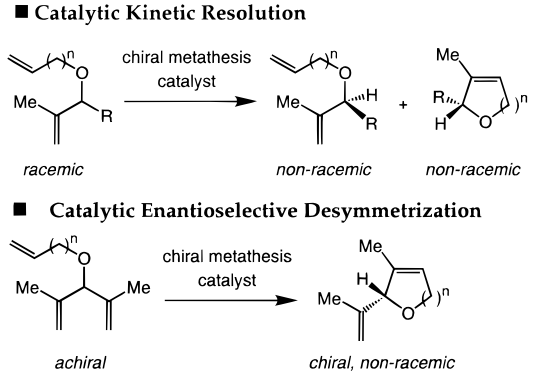


1a R=*i*-Pr
1b R=Me

1,6-dienes that bear an alkoxy or siloxy group undergo asymmetric ring-closing metathesis (ARCM) efficiently and enantioselectively.[1,2] We demonstrated that, depending on the level of alkene substitution, these catalytic kinetic resolutions[3] provide either the recovered dienes or the derived cycloalkenyl products in ≥40% yield and >90% ee.

In addition to the enantioselective synthesis of unsaturated carbocycles, ARCM offers unique opportunities for the preparation of enantiomerically enriched heterocycles.[4] One approach involves the kinetic resolution of acyclic dienes that contain a heteroatom within the cyclizing chain (Scheme 1). A more attractive extension of this strategy would be a catalytic enantioselective desymmetrization[5] that delivers the derived heterocycles in high optical purity and where the maximum yield can be 100% (vs 50% in a typical kinetic resolution). Herein, we report on the ability of complexes **1a** and **1b** to catalytically resolve dienes that can serve as precursors to five-membered heterocycles. Moreover, we present the first examples of efficient and enantioselective desymmetrization reactions that lead to the formation

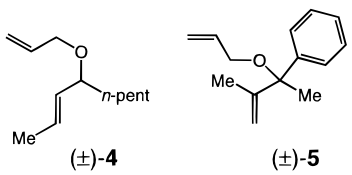
Scheme 1



of chiral furans with high levels of optical purity; in certain cases, the absolute stereochemistry of quaternary carbon centers is controlled.

As illustrated in entry 1 of Table 1, treatment of diene ether **2a** with 5 mol % **1a** in toluene at −25 °C leads to the formation of the derived dihydrofuran (*R*)-**3a**. At 63% conversion, the unreacted starting material, (*S*)-**2a**, is obtained in 92% ee (k_{rel} = 10).[6] Although diene **2d** is resolved with slightly lower enantioselectivity, data in entries 2 and 3 of Table 1 indicate that increasing the size of the α substituent can lead to notable enhancement in resolution selectivity. With **2a**, **2b**, and **2d**, when ARCM is performed at 22 °C, the reaction reaches >80% conversion within one minute. ARCM of the slower reacting **2c** can be carried out at 22 °C (64% conv in 8 min) without a significant diminution in enantioselectivity (entry 3). It is worth noting that although the ARCM processes in Table 1 were effected with 5 mol % catalyst, lower loadings are effective; for example, in the presence of 2.5 mol % **1a**, **2a** is resolved with k_{rel} = 10 (58% conv, 23 h).

In contrast to dienes that carry a 1,1-disubstituted alkene (**2a**−**d**), 1,2-disubstitued substrates such as **4** are not resolved



(±)-**4** (±)-**5**

selectively. After treatment of diene **4** to the above conditions, recovered starting material is obtained in only 27% ee after 54% conversion (k_{rel} = 1.5). In addition, chiral catalysts **1a** and **1b** are ineffective in resolving tertiary ethers, such as **5** (<10% ee after 20% conversion in 24 h under the same conditions as in Table 1).

Next, we turned our attention to catalytic enantioselective desymmetrization processes. As illustrated in Table 2, *when triene* ***6*** *is subjected to 1 mol %* ***1a*** *(C_6H_6, 22* °C*), ARCM proceeds to 94% conversion after 6 h*; dihydrofuran (*R*)-**7** is obtained in 93% ee (chiral GLC) and 86% yield after silica gel chromatography.[7] Similar results are obtained with **1b** as the catalyst. With the more substituted triene **8** as the substrate and with **1a** as the catalyst, enantioselectivity remains high (94% ee) but the rate of formation of **9** suffers significantly (32% conversion after 9 h). However, as also depicted in entry 2 of Table 2, with 5 mol %

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(1) Alexander, J. B.; La, D. S.; Cefalo, D. R.; Hoveyda, A. H.; Schrock, R. R. *J. Am. Chem. Soc.* **1998**, *120*, 4041−4042.

(2) For related studies on ARCM, see: Fujimura, O.; Grubbs, R. H. *J. Org. Chem.* **1998**, *63*, 824−832.

(3) For a recent comprehensive review on metal-catalyzed kinetic resolution, see: Hoveyda, A. H.; Didiuk, M. T. *Curr. Org. Chem.* **1998**, *2*, 537−574.

(4) For recent reviews on catalytic olefin metathesis in organic synthesis, see: (a) Schuster, M.; Blechert, S. *Angew. Chem., Int. Ed. Engl.* **1997**, *109*, 2124−2145. (b) Furstner, A. *Top. Catal.* **1997**, *4*, 285−299. (c) Armstrong, S. K. *J. Chem. Soc., Perkin Trans. 1* **1998**, 371−388. (c) Grubbs, R. H.; Chang, S. *Tetrahedron* **1998**, *54*, 4413−4450.

(5) For select recent examples of metal-catalyzed desymmetrization reactions, see: (a) Schreiber, S. L.; Schreiber, T. S.; Smith, D. B. *J. Am. Chem. Soc.* **1987**, *109*, 1525−1529. (b) Mikami, K.; Narisawa, S.; Shimizu, M.; Terada, M. *J. Am. Chem. Soc.* **1992**, *114*, 6566−6568. For select cases involving meso substrates, see: (c) 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. (d) Iida, T.; Yamamoto, N.; Sasai, H.; Shibasaki, M. *J. Am. Chem. Soc.* **1997**, *119*, 4783−4784. (e) Trost, B. M.; Patterson, D. E. *J. Org. Chem.* **1998**, *63*, 1339−1341.

(6) Relative rates are calculated on the basis of the equation reported by Kagan. See: Kagan, H. B.; Fiaud, J. C. *Top. Stereochem.* **1988**, *18*, 249−330.

(7) For details related to the proof of the stereochemical identity of the reaction products, see the Supporting Information.

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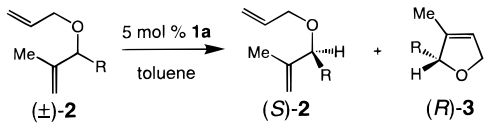
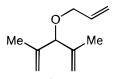
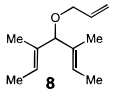
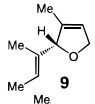
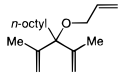
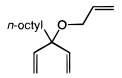
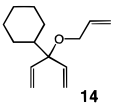
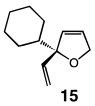
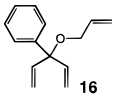
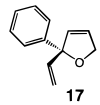
Table 1. Mo-Catalyzed Kinetic Resolution of Allylic Ethers[a]



entry	substrate	temp (°C), time	conv[b] (%)	unreacted subs. ee (%)[c]	k_{rel}
1	(±)-**2a**, R = *n*-Pent	−25, 6 h	63	92	10
2	(±)-**2b**, R = *i*-Bu	−25, 10 h	56	95	23
3	(±)-**2c**, R = Cyhex	−25, 7 h 22, 8 min	62 64	98 97	17 13
4	(±)-**2d**, R = Ph	−25, 6 h	56	75	8

[a] Conditions: 5 mol % **1a**, toluene, Ar atm. [b] Conversion determined by GLC analysis in comparison with dodecane as the internal standard. [c] Enantioselectivity determined by chiral GLC (CHIRALDEX-GTA by Alltech) in comparison with authentic racemic material. Assignments as shown above, except (*R*)-**2d** and (*S*)-**3d** are obtained.

Table 2. Enantioselective Synthesis of Dihydrofurans by Mo-Catalyzed Desymmetrization[a]

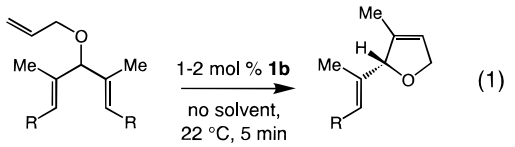
entry	substrate	catalyst	temp (°C), time	product	product ee (%), config.[b]	conv.,[c] yield (%)[d]
1	 **6**	**1a** **1b**	22, 6 h 22, 6 h	 **7**	93, *R* 93, *R*	94, 86 93, 86
2	 **8**	**1a** **1b**	22, 9 h 22, 4 h	 **9**	94, *R* 99, *R*	32, -- 95, 83
3	 **10**	**1a** **1b**	22, 9 h 22, 4 h	 **11**	-- 50,	NO REACTION 36, 28
4	 **12**	**1a** **1b**	22, 15 h 22, 15 h	 **13**	10 10	76, 73 >98, 88
5	 **14**	**1a** **1b**	22, 18 h -20, 18 h	 **15**	17, *S* 73, *S*	87, 85 93, 84
6	 **16**	**1a** **1b**	22, 18 h -20, 18 h	 **17**	16, *S* 82, *S*	36, 34 93, 91

[a] Conditions: 5 mol % catalyst (3 mol %, entry 1), toluene for reactions at −25 °C and C_6H_6 for those at 22 °C, Ar atm. [b] Selectivity determined by chiral GLC (CHIRALDEX-GTA by Alltech for entries 1−4; BETADEX-120 by Alltech for entries 5−6) in comparison with authentic racemic material. [c] Conversion determined by GLC analysis in comparison with dodecane as the internal standard (entries 1−2) or by ^{1}H NMR analysis (400 MHz). [d] Isolated yields after silica gel chromatography or distillation.

1b ARCM proceeds to 95% conversion after only 4 h, and **9** is obtained in 99% ee and 83% isolated yield.

We have examined the possibility of controlling the absolute stereochemistry of quaternary carbon stereogenic centers by our catalytic method.[8] Our efforts to effect the ARCM of triene **10** were thwarted by <2% reaction with **1a** as the initiator; when **1b** was used, the reaction proceeded to 36% conversion to afford **11** in 50% ee. Higher conversions were obtained with the less substituted triene **12**, but selectivity suffered, presumably due to competing initiation at the various olefinic sites. Since our previous studies[1] indicated that it is the formation of the intermediate metallabicyclobutane that is likely the stereochemistry-determining step (vs the initial formation of the metal−alkylidene), we argued that higher levels of enantioselectivity may be obtained with larger alkyl substituents (more effective steric differentiation between a cyclohexyl and a vinyl moiety). These considerations led us to examine the ARCM of triene **14**. We surmised that, with the sterically demanding cyclohexyl unit, Mo−alkylidene formation probably occurs primarily at the less hindered terminal olefin, inducing metallabicycle formation adjacent to the quaternary site. As the data in entries 5 and 6 of Table 2 indicate, in the presence of 5 mol % **1b**, ARCM of tertiary ethers **14** and **16** afford **15** and **17** in 73 and 82% ee and 84 and 91% yield, respectively.[7] It is important to note that, as depicted in entries 5 and 6, reactions with **1a** are less efficient and not as selective.

We thus present the first catalytic and enantioselective synthesis of chiral heterocycles effected through the use of chiral metathesis catalysts **1a** and **1b**. Mo-catalyzed kinetic resolutions are efficient and reliable and deliver chiral dienes in high optical purity. Most noteworthy is the remarkable efficiency of the Mo-catalyzed enantioselective desymmetrization process, where we find that reactions can be run neat. For example, as shown in eq 1,



6 R=H (1 mol % **1b**) (*R*)-**7** *93% ee, 85% yield*
8 R=Me (2 mol % **1b**) (*R*)-**9** *99% ee, 93% yield*

*catalytic ARCM of **6** and **8** can be carried out in the absence of solvent with 1−2 mol % **1b** to afford, within five min, (R)-**7** and (R)-**9** in 85% and 93% isolated yield and 93% and 99% ee after distillation* (>99% conversion in both cases), *respectively*. In both reactions, there is <5% dimer formed (GLC analysis).

Studies on additional applications of ARCM in catalytic enantioselective synthesis and their applications to natural product synthesis 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 (56 pages, print/PDF). See any current masthead page for ordering information and Web access instructions.

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(8) For a review of catalytic enantioselective methods for the synthesis of quaternary carbon stereogenic centers, see: Corey, E. J.; Guzman-Perez, A. *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 388−401.