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Enantioselective Synthesis of Medium-Ring Heterocycles, Tertiary Ethers, and Tertiary Alcohols by Mo−Catalyzed Ring-Closing Metathesis

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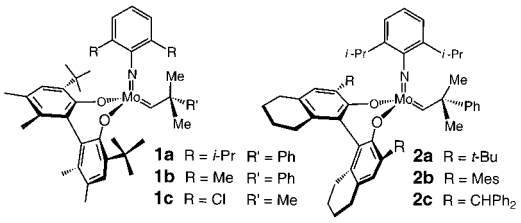
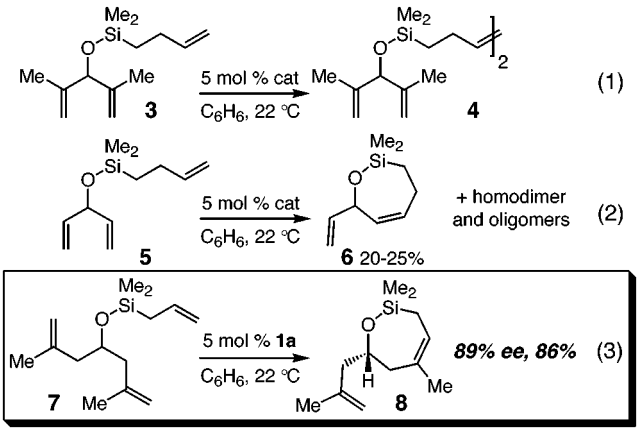
The advent of chiral Mo-based catalysts, represented by **1**−**2**, has provided efficient pathways to optically enriched or pure five- and six-membered ring carbo-[1,2a] and heterocycles.[2,3] In connection to expanding the generality of catalytic asymmetric ring-closing metathesis (ARCM), a number of critical issues remain unresolved. Among these is the need for efficient methods leading to enantioselective synthesis of *medium rings*, formation of which can be hampered by competitive intermolecular homodimerization. Enantioselective syntheses of seven-membered ring oxygen-containing unsaturated heterocycles by Mo-catalyzed ARCM are disclosed herein;[4] this protocol thus significantly expands the utility of catalytic asymmetric metathesis. Tertiary medium-ring siloxanes, a group of products readily accessible by this method, can be easily functionalized to deliver tertiary alcohols of high optical purity—compounds that are often difficult to prepare by any other method.[5]

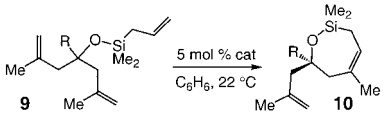


We began our studies by examining the catalytic ARCM of triene **3** (eq 1); this was based on previous success in using this diallyl ether core in highly enantioselective syntheses of five-[2b,c] and six-membered ring heterocycles.[2c,g] As illustrated in eq 1, only homodimeric adduct **4** was formed in the presence of chiral catalysts, which included complexes **1**−**2** (5 mol %). To facilitate ring closure, we turned to all-terminal triene **5** (eq 2); similar screening studies indicated that substantial amounts of homodimeric and oligomeric compounds are still generated. To examine the catalytic ARCM of a substrate with less steric congestion at the olefinic sites, we synthesized triene **7** (eq 3). Although the disubstituted olefins of **7** are homoallylic to the siloxy group and more accessible to the purported terminal Mo−alkylidene (formed by reaction of the catalyst with the monosubstituted olefin), we were not optimistic about the stereochemical outcome of this reaction. This was based on previous studies, indicating that high stereochemical induction may be attained if the initially formed metal−alkylidene reacts with an olefin that is *directly adjacent* to the pro-stereogenic center.[2a] Nonetheless, as depicted in eq 3, catalyst screening revealed that not only is **7** efficiently converted to **8** (90−95% conv in 12 h, 22 °C) but that the seven-membered ring heterocycle can also be isolated in 89% ee and 86% yield.[6]



Next, we turned our attention to the enantioselective synthesis of medium-ring heterocycles that bear *tertiary* ether sites. We established that treatment of triene **9a** with 5 mol % **1a** (22 °C, 12 h) leads to the formation of siloxane **10a** in 93% ee and 92% yield after silica gel chromatography (entry 1, Table 1).[6] Catalytic ARCM

Table 1. Mo-Catalyzed Asymmetric Synthesis of Seven-Membered Siloxanes Bearing Tertiary Ether Centers



entry	R		catalyst	conv (%);[a] yield (%)[b]	ee (%)[c]
1	Ph	**a**	**1a**	>98; 92	93
2	*p*-BrPh	**b**	**1c**	>98; 98	94
3	Cy	**c**	**1a**	>98; 91	83
4	*i*-Pr	**d**	**1a**	>98; 92	90
5	*n*-Bu	**e**	**1b**	>98; 87	66
6	Me	**f**	**2c**	>98; 90	47

[a] Determined by 400 MHz ^{1}H NMR. [b] Isolated yields of products after silica gel chromatography. [c] Determined by chiral HPLC (Chiralcel OJ, entry 1; Chiralcel OD, entry 2) and chiral GLC (β-DEX, entries 3−5 and CDGTA, entry 6). See the Supporting Information for details.

of **9b** (entry 2) proceeds with equal levels of efficiency and selectivity. Although both **1a** and **1c**[2d,7] perform well in effecting the ARCM of **9a**−**b**, the more Lewis acidic **1c** proves to be a more effective catalyst and may be preferable in these cases.[8] As shown in entries 3 and 4 of Table 1, aliphatic tertiary ethers **10c** and **10d** are obtained in 83% and 90% ee (respectively) and >90% isolated yields. It is worthy of note that the sense of stereochemical induction in the formation of **10** is opposite to that seen in the generation of **8** (eq 3); the mechanistic basis for this difference in selectivity is

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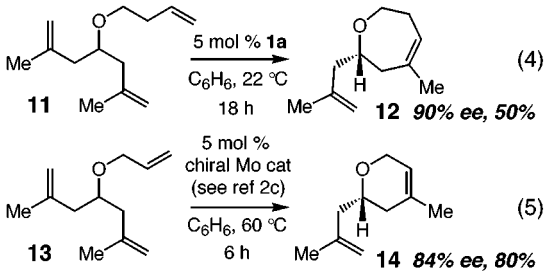
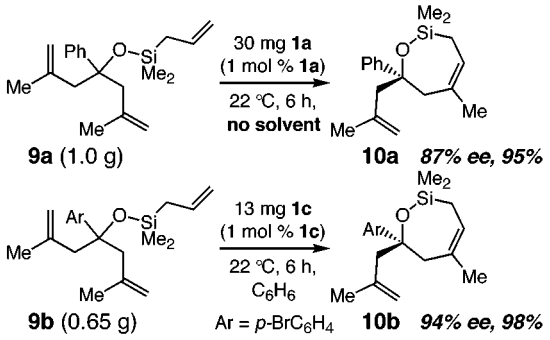
unclear. When substrates **9e** and **9f** (entries 5 and 6) bearing sterically less demanding substituents are used, reactions proceed to >98% conversion but with diminution in enantioselectivity (66% and 47% ee, respectively).[9]

The transformation shown in eq 4 (→**12**) illustrates that medium-ring oxepins can also be prepared enantioselectively and in good isolated yield. However, reactions of the corresponding siloxane **7** are more facile, presumably due to favorable entropic effects imposed by the $SiMe_2$ group. Formation of 20−30% homodimeric products in reaction of **11**, in contrast to <2% generation of such products when the corresponding silyl ethers are used, supports the above hypothesis. As the enantioselective synthesis of dihydropyran **14** indicates (promoted by a binaphtholate-derived catalyst[2c]), unsaturated six-membered ring heterocycles may be prepared by this method as well, allowing access to another class of chiral unsaturated pyrans by Mo-catalyzed ARCM.[2c,g]



The present method provides a practical and cost-effective approach for the synthesis of synthetically versatile tertiary ethers. *Catalytic ARCM of various trienes may be effected efficiently and with excellent enantioselectivity on gram scale, with 1 mol % catalyst loading (10−20 mg of catalyst for 0.5−1 g of products) in the absence of solvent* (Scheme 1); analytically pure product is

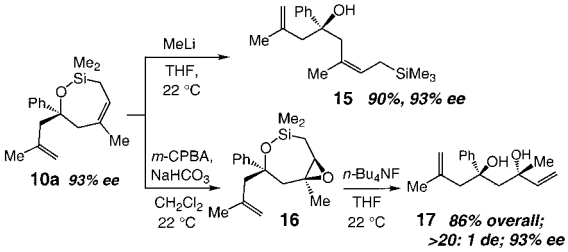
Scheme 1. Cyclic Tertiary Ethers Prepared in Large Scale, without Solvent



obtained by simple distillation. Even in the absence of solvent, no detectable amounts of homodimeric adducts are formed in the synthesis of seven-membered ring **10a**.

The nonracemic chiral medium-ring siloxanes obtained are versatile compounds that can be employed to prepare numerous difficult-to-attain tertiary alcohols. The examples depicted in Scheme 2 are representative. Treatment of **10a** (93% ee) with MeLi in THF (12 h, 22 °C) results in the formation of tertiary alcohol **15** (93% ee), a compound that cannot be prepared by any enantioselective alkylation[5a] or kinetic resolution[10] protocols and is suitable for a variety of hydroxyl-directed reactions.[11] Subjection of siloxane **10a** to *m*-CPBA leads to the diastereoselective formation of epoxide **16** (>20:1);[12] direct treatment of **16** with *n*-Bu_4NF readily delivers **17** in 86% isolated yield (93% ee, >20:1). 1,3-Tertiary diols such as **17** represent important building blocks in natural product

Scheme 2. Functionalization of Non-Racemic Siloxane **10a**



synthesis[13] and are not readily prepared in the nonracemic form by the more traditional approaches.[14]

Supporting Information Available: Experimental procedures and spectral and analytical data for all products (PDF). This material is available free of charge via the Internet at http//:www.acs.pubs.org.

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(6) The stereochemical identities of **8**, **10d**, and **10e** were established through comparison with authentic materials obtained by independent synthesis (see the Supporting Information for details). The remaining stereochemical assignments are by inference.

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(8) That various catalysts are readily prepared and are available for screening to idenify an optimal system should be considered an attractive and positive attribute. It is rare that reactions of different substrates are effected with equal efficiency and selectivity by a single catalyst entity. See: Hoveyda, A. H. *Chem. Biol.* **1998**, *5*, R187−R191.

(9) Use of the derived diphenylsilyl ethers leads to some enhancement in asymmetric induction; as an example, the diphenylsiloxane corresponding to **10f** can be obtained in 57% ee and 86% isolated yield (cf. entry 6, Table 1). Other catalysts or strategies will be required to obtain such compounds with synthetically useful levels of enantiopurity; these and related studies are in progress.

(10) For recent reviews of metal-catalyzed kinetic resolutions, see: (a) Hoveyda, A. H.; Didiuk, M. T. *Curr. Org. Chem.* **1998**, *2*, 537−574. (b) Cook, G. R. *Curr. Org. Chem.* **2000**, *4*, 869−885. (c) Keith, J. M.; Larrow, J. F.; Jacobsen, E. N. *Adv. Synth. Catal.* **2001**, *1*, 5−26.

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(12) The stereochemical identity of the major diastereomer of **16** was ascertained through nOe difference experiments. See the Supporting Information for details.

(13) For an example, see: Semmelhack, M. F.; Shanmugam, P. *Tetrahedron Lett.* **2000**, *41*, 3567−3571.

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