Molecular Design of a Chiral Lewis Acid for the Asymmetric Claisen Rearrangement

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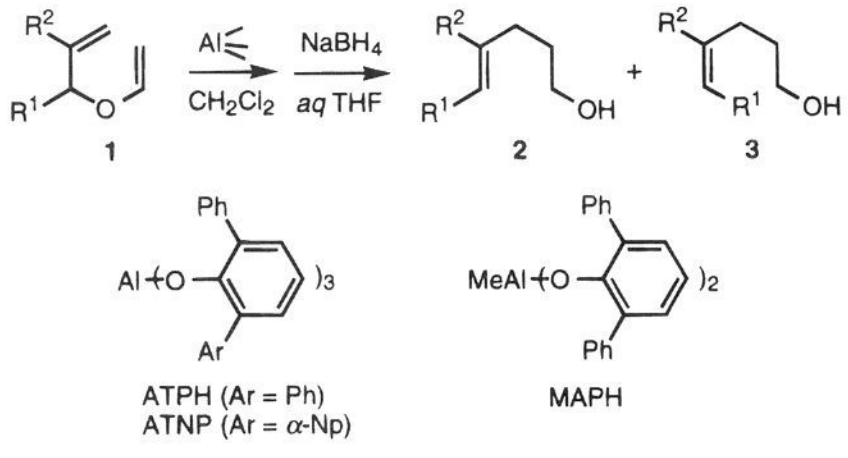
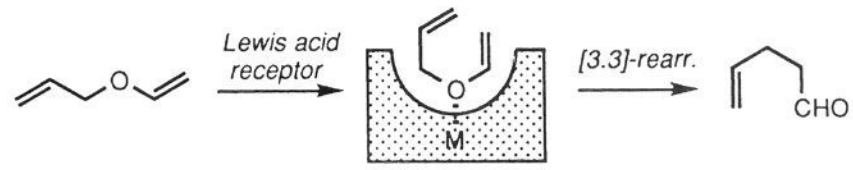
Following its discovery in 1912,[1] the Claisen rearrangement of allyl vinyl ethers has become one of the most powerful tools for stereoselective carbon−carbon bond-forming reactions in organic synthesis. The impact of the Claisen rearrangement on modern synthetic methodology is apparent from a number of recent reports in the literature, the sequential development of new variants of the [3,3]-sigmatropic rearrangement, and numerous applications to the synthesis of natural products.[2] However, many formidable mechanistic and synthetic challenges remain to the entire chemical community regarding this valuable rearrangement. For example, the influence of Lewis acid catalysts on transition state structures of this rearrangement has not been investigated enough to be synthetically useful.[2j] In this report, we describe a new, rational approach to this problem, *i.e.,* the molecular design of a Lewis acid reagent for the Claisen rearrangement and its application to create a new, chiral Lewis acid for an asymmetric Claisen rearrangement, based on our recently developed molecular recognition approach using Lewis acid receptors which are capable of forming preferable six-membered transition state structures for allylic vinyl ether substrates (Scheme 1).

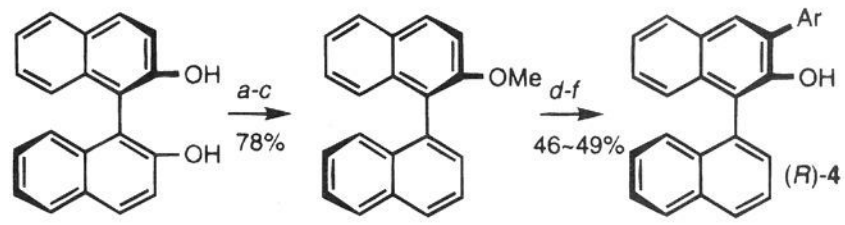
Our recently introduced aluminum tris(2,6-diphenylphenoxide) (ATPH)[3] seems to be ideal for this purpose. Indeed, treatment of allylic vinyl ether **1** (R^1 = Bu; R^2 = H) with ATPH (1.1 equiv) in CH_2Cl_2 at 0 °C for 1.5 h and subsequent reduction with $NaBH_4$ in aqueous THF at 0 °C gave a mixture of (*E*)- and (*Z*)-4-nonenols, **2** and **3** (R^1 = Bu; R^2 = H) (87% combined yield), in a ratio of 16:1.[4] Aluminum tris(2-α-naphthyl-6-phenylphenoxide) (ATNP), which is more sterically hindered than ATPH, gave much higher selectivity (90% yield; **2**:**3** = 47:1). In contrast, our previously reported methylaluminum bis-



Scheme 1



Scheme 2[a]



[a] Me_2SO_4, K_2CO_3, acetone. [b] Tf_2O, Py, CH_2Cl_2. [c] 10% Pd/C, H_2, EtOH. [d] BuLi, TMEDA, ether; Br_2. [e] ArMgBr, $NiCl_2(dppp)_2$, ether. [f] BBr_3, CH_2Cl_2.

(2,6-diphenylphenoxide) (MAPH)[5] gave less satisfactory results in terms of both chemical yield and selectivity under similar reaction conditions (75% yield; 5:1). A similar tendency was also observed for the aluminum-promoted Claisen rearrangement of allyl vinyl ether substrate **1** (R^1 = Bu; R^2 = Me) at 0 °C for 1 h: ATNP (30:1, 85% yield); ATPH (18:1, 89% yield); MAPH (3:1, 75% yield). Apparently, ATPH serves as a tight reaction pocket for allyl vinyl ether substrate **1** (R^1 = Me; R^2 = H) which, on binding with ATPH, forms a preferable six-membered chair-like transition state structure with the R^1 substituent equatorial to ensure the stereoselective [3,3]-sigmatropic rearrangement as shown in Figure 1.

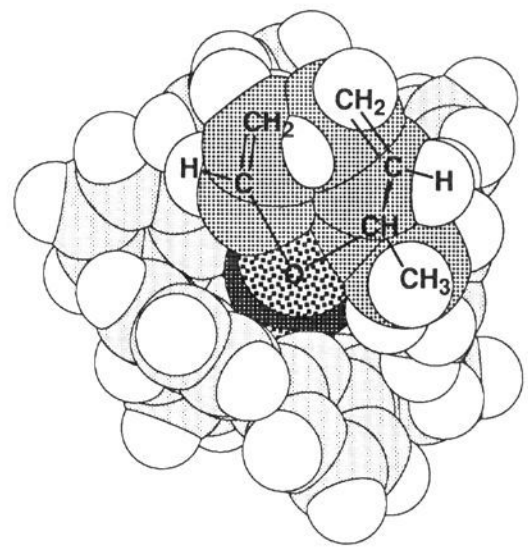
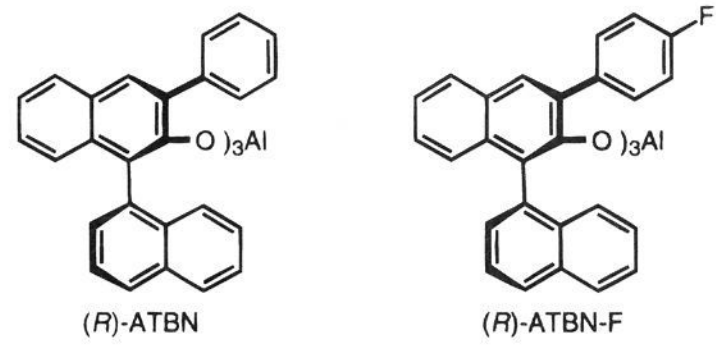


Figure 1. Space-filling model of allylic vinyl ether/ATPH complex.

With this information, we set out to design a chiral ATPH analogue, (*R*)-ATBN, in an optically pure form for use in the asymmetric Claisen rearrangement. The requisite optically pure



phenol, (*R*)-**4**, can be prepared from commercially available (*R*)-binaphthol in six-step sequences, as illustrated in Scheme 2.[6] Treatment of (*R*)-**4** (Ar = Ph) (3 equiv) in toluene with Me_3Al

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(2) Recent reviews: (a) Bartlett, P. A. *Tetrahedron* **1980**, *36*, 3. (b) Gajewski, J. J. *Hydrocarbon Thermal Isomerizations*; Academic Press: New York, 1981. (c) Lutz, R. P. *Chem. Rev.* **1984**, *84*, 205. (d) Hill, R. K. In *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic Press: New York, 1984; Vol. 3, p 503. (e) Murray, A. W. *Org. React. Mech.* **1986**, 429; **1987**, 457. (f) Moody, C. J. *Adv. Heterocycl. Chem.* **1987**, *42*, 203. (g) Ziegler, F. E. *Chem. Rev.* **1988**, *88*, 1423. (h) Kallmerten, J.; Wittman, M. D. *Stud. Nat. Prod. Chem.* **1989**, *3*, 233. (i) Blechert, S. *Synthesis* **1989**, 71. (j) Wipf, P. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Paquette, L. A., Eds.; Pergamon Press: New York, 1991; Vol. 5, Chapter 7.2, p 827.
(3) Maruoka, K.; Imoto, H.; Saito, S.; Yamamoto, H. *J. Am. Chem. Soc.* **1994**, *116*, 4131.
(4) The isomeric ratio was determined by capillary GLC analysis (25-m PEG-HT column) after conversion to its trimethylsilyl ether.
(5) Nonoshita, K.; Banno, H.; Maruoka, K.; Yamamoto, H. *J. Am. Chem. Soc.* **1990**, *112*, 316.
(6) (*R*)-**4** (Ar = Ph): $[\alpha]^{24}_D$ 74.3° (*c* 1.0, $CHCl_3$). (*R*)-**4** (Ar = *p*-F-C_6H_4): $[\alpha]_D$ 61.9° (*c* 0.99, $CHCl_3$).

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Table 1. Asymmetric Claisen Rearrangement of Allyl Vinyl Ether **5** with (*R*)-ATBN Derivatives[a]

entry	substrate **5**	Lewis acid	% yield[b]	% ee[c] (config)
1	R = *t*-Bu	(*R*)-ATBN	63	63 (*S*)[d]
2		(*R*)-ATBN-F	70	91 (*S*)[d]
3	R = c-C_6H_{11}	(*R*)-ATBN	78	61 (*S*)[e]
4		(*R*)-ATBN-F	85	86 (*S*)[e]
5	R = Ph	(*R*)-ATBN	93	61 (*S*)[f]
6		(*R*)-ATBN-F	97	76 (*S*)[f]
7	R = $SiMe_3$	(*R*)-ATBN-F	78	92

[a] The asymmetric Claisen rearrangement of allyl vinyl ether **5** was carried out with 1.1−2 equiv of (*R*)-ATBN or (*R*)-ATBN-F in toluene at −78 °C for 10−40 h. [b] Isolated yield. [c] Determined by capillary GLC analysis after conversion to its acetal of (2*R*,4*R*)-pentanediol. [d] Determined by conversion to (2*S*,4*R*)-4-*tert*-butyl-2-methyltetrahydropyran: (i) enantioselective methylation of (2*R*,4*R*)-pentanediol acetal of **6** (R = *t*-Bu) with Me_2Zn−$TiCl_4$ in CH_2Cl_2 (Mori, A.; Fujiwara, J.; Maruoka, K.; Yamamoto, H. *J. Organomet. Chem.* **1985**, *285*, 83); (ii) hydroboration−oxidation with BH_3·THF and H_2O_2/aqueous NaOH; (iii) PCC oxidation of the resulting diol in CH_2Cl_2; (iv) removal of chiral auxiliary with K_2CO_3 in MeOH; (v) reduction of the lactol with Et_3SiH−BF_3·OEt_2 in CH_2Cl_2. [e] Determined, after hydrogenation, by comparison with the retention time of the known (2*R*,4*R*)-pentanediol acetal of (*R*)-3-cyclohexylpentenal. See ref 7b. [f] Determined by correlation to the known (*S*)-3-phenyl-4-pentenal (Berlan, J.; Besace, Y.; Pourcelot, G.; Cresson, P. *Tetrahedron* **1986**, *42*, 4757).

in hexane at 25 °C for 1 h generated a chiral aluminum reagent, (*R*)-ATBN. This subsequently reacted with allyl vinyl ether **5** (R = cyclohexyl) at −78 °C for 25 h to furnish a rearrangement product **6** (R = cyclohexyl) (78% yield), whose enantiomeric purity was determined to be 61% ee by capillary GLC analysis after conversion to its acetal of (2*R*,4*R*)-pentanediol. Switching the aluminum reagent from (*R*)-ATBN to (*R*)-ATBN-F further increased the enantioselectivity to 86% ee for this substrate. Use of CH_2Cl_2 in place of toluene decreased the enantioselectivity. Other selected examples are listed in Table 1. The ligand effect of chiral aluminum reagents on enantioselectivity was examined in the rearrangement of *trans*-cinnamyl vinyl ether, **5** (R = Ph). Changing the phenyl substituent in (*R*)-ATBN (entry 5, Table 1) to *p*-fluorophenyl (entry 6), *p*-tolyl, 3,5-difluorophenyl, and 3,5-xylyl groups gave Claisen product **6** (R = Ph) at 76, 62, 40, and 7% ee, respectively. In addition, the latter two aluminum reagents (*i.e.*, 3,5-difluorophenyl and 3,5-xylyl derivatives) reduced the rate of the rearrangement. Notably, the fragmentation of **5** takes precedence over Claisen rearrangement with a chiral organoaluminum reagent derived from Me_3Al and (*R*)-3,3′-bis(triphenylsilyl)binaphthol.[7] The present method also provides a facile route to the asymmetric synthesis of functionalized allylic silanes **6** (R = $SiMe_3$), the importance of which has already been delineated in asymmetric synthesis.[8]

On the basis of ^{19}F NMR data of the coordination complexes with (*R*)-ATBN-F and the X-ray structure of the DMF/ATPH complex,[3,9] a plausible structure for (*R*)-ATBN which possesses characteristic C_3 symmetry can be constructed, as shown in the space-filling model in Figure 2. In the transition state for the asymmetric Claisen rearrangement of *trans*-cinnamyl vinyl ether with (*R*)-ATBN, the one conformation of the ether substrate (shown as the ball and stick model in Figure 2) makes a good match for the C_3-symmetric molecular cleft of the chiral aluminum reagent, which leads to the *S* isomer in accord with experimental findings. The enhanced enantioselectivity observed with (*R*)-ATBN-F can be explained by the effective shielding of one side of the aluminum center by three *p*-fluorophenyl groups, which obstruct approach by allylic vinyl ether substrate **5** from the back side in Figure 2.[10]

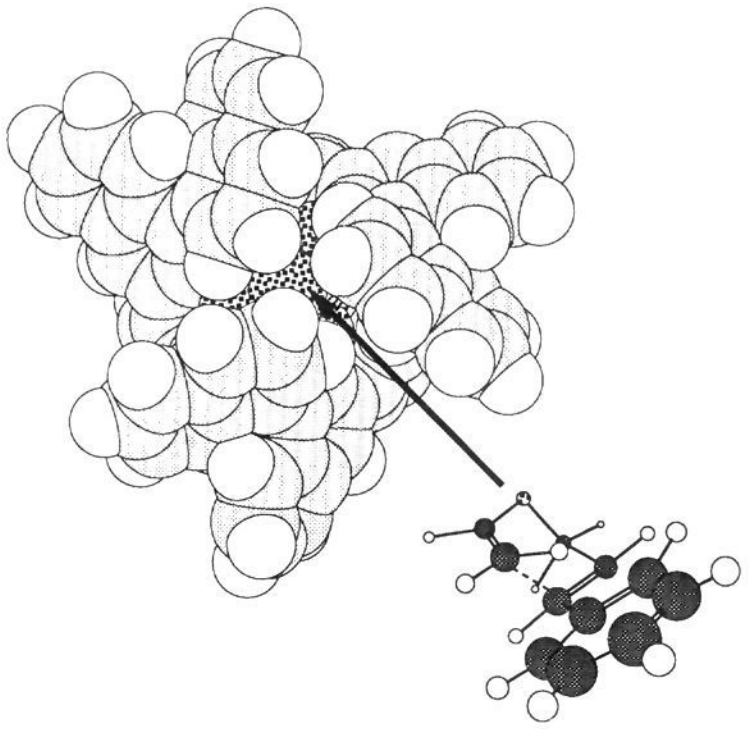
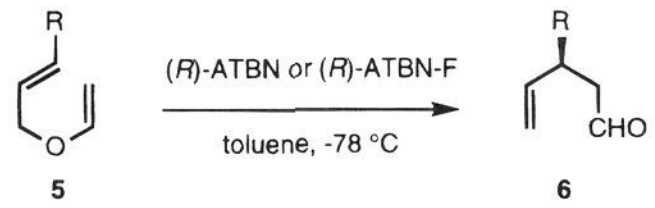


Figure 2. Ball and stick model of *trans*-cinnamyl vinyl ether approaching the space-filling model of (*R*)-ATBN.



5 **6**

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(7) (a) Maruoka, K.; Banno, H.; Yamamoto, H. *J. Am. Chem. Soc.* **1990**, *112*, 7791. (b) Maruoka, K.; Banno, H.; Yamamoto, H. *Tetrahedron: Asymmetry* **1991**, *2*, 647. The α-trimethylsilyl group of allylic vinyl ether substrates is crucial for a smooth Claisen rearrangement in this particular case.

(8) (a) Bhushan, V.; Lohray, B. B.; Enders, D. *Tetrahedron Lett.* **1993**, *34*, 5067. (b) Nishitani, K.; Yamakawa, K. *Ibid.* **1991**, *32*, 387. (c) Panek, J. S.; Cirillo, P. F. *J. Am. Chem. Soc.* **1990**, *112*, 4873. (d) Yi, G.; Wang, D.; Chen, T. H. *Youji Huaxue* **1988**, *8*, 115. (e) Hayashi, T.; Matsumoto, Y.; Ito, Y. *Chem. Lett.* **1987**, 2037. (f) Fleming, I.; Thomas, A. P. *J. Chem. Soc., Chem. Commun.* **1986**, 1456. (g) Hayashi, T.; Konishi, M.; Okamoto, Y.; Kabeta, K.; Kumada, M. *J. Org. Chem.* **1986**, *51*, 3772. (h) Hayashi, T.; Konishi, M.; Kumada, M. *Ibid.* **1983**, *48*, 281. (i) Hayashi, T.; Konishi, M.; Ito, H.; Kumada, M. *J. Am. Chem. Soc.* **1982**, *104*, 4962.

(9) ^{19}F NMR study of cyclopentanone/(*R*)-ATBN-F and acetonitrile/(*R*)-ATBN-F complexes in CD_2Cl_2 have shown single peaks at −116.4 and −117.0 ppm, respectively, implying the existence of a single Al species with a C_3-symmetric ligand in solution. The MM2 calculation for (*R*)-ATBN using the CAChe system suggests that a substrate is prone to coordinate to the aluminum center from the C_3-oriented naphthyl moieties in (*R*)-ATBN.

(10) The MM2 calculation for (*R*)-ATBN-F and its analogues using the CAChe system indicates that one side of the aluminum center is effectively shielded by three *p*-fluorophenyl substituents in (*R*)-ATBN-F, while the three chiral ligands of 3,5-difluorophenyl and 3,5-xylyl derivatives shield both sides of the aluminum center, leading to the eminent loss of enantioselectivity, as well as a reduction in the reaction rate.