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Stereo- and regioselective organic transformations based on main group organometallic reagents— application to the stereocontrolled Claisen rearrangements

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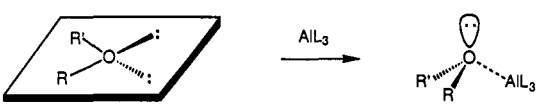
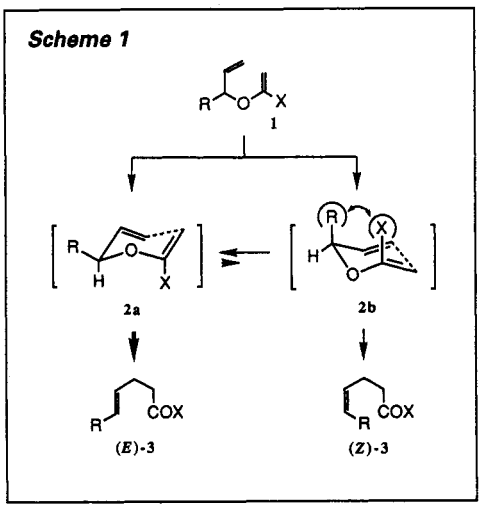
Abstract: Unprecedented stereocontrolled Claisen rearrangement of allylic vinyl ethers has been developed with modified organoaluminum reagents **A** and **B** as an example of diastereoselective activation of ethereal substrates.

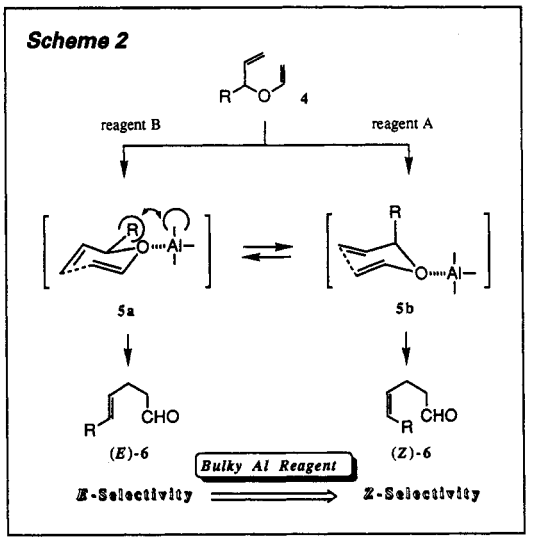
The stereoselective activation of ether moiety is the subject of our current interest. Oxygenophilic organoaluminum reagents are known to exhibit the great tendency to form stable ether-aluminum complexes.[1] Our expectation is *the stereoselective activation of ethereal oxygen by selective coordination of one out of the two lone pair electrons of the oxygen atom to aluminum reagent.* Here, when R and R' are different, ethereal oxygen is prochiral and by the selective coordination to aluminum, this oxygen is now chiral. Hence, with chiral ethers diastereoselective activation of the ether oxygen would be possible, while combination of chiral organoaluminum reagents with prochiral substrates would enable enantioselective activation of ethers.



Chiral Substrates ⟹ *Diastereoselective Activation*
Chiral Al Reagents ⟹ *Enantioselective Activation*

First, we have examined our concept by applying it to the stereo-selective Claisen rearrangement. The Claisen rearrangement and its variants (Carroll, the ortho ester, Eschenmoser, and Ireland rearrangements)[2] provide an excellent stereoselective route to α,β-unsaturated carbonyl compounds (aldehydes, ketones, esters, amides, and acids) from allylic alcohols, and offer a crucial step in the stereo- and regiochemically defined synthesis of a wide variety of natural products.[3] The reactions involve a [3,3]-sigmatropic rearrangement and take place by a concerted mechanism through a cyclic six-membered chairlike transition state.[4] The principle value of these rearrangements in organic synthesis stems from the fact that they are highly stereoselective, particularly when X = H in allyl vinyl ether **1**, leading almost exclusively to the *E*-configuration of the newly created double bond. Examination of the two chairlike transition-state conformations as depicted in Scheme 1 reveals why the *E*-product (*E*)-**3** invariably predominates. Conformation **2a**, with the R substituent equatorial, leads to the (*E*)-olefinic aldehyde (*E*)-**3**, whereas the less likely conformation **2b**, with the R axial, leads to the (*Z*)-olefinic aldehyde (*Z*)-**3**. In fact, the strong preference for *E*-products has been observed for Claisen as well as Carroll, the ortho ester, Eschenmoser, and Ireland rearrangements, and is clearly a general attribute of the Claisen family. In simple Claisen rearrangement of **1** (X = H), the *E*/*Z* ratio in the product is approximately 90:10,[5] but when X is larger than H, as in the Eschenmoser (X = NMe_2), ortho ester (X = OEt), and Ireland (X = $OSiR_3$) rearrangements, the *E*/*Z* ratio can be greater than 99:1 due to the increased 1,3-diaxial interaction in the transition state **2b**, which dramatically decreases its participation.[6] Consequently, it is difficult to obtain the *Z*-selectivity by using conventional methodologies. In this context, we have been interested in the development of organo-aluminum-

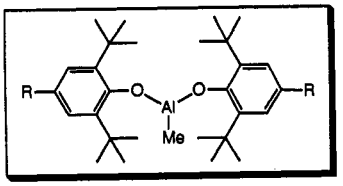




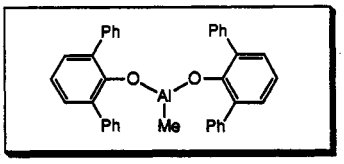
promoted Claisen rearrangement to alter the transition-state structure of the rearrangement, thereby producing the (*Z*)-product (*Z*)-**6** as shown in Scheme 2.[7-9]

The conformation **2a** with the R equatorial, is thermally stable. However, on coordination to aluminum reagent, the resulting conformation **5a** is now destabilized by the steric repulsion between R and the aluminum ligand. In contrast, the thermally unstable conformation **2b** on coordination to aluminum reagent would be stabilized compared to **5a**, thereby producing (*Z*)-**6** preferentially. Apparently, one would expect that the use of more bulky aluminum reagent would give higher Z-selectivity in view of the increased 1,2-steric interaction between R and aluminum reagent. Since we have already succeeded stereoselective activation of carbonyl moiety by using the exceptionally bulky organoaluminum reagents, MAD and MAT,[10] it seems reasonable to utilize these organoaluminum reagents for stereocontrolled Claisen rearrangement.

When allyl vinyl ether **4** (R = *i*-Bu) was treated with methylaluminum bis(2,6-di-*tert*-butyl-4-methylphenoxide) (MAD) in CH_2Cl_2 at -78 °C, the rearrangement proceeded quite reluctantly to furnish 7-methyl-4-octenal **6** (R = *i*-Bu) in only 43% yield. The E/Z ratio of **6** (R = *i*-Bu) was determined to be 19:81 by capillary GLC after conversion of the aldehyde to the corresponding alcohol and then to the trimethylsilyl ether. Apparently, the Lewis acidity of MAD, which is effective for the stereoselective activation of carbonyl moieties,[10] is not strong enough for activation of the ether substrate **4**. Accordingly, the stronger Lewis acidic methylaluminum bis(4-bromo-2,6-di-*tert*-butylphenoxide) (reagent **A**) has been newly prepared and successfully applied to the rearrangement of **4** (R = *i*-Bu) resulting in clean generation of **6** (R = *i*-Bu) in 64% yield in the *E*/*Z* ratio of 7:93. Clearly, the less likely conformation **2b** (R = *i*-Bu; X = H), when complexed with exceptionally bulky organoaluminum reagents, is favored over **5a** as predicted (Scheme 2). In fact, when the bulkiness of the aluminum reagent is decreased from reagent **A** to dimethylaluminum 4-bromo-2,6-di-*tert*-butylphenoxide, the *E*/*Z* selectivity in the rearrangement of the substrate **4** (R = *i*-Bu) is changed dramatically from 7:93 to 71:29, suggesting that the population of the transition state shifts from **5b** to **5a** by decreasing the steric size of aluminum ligands. Surprisingly, treatment of **4** (R = *i*-Bu) in toluene with methylaluminum bis(2,6-diphenylphenoxide) (reagent **B**) at -20 °C gave rise to the *E*-isomer (*E*)-**6** (R = *i*-Bu) almost exclusively (*E*/*Z* = 97:3) in 85% yield. To gain information on the exceedingly high *E*-

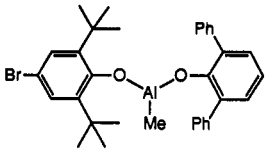


MAD : R = Me
MAT : R = *t*-Bu
reagent A : R = Br

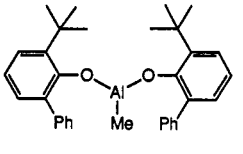


reagent B

selectivity with reagent **B**, the rearrangement of **4** (R = *i*-Bu) was carried out in CH_2Cl_2 at -78 °C under the influence of organoaluminum reagents **C** and **D**. The observed *E*/*Z* ratios of **6** (R = *i*-Bu) with reagents **C** and **D** were 28:72 and 15:85, respectively, indicating the strong effect of the sterically hindered *tert*-butyl moiety on the phenoxy ligands for obtaining *Z*-selectivity. Although the origin of the high *E*-selectivity with reagent **B** remains unclear from these experiments, a series of experimental results seems to imply the importance of the electronic factor of the 2,6-diphenylphenoxy ligand as well as its steric factor.



reagent **C**



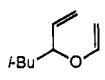
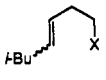
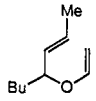
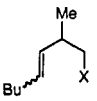
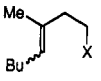
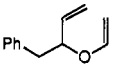
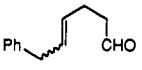
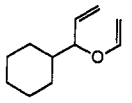
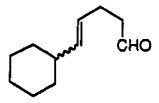
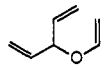
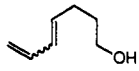
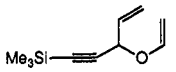
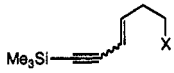
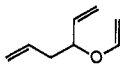
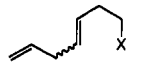
reagent **D**

The generality of the present stereocontrolled Claisen rearrangement is indicated in Table I. Several characteristic features of the reaction has been noted. (1) In general, reagent **A** can be utilized to obtain the *Z*-isomer, while the *E*-isomer can be produced with reagent **B**. (2) Compared to the conventional thermal rearrangement that requires high temperature, the organoaluminum-prompted Claisen rearrangement proceeds under very mild conditions, particularly at strikingly low temperature with very high *E* and *Z*-selectivities. (3) The observed *E*- and *Z*-selectivities appear to increase by lowering the reaction temperature. Reaction of the substrate **4** (R = *i*-Bu) with reagent **A** or **B** at 0 °C results in the *E*/*Z* ratio of 17:83 or 83:17, respectively. (4) The *p*-bromo substituent in reagent **A** is indispensable for rate acceleration of the rearrangement. (5) The rearrangement using reagent **A** is best carried out in CH_2Cl_2. For example, rearrangement of (*E*)-1-butyl-2-butenyl vinyl ether with reagent **A** in toluene, $CHCl_3$, 1,2-dichloroethane, and CH_2Cl_2 gives rise to 3-methyl-4-nonenal in an *E*/*Z* ratio of 33:67, 26:74, 24:76, and 16:84, respectively (cf. entries 8 and 9). Similarly, the *E*-selectivity has been lowered with reagent **B** in CH_2Cl_2 in lieu of toluene (the *E*/*Z* ratio of **6** (R = *i*-Bu) = 94:6 in CH_2Cl_2 and 97:3 in toluene). (6) 2-Butyl-1-methyl-2-propenyl vinyl ether gives the *E*-isomer as a major product even with reagent **A** (entry 11). (7) The conjugated *Z*-enyne units, which are often present in biologically active natural products,[11] can be readily available by this approach (entry 19). (8) In the case of allyl vinyl ether **4** (R = cyclohexyl) possessing a secondary alkyl moiety, both the chemical yield and the selectivity are lowered under the standard conditions using reagent **A** (entry 16).

The stereochemical aspect in the rearrangement of the optically active substrate **7** (78% ee)[12] has been examined in order to elucidate the transition state in the organoaluminum-promoted Claisen rearrangement. Thus, individual treatment of **7** with reagents **A** and **B** under the standard conditions as described above gave the (*S*)-(*Z*)-aldehyde **8** and the (*R*)-(*E*)-aldehyde **9**, respectively, as major products. The absolute configurations of the Claisen products were determined by correlation with optically active citronellal.[13] This was accomplished by catalytic hydrogenation of the Claisen products **8** and **9** with 5% Pd/C in THF under H_2 to furnish 3(*R*)-3,7-dimethyloctanal ($[\alpha]_D$ +5.7° (*c* 0.97, $CHCl_3$)) and its 3(*S*)-isomer ($[\alpha]_D$ -8.4° (*c* 0.99, $CHCl_3$)), respectively. The authentic, optically pure 3(*R*)-3,7-dimethyloctanal ($[\alpha]_D$ +13.6° (*c* 1.05, $CHCl_3$)) and its 3(*S*)-isomer ($[\alpha]_D$ -13.0° (*c* 1.00, $CHCl_3$)) were prepared by the catalytic hydrogenation of (*R*)- and (*S*)-citronellal, respectively.

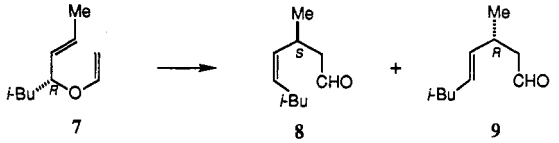
Since the Pd/C catalyst may induce partial racemization of the allylic C-3 chirality in the hydrogenation of **8** and **9**, the optical purities of the Claisen products, **8** and **9** were rigorously established by capillary GLC analysis after conversion to the acetals **10** of (2*R*,4*R*)-2,4-pentanediol. Thus, rearrangement of **7** with reagent **A** gave rise to **8** and **9** in 78% ee and 64% ee, respectively (100% ee and 82% ee based on the optically pure **7**), while **7** was

Table I. Organoaluminum-Promoted Claisen Rearrangement

entry	reagent[a]	product[b]	yield (%)[c]	*E*/*Z*[d,e]
		→ 		
1	MAD	X = CHO	43	19:81
2	**A**	X = CHO	64	7:93
3	**B**	X = CH_2OH	85	97:3 (92:8)
4	**E**	X = CH_2OH	55	87:13
		→ 		
5	MAD	X = CHO	37	15:85
6	**A**	X = CHO	41	9:91
7	**B**	X = CH_2OH	86	97:3
		→ 		
8	**A**	X = CHO	72	16:84
9	**A**[f]	X = CHO	70	12:88
10	**B**	X = CH_2OH	94	99:1 (92:8)
		→ 		
11	**A**	X = CHO	58	61:39
12	**B**	X = CH_2OH	94	95:5 (83:17)
		→ 		
13	**A**		12	40:60
14	**B**		95	92:8
15	**B**[g]		78	99:1
		→ 		
16	**A**		41	60:40
		→ 		
17	**A**		97	24:76
18	**B**		91	90:10
		→ 		
19	**A**	X = CHO	94	3:97
20	**B**	X = CH_2OH	82	69:31
		→ 		
21	**A**	X = CHO	40	7:93
22	**B**	X = CH_2OH	97	95:5
23	**B**[g]	X = CH_2OH	84	97:3 (93:7)

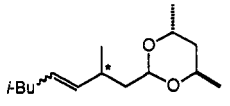
[a] Reagent E: Diisobutylaluminum 4-bromo-2,6-di-*tert*-butylphenoxide. For structures of reagents **A**, **B**, and MAD, see text. [b] When aluminum reagent **B** was utilized, olefinic aldehydes were generally reduced to the corresponding alcohols with $NaBH_4$ in view of the easy product separation from 2,6-diphenylphenol. [c] Isolated yield by column chromatography. [d] Determined by GLC after conversion to the corresponding trimethylsilyl ethers. [e] The *E*/*Z* ratios in parentheses refer to those in the thermal rearrangement (250 °C). [f] At -95 °C. [g] At -78 °C.

transformed by reagent **B** to **9** almost exclusively in 76% ee (98% ee based on the optically pure **7**). These results clearly indicate the rigorous conservation of chirality in the main reaction pathway of the organoaluminum-promoted Claisen rearrangement. Some loss of the optical purity (82% chiral transmission) in the conversion of **7** to **9** with reagent **A** could be ascribed to the participation of the ionic mechanism to some extent. Consequently, the observed selectivities are best accounted for by the two possible chairlike transition-state conformations **5a** and **5b** coordinated to the Lewis acidic aluminum reagent as depicted in Scheme 2. The possibility of the boatlike transition-state conformation with the R substituent equatorial, which leads to (Z)-alkene, cannot be excluded. However, according to the *ab initio* quantum mechanical calculations the intervention of the boatlike transition-state structure seems unlikely because of the high energy compared to the chairlike transition-state structure.[4]



7 **8** **9**

reagent **A** : 74% (84 : 16)
reagent **B** : 90% (2 : 98)



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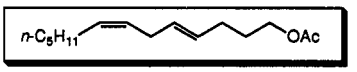
The synthetic utility of the present method in natural product synthesis is illustrated by a simple route to (4*E*,7*Z*)-4,7-tridecadienyl acetate (**15**), a component of the sex pheromone of potato tuberworm moth (*Phthorimaea operculella*).[14] The requisite vinyl ether **13** was prepared from 1-heptyne via 5-step sequences. Thus, lithiation



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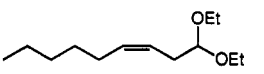

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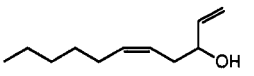

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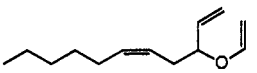

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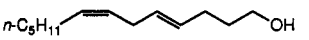

14

of 1-heptyne with BuLi in THF at 0 °C and subsequent alkylation with bromoacetaldehyde diethyl acetal in HMPA gave rise to 3-nonynal diethyl acetal in 52% yield, which was reduced with P-2 nickel and ethylenediamine in ethanol under H_2 to furnish 3-*cis*-nonenal diethyl acetal (**11**) in 77% yield. Hydrolysis of the acetal moiety with oxalic acid in aqueous acetone followed by alkylation with vinylmagnesium bromide in THF afforded allylic alcohol **12** in 75% yield. Transetherification of **12** with ethyl vinyl ether in the presence of $Hg(OAc)_2$ produced the vinyl ether **13** in 63% yield. The Claisen rearrangement of **13** with reagent **B** in toluene at -20 °C and subsequent reduction with $NaBH_4$ in MeOH gave the alcohol **14** in 88% yield in the *E*/*Z* ratio of 95:5. This selectivity was further enhanced to 98:2 by lowering the reaction temperature to -78 °C. It should be noted that the thermal rearrangement of **13** resulted in the *E*/*Z* ratio of 93:7. Finally, simple acetylation of **14** gave the target compound **15** in quantitative yield.

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