Molecular Recognition of Carbonyl Compounds Using Aluminum Tris(2,6-diphenylphenoxide) (ATPH): New Regio- and Stereoselective Alkylation of α,*β*-Unsaturated Carbonyl Compounds

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The regio- and stereoselective synthesis of α,*β*-unsaturated carbonyl compounds is an important goal in organic synthesis.[1] Carbonyl alkylation by dienolates of α,*β*-unsaturated carbonyl compounds is a widely used general method,[2] but problems are frequently encountered controlling the regioselectivity (of both the deprotonation and alkylation steps) and stereoselectivity of the olefin geometry of the new double bond. We report here an entirely new paradigm to solve this problem. The new method depends strongly on aluminum tris(2,6-diphenylphenoxide) (ATPH)[3,4] as the key reagent (Figure 1).

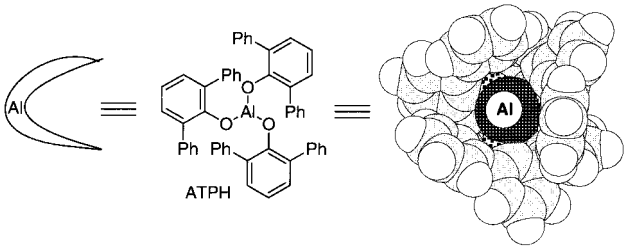
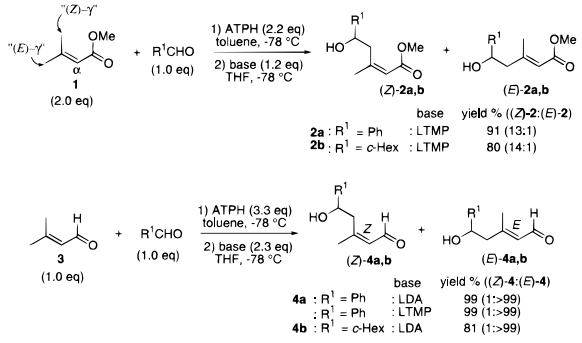


Figure 1. Molecular structure of ATPH.

Sequential treatment of a toluene solution of ATPH (3.3 equiv) with methyl 3-methyl-2-butenoate (**1**) (2.0 equiv) and benzaldehyde (1.0 equiv) at −78 °C was followed by deprotonation with a THF solution of LTMP (2.3 equiv). The reaction mixture was stirred for 30 min and quenched with aqueous NH_4Cl to give homoallyl alcohol **2a** in 91% isolated yield (Scheme 1). The

Scheme 1



predominant alkylation site was at the (*Z*)-*γ* position of **1** ((*Z*)-*γ*:(*E*)-*γ* = 13:1). In sharp contrast, senecialdehyde (**3**) gave the

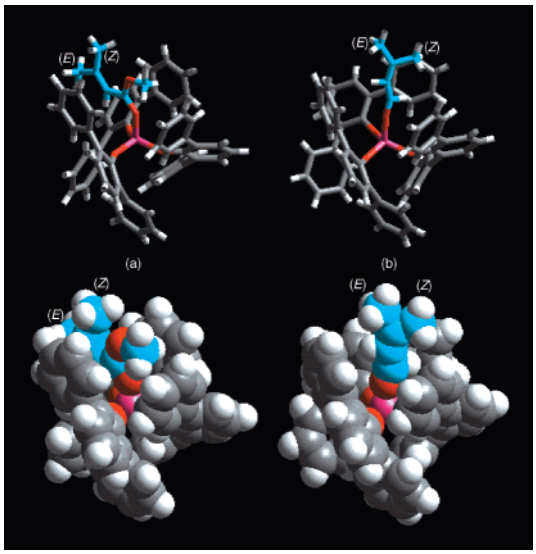


Figure 2. X-ray crystal structures [cylinder (upper) and CPK (lower) models] of (a) ATPH−**1** and (b) ATPH−**3** complexes.

(*E*)-*γ*-products exclusively.[4a,b] None of the α-alkylated product was obtained in either case. Varying the lithium amide or aldehyde does not affect the *E*:*Z* selectivities (Scheme 1).

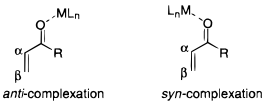
To explain the above striking results, the X-ray crystal structures of the ATPH−**1** and ATPH−**3** complexes were obtained (Figure 2). These two complexes adopt an *s-trans* conformation.[5] Whereas aldehyde **3** (Al−O=C angle (*θ*) of 193.9 (4)°) favors the *anti*-complexation (*θ* > 180°), ester **1** (*θ* = 136.2 (3)°) shows *syn*-complexation (*θ* < 180°) (Table 1).[6] The (*Z*)-*γ*-methyl of **1** and the (*E*)-*γ*-methyl of **3** occupy sterically less hindered space, i.e., rather outside of the cavity of ATPH (Figures 2 and 3).[7]

If interconversion of the extended dienolate conformers (*s-trans* ⇄ *s-cis*)[5] is possible,[8] and if the extended dienolates resemble the corresponding ATPH-carbonyl complexes,[8] the approach of

(1) See ref 3 of Supporting Information.
(2) See ref 4 of Supporting Information.
(3) See ref 5 of Supporting Information.
(4) The present *γ*-aldolization is *not substrate-specific*, but rather showed *substrate generality* using *β*-substituted-α,*β*-unsaturated carbonyl compounds, see: (a) Saito, S.; Shiozawa, M.; Ito, M.; Yamamoto, H. *J. Am. Chem. Soc.* **1998**, *120*, 813. (b) Saito, S.; Shiozawa, M.; Yamamoto, H. *Angew. Chem., Int. Ed.* **1999**, *38*, 1769.

(5) For the general aspects of the conformation (*s-cis* vs *s-trans*) of unsaturated carbonyl compounds, see: *Stereochemistry of Organic Compounds*; Eliel, E. L.; Wilen, S. H. Eds.; John Wiley & Sons: New York; 1994; Chapter 10.2., p 615. Also see the depiction below for two major conformations of an α,*β*-unsaturated carbonyl compound and diene, respectively. The definition for the conformations (*s-trans* and *s-cis*, where "s" denotes a "single bond") of an extended dienolate is based on that for a diene.

(6) For a discussion of the coordination aptitude of a variety of Lewis acids toward carbonyl compounds (e.g., *syn*- vs *anti*-coordination), see: (a) Schreiber, S. L. in *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon Press: Oxford; 1991; Vol. 1, Chapter 1.10 and references therein. (b) Shambayati, S.; Crowe, W. E.; Schreiber, S. L. *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 256. See below for the general definition of *syn* and *anti* complexations of α,*β*-unsaturated carbonyl compounds, which denotes the complexation mode of the Lewis acid (ML_n) with respect to the orientation of the α,*β*-double bond.



(7) To confirm this further, we measured ^{1}H NMR shift changes (Δ*δ*) from free (**1** and **3**) to bound (ATPH−**1** and ATPH−**3**) substrates. See Supporting Information.
(8) Full experimental details (NOE and NMR studies) corroborating the mechanistic models in Figure 3 will be addressed later in a full paper. In fact, a rapid equilibrium (*s-trans* ⇄ *s-cis*) faster than the rate of aldolization is envisioned by complete reversal of the olefin configuration of esters (the *E*-*γ*-methyl of (*E*)-**6** was delivered to the *Z*-*γ*-methylene of **9**).

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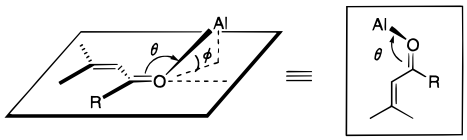
Table 1. Selected Metrical Data for ATPH Complexes



property	ATPH−**1** (R = OMe)	ATPH−**3** (R = H)
C═O, Å	1.249(5)	1.128(6)
Al−O (sp^2), Å	1.833(3)	1.810(3)
θ, (deg)	136.2(3)	193.9(4)
ϕ, (deg)	4.2	16.9

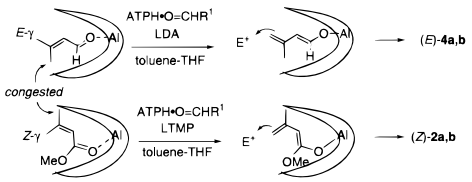
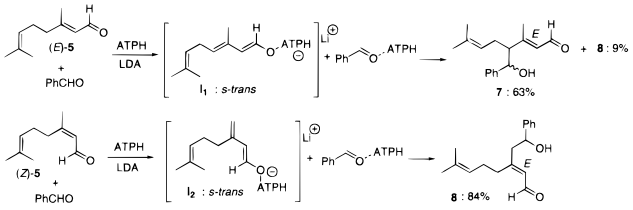


Figure 3. Illustrative depictions of ATPH−**3** and ATPH−**1** complexes and their enolate intermedates as more reactive conformers. E^+ denotes ATPH·O═CHR^1 or R^1CHO, or other reactive species.

electrophiles (E^+)[9] should be influenced by significant steric interactions with ATPH (Figure 3).

By taking advantage of the distinct recognition of ATPH with carbonyl compounds, we next examined the regio- and stereoselectivity of substrates **5** and **6**, which have different substituents at the β-positions. In cases where (*E*)- and (*Z*)-aldehydes **5** were subjected to general conditions using ATPH and LDA, anomalous regio- and chemoselective outcomes were accommodated: (*E*)-γ-*methylene*-selective aldolization predominated with (*E*)-**5** to give (*E*)-product **7**, whereas the (*E*)-γ-*methyl* of (*Z*)-**5** was alkylated exclusively to give (*E*)-product **8** (Scheme 2). These experiments

Scheme 2

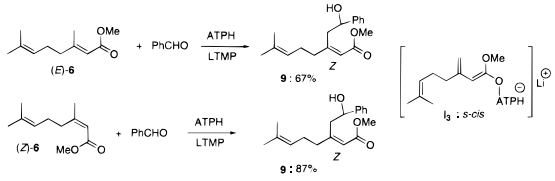


(9) At present, we have no clear evidence to identify the actual electrophilic species. Although ATPH·R^1CHO is formally possible, decomplexed R^1CHO or other possibilities are also nonnegligible.

emphasize that the (*Z*)-γ positions are under the significant influence of the congested environment extended by the cavity of ATPH, since the approach of not only electrophiles but also of LDA is circumvented. Thus, both (*E*)- and (*Z*)-aldehydes **5** must be encapsulated effectively in an *anti*, *s-trans* coordination similar to ATPH−**3**, and *s-trans* dienolate conformers $\mathbf{I_1}$ and $\mathbf{I_2}$ are more reactive species.[10]

In contrast, (*E*)- and (*Z*)-acid esters **6** showed γ-*methyl*-selective deprotonation-aldolization regardless of the original olefin configurations of the esters to give identical (*Z*)-product **9** (Scheme 3). Despite fast equilibrium between the corresponding dienolate

Scheme 3



conformers,[8] *s-cis* conformer $\mathbf{I_3}$ seems more reactive.[11] These results are in agreement with the coordination bias of ATPH−**1**. Furthermore, the observed kinetic attack of LDA or LTMP, which prefers deprotonation at a methyl over methylene, indicates that ATPH has a negligible steric influence on the ester deprotonation steps. Indeed, the cavity can no longer maintain its original propeller-like structure (Figure 1) due to the coordination bias of esters with relatively small θ (Figure 2 (a) and Table 1).

In summary, we have demonstrated that several β,β-disubstituted-α,β-unsaturated carbonyl substrates can be differentiated by complexation with ATPH. We achieved diverse selectivity and reactivity during the reactions, which involve the control of: (1) *syn*- vs *anti*-complexation; (2) *s-cis* vs *s-trans* conformation of carbonyl compounds; (3) the deprotonation site; (4) *s-cis* vs *s-trans* conformation of extended dienolates; and (5) the alkylation site, depending on the α,β-unsaturated carbonyl compounds.

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

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(10) To confirm the influence of ATPH on the dienolate equilibria, deprotonation of ATPH−(*E*)-**5** or ATPH−(*Z*)-**5** with LDA was followed by immediate workup (after ~15 s) with excess MeOH at −78 °C. The original *E*/*Z* ratios of (*E*)-**5** (*E*:*Z* = >99:1) and (*Z*)-**5** (*E*:*Z* = <3:97) were partially preserved to give *E*/*Z* ratios of 80:20 and 19:81, respectively, suggesting that the equilibrium shifted to $\mathbf{I_1}$ and $\mathbf{I_2}$. Note that the rate of aldolization between two carbonyl species at −78 °C is rapid enough that these quenching experiments do not directly reflect the actual product distributions.

(11) A similar workup experiment[10] with the extended dienolates derived from ATPH−(*E*)-**6** and ATPH−(*Z*)-**6** both resulted in the regeneration of (*E*)-**6** and (*Z*)-**6** in a ratio of ~80:20.