Virtually Complete Blocking of α,β-Unsaturated Aldehyde Carbonyls by Complexation with Aluminum Tris(2,6-diphenylphenoxide)

Keiji Maruoka, Hiroshi Imoto, Susumu Saito, and Hisashi Yamamoto*

School of Engineering, Nagoya University Chikusa, Nagoya 464-01, Japan

Received November 3, 1993

The design of new host molecules for application in molecular recognition is a topic of much current interest, and a number of recognition systems capable of reversible binding interactions have been developed for this purpose.[1-4] As part of our continuing effort to broaden the scope of bulky organoaluminum compounds as Lewis acid receptors for synthetic applications, we are interested in the possibility of blocking the aldehyde carbonyl of α,β-unsaturated aldehydes selectively by complexation with such aluminum reagents as a carbonyl stabilizer, thereby permitting the hitherto difficult conjugate addition of reactive nucleophiles to α,β-unsaturated aldehydes. Success in this area would deliver valuable synthetic intermediates, since α,β-unsaturated aldehydes, among various conjugate acceptors, are prone to be more susceptible to 1,2-addition with a number of nucleophiles than α,β-unsaturated ketones, esters, or amides.[5] Here we report the successful conjugate addition of various carbon nucleophiles to α,β-unsaturated aldehydes by complexation with our newly devised aluminum tris(2,6-diphenylphenoxide) (abbreviated to ATPH) as an outstanding aldehyde pocket, as illustrated in Scheme 1.

ATPH is conveniently prepared by treatment of 2,6-diphenylphenol (3 equiv) in CH_2Cl_2 with a 1 M hexane solution of Me_3Al at 25 °C for 30 min. Initial complexation of *trans*-cinnamaldehyde with ATPH (1.1 equiv) in CH_2Cl_2 and subsequent addition of BuMgCl (1.1 equiv) in ether at −78 °C gave rise to a conjugate adduct, 3-phenylheptanal, predominantly in 89% yield along with 10% of 1,2-adduct.[6] Combination of ATPH with BuMI (M = Ca, Sr, Ba)[7] further enhanced the 1,4-selectivity to a great extent (95–98% selectivity), as revealed in Table 1 (entries 4–6). In the absence of ATPH, these reactive organometallics afforded 1,2-adduct as the sole isolable product. Notably, the alkylation with exceptionally bulky methylaluminum bis(2,6-di-*tert*-butyl-4-methylphenoxide) (MAD) and BuMgCl gave only disappointing results (95%; 1,4-/1,2-adducts ratio = 7:93). Our previously designed methylaluminum bis(2,6-diphenylphenoxide) (MAPH)[8] as a carbonyl stabilizer in combination with BuMgCl at −78 °C afforded an equal mixture of 1,4- and 1,2-adducts (98%, ratio = 49:51). Apparently, these results imply that ATPH behaves as an efficient stabilizer of aldehyde carbonyls in the α,β-unsaturated aldehyde systems.[9]

Other examples are listed in Table 1. Two characteristic features of the present methodology in comparison with the organocopper conjugate addition[10] are the successful uses of lithium alkynides (entries 7–9)[11] and the thermally unstable lithium carbenoid reagents (entries 10–13).[12] Interestingly, conjugate addition–cyclization products **2** and **3** are obtainable

Scheme 1

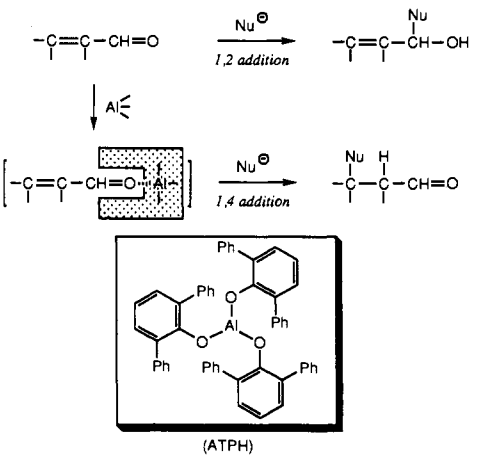


Table 1. Conjugate Addition of Carbon Nucleophiles to α,β-Unsaturated Aldehydes with ATPH[a]

entry	nucleophile	aldehyde[b]	yield,[c] % (ratio)[d]
1	BuM (M = Li)	PhCH=CHCHO	92 (50:50)
2	BuM (M = MgCl)	PhCH=CHCHO	99 (90:10)
3	BuM (M = MgCl)	CH_2=C(Me)CHO	56 (>99:<1)
4	BuM (M = CaI)	PhCH=CHCHO	88 (98:2)
5	BuM (M = SrI)	PhCH=CHCHO	60 (95:5)
6	BuM (M = BaI)	PhCH=CHCHO	97 (97:3)
7	$Me_3SiC{\equiv}CLi$[e]	PhCH=CHCHO	98 (92:8)
8	$Me_3SiC{\equiv}CLi$	PhCH=C(Me)CHO	97 (81:19)
9	$PhC{\equiv}CLi$[f]	PhCH=CHCHO	99 (93:7)
10	Cl_2CHLi[g]	PhCH=CHCHO	93 (98:2)
11	Cl_2CHLi	PhCH=C(Me)CHO	92 (94:6)
12	Br_2CHLi[g,h]	PhCH=CHCHO	86 (94:6)[j]
13	Cl_3CLi[g,h]	PhCH=CHCHO	91 (86:14)
14	*s*-BuMgCl	PhCH=CHCHO	90 (95:5)
15	*s*-BuMgCl	PhCH=C(Me)CHO	54 (98:2)
16	*t*-BuMgCl	PhCH=CHCHO	95 (>99:<1)
17	CH=C(Me)BaI	PhCH=CHCHO	54 (84:16)
18	**4**[i]	PhCH=CHCHO	84 (51:49)
19	**5**[i]	PhCH=CHCHO	85 (90:10)[k]
20	**6**[i]	PhCH=CHCHO	86 (92:8)
21	**7**[i]	PhCH=CHCHO	70 (93:7)[k]
22	**8**[i]	PhCH=CHCHO	60 (85:15)

[a] Unless otherwise noted, the alkylation with carbanions, enolates, or ketene silyl acetals (1.5–3 equiv) was carried out in the presence of ATPH (1.1–1.5 equiv) in CH_2Cl_2 at −78 °C for several hours. [b] (*E*)-Isomer. [c] Isolated yields. [d] Ratio of 1,4-/1,2-adducts. [e] Prepared from $Me_3SiC{\equiv}CH$ and BuLi in DME. [f] $PhC{\equiv}CLi$ in diglyme. See note 11. [g] Generated *in situ* by addition of lithium 2,2,6,6-tetramethylpiperidide (LiTMP) in THF to the reaction mixture containing polyhalomethanes at −78 °C. [h] ATPH in toluene. [i] Prepared from the corresponding ketones or esters with LDA in ether at −78 °C. [j] Conjugate addition–cyclization product **3** was obtained in 31% yield. [k] *Erythro/threo* ratio = 1:1 (entry 19); 3:2 (entry 21).

(1) Polyethers as host: (a) Cram, D. J. *Science* (*Washington, D.C.*) **1983**, *219*, 1177. (b) Lehn, J.-M. *Ibid.* **1985**, *227*, 849. (c) Lehn, J.-M. *Angew. Chem., Int. Ed. Engl.* **1988**, *27*, 89. (d) Cram, D. J. *Ibid.* **1988**, *27*, 1009.

(2) Cyclodextrins as host: (a) Bender, M. L.; Komiyama, M. *Cyclodextrin Chemistry*; Springer-Verlag: New York, 1978. (b) Saenger, W. *Angew. Chem., Int. Ed. Engl.* **1980**, *19*, 344. (c) D'Souza, V. T.; Bender, M. L. *Acc. Chem. Res.* **1987**, *20*, 146.

(3) Cyclophanes as host: Collet, A. *Tetrahedron*, **1987**, *43*, 5725.

(4) Molecular cleft as receptors: (a) Rebek, J., Jr. *Chemtracts: Org. Chem.* **1989**, 337. (b) Rebek, J., Jr. *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 245.

(5) Reviews: (a) Bergman, E. D.; Ginsburg, D.; Pappo, R. *Org. React.* **1959**, *10*, 179. (b) House, H. O. *Modern Synthetic Reactions*, 2nd ed.; W. A. Benjamin: Menlo Park, CA, 1972; p 595. (c) Perlmutter, P. *Conjugate Addition Reactions in Organic Synthesis*; Pergamon Press: Oxford, 1992. (d) Lipshutz, B. H.; Sengupta, S. *Org. React.* **1992**, *41*, 135.

(6) The effect of exact stoichiometry in the reagent was examined with the ATPH/BuMgCl system, and ratios of the 1,4-/1,2-adducts with each 1.1, 1.5, and 2 equiv of ATPH/BuMgCl under similar reaction conditions were 90:10, 91:9, 92:8, respectively. Hence, 1.1–1.5 equiv of ATPH can be satisfactorily utilized for other alkylation experiments.

(7) Prepared from BuLi in hexane and anhydrous MI_2 (M = Ca, Sr, and Ba) in ether.

(8) Maruoka, K.; Saito, S.; Concepcion, A. B.; Yamamoto, H. *J. Am. Chem. Soc.* **1993**, *115*, 1183.

(9) ^{1}H NMR spectrum of the crotonaldehyde/ATPH complex in CD_2Cl_2: δ 2.04 (d, CH_3), 6.36 (br, β-CH=), 4.96 (dd, α-CH=), and 6.26 (d, CH=O···Al). This indicates that the aldehyde hydrogen and α-hydrogen of crotonaldehyde are highly shielded in this complex.

(10) Reviews: (a) Posner, G. H. *Org. React.* **1972**, *19*, 1. (b) Yamamoto, Y. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 947. See also ref 5d.

(11) A profound solvent effect was observed in the addition of $PhC{\equiv}CLi$ to cinnamaldehyde/ATPH complexes: THF, 96% (1,4-/1,2-adducts = 59:41); DME, 97% (78:22); diglyme, 99% (93:7).

0002-7863/94/1516-4131$04.50/0

Scheme 2

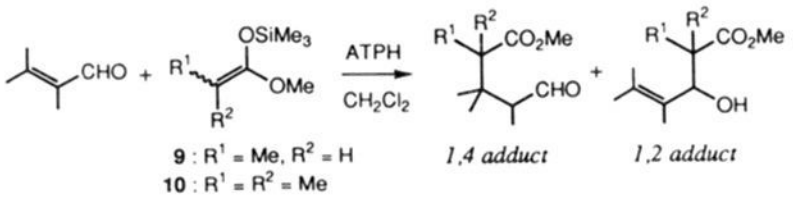
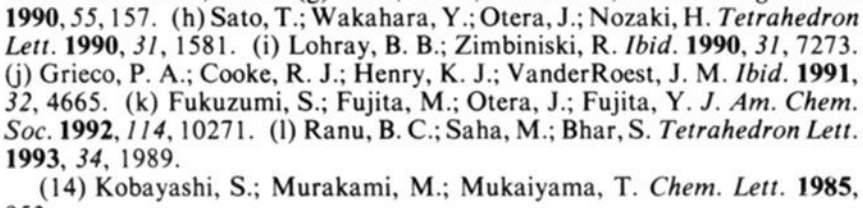


Table 2. Conjugate Addition of Silyl Ketene Acetals to α,β-Unsaturated Aldehydes with ATPH[a]

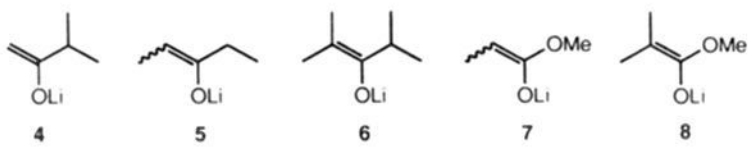
entry	aldehyde	nucleophile	yield,[b] % (ratio)[c]
1	PhCH=CHCHO	**9**	63 (97:3)[d]
2	PhCH=CHCHO	**10**	68 (>99:<1)
3	BuCH=CHCHO	**9**	75 (>99:<1)[d]
4	BuCH=CHCHO	**10**	80 (90:10)
5	CH_2=C(Me)CHO	**10**	34 (>99:<1)
6	PhCH=C(Me)CHO	**10**	36 (>99:<1)

[a] Silyl ketene acetal (1.5 equiv) was added to a solution of α,β-unsaturated aldehyde (1 equiv) and ATPH (1.1–1.5 equiv) in CH_2Cl_2 at −78 °C to 0 °C. [b] Isolated yields. [c] Ratio of 1,4/1,2-adducts. [d] *Erythro/threo* ratio = 4:1 (entry 1); 3:1 (entry 3).

from the intermediary enolates by subsequently increasing the reaction temperature. (1) In general, ATPH exhibited much



better selectivity than MAPH. (2) A series of reactive organometallic reagents is employable for the conjugate alkylation experiments, among which alkylcalcium, alkylstrontium, and alkylbarium reagents are superior for *primary* alkylation. (3) Toluene as solvent lowered the regioselectivity of the alkylation. (4) Conjugate alkylation of various lithium enolates **4**–**8** appeared feasible in the presence of ATPH (entries 18–22).



Even more significant is the application of the α,β-unsaturated aldehyde–organoaluminum complexes to the Mukaiyama–Michael addition reactions, while most of the previous publications deal solely with the Michael addition of silyl enol ethers and silyl ketene acetals to α,β-unsaturated ketones as acceptors.[13] Indeed, little is known about the Mukaiyama–Michael addition to α,β-unsaturated aldehydes, which are prone to be susceptible to 1,2-addition, as reported by Mukaiyama *et al.*,[14] in view of the lack of appropriate Lewis acidic reagents. Here the effective use of ATPH enabled the first example of the Mukaiyama–Michael addition of silyl ketene acetals to α,β-unsaturated aldehydes (Scheme 2). Selected examples are indicated in Table 2. The

(12) (a) Kobrich, G. *Angew. Chem., Int. Ed. Engl.* **1967**, *6*, 41. (b) Taguchi, H, Yamamoto, H, Nozaki, H. *J. Am. Chem. Soc.* **1974**, *96*, 3010.

(13) (a) Heathcock, C. H.; Norman, M. H.; Uehling, D. E. *J. Am. Chem. Soc.* **1985**, *107*, 2797. (b) Kobayashi, S.; Mukaiyama, T. *Chem. Lett.* **1986**, 221. (c) Mukaiyama, T.; Tamura, M.; Kobayashi, S. *Ibid.* **1986**, 1017. (d) Kobayashi, S.; Mukaiyama, T. *Ibid.* **1985**, 1805. (e) Heathcock, C. H.; Uehling, D. E. *J. Org. Chem.* **1986**, *51*, 280. (f) Mukaiyama, T.; Hara, R. *Chem. Lett.* **1989**, 1171. (g) Oare, D. A.; Heathcock, C. H. *J. Org. Chem.* **1990**, *55*, 157. (h) Sato, T.; Wakahara, Y.; Otera, J.; Nozaki, H. *Tetrahedron Lett.* **1990**, *31*, 1581. (i) Lohray, B. B.; Zimbiniski, R. *Ibid.* **1990**, *31*, 7273. (j) Grieco, P. A.; Cooke, R. J.; Henry, K. J.; VanderRoest, J. M. *Ibid.* **1991**, *32*, 4665. (k) Fukuzumi, S.; Fujita, M.; Otera, J.; Fujita, Y. *J. Am. Chem. Soc.* **1992**, *114*, 10271. (l) Ranu, B. C.; Saha, M.; Bhar, S. *Tetrahedron Lett.* **1993**, *34*, 1989.

(14) Kobayashi, S.; Murakami, M.; Mukaiyama, T. *Chem. Lett.* **1985**, 953.

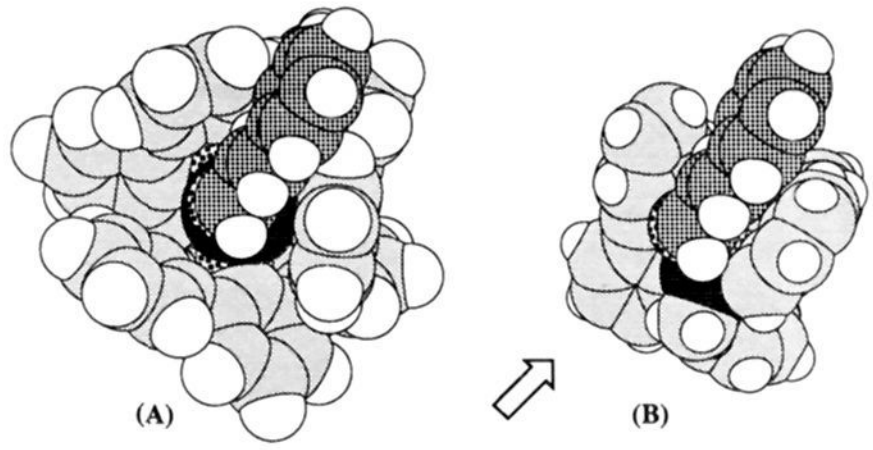


Figure 1. Space-filling models of cinnamaldehyde–ATPH complex (A) and cinnamaldehyde–MAPH complex (B).

low *erythro/threo* selectivity in the present Michael addition is ascribed to the *anti* coordination of aldehyde carbonyl to ATPH.[15]

The existence of hypothetical aldehyde–ATPH complexes was verified by taking the X-ray crystal structure of the *N,N*-dimethylformamide–ATPH complex, in which the arene rings form a propeller-like arrangement around the aluminum, and hence ATPH has a C_3 axis of symmetry.[16] Based on the X-ray data of the DMF–ATPH complex, a plausible cinnamaldehyde–ATPH complex structure **A** is suggested and compared to that of the cinnamaldehyde–MAPH complex **B**. As shown in Figure 1, the cinnamaldehyde–MAPH complex **B** may be susceptible to the nucleophilic attack from the direction of the arrow. In contrast, the third 2,6-diphenylphenoxy group of ATPH in complex **A** shields the nucleophilic attack effectively, thereby serving as a tight aldehyde pocket for the selective 1,4-addition of carbon nucleophiles to α,β-unsaturated aldehydes.

Acknowledgment. We appreciate Mr. Y. Odagaki of Ono Pharmaceutical Company for single crystal X-ray analysis of the DMF–ATPH complex.

(15) (a) Corey, E. J.; Loh, T.-P.; Sarshar, S.; Azimioara, M. *Tetrahedron Lett.* **1992**, *33*, 6945. (b) Denmark, S. E.; Almstead, N. G. *J. Am. Chem. Soc.* **1993**, *115*, 3133. In the Mukaiyama–Michael addition with α,β-unsaturated ketones as acceptors, notable diastereoselection was generally observed in view of the effective *syn* coordination of ketone carbonyls to Lewis acids. See ref 13.

(16) The DMF–ATPH complex was prepared with rigorous exclusion of oxygen and moisture, and crystals were grown from methylene chloride/toluene at 20 °C: space group $R3(h)$, a = 16.458(5) Å, b = 16.458(5) Å, c = 16.241(4) Å, α = 90.00°, β = 90.00°, γ = 120.00°, V = 3809.9(32) Å^3, 3 molecules per unit cell, d = 1.093 g/cm^3, μ(Cu Kα) = 2.208 mm^{-1}, 1210 reflections obtained, R index = 0.068, R_w = 0.087, GOF = 4.454.