# Efficient Conjugate Reduction of α,β-Unsaturated Carbonyl Compounds by Complexation with Aluminum Tris(2,6-diphenylphenoxide)

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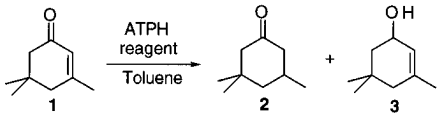
The conjugate reduction of α,β-unsaturated carbonyl compounds remains an active area of organic synthesis.[1] To attain chemoselective reduction[2−5] (1,2 vs 1,4) of these compounds, several methods have been thoroughly investigated, and each method has characteristic advantages. Unfortunately, however, these existing methods also have some disadvantages: strict reaction conditions and the structure of the reaction substrate affect the chemoselectivitiy and yield of the products. Thus, there still seems to be a need for a new, simple, and practical reagent for highly selective 1,4-reduction of various kinds of α,β-unsaturated carbonyl compounds.

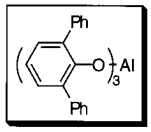
We recently showed that Michael addition of alkyllithium toward a host of α,β-unsaturated carbonyl compounds could be achieved by the complete blocking of carbonyl functions in these substrates with aluminum tris(2,6-diphenylphenoxide) (ATPH).[6] In these reactions, ATPH acted as a receptor to bind carbonyls, inhibiting the attack of nucleophiles in a 1,2-manner with the cooperation of ATPH ligands. These excellent results prompted us to further survey whether this methodology could be extended to the highly selective 1,4-reduction of α,β-unsaturated compounds. We report here that the selective 1,4-reduction of various kinds of α,β-unsaturated compounds was achieved by complexation with ATPH using diisobutylaluminum hydride−butyllithium[5a] (DIBAL−*n*-BuLi) as a reducing agent.

**Table 1. Reduction with Various Kinds of Reducing Agents**[a]




| entry | reagent | conditions (°C, h) | yield(%) ( **2** : **3** )[b] |
|---|---|---|---|
| 1[c] | DIBAL-*n*-BuLi | -78, 0.25 | 90 ( >99 : 1 ) |
| 2[c] | DIBAL--*t*-BuLi | -78, 0.25 | 85 ( >99 : 1 ) |
| 3[d] | 9-BBN-H-*n*-BuLi | -78, 1 | [e] |
| 4 | DIBAL | -78, 1<br>-20, 3 | no reaction |
| 5 | Red-Al | -78, 1<br>-20, 3 | no reaction |

[a] Unless otherwise noted, reaction was performed using 1.2 equiv. of ATPH and the reducing agent in this addition order at -78°C under argon. [b] Yield and ratio are of isolated. [c] Reagent was prepared by treatment of DIBAL with corresponding alkyllitium at -78°C. [d] Reagent was prepared by trearment of 9-BBN-H with n-BuLi at -78°C. [e] Obtained products are a mixture of diastereomers of saturated alcohol ratio of which was not determined.



ATPH

We first evaluated a compatible hydride reducing agent with ATPH in order to obtain the desirable 1,4-reduction of α,β-unsaturated carbonyl compounds. Using isophorone (**1**) as a model substrate, **1** was reduced with various kinds of hydride reagents in the presence of ATPH: the results are presented in Table 1, which shows that tetracoordinated aluminum "ate" complexes were crucial for effective 1,4-reduction. ATPH/DIBAL−*n*-BuLi complex is not the reactive reducing agent, which was demonstrated by the following experiment: after treatment of ATPH with DIBAL−*n*-BuLi at −78 °C, ketone **1** was added and was recovered unchanged (>95%).

A typical procedure is as follows: ATPH was easily prepared from 2,6-diphenylphenol (3.6 equiv) and $Me_3$-Al (1.2 equiv, hexane solution) in toluene at ambient temperature. Treatment of **1** with ATPH (1.2 equiv) in dry toluene at −78 °C under argon, followed by the subsequent addition of DIBAL−*n*-BuLi complex (1.2 equiv) in toluene−THF−hexane solution at −78 °C gave, after 15 min, the desired 1,4-reductant **2** in 90% isolated yield, along with a trace amount of 1,2-reductant **3**. The present reaction was conducted at 0 °C to provide **2** in 88% yield, as well. Using 1.2 equiv of ATPH and 1.2 equiv of the reducing agent was sufficient to complete the reduction within 5 min. The procedure is very simple and could be applied to all of the substrates tested regardless of their substituents (Table 2). In addition, the reaction tolerated only one of the double bonds of the doubly conjugated ketone, and no further reduction was observed (entry 11, Table 2). The generated enolate was reacted with an electrophile: the reduction of ketone **4**, followed by the addition of MeOTf (3.5 equiv) at −78 °C gave, after chromatography on silica gel, α-methylated ketone **5** in 85% yield (eq 1).

(1) Keinan, E.; Greenspoon, N. In *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon Press: Oxford, 1991; Vol. 8, Chapter 3.5 and references cited therein.

(2) Cu reagents: (a) Semmelhalck, M. F.; Staffur, R. D. *J. Org. Chem.* **1975**, *40*, 3619. (b) Semmelhalck, M. F.; Staffur, R. D.; Yamashita, A. *Ibid.* **1977**, *42*, 3180. (c) Osborn, M. E.; Pegues, J. F.; Paquette, L. A. *Ibid.* **1980**, *25*, 167. (d) Saegusa, T.; Kawasaki, K.; Fujii, T.; Tsuda, T. *J. Chem. Soc., Chem. Commun.* **1980**, 1013. (e) Tsuda, T.; Hayashi, T.; Satomi, H.; Kawamoto, T.; Saegusa, T. *J. Org. Chem.* **1986**, *51*, 537. (f) Boeckman, R. K., Jr.; Michalak, R. *J. Am. Chem. Soc.* **1974**, *96*, 1623. (g) Masamune, S.; Bates, G. S.; Georghiou, P. E. *Ibid.* **1974**, *96*, 3686. (h) Ashby, E. C.; Lin, J. J.; Goel, A. B. *J. Org. Chem.* **1978**, 43183. (i) Mahoney, W. S.; Brestensky, D. M.; Stryker, J. M. *J. Am. Chem. Soc.* **1988**, *110*, 291.

(3) Ru reagents: (a) Ohkubo, K.; Terada, I.; Yoshinaga, K. *Inorg. Nucl. Chem. Lett.* **1979**, *15*, 421. (b) Ohkubo, K.; Hirata, K.; Yoshinaga, K.; Okada, M. *Chem. Lett.* **1976**, 183. (c) Ohkubo, K.; Hirata, K.; Yoshinaga, K. *Ibid.* **1976**, 577. (d) Ohkubo, K.; Shoji, T.; Terada, I.; Yoshinaga, K. *Inorg. Nucl. Chem. Lett.* **1976**, *13*, 443. (e) Descotes, G.; Sinou, D. *Tetrahedron Lett.* **1976**, 4083. (f) Descotes, G.; Praly, J. P.; Sinou, D. *J. Mol. Catal.* **1979**, *6*, 421. (g) Beaupére, D.; Bauer, P.; Uzan, R. *Can. J. Chem.* **1979**, *57*, 218. (h) Beaupére, D.; Bauer, P.; Nadjo, L.; Uzan, R. *J. Organomet. Chem.* **1982**, *231*, C49. (i) Beaupére, D.; Bauer, P.; Nadjo, L.; Uzan, R. *J. Mol. Catal.* **1983**, *20*, 185, 195; **1983**, *18*, 73.

(4) Fe reagents: (a) Collman, J. P.; Finke, R. G.; Matlock, P. L.; Wahren, R.; Braumann, J. I. *J. Am. Chem. Soc.* **1976**, *98*, 4685. (b) Collman, J. P.; Finke, R. G.; Matlock, P. L.; Wahren, R.; Komoto, J. I.; Brauman, R. G. *Ibid.* **1978**, *99*, 1119.

(5) Selective 1,2-reducing agents for α,β-unsaturated carbonyl compounds: (a) Kim, S.; Moon, Y. C.; Ahn, K. H. *J. Org. Chem.* **1982**, *47*, 3311. (b) Kim, S.; Ahn, K. H. *Ibid.* **1984**, *49*, 1717. (c) Fuller, J. C.; Stangeland, E.; Goraski, C. T.; Singaram, B. *Tetrahedron Lett.* **1992**, *34*, 257. (d) Bazant, V.; Capka, M.; Cerny, M.; Chvalovsky, V.; Kochloefl, K.; Kraus, M.; Málek, J. *Tetrahedron Lett.* **1968**, 3303. (e) Capka, M.; Chvalovsky, V.; Kochloefl, K.; Kraus, M. *Collect. Czech. Chem. Commun.* **1969**, *34*, 118.

(6) (a) Maruoka, K.; Imoto, H.; Saito, S.; Yamamoto, H. *J. Am. Chem. Soc.* **1994**, *116*, 4131. (b) Maruoka, K.; Shimada, I.; Imoto, H.; Yamamoto, H. *Synlett* **1994**, 519. (c) Maruoka, K.; Shimada, I.; Yamamoto, H. *Ibid.* **1994**, 847. (d) Maruoka, K.; Ito, M.; Yamamoto, H. *J. Am. Chem. Soc.* **1995**, *117*, 9091.

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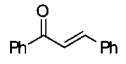
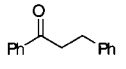
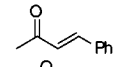
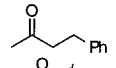
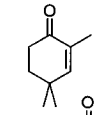
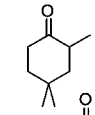
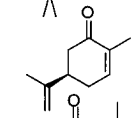
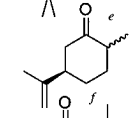
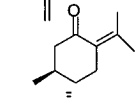
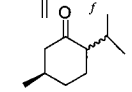
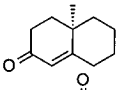
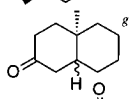
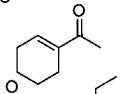
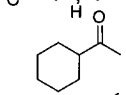
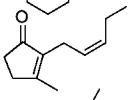
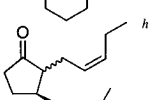
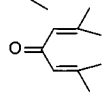
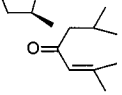
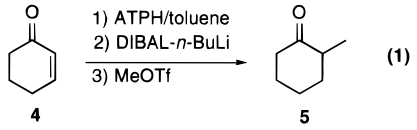
**Table 2. Selective 1,4-Reduction of Various Kinds of α,β-Unsaturated Ketones[a]**

| entry | α,β-unsaturated ketone | product | yield(%)[b] |
|---|---|---|---|
| 1[c] |  |  | 99 |
| 2 |  |  | 98 |
| 3 |  |  | 98 |
| 4 |  |  [d] | 99 |
| 5 |  |  | 99 |
| 6 |  |  [e] | 98 |
| 7 |  |  [f] | 99 |
| 8 |  |  [g] | 99 |
| 9 |  |  | 94 |
| 10 |  |  [h] | 97 |
| 11 |  |  | 99 |

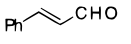
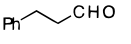
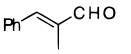
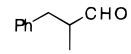
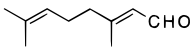
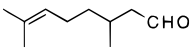
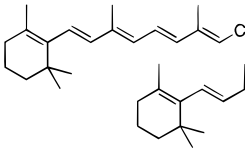
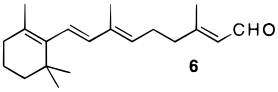
[a] Unless otherwise noted, reactions were performed at -78°C for 15 min, using 1.2 equiv. of ATPH and DIBAL-*n*-BuLi. [b] Yields are of isolated, purified products. [c] Reaction was initiated at -78°C and warmed to r.t. [d] Cis : trans = >99 : 1, Cis : Augustine, R. L. ; Broom, A. D.; *J. Org. Chem.,* **1960**, *25*, 802. Product ratio determined by GC-mass against authentic mixture. [e] Cis : trans = 1 : 3.2, determined by $^1$H NMR compared with authentic samples, see ref.4b. [f] Cis : trans = 1: 2.6, determined by GC-mass compared with (-)-menthone. [g] Cis : trans =11.5 : 1, Gramain, J. G.; Quirion, J. C.; *Mag. Res. Chem.*, **1986**, *24*, 938. [h]Cis : trans = 1 : 10.2, See supplimentary material.




4 5 (1)

Hydride delivery to the less-hindered face of the substrate was observed (entries 4 and 8, Table 2) to give high diastereoselectivites in both cases. These selectivities are quite similar to that of $(PPh_3CuH)_6$[2i]- mediated reduction and thus suggest that coordination of ATPH with the carbonyl has little influence on the attacking site of the reducing agent and that it is instead due to the steric requirements of the reducing agent. However, it seems to be interesting to know that the present stereoselectivity is slightly greater than that in the reduction by Cu(I)H[2g] "ate" complexes. The quenching of enolate/ATPH complex with TfOH (15 equiv) at −78 °C gave low diastereoselectivity (entries 6 and 7, Table 2). The design of a more efficient aluminum reagent for remote stereocontrol is now under investigation.

**Table 3. Selective 1,4-Reduction of α,β-Unsaturated Aldehydes[a]**

| entry | α,β-unsaturated aldehyde | product | yield(%)[b] |
|---|---|---|---|
| 1 |  |  | 90 |
| 2 |  |  | 80<br>93[c] |
| 3 |  |  | 83<br>95[c] |
| 4 |  |  6 | 87[c] |

[a] Unless otherwise noted, reaction was performed at -78°C for 15 min, using 1.2 equiv. of ATPH and DIBAL-*n*-BuLi. [b] Yields are of isolated, purified products. [c] DIBAL-*t*-BuLi was used as a reducing agent.

Reduction of α,β-unsaturated aldehydes with aluminum hydrides is known to give unsaturated and/or saturated primary alcohols.[5d,e] The 1,4-reduction of these substrates also proceeded smoothly to give the corresponding aldehydes in high yields (Table 3). It should be noted that slightly better yields were achieved with diisobutylaluminum hydride−*tert*-butyllithium (DIBAL−*t*-BuLi) than with DIBAL−*n*-BuLi system. Application of this method to *trans*-retinal gave the highly selective delivery of hydride at C-11 to afford the expected 1,6-reduction product[7,8] **6** in 87% isolated yield (entry 4, Table 3).

In summary, a strong preference for the 1,4-reduction of a variety of α,β-unsaturated carbonyl compounds was realized by the combined use of ATPH and tetradentate aluminum hydrides. This method is simple, practical, and general and, thus, has broad applicability in organic synthesis.

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**Supporting Information Available:** Experimental details and spectroscopic and analytical data for the reductants (5 pages).

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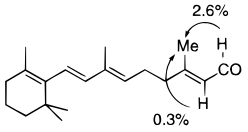
(7) The structure assigned to the compound is in accord with its infrared, 300 MHz $^1$H NMR, $^1$H−$^1$H COSY, and 75 MHz $^{13}$C NMR, as well as elemental analysis. The stereochemical outcome at position C-13 was confirmed to be *E* by NOE experiment as delineated below.




(8) Selective 1,6-addition of alkyllithiums to α,β,γ,δ-unsaturated carbonyl compounds, such as benzophenone or benzaldehyde, was also observed in the presence of ATPH; see ref 6d.