

Manganese Ate Complexes as New Reducing Agents: Perfectly Regiocontrolled Generation and Reactions of the Manganese Enolates with Electrophiles

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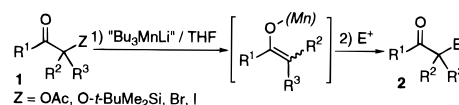
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Among transition metal ate complexes, the organocuprates have been predominantly investigated and utilized in organic synthesis, and reactions using these species are mainly based on their alkylating abilities.¹ The reduction rarely takes place as a side reaction in these alkylations. This reductive nature of cuprates has been utilized for the direct generation of organocuprate reagents in the cases where only a reductive process occurs.^{2,3} The organomanganese reagents were also reported to be alkylating agents.⁴ We report the generation of the enolates from the carbonyl compounds bearing a leaving group such as an acetoxy, silyloxy, or halogen group at the α position by using the organomanganese(II) ate complexes and their characteristic reactions with electrophiles. For the generation of the enolates, a new reactivity of the organomanganese ate complexes as a reductant can thus be exploited (Scheme 1).

We found that "Bu₃MnLi" cleanly reduced α -acetoxypropionophenone (**1b**) to generate an enolate of propionophenone, and it reacted with benzaldehyde to afford the cross aldol adduct **2d** in 87% yield (*syn/anti* = 87:13).⁵ Other aromatic ketones (**1**) bearing an acetoxy group or even a silyloxy group were also efficiently reduced to the enolates, irrespective of their structures. After the aldehydes were added to the reaction mixtures, the

Scheme 1



corresponding aldol adducts **2** were obtained.^{6b,d,7} This reaction is reminiscent of the similar generation of enolates from α -halogeno ketones with organocuprates shown by Posner⁸ and may be possibly related to the partial reductive dimerization of cyclohexenone at β -position in the 1,4-addition to the enone using Bu₃MnLi reported by Cahiez.⁹ Selected results are summarized in Table 1.¹⁰

The oxidative addition and reductive elimination were thought to be the key processes in the present reduction by the following ligand analysis experiments. Protonolysis of lithium tridecylmanganate at -20 °C, prior to the addition of a substrate, resulted in recovery of decane along with a trace amount of decene and eicosane. This suggests there is no generation of a low-valent manganese as a reductant for the substrates **1**.¹¹ On the other hand, the decylmanganate complex reduced **1b** at the same temperature (-20 °C), and the resulting enolate reacted with benzaldehyde to give **2d** in 81% yield (*syn/anti* = 76:24). Interestingly, in the reaction mixture, 46% of decene and 31% of eicosane (based on manganese) were found by NMR and GC analyses together with decane, while decyl acetate was not detected. These observations deserve some comments. Lithium tridecylmanganate, a new manganese ate complex bearing a ligand other than the butyl group, also acts as a reducing agent to **1b**. The fact that decene and eicosane can be detected only during the reduction reaction of **1** suggests a kind of oxidative addition of the substrate to the ate complex in these reductive generation of the enolates, and the subsequent reductive elimination of the ligands on manganese are possibly involved. Since there is no appearance of decyl acetate, a process equivalent to a "metal-halogen exchange" reaction does not seem to be significant.

(1) For the ate complexes in organic synthesis, see: (Cu) (a) Lipshutz, B. H.; Sengupta, S. In *Organic Reactions*; John Wiley & Sons: New York, 1992; Vol. 41, Chapter 2, pp 135–631. (b) Posner, G. H. In *An Introduction to Synthesis Using Organocuprate Reagents*; Wiley: New York, 1980. Organozincates are also known to be alkylating reagents as well as metalating reagents by metal-halogen exchange reaction. For recently reported reactions using organozincates, see: (Zn) (c) Harada, T.; Katsuhira, T.; Osada, A.; Iwazaki, K.; Maejima, K.; Oku, A. *J. Am. Chem. Soc.* **1996**, *118*, 11377–11390. (d) McWilliams, J. C.; Armstrong, J. D., III; Zheng, N.; Bhupathy, M.; Volante, R. P.; Reider, P. J. *J. Am. Chem. Soc.* **1996**, *118*, 11970–11971. (e) Uchiyama, M.; Koike, M.; Kameda, M.; Kondo, Y.; Sakamoto, T. *J. Am. Chem. Soc.* **1996**, *118*, 8733–8734. For 1,4-additions of zincates to α,β -enones, see: (f) Kjonass, R. A.; Hoffer, R. K. *J. Org. Chem.* **1988**, *53*, 4133–4135 and references cited therein. For ate complexes derived from main group elements used in organic synthesis as alkylation agents, see: (B) (g) Vautier, M.; Carboni, B. In *Comprehensive Organometallic Chemistry II*; Abel, E. W., Stone, F. G. A., Wilkinson, G., Eds.; McKillop, A., Vol. Ed.; Pergamon Press: Oxford, 1995; Vol. 11, pp 191–276. (Al) (h) Hauske, J. R. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: Oxford, 1991; Vol. 1, pp 77–106. (Si) (i) Chuit, C.; Corriu, R. J. P.; Reye, C.; Young, J. C. *Chem. Rev.* **1993**, *93*, 1371–1448. (j) Hosomi, A. In *Reviews on Heteroatom Chemistry*; Oae, S., Ed.; MYU: Tokyo, 1992; Vol. 7, pp 214–228.

(2) (a) Corey, E. J.; Kuwajima, I. *J. Am. Chem. Soc.* **1970**, *92*, 395–396. (b) Ibuka, T.; Aoyagi, T.; Kitada, K.; Yoneda, F.; Yamamoto, Y. *J. Organomet. Chem.* **1985**, *287*, C18–C22. (c) Krause, N.; Handke, G. *Tetrahedron Lett.* **1991**, *32*, 7229–7232. (d) Fujii, N.; Habasita, H.; Shigemori, N.; Otake, A.; Ibuka, T.; Tanaka, M.; Yamamoto, Y. *Tetrahedron Lett.* **1991**, *32*, 4969–4972. See also ref 8.

(3) (a) Hojo, M.; Harada, H.; Hosomi, A. *Chem. Lett.* **1994**, 437–440. (b) Hojo, M.; Harada, H.; Watanabe, C.; Hosomi, A. *Bull. Chem. Soc. Jpn.* **1994**, *67*, 1495–1498. (c) Hojo, M.; Harada, H.; Murakami, C.; Hosomi, A. *J. Chem. Soc., Chem. Commun.* **1994**, 2687–2688.

(4) The following are examples for the alkylation with representative electrophiles using monoalkyl- and dialkylmanganese reagents and trialkylmanganate reagents prepared from manganese(II) salts and organolithium or magnesium reagents: (a) Corey, E. J.; Posner, G. H. *Tetrahedron Lett.* **1970**, 315–318. (b) Cahiez, G.; Masuda, A.; Bernard, D.; Normant, J. F. *Tetrahedron Lett.* **1976**, 3155–3156. (c) Cahiez, G.; Normant, J. F. *Tetrahedron Lett.* **1977**, 3383–3384. (d) Cahiez, G.; Alami, M. *Tetrahedron* **1989**, *45*, 4163–4176. (e) Dialkylation of *gem*-dibromocyclopropanes with trialkylmanganates involving a metalation step was recently reported: Inoue, R.; Shinokubo, H.; Oshima, K. *Tetrahedron Lett.* **1996**, *37*, 5377–5380.

(5) The precise structures of the species expressed here as a formula "R₃MnLi" and terms "lithium trialkylmanganate" are not clear at present, and these are tentatively used. As a control experiment, a reaction of **1b** with 3 equiv of halogen-free BuLi in THF at -20 °C afforded a complex mixture.

(6) To date, reported methods for the generation of manganese enolates are as follows. Deprotonation using manganese amides: (a) Cahiez, G.; Figadere, B.; Tozzolino, P.; Cléry, P. *Fr. Pat. Appl.* 88/15,806, 1988; *Eur. Pat. Appl.* EP 373,993, 1990; *Chem. Abstr.* **1991**, *114*, 61550y. (b) Cahiez, G.; Cléry, P.; Laffitte, J. A. *Fr. Pat. Appl.* 90/16,413, 1990; *Chem. Abstr.* **1993**, *118*, 169340b. (c) Cahiez, G.; Figadere, B.; Cléry, P. *Tetrahedron Lett.* **1994**, *35*, 3065–3068. Transmetalation using lithium enolates: (d) Cahiez, G.; Cléry, P.; Laffitte, J. A. *Fr. Pat. Appl.* 91/11,814, 1991; *PCT Int. Appl. WO* 93/06,071, 1993; *Chem. Abstr.* **1993**, *119*, 116519f. (e) Cahiez, G.; Chau, K.; Cléry, P. *Tetrahedron Lett.* **1994**, *35*, 3069–3072. 1,4-Addition to α,β -unsaturated carbonyl compounds: (f) Cahiez, G.; Alami, M. *Tetrahedron Lett.* **1989**, *30*, 3541–3544. (g) Takai, K.; Ueda, T.; Kaihara, H.; Sunami, Y.; Moriwake, T. *J. Org. Chem.* **1996**, *61*, 8728–8729.

(7) The Barbier-type aldol reaction mediated by manganese was reported: Cahiez, G.; Chavant, P.-Y. *Tetrahedron Lett.* **1989**, *30*, 7373–7376.

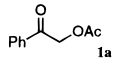
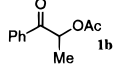
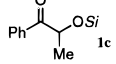
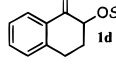
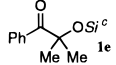
(8) (a) Posner, G. H.; Sterling, J. J. *J. Am. Chem. Soc.* **1973**, *95*, 3076–3077. (b) Wakselmann, C.; Mondon, M. *Tetrahedron Lett.* **1973**, 4285–4288. (c) Posner, G. H.; Sterling, J. J.; Whitten, C. E.; Lentz, C. M.; Brunelle, D. J. *J. Am. Chem. Soc.* **1975**, *97*, 107–118. (d) Lion, C.; Dubois, J.-E. *Tetrahedron* **1975**, *31*, 1223–1226. (e) Dubois, J.-E.; Lion, C. *Tetrahedron* **1975**, *31*, 1227–1231.

(9) Cahiez, G.; Alami, M. *Tetrahedron Lett.* **1986**, *27*, 569–572. This reductive dimerization may be a direct precedent for the present reductive generation of enolates.

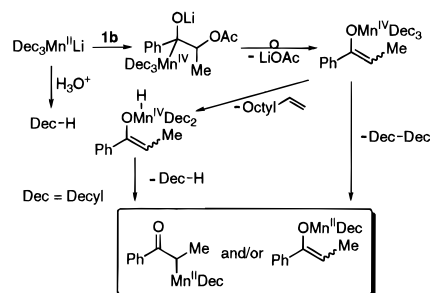
(10) For a general procedure, see: Supporting Information.

(11) As for the stability of Dec₃MnLi (Dec = decyl) in THF, 86% of decene (based on manganese) was formed after a solution of the ate complex was stirred at room temperature (rt) for 10 h and 154% at reflux for 4 h together with <5% of eicosane. When Dec₃MnLi was once refluxed for 4 h to yield decene, the reaction of **1b** with benzaldehyde under the same conditions as those in Table 1 resulted in the formation of α -hydroxypropionophenone (58%) and the recovery of **1b** (32%).

Table 1. Aldol Reaction of the Ketone Enolates Generated from the α -Oxy Ketones **1** Using Manganese(II) Ate Complex^a

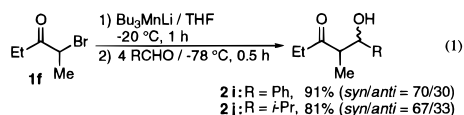
α -oxyketone 1	aldehyde	reduction conditions	aldol adduct 2	% yield ^b (<i>syn/anti</i>)
 1a	PhCHO	-78 °C, 2 h ^d	2a	69
	PhCHO	-78 °C, 2 h ^d	2b	71
 1b	EtCHO	-20 °C, 0.5 h	2c	76 (80/20)
	PhCHO	-20 °C, 0.5 h	2d	87 (87/13)
 1c	PhCHO	-78 - 0 °C, 3 h	2d	81 (63/37)
	<i>i</i> -PrCHO	-78 - 0 °C, 3 h	2e	81 (6/94)
 1d	PhCHO	-78 - 0 °C, 3 h	2f	88 (14/86)
	PhCHO	-78 - 0 °C, 3 h ^e	2g	86
 1e	PhCHO	-78 - 0 °C, 3 h ^e	2h	86

^a For the generation of an enolate, see ref 10. To the enolate, an aldehyde (1 mmol, 4 equiv to **1**) was added, and the mixture was stirred at -78 °C for 30 min. ^b Isolated yield by column chromatography. The isomeric ratio is shown in parentheses. ^c Si = *t*-BuMe₂Si. ^d Bu₃MnLi (0.75 mmol, 1.5 equiv to **1**) was used. ^e Bu₃MnLi (0.65 mmol, 1.3 equiv to **1**) was used.

Scheme 2

One of plausible mechanisms for this novel reduction of α -acetoxyacetophenone (**1b**) with the tridecylmanganese ate complex is shown in Scheme 2, which is consistent with our observations, although further investigations are needed for the elucidation of the precise mechanism.¹²

The reductant Bu₃MnLi was also applicable to the generation of the aliphatic ketone enolates, although in these cases the oxy leaving groups were not appropriate because of their low reactivities, and the halo ketones were used^{13,14} (eq 1).



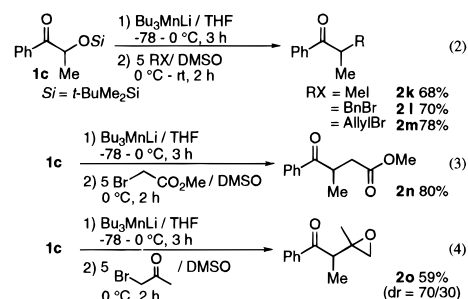
Further advantages of this new species in organic synthesis are exhibited by the following reactions. Alkylations using alkyl halides were attained.^{6a} In these reactions, no polyalkylated products were found^{6,15} (eq 2). As shown in eqs 3 and 4, the enolate derived from **1c** reacted chemoselectively with a halo

(12) The order of the reductive elimination of the ligands and the β -elimination of an acetoxy group is not clear. A mechanism in which a leaving group is directly substituted by a manganese reagent to generate the formally similar intermediate to those in substitution reactions of organic halides with cuprates may be also possible. As pointed out by a referee, an electron transfer process cannot be ruled out without further study.

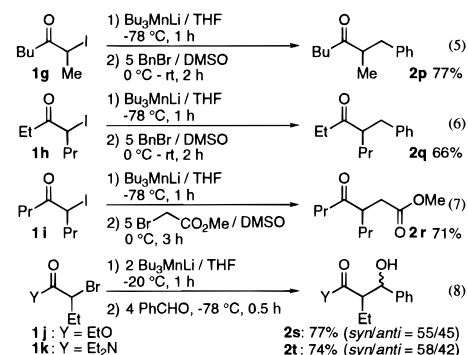
(13) From 4-(*tert*-butyldimethylsilyloxy)-5-nonanone (reduced at rt for 2 h) and 4-chloro-5-nonanone (reduced at -20 °C for 1 h), the yields for the aldol adducts with benzaldehyde (at -78 °C for 1 h) were 38% and 65%, respectively.

(14) When Dec₃MnLi was used in the reaction giving **2i**, 82% of **2i** (*syn/anti* = 70:30) was obtained. In this crude mixture, 24% of 1-decene, 29% of eicosane, and 27% of 1-bromodecane were found, suggesting the competition of a metal-halogen exchange (ca. 27%) with the processes shown in Scheme 2.

ester and a halo ketone to afford the β -keto ester **2n**^{6c} and the β,γ -epoxy ketone **2o**, respectively. These characteristic reactivities strongly suggest that the metal counterion of the enolate in these reactions may be manganese and not lithium.



The absence of any polyalkylation products may stem from the fact that the protonation-deprotonation equilibrium between the alkylated ketone and the unreacted enolate is negligible under the alkylation conditions.⁶ Indeed, the perfectly regiospecific generation and alkylations of the unsymmetrical and non-branched aliphatic ketone enolates were achieved (eqs 5–7). Especially, a regioisomeric pair of the iodo ketones **1g** and **1h**¹⁶ regiospecifically gave the isomeric alkylated products **2p** and **2q**, respectively.¹⁷ In these reactions, the kinetic generation and the subsequent alkylation of each enolate took place without accompanying isomerization. Such transformations are difficult to attain by the deprotonation-alkylation methods under both kinetic and thermodynamic conditions. This protocol can be applicable to the generation of enolates from the α -bromo ester **1j** and amide **1k** (eq 8).



As shown above, the manganese(II) ate complexes cleanly react with carbonyl compounds bearing a leaving group at the α -position to generate the enolates of the original ketones, esters, and amides, irrespective of their structures. In these reactions, the organomanganates serve as a reductant, not an alkylation agent. This direct generation of the enolates can be efficiently applied to the regiospecific generation and reactions of a variety of the enolates of the unsymmetrical and nonbranched ketones.

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Supporting Information Available: Experimental procedures and spectral data for the products (15 pages). See any current masthead page for ordering and Internet access instructions.

JA964054D

(15) Reetz, M. T.; Haning, H. *Tetrahedron Lett.* **1993**, *34*, 7395–7398.

(16) For the preparation of **1g–i**, see: Supporting Information.

(17) Aldol reactions for the enolates of the unsymmetrical and non-branched aliphatic ketones generated in a regiospecific manner were also successful.