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Direct Generation of Thiomethylmanganese Reagents and Their Reactions with Electrophiles[1]

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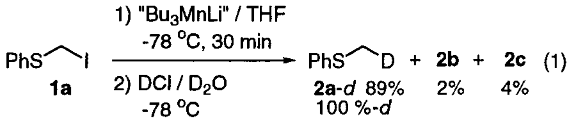
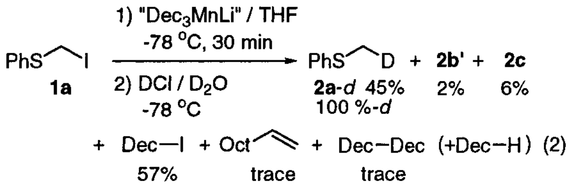
Summary: Trialkylmanganese(II) ate reagents, "R_3MnLi", reacted with iodomethyl sulfides to produce thiomethylmanganese reagents, where the manganate serves as a reductant, not an alkylation agent. In this reductive metalation of halides with alkylmanganese ate complexes, the relationship between oxidative addition and the metal−halogen exchange reaction was revealed. A wide variety of modifications of "thiomethylmanganese reagents" thus generated in reactivity could be made.

In contrast to mono- and dialkylmanganese reagents,[2] the reactivities of alkylmanganese ate-type reagents still remain unexplored.[3] We previously reported that manganate reagents served as a reductant, not as an alkylation agent, toward α-acetoxy ketones and allyl and propargyl bromides to generate enolates and allylic and propargylic reagents, respectively.[4] For the generation of enolates from acetoxy ketones, it was suggested that a kind of oxidative addition was involved in the process, while in the generation from halo ketone, a metal−halogen exchange reaction competed with the oxidative addition to some extent.[4a] These reductive reactions may be affected by a neighboring, unsaturated functional group of substrates, and the generated carbanions possibly have a resonance structure. Therefore, more simple systems are desired to examine the reductive process. In such a context, and also from a synthetic point of view, we were interested in the reductive generation of thiomethylmanganese reagents from halomethyl sulfides. When a reaction of the tributylmanganate reagent "Bu_3MnLi" with iodomethyl phenyl sulfide (**1a**) was examined, we found an interesting feature in the reactivity of the manganate reagent. We describe here the reductive generation of "thiomethylmanganese reagents" and a wide variety of modifications of the reagents thus generated in reactivity toward electrophiles.

We first found that the tributylmanganate reagent "Bu_3MnLi"[5] reacted with iodomethyl phenyl sulfide (**1a**) in THF at −78 °C for 30 min, and after the reaction was quenched with DCl/H_2O, thioanisole (**2a**) was obtained in 89% yield with almost 100% *d* incorporation, along with 2% of a butylated product, pentyl phenyl sulfide (**2b**), and 4% of a dimer, 1,2-bis(phenylthio)ethane (**2c**) (eq 1). The same reaction proceeded even with the tridecylmanganate reagent "Dec_3MnLi", although the reaction was somewhat sluggish. We obtained 45% of **2a**-*d*, 2% of undecyl phenyl sulfide (**2b′**), and 6% of the dimer **2c** in the reaction mixture (eq 2).





As for a decyl ligand of the manganate reagent, 57% of decyl iodide was produced, while only trace amounts of decene and eicosane were detected.[6] This result is in marked contrast to that in the generation of enolate from acetoxy ketone, where decene and eicosane were produced predominantly, suggesting oxidative addition.[4a] Considering that both undecyl phenyl sulfide (**2b′**) and 1,2-bis(phenylthio)ethane (**2c**) are reduced products of **1a**, the above ligand analysis experiment shows that a reaction for the generation of the thiomethylmanganese reagent at −78 °C proceeds through a metal−halogen exchange process. When a reaction of "Dec_3MnLi" with

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[1] Organometallic Ate Compounds in Organic Synthesis. 35. Part 34: Miura, K.; Tamaki, K.; Nakagawa, T.; Hosomi, A. *Angew. Chem., Int. Ed.* **2000**, *39*(11), 1958−1960.

[2] Cahiez, G. In *Encyclopedia of Reagents for Organic Synthesis*; Paquette, L. A., Ed.; Wiley: Chichester, U.K., 1995; pp 925−928.

[3] For reports on reactions of alkylmanganate reagents, see: (a) Fugami, K.; Oshima, K.; Utimoto, K.; Nozaki, H. *Tetrahedron Lett.* **1986**, *27*, 2161−2164. (b) Fugami, K.; Hibino, J.-I.; Nakatsukasa, S.; Matsubara, S.; Oshima, K.; Utimoto, K.; Nozaki, H. *Tetrahedron* **1988**, *44*, 4277−4292. (c) Inoue, R.; Shinokubo, H.; Oshima, K. *Tetrahedron Lett.* **1996**, *37*, 5377−5380. (d) Kakiya, H.; Inoue, R.; Shinokubo, H.; Oshima, K. *Tetrahedron Lett.* **1997**, *38*, 3275−3278. (e) Inoue, R.; Shinokubo, H.; Oshima, K. *J. Org. Chem.* **1998**, *63*, 910−911. (f) Nishikawa, T.; Nakamura, T.; Kakiya, H.; Yorimitu, H.; Shinokubo, H.; Oshima, K. *Tetrahedron Lett.* **1999**, *40*, 6613−6616. (g) Oshima, K. *J. Organomet. Chem.* **1999**, *575*, 1−20. (h) Kakiya, K.; Inoue, R.; Shinokubo, H.; Oshima, K. *Tetrahedron* **2000**, *56*, 2131−2137. (i) Kitagawa, K.: Inoue, A.; Shinokubo, H.; Oshima, K. *Angew. Chem., Int. Ed.* **2000**, *39*, 2481−2483. (j) Usugi, S.; Shinokubo, H.; Oshima, K. *Bull. Chem. Soc. Jpn.* **2000**, *73*, 1903−1904.

[4] (a) Hojo, M.; Harada, H.; Ito, H.; Hosomi, A. *J. Am. Chem. Soc.* **1997**, *119*, 5459−5460. (b) Hojo, M.; Harada, H.; Ito, H.; Hosomi, A. *Chem. Commun.* **1997**, 2077−2078.

[5] The formula "R_3MnLi" and the term "trialkylmanganate" are tentatively used. For the structure of tetraethylmanganate, see: (a) Morris, R. J.; Girolami, G. S. *Organometallics* **1989**, *8*, 1478−1485. (b) Andersen, R. A.; Carmona-Guzman, E.; Gibson, J. F.; Wilkinson, G. *J. Chem. Soc., Dalton Trans.* **1976**, 2204−2211.

[6] In the formation of decene, an equimolar amount of decane would be also produced; however, the amount of decane could not be determined because of a large amount of coproduced decane due to protonolysis of a remaining decyl ligand on manganese in a workup procedure.

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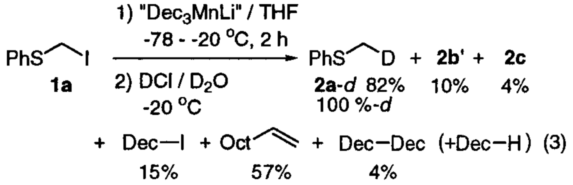
iodomethyl sulfide **1a** in THF was set at −78 °C and the temperature was raised to −20 °C, 82% of **2a**, 10% of **2b′**, and 4% of **2c** were obtained (eq 3). Interestingly in this case, the distribution of the decyl ligand was dramatically changed to 15% of decyl iodide, 57% of decene, and 4% of eicosane. This experimental result suggests that oxidative addition was a major pathway for the reduction of **1a** at −20 °C, since placing "Dec$_3$MnLi" itself in THF at −20 °C without iodomethyl sulfide **1a**, in a control experiment, resulted only in recovery of decane. These results deserve some comments. The exchange reaction proceeds even at −78 °C, while at higher temperature, oxidative addition followed by *β*-elimination or reductive elimination becomes predominant.[7] Considering that the amount of the produced decyl iodide was decreased to 15% at −20 °C, the exchange reaction is reversible and the thiomethyl anion is predominant in the equilibrium.[8]



Hitherto reported methods for the generation of thiomethyl carbanions were based on deprotonation by a strong base,[9] reduction by a one-electron reductant, chromium(II) reagents,[10] reductive lithiation,[11] desilylation by fluoride ion,[12] and a tin−lithium exchange reaction.[13] From a synthetic point of view, the present reaction can be operated under mild conditions using an equimolar amount of the manganate reagent, which formally serves as a two-electron reductant. We tried a reaction of the thiomethylmanganese reagent thus generated with allyl bromides. As shown in Table 1, the thiomethyl reagent reacted with allyl bromides to give the corresponding allylated products **3** (eq 4). In the presence of a catalytic or stoichiometric amount of CuCN, higher yields of allylated products **3** were obtained (entries 1−3).[14] Interestingly, with iodomethyl silyl sulfides **1b**,**c** as starting materials, the generation and reactions of the corresponding silyl-substituted thiomethylmanganese reagents can be also attained. These reagents are synthetically equivalent to a formyl anion, since a silyl-substituted thiomethyl group of the products **3d**,**e** can be oxidatively transformed to a formyl group.[15]

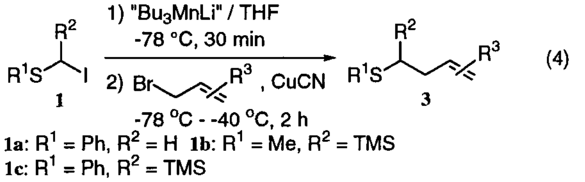
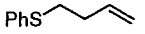
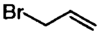
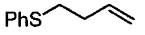
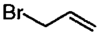
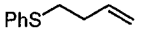
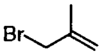
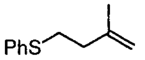
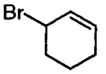
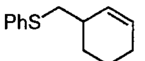
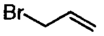
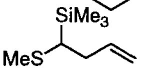
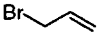
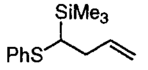
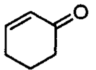
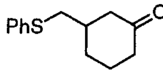
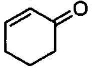
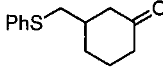
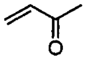
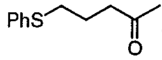
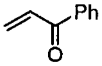
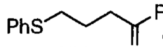
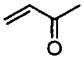
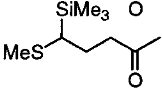


Table 1. Reactions of Thiomethylmanganese Reagents with Allyl Bromides[a]

entry	substrate	allyl bromide	CuCN / eq.	product 3	yield / %[b]
1	**1a**		---	 **3a**	57
2	**1a**		0.1	 **3a**	70
3	**1a**		1	 **3a**	96
4	**1a**		1	 **3b**	87
5	**1a**		1	 **3c**	99
6	**1b**		0.1	 **3d**	69
7	**1c**		1	 **3e**	83

[a] All reactions were carried out under conditions shown in eq 4. Reactions with electrophiles were carried out at −78 °C, and the temperature was elevated to −40 °C for 2 h using 4 equiv of allyl bromide and 1 equiv of CuCN(I). [b] Isolated yield.

Table 2. Reactions of Thiomethylmanganese Reagents with Enones[a]

entry	substrate	enone	product 4	yield / %[b]
1	**1a**		 **4a**	71
2[c]	**1a**		 **4a**	61
3	**1a**		 **4b**	80
4	**1a**		 **4c**	62
5	**1b**		 **4d**	quant.

[a] All reactions were carried out under conditions shown in eq 5, unless otherwise noted. Reactions with enones were carried out at −78 °C, and the temperature was elevated to −40 °C for 2 h using 4 equiv of enone, 1 equiv of CuCN(I), and 4 equiv of TMSCl. [b] Isolated yield. [c] Instead of CuCN and TMSCl, 8 equiv of $BF_3{\cdot}OEt_2$ was used as an additive.

Thiomethylmanganese reagents did not react at all with *α*,*β*-unsaturated ketones. For the 1,4-addition to enones, we found a combination of CuCN and chloro-

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(7) The reaction of liberated butyllithium from tributylmanganate seems not to be significant. The reaction of α-acetoxy ketone with tributylmanganate gave manganese enolate, which reacted with aldehydes to yield aldol adducts in high yield,[4a] while only with butyllithium were α-hydroxy ketone and a starting material, instead of the corresponding aldol adducts, obtained.

(8) When a phenylthiomethyldibutylmanganate reagent, which was prepared by addition of phenylthiomethyllithium to a solution of dibutylmanganese, was stirred with decyl iodide in THF at −78 °C for 30 min, thioanisole was obtained quantitatively along with 31% of decane.

(9) (a) Corey, E. J.; Seebach, D. J. *J. Org. Chem.* **1966**, *31*, 4097−4099. (b) Peterson, D. J. *J. Org. Chem.* **1967**, *32*, 1717−1720. (c) Dolak, T. M.; Bryson, T. A. *Tetrahedron Lett.* **1977**, 1961−1964. (d) Kündig, E. P.; Ripa, A.; Liu, R.; Amurrio, D.; Bernardinelli, G. *Organometallics* **1993**, *12*, 3724−3737.

(10) Nakatsukasa, S.; Takai, K.; Utimoto, K. *J. Org. Chem.* **1986**, *51*, 5045−5046.

(11) Cohen, T.; Zhang, B.; Cherkauskas, J. P. *Tetrahedron* **1994**, *50*, 11569−11584.

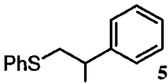
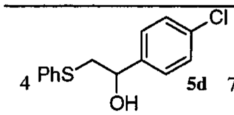
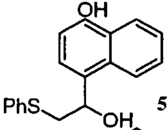
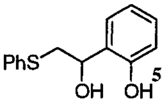
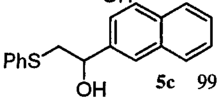
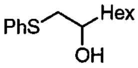
(12) Becke, F.; Heinemann, F. W.; Steinborn, D. *Organometallics* **1997**, *16*, 2736−2739.

(13) (a) Hosomi, A.; Ogata, K.; Hoashi, K.; Kohra, S.; Tominaga, Y. *Chem. Pharm. Bull.* **1988**, *36*(9), 3736−3738. (b) Hojo, M.; Ishibashi, N.; Hosomi, A. *Heteroat. Chem.* **1994**, *5*(3), 229−234.

(14) To "Bu$_3$MnLi" (0.5 mmol) in THF (5 mL), a solution of iodomethyl phenyl sulfide (**1a**) in THF (0.5 M, 0.5 mmol) was introduced to the flask at −78 °C, and the mixture was stirred at −78 °C for 30 min. Allyl bromide (2 mmol) and CuCN (0.5 mmol) were added at −78 °C, and the temperature was raised to −40 °C for 2 h. The reaction was quenched with saturated NH_4Cl at −40 °C. After conventional workup and purification by chromatography, product **3a** was obtained in 96% yield.

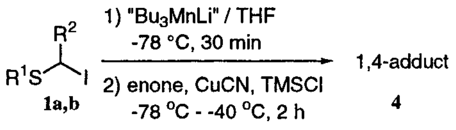
(15) Ager, D. J. *J. Chem. Soc., Perkin Trans. 1* **1983**, 1131−1136.

Table 3. Reactions of Thiomethylmanganese Reagent 1a with Aldehydes

entry	product 5		yield / %[b]	entry	product 5		yield / %[b]
1		**5a**	88	4		**5d**	74
2		**5b**	74	5		**5e**	76
3		**5c**	99	6		**5f**	33

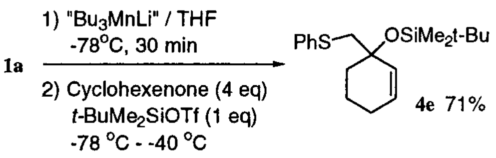
[a] All reactions were carried out under conditions shown in eq 7, unless otherwise noted. Reactions with aldehydes were carried out at −78 °C, and the temperature was elevated to room temperature for 2 h using 4 equiv of aldehyde and 8 equiv of $BF_3{\cdot}OEt_2$. [b] Isolated yield.

trimethylsilane as additives was effective (eq 5, Table 2).[16,17] A silyl-substituted thiomethylmanganese reagent



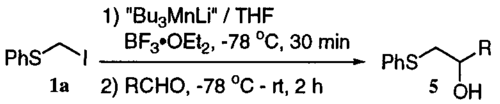
(5)

also successfully added to enones to give **4d** (entry 5). In contras to these results, silyl triflate dramatically changed the reaction mode to 1,2-addition and only **4e** was obtained in 71% yield (eq 6).



(6)

Reactions of the manganese reagent with aldehydes also did not proceed without additives. Upon introduction of $BF_3{\cdot}OEt_2$ into a solution of "Bu_3MnLi" even before the preparation of a thiomethylmanganese reagent, the corresponding adduct with an aldehyde was obtained in high yield. (eq 7, Table 3).[18] It is noteworthy



(7)

that $BF_3{\cdot}OEt_2$ is compatible with "Bu_3MnLi" without deactivation of the manganate in reductive generation of a thiomethylmanganese reagent from iodomethyl sulfide, while in the nucleophilic addition of the thiomethyl group to an aldehyde, the Lewis acid enhances the reactivity of a thiomethyl ligand toward carbonyl compounds.

As shown here, tributylmanganate reagents react with iodomethyl sulfides to generate thiomethylmanganese reagents. The relationship between the exchange reaction and oxidative addition was seen to depend on temperature. The reactivity of the new class of thiomethyl reagents thus reductively generated can be widely modified with additives. Further synthetic applications of the present protocol are now in progress.

Acknowledgment. The present work was partly supported by Grants-in-Aid for Scientific Research on Priority Areas (No. 706: Dynamic Control of Stereochemistry) from the Ministry of Education, Science, Sports and Culture of Japan.

Supporting Information Available: Text giving experimental procedures and ^1H and ^{13}C NMR, IR, and mass spectral data for the products. This material is available free of charge via the Internet at http://pubs.acs.org.

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[16] Nakamura, E.; Matsuzawa, S.; Horiguchi, Y.; Kuwajima, I. *Tetrahedron Lett.* **1986**, *27*, 4029−4032.

[17] Liu, H.; Cohen, T. *J. Org. Chem.* **1995**, *60*, 2022−2025.

[18] Yamamoto, Y. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 947−1038.