

Alkylation of acetals using manganate–BF₃·OEt₂ mixed reagent

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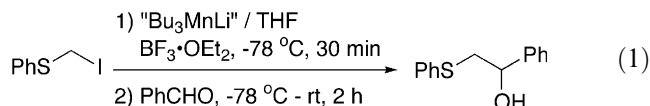
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Abstract—A mixture of ‘R₃MnMgBr’ and BF₃·OEt₂ prepared in advance only by stirring both reagents in ether converted acetals to alkylation products, where an alkoxy group of acetals was substituted by the alkyl group of manganese reagent used. Ketals also reacted with the ‘mixed reagent’ to afford the corresponding alkylation products in high yield. α-Alkoxy-substituted cyclic ethers and acetoxy-substituted cyclic ethers were selectively converted to ring-opening alkylation products and α-alkyl-substituted cyclic ethers, respectively.

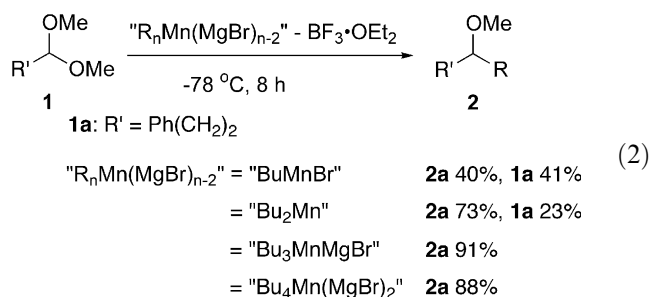
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Introduction of a Lewis acid into the reactions using organometallic reagents often promotes nucleophilic reaction of the organometallic reagent toward electrophiles.¹ Allylation with allylsilanes is representative.² Compared to reactions using less ionic organometallic reagents, alkylation agents with more ionic carbon–metal bond of higher reactivity are used for the nucleophilic introduction of simple alkyl groups. Use of a Lewis acid in simple alkylation is limited because of incompatibility of the simple and ionic alkylation agent with the Lewis acid.³

We previously reported that manganese ate-type reagents reacted with several electrophiles to generate nucleophilic manganese reagents. Manganate reagents served as a reductant in that process.⁴ Unfortunately, thiomethylmanganese reagent that was generated reductively from iodomethyl sulfide with ‘Bu₃MnLi’ did not react with benzaldehyde. However, the corresponding adduct was obtained in the presence of BF₃·OEt₂. Interestingly, even if the manganate reagent ‘Bu₃MnLi’ and BF₃·OEt₂ were mixed in advance, iodomethyl sulfide was reduced to generate thiomethylmanganese reagent without deactivation of the manganese-based reductant by BF₃·OEt₂. Eventually, the Lewis acid enhanced nucleophilic reactivity of thus-generated thiomethylation agent to the aldehyde (Eq. 1).⁵



The above reaction suggests that organomanganese reagents including ate-type reagents were ‘compatible’ with BF₃·OEt₂. Manganese reagents that were generated by transmetalation were employed for preparation of the pre-mixed reagent with BF₃·OEt₂ to examine compatibility of organomanganese reagents with BF₃·OEt₂ in a more general manner. Thus-prepared ‘mixed reagents’ based on mono-, di-, butylmanganese, tri- and tetra-butylmanganate were subjected to a reaction with 3-phenylpropionaldehyde dimethyl acetal (**1a**, R’=Ph(CH₂)₂).⁶ All mixed reagents for butylation (R=‘Bu’) that we examined afforded 2-phenylethyl butyl carbinol methyl ether (**2a**) (Eq. 2). In the reaction with ‘Bu₂Mn’–BF₃·OEt₂, acetal **1a** remained (23% of **1a**) after 8 h at –78 °C, whereas ‘Bu₃MnMgBr’–BF₃·OEt₂ reacted efficiently with **1a** to give the substitution product **2a** in 91% yield.⁷ This efficiency contrasts markedly with that



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Table 1. Reaction of organomanganate–BF₃·OEt₂ mixed reagents with acetals **1**^a

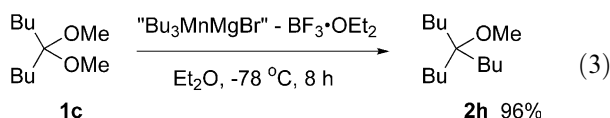
| Entry | R ¹ | R | Conditions | Yield % ^b |
|-------|---|-----------------------------------|-------------|----------------------|
| 1 | Ph(CH ₂) ₂ (1a) | Bu | –78 °C, 4 h | 2a 94 |
| 2 | 1a | Ph(CH ₂) ₃ | –50 °C, 4 h | 2b 90 |
| 3 | 1a | <i>i</i> -Pr | –78 °C, 4 h | 2c 94 |
| 4 | 1a | Ph | –78 °C, 4 h | 2d 71 |
| 5 | <i>c</i> -Hex (1b) | Bu | –50 °C, 4 h | 2e 81 |
| 6 | 1b | <i>i</i> -Pr | –78 °C, 4 h | 2f 80 |

^a BF₃·OEt₂ was added to a solution of 'R₃MnMgBr' in ether at –78 °C. Then the mixture was stirred for 10 min. Acetal **1** (1 mmol) was added to the mixture. The reaction was carried out under the conditions shown in the relevant column.

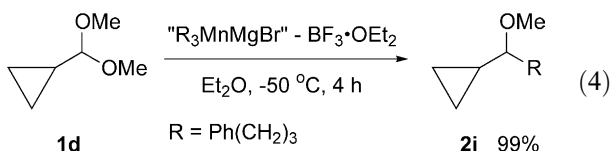
^b Isolated yield.

of the reaction in the absence of BF₃·OEt₂, where the corresponding product **2a** was not obtained.⁸

Table 1 summarizes other reactions of acetals **1** with 'R₃MnMgBr'–BF₃·OEt₂.⁹ Not only acetal **1a**, but also that of α -branched aldehyde **1b** was alkylated to afford *c*-hexyl butyl carbinol methyl ether (**2e**) in 81% (entry 5). *sec*-Alkyl-manganese mixed reagents were also adaptable to the present reaction (entries 3 and 6): especially in entry 6, where both R and R' were *sec*-alkyl group, *c*-hexyl *i*-propyl carbinol methyl ether (**2f**) was obtained in 80% yield. Interestingly, even aromatic groups were delivered onto acetal carbon (entry 4). The present reaction seems not to have suffered from steric hindrance. Moreover, dibutyl ketone dimethyl acetal **1c** was converted to *tert*-alkyl ether **2h** in 96% yield (Eq. 3).

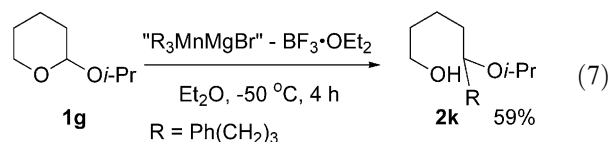
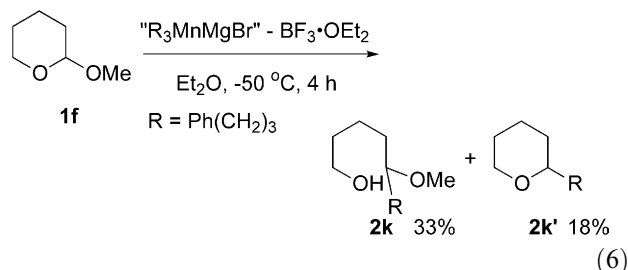
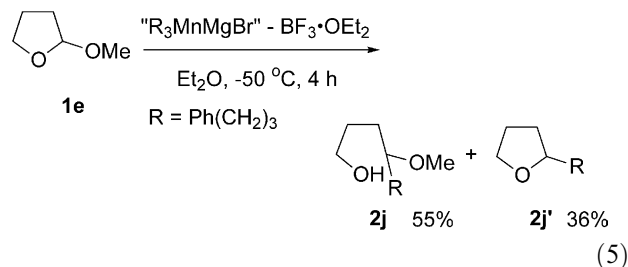


This result suggested that cationic intermediates may have been involved in these reactions and that the generated cationic intermediates were alkylated by the manganate reagent in a stepwise manner. For those reasons, we examined a reaction of acetal that generated *c*-propyl carbinyl cation in the presence of a Lewis acid. Interestingly, in the reaction of *c*-propanecarboxaldehyde dimethyl acetal (**1d**) with 3-phenylpropylmanganese mixed reagent, *c*-propyl phenylpropyl carbinol methyl ether (**2i**) was obtained in high yield without cationic rearrangement (Eq. 4).¹⁰



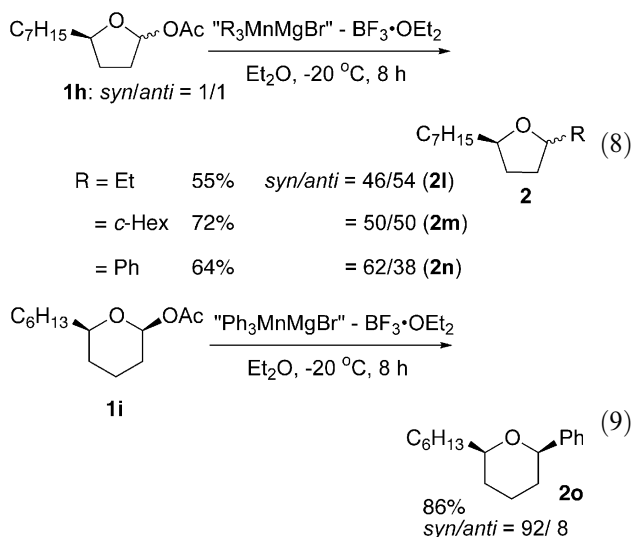
Reactions of unsymmetrical acetals were also examined. When 2-methoxytetrahydrofuran (**1e**) was conducted to the reaction, ring-opening product **2j** and alkylated tetrahydrofuran **2j'** were produced in 55% and 36% yield, respectively (Eq. 5). 2-Methoxytetrahydropyran (**1f**) also gave a mixture of ring-opening product **2k** (33%) and alkylated tetrahydropyran **2k'** (18%) (Eq. 6). In these reactions, ring-opening products were formed through the activation of ring-oxygen of starting mate-

rials with the action of the Lewis acid; activation of methoxy group would engender production of alkylated cyclic ethers. Notably, by merely changing the methoxy group on the tetrahydrofuran ring to *i*-propoxy group affected the product selectivity: only ring-opening product **2k** was obtained (Eq. 7).



Lactol acetates also reacted with the present mixed reagents. In marked contrast to Eq. 7, we found that alkyl-substituted cyclic ethers were obtained without ring-opening products in reactions of cyclic ethers with acetoxy group as a leaving group (Eqs. 8 and 9). *sec*-Alkyl groups and even the phenyl group were able to be introduced to cyclic ethers. A stereoisomeric mixture of 2-acetoxytetrahydrofuran **1h** (*syn/anti* = 1/1) gave 2,5-disubstituted tetrahydrofurans **2l–n**, whose ratio of *syn/anti* varies from 46/54 to 62/38, depending on the R group of manganese-mixed reagents.

A reaction of *syn* 2-acetoxytetrahydropyran **1i** with phenyl-mixed reagent afforded *syn* 2-phenyl-6-hexyl-tetrahydropyran (**2o**) stereoselectively in 86% yield.



Substitution by nonstabilized alkyl group at acetal carbon center was attained using the 'R₃MnMgBr'–BF₃·OEt₂ 'mixed reagent'. Such mixed-use of manganate reagents with BF₃·OEt₂ expands reactivity spectrum of organomanganese reagents, but it remains unclear whether manganate and BF₃·OEt₂ is truly compatible, or whether both reagents form new species for alkylation. Further study of 'mixed reagents' is now in progress.

Acknowledgements

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6. The precise structures of the species expressed here as a formula 'R_nMn(MgX)_{n-2}' and terms 'mono-, di-, and trialkylmanganate' are not clear at present and these 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.
7. 'Bu₂Mn' and 'Bu₃MnMgBr' are possibly in equilibrium through disproportionation. Such a disproportionation would be the reason why clear difference between these reactions was not observed.
8. Previously, copper salt was co-used as a catalyst in reactions of organomanganese reagents for conjugate addition to α,β-unsaturated carbonyl compounds and alkylation with alkyl bromides. In these reactions, transmetalation of alkyl group from manganese to copper may possibly be involved. Therefore, these reactions are closely related to copper chemistry (a) Cahiez, G.; Alami, M. *Tetrahedron Lett.* **1989**, *30*, 3541–3544; (b) Cahiez, G.; Alami, M. *Tetrahedron Lett.* **1989**, *30*, 7365–7368; (c) Cahiez, G.; Alami, M. *Tetrahedron Lett.* **1990**, *31*, 7423–7424; (d) Cahiez, G.; Marquais, S. *Synlett* **1993**, 45–47, Iron catalyst was also used for synthesis of ketones from acid halides and coupling with vinyl halides; (e) Cahiez, G.; Chavant, P.-Y.; Metais, E. *Tetrahedron Lett.* **1992**, *33*, 5245–5248; (f) Cahiez, G.; Marquais, S. *Tetrahedron Lett.* **1996**, *37*, 1773–1776.
9. To a suspension of MnBr₂ (1.1 mmol) and LiBr (2.2 mmol) in ether (10 mL) was added Grignard reagent (3.3 mmol) at –78 °C under argon. The mixture was stirred for 30 min. BF₃·OEt₂ (1.1 mmol) was added to the mixture at –78 °C. The resultant mixture was stirred for another 10 min. Acetal (1.0 mmol) was added to the mixture at –78 °C; the temperature was immediately raised to the reaction temperature. Reaction was quenched with satd NH₄Cl.
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