JOC Article

Chemoselective Conjugate Addition of Dimethylzinc-Mediated Ether and Acetal Radicals to Alkylidenemalonates and Asymmetric Reactions[†]

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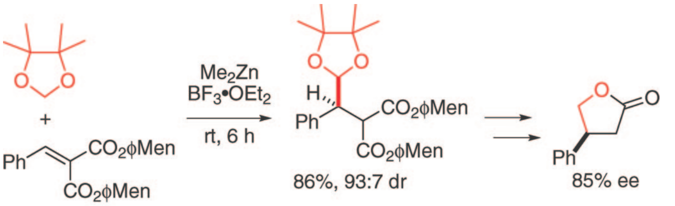

ϕMen = 8-phenylmenthyl

Cyclic and acyclic ether or acetal radicals were generated directly from ethers or acetals by the action of dimethylzinc−air, and their subsequent conjugate addition reaction with alkylidenemalonates afforded the corresponding conjugate adducts in reasonably high yields. The reaction with benzylidenemalonates bearing formyl and imino groups gave chemoselectively the conjugate addition products. The asymmetric reaction of bis(8-phenylmenthyl) benzylidenemalonate proceeded diastereoselectively to provide the adduct with 93:7 dr.

Introduction

A conjugate addition reaction of nucleophilic radicals with olefins activated by an electron-withdrawing group is recognized as a powerful tool in organic synthesis.[1,2] Our recent reports[3] indicated that carbon-centered radicals were generated directly from ethers or acetals,[4] unfunctionalized cycloalkanes,[5] and primary alkyl iodides[6] by the action of dimethylzinc and air. These radicals add to the $C{=}N$ bond of imines to give the adduct amines in good to excellent yields. We have also reported the reactions of carbon-centered radicals with aldehydes,[7] arylamines, alkoxyamines, and dialkylhydrazines.[8] A diastereofaceselective addition of α-alkoxyalkyl radicals to chiral *N*-sulfinylimines provided a reasonably efficient methodology for the asymmetric synthesis of oxygenated amine derivatives.[9] With a view of widening the applicability of the radical reaction, we investigated conjugate addition of carbon-centered ether radicals to Michael acceptors.[10] Although an ene−imine was found to be a good Michael acceptor, a good precursor of ether radical was limited to THF.[11] A wider applicability of ether and acetal

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[†] This paper is dedicated to the memory of Mrs. Joan and Prof. A. I. Meyers.

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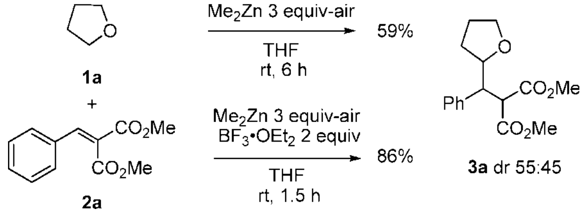
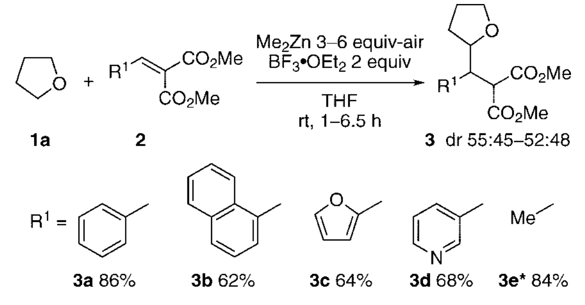
(10) Recent examples for conjugate addition of α-hydroxy or α-alkoxyalkyl radicals: (a) Oka, R.; Nakayama, M.; Sakaguchi, S.; Ishii, Y. *Chem. Lett.* **2006**, *35*, 1104–1105. (b) Bagal, S. K.; Tournier, L.; Zard, S. Z. *Synlett* **2006**, 1485–1490. (c) Geraghty, N. W. A.; Lally, A. *Chem. Commun.* **2006**, 4300–4302. (d) Fernández, M.; Alonso, R. *Org. Lett.* **2005**, *7*, 11–14. (e) Ghosh, A. K.; Leshchenko, S.; Noetzel, M. *J. Org. Chem.* **2004**, *69*, 7822–7829.

10.1021/jo801541m CCC: $40.75

SCHEME 1. Me_2Zn–Air-Initiated Radical Conjugate Addition of THF (1a) to 2a



SCHEME 2. Me_2Zn–Air-Initiated Radical Conjugate Addition of THF (1a) to 2



*Ethyl ester, in place of methyl ester, was used for **3e**.

radicals was found to be possible by the reaction with alkylidenemalonates as a Michael acceptor.

Conjugate Addition of Ether and Acetal Radicals

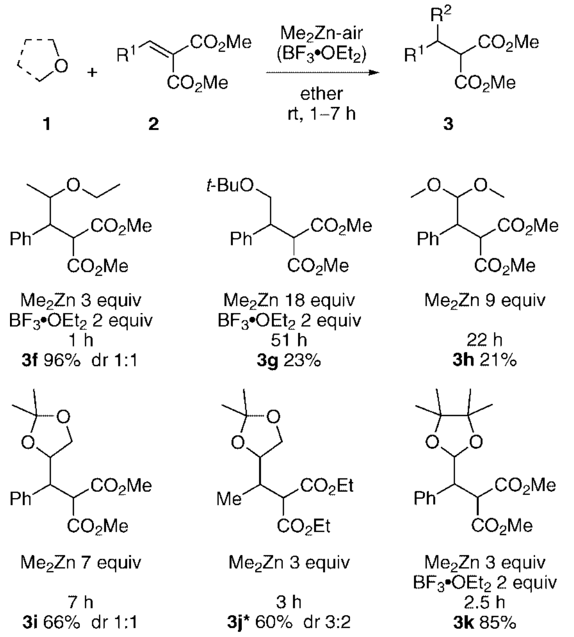
Although attempted radical addition reaction of THF (**1a**) with cinnamate failed to give the desired adduct, dimethyl benzylidenemalonate (**2a)** was found to be a better Michael acceptor to give a 55:45 diastereomeric mixture of THF adduct **3a** in 59% yield at room temperature after 6 h (Scheme 1). The reaction efficiency was improved by the addition of boron trifluoride diethyl etherate. Thus, the reaction of **1a** with **2a** was conducted by the action of 3 equiv of dimethylzinc and 2 equiv of boron trifluoride diethyl etherate in THF at room temperature for 1.5 h to give **3a** in 86% yield.

A plausible mechanism is as follows: Methyl radical, generated by the action of dimethylzinc and air oxygen, would abstract an α-hydrogen of THF to give THF-2-yl radical, which undergoes conjugate addition to **2a** to produce C-centered radical stabilized by the adjacent two ester functionalities. Finally, the radical regenerates methyl radical by the reaction with dimethylzinc to form zinc enolate, which gives product **3a** after aqueous workup.

The reaction is of generality with respect to a variety of alkylidenemalonates **2** as summarized in Scheme 2. Malonates bearing aryl (phenyl, naphthyl), heterocyclic (furyl, pyridyl), and methyl groups (R^1 in **2**) were converted within 6.5 h at room temperature to the corresponding adducts **3** in 62–86% yield.

The reaction of benzylidene- and ethylidenemalonates (R^1 = Ph, Me) **2a**,**e** was also examined using a variety of ethers **1** as summarized in Scheme 3. Among the acyclic ethers examined, diethyl ether was the best donor, giving **3f** in 96% yield, whereas *tert*-butyl methyl ether and methoxymethyl methyl ether were worse donors, giving the corresponding adducts **3g** and **3h** in 23% and 21% yields, respectively. On the contrary, cyclic ethers such as THF, 2,2-dimethyl-1,3-dioxolane, and 4,4,5,5-tetramethyl-1,3-dioxolane were good donors for the Michael reaction. It is important to note that boron trifluoride diethyl etherate was omitted in the reaction when acid-labile ethers were used as radical precursors.

SCHEME 3. Me_2Zn–Air-Initiated Radical Conjugate Addition of Acyclic and Cyclic Ethers 1 to 2



*Ethyl ester, in place of methyl ester, was used for **3j**.

The ability of other radical-generating agents, diethylzinc[12] and triethylborane,[13,14] was comparatively evaluated in the reaction of THF (**1a**) with **2a** (R^1 = Ph) (Scheme 4). The reaction with diethylzinc gave **3a** in 49% yield as well as ethyl adduct **4** in 41% yield. The reaction with triethylborane produced a mixture of much more complex products which comprised **3a** in 34%, its ethylation derivative **5** in 26%, **4** in 14%, and its ethylation derivative **6** in 18% yields. These outcomes clearly indicate the higher efficiency of dimethylzinc in the direct generation of THF radical and also its conjugate addition reaction.

The conjugate addition products **3** are synthetic precursors of antitumor butyrolactones (Scheme 5).[15] Adduct **3i** was converted into 4,5-disubstituted butyrolactones **9** and **10** through acidic hydrolysis to separable **7** and **8** and demethoxycarbonylation. 3,4-Disubstituted butyrolactone **11** was obtained in 86% yield from **3k** via triethylsilane reduction of the acetal moiety and lactonization.

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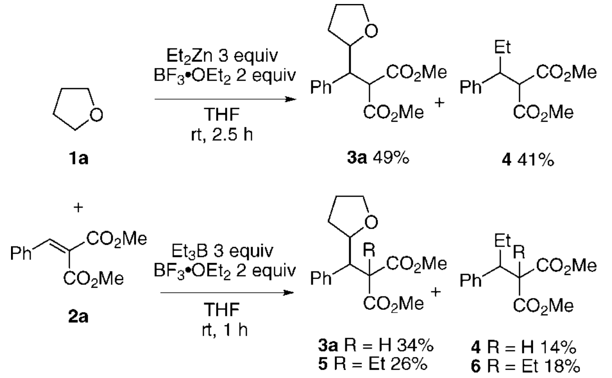
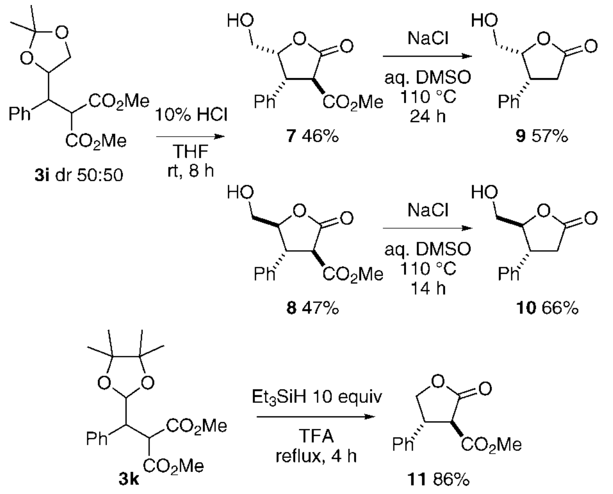
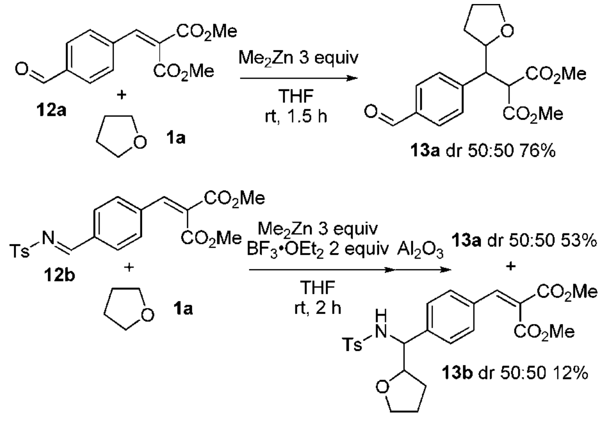
SCHEME 4. Et$_2$Zn- and Et$_3$B-Initiated Radical Reactions of THF (1a) with 2a



SCHEME 5. Conversion into γ-Lactones



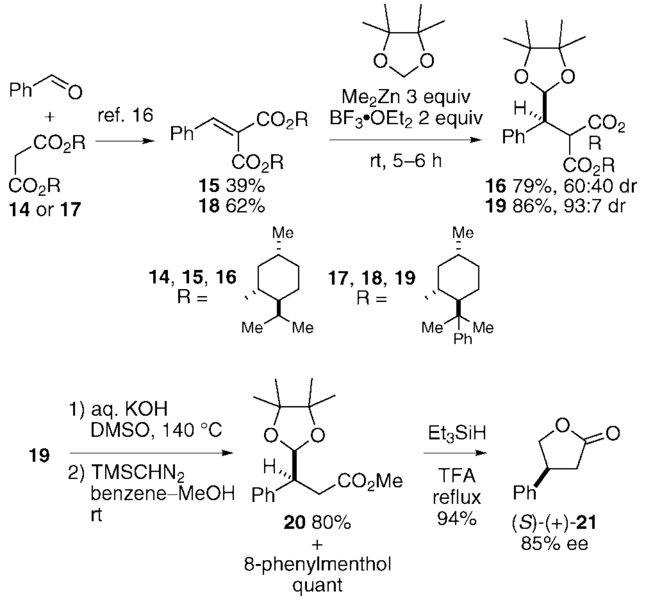
SCHEME 6. Chemoselective Radical Conjugate Addition of THF (1a) to Aldehyde 12a and Imine 12b



Chemoselective Conjugate Addition

The sense of chemoselectivity of the radical conjugate addition reaction was determined by examining the reaction of THF (**1a**) with **12a** bearing a formyl group and its imine **12b** (Scheme 6).[4a,b,7] The reaction of **1a** with aldehyde **12a** was mediated by 3 equiv of dimethylzinc at room temperature for 1.5 h to give chemoselectively the conjugate addition product **13a** in 76% yield. The reaction of imine **12b** also gave, after hydrolysis of the imine moiety through alumina column, **13a** in 53% yield along with amine **13b** in 12% yield. These preferences for conjugate addition as well as that for imine over aldehyde indicate the order of reactivity: Michael acceptor > imine > aldehyde.[4a,b]

SCHEME 7. Asymmetric Conjugate Addition and Conversion to 21



Asymmetric Reaction of Bis(8-phenylmenthyl) Benzylidenemalonate

Extension of the radical conjugate addition reaction to an asymmetric variant was the next challenge. We selected a menthyl malonate as a chiral Michael acceptor. Dimenthyl benzylidenemalonate **15**[16] was prepared from benzaldehyde and dimenthyl malonate **14** (R = *l*-menthyl) according to the reported procedure (Scheme 7). The reaction of **15** with 4,4,5,5-tetramethyl-1,3-dioxolane was conducted under the conditions of 3 equiv of dimethylzinc and 2 equiv of boron trifluoride diethyl etherate at room temperature for 5 h to give adduct **16** in 79% yield. However, it was disappointing to find that the ratio of diastereomers was 60:40, i.e., 20% de. The poor 60:40 dr was dramatically improved using 8-phenylmenthyl[17] ester in place of menthyl ester. Bis(8-phenylmenthyl) benzylidenemalonate **18** was prepared by the reaction of benzaldehyde with bis(8-phenylmenthyl) malonate **17** (R = *l*-8-phenylmenthyl). The radical reaction of **18** was again conducted under the same conditions at room temperature for 6 h to give a conjugate addition product **19** with 93:7 dr in 86% yield. Hydrolysis of sterically bulky 8-phenylmenthyl ester of **19** with KOH in aqueous DMSO at 140 °C for 2 h and methyl esterification with trimethylsilyldiazomethane gave a methyl ester **20** in 80% yield. It is worthy to note that 8-phenylmenthol was recovered quantitatively. Triethylsilane reduction of **20** in trifluoroacetic acid gave lactone (*S*)-(+)-**21**[18] with 85% ee in 94% yield.

Summary

α-Alkoxyalkyl radicals, generated from ethers and acetals by the action of dimethylzinc–air, were chemoselectively reacted

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with Michael acceptors, mainly without addition to aldehyde and imine moieties. Dimethylzinc was confirmed to be a better initiator than triethylborane and diethylzinc, which caused competitive ethyl addition. An efficient asymmetric radical addition was developed by using bis(8-phenylmenthyl) benzylidenemalonate as a chiral Michael acceptor.

Experimental Section

Although a 1.0 M solution of Me_2Zn in hexane is easily handled and we have not experienced spontaneous combustion, dialkylzinc is pyrophoric and there is a potential danger of ignition.

Dimethyl 2-[Phenyl(4,4,5,5-tetramethyl-1,3-dioxolan-2-yl)methyl]malonate (3k). A dry three-necked, round-bottomed flask was equipped with a stir bar and dimethyl 2-benzylidenemalonate (**2a**) (220 mg, 1.0 mmol). The flask was filled with argon by evacuation and refilled three times. 4,4,5,5-Tetramethyl-1,3-dioxolane (36 mL, 250 mmol) was added at room temperature. To the stirred solution were added boron trifluoride diethyl etherate (0.25 mL, 2.0 mmol) and a 1.0 M hexane solution of dimethylzinc (3.0 mL, 3.0 mmol). The argon source was replaced with a NaOH drying tube, and air was injected into the reaction mixture via an air bubbler at a rate of 0.5 mL/h. The reaction mixture was stirred for 2.5 h followed by quenching with saturated ammonium chloride (20 mL). The aqueous layer was extracted with ethyl acetate (3 × 20 mL). The combined organic layers were washed with brine (20 mL), dried over sodium sulfate, filtered, and concentrated under reduced pressure to give a colorless oil. Column chromatography (ethyl acetate/hexane 1/5) gave **3k** (298 mg, 85%) as a colorless solid, which was recrystallized from a mixture of ethyl acetate and hexane to give colorless prisms. Mp: 121.5−122 °C. $R_f = 0.33$ (ethyl acetate/hexane 1/3). ^{1}H NMR δ: 1.03 (s, 3H), 1.11 (s, 3H), 1.12 (s, 3H), 1.14 (s, 3H), 3.39 (s, 3H), 3.69 (dd, $J = 5.8, 11$, 1H), 3.76 (s, 3H), 3.98 (d, $J = 11$, 1H), 5.22 (d, $J = 5.8$, 1H), 7.20−7.29 (m, 5H). ^{13}C NMR δ: 22.0 (CH_3), 22.4 (CH_3), 23.7 (CH_3), 23.8 (CH_3), 50.6 (CH), 52.2 (CH_3), 52.5 (CH_3), 53.8 (CH), 82.3 (C), 82.4 (C), 101.2 (CH), 127.3 (CH), 128.0 (CH), 129.5 (CH), 137.1 (C), 168.0 (C), 168.7 (C). IR (KBr) ν: 2938, 1736, 1157, 1026. EIMS (*m*/*z*): 350 (M^+), 221 ($M - C_7H_{13}O_2$), 129 ($C_7H_{13}O_2$). Anal. Calcd for $C_{19}H_{26}O_6$: C, 65.13; H, 7.48. Found: C, 64.97; H, 7.48.

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Supporting Information Available: Experimental details and characterization data of new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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