



Iron chloride enhancement of dimethylzinc-mediated radical conjugate addition of ethers and an amine to alkylidenemalonates

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ABSTRACT

The addition of FeCl_3 and the use of DMSO as a solvent enabled the radical conjugate addition of a cyclic acetal and a cyclic amine to alkylidenemalonates using a reagent amount (12.5 equiv) of the radical precursors to give Michael addition products in up to 84% yield. This represents a great improvement over the 5% yield obtained under the previously reported conditions.

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Radical chemistry has rapidly progressed in the past two decades and has become one of the most powerful tools of organic synthesis.¹ We previously reported the direct generation of carbon-centered radicals from ethers² or unfunctionalized cycloalkanes³ through C–H bond cleavage by the action of dimethylzinc⁴ and air, and their addition to imines in excellent yields. We also reported their reactions with aldehydes,⁵ arylamines, alkoxyamines, dialkylhydrazines,⁶ and α,β -unsaturated *N*-tosyl imines.⁷ Furthermore, asymmetric addition of a cyclic acetal to chiral *N*-sulfinyl imines has been achieved, providing a reasonably efficient methodology for the asymmetric synthesis of amino alcohol derivatives.⁸ Recently, we developed radical conjugate addition to alkylidenemalonates (Table 1, entry 1).^{9,10} In these radical reactions, however, more than 200 equiv of the ethers was required as radical precursors.¹¹ The reduction of the amount of a radical precursor is a challenging goal in the field of synthetic radical chemistry: to the best of our knowledge, there are only a few examples of radical addition through direct C–H bond cleavage using smaller excess amounts (e.g., 10 equiv) of radical precursors.¹² Herein, we report the promoting effect of iron salts^{13,14} on the radical addition of ethers and an amine to alkylidenemalonates mediated by dimethylzinc, which enabled the use of 12.5 equiv of radical precursors to give products in good to high yield (40–84%).

First, we investigated the reaction of THF (**2a**) with **1a** to determine the suitable conditions. Table 1 shows the effects of the amount of THF (**2a**) on the addition to benzylidenemalonate (**1a**) under the previously reported conditions.⁹ Although the reaction was fast and the yield of product **3a** was high with 250 equiv of **2a**, the yield dramatically dropped and the reaction time increased as the amount of **2a** was decreased from 250 to 100 to 50 equiv (entries 1–3). The reaction with 12.5 equiv of **2a** gave only 5% yield of Michael adduct **3a**, and malonate **1a** was recovered in 15% yield (Table 1, entry 4). In the latter two reactions, α -oxygenated adduct

4a or **6** was produced, indicating that the reaction of dimethylzinc with intermediate radical **A** (Scheme 1), generated by the addition of THF-2-yl radical to **1a**, was inefficient.

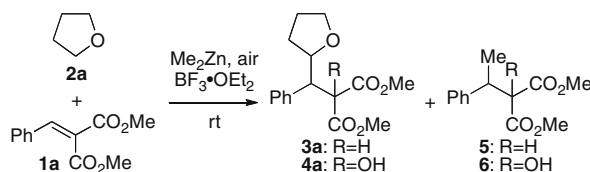
To overcome this problem, we investigated the reaction with transition metal salt as an additive. Transition metal salt would be reduced to lower oxidation state by homolytic methyl–metal bond cleavage (step **a**) following ligand exchange with dimethylzinc. We expected that the reduced metal would facilitate the reduction of **A** to the enolate of malonate (step **b**) to prevent autoxidation and a retro-Michael-type reaction of **A**.

To our delight, the addition of first-row transition metal salts, such as CrCl_3 , MnCl_2 , FeCl_3 , and CoCl_2 , drastically improved the yield of **3a** as well as the reaction rate (Table 2, entries 1–12). Copper salts only promoted the addition of the methyl group to give **5** in good yield (entries 13 and 14).¹⁵ The second-row transition metal salts were less effective (entries 15–19). When FeCl_3 or MnCl_2 was used, the formation of **4a** and **6** was significantly suppressed (entries 3 and 4). Without $\text{BF}_3 \cdot \text{OEt}_2$, the reaction became slower, giving **3a** in low yield (entry 5). Reaction without dimethylzinc failed to proceed and **1a** was recovered in 86% yield (entry 6). These results clearly demonstrate that $\text{BF}_3 \cdot \text{OEt}_2$ significantly accelerated the reaction and that the reaction required dimethylzinc to proceed, even in the presence of the iron salt. The use of other iron(III) salts, such as $\text{FeCl}_3 \cdot 6\text{H}_2\text{O}$, $\text{Fe}(\text{NO}_3)_3 \cdot 9\text{H}_2\text{O}$, and $\text{Fe}(\text{acac})_3$, was not effective (entries 9–11). Air bubbling into a reaction mixture accelerated the reaction to give **3a** in 45% yield (entry 7). Iron(II) salt gave comparable results (entry 8). Thus, among those investigated, the conditions in entries 7 and 8 were the best.

With a suitable additive FeCl_3 in hand, we turned our attention to the reaction using 4,4,5,5-tetramethyl-1,3-dioxolane (**2b**),¹⁶ where the acetal moiety of product **3b** was convertible to a hydroxymethyl group.⁹ The reaction under the conditions mentioned above with 12.5 equiv of **2b** resulted in a 31% yield of the desired adduct **3b**, along with 27% yield of **5** and 24% yield of **7** (Table 3, entry 1). We speculated as follows: The formation of **5** and **7** would indicate that the trapping of initial product **B** with

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Table 1Radical conjugate addition of THF to benzylidenemalonate^a

Entry	2a (equiv)	Me_2Zn (equiv)	Time (h)	3a (%)	4a (%)	5 (%)	6 (%)
1	250	3	1.5	86	0	3	0
2	100	6 ^b	6	72	0	10	0
3	50	6 ^b	24	36	28	13	0
4 ^c	12.5	6	24	5 ^d	0	15	26

^a The indicated amount of a hexane solution of Me_2Zn (1 M) and 1 equiv of $\text{BF}_3 \cdot \text{OEt}_2$ was used. Air, passed through a NaOH tube, was introduced into the reaction mixture through a bubbler at the rate of 0.5 L/(h mol). The isolated yields are presented.

^b Dimethylzinc (3 equiv each) was added portionwise.

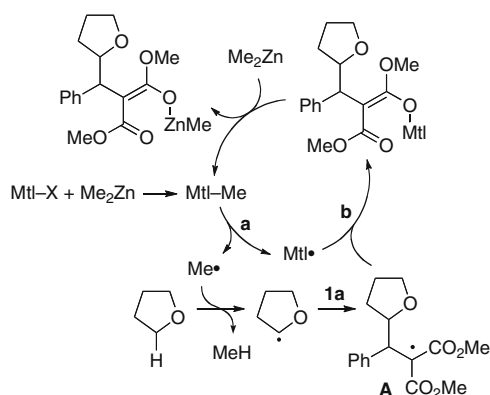
^c The reaction was conducted under ordinary atmosphere without air bubbling.

^d 15% recovery of 1a.

dimethylzinc and/or iron(II) species is inefficient so that **B** undergoes a retro-Michael-type reaction¹⁷ to give back **1a** and a dioxolan-2-yl radical. Methyl adduct intermediate **C**, whose retro-reaction is slow because of the instability of the methyl radical, undergoes coupling with dioxolan-2-yl radical under this highly concentrated condition to give **7** (Scheme 2). Accordingly, we expected that the use of zinc species bearing a ligand that forms a more stable radical than the methyl radical, such as a peroxy radical, would improve the yield of **3b** (Scheme 3). As expected, the addition of *tert*-butylhydroperoxide (TBHP), which would result in the formation of zinc peroxide,¹⁸ prevented the production of **7** (Table 3, entries 2–4).¹⁹ The use of 2 equiv of TBHP gave the best results, giving **3b** in 43% yield (entry 3).

The solvent in the above-mentioned reactions (0.50 mmol of **1a**) was a mixture of **2b** (0.9 mL) and hexane (1.5 mL) due to the use of **2b** (12.5 equiv) and dimethylzinc (3 equiv, 1 M in hexane). Another solvent (5 mL) was added to examine the effect of co-solvents in this reaction (Table 4). Reactions in non-coordinating solvents, toluene and CH_2Cl_2 , as well as coordinating solvents, DMF and CH_3CN , did not improve the yield of **3b** (entries 1–4). The use of DMSO as a co-solvent, however, significantly increased the yield of **3b** to 63%, and suppressed the formation of **5** (entry 5). Again, the necessity for dimethylzinc was clearly confirmed by the reaction under the conditions in entry 5 without dimethylzinc, which resulted in the quantitative recovery of **1a**.

The optimized conditions for the reaction of **2b** with **1a** were also applicable to radical conjugate addition involving substituted

**Scheme 1.** Expected catalytic cycle of transition metal salts.**Table 2**THF addition in the presence of transition metal salts^a

		$\xrightarrow[\text{rt}]{\text{Me}_2\text{Zn 2 equiv}, \text{BF}_3 \cdot \text{OEt}_2 \text{ 1 equiv}, \text{additive 10 mol \%}}$					
1a + 2a		3a + 4a + 5 + 6 + 1a					
12.5 eq							
Entry	Additive	Time (h)	3a (%)	4a (%)	5 (%)	6 (%)	1a (%)
1	None	24	5	0	15	26	15
2	CrCl ₃	2	31	6	45	0	0
3	MnCl ₂	2	32	0	41	0	0
4	FeCl ₃	5	31	0	53	0	0
5 ^b	FeCl ₃	24	14	13	18	10	1
6 ^c	FeCl ₃	24	0	0	0	0	86
7 ^d	FeCl ₃	2	45	0	35	0	0
8 ^d	FeCl ₂	2	43	0	30	0	0
9	FeCl ₃ ·6H ₂ O	5	38	4	27	0	0
10	Fe(NO ₃) ₃ ·9H ₂ O	24	8	0	21	4	0
11	Fe(acac) ₃	4	30	0	39	0	0
12	CoCl ₂	4	21	15	22	10	0
13	CuCl	1	Trace	0	82	0	0
14	CuCl ₂	1	Trace	0	83	0	0
15	MoCl ₃	24	10	15	24	31	15
16	RuCl ₃	24	4	11	16	3	37
17 ^e	PdCl ₂	24	5	4	14	4	10
18	RhCl ₃	24	14	0	18	12	10
19	AgCl	24	7	0	25	5	0

^a The reactions were conducted under an air atmosphere. A 1 M hexane solution of Me_2Zn was used. The isolated yields are presented.

^b Without $\text{BF}_3 \cdot \text{OEt}_2$.

^c Without Me_2Zn .

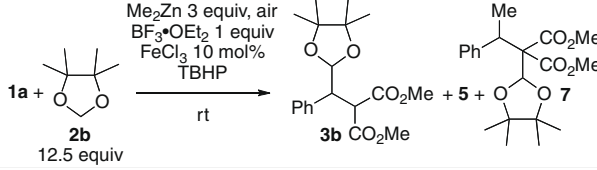
^d Air, passed through a NaOH tube, was introduced into the reaction mixture through a bubbler at a rate of 0.5 L/(h mol).

^e Epoxide of **1a** was obtained in 42% yield.

benzylidenemalonates **1**. The reactions of **1** having a chloro or methyl substituent gave adducts in 43% and 40% yield, respectively (Scheme 4). The optimized conditions, however, were not advantageous for the reaction of THF (**2a**), giving **3a** and **5** in slightly lower yields (36% and 29% yield, respectively) than those in Table 2, entry 7 (45% and 35% yield, respectively).

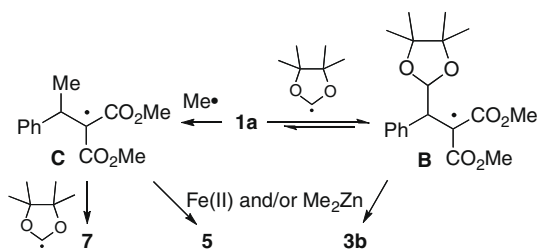
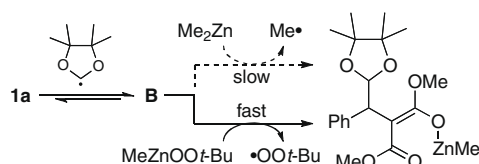
The above-mentioned conditions were applicable to the direct generation and conjugate addition of an α -aminoalkyl radical from pyrrolidine **2c**.^{20,21} The reaction of **2c** with **1a** gave the desired product **3e** in 84% yield after 8 h (Scheme 5).

The reaction of *N*-tosyl imine **8** was also accelerated by the addition of the iron salt (Scheme 6). Although the reaction with **8**

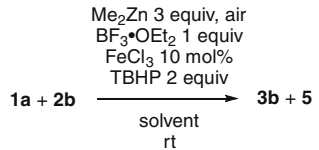
Table 3Reaction with 4,4,5,5-tetramethyldioxolane (**2b**)^a


Entry	TBHP (equiv)	Time (h)	3b (%)	5 (%)	7 (%)
1	0	0.5	31	27	24
2	1	3	32	23	0
3	2	0.5	43	31	0
4	3	3	26	15	0

^a Hexane solutions of Me₂Zn (1 M) and TBHP (4 M) were used. Air, passed through a NaOH tube, was introduced into the reaction mixture through a bubbler at a rate of 0.5 L/(h mol). The isolated yields are presented.

**Scheme 2.** Possible mechanism for the formation of **7**.**Scheme 3.** Expected fast reaction of **B** and zinc peroxide to give zinc enolate.

failed to give the desired product **9b** in DMSO with TBHP, **9b** was obtained in 53% yield after 4 h when a toluene solution of dimethylzinc was used without DMSO and TBHP. When a hexane solution of dimethylzinc was used, a significant amount of hexyl adducts (10%, a regioisomeric and diastereomeric mixture) was isolated

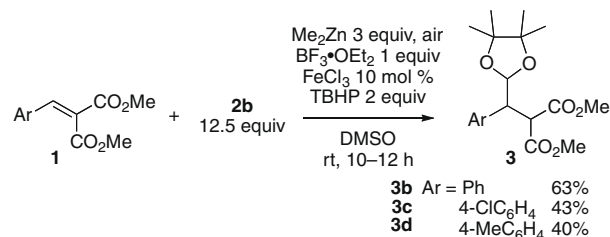
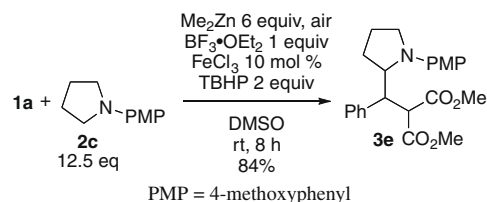
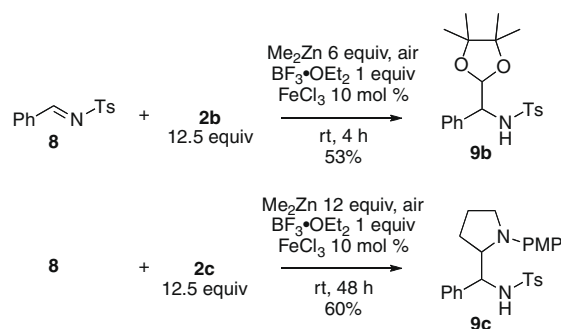
Table 4Co-solvent effect^a


Entry	Solvent	Time (h)	3b (%)	5 (%)
1	CH ₂ Cl ₂	7	39	40
2	Toluene	8	29	30
3 ^b	MeCN	12	14	11
4 ^c	DMF	24	10	10
5	DMSO	12	63	12

^a A hexane solution of TBHP (4 M) was used. Air, passed through a NaOH tube, was introduced into the reaction mixture through a bubbler at a rate of 0.5 L/(h mol). The isolated yields are presented.

^b 5% of **1a** was recovered.

^c 15% of **1a** was recovered.

**Scheme 4.** Production of **3**.**Scheme 5.** Reaction of benzylidenemalonate **1a** with pyrrolidine **2c**.**Scheme 6.** Reactions with *N*-tosyl imine **8**.

as well as **9b** (31%). The reaction of **2c** and *N*-tosyl imine **8** also gave the desired product **9c** in 60% yield.

In summary, the addition of iron salt and TBHP as well as the use of DMSO as a co-solvent is beneficial in dimethylzinc-mediated radical conjugate addition reaction of dioxolane **2b** reducing the amount of required **2b** from 250 to 12.5 equiv, while still giving the desired adduct in 63% yield. This condition was applicable to conjugate addition of the cyclic amine to give the addition product in 84% yield. Furthermore, reactions with the *N*-tosyl imine were similarly improved by the addition of iron salt.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.08.034.

References and notes

1. (a) *Radicals in Synthesis I and II*; Gansäuer, A., Ed. Topics in Current Chemistry 263 and 264; Springer-Verlag: Berlin, Heidelberg, 2006; (b) *Radicals in Organic Synthesis*; Renaud, P., Sibi, M. P., Eds.; Wiley-VCH: Weinheim, 2001; Vols. 1 and 2.
2. (a) Yamada, K.; Yamamoto, Y.; Maekawa, M.; Tomioka, K. *J. Org. Chem.* **2004**, *69*, 1531–1534; (b) Yamada, K.; Yamamoto, Y.; Tomioka, K. *Org. Lett.* **2003**, *5*, 1797–1799; (c) Yamada, K.; Fujihara, H.; Yamamoto, Y.; Miwa, Y.; Taga, T.; Tomioka, K. *Org. Lett.* **2002**, *4*, 3509–3511.
3. Yamada, K.; Yamamoto, Y.; Maekawa, M.; Chen, J.; Tomioka, K. *Tetrahedron Lett.* **2004**, *45*, 6595–6597.
4. Reviews: (a) Akindele, T.; Yamada, K.; Tomioka, K. *Acc. Chem. Res.* **2009**, *42*, 345–355; (b) Yamada, K.; Yamamoto, Y.; Tomioka, K. *J. Synth. Org. Chem. Jpn.* **2004**, *62*, 1158–1165.
5. Yamamoto, Y.; Yamada, K.; Tomioka, K. *Tetrahedron Lett.* **2004**, *45*, 795–797.
6. Yamamoto, Y.; Maekawa, M.; Akindele, T.; Yamada, K.; Tomioka, K. *Tetrahedron* **2005**, *61*, 379–384.
7. Yamada, K.; Umeki, H.; Maekawa, M.; Yamamoto, Y.; Akindele, T.; Nakano, M.; Tomioka, K. *Tetrahedron* **2008**, *64*, 7258–7265.
8. Akindele, T.; Yamamoto, Y.; Maekawa, M.; Umeki, H.; Yamada, K.; Tomioka, K. *Org. Lett.* **2006**, *8*, 5729–5732.
9. (a) Yamada, K.; Maekawa, M.; Akindele, T.; Nakano, M.; Yamamoto, Y.; Tomioka, K. *Tetrahedron* **2009**, *65*, 903–908; (b) Yamada, K.; Maekawa, M.; Akindele, T.; Nakano, M.; Yamamoto, Y.; Tomioka, K. *J. Org. Chem.* **2008**, *73*, 9535–9538.
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. *J. Org. Chem.* **2006**, *71*, 6767–6775.
11. Our efforts to reduce a radical source by using iodoalkanes: (a) Yamada, K.; Nakano, M.; Maekawa, M.; Akindele, T.; Tomioka, K. *Org. Lett.* **2008**, *10*, 3805–3808; (b) Yamada, K.; Yamamoto, Y.; Maekawa, M.; Akindele, T.; Umeki, H.; Tomioka, K. *Org. Lett.* **2006**, *8*, 87–89.
12. (a) Citterio, A.; Filippini, L. *Synthesis* **1986**, 473–474; (b) Iwahama, T.; Sakaguchi, S.; Ishii, Y. *Chem. Commun.* **2000**, 613–614; (c) Hirano, K.; Iwahama, T.; Sakaguchi, S.; Ishii, Y. *Chem. Commun.* **2000**, 2457–2458; (d) Bertrand, S.; Hoffmann, N.; Humbel, S.; Pete, J. P. *J. Org. Chem.* **2000**, *65*, 8690–8703; (e) Kim, S.; Kim, N.; Chung, W.; Cho, C. H. *Synlett* **2001**, 937–940; (f) Mosca, R.; Fagnoni, M.; Mela, M.; Albini, A. *Tetrahedron* **2001**, *57*, 10319–10328; (g) Hirano, K.; Sakaguchi, S.; Ishii, Y. *Tetrahedron Lett.* **2002**, *43*, 3617–3620; (h) Bauer, A.; Westkämper, F.; Grimme, S.; Bach, T. *Nature* **2005**, *436*, 1139–1140; (i) Dondi, D.; Cardarelli, A. M.; Fagnoni, M.; Albini, A. *Tetrahedron* **2006**, *62*, 5527–5535.
13. Review: Bolm, C.; Legros, J.; Le Pailh, J.; Zani, L. *Chem. Rev.* **2004**, *104*, 6217–6254.
14. Iron catalyzed C–C bond formation between ether and diketone or β -ketoester: Li, Z.; Yu, R.; Li, H. *Angew. Chem., Int. Ed.* **2008**, *47*, 7497–7500.
15. Copper-catalyzed conjugate addition is a well-known reaction. For examples, see: Alexakis, A.; Bäckvall, J. E.; Krause, N.; Pàmies, O.; Diéguez, M. *Chem. Rev.* **2008**, *108*, 2796–2823, and references cited therein.
16. Willy, W. E.; Binsch, G.; Eliel, E. L. *J. Am. Chem. Soc.* **1970**, *92*, 5394–5402.
17. 4,4,5,5-Tetramethyl-1,3-dioxolan-2-yl radical is more stable than THF-2-yl radical by ca. 1 kcal/mol in B3LYP/6-31G level DFT calculations. This would be the reason for a more facile retro-reaction in the reaction of 4,4,5,5-tetramethyl-1,3-dioxolane.
18. Peroxyl radical is much more stable than methyl radical based on their C–H bond dissociation energies: t -BuOO–H = 88.2 versus CH_3 –H = 105.0 in kcal/mol. Luo, Y.-R. *Handbook of Bond Dissociation Energies in Organic Compounds*; CRC Press: New York, 2003.
19. Although there is a possibility that alkoxyl radicals are generated from peroxides by the action of the iron salts, the suppressed production of **6** and **7** is not rationalized by the formation of alkoxyl radicals, which would only facilitate the generation of THF-2-yl radical and dioxolan-2-yl radical by hydrogen abstraction.
20. Wolfe, J. P.; Tomori, H.; Sadighi, J. P.; Yin, J.; Buchwald, S. L. *J. Org. Chem.* **2000**, *65*, 1158–1174.
21. Recent examples for addition of α -aminoalkyl radicals: (a) Yoshimitsu, T.; Atsumi, C.; Iimori, E.; Nagaoka, H.; Tanaka, T. *Tetrahedron Lett.* **2008**, *49*, 4473–4475; (b) Angioni, S.; Ravelli, D.; Emma, D.; Dondi, D.; Fagnoni, M.; Albini, A. *Adv. Synth. Catal.* **2008**, *350*, 2209–2214.