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A Flexible, Stereoselective Dimethylzinc-Mediated Radical-Anionic Cascade: Dramatic Influence of Additional Lewis Acids

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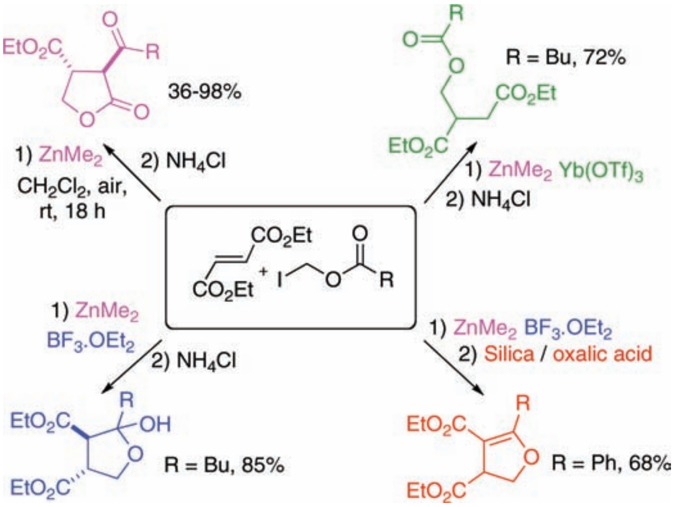
ABSTRACT



Dimethylzinc-mediated addition of acyloxymethyl radicals to diethyl fumarate led to the highly stereoselective formation of disubstituted γ-lactones in mean to good yields; this cascade provides a new example of a one-pot process mediated by dimethylzinc involving a tandem radical-anionic reaction; the chemoselectivity of the reaction was totally modified by additional Lewis acids.

In the context of tin-free radical methodology development, our group is currently investigating the synthetic potential of dialkylzincs as new tools for radical chemistry in aerobic medium.[1] Dialkylzinc-mediated alkyl radical addition to various acceptors such as C═N double bond,[2] C═C activated double bond,[3] and C≡C activated triple bond[4] have been investigated. An interesting feature of dialkylzincs resides in the possibility they offer to generate nucleophilic species from an initial radical elementary step and therefore to

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(1) For a review, see: Bazin, S.; Feray, L.; Bertrand, M. P. *Chimia* **2006**, *60*, 260.

(2) (a) Bertrand, M. P.; Feray, L.; Nouguier, R.; Perfetti, P. *Synlett* **1999**, 1148. (b) Bertrand, M. P.; Feray, L.; Nouguier, R.; Perfetti, P. *J. Org. Chem.* **1999**, *64*, 9189. (c) Bertrand, M. P.; Coantic, S.; Feray, L.; Nouguier, R.; Perfetti, P. *Tetrahedron* **2000**, *56*, 3951. (d) Bertrand, M. P.; Feray, L.; Gastaldi, S. *C. R. Chim.* **2002**, 623.

(3) (a) Bazin, S.; Feray, L.; Naubron, J.-V.; Siri, D.; Bertrand, M. P. *J. Chem. Soc., Chem. Commun.* **2002**, 2506. (b) Bazin, S.; Feray, L.; Vanthuyne, N.; Bertrand, M. P. *Tetrahedron* **2005**, *61*, 4261. (c) Bazin, S.; Feray, L.; Vanthuyne, N.; Siri, D.; Bertrand, M. P. *Tetrahedron* **2007**, *63*, 77.

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perform tandem radical-anionic reactions. Domino processes were devised to prepare in one step trisubstituted γ-lactones such as racemic nephrosteranic acid[3c] or α-alkylidene-γ-lactams.[4] Both dimethylzinc and diethylzinc were used; each reagent presents its own specificity.

The major limitation to the use of the diethylzinc/alkyl iodide couple as the alkyl radical precursor is the risk of competitive addition of ethyl radical when the radical acceptor is highly reactive. Whereas the method can be chemoselective when using secondary and tertiary alkyl iodides, it is not suited to the use of primary alkyl radicals owing to unfavorable enthalpic factors.

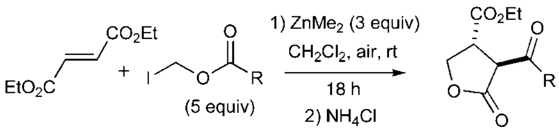
In this respect, even though the oxidation of dimethylzinc is slow compared to that of diethylzinc,[5] the use of dimethylzinc can be advantageous since methyl radical (produced during the reaction of dimethylzinc with oxygen) enables the use of a larger range of radical precursors.[6] At the same time, methyl radical is less reactive than ethyl radical with regard to most radical acceptors. Dimethylzinc was used to generate different types of functionalized primary radicals, including α-alkoxy radicals from methoxymethyl iodide[3c] and from ethers.[7] Only one example of dimethylzinc-mediated generation and addition of pivaloyloxymethyl radical (derived from the corresponding iodide **1a**) to *N*-tosylphenylimine has been reported in the literature.[8,9] The use of dimethylzinc to generate acyloxymethyl radicals from the corresponding iodides can be expanded to conjugate addition.

We report in this paper a new example of a radical-polar crossover reaction, that is, dimethylzinc-mediated γ-lactone synthesis from acyloxymethyl iodides and ethyl fumarate.[10] Through a sequence involving successively iodine atom transfer, radical addition, homolytic substitution at zinc, intramolecular acyl transfer, and lactonization, disubstituted *trans*-γ-lactones **2** were obtained stereoselectively.

Iodomethyl pivalate **1a** was prepared from commercially available chloromethyl pivalate. Iodomethyl esters **1b−e** were prepared in two steps from the corresponding acyl chloride according to a literature procedure.[11]

Optimization of the reaction of iodomethyl pivalate **1a** with ethyl fumarate (Scheme 1)[12] showed that 5 equiv of the starting iodide were needed to completely avoid the competitive addition of methyl radical. Three equivalents of dimethylzinc were necessary to reach completion, within 18 h at room temperature. Under these experimental conditions, disubstituted lactone **2a** was isolated in 98% yield.[13]

Scheme 1



1a, R = *t*-Bu	**2a**, 98%
1b, R = Ph	**2b**, 63%
1c, R = *p*-FPh	**2c**, 72%
1d, R = *p*-OMePh	**2d**, 42%
1e, R = $(CH_2)_3CH_3$	**2e**, 36%

When the reaction was mediated by diethylzinc, under the same experimental conditions, the addition of ethyl radical competed with the addition of acyloxymethyl radical even when only 1.5 equiv of diethylzinc was used.[14] It must be emphasized that dimethylzinc is the mediator of choice for this reaction that could not be performed in the presence of triethylborane.[15]

As shown in Scheme 2, the acyloxymethyl radical formed through iodine atom transfer (step 1)[16] adds to the activated double bond (step 2). The resulting α-acyloxy radical undergoes homolytic substitution at zinc leading to a zinc enolate (step 3) which evolves via intramolecular acyl transfer (step 4).[17] The resulting zinc alkoxide affords the

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(4) Feray, L.; Bertrand, M. P. *Eur. J. Org. Chem.* **2008**, 3164.

(5) Seyferth, D. *Organometallics* **2001**, *20*, 2940, and references cited therein.

(6) For a review, see: Akindele, T.; Yamada, K.-I.; Tomioka, K. *Acc. Chem. Res.* **2009**, *42*, 345.

(7) (a) Yamada, K.-I.; Fujihara, H.; Yamamoto, Y.; Miwa, Y.; Taga, T.; Tomioka, K. *Org. Lett.* **2002**, *4*, 3509. (b) Yamada, K.-I.; Yamamoto, Y.; Tomioka, K. *Org. Lett.* **2003**, *5*, 1797. (c) Yamamoto, Y.; Maekawa, M.; Akindele, T.; Yamada, K.-I.; Tomioka, K. *Tetrahedron* **2005**, *61*, 379. (d) Akindele, T.; Yamamoto, Y.; Maekawa, M.; Umeki, H.; Yamada, K.-I.; Tomioka, K. *Org. Lett.* **2005**, *8*, 5729. For dimethylzinc-mediated direct aminoalkylation of cycloalkanes, see: (e) Yamada, K.-I.; Yamamoto, Y.; Maekawa, M.; Chen, J.; Tomioka, K. *Tetrahedron Lett.* **2004**, *45*, 6595.

(8) Yamada, K.-I.; Nakano, M.; Maekawa, M.; Akindele, T.; Tomioka, K. *Org. Lett.* **2008**, *10*, 3805.

(9) In Tomioka's article, triethylborane was preferred to dimethylzinc to achieve radical additions of acyloxymethyl radicals derived from **1a** and **1b** to *N*-tosylimines; see ref 8.

(10) Acrylic esters are by far less reactive and more sensitive to polymerization than fumaric esters. They led to polymeric materials or to moderate yields in oxidized adducts depending on the nature of the Lewis acid.

(11) (a) Iyer, R. P.; Yu, D.; Ho, N.-H.; Agrawal, S. *Synth. Commun.* **1995**, *25*, 2739. (b) Charette, A. B.; Beauchemin, A.; Francoeur, S. *J. Am. Chem. Soc.* **2001**, *123*, 8139.

(12) The reaction was tested also with chloromethyl pivalate. No evolution was observed in this case.

(13) A typical procedure: To a solution of ethyl fumarate (100 mL, 0.61 mmol) 0.3 M in dichloromethane was added at room temperature 5 equiv of iodomethyl pivalate (**1a**) (740 mg, 3.05 mmol) under an argon atmosphere. Dimethylzinc (3 equiv, 1.8 mL, 1 M in heptane) was then added, whereas air was introduced in the reaction mixture through a syringe pump (40 mL for 2 h). After being stirred for 18 h at room temperature, the reaction was quenched with saturated NH_4Cl. The layers were separated, and the aqueous layer was extracted twice with CH_2Cl_2. The combined organic phases were dried ($MgSO_4$), filtered, and concentrated in vacuo. Flash column chromatography on silica gel using pentane/diethyl ether as eluent afforded 4-(2,2-dimethyl-propionyl)-5-oxo-tetrahydrofuran-3-carboxylic acid ethyl ester (**2a**) in 98% (148 mg, 0,60 mmol, 92:8 mixture of isomers). ^1H NMR ($CDCl_3$, 300 MHz): d 1.27 (s, 9H), 1.29 (t, $J = 7.2$, 3H), 3.85 (dt, $J = 8.7$, 7.6, 1H), 4.22 (q, $J = 7.2$, 2H), 4.42 (dd, $J = 7.4$, 9.1, 1H), 4.5 (d, $J = 7.9$, 1H), 4.65 (t, $J = 9.1$, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz): d 14.4 (CH_3), 26.2 (CH_3), 45.2 (CH), 45.8 (C), 49.7 (CH), 62.4 (CH_2), 68.2 (CH_2), 170.5 (C═O), 171.8 (C═O), 209.0 (C═O). HRMS calcd for $C_{12}H_{19}O_5$ [MH^+]: 243.1227, found 243.1227.

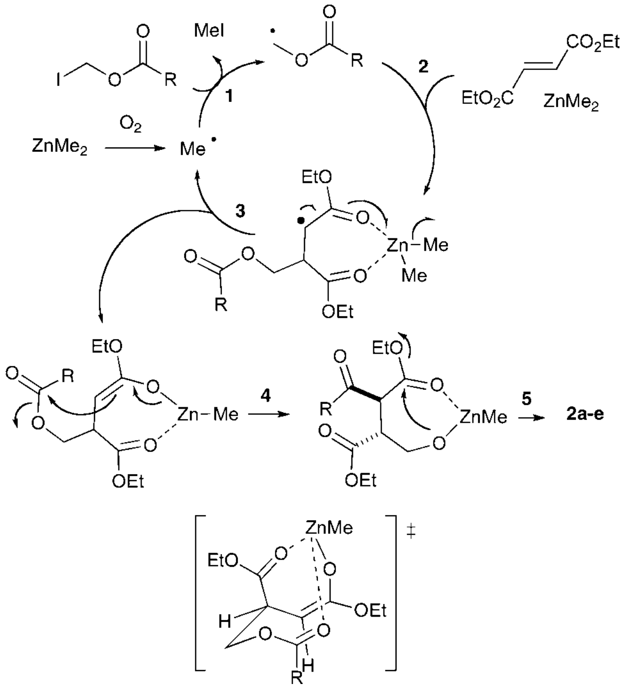
(14) The adduct of ethyl radical was detected with lactone **2a** in a 24:76 NMR ratio.

(15) Reactions were carried out with and without $Et_2O{\cdot}BF_3$. None of these experiments led to any lactone or lactol, only telomeric material was detected from the ^1H NMR spectra of the crude mixture. This result was not surprizing since α-alkoxycarbonyl radicals are known not to undergo homolytic substitution at boron, see: Ollivier, C.; Renaud, P. *Chem. Rev.* **2001**, *101*, 3415.

(16) The intermediacy of bis(pivaloyloxymethyl)zinc, formed through zinc-iodine exchange in the first step, can be ruled out since irradiation was shown to be required to preform this intermediate; see ref 11b.

disubstituted γ-lactone through intramolecular nucleophilic substitution at the ester group (step 5).

Scheme 2. Proposed Mechanism

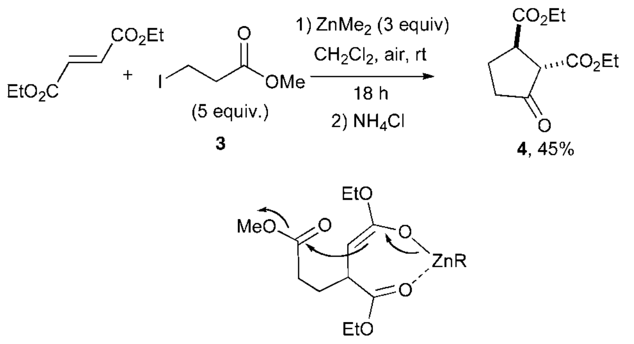


The formation of a seven-membered chelated enolate that fixes the ethoxycarbonyl substituant in the axial position is likely to explain the trans stereoselectivity of the reaction (Scheme 2).[18] Additional activation of the acyl transfer upon zinc tetracoordination can also be envisaged. Moreover, the carbon atom in α position relative to the two carbonyl groups is highly epimerizable, and deprotonation by zinc alkoxides formed in the reaction medium could not be ruled out at this stage.

This mechanism was supported by the experiment conducted on diethyl fumarate in the presence of 5 equiv of iodoester **3** and 3 equiv of dimethylzinc that led to cyclopentanone **4** via Dieckmann cyclization. Ketone **4** was isolated in 45% yield as a single stereoisomer that we assumed to be trans (Scheme 3).

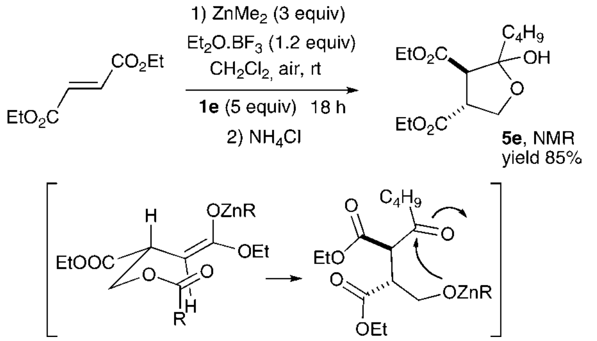
Iodomethyl benzoates **1b**−**d** proved also to be good radical precursors provided that the substituent on the aromatic group was electron-withdrawing (Scheme 1). The presence of the fluorine atom on the aromatic ring in **1c** enhances the electrophilicity of the carbonyl group and favors the transfer of the acyl group in step 4 (Scheme 2). Lactone **2c** was isolated in 72% yield. Conversely, iodomethyl *p*-methoxybenzoate **1d** led to the expected lactone in only 42% yield. When the reaction was conducted with iodide **1e**, the desired lactone was also formed in modest yield.[19]

Scheme 3



It is to be noted that all the reactions were highly stereoselective and led to trans lactones **2b**−**f**.[20] The presence of trace amounts of the cis diastereomers could only be suspected from the proton NMR spectra of the crude mixtures; none could be isolated or fully characterized.[21]

Scheme 4



The introduction of a stronger Lewis acid, i.e., BF_3•OEt_2, with the prospect of activating the acyl group transfer, and consequently to increase the yield in lactone **2**, resulted in a

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(17) A mechanism involving intramolecular acyl group transfer has been proposed recently for the bis(iodozincio)methane mediated 1,3-diketone synthesis, see: Sada, M.; Matsubara, S. *J. Am. Chem. Soc.* **2010**, *132*, 432.

(18) Such an intermediate has already been proposed to explain the formation of the major stereoisomer in diethylzinc-mediated radical-polar cascade leading to trisubstituted lactones; see ref 3b,c. For their involvement in the syn selective aldol consensation of zinc enolates, see also: Lai, S.; Zercher, C. K.; Jasinski, J. P.; Reid, S. N.; Staples, R. J. *Org. Lett.* **2001**, *3*, 4169.

(19) In this case, the adduct of α-acyloxy radical, resulting from the hydrolysis of the corresponding zinc enolate intermediate before the acyl group transfer has occurred, was isolated in a 1:1 ratio with **2e** while the starting material was recovered in 30% yield.

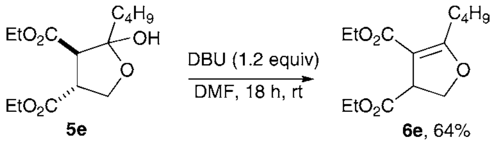
(20) In order to determine which stereoisomer of the lactone **2** was formed during the process, epimerization reactions were conducted on lactones **2c** and **2e** in the presence of 1.2 equiv of DBU in DMF (0.1 M). After one night, no evolution was observed in both cases. This strongly suggested that the starting lactones were already in the most stable trans configuration. In addition, the coupling constants between H2 and H3 in lactones **2b**−**e** were close to 6.8 Hz, and this is in agreement with a trans relationship, see: (a) Yamauchi, S.; Sugahara, T.; Nakashima, Y.; Okada, A.; Akiyama, K.; Kishida, T.; Maruyama, M.; Masuda, T. *Biosci. Biotechnol. Biochem.* **2006**, *70*, 1934. (b) Bennett, S. A.; Rickards, R. W. *Tetrahedron Lett.* **2003**, *44*, 6927.

(21) The presence in trace amount of the cis isomer could not be ascertained. A doublet (J = 8−9 Hz) was detected in the proton NMR spectra of the crude mixtures. However, no evolution of the spectra was observed when either **2c** or **2e** was treated with DBU.

complete change in the chemoselectivity of the reaction. It may be envisaged that BF_3 inhibits the chelation of the ethoxycarbonyl group which adopts preferentially an equatorial position in the transition state of the acyl group transfer. In such a situation, severe steric interactions in the eclipsed conformation prevent the formation of the *cis*-lactone, and only lactol **5e** was detected in the crude mixture instead. The absence of any *trans*-**2e** in the crude mixture, which also contains zinc alkoxides in excess, argues against the zinc alkoxide promoted formation of the latter through epimerization of any *cis*-**2e**.

Lactol **5e** was isolated in 60% yield after purification on silica gel (Scheme 4).[22] Treating the crude mixture with DBU did not lead to any epimerization susceptible to induce the formation of lactone **2e**. The only product was dihydrofuran **6e**, isolated in 64% yield (Scheme 5).

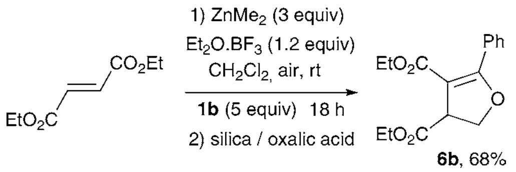
Scheme 5



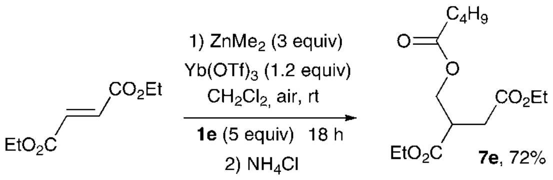
An improved experimental protocol in which both hydrolysis and dehydration were achieved during workup is described in Scheme 6; **6b** was directly isolated in 68% yield.

The outcome of the reaction was changed upon addition of 1.2 equiv of $Yb(OTf)_3$. In this case, the acyl group transfer was suppressed, and only the adduct of acyloxymethyl radical was isolated in 72% yield from **1e** (Scheme 7).

Scheme 6



Scheme 7



In conclusion, this paper describes a new tandem radical-anionic reaction mediated by dimethylzinc. The use of iodomethyl esters as radical precursors was extended to fumaric ester radical acceptors. The reaction resulted in a straightforward stereoselective synthesis of trans 2,3-disubstituted γ-lactones. The addition of monodentate or polydentate Lewis acids resulted in a dramatic change in the chemoselectivity of the reaction.

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Supporting Information Available: Experimental procedures 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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[22] During purification on silica gel, lactol **5e** was partially dehydrated and degraded. Therefore, the signals of impurities appeared in the corresponding NMR spectra. This is the reason why complete transformation into **6e** was preferred before purification.