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Dimethylzinc-Mediated, Oxidatively Promoted Reformatsky Reaction of Ethyl Iodoacetate with Aldehydes and Ketones

Pier Giorgio Cozzi,[a,*] Alessandro Mignogna,[a] and Paola Vicennati[a]

[a] Dipartimento di Chimica "G. Ciamician", Università di Bologna, Via Selmi 2, 40126 Bologna, Italy
Fax: (+39)-051-209-9456; e-mail: piergiorgiogcozzi@.unibo.it

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Dedicated to Professor Andreas Pfaltz on the occasion of his 60th birthday.

Supporting information for this article is available on the WWW under http://asc.wiley-vch.de/home/.

Abstract: A practical and general Reformatsky reaction, promoted by oxidants and mediated by dimethylzinc, is described. The reaction is fast and runs at 0 °C with aldehydes and ketones, under mild reaction conditions. Preliminary results obtained for the enantioselective version show that inexpensive chiral amino alcohols could be used in the challenging formation of enantioenriched quaternary stereogenic centers.

Keywords: aldehydes; dimethylzinc; enantioselective; ephedrine; ketones; Reformatsky reaction

The Reformatsky reaction[1] represents a valuable tool for the synthetic chemist as it allows the facile addition of zinc enolates to aldehydes, ketones, or imines.[2] In general the reaction is heterogeneous, and efficient methodology has been introduced for the activation of the zinc. A great advance in the Reformatsky-type reaction was realized by Honda[3] and Adrian[4] who have suggested using Me_2Zn and transition metals (Rh, Ni) for the homogeneous preparation of zinc enolates. On the other hand, zinc enolates could be obtained by transmetallation of Et_2Zn[5] and i-Pr_2Zn[6] with iodoacetate, or by the reaction of a silyl-enolate with ZnF_2.[7] In addition, many other metals have been considered in the Reformatsky-type reaction, and the corresponding enolates have been formed *via* transmetallation with alkylmetals or by the use of the metal in low oxidation state.[1,2] Recently, we have shown that an enantioselective Reformatsky reaction in the presence of a catalytic amount of metal complexes[8] or ligands,[9] could be effectively realized with a simple concept: performing the trasmetallation reaction between iodoacetate and Me_2Zn in the presence of a chiral ligand able to control the mild formation of the enolate and its successive reaction with electrophiles. In this contribution, we report a practical and straightforward formation of zinc enolates promoted by air, their effective use in Reformatsky reactions with aldehydes and ketones, and preliminary results towards the development of the corresponding enantioselective variants.

The addition of Me_2Zn to aldehydes is scarcely developed, due to the lower reactivity of Me_2Zn that is well documented in the literature.[10] Following our studies in imino-Reformatsky reactions, we have discovered that the transmetallation of iodoacetate and Me_2Zn is accelerated by the presence of air,[9] through a cycle in which Me_2Zn is acting as a source of Me radicals, and as a source of zinc (Figure 1).

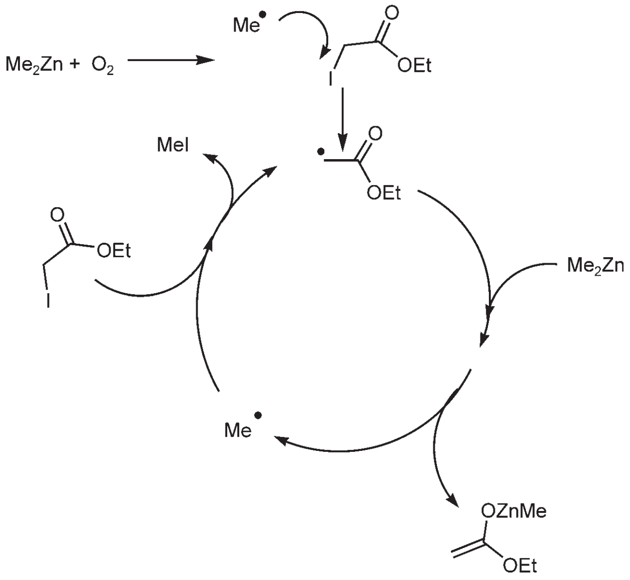
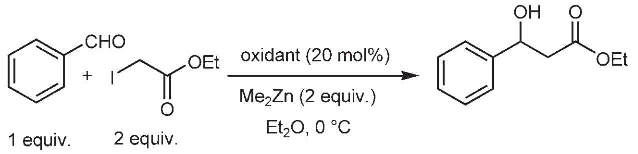


Figure 1. Proposed catalytic cycle for the oxidatively promoted Reformatsky reactions.



Scheme 1. Model reaction performed with benzaldehyde in the presence of different oxidants.

Table 1. Oxidatively promoted Reformatsky reaction with benzaldehyde.

Entry[a]	Oxidant	Yield[b] [%]
1	air	88
2	H_2O_2/Urea	73
3	*t*-BuOOH[c]	91
4	DDQ	20
5	$Fe^+Cp_2BF_4^-$	89
6	Oxone	40
7	$PhI(OAc)_2$	61
8	PhI=O	33
9	CAN	91

[a] All the reactions were carried out in anhydrous Et_2O on a 0.2 mmol scale at 0 °C for 4 h employing 2 equiv. of Me_2Zn (commercially available 2 M solution in toluene) and 20 mol% of the oxidant. In the case of entry 1, air was allowed to enter in the reaction flask *via* a $CaCl_2$ drying tube.

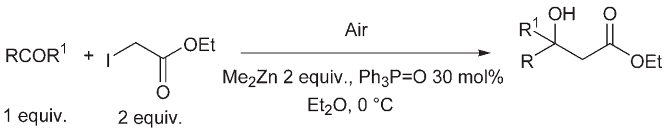
[b] Isolated yield after chromatographic purification.

[c] A commercially available 5–6 M solution of *t*-BuOOH in decane was used for the reaction.

For this reason, we have investigated, with a model reaction (Scheme 1, Table 1), whether oxidizing agents were able to accelerate the iodo-zinc exchange, making our reaction conditions suitable for the addition of zinc enolate to carbonyls. Benzaldehyde (1 equiv.), ethyl iodoacetate (2 equiv.) and Me_2Zn (2 equiv.) were reacted in a flask in diethyl ether at 0 °C in the presence of many different oxidants.

In general, good isolated yields were obtained with *t*-BuOOH, air[11] and CAN (cerium ammonium nitrate). No by-products derived from the addition of Me_2Zn to aldehyde were detected. From the point of view of the simplicity of the reaction, opening the reaction to the air represents an effective and economic methodology for promoting the homogeneous Reformatsky reaction, as nickel or rhodium metal complexes are absent. Therefore, these reaction conditions were tested with a variety of aromatic, heterocyclic, and aliphatic aldehydes. However, we found quite a slow reaction with electron-rich aromatic aldehydes, and, in order to accelerate the reaction and improve yields, we studied the model reaction in the presence of different additives. As suggested by the work of Shibasaki[12], $Ph_3P{=}O$ and $Ph_3P{=}S$ are suitable additives for reactions conducted in the presence of zinc reagents. In fact, we found the admission of 30 mol% of $Ph_3P{=}O$ in the reaction mixture considerably accelerates the Reformatsky reaction (Scheme 2, Table 2).

Two general protocols were investigated, and allowed good to excellent yields to be obtained in 2 h at 0 °C (Table 1). For non-enolizable aldehydes the addition of the carbonyl substrate was performed after 30–40 min from the mixing at 0 °C of iodoacetate and Me_2Zn, connecting the reaction flask to air



Scheme 2. Reformatsky reaction promoted by air.

Table 2. Me_2Zn-mediated Reformatsky reaction promoted by air, with different aldehydes and ketones.

Entry[a]	$RCOR^1$	Yield [%][b]
1	PhCHO	94
2	FerrocenylCHO	90
3	$4\text{-}MeOC_6H_4CHO$	90
4[c]	$4\text{-}BrC_6H_4CHO$	77
5[c]	$3\text{-}BrC_6H_4CHO$	77
6	$2\text{-}IC_6H_4CHO$	92
7	$4\text{-}PhC_6H_4CHO$	89
8	$4\text{-}MeC_6H_4CHO$	98
9[c]	FurfuralCHO	98
10[c]	2-ThiopheneCHO	93
11[c]	3-ThiopheneCHO	92
12[c]	(*E*)-PhCH=CHCHO	77
13[c,d]	*n*-$C_8H_{17}CHO$	95
14[d]	CyclohexylCHO	90
15[d]	*t*-ButylCHO	66
16[d]	$PhCOCH_3$	95
17[d]	$PhCOCH_2Br$	97
18[d]	$4\text{-}ClPhCOCH_2Cl$	92
19[d]	$(CH_3)_2C{=}CHCH_2CH_2COCH_3$	93
20[d]	$PhCH_2CH_2COCH_3$	80

[a] All the reactions were performed at 0 °C , on a 0.2–0.3 mmol scale for 2 h following the procedure A (Me_2Zn mixed with iodoacetate in Et_2O and air allowed to enter in the reaction flask at room temperature, followed after 30 min by the addition of the carbonyl substrates at 0 °C; see Supporting Information for further details), and employing 30 mol% of $Ph_3P{=}O$ as the additive.

[b] Isolated yield after chromatographic purification

[c] Three equivalents of Me_2Zn and three equivalents of iodoacetate were used in the reaction.

[d] The reaction was carried out employing procedure B (which consists of the rapid and consecutive addition of all the reagents at 0 °C; see Supporting Information for further details).

(Method A, see Supporting Information for details). Instead, in Method B, all reagents are added consecutively in the reaction flask. This method is more appropriate for aliphatic enolizable aldehydes and ketones, and avoids the formation of by-products derived from the enolization of the carbonyl and their successive reaction with themselves. Not only does the addition of $Ph_3P{=}O$ shorten the reactions, but it permits the use of the rather unreactive and challenging ketones with our reaction conditions.[8]

We have also evaluated the possibility of performing an oxidative catalytic enantioselective Reformatsky reaction, by adding a chiral ligand in a catalytic amount. The lower reactivity of Me_2Zn,[13] compared to i-Pr_2Zn, and the controlled transmetallation, are key points for these enantioselective variants. After an extensive evaluation of chiral amino alcohols as ligands, and of the reaction conditions, (see Supporting Information for details), we performed the reactions with benzaldehyde and acetophenone between 0 and −25 °C, stirring the reaction mixture in the presence of 25 mol% of (1*R*,2*S*)-*N*-pyrrolidinylephedrine (Scheme 3).

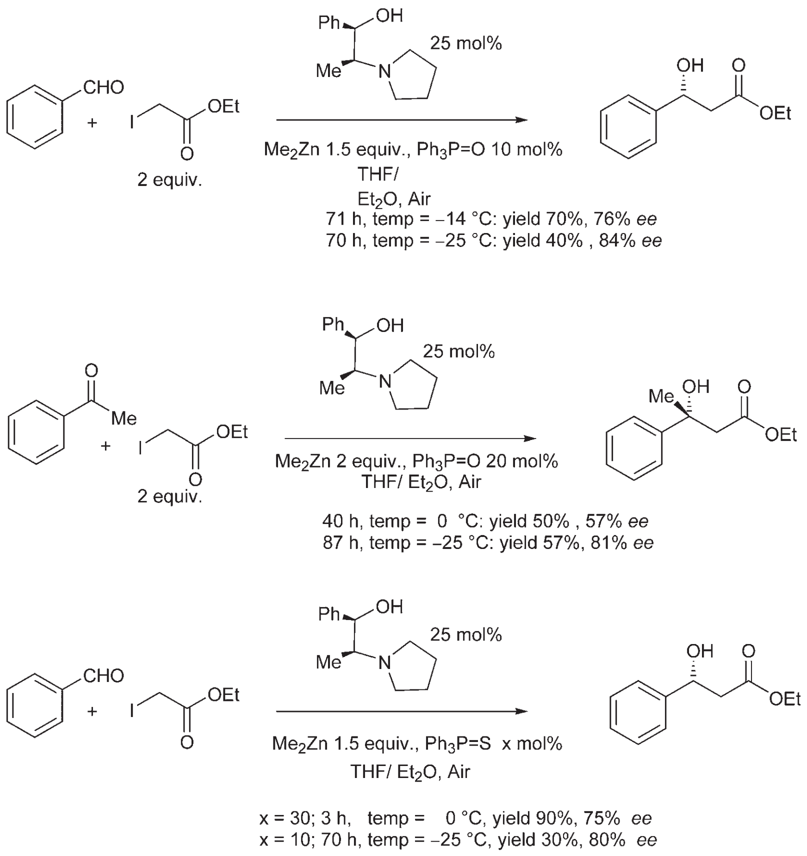
The desired products were isolated in moderate to good yields, and in good enantiomeric excesses.[13] Particularly promising appear to be the results obtained with acetophenone, which indicate that, with a fine tuning of the amino alcohol ligand and of the reaction conditions, it will be possible to achieve a straightforward access to enantioenriched quaternary stereogenic centers.[14] Work towards these goals is presently in progress in our laboratory.

To summarize, we have developed a simple, direct and effective Reformatsky reaction mediated by Me_2Zn and promoted by air, with aldehydes and ketones employing commercially available reagents. The enantioselective variant of these reactions looks quite promising, allowing the simple addition of acetate for solving difficult synthetic problems using inexpensive and commercially available amino alcohols as chiral ligands.[15] The facility of execution makes this reaction adapt to became a benchmark reaction for the evaluation of newly synthesized chiral amino alcohols for asymmetric catalysis.

Experimental Section

Method B (for Enolizable Aldehydes and Ketones)

A flame-dried, 25-mL, two-necked, round-bottom flask, equipped with magnetic stirring bar and nitrogen inlet was



Scheme 3. Examples of catalytic enantioselective Reformatsky reaction performed with 25 mol% of pyrrolidinylephedrine with PhCHO and $PhCOCH_3$.

charged with Et_2O (3 mL), THF (2 mL), Me_2Zn (150 μL, 1,5 equiv.) The mixture was then cooled to 0 °C in an ice-water bath and aldehyde or ketone (0.2 mmol), ethyl iodoacetate (50 μL, 0.4 mmol, 2 equiv.) and Ph_3PO (20 mol%, 11.2 mg) were added in sequence. The flask was connected to air through a calcium chloride drying tube and the mixture was stirred for 24 h, then quenched with 1 N HCl and diluted with Et_2O. The phases were separated, and the aqueous phase was extracted with Et_2O (3×3 mL). The organic phases were reunited, dried over Na_2SO_4 and evaporated under reduced pressure to give a pale yellow pale oil that was purified by chromatography (Et_2O:cyclohexane).

Acknowledgements

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