

Me₂Zn mediated, *tert*-butylhydroperoxide promoted, catalytic enantioselective Reformatsky reaction with aldehydes†

Pier Giorgio Cozzi,* Fides Benfatti, Montse Guiteras Capdevila and Alessandro Mignogna

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A practical and highly enantioselective catalytic Reformatsky reaction with aldehydes using a cheap, commercially available aminoalcohol as ligand is described.

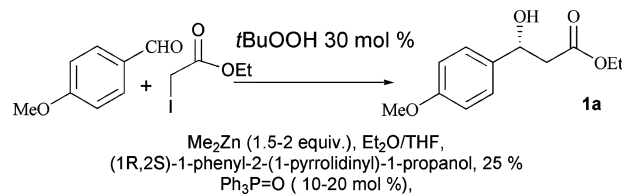
The classical Reformatsky reaction,¹ which consists of the zinc-induced formation of β-hydroxy derivatives by the reaction of α-halogenated carbonyl compounds with aldehydes or ketones, represents a formidable synthetic tool. Recently, we have described the first catalytic enantioselective Reformatsky reactions of Me₂Zn and iodoacetate, with ketones in the presence of a catalytic amount of CIMn(salen) (20 mol%),² or with imines in the presence of a catalytic amount of *N*-methylphedrine (20–30 mol%)^{3a} as the chiral ligand. Feringa and co-workers have developed the first catalytic enantioselective Reformatsky reaction with aldehydes, by the use of Me₂Zn/air and iodoacetate, in the presence of 20 mol% of 3,3'-trimethylsilylBINOL derivative as the chiral catalyst.⁴ This interesting procedure suffered from the fact that 8 equiv. of Me₂Zn were necessary for achieving good yields and enantioselectivities. Herein, we report that activation towards a faster halogen–zinc exchange can be realized, with a catalytic amount of *t*BuOOH as promoter, and by using inexpensive, commercially available (1*R*,2*S*)-1-phenyl-2-(1-pyrrolidinyl)-1-propanol (*N*-pyrrolidinylnorephedrine) as the chiral ligand, just with 2 equivalent of Me₂Zn, from good to very high enantioselectivities can be obtained in the Reformatsky reaction with aldehydes. Following our studies in imino-Reformatsky reactions, we have discovered that the metallation of iodoacetate by Me₂Zn is accelerated by the presence of air,³ through a cycle in which Me₂Zn is acting as a source of the Me radicals, and as a source of zinc. Therefore, we have investigated, with a model reaction, whether aminoalcohols were suitable ligands for a catalytic enantioselective addition of zinc enolate to aldehydes. After an extensive evaluation of chiral aminoalcohols as ligands, we performed the reactions with benzaldehyde under air, between 0 and –25 °C, stirring the reaction mixture in the presence of 25 mol% of (1*R*,2*S*)-1-phenyl-2-(1-pyrrolidinyl)-1-propanol and encouraging preliminary results were obtained for the corresponding enantioselective variant.⁵ Unfortunately, the scope of the reaction was quite limited as electron-rich aromatic aldehydes were rather unreactive, when the reaction was performed at –25 °C. The

enantiomeric excess was only moderate (50–70% ee) performing the reaction at higher temperature. We recognized that these difficulties were related to the generation of the radical cycle with oxygen. As when *t*Bu₂Zn is reacted with oxygen the unstable *t*BuZnOO*t*Bu is formed,⁶ we reasoned that using homogeneous conditions and adding a solution of *t*BuOOH as promoter, we could favour the establishment of a radical catalytic cycle at lower temperature.

Therefore, by selecting the electron-rich *p*MeOPhCHO as model substrate, we have carefully studied the reaction conditions of the catalytic Reformatsky reaction, as illustrated in Table 1. The enantiomeric excess of the model reaction is a function of the equivalents of Me₂Zn used, and of the temperature, and this is due to background reaction. In order to accelerate the reaction, Ph₃P=O was found to be a suitable additive, particularly when the reaction was operating at low temperature.^{5,7} The scope of the reaction was investigated with different aldehydes, as illustrated in Table 2.

In general, good ee and from moderate to good yields were obtained with electron-rich or -poor aromatic aldehydes. No by-products were detected by GC or NMR. Ferrocenyl aldehyde gave modest ee due its low solubility at –25 °C. Aliphatic aldehydes gave, in the examined reaction conditions, low yields due to formation of by-products derived from enolization of the aldehydes. In order to further accelerate the reaction, and avoid the formation of by-products, we found that the contemporary use of *t*BuOOH and air was necessary; however very low enantioselectivity was still

Table 1 Model reaction performed with *p*-MeOPhCHO



<i>T</i> /°C	<i>t</i> /h	Me ₂ Zn (eq.) ^a	Ph ₃ PO (mol%)	Yield ^b (%)	Ee ^c (%)
0	5	2	10	42	71
0	31	1.5	10	29	73
0	5	2	10	42	64
0	5	2	20	49	72
0	5	2	20	51	60
–25	127	2	20	54	81

^a All the reactions were performed in an Et₂O–THF (3 : 2) mixture at the indicated temperature, for the indicated time. ^b Yield of isolated product after chromatographic purification. ^c Determined by chiral HPLC (see ESI† for details).

Dipartimento di Chimica “G. Ciamician” ALMA MATER
STUDIORUM, Università di Bologna, Bologna, Italy.
E-mail: piergiorgio.cozzi@unibo.it; Fax: +39 051 2099456;
Tel: +39 051 2099456

† Electronic supplementary information (ESI) available: Typical experimental procedure and analytical data for compounds **1a–1p**. See DOI: 10.1039/b805197f

Table 2 Scope of the Reformatsky reaction

Entry ^a	R	Product	Yield ^b (%)	Ee ^c (%)
1	2-Thienyl	1b	80	77
2 ^d	Phenyl	1c	70	40
3	2-Iodophenyl	1d	60	60
4	4-Phenylphenyl	1e	90	80
5	4-Bromophenyl	1f	40	84
6	4-Methylphenyl	1g	53	81
7 ^e	Ferrocenyl	1h	88	40
8 ^f	<i>n</i> -Nonyl	1i	65	11
9	<i>tert</i> -Butyl	1j	50	93
10 ^f	Cyclohexylallyl	1k	30	50
11 ^f	Dimethylphenyl	1l	40	43
12 ^f	Dimethylallyl	1m	57	52
13 ^f	Dimethylbenzyl	1n	60	54
14 ^f	2-Methyl-3-oxo-2-butyl	1o	40	52
15 ^f	2-Methyl-3-oxo-2-pentyl	1p	40	40

^a All the reactions were performed at $-25\text{ }^{\circ}\text{C}$ for 100–120 h. ^b Yield of isolated product after chromatographic purification. ^c Determined by chiral GC, HPLC or NMR analysis (see ESI† for details). Absolute configurations of products were established based on rotation values; see ref. 4. ^d Reaction performed at $-35\text{ }^{\circ}\text{C}$ using 1 mL of Et_2O as the reaction solvent. ^e Reaction performed at $0\text{ }^{\circ}\text{C}$. ^f Reaction performed at $0\text{ }^{\circ}\text{C}$, with 30 mol% of *t*BuOOH and air, introduced by a CaCl_2 drying tube.

observed (entry 8). With pivalaldehyde 93% ee was obtained. Other hindered aldehydes were prepared⁸ (see ESI†) and tested in the reaction (entries 10–15). With these hindered aldehydes the optimal reaction conditions consisted in the use of *t*BuOOH/air at $0\text{ }^{\circ}\text{C}$. Lower reaction temperature, or the use of *t*BuOOH without air, gave low conversions. Selective reactions are possible with our Reformatsky conditions. In fact, the aldehydes 2,2-dimethyl-3-oxobutanal (Table 2, entry 14), and 2,2-dimethyl-3-oxopentanal (Table 2, entry 15), starting compounds used in the total synthesis of epothilones,⁹ were submitted to our reaction conditions, and in the reaction

with iodoacetate the corresponding products were isolated with ee of 52 and 40%, respectively. No by-products derived from addition of Me_2Zn to aldehyde or ketone, nor by-products generated by the addition of enolate to ketones were detected by GC-MS analysis performed on the crude reaction mixture. To summarize, we have developed a practical and high enantioselective catalytic Reformatsky reaction with aldehydes. Further studies in order to improve the enantiomeric excess with linear aliphatic aldehydes are in progress in our laboratory.

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