Me_2Zn mediated, *tert*-butylhydroperoxide promoted, catalytic enantioselective Reformatsky reaction with aldehydes†

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Received (in Cambridge, UK) 27th March 2008, Accepted 22nd April 2008
First published as an Advance Article on the web 27th May 2008
DOI: 10.1039/b805197f

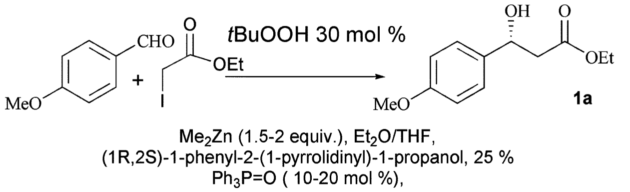
A practical and highly enantioselective catalytic Reformatsky reaction with aldehydes using a cheap, commercially available aminoalcohol as ligand is described.

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 Me_2Zn and iodoacetate, with ketones in the presence of a catalytic amount of ClMn(salen) (20 mol%),[2] or with imines in the presence of a catalytic amount of *N*-methylephedrine (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 Me_2Zn/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 Me_2Zn 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 Me_2Zn, 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 Me_2Zn is accelerated by the presence of air,[3] through a cycle in which Me_2Zn 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 tBu_2Zn 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 Me_2Zn used, and of the temperature, and this is due to background reaction. In order to accelerate the reaction, $Ph_3P{=}O$ 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



T/°C	*t*/h	Me_2Zn (eq.)[a]	Ph_3PO (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 Et_2O–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).

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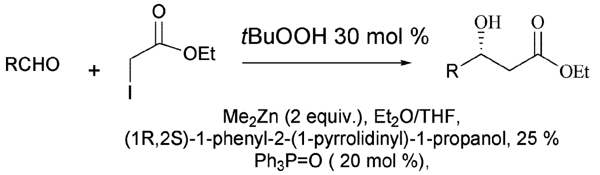
† Electronic supplementary information (ESI) available: Typical experimental procedure and analytical data for compounds **1a–1p**. See DOI: 10.1039/b805197f

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]	*n*-Nonyl	**1i**	65	11
9	*tert*-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 °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 °C using 1 mL of Et_2O as the reaction solvent. [e] Reaction performed at 0 °C. [f] Reaction performed at 0 °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 prepared[8] (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 °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.

This work was supported by PRIN 2005 (Progetto Nazionale: Sintesi e Stereocontrollo di Molecole Organiche per lo Sviluppo di Metodologie Innovative di Interesse Applicativo). Financial support form European Community (IBAAC project) is acknowledged for a fellowship to M. G. C. Antonio Zanotti Gerosa and Johnson Matthey Catalysis are acknowledged for the generous gift of chemicals.

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