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

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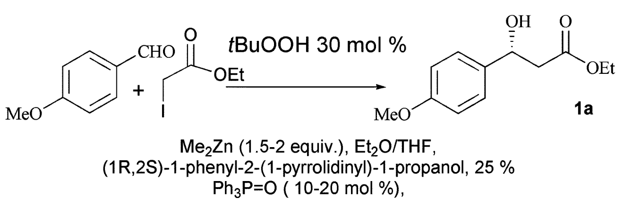
A practical and highly enantioselective catalytic Reformatsky reaction with aldehydes using a cheap, commercially available aminoalcohol as ligand is described.

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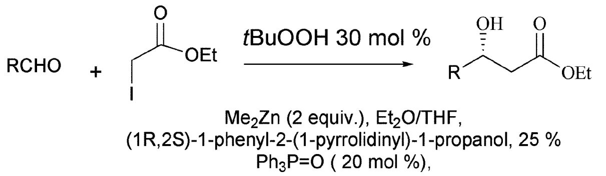
† Electronic supplementary information (ESI) available: Typical experimental procedure and analytical data for compounds **1a–1p**. See DOI: 10.1039/b805197f

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.

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