Pergamon

Tetrahedron, Vol. 53, No. 17, pp. 6065-6072, 1997

0040-4020/97 $17.00 + 0.00

PII: S0040-4020(97)00267-6

The Asymmetric Reformatsky Reaction: an NMR Investigation about the Nature of some Organozinc Reaction Species

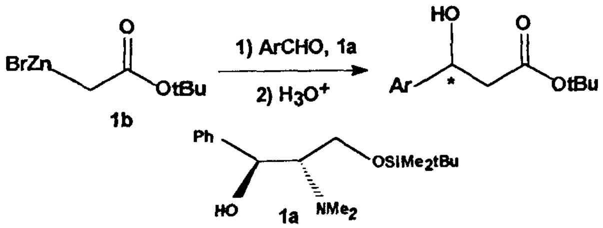
Dario PINI, Gloria UCCELLO-BARRETTA, Alberto MASTANTUONO and Piero SALVADORI*

Centro di Studio del CNR per le Macromolecole Stereordinate ed Otticamente Attive, Dipartimento di Chimica e Chimica Industriale, via Risorgimento, 35, 56126 Pisa, Italy.

Abstract: In order to obtain some information about the nature of the intermediate organometallic species formed during the asymmetric reaction between the Reformatsky reagent **1b**, and benzaldehyde,**1c**, in the presence of (1S,2S)-1-phenyl-2-N,N-dimethylamino-3-tbutyl-dimethylsilyloxy-1-propanol,**1a**, a spectroscopic NMR investigation has been carried out directly on the mixtures of **1b**, **1c** and the chiral ligand **1a**. To semplify ternary mixture analysis, binary mixtures containing **1b** and **1c** or **1b** and **1a** have been studied. Some hypotheses, about the plausible nature of the intermediates reaction species, which seem to justify the chiral discrimination results so far reached by using the above optically active ligands, are reported. © 1997 Elsevier Science Ltd.

INTRODUCTION

Although the synthetic relevance of the Reformatsky reaction has been recognized for a long time, its mechanicistic aspects have not been exhausted. Some pathways have been proposed , by analysing the correlation between the experimental parameters and the reaction kinetics or thermodynamics.[1] Alternatively, theoretical calculations led to the hypothesis of transition state structures.[2] Spectroscopic investigations, which are very attractive in principle because of the possibility to probe directly the reaction medium, were not encouraged due to the complexity of the systems under analysis. So far only the nature of the Reformatsky reagent in solution has been investigated by Nuclear Magnetic Resonance (NMR).[3]



Scheme 1

Recently we developed a new chiral auxiliary,(1S,2S)-2-N,N-dimethylamino-1-phenyl-3-tbutyl-dimethylsilyloxy-1-propanol (**1a**) , to be employed in the asymmetric Reformatsky reaction for the synthesis of enantiomerically enriched β-hydroxy esters from aldehydes[4] (Scheme 1).

In an attempt to contribute to the knowledge of the reaction mechanism in order to improve the stereoselectivity of such an asymmetric reaction, we were prompted to carry out an NMR spectroscopic investigation directly on mixtures containing the Reformatsky reagent (**1b**), benzaldehyde (**1c**) and the asymmetric ligand **1a**. The results obtained are reported and discussed here.

RESULTS AND DISCUSSION

All the NMR analyses were performed in THF-d_8, THF being the solvent employed in the corresponding synthetic procedures. As a first step of the NMR investigation we simply compared the proton spectra (300 MHz) of the pure compounds **1a**, **1b** and **1c** to the spectrum of their 1:2:1 mixture (this molar ratio is the most frequently employed for synthetic aims[4]) (Figure 1).

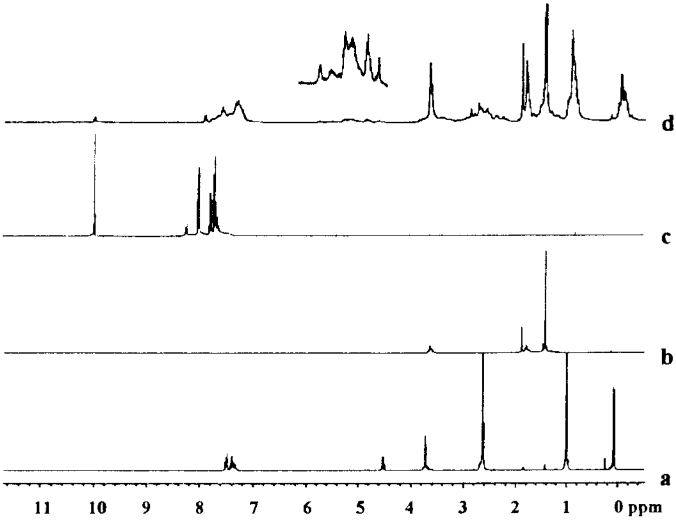


Fig.1 . ^{1}H NMR (300 MHz, THF-d_8, 0 °C) spectra of: a) asymmetric ligand **1a** ,b) Reformatsky reagent **1b**,c) benzaldehyde **1c**,d) mixture **1a**:**1b**:**1c** (molar ratio 1:2:1).

Each pure component showed well resolved and recognizable absorptions: for **1a** these were four sharp singlets at 0.08 and 0.06 ppm (<u>Me</u>-Si), 0.99 ppm (<u>t-Bu</u>-Si) and 2.63 ppm (N<u>Me</u>$_2$), a doublet at 4.51 ppm (C<u>H</u>-OH) and three structured signals at 2.66 ppm (C<u>H</u>- NMe$_2$), 3.74 ppm (C<u>H</u>H-O) and 3.69 ppm (CH<u>H</u>-O); finally the absorptions between 7.25 ppm to 7.50 ppm originated from the phenyl protons. The proton spectra of **1b** and **1c** were even more simple, the first showing two singlets at 1.48 ppm (<u>t-Bu</u>) and 1.89 ppm (<u>CH$_2$</u>) and the latter a singlet at 10 ppm (C<u>H</u>O) and a multiplet at 7.6-7.9 ppm (<u>Ph</u>). By contrast, their mixture showed very complex signals, dispersed over the spectrum, which were constituted by the above described absorptions due to the free compounds, but diminished in intensity, and also flanked with other broad signals. In addition, the aldehyde proton absorption remained sharp, its intensity decreased with time and, concomitantly, new broad absorptions rose in the high frequency (7.0 ppm to 7.6 ppm) region and in the methine (4.6 ppm to 5.6 ppm) and methylene (2.6 ppm to 3.2 ppm) regions. Therefore we hypothesized that the interaction between the Reformatsky reagent and the asymmetric ligand resulted in complexation, exchanging slowly with the free compounds on the NMR time scale; any coordinated aldehyde species is not detected (the CHO signal remains sharp and it is not flanked with similar broad signals) which indicates that the new species observed are the precursors of the final product, having in their structure a methine, a methylene and a phenyl group. All these absorptions were significatively broadened probably because they take part in more than one slow exchanging complexed form.

In order to lower the complexity level in the system under investigation and to confirm the above qualitative conclusions we analysed binary mixtures containing the Reformatsky reagent and the aldehyde or the Reformatsky reagent and the asymmetric ligand.

Firstly, we analysed solutions containing a fixed amount of Reformatsky reagent **1b** and increasing amounts of the aldehyde **1c** as shown in Figure 2, we observed the appearance of broad absorptions in the aromatic region between 7.2 ppm to 7.6 ppm and in the remaining spectral region two sets of signals, having constant 1 to 3 intensities, were originated. The signals of the prevailing species were at 5.50 ppm, 2.86 ppm and 1.10 ppm, whereas the less abundant component was found at 5.66 ppm, 3.06 ppm and 1.02 ppm. The total integrated areas of these signals were in the ratio 1:2:9.

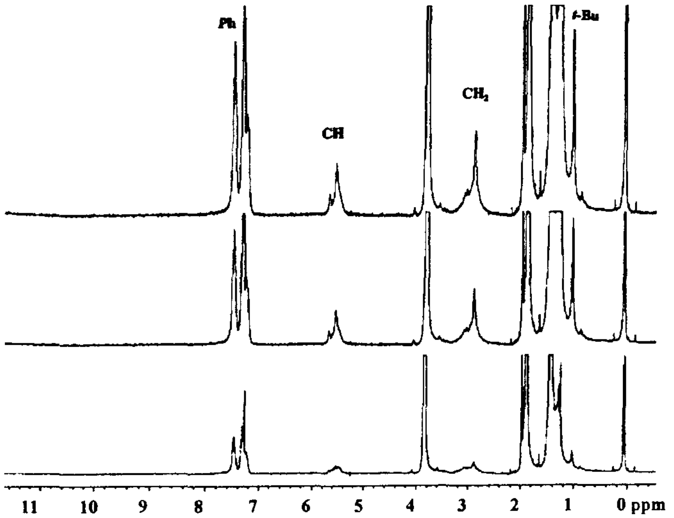


Fig.2 . ^{1}H NMR (300 MHz, THF-d_8, 25°C) of mixtures **1b**:**1c** ([**1b**] = 77 mM) at different molar ratios:
a) 1:0.1, **b)** 1:0.3, **c)** 1:0.5.

Similarly, the carbon spectrum (Figure 3a) revealed the presence of two sets of absorptions which were identified by DEPT analysis (Figure 3b) as two methyl carbons at 27.78 ppm and 27.41 ppm, two methylene carbons at 45.43 ppm and 44.85 ppm respectively and two methine carbons at 73.55 ppm and 73.30 ppm , in addition to a group of methine signals in the aromatic region.

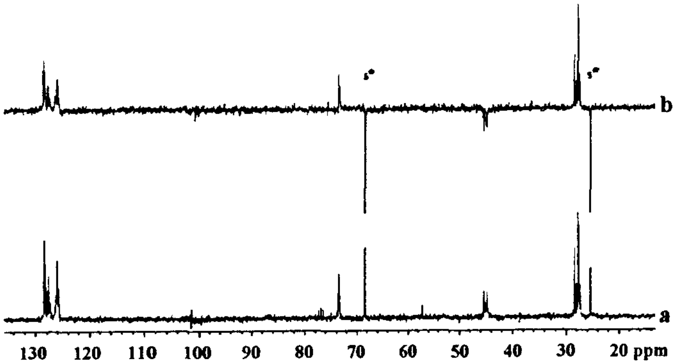


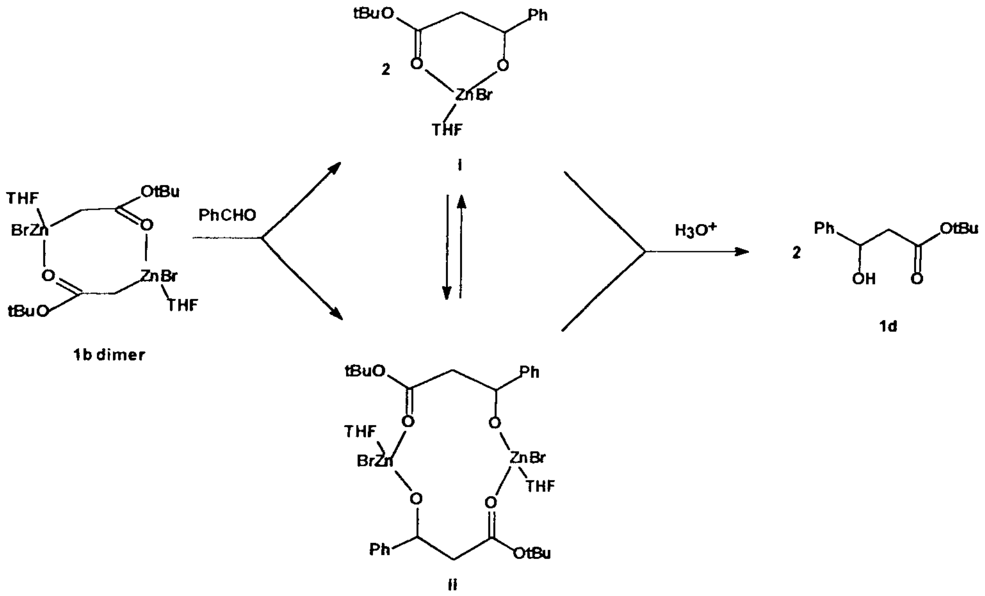
Fig.3 . ^{13}C NMR (75 MHz, THF-d_8, 25° C) analysis of the mixture **1b**:**1c** (molar ratio 1:0.5):
a) ^{13}C NMR spectrum,
b) ^{13}C DEPT spectrum
(S* = THF) .

By 2D H/C correlation (HETCOR) these carbon absorptions were correlated to the above mentioned proton resonances, thus allowing us to confirm that the two species are both constituted by methine, methylene and t-butyl groups, in addition to a phenyl moiety.

The analysis of the dipolar interaction in the rotating frame (2D ROESY analysis) clearly showed the presence of cross-peaks due to exchange between the methine protons at 5.50 ppm and 5.66 ppm, between the methylene protons at 2.86 ppm and 3.06 ppm and, finally, between the two peaks at 1.10 ppm and 1.02 ppm, i.e. between corresponding signals of the two species formed.

Therefore we can conclude that, as previously supposed, the interaction between the organometallic reagent and the aldehyde leads to the formation of two slowly exchanging species both having the structure of the final product. The differences in their stereochemical arrangements are well reflected in the proton spectrum; indeed in the prevalent form the methine and methylene protons are shifted to high frequency relatively to the corresponding signals in the less abundant one, the reverse is true for the t-butyl group. Interestingly, the diastereotopic methylene protons of the less abundant species are more differentiated, i.e. show a greater chemical shift non-equivalence. Finally, in the 2D ROESY spectrum inter-n.O.e.s are measured between the phenyl group of the prevalent species and its methylene and t-Butyl groups not directly bound to it. This kind of dipolar interaction is not detected for the other species, where the expected inter-n.O.e. between the phenyl and methine protons is still observed. It should be noticed that such NMR measurements do not furnish any evidence about the coordination state of benzaldehyde to Reformatsky reagent: indeed, during the addition of increasing amounts of benzaldehyde, even though the aldehydic proton signal looses so much intensity that it disappeared for a molar ratio of 1 to 1, it remained very sharp.

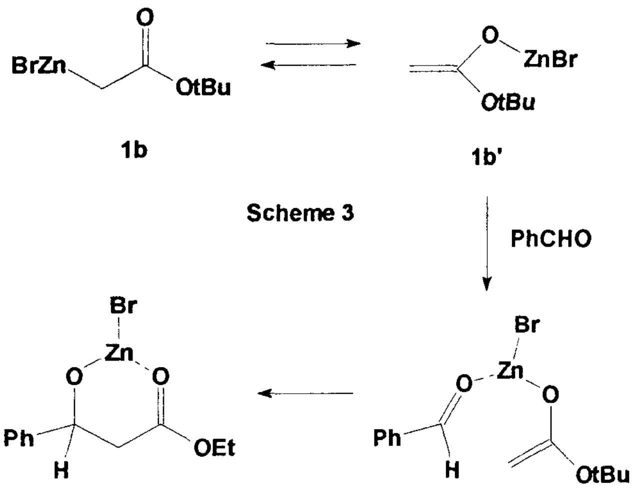
These data would show (Scheme 2) that the Reformatsky reagent, now also considered dimeric in solution[3], reacts very quickly with benzaldehyde[5] giving rise to the slowly exchanging species **i** and **ii**, precursors of the final product **1d**.



Scheme 2

The less abundant species, showing the diastereotopic methylene protons as more differentiated, could be **i** having a major conformational rigidity. In addition the dimeric structure **ii** for the most abundant species could justify the inter-n.O.e.s. measured in the 2D ROESY spectrum between the phenyl and t-butyl protons.

Previous theoretical studies[2] in the absence of asymmetric ligands pointed out the role of a O-metallated monomeric Reformatsky reagent having the aldehyde coordinated (Scheme 3).



Scheme 3

However any enolate species was not detected by us and our experimental data are in keeping with the simultaneous presence of both monomeric and dimeric forms.

Then we analysed binary solutions containing the Reformatsky reagent and the asymmetric ligand and we found that by adding the organozinc reagent to the asymmetric ligand there is formation of new and numerous species slowly exchanging and having the same skeleton of the asymmetric ligand. In fact, the proton spectra of mixtures (Figure 4) showed the peaks of the free compounds flanked by a great number of broad signals; the analysis of their 2D ROESY spectra showed the presence of cross peaks due to exchange between each signal of the free ligand and other peaks of the same kind (methine, methylene or methyl) and also cross peaks due to dipolar interaction between protons belonging to the same molecular species.

Fig.4 . ^{1}H NMR (300 MHz, THF-d_8, 25°C) spectral regions corresponding to the methine absorptions of **1a** in mixtures **1a**:**1b** ([**1a**] = 77 mM) at different molar ratios: **a**) free **1a**, **b**) 1:0.3, **c**) 1:0.5, **d**) 1:0.7, **e**) 1:1.

The new species formed have proton longitudinal relaxation rates remarkably higher (Table), thus probably reflecting the minor mobility of the new species formed or the effect of exchange processes. The interaction site is the OH group of the ligand, which remains coordinated by the oxygen probably to Zn without loss of the proton; in fact the greatest complexation shifts for the new species, relative to the free compound (see Table), are measured for the methine proton bound to the OH, followed by the methine proton bound to the nitrogen and, finally, the lowest complexation shifts are measured for the methylene protons.

Table . ^{1}H NMR (300MHz, THF-d_8, 25 °C) Complexation Shifts ($\Delta\delta^a$) of the Methine and Methylene Protons of some Complexed Species **1a** (indicated as **A**, **B**, **C** and **D**) Detected in the Presence of an Equimolar Amount of **1b** and Proton Longitudinal Relaxation Rates (R) of the Methine Proton Bound to the OH group in the Free Compound **1a** and in the Same Complexed Species.

		A	B	C	D	free
$\Delta\delta$, ppm	-C$\underline{H}$-OH	+ 0.30	+ 0.73	+ 0.77	+ 0.98	
	-C$\underline{H}$-NMe$_2$	+ 0.22	+ 0.40	+ 0.45	+ 0.73	
	-C$\underline{H}_2$-O-	- 0.12	- 0.12	- 0.19	- 0.29	
R, s^{-1}	-C$\underline{H}$-OH	1.56	1.72	2.22	3.70	1.35

[a] $\Delta\delta = \delta_{\text{complexed species}} - \delta_{\text{free}}$; the complexed species have been characterized by bidimensional DQF-COSY analysis of the equimolar mixture **1a**/**1b** (1:1).

This point has been clearly revealed by analysing the ^{2}H NMR spectra of solutions containing the asymmetric ligand **1a** deuterated at the oxygen and increasing amounts of the Reformatsky reagent: as shown in Figure 5, the free ligand shows only the expected broad signal due to the OD group at 2.40 ppm, but in the presence of increasing amounts of the Reformatsky reagent there is appearance of a new broad signal at 0.82 ppm and a concomitant intensity decrease of the above signal at 2.40 ppm.

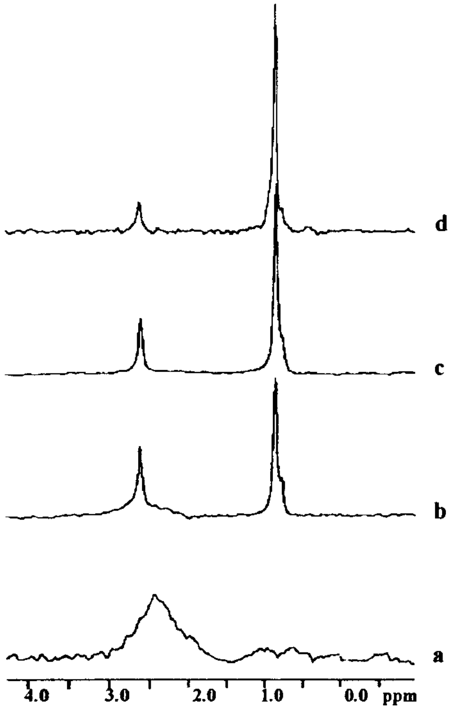
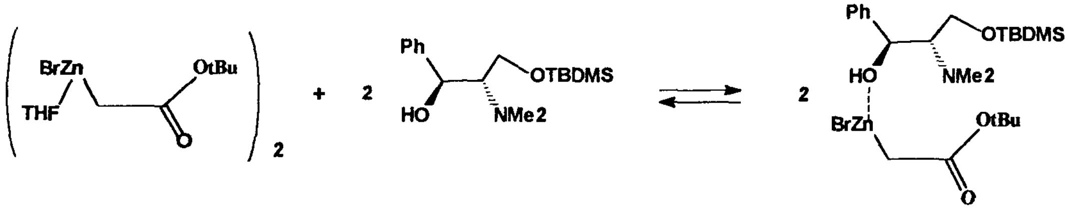


Fig.5 . ^{2}H NMR (46 MHz, THF, 25°C) spectra of deuterated **1a**: **a)** free compound,**b)** mixture **1a**:**1b** = 1:0.3, **c)** mixture **1a**:**1b** = 1:1, **d)** mixture **1a**:**1b**:**1c** = 1:2:1.

The signals of the free asymmetric ligand completely desappeared in the presence of one equivalent of reagent. This fact can be rationalized by supposing that the chiral ligand **1a** interacts with the organometallic compound according to a reversible equilibrium between its free and complexed form by the oxygen atom of the hydroxylic group, without proton abstraction (Scheme 4).



Scheme 4

The multiplicity of coordinated species, detected in solution, is probably determined by the large number of coordination possibilities of the Reformatsky reagent to chiral ligand **1a**, in virtue of its existence as a dimeric structure equilibrating with the monomeric one. Then it is possible to conclude that the interaction of the organozinc reagent with benzaldehyde is stronger than that with chiral ligand; this latter indeed gives rise, with the Reformatsky reagent, to some transient species, coordinatively weak at no univocal stereochemistry, not having a high extent of enantiodifferentiating ability. It should also be considered that the proton spectrum of the ternary mixture (Figure 1) containing the Reformatsky reagent in the presence both of the aldehyde and asymmetric ligand, although very complex, seems to be constituted by the sum of the signals obtained in the two binary mixtures formed by the Reformatsky reagent and the aldehyde or asymmetric ligand. Therefore, probably, the organometallic species prefers interacting independently with each of the two other compounds. The results of this spectroscopic investigation can help to justify experimental data previously reported[4] by us, showing that, even if **1a** or the other N-derivatives of (1S,2S)-1-phenyl-2-amino-3-tbutyl-dimethylsilyloxy-1,3-propanediol are useful chiral auxiliaries in the asymmetric Reformatsky reaction, a given threshold of enantioselectivity cannot be exceeded.

This is probably due to the fact that the interaction of the Reformatsky reagent with the asymmetric ligand is less strong relative to its interaction with the aldehyde and the chiral auxiliary is probably not strongly involved in the same moiety containing the aldehyde. Therefore, more efficient chiral auxiliaries could be projected to attain a stronger complexing ability towards the organozinc reagent.

EXPERIMENTAL

All NMR spectra were recorded using a Varian VXR-300 spectrometer and the temperature was controlled to ±0.1 °C.

The non-selective relaxation rates were measured using the inversion-recovery pulse sequence. The $^{13}C/^{1}H$ heterocorrelated 2D HETCOR spectra were acquired with a spectral width of 16500 Hz in F_2 and 3000 Hz in F_1, with 2K data points, 256 increments of 32 scans; a relaxation delay of 5s was used. The data were zero-filled to 2K x 1K.

The phase sensitive 2D ROESY were acquired with a spectral width of 3000 Hz in 2K data points using 32 scans for each of the 512 increments. The spin-lock time was set to 400 ms, the data matrix was zero-filled to

2K x 1K and a Gaussian function was applied for processing in both dimensions.

(1S,2S)-2-N,N-dimethylamino-1-phenyl-3-t-butyl-dimethylsilyloxy-1-propanol, 1a.

The procedure was that reported in Ref.4: a solution of 50 mmol of t-butyldimethylsilylchloride in 20 ml of dry dichloromethane was added to a solution of 50 mmol of (1S,2S)-2-N,N-dimethylamino-1-phenyl-1,3-propanediol (prepared from (1S,2S)-2-amino-1-phenyl-1,3-propanediol, commercial formalin and formic acid), 56 mmol of Et_3N and 0.4 mmol of 4-dimethylaminopyridine in 30 ml of dry dichloromethane. After the reported workup, pure **1a** was isolated with 90% yield.

$[\alpha]_D^{18}$ + 52.75(c 1.45, $CHCl_3$; ^1H NMR (200MHz,δ, $CDCl_3$): 7.5-7.3 (m, 5H); 5.0 (bs, 1H); 4.4 (d, 1H); 3.7-3.5 (m, 2H); 2.8-2.6 (m, 1H); 2.5 (s, 6H); 0.9 (s, 9H); -0.1 (d, 6H).

Preparation of Reformatsky reagent, 1b.

Following the procedure reported in Ref.4, from 38 mmol of t-butyl bromoacetate in 19 ml of THF and 38 mmol of activated Zn dust, was obtained 30 mmol of crystalline pure Reformatsky reagent.

REFERENCES AND NOTES

1. See review: Fürstner,A. *Synthesis* **1989**, 571.
2. Dewar,M.J.S.; Merz,K.M., Jr. *J.Am.Chem.Soc.* **1987**, *109*, 6553; Lopez,X.; Ugalde,J.M.; Cossio, F.P. *Tetrahedron Lett.* **1993**, *34*, 6111.
3. Dekker,J.; Budzelaar,P.H.M.; Boersma,J.; van Der Kerk,G.J.M. *Organometallics* **1984**, *3*, 1403.
4. Pini,D.; Mastantuono,A.; Salvadori,P. *Tetrahedron: Asymmetry* **1994**, *5*, 1875; Mastantuono,A.; Pini,D.; Rolfini,C.; Salvadori,P. *Chirality* **1995**, *7*, 499.
5. By reaction of benzaldehyde with **1b** using both an excess of this latter (molar ratio 1 to 3 or 1 to 2) and an equimolar amount, the conversion to β-hydroxyester was ≥85% just after 5 minutes and complete after 10-15 minutes.

(*Received in UK* 8 *October* 1996; *revised* 31 *December* 1996; *accepted* 13 *March* 1997)