

Catalytic Enantioselective Reformatsky Reaction with Aldehydes**

M. Ángeles Fernández-Ibáñez, Beatriz Maciá, Adriaan J. Minnaard, and Ben L. Feringa*

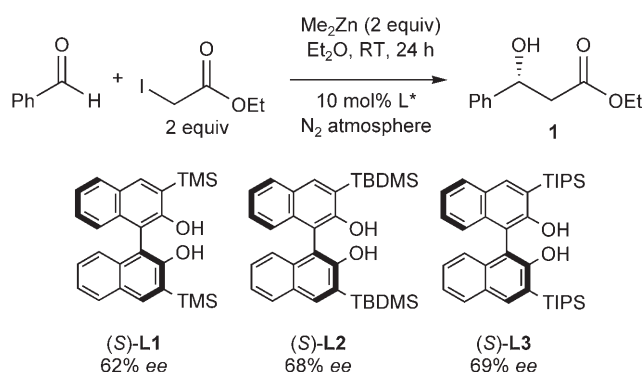
The classical Reformatsky reaction,^[1] introduced for the first time in 1887, consists of the zinc-induced formation of β -hydroxyesters by the reaction of α -halogenated esters with aldehydes or ketones.^[2] Currently, Reformatsky reactions are defined as transformations that result from metal insertions into carbon–halogen bonds activated by carbonyl groups and subsequent addition of different kinds of electrophiles. The Reformatsky reaction is among the most useful methods for the formation of carbon–carbon bonds and an important alternative to the base-induced aldol reaction. Its excellent functional-group tolerance and mild reaction conditions have contributed to its success. The reaction is typically heterogeneous in nature; however, in recent years homogeneous Reformatsky reactions based on the use of Me_2Zn or Et_2Zn have been described.^[3]

The asymmetric version of the Reformatsky reaction has been achieved using chiral auxiliaries^[4] or ligands.^[5] Recently, a catalytic enantioselective version of this transformation has been reported by Cozzi, employing ketones or imines as electrophiles.^[6] High enantioselectivities have been reached using chiral $[\text{MnCl}(\text{salen})]$ complexes (20 mol %) in the reaction with ketones and *N*-methylephedrine (20–30 mol %) in the imino-Reformatsky reaction. However, both methods provide low levels of enantioselectivity in the reaction with benzaldehyde.

Herein, we report the first effective catalytic enantioselective Reformatsky reaction with aldehydes using a catalyst based on binol derivatives as the chiral ligand.

Several chiral ligands (10 mol %) were tested in a model reaction with benzaldehyde in the presence of Me_2Zn and ethyl iodoacetate in a nitrogen atmosphere (Scheme 1). Chiral ligands (S)-L1, (S)-L2, and (S)-L3 gave the highest enantioselectivities (62–69 % ee), but unfortunately the conversion into the desired product **1** was only 10–20 %. The remaining starting material was recovered, and no 1,2-addition product of Me_2Zn to benzaldehyde was detected. Therefore, we initially focussed our efforts on the key issue of conversion and chemoselectivity.

To increase the conversion, the more reactive Et_2Zn and $i\text{Pr}_2\text{Zn}$ were used as the zinc source in the model reaction with



Scheme 1. Model reaction using chiral binol derivatives. TMS = trimethylsilyl, TBDMS = *tert*-butyldimethylsilyl, TIPS = triisopropylsilyl.

(S)-L2 as the chiral ligand. Full conversion was obtained in these cases although the enantioselectivity dropped to 26 and 8 % ee, respectively. Addition of catalytic amounts of $[\text{NiCl}_2(\text{PPh}_3)_2]$ or $[\text{RhCl}(\text{PPh}_3)_3]$, which are expected to give faster halogen–zinc exchange compared to the direct insertion of Me_2Zn ,^[3] gave nonreproducible results in the addition of ethyl bromoacetate^[7] to benzaldehyde using (S)-L2 as the chiral ligand. Finally, to activate the Me_2Zn reagent, we decided to exchange the nitrogen atmosphere with air. It is known that Me_2Zn in the presence of oxygen forms the more reactive alkyl peroxides (RZnOOR),^[8] which are able to initiate radical reactions.^[6b,8,9] Under these conditions, by using 10 mol % of (S)-L2, complete conversion and a promising level of enantioselectivity (58 % ee) were obtained (Table 1, entry 1). It is important to note that the reaction was complete in less than 1 h, in sharp contrast with the reaction under nitrogen. Lower and higher temperatures and different additives and iodoacetates were evaluated, and in all cases lower enantioselectivities were obtained.

Table 1: Effect of the amount of ligand on the enantioselectivity.

Entry	Ligand (L*)	mol % L*	ee [%] ^[a]
1	(S)-L2	10	58
2	(S)-L2	20	70
3	(S)-L2	30	80
4	(S)-L2	50	74
5	(S)-L1	10	62
6	(S)-L1	20	74

[a] Determined by chiral HPLC analysis (Chiralcel OD-H).

[*] Dr. M. Á. Fernández-Ibáñez, Dr. B. Maciá, Prof. Dr. A. J. Minnaard, Prof. Dr. B. L. Feringa
Stratingh Institute for Chemistry
University of Groningen Nijenborgh 4
9747 AG, Groningen (The Netherlands)
Fax: (+31) 50-363-4296
E-mail: b.l.feringa@rug.nl

[**] This research was financially supported by the Dutch Ministry of Economic Affairs. M.A.F.-I. thanks the Spanish Ministry of Education and Science for a postdoctoral fellowship.

Supporting information for this article is available on the WWW under <http://www.angewandte.org> or from the author.

Next, the effect on the enantioselectivity of different catalyst loadings was studied (Table 1). We found that the enantioselectivity increased to 80% *ee* when the amount of ligand was raised (Table 1, entries 1–3). This effect might be explained by competition between catalytic and uncatalyzed reactions. Surprisingly, with 50 mol % of (*S*)-**L2** the enantioselectivity did not improve, but dropped to 74% *ee*. Both ligands (*S*)-**L1** and (*S*)-**L2** gave very similar results under the same conditions, but enantioselectivities were slightly higher for (*S*)-**L1** (Table 1, entries 5 and 6).

To suppress the uncatalyzed reaction we decided to adopt a slow-addition protocol for benzaldehyde in this reaction. Thus, the addition of benzaldehyde over 3 h to the reaction mixture using 10 mol % of (*S*)-**L2**, ethyl iodoacetate, and Me₂Zn in Et₂O provided **1** with high enantioselectivity (86% *ee*). Unfortunately, the conversion dropped dramatically. Analysis of the reaction mixture by GC–MS showed the formation of diethyl succinate (see Figure 1). The presence of this product can be attributed to homocoupling of two ethyl acetate radicals, which in the absence of an electrophile are engaged in the termination step, thus explaining the low conversion observed.^[10]

To solve the problem of competing reactions, different addition rates of RCHO were evaluated. Finally, the optimal reaction conditions were obtained by using 20 mol % of (*S*)-**L1** while adding benzaldehyde over 10 min. Gratifyingly, these conditions provided nearly full conversion into **1** and an enantioselectivity of 84% *ee* (Table 2, entry 1).

The scope of the reaction was examined with several aldehydes (Table 2). The new catalytic asymmetric version of the Reformatsky reaction proceeded with good yields, and no

Table 2: Catalytic enantioselective Reformatsky reaction with various aldehydes.

$\text{R-CHO} + \text{I-CH}_2\text{CO}_2\text{Et} \xrightarrow[\text{air}]{\text{Me}_2\text{Zn (8 equiv), Et}_2\text{O, RT, 1 h, 20 mol\% (S)-L1}} \text{R-CH(OH)-CH}_2\text{CO}_2\text{Et} \quad \mathbf{1}$				
Entry	R	Product	Yield ^[a] [%] (Conversion) ^[b] [%]	<i>ee</i> [%] ^[c]
1 ^[d]	phenyl	1a	72 (87)	84 (<i>R</i>)
2 ^[d]	4-chlorophenyl	1b	75 (81)	80 (<i>R</i>)
3 ^[d]	4-bromophenyl	1c	70 (83)	80 (<i>R</i>)
4	4-cyanophenyl	1d	72 (98)	76
5	4-isopropylphenyl	1e	87 (98)	80
6 ^[d]	4-methoxyphenyl	1f	73 (84)	80 (<i>R</i>)
7	mesityl	1g	72 (86)	76
8 ^[d]	2-furyl	1h	75 (88)	54 (<i>R</i>)
9	2-thienyl	1i	69 (86)	84
10 ^[d]	2-phenylvinyl	1j	82 (95)	42 (<i>R</i>)
11	2-naphthyl	1k	61 (76)	80
12	<i>n</i> -heptyl	1l	56 (75)	7
13 ^[d]	isopropyl	1m	87 (n.d.)	30 (<i>R</i>)
14	<i>tert</i> -butyl	1n	70 (n.d.)	50 ^[e]

[a] Yield of isolated product. [b] Determined by GC–MS. [c] Determined by chiral GC or HPLC (see the Supporting Information for further details). [d] Absolute stereochemistry was determined by comparison of the sign of specific rotation with those of literature values (see the Supporting Information for further details). [e] Determined by formation of the corresponding Mosher esters. n.d. = not determined.

by-products were detected by NMR or GC–MS analysis. Aromatic aldehydes with electron-poor and electron-rich substituents at the *para* position gave enantioselectivities in the range 76–80% *ee* (Table 2, entries 2–6). The bulky mesitaldehyde provided 76% *ee* (Table 2, entry 7). The enantioselectivity of the reaction using 2-furaldehyde was modest (54% *ee*; Table 2, entry 8), in contrast with 2-thienylaldehyde, which gave 84% *ee* (Table 2, entry 9). The reaction with cinnamic aldehyde provided a moderate enantioselectivity (Table 2, entry 10), whereas 2-naphthaldehyde gave 80% *ee* and a slightly lower conversion compared to other aldehydes (Table 2, entry 11). The lowest enantioselectivity was observed with the linear aliphatic aldehyde *n*-octanal (Table 2, entry 12). However, the use of more-hindered aliphatic aldehydes (isobutyraldehyde and pivaldehyde) gave an increase in the enantioselectivity (30% and 50% *ee*, respectively; Table 2, entries 13 and 14) compared to the linear substrate.

To explain the results obtained in this work we suggest a possible mechanism for our catalytic system that is based on a catalytic cycle proposed by Cozzi for the imino-Reformatsky reaction^[6b,11] and the zinc species proposed by Noyori^[12] (Figure 1).

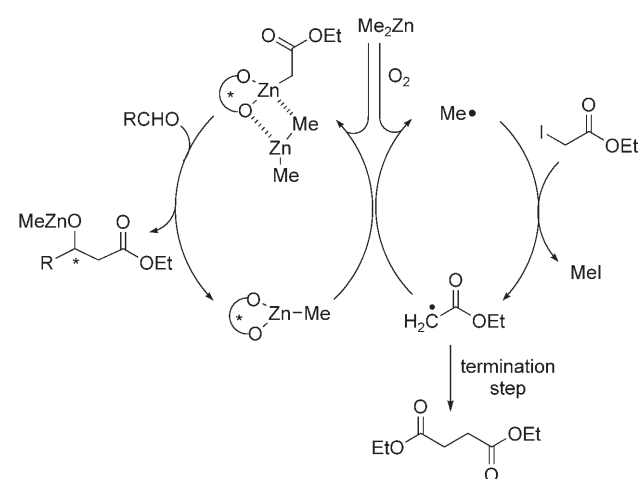


Figure 1. Proposed catalytic cycle for the Reformatsky reaction in air.

In conclusion, we have developed the first catalytic chemo- and enantioselective Reformatsky reaction with aldehydes, proceeding with high levels of asymmetric induction in several cases. A readily available binol derivative was used as a chiral catalyst, and the reaction was performed with ethyl iodoacetate and Me₂Zn as the zinc source. The presence of air was found to be crucial, presumably to initiate a radical mechanism. Currently, efforts are directed towards expanding the scope and elucidating the mechanism of this new asymmetric transformation.

Experimental Section

In a two-neck, 100-mL round-bottom flask equipped with a CaCl₂ tube, Et₂O (5 mL), (*S*)-**L1** (0.025 mmol, 20 mol %), and ethyl

iodoacetate (0.5 mmol, 2 equiv) were added at room temperature. Me_2Zn (1 mmol, 4 equiv, 2 M in toluene) was added, and immediately a solution of aldehyde (0.25 mmol) in Et_2O (1 mL) was added over a 10-min period by using a syringe pump. At the same time that the addition of aldehyde was started, again Me_2Zn (1 mmol, 4 equiv, 2 M in toluene) was added. The resulting solution was stirred for 1 h and quenched with aqueous HCl (1 M). The organic phase was separated, and the aqueous phase was extracted with Et_2O (5 mL). The combined organic phases were dried over MgSO_4 , and the solvent was evaporated under reduced pressure to give β -hydroxyesters **1**. The products were purified by flash chromatography (see the Supporting Information for further details).

Received: October 18, 2007

Published online: January 4, 2008

Keywords: enantioselectivity · O ligands · oxygen · radical reactions · zinc

- [1] S. Reformatsky, *Ber. Dtsch. Chem. Ges.* **1887**, 20, 1210–1211; for a review, see: a) R. Ocampo, W. R. Dolbier, Jr., *Tetrahedron* **2004**, 60, 9325–9374; b) S. A. Babu, M. Yasuda, I. Shibata, A. Baba, *J. Org. Chem.* **2005**, 70, 10408–10419; c) P. G. Cozzi, *Angew. Chem.* **2007**, 119, 2620–2623; *Angew. Chem. Int. Ed.* **2007**, 46, 2568–2571.
- [2] a) A. Fürstner, *Synthesis* **1989**, 571–590; b) A. Fürstner in *Organozinc Reagents* (Eds.: P. Knochel, P. Jones), Oxford University Press, New York, **1999**, pp. 287–305; c) J. A. Marshall, *Chemtracts* **2000**, 13, 705–707; d) J. Podlech, T. C. Maier, *Synthesis* **2003**, 633–655; e) E. Nakamura in *Organometallics in Synthesis: A Manual* (Ed.: M. Schlosser), Wiley, New York, **2002**, pp. 579–664; f) F. Orsini, G. Sello, *Curr. Org. Synth.* **2004**, 1, 111–135; g) Y. Suh, R. D. Rieke, *Tetrahedron Lett.* **2004**, 45, 1807–180; h) L. Kürti, B. Czako in *Strategic Applications of Named Reactions in Organic Synthesis* (Eds.: L. Kürti, B. Czako), Elsevier Academic Press, **2005**, pp. 374–375.
- [3] a) J. C. Adrian, Jr., M. L. Snapper, *J. Org. Chem.* **2003**, 68, 2143–2150; b) A. Dondoni, A. Massi, S. Sabbatini, *Chem. Eur. J.* **2005**, 11, 7110–7125; c) K. Kanai, H. Wakabayashi, T. Honda, *Org. Lett.* **2000**, 2, 2549–2551; d) K. Kanai, H. Wakabayashi, T. Honda, *Heterocycles* **2002**, 58, 47–51; e) K. Sato, A. Tarui, T. Kita, Y. Ishida, H. Tamura, M. Omote, A. Ando, I. Kumadaki, *Tetrahedron Lett.* **2004**, 45, 5735–5737; f) M.-F. Laroche, D. Belotti, J. Cossy, *Org. Lett.* **2005**, 7, 171–173.
- [4] a) J. D. Clark, G. A. Weisenburger, D. K. Anderson, P.-J. Colson, A. D. Edney, D. J. Gallagher, H. P. Kleine, C. M. Knable, M. K. Lantz, C. M. V. Moore, J. B. Murphy, T. E. Rogers, P. G. Ruminiski, A. S. Shah, N. Storer, B. E. Wise, *Org. Process Res. Dev.* **2004**, 8, 51–61; b) L.-T. Yu, M.-T. Ho, C.-Y. Chang, T.-K. Yang, *Tetrahedron: Asymmetry* **2007**, 18, 949–962; c) F. Orsini, G. Sello, A. M. Manzo, E. M. Lucci, *Tetrahedron: Asymmetry* **2005**, 16, 1913–1918.
- [5] a) For a review, see: C. M. R. Ribeiro, F. M. Cordeiro de Farias, *Mini-Rev. Org. Chem.* **2006**, 3, 1–10, and references therein; b) for other recent papers, see: D. P. G. Emmerson, W. P. Hems, B. G. Davis, *Tetrahedron: Asymmetry* **2005**, 16, 213–221; c) P. G. Cozzi, E. Rivalta, *Angew. Chem.* **2005**, 117, 3666–3669; *Angew. Chem. Int. Ed.* **2005**, 44, 3600–3603; d) E.-k. Shin, H. J. Kim, Y. Kim, Y. Kim, Y. S. Park, *Tetrahedron Lett.* **2006**, 47, 1933–1935; e) R. J. Kloetzing, T. Thaler, P. Knochel, *Org. Lett.* **2006**, 8, 1125–1128.
- [6] a) For ketones, see: P. G. Cozzi, *Angew. Chem.* **2006**, 118, 3017–3020; *Angew. Chem. Int. Ed.* **2006**, 45, 2951–2954; b) for imines, see: P. G. Cozzi, *Adv. Synth. Catal.* **2006**, 348, 2075–2079.
- [7] These experiments were carried out with ethyl bromoacetate instead of ethyl iodoacetate in order to follow faithfully the procedure described in the literature (see reference [3]).
- [8] a) J. Lewiński, W. Śliwiński, M. Dranka, I. Justyniak, J. Lipkowski, *Angew. Chem.* **2006**, 118, 4944–4947; *Angew. Chem. Int. Ed.* **2006**, 45, 4826–4829; b) J. Lewiński, Z. Ochla, E. Bojarski, E. Tratkiewicz, I. Justyniak, J. Lipkowski, *Angew. Chem.* **2003**, 115, 4791–4794; *Angew. Chem. Int. Ed.* **2003**, 42, 4643–4646; c) for a review, see: M. Bertrand, L. Feray, S. Gastaldi, *C. R. Chim.* **2002**, 5, 623–638.
- [9] For reactions promoted by the combination of oxygen and R_2Zn , see: a) K.-i. Yamada, Y. Yamamoto, M. Maekawa, T. Akindele, H. Umeki, K. Tomioka, *Org. Lett.* **2006**, 8, 87–89; b) Y. Yamamoto, M. Maekawa, T. Akindele, K.-i. Yamada, K. Tomioka, *Tetrahedron* **2005**, 61, 379–384; c) K.-i. Yamada, Y. Yamamoto, M. Maekawa, K. Tomioka, *J. Org. Chem.* **2004**, 69, 1531–1534; d) K.-i. Yamada, Y. Yamamoto, K. Tomioka, *Org. Lett.* **2003**, 5, 1797–1799; e) Y. Yamamoto, K.-i. Yamada, K. Tomioka, *Tetrahedron Lett.* **2004**, 45, 795–797; f) T. Akindele, Y. Yamamoto, M. Maekawa, H. Umeki, K.-i. Yamada, K. Tomioka, *Org. Lett.* **2006**, 8, 5729–5732; g) S. Bazin, L. Feray, N. Vanthuyne, D. Siri, M. P. Bertrand, *Tetrahedron* **2007**, 63, 77–85; h) H. van der Deen, R. M. Kellogg, B. L. Feringa, *Org. Lett.* **2000**, 2, 1593–1595; i) M. P. Bertrand, L. Feray, R. Nougier, P. Perfetti, *J. Org. Chem.* **1999**, 64, 9189–9193; j) K.-i. Yamada, Y. Yamamoto, M. Maekawa, J. Chen, K. Tomioka, *Tetrahedron Lett.* **2004**, 45, 6595–6597; k) K.-i. Yamada, H. F. Fujihara, Y. Yamamoto, Y. Miwa, T. Taga, K. Tomioka, *Org. Lett.* **2002**, 4, 3509–3511.
- [10] We rule out the formation of diethyl succinate by attack of Reformatsky reagent on ethyl iodoacetate, because no ethyl iodoacetate is detected after 6 min of reaction by GC–MS, and the diethyl succinate starts to be formed later on.
- [11] The formation of the methyl radical from dimethylzinc (or, in general, alkyl radical from dialkyl zinc) and oxygen has been previously reported by several authors; see reference [9].
- [12] M. Kitamura, S. Suga, M. Niwa, R. Noyori, *J. Am. Chem. Soc.* **1995**, 117, 4832–4842.