

Catalytic enantioselective Reformatsky reaction with ketones†

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Received (in Cambridge, UK) 31st January 2008, Accepted 7th March 2008

First published as an Advance Article on the web 1st April 2008

DOI: 10.1039/b801749b

Chiral tertiary alcohols were obtained with good yields and enantioselectivities via a catalytic Reformatsky reaction with ketones, including the challenging diaryl ketones, using chiral BINOL derivatives.

Chiral tertiary alcohols are important structural units present in many biologically active compounds and pharmaceutical intermediates. An important strategy for the construction of this moiety is the catalytic enantioselective addition of carbon nucleophiles to ketones.¹ However, this approach is difficult due to the lower reactivity of ketones and the decreased steric discrimination compared to aldehydes. Very few examples have been reported describing catalytic enantioselective aldol reactions to ketones.^{1,2}

The Reformatsky reaction³ consists of the zinc-induced formation of β -hydroxy esters by the reaction of α -halogenated esters with aldehydes or ketones.⁴ Its excellent functional group tolerance makes it an important alternative to the base-induced aldol reaction. Recently, the first example of a catalytic enantioselective Reformatsky reaction to ketones was reported by Cozzi.⁵ This pioneering work also revealed some of the limitations so far, including moderate to low yields and long reaction times. We report here a general enantioselective catalytic Reformatsky reaction to ketones.

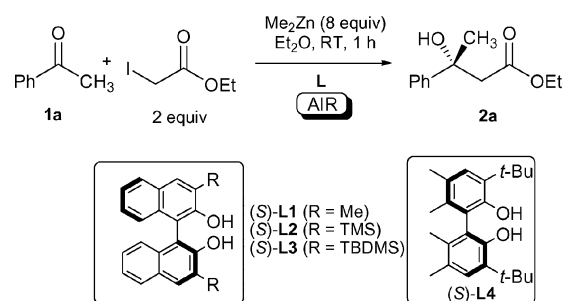
Recently, we developed a new catalytic system for the Reformatsky reaction with aldehydes based on the use of BINOL derivative (*S*)-L2, Me₂Zn and ethyl iodoacetate as a nucleophile in the presence of air.⁶ It is known that Me₂Zn in the presence of oxygen forms the more reactive alkyl peroxides (RZnOOR)⁷ which are able to initiate radical reactions.⁸ In order to avoid the uncatalyzed reaction, we found that the slow addition of aldehyde over 10 min was crucial to get high enantioselectivities.

On the basis of these findings, several BINOL-derivatives (10 mol%) were tested at room temperature in a model reaction with acetophenone (**1a**), ethyl iodoacetate and Me₂Zn in the presence of air. Full conversion was achieved in 1 h, and among the chiral ligands screened, (*S*)-L2 gave the highest enantioselectivity (52%) for this Reformatsky reaction (Table 1, entries 1–4). Lower and higher temperatures were evaluated but lower enantioselectivities were obtained in both cases (entries 5–6). The enantioselectivity increased to 62% when

the amount of ligand was raised to 20 mol% (entry 7). This effect might be explained by the competition between the catalytic and the uncatalyzed reaction. To suppress the uncatalyzed reaction, we decided to adopt a slow addition protocol for the ketone in this reaction. Thus, the slow addition of acetophenone (**1a**) over 10 min to the reaction mixture gave 87% conversion and a slight improvement in the enantioselectivity (68%) (entry 8). However, when the slow addition of acetophenone (**1a**) was performed over 30 min, 85% conversion and an important improvement in the enantioselectivity (77%) were observed (entry 9).

Under these conditions (addition of the ketone over 30 min in the presence of air at room temperature) we investigated the substrate scope. Unfortunately, for some substrates the conversions were lower than expected (*ca.* 50%). GC-MS analysis of these samples taken after 1 h showed the disappearance of ethyl iodoacetate (Fig. 1). The origin of the low conversions might be attributed to the total oxidation of Me₂Zn as a consequence of the slow addition of the electrophile. On the other hand, some reaction with oxygen is necessary for the reaction to proceed. In order to solve this problem, we decided

Table 1 Ligand screening and optimization



Entry	Catalyst (mol%)	T/°C	Addition time of 1a	Conv. (%) ^a	ee (%) ^b
1	(<i>S</i>)-L1 (10)	20	—	100	0
2	(<i>S</i>)-L2 (10)	20	—	100	52
3	(<i>S</i>)-L3 (10)	20	—	100	30
4	(<i>S</i>)-L4 (10)	20	—	100	22
5	(<i>S</i>)-L2 (10)	0	—	100	30
6	(<i>S</i>)-L2 (10)	30	—	100	44
7	(<i>S</i>)-L2 (20)	20	—	100	62
8	(<i>S</i>)-L2 (20)	20	10 min	87	68
9	(<i>S</i>)-L2 (20)	20	30 min	85	77

^a Determined by GC-MS. ^b Determined by chiral HPLC analysis (Chiralpak OJ-H).

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† Electronic supplementary information (ESI) available: Experimental procedures and characterizations. See DOI: 10.1039/b801749b

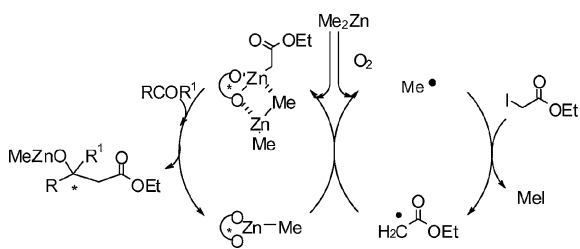
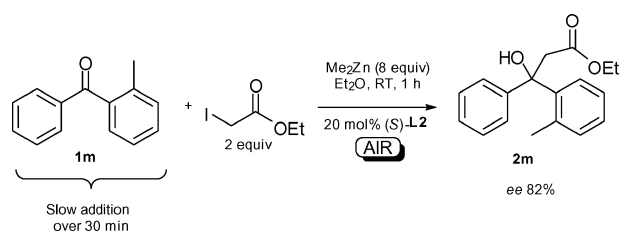


Fig. 1 Proposed catalytic cycle for the Reformatsky reaction promoted by Me_2Zn and air.

to add Me_2Zn in two portions, the first one at the beginning of the reaction and the second one after 15 min. Under these conditions, good yields and enantioselectivities were achieved and the results are summarized in Table 2.

The new catalytic asymmetric version of the Reformatsky reaction provides good yields, and no by-products were detected by GC-MS analysis. The remaining starting material and the ligand were recovered after flash chromatography. The reaction with aromatic ketones gave high enantioselectivities (74–90% ee, Table 2, entries 1–6). The highest ee was achieved with the rigid substrate 1-tetralone (**1b**). The reaction with furylacetone (**1g**) gave modest enantioselectivity (entry 7); in contrast, the reaction with thienylacetone (**1h**) provided a good yield and enantioselectivity (entry 8). α,β -Unsaturated ketones, both aromatic and non aromatic, provided moderate ee's (entries 9–10). Different levels of ee were achieved with aliphatic ketones, reaching a high ee (80%) for the more rigid substrate 2,2-dimethylcyclopentanone (**1i**) (entries 11–12).

To the best of our knowledge, there have been no reports of enantioselective nucleophilic addition of carbon nucleophiles to diaryl ketones. This is extremely difficult due to the similarity of the substituents at the ketone functionality. In order to prove the efficiency of our catalytic system, we examined the



Scheme 1 Reformatsky reaction with phenyl(*o*-tolyl)methanone (**1m**).

reaction with phenyl(*o*-tolyl)methanone (**1m**) (Scheme 1). Under the optimal conditions, moderate yield (40%) but an excellent ee (82%) for this type of substrate were obtained.

Based on the catalytic cycle proposed by Cozzi for the imino-Reformatsky reaction^{8f} and the zinc species proposed by Noyori,⁹ we suggested a possible mechanism for the Reformatsky reaction with aldehydes.⁶ For the reaction with ketones, we propose a similar radical mechanism¹⁰ as shown in Fig. 1.

In conclusion, we have developed a new catalytic system for the enantioselective Reformatsky reaction with ketones. Also, the first enantioselective carbon nucleophile addition to a diaryl ketone with excellent ee is reported. Chiral tertiary alcohols were obtained with good yields and enantioselectivities. A readily available BINOL-derivative is used as a chiral catalyst and the reactions are performed with ethyl iodacetate as the nucleophile and Me_2Zn as the zinc source. The presence of air was found to be crucial to initiate a radical mechanism. Currently, efforts are directed towards expanding the scope and elucidating the mechanism of this new asymmetric transformation.

We thank the Dutch Ministry of Economic Affairs for the financial support. M. A. F.-I. thanks the Spanish Ministry of Education and Science for a postdoctoral fellowship.

Table 2 Catalytic enantioselective Reformatsky reaction to ketones

Entry	Ketone	Product (2)	Yield (%) ^a	ee (%) ^{b,c}
1	Acetophenone	2a	73	77 (R)
2	1-Tetralone	2b	65	90
3	1-Indanone	2c	64	80 (R)
4	4-Chloroacetophenone	2d	80	85
5	4-Bromoacetophenone	2e	85	74 (R)
6	1-Acetonaphthone	2f	73	76
7	2-Furylacetone	2g	60	50
8	2-Thienylacetone	2h	79	77
9	(<i>E</i>)-4-Phenyl-3-buten-2-one	2i	89	50
10	3-Penten-2-one	2j	72	48 (R)
11	3-Methylbutan-2-one	2k	53	28
12	2,2-Dimethylcyclopentanone	2l	85	80

^a Isolated yield. ^b Determined by chiral GC or HPLC (see ESI).

^c Absolute stereochemistry was determined by comparison of the sign of specific rotation with those of the literature values (see ESI for further details).

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- 10 Preliminary EPR studies showed the presence of radicals in the reaction mixture. The addition of TEMPO gave no conversion after 4 h of reaction.