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Catalytic Enantioselective Reformatsky Reaction with *ortho*-Substituted Diarylketones

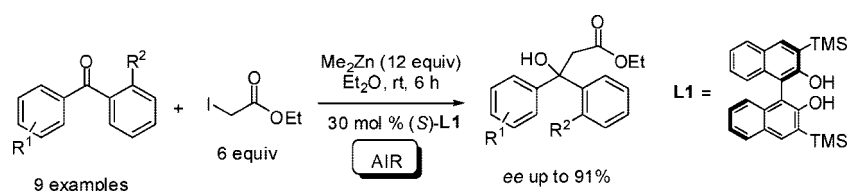
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ABSTRACT



The catalytic enantioselective Reformatsky reaction with *ortho*-substituted diarylketones with good enantioselectivities and moderate to good yields is reported. A readily available BINOL derivative is used as a chiral catalyst, and the reactions are performed with ethyl iodoacetate as a nucleophile and Me₂Zn as the zinc source. The presence of air was found to be crucial to achieve an effective C–C bond formation pointing to a radical mechanism.

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. A range of highly effective catalysts have been developed for the enantioselective nucleophilic addition to ketones.¹ Furthermore, several approaches toward catalytic enantioselective hydrogenation of diarylketones have been described to provide the corresponding diaryl-methanols.² However, to the best of our knowledge, there have been no reports of efficient asymmetric catalytic nucleophilic addition to diarylketones. Such enantioselective

C–C bond formation via nucleophilic addition to diarylketones is extremely difficult due to the similarity of the substituents at the ketone functionality. Herein, we disclose a catalytic asymmetric process providing chiral tertiary alcohols with two aryl substituents.

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 Recently, we developed a new catalytic system for the Reformatsky reaction with aldehydes based on the use of BINOL

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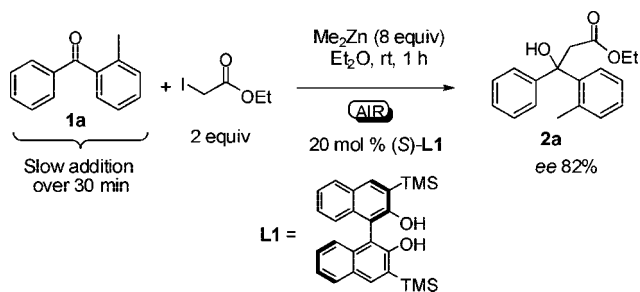
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derivative (*S*)-**L1**, Me₂Zn, and ethyl iodoacetate as a nucleophile in the presence of air.⁵ The presence of oxygen was found to be crucial to initiate a radical pathway.^{6,7} A similar catalytic system was also developed for the reaction with ketones.⁸ Preliminary experiments with phenyl *o*-tolyl ketone (**1a**), using 20 mol % of (*S*)-**L1**, 2 equiv of ethyl iodoacetate, 8 equiv of Me₂Zn in two portions, and the slow addition of the ketone over 30 min in the presence of air provided the chiral alcohol **2a** in 40% yield with 82% ee (Scheme 1).⁸

Scheme 1. Reformatsky Reaction with Phenyl *o*-Tolyl Ketone



Inspired by this amazing result, we decided to study several of the key parameters of this new transformation (Table 1).

Although, unfortunately, the *para*- and *meta*-substituted diarylketones provided the racemic carbinol (Table 1, entries 1–3), the reaction with the *ortho*-substituted ketone **1e** gave the corresponding carbinol with high enantioselectivity, albeit initially in low yield (entry 4). No byproducts were detected in the reaction mixture, and the starting material could be recovered. To improve the conversion, we tested several Lewis acids and additives (TMSCl, BF₃·OEt₂, TiCl₄, PPh₃, 4-phenylpyridine *N*-oxide, LiCl, and CuTC), but none of these induced any improvement.

The slow addition of the electrophile to the reaction mixture was used in our previous work with aldehydes⁵ and

Table 1. Reformatsky Reaction with Diarylketones

entry	substrate	yield (%) ^a	ee (%) ^b
1	1b	72	0
2	1c	n.d.	0
3	1d	n.d.	0
4	1e	<12 ^c	84
5 ^d	1e	40 ^c	77
6 ^e	1e	40 ^c	84

^a Isolated yield after column chromatography. ^b Determined by chiral HPLC. ^c Conversion determined by GC-MS. ^d Direct addition of **1e**. ^e Using 30 mol % of (*S*)-**L1** and direct addition of **1e**.

ketones⁸ to suppress the uncatalyzed reaction. This protocol, however, generally gives lower conversions than that based on direct addition of the electrophile. Direct addition of the diarylketone **1e** indeed provided better conversion (40%) and, as expected, lower enantioselectivity (77% ee) (Table 1, entry 5). For this reason, we decided to perform direct addition of the ketone and to increase the amount of ligand to 30 mol %. Under these conditions we obtained higher enantioselectivity (84% ee) and similar conversion (40%) (Table 1, entry 6). We also tested differing amounts of Me₂Zn and ethyl iodoacetate. The optimal reaction conditions were found to be 30 mol % of (*S*)-**L1**, 6 equiv of ethyl iodoacetate, and 12 equiv of Me₂Zn (in three portions) to provide the carbinol **2e** in 52% yield and 84% ee (Table 2, entry 3).

While we were screening different diarylketones under the optimal conditions, Cozzi et al. reported the use of triphenylphosphine oxide as an additive in the Reformatsky reaction with aldehydes and ketones to improve yields.⁹ In our catalytic system, the use of 20 mol % of Ph₃PO afforded similar yields but higher enantioselectivities (Table 2, compare entries 1–2, 3–4, 5–6, 7–8, 9–10).¹⁰

The reaction of the diarylketone **1a** gave 68% yield and 85% ee (Table 2, entry 1). The use of 20 mol % of Ph₃PO (entry 2) slightly improved the yield (74%), whereas the

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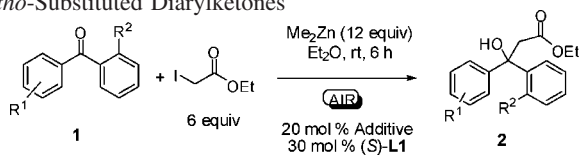
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(10) The use of 10 or 30 mol % of Ph₃PO provided 88% ee in both cases for substrate **1a**.

Table 2. Scope of the Reformatsky Reaction with *ortho*-Substituted Diarylketones



entry	substrate	additive	yield (%) ^a	ee (%) ^b
1		-	68	85
2	1a	Ph ₃ PO	74	91
3		-	52	84
4	1e	Ph ₃ PO	56	89
5		-	38	84
6	1f	Ph ₃ PO	58	89
7		-	84	60
8	1g	Ph ₃ PO	76	66
9		-	n.d.	30
10	1h	Ph ₃ PO	41	32
11		Ph ₃ PO	<5 ^c	n.d.
12		Ph ₃ PO	<5 ^c	n.d.
13		Ph ₃ PO	40	91
14		Ph ₃ PO	70	88
15		Ph ₃ PO	<5 ^c	n.d.
16	1m	Ph ₃ PO	33	91
17		Ph ₃ PO	63	88
18		Ph ₃ PO	<5 ^c	n.d.
	1p			

^a Isolated yield after column chromatography. ^b Determined by chiral HPLC. ^c Conversion determined by GC-MS.

enantioselectivity was significantly enhanced (91% ee). The Reformatsky reaction of the *ortho*-halogen-substituted diarylketones **1e–1f** (entries 3–6) gave the corresponding carbinols with good yields and excellent enantioselectivities (84–89% ee). The presence of a donating group (OMe) in the *ortho* position of the diarylketone provided the carbinol **2g** with good yield, although the enantioselectivity was slightly lower (60–66% ee) (entries 7 and 8). The presence of a linear and electron-withdrawing group (CN) in the *ortho* position gave the lowest enantioselectivity (30–32% ee) seen for this type of substrates (entries 9 and 10). No conversion was detected when strongly electron-withdrawing *ortho* substituents were present (CO₂Me or NO₂) (entries 11 and 12). The reaction with an alkyl (Et) substituent in the *ortho* position gave excellent enantioselectivity (91% ee) (entry 13). With 2-naphthyl as one of the aryl groups of the diarylketone, the reaction proceeded with excellent enantioselectivity (88% ee) and good yield (70%) (entry 14). No conversion was detected with the hindered substituted diarylketones **1m** (*p*-tolyl group in the *ortho* position) or **1p** (two substituents in the *ortho* position) (entries 15, 18). Finally, we also tested the reaction of diarylketones with an *ortho* substituent in one aryl group and a *para* substituent in the other aryl group (entries 16 and 17). The reaction of this type of substrates provided the corresponding carbinols with good to moderate yields and excellent enantioselectivities (88–91% ee).

On the basis of the catalytic cycle proposed by Cozzi for the imino–Reformatsky reaction^{7c} and the zinc intermediates proposed by Noyori et al.,¹¹ we suggest a possible mechanism for the Reformatsky reaction with ketones as depicted in Figure 1.

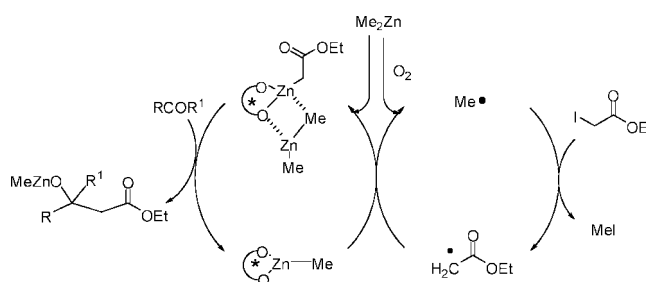


Figure 1. Proposed catalytic cycle for the Reformatsky reaction promoted by Me₂Zn and air.

In conclusion, we have developed the first enantioselective Reformatsky reaction to the highly challenging class of diarylketones with, in several cases, excellent enantioselectivities. The use of *ortho*-substituted diarylketones is necessary to achieve high levels of stereocontrol. Chiral tertiary alcohols with two aryl groups were obtained. A readily available BINOL derivative is used as a chiral catalyst, and the reactions are performed with ethyl iodoacetate as

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nucleophile and Me_2Zn as the zinc source while the presence of air was found to be crucial. Currently, efforts are directed toward expanding the scope of this new asymmetric transformation.

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Supporting Information Available: Experimental procedures and spectroscopic data of the products. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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