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# Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry

Publication details, including instructions for authors and subscription information: http://www.tandfonline.com/loi/lsyc20

# Asymmetric Reformatsky Reaction of Aldehydes Catalyzed by Novel β-Amino Alcohols and Zinc Complexes

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To cite this article: Yan Li & Bin He (2014) Asymmetric Reformatsky Reaction of Aldehydes Catalyzed by Novel  $\beta$ -Amino Alcohols and Zinc Complexes, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 44:13, 1938-1943, DOI: 10.1080/00397911.2013.879898

To link to this article: http://dx.doi.org/10.1080/00397911.2013.879898

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*Synthetic Communications*<sup>®</sup>, 44: 1938–1943, 2014 Copyright © Taylor & Francis Group, LLC ISSN: 0039-7911 print/1532-2432 online DOI: 10.1080/00397911.2013.879898

# ASYMMETRIC REFORMATSKY REACTION OF ALDEHYDES CATALYZED BY NOVEL $\beta$ -AMINO ALCOHOLS AND ZINC COMPLEXES

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#### **GRAPHICAL ABSTRACT**



**Abstract** A series of  $\beta$ -amino alcohols derived from (1R, 2S)-2-amino-1,2-diphenylethanol and substituted salicylaldehydes as novel chiral tridentate ligands has been applied to an asymmetric Reformatsky reaction of aldehydes with ethyl iodoacetate in the presence of ZnMe<sub>2</sub>. This novel catalytic system produced the desired -hydroxyl esters with moderate to good enantioselectivities (up to 81% ee) and yields for many aldehydes, including aromatic, heteroaromatic, conjugated, and aliphatic aldehydes.

Keywords  $\beta$ -Amino alcohols; aldehydes; asymmetric Reformatsky; chiral tridentate ligands

Received November 20, 2013.

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#### ASYMMETRIC REFORMATSKY REACTION

#### INTRODUCTION

The Reformatsky reaction is a classical carbon-carbon bond-forming reaction that was introduced for the first time in 1887.<sup>[1]</sup> The Reformatsky reaction involves the zinc-induced formation of  $\beta$ -hydroxyesters by the reaction of  $\alpha$ -halo esters with aldehydes or ketones.<sup>[2,3]</sup> Because of the importance of the Reformatsky products, β-hydroxy esters, as versatile intermediates for the synthesis of such natural products as macrolides<sup>[4]</sup> and polyether antibiotics,<sup>[5]</sup> there has been continuous effort to conduct these reactions with asymmetric versions. Many existing chiral auxiliaries<sup>[6-9]</sup> and catalysts<sup>[10-14]</sup> can induce useful levels of diastereoselectivity or enantioselectivity. A recent review summarized the results of work showing that by using a large variety of chiral auxiliaries,<sup>[15]</sup> the diastereoselective Reformatsky reactions have excellent diastereochemical control with regard to the synthesis of specific cyclic and acyclic chiral moieties and have been successfully applied to the total synthesis of natural products.<sup>[15]</sup> Conversely, the improved homogeneous asymmetric versions by chiral ligands have also been reported in recent years. The first catalytic enantioselective Reformatsky reaction of ethyl iodoacetate was reported in 2006 using 20 mol% of a chiral manganese salen catalyst and dimethylzinc to homogeneously generate the zinc reagent.<sup>[16,17]</sup> The catalytic enantioselective Reformatsky reactions of  $\alpha$ -halogenated esters with aldehydes and ketones have subsequently been promoted by BINOL derivatives,<sup>[18]</sup> chiral aminoalcohols,<sup>[19,20]</sup> a chiral Schiff base,<sup>[21]</sup> and a chiral bisoxazolidine.<sup>[22]</sup> Despite the abovementioned progress in this field, efforts to seek novel effective chiral ligands for the asymmetric catalysis of this practical carbon-carbon bond-forming reaction are ongoing.

Previously, we reported that novel  $\beta$ -amino alcohols as chiral tridentate ligands can efficiently catalyze the enantioselective cyanosilylation of aldehydes.<sup>[23]</sup> Because most ligands for asymmetric Reformatsky reaction are bidentate ligands, there are few reports of tridentate ligands. To extend the applications of these novel  $\beta$ -amino alcohols, we tested whether they could be good chiral tridentate ligands for an asymmetric Reformatsky reaction.

In this study, we report that these  $\beta$ -amino alcohols as novel chiral tridentate ligands can indeed catalyze the asymmetric Reformatsky reaction of aldehydes with moderate to good enantioselectivities and yields.

#### **RESULTS AND DISCUSSION**

From previous studies, we know that the steric effect of the ligand has a greater contribution than the electronic effect to enhance the entioselectivity.<sup>[23]</sup> On the other hand, based on the pioneering works of Refs. 16–18 and 22, it was established that the Reformatsky reaction can be carried out with high conversion and excellent chemoselectivity by using ZnMe<sub>2</sub> and ethyl iodoacetate with air in an hour. Therefore, under these optimum conditions, by using benzaldehyde as standard substrate, we first evaluated the effects of ligands **1a–1e** with different sized substituents of  $R_1$  or  $R_2$  on the asymmetric Reformatsky reaction (Figure 1 and Table 1).

We performed the asymmetric Reformatsky reaction by using 20 mol% ligand, 2.25 equiv  $ZnMe_2$ , and 2 equiv ethyl iodoacetate. After 1 h of reaction, we isolated the desired product **3a**, and no 1, 2-addition product of  $ZnMe_2$  to benzaldehyde was



Figure 1. Structures of chiral amino alcohol ligands 1a-1e.

detected by LC-MS. Therefore, it is confirmed that the conditions described can provide excellent chemoselectivity in the Reformatsky reaction. In support of our original hypothesis, the results indicated that the enantioselectivity was highly influenced by the structures of the ligands (Table 1). The reaction catalyzed by ligand **1d** ( $R_1 = tert$ -butyl,  $R_2 = tert$ -butyl) gave the greatest enantioselectivity (63% *ee*) (entry 4, Table 1). More or less bulky substitutes all led to less enantioselectivity (entries 1–5, Table 1). The most bulky  $R_1$ , adamantanyl, was detrimental for both the enantioselectivity and reactivity. Lower temperature can facilitate an increase in the enantioselectivity in many cases of asymmetric catalysis. Therefore, we investigated the temperature effect on this reaction. Lower temperature, which caused dramatic decreases in both the enantioselectivity and the yield, actually disadvantaged this reaction (entry 4 vs. entries 9 and 10, Table 1). Additionally, we investigated the loading amount of the ligand **1d**. By lowering the ligand to 10 mol% **1d**, the reaction

	0 H 2a	ICH <sub>2</sub> COOEt — (2 equiv)	<b>1a-1e</b> ZnMe <sub>2</sub> (2.25 equiv) Et <sub>2</sub> O	HO H 3a	COOEt
Entry	Ligand (L*)	L* (mol%)	) Temp. (°C)	Yield $(\%)^b$	<i>Ee</i> $(\%)^{c}$
1	1a	20	RT	54	34
2	1b	20	RT	63	50
3	1c	20	RT	72	61
4	1d	20	RT	68	63
5	1e	20	RT	23	54
6	1d	10	RT	53	56
7	1d	30	RT	68	59
8	1d	50	RT	65	53
9	1d	20	0	18	28
10	1d	20	-10	Trace <sup>d</sup>	nd <sup>e</sup>

Table 1. Screening of different ligands 1a-1e for asymmetric Reformatsky<sup>a</sup>

<sup>*a*</sup>All reactions were carried out using 2 equiv ethyl iodoacetate and 2.25 equiv  $ZnMe_2$  in Et<sub>2</sub>O at RT for 1 hour with air.

<sup>b</sup>Isolated yield.

<sup>c</sup>The enantiomeric excess was determined by chiral HPLC analysis using a Chiralcel OD column.

<sup>d</sup>Determined by LC-MS.

<sup>e</sup>nd, not determined.

	0 ICH COOEt -	<b>1d</b> (20 mol%) ZnMe <sub>2</sub> (2.25 equiv)		
R	$\frac{1}{2}$ + $10H_2COOR$ = (2 equiv)	Et <sub>2</sub> O, RT		DODEL
Entry	Aldehydes	Yield $(\%)^b$	ee (%) <sup>c</sup>	Config. <sup>d</sup>
1	Benzaldehyde ( <b>2a</b> )	68	63	R
2	4-Chlorobenzaldehyde (2b)	63	61	R
3	4-Bromobenzaldehyde (2c)	60	60	R
4	4-Methylbenzaldehyde (2d)	60	60	R
5	4-Methoxybenzaldehyde (2e)	60	60	R
6	1-Naphthaldehyde (2f)	65	81	
7	2-Naphthaldehyde (2g)	68	80	
8	2-Furaldehyde (2h)	45	53	R
9	2-Thienylaldehyde (2i)	58	63	
10	(E)-Cinnamaldehyde (2j)	62	33	
11	Phenylpropyl aldehyde (2k)	52	25	
12	Isopropyl aldehyde (21)	56	45	

**Table 2.** Asymmetric Reformatsky reaction of aldehydes catalyzed by  $1d/2nMe_2$  with ethyl iodoacetate<sup>*a*</sup>

"All reactions were carried out using 10 mol% 1d, 2 equiv ethyl iodoacetate, and 2.25 equiv ZnMe<sub>2</sub> in Et<sub>2</sub>O at RT for 1 h with air.

<sup>b</sup>Isolated yield.

"The enantiomeric excess was determined by chiral HPLC analysis using Chiralcel OD column and Chiralpak AS column, or by chiral GC analysis using Chiralsil Dex CB column.

<sup>d</sup>The absolute configuration of the product was assigned by comparison of HPLC retention time with values in the literature.[18,22]

showed lower enantioselectivity, whereas there was little enhancement of enantioselectivity with 30 mol% or 50 mol% 1d (entry 4 vs. entries 6–8, Table 1).

Encouraged by the results obtained from these model reactions, the scope of this novel catalytic system was examined with different aldehydes, including aromatic, heteroaromatic, conjugated, and aliphatic aldehydes (Table 2). Aldehydes with substituents on the aromatic ring gave similar ee values as benzaldehyde (entries 1–5, Table 2). Heteroaromatic aldehydes also gave similar ee values with benzaldehyde (entries 8 and 9, Table 2). Among all tested aldehydes, 1-naphthaldehyde and 2-naphthaldedyde gave the best enantioselectivities, with 81% and 80% ee, respectively (entries 6 and 7, Table 2).  $\alpha$ ,  $\beta$ -Unsaturated aldehyde and aliphatic aldehydes gave relatively lower enantioselectivities, from 25% to 45% ee (entries 10–12, Table 2).

#### **EXPERIMENTAL**

#### General Procedure for Preparation of Chiral Amino-Alcohol Ligands 1a–1e

According to our previous report,<sup>[23]</sup> it is easy to synthesize the chiral amino alcohol ligands 1a-1e (Fig. 1). A typical procedure for the synthesis of ligand 1d was shown as following: A mixture of 2,5-di-tertbutylsalicylaldehyde (1 mmol) and chiral (1R,2S)-2-amino-1,2-diphenylethanol (1 mmol) in absolute EtOH was stirred for 24 h. Then NaBH<sub>4</sub> (114 mg, 3 mmol) was directly added in it. After the mixture was stirred for an additional 4 h, it was quenched by water. The resulting mixture was extracted with  $CH_2Cl_2$ , and the organic layer was washed with brine. After drying over anhydrous sodium sulfate, the solvent was removed and the residue was purified by silica-gel column chromatography to afford the title ligand 1d.<sup>[23]</sup>

Yield: 85%. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$  7.18–7.36 (m, 11H), 6.65 (s, 1H), 4.92 (d, J = 6.0 Hz, 1H), 3.88 (d, J = 6.4 Hz, 1H), 3.78 (d, J = 13.2 Hz, 1H), 3.56 (d, J = 13.2 Hz, 1H), 1.41 (s, 9H), 1.21 (s, 9H); <sup>13</sup>C NMR (100 MHz, CDCl3):  $\delta$  154.3, 140.5, 137.8, 135.9, 128.6, 128.4, 128.2, 128.1, 126.8, 123.3, 122.9, 122.0, 68.3, 51.1, 34.9, 34.1, 31.6, 29.6.

#### General Procedure for Asymmetric Reformatsky Reaction

In a two-neck 100-mL flame-dried flask equipped with a CaCl<sub>2</sub> tube, Et<sub>2</sub>O (5 mL), ligand **1d** (0.05 mmol, 20 mol%) and ethyl iodoacetate (0.5 mmol, 2 equiv) were added at room temperature. ZnMe<sub>2</sub> (0.5 mmol, 2 equiv, 2 M solution in toluene) was added and immediately followed by the addition over 10 min of a solution of aldehyde (0.25 mmol) in Et<sub>2</sub>O (1 mL). In the meantime, additional ZnMe<sub>2</sub> (0.25 mmol, 0.25 equiv, 2 M solution 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<sub>2</sub>O (20 mL). The product was analyzed by chiral high-performance liquid chromatography (HPLC) or gas chromatography (GC). Absolute configurations were determined by comparison of the known order of elution of the two enatiomers or the sign of optical rotation with literature data.<sup>[18,22]</sup>

#### CONCLUSIONS

In summary, this report describes the first attempt to use  $\beta$ -amino alcohols as novel chiral tridentate ligands for asymmetric Reformatsky reaction of aldehydes. The asymmetric Reformatsky reaction of aldehydes was achieved by the catalysis of 20 mol%, chiral  $\beta$ -amino alcohol, and ZnMe<sub>2</sub> with moderate to good enantioselectivities (up to 81% *ee*) and yields.

#### FUNDING

We are grateful for financial support from National Natural Science Foundation of China (No. 21302027) and the Special Support in Guizhou Province for Research and Development of Modern Science and Technology Industrialization in TCM (QKHGZ[2013] 4001).

#### SUPPORTING INFORMATION

Full experimental details and <sup>1</sup>H and <sup>13</sup>C NMR, HPLC, and GC data for this article can be accessed on the publisher's website.

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