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Zinc Acetate Catalyzed Enantioselective Reductive Aldol Reaction of Ketones

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Abstract. A highly enantioselective method for the synthesis of β-hydroxy esters *via* reductive aldol reaction of acrylates with aryl and heteroaromatic ketones is described. In situ generated catalyst composed of zinc acetate and chiral diamine afforded enantioenriched tertiary alcohols in high yields and with excellent enantioselectivity (up to 91% *ee*). This is also the first successful application of the zinc hydride reagent in stereoselective reductive aldol reactions of ketones.

Keywords: asymmetric synthesis; aldol reaction; zinc; hydrosilylation; ketones

The asymmetric reductive aldol reaction of carbonyl compounds with α,β-unsaturated esters provides a convenient and efficient way to optically active β-hydroxy esters, which are valuable building blocks in organic synthesis.[1] Resulting chiral secondary and tertiary alcohols prepared from aldehydes and ketones are an important class of organic compounds which have found wide applications in both academia and industry.[2] Therefore, numerous catalytic strategies towards asymmetric reductive aldol reaction of carbonyl compounds have already been developed.[3]

While transition metal-catalyzed enantioselective variant of the reductive aldol addition reaction with aldehydes promoted by the combination of Rh-,[4] Co-,[5] or Cu-based complexes[6] with silanes is well established, only limited success has been achieved in asymmetric addition to ketones, mostly restricted to intramolecular reaction.[3b,7] Therefore, further development in this area deserves continuous attention.

In 2006, Shibasaki and co-workers reported a breakthrough in the intermolecular enantioselective reductive aldol reaction of α,β-unsaturated esters to ketones.[8a] Application of CuF complex with chiral diphosphine ligands and triethoxysilane (TES), resulted in a low yield and low enantioselectivity (up to 30% *ee*) for the reaction between acetophenone and methyl acrylate.[8a] Following this achievement, a few efficient protocols based on copper(I) complexes have been then developed.[8] Riant[8b] and Fukuzawa[8c] elaborated catalytic method for the highly stereoselective construction of stereogenic quaternary carbon centers through domino conjugated reduction/aldol reaction of methyl acrylate with various alkyl aryl ketones promoted by Cu-ferrophos and taniaphos complexes. The alternative approach to asymmetric copper(I)-catalyzed reductive aldol-type reaction of acrylates with ketones was showed by Nishiyama.[9] Although the use of a chiral rhodium-bis(oxazolinylphenyl) catalyst proceeded highly enantioselective (57-98% *ee*), the substrate scope was mainly limited to few examples of aliphatic ketones.[9]

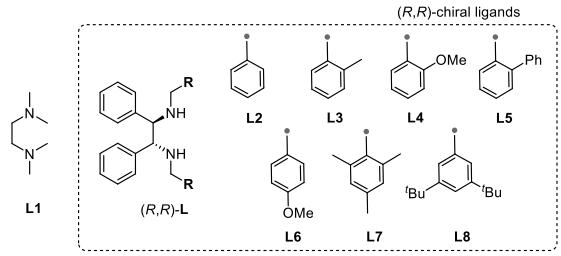
In all these examples copper complexes have been documented as the catalyst of choice. These findings fit the overall supremacy of copper in the reduction reactions. For a long time copper continues to dominate the catalytic chemistry of the coinage metal hydrides[10] and copper hydrides were best known as reagents or as catalytic intermediates in selective reduction chemistry. While broad array of structures of hydride complexes of copper (and also silver, and gold – so called coinage metals) inspired recent advances in synthesis and catalysis, application of zinc hydride intermediate is far less documented. This paper support our thesis that zinc complexes can also promote the asymmetric reductive aldol reaction and zinc may be also used in the catalytic processes in which coinage metal hydrides act as intermediates.

While an example of the chiral Rh complex in presence of zinc salt has been presented by Ando in 2014, the role of Et_2Zn was limited only to generation of rhodium hydride complex.[11] Previously, we elaborated expedient protocols for the asymmetric hydrosilylation of prochiral ketones and imines by using readily available chiral $Zn(OAc)_2$ complexes *in situ* forming zinc hydride as an active intermediate.[12] This prompted us to predict that the chiral zinc hydride complex may be a cheaper and easy formed equivalent of Cu-based catalysts. Here, we describe the first

10.1002/adsc.201901457

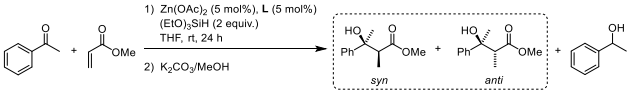
example of a highly efficient and enantioselective zinc acetate-catalyzed reductive aldol reaction of broad range of aryl and heteroaromatic ketones with α,β-unsaturated esters.

Figure 1. Structures of diamine ligands used in this study.



After initial study, we found that $Zn(OAc)_2$ was the most promising zinc salt in a model reaction of acetophenone (**1a**) with methyl acrylate (**2a**) in presence of TES as a reducing agent. After confirming the efficiency of the non-chiral *N*,*N*,*N'*,*N'*-tetramethylethylenediamine (TMEDA, Figure 1, **L1**) in reaction (Table 1, entries 1–3), many chiral ligand based on (*R*,*R*)-diphenylethylenediamine (DPEDA, Figure 1, **L2– L8**) have been prepared and screened in reductive aldol reaction of acetophenone.

Table 1. Initial screening of diamine ligands in asymmetric reductive aldol reaction between acetophenone and methyl acrylate.[a]



Entry	Ligand	Yield (%)[b]		*dr*[c]	*ee* (%)[d]	
		3a	**4a**		*syn*	*anti*
1	**L1**	63	25	1.6 : 1	rac	rac
2[e]	**L1**	84	15	2.0 : 1	rac	rac
3[f]	**L1**	95	trace	2.2 : 1	rac	rac
4	**L2**	70	24	1.3 : 1	14	16
5	**L3**	68	31	2.5 : 1	15	12
6	**L4**	75	15	1.7 : 1	10	15
7	**L5**	54	33	3.8 : 1	9	16
8	**L6**	73	trace	1.8 : 1	8	10
9	**L7**	54	23	2.7 : 1	9	16
10	**L8**	**55**	**21**	**1.6 : 1**	**22**	**48**
11[g]	**L8**	48	18	1.8:1	15	35
12[h]	**L8**	trace	32	-	-	-
13[i]	**L8**	0	trace	-	-	-

[a] Reactions were carried out by stirring $Zn(OAc)_2$ (5 mol%) with **L1–L8** diamine ligands (5 mol%) in THF (1 mL) at room temperature for 24 h, containing TES (1.0 mmol), acetophenone **1a** (0.5 mmol) and methyl acrylate **2a** (0.6 mmol) unless otherwise stated. [b] Isolated yield after silica gel chromatography. [c] *syn*/*anti* ratio determined by ^{1}H NMR spectroscopy. [d] Determined by chiral HPLC analysis. [e] Catalyst loading: 10 mol%. [f] Reaction carried out at 4 °C for 48 h with 10 mol% of catalyst loading. [g] $Zn(OCOEt)_2$, [h] $Zn(OTf)_2$, [i] $Fe(OAc)_2$ or $Fe(OTf)_2$ or $Cu(OTf)_2$ were used instead of $Zn(OAc)_2$.

Data collected in Table 1 indicate that slightly changing the (*R*,*R*)-diamine ligand structure had immense impact on the reaction enantioselectivity. From among tested benzyl derivatives of DPEDA (**L2–L8**, entries 4–10), only ligand **L8** bearing four bulky *tert*-butyl groups at the *meta* positions resulted in moderate yield and promising enantioselectivity (up to 48% *ee* for *anti*-isomer **3a**). While the diastereoselectivity of this reaction was poor, the chemoselectivity was acceptable in all examples and the minor product **4a** formed in very low yield.

Having the best type of ligand in hand, several commercially available Lewis acids were tested and results are also collected in Table 1. Metal salts screening demonstrated that only $Zn(OAc)_2$ and zinc propionate (entry 12) effectively promotes this reaction, while the iron(II)- and copper(II) complexes turned out to be entirely inactive in the asymmetric reductive aldol reaction (Table 1, entry 13). Other zinc salts as zinc triflate (entry 12) or zinc chloride were identified as not promising catalyst precursors. Catalyst composed of diethylzinc with ligand **L8** have also been unreactive under conditions described in Table 1. Despite the fact that the diastereoselectivity of this reaction was in favor of *syn*-**3a**, the promising attempt of the chiral $Zn(OAc)_2$ catalyst based on the ligand **L8** encouraged us to pursue further optimization of the reaction conditions. Although changing solvent from THF to *m*-xylene gave a higher yield of the newly

Table 2. Asymmetric reductive aldol reaction between acetophenone and methyl acrylate under various conditions.[a]

Entry	T (°C)	Time (h)	Cat. (mol%)	Yield (%)[b]	*dr*[c]	*ee* (%)[d]	
						syn	*anti*
1[e]	rt	24	5	55	1.6:1	22	48
2[f]	rt	24	5	72	1.3:1	22	56
3[g]	rt	24	5	67	1.7:1	29	46
4	rt	24	5	68	1.4:1	26	58
5	4	24	5	68	1.3:1	24	62
6	4	48	5	76	1.2:1	26	66
7	-30	48	5	trace	-	-	-
8	-30	48	10	21	1.9:1	16	80
9	-30	72	10	46	1.8:1	23	77
10	-30	48	15	40	1.4:1	16	78
11	**-30**	**72**	**15**	**73**	**1.4:1**	**6**	**82**
12[f]	-30	72	15	63	1.6:1	10	78
13[h]	-30	72	15	69	1.4:1	20	76
14	-30	48	20	75	1.8:1	22	77

[a] Reactions were performed with $Zn(OAc)_2$ (5–20 mol%) and chiral **L8**-ligand (5–20 mol%) in *m*-xylene (1 mL) at the specified time and temperature, containing TES (1.0 mmol), acetophenone **1a** (0.5 mmol) and methyl acrylate **2a** (0.6 mmol) unless otherwise stated. [b] Isolated yield after silica gel chromatography. [c] *syn*/*anti* ratio determined by ^{1}H NMR spectroscopy. [d] Determined by chiral HPLC analysis. [e] THF, [f] toluene, [g] DCM and [h] THF/*m*-xylene (6:1) were used instead of *m*-xylene.

10.1002/adsc.201901457

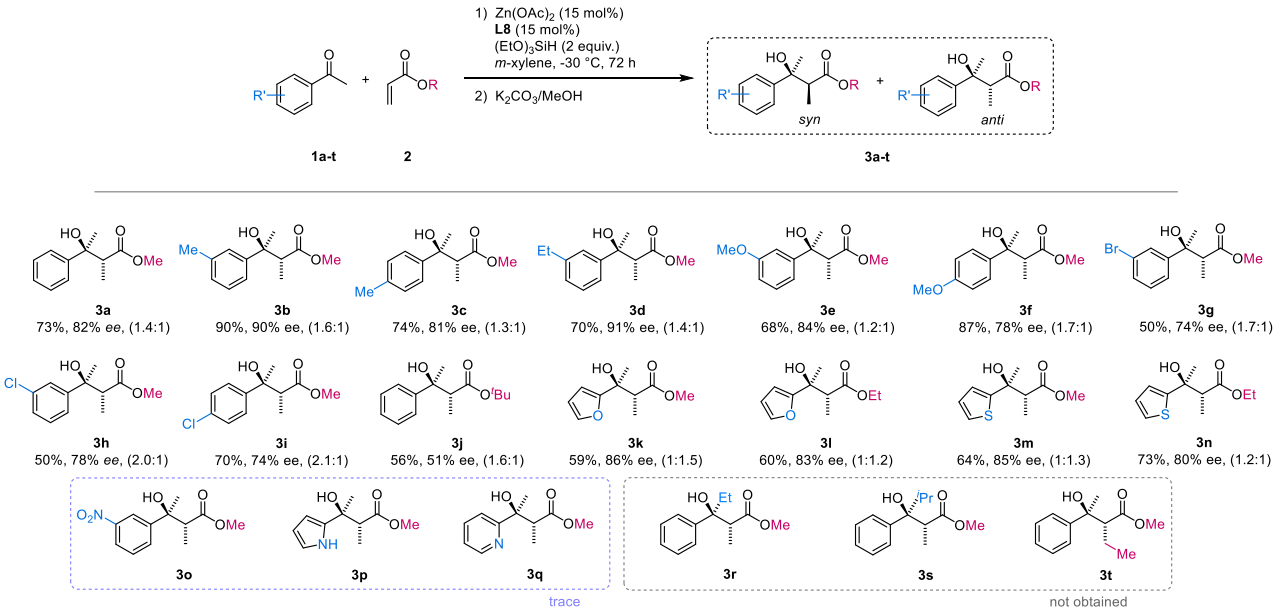
formed *anti*-3**a** product, still the relatively low level of enantioselectivity left much to be desired (Table 2, entry 1 vs. 4).

Further investigations showed that conditions such as temperature and catalyst loading have a significant impact on the control of the reaction stereoselectivity. Based on the initial screening performed at room temperature, cooling down to 4 °C increased the *ee* to 66% (Table 2, entry 5). However, we noticed that reaction performed below 0 °C was unfortunately unsuccessful in the case of 5 mol% of the catalyst (Table 2, entry 7). Considering further improvement of the reaction enantioselectivity, the optimal amount of employed catalyst was evaluated in low reaction temperature. We found that increasing the catalyst loading was required to reactions proceed, and played a crucial role in asymmetric induction and reaction efficiency. To our delight, higher catalyst loading (10 mol%) resulted in formation of desired *anti*-**3a** with a high level of enantioselectivity to 80% *ee*, albeit the efficiency suffered (Table 2, entry 8). A satisfactory yield up to 73% was obtained without loss of *ee* by employing 15 mol% of the catalyst loading and prolonged reaction time to 72 h (Table 2, entry 11). Interestingly, further loading (20 mol%), resulted in a slight decrease of the zinc-complex activity.

At the established optimal conditions, the scope of the zinc-catalyzed asymmetric reductive aldol reaction with respect to the ketones and unsaturated esters was examined, as presented in Scheme 1. For the range of substrates studies, a variety of aryl and heteroaromatic ketones participated successfully in the reaction with high enantioselectivities and very good yields. The investigations revealed that the position of the substituent attached to the aromatic ring has a decisive influence on the reaction enantioselectivity. Substrates possessing groups placed in the *meta* position gave higher *ee* (74–91%), whereas the *para*-substituted products formed with slightly lower selectivities for each cases (up to 81% *ee*). Moreover, the switch of electron-withdrawing groups (**3g–3i**) by electron-donating groups (**3b**–**3f**) on acetophenone significantly increased both the *ee* and yield of the corresponding *anti*-products. Interestingly, the presence of alkyl substituents on the *meta* position afforded the desired products (**3b**, **3d**) with excellent enantioselective control (around 91% *ee*), whereas replacing by a strongly activating group decreased both yield and enantioselectivity of **3e** to 78% *ee*. The replacement of the relatively small methyl group by the *tert*-butyl group in the ester fragment led to significantly lower level of enantioselectivity (51% *ee*) of the corresponding **3j**. In addition to the above-mentioned substrates, attempts to the reaction of 3'-nitroacetophenone (**3o**) were unsuccessful and gave only trace of desired product. Aryl ketones bearing the nitro groups are known to be problematic in hydrosilylations, as shown for instance by Adolfsson.[13] We also examined substrates with longer alkyl chain derivatives (**3r**–**3t**), but products were not observed, since appear to be more sterically hindered. Application of aliphatic ketones (acetone, butan-2-one, benzyl methyl ketone) was also not successful unfortunately.

Although the reductive aldol reaction of aryl ketones proceeded in favor of the *syn*-diastereomer,

Scheme 1. Asymmetric zinc-catalyzed reductive aldol reaction of various ketones with α,β-unsaturated esters.[a], [b], [c], [d]

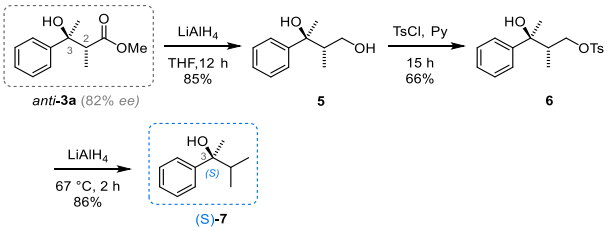


[a] Reactions were performed with $Zn(OAc)_2$ (15 mol%) and chiral **L8**-ligand (15 mol%) in *m*-xylene (1 mL) at –30 °C for 72 h, containing TES (1.0 mmol), aryl or heteroaromatic ketone **1a-t** (0.5 mmol) and specified acrylate **2** (0.6 mmol). [b] Isolated yield after silica gel chromatography. [c] *syn*/*anti* ratio is shown in the parentheses and was determined by ^{1}H NMR spectroscopy. [d] The *ee* values of *anti*-isomers were determined by chiral HPLC analysis.

10.1002/adsc.201901457

substantially improved diastereocontrol of the reaction was achieved *via* the application of heteroaromatic ketones. As shown in Scheme 1, zinc complex promoted the reaction of 2-acetylfuran (**3k**, **3l**) in enantioselective (up to 86% *ee*) and *anti*-diastereoselective manner (*dr* up to 1.5:1 for *anti*-**3k**). While the actual cause of such reversal is not fully understood, the similar tendency in terms of *dr* and *ee* was observed for product formation of reaction between 2-acetylthiophene and methyl acrylate (**3m**). Surprisingly, a methyl-group exchange in larger ethyl group in the acrylate fragment of **3n**, resulted in reversal of diastereoselectivity in favor of *syn*-isomer once again and decrease in enantioselectivity to 80% *ee*. In contrast to reactivity of furan- and thiophene-type ketones, similar investigation made for pyrrole (**3p**) and pyridine (**3q**) derivatives were unsuccessful.

Finally, we determined an absolute configuration of isolated *anti*-β-hydroxy ester **3a** by conversion to described in literature alcohol **7** with a single chiral center at C-3 position (Scheme 2).[8b,14] Based on comparison of the optical rotation of reduced (*S*)-3-methyl-2-phenyl-butan-2-ol (**7**) with the literature value, the absolute configuration of *anti*-**3a** was determined to be (2*R*,3*S*).



Scheme 2. Absolute configuration of *anti*-**3a** product.

In summary, we have developed a new strategy for the asymmetric reductive aldol reaction of ketones with α,β-unsaturated esters promoted by the chiral zinc catalyst. This is also the first successful application of zinc hydride reagent in stereoselective reductive aldol reaction of ketones. The elaborated catalytic system is based on cost-effective, environmentally benign and easily accessible zinc acetate complex with the readily available chiral diamine ligands. Furthermore, presented method provides a facile access to a broad range of highly functionalized enantioenriched β-hydroxy esters with very good yields and high enantioselectivities. Although the reaction diastereoselectivity is substrate-dependent and requires further improvement, this efficient protocol offers application of various aryl and heteroaromatic ketones without the use of high-priced catalysts previously reported.

Experimental Section

General procedure for Asymmetric Reductive Aldol Reaction of Ketones with Acrylates

Under an argon atmosphere at room temperature, $Zn(OAc)_2$ (13.8 mg, 0.075 mmol) and diamine ligand (45.0 mg, 0.075 mmol) were dissolved in anhydrous *m*-xylene (1 mL) and stirred for 60 min. Triethoxysilane (0.185 mL, 1.0 mmol) was then added, the mixture was cooled down to –30 °C and stirred for additional 5 min. Then, the corresponding ketone (0.5 mmol) followed by methyl acrylate (0.6 mmol) were added to the solution. After specified time, the reaction mixture was quenched by addition of 5 mL of saturated K_2CO_3 in methanol. The resulting mixture was stirred for 30 min, then 10 mL of ethyl acetate was added and the aqueous layer was extracted three times. The combined organic layers were washed with brine, then dried over anhydrous $MgSO_4$. The residue obtained after evaporation of the solvent under reduced pressure was purified by column chromatography on silica gel using hexane-ethyl acetate (6:1, v/v) as eluent. The *ee* values and *dr* ratios were then determined by HPLC methods and NMR spectroscopy. Part of isolated mixtures of diastereomers were separated by additional column chromatography on silica gel, eluted with hexanes-ethyl acetate (9:1, v/v) and the *ee* values of particular diastereomers were determined by chiral HPLC analysis.

Acknowledgements

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UPDATE

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Adv. Synth. Catal. **Year**, *Volume*, Page – Page

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