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Magnesium-Catalyzed Asymmetric Direct Aldol Addition of Ethyl Diazoacetate to Aromatic, Aliphatic, and α,β-Unsaturated Aldehydes

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The asymmetric catalytic direct aldol reaction constitutes a powerful strategy toward the atom economical synthesis of enantiomerically pure compounds. Several methods using both organic[1] and organometallic[2] catalysts have been developed obviating the need for stoichiometric quantities of preactivated intermediates such as enol silyl ethers or (thio)ketene acetals.[3] Although much progress has been made in the development of a direct ketone aldol, few methods exist for the equivalent ester aldol reaction.[4]

The nature of esters precludes their use in enamine catalysis. The higher pK_a values of α-protons of esters relative to aldehydes or ketones also makes them less reactive substrates in direct aldol reactions. Several strategies to address these issues have been developed; for example, the Baeyer−Villiger oxidation of β-hydroxy ketones affords the corresponding ester.[5] Another method involves the asymmetric reductive aldol reaction; however, this method is limited to the formation of α-alkyl-β-hydroxy esters.[6] A third strategy involves the asymmetric addition of an ester equivalent into a carbonyl acceptor.[4]

The direct aldol reaction between commercially available ethyl diazoacetate (EDA) and an aldehyde represents an attractive and an atom economical method toward products possessing synthetic utility. Unfortunately, this reaction is limited by the competitive formation of the β-ketoester via a process described by Roskamp.[7] The groups of Wang[4a] and Arai[4b] have made progress in this area; however, there still remains a need for a practical process with higher ee's.

In the context of a natural product synthesis we were inspired by the utility of the ProPhenol ligand **1** in the development of an asymmetric catalytic aldol between EDA and an aldehyde. Herein described is a highly enantioselective and general method toward α-diazo-β-hydroxy esters and the utility of these products toward the synthesis of diverse chiral building blocks (Figure 1). Furthermore, we expand the utility of the ProPhenol ligand using dinuclear species other than zinc, most notably magnesium.

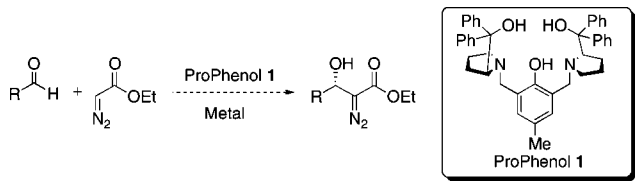
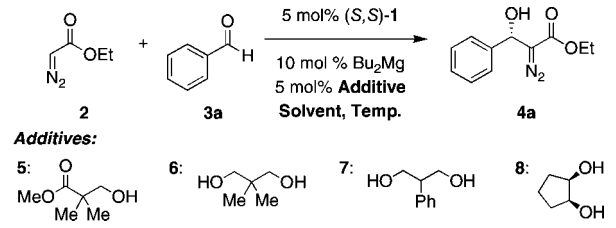


Figure 1. Bu_2Mg-ProPhenol **1**-catalyzed aldol reaction.

The addition of diethylzinc to (*S*,*S*)-ProPhenol **1** catalyzed the formation of product **4a**, however, in low enantioselectivity. After a survey of other metals, the di-*n*-butylmagnesium/**1**-derived catalyst system was found to give the highest enantioselectivity (Table 1, entry 1). A survey of solvents revealed that the enantioselectivity was solvent dependent where DME and dioxane afforded the opposite enantiomer of product **4a** (Table 1, entries 2 and 3)

Table 1. Selected Optimization Study[a]



entry	solvent	temp (°C)	additive	% ee[b]
1	THF	rt	−	27
2	dioxane	rt	−	−11
3	DME	rt	−	−16
4	THF	rt	**5**	37
5	THF	rt	**6**	47
6	THF	rt	**7**	51
7	THF	rt	**8**	65
8	THF	0	**8**	78
9	**THF**	**−20**	**8**	**82**
10	THF	−40	**8**	72

[a] Reactions were conducted on a 0.47 mmol scale at 0.5 M using equimolar quantities of **2** and **3a**. The catalyst was prepared by adding Bu_2Mg to a solution of the ligand. Where additives were employed, the additive and the catalyst were stirred for 45 min prior to the addition of the acceptor and donor. [b] Determined by chiral HPLC.

compared to THF. This solvent effect may derive from the metal remaining coordinatively unsaturated in the complex. Therefore, the addition of potential complexing agents (additives) that can compete for binding to the catalyst may lead to a more selective pathway.[8]

Focus was directed to bidentate coordinators which may span both magnesium ions in the complex. Adding such a modifier to a solution of di-*n*-butylmagnesium and (*S*,*S*)-ProPhenol **1** had a marked influence on the enantioselectivity (Table 1). Although hydroxy ester **5** gave only a modest enhancement in the enantiomeric ratio (entry 4), 2-substituted-1,3-propanediols **6** and **7** almost doubled the enantiomeric excess of product **4a** (entries 5 and 6). Gratifyingly, the addition of *cis*-1,2-cyclopentanediol **8**, presumably the best bidentate chelator, gave the greatest enhancement in the enantiomeric ratio (entry 7). Using additive **8**, the dependence of temperature on the selectivity of the reaction was studied (entries 7−10). It was found that −20 °C was the optimal temperature for this reaction (entry 9).

Furthermore, it was found that the slow addition of EDA to the reaction conducted at a concentration of 1.0 M afforded product **4a** in 92% yield and 95% ee (Table 2, entry 1). These conditions were then used to determine the generality of this process.

Evaluation of the reaction scope revealed that high levels of enantioselectivity could be achieved for a wide range of aldehydes (Table 2). Carbocyclic aromatic aldehydes with highly electron-donating groups (entries 2−3), electron-withdrawing groups (entries

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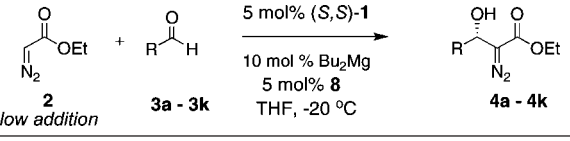
Table 2. Asymmetric Diazoester Aldol Reaction



entry	R	product	time (h)	yield[b]	% ee[c]
1	Ph (**3a**)	**4a**	18	92	95
2	*m*-$CH_3OC_6H_4$ (**4b**)	**4b**	18	83	90
3	*p*-$CH_3OC_6H_4$ (**3c**)	**3c**	18	70	87
4	*o*-ClC_6H_4 (**3d**)	**4d**	18	91	89
5	*m*-ClC_6H_4 (**3e**)	**4e**	18	88	98
6	*p*-ClC_6H_4 (**3f**)	**4f**	18	78	93
7	2-furyl (**3g**)	**4g**	18	83	96
8[d]	$(CH_3)_2CH$ (**3h**)	**4h**	24	56	97
9[d]	$CH_3(CH_2)_3$ (**3i**)	**4i**	24	50	97
10[d]	$PhCH_2CH_2$ (**3j**)	**4j**	24	76	90
11	PhCHCH (**3k**)	**4k**	18	50	94

[a] All reactions were conducted on a 0.94 mmol scale at 1 M using equimolar quantities of **2** and **3a**−**3k** unless otherwise noted. [b] Isolated yields. [c] Determined by chiral HPLC. [d] Reactions conducted at 0.5 M.

4−6), and a heteroaromatic aldehyde (entry 7) afforded products in 70−92% yield and 87−98% ee. Aliphatic aldehydes (entries 8−10) are known to be challenging substrates in metal-catalyzed direct aldol reactions.[9] In particular, α-unbranched aliphatic aldehydes typically require a 10-fold excess of the donor and result in modest yields and enantioselectivities. It is, therefore, noteworthy that this process affords yields ranging from 50 to 76% and in 90−98% ee using 1 equiv of both EDA and the respective aldehydes **3h**−**3j**. In addition, an α,β-unsaturated aldehyde (**3k**) also provides the normal adduct in high ee (Table 2, entry 11).

Transformation of diazoester **4a** to products **9**−**11** demonstrates the synthetic utility of the obtained products and establishes the absolute configuration (Figure 2). Treatment of **4a** with Et_3B

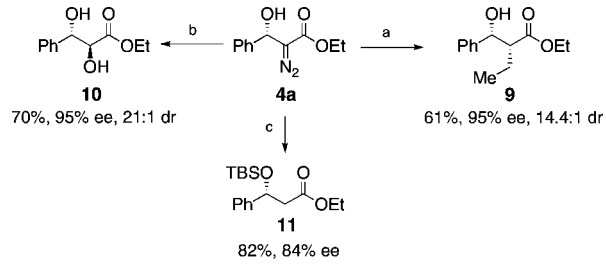


Figure 2. Conditions: (a) Et_3B, THF, rt; (b) DMDO, CH_2Cl_2, −35 °C; then $NaBH_4$, CH_2Cl_2, −78 °C; (c) (i) TBDMSCl, Imidazole, CH_2Cl_2; (ii) Pd(C), H_2, EtOAc.

afforded ester **9** in 61% yield, 14:1 dr, and with no degradation in ee.[10] Oxidative cleavage and subsequent reduction of product **4a** afforded **10**.[11] The reaction proceeded without epimerization and is a novel entry into enantiomerically pure *anti*-diols. Furthermore, silyl protection of **4a** followed by hydrogenation gave ester **11** in 82% yield with some loss in enantiomeric purity. Compounds **4a**[4b] and **11**[12] confirm that the product obtained using (*S*,*S*)-**1** furnishes *S*-**4a** by comparison to the literature.

In conclusion, we have developed a highly enantioselective method for the catalytic direct ester aldol between EDA and aromatic, aliphatic, and α,β-unsaturated aldehydes. The broad substrate scope, commercial availability of the reagents, and the high concentrations at which the reactions are performed make this a powerful method. The synthetic utility of the products obtained highlights processes where both carbon and heteroatom substituents can be introduced with high diastereo- and enantioselectivities. Further development of the synthetic potential of these aldol adducts is underway.

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Supporting Information Available: Experimental details and analytical data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org

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