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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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Abstract

Magnesium-catalyzed enantioselective aldol between ethyl diazoacetate and aromatic, aliphatic, and α,β -unsaturated aldehydes affords α -diazo- β -hydroxy-esters in high enantioselectivities. Aldol adducts resulting from this asymmetric transformation are versatile intermediates towards the synthesis of several ester containing chiral building blocks.

The asymmetric catalytic direct aldol reaction constitutes a powerful strategy towards the atom economical synthesis of enantiomerically pure compounds. Several methods using both organic¹ and organometallic² 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 $\text{p}K_{\text{a}}$ 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 towards 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 towards α -diazo- β -hydroxy esters and the utility of these products towards 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.

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) 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 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 – 76 % and in 90 – 98% ee using one equivalent of both EDA and the respective aldehydes **3h** – **3k**. In addition, an α,β -unsaturated aldehyde 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. Treatment of **4a** with Et₃B 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.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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References

1. Notz W, Tanaka F, Barbas CF III. *Acc Chem Res* 2004;37:580. [PubMed: 15311957] (b) Northrup AB, MacMillan DWC. *J Am Chem Soc* 2002;124:6798. [PubMed: 12059180]
2. (a) Trost BM, Ito H. *J Am Chem Soc* 2000;122:12033. (b) Trost BM, Ito H, Silcoff ER. *J Am Chem Soc* 2001;123:3367. [PubMed: 11457073] (c) Suzuki T, Yamagiwa N, Matsuo Y, Sakamoto S, Yamaguchi K, Shibasaki M, Noyori R. *Tetrahedron Lett* 2001;42:4669. (d) Gnanadesikan V, Horiuchi Y, Ohshima T, Shibasaki M. *J Am Chem Soc* 2004;126:7782. [PubMed: 15212518] and references therein (e) Li H, Da CS, Xiao YH, Li X, Su YN. *J Org Chem* 2008;73:7398. [PubMed: 18700798]
3. (a) Denmark SE, Stavenger RA. *Acc Chem Res* 2000;33:432. [PubMed: 10891061] and references therein (b) Carreira EM, Singer RA, Lee W. *J Am Chem Soc* 1994;116:8837. (c) Mikami K, Matsukawa S. *J Am Chem Soc* 1994;116:4077.
4. (a) Yao W, Wang J. *Org Lett* 2003;5:1527. [PubMed: 12713315] (b) Hasegawa K, Arai S, Nishida A. *Tetrahedron* 2006;62:1390. (c) Suto Y, Tsuji R, Kanai M, Shibasaki M. *Org Lett* 2005;7:3757. [PubMed: 16092868] (d) Li L, Klauber EG, Seidel D. *J Am Chem Soc* 2008;130:12248. [PubMed: 18722434] (e) Magdziak D, Lalic G, Lee HM, Fortner KC, Aloise AD, Shair MD. *J Am Chem Soc* 2005;127:7284. [PubMed: 15898756] (f) Evans DA, Downey CW, Hubbs JL. *J Am Chem Soc* 2003;125:8706. [PubMed: 12862448] (g) Ooi T, Kameda M, Taniguchi M, Maruoka K. *J Am Chem Soc* 2004;126:9685. [PubMed: 15291572] (h) Saito S, Kobayashi S. *J Am Chem Soc* 2006;128:8704. [PubMed: 16819844]
5. Kumagai N, Matsunaga S, Kinoshita T, Harada S, Okada S, Sakamoto S, Yamaguchi K, Shibasaki M. *J Am Chem Soc* 2003;125:2169. [PubMed: 12590545]
6. (a) Taylor SJ, Duffey MO, Morken JP. *J Am Chem Soc* 2000;122:4528. (b) Nishiyama H, Shiomi T, Tsuchiya Y, Matsuda I. *J Am Chem Soc* 2005;127:6972. [PubMed: 15884939] (c) Zhao CX, Duffey MO, Taylor SJ, Morken JP. *Org Lett* 2001;3:1829. [PubMed: 11405722] (d) Zhao D, Oisaki K, Kanai M, Shibasaki M. *Tetrahedron Lett* 2006;47:1403. (e) Deschamp J, Chuzel O, Hannedouche J, Riant O. *Angew Chem Int Ed* 2006;45:1292. (f) Lipshutz BH, Amorelli B, Unger JB. *J Am Chem Soc* 2008;130:14378. [PubMed: 18847266]
7. Holmquist CR, Roskamp EJ. *J Org Chem* 1989;54:3258.
8. Trost BM, Fettes A, Shireman BT. *J Am Chem Soc* 2004;126:2660. [PubMed: 14995157]
9. List B, Pojarliev P, Castello C. *Org Lett* 2001;3:573. [PubMed: 11178828]
10. Hooz J, Linke S. *J Am Chem Soc* 1968;90:6891.
11. Liao M, Yao W, Wang J. *Synthesis* 2004;16:2633.
12. Manzocchi A, Casati R, Fiecchi A, Santaniello E. *J Chem Soc, Perkin Trans 1* 1987;12:2753.

Figure 1.
Bu₂Mg-ProPhenol **1**-catalyzed aldol reaction.

Figure 2.

Conditions: (a) Et₃B, THF, rt; (b) DMDO, CH₂Cl₂, -35 °C; then NaBH₄, CH₂Cl₂, -78 °C; (c) (i) TBDMSCl, Imidazole, CH₂Cl₂; (ii) Pd(C), H₂, EtOAc.

Table 1

Selected Optimization Study.^a

Additives: 5: 6: 7: 8:
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 0.5M using equimolar quantities of **2** and **3a**. The catalyst was prepared by adding Bu₂Mg to a solution of the ligand. Where additives were employed, the additive and the catalyst were stirred for 45 minutes prior to the addition of the acceptor and donor.

^b Determined by chiral HPLC.

Table 2

Asymmetric diazoester aldol reaction.

<div> <div> $\begin{array}{c} \text{O} \\ \parallel \\ \text{C} \\ \mid \\ \text{CH}=\text{N}_2 \\ \mid \\ \text{OEt} \end{array} + \begin{array}{c} \text{O} \\ \parallel \\ \text{R}-\text{C}-\text{H} \end{array} \xrightarrow[\text{THF, -20 } ^\circ\text{C}]{\begin{array}{l} 5 \text{ mol\% (S,S)-1} \\ 10 \text{ mol \% Bu}_2\text{Mg} \\ 5 \text{ mol\% } \mathbf{13} \end{array}} \begin{array}{c} \text{OH} \quad \text{O} \\ \mid \quad \parallel \\ \text{R}-\text{C} \quad \text{C} \\ \mid \quad \mid \\ \text{N}_2 \quad \text{OEt} \end{array} \quad \mathbf{4a-4k}$ </div> <div> $\mathbf{2}$ </div> <div> $\mathbf{3a-3k}$ </div> <div> <i>slow addition</i> </div> </div>				
Entry	R	Product	Time (h)	Yield ^b
1	Ph (3a)	4a	18	92
2	<i>m</i> -CH ₃ OC ₆ H ₄ (3b)	4b	18	83
3	<i>p</i> -CH ₃ OC ₆ H ₄ (3c)	4c	18	70
4	<i>o</i> -ClC ₆ H ₄ (3d)	4d	18	91
5	<i>m</i> -ClC ₆ H ₄ (3e)	4e	18	88
6	<i>p</i> -ClC ₆ H ₄ (3f)	4f	18	78
7	2-Furyl (3g)	4g	18	83
8 ^d	(CH ₃) ₂ CH (3h)	4h	24	56
9 ^d	CH ₃ (CH ₂) ₃ (3i)	4i	24	50
10 ^d	PhCH ₂ CH ₂ (3j)	4j	24	76
11	PhCHCH (3k)	4k	18	50

^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.