

Diastereoselective Aldol Reaction of *N,N*-Dibenzyl- α -amino Aldehydes with Ketones Catalyzed by Proline

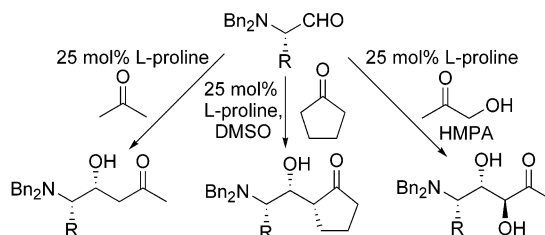
Qiangbiao Pan,[†] Benli Zou,[†] Yuji Wang,[†] and Dawei Ma^{*,†}

Department of Chemistry, Fudan University, Shanghai 200433, China, and State Key Laboratory of Bioorganic and Natural Products Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, 354 Fenglin Lu, Shanghai 200032, China

madw@pub.sioc.ac.cn

Received January 13, 2004

ABSTRACT



L-Proline-catalyzed direct aldol reaction of L-amino acid-derived *N,N*-dibenzyl amino aldehydes with acetone, cyclopentanone, or hydroxyacetone provides γ -amino- β -hydroxy- or γ -amino- α,β -dihydroxy-ketones with moderate to excellent yields and diastereoselectivities.

Development of new asymmetric carbon–carbon formation reactions is one of the most important problems of contemporary chemistry. Among recent achievements in this field, proline-catalyzed direct enantioselective aldol reaction between aldehydes and ketones is more attractive because of its operational simplicity and cheaper catalytic system.^{1,2} However, the scope of this catalytic reaction is still narrow and more substrates, especially functionalized aldehydes or ketones, need to be explored in order to expand its application in the synthesis of useful chemicals.

Due to their convenient availability, enantiopure α -amino aldehydes have received considerable attention in organic synthesis.³ Aldol-type reactions of α -amino aldehydes with

several different nucleophiles have been investigated and used for assembly of some biologically important molecules.³ However, these nucleophiles were limited to air- and moisture-sensitive agents such as silyl ketene acetals,⁴ titanium homoenolates,⁵ as well as boron enolates.⁶ One

(3) For reviews, see: (a) Gryko, D.; Chalko, J.; Jurczak, J. *Chirality* **2003**, *15*, 514. (b) Reetz, M. T. *Chem. Rev.* **1999**, *99*, 1121. (c) Reetz, M. T. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 1531. (d) Jurczak, J.; Golebiowski, A. *Chem. Rev.* **1989**, *89*, 149.

(4) (a) Takemoto, Y.; Matsumoto, T.; Ito, Y.; Terashima, S. *Tetrahedron Lett.* **1990**, *31*, 217. (b) Mikami, K.; Kaneko, M.; Loh, T.-P.; Terada, M.; Nakai, T. *Tetrahedron Lett.* **1990**, *31*, 3909. (c) Kiyooka, S.; Suzuki, K.; Shirouchi, M.; Kaneko, Y.; Tanimori, S. *Tetrahedron Lett.* **1993**, *34*, 5729. (d) Kiyooka, S.; Goh, K.; Nakamura, Y.; Takeuse, H.; Hena, M. *Tetrahedron Lett.* **2000**, *41*, 6599.

(5) (a) DeCamp, A. E.; Kawaguchi, A. T.; Volante, R. P.; Shinkai, I. *Tetrahedron Lett.* **1991**, *32*, 1867. (b) Campbell, J. A.; Lee, W. K.; Rapoport, H. J. *Org. Chem.* **1995**, *60*, 4602. (c) Armstrong, J. D.; Hartner, F. W.; DeCamp, A. E.; Volante, R. P.; Shinkai, I. *Tetrahedron Lett.* **1992**, *33*, 6599. (d) McWilliams, J. C.; Armstrong, J. D.; Zheng, N.; Bhupathy, M.; Volante, R. P.; Reider, P. J. *Am. Chem. Soc.* **1996**, *118*, 11970.

(6) (a) Reetz, M. T.; Rivadeneira, E.; Niemeyer, C. *Tetrahedron Lett.* **1990**, *31*, 3863. (b) Hamada, Y.; Hayashi, K.; Shioiri, T. *Tetrahedron Lett.* **1991**, *32*, 931. (c) Hayashi, K.; Hamada, Y.; Shioiri, T. *Tetrahedron Lett.* **1991**, *32*, 7287. (d) Gennari, C.; Moresca, D.; Vulpetti, A.; Pain, G. *Tetrahedron* **1997**, *53*, 5593.

[†] Fudan University.

[‡] Shanghai Institute of Organic Chemistry.

(1) For reviews, see: (a) List, B. *Synlett* **2001**, 1675. (b) List, B. *Tetrahedron* **2002**, *58*, 5573. (c) Alcaide B.; Almendros, P. *Angew. Chem., Int. Ed.* **2003**, *42*, 858.

(2) (a) List, B.; Lerner, R. A.; Barbas, C. F., III. *J. Am. Chem. Soc.* **2000**, *122*, 2395. (b) Notz, W.; List, B. *J. Am. Chem. Soc.* **2000**, *122*, 7386. (c) List, B.; Pojarliev, P.; Castello, C. *Org. Lett.* **2001**, *3*, 573. (d) Sakthivel, K.; Notz, W.; Bui, T.; Barbas, C. F., III. *J. Am. Chem. Soc.* **2001**, *123*, 5260.

Table 1. Proline-Catalyzed Reaction of *N*-Protected Phenylalaninals with Acetone^a

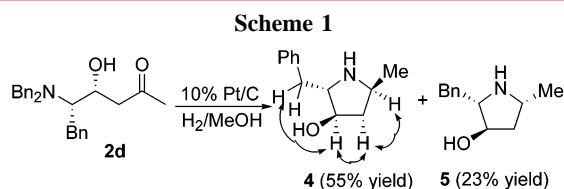
a: R = Tr, R' = H; b: R = Boc, R' = H;
c: R = Cbz, R' = H; d: R = R' = Bn

entry	aldehyde	catalyst	yield (%) ^b	2:3 ^c
1	1a	L-proline	48	98:2
2	1b	L-proline	93	84:16
3	1c	L-proline	82	76:24
4	1d	L-proline	98	95:5
5	1d	D-proline	78	33:67
6	1d	L-proline	77	92:8 ^d

^a Reaction conditions: aldehyde (1 mmol), proline (0.25 mmol) in acetone (10 mL). ^b Isolated yield for **2** and **3**. ^c Determined by weighing the separated isomers **2** and **3**. ^d Reaction was carried out in a mixture of 2 mL of acetone and 8 mL of DMSO.

exception was nitroalkanes, which have been studied by several groups to give Henry reaction products.⁷ In this communication, we wish to describe a direct aldol reaction of α -amino aldehydes with ketones catalyzed by proline, which delivers synthetically useful γ -amino- β -hydroxy- or γ -amino- α,β -dihydroxy-ketones diastereoselectively.

As summarized in Table 1, we initially checked the proline-catalyzed direct aldol reaction of acetone with several *N*-substituted phenylalaninals in order to identify a favored *N*-protecting group. It was found that *N*-trityl phenylalaninal gave the best diastereoselectivity but the lowest yield (entry 1). This drawback might come from its poor reactivity resulting from the steric hindrance of the trityl group. Both *N*-Boc phenylalaninal and *N*-Cbz phenylalaninal showed lower diastereoselectivity, although their reaction yields were satisfactory (entries 2 and 3). The most acceptable result was observed in the case of *N,N*-dibenzyl phenylalaninal as a substrate and L-proline as a catalyst, which provided aldol products **2d** and **3d** in 98% combination yield and 90% de (entry 4). To establish the stereochemistry of the major product, **2d** was subjected to Pt/C-catalyzed hydrogenation to afford pyrrolidines **4** and **5** (Scheme 1). By NOE analysis

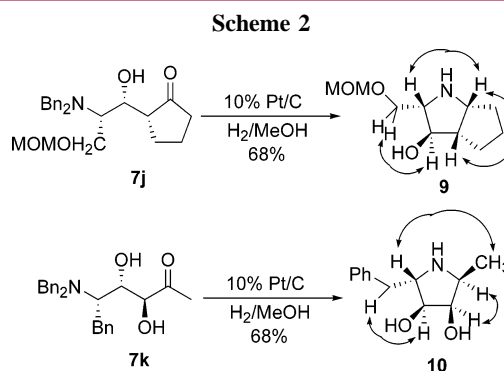


it was found that the 2-benzyl group and the 3-hydroxy group in **4** were trans to each other, which implied that the configuration of the newly generated stereocenter in **2d** was *R*. The chirality of proline should be essential for diastereoselectivity because in the case of **1d** as a substrate, L-proline-

catalyzed reaction provided good diastereoselectivity in favor of syn product **2d** (entry 4), while D-proline-catalyzed reaction gave poor diastereoselectivity in favor of anti product **3d** (entry 5). These results implied that (*S*)-*N,N*-dibenzyl amino aldehydes and L-proline are a matched pair for diastereoselectivity induction. In addition, the solvent was another noticeable factor because a slightly lower yield was obtained when mixed acetone and DMSO were utilized (entry 6).

In view of the above encouraging result, the scope of this reaction was explored by varying ketones and *N,N*-dibenzyl amino aldehydes, and the results are summarized in Table 2. Good to excellent yields were observed for reaction of acetone with several *N,N*-dibenzyl amino aldehydes except for valinal **6b** (entries 1–6). We reasoned that this problem resulted from steric hindrance of **6b**. The ratios for syn products **7** and anti products **8** were very close for simple and some functionalized aldehydes (entries 1–5). However, this value changed drastically when serine-derived aldehyde **6f** was employed, which might be due to formation of additional interaction of MOM group with catalyst in the transition state.

We found that cyclopentanone also worked for this reaction if DMSO was used as the solvent, producing separable aldol products **7g–j** in moderate yields, together with some unidentified isomers (entries 7–10). The γ -amino ketone **7j** was subjected to a hydrogenolysis/cyclization/hydrogenation process and afforded a fused bicyclic compound **9**. By NOE analysis of **9**, we established the stereochemistry of **7j** (Scheme 2).



Proline-catalyzed aldol reaction of hydroxyacetone with aldehydes is a more attractive transformation for organic synthesis because, in this way, a 1,2-diol unit could be formed concurrently with carbon–carbon bond formation.^{2b,d} We were pleased to find that L-proline-catalyzed reaction of hydroxyacetone with *N,N*-dibenzyl phenylalaninal in DMSO produced **7k** in 79% yield, together with other minor isomers (entry 11). The stereochemistry assignment of **7k** was

(7) (a) Sasai, H.; Kim, W.-S.; Suzuki, T.; Shibasaki, M. *Tetrahedron Lett.* **1994**, 35, 6123. (b) Corey, E. J.; Zhang, F.-Y. *Angew. Chem., Int. Ed.* **1999**, 38, 1931. (c) Misumi, Y.; Matsumoto, K. *Angew. Chem., Int. Ed.* **2002**, 41, 1031. (d) Ma, D.; Pan, Q.; Han, F. *Tetrahedron Lett.* **2002**, 43, 9401.

Table 2. L-Proline-Catalyzed Direct Aldol Reaction of *N,N*-Dibenzyl Aldehydes with Ketones^a

Entry	Aldehyde	Ketone	Solvent	Time (day)	Product (yield ^b)	
1			-	3		
2			-	6		
3			-	3		
4			-	3		
5			-	3		
6			-	3		
7			DMSO	1.5		
8			DMSO	2		other isomers (2%) ^c
9			DMSO	1.5		other isomers (3%)
10			DMSO	2		other isomers (10%)
11			DMSO	1		other isomers (6%)
12			HMPA	1		other isomers (4%)
13			HMPA	1		other isomers (4%) ^c
14			HMPA	1.5		other isomers (4%)
15			HMPA	2		other isomers (11%)
16			HMPA	1.5		other isomers (9%) ^c

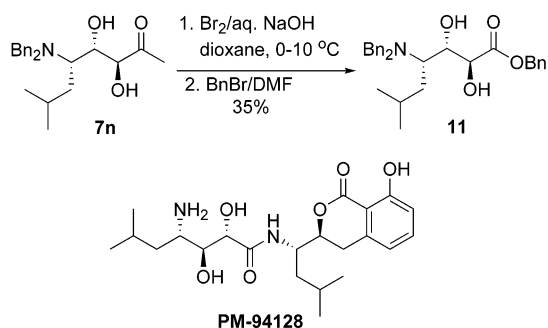
^a Reaction conditions: aldehyde (1 mmol) with either L-proline (0.25 mmol) in 10 mL of acetone (entries 1–6), 2 mL of cyclopentanone and 8 mL of DMSO (entries 7–10), 2 mL of hydroxyacetone and 8 mL of DMSO (entry 11), or 2 mL of HMPA (entries 12–16). ^b Isolated yield. ^c Yield was calculated from the ratio of major product and its inseparable isomers determined by ¹H NMR.

accomplished by hydrogenating it to pyrrolidine **10** as indicated in Scheme 2. Among solvents tested, HMPA showed some improvement for diastereoselectivity (compare entries 11 and 12), while THF and CH₂Cl₂ gave worse results. Using these conditions, we tested other amino aldehydes and observed that good diastereoselectivities were

obtained for simple amino aldehydes (entries 12–14), while functionalized amino aldehydes showed lower diastereoselectivities (entries 15 and 16).

As shown in Scheme 3, compound **7n**, a major aldol product of hydroxyacetone with *N,N*-dibenzyl isoleucinal, was subjected to oxidative cleavage⁸ with sodium hypobro-

Scheme 3



mite to produce an amino acid, which was treated with benzyl bromide and K_2CO_3 in DMF to provide enantiopure (2*S*,3*S*,4*S*)-4-amino-2,3-dihydroxyester **11** in 35% yield. This compound is obviously a suitable intermediate for assembling PM-94128, an antitumor agent synthesized by Vallee and co-workers.⁹ This fact, together with the ready transformation

(8) Stacy, G. W.; Klundt, I. L.; Davis, G. T.; Nielsen, N. A.; Power, M. S.; Rector, D. L.; Razniak, S. L. *J. Org. Chem.* **1966**, *31*, 1753.

of the present reaction products to the polysubstituted pyrrolidines¹⁰ as outlined in Schemes 1 and 2, clearly shows that proline-catalyzed aldol reaction of *N,N*-dibenzyl amino aldehydes with ketones could find considerable use in organic synthesis. Further studies in this direction are in progress and will be reported in due course.

Acknowledgment. The authors are grateful to the Chinese Academy of Sciences, National Natural Science Foundation of China (Grant 20242003), and Science and Technology Commission of Shanghai Municipality (Grants 02JC14032 and 03XD14001) for their financial support.

Supporting Information Available: Experimental procedures and characterizations for compounds **2d**, **4**, **7a–p**, and **9–11**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

OL049927K

(9) Synthesis: (a) Patel, S. K.; Murat, K.; Py, S.; Vallee, Y. *Org. Lett.* **2003**, *5*, 4081. Isolation: (b) Canedo, L. M.; Fernandez Puentes, J. L.; Perez Baz, J.; Acebal, C.; de la Calle, F.; Garcia Gravalos, D.; Garcia de Quesada, T. *J. Antibiot.* **1997**, *50*, 175.

(10) For recent reviews on the biology and synthetic usages of polysubstituted pyrrolidines, see: (a) O'Hagen, D. *Nat. Prod. Rep.* **2000**, *17*, 435. (b) Broggini, G.; Zecchi, G. *Synthesis* **1999**, 905.