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Vicinal Amino Alcohols as Organocatalysts in Asymmetric Cross-Aldol Reaction of Ketones: Application in the Synthesis of Convolutamydine A†

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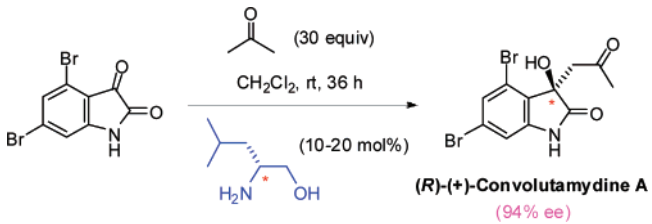
ABSTRACT



Leucinol and valinol have been identified as efficient organocatalysts for the aldol reaction of isatin and its derivatives (as examples of activated, non-enolizable ketones) with acetone. Uncommon mechanistic features were observed and used in the formulation of the transition state of the reaction.

The aldehyde−aldehyde and aldehyde−ketone aldol reaction, proceeding via an enamine intermediate, is one of the pillars of synthetic chemistry.[1] Recent years have witnessed a boom of its catalytic version, with proline and its congeners acting as highly enantioselective catalysts.[2] On the other hand, catalytic, intermolecular ketone−ketone cross-aldol reactions are rare and represent a significant challenge.[1,2]

While secondary amines are usually employed to mediate these aldol-type reactions,[2,3] the use of primary amines is less common,[2,3] presumably owing to their tendency to form stable imines rather than enamines. Furthermore, the dominant position of proline (itself a secondary amine) is partly related to the key function of its carboxyl group in steering the reactants,[2,4,5] whereas amines lacking the carboxyl or its equivalent operate mainly on steric grounds.[2] Herein, we report that vicinal amino alcohols,[3a−c] derived from common α-amino acids, act as superior catalysts in the cross-aldol reaction of isatins **1a**−**c** with acetone to produce 3-hydroxyindolones **2a**−**c**.

The aldol reaction of isatin with acetone, catalyzed by proline, has been reported to give inferior results, whereas

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(1) Carreira, E. M.; Fettes, A.; Marti, C. *Org. React.* **2006**, *67*, 1.

(2) (a) Dalko, P. I.; Moisan, L. *Angew. Chem., Int. Ed.* **2001**, *40*, 3726. (b) Dalko, P. I.; Moisan, L. *Angew. Chem., Int. Ed.* **2004**, *43*, 5138. (c) Berkessel, A.; Gröger, H. *Asymmetric Organocatalysis*; Wiley-VCH: Weinheim, 2005. (d) Dalko, P. I., Ed. *Enantioselective Organocatalysis*; Wiley-VCH: Weinheim, 2007. (d) For kinetic studies on the aldol reaction of acetophenone with acetone and related examples, see: Guthrie, J. P.; Wang, X.-P. *Can. J. Chem.* **1991**, *69*, 339 and references therein.

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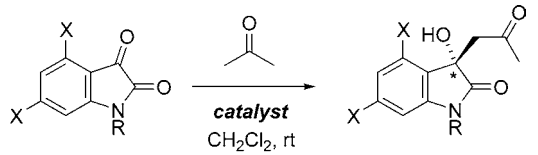
dipeptides with proline at the N-terminus were more effective (≤73% ee).[6,7] Using *N*-methylisatin (**1a**) and acetone as a model pair of ketones (Scheme 1), we embarked on the

Scheme 1. Aldol Condensation of Isatins with Acetone[a]



1a, R = Me, X = H
1b, R = H, X = H
1c, R = H, X = Br

2a, R = Me, X = H
2b, R = H, X = H
2c, R = H, X = Br

[a] For catalysts, see Table 1.

development of a more efficient catalyst, hoping to increase the enantioselectivity and turnovers (Table 1) and to gain a more detailed mechanistic picture.

Consistent with the Tomasini report,[6a,b] proline, its methyl ester, and prolinol exhibited low enantioselectivity (Table 1, entries 1−3), whereas diphenylprolinol and valine failed to catalyze the reaction.[8] By contrast, vicinal amino alcohols with primary amino and hydroxy groups, namely, valinol and its analogues, turned out to catalyze the reaction very efficiently, with 88−95% ee (entries 4−10).[9] Leucinol was identified as the most effective catalyst, both in terms of the reaction rate and enantioselectivity (entry 9). The highest enantioselectivities were attained in CH_2Cl_2; in pure acetone, the reaction was faster but at the expense of the asymmetric induction (entry 11), whereas in methanol, further acceleration was observed but the product was racemic (entry 12).

We then returned to isatin **1b** with a view that the 3-hydroxyindol-2-one motif constitutes a core structural feature of a number of natural products, such as convolutamydines A−E,[10] diazonamide,[11] and other densely functionalized molecules.[12] As expected, L-leucinol (20 mol %) exhibited excellent reactivity and enantioselectivity, affording

Table 1. Aldol Reaction of Isatins **1a**−**c** with Acetone Catalyzed by Selected Amino Acids and Amino Alcohols[a]

entry	isatin	catalyst	solvent	yield[b] (%)	**2**, % ee[c] (configuration)[d]
1	**1a**	L-proline	CH_2Cl_2	18	40 (*S*)-(−)
2	**1a**	L-proline methyl ester	CH_2Cl_2	12	25 (*R*)-(+)
3	**1a**	L-prolinol	CH_2Cl_2	20	20 (*S*)-(−)
4	**1a**	L-valinol	CH_2Cl_2	84	95 (*S*)-(−)
5	**1a**	D-cyclohexylglycinol	CH_2Cl_2	50	95 (*R*)-(+)
6	**1a**	L-phenylglycinol	CH_2Cl_2	70	88 (*S*)-(−)
7	**1a**	L-phenylalaninol	CH_2Cl_2	50	94 (*S*)-(−)
8	**1a**	L-*tert*-leucinol	CH_2Cl_2	50	95 (*S*)-(−)
9	**1a**	L-leucinol	CH_2Cl_2	98	95 (*S*)-(−)
10	**1a**	L-leucinol[e]	CH_2Cl_2	88	94 (*S*)-(−)
11	**1a**	L-leucinol	Me_2CO	98	72 (S)-(−)
12	**1a**	L-leucinol	MeOH	98	racemic
13	**1b**	L-leucinol	CH_2Cl_2	98	94 (*S*)-(−)[f]
14	**1c**	L-leucinol	CH_2Cl_2	98	95 (*S*)-(−)[f]

[a] The reaction was carried out at 0.6 mol scale (**1**) with 30 equiv of acetone in the presence of 20 mol % of the catalyst and water (1 equiv) at room temperature for 36 h (12 h for entries 11 and 12). The crude product was purified by chromatography on aluminum oxide pretreated with Et_3N to suppress racemization. [b] Determined by NMR. [c] Determined by chiral HPLC (see Supporting Information for details). [d] The absolute configuration was inferred from the assignment for **2a**−**c** (ref 6a,b), which was based on the CD spectra and X-ray crystallography. [e] At 40 °C in 8 h. [f] The product was obtained as a pure enantiomer (>99% ee) on a single crystallization from a mixture of hexane, CH_2Cl_2, and MeOH.

(3) Amino alcohols and vicinal diamines have been previously shown to catalyze aldol-type reactions. For examples of the aldol reaction of aldehydes with α-fluoro-acetone, catalyzed by prolinol, see: (a) Zhong, G.; Fan, J.; Barbas, C. F. *Tetrahedron Lett.* **2004**, *45*, 5681. For Robinson annulation, catalyzed by prolinol and its congeners (though lacking the information on enantioselectivity), see: (b) Bui, T.; Barbas, C. F. *Tetrahedron Lett.* **2000**, *41*, 6951. For hydroxyamination of aldehydes, catalyzed by amino alcohols, see: (c) Kano, T.; Ueda, M.; Takai, J.; Maruoka, K. *J. Am. Chem. Soc.* **2006**, *128*, 6046. For aldol reaction of ArCHO with acetone and its derivatives, catalyzed by vicinal diamines, see: (d) Luo, S.; Xu, H.; Li, J.; Zhang, L.; Cheng, J.-P. *J. Am. Chem. Soc.* **2007**, *129*, 3074. For an overview of diamine catalysts, see: (e) Notz, W.; Tanaka, F.; Barbas, C. F. *Acc. Chem. Res.* **2004**, *37*, 580. The amino alcohols typically featured a secondary amine moiety, whereas the diamines typically contained a combination of one secondary and one tertiary amino group or one primary and one tertiary. For the use of amino acids with a primary amino group as catalysts for aldol reaction, see for example: (f) Eder, U.; Sauer, G.; Wiechert, R. *Angew. Chem., Int. Ed. Engl.* **1971**, *10*, 496. (g) Tanaka, F.; Thayumanava, R.; Mase, N.; Barbas, C. F. *Tetrahedron Lett.* **2004**, *45*, 325. (h) Córdova, A.; Zou, W.; Dziedzic, P.; Ibrahem, I.; Reyes, E.; Xu, Y. *Chem. Eur. J.* **2006**, *12*, 5383 and references therein. (i) Ramasastry, S. S. V.; Zhang, H.; Tanaka, F.; Barbas, C. F. *J. Am. Chem. Soc.* **2007**, *129*, 288. For a general overview, see: (j) Tanaka, F.; Barbas, C. F. Enamine Catalysis, In *Enantioselective Organocatalysis*; P. I. Dalko, P. I., Ed.; Wiley-VCH: Weinheim, 2007; p 19.

(4) (a) Cheong, P. H.-Y.; Houk, K. N. *J. Am. Chem. Soc.* **2004**, *126*, 13912. (b) Allemann, C.; Gordillo, R.; Clemente, F. R.; Cheong, P. H.-Y.; Houk, K. N. *Acc. Chem. Res.* **2004**, *37*, 558. (c) Seebach, D.; Beck, A. K.; Badine, D. M.; Linbach, M.; Eschenmoser, A.; Treasurywala, A. M.; Hobi, R.; Prikoszovich, W.; Linder, B. *Helv. Chim. Acta* **2007**, *90*, 425.

(5) A similar effect has been attributed to the OH in prolinol[3a] and to NH in 5-pyrrolidine-2-yl-1*H*-tetrazole.[3j]

(6) (a) Luppi, G.; Cozzi, P. G.; Monari, M.; Kaptein, B.; Broxterman, Q. B.; Tomasini, C. *J. Org. Chem.* **2005**, *70*, 7418−7421. (b) Luppi, G.; Monari, M.; Corrêa, R. J.; Violante, F. A.; Pinto, A. C.; Kaptein, B.; Broxterman, Q. B.;. Garden, S. J.; Tomasini, C. *Tetrahedron* **2006**, *62*, 12017. (c) Chen, G.; Wang, Y.; He, H.; Gao, S.; Yang, X.; Hao, X. *Heterocycles* **2006**, *68*, 2327.

(7) For aldol reaction of isatin with acetone, mediated by non-chiral secondary amines or K_2CO_3, see: (a) Braude, F.; Lindwall, H. G. *J. Am. Chem. Soc.* **1933**, *55*, 325. (b) Garden, S. J.; Torres, J. C.; Ferreira, A. A.; da Silva, R. B.; Pinto, A. C. *Tetrahedron Lett.* **1997**, *38*, 1501. (c) Garden, S. J.; da Silva, R. B.; Pinto, A. C. *Tetrahedron* **2002**, *58*, 8399.

(8) MacMillan's imidazolone salt and Jørgensen's TMS ether of diarylprolinol[2] produced only traces of (±)-**2b** in pure acetone.

(9) Partial racemization of the product was observed on column chromatography on silica gel; alumina proved to be a safer adsorbent. The enantiomeric enrichment on chromatography, reported by Tomasini,[6a] could not be confirmed.

(10) (a) Kamano, Y.; Zhang, H.; Ichihara, Y.; Kizu, H.; Komiyama, K.; Pettit, G. R. *Tetrahedron Lett.* **1995**, *36*, 2783. (b) Zhang, H.; Kamano, Y.; Ichihara, Y.; Kizu, H.; Komiyama, K.; Itokawa, H.; Pettit, G. R. *Tetrahedron* **1995**, *51*, 5523. (c) Takayama, H.; Shimizu, T.; Sada, H.; Harada, Y.; Kitajima, M.; Aimi, N. *Tetrahedron* **1999**, *55*, 6841. (d) Kamano, Y.; Kotake, A.; Hashima, H.; Hayakawa, I.; Hiraide, H.; Zhang, H. P.; Kizu, H.; Kizu, Komiyama, K.; Hayashi, M.; Pettit, G. R. *Collect. Czech. Chem. Commun.* **1999**, *64*, 1147.

(11) (a) Nicolaou, K. C.; Huang, X.; Giuseppone, N.; Rao, P. B.; Bella, M.; Reddy, M. V.; Snyder, S. A. *Angew. Chem., Int. Ed.* **2001**, *40*, 4705. (b) Nicolaou, K. C.; Bella, M.; Che, D. Y.-K.; Huang, X.; Ling, T.; Snyder, S. A. *Angew. Chem., Int. Ed.* **2002**, *41*, 3495. (c) Nicolaou, K. C.; Snyder, S. A.; Giuseppone, N.; Huang, X. H.; Bella, B.; Reddy, M. V.; Rao, P. B.; Koumbis, A. E.; Giannakakou, P.; O'Brate, A. *J. Am. Chem. Soc.* **2004**, *126*, 10174. (d) Nicolaou, K. C.; Chen, D. Y.-K.; Huang, X. H.; Ling, T. T.; Bella, M.; Snyder, S. A. *J. Am. Chem. Soc.* **2004**, *126*, 12888.

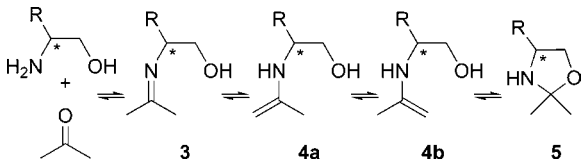
the aldol product **2b** in 94% ee (entry 13) at room temperature over 36 h.[9,13] With 10 mol % of leucinol, the reaction was still effective, although at the expense of the rate (4 days at rt) and a marginal loss of enantioselectivity (by ~2% ee). However, further decrease in the catalyst loading to 5 mol % rendered the reaction unacceptably slow.

This high-yielding aldol reaction opened a straightforward route to convolutamydine A (**2c**), whose (*R*)-(+)-enantiomer[6a,b,10] was isolated from the marine bryozoan species *Amathia convoluta* and identified as an anti-leukemia agent.[10] The L-leucinol-catalyzed reaction afforded its unnatural (*S*)-(−)-enantiomer (entry 14). The natural convolutamydine A (*R*)-(+)-**2c** was then prepared on a larger scale by an aldol reaction using D-leucinol (20 mol %) as catalyst (80% isolated yield, 94% ee) and found identical with the natural product.[14,15]

The aldol reaction of **1b** with Me_2CO in the presence of leucinol (20 mol %) proved to be first-order in **1b** and irreversible under the reaction conditions.[16] The reaction can also be catalyzed by $BuNH_2$ or Et_2NH, whereas Et_3N was found to be inert, suggesting an enamine intermediate.[17] Accordingly, *N*-methylleucinol failed to catalyze the reaction at an appreciable rate, showing the key importance of the primary amino group. On the other hand, the methyl ether of leucinol and *O*-trimethylsilylleucinol turned out to catalyze the reaction but more slowly and far less selectively than leucinol (both reached ~50% conversion over 36 h at rt, with 50% ee). A linear correlation was found between the enantiopurity of leucinol and that of the product **2b**, which indicates that only one molecule of the catalyst is likely to be involved in the stereodiscriminating step.

On mixing acetone and leucinol, formation of species **3**−**5** can be a priori expected (Scheme 2). Monitoring of a 30:1 acetone−leucinol mixture in $CDCl_3$ by ^1H NMR at 37 °C revealed a gradual disappearance of leucinol with a concomitant build-up of oxazolidine **5**. The reaction was complete within 2 h, and no other species could be detected during this process. The presence of water (1 equiv with respect to leucinol) did not have any noticeable effect on the formation of **5**. On the other hand, when isatin (**1b**) (5-fold excess to leucinol) was added to a 150:1 acetone−leucinol mixture (this ratio mimics the concentrations in the catalytic reaction) in $CDCl_3$ at room temperature, a quantitative conversion into **5** was observed within several minutes, demonstrating the catalytic effect of isatin. On the other hand, the isolated oxazolidine **5** proved unstable in the absence of an excess of acetone, as its solution in (wet) $CDCl_3$ slowly decomposed back to acetone and leucinol, possibly via enamine **4**.

Scheme 2. Equilibrium in the Acetone−Leucinol Mixture (R = Me_2CHCH_2)



The aldol reaction of **1b** with acetone in $CHCl_3$ at 37 °C was found to be catalyzed by oxazolidine **5** as effectively as by leucinol, with the same rate constant (at 20 mol % catalyst loading). By contrast, in CH_2Cl_2, the reaction catalyzed by leucinol was 3 times slower than that in $CHCl_3$, and 10 times slower with **5**.[18] Only marginal differences in the enantioselectivity were observed for $CHCl_3$ (86% vs 90% ee), whereas in CH_2Cl_2 both reactions gave the same result (90% ee).[19]

Monitoring the enantiomeric ratio while the reaction was in progress (at 37 °C) revealed little enantioselectivity in the initial stages, whereas after ca. 20−30 min, one enantiomer began to dominate (Figure 1). This intriguing behavior

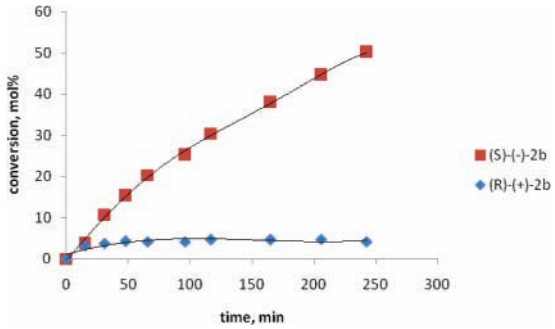


Figure 1. Monitoring the enantioselectivity for the reaction of isatin (**1b**) with acetone catalyzed by L-valinol.

may seem to suggest an autocatalysis by the product (**2b**), but this mechanism was ruled out by a control experiment, carried out in the presence of (*S*)-(−)-**2b** (20 mol %), added at the onset of the reaction. The latter additive neither catalyzed the reaction nor altered the enantiomeric ratio of the gradually produced **2b** when L-leucinol was also added to the mixture.[20−22]

As discussed above, isatin **1b** accelerates the formation of oxazolidine **5** from acetone and leucinol, thereby dramati-

(12) (a) Franz, A. K.; Dreyfuss, P. D.; Schreiber, S. L. *J. Am. Chem. Soc.* **2007**, *129*, 1020. (b) Schulz, V.; Davoust, M.; Lemarié, M.; Lohier, J.-F.; Sopkova de Oliveira Santos, J.; Metzner, P.; Brière, J.-F. *Org. Lett.* **2007**, *9*, 174. (c) Kumar, R. R.; Perumal, S. *Tetrahedron* **2007**, *63*, 12220.

(13) 2-Butanone was found to react readily with **1b**, giving a 5:1 mixture of regioisomers in favor of R-CH_2COEt (88% ee).

(14) Our synthetic, enantiopure (*R*)-(+)-**2c** showed $[\alpha]_D$ +48.9 (*c* 0.33, MeOH), whereas the natural product, isolated from *Amathia convoluta*, had $[\alpha]_D$ +27.4 (*c* 0.06, MeOH),[10a] suggesting a partial racemization during the isolation process or that the natural product might not be enantiopure.

(15) A single crystallization from a CH_2Cl_2−hexane−methanol mixture provided enantiopure (*R*)-(+)-**2c**.

(16) Treatment of (±)-**2b** with a mixture of leucinol and Me_2CO in CH_2Cl_2 did not lead to deracemization. Hence, the partial racemization observed on silica[9] can be attributed to dehydration−rehydration rather then the retroaldol−aldol sequence.

(17) A slow conversion of **1b** into (±)-**2b** was observed with quinine as catalyst in pure acetone; the reaction was completed in 4 days.

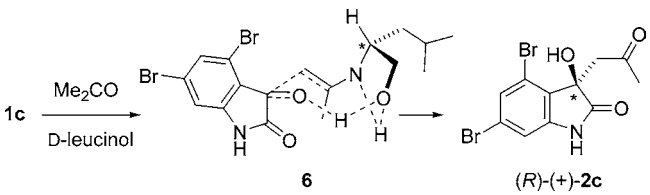
(18) The reaction rate in this case presumably depends on the rate of equilibration **5** ⇆ **4a**,**b**, which is apparently faster in $CHCl_3$ than in CH_2Cl_2.

(19) Note that the related oxazolidinone species, generated from proline and cyclohexanone and regarded as "parasitic", has recently been suggested to be an active participant of the catalytic cycle.[4c]

cally lowering the concentration of free leucinol within minutes. Therefore, it can be speculated that the aldol reaction of **1b** with acetone is initially catalyzed by free leucinol (note that both $BuNH_2$ and K_2CO_3[7] are also catalytically active). However, as the concentration of leucinol gradually decreases, the latter process is eventually suppressed in favor of a different, highly enantioselective reaction that uses enamine **4** as a reactive intermediate, while oxazolidine **5** serves as a nonreactive resting state.[18] This scenario is consistent with the linear dependence of the product enantiopurity on that of leucinol (at full conversion; vide supra) and with the observed increase of enantiomeric excess as the reaction progresses. The key role of the hydroxy group in the catalyst, demonstrated by its O-methylation (vide supra), is consistent with the formation of **5**. This also suggests that hydrogen bonding between the keto group of **1** and the reactive intermediate[2,4,6b,c] is a prerequisite for the highly enantioselective process, which is in line with the formation of a racemic product in MeOH, an interfering protic solvent (entry 12) and with a much reduced enantioselectivity attained with *O*-methyl- and *O*-trimethylsilylleucinol (from ≥90% to 50% ee; vide supra). Accordingly, transition state **6**, using the *syn*-form of the intermediate enamine (**4b**), can be proposed to account for these effects (Scheme 3).[23] Preliminary quantum chemistry calculations (DFT with TPSS functional in cc-PVDZ basis) lend additional support to this pathway.[24]

In conclusion, primary amino alcohols, available from natural α-amino acids in one step, have been shown to act as efficient, enantioselective organocatalysts for the cross-aldol reaction of isatins **1a**−**c** (activated, non-enolizable ketones) with acetone (an enolizable, sterically undemanding ketone).[13,25] Oxazolidine **5** has been suggested as the resting state of the catalyst. Its quick formation, catalyzed by isatin, has been found to be the prerequisite for a highly enantioselective aldol reaction, since this process sequesters the free leucinol, which itself would act as a nonselective catalyst. Both enantiomers of convolutamydine A (**2c**) were synthesized in an enantiomerically pure form.[26]

Scheme 3. Condensation of **1c** with Acetone Catalyzed by D-Leucinol To Produce Natural Convolutamydine A (*R*)-(+)-**2c**



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Supporting Information Available: Experimental methods and ^1H and ^{13}C NMR spectra and HPLC traces for key compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(20) The overall ee of the product (80% ee after 2 h) in this instance was a mathematical combination of the enantiopurity of the added (*S*)-(−)-**2b** (20 mol% of 99% ee) and that normally produced on catalysis with leucinol (35% conversion, 70% ee).

(21) For a discussion of another case of gradual amplification (operating via a different mechanism), see: Mathew, S. P.; Iwamura, H.; Blackmond, D. G. *Angew. Chem., Int. Ed.* **2004**, *43*, 3317 and references therein.

(22) Pihko has observed an interesting increase in enantioselectivity in the proline-catalyzed aldehyde−ketone aldol reactions when triethylamine was added to the reaction mixture (Pihko, P. M.; Laurikainen, K. M.; Usano, A.; Nyberg, A. I.; Jatta, A.; Kaavi, J. A. *Tetrahedron* **2006**, *62*, 317); however, this effect does not appear to be related to our reactions.

(23) A similar transition state was proposed by Barbas for an aldehyde-ketone aldol reaction, catalyzed by prolinol.[3a] However, leucinol, being a primary amine, offers further stabilization of the transition state by an additional hydrogen bonding between the NH and OH, not available in the case of prolinol.

(24) The reaction of the *syn*-enamine **4b** (featuring in **6**) appears to be the lowest-energy pathway. For a discussion of this effect, see ref 6b and Cheong, P. H. Y.; Zhang, H. L.; Thayumanavan, R.; Tanaka, F.; Houk, K. N.; Barbas, C. F. *Org. Lett.* **2006**, *8*, 811.

(25) Other activated, non-enolizable ketones, such as X-$C_6H_4COCY_3$ (X = F, Cl, MeO; Y = F, Cl) reacted with acetone in the presence of L-valinol as catalyst to afford the corresponding aldol products with 64−82% ee; details will be revealed in a full paper.

(26) For the synthesis of racemic convolutamydine A, see ref 7c and the following: (a) Jnaneshwar, G. K.; Deshpande, V. H. *J. Chem. Res., Synop.* **1999**, 632. (b) Jnaneshwara, G. K.; Bedekar, A. V.; Deshpande, V. H. *Synth. Commun.* **1999**, *29*, 3627. For the synthesis of racemic convolutamydine C, see: (c) Miah, S.; Moody, C. J.; Richards, I. C.; Slawin, A. M. Z. *J. Chem. Soc., Perkin Trans. 1* **1997**, 2405. For the synthesis of both enantiomers of convolutamydine B and E using a stoichiometric chiral auxiliary, see: (d) Nakamura, T.; Shirokawa, S.; Hosokawa, S.; Nakazaki, A.; Kobayashi, S. *Org. Lett.* **2006**, *8*, 677.