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Proline-Catalyzed Diastereoselective Direct Aldol Reaction between 4-Oxoazetidine-2-carbaldehydes and Ketones

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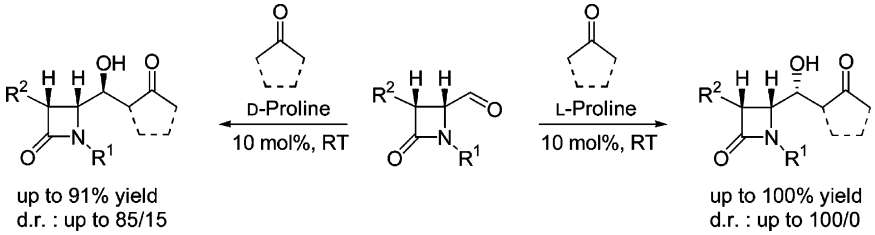

The reaction of enantiopure 4-oxoazetidine-2-carbaldehydes with unmodified ketones was catalyzed by L-proline as well as by D-proline, to give the corresponding γ-amino-β-hydroxy ketones with good yields and diastereoselectivities. The obtained results implied that (2*R*,3*R*)-4-oxoazetidine-2-carbaldehydes and L-proline are a matched pair for diastereoselective induction.

Introduction

β-Lactams are among the most important pharmacophores for treatment of diseases caused by bacterial infections.[1] In addition, there are many important nonantibiotic uses of 2-azetidinones in fields ranging from enzyme inhibition[2] to gene activation.[3] These biological activities, combined with the use of these products as starting materials to prepare α- and β-amino acids, alkaloids, heterocycles, taxoids, and other types of compounds of biological and medicinal interest,[4] provide the motivation to explore new methodologies for the synthesis of substances based on the β-lactam core. In addition, the chiral β-amino alcohol moiety is present in many biologically important molecules such as dipeptide isosteres, statine, and its analogues, and therefore, its stereocontrolled synthesis remains an intensive research area.[5] On the other hand, nucleophilic carbonyl addition reactions can be ranked among the premier transformations in organic synthesis for stereoselective carbon−carbon bond formation. In particular, the aldol reaction constitutes a fundamental synthetic methodology.[6] Small organic molecules, especially proline, have been shown to catalyze the direct aldol reaction between aldehydes and aldehyde or ketone donors,[7] mimicking the type I aldolase mechanism. A major limitation of the proline-promoted aldol reaction has been the rather narrow substrate scope. The majority of examples reported to date has involved simple achiral reactants. Functionalized aldehydes or ketones need to be explored to expand their application in the synthesis of useful chemicals. In connection

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§ To whom correspondence regarding the X-ray crystal structure should be adressed.

(1) See, for example: (a) Niccolai, D.; Tarsi, L.; Thomas, R. J. *Chem. Commun.* **1997**, 2333. (b) Southgate, R. *Contemp. Org. Synth.* **1994**, *1*, 417. (c) Southgate, R.; Branch, C.; Coulton, S.; Hunt, E. In *Recent Progress in the Chemical Synthesis of Antibiotics and Related Microbial Products*; Lukacs, G., Ed.; Springer: Berlin, 1993; Vol. 2, p 621. (d) *The Chemistry of β-Lactams*; Page, M. I., Ed.; Chapman and Hall: London, 1992A. (e) *Chemistry and Biology of β-Lactam Antibiotics*; Morin, R. B., Gorman, M., Eds.; Academic: New York, 1982; Vols. 1−3.

(2) Some of the more notable advances concern the development of mechanism-based serine protease inhibitors of elastase, cytomegalovirus protease, thrombin, prostate-specific antigen, and cell metastasis and inhibitors of acyl-CoA cholesterol acyl transferase. For a review, see: (a) Veinberg, G.; Vorona, M.; Shestakova, I.; Kanepe, I.; Lukevics, E. *Curr. Med. Chem.* **2003**, *10*, 1741. For selected examples, see: (b) Hogan, P. C.; Corey, E. J. *J. Am. Chem. Soc.* **2005**, *127*, 15386. (c) Clader, J. W. *J. Med. Chem.* **2004**, *47*, 1. (d) Kvaerno, L.; Ritter, T.; Werder, M.; Hauser, H.; Carreira, E. M. *Angew. Chem., Int. Ed.* **2004**, *43*, 4653. (e) Burnett, D. A. *Curr. Med. Chem.* **2004**, *11*, 1873. (f) Page, M. I.; Laws, A. P. *Tetrahedron* **2000**, *56*, 5631. (g) Haley, T. M.; Angier, S. J.; Borthwick, A. D.; Singh, R.; Micetich, R. G. *Drugs* **2000**, *3*, 512. (h) Bonneau, P. R.; Hasani, F.; Plouffe, C.; Malenfant, E.; LaPlante, S. R.; Guse, I.; Ogilvie, W. W.; Plante, R.; Davidson, W. C.; Hopkins, J. L.; Morelock, M. M.; Cordingley, M. G.; Deziel, R. *J. Am. Chem. Soc.* **1999**, *121*, 2965. (i) Ogilvie, W. W.; Yoakim, C.; Do, F.; Hache, B.; Lagace, L.; Naud, J.; O'Meara, J. A.; Deziel, R. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 1521. (j) Vaccaro, W. D.; Davis, H. R., Jr. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 313. (k) Borthwick, A. D.; Weingarte, G.; Haley, T. M.; Tomaszewski, M.; Wang, W.; Hu, Z.; Bedard, J.; Jin, H.; Yuen, L.; Mansour, T. S. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 365. (l) Han, W. T.; Trehan, A. K.; Wright, J. J. K.; Federici, M. E.; Seiler, S. M.; Meanwell, N. A. *Bioorg. Med. Chem.* **1995**, *3*, 1123.

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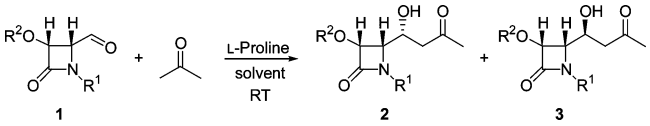
with our current research interest in the preparation and synthetic utility of β-lactams,[8] here we examine the feasibility and efficiency of the direct organocatalytic asymmetric aldol reaction of enantiopure 4-oxoazetidine-2-carbaldehydes.

Results and Discussion

Starting substrates, 4-oxoazetidine-2-carbaldehydes **1a**−**f**, were prepared as single cis enantiomers from imines of (*R*)-2,3-*O*-isopropylideneglyceraldehyde, through Staudinger reaction with the appropriate alkoxyacetyl chloride in the presence of Et_3N, followed by sequential acidic acetonide hydrolysis and oxidative cleavage, using standard methodology.[8] Compounds **1** are protected α-amino aldehydes. These substrates are notoriously unstable and easily racemized.[9]

One of the rapidly growing research areas in the field of asymmetric synthesis is catalytic transformations using simple organic molecules called organocatalysts.[10] Because proline-based reagents have emerged as particularly efficient catalysts,[7] we decided to explore the proline-catalyzed direct aldol reaction between 4-oxoazetidine-2-carbaldehydes **1** and ketones. A model reaction of 4-oxoazetidine-2-carbaldehyde (+)-**1a** was carried out by mixing acetone, 10 mol % of L-proline, and the β-lactam aldehyde in the corresponding solvent at ambient temperature. Indeed, the desired adduct (+)-**2a** was formed when the reaction was conducted in DMSO (yield 85%, de 40%), DMF (yield 80%, de 60%), or acetone (yield 94%, de 100%). Acetone was selected as the solvent for all further reactions because a higher yield and better diastereoselectivity were obtained for aldol (+)-**2a**. The effect of the amount of the organocatalyst on the conversion rate as well as on the product ratio was studied. Lower yields were obtained when the amount of catalyst was decreased (5 mol %). It was found that the efficiency of the process did not increase on increasing the amount of catalyst (20 mol %). Subsequently, it was found that 4-oxoazetidine-2-carbaldehydes **1b**−**f** reacted with acetone using L-proline catalysis under standardized conditions to yield β-lactam aldols **2b**−**f** as single isomers in good to excellent yields (60−100%) (Scheme 1, Table 1). Because total asymmetric induction is observed for reactions between aldehydes **1a**−**f** and acetone in the presence of catalytic amounts of L-proline, it was decided to test the effect of the chirality of proline on the aldol process. Would the stereoselectivity be controlled by the organocatalyst, in which case the **3** isomer should be the major product for D-proline-catalyzed direct aldol reactions, or would the configuration of the 4-oxoazetidine-2-carbaldehyde control the facial selectivity, in which case matching and mismatching with the catalyst would be observed? In the event, useful stereocontrol was not observed because D-proline-catalyzed reactions gave poor diastereoselectivities in favor of products **3** generally (Table 1, entries 6, 8, and 12). The above results implied that β-lactam aldehydes **1** and L-proline are a matched pair for diastereoselective induction. Conversely, β-lactam aldehydes **1** and D-proline are a mismatched pair for diastereoselective induction.

SCHEME 1



The scope of the aldol reaction by varying the ketone component was explored next. Disappointingly, proline was unable to promote the direct aldol reaction of 4-oxoazetidine-2-carbaldehydes **1** with cyclobutanone. After several days of reaction, the analysis of the ^1H NMR spectra of the crude reaction mixtures revealed partial epimerization of the starting aldehyde. Fortunately, it was found that cyclopentanone worked well, affording the corresponding aldol products in good yields and with reasonable stereoselectivity (Scheme 2, Table 2). Again, the highest diastereoselectivities were realized when cyclopentanone was used as solvent. L-Proline-catalyzed direct aldol reaction between 4-oxoazetidine-2-carbaldehydes **1** and cyclopentanone provided reasonable diastereoselectivity in favor of adducts **4a**−**d** (Table 2, entries 1, 2, 4, 6, and 7), whereas in the case of compounds **1** as substrates, the D-proline-catalyzed reaction gave useful diastereoselectivity in favor of adducts (+)-**6a**−**c** (Table 2, entries 3, 5, and 8). Remarkably, both L- and D-proline exert total diastereocontrol at the carbinolic carbon, respectively. The minor products, **5a**−**d** and (+)-**7a**−**c**, are epimers of the major compounds at the newly formed α-keto stereocenter. Usually, the diastereomeric aldols **3**/**4** and **5**/**6** could be easily separated by gravity flow chromatography.

No partial configuration inversion was involved in the transformation of aldehydes **1** to alcohols **2**−**6**. The assignment of the cis stereochemistry to β-lactams **2**−**6** was based on the observed coupling constants of about 5.0 Hz for methine protons

(3) It has been reported that β-lactams act to modulate the expression of glutamate neurotransmitter transporters via gene activation. See: Rothstein, J. D.; Patel, S.; Regan, M. R.; Haenggeli, C.; Huang, Y. H.; Bergles, D. E.; Jin, L.; Hoberg, M. D.; Vidensky, S.; Chung, D. S.; Toan, S. V.; Bruijn, L. I.; Su, Z.-z.; Gupta, P.; Fisher, P. B. *Nature* **2005**, *433*, 73.

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(5) See, for example: (a) Enders, D.; Reinhold, U. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 1219. (b) Rich, D. H. Peptidase Inhibitors. In *Comprehensive Medicinal Chemistry*; Sammes, P. G., Ed.; Pergamon Press: Oxford, 1990; Vol. 2, p 391. (c) Huff, J. R. *J. Med. Chem.* **1991**, *34*, 2305. (d) Thaisrivongs, S.; Pals, D. T.; Kroll, L. T.; Turner, S. R.; Han, F.-S. *J. Med. Chem.* **1987**, *30*, 976.

(6) Reviews: (a) *Modern Aldol Reactions*; Mahrwald, R., Ed.; Wiley-VCH: Weinheim, 2004. (b) Palomo, C.; Oiarbide, M.; García, J. M. *Chem. Soc. Rev.* **2004**, *33*, 65. (c) Palomo, C.; Oiarbide, M.; García, J. M. *Chem.*−*Eur. J.* **2002**, *8*, 37. (d) Machajewski, T. D.; Wong, C.-H. *Angew. Chem., Int. Ed.* **2000**, *39*, 1352.

(7) For selected reviews, see: (a) List, B. *Acc. Chem. Res.* **2004**, *37*, 548. (b) Notz, W.; Tanaka, F.; Barbas, C. F., III. *Acc. Chem. Res.* **2004**, *37*, 580. (c) Alcaide B.; Almendros, P. *Angew. Chem., Int. Ed.* **2003**, *42*, 858. (d) Jarvo, E. R.; Miller, S. J. *Tetrahedron* **2002**, *58*, 2481. (e) List, B. *Tetrahedron* **2002**, *58*, 5573. (f) Alcaide, B.; Almendros, P. *Eur. J. Org. Chem.* **2002**, 1595.

(8) (a) Alcaide, B.; Almendros, P.; Aragoncillo, C.; Redondo, M. C.; Torres, M. R. *Chem.*−*Eur. J.* **2006**, *12*, 1539. (b) Alcaide, B.; Almendros, P.; Redondo, M. C.; Ruiz, M. P. *J. Org. Chem.* **2005**, *70*, 8890. (c) Alcaide, B.; Almendros, P.; Rodríguez-Acebes, R. *Chem.*−*Eur. J.* **2005**, *11*, 5708. (d) Alcaide, B.; Almendros, P.; Rodríguez-Acebes, R. *J. Org. Chem.* **2005**, *70*, 2713. (e) Alcaide, B.; Almendros, P.; Cabrero, G.; Ruiz, M. P. *Org. Lett.* **2005**, *7*, 3981.

(9) 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.

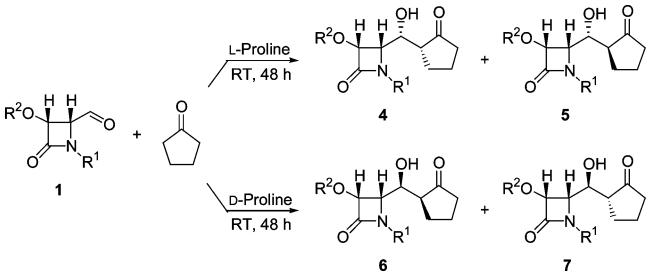
(10) For recent selected reviews, see: (a) *Tetrahedron* **2006**, *62*, issues 2 and 3: *Organocatalysis in organic synthesis*; Kočovský, P., Malkov, A. V., Guest Eds. (b) *Asymmetric Organocatalysis*; Berkessel, A., Gröger, H., Eds.; Wiley-VCH: Weinheim, 2005. (c) Seayad, J.; List, B. *Org. Biomol. Chem.* **2005**, *3*, 719−724. (d) Dalko, P. I.; Moisan, D. L. *Angew. Chem., Int. Ed.* **2004**, *43*, 5138−5175. (e) Johnson, J. S. *Angew. Chem., Int. Ed.* **2004**, *43*, 1326. (f) Dalko, P. I.; Moisan, L. *Angew. Chem., Int. Ed.* **2001**, *40*, 3726.

TABLE 1. Direct Aldol Reaction between 4-Oxoazetidine-2-carbaldehydes 1 and Acetone[a]

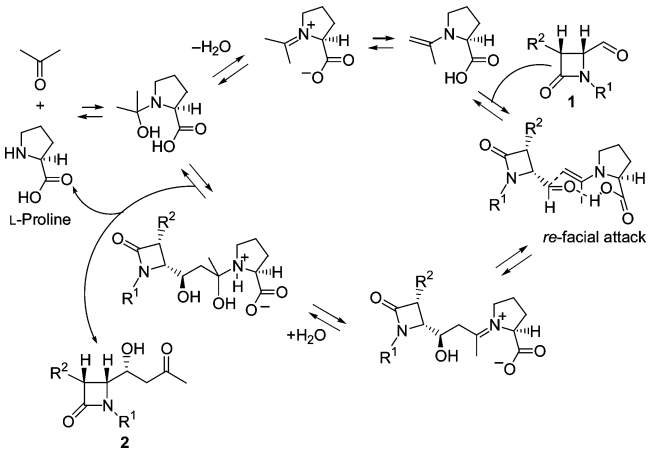
entry	aldehyde	R^1	R^2	solvent	catalyst	*t* (h)	product	**2**/**3** ratio[b]	yield (%)[c]
1	(+)-**1a**	Me	PMP	DMSO	L-proline	48	(+)-**2a**	70:30	85
2	(+)-**1a**	Me	PMP	DMF	L-proline	48	(+)-**2a**	80:20	80
3	(+)-**1a**	Me	PMP	acetone	L-proline	48	(+)-**2a**	100:0	94
4	(+)-**1a**	Me	PMP	acetone	L-proline[d]	72	(+)-**2a**	100:0	80
5	(+)-**1a**	Me	PMP	acetone	L-proline[e]	48	(+)-**2a**	100:0	94
6	(+)-**1a**	Me	PMP	acetone	D-proline	48	(+)-**3a**	40:60	60
7	(+)-**1b**	Ph	PMP	acetone	L-proline	48	(+)-**2b**	100:0	90
8	(+)-**1b**	Ph	PMP	acetone	D-proline	48	(+)-**3b**	40:60	91[f]
9	(+)-**1c**	PMPCO	PMP	acetone	L-proline	48	(+)-**2c**	100:0	94
10	(+)-**1d**	Me	allyl	acetone	L-proline	48	(+)-**2d**	100:0	56
11	(+)-**1e**	Ph	allyl	acetone	L-proline	48	(+)-**2e**	100:0	100
12	(+)-**1e**	Ph	allyl	acetone	D-proline	48	(+)-**2e**	60:40	62
13	(+)-**1f**	Ph	2-Br-allyl	acetone	L-proline	48	(+)-**2f**	100:0	82

[a] 10 mol % of proline was used unless otherwise stated. PMP = 4-$MeOC_6H_4$. [b] A reviewer suggested the possibility of a change in diastereomeric ratio over the very long course of the reaction. The ratio was determined by integration of well-resolved signals in the ^1H NMR spectra (300 MHz) of the crude reaction mixtures before purification. [c] Combined yield of isolated aldol products with correct analytical and spectral data. [d] 5 mol % of proline was used. [e] 20 mol % of proline was used. [f] The diastereomeric aldols (+)-**2b** and (+)-**3b** could be easily separated by gravity flow chromatography.

SCHEME 2



SCHEME 3



H3 and H4, whereas the trans stereochemistry is consistent with methine coupling constants of ca. 2.0 Hz in their ^1H NMR spectra.[11] Derivatizing the hydroxyketones **2**−**6** with (*R*)- and (*S*)-*O*-acetylmandelic acids would allow assignment of the configuration at the carbinolic stereocenter. However, sluggish and low yielding reactions were observed. This behavior of the β-lactam aldol adducts is in sharp contrast to the good yields observed by us for related *O*-acetylmandelates derived from α-allenic or bromohomoallylic alcohols.[8a,d] The configurational assignment for the acetone series was established by X-ray crystallography of the adduct (+)-**3b** (see Supporting Information).[12] The stereochemical relationship of aldol (+)-**6b** was established via an X-ray diffraction analysis (see Supporting Information).[13]

The absolute configurations of the aldol products were in good agreement with previously proposed models on proline-catalyzed aldol reactions (Scheme 3).[14] According to this proposal, proline functions as a microaldolase, with the secondary amine acting as a nucleophilic enamine catalyst and the carboxylic acid moiety acting as a general Brønsted cocatalyst. The observed stereochemistry can be explained by invoking a metal-free Zimmerman−Traxler-like transition state. A hydrogen bond involving the carboxylate, enamine, and aldehyde organizes the transition state.[7d] Steric interactions between the aldehyde and enamine substituents may be the most important, accounting for the enantiofacial selectivity exhibited by this reaction. The observed

(11) The assignment of relative stereochemistry based on the observed coupling constant for methine protons H3 and H4 is a very well-established criterion in β-lactam chemistry. See, for example: (a) Alcaide, B.; Almendros, P.; Salgado, N. R.; Rodríguez-Vicente, A. *J. Org. Chem.* **2000**, *65*, 4453. (b) Alcaide, B.; Aly, M. F.; Rodríguez, C.; Rodríguez-Vicente, A. *J. Org. Chem.* **2000**, *65*, 3453.

(12) X-ray data of (+)-**3b**: crystallized from ethyl acetate/*n*-hexane at 20 °C; $C_{20}H_{21}NO_5$ (M_r = 355.38); monoclinic; space group = *P*2(1); *a* = 12.5066(11) Å, *b* = 6.4952(6) Å; *c* = 12.8842(12) Å; β = 116.588(2)°; *V* = 935.94(15) Å^3; *Z* = 2; d_c = 1.261 mg m^{-3}; μ = 0.091 mm^{-1}; *F*(000) = 376. A transparent crystal of 0.19 × 0.13 × 0.13 mm^3 was used. 4235 [*R*(int) = 0.0373] independent reflections were collected on a Bruker Smart CCD diffractometer using graphite-monochromated Mo Kα radiation (λ = 0.710 73 Å) operating at 50 kV and 30 mA. Data were collected over a hemisphere of the reciprocal space by combination of three exposure sets. Each exposure of 20 s and 30 s covered 0.3 in ω. The structure was solved by direct methods and Fourier synthesis. It was refined by full-matrix least-squares procedures on F^2 (SHELXL-97). All non-hydrogen atoms were refined anisotropically, and all hydrogen atoms were included in calculated positions and refined riding on the respective carbon or oxygen atoms. Final $R(R_w)$ values were 4.06 (8.54) and 5.19 (13.30). CCDC-274849 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.can.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Centre, 12 Union Road, Cambridge CB21EZ, U.K.; fax (+44)1223-336033; or deposit@cccdc.cam.ac.uk).

(13) X-ray data of (+)-**6b**: crystallized from ethyl acetate/*n*-hexane at 20 °C; $C_{22}H_{23}NO_5$ (M_r = 381.41); monoclinic; space group = *P*2(1); *a* = 13.592(2) Å, *b* = 5.9800(9) Å; *c* = 13.892(2) Å; β = 119.223(2)°; *V* = 985.4(3) Å^3; *Z* = 2; d_c = 1.285 mg m^{-3}; μ = 0.091 mm^{-1}; *F*(000) = 404. A transparent crystal of 0.43 × 0.10 × 0.06 mm^3 was used. 4734 [*R*(int) = 0.0914] independent reflections were collected on a Bruker Smart CCD diffractometer using graphite-monochromated Mo Kα radiation (λ = 0.710 73 Å) operating at 50 kV and 30 mA. Data were collected over a hemisphere of the reciprocal space by combination of three exposure sets. Each exposure of 20 s and 30 s covered 0.3 in ω. The structure was solved by direct methods and Fourier synthesis. It was refined by full-matrix least-squares procedures on F^2 (SHELXL-97). All non-hydrogen atoms were refined anisotropically, and all hydrogen atoms were included in calculated positions and refined riding on the respective carbon or oxygen atoms. Final $R(R_w)$ values were 4.06 (8.54) and 5.19 (13.30). CCDC-274850 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.can.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Centre, 12 Union Road, Cambridge CB21EZ, U.K.; Fax (+44)1223-336033; or deposit@cccdc.cam.ac.uk).

(14) (a) List, B. *Chem. Commun.* **2006**, 819. (b) Hoang, L.; Bahmanyar, S.; Houk, K. N.; List, B. *J. Am. Chem. Soc.* **2003**, *125*, 16.

TABLE 2. Direct Aldol Reaction between 4-Oxoazetidine-2-carbaldehydes 1 and Cyclopentanone[a]

entry	aldehyde	R^1	R^2	solvent	catalyst	product	**4**/**5**/**6**/**7** ratio[b]	yield (%)[c]
1	(+)-**1a**	Me	PMP	DMSO	L-proline	(+)-**4a**	70:30:0:0	80[d]
2	(+)-**1a**	Me	PMP	CP	L-proline	(+)-**4a**	90:10:0:0	85[d]
3	(+)-**1a**	Me	PMP	CP	D-proline	(+)-**6a**	0:0:80:20	80[e]
4	(+)-**1b**	Ph	PMP	CP	L-proline	(+)-**4b**	90:10:0:0	100[f]
5	(+)-**1b**	Ph	PMP	CP	D-proline	(+)-**6b**	0:0:85:15	77[g]
6	(+)-**1c**	PMPCO	PMP	CP	L-proline	(+)-**4c**	90:10:0:0	68
7	(+)-**1e**	Ph	allyl	CP	L-proline	(+)-**4d**	80:20:0:0	62
8	(+)-**1e**	Ph	allyl	CP	D-proline	(+)-**6c**	0:0:80:20	73[h]

[a] CP = cyclopentanone. 10 mol % of proline was used. PMP = 4-$MeOC_6H_4$. [b] The ratio was determined by integration of well-resolved signals in the ^1H NMR spectra (300 MHz) of the crude reaction mixtures before purification. [c] Combined yield of isolated aldol products with correct analytical and spectral data. [d] The diastereomeric aldols (+)-**4a** and (+)-**5a** could be easily separated by gravity flow chromatography. [e] The diastereomeric aldols (+)-**6a** and (+)-**7a** could be easily separated by gravity flow chromatography. [f] The diastereomeric aldols (+)-**4b** and (+)-**5b** could be easily separated by gravity flow chromatography. [g] The diastereomeric aldols (+)-**6b** and (+)-**7b** could be easily separated by gravity flow chromatography. [h] The diastereomeric aldols (+)-**6c** and (+)-**7c** could be easily separated by gravity flow chromatography.

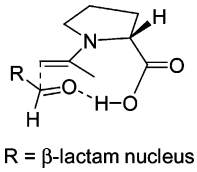


FIGURE 1.

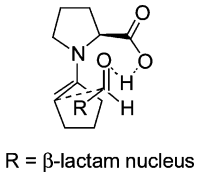


FIGURE 2.

high selectivity for the L-proline-catalyzed reaction of 4-oxoazetidine-2-carbaldehydes can be rationalized as the cumulative effect of steric inhibitions posed by the chiral aldehyde and the facial preference of the organocatalyst (favored, match). The poorer selectivity encountered in the case of D-proline could be explained by the opposite preference of the β-lactam aldehyde and the organocatalyst, thus making both faces available (disfavored, mismatch) for the enolate attack (Figure 1).

The observed relative stereochemistry for the cyclopentanone case can be explained by the Houk−List model for proline-catalyzed aldol reactions with cyclic ketones,[15] where a cyclic enamine intermediate and an intermolecular hydrogen bond play the decisive role. The postulated transition state for the L-proline-catalyzed reaction of 4-oxoazetidine-2-carbaldehydes with cyclopentanone is depicted in Figure 2, favoring addition from the *re* face of the β-carbon in an *anti*-oriented enamine to the *re* face of the aldehyde. Facial selectivity for addition to the enamine is controlled by the absolute configuration of the proline catalyst, and facial selectivity for addition to the aldehyde is dictated by the closed transition state. In our case, the rigidity of the transition state imposed by the *anti*-enamine overwhelmed the facial preference of the chiral aldehyde, explaining the selectivity difference at the carbinol center between acetone and cyclopentanone.

Conclusions

In conclusion, the present study provides the first insight into the asymmetric manner in which 4-oxoazetidine-2-carbaldehydes and ketones undergo a direct organocatalyzed coupling to give aldol adducts, being the β-lactam aldehyde/L-proline couple, a matched pair for diastereoselectivity induction. This novel synthetic approach is inexpensive and operationally simple, allowing for the creation of up to two contiguous new stereocenters with good stereocontrol.

Experimental Section

General. The same experimental techniques as those previously reported were used.[8]

Proline-Catalyzed Reaction between Unmodified Ketones and 4-Oxoazetidine-2-carbaldehydes 1. General Procedure for the Synthesis of Aldols 2−6. l-Proline or D-proline (10.4 mg, 0.09 mmol) was added to a well-stirred suspension of the appropriate aldehyde **1** (0.90 mmol) in the corresponding ketone (9 mL) at room temperature. After disappearance of the starting material (TLC), saturated aqueous sodium hydrogen carbonate (5 mL) was added before being extracted with ethyl acetate (3 × 10 mL). The organic extract was washed with brine, dried ($MgSO_4$), and concentrated under reduced pressure. Chromatography of the residue and eluting with hexane/ethyl acetate mixtures gave analytically pure compounds **2**−**6**. Spectroscopic and analytical data for some representative forms of **2**−**6** follow.[16]

Aldol (+)-2a. From 210 mg (0.89 mmol) of 4-oxoazetidine-2-carbaldehyde (+)-**1a** and 10 mg (0.089 mmol) of L-proline, 243 mg (94%) of compound (+)-**2a** was obtained as a colorless solid after purification by flash chromatography (hexanes/ethyl acetate, 1:2). Mp: 124−125 °C (hexanes/ethyl acetate). $[\alpha]_D = +179.6$ (*c* 0.5, $CHCl_3$). ^1H NMR: δ 2.15 (s, 3H), 2.75 (m, 2H), 3.67 (s, 3H), 3.78 (br s, 1H), 3.79 (s, 3H), 4.35 (t, 1H, $J = 5.1$ Hz), 4.54 (m, 1H), 4.63 (d, 1H, $J = 5.1$ Hz), 6.86 and 7.40 (d, each 2H, $J = 9.0$ Hz). ^{13}C NMR: δ 208.2, 165.1, 156.9, 130.8, 120.1, 114.4, 82.8, 67.5, 59.9, 59.7, 55.6, 46.3, 30.8. IR (KBr, cm^{-1}): ν 3458, 1744, 1710. MS (EI), *m*/*z*: 294 ($M^+ + 1$, 9), 293 (M^+, 48), 149 (100). Anal. Calcd for $C_{15}H_{19}NO_5$: C, 61.42; H, 6.53; N, 4.78. Found: C, 61.67; H, 6.44; N, 4.70.

Aldol (+)-2b. From 40 mg (0.13 mmol) of 4-oxoazetidine-2-carbaldehyde (+)-**1b** and 1.5 mg (0.013 mmol) of L-proline, 40 mg (90%) of compound (+)-**2b** was obtained as a colorless solid after purification by flash chromatography (hexanes/ethyl acetate, 2:1). Mp: 112−113 °C (hexanes/ethyl acetate). $[\alpha]_D = +219.4$ (*c* 1.0, CH_2Cl_2). ^1H NMR: δ 2.16 (s, 3H), 2.79 (m, 2H), 3.79 (s, 3H), 4.52 (t, 1H, $J = 5.1$ Hz), 4.65 (m, 1H), 5.37 (d, 1H, $J = 5.1$ Hz), 6.88 and 7.50 (d, each 2H, $J = 9.0$ Hz), 7.11 (m, 3H), 7.36 (m, 2H). ^{13}C NMR: δ 208.3, 163.5, 157.7, 157.4, 131.0, 130.2, 123.4, 120.6, 116.4, 114.7, 80.2, 68.1, 60.6, 55.9, 46.9, 31.2. IR (KBr, cm^{-1}): ν 3461, 1745, 1708. MS (EI), *m*/*z*: 356 ($M^+ + 1$, 10), 355

(15) Bahmanyar, S.; Houk, K. N.; Martin, H. J.; List, B. *J. Am. Chem. Soc.* **2003**, *125*, 2475.

(16) Full spectroscopic and analytical data for compounds not included in this Experimental Section are described in the Supporting Information.

(M^+, 42), 149 (100). Anal. Calcd for $C_{20}H_{21}NO_5$: C, 67.59; H, 5.96; N, 3.94. Found: C, 67.70; H, 5.92; N, 3.91.

Aldol (+)-2e. From 38 mg (0.16 mmol) of 4-oxoazetidine-2-carbaldehyde (+)-**1e** and 1.9 mg (0.016 mmol) of L-proline, 47 mg (100%) of compound (+)-**2e** was obtained after purification by flash chromatography (hexanes/ethyl acetate, 1:1). Colorless solid. Mp: 65−66 °C (hexanes/ethyl acetate). $[\alpha]_D = +160.6$ (*c* 0.5, CH_2Cl_2). ^{1}H NMR: δ 2.17 (s, 3H), 2.63 (dd, 1H, $J = 17.6$, 8.5 Hz), 2.84 (dd, 1H, $J = 17.6$, 3.2 Hz), 3.61 (br s, 1H), 3.91 (m, 2H), 4.20 (dd, 1H, $J = 15.4$, 5.1 Hz), 4.47 (dd, 1H, $J = 8.5$, 3.2 Hz), 5.22 (d, 1H, $J = 4.9$ Hz), 5.29 (m, 2H), 5.83 (m, 1H), 7.05 (m, 3H), 7.30 (m, 2H). ^{13}C NMR: δ 208.4, 165.9, 157.4, 131.8, 129.7, 122.7, 118.8, 115.8, 79.9, 68.3, 59.9, 46.5, 44.5, 30.8. IR (KBr, cm^{-1}): ν 3465, 1748, 1714. MS (EI), *m*/*z*: 290 ($M^+ + 1$, 7), 289 (M^+, 100). Anal. Calcd for $C_{16}H_{19}NO_4$: C, 66.42; H, 6.62; N, 4.84. Found: C, 66.53; H, 6.65; N, 4.81.

Preparation of Aldol (+)-3b. From 40 mg (0.13 mmol) of 4-oxoazetidine-2-carbaldehyde (+)-**1b** and 3.7 mg (0.033 mmol) of D-proline, after column chromatography and eluting with hexanes/ethyl acetate (2:1), 16 mg (35%) of the less polar compound (+)-**2b** and 26 mg (56%) of the more polar compound (+)-**3b** were obtained.

Aldol (+)-3b. Colorless solid. Mp: 115−116 °C (hexanes/ethyl acetate). $[\alpha]_D = +42.2$ (*c* 1.0, CH_2Cl_2). ^{1}H NMR: δ 2.16 (s, 3H), 2.64 and 3.00 (m, each 1H), 3.81 (s, 3H), 4.60 (m, 3H), 5.40 (d, 1H, $J = 5.4$ Hz), 6.90 and 7.69 (d, each 2H, $J = 9.0$ Hz), 7.08 (m, 2H), 7.34 (m, 3H). ^{13}C NMR: δ 209.5, 163.5, 157.7, 157.2, 131.3, 130.2, 123.4, 119.9, 116.1, 114.8, 79.9, 66.7, 62.1, 55.9, 46.1, 31.1. IR (KBr, cm^{-1}): ν 3460, 1745, 1709. MS (EI), *m*/*z*: 356 ($M^+ + 1$, 11), 355 (M^+, 40), 149 (100). Anal. Calcd for $C_{20}H_{21}NO_5$: C, 67.59; H, 5.96; N, 3.94. Found: C, 67.71; H, 6.00; N, 3.91.

Preparation of Aldols (+)-4a (+)-5a. From 32 mg (0.14 mmol) of 4-oxoazetidine-2-carbaldehyde (+)-**1a** and 1.6 mg (0.014 mmol) of L-proline, after column chromatography and eluting with hexanes/ethyl acetate (1:1), 4 mg (9%) of the less polar compound (+)-**5a** and 34 mg (76%) of the more polar compound (+)-**4a** were obtained.

Aldol (+)-4a. Colorless oil. $[\alpha]_D = +129.6$ (*c* 1.1, CH_2Cl_2). ^{1}H NMR: δ 2.05 (m, 7H), 2.60 (br s, 1H), 3.63 (s, 3H), 3.76 (s, 3H), 4.22 (dd, 1H, $J = 6.3$, 5.0 Hz), 4.58 (d, 1H, $J = 5.3$ Hz), 4.68 (t, 1H, $J = 5.3$ Hz), 6.82 and 7.44 (d, each 2H, $J = 9.0$ Hz). ^{13}C NMR: δ 219.5, 165.2, 156.6, 130.7, 120.3, 114.0, 82.3, 69.7, 59.5, 58.9, 55.3, 51.2, 38.8, 25.5, 20.3. IR ($CHCl_3$, cm^{-1}): ν 3460, 1745, 1709. MS (ES), *m*/*z*: 320 ($M^+ + 1$, 100), 319 (M^+, 18). Anal. Calcd for $C_{17}H_{21}NO_5$: C, 63.94; H, 6.63; N, 4.39. Found: C, 64.05; H, 6.60; N, 4.42.

Aldol (+)-5a. Colorless oil. $[\alpha]_D = +45.3$ (*c* 0.8, CH_2Cl_2). ^{1}H NMR: δ 2.00 (m, 6H), 2.65 (m, 1H), 3.63 (s, 3H), 3.78 (s, 3H), 4.26 (t, 1H, $J = 6.1$ Hz), 4.70 (m, 2H), 6.86 and 7.42 (d, each 2H, $J = 9.0$ Hz). ^{13}C NMR: δ 218.9, 165.3, 156.6, 130.9, 119.5, 114.3, 83.1, 71.7, 59.6, 59.1, 55.5, 50.6, 38.8, 27.0, 20.9. IR ($CHCl_3$, cm^{-1}): ν 3462, 1747, 1711. MS (ES), *m*/*z*: 320 ($M^+ + 1$, 100), 319 (M^+, 12). Anal. Calcd for $C_{17}H_{21}NO_5$: C, 63.94; H, 6.63; N, 4.39. Found: C, 64.07; H, 6.68; N, 4.43.

Preparation of Aldols (+)-6b and (+)-7b. From 32 mg (0.10 mmol) of 4-oxoazetidine-2-carbaldehyde (+)-**1b** and 1.2 mg (0.01 mmol) of D-proline, after column chromatography and eluting with hexanes/ethyl acetate (2:1), 5 mg (12%) of the less polar compound (+)-**7b** and 25 mg (65%) of the more polar compound (+)-**6b** were obtained.

Aldol (+)-6b. Colorless solid. Mp: 138−139 °C (hexanes/ethyl acetate). $[\alpha]_D = +131.3$ (*c* 0.6, CH_2Cl_2). ^{1}H NMR: δ 2.11 (m, 7H), 3.80 (s, 3H), 4.53 (dd, 1H, $J = 5.4$, 4.8 Hz), 4.76 (t, 1H, $J = 4.8$ Hz), 5.47 (d, 1H, $J = 5.4$ Hz), 6.90 and 7.43 (d, each 2H, $J = 9.0$ Hz), 7.12 (m, 3H), 7.33 (m, 2H). ^{13}C NMR: δ 219.2, 163.3, 157.3, 157.1, 130.1, 129.9, 123.3, 120.0, 116.2, 114.7, 80.9, 68.7, 59.7, 55.6, 52.3, 38.6, 25.4, 20.8. IR ($CHCl_3$, cm^{-1}): ν 3461, 1745, 1709. MS (EI), *m*/*z*: 381 (M^+, 26), 149 (100). Anal. Calcd for $C_{22}H_{23}NO_5$: C, 69.28; H, 6.08; N, 3.67. Found: C, 69.40; H, 6.04; N, 3.64.

Aldol (+)-7b. Colorless oil. $[\alpha]_D = +34.5$ (*c* 1.4, CH_2Cl_2). ^{1}H NMR: δ 2.00 (m, 7H), 3.80 (s, 3H), 4.32 (dd, 1H, $J = 5.6$, 5.1 Hz), 4.87 (t, 1H, $J = 5.1$ Hz), 5.41 (d, 1H, $J = 5.6$ Hz), 6.90 and 7.62 (d, each 2H, $J = 9.0$ Hz), 7.10 (m, 3H), 7.35 (m, 2H). ^{13}C NMR: δ 221.8, 163.3, 157.0, 156.7, 130.5, 129.7, 122.9, 119.5, 115.8, 114.4, 79.9, 70.9, 60.1, 55.4, 50.0, 38.9, 27.3, 20.7. IR ($CHCl_3$, cm^{-1}): ν 3457, 1748, 1712. MS (EI), *m*/*z*: 381 (M^+, 18), 149 (100). Anal. Calcd for $C_{22}H_{23}NO_5$: C, 69.28; H, 6.08; N, 3.67. Found: C, 69.17; H, 6.05; N, 3.70.

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Supporting Information Available: Compound characterization data and experimental procedures for compounds (+)-**2c**, (+)-**2d**, (+)-**2f**, (+)-**3a**, (+)-**3e**, (+)-**4b**−**d**, (+)-**5b**, (+)-**6a**, (+)-**6c**, (+)-**7a**, and (+)-**7c**. This material is available free of charge via the Internet at http://pubs.acs.org.

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