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Organocatalytic Entry to Chiral Bicyclo[3.*n*.1]alkanones via Direct Asymmetric Intramolecular Aldolization

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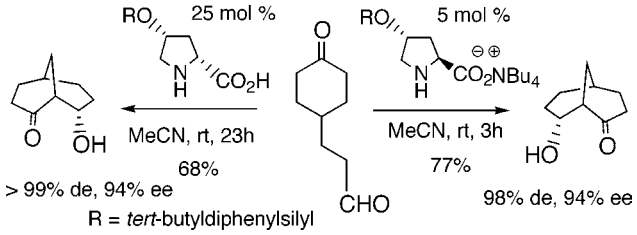
ABSTRACT



The facile stereoselective syntheses of *endo*-8-hydroxybicyclo[3.3.1]nonan-2-one and *endo*-7-hydroxybicyclo[3.2.1]octan-2-one, featuring an α-amino acid catalyzed intramolecular aldolization of *σ*-symmetric substrates, are described. A high enantioselectivity and a high catalytic efficiency have been exhibited by (4*R*,2*S*)-tetrabutylammonium 4-TBDPSoxy-prolinate in the aldolization of 3-(4-oxocyclohexyl)propionaldehyde to give highly enantiomerically enriched (1*S*,5*R*,8*R*)-8-hydroxybicyclo[3.3.1]nonan-2-one.

Reaction processes that bring about significant increases in molecular complexity play enormous roles in synthetic organic chemistry.[1,2] In this regard, the direct aldol reaction[3] is noteworthy because it offers access to a variety of cyclic and acyclic molecules via the generation of a new C−C bond and up to two new adjacent stereocenters with ideal atom efficiency.[4] The landmark discoveries in the early 1970s by Hajos−Parrish[5] and Eder−Sauer−Wiechert[6] and in 2000 by List−Lerner−Barbas[7] showing that proline catalyzes highly enantioselective direct asymmetric aldol reactions spurred extensive research on the use of proline and its derivatives in catalyzing aldol and related reactions.[8−10] Proline is now widely recognized as the simplest enzyme[11] whose suitable modifications could principally bring about evolution in catalytic activity.[12] With this encouraging prospect in mind,

(1) Whitlock, H. W. *J. Org. Chem*. **1998**, *63*, 7982.
(2) Taylor, M. S.; Jacobsen, E. N. *Proc. Nat. Acad. Sci. U.S.A*. **2004**, *101*, 5368.
(3) Recent reviews: (a) Machajewski, T. D.; Wong, C.-H. *Angew. Chem., Int. Ed*. **2000**, *39*, 1353. (b) Palomo, C.; Oiarbide, M.; García, J. M. *Chem. Eur. J*. **2002**, *8*, 37. (c) Alcaide, B.; Almendros, P. *Angew. Chem., Int. Ed*. **2003**, *42*, 858.
(4) Trost, B. M. *Science* **1991**, *254*, 1471.
(5) (a) Hajos, Z. G.; Parrish, D. R. German Patent DE 2102623, July 29, 1971. (b) Hajos, Z. G.; Parrish, D. R. *J. Org. Chem*. **1974**, *39*, 1615.
(6) (a) Eder, U.; Sauer, G.; Wiechert, R. (Schering, A.-G.) German Patent DE 2014757, Oct 7, 1971. (b) Eder, U.; Sauer, G.; Wiechert, R. *Angew. Chem., Int. Ed. Engl*. **1971**, *10*, 496.
(7) List, B.; Lerner, R. A.; Barbas, C. F., III. *J. Am. Chem. Soc*. **2000**, *122*, 2395.
(8) Reviews: (a) Drauz, K.; Kleeman, A.; Martens, J. *Angew. Chem., Int. Ed. Engl*. **1982**, *21*, 584. (b) List, B. *Synlett* **2001**, 1675. (c) Gröger, H.; Wilken, J. *Angew. Chem., Int. Ed*. **2001**, *40*, 529. (d) Dalko, P. I.; Moisan, L. *Angew. Chem., Int. Ed*. **2001**, *40*, 3727 (e) Jarvo, E. R.; Miller, S. J. *Tetrahedron* **2002**, *58*, 2481. (f) List, B. *Tetrahedron* **2002**, *58*, 5573. (g) List, B. *Acc. Chem. Res*. **2004**, *37*, 548 (h) Saito, S.; Yamamoto, H. *Acc. Chem. Res*. **2004**, *37*, 548; *Acc. Chem. Res*. **2004**, *37*, 570. (i) Notz, W.; Tanaka, F.; Barbas, C. F., III. *Acc. Chem. Res*. **2004**, *37*, 580. (j) Dalko, P. I.; Moisan, L. *Angew. Chem., Int. Ed*. **2004**, *43*, 5138, 5175. (k) Seayad, J.: List, B. *Org. Biomol. Chem*. **2005**, *3*, 719.
(9) For selected references on intramolecular asymmetric aldolization, see: (a) Hiroi, K.; Yamada, S.-i. *Chem. Pharm. Bull*. **1975**, *23*, 1103. (b) Terashima, S.; Sato, S.; Koga, K. *Tetrahedron Lett*. **1979**, *36*, 3469. (c) Bui, T.; Barbas, C. F., III. *Tetrahedron Lett*. **2000**, *41*, 6951. (d) Li, Y.; Nassim, B.; Crabbé, P. *J. Chem. Soc., Perkin Trans. 1* **1983**, 2349. (e) Hagiwara, H.; Uda, H. *J. Org. Chem*. **1988**, *53*, 2308. (f) Pidathala, C.; Hoang, L.; Vignola, N.; List, B. *Angew. Chem., Int. Ed*. **2003**, *42*, 2785, 2788. (g) Mans, D. M.; Pearson, W. H. *Org. Lett*. **2004**, *6*, 3305−3308. (h) Inomata, K.; Barragué, M.; Paquette, L. A. *J. Org. Chem*. **2005**, *70*, 533−539. (i) Kurteva, V. B.; Afonso, C. A. M. *Tetrahedron* **2005**, *61*, 267. (j) Shigehisa, H.; Mizutani, T.; Tosaki, S.; Ohshima, T.; Shibasaki, M. *Tetrahedron* **2005**, *61*, 5057.

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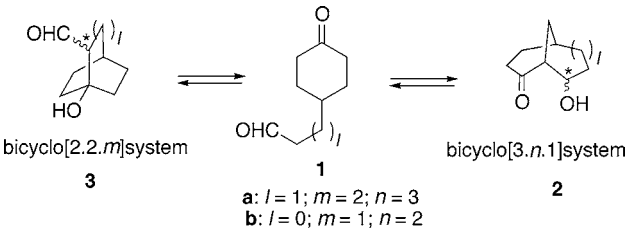
we envisaged the enantioselective synthesis of bicyclo[3.*n*.1]-alkanones ($n = 3$ or 2) **2**[13] from σ-symmetric keto-aldehydes **1** via *enolexo* mode[9f] of intramolecular aldolization with amino acid catalysis (Scheme 1).

Scheme 1. Issues in the Selectivity of the Aldolization of **1**

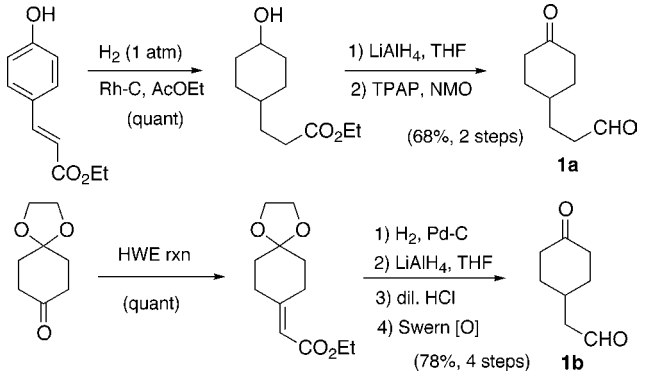


Our hope of using **2** as building blocks and the mechanistic interest in the issue of selectivity prompted us to investigate the feasibility of the process. We report herein an organocatalytic entry to chiral bicyclo[3.*n*.1]alkanones ($n = 3$ or 2) and the discovery of several interesting factors that markedly enhance the efficiency of aldolization.

The σ-symmetric keto-aldehydes **1a** and **1b** were prepared from ethyl 4-hydroxycinnamate and 1,4-cyclohexanedione monoethylene acetal, respectively, as shown in Scheme 2.[14]

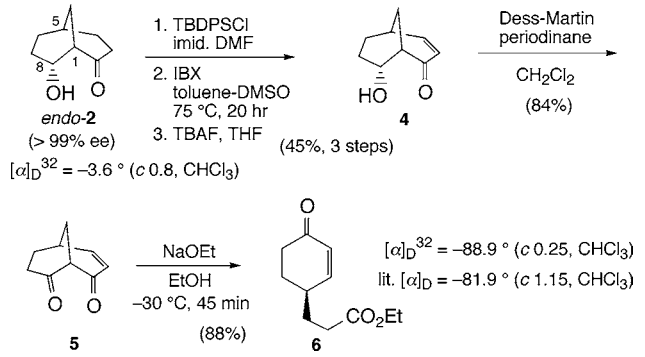
To scout the inherent reactivity toward aldolization, **1a** and **1b** were subjected to typical conditions employing K_2CO_3[12] or pyrrolidine as the catalyst. In both cases, bicyclo[3.*n*.1]-type products **2** were produced as the mixtures of *endo*-/*exo*-diastereomers, and bicyclo[2.2.*m*]-type products **3** were not detected (entries 1−4). It was, therefore, interesting to find that L-proline catalyzed the highly diastereoselective aldolization of **1b** to furnish *endo*-**2b** in 52% yield with 94% de, although ee was 10% (entry 5). To our satisfaction, the L-proline-catalyzed aldolization of **1a** to furnish (−)-*endo*-8-hydroxy-bicyclo[3.3.1]nonan-2-one (*endo*-**2a**) in 60% yield with an excellent de of 98% and a high ee of 78% under the standard conditions (25 mol % catalyst, DMSO, rt, 72 h, entry 6), which was easily optically purified

Scheme 2. Preparation of the Substrates



(>99% ee) by single recrystallization (diisopropyl ether/hexane). The absolute stereochemistry of (−)-*endo*-**2** was unequivocally established to be 1*S*,5*R*,8*R* by connecting to the known compound (*R*)-**6**[15] via a retro-Dieckmann reaction of **5** as shown in Scheme 3.[14]

Scheme 3. Determination of Absolute Stereochemistry of (−)-**2**



Since the preliminary experiments revealed that L-proline cannot be used to examine various reaction conditions because of its inherent low solubility in conventional organic solvents, we designed a series of proline derivatives **7**−**11**[14] with the hope of conferring a lipophilic property onto the proline motif, thereby securing the basis for the evolution of the catalytic activity.[16] It was found that both **7** and **8** showed improved solubilities[17] in MeCN and enhanced catalytic potencies to convert **1a** to a bicyclo[3.3.1]-type product with opposite enantiopreferences and different enantiocontrolling proficiencies. Thus, although **7** gave diastereo- and enantioselectivities almost comparable with those of

(10) For selected references on intermolecular aldolization, see: (a) Notz, W.; List, B. *J. Am. Chem. Soc.* **2000**, *122*, 7386. (b) List, B.; Pojarliev, P.; Castello, C. *Org. Lett.* **2001**, *3*, 573. (c) Sakthivel, K.; Notz, W.; Bui, T.; Barbas, C. F., III. *J. Am. Chem. Soc.* **2001**, *123*, 5260. (d) Northup, A. B.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2002**, *124*, 6798. (e) Chowdari, N. S.; Ramachary, D. B.; Córdova, A.; Barbas, C. F., III. *Tetrahedron Lett.* **2002**, *43*, 9591. (f) Casas, J.; Engqvist, M.; Ibrahem, I.; Kaynak, B.; Córdova, A. *Angew. Chem., Int. Ed.* **2004**, *43*, 2−4. (g) Northup, A. B.; Mangion, I. K.; Hettche, F.; MacMillan, D. W. C. *Angew. Chem., Int. Ed.* **2004**, *43*, 2152 (h) Chan, V.; Kim, J. G.; Jimeno, C.; Carroll, P. J.; Walsh, P. J. *Org. Lett.* **2004**, *6*, 2051. (i) Thayumanavan, R.; Tanaka, F.; Barbas, C. F., III. *Org. Lett.* **2004**, *6*, 3541. (j) Northup, A. B.; MacMillan, D. W. C. *Science* **2004**, *305*, 1752. (k) Ward, D. E.; Jheengut, V.; Akinnusi, O. T. *Org. Lett.* **2005**, *7*, 1181. (l) Suri, J. T.; Ramachary, D. B.; Barbas, C. F., III. *Org. Lett.* **2005**, *7*, 1383.

(11) Movassaghi, M.; Jacobsen, E. N. *Science* **2002**, *298*, 1904.

(12) (a) Saito, S.; Nakadai, M.; Yamamoto, H. *Synlett* **2001**, 1245. (b) Tang, Z.; Jiang, F.; Yu, L.-T.; Cui, X.; Gong, L.-Z.; Mi, A.-Q.; Jiang, Y.-Z.; Wu, Y.-D. *J. Am. Chem. Soc.* **2003**, *125*, 5263. (c) Cobb, A. J. A.; Shaw, D. M.; Ley, S. V. *Synlett* **2004**, 558. (d) Mase, N.; Tanaka, F.; Barbas, C. F., III. *Angew. Chem., Int. Ed.* **2004**, *43*, 2420.

(13) A highly enantioselective synthesis of (+)-*endo*-**2** by yeast-mediated asymmetric reduction of bicyclo[3.3.1]nonan-2,8-dione has been reported. Mori, K.; Takayama, S.; Kido, M. *Bioorg. Med. Chem.* **1994**, *2*, 395.

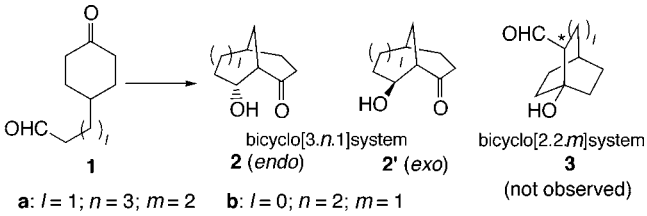
(14) See Supporting Information.

(15) Elliot, M. L.; Urban, F. J. Border. *J. Org. Chem.* **1985**, *50*, 1752.

(16) (a) Hoang, L.; Bahmanya, S.; Houk, K. N.; List, B. *J. Am. Chem. Soc.* **2003**, *125*, 16. (b) Allemann, C.; Gordillo, R.; Clemente, F. R.; Cheong, P. H.-E.; Houk, N. K. *Acc. Chem. Res.* **2004**, *37*, 558. (c) Bahmanyar, S.; Houk, K. N. *J. Am. Chem. Soc.* **2001**, *123*, 11273. (d) Bahmanyar, S.; Houk, K. N.; Martin, H. J.; List, B. *J. Am. Chem. Soc.* **2003**, *125*, 2475.

(17) For discussions on solubility and reactivity of organocatalysts, see: (a) Cobb, A. J. A.; Shaw, D. M.; Longbottom, D. A.; Gold, J. B.; Ley, S. L. *Org. Biomol. Chem.* **2005**, *3*, 84. (b) Darbre, T.; Machuqueiro, M. *Chem. Commun.* **2003**, 1090.

Table 1. Exploratory Studies of Intramolecular Aldolization of *s*-Symmetric Keto-aldehydes **1**[a]



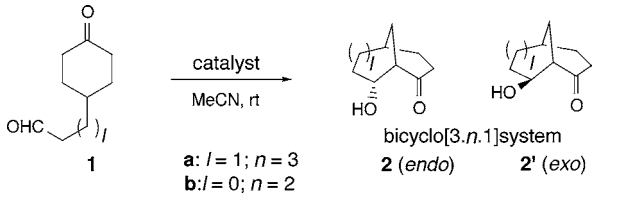
entry	substrate	catalyst (mol %)	solvent	time (h)	product	yield[b] (%)	de[c]	ee[d]
1	**1a**	K_2CO_3 (9)	MeOH	1	**2a**	60	0	
2	**1b**	K_2CO_3 (9)	MeOH	12	**2b**	83	−24	
3	**1a**	pyrrolidine (25)	MeCN	8	**2a**	70	59	
4	**1b**	pyrrolidine (25)	MeCN	24	**2b**	38	0	
5	**1b**	L-proline (25)	DMF	54	**2b**	52	94	10
6	**1a**	L-proline (25)	DMSO	72	**2a**	60	99	78

[a] Reactions were carried out in the indicated solvent (0.125 or 0.18 M). [b] Isolated after chromatographic purification. [c] Determined by ^{1}H NMR; refers to preference of *endo* selectivity. Negative value corresponds to enrichment in the *exo* isomer. [d] Determined by ^{1}H NMR analysis of the (*R*)- and (*S*)-MTPA derivatives of **2** or chiral HPLC analysis of the benzoyl ester of **2**.

proline, **8** exhibited a high enantioselectivity of 94% ee, suggesting some productive role of the *cis*-oriented TBDPSoxy group in crucial enantio-discriminating events (Table 2, entries 1−3). It was also an important clue in this venture that the tetrabutylammonium salt **9** was found not only to exist as an oil at ambient temperature and be miscible in MeCN but also to markedly enhance the aldolization rate (entry 4). We then surveyed factors leading to the further improvement of catalysis. Regarding **7**, the addition of some portions of H_2O[18] brought about a notable rate acceleration and an increment in enantioselectivity (entries 5 and 6), while excess (50 equiv) H_2O in turn attenuated the enantioselectivity to 76% ee (entry 7). No such phenomenon was observed in proline, indicating the supportive role played by the TBDPS group in enantio-discriminating events (entry 8). We found that the tetrabutylammonium salt **10**[19,20] gave good results as the use of 5 mol % of **10** completed the reaction within 3 h at room temperature to furnish 77% **2a** with 94% ee (entry 9). In contrast, the use of **11** resulted in a slight decrease in enantioselectivity (entry 10). On the other hand, any modification proved less effective for the aldolization of **1b** to **2b**. To date, the catalyst **12** was found to mark 33% ee at best (entries 11 and 12).

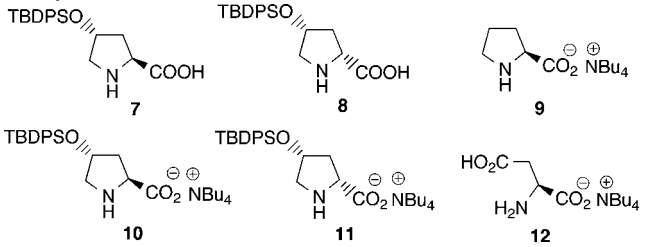
Although the roles of the TBDPSoxy group, H_2O, and tetrabutylammonoium salt in the reaction system are not yet clear,[20,21] the following mechanistic rationale would explain

Table 2. Organocatalytic Desymmetric Aldolization of *σ*-Symmetric Keto-aldehydes **1**



entry	substrate	catalyst (mol %)	additive (equiv)	time (h)	product	yield[b] (%)	de[c]	ee[d]
1	**1a**	L-proline (25)		92	**2a**	45	88	77
2	**1a**	**7** (15)		16	**2a**	84	98	78
3	**1a**	**8 (25)**		**23**	*ent*-**2a**	**68**	**>99**	**94**
4	**1a**	**9** (5)		3	**2a**	70	96	72
5	**1a**	**7** (15)	H_2O (1)	8	**2a**	71	99	89
6	**1a**	**7** (15)	H_2O (10)	7	**2a**	81	99	95
7	**1a**	**7** (15)	H_2O (50)	96	**2a**	85	85	76
8	**1a**	L-proline (25)	H_2O (1)	48	**2a**	68	99	76
9	**1a**	**10 (5)**		**3**	**2a**	**77**	**98**	**94**
10	**1a**	**11** (25)		18	*ent*-**2a**	74	99	81
11	**1b**	**9** (25)		2	**2b**	46	84	0
12	**1b**	**12** (25)		2	**2b**	40	98	33

[a] Reactions were carried out in the indicated solvent (0.1 or 0.125 M). [b] Isolated after chromatographic purification. [c] Determined by ^{1}H NMR; refers to preference of *endo* selectivity. [d] Determined by ^{1}H NMR analysis of the (*R*)-and (*S*)-MTPA derivatives of **2** or chiral HPLC analysis of the benzoyl ester of **2**.



the observed chemo-, diastereo-, and enantioselectivities in the amino acid catalyzed reaction of **1a** to *endo*-**2a** (Figure 1). The reaction of the catalyst **7** with **1a** furnishes an equilibrium mixture[22] of several enamines and H_2O. Under the provided conditions, transition state **B** is allowed to enjoy both a dipole interaction between the developing oxyanion and the iminium ion as well as a hydrogen bonding between the oxyanion and the carboxy group on the catalyst within a less strained chairlike conformation on the way to (1*S*,5*R*,8*R*)-**2a**. On the other hand, transition state **A** is discouraged as a result of the lack of an intramolecular hydrogen bonding between oxy-anion and carboxy group. The nonappearance of the bicyclo[2.2.2]octane **3** in the reaction products could be attributed to the constrained nature of the transition state **C**.[24]

To summarize, we have described the facile diasetereoselective synthesis of the bicyclo[3.3.1]nonane **2a** and

(18) For the unique effect of H_2O on organocatalysis, see: (a) Itoh, T.; Yokoya, M.; Miyauchi, K.; Nagata, K.; Ohsawa, A. *Org. Lett.* **2003**, *5*, 4301. (b) Torii, H.; Nakadai, M.; Ishihara, K.; Saito, S.; Yamamoto, H. *Angew. Chem., Int. Ed.* **2004**, *43*, 1983.

(19) Yamaguchi et al. reported that **9** catalyzes the Hajos−Wiechert reaction much faster than proline itself but with low ee. Yamaguchi, M.; Shiraishi, T.; Hirama, M. *J. Org. Chem.* **1996**, *61*, 3520.

(20) The remarkable rate acceleration exhibited by the tetrabutylammonium salt **10** would be attributed to the increment in the effective concentration of the catalytically active, nucleophilic secondary amine form compared with that of **7**, most of which tends to equilibrate to zwitterionic form under typical conditions.

(21) For the amino group to be nucleophilic, it must be in its unchanged form. We presumed that the hydrophobic environment generated by the TBDPS group and the tetrabutylammonium ion perturbed the pK_a of the amino group. (a) Barbas, C. F., III; Heine, A.; Zhong, G.; Hoffman, T.; Gramatikova, S.; Björnested, R.; List, B.; Anderson, J.; Stura, E. A.; Wilson, I.; Lerner, R. A. *Science* **1997**, *278*, 2085. (b) Lee, J. K.; Houk, K. N. *Science* **1997**, *276*, 942.

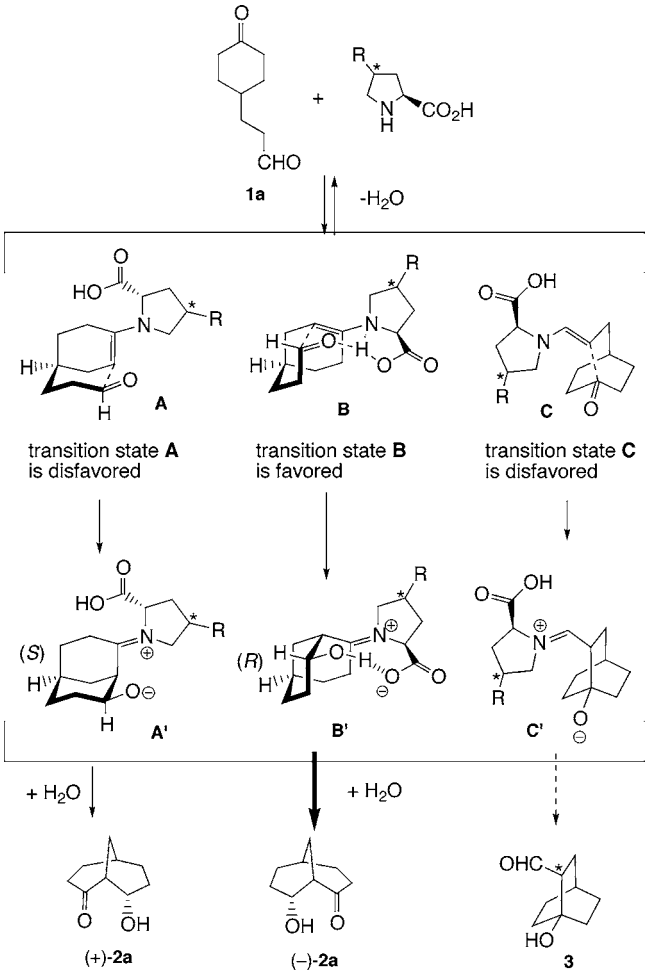


Figure 1. Mechanistic rationale on chemo-, diastereo-, and enantioselectivity.

bicyclo[3.2.1]octanone **2b** entailing an amino acid catalyzed aldolization as the key step, in which the former is efficiently constructed in a highly enantiomerically enriched fashion using **10**. This methodology complements the highly enantioselective Baker's yeast reduction.[13] The product is potentially useful as a chiral building block in target-oriented synthesis. The elucidation of the roles of TBDPSoxy group, H_2O, and tetrabutylammonoium salt in amino acid catalyzed aldolization and the search for a catalyst that enables asymmetric construction of chiral bicyclo[3.2.1]octane-type products are now the subjects of our extensive studies.

Acknowledgment. The authors are grateful to Prof. Masahiko Yamaguchi for useful suggestions and discussions.

Supporting Information Available: Experimental procedures, compound characterization, and analytical data (^{1}H NMR, ^{13}C NMR, and HRMS) for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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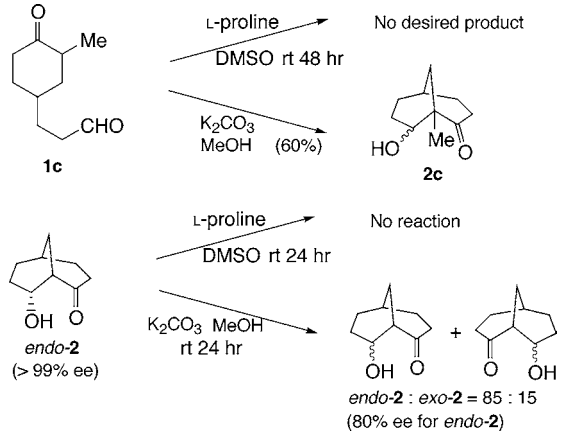
(22) It is important to point out that all of the amino acid catalysts described in this study promoted neither the aldolization of the α-methyl congeners **1c** to **2c** nor the reverse aldolization of **2a**, whereas methanolic K_2CO_3 promoted both reactions with considerable efficacies. These observations suggest that (i) proline-catalyzed aldolization is sensitive to steric hindrance around the carbonyl group and thus suffers from the formation of an enamine moiety,[23] (ii) the reverse aldolization of **2a** to **1a** is not operative under proline-type catalysis, and (iii) the enantioselectivity is not a result of thermodynamically equilibrated processes but is determined by a kinetically controlled step.



(23) It has been reported that proline catalyzes the asymmetric transfer aldol reaction between diacetone alcohol and aldehydes but not the reaction of 5-ethyl-5-hydroxy-4-methyl-3-heptanone. Chandrasekhar, S,; Narsihmulu, C.; Reddy, N. R.; Sultana, S. *Chem. Commun.* **2004**, 2450.

(24) The main reason that **3** was not formed could be the constraint of the bicyclo[2.2.2]-product and not because of the proline-based catalysts, since K_2CO_3 and pyrrolidine also did not afford **3**.