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A New Powerful Strategy for the Organocatalytic Asymmetric Construction of a Quaternary Carbon Stereogenic Center

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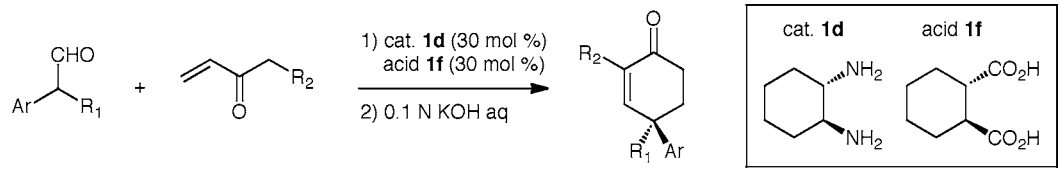
ABSTRACT



A new method for chiral diamine-catalyzed Robinson-type annulation was developed to construct cyclohexenone derivatives bearing a quaternary carbon stereogenic center at the 4-position in high enantiomeric excess. This method was successfully applied to the short synthesis of (+)-sporochnol A.

The catalytic asymmetric synthesis of quaternary carbon stereogenic centers, particularly all-carbon substituted centers, represents a significant synthetic challenge in modern organic chemistry.[1] A number of methods have been reported, which can be categorized into five major classes: enolate alkylation, Michael addition, cycloaddition reaction, sigmatropic rearrangement, and C−H insertion.[2] Organocatalytic asymmetric versions of these reactions have recently attracted considerable attention because of their environmentally friendly characteristics.[3] In our ongoing research, we anticipated that an organocatalytic Robinson-type annulation could provide an elegant approach to satisfy the desired stereochemical requirement, since this method can be frequently used to obtain complex cyclohexenone derivatives including polycyclic terpenes, steroids, and other natural products.[4] However, except for the examples using a Hajos−Parrish−Eder−Sauer−Wiechert reaction,[5] there has been very limited success with a practical and straightforward approach to construct a quaternary carbon stereogenic center at the 4-position on a nonfused cyclohexenone framework with high enantiomeric excess.[6]

In 1969, Yamada and Otani reported an asymmetric synthesis of 4,4-disubstituted cyclohexenone derivatives via a stepwise strategy in which L-proline enamines were used as nucleophiles.[7] However, our preliminary studies revealed

(1) *Quaternary Stereocenters: Challenge and Solutions for Organic Synthesis*; Christoffers, J., Baro, A., Eds.; Wiley-VCH: Weinheim, 2005.

(2) For recent reviews, see: (a) Denissova, I.; Barriault, L. *Tetrahedron* **2003**, *59*, 10105. (b) Douglas, C. J.; Overman, L. E. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 5363. (c) Trost, B. M.; Jiang, C. *Synthesis* **2006**, 369. (d) Cozzi, P. G.; Hilgraf, R.; Zimmermann, N. *Eur. J. Org. Chem.* **2007**, 5969.

(3) Review : Bella, M.; Gasperi, T. *Synthesis* **2009**, 1583.

(4) Review: Varner, M. A.; Grossman, R. B. *Tetrahedron* **1999**, *55*, 13867.

(5) Christen, D. P. In *Name Reactions for Homologations*; Li, J. J., Ed.; Wiley-VCH: Weinheim, 2009; Part 2, pp 554−582.

(6) For related works, see: (a) Carlone, A.; Marigo, M.; North, C.; Landa, A.; Jørgensen, K. A. *Chem. Commun.* **2006**, 4928. (b) Zhou, J.; Wakchaure, V.; Kraft, P.; List, B. *Angew. Chem., Int. Ed.* **2008**, *47*, 7656. (c) Akiyama, T.; Katoh, T.; Mori, K. *Angew. Chem., Int. Ed.* **2009**, *48*, 4226. (d) Mori, K.; Katoh, T.; Suzuki, T.; Noji, T.; Yamanaka, M.; Akiyama, T. *Angew. Chem., Int. Ed.* **2009**, *48*, 9652. (e) Li, P.; Yamamoto, H. *Chem. Commun.* **2009**, 5412.

(7) Yamada, S.; Otani, G. *Tetrahedron Lett.* **1969**, *10*, 4237.

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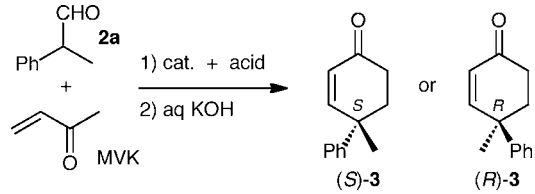
Table 1. Catalytic Asymmetric Robinson Annulation: Optimization Study[a]



entry	cat. (mol %)	acid (mol %)	time (days)	yield (%)	ee[b] (%)
1	L-Lys (10)		1	48 (*S*)	55
2	L-Orn (10)		6	25 (*S*)	31
3	L-Arg (10)		7	45 (*S*)	60
4	**1a** (10)	**1e** (5)	2	47 (*R*)	52
5	**1a** (10)	**1g** (5)	2	53 (*R*)	52
6	**1a** (10)	(±)-**1e** (5)	2	47 (*R*)	50
7	**1b** (10)	(±)-**1e** (5)	2	55 (*S*)	50
8	**1c** (10)		8	51 (*S*)	41
9	**1c** (10)	**1e** (10)	3	54 (*S*)	74
10	**1c** (30)	**1e** (15)	0.38	50 (*S*)	67
11	**1c** (30)	**1e** (30)	**0.33**	**45 (*S*)**	**82**
12	**1c** (10)	**1f** (10)	3	60 (*S*)	68
13	**1c** (10)	(±)-**1e** (10)	2	38 (*S*)	63
14	**1c** (10)	phthalic acid (10)	7	53 (*S*)	61
15	**1c** (10)	**1g** (10)	3	46 (*S*)	68
16	**1c** (10)	L-tartaric acid (10)	3	43 (*S*)	65
17	**1c** (10)	D-tartaric acid (10)	3	40 (*S*)	21
18	**1d** (30)	**1f** (30)	**0.33**	**49 (*R*)**	**87**

[a] Conditions: **2a** (1 mmol), MVK (1.5 mmol) in *i*-PrOH (1.0 mL) in the presence of catalyst and acid. [b] Determined by chiral HPLC analysis using a Chiralpak AD.

that the direct treatment of 2-phenylpropionaldehyde (**2a**) with methyl vinyl ketone (MVK) in the presence of a catalytic amount of L-proline (30 mol %) was unsuccessful. Furthermore, the use of diphenylprolinol methyl ether as a chiral catalyst under Gellman's conditions[8] was also unsatisfactory (7 days, 20% yield, 20% ee).[9] These results clearly suggest that it is inherently difficult to form a sterically congested enamine species from **2a** and secondary amines. To overcome this difficulty, we sought to devise a new methodology based on chiral primary amine catalysis[10] that might address the steric-constraint problems.

We report here an efficient method for the construction of cyclohexenone derivatives bearing a quaternary carbon stereogenic center at the 4-position based on a novel chiral diamine-catalyzed Robinson-type annulation.

First, we screened various combinations of chiral primary amines and carboxylic acids to transform 2-phenylpropionaldehyde (**2a**) to the desired cyclohexenone **3** by exposure to MVK (Table 1).[9] In all cases, the use of naturally occurring basic amino acids or commercially available primary amines like **1a** and **1b** (Figure 1) was less efficient (entries 1−7). To our delight, the combined use of (1*R*,2*R*)-1,2-cyclohexanediamine (**1c**) with (1*R*,2*R*)-1,2-cyclohexanedicarboxylic acid (**1e**) in *i*-PrOH[11]led to a significant improvement in enantioselectivity (entries 9−11), and with an increase in catalyst loading (30 mol %) the reaction went to completion within 8 h to give the cyclohexenone (*S*)-**3** in 45% yield with 82% ee (entry 11).[12,13] The lower efficiency for (*R*,*R*)-**1c**/(*S*,*S*)-**1f** and (*R*,*R*)-**1c**/racemic-**1e** highlights the importance of the compatibility of chirality between the amine and acid catalysts (entries 12 and 13). Similar phenomena were observed for the use of L- or D-tartaric acid as an acid additive (entries 16 and 17). The superiority of (*R*,*R*)-**1e** as a cocatalyst in this catalyst system is clear based on the results shown in entries 8 and 14−17. As expected, the combination of (*S*,*S*)-**1d** and (*S*,*S*)-

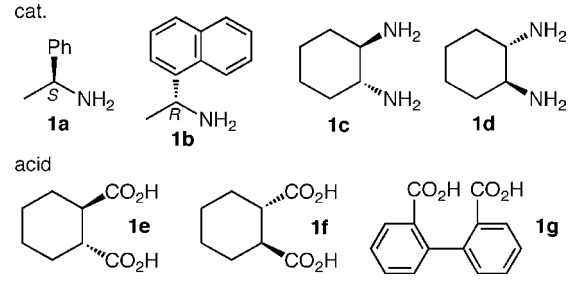


Figure 1. Organocatalysts and acid additives examined in the present study.

(8) Chi, Y.; Gellman, S. H. *Org. Lett.* **2005**, *7*, 4253.
(9) For a comprehensive compilation of the catalyst-screening results, see the Supporting Information.

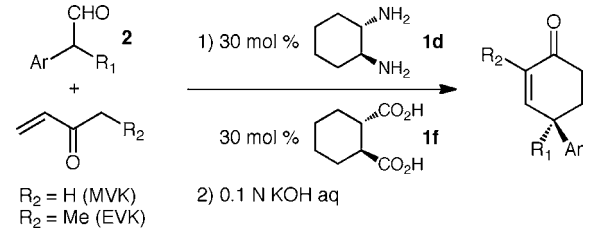
1f produced cyclohexenone (*R*)-**3** with a completely opposite configuration (49% yield, 87% ee) (entry 18).[14]

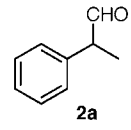
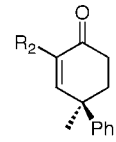
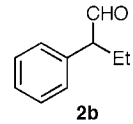
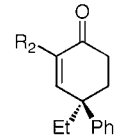
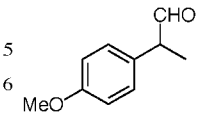
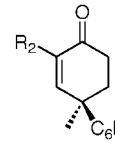
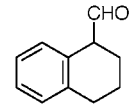
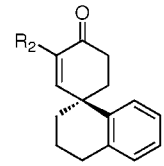
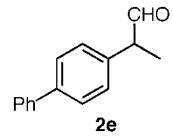
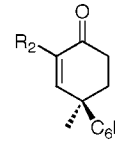
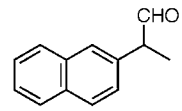
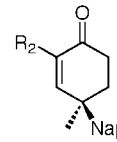
With the optimal conditions in hand, we then examined a variety of α-aryl-substituted propionaldehydes to establish the general utility of this asymmetric transformation (Table 2). All reactions were performed in *i*-PrOH at 0 °C in the presence of 30 mol % of the respective diamine (*S*,*S*)-**1d** and dicarboxylic acid (*S*,*S*)-**1f**.

Various aldehydes reacted smoothly with MVK or ethyl vinyl ketone (EVK) in moderate yields (up to 65%) and with high enantioselectivity (up to 97%) (entries 1−12).[13,15,16]

A probable mechanism that may account for the observed absolute configuration of product (*R*)-**3** and this highly effective catalytic asymmetric process is outlined in Scheme 1. Thus, condensation of bifunctional catalyst **1d** with both **2a** and MVK in the presence of cocatalyst **1f** proceeds through the formation of an enamine−iminium double-activation intermediate **A**, which then causes an intramolecular Michael addition to afford the cyclic enamine−iminium ion intermediate **B**. This intermediate collapses spontaneously via hydrolysis to give the keto-aldehyde precursor **C**[17] and

Table 2. Catalytic Asymmetric Robinson Annulation:Generality[a]



entry	substrate	time (h)	product	yield[b] (%)	ee (%)
1		8	 **3**, R_2 = H	49	87[c]
2	**2a**	4	**4**, R_2 = Me	51	70[d]
3		48	 **5**, R_2 = H	40	85[c]
4	**2b**	72	**6**, R_2 = Me	65	72[d]
5		12	 **7**, R_2 = H	62	91[e]
6	**2c**	8	**8**, R_2 = Me	59	91[e]
7		2	 **9**, R_2 = H	48	90[e]
8	**2d**	3	**10**, R_2 = Me	56	82[e]
9		4	 **11**, R_2 = H	56	92[d]
10	**2e**	3	**12**, R_2 = Me	54	94[d]
11		4	 **13**, R_2 = H	50	97[c]
12	**2f**	3	**14**, R_2 = Me	61	84[c]

[a] Conditions: aldehyde **2** (1 mmol), MVK or EVK (1.5 mmol) in *i*-PrOH (1 mL) at 0 °C in the presence of 30 mol % of catalyst **1d** and 30 mol % of acid **1f**. [b] Isolated yield. [c] Determined by chiral HPLC analysis using a Chiralpak AD. [d] Determined by chiral HPLC analysis using a Chiralpak AS-H. [e] Determined by chiral HPLC analysis using a Chiralpak AD-H.

the catalyst/cocatalyst system composed of **1d** and **1f**, which leads back to the catalytic cycle. In this sequence, the vicinal *trans*-diamine arrangement in catalyst **1d** is essential not only to activate both the Michael donor and acceptor components but also to bring them together in close proximity to achieve carbon−carbon bond formation with the observed enantiocontrol.[18]

To demonstrate the synthetic value of this organocatalytic asymmetric process, (+)-sporochnol A (**15**), a chemical fish

(10) For reviews, see: (a) Peng, F.; Shao, Z. *J. Mol. Catal. A: Chem.* **2008**, *285*, 1. (b) Bartoli, G.; Melchiorre, P. *Synlett* **2008**, 1759. (c) Xu, L.-W.; Luo, J.; Lu, Y. *Chem. Commun.* **2009**, 1807. For recent selected examples, see: (d) Luo, S.; Qiao, Y.; Zhang, L.; Li, J.; Li, X.; Cheng, J.-P. *J. Org. Chem.* **2009**, *74*, 9521, and references cited therein. (e) Jiang, X.; Zhang, Y.; Chan, A. S. C.; Wang, R. *Org. Lett.* **2009**, *11*, 153. (f) Li, P.; Wen, S.; Yu, F.; Liu, Q.; Li, W.; Wang, Y.; Liang, X.; Ye, J. *Org. Lett.* **2009**, *11*, 753. (g) Zhang, X.; Liu, S.; Li, X.; Yan, M.; Chan, A. S. C. *Chem. Commun.* **2009**, 833. (h) Li, J.; Luo, S.; Cheng, J.-P. *J. Org. Chem.* **2009**, *74*, 1747. (i) Kano, T.; Tanaka, Y.; Osawa, K.; Yurino, T.; Maruoka, K. *Chem. Commun.* **2009**, 1956. (j) Da, C.-S.; Che, L.-P.; Guo, Q.-P.; Wu, F.-C.; Ma, X.; Jia, Y.-N. *J. Org. Chem.* **2009**, *74*, 2541. (k) Wu, F.-C.; Da, C.-S.; Du, Z.-X.; Guo, Q.-P.; Li, W.-P.; Yi, L.; Jia, Y.-N.; Ma, X. *J. Org. Chem.* **2009**, *74*, 4812. (l) Gogoi, S.; Zhao, C.-G.; Ding, D. *Org. Lett.* **2009**, *11*, 2249. (m) Mei, K.; Jin, M.; Zhang, S.; Li, P.; Liu, W.; Chen, X.; Xue, F.; Duan, W.; Wang, W. *Org. Lett.* **2009**, *11*, 2864. (n) Rasappan, R.; Reiser, O. *Eur. J. Org. Chem.* **2009**, 1305. (o) Ma, X.; Da, C.-S.; Yi, L.; Jia, Y.-N.; Guo, Q.-P.; Che, L.-P.; Wu, F.-C.; Wang, J.-R.; Li, W.-P. *Tetrahedron: Asymmetry* **2009**, *20*, 1419. (p) Dong, L.; Lu, R.; Du, Q.; Zhang, J.; Liu, S.; Xuan, Y.; Yan, M. *Tetrahedron* **2009**, *65*, 4142. (q) Gu, Q.; Guo, X.-T.; Wu, X.-Y. *Tetrahedron* **2009**, *65*, 5265. (r) Luo, G.; Zhang, S.; Duan, W.; Wang, W. *Synthesis* **2009**, 1564. (s) Liu, J.; Yang, Z.; Liu, X.; Wang, Z.; Liu, Y.; Bai, S.; Lin, L.; Feng, X. *Org. Biomol. Chem.* **2009**, *7*, 4120. (t) Li, J.; Li, X.; Zhou, P.; Zhang, L.; Luo, S.; Cheng, J.-P. *Eur. J. Org. Chem.* **2009**, 4486. (u) He, T.; Qian, J.-Y.; Song, H.-L.; Wu, X.,-Y. *Synlett* **2009**, 3195. (v) Galzerano, P.; Bencivenni, G.; Pesciaioli, F.; Mazzanti, A.; Giannichi, B.; Sambri, L.; Bartoli, G.; Melchiorre, P. *Chem.—Eur. J.* **2009**, *15*, 7846. (w) Wu, L.-Y.; Bencivenni, G.; Mancinelli, M.; Mazzanti, A.; Bartoli, G.; Melchiorre, P. *Angew. Chem., Int. Ed.* **2009**, *48*, 7196. (x) Galzerano, P.; Pesciaioli, F.; Mazzanti, A.; Bartoli, G.; Melchiorre, P. *Angew. Chem., Int. Ed.* **2009**, *48*, 7892. (y) Zhang, E.; Fan, C.-A.; Tu, Y.-Q.; Zhang, F.-M.; Song, Y. L. *J. Am. Chem. Soc.* **2009**, *131*, 14626.

(11) Other solvents found to be less efficient for the present purpose: MeOH (32 h at 0 °C, 42%, 88% ee), MeCN (42 h at 0 °C, 50%, 61% ee), DMSO (15 h at rt, 35%, 82% ee).

(12) In contrast, the use of (1*R*,2*R*)-1,2-diphenylethylenediamine with *rac*-**1e** caused no asymmetric induction (Supporting Information).

(13) Due to the instability of the starting aldehyde **2** under the conditions, unidentified complex byproducts were formed.

(14) The absolute stereochemical sequence in these asymmetric transformations was determined by comparison of the optical rotation data with those reported in the literature: Meyers, A. I.; Lefker, B. A.; Wanner, K. Th.; Aitken, R. A. *J. Org. Chem.* **1986**, *51*, 1936.

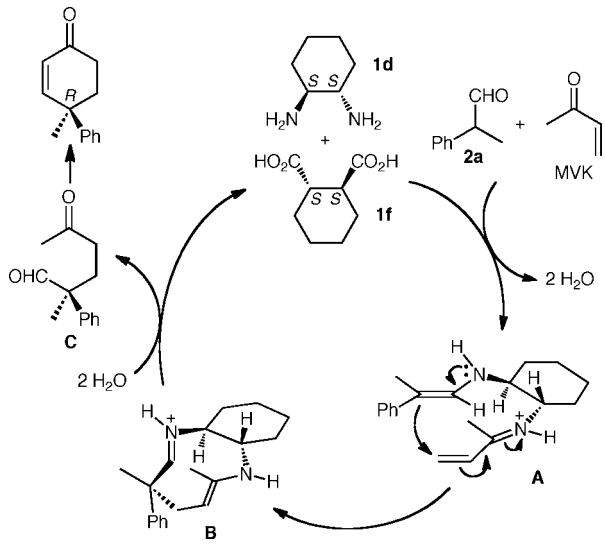
(15) The absolute configurations of unknown products were surmised by analogy.

(16) Unfortunately, similar reactions using α-alkyl-substituted analogues as donor molecules were disappointingly very slow, suggesting the importance of enough acidity for an active α-hydrogen atom.

(17) Although we did not examine this point in detail, it was possible to isolate the intermediary Michael adduct from the reaction mixture; see the Supporting Information. See also ref 10g.

(18) Although we did not try, it might be possible to recover the catalyst/cocatalyst system from the reaction mixture by column purification.

Scheme 1. Proposed Catalytic Cycle of Asymmetric Robinson Annulation



deterrent isolated from the Caribbean marine alga *Sporochnus bolleanus*, was targeted (Scheme 2).[19] The reaction of 2-(4-methoxyphenyl)propionaldehyde with MVK under the standardized conditions using catalyst **1c** and acid **1e** gave cyclohexenone (*S*)-**7** (62%, 91% ee). Conjugate addition of the silyl zincate, developed by Oestreich,[20] followed by Hudrlik's silicon-directed fragmentation (*m*-CPBA oxidation; BF_3•OEt_2-mediated β-elimination)[21] and subsequent esterification gave methyl ester **18** (41% total yield), which can be converted into (+)-sporochnol A (**15**) as described in the literature.[22]

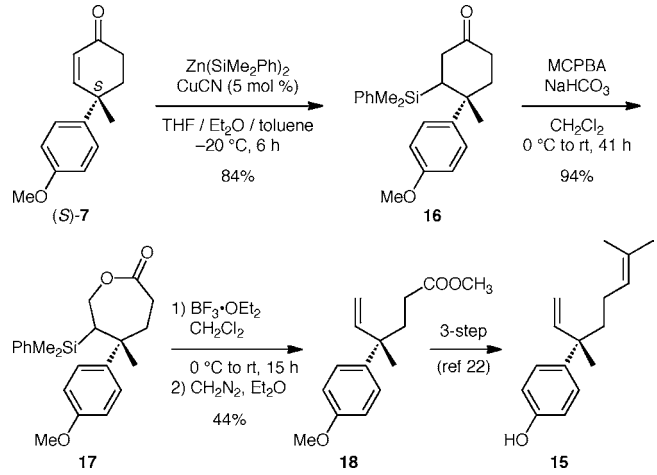
(19) (a) Martín, R.; Buchwald, S. L. *Org. Lett.* **2008**, *10*, 4561, and references cited therein. (b) Yamamoto, D.; Kawano, K.; Takahashi, K.; Ishihara, J.; Hatakeyama, S. *Heterocycles* **2009**, *77*, 249.

(20) (a) Oestreich, M.; Weiner, B. *Synlett* **2004**, 2139. (b) Auer, G.; Weiner, B.; Oestreich, M. *Synthesis* **2006**, 2113.

(21) (a) Hudrlik, P. F.; Hudrlik, A. M.; Nagendrappa, G.; Yimenu, T.; Zellers, E. T.; Chin, E. *J. Am. Chem. Soc.* **1980**, *102*, 6894. (b) Hudrlik, P. F.; Hudrlik, A. M.; Yimenu, T.; Waugh, M. A.; Nagendrappa, G. *Tetrahedron* **1988**, *44*, 3791.

(22) Fadel, A.; Vandromme, L. *Tetrahedron: Asymmetry* **1999**, *10*, 1153.

Scheme 2. Total Synthesis of (+)-Sporochnol A (**15**)[a]



In conclusion, we have developed an unprecedented organocatalytic asymmetric synthesis of cyclohexenone derivatives with a quaternary carbon stereogenic center at the 4-position with complete control via chiral diamine/dicarboxylic acid-catalyzed Robinson-type annulation. In addition, this new methodology was successfully applied to the short synthesis of (+)-sporochnol A. This method should be of great value in terms of simplicity, ready availability of the respective catalysts, and utility in natural product synthesis. Further studies to extend the scope of this method are now in progress.

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Supporting Information Available: Experimental details and spectral data. This material is available free of charge via the Internet at http://pubs.acs.org.

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