

Primary-Amine-Catalyzed Enantioselective Intramolecular Aldolizations**

Jian Zhou, Vijay Wakchaure, Philip Kraft, and Benjamin List*

Dedicated to Professor Manfred T. Reetz on the occasion of his 65th birthday

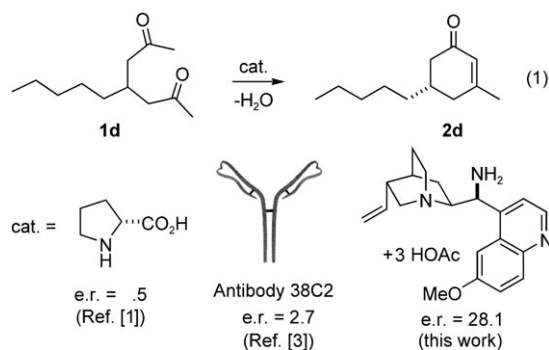
The enantioselective aldol cyclodehydration of 4-substituted 2,6-heptandiones **1** to cyclohexenones **2** [e.g., **1d** to **2d**, Eq. (1)] has been a long-term challenge in asymmetric catalysis. Pioneering investigations by Agami et al.^[1] using proline catalysis, in analogy to the Hajos–Parrish–Eder–Sauer–Wiechert reaction,^[2] have led to only moderate enantioselectivity and poor yields. Catalytic antibody 38C2, developed by Lerner, Barbas et al., turned out to be more active, but the enantioselectivity remained moderate.^[3] We have now reinvestigated this reaction concentrating on catalysis with primary amines, and have identified quinine derivative **5**·3HOAc, which gives high yields, excellent enantioselectivity, and has a broad substrate scope.

As fragrances and building blocks for natural product synthesis,^[4] chiral non-racemic enones **2** are valuable synthetic targets. In particular, the desymmetrizing intramolecular aldol reaction of 4-substituted 2,6-heptandiones **1** represents a potentially attractive approach. First attempts to conduct such aldol reactions by differentiating enantiotopic groups were made in the 1980s by Agami et al. using proline as catalyst. However, in these aldolizations, proline is rather inefficient, giving only low yields of moderately enantioenriched aldol condensation products, along with the corre-

sponding aldol addition products and starting material.^[1] The other catalyst investigated, aldolase antibody 38C2, catalyzes the aldol condensation of three diketones **1** to the corresponding enones **2** in high yields (>95%), but the reactions have only been investigated on an analytical scale, and enantioselectivity remained low (e.r. ≤ 4.2).^[3] Clearly, there still remains much room for improvement regarding practicality, enantioselectivity, and substrate scope.

Recently, low molecular weight primary amines have been described as being effective aminocatalysts for transformations involving enamine and iminium ions.^[5,6] Although only limited success has previously been achieved in aldolizations of ketones,^[2,7] we reasoned that primary amines should be suitable catalysts for such reactions. The generally lower nucleophilicity of enamines derived from primary amines was expected to be counterbalanced by two factors: 1) a higher concentration of the iminium ion and enamine intermediates owing to reduced steric requirements, and 2) possible general Brønsted acid co-catalysis by the N–H bond of the enamine in the C–C-bond-forming transition state, as proposed by Houk et al. for primary amine-catalyzed aldol reactions.^[8] With this hypothesis in mind, and encouraged by the high activity of aldolase antibody 38C2, which also features a primary amino group at its active site, we decided to reexamine the desymmetrization of acyclic heptandiones **1** to chiral enones **2** using primary aminocatalysts.

Initial studies confirmed that in addition to proline, most other tested secondary amine catalysts are only moderately active. Phenylalanine was also investigated as a primary amino acid but gave unsatisfactory results. In contrast, salts of primary amines **3–7** proved to be rather efficient. Whereas the (*S*)-TRIP salt of *p*-anisidine (**3**), which we have employed in the catalysis of a very similar 6-*endo* aldolization in an organocatalytic cascade sequence,^[9] proved particularly active, its enantioselectivity was poor (Table 1, entry 1). Remarkably, chiral diamines **4–6**, used recently used as bifunctional primary amine catalysts in the epoxidation of cyclic enones, also turned out to be highly enantioselective in the aldolization of **1d**.^[6g] Although chiral diamine **4** in combination with (*S*)-TRIP failed to promote the reaction (entry 2), it gave a promising enantioselectivity (e.r. = 9.3) as the trichloroacetate salt (entry 3), although the reactivity of this salt was still insufficient. Gratifyingly, 9-amino-9-deoxyepiquinine **5**, recently introduced to primary iminium^[6d–g] and enamine catalysis,^[5g,h] proved to be particularly powerful in this reaction. At room temperature, it afforded comparable enantioselectivity, as with catalyst **4**, but had an improved reaction rate (entry 4). Lowering the temperature to –15°C improved the e.r. to



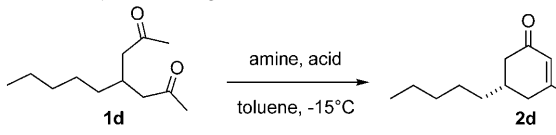
[*] Dr. J. Zhou, Dr. V. Wakchaure, Prof. Dr. B. List
Max-Planck-Institut für Kohlenforschung
Kaiser Wilhelm-Platz 1, 45470 Mülheim an der Ruhr (Germany)
Fax: (+49) 208-306-2982
E-mail: list@mpi-muelheim.mpg.de

Dr. P. Kraft
Givaudan Schweiz AG
8600 Dübendorf (Switzerland)

[**] The authors acknowledge generous funding from the Max Planck Society, the DFG (SPP 1179, Organocatalysis), the Fonds der Chemischen Industrie, and Wacker Chemie AG.

Supporting information for this article is available on the WWW under <http://dx.doi.org/10.1002/anie.200802497>.

Table 1: Catalyst screening.



Reaction scheme: 2,6-diketone **1d** reacts with an amine and acid in toluene at -15°C to form enone **2d**.

Chemical structures of catalysts **3**, **4**, **5**, **6** (R = OMe), and **7** (R = H) are shown.

Entry	Catalyst ^[f] amine, acid	t [h]	Conv. [%] ^[a]	e.r. ^[b]	(ee [%])
1 ^[c]	3 ·(S)-TRIP ^[d]	48	full	1.0	(2)
2 ^[c]	4 ·2 (S)-TRIP	48	trace	—	—
3 ^[c]	4 ·2 Cl ₃ CCO ₂ H	96	full	9.3	(80)
4 ^[c]	5 ·2 Cl ₃ CCO ₂ H	10	full	8.5	(79)
5	5 ·2 Cl ₃ CCO ₂ H	96	full	16.5	(88)
6	5 ·3 Cl ₃ CCO ₂ H	80	full	16.5	(88)
7	6 ·3 Cl ₃ CCO ₂ H	80	full	16.0	(88) ^[e]
8	7 ·3 Cl ₃ CCO ₂ H	80	full	7.3	(76) ^[e]
9	5 ·3 CH ₃ CO ₂ H	48	full	28.1	(93)
10	5 ·3 CF ₃ CO ₂ H	96	80	9.8	(81)
11	5 ·3 <i>p</i> TsOH	96	40	4.9	(66)
12	5 ·3 EtCO ₂ H	36	full	25.3	(92)
13	5 ·3 <i>i</i> PrCO ₂ H	36	full	23.4	(91)
14	5 ·3 PhCO ₂ H	48	full	17.8	(89)

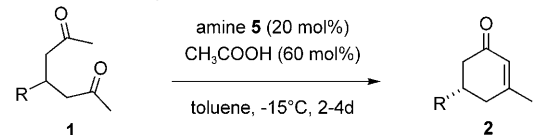
[a] From GC analysis. [b] From chiral-phase HPLC analysis. [c] At room temperature. [d] TRIP = 3,3'-bis(2,4,6-triisopropylphenyl)-1,1'-bi-2-naphthol cyclic monophosphate. [e] Opposite enantiomer. [f] 20 mol% of each amine was used.

16.5 (entry 5). As expected, quinidine-derived catalyst **6** afforded the opposite enantiomer with equally high enantioselectivity (entry 7). Cinchonine-derived primary amine **7** was also tested, but resulted in lower enantioselectivity than the quinine-derived amine catalyst **6** (entry 8).

The acid co-catalyst significantly influenced both reactivity and enantioselectivity (entries 5–6 and 9–14). The use of three rather than two equivalents of acid slightly improved the reactivity without loss of enantioselectivity (entry 5). The general tendency is that salts of amine **5** with stronger acids are less reactive and give lower enantioselectivity.^[10] Acetic acid turned out to be the best co-catalyst in terms of enantioselectivity (entry 9), although the corresponding propionic acid and isobutyric acid salts are slightly more active. We also investigated a variety of solvents, and toluene turned out to be optimal.

Based on these optimization studies, we investigated the reaction of different 2,6-diketones **1** in toluene at -15°C using 20 mol% of quinine catalyst **5** in combination with three equivalents of acetic acid (Table 2). A variety of aliphatic and aromatic substituted 2,6-heptandiones **1** were effectively processed under the optimized reaction conditions, and furnished the desired products in excellent yields. In general, diones **1** with an aliphatic substituent in the 4-position reacted faster than those with an aromatic group. Of the eleven substrates examined, ten afforded the desired enone **2** with e.r. > 19.0. It should be noted that the pseudoenantiomeric catalyst **6** also delivered excellent

Table 2: Substrate scope.



Reaction scheme: 2,6-diketone **1** reacts with amine **5** (20 mol%) and CH₃COOH (60 mol%) in toluene at -15°C for 2–4 d to form enone **2**.

Entry ^[a]	R	Product	Yield [%] ^[b]	e.r. ^[c]	(ee [%])
1	Me	2a	91	23.9	(92)
2	Me	2a	87	26.1	(92) ^[d]
3	Et	2b	80	20.6	(90)
4	<i>i</i> Pr	2c	97	13.4	(86)
5	<i>n</i> -C ₅ H ₁₁	2d	96	28.1	(93)
6	CH ₂ CH ₂ Ph	2e	98	19.8	(90)
7	Ph	2f	93	21.6	(91)
8	<i>p</i> -ClC ₆ H ₄	2g	94	22.0	(91)
9	<i>m</i> -ClC ₆ H ₄	2h	92	26.4	(92)
10	<i>p</i> -MeC ₆ H ₄	2i	94	24.5	(91)
11	2-thienyl	2j	92	25.2	(92)
12	2-furanyl	2k	95	36.3	(94)

[a] Reaction scale: 0.5 mmol. [b] Yield of isolated product. [c] From chiral-phase HPLC or GC analysis. [d] Opposite enantiomer.

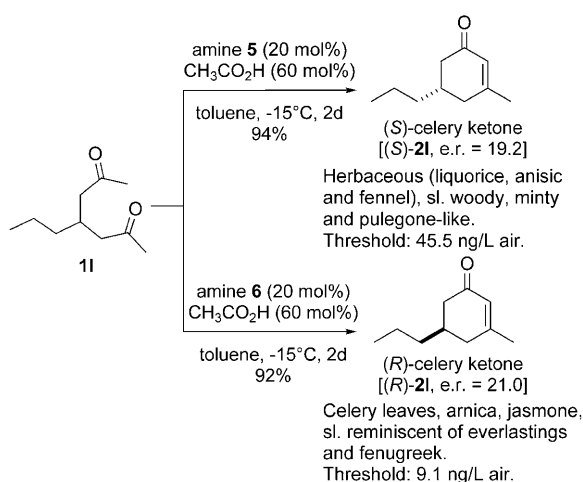
enantioselectivity in providing the opposite enantiomer, as demonstrated with **2a** (entry 2).

Chiral enones **2** are valuable synthetic building blocks. Enone **2a**, for instance, has been used in the synthesis of 9-isocyanopupukeanane^[4d] and HIV-1 protease-inhibitive didemnaketals.^[11] Previously, at least five steps were required to obtain (*R*)-**2a** from (*R*)-pulegone.^[11,12] With our current approach, both of its enantiomers can be easily accessed in two steps from 2,4,6-lutidine.^[13]

The synthetic utility of our reaction was further exemplified by the first asymmetric synthesis of both enantiomers of celery ketone **2i** (*syn.* Livescone), a synthetic fragrance material with typical lovage and celery character, used as modifier with basil and tarragon top notes, and to support jasmine complexes in perfumery.^[4a] The enantiomers of **2i** differ as strikingly in their olfactory properties as in the rare case of carvone.^[14] Only the stronger *R* enantiomer (odor threshold 9.1 ng L⁻¹ air) is responsible for the characteristic celery note of the racemate, whereas the *S* enantiomer, which is five times weaker (odor threshold 45.5 ng L⁻¹ air), has an aniseed-like liquorice smell with minty facets (Scheme 1).

It should be noted that, in the reaction catalyzed by salts **3** and **4**, a substantial amount of the intermediate aldol addition product could be detected during the reaction course. Using the quinine-derived amine **5**, only traces of the aldol product were detected, suggesting that the higher reactivity obtained by catalyst **5** may at least in part be due to faster dehydration.

The absolute configuration of the product obtained using catalyst **5** was determined by comparison of the optical rotation of compound **2a** with the literature value.^[12] As has been proposed in related aldol reactions catalyzed by a combination of diamine and protonic acid,^[15] the protonated quinine moiety of catalyst **5** might act as synergistic Brønsted acid for the direction and activation of the electrophilic carbonyl group by hydrogen bonding. This double-activation model was also supported by the fact that when only one equivalent of acid co-catalyst is used, the reaction is much slower.



Scheme 1. Synthesis of both enantiomers of celery ketone (**2**).

In conclusion, we have reported a solution to the long-standing problem of enantioselective aldolizations of 4-substituted-2,6-heptanediones **1** to enantiomerically enriched 5-substituted-3-methyl-2-cyclohexene-1-ones **2**. Both 9-amino-9-deoxyepiquinine **5** and its pseudoenantiomeric, quinidine-derived analogue **6**, in combination with acetic acid, proved to be efficient and highly enantioselective catalysts for this transformation, giving both enantiomers of enone **2** with high e.r. values. Mechanistic investigations towards a better understanding of the details of this reaction as well as investigations towards developing modular combinations of the process with other reactions by iminium ion or enamine catalysis to develop new organocatalytic cascades are ongoing.

Experimental Section

Acetic acid (18.0 mg, 0.3 mmol) was added to a solution of amine **5** (32.5 mg, 0.1 mmol) in toluene (0.5 mL). After cooling to -15°C, diketone **1** (0.5 mmol) was added. The resulting mixture was stirred at -15°C until TLC analysis indicated complete conversion of the diketone. The reaction mixture was then directly subjected to column chromatography to afford the desired product **2**, using hexane or pentane/diethyl ether (10:1→10:2) as eluent. To obtain pure compounds, volatile enones **2** were carefully dried under vacuum at -78°C to remove residual solvent.

Received: May 28, 2008

Published online: August 20, 2008

Keywords: aldol reaction · asymmetric catalysis · bifunctional catalysis · enamines · organocatalysis

- [1] a) C. Agami, H. Sevestre, *J. Chem. Soc. Chem. Commun.* **1984**, 1385–1386; b) C. Agami, N. Platzer, H. Sevestre, *Bull. Soc. Chim. Fr.* **1987**, 2, 358–360.
- [2] a) Z. G. Hajos, D. R. Parrish, Germany Patent DE 21022623, **1971**; b) U. Eder, G. R. Sauer, R. Wiechert, Germany Patent DE 2014757, **1971**; c) U. Eder, G. Sauer, R. Wiechert, *Angew. Chem.* **1971**, 83, 492; *Angew. Chem. Int. Ed. Engl.* **1971**, 10, 496; d) G. Hajos, D. R. Parrish, *J. Org. Chem.* **1974**, 39, 1615–1621. For a general review, see: e) S. Mukherjee, J. W. Yang, S. Hoffmann, B. List, *Chem. Rev.* **2007**, 107, 5471–5569.

- [3] B. List, R. A. Lerner, C. F. Barbas III, *Org. Lett.* **1999**, 1, 59–61.
- [4] See, for example: a) C. S. Letizia, J. Cocchiara, G. A. Wellington, C. Funk, A. M. Api, *Food Chem. Toxicol.* **2000**, 38, S153–S155; b) M. A. González, S. Ghosh, F. Rivas, D. Fischer, E. A. Theodorakis, *Tetrahedron Lett.* **2004**, 45, 5039–5041; c) B. H. Bae, K. S. Im, W. C. Choi, J. Hong, C.-O. Lee, J. S. Choi, B. W. Son, J.-I. Song, J. H. Jung, *J. Nat. Prod.* **2000**, 63, 1511–1514; d) H. Yamamoto, H. L. Sham, *J. Am. Chem. Soc.* **1979**, 101, 1609–1611.
- [5] For examples of asymmetric enamine catalysis using primary amines, see: a) S. Danishefsky, P. Cain, *J. Am. Chem. Soc.* **1976**, 98, 4975–4983; b) S. G. Davies, R. L. Sheppard, A. D. Smith, J. E. Thomson, *Chem. Commun.* **2005**, 3802–3804; c) W. Zou, I. Ibrahim, P. Dziedzic, H. Sundén, A. Córdova, *Chem. Commun.* **2005**, 4946–4948; d) M. Amedjkouh, *Tetrahedron: Asymmetry* **2005**, 16, 1411–1414; e) S. B. Tsogoeva, S. Wei, *Chem. Commun.* **2006**, 1451–1453; f) H. Huang, E. N. Jacobsen, *J. Am. Chem. Soc.* **2006**, 128, 7170–7171; g) T.-Y. Liu, H.-L. Cui, Y. Zhang, K. Jiang, W. Du, Z.-Q. He, Y.-C. Chen, *Org. Lett.* **2007**, 9, 3671–3674; h) S. H. McCoey, S. J. Conon, *Org. Lett.* **2007**, 9, 599–602; i) S. S. V. Ramasastri, H. Zhang, F. Tanaka, C. F. Barbas III, *J. Am. Chem. Soc.* **2007**, 129, 288–289; j) S. Luo, H. Xu, J. Li, L. Zhang, J.-P. Cheng, *J. Am. Chem. Soc.* **2007**, 129, 3074–3075; k) B.-L. Zheng, Q.-Z. Liu, C.-S. Guo, X.-L. Wang, L. He, *Org. Biomol. Chem.* **2007**, 5, 2913–2915. For a review on primary amino acids as catalysts, see: l) L.-W. Xu, Y. Lu, *Org. Biomol. Chem.* **2008**, 6, 2047–2053.
- [6] For examples of asymmetric iminium ion catalysis using primary amines, see: a) K. Ishihara, K. Nakano, *J. Am. Chem. Soc.* **2005**, 127, 10504–10505; b) N. J. A. Martin, B. List, *J. Am. Chem. Soc.* **2006**, 128, 13368–13369; c) H. Kim, C. Yen, P. Preston, J. Chin, *Org. Lett.* **2006**, 8, 5239–5242; d) J.-W. Xie, W. Chen, R. Li, M. Zeng, W. Du, L. Yue, Y.-C. Chen, Y. Wu, J. Zhu, J.-G. Deng, *Angew. Chem.* **2007**, 119, 393–396; *Angew. Chem. Int. Ed.* **2007**, 46, 389–392; e) G. Bartoli, M. Bosco, A. Carlone, F. Pescioli, L. Sambri, P. Melchiorre, *Org. Lett.* **2007**, 9, 1403–1405; f) R. P. Singh, K. Bartelson, Y. Wang, H. Su, X. Lu, L. Deng, *J. Am. Chem. Soc.* **2008**, 130, 2422–2423; g) X. Wang, C. M. Reisinger, B. List, *J. Am. Chem. Soc.* **2008**, 130, 6070–6071.
- [7] For enamine catalysis of intermolecular aldolizations of ketones, see: a) O. Tokuda, T. Kano, W.-G. Gao, T. Ikemoto, K. Maruoka, *Org. Lett.* **2005**, 7, 5103–5105; b) S. Samanta, C. G. Zhao, *J. Am. Chem. Soc.* **2006**, 128, 7442–7443; c) Z. Tang, L.-F. Cun, X. Cui, A.-Q. Mi, Y.-Z. Jiang, L.-Z. Gong, *Org. Lett.* **2006**, 8, 1263–1266; d) J. Liu, Z. Yang, Z. Wang, F. Wang, X. Chen, X. Liu, X. Feng, Z. Su, C. Hu, *J. Am. Chem. Soc.* **2008**, 130, 5654–5655.
- [8] S. Bahmanyar, K. N. Houk, *J. Am. Chem. Soc.* **2001**, 123, 11273–11283.
- [9] J. Zhou, B. List, *J. Am. Chem. Soc.* **2007**, 129, 7498–7499.
- [10] CH₃CO₂H (pK_a = 4.76, e.r. = 28.1); PhCO₂H (pK_a = 4.31, e.r. = 17.8); Cl₃CCO₂H (pK_a = 0.65, e.r. = 16.5); CF₃CO₂H (pK_a = -0.25, e.r. = 9.8); pTsOH (pK_a = -2.80, e.r. = 4.9). For a discussion of acid co-catalyst effects in enamine catalytic aldolizations, see: A. Erkkilä, P. M. Pihko, *Eur. J. Org. Chem.* **2007**, 4205–4216.
- [11] a) X. Z. Zhao, L. Peng, M. Tang, Y. Q. Tu, S. H. Gao, *Tetrahedron Lett.* **2005**, 46, 6941–6944; b) Y. X. Jia, X. Li, B. Wu, X. Z. Zhao, Y. Q. Tu, *Tetrahedron* **2002**, 58, 1697–1708; c) Y. X. Jia, B. Wu, X. Li, S. K. Ren, Y. Q. Tu, A. S. C. Chan, W. Kitching, *Org. Lett.* **2001**, 3, 847–849.
- [12] N. L. Allinger, C. K. Riew, *J. Org. Chem.* **1975**, 40, 1316–1321.
- [13] For the one-step synthesis of diketone **2a**, see the Supporting Information.
- [14] a) L. Friedman, J. G. Miller, *Science* **1971**, 172, 1044–1046; b) C. S. Sell, *Chem. Biodiversity* **2004**, 1, 1899–1920; c) P. Kraft, G. Fráter, *Chirality* **2001**, 13, 388–394.
- [15] For a review, see: S. Saito, H. Yamamoto, *Acc. Chem. Res.* **2004**, 37, 570–579.