

Asymmetric Synthesis

Direct Catalytic Enantioselective α -Aminomethylation of Ketones**

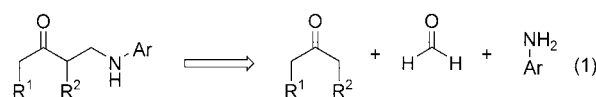
Ismail Ibrahim, Jesús Casas, and Armando Córdova*

The classical Mannich reaction,^[1] in which an aminomethyl group is introduced in the position α to a carbonyl function, has found a multitude of applications in organic chemistry.^[2] The resulting Mannich bases are of particular interest due to their biological activity as analgesics, antioplastics, and antibiotics, and as synthetic building blocks and precursors of pharmaceutically valuable γ -amino alcohols.^[2] However, regardless of the immense importance of this reaction only a few stereoselective α -aminomethylation reactions have been developed.^[3] For example, Enders et al. employed enantiomerically pure α -silyl ketones in diastereoselective α -aminomethylation reactions.^[4]

Chemists have developed several stoichiometric, indirect, stereoselective Mannich transformations that utilize preformed enol equivalents or imines.^[5] More recently, the first successful examples of catalytic asymmetric additions of enolates to imines were reported by Kobayashi and co-workers,^[6] which has led to intense research into catalytic indirect Mannich reactions.^[7] For example, Hoveyda and co-workers developed an elegant one-pot three-component silver-mediated Mannich-type reaction.^[8] Recently, Shibasaki and co-workers reported that heterodimetallic complexes are catalysts for the direct asymmetric Mannich reaction.^[9] Shibasaki and co-workers^[10] and Trost and Terrell^[11] also developed binuclear organozinc complexes that catalyze

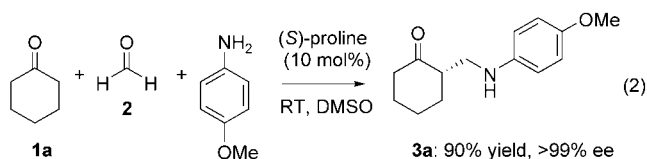
highly enantioselective Mannich-type reactions between hydroxyaryl ketones and preformed imines. Jørgensen and co-workers developed direct asymmetric Mannich reactions involving activated ketones as donors which are catalyzed by chiral copper(II) bisoxazoline (BOX) complexes.^[12] It was not until recently that researchers demonstrated that amino acid derivatives function as metal-free catalysts for direct asymmetric intermolecular reactions.^[13,14] List et al.,^[15] Barbas and co-workers,^[16] and we have developed direct organocatalytic asymmetric Mannich reactions of this type that involve ketones as donors.^[17] Asymmetric Mannich-type reactions with aldehydes as nucleophiles and preformed α -imino glyoxylate esters as the electrophiles have also been developed.^[18] More recently, we developed direct organocatalytic one-pot three-component cross-Mannich reactions.^[19] In addition, Jacobsen and Wenzel,^[20a] Terada and Uruguchi,^[20b] and others have reported excellent organocatalytic asymmetric Mannich-type reactions.^[20]

Despite the intense research on the catalytic enantioselective Mannich reaction, there is to our knowledge only one example of a catalytic one-pot three-component α -aminomethylation reaction. In this example, Shibasaki and co-workers demonstrated a catalytic enantioselective reaction between a ketone, amine, and formaldehyde, which furnished the corresponding Mannich base in 16 % yield with 64 % *ee*.^[9] Based on this initial investigation and our recently developed organocatalytic asymmetric α -hydroxymethylation reaction,^[21] we became interested in whether organocatalysis could be applied to this transformation. An amino acid catalyzed one-pot three-component reaction would be a more effective and economical process, which would provide a new tool for the α -aminomethylation of ketones [Eq. (1)].



Herein, we disclose one-pot three-component direct organocatalytic Mannich reactions between aqueous formaldehyde and ketones that furnished α -aminomethylated ketones with yields of up to 94 % and > 99 % *ee*. The reactions were catalyzed by proline and its derivatives with excellent chemo- and enantioselectivity.

In an initial experiment we treated cyclohexanone **1a** (2 mmol) with formaldehyde **2** (1 mmol, 36 % aqueous solution) and *para*-anisidine (1.1 mmol) in the presence of a catalytic amount of (*S*)-proline (10 mol %) in dimethylsulfoxide (DMSO, 4 mL) at room temperature [Eq. (2)]. The reaction was quenched after 20 h, and α -aminomethylated ketone **3a** was isolated in 90 % yield with > 99 % *ee* by column chromatography using neutral aluminium oxide as the



[*] I. Ibrahim, Dr. J. Casas, Prof. Dr. A. Córdova
Department of Organic Chemistry
The Arrhenius Laboratory, Stockholm University
10691 Stockholm (Sweden)
Fax: (+46) 8-154-908
E-mail: acordova@organ.su.se

[**] We gratefully acknowledge the Swedish National Research council and Wenner-Gren-Foundation for financial support.

stationary phase.^[22] The reactions were also readily performed in *N,N*-dimethylformamide (DMF) and *N*-methylpyrrolidinone (NMP) without decreasing the enantioselectivity.

We also performed a catalyst screen using high-throughput chiral-phase high-performance liquid chromatography (HPLC) analyses and found that hydroxyproline derivatives, 5-pyrrolidine-2-yltetrazole, and proline-derived dipeptides catalyzed the α -aminomethylation reactions. For example, *trans*-4-hydroxyproline catalyzed the reaction between ketone **1a**, formaldehyde **2**, and anisidine furnishing **3a** with 90% *ee*.

Next, we performed the corresponding reaction with a set of different aliphatic ketones (Table 1). The reactions were effective, and the corresponding α -aminomethylated ketones **3a–3f** were isolated in high yield with predominantly >99% *ee*. The reactions proceeded with excellent chemoselectivity, and no aldol adducts could be detected. For acyclic ketones, the reactions were regioselective and the α -aminomethylation occurred predominantly at the methylene carbon atoms of the ketones. For example, α -aminomethylated

Table 1: Proline-catalyzed one-pot three-component direct α -aminomethylation of different ketones.^[a]

Entry	Ketone	Product	Yield [%] ^[b]	3:3' [%]	Sel. 3 [% <i>ee</i>] ^[c]
1			90	–	>99
2			85	–	>99
3			85 ^[d]	–	>99 ^[e]
4			80	2:1	>99
5			94	4:1	84
6			72	6:1	>99

[a] Experimental conditions: a mixture of **1** (2 mmol, 2 equiv), **2** (1 mmol), and (*S*)-proline was stirred at room temperature for 16–17 h. The crude product obtained after aqueous workup was purified by column chromatography. PMP = *para*-methoxyphenyl. [b] Yield of the pure products isolated after column chromatography using neutral alumina as the stationary phase. [c] Determined by chiral-phase HPLC analyses. [d] *trans/cis* = 3:1. [e] *ee* of the *trans* isomer.

ketones **3f** and **3f'** were isolated (**3f/3f'** 6:1) in 72% yield for the combined products and with >99% *ee* for **3f**. The reactions were readily performed on a 10-gram scale in aqueous solvents and in the presence of air without decreasing the yield and the *ee* of the product.

We also examined the variation of the amine component for the catalytic α -aminomethylation reaction. Hence, substituted aniline derivatives were treated with cyclohexanone and formaldehyde in the presence of a catalytic amount of (*S*)-proline (10 mol%; Table 2). In all cases, the reaction furnished the α -arylaminoethylated ketones with >99% *ee*.

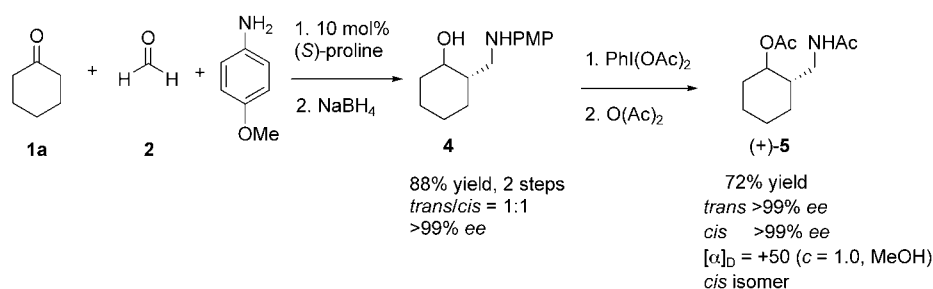
Table 2: Direct catalytic one-pot three-component α -aminomethylation reactions with different aromatic amines.^[a]

Entry	Ar	Product	Yield [%] ^[b]	Sel. [% <i>ee</i>] ^[c]
1			90	>99
2			45	>99
3			71	>99
4			92	>99

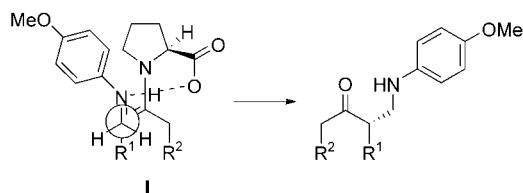
[a] Experimental conditions: a mixture of **1** (2 mmol, 2 equiv), **2** (1 mmol), and (*S*)-proline was stirred at room temperature for 16–24 h. The crude product obtained after aqueous workup was purified by column chromatography. [b] Combined yield of products isolated after column chromatography using neutral alumina as the stationary phase. [c] Determined by chiral-phase HPLC analyses.

The α -aminomethylated ketone **3a** was readily reduced with NaBH₄ in situ to give the corresponding monoprotected amino alcohol **4**, which was isolated in 88% yield over the two steps with d.r. (*trans/cis*) 1:1 and >99% *ee* (Scheme 1). Removal of the *para*-methoxyphenyl (PMP) group under oxidative conditions followed by acetylation afforded the *cis*- and *trans*-diacetylated amino alcohols **5** in 72% yield for the combined products. Optical rotation studies of the *cis* isomer and comparison with published reports revealed that the absolute configuration of the product was *cis*-(1*S*,2*S*)-**5**.^[23] As selective reduction of β -amino ketones to both *syn*- and *anti*-1,3-amino alcohols is known, the present procedure is one practical route for the preparation of all of the possible stereoisomers of chiral 1,3-amino alcohols.^[24]

Based on the absolute configuration of the product, we propose transition-state model **I** to account for the regio- and enantioselectivity of the α -aminomethylation reaction of unmodified substituted ketones (Scheme 2). Hence, the (*S*)-



Scheme 1. Asymmetric synthesis of diacetylated *cis*- and *trans*-5.



Scheme 2. Transition-state model I is evoked to account for the enantioselectivity of the (S)-proline-catalyzed reaction.

proline derivative forms an enamine with the ketone that is attacked by the imine from its *si* face, providing (2*S*)- α -aminomethylated ketones. This is in accordance with the transition states of previously reported proline-catalyzed Mannich reactions, in which a *si*-facial attack occurs.^[15–19,25]

In conclusion, we have developed a direct catalytic enantioselective method that provides α -aminomethylated ketones in high yield with up to > 99% *ee*. The reactions were performed without tedious elaboration in wet solvents, were carried out in the presence of air, and could be readily scaled-up. In addition, a high-throughput screen revealed that other proline-derivatives including dipeptides catalyze the reaction with excellent enantioselectivity. To the best of our knowledge, this procedure is the first practical applicable a one-pot three-component catalytic asymmetric α -aminomethylation reaction. Further elaboration of this transformation and its synthetic applications is ongoing in our laboratory.

Experimental Section

Typical experimental procedure (Table 1, entry 1): Ketone **1a** (2 mmol) was added to a vial containing **2** (1 mmol, 36% aqueous solution) and a catalytic amount of (S)-proline (10 mol%) in DMSO (4 mL). After 20 h of vigorous stirring, the reaction was quenched by addition of aqueous NH₄Cl, and the aqueous phase was extracted three times with EtOAc. The combined organic layers were dried with MgSO₄, which was subsequently removed by filtration. Next, the solvent was removed under reduced pressure, and the crude product mixture was purified by column chromatography using neutral aluminum oxide as the stationary phase (EtOAc/pentane 1:10) to afford α -aminomethylated ketone **3a** in 90% yield as pale yellow solid. The *ee* value of **3a** was > 99% as determined by chiral-phase HPLC analysis. **3a**: ¹H NMR (CDCl₃): δ = 1.49 (m, 2H), 1.67 (m, 2H), 2.10 (m, 2H), 2.35 (m, 2H), 3.05 (dd, *J* = 13.3, 9.3 Hz, 1H), 3.37 (dd, *J* = 12.8, 7.8 Hz, 1H), 3.74 (s, 3H), 6.63 (d, *J* = 8.4 Hz, 2H), 6.77 ppm (d, *J* = 8.4 Hz, 2H); ¹³C NMR: δ = 25.1, 28.0, 32.3, 42.5, 45.6,

50.0, 56.1, 114.9, 115.18, 142.2, 152.6, 213.56 ppm; HPLC (Daicel Chiralpak AD, hexanes/*i*PrOH (96:4), flow rate = 0.5 mL min⁻¹, λ = 254 nm): major isomer: *t*_R = 44.31 min; minor isomer: *t*_R = 58.79 min; [α]_D = +4.1 (c = 2.0, CHCl₃); MALDI-TOF-MS: *m/z* = 256.1008; C₁₄H₁₉NO₂ (M + Na⁺: calcd 256.1313).

Received: May 15, 2004

Keywords: amino alcohols · asymmetric catalysis · ketones · Mannich reaction

- [1] C. Mannich, W. Krösche, *Arch. Pharm.* **1912**, 250, 647.
- [2] For excellent reviews see: a) E. F. Kleinmann in *Comprehensive Organic Synthesis*, Vol. 2 (Eds.: B. M. Trost, I. Fleming), Pergamon Press, New York, **1991**, Chapter 4.1; b) M. Arend, B. Westerman, N. Risch, *Angew. Chem.* **1998**, 110, 1096; *Angew. Chem. Int. Ed.* **1998**, 37, 1044; c) S. Denmark, O. J.-C. Nicaise in *Comprehensive Asymmetric Catalysis*, Vol. 2 (Eds.: E. N. Jacobsen, A. Pfaltz, H. Yamamoto), Springer, Berlin, **1999**, p. 93; d) M. Tramontini, L. Angiolini, *Tetrahedron* **1990**, 46, 1791; e) H. Hellmann, G. Opitz, α -Aminoalkylierung, Verlag Chemie, Weinheim, **1960**, p. 1; f) For examples, see: *Enantioselective Synthesis of β -Amino Acids* (Ed.: E. Juaristi), Wiley-VCH, Weinheim, **1997**.
- [3] a) N. Risch, A. Esser, *Liebigs Ann.* **1992**, 233; b) N. Risch, M. Arend in *Houben-Weyl: Methoden der Organischen Chemie*, Vol. E21b (Ed.: E. Müller), Thieme, Stuttgart, **1995**, p. 1908; c) V. Vinkovic, V. Sunjic, *Tetrahedron* **1997**, 53, 689.
- [4] a) D. Enders, D. Ward, J. Adam, G. Raabe, *Angew. Chem.* **1996**, 108, 1059; *Angew. Chem. Int. Ed. Engl.* **1996**, 35, 981; b) D. Enders, S. Oberbörsh, J. Adam, D. Ward, *Synthesis* **2002**, 18, 1737.
- [5] a) R. Kober, K. Papadopoulos, W. Miltz, D. Enders, W. Steglich, H. Reuter, H. Puff, *Tetrahedron* **1985**, 42, 1963; b) D. Enders, S. Oberbörsh, J. Adam, *Synlett* **2000**, 644; c) D. Seebach, M. Hoffmann, *Eur. J. Org. Chem.* **1998**, 1337; d) Y. Aoyagi, R. P. Jain, R. M. Williams, *J. Am. Chem. Soc.* **2001**, 123, 3472, and references therein; e) U. Schöllkopf in *Topics in Current Chemistry*, Vol. 109 (Ed.: F. L. Boschke), Springer, Berlin, **1983**, pp. 45–85; f) D. A. Evans, F. Urpi, T. C. Somers, J. S. Clark, M. T. Bilodeau, *J. Am. Chem. Soc.* **1990**, 112, 8215; g) C. Palomo, M. Oiarbide, A. Landa, M. C. Gonzales-Rego, J. M. Garcia, A. Gonzalez, J. M. Odriozola, M. Martin-Pastor, A. Linden, *J. Am. Chem. Soc.* **2002**, 124, 8637, and references therein.
- [6] a) S. Kobayashi, H. Ishitani, *Chem. Rev.* **1999**, 99, 1069; b) H. Ishitani, M. Ueno, S. Kobayashi, *J. Am. Chem. Soc.* **1997**, 119, 7153; c) S. Kobayashi, T. Hamada, K. Manabe, *J. Am. Chem. Soc.* **2002**, 124, 5640; d) H. Ishitani, M. Ueno, S. Kobayashi, *Org. Lett.* **2002**, 4, 143; e) H. Ishitani, S. Ueno, S. Kobayashi, *J. Am. Chem. Soc.* **2000**, 122, 8180.
- [7] a) E. Hagiwara, A. Fujii, M. Sodeoka, *J. Am. Chem. Soc.* **1998**, 120, 2474; b) A. Fujii, E. Hagiwara, M. Sodeoka, *J. Am. Chem. Soc.* **1999**, 121, 545; c) Y. Hamashima, K. Yagi, H. Tamas, M. Sodeoka, *J. Am. Chem. Soc.* **2002**, 124, 14530; d) Y. Hamashima, M. Hotta, M. Sodeoka, *J. Am. Chem. Soc.* **2002**, 124, 11240; e) D. Ferraris, B. Young, T. Dudding, T. Lectka, *J. Am. Chem. Soc.* **1998**, 120, 4548; f) D. Ferraris, B. Young, C. Cox, W. J. Drury III, T. Dudding, T. Lectka, *J. Org. Chem.* **1998**, 63, 6090; g) D. Ferraris, B. Young, C. Cox, T. Dudding, W. J. Drury III, L. Ryzhkov, T. Taggi, T. Lectka, *J. Am. Chem. Soc.* **2002**, 124, 67.
- [8] W. S. Josephsohn, M. L. Snapper, A. H. Hoveyda, *J. Am. Chem. Soc.* **2004**, 126, 3734.

- [9] S. Yamasaki, T. Iida, M. Shibasaki, *Tetrahedron Lett.* **1999**, *40*, 307.
- [10] S. Matsunaga, N. Kumagai, N. Harada, S. Harada, M. Shibasaki, *J. Am. Chem. Soc.* **2003**, *125*, 4712.
- [11] B. M. Trost, L. M. Terrell, *J. Am. Chem. Soc.* **2003**, *125*, 338.
- [12] a) K. Juhl, N. Gathergood, K. A. Jørgensen, *Angew. Chem.* **2001**, *113*, 3083; *Angew. Chem. Int. Ed.* **2001**, *40*, 2995; b) M. Marigo, A. Kjaersgaard, K. Juhl, N. Gathergood, K. A. Jørgensen, *Chem. Eur. J.* **2003**, *9*, 2395; c) L. Bernardi, A. S. Gothelf, R. G. Hazell, K. A. Jørgensen, *J. Org. Chem.* **2003**, *68*, 2583.
- [13] a) P. I. Dalko, L. Moisan, *Angew. Chem.* **2001**, *113*, 3840; *Angew. Chem. Int. Ed.* **2001**, *40*, 3726; b) B. List, *Tetrahedron* **2002**, *58*, 5573; c) E. R. Jarvo, S. J. Miller, *Tetrahedron* **2002**, *58*, 2481; d) R. O. Duthaler, *Angew. Chem.* **2003**, *115*, 1005; *Angew. Chem. Int. Ed.* **2003**, *42*, 975.
- [14] Aldol reactions see: a) B. List, R. A. Lerner, C. F. Barbas III, *J. Am. Chem. Soc.* **2000**, *122*, 2395; b) W. Notz, B. List, *J. Am. Chem. Soc.* **2000**, *122*, 7386; c) K. Saktihvel, W. Notz, T. Bui, C. F. Barbas III, *J. Am. Chem. Soc.* **2001**, *123*, 5260; d) A. Córdova, W. Notz, C. F. Barbas III, *J. Org. Chem.* **2002**, *67*, 301; e) B. List, P. Pojarliev, C. Castello, *Org. Lett.* **2001**, *3*, 573; f) A. Córdova, W. Notz, C. F. Barbas III, *Chem. Commun.* **2002**, *67*, 3034; g) A. Bøgevig, K. Juhl, N. Kumaragurubaran, K. A. Jørgensen, *Chem. Commun.* **2002**, 620; h) A. B. Northrup, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2002**, *124*, 6798; i) N. S. Chowdari, D. B. Ramachary, A. Córdova, C. F. Barbas III, *Tetrahedron Lett.* **2002**, *43*, 9591; j) C. Pidathala, L. Hoang, N. Vignola, B. List, *Angew. Chem.* **2003**, *115*, 2797; *Angew. Chem. Int. Ed.* **2003**, *42*, 2785; k) Z. Tang, F. Jiang, L.-T. Yu, X. Cui, L.-Z. Gong, A.-Q. Mi, Y.-Z. Jiang, Y.-D. Wu, *J. Am. Chem. Soc.* **2003**, *125*, 5262; α -Aminations see: a) A. Bøgevig, K. Juhl, N. Kumaragurubaran, W. Zhuang, K. A. Jørgensen, *Angew. Chem.* **2002**, *114*, 1868; *Angew. Chem. Int. Ed.* **2002**, *41*, 1790; b) B. List, *J. Am. Chem. Soc.* **2002**, *124*, 5656; c) N. Kumaragurubaran, K. Juhl, W. Zhuang, A. Bøgevig, K. A. Jørgensen, *J. Am. Chem. Soc.* **2002**, *124*, 6254; α -Oxidations see: a) A. Bøgevig, H. Sundén, A. Córdova, *Angew. Chem.* **2004**, *116*, 1129; *Angew. Chem. Int. Ed.* **2004**, *43*, 1109; b) M. Hayashi, J. Yamaguchi, T. Sumaiya, M. Shoji, *Angew. Chem.* **2004**, *116*, 1132; *Angew. Chem. Int. Ed.* **2004**, *43*, 1112; c) G. Zhong, *Angew. Chem.* **2003**, *115*, 4379; *Angew. Chem. Int. Ed.* **2003**, *42*, 4247; d) S. P. Brown, M. P. Brochu, C. J. Sinz, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2003**, *125*, 10808; Michael reactions see: a) B. List, P. Pojarliev, H. J. Martin, *Org. Lett.* **2001**, *3*, 2423; b) S. Hanessian, V. Pham, *Org. Lett.* **2000**, *2*, 2975; c) J. M. Betancort, K. Saktihvel, R. Thayumanavan, C. F. Barbas III, *Tetrahedron Lett.* **2001**, *42*, 4441; d) J. M. Betancort, C. F. Barbas III, *Org. Lett.* **2001**, *3*, 3737; e) D. J. Hortsmann, D. J. Guerin, S. J. Miller, *Angew. Chem.* **2000**, *112*, 3781; *Angew. Chem. Int. Ed.* **2000**, *39*, 3635; f) A. Alexakis, O. Andrey, *Org. Lett.* **2002**, *4*, 3611; g) D. J. Guerin, S. J. Miller, *J. Am. Chem. Soc.* **2002**, *124*, 2134; h) N. Halland, P. S. Aburel, K. A. Jørgensen, *Angew. Chem.* **2003**, *115*, 685; *Angew. Chem. Int. Ed.* **2003**, *42*, 661; i) N. Halland, R. G. Hazell, K. A. Jørgensen, *J. Org. Chem.* **2002**, *67*, 8331; j) O. Andrey, A. Alexakis, G. Bernardinelli, *Org. Lett.* **2003**, *5*, 2559; k) D. Enders, A. Seki, *Synlett* **2002**, 26; Diels–Alder reactions see: a) A. B. Northrup, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2002**, *124*, 2458; b) K. A. Ahrendt, C. J. Borths, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2000**, *122*, 4243; hetero-Diels–Alder reactions see: a) K. Juhl, K. A. Jørgensen, *Angew. Chem.* **2003**, *115*, 1536; *Angew. Chem. Int. Ed.* **2003**, *42*, 1498; b) Y. Huang, K. Unni, A. N. Thadani, V. H. Rawal, *Nature* **2003**, *424*, 146; alkylation of electron-rich benzene systems see: a) N. A. Paras, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2001**, *123*, 4370; b) J. F. Austin, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2002**, *124*, 1172; c) N. A. Paras, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2002**, *124*, 7894; 1,3-dipolar cycloadditions see: a) W. S. Jen, J. J. M. Wiener, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2000**, *122*, 9874; b) S. Karlsson, H. Högberg, *Tetrahedron: Asymmetry* **2002**, *13*, 923; other reactions see: a) A. E. Taggi, A. M. Hafez, H. Wack, B. Young, W. J. Drury III, T. Lectka, *J. Am. Chem. Soc.* **2000**, *121*, 7831; b) B. R. Sculimbrene, A. J. Morgan, S. J. Miller, *J. Am. Chem. Soc.* **2002**, *124*, 11653; c) M. Harmata, S. K. Ghosh, X. Hong, S. Wacharasindhu, P. Kirchhoefer, *J. Am. Chem. Soc.* **2003**, *125*, 2058; d) N. Bremeyer, S. C. Smith, S. V. Ley, M. J. Gaunt, *Angew. Chem.* **2004**, *116*, 2735; *Angew. Chem. Int. Ed.* **2004**, *43*, 2681.
- [15] a) B. List, *J. Am. Chem. Soc.* **2000**, *122*, 9336; b) B. List, P. Porjaliev, W. T. Biller, H. J. Martin, *J. Am. Chem. Soc.* **2002**, *124*, 827.
- [16] W. Notz, K. Saktihvel, T. Bui, G. Zhong, C. F. Barbas III, *Tetrahedron Lett.* **2001**, *42*, 199.
- [17] A. Córdova, W. Notz, G. Zhong, J. M. Betancort, C. F. Barbas III, *J. Am. Chem. Soc.* **2002**, *124*, 1842.
- [18] a) A. Córdova, S. Watanabe, F. Tanaka, W. Notz, C. F. Barbas III, *J. Am. Chem. Soc.* **2002**, *124*, 1866; b) A. Córdova, C. F. Barbas III, *Tetrahedron Lett.* **2002**, *43*, 7749; c) A. Córdova, C. F. Barbas III, *Tetrahedron Lett.* **2003**, *44*, 1923; d) S.-i. Watanabe, A. Córdova, F. Tanaka, C. F. Barbas III, *Org. Lett.* **2002**, *4*, 4519.
- [19] a) A. Córdova, *Chem. Eur. J.* **2004**, *10*, 1987; b) A. Córdova, *Synlett* **2003**, 1651; c) Y. Hayashi, W. Tsuboi, I. Ashimine, T. Urushima, M. Shoji, K. Sakai, *Angew. Chem.* **2003**, *115*, 3805; *Angew. Chem. Int. Ed.* **2003**, *42*, 3677; d) A. Córdova, *Acc. Chem. Res.* **2004**, *37*, 102.
- [20] a) E. N. Wenzel, E. N. Jacobsen, *J. Am. Chem. Soc.* **2002**, *124*, 12964; b) D. Uraguchi, M. Terada, *J. Am. Chem. Soc.* **2004**, *126*, 5356; c) T. Akiyama, J. Itoh, K. Yokota, K. Fuchibe, *Angew. Chem.* **2004**, *116*, 1592; *Angew. Chem. Int. Ed.* **2004**, *43*, 1566; d) A. J. A. Cobb, D. M. Shaw, S. V. Ley, *Synlett* **2004**, 558; e) T. Itoh, M. Yokoya, K. Miyauchi, K. Nagata, A. Ohsawa, *Org. Lett.* **2003**, *5*, 4301.
- [21] a) J. Casas, H. Sünden, A. Córdova, *Tetrahedron Lett.* **2004**, *45*, 6117; b) Yamamoto, Saito and co-workers have also reported two excellent examples of organocatalytic asymmetric α -hydroxymethylation of ketones see: H. Torii, M. Nakadai, K. Ishihara, S. Saito, H. Yamamoto, *Angew. Chem.* **2004**, *116*, 2017; *Angew. Chem. Int. Ed.* **2004**, *43*, 1983.
- [22] The compounds are sensitive and racemize upon column chromatography with silica gel as the stationary phase. The Mannich base products should be stored at -35°C .
- [23] $[\alpha]_{\text{D}} = +50$ ($c = 1.0$, MeOH), (literature: $[\alpha]_{\text{D}} = +49.5$ ($c = 0.8$, MeOH), J. Kaman, E. Forro, F. Fülöp, *Tetrahedron: Asymmetry* **2001**, *12*, 1881).
- [24] R. A. Pili, D. Russowsky, L. C. Dias, *J. Chem. Soc. Perkin Trans. I* **1990**, 213.
- [25] S. Bahmanyar, K. N. Houk, *Org. Lett.* **2003**, *5*, 1249 and references therein.