Research Article

Open Access

Guillem Valero, Carlos M. León, Albert Moyano*

Solvent-controlled diastereoselectivity in tryptophan-catalyzed Mannich reactions

Abstract: Solvent effects in the L-tryptophan-catalyzed Mannich reaction between hydroxyacetone and glyoxylate imines have been examined. The use of a DMSO/1-butanol (4:1 v/v) mixture as solvent at rt provided the expected Mannich adducts in good yields, high *anti*-diastereoselectivity (up to 10.3:1 *anti/syn* ratio) and excellent enantioselectivities (up to >99.9% ee for the *anti* isomer)

1 Introduction

The Mannich reaction[1] constitutes a direct and efficient method for the synthesis of β-amino carbonyl compounds, and is one of the most important carbon–carbon bond–forming reactions in organic chemistry [2,3]. Since the pioneering work of List [4,5] and Barbas III [6] on the enantioselective, proline-catalyzed direct Mannich reaction, asymmetric organocatalytic Mannich reactions have become an extraordinarily active area of research. [7-10] High *syn*-diastereoselectivity and enantioselectivity can easily be achieved for Mannich adducts derived from substituted aldehyde or ketone donors, [4-22] but a general organocatalyst that can achieve high levels of *anti*-diastereoselectivity (together with high yields and enantioselectivities) for a wide range of substrates is still yet to be developed [23-32]. In particular, none of the presently known catalysts, with the possible exception of *O*-(*tert*-butyl)-L-threonine, [28] are suitable for the stereocontrolled preparation of *anti*-Mannich adducts derived from hydroxyacetone (**1**).
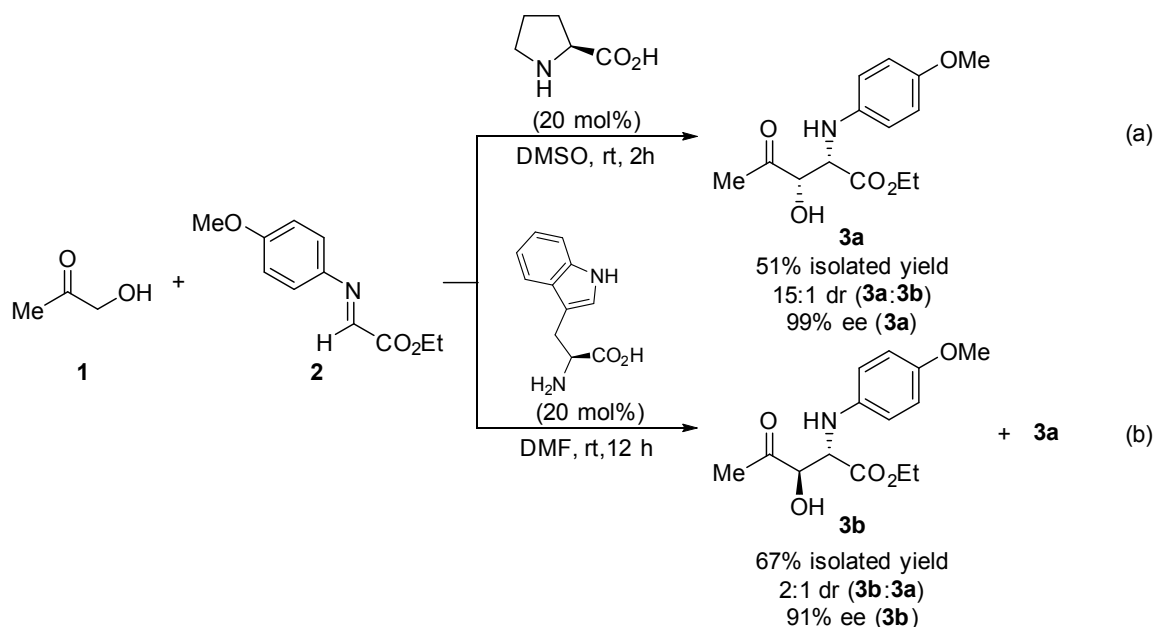
In the course of a research program devoted to spontaneous mirror-symmetry breaking and asymmetric organoautocatalysis, [33-40] we needed to prepare both the *syn* (**3a**) and the *anti* (**3b**) stereoisomers of the Mannich adduct from hydroxyacetone (**1**) and the glyoxylate-derived imine **2**. Whereas **3a** was easily obtained by L-proline catalysis under the reaction conditions previously described by Barbas III (Scheme 1, (a)),[11] the preparation of **3b** proved more troublesome, since in our hands the L-tryptophan (L-Trp) catalysis of the reaction between **1** and **2**[28] afforded (as reported) an inseparable 2:1 (*anti:syn*) mixture of **3b** and **3a** in 67% yield, after chromatographic purification (Scheme 1, (b)). Although it had been described that the use of *O*-(*tert*-butyl)-L-threonine as a catalyst in the Mannich reaction of **1** with a 4-nitrobenzaldehyde-derived imine gave improved *anti:syn* ratios (up to 8:1 dr, determined by NMR analysis of the crude reaction mixture),[28] both the easier availability of L-tryptophan and the instability of the Mannich adduct **3b** (that precludes its careful chromatographic purification) spurred us on to optimize the *anti*-stereoselectivity of the L-Trp-catalyzed process.

2 Experimental Procedure

2.1 General methods

Reactions were generally run in loosely-stoppered 5 mL flasks under open air with magnetic stirring. Commercially available reagents, catalysts, and solvents were purchased from Panreac, Scharlab and Aldrich and used as supplied, with the exception of dichloromethane (DCM), which was distilled from calcium hydride [41].

The reaction progress was monitored by thin layer chromatography on silica gel (aluminium foils) and

*Corresponding author: Albert Moyano: Departament de Química Orgànica, Universitat de Barcelona, Facultat de Química, C. Martí i Franquès 1-11, 08028-Barcelona, Catalonia, Spain, E-mail: amoyano@ub.edu

Guillem Valero, Carlos M. León: Departament de Química Orgànica, Universitat de Barcelona, Facultat de Química, C. Martí i Franquès 1-11, 08028-Barcelona, Catalonia, Spain

Scheme 1. Initial preparation of Mannich adducts **3a** (*syn*, (a)) and **3b** (*anti*, (b))

spotted under UV light (254 nm). Purification by column chromatography was carried out on silica gel Merck 60 (particle size: 0.0040-0.063 nm) using mixtures of DCM/EtOAc as eluent. ^{1}H (400 MHz) and ^{13}C (100.6 MHz) NMR spectra were recorded using Varian Mercury 400 and VNRMS 400 spectrometers. Chemical shifts (δ) are given in ppm relative to tetramethylsilane (TMS), and coupling constants (*J*) are given in Hz. The spectra were recorded in CDCl$_3$ and DMSO-d$_6$ solvents at room temperature. CDCl$_3$ served as an internal standard (δ = 7.26 ppm) for ^{1}H NMR spectra. CDCl$_3$ (δ = 77.0 ppm) and DMSO-d$_6$ (δ = 39.5 ppm) served as an internal standard for ^{13}C NMR spectra. Data are reported as follows: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad signal; dd, doublet of doublet; ddd, doublet of doublet of doublet. High-resolution mass spectra (HRMS) were obtained with the ESI (+ or -) technique at the 'Unitat d'Espectrometria de Masses' of Barcelona University in a Bruker MicrOTOF spectrometer. Chiral HPLC analyses were performed with a Shimadzu LC Series 20 apparatus with an M20 diode array UV/Vis detector, using Chiralpak® IA, IB and IC columns. The homogeneity of the peaks corresponding to the two enantiomers of the products was thoroughly checked by comparison of the UV spectra.

2.2 General procedure for the preparation of aldimines [42]

A solution of ethyl glyoxylate (1.98 mL, 10.0 mmol, 1.23 eq.) (50% in toluene) was slowly added *via* syringe to a stirred solution of the desired aniline derivative (8.1 mmol, 1 equiv.) in dry DCM (14 mL) over 45 minutes, in the presence of pre-activated molecular sieves (4Å) (15.00 g) under an Argon atmosphere. The reaction mixture was subsequently stirred at room temperature for 2 h. The mixture was then filtered through a short pad of Celite® and the solvent was removed under reduced pressure. Toluene (5 mL) was added to the crude product and the solvent was removed under reduced pressure. The resulting brownish oil was directly used for synthetic purposes without further purification.

The crude product of the reaction between ethyl glyoxylate and *p*-methoxyaniline was purified by flash column chromatography (DCM as eluent) to afford the desired aldimine **2**. Products **8** and **9** were synthesized using the general procedure for the preparation of aldimines, however the reactions were stirred overnight.

Ethyl 2-(4-methoxyphenylimino)acetate (2) [43]:
 2.35 g, 70% yield. ^{1}H-NMR (400 MHz, CDCl$_3$): δ (ppm) = 7.94 (s, 1H), 7.39-7.32 (m, 2H), 6.96-6.89 (m, 2H), 4.41 (q, *J* = 7.1 Hz, 2H), 3.83 (s, 3H), 1.40 (t, *J* = 7.1, 3H).

Ethyl 2-(*p*-tolylimino)acetate (4) [43]:
1.50 g, 70% yield (crude product). ^{1}H-NMR (400 MHz, CDCl$_3$): δ (ppm) = 7.93 (s, 1H), 7.22 (br, 4H), 4.42 (q, *J* = 7.1 Hz, 2H), 2.38 (s, 3H), 1.41 (t, *J* = 7.1 Hz, 3H).

Ethyl 2-(phenylimino)acetate (5) [43]:
1.51 g, 79% yield (crude product). ^{1}H-NMR (400 MHz, CDCl$_3$): δ (ppm)= 7.92 (s, 1H), 7.45-7.38 (m, 2H), 7.37-7.32 (m,

1H), 7.31-7.26 (m. 2H), 4.43 (q, J = 7.0, 2H), 1.42 (t, J = 7.1 Hz, 3H).

Ethyl 2-(4-chlorophenylimino)acetate (6) [43]:
1.06 g, 58% yield (crude product). ^{1}H-NMR (400 MHz, CDCl$_3$): δ (ppm)= 7.89 (s, 1H), 7.41-7.36 (m, 2H), 7.25-7.20 (m, 2H), 4.43 (q, J = 7.1 Hz, 2H), 1.41 (t, J = 7.1 Hz, 3H).

Ethyl 2-(3-chlorophenylimino)acetate (7):
309 mg, 46% yield (crude product). ^{1}H-NMR (400 MHz, CDCl$_3$): δ (ppm) 7.88 (s, 1H), 7.35 (ddd, J^1 = 7.8 Hz, J^2 = 7.5 Hz, J^3 = 0.5 Hz, 1H), 7.31 (ddd, J^1 = 8.0 Hz, J^2 = 2.0 Hz, J^3 = 1.5 Hz, 1H), 7.25 (ddd, J^1 = 1.9 Hz, J^2 = 1.9 Hz, J^3 = 0.5 Hz, 1H), 7.16 (ddd, J^1 = 7.5 Hz, J^2 = 2.0 Hz, J^3 = 1.5 Hz, 1H), 4.43 (q, J = 7.1 Hz, 2H), 1.41 (t, J = 7.1 Hz, 3H).

Ethyl 2-(2-chlorophenylimino)acetate (8):
509 mg, 59% yield (crude product). ^{1}H-NMR (400 MHz, CDCl$_3$): δ (ppm)= 7.83 (s, 1H), 7.46 (dd, J^1 = 7.7 Hz, J^2 = 1.6 Hz, 1H), 7.29 (ddd, J^1 = 7.6 Hz, J^2 = 7.6 Hz, J^3 = 1.4 Hz, 1H), 7.23 (ddd, J^1 = 7.7 Hz, J^2 = 7.5 Hz, J^3 = 1.7 Hz, 1H), 6.99 (dd, J^1 = 7.8 Hz, J^2 = 1.6 Hz, 1H), 4.44 (q, J = 7.1 Hz, 2H), 1.42 (t, J = 7.1 Hz, 3H).

Ethyl 2-(4-trifluoromethylphenylimino)acetate (9):
813 mg, 89% yield (crude product). ^{1}H-NMR (400 MHz, CDCl$_3$): δ (ppm)= 7.88 (s, 1H), 7.68 (d, J = 8.3 Hz, 2H), 7.31 (d, J = 8.7 Hz, 2H), 4.44 (q, J = 7.1 Hz, 2H), 1.42 (t, J = 7.1 Hz, 3H).

2.3 General procedure for the catalytic asymmetric Mannich reaction of hydroxyace-tone and preformed imines

A mixture of 4:1 DMSO/1-butanol (1.7 mL), hydroxyacetone (4.83 mmol, 10 equiv.) and L-tryptophan (0.16 mmol, 0.33 equiv.) was vigorously stirred at 22 °C. When L-tryptophan was completely dissolved, the preformed imine (0.48 mmol, 1 equiv.) was added and the mixture was stirred for 3-4 h (reaction progress was monitored by TLC). The mixture was diluted with DCM (10 mL) and half-saturated ammonium chloride solution (10 mL) was added. The mixture was extracted with ethyl acetate (3 x 10 mL). The combined organic layers were washed with water, brine, dried over anhydrous MgSO$_4$, concentrated *in vacuo*, and purified by flash column chromatography (DCM/EtOAc mixtures) to afford the desired Mannich addition product as an *anti/syn* diastereomer mixture.

Racemic products were similarly prepared using *dl*-tryptophan as catalyst.

(2*S*,3*S*)- and (2*S*,3*R*)-Ethyl-2-(*p*-methoxyphenylamino)-3-hydroxy-4-oxo-pentanoate (3a,b) [28]**.**
Brown oil, 108 mg, 80% yield (crude product), 7.6:1 dr, 99% *ee*.(*anti* diastereomer **3b**). ^{1}H-NMR (400 MHz, CDCl$_3$): δ (ppm) = 6.88-6.79 (m, 4H, both), 4.63 (d, J= 2.7 Hz, 1H, minor), 4.56 (br s, 1H, major), 4.51 (d, J= 2.7 Hz, 1H, major), 4.45 (d, J = 2.7 Hz, 1H, minor), 4.23-4.09 (m, 2H, both), 3.75 (s, 3H, major), 2.38 (s, 3H, major), 2.30 (s, 3H, minor), 1.20 (t, J = 7.1 Hz, 3H, major). ^{13}C-NMR (100 MHz, CDCl$_3$): (major isomer) δ(ppm)= 206.3, 169.7, 153.4, 139.9, 116.0, 114.9, 77.6, 61.8, 60.7, 55.6, 26.0, 14.0. HRMS (ESI): Calcd. for C$_{14}$H$_{20}$NO$_5$ (M + H)$^+$: 282.1336, found 282.1332. HPLC (Daicel Chiralpak® IA column, *i*-PrOH/*n*-hexane= 5:95, λ= 254 nm, 1.0 mL/min): t$_R$ (*anti* major enantiomer) = 41.4 min, t$_R$ (*anti* minor enantiomer) = 46.7 min, t$_R$ (*syn* major enantiomer) = 34.8 min, t$_R$ (*syn* minor enantiomer) = 30.9 min.

(2*S*,3*S*)- and (2*S*,3*R*)-Ethyl-2-(*p*-methylphenylamino)-3-hydroxy-4-oxo-pentanoate (10a,b).
Yellow oil, 96 mg, 66% yield, 9.6:1 dr, > 99.9% *ee* (*anti* diastereomer **10b**). ^{1}H-NMR (400 MHz, CDCl$_3$): δ (ppm) = 7.03 (d, J = 8.0 Hz, 2H, major), 6.99 (d, J = 8.0 Hz, 2H, minor), 6.65 (d, J = 8.5 Hz, 2H, major), 6.56 (d, J = 8.4 Hz, 2H, minor), 4.65 (br, 1H, minor), 4.57 (s, 1H, major), 4.50 (d, J = 5.5 Hz, 1H, major), 4.26-4.21 (m, 2H, minor), 4.21-4.11 (m, 2H, major), 3.86 (d, J = 4.1 Hz, 1H, minor), 3.62 (d, J = 5.1 Hz, 1H, major), 2.40 (s, 3H, major), 2.30 (s, 3H, minor), 2.25 (s, 3H, major), 2.23 (s, 3H, minor), 1.21 (t, J= 7.1 Hz, 3H, major). ^{13}C-NMR (100 MHz, CDCl$_3$): (major *anti* isomer **10b**) δ (ppm)= 206.4, 169.7, 143.7, 130.1, 128.7, 114.5, 77.8, 62.0, 59.9, 26.2, 20.6, 14.1. HRMS (ESI): Calcd for C$_{14}$H$_{20}$NO$_4$ (M + H)$^+$: 266.1387, found 266.1385. HPLC (Daicel Chiralpak® IA column, *i*-PrOH/*n*-hexane= 7:93, λ= 254 nm, 1.0 mL/min): t$_R$ (*anti* major enantiomer) = 19.4 min, t$_R$ (*syn* major enantiomer) = 16.9 min, t$_R$ (*syn* minor enantiomer) = 14.6 min.

(2*S*,3*S*)- and (2*S*,3*R*)-Ethyl-2-phenylamino-3-hydroxy-4-oxo-pentanoate (11a,b).
Yellow oil, 75 mg, 58% yield, 10.3:1 dr, 99% *ee*.(*anti* diastereomer **11b**). ^{1}H-NMR (400 MHz, CDCl$_3$): δ (ppm) = 7.25-7.26 (m, 2H, both), 6.84-6.79 (m, 1H, major), 6.72 (dd, J^1 = 8.6 Hz, J^2 = 1.0 Hz, 2H, major), 6.64 (dd, J^1 = 8.6 Hz, J^2 = 1.0 Hz, 2H, minor), 4.67 (br, 1H, minor), 4.62 (d, J = 2.7 Hz, 1H, major), 4.56 (d, J = 2.5 Hz, 1H, minor), 4.51 (dd, J^1 = 4.5 Hz, J^2 = 2.7 Hz, 1H, major), 4.27-4.10 (m, 2H, both), 3.87 (d, J = 3.1 Hz, 1H, minor), 3.63 (d, J = 5.1 Hz, 1H, major), 2.41 (s, 3H, major), 2.30 (s, 3H, minor), 1.21 (t, J = 7.1 Hz, 3H, major). ^{13}C-NMR (100 MHz, CDCl$_3$): (major *anti* isomer **11b**) δ (ppm) = 206.2, 169.6, 146.0, 129.6, 119.4, 114.2, 77.8, 62.1, 59.5, 26.2, 14.1. HRMS (ESI): calcd for C$_{13}$H$_{18}$NO$_4$ (M

+ H)⁺: 252.1230, found 252.1231. HPLC (Daicel Chiralpak® IB column, *i*-PrOH/*n*-hexane= 7:93, λ= 254 nm, 1.0 mL/min): t$_R$ (*anti* major enantiomer) = 27.2 min, t$_R$ (*anti* minor enantiomer) = 26.3 min, t$_R$ (*syn* major enantiomer) = 20.5 min, t$_R$ (*syn* minor enantiomer) = 18.4 min.

(2*S*,3*S*)- and (2*S*,3*R*)-Ethyl-2-(*p*-chlorophenylamino)-3-hydroxy-4-oxo-pentanoate (12a,b).

Yellow oil, 32 mg, 59% yield, 10.3:1 dr, 92% *ee*.(*anti* diastereomer **12b**). ¹H-NMR (400 MHz, CDCl₃): δ (ppm) = 7.17 (d, *J* = 8.7 Hz, 2H, major), 7.14 (d, *J* = 8.8 Hz, 2H, minor), 6.64 (d, *J* = 8.8 Hz, 2H, major), 6.56 (d, *J* = 8.8 Hz, 2H, minor), 4.66 (br, 1H, minor), 4.55 (d, *J* = 2.5 Hz, 1H, major), 4.49 (br, 1H, major), 4.27-4.12 (m, 2H, both), 3.85 (d, *J* = 3.7 Hz, 1H, minor), 3.64 (d, *J* = 4.9 Hz, 1H, major), 2.41 (s, 3H, major), 2.30 (s, 3H, minor), 1.21 (t, *J* = 7.1 Hz, 3H, major). ¹³C-NMR (100 MHz, CDCl₃): (major *anti* isomer **12b**) δ (ppm) = 205.9, 169.4, 144.7, 129.5, 124.1, 115.3, 77.7, 62.2, 59.5, 26.1, 14.1. HRMS (ESI): calcd for C₁₃H₁₇ClNO₄ (M + H)⁺: 286.0841, found 286.0845. HPLC (Daicel Chiralpak® IB column, *i*-PrOH/*n*-hexane= 4:96, λ= 254 nm, 1.0 mL/min): t$_R$ (*anti* major enantiomer) = 28.7 min, t$_R$ (*anti* minor enantiomer) = 18.9 min, t$_R$ (*syn* major enantiomer) = 21.6 min, t$_R$ (*syn* minor enantiomer) = 17.6 min.

(2*S*,3*S*)- and (2*S*,3*R*)-Ethyl-2-(*m*-chlorophenylamino)-3-hydroxy-4-oxo-pentanoate (13a,b).

Yellow oil, 96 mg, 72% yield, .6:1 dr, 95% *ee*.(*anti* diastereomer **13b**). ¹H-NMR (400 MHz, CDCl₃): δ (ppm) = 7.12 (dd, *J¹* = 8.0 Hz, *J²* = 8.0 Hz, 1H, both), 6.77 (ddd, *J¹* = 7.9 Hz, *J²* = 1.9 Hz, *J³* = 0.9 Hz, 1H, both), 6.68 (dd, *J¹* = 2.1 Hz, *J²* = 2.1 Hz, 1H, major), 6.59 (ddd, *J¹* = 8.2 Hz, *J²* = 2.4 Hz, *J³* = 0.9 Hz, 1H, major), 6.51 (ddd, *J¹* = 8.2 Hz, *J²* = 2.4 Hz, *J³* = 0.9 Hz, 1H, minor), 4.67 (br s, 1H, minor), 4.57 (d, *J* = 2.6 Hz, 1H, major), 4.52-4.47 (m, 1H, major), 4.28-4.11 (m, 1H, both), 3.86 (d, *J* = 3.5 Hz, 1H, minor), 3.66 (d, *J* = 5.0 Hz, 1H, major), 2.42 (s, 3H, major), 2.30 (s, 3H, minor), 1.21 (t, *J* = 7.1 Hz, 3H). ¹³C-NMR (100 MHz, CDCl₃): (major *anti* isomer **13b**) δ (ppm) = 205.8, 147.3, 135.3, 130.6, 119.2, 113.8, 112.4, 77.7, 62.2, 59.1, 26.1, 14.1. HRMS (ESI): calcd for C₁₃H₁₇ClNO₄ (M + H)⁺: 286.0841, found 286.0840. HPLC (Daicel Chiralpak® IC column, *i*-PrOH/*n*-hexane= 8:92, λ= 240 nm, 1.0 mL/min): t$_R$ (*anti* major enantiomer) = 12.5 min, t$_R$ (*anti* minor enantiomer) = 10.3 min, t$_R$ (*syn* major enantiomer) = 9.6 min, t$_R$ (*syn* minor enantiomer) = 10.8 min.

(2*S*,3*S*)- and (2*S*,3*R*)-Ethyl-2-(*o*-chlorophenylamino)-3-hydroxy-4-oxo-pentanoate (14a,b).

Yellow oil, 95 mg, 72% yield, 2.5:1 dr, 86% *ee*.(*anti* diastereomer **14b**). ¹H-NMR (400 MHz, CDCl₃): δ (ppm) = 7.31 (dd, *J¹* = 7.9 Hz, *J* 2= 1.5 Hz, 1H, major), 7.28 (dd, *J¹* = 8.0

Hz, *J²* = 1.5 Hz, 1H, minor), 7.18-7.09 (m, 1H, both), 6.76-6.68 (m, 2H, both), 6.60 (dd, *J¹* = 8.2 Hz, *J²* = 1.3 Hz, 1H, minor), 5.35 (d, *J* = 8.9 Hz, 1H, major), 4.96 (d, *J* = 10.7 Hz, 1H, minor), 4.70 (dd, *J¹* = 3.9 Hz, *J²* = 2.4 Hz, 1H, minor), 4.64 (dd, *J¹* = 8.9 Hz, *J²* = 2.7 Hz, 1H, major), 4.59 (dd, *J¹* = 10.8 Hz, *J²* = 2.4 Hz, 1H, minor), 4.52 (dd, *J¹* = 5.1 Hz, *J²* = 2.7 Hz, 1H, major), 4.27-4.12 (m, 2H, both), 3.92 (d, *J* = 4.0 Hz, 1H, minor), 3.65 (d, *J* = 5.1 Hz, 1H, major), 2.42 (s, 1H, major), 2.30 (s, 1H, minor), 1.22 (t, *J*= 7.1 Hz, 3H, both). ¹³C-NMR (100 MHz, CDCl₃): δ(ppm) = 206.1 (major), 206.0 (minor), 170.3 (minor), 169.3 (major), 142.5 (minor), 142.2 (major), 129.9 (major), 129.8 (minor), 127.9 (major), 127.8 (minor), 121.1 (minor), 120.8 (major), 199.5 (minor), 199.3(major), 112.4 (minor), 112.2 (major), 77.8 (major), 77.4 (minor), 62.3 (major), 62.2 (minor), 59.3 (major), 58.1 (minor), 26.2 (major), 25.2 (minor), 14.2 minor), 14.1 (major). HRMS (ESI): calcd for C₁₃H₁₇ClNO₄ (M + H)⁺: 286.0841, found 286.0849. HPLC (Daicel Chiralpak® IB column, *i*-PrOH/*n*-hexane= 4:96, λ= 220 nm, 1.0 mL/min): t$_R$ (*anti* major enantiomer) = 18.9 min, t$_R$ (*anti* minor enantiomer) = 18.2 min, t$_R$ (*syn* enantiomer) = 13.0 min.

(2*S*,3*S*)-and(2*S*,3*R*)-Ethyl-2-(*p*-trifluoromethylphenylamino)-3-hydroxy-4-oxo-pentanoate (15a,b).

Yellow oil, 72 mg, 56% yield, 7.5:1 dr, 97% *ee*.(*anti* diastereomer **15b**). ¹H-NMR (400 MHz, CDCl₃): δ(ppm) = 7.45 (d, *J*= 8.5 Hz, 2H, both), 6.73 (d, *J* = 8.5 Hz, 2H, major), 6.66 (d, *J* = 8.6 Hz, 2H, minor), 5.01 (d, *J* = 9.8 Hz, 1H, major), 4.70 (d, *J* = 3.5 Hz, 1H, minor), 4.65 (dd, *J¹* = 9.1 Hz, *J²* = 2.5 Hz, 1H, major), 4.58 (br, 1H, minor), 4.50 (dd, *J¹* = 4.9 Hz, *J²* = 2.6 Hz, 1H, major), 4.28-4.11 (m, 2H, both), 3.87 (d, *J*= 3.9 Hz, 1H, minor), 3.68 (d, *J* = 5.0 Hz, 1H, major), 2.43 (s, 1H, major), 2.30 (s, 1H, minor), 1.22 (t, *J* = 7.1 Hz, 3H, major). ¹³C-NMR (100 MHz, CDCl₃): (major *anti* isomer **15b**) δ(ppm)= 205.6, 169.0, 148.7, 127.1, 127.0, 126.9, 126.8, 113.2, 77.7, 62.4, 58.7, 26.1, 14.1. HRMS (ESI): calcd for C₁₄H₁₇FNO₄ (M + H)⁺: 320.1104, found 320.1117. HPLC (Daicel Chiralpak® IC column, *i*-PrOH/*n*-hexane= 1:99, λ= 254 nm, 1.0 mL/min): t$_R$ (*anti* major enantiomer) = 61.5 min, t$_R$ (*anti* minor enantiomer) = 41.4 min.

3 Results and discussion

3.1 Optimization of the reaction conditions

In order to improve the *anti*-diastereoselectivity of the L-Trp-catalyzed reaction between **1** and **2**, we initially decided to change the solvent from DMF to DMSO (Scheme 2). In DMSO alone, the **3b:3a** ratio, determined

by ^{1}H NMR of the reaction mixture, showed a marginal improvement relative to DMF (2.3:1 *vs.* 2:1, respectively). We reasoned that the use of ethylene glycol (EG) as a co-solvent would allow us to perform the reaction at lower temperatures, hopefully increasing the *anti:syn* ratio. When we performed the reaction using a DMSO/EG (20% v/v) solvent mixture *at room temperature*, we were pleased to observe an improved 3.2:1 **3b:3a** ratio.

In the light of this result, we decided to perform a study with different DMSO/EG ratios; moreover, we modified both the equivalents of hydroxyacetone and the catalyst loading employed (Table 1).
By using 5 equivalents of **1** and 20 mol% of L-Trp (relative to **2**) the *anti:syn* ratio of the Mannich adducts did not change significantly between 10 to 30% vol of EG (entries 1-4, Table 1). Using 40% vol of EG a slight decrease in diastereoselectivity was observed (entry 5). The effect of the amounts of hydroxyacetone employed was examined (entries 6-8, Table 1) using 20% vol of EG. The best

results were obtained with 10 equivalents of **1** (entry 7). A further improvement was observed (7.5:1 dr) under these conditions when the catalyst loading was increased to 33 mol% (entry 9, Table 1).

We subsequently studied the effect of the reaction temperature under these partially optimized conditions (Table 2).

At reaction temperatures of 0 °C or lower (entries 1 and 2, Table 2), the reaction was very slow, and no product was detected after 16 h. Both at 4 °C (entry 3) and at 35 °C (entry 4) a slight decrease of the diastereoselectivity was observed, thus, we selected room temperature (22 °C) as the optimal temperature.

We were disappointed to find that under these optimized reaction conditions the *anti:syn* dr was not reproducible. Thus, in a series of eight independent experiments performed under the conditions of entry 9 in Table 1 we obtained **3b:3a** ratios ranging from 4.2:1 to 7.3:1, even when freshly distilled hydroxyacetone **1** was
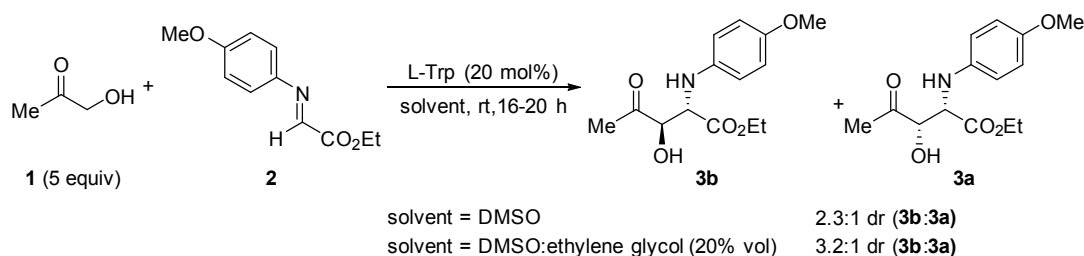
Scheme 2. Initial observation of the effect of the presence of ethylene glycol as a co-solvent in the Mannich reaction.

Table 1. Effect of the DMSO/EG ratio, catalyst loading and equivalents of hydroxyacetone **2** on the diastereoselectivity of the Mannich reaction between **1** and **2**.[a]

Entry	Equiv of 1	L-Trp (mol %)	% vol EG in DMSO	Dr (3b:3a)[b]
1	5	20	10	3.2:1
2	5	20	15	3.4:1
3	5	20	20	3.2:1
4	5	20	30	3.4:1
5	5	20	40	2.9:1
6	2	20	20	3.1:1
7	10	20	20	5.8:1
8	20	20	20	4.2:1
9	10	33	20	7.5:1

[a] Reaction performed in DMSO as the main solvent at rt, 2-4 h. [b] Determined by ^{1}H-NMR analysis of the crude reaction mixture.

Table 2. Study of the effect of the temperature on the diastereoselectivity of the reaction.[a]

Entry	Temperature (°C)	Time (h)	Dr (3b:3a)[b]
1	-23	16	–[c]
2	0	16	–[c]
3	4	17	5.6:1
4	35	1	5.3:1

[a] Reaction conditions: 10 equiv **1**, 1 equiv **2**, 33 mol% L-Trp, DMSO/EG (20% vol).
[b] Determined by ^{1}H-NMR analysis of the crude reaction mixture at the time indicated in. [c] No product was detected by ^{1}H-NMR.

employed. Further work demonstrated that the presence of water in the reaction medium led to lower dr's, thus highly hygroscopic EG was replaced by other alcohols as the DMSO co-solvent (Table 3).

Glycerol (entry 1, Table 3) gave much poorer dr's than ethylene glycol (entry 2), so we turned our attention to easily available monoalcohols. Anhydrous methanol (entry 3) gave a better *anti:syn* ratio (6.6:1). This parameter increased linearly from ethanol to 1-butanol (entries 3 to 6), but 1-pentanol (entry 7) gave much poorer results. Both secondary (entries 8, 10, and 11, Table 3) and tertiary (entry 9) alcohols also gave inferior diastereoselectivities. Thus, 1-butanol (entry 6) was selected as the best DMSO co-solvent in our Mannich reaction.

Subsequently, we tested the effect of different proportions of 1-butanol (Table 4).

Using 3% vol of 1-butanol (corresponding to one equivalent of alcohol relative to the imine **2** under the actual reaction conditions) an improved *anti:syn* ratio was readily observed (entry 1, Table 4), however, the best dr corresponded to the initially used value of 20% vol of 1-butanol (entry 3, Table 4). When the imine **2** was added in three portions, the *anti:syn* ratio deteriorated (entry 5, Table 4), suggesting that a pre-equilibrium between the imine and the alcohol improves the stereochemical outcome of the Mannich reaction. In conclusion, the addition of 10 equivalents of hydroxyacetone **1** to a solution of the imine **2** and of L-tryptophan (33 mol%) in DMSO/1-butanol (20% vol) at room temperature (22 °C) was chosen as the optimal set of reaction parameters. We were pleased to find that under these conditions the 7.6:1 ratio of **3b** to **3a** was perfectly reproducible.

3.2 Scope of the reaction

Subsequently, we applied these conditions to the Mannich reaction of hydroxyacetone **1** with a set of glyoxylate-derived imines (**2**, **4**-**9**) having different aryl substituents (Scheme 3). We determined not only the diastereomer ratios of the resulting Mannich adducts (**3**, **10**-**15**) but also the corresponding yields and the enantiomeric purities of the major *anti* isomers (Table 5).

In general, the Mannich adducts were obtained in good yields (56-72%) after chromatographic purification. Adduct **3** (entry 1, Table 5) was not purified by chromatography due to the instability of the *anti* isomer

Table 3. Study of different alcohols as DMSO co-solvents in the Mannich reaction.[a]

Entry	Co-solvent (20% vol)	Dr (3b:3a)[b]
1	Glycerol	3.1:1
2	EG	6.2:1
3	MeOH	6.6:1
4	EtOH	5.7:1
5	1-Propanol	7.0:1
6	1-Butanol	7.6:1
7	1-Pentanol	6.4:1
8	2-Propanol	4.8:1
9	*tert*-Butyl alcohol	5.2:1
10	2-Butanol	6.0:1
11	Isobutyl alcohol	7.0:1

[a] Reaction conditions: 10 equiv **1**, 1 equiv **2**, 33 mol% L-Trp, DMSO/co-solvent (20% vol), rt, 4 h. All co-solvent alcohols were used as received («dry»), without further purification. [b] Determined by ^{1}H-NMR analysis of the crude reaction mixture.

Table 4. Study of different proportions of 1-butanol as DMSO co-solvent in the Mannich reaction.[a]

| Entry	% vol of 1-butanol	Dr (3b:3a)[b]
1	3	4.6:1
2	10	6.4:1
3	20	7.6:1
4	30	6.1:1
5[c]	20	3.3:1

[a] Reaction conditions: 10 equiv **1**, 1 equiv **2**, 33 mol% L-Trp, DMSO/1-butanol (x% vol), rt, 4 h. [b] Determined by ^{1}H-NMR analysis of the crude reaction mixture. [c] Imine **2** was added in three portions (1 h intervals)

3b on silica gel, thus the yield corresponds to the crude mixture of Mannich products (>98% pure by ¹H-NMR).

The diastereoselectivity of the reaction is clearly dependent on the nature of the imine aromatic ring. The highest *anti:syn* ratios were obtained for relatively electroneutral aryl groups (entries 2-4, Table 5). The diastereomeric ratios were somewhat lower either for electron-donating (entry 1) or for electron-withdrawing (entry 7) *p*-substituents. A clear decrease in the diastereoselectivity was observed when the chloro substituent was shifted from *para* (entry 4) to *meta* (entry 5) to *ortho* (entry 6) positions on the ring. On the other hand, the enantiomeric purities of the major *anti* isomers were uniformly high (92% to > 99.9% ee), and only in the case of the *o*-substituted adduct **14b** was a decrease in the enantiomeric purity observed (entry 6).

The absolute configurations of the major enantiomers of the *anti* and *syn* Mannich adducts obtained with L-Trp
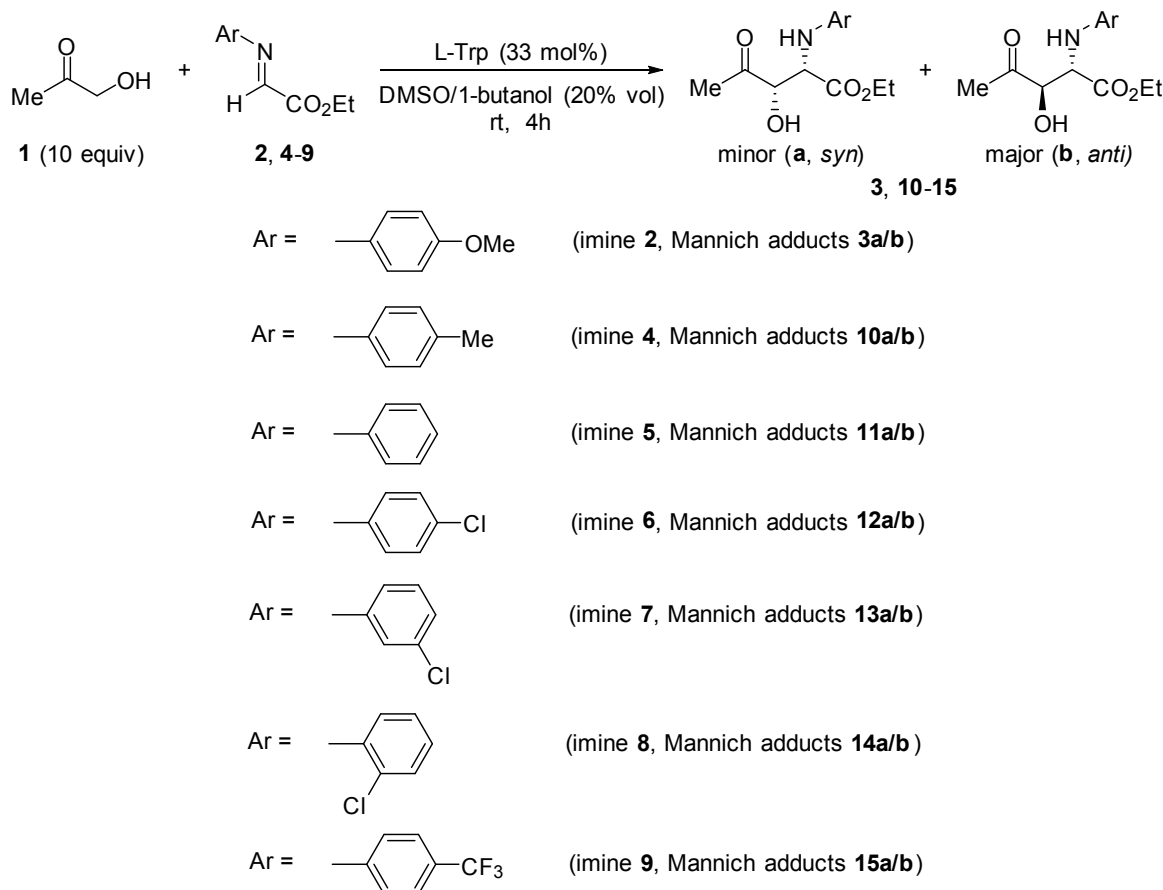
Scheme 3. Mannich reaction of hydroxyacetone **1** with a set of glyoxylate-derived imines under the optimized reaction conditions.

Table 5. Scope of the L-Trp-catalyzed Mannich reaction between hydroxyacetone **1** and a set of glyoxylate-derived imines.[a]

Entry	Imine	Products	Yield (%)[b]	Dr (*anti:syn*)[c]	Ee (*anti*, %)[d]
1	**2**	**3a,b**	80[e]	7.6:1	99
2	**4**	**10a,b**	66	9.6:1	> 99.9[f]
3	**5**	**11a,b**	58	10.3:1	99
4	**6**	**12a,b**	59	10.3:1	92
5	**7**	**13a,b**	72	6.6:1	95
6	**8**	**14a,b**	76	2.5:1	86
7	**9**	**15a,b**	56	7.2:1	97

[a] Reaction conditions: 10 equiv **1**, 1 equiv imine, 33 mol% L-Trp, DMSO/1-butanol (20% vol), rt, 2-4 h. [b] Yield of isolated product (diastereomer mixture) after chromatographic purification. [c] Determined by ¹H-NMR analysis of the crude reaction mixture. [d] Determined by chiral HPLC analysis. [e] Yield obtained without chromatographic purification. [f] The minor enantiomer of **10b** could not be detected.

were assigned as (2*S*,3*R*) and (2*S*,3*S*), respectively, by comparison of our data with those reported by Barbas III and co-workers [28].

In order to ascertain if the increase in the *anti:syn* ratio observed upon the use of alcohols as DMSO co-solvents was specific to glyoxylate-derived imines, we examined the diastereoselectivity of the Mannich reaction between hydroxyacetone **1** and imine **16** (derived from *p*-chlorobenzaldehyde and *p*-anisidine)[28] under different conditions (Scheme 4 and Table 6).

The addition of 1-butanol as co-solvent of DMSO (20% vol) led to a marginal increase in diastereoselectivity (entry 1 vs 2, Table 6). When DMF was used as a solvent, a further improvement was obtained (entry 3). Running the reaction at low temperature (4 °C, entries 4 and 5) gave a slight improvement over the original ratio of 2.0:1.

It is worth noting here that in the conditions of entry 5 in Table 6, Barbas III and co-workers reported a higher *anti:syn* ratio for this adduct (> 10:1), but the diastereomer ratio was determined *after* chromatographic purification [28].

The involvement of the alcohol co-solvent in the formation of hemiaminal or other covalent species with the starting imine was ruled out when ¹H-NMR monitoring did not reveal the formation of any new species (within the limits of detection) upon addition of 1-butanol (20% vol) to a DMSO solution of hydroxyacetone **1** and imine **2** (or **16**).

As a working hypothesis, we propose that the role of the alcohol co-solvent is that of destabilizing the (*E*)-enamine in the transition state of the Mannich reaction (Scheme 5). In the absence of the co-solvent (A), the transition state involving the (*E*)-enamine (that leads to the *syn*-Mannich adduct) is somewhat stabilized relative to the transition state arising from the (*Z*)-enamine leading to the production of the major *anti* isomer by an intramolecular hydrogen bond between the hydroxyl of the hydroxyacetone and the carbonyl oxygen of the imine. In the presence of the alcohol co-solvent (B) this intramolecular hydrogen bond is disrupted, destabilizing the transition state involving the (*E*)-enamine and increasing the *anti:syn* diastereoselectivity of the reaction. These alcohol co-solvent effects obviously do not play any role in the case of benzaldehyde-derived imines, in accordance to our observations.

4 Conclusions

In summary, we have found that the use of a DMSO/1-butanol (4:1 v/v) mixture as solvent at room temperature in the L-tryptophan-catalyzed Mannich reaction between hydroxyacetone and glyoxylate imines leads to a high diastereoselectivity favoring the *anti* isomer. The expected Mannich adducts are obtained in good yields, high *anti*-diastereoselectivity (up to 10.3:1 *anti/syn* ratio) and excellent enantioselectivities (up to >99.9% ee for the *anti* isomer). When the reaction is performed in DMSO alone much lower *anti/syn* ratios (~ 2:1) are obtained.

This increased *anti* diastereoselectivity upon the addition of an alcohol co-solvent is not observed for
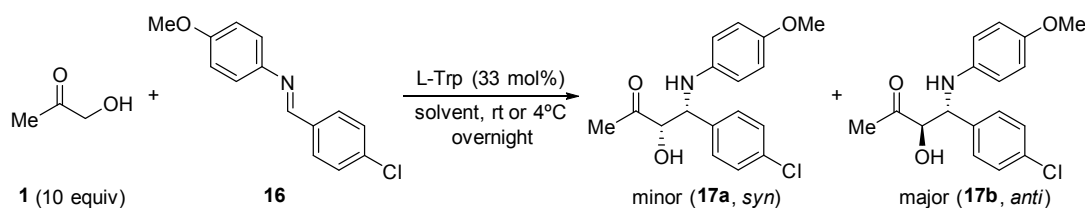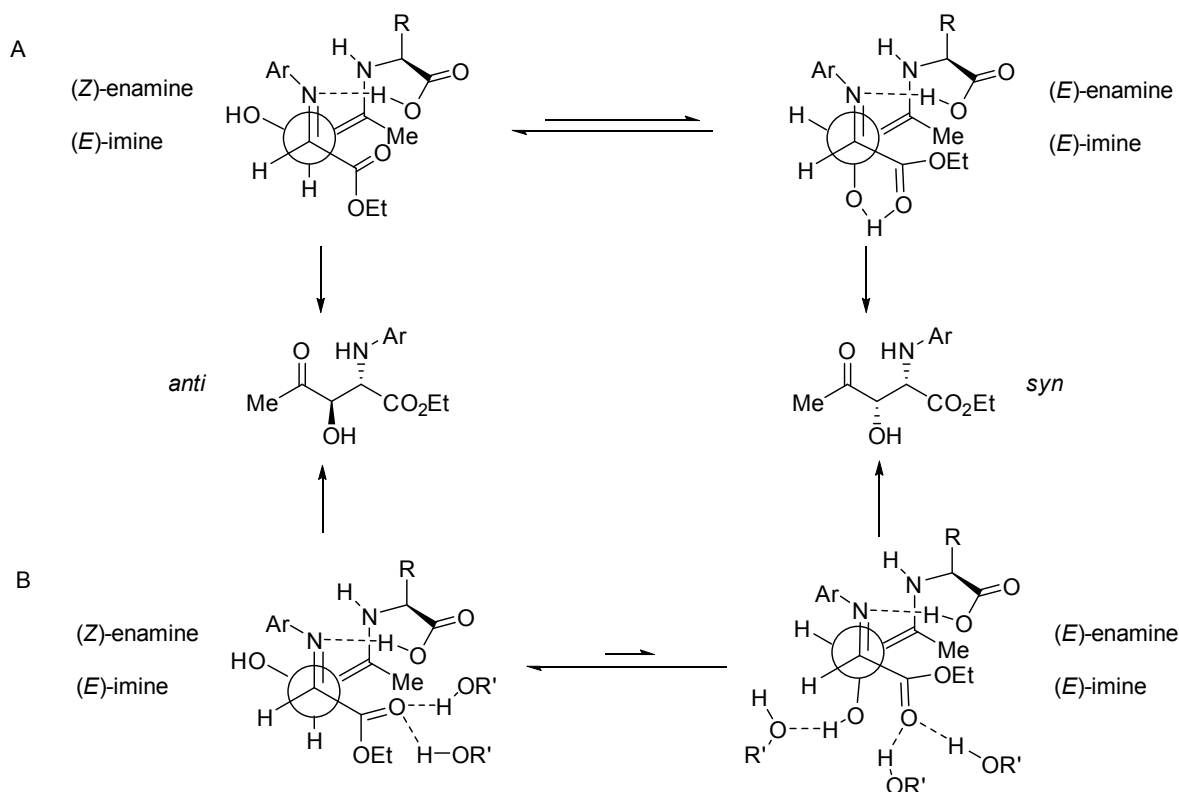

Scheme 4. Mannich reaction of hydroxyacetone **1** with the aromatic imine **16**.

Table 6. Solvent effects in the diastereoselectivity of the L-Trp-catalyzed Mannich reaction between hydroxyacetone **1** and the *p*-chlorobenz-aldehyde-derived imine **16**.

Entry	Solvent	Temperature (°C)	Dr (*anti:syn*)[a]
1[b]	DMSO	22	2.0:1
2[b]	DMSO/1-butanol (20% vol)	22	2.2:1
3[c]	DMF	22	3.0:1
4[c]	DMSO	4	2.4:1
5[c]	DMF	4	3.5:1

[a] Determined by ¹H-NMR analysis of the crude reaction mixture. [b] Reaction conditions: 10 equiv **1**, 1 equiv imine **16**, 33 mol% L-Trp, rt, 12 h. [c] The imine was generated *in situ* from *p*-chlorobenzaldehyde (1.1 equiv) and *p*-anisidine (1.0 equiv).

Scheme 5. Proposed role of the alcohol co-solvent in the diastereoselectivity of the L-Trp-catalyzed Mannich reaction between hydroxyacetone **1** and glyoxylate-derived imines.

benzaldehyde-derived imines.

References

[1] Mannich C., Krösche, W. Ueber ein Kondensationsprodukt aus Formaldehyd, Ammoniak und Antipyrin, Arch. Pharm. Pharm. Med. Chem., 1912, 250, 647-667.

[2] Hart D.J., Ha D.C., The ester enolate-imine condensation route to beta-lactams, Chem. Rev., 1989, 89, 1447-1465.

[3] Kobayashi S., Mori Y., Fossey J.S., Salter M.M., Catalytic Enantioselective Formation of C−C Bonds by Addition to Imines and Hydrazones: A Ten-Year Update, Chem. Rev., 2011, 111, 2626-2704.

[4] List, B., The Direct Catalytic Asymmetric Three-Component Mannich Reaction, J. Am. Chem. Soc. 2000, 122, 9336-9337.

[5] List B., Pojarliev P., Biller W.T., Martin H.J., The Proline-Catalyzed Direct Asymmetric Three-Component Mannich Reaction: Scope, Optimization, and Application to the Highly Enantioselective

Synthesis of 1,2-Amino Alcohols, J. Am. Chem. Soc. 2002, 124, 827-833.

[6] Notz W., Sakthivel K., Bui T., Zhong G., Barbas III C.F., Amine-catalyzed direct asymmetric Mannich-type reactions, Tetrahedron Lett., 2001, 42, 199-201.

[7] Ting A., Schaus S.E., You have full text access to this content Organocatalytic Asymmetric Mannich Reactions: New Methodology, Catalyst Design, and Synthetic Applications, Eur. J. Org. Chem., 2007, 5797-5815.

[8] Verkade J.M.M., van Hemert L.C.J., Quadflieg P.J.L. M., Rutjes F. P.J. T., Organocatalysed asymmetric Mannich reactions, Chem. Soc. Rev., 2008, 37, 29-41.

[9] Córdova A., In: Rios Torres R. (Ed.), Stereoselective Organocatalysis: Bond Formation Methodologies and Activation Modes, John Wiley & Sons, Hoboken, 2013, pp. 129-146.

[10] Mase N., Barbas III C.F., In: Dalko P.I. (Ed.), Comprehensive Enantioselective Organocatalysis: Catalysts, Reactions, and Applications, Wiley-VCH, Weinheim, 2013, Vol. 3, pp. 793-840.

[11] Córdova A., Notz W., Zhong G., Betancort J.M., Barbas III C.F., A Highly Enantioselective Amino Acid-Catalyzed Route to Functionalized α-Amino Acids, J. Am. Chem. Soc., 2002, 124, 1842-1843.

[12] Córdova A., Watanabe S., Tanaka F., Notz W., Barbas III C.F., A Highly Enantioselective Route to Either Enantiomer of Both α- and β-Amino Acid Derivatives, J. Am. Chem. Soc., 2002, 124, 1866-1867.

[13] Hayashi Y., Tsuboi W., Ashimine I., Urushima T., Shoji M., Sakai K., The Direct and Enantioselective, One-Pot, Three-Component, Cross-Mannich Reaction of Aldehydes, Angew. Chem. Int. Ed., 2003, 42, 3677-3680.

[14] Córdova A., The Direct Catalytic Asymmetric Cross-Mannich Reaction: A Highly Enantioselective Route to 3-Amino Alcohols and α-Amino Acid Derivatives, Chem. Eur. J., 2004, 10, 1987-1997.

[15] Zhuang W., Saaby S., Jørgensen K.A., Direct Organocatalytic Enantioselective Mannich Reactions of Ketimines: An Approach to Optically Active Quaternary α-Amino Acid Derivatives, Angew. Chem. Int. Ed., 2004, 43, 4476-4478.

[16] Akiyama T., Itoh J., Yokota K., Fuchibe K., Enantioselective Mannich-Type Reaction Catalyzed by a Chiral Brønsted Acid, Angew. Chem. Int. Ed., 2004, 43, 1566-1568.

[17] Uraguchi D., Terada M., Chiral Brønsted Acid-Catalyzed Direct Mannich Reactions via Electrophilic Activation, J. Am. Chem. Soc., 2004, 126, 5356-5357.

[18] Enders D., Grondal C., Vrettou M., Raabe G., Dihydroxyacetone in Amino Acid Catalyzed Mannich-Type Reactions, Angew. Chem. Int. Ed., 2005, 44, 4079-4083.

[19] Lou S., Taoka B.M., Ting A., Schaus S., Asymmetric Mannich Reactions of β-Keto Esters with Acyl Imines Catalyzed by Cinchona Alkaloids, J. Am. Chem. Soc., 2005, 127, 11256-11257.

[20] Ibrahem I., Zou W., Engqvist M., Xu Y., Córdova A., Acyclic Chiral Amines and Amino Acids as Inexpensive and Readily Tunable Catalysts for the Direct Asymmetric Three-Component Mannich Reaction, Chem. Eur. J., 2005, 11, 7024-7029.

[21] Alza E., Rodríguez-Escrich C., Salayero S., Bastero A., Pericàs M.A., A Solid-Supported Organocatalyst for Highly Stereoselective, Batch, and Continuous-Flow Mannich Reactions, Chem. Eur. J., 2009, 15, 10167-10172.

[22] Perera S., Sinha D., Rana N.K., Trieu-Do V., Zhao J.C.-G., List–Barbas–Mannich Reaction Catalyzed by Modularly Designed Organocatalysts, J. Org. Chem., 2013, 78, 10947-10953; and references cited therein.

[23] Córdova A., Barbas III C.F., *Anti*-Selective SMP-catalyzed direct asymmetric Mannich-type reactions: synthesis of functionalized amino acid derivatives, Tetrahedron Lett., 2002, 43, 7749-7752.

[24] Franzén J., Marigo M., Fielenbach D., Wabnitz T.C., Kjaersgaard A., Jørgensen K.A., A General Organocatalyst for Direct α-Functionalization of Aldehydes: Stereoselective C–C, C–N, C–F, C–Br, and C–S Bond-Forming Reactions. Scope and Mechanistic Insights, J. Am. Chem. Soc., 2005, 127, 18296-18304.

[25] Kano T., Yamaguchi Y., Tokuda O., Maruoka K., *Anti*-Selective Direct Asymmetric Mannich Reactions Catalyzed by Axially Chiral Amino Sulfonamide as an Organocatalyst, J. Am. Chem. Soc., 2005, 127, 16408-16409.

[26] Mitsumori S., Zhang H., Cheong P.H.-Y., Houk K.N., Tanaka F., Barbas III C.F., Direct Asymmetric *anti*-Mannich-Type Reactions Catalyzed by a Designed Amino Acid, J. Am. Chem. Soc., 2006, 128, 1040-1041.

[27] Zhang H, Mifsud M., Tanaka F., Barbas III C.F., 3-Pyrrolidinecarboxylic Acid for Direct Catalytic Asymmetric anti-Mannich-Type Reactions of Unmodified Ketones, J. Am. Chem. Soc. 2006, 128, 9630-9631.

[28] Ramasastry S.S.V., Zhang H., Tanaka F., Barbas III C.F., Direct Catalytic Asymmetric Synthesis of anti-1,2-Amino Alcohols and syn-1,2-Diols through Organocatalytic anti-Mannich and *syn*-Aldol Reactions, J. Am. Chem. Soc., 2007, 129, 288-289.

[29] Zhang H., Mitsumori S., Utsumi N., Imai M., García-Delgado N., Mifsud M., Albertshofer K., Cheong P.H.-Y., Houk K.N., Tanaka F., Barbas III C.F., Catalysis of 3-Pyrrolidinecarboxylic Acid and Related Pyrrolidine Derivatives in Enantioselective anti-Mannich-Type Reactions: Importance of the 3-Acid Group on Pyrrolidine for Stereocontrol, J. Am. Chem. Soc., 2008, 130, 875-886.

[30] Pouliquen M., Blanchet J., Lasne M.-C., Rouden J., 3-Trifluoro-methanesulfonamido-pyrrolidine: A General Organocatalyst for anti-Selective Mannich Reactions, Org. Lett., 2008, 10, 1029-1032.

[31] Kano T., Yamaguchi Y., Maruoka K., A Designer Axially Chiral Amino Sulfonamide as an Efficient Organocatalyst for Direct Asymmetric Mannich Reactions of *N*-Boc-Protected Imines, Angew. Chem. Int. Ed., 2009, 48, 1838-1840.

[32] Martín-Rapún R., Fan X., Salayero S., Bahramnejad M., Cuevas F., Pericàs M.A., Highly Active Organocatalysts for Asymmetric anti-Mannich Reactions, Chem. Eur. J. 2011, 17, 8780-8783; and references cited therein.

[33] Crusats J., Hochberg D., Moyano A., Ribó J. M., Frank Model and Spontaneous Emergence of Chirality in Closed Systems, ChemPhysChem, 2009, 10, 2123-2131.

[34] Blanco C., Ribó J. M., Crusats J., El-Hachemi Z., Moyano A., Hochberg D., Mirror symmetry breaking with limited enantio-selective autocatalysis and temperature gradients: a stability survey, Phys. Chem. Chem. Phys., 2013, 15, 1546-1556.

[35] Blanco C., Crusats J., El-Hachemi Z., Moyano A., Hochberg D., Ribó J. M., Spontaneous Emergence of Chirality in the Limited Enantioselectivity Model: Autocatalytic Cycle Driven by an External Reagent, ChemPhysChem 2013, 14, 2432-2440.

[36] Blanco C., Crusats J., El-Hachemi Z., Moyano A., Veintemillas-Verdaguer S., Hochberg D., Ribó J.M., The Viedma Deracemization of Racemic Conglomerate Mixtures as a Paradigm of Spontaneous Mirror Symmetry Breaking in Aggregation and Polymerization, ChemPhysChem 2013, 14, 3982-3993.

[37] Valero G., Ribó J.M., Moyano A., A Closer Look at Spontaneous Mirror Symmetry Breaking in Aldol Reactions, Chem. Eur. J., 2014, 20, 17395-17408.

[38] Ribó J.M., Blanco C., Crusats J., El-Hachemi Z., Hochberg D., Moyano A., Absolute Asymmetric Synthesis in Enantiose-lective Autocatalytic Reaction Networks: Theoretical Games, Speculations on Chemical Evolution and Perhaps a Synthetic Option, Chem.-Eur. J., 2014, 20, 17250-17271.

[39] Tsogoeva S.B., Organoautocatalysis: Challenges for experiment and theory, J. Systems Chem., 2010, 1:8.

[40] Tsogoeva S.B., When chiral product and catalyst are the same: discovery of asymmetric organoautocatalysis, Chem. Commun., 2010, 46, 7662-7669.

[41] Perrin D.D.A., Armarego W.L.F., Purification of Laboratory Chemicals, 4th Ed., Butterworth-Heinemann, Oxford, 1996.

[42] Held F.E., Fingerhut A., Tsogoeva S.B., Insights into the spontaneous emergence of enantioselectivity in an asymmetric Mannich reaction carried out without external catalyst, Tetrahedron: Asymmetry, 2012, 23, 1663-1669.

[43] Zhu S., Dong J., Fu S., Jiang H., Zeng W., Cu(II)-Catalyzed Intermolecular Amidation of C-Acylimine: A Convenient Access to gem-Diamino Acid Derivatives, Org. Lett., 2011, 13, 4914-4917.