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Evaluation of 6-APA as a New Organocatalyst for a Direct Cross-Aldol Reaction

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6-Aminopenicillanic acid (6-APA) and two of its derivatives, 6-APA benzyl ester (6-APA-OBn) and Penicillin G (PenG), have been evaluated as catalysts for use in direct cross-aldol reactions in different solvents and mixtures. The effects of catalyst loading, reaction time, pH and temperature on the yield and stereoselectivity have been studied. 6-APA proved to be an effective catalyst in terms of yield for the reaction between cyclohexanone and *p*-nitrobenzaldehyde, especially in neat conditions. The stereoselectivity of the reaction was conditioned by the presence of two competing mechanisms: one an imine–enamine pathway and the other a Brønsted acid catalysis.

Introduction

The organocatalysed aldol reaction has been the object of extraordinary efforts in recent years.[1] Many kinds of small organic molecules, such as amines,[2] proline[3] and other amino acids[4] and small peptides,[5] have been used as catalysts to promote asymmetric C–C bond formation.

6-Aminopenicillanic acid (6-APA)[6] is a particular kind of amino acid produced by several species of *Penicillium* and *Aspergillus* and it is the active nucleus common to all penicillins. 6-APA is the basic material used for the industrial production of antibiotics. The year 2007 marked the 50th anniversary of the discovery of 6-APA, which made possible the development of semi-synthetic penicillins that have become one of the most important groups of antibiotics in clinical practice. 6-APA is a very cheap, easily available, enantiopure chiral compound. It is industrially produced either by chemical or enzymatic deacylation using penicillin amidase from Penicillin G or V, which are in turn efficiently obtained from biotechnological processes.[7] For many years we have been working on the synthesis of biologically active β-lactam derivatives and on their use as synthons.[8] Herein, we present our results on the evaluation of 6-APA and two of its derivatives, 6-APA benzyl ester (6-APA-OBn) and Penicillin G (PenG; see Figure 1), as catalysts in direct cross-aldol reactions. To the best of our knowledge, this is the first application of penicillins as organocatalysts in asymmetric synthesis.

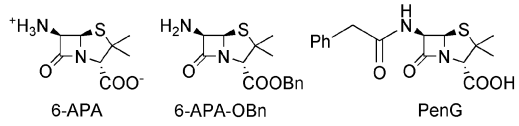

Figure 1. 6-APA and derivatives evaluated as catalyst.

Results and Discussion

As a model reaction, we explored the aldol condensation between cyclohexanone and *p*-nitrobenzaldehyde. In a preliminary combinatorial screening we tested some polar aprotic solvents and mixtures with water using 6-APA (30 mol-% with respect to the aldehyde) as the catalyst (see Table 1). Products were detected in minimal amounts except for when the reaction was conducted in water, in which case a yield of 36% was obtained. Notably, better yields were obtained when the reaction was conducted in solvent-free conditions in an excess of ketone: complete conversion was achieved and *syn*/*anti* products were obtained in 86% yield with a 23:77 diastereomeric ratio in favour of the *anti* isomer. In this case, the addition of 6-APA seemed to improve the homogeneity of the reaction mixture.

These results prompted us to undertake a more detailed study of the 6-APA-catalysed aldol reaction in water and in solvent-free conditions, considering the influence of the amount of catalyst, time, pH and temperature on the yield and stereoselectivity. The course of the reaction at different temperatures and with different amounts of catalyst was carefully monitored by HPLC and ^{1}H NMR analysis at various reaction times (Table 2 and Figure 2).

As expected, in the absence of the catalyst the reaction did not proceed. When 6-APA was used in a stoichiometric amount, there was complete conversion into the products;

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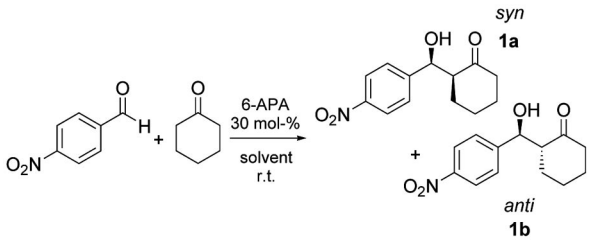
Table 1. Aldol condensation between cyclohexanone and *p*-nitrobenzaldehyde catalysed by 6-APA in different solvents.[a]



Entry	Solvent	% Yield of **1a** + **1b**	*syn*/*anti*[b]
1	THF/H_2O (1:1)	7	57:43
2	THF	13	66:34
3	DMF/H_2O (1:1)	13	51:49
4	DMF	12	58:42
5	$DMSO/H_2O$ (1:1)	7	50:50
6	DMSO	7	56:44
7	H_2O	36	58:42
8	BMIM NTf_2	4	54:46
9	Neat[c]	86	23:77

[a] Experimental conditions: *p*-nitrobenzaldehyde (0.5 mmol), cyclohexanone (1.5 mmol), 6-APA (0.15 mmol, 30 mol-%), solvent (2 mL), T = 27 °C, time = 84 h. [b] The *syn*/*anti* ratio was evaluated by HPLC analysis. [c] In this case the cyclohexanone was used in excess: *p*-nitrobenzaldehyde (0.5 mmol) and cyclohexanone (2.5 mmol).

by lowering the amount of catalyst, good conversions could be still obtained by extending the reaction times (Table 2, entries 8, 10 and 15). From 100 to 10 mol-% catalyst, the *anti* diastereoisomer was preferentially formed, even if with a low diastereoselectivity (Table 2, entries 2, 5, 8 and 10). In these cases, we also recorded the presence of variable amounts of the dehydrated aldol adduct **2** as a byproduct.[9] The distribution between aldols and enone **2** did not depend on the amount of 6-APA, but the enantiomeric excess varied with the best values for both the *syn* and *anti* diastereoisomers being obtained with 10 mol-% 6-APA. Note that at low conversion, the *syn* isomer was the preferred diastereoisomer, but its relative amount progressively diminished because of the concomitant formation of enone **2**, and ultimately the *anti* diastereoisomer predominated on disappearance of the aldehyde (Table 2, entries 5, 8 and 10). Even at low temperatures the preferred diastereoisomer was the *syn* isomer. Thus, the *syn* isomer can be considered the kinetically controlled diastereoisomer.

By monitoring the ongoing reaction, we noticed the presence of transient byproducts **A** and **A′**. They appeared as a double peak in the HPLC analysis, and their amount decreased as the starting aldehyde was consumed. The ^1H NMR spectra of the crude products at lower aldehyde conversions showed the presence of two signal pairs at 6.53, 6.41, 5.76, and 5.07 ppm, which suggests the presence of at least two stereoisomers of the hemiacetal structure **A** depicted in Figure 2. Attempts to isolate the products by flash chromatography failed, but identical HPLC and NMR signals were obtained by mixing the final aldols **1a**,**b** and the starting aldehyde, which supports the proposed structure. Mass spectra consistent with these findings were obtained in negative ionization mode (ESI HPLC–MS): the peak at m/z = 435 was attributed to the $[M - H + 2H_2O]^-$ ion. The same typical ionization cluster was recognized in the MS of aldols **1a**,**b** (peak at m/z = 284)**.** To the best of our knowledge, this is the first case in which these kinds of byproducts have been reported. To trace the presence of any other intermediates, imines of 6-APA with the aldehyde and cyclohexanone were prepared for comparison, but no iminic-enaminic intermediates formed between 6-APA and the aldehyde or ketone were observed.

Some experiments were conducted to examine the scope of the 6-APA catalytic system in neat conditions, and the

Table 2. Influence of amount of catalyst, time and temperature on the aldol condensation between cyclohexanone and *p*-nitrobenzaldehyde catalysed by 6-APA in "neat" conditions.[a]

Entry	Cat. [mol-%]	T [°C]	t [h]	% Yield			*syn*/*anti*	% ee_{syn}	% ee_{anti}
				1a + **1b**	**2**	**A** + **A′**			
1	–	27	96	–	–	–	–	–	–
2	100	27	24	87	10	3	32:68	34	22
3	30	27	17	67	1	33	72:28		
4	30	27	25	74	4	16	66:34		
5	30	27	58	87	13	–	23:77	51	16
6	20	27	17	33	–	8	75:25		
7	20	27	41	79	5	16	52:48		
8	20	27	96	85	12	2	30:70	46	29
9	10	27	56	76	5	5	51:49		
10	10	27	96	85	15	–	33:67	53	59
11	5	27	21	22	1	13	72:28		
12	5	27	40	34	3	20	69:31		
13	5	27	64	48	6	34	65:35		
14	5	27	88	57	10	14	61:39		
15	5	27	97	67	10	10	58:42	18	36
16	10	0	117	32	–	–	78:22		
17	10	0	243	68	–	–	78:22	59	60

[a] Experimental conditions: *p*-nitrobenzaldehyde (0.5 mmol), cyclohexanone (2.5 mmol). The *syn*/*anti* ratio and *ee* were determined by HPLC.

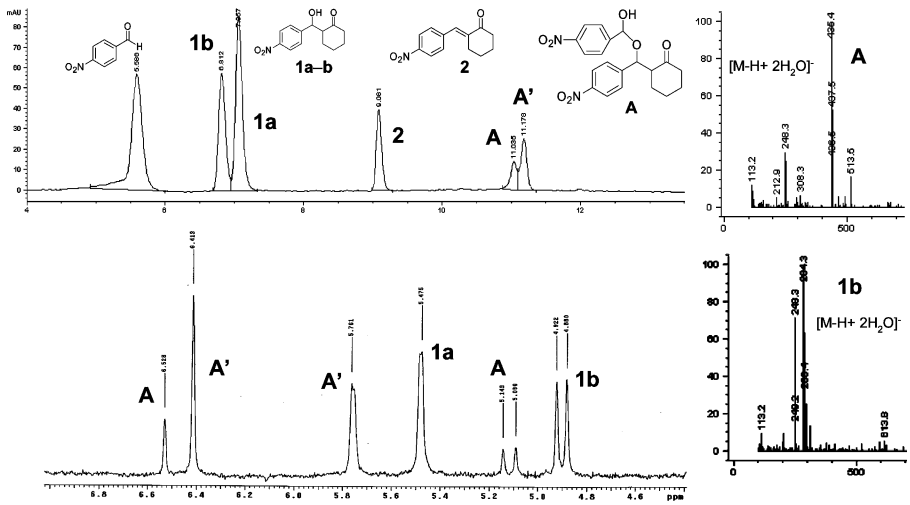
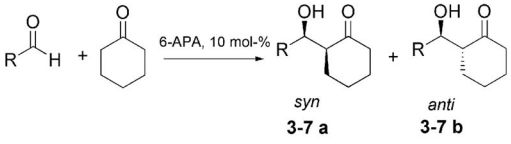


Figure 2. HPLC–MS chromatogram (mass spectra in negative ionization mode) and ^{1}H NMR (200 MHz) spectrum of a typical reaction mixture.

results are summarized in Table 3. It appears that electron-poor aromatic aldehydes are better substrates than electron-rich ones, but the stereoselectivity is poor.

Table 3. Aldol condensations between cyclohexanone and aromatic aldehydes catalysed by 10 mol-% 6-APA.[a]



Entry	R	Prod.	*t* [h]	% Yield	*syn*/*anti*	% ee_{syn}	% ee_{anti}
1	*p*CNC_6H_5	**3a**,**b**	72	82[b]	62:38	23	20
2	*p*ClC_6H_5	**4a**,**b**	162	61	54:46	20	21
3	C_6H_5	**5a**,**b**	76	43	57:43	11	19
4	*p*$CH_3OC_6H_5$	**6a**,**b**	90	traces	–	–	–
5	C_6F_5	**7a**,**b**	48	86	51:49	18	13

[a] Experimental conditions: aldehyde (0.5 mmol), cyclohexanone (2.5 mmol), 6-APA (0.05 mmol; 10 mol-%), T = 27 °C. [b] With this aldehyde, enone and byproducts were detected.

6-APA can be considered a sort of dipeptide with terminal acid–base functionalities. It is possible to calculate the pH-dependent distribution of the protonation of 6-APA from the constants pK_1 = 2.5 and pK_2 = 4.75, which are unusually low compared with values for α-amino acids.[10] Site-specific protonation of the amine and carboxylate groups gives rise to a set of four microspecies: anionic, cationic, uncharged and zwitterionic. It has been found that for 6-APA, the zwitterionic species dominates the uncharged form by a factor of 110.[11] Thus, only three microspecies need be considered. To explore the influence of pH, the reaction was performed in "in water" conditions, buffering the pH in the range 1.9–8.2, which favours the presence of the cationic, zwitterionic or anionic form (Table 4, entries 1–7), and in "on water" conditions, performing the reaction in the presence of 5 equiv. of ketone and a small amount of water (50 μL; Table 4, entries 8 and 9). The plots of product yields, diastereoselectivity and enantioselectivity for entries 1–7 are presented in Figure 3 as a function of pH. The expected pH-dependent distribution of the 6-APA microspecies is also reported.

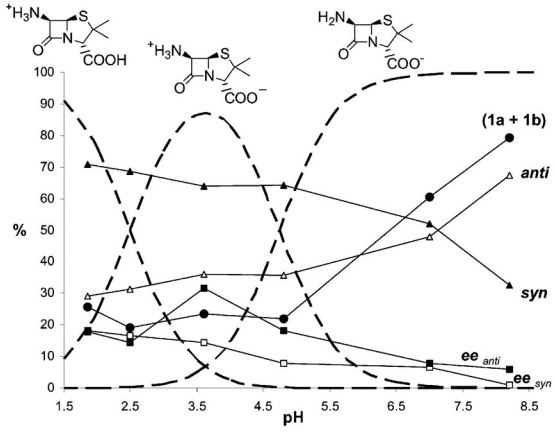


Figure 3. pH-dependent distribution of the three major species of 6-APA (cationic, zwitterionic and anionic): aldol yields (●), *anti* % (Δ), *syn* % (▲), ee_{anti} (■) and ee_{syn} (□) data as function of aqueous buffer pH.

Conversions in the range of pH 1.9–4.8 were lower than those obtained in neat conditions, whereas at higher pH we observed higher yields. The diastereoselectivity was almost constant in the pH range 2–5 with a predominance of the *syn* aldol. In this respect, 6-APA behaves in water like primary amines or some reduced dipeptides, which catalyse the direct asymmetric aldol reaction with *syn* selectivity.[12] For pH values higher than 7, the diastereomeric ratio was strongly affected by the concomitant elimination reaction, which eroded the *syn* aldol. The enantioselectivity was always low and reached its highest value for the *anti* diastereoisomer at pH 3.6, at which pH the zwitterionic form is predominant, whereas for the *syn* diastereoisomer the *ee* was almost constant in the range of pH 1.9–3.6. Thus, for both the *syn* and *anti* isomers, the *ee* is higher in the pres-

Table 4. Influence of pH and the amount of water present in the aldol condensation between cyclohexanone and *p*-nitrobenzaldehyde catalysed by 6-APA.[a]

Entry	pH[b]	Water	*t* [h]	% Yield		*syn*/*anti*	% ee_{syn}	% ee_{anti}
				1a + **1b**	**2**			
1	–[c]	2 mL	70	36	–	58:42	9	12
2	1.9	2 mL	64	26	1	71:29	18	18
3	2.5	2 mL	64	19	1	69:31	17	14
4	3.6	2 mL	66	24	1	64:36	15	32
5	4.8	2 mL	56	22	1	64:36	8	18
6	7.0	2 mL	56	61	31	52:48	7	8
7	8.2	2 mL	56	79	7	33:68	1	6
8	–[c]	50 μL	138	76	14	32:68	36	18
9	2.1	50 μL	97	73	20	38:62	31	20

[a] Experimental conditions (entries 1–7): *p*-nitrobenzaldehyde (0.5 mmol), cyclohexanone (1.5 mmol), 6-APA (30 mol-%), aqueous buffer (2 mL), T = 27 °C. Experimental conditions (entries 8 and 9): *p*-nitrobenzaldehyde (0.5 mmol), cyclohexanone (2.5 mmol), 6-APA (10 mol-%), T = 27 °C. [b] Buffers: AcOH/AcONa: pH 1.9; Na_3PO_4/citric acid: pH 2.5; citric acid/sodium citrate: pH 3.6 and 4.0; KH_2PO_4/Na_2HPO_4: pH 7; boric acid/borax: pH 8.2. [c] No buffer.

ence of the cationic form of 6-APA. From these data it appears that 6-APA is catalytically active in its cationic or zwitterionic form in the pH range 2–5, whereas at pH 7 and 8 it is more likely that the reaction follows a general base catalysis mechanism. When the water content was lowered (Table 4, entries 8 and 9), the yields remained good, although higher amounts of elimination product **2** were obtained, thus giving rise to predominantly the *anti* isomer; the enantiomeric excesses were better, but they still did not reach those obtained in neat conditions.

The enamine mechanism is largely accepted to be the most important activation method in asymmetric organocatalysis with proline.[13] However, for a primary amino acid promoted enamine catalysis, an efficient imine–enamine tautomerism is essential.[14] To verify the imine–enamine mechanism and to clarify the catalytic role of the amino and carboxylic acid groups of 6-APA, we performed the reaction with Penicillin G (PenG) and 6-APA benzyl ester (6-APA-OBn; Table 5, entries 1 and 3). PenG and 6-APA-OBn are less effective than 6-APA in terms of reaction yield, but, surprisingly, the best result in terms of enantioselectivity was obtained with Penicillin G (entry 1, ee_{anti} = 80%), in the absence of the primary amino group, whereas with the 6-APA *O*-benzyl ester, the *ee* was low and, notably, with a reversed enantioselectivity in the case of the *anti* isomer (Table 5, entry 3). By using the Penicillin G potassium salt, just traces of aldols could be detected (entry 2), which indicates that the carboxylic group must be protonated to exert catalytic activity. To force the presence of the protonated carboxylic group, we added two acid additives, benzoic acid (pK_a = 4.21) and/or trifluoroacetic acid (pK_a = 0.3). Unfortunately, the stereoselectivity did not improve, especially when CF_3COOH, which catalyses the achiral aldol condensation by itself to some extent, was used (Table 5, entries 6–8 and 10).

Proline is considered a "bifunctional catalyst" in cross-aldol reactions, and a joint action of the two proximal functional groups is proposed in some of the mechanistic models: the secondary amine in the enamine formation and the carboxylic acid in the hydrogen-bond activation of the acceptor carbonyl group.[15] In organocatalysis by peptides, the spatial arrangement of the amine and the carboxylic acid groups has been examined and it was demonstrated that even in this case it was quite critical for an efficient catalysis.[16] The bicyclic core of 6-APA is a rigid and bent structure with the amino and carboxylic acid functions pointing in opposite directions with respect to the azetidinone plane, and hence an intramolecular cooperation of the two functional groups in catalysis should be highly limited by their geometrical arrangement.

Table 5. Aldol condensation between cyclohexanone and *p*-nitrobenzaldehyde with different catalysts and catalyst activation mode.[a]

Entry	Catalyst [10 mol-%]	Additive [mol-%]	*t* [h]	% Yield		*syn*/*anti*	% ee_{syn}	% ee_{anti}
				1a + **1b**	**2**			
1	PenG	–	214	21	–	50:50	27	80
2	PenG (K^+ salt)	–	310	3	–	75:35	Nd[b]	Nd[b]
3	6-APA-OBn	–	238	54	1	52:48	16	–9
4	6-APA	PhCOOH 5%	134	87	–	27:73	47	32
5	6-APA	CF_3COOH 5%	185	83	4	64:36	14	27
6	PenG	CF_3COOH 10%	112	20	1	55:45	5	52
7	6-APA	CF_3COOH 10%	142	64	8	64:36	10	20
8	6-APA-OBn	CF_3COOH 10%	145	90	2	56:44	9	–14
9	–	PhCOOH 5%	195	traces	–	–	–	–
10	–	CF_3COOH 5%	195	15	–	>99:1	–	–

[a] Experimental conditions: aldehyde (0.5 mmol), cyclohexanone (2.5 mmol), T = 27 °C. [b] Nd = not detectable.

The experimental results obtained with 6-APA at different pH values, and with the 6-APA benzyl ester and PenG, suggest the possibility of there existing two competing mechanisms: one an imine–enamine mechanism (6-APA or 6-APA-OBn) and the other a Brønsted acid catalysis (6-APA or PenG). With PenG and 6-APA-OBn the two mechanisms act separately, whereas with 6-APA they operate simultaneously. Brønsted acid catalysis appeared to be less effective in terms of yield, but gave quite a good enantioselectivity with respect to the *anti* isomer (Table 5 entry 1), whereas the imine–enamine catalysis mode was more effective, but had a low enantioselectivity with an opposite stereoinduction in the case of the *anti* isomer (Table 5, entry 3). The competition between the two mechanisms in 6-APA catalysis provides a rationale for the limits we found in the asymmetric catalysis.

Conclusions

6-Aminopenicillanic acid (6-APA) has been evaluated for the first time as a catalyst for a direct cross-aldol reaction. The best results were obtained in neat conditions in which 6-APA proved to be an effective catalyst in terms of yield. The competition between two different catalysis mechanisms, one an imine–enamine mechanism and the other a Brønsted acid catalysis, limited the performance with respect to the diastereo- and enantioselectivity. Work is in progress to design and synthesize more efficient 6-APA derivatives as organocatalysts.

Experimental Section

General: Solvents were of HPLC grade and were purchased from commercial suppliers. TLC: Merck 60 F254. Column chromatography: Merck silica gel 20–300 mesh. ^{1}H and ^{13}C NMR spectra were obtained with Varian GEMINI 200 and INOVA 300 spectrometers with a 5 mm probe. All chemical shifts have been quoted relative to deuteriated solvent signals with δ in parts per million and J in hertz. HPLC–MS: Agilent Technology HP1100, column ZOBRAX-Eclipse XDB-C8 Agilent Technologies coupled with a Agilent Technologies MSD1100 single-quadrupole mass spectrometer, full-scan mode from m/z = 50–2600, scan time 0.1 s, ESI spray voltage 4500 V in positive ion mode (3000 V in negative ion mode), nitrogen gas 35 psi, drying gas flow 11.5 mL/min, fragmentor voltage 20 V. HPLC: Agilent Technology HP1100, column ZOBRAX-Eclipse XDB-C8 Agilent Technologies. The compounds were eluted with CH_3CN/H_2O, gradient from 10–100% of CH_3CN in 15 min, then 100% of CH_3CN for 10 min. Chiral HPLC: Hewlett–Packard HP1090 Series II, columns Daicel's Chiralpack (25 cm × 0.46 cm Ø) AD, OD and OJ. The compounds were eluted with hexane/*i*PrOH. To set and maintain the temperature in the range of ±1 °C, a Techne TE-10D Tempunit and Fison Haake K15 were used.

General Procedure for the Organocatalysed Aldol Reaction: In a typical experiment, the solvent (2 mL) was placed in a 20 mL test-tube equipped with a screw cap and magnetic bar. The desired temperature was reached and kept constant by use of a temperature control apparatus. Catalyst (0.15 mmol) and aldehyde (0.5 mmol) were added to the test-tube with freshly distilled cyclohexanone (1.5 mmol) under constant stirring. After the time indicated in Tables 1–5, the reaction mixture was diluted with water and extracted with dichloromethane (3 × 20 mL). The combined organic phases were dried with anhydrous sodium sulfate and after removal of the solvent the crude was analysed to determine the yields and diastereomeric ratios. The residue was purified by flash chromatography on silica gel (cyclohexane/ethyl acetate, 85:15) to give a mixture of two aldols, which was analysed by chiral HPLC to determine the enantiomeric ratios.

When the reactions were conducted in "neat" conditions, the chosen amount of catalyst, aldehyde (0.5 mmol) and freshly distilled cyclohexanone (2.5 mmol) were mixed. After the times indicated in Tables 1–5 the reactions were worked up as described above.

Aldols **1a**,**b**, **3**–**7a**,**b** and enone **2**[17] are known products[18,19] and their NMR spectra agreed with reported data.

The *syn*/*anti* ratios were generally determined by HPLC. In the cases of products **5a**,**b** and **6a**,**b**, the diastereomeric ratios were determined by ^{1}H NMR analysis of the crude product. Enantiomeric excesses were obtained by HPLC on chiral columns and peak assignment was carried out by comparison with reported literature data.[15]

1a,**b:** Reversed phase HPLC: t_R = 12.90 (**1b**, *anti*), 13.10 (**1a**, *syn*), 14.91 (**2**), 16.40 and 16.56 min (**A** and **A′**). Chiral HLPC conditions: column AD, hexane/*i*PrOH (90:10), flow 0.8 mL/min, λ = 210 nm: t_R = 21.50 (**1a**, *syn* minor isomer), 26.79 (**1a**, *syn* major isomer), 29.29 (**1b**, *anti* major isomer, 2*S*,1′*R*), 39.00 min (**1b**, *anti* minor isomer, 2*R*,1′*S*).

3a,**b:** Reversed phase HPLC: t_R = 12.87 (**3b**, *anti*), 13.08 (**3a**, *syn*), 15.10 (enone), 16.25 and 16.39 min (hemiacetals). Chiral HLPC conditions: column AD, hexane/*i*PrOH (from 99:1 to 90:10 in 20 min), flow 1.0 mL/min, λ = 214 nm: t_R = 22.90 (**3a**, *syn* minor isomer), 26.21 (**3a**, *syn* major isomer), 28.40 (**3b**, *anti* major isomer), 33.30 min (**3b**, *anti* minor isomer).

4a,**b:** Reversed phase HPLC (from 10% to 80% of CH_3CN in 25 min): t_R = 22.34 (**4b**, *anti*), 22.50 min (**4a**, *syn*). Chiral HLPC conditions: column AD, hexane/*i*PrOH (from 99:1 to 90:10 in 20 min), flow 1.0 mL/min, λ = 214 nm: t_R = 13.80 (**4a**, *syn* minor isomer), 16.60 (**4a**, *syn* major isomer), 19.10 (**4b**, *anti* major isomer), 21.50 min (**4b**, *anti* minor isomer).

5a,**b:** Reversed phase HPLC: t_R = 13.55 min (**5a** + **5b**). Chiral HLPC conditions: column OD, hexane/*i*PrOH (98:2), flow 0.7 mL/min, λ = 210 nm: t_R = 21.26 (**5a**, *syn* major isomer), 24.67 (**5a**, *syn* minor isomer), 30.15 (**5b**, *anti* minor isomer), 47.21 min (**5b**, *anti* major isomer).

6a,**b:** Reversed phase HPLC: t_R = 13.30 min (**5a** + **5b**). Chiral HLPC conditions: column AD, hexane/*i*PrOH (92:8), flow 1.0 mL/min, λ = 210 nm: t_R = 30.50 (**6a**, *syn* minor isomer), 37.06 (**6a**, *syn* major isomer), 57.72 (**6b**, *anti* major isomer), 64.19 min (**6b**, *anti* minor isomer).

7a,**b:** Reversed phase HPLC: t_R = 15.42 (**7b**, *anti*), 15.13 min (**7a**, *syn*). Chiral HLPC conditions: column OJ, hexane/*i*PrOH (99:1), flow 1.0 mL/min, λ = 214 nm: t_R = 8.45 (**7b**, *anti* major isomer), 10.25 (**7b**, *anti* minor isomer), 18.11 (**7a**, *syn* minor isomer), 19.37 min (**7a**, *syn* major isomer).

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[1] a) B. List, R. A. Lerner, C. F. Barbas III, *J. Am. Chem. Soc.* **2000**, *122*, 2395–2396; b) K. Sakthivel, W. Notz, T. Bui, C. F. Barbas III, *J. Am. Chem. Soc.* **2001**, *123*, 5260–5267; c) D. W. C. MacMillan, *Nature* **2008**, *455*, 304–308; for recent reviews, see also: d) P. I. Dalko, L. Moisan, *Angew. Chem. Int. Ed.* **2004**, *43*, 5138–5175; e) J. Seayad, B. List, *Org. Biomol. Chem.* **2005**, *3*, 719–724; f) A. Berkssel, H. Gröger, in: *Asymmetric Organocatalysis*, Wiley-VCH, Weinheim, **2005**; g) M. J. Gaunt, C. C. C. Johansson, A. McNally, N. C. Vo, *Drug Discovery Today* **2007**, *12*, 8–27; h) P. I. Dalko in *Enantioselective Organocatalysis*, Wiley-VCH, Weinheim, **2007**; i) B. List, *Chem. Rev.* **2007**, *107*, 5413–5415; j) H. Pellissier, *Tetrahedron* **2007**, *63*, 9267–9331; k) D. G. Blackmond, A. Armstrong, V. Coombe, A. Wells, *Angew. Chem. Int. Ed.* **2007**, *46*, 3798–3800.

[2] a) B.-L. Zheng, Q.-Z. Liu, C.-S. Guo, X.-L. Wang, L. He, *Org. Biomol. Chem.* **2007**, *5*, 2913–2915; b) S.-Z. Luo, H. Xu, J.-Y. Li, L. Zhang, J.-P. Chen, *J. Am. Chem. Soc.* **2007**, *129*, 3074–3075.

[3] G. Guillena, M. C. Nájera, D. J. Ramòn, *Tetrahedron: Asymmetry* **2007**, *18*, 2249–2293.

[4] a) M. Amedjkouh, *Tetrahedron: Asymmetry* **2005**, *16*, 1411–1414; b) A. Cordova, W. Zou, P. Dziedzic, I. Ibrahem, E. Reyes, Y. Xu, *Chem. Eur. J.* **2006**, *12*, 5383–5397; c) D. Deng, J. Cai, *Helv. Chim. Acta* **2007**, *90*, 114–120.

[5] a) G. Carrea, G. Ottolina, A. Lazcano, V. Pironti, S. Colonna, *Tetrahedron: Asymmetry* **2007**, *18*, 1265–1268; b) M. Lei, L. Shi, G. Li, S. Chen, W. Fang, Z. Ge, T. Cheng, R. Li, *Tetrahedron* **2007**, *63*, 7892–7898.

[6] a) G. N. Rolinson, A. M. Geddes, *Int. J. Antimicrob. Agents* **2007**, *29*, 3–8.

[7] A. Liese, K. Seelbach, C. Wandrey, *Industrial Biotransformations*, Wiley-VCH, Weinheim, **2000**.

[8] a) G. Cainelli, D. Giacomini, P. Galletti, A. Quintavalla, *Eur. J. Org. Chem.* **2003**, 1765–1774; b) G. Cainelli, D. Giacomini, P. Galletti, *Synthesis* **2000**, *2*, 289–294.

[9] a) K. Shokat, T. Uno, P. G. Schultz, *J. Am. Chem. Soc.* **1994**, *116*, 2261; b) M. Nakadai, S. Saito, H. Yamamoto, *Tetrahedron* **2002**, *58*, 8167–8177.

[10] F. S. Richardson, C. Y. Yeh, T. C. Troxell, D. B. Boyd, *Tetrahedron* **1977**, *33*, 711–721.

[11] K. Kóczián, Z. Szakács, J. Kökösi, B. Noszál, *Eur. J. Pharm: Sci.* **2007**, *32*, 1–7.

[12] a) A. Cordova, W. Zou, I. Ibrahem, E. Reyes, M. Engqvist, W.-W. Liao, *Chem. Commun.* **2005**, 3586–3588; b) A. Cordova, W. Zou, P. Dziedzic, I. Ibrahem, E. Reyes, Y. Xu, *Chem. Eur. J.* **2006**, *12*, 5383–5397.

[13] C. Allemann, R. Gordillo, F. R. Clemente, P.-H.-Y. Cheong, K. N. Houk, *Acc. Chem. Res.* **2004**, *37*, 558–569, and references cited therein.

[14] a) F. Tanaka, R. Thayumanavan, N. Mase, C. F. Barbas III, *Tetrahedron Lett.* **2004**, *45*, 325; b) A. Heine, G. DeSanctis, J. G. Luz, M. Mitchell, C.-H. Wong, I. A. Wilson, *Science* **2001**, *294*, 369; c) M. Amedjkouh, *Tetrahedron: Asymmetry* **2005**, *16*, 1411; d) Y. Hayashi, T. Itoh, N. Nagae, M. Okukub, H. Ishikawa, *SynLett* **2008**, 1565–1570; e) J. Zhou, V. Wakchaure, P. Kraft, B. List, *Angew. Chem. Int. Ed.* **2008**, *47*, 7656–7658.

[15] See, for instance: S. Mukherjee, J. W. Yang, S. Hoffmann, B. List, *Chem. Rev.* **2007**, *107*, 5471–5569.

[16] J. D. Revell, H. Wennemers, *Adv. Synth. Catal.* **2008**, *350*, 1046–1052.

[17] U. Das, A. Doroudi, S. Das, B. Bandy, J. Balzarini, E. De Clercq, J. R. Dimmock, *Bioorg. Med. Chem.* **2008**, *16*, 6261–6268.

[18] N. Mase, Y. Nakai, N. Ohara, H. Yoda, K. Takabe, F. Tanaka, C. F. Barbas III, *J. Am. Chem. Soc.* **2006**, *128*, 734–735.

[19] M. Gruttadauria, F. Giacalone, A. Mossuto Marculescu, P. Lo Meo, S. Riela, R. Noto, *Eur. J. Org. Chem.* **2007**, 4688–4698.

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