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Sulfonamides of homoproline and dipeptides as organocatalysts for Michael and aldol reactions

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ABSTRACT

Sulfonamides of the non-natural amino acid homoproline and the dipeptide Pro–Phe were synthesised and evaluated for their catalytic activity in Michael and aldol reactions. Sulfonamides of homoproline outperform proline and Pro–Phe in the Michael reaction, whereas sulfonamides of Pro–Phe lead to better results in the aldol reaction. The results of the present study show that the conversion of the carboxylic group of either homoproline or dipeptide Pro–Phe to the bioisosteric acyl sulfonamide group lead to improved organocatalysts.

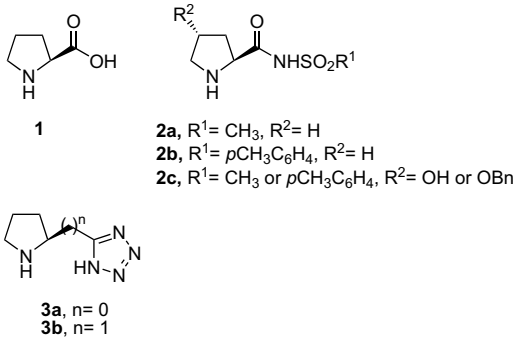
1. Introduction

During the last few years organocatalysis has emerged as a powerful tool in modern organic synthesis.[1] Since the pioneering work of List et al. on the application of the amino acid proline as a catalyst for the aldol reaction (**1**, Fig. 1),[2] a number of organocatalysts have been synthesised and employed in various organic transformations.[3] Recently, we and others have shown that acyl sulfonamides of proline (**2a**, **b**) and 4-substituted proline (**2c**) are excellent organocatalysts for the asymmetric aldol reaction.[4–7] The tetrazolyl derivative of proline (**3a**) was also studied as an organocatalyst for the aldol reaction.[7,8] In addition, homoproline[9] and homoproline tetrazole[10] (**3b**) have been reported to give improved results as catalysts for the Michael reaction.

Apart from amino acids and amino acid derivatives, peptides have also been employed successfully as organocatalysts in a number of reactions.[11] The reaction that peptides are most commonly used as catalysts is the aldol reaction.[12] In particular, dipeptide Pro–Phe was used in the aldol reaction of acetone with 4-nitrobenzaldehyde leading to high yield but moderate enantioselectivity.[12d] Furthermore, in the same reaction, the dipeptide Pro–Phe–OMe led to high yield but with lower enantioselectivity.[13] Continuing our work on acyl sulfonamide derivatives[4] and 4-substituted proline derivatives,[14,15] the aim of the present work was to synthesise sulfonamide derivatives of homoproline and sulfonamide derivatives of the dipeptide Pro–Phe–OH and evaluate their ability to catalyse Michael and aldol reactions.

2. Results and discussion

The synthesis of homoproline sulfonamides is depicted in Scheme 1. *tert*-Butoxycarbonyl-L-homoproline (**4**), prepared according to a literature procedure,[16] was coupled with methanesulfonamide and *p*-toluenesulfonamide using *N*,*N*′-dicyclohexylcarbodiimide (DCC) as a coupling reagent in the presence of 4-(dimethylamine)-pyridine (DMAP)[4] in dichloromethane to produce derivatives **5a**, **b**.



1

2a, R^1= CH_3, R^2= H
2b, R^1= $pCH_3C_6H_4$, R^2= H
2c, R^1= CH_3 or $pCH_3C_6H_4$, R^2= OH or OBn

3a, n= 0
3b, n= 1

Figure 1. Structures of proline and related organocatalysts.

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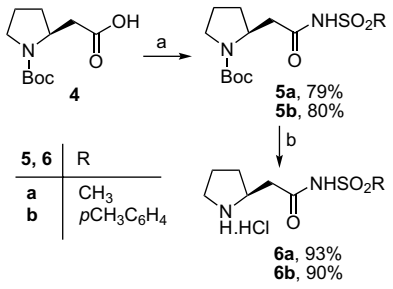
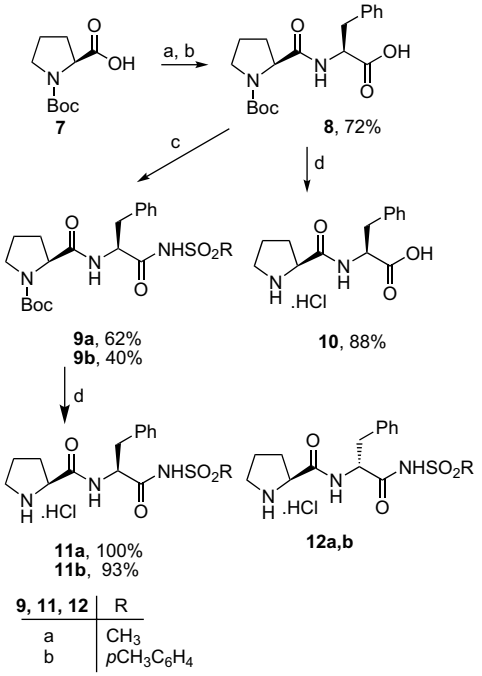
Removal of the Boc protecting group by treatment with HCl in MeOH afforded homoprolyl sulfonamides **6a**, **b** in almost quantitative yield.



Scheme 1. Reagents and conditions: (a) methanesulfonamide or *p*-toluenesulfonamide, DCC, DMAP, DCM, rt, 48 h; (b) 5 N HCl/MeOH, rt, 30 min.

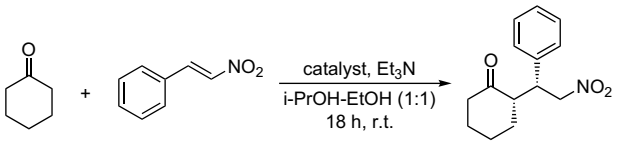
Boc-Proline (**7**) was coupled with the methyl ester of L-phenylalanine in good yield using 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide (WSCI) as a condensing agent in the presence of 1-hydroxybenzotriazole (HOBt) (Scheme 2). After saponification, dipeptide **8** was coupled with methanesulfonamide in the presence of DCC and DMAP to afford sulfonamide **9a** or with *p*-toluenesulfonamide to afford sulfonamide **9b** in respectable yields. Dipeptide **10** was prepared by treatment of **8** with a methanolic solution of HCl and was used in our study as a test organocatalyst in the aldol reaction of acetone with 4-nitrobenzaldehyde. Sulfonamides **9a** and **9b** were also deprotected with a methanolic solution of HCl to afford organocatalysts **11a** and **11b** in almost quantitative yields. To study the role of the chiral centre of the dipeptide in the asymmetric transformations, we also synthesised dipeptides **12a** and **12b** containing D-phenylalanine by similar procedures.



Scheme 2. Reagents and conditions: (a) (L)-Phe–OMe, WSCI, HOBt, Et_3N, CH_2Cl_2, 0 °C, 1 h, then rt for 18 h; (b) 1 N NaOH, MeOH, rt, 18 h; (c) methanesulfonamide or *p*-toluenesulfonamide, DCC, DMAP, CH_2Cl_2, rt, 18 h; (d) 5 N HCl/MeOH, rt, 1 h.

The asymmetric Michael addition of carbonyl compounds to nitro-olefins is a useful synthetic transformation.[17] First, the Michael reaction between cyclohexanone and β-nitrostyrene was studied and the results are summarised in Table 1. L-Proline is known to catalyse this reaction in high yields but low selectivities.[18] Indeed, in our hands the product was isolated in 89% yield with a 15:1 dr and low ee (entry 1, Table 1). In all cases where sulfonamides of homoproline or dipeptide Pro–Phe were utilised, the diastereoselectivity of the reaction was extremely high >19:1 (entries 2–8, Table 1). The methanesulfonamide of homoproline (**6a**) gave the best results among the catalysts used in this study. As we observed, the loading of the catalyst was crucial for the reaction yield and enantioselectivity (entries 2–4, Table 1). After identifying 10% catalyst loading as the optimal for the reaction, the effect of the temperature was studied leading to similar results as far as selectivities are concerned but a lower yield was obtained (entry 5, Table 1). Sulfonamide **6b** afforded the product in high diastereo- and enantioselectivities but in low yields in all cases (entries 6 and 7, Table 1). Finally, dipeptide methanesulfonamide **11a** was also tested, leading to low yield and enantioselectivity (entry 8, Table 1). Thus, using methanesulfonamide **6a** at 10% catalyst loading and at room temperature, the product of the reaction between cyclohexanone with β-nitrostyrene was obtained in good yield, excellent diastereoselectivity and high enantioselectivity. The enantioselectivity is far higher than that observed with proline and comparable to that using tetrazolyl homoproline as a catalyst.[10] It should be noticed that homoproline by itself cannot catalyse this particular Michael reaction.[10]

Table 1
Michael reaction of cyclohexanone with β-nitrostyrene using sulfonamide organocatalysts

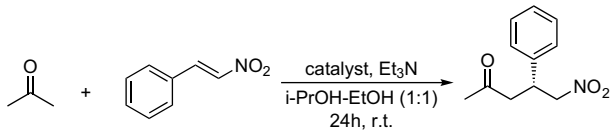


Entry	Catalyst	Catalyst loading (%)	Yield[a] (%)	dr[b]	ee[c] (%)
1	(L)-Pro[d,e]	15	89	15:1	25
2	**6a**	20	70	>19:1	83
3	**6a**	10	64	>19:1	90
4[f]	**6a**	5	16	>19:1	84
5[g]	**6a**	10	33	>19:1	92
6	**6b**	20	21	>19:1	79
7	**6b**	10	19	>19:1	81
8	**11a**	10	33	>19:1	13

[a] Isolated yield after column chromatography.
[b] The dr was measured from the ^1H NMR spectrum of the crude mixture.
[c] The ee was determined by HPLC on a Daicel Chiralpak AD-H column.
[d] In the absence of Et_3N.
[e] Using DMSO as solvent.
[f] The reaction time was 48 h.
[g] The reaction was carried out at −20 °C for 48 h.

The reaction of acetone with β-nitrostyrene using sulfonamides of homoproline as catalysts was also studied (Table 2). Under the reaction conditions used (see Table 2), the addition product was obtained in very low ee, when proline was used at 20% catalyst loading in accordance with the literature data[18] (entry 1, Table 2). However, at the same catalyst loading sulfonamides **6a** and **6b** gave the products in high yields and outperformed proline in the context of enantioselectivity (entries 2 and 6, Table 2). The effect of the catalyst loading on the conversion and enantioselectivity for this Michael reaction was also studied (entries 2–5, Table 2). The use of methanesulfonamide of homoproline (**6a**) led to the formation of the product in 87% yield and 48% ee, when 5% catalyst loading was employed (entry 4, Table 2). At an even lower catalyst loading both yield and enantioselectivity dropped (entry 5, Table 2). Catalyst **6b** in lower loadings led to significant decreased yields (entries 7 and 8, Table 2).

Table 2
Michael reaction of acetone with β-nitrostyrene using derivatives of homoproline as catalysts



Entry	Catalyst	Catalyst loading (%)	Yield[a] (%)	ee[b] (%)
1	L-Pro[c]	20	63	7
2	**6a**	20	88	13
3	**6a**	10	84	30
4	**6a**	5	87	48
5	**6a**	2	68	29
6	**6b**	20	70	16
7	**6b**	10	15	42
8	**6b**	5	8	38

[a] Isolated yield after column chromatography.
[b] The ee was determined by HPLC on a Daicel Chiralpak AD-H column.
[c] In the absence of Et_3N.

As described in the literature, under the same conditions the Michael product of the reaction between acetone and β-nitrostyrene was obtained in 68% yield and 42% ee, when the tetrazole analogue of homoproline **3b** was used as a catalyst.[10] Using homoproline as a catalyst in different solvents, the product was isolated in 5–88% yield and 13–42% ee.[9] Homoprolyl methanesulfonamide **6a** leads to better yield and enantioselectivity in comparison to tetrazolyl catalyst **3b**, clearly indicating that the conversion of the carboxyl group into sulfonamide functionality provides results at least comparable or even better than those obtained by the tetrazole functionality. However, according to recent findings a chiral thiourea may catalyse the reaction between acetone and β-nitrostyrene giving the product in both high yield and enantioselectivity.[19]

Two possible transition states have been proposed to explain the enantioselectivity observed in Michael additions catalysed by proline derivatives.[10,20,21] In accordance with those literature data, two similar frameworks may be proposed for homoprolyl sulfonamides (Fig. 2). In both models, an electrostatic interaction between the nitro group and the nitrogen of the enamine is involved. The first model (A) suggests that it may be an extended hydrogen-bonded transition state. The second model (B) proposes that the selectivity is determined by the steric hindrance of the pyrrolidine ring substituent.

The reaction of acetone with 4-nitrobenzaldehyde is a usual model reaction to study the efficacy of dipeptide sulfonamides organocatalysts. L-Proline is known to catalyse this reaction in good yield and enantioselectivity. In our hands, when L-proline was used as a catalyst in DMSO for 18 h, the product was obtained in 73% yield and 73% ee (entry 1, Table 3). Both sulfonamides of homoproline **6a** and **6b** led to decreased yields and enantioselectivities (entries 2 and 3, Table 3). We and others have previously shown that proline sulfonamides **2a** and **2b** outperform proline in the aldol reaction between acetone and *p*-nitrobenzaldehyde.[4,7] The

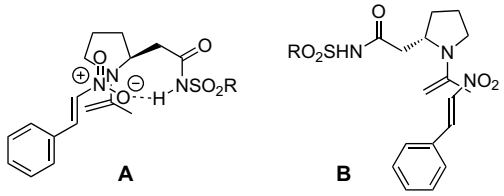
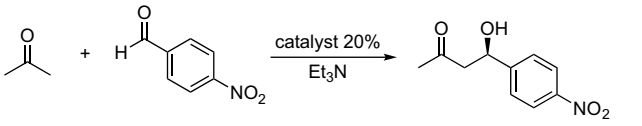


Figure 2. Transition state models for the reaction of acetone with β-nitrostyrene.

Table 3
Direct asymmetric aldol reaction of acetone with 4-nitrobenzaldehyde using sulfonamide catalysts



Entry	Catalyst	Solvent	Reaction time (h)	Temperature	Yield[a] (%)	ee[b] (%)
1	L-Pro[c]	DMSO	18	rt	73	73
2	**6a**	DMSO	18	rt	68	44
3	**6b**	DMSO	18	rt	47	35
4	**10**	DMSO	18	rt	62	27
5	**10**[d]	DMSO	18	rt	61	54
6	**10**[d]	DMSO	48	rt	64	54
7	**10**	CH_2Cl_2	18	rt	67	34
8	**11a**	CH_2Cl_2	18	rt	74	77
9	**11a**	DMSO	48	rt	40	79
10	**11b**	CH_2Cl_2	18	rt	72	61
11	**11b**	DMSO	18	rt	29	84
12	**12a**	CH_2Cl_2	18	rt	62	31
13	**12b**	CH_2Cl_2	18	rt	47	37
14	**11a**	Acetone	18	rt	65	77
15	**11a**	Toluene	18	rt	57	48
16	**11a**	MeOH	18	rt	56	38
17	**11a**	H_2O	18	rt	81	10
18	**11a**	DMSO	48	0 °C	10	80
19	**11a**	CH_2Cl_2	48	−20 °C	79	84
20	**11a**[d]	CH_2Cl_2	48	−20 °C	82	82
21	**11a**[e]	CH_2Cl_2	48	−20 °C	48	77
22	**11a**[f]	CH_2Cl_2	48	−20 °C	49	87
23	**11a**	CH_2Cl_2	48	−78 °C	13	74
24	**11a**	Acetone	48	−20 °C	35	75
25	**11a**	Acetone	48	−78 °C	16	73
26	**11b**	CH_2Cl_2	48	−20 °C	60	75

[a] Isolated yield after column chromatography.
[b] The ee was determined by HPLC on a Daicel Chiralpak AD-RH column.
[c] In the absence of Et_3N.
[d] In the presence of NMM instead of Et_3N.
[e] Catalyst loading: 10%.
[f] Catalyst loading: 5% .

results obtained in the present study for the homoproline sulfonamides **6a** and **6b** indicate that increase of the distance between the sulfonamide group and the pyrrolidine scaffold by one carbon atom leads to a substantial decrease in both yield and enantioselectivity in this particular aldol reaction. Probably the formation of the hydrogen bond network is disfavoured. This is in plain contrast to the beneficial effect of the longer distance between the sulfonamide group and the pyrrolidine scaffold observed in this study for the Michael reaction.

Although dipeptide **10** is known to catalyse this reaction in high yield but with moderate enantioselectivity,[12d] our attempts failed to reproduce this result in DMSO and the product was obtained in moderate yield (62%) and low enantiomeric excess (entry 4, Table 3). When *N*-methyl morpholine (NMM) was used as a base, the yield did not improve but the enantiomeric excess increased, in accordance with the literature[12d] (entry 5, Table 3). The reaction time as well as the change of solvent did not improve either the yield or the selectivity (entries 6 and 7, Table 3). When the novel organocatalysts **11a** and **11b** were used, the yield was highly dependent on the solvent of the reaction. Using methanesulfonamide **11a** in dichloromethane for 18 h at room temperature, the product was obtained in 74% yield and 77% ee, while when DMSO was used as a solvent and even at prolonged reaction times, the yield dropped to 40% with an enantiomeric excess of 79% (entries 8 and 9, Table 3). When sulfonamide **11b** was used in dichloromethane the product was produced in 72% yield and 61% ee, while in DMSO the yield was far lower (29%) and the enantiomeric excess was

increased (84%, entries 10 and 11, Table 3). When the diastereomeric sulfonamides **12a** and **12b** were used, both yield and enantiomeric excess dropped significantly (entries 12 and 13, Table 3). Methanesulfonamide **12a** containing D-phenylalanine afforded the product in 62% yield and in 31% ee, while sulfonamide **12b** gave similar results (47% yield, 37% ee). It is quite clear that the asymmetric efficacy of the catalyst also depends on the chirality of the second amino acid of the catalyst and the (*S*)-configuration leads to better results. Since sulfonamide **11a** afforded the best results as far as both yield and enantioselectivity are concerned, we decided to study the effect of the solvent in the catalytic efficiency of **11a** (entries 14–17, Table 3). When acetone was used, the yield dropped slightly (65%) but the enantiomeric excess was the same (77%, entry 14, Table 3). Toluene as well as methanol proved to give lower yields and ees (entries 15 and 16, Table 3), while water afforded the product in good yield (81%) but in very low ee (entry 17, Table 3). The effect of the temperature was also studied (entries 18–26, Table 3). When DMSO was used with sulfonamide **11a** at 0 °C, the yield was decreased (10%) but the enantiomeric excess was almost the same (80%, entry 18 vs entry 9, Table 3). Sulfonamide **11a** in dichloromethane afforded the best results, so it was decided to drop the temperature and extend the reaction time. At −20 °C the product was obtained in higher yield (79%) and improved enantiomeric excess (84%, entry 19, Table 1). Earlier, we had observed that in the case of dipeptide **10** when *N*-methyl morpholine was used instead of triethylamine as a base, an increase in the enantioselectivity was observed (entry 5 vs entry 4, Table 3). Thus, we decided to explore whether the change of the base had any significant implication with sulfonamide **11a** (entry 20, Table 3); however, similar results were obtained. When the catalyst loading was decreased, the yield dropped, while the enantioselectivity was maintained at the same levels (entries 21 and 22, Table 3). When the temperature was dropped down to −78 °C, the yield was significantly decreased, while the ee was maintained at the same levels (entry 23, Table 3). In acetone, low temperatures led to decreased yield, while the enantiomeric excess was left intact (entries 24 and 25, Table 3). Finally, sulfonamide **11b** was also used in dichloromethane at −20 °C leading to decreased yield (60%) and increased selectivity (entry 26 vs entry 10, Table 1).

From the results of Table 3 and in accordance with the results observed for the Michael reaction, the conversion of the carboxylic group of Pro–Phe into the methanesulfonamide functionality has a profound effect in the enantioselectivity in the aldol reaction between acetone and *p*-nitrobenzaldehyde. Fine tuning of solvent and temperature showed that CH_2Cl_2 and −20 °C are optimal for this reaction. Similarly as in the Michael reaction, the higher selectivities obtained in the aldol reaction using sulfonamides of dipeptide Pro–Phe can be attributed to the extended hydrogen bonding between the carbonyl group of 4-nitrobenzaldehyde and the NHs of dipeptide sulfonamides (Fig. 3). To the best of our knowledge, this is the first example of dipeptide sulfonamides used as organocatalysts.

In conclusion, the results of the present study show that the conversion of the carboxyl group of either homoproline or dipeptide Pro–Phe to the bioisosteric acyl sulfonamide group lead to improved organocatalysts. Using methanesulfonamide of homoproline, the Michael addition product of cyclohexanone to β-nitrostyrene was obtained in high chemical yield, high diastereoselectivity and enantioselectivity, whereas the product of the reaction between acetone and β-nitrostyrene was produced in high yield and moderate enantioselectivity. However, even in this case, the sulfonamide of homoproline outperformed proline itself as a catalyst. Methanesulfonamide of the dipeptide Pro–Phe was also proved better catalyst in comparison to either proline or the dipeptide Pro–Phe in the aldol reaction between acetone and *p*-nitrobenzaldehyde.

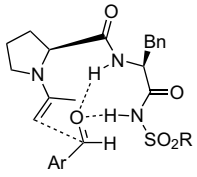


Figure 3. Proposed transition state model for the reaction of acetone with β-nitrostyrene.

3. Experimental

3.1. General

All chemicals were purchased from Aldrich, Fluka or Alfa. Anhydrous solvents were prepared according to the literature known procedures. Flash chromatography was performed on silica gel (Merck Kieselgel 60 F_{254} 230–400 mesh). TLC was performed on aluminium backed silica plates (0.2 mm, 60 F_{254}), which were developed using standard visualising agents: UV fluorescence (254 and 366 nm), phosphomolybdic acid/Δ, anisaldehyde/Δ. Melting points were determined on a Buchi 530 hot stage apparatus. ^{1}H NMR spectra were recorded at 200 MHz Varian Mercury instrument. Chemical shifts (δ_H) are quoted in parts per million (ppm), referenced to $CDCl_3$. ^{13}C NMR spectra were recorded at 50 MHz Varian Mercury instrument. Chemical shifts (δ_C) are quoted in parts per million (ppm), referenced to the appropriate solvent peak. Where rotamers are apparent and resolved, peaks for major and minor rotamers are reported. IR spectra were recorded on a Nicolet IR6700 FT-IR spectrometer. Only selected absorbencies (ν_{max}) are reported. Mass spectra were recorded on a Finnigan Surveyor MSQ Plus, with only molecular ions (M^+ or MH^+) and major peaks being reported with intensities quoted as percentages of the base peak.

3.2. General procedure for the coupling of a carboxylic acid with methanesulfonamide or *p*-toluenesulfonamide

To a stirring solution of carboxylic acid (1 mmol) in CH_2Cl_2 (10 mL), DCC (206 mg, 1 mmol), the corresponding sulfonamide (1 mmol) and DMAP (122 mg, 1 mmol) were added consecutively. The reaction mixture was left stirring for 18 h at room temperature. After filtration, the solvent was removed and the residue was purified by column chromatography eluting with the appropriate CH_2Cl_2/MeOH mixture to give the product.

*3.2.1. (S)-tert-Butyl-2-[2-(methylsulfonamido)-2-oxoethyl]-pyrrolidine-1-carboxylate (**5a**)*

White solid (242 mg, 79%); mp 49–50 °C; $[\alpha]_D^{25}$ +43.9 (*c* 1, $CHCl_3$); IR (KBr, cm^{-1}) 1720, 1332, 1167; ^{1}H NMR (200 MHz, $CDCl_3$) δ 10.84–10.67 (br s, 1H, NH), 4.17–4.06 (m, 1H, CH), 3.33 (t, *J*=6.0 Hz, 2H, NCH_2), 3.25 (s, 3H, CH_3), 2.79 (dd, *J*=14.0 and 4.0 Hz, 1H, COC*H*H), 2.39 (dd, *J*=14.0 and 8.0 Hz, 1H, COC*H*H), 2.12–1.97 (m, 1H, C*H*H), 1.96–1.73 (m, 3H, 3×C*H*H), 1.45 [br s, 9H, $C(CH_3)_3$]; ^{13}C NMR (50 MHz, $CDCl_3$) δ 171.0 (CONH), 155.7 (OCONH), 80.8 [*C*(CH_3)], 54.4 (CH), 46.9 (NCH_2), 42.9 (CH_2CO), 41.5 (SO_2CH_3), 31.7 (CH_2CH_2CH), 28.7 [C(CH_3)], 23.6 (CH_2CH_2CH); MS (ESI): *m*/*z* (%) 305 (100) $[M-H]^-$. Anal. Calcd for $C_{12}H_{22}N_2O_5S$: C, 47.04; H, 7.24; N, 9.14. Found: C, 46.85; H, 7.33; N, 9.03.

*3.2.2. (S)-tert-Butyl-2-[2-(4-methylphenylsulfonamido)-2-oxoethyl]pyrrolidine-1-carboxylate (**5b**)*

White solid (306 mg, 80%); mp 52–54 °C; $[\alpha]_D^{25}$ +27.9 (*c* 1, $CHCl_3$); IR (KBr, cm^{-1}) 1726, 1337, 1174; ^{1}H NMR (200 MHz, $CDCl_3$) δ 10.73–10.47 (br s, 1H, NH), 7.90 (d, *J*=8.2 Hz, 2H, Ar),

7.28 (d, *J*=8.2 Hz, 2H, Ar), 4.07–3.95 (m, 1H, CH), 3.35–3.16 (m, 2H, NCH_2), 2.72 (dd, *J*=15.8 and 4.2 Hz, 1H, COC*H*H), 2.39 (s, 3H, CH_3), 2.34 (dd, *J*=15.8 and 7.8 Hz, 1H, COC*H*H), 2.03–1.87 (m, 1H, C*H*H), 1.84–1.62 (m, 3H, 3×C*H*H), 1.42 [br s, 9H, $C(CH_3)_3$]; ^{13}C NMR (50 MHz, $CDCl_3$) δ 169.7 (CONH), 155.9 (OCONH), 144.9 (Ar), 136.3 (Ar), 129.6 (Ar), 128.5 (Ar), 80.6 [*C*(CH_3)], 54.2 (CH), 46.8 (NCH_2), 42.4 (*C*H_2CO), 31.6 (CH_2CH_2CH), 28.7 [C(*C*H_3)], 23.5 (CH_2CH_2CH), 21.8 (CH_3); MS (ESI): *m*/*z* (%) 381 (100) $[M-H]^-$. Anal. Calcd for $C_{18}H_{26}N_2O_5S$: C, 56.52; H, 6.85; N, 7.32. Found: C, 56.21; H, 6.98; N, 7.21.

*3.2.3. (S)-tert-Butyl-2-[(S)-1-(methylsulfonamido)-1-oxo-3-phenylpropan-2-ylcarbamoyl]pyrrolidine-1-carboxylate (**9a**)*

White solid (272 mg, 62%); mp 78–79 °C; $[\alpha]_D^{25}$ −45.9 (*c* 1, CH_2Cl_2); IR (KBr, cm^{-1}) 1719, 1679, 1339, 1142; ^1H NMR (200 MHz, $CDCl_3$) δ 10.44–10.11 (br s, 1H, NH), 7.36–7.03 (m, 5H, Ar), 6.91 (br d, *J*=8.0 Hz, 1H, NHCO), 4.87–4.69 (m, 1H, CH), 4.29–4.02 (m, 1H, CH), 3.38–3.21 (m, 3H, NCH_2 and C*H*H), 3.16–2.96 (m, 4H, CH_3 and C*H*H), 2.13–1.52 (m, 4H, 4×C*H*H), 1.37 [br s, 9H, $C(CH_3)_3$]; ^{13}C NMR (50 MHz, $CDCl_3$) δ 173.6 (CONH), 173.0 (CONH), 155.4 (155.3) (OCONH), (136.0) 135.8 (Ar), 129.5 (Ar), 128.9 (Ar), 127.5 (127.4) (Ar), 81.5 (81.0) [*C*(CH_3)], 60.9 (60.5) (CH), (54.9) 54.4 (CH), 47.3 (NCH_2), 41.3 (SO_2CH_3), 37.4 (CH_2Ph), 29.8 (29.7) (CH_2CH_2CH), 28.5 (28.4) [C(*C*H_3)], 24.6 (*C*H_2CH_2CH); MS (ESI): *m*/*z* (%) 438 (100) $[M-H]^-$. Anal. Calcd for $C_{20}H_{29}N_3O_6S$: C, 54.65; H, 6.65; N, 9.56. Found: C, 54.33; H, 6.84; N, 9.46.

*3.2.4. (S)-tert-Butyl-2-[(S)-1-(4-methylphenylsulfonamido)-1-oxo-3-phenylpropan-2-ylcarbamoyl]pyrrolidine-1-carboxylate (**9b**)*

White solid (206 mg, 40%); mp 83–84 °C; $[\alpha]_D^{25}$ −43.0 (*c* 1, CH_2Cl_2); IR (KBr, cm^{-1}) 1726, 1680, 1344, 1162; ^1H NMR (200 MHz, $CDCl_3$) δ 10.49–10.00 (br s, 1H, NH), 7.89 (d, *J*=8.0 Hz, 2H, Ar), 7.27 (d, *J*=8.0 Hz, 2H, Ar), 7.22–7.08 (m, 3H, Ar), 7.02–6.89 (m, 2H, Ar), 6.73 (br d, *J*=8.0 Hz, 1H, NHCO), 4.92–4.67 (m, 1H, CH), 4.28–4.09 (m, 1H, CH), 3.42–3.19 (m, 2H, 2×C*H*H), 3.08–2.89 (m, 2H, 2×C*H*H), 2.40 (s, 3H, CH_3), 2.07–1.63 (m, 4H, 4×C*H*H), 1.39 [br s, 9H, $C(CH_3)_3$]; ^{13}C NMR (50 MHz, $CDCl_3$) δ 172.5 (CONH), 169.9 (CONH), 155.5 (OCONH), 144.9 (Ar), 136.1 (Ar), 135.6 (Ar), 129.6 (Ar), 129.4 (Ar), 128.9 (Ar), 128.8 (Ar), 127.4 (Ar), 81.6 (81.1) [*C*(CH_3)], 60.9 (60.7) (CH), (54.3) 53.7 (CH), 47.3 (NCH_2), 37.3 (CH_2Ph), 29.9 (29.6) (CH_2CH_2CH), 28.5 [C(*C*H_3)], 24.8 (*C*H_2CH_2CH), 21.8 (CH_3); MS (ESI): *m*/*z* (%) 538 (100) $[M+Na]^+$. Anal. Calcd for $C_{26}H_{33}N_3O_6S$: C, 60.56; H, 6.45; N, 8.15. Found: C, 60.38; H, 6.52; N, 8.04.

3.3. General procedure for the deprotection of Boc group

To a stirring solution of Boc protected compound (0.80 mmol) in MeOH (2 mL), a methanolic solution of HCl 6 N (6.7 mL) was added. The reaction mixture was left stirring for 1 h at room temperature. The solvent was removed in vacuo, methanol (5×10 mL) was added and the solvent was removed in vacuo. The residue was recrystallised from MeOH/cold Et_2O to afford the product.

*3.3.1. (S)-N-(Methylsulfonyl)-2-(pyrrolidin-2-yl)acetamide hydrochloride (**6a**)*

White solid (180 mg, 93%); mp 246–247 °C; $[\alpha]_D^{25}$ +39.2 (*c* 1, CH_3OH); IR (KBr, cm^{-1}) 1718, 1330, 1169; ^1H NMR (200 MHz, CD_3OD) δ 3.96–3.80 (m, 1H, CH), 3.34–3.27 (m, 2H, NCH_2), 3.26 (s, 3H, CH_3), 2.95 (dd, *J*=17.2 and 4.2 Hz, 1H, COC*H*H), 2.77 (dd, *J*=17.2 and 8.6 Hz, 1H, COC*H*H), 2.34–2.18 (m, 1H, C*H*H), 2.12–1.88 (m, 2H, 2×C*H*H), 1.80–1.62 (m, 1H, C*H*H); ^{13}C NMR (50 MHz, CD_3OD) δ 171.2 (CONH), 55.9 (CH), 45.4 (NCH_2), 40.3 (SO_2CH_3), 37.4 (*C*H_2CO), 29.9 (CH_2CH_2CH), 23.4 (*C*H_2CH_2CH); MS (ESI): *m*/*z* (%) 207 (100) $[M+H]^+$. Anal. Calcd for $C_7H_{15}N_2O_3SCl$: C, 34.64; H, 6.23; N, 11.54. Found: C, 34.42; H, 6.48; N, 11.37.

*3.3.2. (S)-N-(4-Methylphenylsulfonyl)-2-(pyrrolidin-2-yl)-acetamide hydrochloride (**6b**)*

White solid (229 mg, 90%); mp 192–194 °C; $[\alpha]_D^{25}$ +41.0 (*c* 1, CH_3OH); IR (KBr, cm^{-1}) 1724, 1339, 1174; ^1H NMR (200 MHz, CD_3OD) δ 7.86 (d, *J*=8.2 Hz, 2H, Ar), 7.35 (d, *J*=8.2 Hz, 2H, Ar), 3.79–3.62 (m, 1H, CH), 3.48–3.11 (m, 2H, NCH_2), 2.81 (dd, *J*=17.4 and 3.8 Hz, 1H, COC*H*H), 2.64 (dd, *J*=17.4 and 9.4 Hz, 1H, COC*H*H), 2.39 (s, 3H, CH_3), 2.03–1.49 (m, 4H, 4×C*H*H); ^{13}C NMR (50 MHz, CD_3OD) δ 169.5 (CONH), 145.0 (Ar), 136.8 (Ar), 129.3 (Ar), 128.1 (Ar), 55.9 (CH), 45.4 (NCH_2), 37.4 (*C*H_2CO), 29.9 (CH_2CH_2CH), 23.2 (*C*H_2CH_2CH), 20.3 (CH_3); MS (ESI): *m*/*z* (%) 283 (100) $[M+H]^+$. Anal. Calcd for $C_{13}H_{19}N_2O_3SCl$: C, 48.97; H, 6.01; N, 8.79. Found: C, 48.67; H, 6.28; N, 8.62.

*3.3.3. (S)-N-[(S)-1-(Methylsulfonamido)-1-oxo-3-phenylpropan-2-yl]pyrrolidine-2-carboxamide hydrochloride (**11a**)*

White solid (300 mg, 100%); mp 135–136 °C; $[\alpha]_D^{25}$ −17.6 (*c* 1, CH_3OH); IR (KBr, cm^{-1}) 1718, 1677, 1337, 1140; ^1H NMR (200 MHz, CD_3OD) δ 7.36–7.12 (m, 5H, Ar), 4.79–4.59 (m, 1H, CH), 4.29–4.14 (m, 1H, CH), 3.74–2.87 (m, 7H, CH_3 and 4×C*H*H), 2.28–1.42 (m, 4H, 4×C*H*H); ^{13}C NMR (50 MHz, CD_3OD) δ (172.9) 172.6 (CONH), 169.9 (169.5) (CONH), (137.9) 137.3 (Ar), 130.4 (130.3) (Ar), 129.6 (129.5) (Ar), 128.2 (128.0) (Ar), 60.9 (60.8) (CH), 56.9 (55.0) (CH), 48.2 (47.5) (NCH_2), 43.3 (41.4) (SO_2CH_3), 38.5 (38.0) (CH_2Ph), 31.2 (31.1) (CH_2CH_2CH), 25.0 (24.7) (*C*H_2CH_2CH); MS (ESI): *m*/*z* (%) 340 (100) $[M+H]^+$. Anal. Calcd for $C_{15}H_{22}N_3O_4SCl$: C, 47.93; H, 5.90; N, 11.18. Found: C, 47.64; H, 6.18; N, 11.03.

*3.3.4. (S)-N-[(S)-1-(4-Methylphenylsulfonamido)-1-oxo-3-phenylpropan-2-yl]pyrrolidine-2-carboxamide hydrochloride (**11b**)*

White solid (336 mg, 93%); mp 110–113 °C; $[\alpha]_D^{25}$ −18.6 (*c* 1, CH_3OH); IR (KBr, cm^{-1}) 1724, 1677, 1343, 1159; ^1H NMR (200 MHz, CD_3OD) δ 7.83 (d, *J*=8.2 Hz, 2H, Ar), 7.37 (d, *J*=8.2 Hz, 2H, Ar), 7.27–7.05 (m, 5H, Ar), 4.73–4.51 (m, 1H, CH), 4.21–4.11 (m, 1H, CH), 3.75–3.67 (m, 1H, C*H*H), 3.32–3.19 (m, 1H, C*H*H), 3.01 (dd, *J*=14.0 and 5.8 Hz, 1H, PhC*H*H), 2.80 (dd, *J*=14.0 and 8.2 Hz, 1H, PhC*H*H), 2.41 (s, 3H, CH_3), 2.08–1.79 (m, 4H, 4×C*H*H); ^{13}C NMR (50 MHz, CD_3OD) δ 170.5 (170.4) (CONH), 168.6 (168.4) (CONH), 145.1 (Ar), 136.5 (Ar), 136.1 (135.9) (Ar), 129.5 (Ar), 129.2 (Ar), 128.4 (Ar), 128.1 (Ar), 126.9 (Ar), 59.8 (59.6) (CH), 55.7 (54.9) (CH), 46.4 (46.3) (NCH_2), (37.4) 36.9 (CH_2Ph), (30.1) 29.9 (CH_2CH_2CH), 23.7 (23.7) (*C*H_2CH_2CH), 20.6 (CH_3); MS (ESI): *m*/*z* (%) 416 (100) $[M+H]^+$. Anal. Calcd for $C_{21}H_{26}N_3O_4SCl$: C, 55.81; H, 5.80; N, 9.30. Found: C, 55.57; H, 5.98; N, 9.13.

3.4. General procedure for the Michael reaction of cyclohexanone with β-nitrostyrene catalysed by methanesulfonamides or *p*-toluenesulfonamides

To a suspension of catalyst (depending on the catalyst loading) in a mixture of isopropanol and ethanol (1:1) (1 mL) was added triethylamine (equimolar amount with the catalyst). *trans*-β-Nitrostyrene (37.3 mg, 0.25 mmol) was added followed by cyclohexanone (0.04 mL, 0.38 mmol). The resulting mixture was allowed to stir at room temperature for 18 h and the solvents were evaporated in vacuo. EtOAc (10 mL) was added and the organic layer was washed with a saturated solution of NH_4Cl (2×10 mL). The combined aqueous layers were extracted with EtOAc (5×10 mL). The combined organic layers were dried (Na_2SO_4), and the solvent was removed in vacuo. The residue was purified by column chromatography eluting with a mixture of petroleum ether 40–60/EtOAc 80:20 affording the product as a white solid.

3.4.1. (S)-2-[(R)-3-Nitro-1-phenylethyl]cyclohexanone[18]

^{1}H NMR (200 MHz, $CDCl_3$) δ 7.38–7.05 (m, 5H, Ar), 4.93 (dd, J=12.5 and 4.5 Hz, 1H, C*H*HNO_2), 4.59 (dd, J=12.5 and 9.9 Hz, 1H, C*H*HNO_2), 3.76 (m, 1H, CHPh), 2.69 (m, 1H, CHCO), 2.50–2.35 (m, 2H, CHH), 2.16–2.05 (m, 1H, C*H*H), 1.81–1.52 (m, 4H, 4×C*H*H), 1.32–1.16 (m, 1H, C*H*H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 212.2 (CO), 138.0 (Ar), 129.1 (Ar), 128.4 (Ar), 127.9 (Ar), 79.1 (CH_2NO_2), 52.7 (*C*HCO), 44.2 (*C*H_2CO), 42.9 (CHPh), 33.4 (CH_2), 28.8 (CH_2), 25.2 (CH_2); HPLC analysis: Daicel Chiralpak AD-H, hexane/*i*-PrOH 95:5, flow rate 1 mL/min, retention time: 14.06 (minor) and 17.7 (major).

3.5. General procedure for the Michael reaction of acetone with β-nitrostyrene catalysed by methanesulfonamides or *p*-toluenesulfonamides

To a suspension of catalyst (depending on the catalyst loading) in a mixture of isopropanol and ethanol (1:1) (1.6 mL) was added triethylamine (equimolar amount with the catalyst). *trans*-β-Nitrostyrene (30.0 mg, 0.20 mmol) was added followed by acetone (0.4 mL, 5.45 mmol). The resulting mixture was allowed to stir at room temperature for 18 h and the solvents were evaporated in vacuo. EtOAc (10 mL) was added and the organic layer was washed with a saturated solution of NH_4Cl (2×10 mL). The combined aqueous layers were extracted with EtOAc (5×10 mL). The combined organic layers were dried (Na_2SO_4), and the solvent was removed in vacuo. The residue was purified by column chromatography eluting with a mixture of petroleum ether 40–60/EtOAc 80:20 affording the product as a white solid.

3.5.1. (R)-5-Nitro-4-phenylpentan-2-one[18]

^{1}H NMR (200 MHz, $CDCl_3$) δ 7.38–7.07 (m, 5H, Ar), 4.69 (dd, J=12.2 and 7.0 Hz, 1H, C*H*HNO_2), 4.57 (dd, J=12.2 and 7.8 Hz, 1H, C*H*HNO_2), 3.99 (m, 1H, CHPh), 2.89 (d, J=7.4 Hz, 2H, CH_2CO), 2.09 (s, 3H, CH_3); ^{13}C NMR (50 MHz, $CDCl_3$) δ 205.6 (CO), 139.1 (Ar), 129.3 (Ar), 128.1 (Ar), 127.6 (Ar), 79.7 (CH_2NO_2), 46.3 (*C*H_2CO), 39.3 (CH), 30.6 (CH_3); HPLC analysis: Daicel Chiralpak AD-H, hexane/*i*-PrOH 94:6, flow rate 1 mL/min, retention time: 12.82 (minor) and 14.07 (major).

3.6. General procedure for the aldol reaction of acetone with 4-nitrobenzaldehyde catalysed by methanesulfonamides or *p*-toluenesulfonamides

To a suspension of catalyst (depending on the catalyst loading) in dichloromethane (8 mL) was added triethylamine (equimolar amount with the catalyst) followed by acetone (2.0 mL, 27.2 mmol). 4-Nitrobenzaldehyde (151.1 mg, 1 mmol) was added to the reaction mixture and left stirring for 18 h at room temperature and the solvents were evaporated in vacuo. EtOAc (10 mL) was added and the organic layer was washed with a saturated solution of NH_4Cl (2×10 mL). The combined aqueous layers were extracted with EtOAc (5×10 mL). The combined organic layers were dried (Na_2SO_4), and the solvent was removed in vacuo. The residue was purified by column chromatography eluting with a mixture of petroleum ether 40–60/EtOAc 50:50 affording the product as a yellow oil.

3.6.1. (R)-4-Hydroxy-4-(4-nitrophenyl)butan-2-one[22]

^{1}H NMR (200 MHz, $CDCl_3$) δ 8.20 (d, J=7.0 Hz, 2H, Ar), 7.52 (d, J=7.0 Hz, 2H, Ar), 5.25 (m, 1H, CH), 3.56 (br s, 1H, OH), 2.83 (m, 2H, CH_2CO), 2.21 (s, 3H, CH_3CO); ^{13}C NMR (50 MHz, $CDCl_3$) δ 208.6 (CO), 149.9 (Ar), 147.4 (Ar), 126.4 (Ar), 123.8 (Ar), 68.9 (CH), 51.5 (CH_2), 30.7 (CH_3); HPLC analysis: Daicel Chiralpak AD-RH, MeCN/H_2O 30:70, flow rate 0.5 mL/min, retention time: 17.45 (major) and 20.75 (minor).

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References and notes

1. For books, see: (a) Berkessel, A.; Groger, H. *Asymmetric Organocatalysis—From Biomimetic Concepts to Powerful Methods for Asymmetric Synthesis*; Wiley-VCH: Weinheim, 2005; (b) Dalko, P. I. *Enantioselective Organocatalysis: Reactions and Experimental Procedures*; Wiley-VCH: Weinheim, 2007.
2. List, B.; Lerner, R. A.; Barbas, C. F., III. *J. Am. Chem. Soc.* **2000**, *122*, 2395–2396.
3. For reviews, see: (a) Dalko, P. I.; Moisan, L. *Angew. Chem., Int. Ed.* **2004**, *43*, 5138–5175; (b) Taylor, M. S.; Jacobsen, E. N. *Angew. Chem., Int. Ed.* **2006**, *45*, 1520–1543; (c) List, B. *Chem. Commun.* **2006**, 819–824; (d) Doyle, A. G.; Jacobsen, E. N. *Chem. Rev.* **2007**, *107*, 5713–5743; (e) Pellissier, H. *Tetrahedron* **2007**, *63*, 9267–9331; (f) Guillena, G.; Najera, C.; Ramon, D. J. *Tetrahedron: Asymmetry* **2007**, *18*, 2249–2293; (g) Mukherjee, S.; Yang, J. W.; Hoffmann, S.; List, B. *Chem. Rev.* **2007**, *107*, 5471–5569; (h) Sulzer-Mosse, S.; Alexakis, A. *Chem. Commun.* **2007**, 3123–3135; (i) Longbottom, D. A.; Franckevicius, V.; Kumarn, S.; Oelke, A. J.; Wascholowski, V.; Ley, S. V. *Aldrichimica Acta* **2008**, *41*, 3–11.
4. Bellis, E.; Vasilatou, K.; Kokotos, G. *Synthesis* **2005**, 2407–2413.
5. Hartikka, A.; Arvidsson, P. I. *Tetrahedron: Asymmetry* **2004**, *15*, 1831–1834.
6. Berkessel, A.; Koch, B.; Lex, J. *Adv. Synth. Catal.* **2004**, *346*, 1141–1146.
7. Cobb, A. J. A.; Shaw, D. M.; Longbottom, D. A.; Gold, J. B.; Ley, S. V. *Org. Biomol. Chem.* **2005**, *3*, 84–96.
8. (a) Torii, H.; Nakadai, M.; Ishihara, K.; Saito, S.; Yamamoto, H. *Angew. Chem., Int. Ed.* **2004**, *43*, 1983–1986; (b) Yamamoto, Y.; Momiyama, N.; Yamamoto, H. *J. Am. Chem. Soc.* **2004**, *126*, 5962–5963.
9. Terakado, D.; Takano, M.; Oriyama, T. *Chem. Lett.* **2005**, *34*, 962–963.
10. Mitchell, C. E. T.; Cobb, A. J. A.; Ley, S. V. *Synlett* **2005**, 611–614.
11. For reviews, see: (a) Miller, S. J. *Acc. Chem. Res.* **2004**, *37*, 601–610; (b) Revell, J. D.; Wennemers, H. *Curr. Opin. Chem. Biol.* **2007**, *11*, 269–278; (c) Colby Davie, E. A.; Mennen, S. M.; Xu, Y.; Miller, S. J. *Chem. Rev.* **2007**, *107*, 5759–5812.
12. (a) Kofoed, J.; Nielsen, J.; Reymond, J.-L. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 2445–2447; (b) Martin, H. J.; List, B. *Synlett* **2003**, 1901–1902; (c) Tang, Z.; Yang, Z.-H.; Cun, L.-F.; Gong, L.-Z.; Mi, A.-Q.; Jiang, Y.-Z. *Org. Lett.* **2004**, *6*, 2285–2287; (d) Shi, L.-X.; Sun, Q.; Ge, Z.-M.; Zhu, Y.-Q.; Cheng, T.-M.; Li, R.-T. *Synlett* **2004**, 2215–2217; (e) Luppi, G.; Cozzi, P. G.; Monari, M.; Kaptein, B.; Broxterman, Q. B.; Tomasini, C. *J. Org. Chem.* **2005**, *70*, 7418–7421; (f) Krattiger, P.; Kovasy, R.; Revell, J. D.; Ivan, S.; Wennemers, H. *Org. Lett.* **2005**, *7*, 1101–1103; (g) Zou, W.; Ibrahem, I.; Dziedzic, P.; Sunden, H.; Cordova, A. *Chem. Commun.* **2005**, 4946–4948; (h) Akagawa, K.; Sakamoto, S.; Kudo, K. *Tetrahedron Lett.* **2005**, *46*, 8185–8187; (i) Tsogoeva, S. B.; Wei, S. *Tetrahedron: Asymmetry* **2005**, *16*, 1947–1951; (j) Zheng, J.-F.; Li, Y.-X.; Zhang, S.-Q.; Yang, S.-T.; Wang, X.-M.; Wang, Y.-Z.; Bai, J.; Liu, F.-A. *Tetrahedron Lett.* **2006**, *47*, 7793–7796; (k) Dziedzic, P.; Zou, W.; Hafren, J.; Cordova, A. *Org. Biomol. Chem.* **2006**, *4*, 38–40; (l) Lei, M.; Shi, L.; Li, G.; Chen, S.; Fang, W.; Ge, Z.; Cheng, T.; Li, R. *Tetrahedron* **2007**, *63*, 7892–7898.
13. Tang, Z.; Jiang, F.; Gong, L.-Z.; Mi, A.-Q.; Jiang, Y.-Z.; Wu, Y.-D. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 5755–5760.
14. Bellis, E.; Kokotos, G. *Tetrahedron* **2005**, *61*, 8669–8676.
15. Bellis, E.; Kokotos, G. *J. Mol. Catal. A: Chem.* **2005**, *241*, 166–174.
16. Cassal, J.-M.; Furst, A.; Meier, W. *Helv. Chim. Acta* **1976**, *59*, 1917–1924.
17. For recent reviews, see: (a) Tsogoeva, S. B. *Eur. J. Org. Chem.* **2007**, 1701–1716; (b) Vicario, J. L.; Badia, D.; Carillo, L. *Synthesis* **2007**, 2065–2092.
18. List, B.; Pojarliev, P.; Martin, H. J. *Org. Lett.* **2001**, *3*, 2423–2425.
19. Huang, H.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2006**, *128*, 7170–7171.
20. Enders, D.; Seki, A. *Synlett* **2002**, 26–28.
21. Hayashi, Y.; Gotoh, H.; Hayashi, T.; Shoji, M. *Angew. Chem., Int. Ed.* **2005**, *43*, 4212–4215.
22. Sakthivel, K.; Notz, W.; Bui, T.; Barbas, C. F., III. *J. Am. Chem. Soc.* **2001**, *123*, 5260–5267.