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Synthesis of Substituted 5-(Pyrrolidin-2-yl)tetrazoles and Their Application in the Asymmetric Biginelli Reaction

Yong-Yong Wu,[a,b] Zhuo Chai,[a] Xin-Yuan Liu,[a] Gang Zhao,*[a] and Shao-Wu Wang*[b]

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A series of chiral substituted 5-(pyrrolidin-2-yl)tetrazoles have been synthesized and evaluated as organocatalysts for the asymmetric Biginelli reaction. The relationship between catalytic activity and the different catalyst structures is briefly discussed. By using the optimized catalyst **C^{10}** (10 mol-%), a series of 3,4-dihydropyrimidin-2(1*H*)-one (DHPM) derivatives have been obtained in 63–88 % yields and 68–81 % *ee* values within 24 h at room temperature.

Introduction

Chiral tetrazoles as organocatalysts have received increasing interest since the pioneering works of Yamamoto,[1] Ley,[2] and Arvidsson[3] and their co-workers in 2004. So far tetrazole catalysts have been applied successfully to a variety of organic reactions, including Mannich-type reactions,[4] Michael additions,[5] and aldol[6] and *o*-nitroso-aldol/Michael reactions.[7] Meanwhile, Barbas[8] and Ward[9] and their co-workers have also successfully utilized tetrazole catalysts in the total synthesis of BIRT-377 and serricornin, respectively. Tetrazoles were initially synthesized out of consideration for a better solubility in conventional organic solvents than the corresponding amino acids while retaining their properties. In fact, it has been well documented[1–9] that in many cases tetrazoles are more efficient catalysts than the parent amino acids, which makes them a valuable member of the organocatalyst family. However, until now, in contrast to the huge number of amino acid catalysts available, only a handful of chiral tetrazole catalysts[10] (Figure 1, **A**–**E**) have been synthesized and investigated in asymmetric reactions.

As one of the most useful multicomponent reactions and originally described by Biginelli in 1891,[11] the Biginelli reaction offers an efficient way to obtain pharmacologically and biologically important 3,4-dihydropyrimidin-2(1*H*)-ones (DHPMs) through the simple condensation reaction of an aldehyde, a urea or thiourea, and an easily enolizable carbonyl compound.[12] However, besides chemical resolution and enzymatic strategies,[13] procedures for the enantioselective synthesis of DHPMs are rather limited,[14] especially by the catalytic asymmetric Biginelli reaction.[15–17] In 2005, a catalytic highly enantioselective version of the Biginelli reaction was realized by Zhu and co-workers using a recyclable new chiral ytterbium catalyst.[15] In the field of organocatalysis, Gong and co-workers successfully applied BINOL-derived phosphoric acids to this reaction with excellent enantiocontrol.[16] Feng and co-workers utilized a readily available *trans*-4-hydroxyproline-derived secondary amine Brønsted acid as a catalyst to catalyze this reaction, however, an organic amino salt was usually required as an additive to obtain good results in this case.[17] In view of these few successful examples, it is still desirable to develop other new organocatalysts for this important transformation. As a part of our continued interest in the development of novel asymmetric organocatalytic reactions,[18] we report herein the synthesis of a series of novel proline-derived tetrazole catalysts and their application in these reactions.

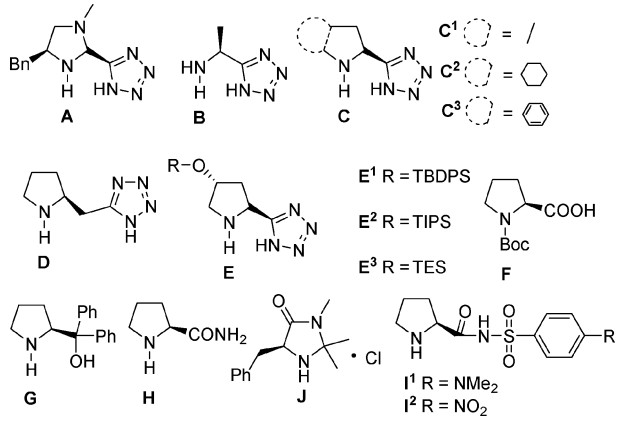


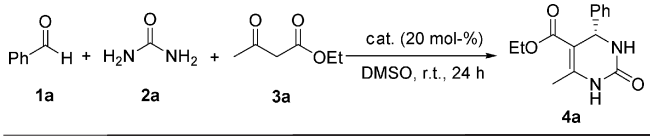
Figure 1. Structures of known organocatalysts.

[a] Laboratory of Modern Organic Synthetic Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, 354 Fenglin Lu, Shanghai 200032, P. R. China
Fax: +86-21-64166128
E-mail: zhaog@mail.sioc.ac.cn
swwang@mail.ahnu.edu.cn
[b] Institute of Organic Chemistry, School of Chemistry and Materials Science, Anhui Normal University, Wuhu, Anhui 241000, P. R. China

Results and Discussion

Our study began with a preliminary screening of several different known catalysts (Figure 1). By using benzaldehyde (1.1 mmol), ethyl acetoacetate (1.0 mmol), and urea (1.5 mmol) as the probing substrates, the reactions were performed in DMSO at room temperature and the results are summarized in Table 1. Although L-proline could catalyze this reaction to provide the desired product **4a** in moderate yield, the enantioselectivity was rather poor (Table 1, entry 1). Moreover, the *N*-Boc-protected L-proline **F**, the diphenyl prolinol **G**, and prolinamide **H**, in which the carboxylic acid group of L-proline is replaced by less acidic groups, all failed to catalyze this reaction (Table 1, entries 4–6). Although the desired product could be obtained in good yields when catalysts **I** and **J** with a stronger acidic moiety were used, the enantioselectivities were poor (Table 1, entries 7–9). These results suggested that both the basic amine and the acidic moieties in L-proline are essential to effect this reaction. Encouragingly, we found that 5-(pyrrolidin-2-yl)tetrazole (**C**^{1}) could catalyze this reaction effectively to provide **4a** in 65% yield and 23% *ee*. Consequently, we directed our optimization efforts towards both the structural modification of **C**^{1} and the optimization of the reaction conditions.

Table 1. Preliminary catalyst screening for the asymmetric Biginelli reaction.[a]



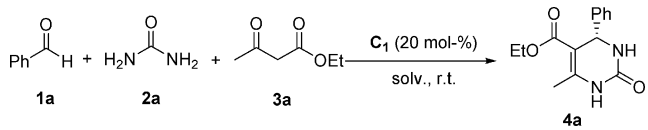
Entry	Catalyst	Yield [%][b]	*ee* [%][c]
1	L-proline	57	8
2	**C**^{1}	65	23
3	**D**	<5	n.d.
4	**F**	<5	n.d.
5	**G**	–[d]	–[d]
6	**H**	–[d]	–[d]
7	**I**^{1}	75	4
8	**I**^{2}	81	2
9	**J**	87	11

[a] **1a**:**2a**:**3a** = 1.1:1:1.5. [b] Isolated yields. [c] Determined by HPLC using a chiral column. [d] No reaction was detected.

First, solvent effects were evaluated with the catalyst **C**^{1} and the results are shown in Table 2. In terms of both yield and enantioselectivity, *i*PrOH as the solvent gave the best results (Table 2, entry 5). Longer- and shorter-chained alcohols all gave inferior results. In addition, reducing the catalyst loading to 10 mol-% led to a longer reaction time without any significant change in the enantioselectivity (Table 2, entry 6).

In the meantime, our efforts to structurally modify the tetrazole catalyst **C**^{1} commenced with the synthesis of the known catalysts **C**^{2}, **C**^{3}, and **E**^{1} (Figure 1). For reasons of solubility, these three catalysts together with **C**^{1} were investigated in a co-solvent of DMSO/*i*PrOH (1:5, v/v) in the

Table 2. Optimization of the reaction conditions with catalyst **C**^{1}.[a]



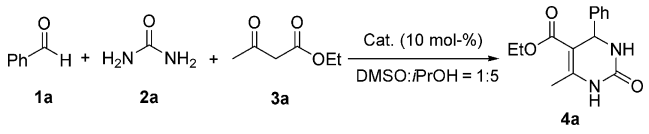
Entry	Solvent	Yield [%][b]	*ee* [%][c]
1	MeOH	75	30
2	DMSO	65	23
3[d]	THF	73	20
4	EtOH	84	44
5	*i*PrOH	58	52
6[d,e]	*i*PrOH	68	51
7	*i*BuOH	55	32
8	*t*BuOH	65	27

[a] The reaction was performed with **C**^{1} (0.05 mmol), **1a** (0.27 mmol), **2a** (0.30 mmol), and **3a** (0.25 mmol) in 1 mL of solvent at room temperature for 24 h. [b] Isolated yields. [c] Determined by HPLC using chiral columns. [d] A reaction time of 48 h was used. [e] 10 mol-% of catalyst **C**^{1} was used.

model reaction. Disappointingly, none of the three catalysts led to any significant improvement in the enantioselectivity compared with **C**^{1} (Table 3, entries 1–4). With the intention of achieving better enantioselectivity, we continued our endeavors in the synthesis of novel catalysts based on **C**^{1}. Starting from the commercially available 4-hydroxy-L-proline, the known compound **5a** was prepared according to literature procedures.[1,19] The reaction of **5a** with TsCl provided compound **6a**, which was subjected to a sequence of ammonolysis, dehydration with $POCl_3$, and a click reaction with sodium azide to afford the desired catalyst **C**^{4} (Scheme 1). In a similar way, **C**^{5}, the *N*-methylated analogue of **C**^{4}, was also prepared. To ascertain whether the relative stereochemistry of the catalyst would have an influence on the enantioselectivity, we also synthesized the 2,4-*trans*-disubstituted catalysts **C**^{6} and **C**^{7}, namely the 2-epimers of **C**^{4} and **C**^{5} (Figure 2). Subsequently, the newly prepared catalysts **C**^{4}–**C**^{7} were tested in the model reaction. It was found that the 2,4-*trans*-disubstituted pyrrolidinyltetrazoles **C**^{6} and **C**^{7} provided higher enantioselectivities than their *syn* counterparts **C**^{4} and **C**^{5} with an inverted absolute configuration of the product **4a**. In addition, no considerable difference in the enantioselectivity was observed between **C**^{6} and **C**^{7}, which suggests that the hydrogen atom on the N-4 atom might not participate in the enantiodiscriminating process.

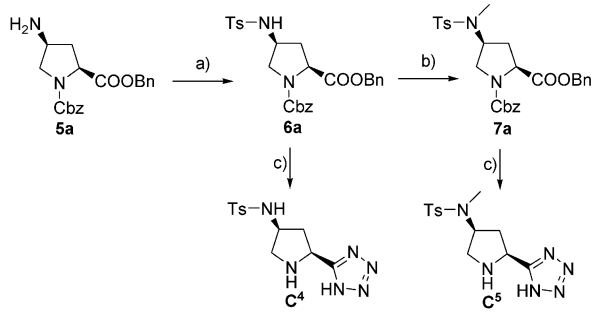
Next we changed the protecting group of **C**^{6} from tosyl to a mesyl (**C**^{8}) or mesityl (**C**^{9}) group to examine the steric effect of this position. Moreover, because some proline-derived organocatalysts with long alkyl chains on the nitrogen atom have recently been found to be highly effective in aldol and Michael reactions,[20] we also modified the N-4 atom of **C**^{6} with four-, eight- and twelve-carbon alkyl chains, namely catalysts **C**^{10}–**C**^{12} (Scheme 2). Then the five novel catalysts **C**^{8}–**C**^{12} were examined in the model reaction: **C**^{10} with a four-carbon alkyl chain gave the highest enantioselectivity (63%) and the *ee* values of the product dropped

Table 3. Further evaluation of catalysts for the asymmetric Biginelli reaction.[a]



Entry	Catalyst	Time [h]	Yield [%][b]	*ee* [%][c]	Config.[d]
1	**C**[1]	48	68	47	*S*
2	**C**[2]	48	75	51	*S*
3	**C**[3]	48	84	49	*S*
4	**E**[1]	48	48	49	*S*
5	**C**[4]	24	80	42	*S*
6	**C**[5]	24	63	45	*S*
7	**C**[6]	24	85	59	*R*
8	**C**[7]	24	78	58	*R*
9	**C**[8]	24	90	50	*R*
10	**C**[9]	48	77	58	*R*
11	**C**[10]	24	74	63	*R*
12[e]	**C**[11]	24	68	54	*R*
13[f]	**C**[12]	24	72	51	*R*

[a] The reaction was performed with catalyst (0.025 mmol), **1a** (0.27 mmol), **2a** (0.30 mmol), and **3a** (0.25 mmol) in 1.2 mL of solvent at room temperature. [b] Isolated yields. [c] Determined by HPLC using a chiral column. [d] The absolute configuration was determined by comparison of the optical rotation value with literature values.[17] [e] DMSO/*i*PrOH = 1:3 was used as the solvent due to poor catalyst solubility. [f] DMSO/*i*PrOH = 1:2 was used as the solvent due to poor catalyst solubility.



a) TsCl, Et_3N/ DCM; b) CH_3I, K_2CO_3/ CH_3COCH_3, DMF; c) i)NH_3/MeOH; ii) $POCl_3$, pyr./DCM, 0 °C; iii) NaN_3, NH_4Cl/DMF, 70 °C; iv) Pd/C, H_2 (1atm)/MeOH.

Scheme 1. Synthesis of catalysts **C**[4] and **C**[5].

as the alkyl chain became longer (Table 3, entries 10–13). Although the catalyst **C**[8] provided the best chemical yield, the *ee* was poor (Table 3, entry 9).

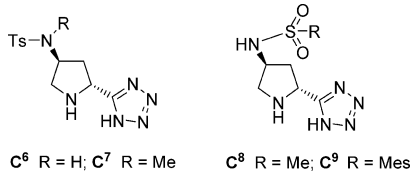
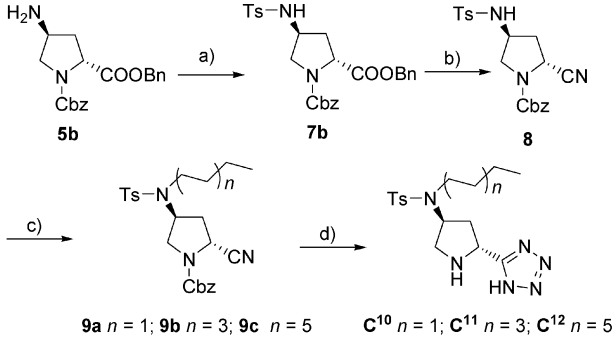


Figure 2. Structures of catalysts **C**[6]–**C**[9].

To optimize the reaction conditions further, the solvent effect was reinvestigated with the optimum catalyst **C**[10], and the best result was obtained in EtOH (Table 4, entry 4). Similar to the instance of catalyst **C**[1], DMSO and THF again gave very poor enantioselectivity (Table 4, entries 3 and 6). When the reaction was performed in DCM, a very low yield was obtained even with a prolonged reaction time, probably due to low catalyst solubility, although the *ee* was comparable to that of EtOH. Thus, the optimal reaction conditions for this transformation were determined to be 10 mol-% of **C**[10] in EtOH at room temperature (Table 4, entry 4).

With the optimized conditions in hand, the substrate scope of this reaction was probed (Table 5). In general, all the examined substrates could furnish the desired products in good yields and with moderate-to-good enantioselectivities. Notably, although the enantioselectivities are not very satisfying, the catalytic system described in this work required a markedly shorter reaction time (24 h) compared with two previous organocatalytic systems (36–72 h).[16,17] Changes to the substituents in both the aldehyde and the acylacetate components seemed not to have any striking effect on either the yields or the *ee* values. In addition, a comparable result was obtained when thiourea **2b** was employed instead of urea **2a** (Table 5, entry 10).

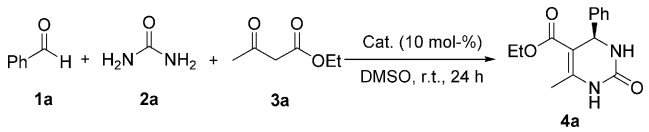
Based on previous studies of the mechanism of the Biginelli reaction[12,15–17] and the experimental results, a possible transition state with catalyst **C**[10] as an example has



a) TsCl, Et_3N/ DCM; b) i)NH_3/MeOH; ii) $POCl_3$, pyr./DCM, 0 °C; c) $CH_3CH_2(CH_2CH_2)_nBr$, K_2CO_3, nBu_4NBr/ CH_3COCH_3, DMF; d) i) NaN_3, NH_4Cl/DMF, 70 °C; ii) Pd/C, H_2(1atm)/ MeOH.

Scheme 2. Synthesis of catalysts **C**[10]–**C**[12].

Table 4. Screening of solvents for catalyst **C**[10].[a]

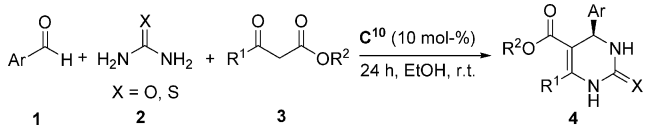


1a 2a 3a 4a

Entry	Solvent	Time [h]	Yield [%][b]	*ee* [%][c]
1	DMSO/*i*PrOH, 1:5	24	74	63
2	MeOH	24	70	65
3	DMSO	24	73	35
4	EtOH	24	75	72
5[d,e]	EtOH	24	55	70
6[e]	THF	48	73	20
7[e]	CH_2Cl_2	120	22	69

[a] The reaction was performed with **C**[10] (0.025 mmol), **1a** (0.27 mmol), **2a** (0.30 mmol), and **3a** (0.25 mmol) in 1.2 mL of solvent at room temperature. [b] Isolated yields. [c] Determined by HPLC using a chiral column. [d] Catalyst **C**[11] was used. [e] The catalyst did not dissolve completely.

Table 5. Scope of the asymmetric Biginelli reaction catalyzed by **C**[10].[a]



1 2 3 4

Entry	Ar (**1**)	R^1/R^2 (**3**)	**4**	Yield [%][b]	*ee* [%][c]
1	C_6H_5 (**1a**)	Me/Et (**3a**)	**4a**	75	72
2	4-BrC_6H_4 (**1b**)	Me/Et (**3a**)	**4b**	63	69
3	4-CNC_6H_4 (**1c**)	Me/Et (**3a**)	**4c**	82	75
4	4-$NO_2C_6H_4$ (**1d**)	Me/Et (**3a**)	**4d**	78	76
5	3-$NO_2C_6H_4$ (**1e**)	Me/Et (**3a**)	**4e**	75	78
6	C_6H_5 (**1a**)	Ph/Et (**3b**)	**4f**	88	81
7	C_6H_5 (**1a**)	Me/Me (**3c**)	**4g**	81	69
8	C_6H_5 (**1a**)	Me/*i*Pr (**3d**)	**4h**	78	68
9	C_6H_5 (**1a**)	Me/*t*Bu (**3e**)	**4i**	76	72
10[d]	4-CNC_6H_4 (**1c**)	Me/Et (**3a**)	**4j**	71	80

[a] The reaction was performed with **C**[10] (0.025 mmol), **1** (0.27 mmol), **2** (0.30 mmol), and **3** (0.25 mmol) in 1 mL of EtOH at room temperature. [b] Isolated yields. [c] Determined by HPLC using chiral columns. The absolute configuration was determined by comparison of the optical rotation value or the sequence of HPLC peaks with literature values.[17] [d] Thiourea was used instead of **2a**.

been proposed to explain the stereochemical results of the transformation described in this work (Figure 3). Similarly to the widely accepted catalytic mode of the L-proline-catalyzed aldol reaction, the catalyst may catalyze the reaction in a dual-activation way: The acidic tetrazole moiety activates the electrophilic imine formed from urea and aldehyde by a hydrogen-bonding interaction and the secondary amine moiety activated the nucleophilic keto ester via the formation of an enamine intermediate. Such a transition state implies that the enantiodetermining element in the catalyst mainly resides in the stereochemistry of the acidic tetrazole moiety, which is supported by the following two observations: (a) The inversion of the absolute configuration of the product when catalysts **C**[1]–**C**[5] were used (Table 3) and (b) modification of the substituents at the 4-position of the catalysts had no remarkable influence on product enantioselectivity.

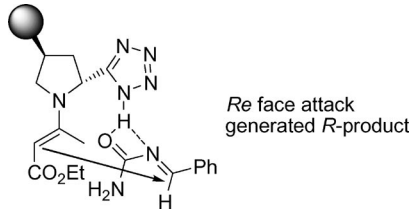


Figure 3. Possible catalytic transition state for the present catalytic system.

Conclusions

We have synthesized a series of novel chiral substituted 5-(pyrrolidin-2-yl)tetrazoles for application in the enantioselective Biginelli reaction. The optimization of catalyst structures, including different absolute and relative configurations and different substituents with varied electronic and steric properties, furnished **C**[10] as the best catalyst, which provides the corresponding 3,4-dihydropyrimidin-2(1*H*)-one (DHPM) derivatives in good yields and enantioselectivities under mild reaction conditions. These novel tetrazole catalysts allow facile adjustments to both electronic and steric properties for further optimization and expand the existing library of tetrazole catalysts.

Experimental Section

General Remarks: ^{1}H NMR spectra were recorded with a Bruker DPX-300 or Varian EM-360 (300 MHz) instrument. All chemical shifts (δ) are given in ppm. ^{13}C NMR spectra were recorded with a Bruker DPX-300 (75 MHz) or DPX-400 (100 MHz) instrument. IR spectra were recorded with a Perkin–Elmer 983G instrument. Flash column chromatography was performed by using 300–400-mesh silica gel. For thin-layer chromatography (TLC), silica gel plates (HSGF 254) were used and compounds were visualized by irradiation with UV light or by treatment with a solution of phosphomolybdic acid in ethanol followed by heating. Mass spectra (EI) were recorded at an ionizing voltage of 70 eV.

Synthesis of Esters 6a–d: A solution of *p*-toluenesulfonyl chloride (1.14 g, 6.0 mmol) in dry DCM (5.0 mL) was slowly added to a stirred solution of dibenzyl (2*S*,4*R*)-4-aminopyrrolidine-1,2-dicarboxylate (**5a**) (1.416 g, 4.0 mmol) and Et_3N (1.12 mL, 8.0 mmol) in dry DCM (20 mL) under cooling in an ice/water bath. The stirring was continued for 12 h at room temperature. Then saturated $NaHCO_3$ (10 mL) was added to quench the reaction. The reaction mixture was extracted with DCM (2 × 10 mL). The combined organic portions were washed with saturated brine (20 mL), dried with Na_2SO_4, and concentrated in vacuo. The crude product was purified by flash column chromatography (PE/EA, 1:1) to give **6a** as a white solid.

Dibenzyl (2*S*,4*S*)-4-(4-Methylphenylsulfonamido)pyrrolidine-1,2-dicarboxylate (6a): Yield 1.585 g, 78%. $[\alpha]_D^{27}$ = –13.1 (*c* = 4.57, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ = 7.75–7.64 (m, 2 H), 7.35–7.12 (m, 12 H), 6.08 (d, *J* = 9.0 Hz, 1 H), 5.22–4.92 (m, 4 H), 4.36–4.17 (m, 1 H), 3.89 (br., 1 H), 3.63–3.50 (m, 1 H), 3.40–3.30 (m, 1 H), 2.34 and 2.32 (s, 3 H), 2.35–2.20 (m, 1 H), 2.00–1.75 (m, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, the signals in parentheses refer to the rotamer): δ = 173.3 (173.1), 154.6 (153.9), 143.6, 137.6, 136.2 (136.1), 135.2 (135.0), 130.0 (129.9), 128.7, 128.5, 128.3, 128.2, 128.1, 127.8, 127.0, 67.4, 67.3, 57.9 (57.5), 52.5, 52.2 (51.7), 36.5 (35.3), 21.5 ppm. IR (KBr): $\tilde{\nu}$ = 3271, 2953, 1709, 1417, 1354, 1163, 698 cm^{-1}. MS (ESI): *m*/*z* = 531.2 $[M + Na]^+$. HRMS (ESI): calcd. for $C_{27}H_{28}N_2O_6SNa^+$ $[M + Na]^+$ 531.1560; found 531.1575.

Dibenzyl (2*R*,4*S*)-4-(4-Methylphenylsulfonamido)pyrrolidine-1,2-dicarboxylate (6b): Yield 1.748 g, 86%. $[\alpha]_D^{27}$ = 23.0 (*c* = 4.27, $CHCl_3$). ^1H NMR (300 MHz $CDCl_3$): δ = 7.68 (dd, *J* = 8.4, 4.5 Hz, 2 H), 7.32–7.12 (m, 12 H), 6.17 (dd, *J* = 9.9, 7.2 Hz, 1 H), 5.14–4.86 (m, 4 H), 4.46–4.32 (m, 1 H), 3.65 (br., 1 H), 3.66–3.56 (m, 1 H), 3.28 (m, 1 H), 2.33 and 2.31 (s, 3 H), 2.24–1.92 (m, 2 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, the signals in parentheses refer to the rotamer): δ = 172.0 (171.8), 154.8 (154.2), 143.7, 137.3 (137.1), 136.2 (136.1), 135.5 (135.3), 130.0 (129.9), 128.6, 128.5, 128.4, 128.2, 128.1, 127.7, 127.0, 67.3, 67.1 (67.0), 57.8 (57.6), 51.8 (51.7), 51.6 (51.1), 36.8 (35.6), 21.5 ppm. IR (KBr): $\tilde{\nu}$ = 3255, 2954, 1745, 1708, 1420, 1162, 698 cm^{-1}. MS (ESI): *m*/*z* = 531.2 $[M + Na]^+$. HRMS (ESI): calcd. for $C_{27}H_{28}N_2O_6SNa^+$ $[M + Na]^+$ 531.1560; found 531.1574.

Dibenzyl (2*R*,4*S*)-4-(Methylsulfonamido)pyrrolidine-1,2-dicarboxylate (6c): Yield 1.123 g, 65%, m.p. 89–90 °C. $[\alpha]_D^{29}$ = 26.1 (*c* = 1.20, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ = 7.45–7.16 (m, 10 H), 5.73 (t, *J* = 7.2 Hz, 1 H), 5.20–4.95 (m, 4 H), 4.54–4.40 (m, 1 H), 4.10–4.00 (m, 1 H), 3.88–3.80 (m, 2 H), 3.48–3.34 (m, 1 H), 2.86 and 2.83 (s, 3 H), 2.30–2.14 (m, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, the signals in parentheses refer to the rotamer): δ = 171.9 (171.8), 154.8 (154.2), 136.2 (136.1), 135.4 (135.2), 128.7 (128.6), 128.5, 128.2, 128.2 (128.1), 127.9, 127.7, 67.5 (67.4), 67.2, 57.8 (57.6), 52.1 (52.0), 51.8 (51.1), 41.1, 37.3 (36.1) ppm. IR (KBr): $\tilde{\nu}$ = 3281, 2927, 1747, 1498, 1463, 745, 697 cm^{-1}. MS (ESI): *m*/*z* = 433.2 $[M + H]^+$. HRMS (ESI): calcd. for $C_{21}H_{24}N_2O_6SNa^+$ $[M + Na]^+$ 455.1239; found 455.1247.

Dibenzyl (2*R*,4*S*)-4-(2,4,6-Trimethylphenylsulfonamido)pyrrolidine-1,2-dicarboxylate (6d): Yield 1.672 g, 78%. $[\alpha]_D^{27}$ = 24.2 (*c* = 3.95, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ = 7.36–7.12 (m, 10 H), 6.93 and 6.90 (s, 2 H), 5.18–4.90 (m, 5 H), 4.47–4.33 (m, 1 H), 3.94–3.84 (m, 1 H), 3.68–3.58 (m, 1 H), 3.28–3.20 (m, 1 H), 2.57 and 2.56 (s, 6 H), 2.29 and 2.26 (s, 3 H), 2.25–2.06 (m, 2 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, the signals in parentheses refer to the rotamer): δ = 172.0 (171.8), 154.7 (154.1), 142.6, 139.1, 136.2 (136.1), 135.4 (135.2), 133.8 (133.7), 132.2 (132.1), 128.6, 128.5, 128.4, 128.2, 128.1, 127.8, 67.3, 67.1, 57.8 (57.6), 51.6 (51.4), 51.3 (50.6), 36.8 (35.7), 22.9, 21.0 ppm. IR (KBr): $\tilde{\nu}$ = 3276, 2939, 1747, 1714, 1604, 1455, 1156, 746, 698, 659 cm^{-1}. MS (ESI): *m*/*z* = 537.3 $[M + H]^+$. HRMS (ESI): calcd. for $C_{29}H_{32}N_2O_6SNa^+$ $[M + Na]^+$ 559.1873; found 559.1885.

Synthesis of Compounds 7a–d: MeI (1.4 mL, 15.0 mmol, 3.0 equiv.) was slowly added to a stirred solution of **6a** (2.54 g, 5.0 mmol, 1.0 equiv.) and K_2CO_3 (0.828 g, 6.0 mmol, 1.2 equiv.) in acetone (40 mL) and DMF (6 mL). The stirring was continued for 2 d at room temperature. Then the reaction mixture was concentrated in vacuo before HCl (1.0 M, 50 mL) was added. The mixture was extracted with EA (2 × 40 mL). The combined organic portions were washed with saturated brine (40 mL), dried with Na_2SO_4, and concentrated in vacuo. The crude product was purified by flash column chromatography (PE/EA, 3:1) to give **7a** as a colorless oil.

Dibenzyl (2*S*,4*S*)-4-(*N*,4-Dimethylphenylsulfonamido)pyrrolidine-1,2-dicarboxylate (7a): Yield 2.558 g, 98%. $[\alpha]_D^{27}$ = –31.8 (*c* = 4.97, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ = 7.62 (d, *J* = 6.9 Hz, 2 H), 7.34–7.12 (m, 12 H), 5.15–4.88 (m, 4 H), 4.57–4.40 (m, 1 H), 4.36–4.17 (m, 1 H), 3.62 (dd, *J* = 10.5, 8.1 Hz, 1 H), 3.26–3.14 (m, 1 H), 2.61 and 2.57 (s, 3 H), 2.32 (s, 3 H), 2.30–2.12 (m, 1 H), 1.86–1.64 (m, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, the signals in parentheses refer to the rotamer): δ = 171.9 (171.7), 154.5 (153.9), 143.8, 136.3 (136.2), 135.5 (135.3), 130.0, 128.5, 128.5, 128.4, 128.3, 128.2, 128.1, 127.8, 127.1, 67.2, 66.9, 57.5 (57.1), 54.7 (54.1), 46.6, 32.2 (30.7), 29.3 (29.2), 21.4 ppm. IR (KBr): $\tilde{\nu}$ = 2954, 1747, 1712, 1417, 1348, 1166, 663 cm^{-1}. MS (ESI): *m*/*z* = 523.2 $[M + H]^+$. HRMS (ESI): calcd. for $C_{28}H_{30}N_2O_6SNa^+$ $[M + Na]^+$ 545.1717; found 545.1732.

Dibenzyl (2*R*,4*S*)-4-(*N*,4-Dimethylphenylsulfonamido)pyrrolidine-1,2-dicarboxylate (7b): Yield 2.480 g, 95%. $[\alpha]_D^{25}$ = 17.7 (*c* = 4.20, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ = 7.58 (dd, *J* = 8.1, 4.5 Hz, 2 H), 7.40–7.16 (m, 12 H), 5.22–4.96 (m, 4 H), 4.76–4.55 (m, 1 H), 4.48–4.34 (m, 1 H), 3.70–3.50 (m, 1 H), 3.24–3.13 (m, 1 H), 2.69 and 2.67 (s, 3 H), 2.40 and 2.38 (s, 3 H), 2.24–1.83 (m, 2 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, the signals in parentheses refer to the rotamer): δ = 171.7 (171.5), 154.6 (153.9), 143.8, 136.3 (136.2), 135.5 (135.4), 135.2, 130.0, 128.7, 128.5, 128.3, 128.2, 128.1, 127.8, 127.1, 67.2, 67.1, 57.9 (57.6), 54.8 (54.0), 46.9 (46.8), 32.5 (31.0), 29.2 (29.1), 21.5 ppm. IR (KBr): $\tilde{\nu}$ = 2956, 1745, 1712, 1455, 1416, 1348, 1162, 663 cm^{-1}. MS (ESI): *m*/*z* = 523.2 $[M + H]^+$. HRMS (ESI): calcd. for $C_{28}H_{30}N_2O_6SNa^+$ $[M + Na]^+$ 545.1717; found 545.1729.

Synthesis of Compounds 9: *n*BuBr (0.65 mL, 6.0 mmol, 2.0 equiv.) was slowly added to a stirred solution of **8** (1.20 g, 3.0 mmol, 1.0 equiv.), K_2CO_3 (0.496 g, 3.6 mmol, 1.2 equiv.), and nBu_4NBr (0.097 g, 0.3 mmol, 0.1 equiv.) in acetone (30 mL) and DMF (5 mL). The stirring was continued for 5 d at room temperature. Then the reaction mixture was concentrated in vacuo before water (50 mL) was added. The mixture was extracted with DCM (2 × 25 mL). The combined organic portions were washed with saturated brine (40 mL), dried with Na_2SO_4, and concentrated in vacuo. The crude product was purified by flash column chromatography (PE/EA, 3:1) to give **9** as a white solid.

Benzyl (2*R*,4*S*)-4-(*N*-Butyl-4-methylphenylsulfonamido)-2-cyanopyrrolidine-1-carboxylate (9a): Yield 1.228 g, 90%. $[\alpha]_D^{23}$ = 18.7 (*c* = 1.75, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ = 7.67 (d, *J* = 8.4 Hz, 2 H), 7.38–7.22 (m, 7 H), 5.13 (d, *J* = 5.7 Hz, 2 H), 4.64–4.47 (m, 2 H), 3.67–3.46 (m, 1 H), 3.23–3.10 (m, 1 H), 3.10–2.95 (m, 2 H), 3.05 (s, 3 H), 2.40–2.10 (m, 2 H), 1.56 (m, 2 H), 1.25 (q, *J* = 7.5 Hz, 2 H), 0.87 (t, *J* = 7.5 Hz, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, the signals in parentheses refer to the rotamer): δ = 162.5, 154.0 (153.1), 144.0, 136.8 (135.6), 130.0, 128.6, 128.4, 128.2, 127.0, 118.0 (117.8), 68.1 (68.0), 55.7 (54.8), 47.3 (46.9), 45.5 (45.2), 45.1, 36.4 (34.3), 33.5 (33.4), 33.1 (31.4), 21.5 (20.0), 13.7 ppm. IR (film): $\tilde{\nu}$ = 2957, 2927, 1713, 1455, 1410, 1353, 1162, 550 cm^{-1}. MS (ESI): *m*/*z* = 473.2 $[M + NH_4]^+$. HRMS (ESI): calcd. for $C_{24}H_{29}N_3O_4SNa^+$ $[M + Na]^+$ 478.1771; found 478.1777.

Benzyl (2*R*,4*S*)-2-Cyano-4-(*N*-octyl-4-methylphenylsulfonamido)pyrrolidine-1-carboxylate (9b): Yield 1.318 g, 86%. $[\alpha]_D^{23}$ = 16.7 (*c* = 2.56, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ = 7.61 (d, *J* = 9.0 Hz, 2 H), 7.42–7.17 (m, 7 H), 5.06 (d, *J* = 6.6 Hz, 2 H), 4.60–4.40 (m, 2 H), 3.61–3.38 (m, 1 H), 3.18–3.03 (m, 1 H), 3.03–2.90 (m, 2 H), 2.34 (s, 3 H), 2.23–2.07 (m, 2 H), 1.50 (br., 2 H), 1.16 (m, 10 H), 0.80 (t, *J* = 6.6 Hz, 3 H) ppm. ^{13}C NMR (75 MHz,

$CDCl_3$, the signals in parentheses refer to the rotamer): δ = 162.4, 153.9 (153.1), 143.9, 136.8 (135.6), 130.0, 128.5, 128.4, 128.1, 126.9, 117.9 (117.8), 68.0 (67.9), 55.6 (54.8), 47.2 (46.9), 45.5 (45.3), 36.4, 34.3 (33.0), 31.7, 31.4 (31.3), 29.1, 29.0, 26.7, 22.5, 21.5, 14.0 ppm. IR (film): ṽ = 2927, 2856, 1716, 1455, 1410, 1353, 1161, 550 cm^{-1}. MS (ESI): *m*/*z* = 529.2 $[M + NH_4]^+$. HRMS (ESI): calcd. for $C_{28}H_{37}N_3O_4SNa^+$ $[M + Na]^+$ 534.2397; found 534.2395.

Benzyl (2*R*,4*S*)-2-Cyano-4-(*N*-dodecyl-4-methylphenylsulfonamido)-pyrrolidine-1-carboxylate (9c): Yield 1.361 g, 80%. $[\alpha]_D^{23}$ = 16.2 (*c* = 0.92, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ = 7.62 (d, *J* = 8.7 Hz, 2 H), 7.30–7.16 (m, 7 H), 5.07 (m, 2 H), 4.63–4.42 (m, 2 H), 3.60–3.42 (m, 1 H), 3.22–3.05 (m, 1 H), 3.05–2.83 (m, 2 H), 2.35 (s, 3 H), 2.27–2.10 (m, 2 H), 1.51 (br., 2 H), 1.17 (m, 18 H), 0.81 (t, *J* = 6.6 Hz, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, the signals in parentheses refer to the rotamer): δ = 162.0, 153.9 (153.2), 144.0, 136.8 (135.7), 130.0, 128.6, 128.5 (128.4), 128.3 (128.1), 127.0, 117.9, 68.0, 55.7 (54.9), 47.3 (46.9), 45.5 (45.2), 34.4, 33.1, 31.9 (31.4), 29.6, 29.5, 29.3, 29.2, 26.8, 22.7, 21.5, 14.1 ppm. IR (film): ṽ = 2925, 2854, 1716, 1456, 1410, 1353, 1161, 550 cm^{-1}. MS (ESI): *m*/*z* = 585.4 $[M + NH_4]^+$. HRMS (ESI): calcd. for $C_{32}H_{45}N_3O_4SNa^+$ $[M + Na]^+$ 590.3023; found 590.3024.

Synthesis of Catalysts C[1]–C[12] and E[1]: A solution of the ester (5 mmol) and MeOH saturated with NH_3 (100 mL) in a tightly sealed bottle (250 mL) at room temperature was stirred for 5 d. The solvent was then removed under reduced pressure to give the corresponding acylamide without further purification.

Under dry N_2, a solution of $POCl_3$ (2.8 mL, 30 mmol) in DCM (10 mL) was added dropwise to a stirred solution of the acylamide (5 mmol) and pyridine (10 mL) in DCM (20 mL) under cooling in an ice/water bath. Stirring was continued for 3 h at the same temperature. The resulting mixture was poured into ice/water (100 mL) and the water portion was extracted with DCM (2 × 30 mL). The combined organic portions were washed with saturated Cu_2SO_4 (2 × 80 mL) and saturated brine (40 mL), dried with Na_2SO_4, and concentrated in vacuo. The crude product was purified by flash column chromatography (PE/EA, 4:1) to give the corresponding nitrile.

NaN_3 (0.52 g, 8 mmol) and NH_4Cl (0.432 g, 8 mmol) were added to a stirred solution of nitrile (4 mmol) in DMF (40 mL). Stirring was continued for 1 d at 70 °C. The resulting mixture was concentrated in vacuo to remove most of the DMF, then water (100 mL) was added, and the water phase was extracted with DCM (2 × 50 mL). The combined organic portions were washed with saturated brine (2 × 50 mL), dried with Na_2SO_4, and concentrated in vacuo. The crude product was purified by flash column chromatography (DCM/MeOH, 10:1) to give the Cbz-protected tetrazole.

10% Pd/C (10 wt.-%) was added to a solution of the Cbz-protected tetrazole (2 mmol) in methanol and the mixture was subjected to hydrogenation under a pressure of 1 atmosphere at room temperature. The reaction was monitored by TLC. After completion of the reaction, the reaction mixture was filtered and concentrated in vacuo to afford the crude product. The pure catalysts **C** were obtained by recrystallization from methanol.

(*S*)-5-(Pyrrolidin-2-yl)-1*H*-tetrazole (C[1]):[1] Yield 0.234 g, 84%. $[\alpha]_D^{25}$ = –27.5 (*c* = 1.30, DMSO). ^1H NMR (300 MHz, $[D_4]$MeOH): δ = 5.02–4.96 (m, 1 H), 3.55–3.42 (m, 2 H), 2.62–2.47 (m, 1 H), 2.46–2.10 (m, 3 H) ppm. IR (KBr): ṽ = 2962, 2586, 2466, 1627, 1456, 1418, 1397, 954 cm^{-1}.

(2*S*,3*R*,7*R*)-5-(Octahydro-1*H*-indol-2-yl)-1*H*-tetrazole (C[2]): Yield 0.317 g, 82%. $[\alpha]_D^{24}$ = –6.0 (*c* = 0.77, DMSO). ^1H NMR (300 MHz, $[D_4]$MeOH): δ = 4.98 (t, *J* = 8.4 Hz, 1 H), 3.70 (dd, *J* = 15.3, 6.6 Hz, 1 H), 2.74–2.40 (m, 3 H), 1.96–1.26 (m, 8 H) ppm. IR (KBr): ṽ = 2930, 2530, 1617, 1443, 1397, 1097, 889 cm^{-1}.

(*S*)-5-(Indolin-2-yl)-1*H*-tetrazole (C[3]): Yield 0.329 g, 88%. $[\alpha]_D^{24}$ = –21.1 (*c* = 0.80, DMSO). ^1H NMR (300 MHz, $[D_4]$MeOH): δ = 7.16–7.02 (m, 2 H), 6.82–6.70 (m, 2 H), 5.29 (t, *J* = 9.0 Hz, 1 H), 3.68–3.57 (m, 1 H), 3.28–3.17 (m, 1 H) ppm. IR (KBr): ṽ = 3349, 2935, 2598, 1882, 1605, 1569, 1484, 1244, 1054, 747 cm^{-1}.

(2*S*,4*S*)-5-[4-(4-Methylphenylsulfonamido)pyrrolidin-2-yl]-1*H*-tetrazole (C[4]): Yield 0.554 g, 90%, m.p. 169–170 °C. $[\alpha]_D^{25}$ = –11.4 (*c* = 1.05, DMSO). ^1H NMR (300 MHz, $[D_6]$DMSO): δ = 8.26 (br., 1 H), 7.73 (d, *J* = 8.1 Hz, 2 H), 7.43 (d, *J* = 8.1 Hz, 2 H), 4.76–4.62 (m, 1 H), 4.00–3.84 (m, 1 H), 3.34–3.20 (m, 1 H), 3.00–2.82 (m, 1 H), 2.40 (s, 3 H), 2.10–1.90 (m, 2 H) ppm. ^{13}C NMR (75 MHz, $[D_6]$DMSO): δ = 157.8, 143.6, 138.2, 130.4, 127.2, 53.6, 51.9, 49.7, 36.5, 21.5 ppm. IR (KBr): ṽ = 3559, 3107, 2895, 2448, 1653, 1449, 1312, 1152, 1093, 661 cm^{-1}. MS (ESI): *m*/*z* = 309.2 $[M + H]^+$. HRMS (ESI): calcd. for $C_{12}H_{17}N_6O_2S^+$ $[M + H]^+$ 309.1128; found 309.1133.

(2*S*,4*S*)-5-[4-(*N*,4-Dimethylphenylsulfonamido)pyrrolidin-2-yl]-1*H*-tetrazole (C[5]): Yield 0.547 g, 85%, m.p. 162–163 °C. $[\alpha]_D^{25}$ = –19.2 (*c* = 0.95, DMSO). ^1H NMR (300 MHz, $[D_6]$DMSO): δ = 7.73 (d, *J* = 8.4 Hz, 2 H), 7.45 (d, *J* = 8.4 Hz, 2 H), 4.93–4.80 (m, 1 H), 4.80–3.68 (m, 1 H), 3.29 (m, 1 H), 3.00–2.84 (m, 1 H), 2.72 (s, 3 H), 2.40 (s, 3 H), 2.26–2.14 (m, 1 H), 2.10–1.94 (m, 1 H) ppm. IR (KBr): ṽ = 3548, 2972, 2451, 1657, 1597, 1343, 1153, 1091, 983, 665 cm^{-1}. MS (ESI): *m*/*z* = 323.2 $[M + H]^+$. $C_{13}H_{18}N_6O_2S$: C 48.43, H 5.63, N 26.07; found C 48.20, H 5.44, N 26.31.

(2*R*,4*S*)-5-[4-(4-Methylphenylsulfonamido)pyrrolidin-2-yl]-1*H*-tetrazole (C[6]): Yield 0.536 g, 87%, m.p. 217–218 °C. $[\alpha]_D^{27}$ = –8.6 (*c* = 1.80, DMSO). ^1H NMR (300 MHz, $[D_6]$DMSO): δ = 8.18 (br., 1 H), 7.72 (m, 2 H), 7.42 (m, 2 H), 4.95–4.82 (m, 1 H), 3.93 (br., 1 H), 3.46–3.32 (m, 1 H), 3.10–2.97 (m, 1 H), 2.37 (s, 3 H), 2.30–2.07 (m, 2 H) ppm. ^{13}C NMR (75 MHz, $[D_6]$DMSO): δ = 157.9, 143.7, 137.8, 130.4, 127.2, 53.7, 52.3, 50.9, 36.8, 21.5 ppm. IR (KBr): ṽ = 3543, 3112, 2430, 1594, 1450, 1314, 1159, 1094, 706 cm^{-1}. MS (ESI): *m*/*z* = 309.2 $[M + H]^+$. HRMS (ESI): calcd. for $C_{12}H_{17}N_6O_2S^+$ $[M + H]^+$ 309.1128; found 309.1132.

(2*R*,4*S*)-5-[4-(*N*,4-Dimethylphenylsulfonamido)pyrrolidin-2-yl]-1*H*-tetrazole (C[7]): Yield 0.560 g, 87%, m.p. 156–157 °C. $[\alpha]_D^{25}$ = –8.0 (*c* = 1.45, DMSO). ^1H NMR (300 MHz, $[D_6]$DMSO): δ = 7.69 (d, *J* = 8.4 Hz, 2 H), 7.45 (d, *J* = 8.4 Hz, 2 H), 4.92–4.80 (m, 2 H), 3.28 (m, 1 H), 3.05–2.96 (m, 1 H), 3.00 (s, 3 H), 2.40 (s, 3 H), 2.13–2.05 (m, 2 H) ppm. IR (KBr): ṽ = 3611, 3430, 2962, 2423, 1649, 1597, 1337, 1158, 1087, 669 cm^{-1}. MS (ESI): *m*/*z* = 323.2 $[M + H]^+$. $C_{13}H_{18}N_6O_2S$: C 48.43, H 5.63, N 26.07; found C 48.25, H 5.50, N 26.19.

(2*R*,4*S*)-5-(4-Methylsulfonamidopyrrolidin-2-yl)-1*H*-tetrazole (C[8]): M.p. 204–205 °C. Yield 0.399 g, 86%. $[\alpha]_D^{26}$ = –26.4 (*c* = 1.05, DMSO). ^1H NMR (300 MHz, $[D_6]$DMSO): δ = 7.69 (br., 1 H), 4.98 (m, 1 H), 4.26 (br., 1 H), 3.67–3.56 (m, 1 H), 3.22 (m, 1 H), 3.02 (s, 3 H), 2.55–2.45 (m, 1 H), 2.44–2.32 (m, 1 H) ppm. ^{13}C NMR (75 MHz, $[D_6]$DMSO): δ = 158.1, 54.1, 52.3, 51.6, 40.8, 37.7 ppm. IR (KBr): ṽ = 3295, 3000, 2472, 1602, 1462, 1328, 1154, 1029, 764 cm^{-1}. MS (ESI): *m*/*z* = 233.1 $[M + H]^+$. HRMS (ESI): calcd. for $C_6H_{12}N_6O_2SNa^+$ $[M + Na]^+$ 255.0635; found 255.0643.

(2*R*,4*S*)-5-[4-(2,4,6-Trimethylphenylsulfonamido)pyrrolidin-2-yl]-1*H*-tetrazole (C[9]): Yield 0.558 g, 83%, m.p. 238 °C (dec.). $[\alpha]_D^{25}$ = –8.8 (*c* = 1.70, DMSO). ^1H NMR (300 MHz, $[D_6]$DMSO): δ = 8.03 (br., 1 H), 7.10–7.00 (m, 2 H), 4.89 (t, *J* = 8.7 Hz, 1 H), 3.98 (t, *J* = 8.7 Hz, 1 H), 3.45 (m, 1 H), 3.05–2.95 (m, 1 H), 2.58 (s, 6 H), 2.27 (s, 3 H), 2.30–2.16 (m, 1 H), 2.16–1.99 (m, 1 H) ppm. ^{13}C

NMR (75 MHz, [D$_6$]DMSO): δ = 158.1, 142.5, 139.0, 134.4, 132.4, 53.7, 51.5, 50.5, 36.7, 23.1, 20.9 ppm. IR (KBr): $\tilde{\nu}$ = 3536, 3112, 2974, 1604, 1456, 1328, 1160, 660 cm^{-1}. MS (ESI): *m*/*z* = 337.1 [M + H]$^+$. HRMS (ESI): calcd. for $C_{14}H_{20}N_6O_2S^+$ [M + H]$^+$ 337.1441; found 337.1438.

(2*R*,4*S*)-5-[4-(*N*-Butyl-4-methylphenylsulfonamido)pyrrolidin-2-yl]-1*H*-tetrazole (C^{10}): Yield 0.612 g, 84%, m.p. 244–245 °C. $[\alpha]_D^{24}$ = 15.5 (*c* = 0.60, DMSO). ^{1}H NMR (300 MHz, [D$_4$]MeOH): δ = 7.80 (d, *J* = 8.4 Hz, 2 H), 7.45 (d, *J* = 8.1 Hz, 2 H), 5.20 (t, *J* = 6.9 Hz, 1 H), 4.96–4.80 (m, 1 H), 3.72–3.62 (m, 1 H), 3.43–3.30 (m, 1 H), 3.25–3.17 (m, 2 H), 2.57–2.40 (m, 2 H), 2.46 (s, 3 H), 1.69 (m, 2 H), 1.38 (q, *J* = 7.5 Hz, 2 H), 0.98 (t, *J* = 7.5 Hz, 3 H) ppm. ^{13}C NMR (75 MHz, [D$_6$]DMSO): δ = 158.4, 144.0, 136.8, 130.5, 127.4, 56.0, 53.5, 46.7, 44.4, 34.0, 32.9, 21.4, 20.0, 14.1 ppm. IR (KBr): $\tilde{\nu}$ = 3169, 2925, 2855, 1597, 1468, 1345, 1160, 1091, 673, 571 cm^{-1}. MS (ESI): *m*/*z* = 365.2 [M + H]$^+$. HRMS (ESI): calcd. for $C_{16}H_{25}N_6O_2S^+$ [M + H]$^+$ 365.1754; found 365.1769.

(2*R*,4*S*)-5-[4-(*N*-Octyl-4-methylphenylsulfonamido)pyrrolidin-2-yl]-1*H*-tetrazole (C^{11}): Yield 0.638 g, 76%, m.p. 183–184 °C. $[\alpha]_D^{24}$ = –2.80 (*c* = 1.15, DMSO). ^{1}H NMR (300 MHz, [D$_4$]MeOH): δ = 7.81 (d, *J* = 8.1 Hz, 2 H), 7.45 (d, *J* = 8.1 Hz, 2 H), 5.24 (t, *J* = 6.9 Hz, 1 H), 4.94–4.82 (m, 1 H), 3.75–3.64 (m, 1 H), 3.43–3.35 (m, 1 H), 3.26–3.13 (m, 2 H), 2.55–2.42 (m, 2 H), 2.46 (s, 3 H), 1.69 (m, 2 H), 1.33 (m, 10 H), 0.94 (t, *J* = 6.9 Hz, 3 H) ppm. ^{13}C NMR (75 MHz, [D$_6$]DMSO): δ = 158.3, 144.0, 136.8, 130.5, 127.4, 56.0, 53.5, 46.6, 44.6, 32.9, 31.8, 31.7, 29.1, 28.1, 26.7, 22.5, 21.4, 14.4 ppm. IR (KBr): $\tilde{\nu}$ = 2955, 2871, 2525, 1594, 1409, 1346, 1161, 1137, 663, 548 cm^{-1}. MS (ESI): *m*/*z* = 421.2 [M + H]$^+$. HRMS (ESI): calcd. for $C_{20}H_{33}N_6O_2S^+$ [M + H]$^+$ 421.2380; found 421.2390.

(2*R*,4*S*)-5-[4-(*N*-Dodecyl-4-methylphenylsulfonamido)pyrrolidin-2-yl]-1*H*-tetrazole (C^{12}): Yield 0.639 g, 67%, m.p. 190–191 °C. $[\alpha]_D^{24}$ = –11.8 (*c* = 0.95, DMSO). ^{1}H NMR (300 MHz, [D$_4$]MeOH): δ = 7.80 (d, *J* = 8.4 Hz, 2 H), 7.44 (d, *J* = 7.8 Hz, 2 H), 5.19 (t, *J* = 6.6 Hz, 1 H), 4.96–4.82 (m, 1 H), 3.72–3.58 (m, 1 H), 3.46–3.35 (m, 1 H), 3.25–3.14 (m, 1 H), 2.55–2.36 (m, 2 H), 2.46 (s, 3 H), 1.69 (m, 2 H), 1.32 (m, 18 H), 0.93 (t, *J* = 6.6 Hz, 3 H) ppm. ^{13}C NMR (75 MHz, [D$_6$]DMSO): δ = 158.4, 143.9, 136.8, 130.4, 127.3, 56.0, 53.4, 46.4, 44.6, 32.9, 31.7, 29.5, 29.5, 29.2, 26.7, 22.5, 21.3, 14.3 ppm. IR (KBr): $\tilde{\nu}$ = 2924, 2854, 1598, 1459, 1341, 1159, 1091, 814, 661 cm^{-1}. MS (ESI): *m*/*z* = 477.3 [M + H]$^+$. HRMS (ESI): calcd. for $C_{24}H_{41}N_6O_2S^+$ [M + H]$^+$ 477.3006; found 477.3015.

(2*S*,4*R*)-5-[4-(*tert*-Butyldiphenylsilyloxy)pyrrolidin-2-yl]-1*H*-tetrazole (E^1): Yield 0.707 g, 90%, m.p. 128–129 °C. $[\alpha]_D^{26}$ = –14.0 (*c* = 1.43, DMSO). ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ = 8.03 (s, 1 H), 7.66–7.58 (m, 4 H), 7.50–7.40 (m, 6 H), 5.25 (t, *J* = 7.2 Hz, 1 H), 4.69–4.63 (m, 1 H), 3.42–3.29 (m, 2 H), 2.43–2.32 (m, 1 H), 2.24–2.16 (m, 1 H), 1.03 (s, 9 H) ppm. IR (KBr): $\tilde{\nu}$ = 3432, 2956, 1653, 1471, 1428, 1090, 1020, 702 cm^{-1}.

General Procedure for the Enantioselective Biginelli Reaction: Compound **3** (0.26 mmol) was added to a stirred solution of catalyst (10 mol-%, 0.25 mmol) and **2** (0.30 mmol) in EtOH (1.0 mL). The reaction mixture was stirred at 25 °C for the time given in Tables 1, 2, 3, 4, and 5. After removal of the solvent, the crude product was purified by flash column chromatography (PE/EA = 1:1) to afford the corresponding product. The enantiomeric excesses were determined by HPLC using a chiral column (OD or OD-H).

Supporting Information (see also the footnote on the first page of this article): ^{1}H and ^{13}C NMR spectra and HPLC chromatograms.

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[1] a) H. Torii, M. Nakadai, K. Ishihara, S. Saito, H. Yamamoto, *Angew. Chem. Int. Ed.* **2004**, *43*, 1983–1986; b) Y. Yamamoto, N. Momiyama, H. Yamamoto, *J. Am. Chem. Soc.* **2004**, *126*, 5962–5963.
[2] a) A. J. A. Cobb, D. M. Shaw, S. V. Ley, *Synlett* **2004**, *3*, 558–560; b) C. E. T. Mitchell, S. E. Brenner, J. García-Fortanet, S. V. Ley, *Org. Biomol. Chem.* **2006**, *4*, 2039–2049; c) A. J. A. Cobb, D. A. Longbottom, D. M. Shaw, S. V. Ley, *Chem. Commun.* **2004**, 1808–1809.
[3] A. Hartikka, P. I. Arvidsson, *Tetrahedron: Asymmetry* **2004**, *15*, 1831–1834.
[4] a) A. J. A. Cobb, D. M. Shaw, D. A. Longbottom, J. B. Gold, S. V. Ley, *Org. Biomol. Chem.* **2005**, *3*, 84–96; b) N. S. Chowdari, M. Ahmad, K. Albertshofer, F. Tanaka, C. F. Barbas III, *Org. Lett.* **2006**, *8*, 2839–2842; c) Y. Hayashi, T. Urushima, S. Aratake, T. Okano, K. Obi, *Org. Lett.* **2008**, *10*, 21–24.
[5] a) C. E. T. Mitchell, S. E. Brenner, S. V. Ley, *Chem. Commun.* **2005**, 5346–5348; b) K. R. Knudsen, C. E. T. Mitchell, S. V. Ley, *Chem. Commun.* **2006**, 66–68.
[6] a) A. Hartikka, P. I. Arvidsson, *Eur. J. Org. Chem.* **2005**, *11*, 4287–4295; b) I. Ibrahem, W. Zou, Y. Xu, A. Córdova, *Adv. Synth. Catal.* **2006**, *348*, 211–222.
[7] a) S.-G. Kim, T.-H. Park, *Tetrahedron Lett.* **2006**, *47*, 9067–9071; b) S. Kumarn, D. M. Shaw, S. V. Ley, *Chem. Commun.* **2006**, 3211–3213; c) S. Kumarn, D. M. Shaw, D. A. Longbottom, S. V. Ley, *Org. Lett.* **2005**, *7*, 4189–4191; d) N. Momiyama, Y. Yamamoto, H. Yamamoto, *J. Am. Chem. Soc.* **2007**, *129*, 1190–1195.
[8] N. S. Chowdari, C. F. Barbas III, *Org. Lett.* **2005**, *7*, 867–870.
[9] D. E. Ward, V. Jheengut, G. E. Beye, *J. Org. Chem.* **2006**, *71*, 8989–8992.
[10] a) A. Prieto, N. Halland, K. A. Jorgensen, *Org. Lett.* **2005**, *7*, 3897–3900; b) L. Hojabri, A. Hartikka, F. M. Moghaddam, P. I. Arvidssona, *Adv. Synth. Catal.* **2007**, *349*, 740–748; c) A. Córdova, W. B. Zou, P. Dziedzic, I. Ibrahem, E. Reyes, Y. M. Xu, *Chem. Eur. J.* **2006**, *12*, 5383–5397; d) I. Ibrahem, W. B. Zou, M. Engqvist, Y. M. Xu, A. Córdova, *Chem. Eur. J.* **2005**, *11*, 7024–7029; e) A. Hartikka, P. I. Arvidsson, *J. Org. Chem.* **2007**, *72*, 5874–5877; f) H. Sunden, I. Ibrahem, A. Córdova, *Tetrahedron Lett.* **2006**, *47*, 99–103; g) C. E. T. Mitchell, A. J. A. Cobb, S. V. Ley, *Synlett* **2005**, *4*, 611–614; h) M. Limbach, *Chem. Biodivers.* **2006**, *3*, 119–133.
[11] a) P. Biginelli, *Ber. Dtsch. Chem. Ges.* **1891**, *24*, 1317–2962; b) P. Biginelli, *Ber. Dtsch. Chem. Ges.* **1893**, *26*, 447.
[12] a) C. O. Kappe, *Acc. Chem. Res.* **2000**, *33*, 879–888; b) C. O. Kappe, *Org. React.* **2004**, *63*, 1; c) C. O. Kappe, *Tetrahedron* **1993**, *49*, 6937–6963; d) C. O. Kappe, *J. Org. Chem.* **1997**, *62*, 7201–7204; e) E. H. Hu, D. R. Sidler, U. H. Dolling, *J. Org. Chem.* **1998**, *63*, 3454–3457; f) D. S. Bose, L. Fatima, H. B. Mereyala, *J. Org. Chem.* **2003**, *68*, 587–590.
[13] a) A. Dondoni, A. Massi, S. Sabbatini, V. Bertolasi, *J. Org. Chem.* **2002**, *67*, 6979–6994; b) B. Schnell, U. T. Strauss, P. Verdino, K. Faber, C. O. Kappe, *Tetrahedron: Asymmetry* **2000**, *11*, 1449–1453; c) A. Dondoni, A. Massi, S. Sabbatini, *Tetrahedron Lett.* **2002**, *43*, 5913–5916; d) B. Schnell, W. Krenn, K. Faber, C. O. Kappe, *J. Chem. Soc. Perkin Trans. 1* **2000**, 4382–4389.
[14] For reviews, see: a) C. O. Kappe, *QSAR Comb. Sci.* **2003**, *22*, 630–645; b) C. O. Kappe, *Eur. J. Med. Chem.* **2000**, *35*, 1043–1052; for a recent example,see: c) S. Lou, B. M. Taoka, A. Ting, S. E. Schaus, *J. Am. Chem. Soc.* **2005**, *127*, 11256–11257.

[15] Y. J. Huang, F. Y. Yang, C. J. Zhu, *J. Am. Chem. Soc.* **2005**, *127*, 16386–16387.
[16] a) X. H. Chen, X. Y. Xu, H. Liu, L. F. Cun, L. Z. Gong, *J. Am. Chem. Soc.* **2006**, *128*, 14802–14803; b) L. Z. Gong, X. H. Chen, X. Y. Xu, *Chem. Eur. J.* **2007**, *13*, 8920–8926.
[17] J. G. Xin, L. Chang, Z. R. Hou, D. J. Shang, X. H. Liu, X. M. Feng, *Chem. Eur. J.* **2008**, *14*, 3177–3181.
[18] a) Y.-Y. Wu, Y.-Z. Zhang, M.-L. Yu, G. Zhao, S.-W. Wang, *Org. Lett.* **2006**, *8*, 4417–4420; b) L.-Q. Gu, Y.-Y. Wu, Y.-Z. Zhang, G. Zhao, *J. Mol. Catal. A: Chem.* **2007**, *263*, 186–194; c) L.-Q. Gu, G. Zhao, *Adv. Synth. Catal.* **2007**, *349*, 1629–1632; d) L.-Q. Gu, Y. Z. Zhang, X. Y. Wu, M. L. Yu, G. Zhao, *Adv. Synth. Catal.* **2006**, *348*, 2223–2228.
[19] M. Tamaki, G. Han, V. J. Hruby, *J. Org. Chem.* **2001**, *66*, 1038–1042.
[20] a) N. Mase, Y. Nakai, N. Ohara, H. Yoda, K. Takabe, F. Tanaka, C. F. Barbas III, *J. Am. Chem. Soc.* **2006**, *128*, 734–735; b) N. Mase, K. Watanabe, H. Yoda, K. Takabe, F. Tanaka, C. F. Barbas III, *J. Am. Chem. Soc.* **2006**, *128*, 4966–4967.

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