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Asymmetric Organocatalysis with Novel Chiral Thiourea Derivatives: Bifunctional Catalysts for the Strecker and Nitro-Michael Reactions

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Novel bifunctional organocatalysts bearing both a thiourea moiety and an imidazole group on a chiral scaffold were synthesized and applied to the Strecker synthesis and nitro-Michael reaction. The addition of acetone to nitroolefins in the presence of these novel bifunctional organocatalysts gave enantioselectivities (up to 87 % *ee*) that are superior to those generated by the proline and/or homo-proline tetrazole catalysts described in the literature.

Introduction

The continually increasing number of contributions to the field of asymmetric synthesis with chiral bifunctional catalysts undoubtedly confirms the importance of this area of research for chemists from both academia as well as industry.[1,2]

A large body of results from Jacobsen's laboratory clearly demonstrated peptide-like thiourea based molecules to be excellent bifunctional chiral catalysts for the asymmetric Strecker synthesis,[3–5] enantioselective hydrophosphonylation of imines,[6] Acyl-Pictet–Spengler[7] and nitro-Mannich[8] reactions.

Furthermore, examples of enantioselective Michael additions,[9–13] Aza-Henry,[14] Baylis–Hillman[15,16] reactions and dynamic kinetic resolution of azlactones[17] have recently been reported in which chiral bifunctional organocatalysts have been employed.

However, the design and development of new, effective and easily accessible bifunctional chiral organic catalysts continues to be a major challenge.

Based on our previous results and the observation[18] that imidazole as a base is essential for thiourea catalytic activity, we report here on the syntheses and application of some novel chiral imidazole-based thiourea catalysts for C–C bond formation reactions. Initially, these bifunctional organocatalysts were tested in the asymmetric Strecker reaction,[19] one of the most direct and efficient methods for the asymmetric synthesis of natural and unnatural α-amino acids. Furthermore, the high potential of these bifunctional organocatalysts for conjugate addition reactions, for example in the Michael addition of acetone to β-nitrostyrene, is demonstrated.

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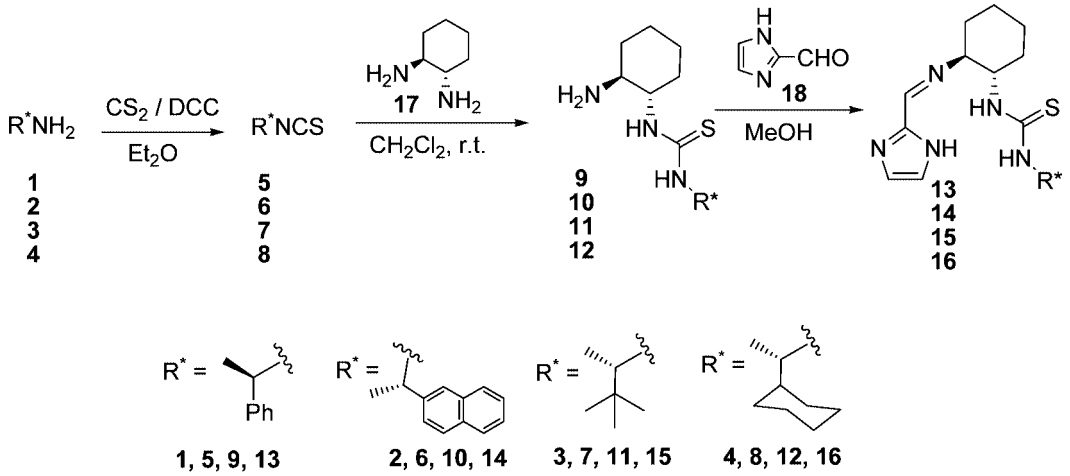
Results and Discussion

Our investigation began with the preparation of novel thiourea compounds **13**–**16** from four different chiral amines: (*R*)-(+)-1-phenylethylamine (**1**), (*S*)-1-(2-naphthyl) ethylamine (**2**), (*S*)-3,3-dimethyl-2-aminobutane (**3**) and (*S*)-1-cyclohexylethylamine (**4**) by known methods[5,20,21] as summarised in Scheme 1. These derivatives were then examined for their ability to mediate the enantioselective Strecker reaction.

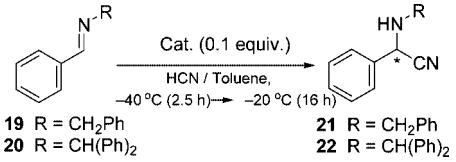
As a model transformation we studied the addition of hydrogen cyanide to aldimines **19** and **20** in the presence of 0.1 equiv. of the appropriate thiourea derivative, with the reaction proceeding for 2.5 h at –40 °C and subsequently for a further 16 h at –20 °C (Scheme 2).

The results obtained show that the nature of the substrate influences both the reaction rate and enantioselectivity to a large extent. Notably, catalysts **13**–**16** afforded low to moderate conversions (up to 47%) and enantioselectivities (up to 39% *ee*) with substrate **19** over 2.5 h at –40 °C (Entries 1, 3, 5, 7 of Table 1). Better enantioselectivities (up to 68% *ee*), but worse conversions (up to 24%) were observed under the same reaction conditions with the aldimine substrate **20**. The bulkier *N*-benzhydryl subunit present in substrate **20** seems to have a beneficial effect on the enantioselectivity (Entries 2 and 6 of Table 1).

A longer reaction time (16 h at –20 °C) provided high conversions with the aldimine substrate **19** (93–100%, Entries 1, 3, 5, 7 of Table 1) and low to good conversions with the bulkier substrate **20** (12–73%, Entries 2, 4, 6, 8 of Table 1). At the same time, the enantiomeric excess values



Scheme 1.



Scheme 2.

of all products were reduced during the course of the reaction, indicating that racemization of the product takes place under the reaction conditions.

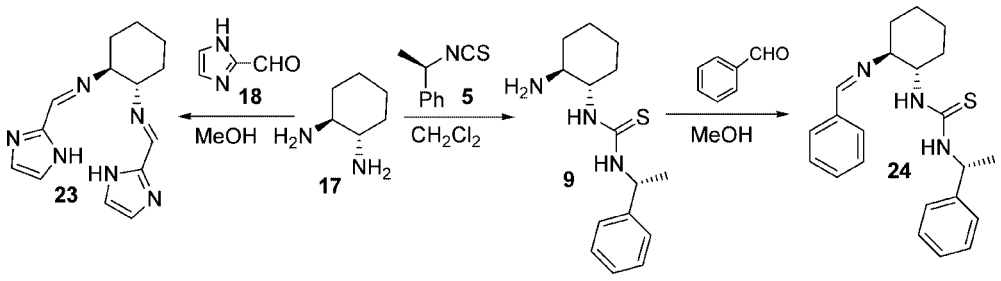
The contribution of the thiourea and imidazole subunits to the activity of the catalyst was then investigated. Replacing the thiourea moiety of **13** with an imidazole ring (compound **23**, Scheme 3) led to a reduction in the conversion of aldimine **19** from 96% to 74%, as well as a corresponding reduction in enantiomeric excess of the product from 12% to 3% (Table 1, Entry 1 vs. Entry 9). Whereas thiourea derivative **24**, which has no imidazole moiety (prepared according to Scheme 3), provides a comparatively high conversion of substrate **19** to that generated by catalyst **13** (Table 1, Entry 10 vs. Entry 1), only 10% conversion and 4% *ee* were observed with catalyst **24** for substrate **20** (Table 1, Entry 11 vs. Entry 2). This represents a 63% reduction in the conversion and a 20% reduction in the *ee* value compared to the imidazole-based chiral thiourea **13**. These results indicate that for a high conversion the catalyst should possess both an imidazole group and a thiourea moiety.

In order to explain the low enantioselectivities observed we examined the reaction of aldimine substrates **19** and **20** in the absence of catalyst under the standard reaction conditions (–20 °C, 16 h). The rate of the noncatalysed racemic reaction was found to be very low for the *N*-benzhydryl imine **20** but significant for the *N*-benzyl benzaldehyde imine **19** (5% and 54% conversion, respectively, Entries 12, 13 in Table 1). Taking these results into consideration we speculated that complete suppression of the noncatalysed racemic reaction pathway might occur at a reduced temperature. Indeed, a slight enhancement in the *ee* value from

Table 1. Strecker reactions catalyzed by thiourea derivatives **13**–**16** and compounds **23** and **24**.

Entry	Catalyst	Substrate	2.5 h at –40 °C		16 h at –20 °C	
			conv. [%][a]	*ee* [%][a]	conv. [%][a]	*ee* [%][a]
1	**13**	**19**	27	22	96	12
2	**13**	**20**	24	63	73	24
3	**14**	**19**	14	39	93	17
4	**14**	**20**	2	–	12	15
5	**15**	**19**	47	24	100	10
6	**15**	**20**	17	68	71	20
7	**16**	**19**	16	13	99	5
8	**16**	**20**	0	–	47	2
9	**23**	**19**	8	2	74	3
10	**24**	**19**	20	2	97	4
11	**24**	**20**	0	–	10	4
12	none	**20**	0	–	5	–
13	none	**19**	6	–	54	–
14	**13**	**19**	–	–	50[b]	31[b]

[a] Determined by HPLC after reaction proceeded for 16 h at –20 °C. Reported conversions and *ee* values are the average of 2 runs. [b] Reaction was carried out at –78 °C for 120 h.



Scheme 3.

12% to 31% was observed when the conversion of **19** was carried out at –78 °C (Table 1, Entry 1 vs. Entry 14). Unfortunately, this improved enantioselectivity was paid for by a much lower reaction rate (50% conversion in 120 h).

The novel thiourea derivatives **13**–**16** subsequently proved to be effective catalysts in the nitro-Michael reaction. The addition of acetone to *trans*-β-nitrostyrene was chosen as a model reaction to determine the catalytic activity of the thiourea compounds. Barbas and coworkers were the first to report the organocatalytic version of this reaction. Using L-proline as the catalyst in DMSO[22] they were only able to isolate the product in the racemic form. As a result, considerable effort has been directed towards the development of a catalytic asymmetric version of this reaction over the past several years, although only low enantioselectivities (up to 31% *ee*) have been obtained so far.[23–25] The best results to date have been achieved very recently using a homo-proline tetrazole catalyst in the addition of acetone to *trans*-β-nitrostyrene with up to 42% *ee*.[13b]

We first screened a range of solvents for the reaction catalysed by the novel bifunctional organocatalyst **13** (Table 2, Entries 1–5). The optimum result was observed in nonpolar toluene, providing high conversion (89%) and very good enantioselectivity (87% *ee*) (Table 2, Entry 1). This represents a 45% improvement in the *ee* value over the reported homo-proline tetrazole catalyst.[13b] Interestingly, the results in CH_2Cl_2 and $CHCl_3$ resemble those in toluene, with the sole exception of the reduced conversion achieved in CH_2Cl_2 (Table 2, Entries 2, 3). In more polar solvents (acetone, MeOH) the adduct was obtained with lower conversions and enantioselectivities, since these solvents might inhibit the hydrogen-bonding interaction between *trans*-β-nitrostyrene and the thiourea moiety of **13** (Table 2, Entries 4, 5).

It is necessary to note that the urea derivative of compound **13** gave a lower conversion (78%) and enantioselectivity (72% *ee*) in toluene with respect to thiourea **13**, which is in agreement with results reported in the literature (the interaction in the catalyst-substrate complex is stronger for thiourea than for urea).[5]

When the bifunctional thioureas **14**–**16** with the *S*-configuration in the naphthyl-, *tert*-butyl- and cyclohexylethylamine moieties were studied as catalysts in the same reaction, we found that the Michael product was formed with slightly reduced enantioselectivities (73–77% *ee*, Entries 2–4 of Table 3). The stereoselectivity of this reaction has been shown to be dependent on the presence of a suitable combination of the absolute configurations of the stereogenic centres in the catalyst molecule.

Table 2. Michael addition of acetone to *trans*-β-nitrostyrene in different solvents.

Entry	Solvent	Conversion [%][a]	*ee* [%][b] (*R*)
1	toluene	89	87
2	CH_2Cl_2	58	86
3	$CHCl_3$	86	85
4	acetone	48	79
5	MeOH	39	56

[a] Determined from the ^{1}H NMR spectrum of the crude reaction mixture. [b] Enantioselectivities were determined by chiral HPLC analysis (Daicel Chiralpak AS) in comparison with authentic racemic material.

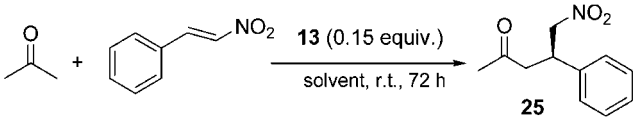
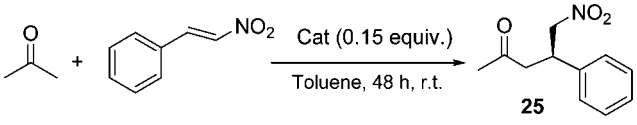


Table 3. Michael addition of acetone to *trans*-β-nitrostyrene.

Entry	Catalyst	Yield [%][a]	*ee* [%][b] (*R*)
1	**13**	55[c]	87
2	**14**	49	73
3	**15**	60	73
4	**16**	61	77
5	imidazole	n.r	–
6	**23**	n.r.	–
7	**24**	n.r	–

[a] Yield of isolated product after column chromatography on SiO_2. [b] Enantioselectivities were determined by chiral HPLC analysis (Daicel Chiralpak AS) in comparison with authentic racemic material. [c] Yield and % *ee* were determined after 40 h.

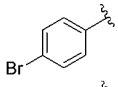
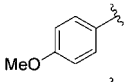


The similarity of the results using the thiourea catalysts **14**–**16** is also noteworthy, suggesting that the functionality attached to the thiourea moiety has little effect on the outcome of this reaction.

In order to gain an insight into the mechanism of catalysis, imidazole alone as well as compounds **23** and **24** were tested as catalysts. Whereas thioureas **13**–**16** gave the Michael product in up to 61% yield (Entries 1–4), no reaction was observed in the presence of imidazole, or compounds **23** and **24** (Entries 5–7, Table 3). These experiments show that neither the imidazole ring nor the thiourea moiety are able to facilitate the Michael addition on their own, and thus the prerequisite for successful conversion to product is that the catalyst possess both functionalities. Both of these groups most probably act in a synergistic manner within the catalyst.

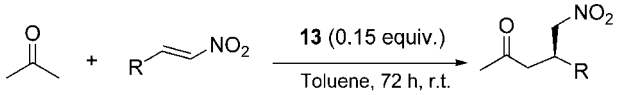
Once the optimal catalyst and solvent conditions had been established, various nitroolefins were then evaluated as substrates (Table 4).

Table 4. Michael addition of acetone to nitroolefins under optimised conditions.

Entry	Substrate (R)	Yield [%][a]	*ee* [%][b]
1		57	84
2		62	83
3		46	86
4		55[c]	87

[a] Yield of isolated product after column chromatography on SiO_2. [b] Enantioselectivities were determined by chiral HPLC analysis (Daicel Chiralpak AS) in comparison with authentic racemic material. [c] Yield and % *ee* were determined after 40 h.

The introduction of electron-withdrawing or electron-donating groups on the aromatic ring of the nitroolefins did not affect the enantioselectivities (83–87% *ee*, Table 4, Entries 1–4) or the yields (46–62%) significantly.



Although further studies are needed to firmly elucidate the reaction mechanism of this Michael addition, we postulate the sequence shown in Scheme 4.[25] Acetone in the enol/enolate form, stabilised by the imidazole group, attacks the nitrostyrene molecule enantioselectively from one face of the double bond. According to our results and the proposed model, the *Re* approach is favoured for acetone. The nitrostyrene substrate is held in place by hydrogen bonding between the nitro group and the thiourea moiety. The hydrogen bonding strength is, evidently, affected by the solvent polarity and this is consistent with the observed range of conversions and enantioselectivities found in the various solvents investigated (Table 2).

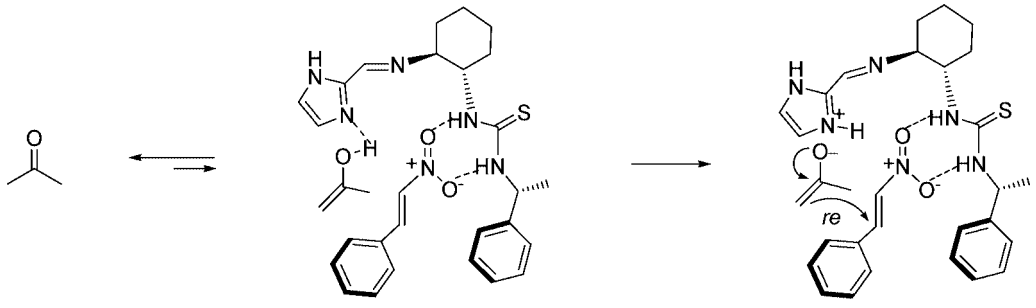
Conclusions

The novel imidazole-based chiral thiourea derivatives **13**–**16** have been shown to catalyse the nitro-Michael reaction with much higher stereoselectivity than the Strecker synthesis. In the case studied (addition of acetone to *trans*-β-nitrostyrene) these novel catalysts gave superior results in terms of enantioselectivity (up to 87% *ee*) than the known proline derivatives described in the literature.

Experimental Section

General: All solvents were purified by standard procedures and distilled prior to use. Reagents obtained from commercial sources were used without further purification. TLC chromatography was performed on precoated aluminium silica gel SIL G/UV_{254} plates (Marcherey–Nagel & Co.) or silica gel 60-F_{254} precoated glass plates (Merck). All reactions were conducted under argon or nitrogen. ^{1}H NMR spectra were recorded with a Varian Unity 300. EI mass spectra were measured with a Finnigan MAT 95: Alpha AXP DEC station 3000–300LX. ESI mass spectra were recorded with a LCQ Finnigan spectrometer. High-resolution mass spectra were measured with a Bruker APEX IV 7T FT-ICR instrument. A Perkin–Elmer 241 polarimeter was used for optical rotation measurements.

Compound 5: CS_2 (1.26 mL) and DCC (680 mg, 3.3 mmol) were added to a solution of (*R*)-1-phenylethylamine (**1**) (0.42 mL, 399.8 mg, 3.3 mmol) in dry ether (4.2 mL) at –10 °C. The reaction mixture was allowed to warm slowly to room temperature over a period of 3 h and then was stirred for a further 12 h at room temperature. After separation of the precipitated thiourea by filtration, the solvent was removed under vacuum. The residue was taken up in ether and more of the thiourea was removed by filtration. Evaporation of the solvent and rapid filtration through silica gel (with hexane) gave product **5** (506 mg, 94%) as a liquid. $[\alpha]_D^{20}$ = –4.3 (*c* = 1.0, acetone). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.30–7.43 (m, 5



Scheme 4. Proposed transition state.

H), 4.93 (q, 1 H), 1.69 (d, J = 6.6 Hz, 3 H) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 140.11, 128.84, 128.14, 125.35, 56.98, 24.90 ppm. EI-MS (70 eV); m/z (%): 163.1 (16) [M^+], 105.1 (100), 77.1 (13), 51.0 (6).

Compound 6: This compound was prepared in 51% (1.3 g) yield as a white solid, analogously with the above procedure, starting from (*S*)-1-(2-naphthyl)ethylamine (**2**). $[\alpha]_D^{20}$ = +24.9 (c = 0.095, $CHCl_3$). ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ = 7.91–7.99 (m, 4 H), 7.53–7.56 (m, 3 H), 5.42 (q, J = 6.9 Hz, 1 H), 1.71 (d, J = 6.6 Hz, 3 H) ppm. ^{13}C NMR (75.5 MHz, [D$_6$]DMSO): δ = 137.47, 132.60, 132.45, 128.60, 127.80, 127.48, 126.49, 126.32, 124.20, 123.53, 56.51, 23.86 ppm.

Compound 7: This compound was prepared from (*S*)-3,3-dimethyl-2-aminobutane (**3**) in a manner analogous to **5** and was obtained as a liquid in 80% (2.27 g) yield. $[\alpha]_D^{20}$ = +36.9 (c = 0.85, $CHCl_3$). ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ = 3.76 (q, J = 6.6 Hz, 1 H), 1.26 (d, J = 6.9 Hz, 3 H), 0.93 (s, 9 H) ppm. ^{13}C NMR (75.5 MHz, [D$_6$]DMSO): δ = 62.73, 35.20, 25.33, 16.25 ppm.

Compound 8: This compound was prepared from (*S*)-1-cyclohexylethylamine (**4**) in a manner analogous to **5** and was isolated as a liquid in 66% (1.74 g) yield. $[\alpha]_D^{20}$ = +53.5 (c = 0.095, $CHCl_3$). ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ = 3.81 (q, 1 H), 1.62–1.76 (m, 5 H), 1.42–1.52 (m, 1 H), 1.29 (d, J = 6.6 Hz, 3 H), 0.96–1.26 (m, 5 H) ppm. ^{13}C NMR (75.5 MHz, [D$_6$]DMSO): δ = 58.39, 42.83, 28.93, 27.39, 25.63, 25.27, 25.16, 18.45 ppm.

Compound 9: (*R*)-1-Phenylethyl isothiocyanate (**5**) (1.43 g, 8.75 mmol) was added over a period of 1 h to a stirred solution of (*S*,*S*)-1,2-diaminocyclohexane (**17**) (1 g, 8.75 mmol) in dry dichloromethane (17 mL). The reaction mixture was stirred for a further 2 h at room temperature. The solvent was removed under reduced pressure and the residue was purified by flash chromatography on SiO_2 (EtOAc/EtOH, 3:1) to give **9** as a yellow solid in 57% (1.38 g) yield. $[\alpha]_D^{20}$ = –85.0 (c = 1, $CHCl_3$). ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ = 7.17–7.35 (m, 5 H), 5.42–5.49 (m, 1 H), 3.68–3.69 (m, 1 H), 2.41–2.49 (m, 1 H), 1.94–1.99 (m, 1 H), 1.76–1.83 (m, 1 H), 1.54–1.62 (m, 2 H), 1.41 (d, J = 6.9 Hz, 3 H), 0.99–1.26 (m, 4 H) ppm. ^{13}C NMR (75.5 MHz, [D$_6$]DMSO): δ = 181.57, 144.39, 128.12, 126.48, 125.97, 59.43, 54.20, 52.21, 34.40, 31.37, 24.42, 24.29, 22.30 ppm. ESI-MS (positive ion): m/z = 278.1 [M + H]$^+$, 554.9 [2M + H]$^+$. ESI-MS (negative ion): m/z = 276.1 [M – H]$^-$. HRMS (ESI): calcd. for $C_{15}H_{23}N_3S$ [M + H]$^+$ 278.16854; found 278.16866.

Compound 10: This compound was prepared in a 50% (384 mg) yield analogously with the above procedure, starting from **6**. ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ = 7.80–7.89 (m, 4 H), 7.44–7.52 (m, 3 H), 5.61–5.63 (m, 1 H), 3.76–3.77 (m, 1 H), 2.50–2.54 (m, 1 H), 1.98–2.00 (m, 1 H), 1.80–1.83 (m, 1 H), 1.51–1.61 (m, 2 H), 1.51 (d, J = 6.6 Hz, 3 H), 1.15–1.22 (m, 4 H) ppm. ^{13}C NMR (75.5 MHz, [D$_6$]DMSO): δ = 181.65, 141.99, 132.78, 131.95, 127.72, 127.54, 127.33, 125.96, 125.46, 124.95, 123.99, 59.17, 33.91, 31.27, 24.37, 24.21, 22.23 ppm. ESI-MS (positive ion): m/z = 328.1 [M + H]$^+$, 655.0 [2M + H]$^+$.

Compound 13: Na_2SO_4 (2 g) and imidazole-2-carbaldehyde (**18**) (3.24 mmol) were added to a solution of **9** (899 mg, 3.24 mmol) in anhydrous methanol (50 mL) at room temperature under argon. The reaction mixture was stirred for 2 h at room temperature, then filtered and the collected sodium sulphate was washed with anhydrous methanol (3 × 20 mL). The organic phase was concentrated to afford product **13** in a quantitative yield as a white solid. $[\alpha]_D^{20}$ = +98.2 (c = 0.44, $CHCl_3$). IR (KBr): $\tilde{\nu}$ = 3255, 3061, 2929, 2855, 1646, 1543, 1494, 1447, 1357, 1232, 1097, 946, 863, 756, 698, 535 cm^{-1}. ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ = 8.20 (s, 1 H), 7.68 (br. s, NH), 7.25 (br. s, NH), 7.10–7.20 (m, 5 H), 7.11 (s, 2 H), 5.36–5.37 (m, 1 H), 4.16 (m, 1 H), 3.13–3.21 (m, 1 H), 2.17–2.20 (m, 1 H), 1.55–1.71 (m, 4 H), 1.39 (d, J = 6.9 Hz, 3 H), 1.2–1.41 (m, 2 H), 1.11–1.32 (m, 1 H) ppm. ^{13}C NMR (75.5 MHz, [D$_6$]DMSO): δ = 181.2, 152.24, 145.04, 144.37, 127.98, 126.22, 125.94, 125.81, 72.47, 56.51, 51.85, 48.50, 33.45, 31.17, 24.21, 23.65, 22.03 ppm. ESI-MS (positive ion): m/z = 356.1 [M + H]$^+$, 710.9 [2M + H]$^+$. HRMS (ESI): calcd. for $C_{19}H_{25}N_5S$ [M + H]$^+$ 356.19034; found 356.19032.

Compound 14: This compound was prepared from **10** by the same procedure as described above for **13**, to give **14** as a white solid in a quantitative yield. $[\alpha]_D^{20}$ = +70.3 (c = 0.65, CH_3OH). IR (KBr): $\tilde{\nu}$ = 3259, 3053, 2930, 2856, 1647, 1543, 1446, 1353, 1269, 1131, 1107, 1005, 945, 856, 819, 760, 656, 578, 476 cm^{-1}. ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ = 8.18 (s, 1 H), 7.72–7.91 (m, 4 H), 7.39–7.56 (m, 3 H), 7.08 (s, 2 H), 5.49–5.59 (m, 1 H), 4.12–4.18 (m, 1 H), 3.14–3.20 (m, 1 H), 2.21–2.24 (m, 1 H), 1.46–1.79 (m, 4 H), 1.39 (d, J = 6.9 Hz, 3 H), 1.20–1.39 (m, 2 H), 1.05–1.19 (m, 1 H) ppm. ^{13}C NMR (75.5 MHz, [D$_6$]DMSO): δ = 181.30, 152.82, 145.90, 142.01, 132.78, 131.91, 127.68, 127.56, 127.31, 125.92, 125.42, 125.02, 123.93, 72.25, 56.71, 52.25, 33.54, 31.02, 24.15, 23.70, 22.07 ppm. ESI-MS (positive ion): m/z = 406.1 [M + H]$^+$, 428.2 [M + Na]$^+$, 810.8 [2M + H]$^+$, 832.8 [2M + Na]$^+$. HRMS (ESI): calcd. for $C_{23}H_{27}N_5S$ [M + H]$^+$ 406.20599; found 406.20621.

Compound 15: This compound was prepared from **11** (2.20 g, 8.56 mmol) by the same procedure as described above for **13**, to give **15** in a quantitative yield as a white solid. $[\alpha]_D^{20}$ = +151.8 (c = 0.38, CH_3OH). IR (KBr): $\tilde{\nu}$ = 3280, 3058, 2933, 2856, 1649, 1541, 1447, 1397, 1365, 1269, 1202, 1134, 1101, 994, 947, 866, 763, 724, 573 cm^{-1}. ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ = 12.6 (br. s, NH), 8.18 (s, 1 H), 7.13 (s, NH), 7.12 (s, 2 H), 6.86 (d, NH), 4.12–4.21 (m, 2 H), 3.14–3.21 (m, 1 H), 2.26–2.31 (m, 1 H), 1.58–1.74 (m, 4 H), 1.26–1.40 (m, 2 H), 1.00–1.12 (m, 1 H), 0.83 (d, J = 6.9 Hz, 3 H), 0.79 (s, 9 H) ppm. ^{13}C NMR (75.5 MHz, [D$_6$]DMSO): δ = 151.54, 144.33, 72.52, 56.59, 56.37, 45.49, 34.31, 33.53, 31.16, 26.18, 24.14, 23.68, 15.38, 8.45 ppm. ESI-MS (positive ion): m/z = 336.2 [M + H]$^+$, 358.2 [M + Na]$^+$, 670.9 [2M + H]$^+$, 692.9 [2M + Na]$^+$. HRMS (ESI): calcd. for $C_{17}H_{29}N_5S$ [M + H]$^+$ 336.22164; found 336.22170.

Compound 16: This compound was prepared from **12** in a manner analogous to **13** and was isolated in a quantitative yield. $[\alpha]_D^{20}$ = +126.0 (c = 0.96, CH_3OH). IR (KBr): $\tilde{\nu}$ = 3259, 3056, 2924, 2853, 1649, 1544, 1449, 1366, 1271, 1236, 1203, 1149, 1100, 987, 955, 914, 857, 811, 759, 722, 671, 573 cm^{-1}. ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ = 12.6 (br. s, NH), 8.17 (s, 1 H), 7.12 (s, 2 H), 6.9–7.0 (m, 2 H, 2 × NH), 4.2 (m, 1 H), 3.95 (m, 1 H), 3.2 (m, 1 H), 2.23 (m, 1 H), 1.42–1.8 (m, 10 H), 1.19–1.4 (m, 3 H), 0.98–1.18 (m, 4 H), 0.89 (d, J = 6.9 Hz, 3 H), 0.8–0.98 (m, 1 H) ppm. ^{13}C NMR (75.5 MHz, [D$_6$]DMSO): δ = 151.64, 144.36, 72.40, 52.75, 42.45, 33.61, 31.16, 28.79, 28.38, 25.89, 25.57, 24.20, 23.74, 17.19 ppm. ESI-MS (positive ion): m/z = 384.4 [M + Na]$^+$. ESI-MS (negative ion): m/z = 360.1 [M – H]$^-$. HRMS (ESI): calcd. for $C_{19}H_{31}N_5S$ [M + H]$^+$ 362.23729; found 362.23741.

Compound 23: This compound was prepared from (*S*,*S*)-1,2-diaminocyclohexane (**17**) (300 mg, 2.63 mmol) and imidazole-2-carbaldehyde (**18**) (505 mg, 5.26 mmol) by the same procedure as described above for **13**, to give **19** in quantitative yield as a white solid. $[\alpha]_D^{20}$ = +393.6 (c = 0.41, CH_3OH). IR (KBr): $\tilde{\nu}$ = 3025, 2921, 2854, 1649, 1554, 1446, 1388, 1344, 1307, 1153, 1113, 1090, 996, 935, 857, 815, 753, 712, 507 cm^{-1}. ^{1}H NMR (300 MHz, [D$_6$]-DMSO): δ = 8.04 (s, 2 H), 7.03 (s, 4 H), 3.30–3.39 (m, 2 H), 1.39–

1.81 (m, 8 H) ppm. ^{13}C NMR (75.5 MHz, [D$_6$]DMSO): δ = 150.86, 144.12, 123.72, 72.48, 32.37, 23.55 ppm. ESI-MS (positive ion): *m*/*z* = 271.2 [M + H]$^+$, 293.2 [M + Na]$^+$. ESI-MS (negative ion): *m*/*z* = 269.2 [M – H]$^-$. HRMS (ESI): calcd. for $C_{14}H_{18}N_6$ [M + H]$^+$ 271.16657; found 271.16666.

Compound 24: This compound was prepared from **9** (400 mg, 1.44 mmol) and benzaldehyde (0.147 ml, 1.44 mmol) in a manner analogous to that used for **13** with the difference being that the reaction mixture was stirred at 40–45 °C for 5 h. The desired product **21** was obtained in a quantitative yield as a white solid. $[\alpha]_D^{20}$ = +59.3 (*c* = 0.84, CH_3OH). IR (KBr): $\tilde{\nu}$ = 3311, 3057, 2973, 2925, 2856, 2807, 1642, 1536, 1493, 1448, 1354, 1338, 1315, 1262, 1234, 1201, 1132, 1087, 1072, 1002, 946, 916, 828, 797, 773, 753, 719, 692, 649, 558 cm^{-1}. ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ = 8.35 (s, 1 H), 7.7 (m, 2 H), 7.45 (m, 4 H), 7.1–7.18 (m, 4 H), 7.0 (br. s, 2 H, 2 × NH), 5.32–5.36 (m, 1 H), 4.14–4.21 (m, 1 H), 3.14–3.22 (m, 1 H), 2.06–2.09 (m, 1 H), 1.55–1.74 (m, 4 H), 1.17–1.40 (m, 3 H), 1.31 (d, *J* = 6.9 Hz, 3 H) ppm. ^{13}C NMR (75.5 MHz, [D$_6$]DMSO): δ = 160.01, 144.77, 136.25, 130.26, 128.37, 127.84, 127.78, 126.30, 126.01, 125.71, 72.36, 56.27, 51.95, 48.38, 33.11, 31.15, 24.25, 23.61, 22.15 ppm. ESI-MS (positive ion): *m*/*z* = 366.2 [M + H]$^+$, 388.1 [M + Na]$^+$, 752.9 [2M + Na]$^+$. HRMS (ESI): calcd. for $C_{22}H_{27}N_3S$ [M + H]$^+$ 366.19985; found 366.20006.

General Procedure for the Addition of Hydrogen Cyanide to Substituted Imines 19 and 20: A solution of hydrogen cyanide (1.5 mmol) in dry toluene (1.5 mL) was added in one batch to a suspension of catalyst (10 mol-%) and an aldimine (**19** or **20**, 1 mmol) in dry toluene (3.5 mL) under argon at –40 °C. The mixture was then stirred at –40 °C for 2.5 h and subsequently at –20 °C for a further 16 h. The crude reaction mixture was analysed by HPLC using a Daicel Chiralpak AS 250 column at 22 °C (*n*-hexane/2-propanol, 90:10, flow rate 1 mL/min, λ = 210 nm; amino nitrile (**21**): t_{R1} = 9.8 min, t_{R2} = 8.7 min); amino nitrile (**22**): t_{R1} = 8.9 min, t_{R2} = 14.4 min.

21: ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ = 7.56–7.23 (m, 10 H), 5.0 (d, 1 H, NH), 3.89–3.75 (m, 2 H), 3.62–3.57 (m, 1 H) ppm. EI-MS (70 eV): *m*/*z* (%) = 222.1(5), 116.0 (70), 91.0 (91), 77.0 (62), 65.0 (56), 51.0 (100).

22: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.2–7.6 (m, 15 H), 5.25 (s, 1 H), 4.60 (s, 1 H), 2.15 (d, 1 H) ppm. EI-MS (70 eV): *m*/*z* (%) = 298.2 (2), 221.1 (48), 182.1 (58), 167.1 (67), 116.0 (100), 77.0(18), 51.0(6).

General Procedure for the Preparation of the Michael Adduct, 1-Nitro-2-phenylpentan-4-one (25): Acetone (0.27 mL) was added to a stirred solution of *trans*-β-nitrostyrene (20 mg, 0.13 mmol) and catalyst (15 mol-%) in toluene (0.5 mL), and the reaction mixture was stirred at room temperature for 48 h. The solvent was evaporated and the residue was purified by TLC or chromatography on a SiO_2-column (hexane/ethyl acetate, 1:1) to afford the desired product. The enantiomeric excess of the product was determined by chiral HPLC analysis (Daicel Chiralpak AS) in comparison with authentic racemic material: *n*-hexane/2-propanol = 65:35, flow rate 1 mL/min, λ = 210 nm: t_R(minor) = 13.43 min, t_R(major) = 16.98 min. ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ = 7.20–7.50 (m, 5 H), 4.80 (m, 2 H), 3.80 (m, 1 H), 2.91 (d, *J* = 8.0 Hz, 2 H), 2.10 (s, 3 H) ppm. ESI-MS (positive ion): *m*/*z* = 230.1 [M + Na]$^+$. HRMS (ESI): calcd. for $C_{11}H_{13}NO_3$ [M + Na]$^+$ 230.07876; found 230.07878.

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