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Bioorganic & Medicinal Chemistry 13 (2005) 5680–5685
Bioorganic & Medicinal Chemistry

Thiourea-based non-nucleoside inhibitors of HIV reverse transcriptase as bifunctional organocatalysts in the asymmetric Strecker synthesis

Svetlana B. Tsogoeva,[a,*] Martin J. Hateley,[b] Denis A. Yalalov,[a] Kathrin Meindl,[c] Christoph Weckbecker[b] and Klaus Huthmacher[b]

[a]*Institut für Organische und Biomolekulare Chemie der Georg-August-Universität Göttingen, Tammannstrasse 2, 37077 Göttingen, Germany*
[b]*Degussa AG, Feed Additives, Rodenbacher Chaussee 4, 63457 Hanau-Wolfgang, Germany*
[c]*Institut für Anorganische Chemie der Georg-August-Universität Göttingen, Tammannstrasse 4, 37077 Göttingen, Germany*

Received 15 March 2005; revised 6 May 2005; accepted 10 May 2005
Available online 16 June 2005

Abstract—The potential of novel and known pyridyl thiourea derivatives (non-nucleoside inhibitors (NNI) of HIV reverse transcriptase) as bifunctional organic catalysts in the asymmetric Strecker synthesis was investigated. It was shown that incorporation of the imidazolyl moiety in place of a pyridyl group results in a new thiourea derivative that displays a much higher catalytic activity.

1. Introduction

Chiral catalysts that contain both an acidic and a basic/nucleophilic structural unit are of growing importance in the development of asymmetric catalysis.[1,2]

Recently, several enantioselective bifunctional organic catalysts have been identified.[3] Among them are chiral organic catalysts for the Strecker synthesis, including a guanidine-bearing diketopiperazine,[4] a C_2-symmetric guanidine catalyst[5] and the chiral peptide-like catalysts described by Jacobsen, which possess both acidic (urea and/or thiourea moiety) as well as basic functionality (Schiff base).[6–9] Furthermore, the use of chiral bifunctional thiourea-based organocatalysts in the enantioselective Michael addition,[10] the Aza-Henry,[11] Baylis–Hillman,[12,13] Acyl-Pictet-Spengler[14] and Nitro-Mannich[15] reactions as well as for the dynamic kinetic resolution of azalactones[16] has recently been reported.

Many known compounds displaying important biological activity contain both a thiourea moiety as well as a pyridine residue.[17–21] For instance, chiral α-methyl benzyl pyridyl thiourea compounds **1** and **2** (Fig. 1) were reported by Uckun and co-workers to be non-nucleoside inhibitors (NNI) of the reverse transcriptase enzyme of the human immunodeficiency virus (HIV).[22–25]

These structures incorporate both the acidic and the basic/nucleophilic bifunctionality of interest with respect to potential enantioselective bifunctional organocatalysts.

This prompted us to apply these pyridine based thiourea compounds, as well as the novel thiourea derivatives **3**–**5** (Fig. 1), synthesised in our laboratory, as catalysts for C–C bond formation reactions.

In particular, we were interested in the Strecker synthesis,[26,27] which provides synthetically useful building blocks and has many important applications both in natural product synthesis as well as in the industrial preparation of pharmaceuticals and agrochemicals.

2. Results and discussion

The syntheses of the thiourea compounds were accomplished by known methods[28,29] as summarised in

Keywords: NNI; Inhibitor; Thiourea derivative; Strecker synthesis; Bifunctional organocatalyst.
* Corresponding author. Tel.: +49 0 551 393285; fax: +49 0 551 399660; e-mail: stsogoe@gwdg.de

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doi:10.1016/j.bmc.2005.05.014

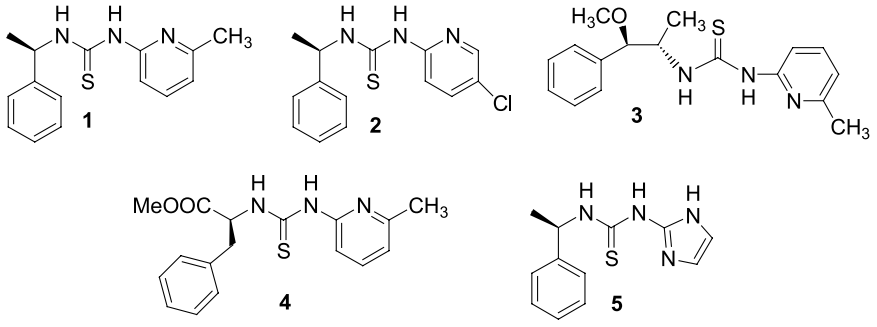


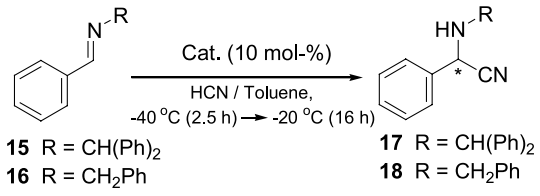
Figure 1.

Scheme 1. Three different amines: (*R*)-(+)-1-phenylethylamine (**6**), (1*R*,2*S*)-(−)-2-amino-1-methoxy-1-phenylpropane (**7**) and (*S*)-phenylalanine methyl ester (**8**) were employed for the synthesis of chiral isothiocyanates **9**–**11**. Subsequent treatment of these chiral isothiocyanates with 2-amino-6-methylpyridine (**12**) and 2-amino-5-chloropyridine (**13**) gave the target pyridyl thioureas **1**–**4**.

The addition of hydrogen cyanide to aldimines **15** and **16** (Scheme 2) was employed to determine the catalytic activity of the pyridyl thiourea derivatives **1**–**4** (Fig. 1) and thus their potential as bifunctional organocatalysts. Aldimines **15** and **16** were selected as the substrates of choice to enable an effective comparison with earlier investigations in the literature.[5,9] All reactions were performed as solutions in toluene with 10 mol % of the appropriate catalyst and were stirred for 2.5 h at −40 °C and subsequently for a further 16 h at −20 °C.

Low conversions (up to 25%) and enantioselectivities (up to 14%) were observed in all cases (entries 1–4, Table 1).

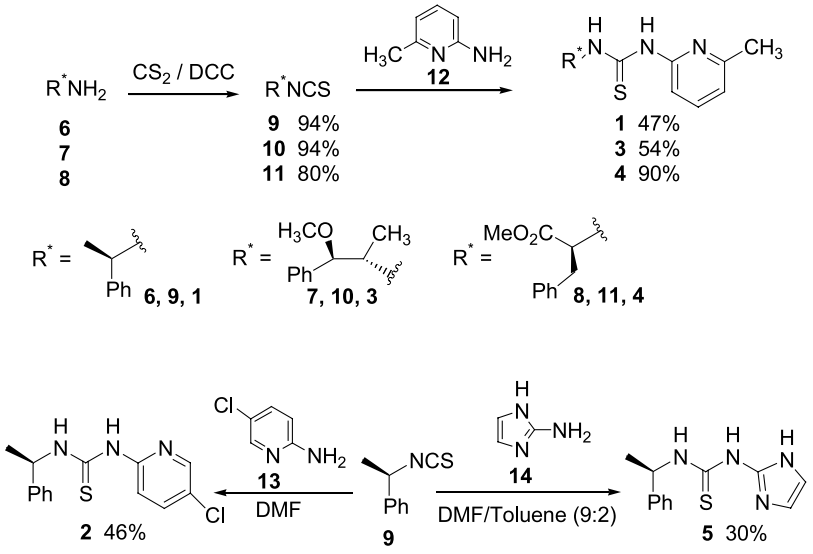
In searching for ways to improve the catalyst activity, we were drawn to the strategy of base variation. Therefore, we continued our investigation with an examination of the catalytic efficacy of some available organic bases (entries 5–8, Table 1). We have found that use of imidazole as a base generally gave a better conversion (32%, entry 8) than pyridine (5%, entry 5), pyrrolidine (11%, entry 6) or Et_3N (6%, entry 7).



Scheme 2.

Thus, in the chiral thiourea **5** (Scheme 1), the methylpyridyl group of **1** was replaced by an imidazolyl substituent.

Intriguingly, whereas imidazole and/or biotin alone, as well as their mixture gave the Strecker product from the substrate **15** in only 32%, 10% and 37% yields, respectively (entries 8–10), high conversion was observed with substrates **15** and **16** under the same



Scheme 1.

Table 1. Strecker reactions catalyzed by thiourea derivatives **1**–**5**

Entry	Catalyst (10 mol %)	Substrate	2.5 h at −40 °C; 16 h at −20 °C	
			Conversion (%)[a]	ee (%)[a]
1	**1**	**15**	17	14
2	**2**	**15**	25	12
3	**3**	**15**	9	6
4	**4**	**15**	9	4
5	Pyridine	**15**	5	—
6	Pyrrolidine	**15**	11	—
7	Et_3N	**15**	6	—
8	Imidazole	**15**	32	—
9	Biotin	**15**	10	4
10	Biotin[b] + Imidazole[b]	**15**	37	4
11	**5**	**15**	85	6
12	**5**	**16**	100	7

[a] Determined by HPLC after 16 h of reaction at −20 °C. Reported conversions and ee values are the average of 2 runs.
[b] 10 mol % of co-catalyst.

conditions in the presence of imidazolyl thiourea catalyst **5** (85% and 100%, respectively, entries 11 and 12, Table 1), which represented up to 76% improvement in the conversion of imine **15** over the corresponding pyridyl thiourea based catalysts **1**–**4** (entries 1–4). These results indicate that for a high conversion the catalyst should possess both an imidazole group and a urea/thiourea moiety within one molecule. More probably, the basic group and the thiourea reaction centre act in a synergistic manner within the catalyst.

The enantioselectivities obtained with imidazolyl thiourea **5**, however, proved to be in the same range as those observed with pyridyl thioureas **1**–**4**.

The X-ray crystal structure of the new thiourea derivative **3** (chiral methylpyridyl thiourea) sheds light on the cause of the low chiral induction observed in the Strecker reaction using bifunctional catalysts **1**–**5**.

As already reported by Vachal and Jacobsen[9] and Schreiner and Wittkopp,[31] ureas and thioureas are able to provide two hydrogen bonds to bind the H-bond acceptors (carbonyl or imine groups). It appears likely that a bridged structure, in which the imine forms hydrogen-bonds to both thiourea hydrogen atoms simultaneously, is important for catalyst activity and selectivity.[9] The X-ray structure[30] of methylpyridyl thiourea **3** shows, however, that an intramolecular hydrogen bond is formed between the thiourea N^{10}–H group and the basic nitrogen atom (N^7) of the pyridyl group as well as an intermolecular hydrogen bond from N^8–H to the sulfur of a crystallographic independent second molecule leading to a dimer. There are two of these nearly identical dimers in the asymmetric unit (Fig. 2).

As a result, the imine substrate cannot be placed in a bridging mode between the two thiourea hydrogen atoms, which might serve to explain the low enantiose-

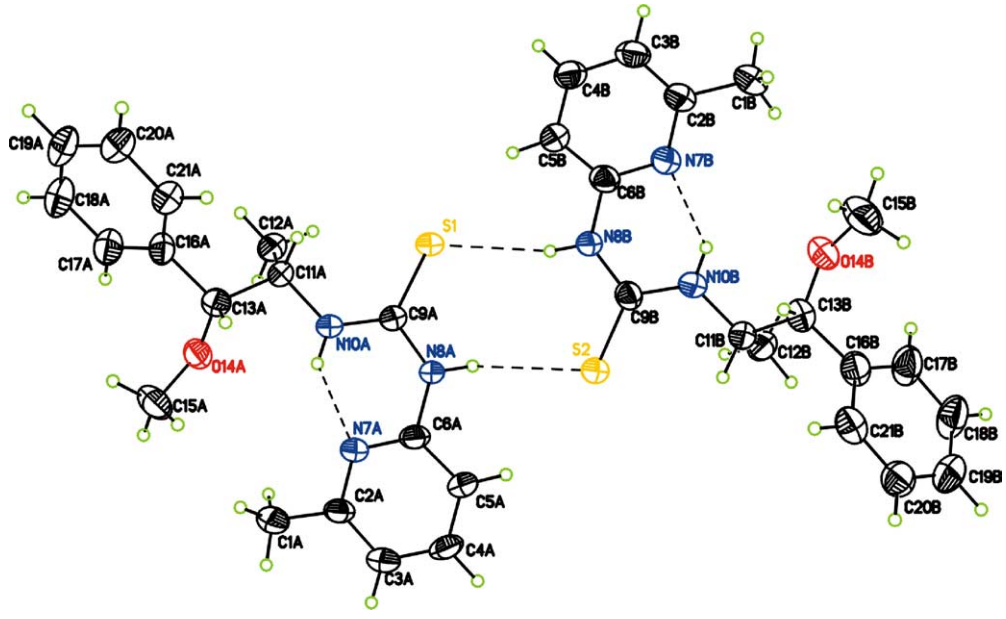


Figure 2. X-ray crystal structure of two molecules of compound **3**; thermal ellipsoids are shown at 50% probability level.

lectivities obtained with catalyst **3**, as well as with all the other thiourea derivatives presented here (since structural similarities are evident). These observations are consistent with the postulation that H-bonding interactions are central to reaction selectivity.[9]

Based on these results and the observation that imidazole as a base is essential for catalyst activity, we have targeted imidazolyl thiourea derivative **5** as a candidate that might be further modified to improve catalyst enantioselectivity.

3. Conclusion

The examination of the catalytic potential of the pyridyl thiourea derivatives **1**–**4**, as well as an X-ray analysis of the new compound **3** proved that the formation of H-bonding interactions between imine substrates and the thiourea moiety of the catalysts is crucial for good yields and enantioselectivities.

Furthermore, we established that the substitution of an imidazolyl moiety for a pyridyl group (derivative **5**) resulted in a much more active catalyst.

The results presented herein indicate that the combination of an imidazolyl group with suitable chiral aliphatic or aromatic substituents leads to substantial improvements in the catalytic activity of the thiourea catalyst.

Further design, synthesis and application of new improved bifunctional organocatalysts are presently underway in our laboratories.

4. Experimental

4.1. General

All solvents were purified by standard procedures and distilled prior to use. Reagents obtained from commercial sources were used without further purification. TLC 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 an argon or nitrogen atmosphere. ^{1}H NMR spectra were recorded on a Varian Unity 300 spectrometer. 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. A Perkin-Elmer 241 polarimeter was used for optical rotation measurements.

4.2. Compound 1

(*R*)-1-Phenylethylisothiocyanate (**9**) (350 mg, 2.14 mmol) was added to a stirred solution of 2-amino-6-methylpyridine (**12**) (231 mg, 2.14 mmol) in ethanol (10.7 ml). The reaction mixture was heated to reflux for 5 h. The solvent was removed under reduced pressure and the residue was allowed to cool. The precipitate formed was filtered off and washed with ethanol. Further purification by flash chromatography on SiO_2 (hexane/EA, 3:0.5) gave **1** as a white solid. Yield 47%; $[\alpha]_D^{20}$ −134.8 (*c* 0.25, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 12.4 (br s, 1H, NH), 8.1 (s, 1H, NH), 7.47–7.52 (m, 1H), 7.26–7.43 (m, 5H), 6.78 (d, J = 6.9, 1H), 6.46 (d, J = 8.1 Hz, 1H), 5.56–5.61 (m, 1H), 2.39 (s, 3H), 1.67 (d, J = 7.2, 3H); ^{13}C NMR ($CDCl_3$) δ 178.50, 154.87, 152.96, 142.93, 138.89, 128.59, 127.23, 126.26, 117.08, 108.92, 55.08, 23.74, 22.47. EI-MS *m*/*z* (rel intensity) 271.2 (M^+, 100), 151.1 (33), 120.1 (53), 109.1 (42), 92.1 (25); the exact molecular mass *m*/*z* = 271.1143 ± 2 ppm (M^+) was confirmed by HRMS (EI, 70 eV).

4.3. Compound 2

This compound was prepared from (*R*)-1-phenylethylisothiocyanate (**9**) and 2-amino-5-chloropyridine (**13**) in a manner analogous to that used for **1** with the difference that the reaction was carried out in DMF and that the reaction mixture was stirred at 65 °C for 5 days. Product **2** was obtained as a colourless solid. Yield 46%; $[\alpha]_D^{20}$ −189.0 (*c* 0.5, $CHCl_3$); ^{1}H NMR (DMSO-d_6) δ 11.74 (d, 1H, NH), 10.7 (s, 1H, NH), 8.32 (d, J = 2.7, 1H), 7.87–7.91 (dd, 1H), 7.36–7.38 (m, 5H), 7.22 (m, 1H), 5.53–5.62 (m, 1H), 1.55 (d, J = 6.6, 3H). ESI-MS (positive ion): *m*/*z* 314.1 $[M+Na]^+$. ESI-MS (negative ion): *m*/*z* 290.1 $[M-H]^-$; EI-MS *m*/*z* (rel intensity) 291 (M^+, 90), 149.1 (25), 129.0 (39), 120.1 (100), 105.1 (44); the exact molecular mass *m*/*z* = 291.0597 ± 2 ppm (M^+) was confirmed by HRMS (EI, 70 eV).

4.4. Compound 3

This compound was prepared from isothiocyanate **10** and 2-amino-6-methylpyridine (**12**) in a manner analogous to that used for **1** with the difference that the reaction was carried out in toluene and that the reaction mixture was stirred at 60 °C for 4 days. Product **3** was obtained as a white solid. Yield 54%; $[\alpha]_D^{20}$ −11.5 (*c* 0.4, $CHCl_3$); ^{1}H NMR (DMSO-d_6) δ 12.18 (d, 1H, NH), 10.45 (s, 1H, NH), 7.62 (t, 1H), 7.28–7.43 (m, 5H), 6.95 (dd, 2H), 4.57–4.61 (m, 2H), 3.31 (s, 3H, CH_3O), 2.43 (s, 3H), 1.02 (d, J = 6.3, 3H); ^{13}C NMR (DMSO-d_6) δ 178.42, 154.31, 153.25, 139.02, 138.60, 128.26, 127.44, 126.40, 116.72, 109.28, 84.12, 57.32, 55.44, 23.37, 12.99. EI-MS *m*/*z* (rel intensity) 315.2 (M^+, 4), 283.2 (12), 194.1 (54), 151.1 (100), 92.1 (42); the exact molecular mass *m*/*z* = 315.1405 ± 2 ppm (M^+) was confirmed by HRMS (EI, 70 eV). Anal. Calcd for $C_{17}H_{21}N_3OS$: C, 64.73; H, 6.71; N, 13.32. Found: C, 64.84; H, 6.46, N, 13.78.

4.5. Compound 4

This compound was prepared from isothiocyanate **11** and 2-amino-6-methylpyridine (**12**) in a manner analogous to **3** and was obtained as a white solid. Yield 90%; $[\alpha]_D^{20}$ −2.8 (*c* 1, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 12.55 (d, 1H, NH), 8.88 (s, 1H, NH), 7.50 (t, 1H), 7.11–7.21 (m, 5H), 6.74 (d, J = 7.5, 1H), 6.47 (d, J = 9.0, 1H), 5.45–5.55 (m, 1H), 3.71 (s, 3H), 3.30–3.35 (m, 2H), 2.21 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 178.98, 171.45, 155.47, 152.47, 138.82, 136.01, 129.38, 128.30, 126.00, 117.36, 108.54,

59.47, 52.18, 37.81, 23.44. ESI-MS (positive ion): *m/z* 352.1 $[M + Na]^+$. EI-MS *m/z* (rel intensity) 329.2 (M^+, 38), 167.1 (100), 151.1 (95), 134.1 (56), 108.1 (81), 92.1 (71); the exact molecular mass *m/z* = 329.1198 ± 2 ppm (M^+) was confirmed by HRMS (EI, 70 eV).

4.6. Compound 5

This compound was prepared from (*R*)-1-phenylethylisothiocyanate (**9**) and 2-aminoimidazole (**14**) in a manner analogous to that used for **1** with the difference that the reaction was carried out in a 9:2 mixture of DMF and toluene and that the reaction mixture was stirred at 60 °C for 20 h. The desired product was obtained as a colourless solid. Yield 30%; $[\alpha]_D^{20}$ −238.0 (*c* 0.2, $CHCl_3$); ^1H NMR (DMSO-d_6) δ 11.26 (br s, NH), 10.6 (br s, 2H, 2× NH), 7.22–7.40 (m, 5H), 6.78 (br s, 2H of imidazole), 5.50–5.60 (m, 1H), 1.52 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (DMSO-d_6, 150.8 MHz) δ 176.27, 143.22, 142.85, 128.41, 126.87, 125.93, 53.31, 22.25. ESI-MS (positive ion): *m/z* 247.1 $[M+H]^+$, 269.1 $[M+Na]^+$: ESI-MS (negative ion): *m/z* 245.2 $[M-H]^-$; EI-MS *m/z* (rel intensity) 246.2 (M^+, 100), 126.0 (38), 120.1 (30), 105.1 (83), 84.0 (52), 83.0 (72), 77.0 (32); the exact molecular mass *m/z* = 246.0939 ± 2 ppm (M^+) was confirmed by HRMS (EI, 70 eV).

4.7. Compound 9

To a solution of (*R*)-1-phenylethylamine (**6**) (0.42 ml, 3.3 mmol) in dry ether (4.2 ml) at −10 °C were added CS_2 (1.26 ml) and DCC (680 mg, 3.3 mmol). The reaction mixture was allowed to warm slowly to room temperature over a period of 3 h and was then stirred for a further 12 h at room temperature. The thiourea which precipitated was removed by filtration and the solvent was subsequently removed under vacuum. The residue was taken up in ether and more of the thiourea was able to be removed by filtration. Evaporation of the solvent and rapid filtration on silica gel (with hexane) gave product **9** as a liquid. Yield 94%; $[\alpha]_D^{20}$ −4.3 (*c* 1.0, acetone); ^1H NMR ($CDCl_3$) δ 7.30–7.43 (m, 5H), 4.93 (q, 1H), 1.69 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR ($CDCl_3$, 150.8 MHz) δ 140.11, 128.84, 128.14, 125.35, 56.98, 24.90. EI-MS *m/z* (rel intensity) 163.1 (M^+, 16), 105.1 (100), 77.1 (13), 51.0 (6).

4.8. Compound 10

This compound was prepared from (1*R*,2*S*)-(−)-2-amino-1-methoxy-1-phenylpropane (**7**) in a manner analogous to **9** and was isolated as a yellowish solid. Yield 94%; $[\alpha]_D^{20}$ −100.0 (*c* 1, acetone); ^1H NMR (DMSO-d_6) δ 7.32–7.42 (m, 5H), 4.35 (d, *J* = 4.8, 1H), 4.25–4.27 (m, 1H), 3.22 (s, 3H, CH_3O), 1.17 (d, *J* = 6.3, 3H); ^{13}C NMR (DMSO-d_6) δ 136.76, 128.15, 127.33, 84.11, 57.20, 56.54, 16.88. Anal. Calcd for $C_{11}H_{13}NOS$: C, 63.73; H, 6.32; N, 6.76. Found: C, 63.89; H, 6.37; N, 6.80.

4.9. Compound 11

This compound was prepared from (*S*)-phenylalanine methyl ester (**8**) in a manner analogous to that used for **9** with the difference that the reaction was carried out in dry DMF. Product **11** was obtained as a liquid. Yield 80%; $[\alpha]_D^{20}$ −60.0 (*c* 1, toluene); ^1H NMR (DMSO-d_6) δ 7.22–7.34 (m, 5H), 5.09–5.13 (m, 1H), 3.74 (s, 3H), 3.13–3.23 (m, 2H); ^{13}C NMR (DMSO-d_6), δ 167.92, 135.32, 129.22, 128.37, 127.15, 60.04, 52.94, 38.17. EI-MS *m/z* (rel intensity) 221.1 (M^+, 9.5), 162.1 (100), 128.1 (20), 91.1 (72).

4.10. General procedure for the addition of hydrogen cyanide to substituted imines 15 and 16

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 (**15** or **16**, 1 mmol) in dry toluene (3.5 ml) under an argon atmosphere 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 **17**: t_R (major) = 8.9 min, t_R (minor) = 14.4 min; amino nitrile **18**: t_{R1} (major) = 9.8 min, t_{R2} (minor) = 8.7 min).

Compound **17**: ^1H NMR ($CDCl_3$) δ 7.2–7.6 (m, 15H), 5.25 (s, 1H), 4.60 (s, 1H), 2.15 (d, 1H).

Compound **18**: ^1H NMR (DMSO-d_6) δ 7.56–7.23 (m, 10H), 5.0 (d, 1H, NH), 3.89–3.75 (m, 2H), 3.62–3.57 (m, 1H).

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30. Crystal data of **3**: $C_{17}H_{21}N_3OS$, $M_r = 315.43$, crystal size $0.5 \times 0.15 \times 0.05\ mm^3$, monoclinic, space group $P2_1$, $a = 9.863(2)$, $b = 23.217(2)$, $c = 15.423(2)$ Å, $\beta = 97.31(3)°$, $V = 3503.0(9)$ Å^3, $T = 100(2)$ K, $Z = 8$, $D_x = 1.196\ Mg\ m^{-3}$, $\mu = 1.675\ mm^{-1}$. A total of 47,774 reflections were collected, final R_1 ($I > 2\sigma(I)$) = 0.0319, wR_2 (all data) = 0.0833 for 839 parameters and 9899 reflections, GOF = 1.025, $\theta = 2.89–59.56°$. Absolute structure parameter = −0.005(8), maximum and minimum residual electron density 0.332 and $-0.209\ eÅ^{-3}$. Data were collected on a Bruker three-circle diffractometer ($Cu_{K\alpha}$ radiation, $\lambda = 1.54178$ Å) equipped with a SMART 6000 area detector. The structure was solved by using direct methods and refined by full-matrix least squares on F^2 for all data. All non-hydrogen atoms were refined anisotropically. H atoms at nitrogens were located in the difference Fourier map and refined isotropically with distance restraints. All other H atoms were placed at calculated positions and refined using a riding model. (G. M. Sheldrick, *SHELXS97* and *SHELXL97*, University of Göttingen, Germany, **1997**). Data were collected on a non-merohedrally twinned crystal. The fractional contribution of the second twin domain was refined to 0.0609(6). CCDC-266193 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge at www.ccdc.cam.ac.uk/data_request/cif (or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; e-mail: deposit@ccdc.cam.ac.uk).
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