Asymmetric organocatalytic Strecker-type reactions of aliphatic N,N-dialkylhydrazones†

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The enantioselective organocatalytic Strecker-type reaction of aliphatic N,N-dialkylhydrazones is presented. Using trimethylsilyl cyanide (TMSCN) as the cyanide source, the reaction can be efficiently catalyzed by a tert-leucine-derived bifunctional thiourea to afford the corresponding hydrazino nitriles in good to excellent yields (50–96%) and moderate to good enantioselectivities, up to 86% ee. Further transformations of the nitrile functionality allow access to useful protected hydrazino acids and imidazolidinones. Interestingly, some of the hydrazino nitriles and their derivatives could be recrystallized in high recovery, yielding essentially pure enantiomers.

Introduction

Hydrazino acids are important bioactive molecules in medicinal chemistry (Fig. 1). Some of their derivatives containing the N–N–C–C═O fragment have been identified as inhibitors of several amino acid metabolizing enzymes with potential applications.1 For example, L-Carbidopa is an inhibitor of the peripheral aromatic L-amino acid decarboxylase (DDC), an enzyme responsible for the metabolism of levodopa to dopamine, and has improved the efficiency of Parkinson’s treatment in combination with L-DOPA.2 Additionally, cyclic α-hydrazino acids are present in a variety of natural peptides with remarkable biological properties (antibacterial, antitumour or even anti-HIV therapeutics).3

The L-enantiomer of hexahydropyridazine-3-carboxylic acid (piperazic acid) also resides within the bicyclic ring system of many bioactive synthetic products such as cilazapril,4 a drug widely used in the treatment of hypertension. Furthermore, α-hydrazino acids have attracted a great deal of interest in recent years as valuable precursors of conformationally restricted,5 protease-resistant peptidomimetics.6

Existing routes to enantiopure derived hydrazino acids7 rely generally on elaboration of amino acid derivatives,8 sporadic catalytic hydrogenation of hydrazones,9 and electrophilicamination of enolates with azodicarboxylates.10 In this context, the development of asymmetric catalytic versions of hydrazone cyanation, which enables direct access to hydrazino acids, appears to be a very challenging task. In contrast to the Strecker-type reaction of imines,11 approaches involving catalytic hydrocyanation of hydrazone derivatives have received relatively little attention. The few inventions reported relied on N-acylhydrazones as imine surrogates (eqn (1), Scheme 1).12

The first asymmetric variant of the reaction was reported in 2004 by Jacobsen and co-workers employing lanthanide-PYBOX complexes as the catalysts.12a Recently, the group of

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†Electronic supplementary information (ESI) available: Experimental procedures, characterization data, NMR spectra for new compounds, HPLC traces and CIF data for (S)-8. CCDC 945611. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c3ob41437j

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Tsogoeva reported an enantioselective organocatalytic hydrazone hydrocyanation by an O-silylated BINOL-phosphate.\textsuperscript{12b} Considering that the higher basicity of \textit{N},\textit{N}-dialkylhydrazones over acyl hydrazones offers different interaction opportunities with acidic organocatalysts, we envisioned an alternative procedure from \textit{N},\textit{N}-dialkylhydrazones (eqn (2), Scheme 1). To the best of our knowledge, a catalytic reaction for this system has not been described to date.\textsuperscript{13} On the other hand, we have investigated the ambiphilic reactivity of aldehyde \textit{N},\textit{N}-dialkylhydrazones.\textsuperscript{14} Their imine-type reactivity has been exploited in Mannich-type additions of ketene silyl acetals and thioacetals,\textsuperscript{15} in Staudinger-like cycloadditions\textsuperscript{16} and cyanosilylations\textsuperscript{13c} employing \textit{C}\textsubscript{2}-symmetric dialkylamino groups as chiral auxiliaries. The development of a catalytic system for this last reaction was problematic for the tendency of nitrogen-containing reagents to bind acidic metals and undergo side reactions, decomposition, dimerization or catalyst deactivation.\textsuperscript{17} The mild nature of H-bonding and Brønsted acid organocatalytic activations,\textsuperscript{18} however, appears to be more compatible with hydrazones, and applications have been developed in other contexts.\textsuperscript{19} We now report on a novel enantioselective Strecker-type reaction of \textit{N},\textit{N}-dialkylhydrazones using bifunctional H-bonding activation.

**Results and discussion**

We started studies on Strecker-type reactivity employing piperidine-containing (\textit{1A}, \textit{R} = \textit{i}-Bu) or \textit{N},\textit{N}-dibenzyl (\textit{1B}, \textit{R} = \textit{i}-Bu) hydrazones and trimethylsilyl cyanide (TMSCN) as model reactions. At room temperature, the non-catalyzed reaction hardly took place after 72 hours in toluene (<5% conv.) or CH\textsubscript{3}Cl\textsubscript{2} (<15% conv.), while a polar protic solvent like MeOH afforded cleanly the corresponding hydrazino nitriles over acyl hydrazones offers different interaction opportunities with acidic organocatalysts, we envisioned an alternative procedure from \textit{N},\textit{N}-dialkylhydrazones (eqn (2), Scheme 1). To the best of our knowledge, a catalytic reaction for this system has not been described to date.\textsuperscript{13} On the other hand, we have investigated the ambiphilic reactivity of aldehyde \textit{N},\textit{N}-dialkylhydrazones.\textsuperscript{14} Their imine-type reactivity has been exploited in Mannich-type additions of ketene silyl acetals and thioacetals,\textsuperscript{15} in Staudinger-like cycloadditions\textsuperscript{16} and cyanosilylations\textsuperscript{13c} employing \textit{C}\textsubscript{2}-symmetric dialkylamino groups as chiral auxiliaries. The development of a catalytic system for this last reaction was problematic for the tendency of nitrogen-containing reagents to bind acidic metals and undergo side reactions, decomposition, dimerization or catalyst deactivation.\textsuperscript{17} The mild nature of H-bonding and Brønsted acid organocatalytic activations,\textsuperscript{18} however, appears to be more compatible with hydrazones, and applications have been developed in other contexts.\textsuperscript{19} We now report on a novel enantioselective Strecker-type reaction of \textit{N},\textit{N}-dialkylhydrazones using bifunctional H-bonding activation.

**Results and discussion**

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Several alkoaid-derived quaternary ammonium salts (bearing a free OH group), (\textit{S})-BINOL, (\textit{S})-BINOL-derived phosphoric acid and \textit{N},\textit{N}-bis[3,5-bis(trifluoromethyl)]phenyl thiourea (\textit{I}) were chosen as model organocatalysts for their ability to establish H-bonding cooperative networks to activate reagents. Phase transfer catalysts (PTCs) showed a moderate catalytic activity in Et\textsubscript{2}O, toluene or CH\textsubscript{3}Cl\textsubscript{2} (40–50% conv. after 72 hours), but afforded \textit{2} in racemic form, whereas (\textit{S})-BINOL phosphoric acid derivatives were less active (22–30% conv., 72 h, racemic). Thiourea \textit{I}, however, efficiently accelerated the model reactions with respect to the background reaction in several solvents (CH\textsubscript{3}Cl\textsubscript{2}: 46–67%, 72 h; CH\textsubscript{2}Cl\textsubscript{2}: 58%, 72 h; toluene: 35–47%, 72 h; CH\textsubscript{3}CN: 72%, 72 h), thereby opening opportunities for the development of an asymmetric catalytic version. Aliphatic \textit{N},\textit{N}-dibenzylhydrazones \textit{1B} (slightly superior) and piperidin-1-yl derivatives \textit{1A} proved to be better substrates than other considered \textit{N},\textit{N}-dialkylhydrazones such as pyrrolidine or \textit{N},\textit{N}-dimethylamino derivatives \textit{1C} and \textit{1D}, respectively, while TMSCN provided higher reactivities over KCN or CH\textsubscript{3}CO\textsubscript{2}N. Finally, addition of 2–3 equivalents of PhOH as aprotic additive to the reaction mixtures in toluene improved the catalytic efficiency, leading to the desired hydrazino nitriles \textit{rac-2} in full conversions (>95%) and shorter reaction times (48 h). Unfortunately, aromatic-substituted hydrazones showed no reactivity under these conditions.

Previous studies have shown that chiral thiourea-based catalysts are effective promoters for conducting the activation of imines towards cyanide attack in highly enantioselective Strecker-type reactions.\textsuperscript{21} Hence we performed a screening of representative thiourea catalysts (Fig. 2) employing the reaction between \( (E)-1,1\)-dibenzyl-2-(3-methylbutylidene)hydrazine (\textit{1a} = \textit{1B}, \textit{R} = \textit{i}-Bu) and TMSCN–PhOH 3 : 2 in toluene [0.1 M] at 0 °C as the model system and the results are presented in Table 1.

Initially we explored the behavior of bifunctional catalysts \textit{3a} and \textit{3b} for the simultaneous activation of the hydrazone (by the thiourea as a hydrogen-bond donor moiety) and the cyanide reagent (by the amino nitrogen in \textit{3a} or the hydroxyl group in \textit{3b}).\textsuperscript{22} Unfortunately, the reaction proceeded with low enantioselectivity after prolonged reaction times (entries 1 and
groups attached to both N atoms. Finally, Jacobsen-type thiourea catalysts 3e-h were tested (entries 5-6 and 8-9) and the results revealed 3h as the best catalyst, reaching conversions of around 75% in 3 days (entry 9) and affording 2a with good enantioselectivity (72% ee). Control experiments conducted without PhOH (entries 7 and 10) revealed the role of this additive as an activator of TMSCN, affording similar conversions in prolonged reaction times (7 days). It is noteworthy that the catalyst loading could be reduced to 10 mol% without compromising the selectivity or the reactivity, as shown in entry 11. A further optimization was then performed to identify the best solvent, reaction temperature, and protic additives (see ESI†). From this study, reactions performed in toluene at 0 °C in the presence of PhOH (2 equivalents) afforded the best results (>95%, 72% ee). Substitution of PhOH by different alcohols such as iPrOH (>95%, 66% ee), HFIP (>95%, 64% ee) or 1-naphthol (>95%, 54% ee) PhOH is also possible, whereas bulkier BuOH or 2,6-di-tert-butyl-p-cresol are less efficient, affording 2a in 4 days with 22 and 57% conversion, respectively. These data are in agreement with a nucleophilic preactivation of TMSCN to generate HCN; 24 the assistance of the dialkylamino group N atom should not be ruled out, as related N-acyl hydrazones exhibited no reactivity. 825

Under the optimized conditions, the reaction was performed on a 0.5 mmol scale for the synthesis of hydrazino nitrile 2a in 93% yield and matching the same 72% ee (entry 1, Table 2), and the scope of the methodology was explored with a representative set of aliphatic hydrazones 1b-h. The results summarized in Table 2 indicate a uniform behaviour for the synthesis of hydrazino nitriles 2a-h, obtained in good yields (89–98%) and moderate enantioselectivities (62–86% ee). As an exception, tert-butyl-substituted hydrazone 1g required 7 days to afford adduct 2g in 40% yield and 68% ee (entry 7). This result could be slightly improved by making use of the superior reactivity observed in trifluorotoluene, 50% yield and 68% ee in 4 days (entry 8). It is noteworthy that products 2e and 2f proved to be fairly crystalline, and this circumstance was exploited to obtain essentially pure enantiomers (98% ee) after a single crystallization.

Furthermore, the cyano group in adducts 2 can be conveniently transformed into a variety of valuable functional groups. Attempts to hydrolyze directly adducts 2 under acidic or basic conditions were unsuccessful as a result of a

Fig. 2 Thiourea organocatalysts tested.

![Thiourea organocatalysts](image)

Table 1 Screening of catalysts for the enantioselective Strecker-type reaction of 1a

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst</th>
<th>t (days)</th>
<th>Conv. (%)</th>
<th>ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>3a</td>
<td>7</td>
<td>48</td>
<td>10</td>
</tr>
<tr>
<td>2</td>
<td>3b</td>
<td>7</td>
<td>&gt;95</td>
<td>16</td>
</tr>
<tr>
<td>3</td>
<td>3c</td>
<td>7</td>
<td>63</td>
<td>16</td>
</tr>
<tr>
<td>4</td>
<td>3d</td>
<td>1</td>
<td>&gt;95</td>
<td>18</td>
</tr>
<tr>
<td>5</td>
<td>3e</td>
<td>7</td>
<td>40</td>
<td>40</td>
</tr>
<tr>
<td>6</td>
<td>3f</td>
<td>3</td>
<td>71</td>
<td>40</td>
</tr>
<tr>
<td>7f</td>
<td>3f</td>
<td>7</td>
<td>76</td>
<td>46</td>
</tr>
<tr>
<td>8</td>
<td>3g</td>
<td>3</td>
<td>22</td>
<td>rac</td>
</tr>
<tr>
<td>9</td>
<td>3h</td>
<td>3</td>
<td>75</td>
<td>72</td>
</tr>
<tr>
<td>10f</td>
<td>3h</td>
<td>7</td>
<td>79</td>
<td>44</td>
</tr>
<tr>
<td>11†</td>
<td>3h</td>
<td>3</td>
<td>&gt;95</td>
<td>72</td>
</tr>
</tbody>
</table>

†Interestingly, reaction performed with bulkier tert-butyl dimethylsilyl cyanide (TBDMSCN), under optimized conditions, afforded no product after 4 days.

‡Reactions performed with acyl hydrazones 1-I-III (0.1 mmol), TMSCN (0.3 mmol), 3h (10 mol%) and PhOH (0.2 mmol) in toluene (1 mL) afforded no product after 4 days at rt.

2). Bis-thioureas 3e and 3d also afforded product 2a with poor enantiomeric ratios (entries 3 and 4). Notably, (R)-BINAM derived bis-thiourea 3d proved to be the most active catalyst, as a significantly shorter reaction time was observed (from 7 days to 1 day); the enhanced reactivity in this case might be attributed to the superior acidity associated with the aromatic groups attached to both N atoms. Finally, Jacobsen-type
competing retro-Strecker reaction. Therefore, representative products 2a, b were transformed into the corresponding formyl hydrazines 4a, b via a "one-pot" Strecker/formylation sequence in excellent 86 and 98% yield, respectively (Scheme 3), and these products were selectively hydrolyzed with concentrated sulfuric acid at 45 °C to afford hydrazino acids 5a, b in excellent yields. Alternatively, hydrolysis of the cyano and formyl groups of 4a was performed by sequential treatment with sulfuric and hydrochloric acid to yield hydrazino acid 6a in 60% yield, although with slight racemization. Unfortunately, attempts to achieve selective removal of the N-benzyl groups were unsuccessful.

Importantly, single crystallizations made it possible to improve the enantioselectivities (5a: 82% ee; 5b: >99% ee) while slightly compromising the chemical yields. Alternatively, hydrazino nitriles 2a, b were subjected to reduction with lithium aluminum hydride and subsequent condensation with triphosgene leading to imidazolidinones 7a, b in good overall yields and without racemization. These are also valuable products containing an unsymmetrical vicinal diamine moiety, often present in biologically active compounds.

**Absolute configuration and stereochemical model**

The absolute configuration of acylated derivative (S)-8 (the major enantiomer isolated by chiral semi-preparative HPLC) was assigned by X-ray diffraction analysis as shown in Scheme 4.28

The absolute configurations of hydrazino nitriles 2 and derivatives 4–7 were assigned by analogy assuming a uniform reaction pathway by which the cyanide attacks from the Re face to the azomethine C=\(\equiv\)N bond of hydrazone 1 (Fig. 3).

Jacobsen and co-workers have performed extensive computational and experimental studies to elucidate the mode of action of this class of chiral thiourea catalysts in hydrocyanations of imines,29 concluding that the transformation proceeds via anion-binding catalysis.30 On this basis, a similar mode of activation is suggested in Fig. 3. In the proposed pathway, an initial catalyst-promoted hydrazone protonation by HCN is believed to generate a catalyst-bound hydrazonium–cyanide ion pair. Collapse of this ion pair and selective C–C bond formation leading to (S) hydrazino nitrile 2 then occur where the preferred orientation of the hydrazonium cation might be additionally stabilized by \(\pi\)–\(\pi\) interactions between the

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**Table 2** Scope of the synthesis of enantioenriched hydrazino nitriles 2

<table>
<thead>
<tr>
<th>Entry</th>
<th>R</th>
<th>t (days)</th>
<th>2 Yield (%)</th>
<th>ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>i-Bu, 1a</td>
<td>3</td>
<td>2a 93</td>
<td>72</td>
</tr>
<tr>
<td>2</td>
<td>i-Pr, 1b</td>
<td>3</td>
<td>2b 98</td>
<td>76</td>
</tr>
<tr>
<td>3</td>
<td>Et, 1c</td>
<td>3</td>
<td>2c 89</td>
<td>62</td>
</tr>
<tr>
<td>4</td>
<td>(CH(_2))(_2), 1d</td>
<td>3</td>
<td>2d 93</td>
<td>86</td>
</tr>
<tr>
<td>5</td>
<td>CH(_2)Ph, 1e</td>
<td>3</td>
<td>2e 91</td>
<td>82 (98)</td>
</tr>
<tr>
<td>6</td>
<td>CH(_2)CH(_2)Ph, 1f</td>
<td>3</td>
<td>2f 96</td>
<td>74 (98)</td>
</tr>
<tr>
<td>7</td>
<td>t-Bu, 1g</td>
<td>4</td>
<td>2g 50</td>
<td>68</td>
</tr>
<tr>
<td>8</td>
<td>t-Bu, 1g</td>
<td>7</td>
<td>2g 40</td>
<td>68</td>
</tr>
<tr>
<td>9</td>
<td>C(_8)H(_11), 1h</td>
<td>3</td>
<td>2h 90</td>
<td>72</td>
</tr>
</tbody>
</table>

* a Unless otherwise stated, reactions were performed with 1 (0.5 mmol), TMSCN (1.5 mmol), 3 h (10 mol%) and PhOH (1 mmol) in toluene (5 mL) at 0 °C. * b Isolated yield after column chromatography. * c Determined by HPLC on chiral stationary phases. In parentheses, ee after a single crystallization. * d Reaction performed in trifluorotoluene.
benzhydryl moiety of the optimum catalyst 3h and benzyl groups of hydrazone 1.**

**Conclusions**

In summary, an enantioselective Strecker-type transformation of aliphatic N,N-dibenzyldihydrazone 1 has been developed. The reaction can be efficiently catalyzed by a tert-leucine derived bifunctional amide-thiourea to afford the corresponding hydrazino nitriles 2 in good to excellent yields (50–96%) and moderate to good enantioselectivities, up to 86% ee. The protocol requires a combination of TMSCN and PhOH for the in situ generation of HCN as a cyanide source. The synthetic potential of adducts 2 has been illustrated by transformation into protected hydrazino acids 5–6 and imidazolidiones 7.

**General methods**

1H NMR spectra were recorded at 300 MHz or 500 MHz; 13C NMR spectra were recorded at 75 MHz or 125 MHz, with the solvent peak used as the internal standard. The following abbreviations are used to indicate the multiplicity in 1H NMR spectra: s, singlet; d, doublet; t, triplet; q, quartet; dd, double doublet; m, multiplet; bs, broad signal. Analytical thin layer chromatography (TLC) was performed on 0.25 mm silica gel 60-F plates and visualized by ultraviolet irradiation or by dipping the plates in solutions of Mostain, anisaldehyde or phosphomolibdic acid stains followed by heating. Optical rotations were measured using a Perkin-Elmer 341 MC polarimeter.

[†] In the X-ray structure of compound (S)-8 a π–π stabilizing interaction between one phenyl ring and the other p-bromo phenyl ring is also observed (see Scheme 4).

[**] Supporting this hypothesis, substitution of the N,N-dibenzalamino by the piperidino group of 1A, (R = i-Pr) resulted in a lower reactivity (70% conversion after 4 days) and enantioselectivity (20% ee) under the conditions described in Table 2. No reactivity was observed using 1D.

**Materials**

Unless otherwise noted, analytical grade solvents and commercially available reagents, or catalysts, were used without further purification. For flash chromatography (FC) silica gel (0.040–0.063 mm) was used. TMSCN was distilled under argon. Non-commercially available catalysts 3c, d, g, h1 were synthesized according to the literature. Synthesis and characterization data of hydrazones 1 are described in the ESI.

**General procedure for the enantioselective addition of TMSCN to N,N-dibenzyldihydrazone 1**

TMSCN (0.2 mL, 1.5 mmol, freshly distilled) was added to a solution of hydrazone 1 (0.5 mmol), catalyst 3h (29 mg, 0.05 mmol) and PhOH (94 mg, 1.0 mmol) in toluene (5 mL) at 0°C under an argon atmosphere. The mixture was stirred for 3–5 days. The enantiomerically enriched products 2 were purified by FC (cyclohexane–EtO, 6:1). Enantiomeric excesses were determined by HPLC analysis.

(S)-2-(2,2-Dibenzhydrazinyl)-4-methylpentanenitrile (2a).

Colourless oil (93% yield); [α]25D **−8.7 (c 1.3, CHCl3) (72% ee);
1H NMR (300 MHz, CDCl3) δ 7.33–7.17 (m, 10H), 3.86 (d, J = 12.9 Hz, 2H), 3.60 (d, J = 12.9 Hz, 2H), 3.33 (t, J = 7.5 Hz, 1H), 2.67 (bs, 1H), 1.57–1.47 (m, 1H), 1.40–1.31 (m, 1H), 1.23–1.13 (m, 1H), 0.65 (d, J = 6.7 Hz, 3H), 0.62 (d, J = 6.6 Hz, 3H); 13C NMR (125 MHz, CDCl3) δ 137.6, 129.7, 128.5, 127.6, 121.4, 61.9, 50.6, 47.8, 22.3, 22.1; HRMS (CI): calculated for [C20H25N3]+ 307.2048; found: 307.2050. The enantiomeric excess was determined by HPLC using a Chiralpak AD-H column [hexane–iPrOH (98:2)]; flow rate 1.0 mL min−1; τminore = 10.3 min, τmajor = 9.4 min.

(S)-2-(2,2-Dibenzhydrazinyl)-3-methylbutanenitrile (2b).

Colourless oil (98% yield); [α]25D −14.5 (c 0.9, CHCl3) (76% ee);
1H NMR (500 MHz, CDCl3) δ 7.42–7.29 (m, 10H), 3.96 (d, J = 12.9 Hz, 2H), 3.72 (d, J = 12.9 Hz, 2H), 3.29 (d, J = 5.1 Hz, 1H), 2.80 (bs, 1H), 1.83–1.73 (m, 1H), 0.92 (d, J = 6.7 Hz, 3H), 0.87 (d, J = 6.7 Hz, 3H); 13C NMR (125 MHz, CDCl3) δ 137.5, 129.8, 128.4, 127.6, 120.1, 61.6, 58.7, 30.2, 19.3, 18.2; HRMS (CI) calculated for [C14H23N3]+ 293.1905; found: 293.1904. The enantiomeric excess was determined by HPLC using a Chiralpak AD-H column [hexane–iPrOH (98:2)]; flow rate 1.0 mL min−1; τminore = 7.7 min, τmajor = 8.2 min.

(S)-2-(2,2-Dibenzhydrazinyl)butanenitrile (2c).

Colourless oil (89% yield); [α]25D −16.6 (c 0.8, CHCl3) (62% ee);
1H NMR (300 MHz, CDCl3) δ 7.42–7.27 (m, 10H), 3.93 (d, J = 12.9 Hz, 2H), 3.74 (d, J = 12.9 Hz, 2H), 3.39 (t, J = 6.7 Hz, 1H), 2.82 (s, 1H), 1.66–1.45 (m, 2H), 0.88 (t, J = 7.4 Hz, 3H); 13C NMR (125 MHz, CDCl3) δ 137.5, 129.8, 128.5, 127.6, 121.0, 61.6, 53.4, 25.1, 10.0; HRMS (CI): calculated for [C13H21N3]+ 279.1735; found: 279.1731. The enantiomeric excess was determined by HPLC using a Chiralpak AD-H column [hexane–iPrOH (98:2)]; flow rate 1.0 mL min−1; τminore = 11.6 min, τmajor = 10.4 min.

(S)-2-(2,2-Dibenzhydrazinyl)-4,4-dimethylpentanenitrile (2d).

White solid (93% yield); MP: 77–79°C; [α]25D −23.1 (c 0.3, CHCl3) (86% ee); 1H NMR (300 MHz, CDCl3) δ 7.44–7.28 (m,
general procedure for the one pot Strecker/formylation protocol

Mixed acetic formic amine, prepared from acetic anhydride (1.5 mL) and formic acid (0.6 mL) by heating at 60 °C for 2 hours, was cooled to 0 °C and added to the crude Strecker reaction described above (on a 0.5 mmol scale). The reaction mixture was allowed to stir for 1 hour and poured into ice/water (15 mL) and extracted with dichloromethane (3 × 10 mL). Combined organic extracts were washed with 10% aqueous solution of sodium bicarbonate (2 × 10 mL) and brine (10 mL). The organic extracts were dried over Na₂SO₄ and the solvents were removed in vacuo. Flash chromatography (cyclohexane–Et₂O, 4:1) afforded the corresponding formamide derivatives 4.

(S)-N,N’-Dibenzyl-N(1-cyano-3-methylbutyl)formo-hydrazide (4a). Colourless oil (86% yield); [α]D²⁵ +7.4 (c 1.0, CHCl₃) (70% ee); a mixture of rotamers: 1H NMR (300 MHz, CDCl₃) δ 8.26 (s, 0.3H), 8.10 (s, 0.7H), 7.45–7.30 (m, 10H), 4.80 (dd, J = 10.1, 5.5 Hz, 0.7H), 4.52–4.36 (m, 3H), 3.87 (dd, J = 10.1, 5.5 Hz, 0.3H), 1.91–1.82 (m, 0.7H), 1.77–1.64 (m, 0.7H), 1.51–1.39 (m, 0.3H), 1.37–1.29 (m, 0.3H), 1.15–1.01 (m, 0.7H), 0.89 (dd, J = 6.6, 1.8 Hz, 5H), 0.72 (d, J = 6.6 Hz, 0.4H), 0.61 (d, J = 6.6 Hz, 0.6H), 0.59–0.49 (m, 0.3H); 13C NMR (125 MHz, CDCl₃) δ 163.8, 161.3, 137.5, 137.4, 135.7, 135.6, 133.0, 129.8, 129.7, 129.5, 129.0, 128.9, 128.8, 128.5, 128.4, 128.1, 128.0, 117.1, 60.5, 59.5, 59.2, 57.4, 52.3, 43.9, 41.1, 39.4, 25.2, 24.6, 22.8, 22.7, 21.4, 20.9; HRMS (CI): calculated for [C₂₉H₂₉N₂O³⁺] 336.2076; found: 336.2065. The enantio-meric excess was determined by HPLC using a Chiralpak OD column [hexane–i-PrOH (98:2)]; flow rate 1 mL min⁻¹; τminor = 22.2 min, τmajor = 25.7 min.

(S)-N,N’-Dibenzyl-N(1-cyano-2-methylpropyl)formo-hydrazide (4b). White solid (98% yield); MP: 110–112 °C; [α]D²⁵ +13.8 (c 1.0, CHCl₃) (76% ee); a mixture of rotamers: 1H NMR (300 MHz, DMSO, 363 K) δ 8.26 (s, 0.8H), 8.20 (s, 0.2H), 7.51–7.16 (m, 10H), 4.73 (d, J = 9.6 Hz, 0.8H), 4.56–4.29 (m, 0.8H), 4.16–3.95 (m, 3.4H), 2.41–2.24 (m, 0.8H), 1.56–1.42 (m, 0.2H), 1.00 (d, J = 6.7 Hz, 2.3H), 0.86 (d, J = 6.7 Hz, 0.7H), 0.71 (d, J = 6.7 Hz, 2.3H), 0.41 (d, J = 6.7 Hz, 0.7H); 13C NMR (75 MHz, DMSO, 363 K) δ 165.2, 162.8, 132.6, 137.3, 136.8, 136.2, 129.3, 129.2, 129.0, 128.6, 128.4, 128.3, 128.1, 127.7, 117.6, 117.5, 59.8, 58.3, 58.5, 57.9, 49.9, 29.4, 19.3, 18.8, 18.4, 18.1; HRMS (CI): calculated for [C₂₉H₂₈N₂O³⁺] 322.1919; found: 322.1915. The enantio-meric excess was determined by HPLC using a Chiralpak OJ-H column [hexane–i-PrOH (96:4)]; flow rate 1 mL min⁻¹; τminor = 25.5 min, τmajor = 35.7 min.

General procedure for the transformation of 4 into acids 5

Sulfuric acid (65% w/v, 17.5 mL) was added to a solution of 4 (0.5 mmol) in the minimal amount of CH₃Cl₂. The reaction was stirred at 45 °C for 24 h, followed by pouring into ice/water and extracted with Et₂O (3 × 15 mL). The organic extracts were dried over Na₂SO₄ and the solvents were removed in vacuo. Crystallization from pentane afforded the corresponding acids 5.
The solvent was removed in vacuo. The reaction mixture was allowed to warm to room temperature and stirred overnight. AcOEt (5 mL) and water (0.2 mL) were sequentially added dropwise to the reaction mixture until a white solid was formed. The mixture was filtered through Celite and the solvent was removed in vacuo. The crude amine was taken in anhydrous CH2Cl2 (4.0 mL), and DIPEA (0.3 mL, 1.5 mmol) was added dropwise at 0 °C. After 15 minutes, a solution of triphosgene (178 mg, 0.6 mmol) in anhydrous CH2Cl2 (2 mL) was added dropwise and the reaction mixture was allowed to warm to room temperature and stirred overnight. The reaction was diluted with CH2Cl2 (2 mL), washed with water (5 mL), brine (5 mL), dried over Na2SO4 and the solvent was removed in vacuo. Flash chromatography (cyclohexane–Et2O, 2:1) afforded the corresponding imidazolidinones 7.

(S)-1-(Dibenzylamino)-3-isobutylimidazolidin-2-one (7a). White solid (67% yield); MP: 129–131 °C; [α]D 25 +17.2 (c 0.2, CHCl3) (70% ee); 1H NMR (500 MHz, CDCl3) δ 7.31–7.16 (m, 10H), 4.33–3.94 (m, 4H), 3.03 (t, J = 7.9 Hz, 1H), 2.80–2.74 (m, 1H), 2.63–2.59 (m, 1H), 1.42–1.37 (m, 1H), 1.26–1.19 (m, 1H), 0.66 (d, J = 6.6 Hz, 3H), 0.58 (d, J = 6.6 Hz, 3H), 0.55–0.49 (m, 1H), 13C NMR (125 MHz, CDCl3) δ 162.0, 138.8, 138.6, 129.7, 128.4, 128.2, 127.3, 61.4, 56.7, 56.3, 44.7, 41.7, 24.5, 23.8, 21.7; HRMS (Cl) (calculated for [C20H23N2O]+): 338.1727; found: 338.1720. The enantiomeric excess was determined by HPLC using a Chiralpak AD-H column [hexane–i-PrOH (90:10)]; flow rate 1.0 mL min−1; [α]D 25 = −5.0, [β]D 25 = +4.8.

(S)-1-(Dibenzylamino)-3-isopropylimidazolidin-2-one (7b). White solid (64% yield); MP: 98–100 °C; [α]D 25 −57.8 (c 0.9, CHCl3) (76% ee); 1H NMR (300 MHz, CDCl3) δ 7.43–7.32 (m, 32H), 4.58 (d, J = 11.1 Hz, 1H), 4.35 (d, J = 11.1 Hz, 2H), 3.88 (d, J = 11.8 Hz, 1H), 3.43–3.28 (m, 2H), 2.57–2.51 (m, 1H), 2.16–2.06 (m, 1H), 0.73 (d, J = 7.2 Hz, 3H), 0.65 (d, J = 7.2 Hz, 3H), 13C NMR (75 MHz, CDCl3) δ 151.4, 144.8, 137.7, 137.1, 129.8, 120.9, 128.6, 121.7, 60.5, 59.6, 55.5, 43.8, 27.4, 18.4, 14.4; HRMS (Cl) (calculated for [C20H30N2O]+): 324.2076; found: 324.2070. The enantiomeric excess was determined by HPLC using a Chiralpak AD-H column [hexane–i-PrOH (90:10)]; flow rate 1.0 mL min−1; [α]D 25 = +5.6 min, [β]D 25 = −5.1.

**Determination of absolute configuration (Scheme 4): synthesis of (S)-4-bromo-N-(1-cyan-2-methylpropyl)-N-(1,3-diphenylpropan-2-yl)benzamide (8)**

Et3N (0.7 mL, 5 mmol) and 4-bromobenzoyl chloride (1 g, 5 mmol) were sequentially added to a solution of 2b (150 mg, 0.5 mmol) in anhydrous CH2Cl2 (2.5 mL). The reaction was stirred at reflux for 48 h, neutralized with a saturated solution of NaHCO3, and extracted with dichloromethane (3 × 10 mL). Combined organic extracts were dried over Na2SO4 and the solvent was removed in vacuo. Flash chromatography (cyclohexane–Et2O, 6:1) afforded 8 as a yellow solid (73 mg, 70%, 70% ee). 1H NMR (300 MHz, DMSO D6) δ 7.88–7.84 (m, 1H), 7.72–7.67 (m, 1H), 7.51–7.46 (m, 2H), 7.38–7.15 (m, 5H), 7.08–7.03 (m, 2H), 7.00–6.96 (m, 2H), 6.82 (d, J = 7.2 Hz, 2H), 4.73 (d, J = 9.6 Hz, 1H), 4.33 (d, J = 12.5 Hz, 1H), 4.20 (d, J = 12.5 Hz, 1H), 3.83 (d, J = 14.0 Hz, 1H), 3.60 (d, J = 14.0 Hz, 1H).
The enantioenriched mixture was resolved by semi-preparative HPLC on a Chiralpak OJ-H column, [hexane–i-ProH (80:20)], 6 mL min$^{-1}$. Analytical OJ-H, [hexane–i-ProH (80:20)], 1 mL min$^{-1}$.

$\{S\}$-$\delta$: $t_R = 10.7$ min (47 mg, 45%). X-ray quality crystals were obtained by crystallization in hexane–AcOEt at room temperature. MP: 172–174°C. $[\alpha]^2_28 = -14.3$ (c 1.0, CHCl$_3$) (99.8% ee).

$\{R\}$-$\delta$: $t_R = 21.3$ min (10 mg, 11%). $[\alpha]^2_28 = +12.6$ (c 0.7, CHCl$_3$) (99.8% ee).

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Notes and references


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For interesting NMR control experiments where the generation of HCN from ipROH and TMSCN (under diluted conditions) is strongly accelerated by the presence of basic nitrogens, see: J. Wang, W. Wang, W. Li, X. Hu, K. Shen, C. Tan, X. Liu and X. Feng, Chem.–Eur. J., 2009, 15, 11642.


Crystal data for (S)-7: C_{26}H_{26}BrN_{3}O, M = 476.41, tetragonal, a = 10.8070(4) Å, b = 10.8070(4) Å, c = 40.3063(3) Å, α = 90.00°, β = 90.00°, γ = 90.00°, V = 4707.3(4) Å^3, T = 173(2) K, space group P 4_{1}2_{1}2, Z = 8, μ(MoKα) = 1.769 mm⁻1, 96964 reflections measured, 7175 independent reflections (R_{int} = 0.0579). The final R_{1} values were 0.0314 (I > 2σ(I)). The final wR(F²) values were 0.0680 (I > 2σ(I)). The final R_{1} values were 0.0492 (all data). The final wR(F²) values were 0.0741 (all data). The goodness of fit on F² was 1.008. Flack parameter = 0.004(5).

