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 enantioenriched hydrazino acids7 rely generally on elaboration of amino acid derivatives,8 sporadic catalytic hydrogenation of hydrazones,9 and electrophilic amination 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...
Tsogoeva reported an enantioselective organocatalytic hydrazone hydrocyanation by an O-silylated BINOL-phosphate.\textsuperscript{12b}

Considering that the higher basicity of $N,N$-dialkylhydrazones over acyl hydrazones offers different interaction opportunities with acidic organocatalysts, we envisioned an alternative procedure from $N,N$-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 $N,N$-dialkylhydrazones.\textsuperscript{14} Their imine-type reactivity has been exploited in Mannich-type additions of ketene silyl acetics and thioacetics,\textsuperscript{15} in Staudinger-like cycloadditions\textsuperscript{16} and cyanosilylations\textsuperscript{13e} employing $C_2$-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 $N,N$-dialkylhydrazones using bifunctional H-bonding activation.

Results and discussion

We started studies on Strecker-type reactivity employing piperidine-containing \((1 \text{A, } R = i \text{Bu})\) or $N,N$-dibenzyl \((1 \text{B, } R = i \text{Bu})\) 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 CHCl$_3$ (<15% conv.), while a polar protic solvent like MeOH afforded cleanly the corresponding hydrazino nitriles in full conversions (>95%) and shorter reaction times (<4 h).\textsuperscript{20} suggesting that HCN, produced \textit{in situ}, spontaneously adds to the hydrazone C=N bond. Preliminary screenings were then performed to identify the best cyanide source, structure of the $N,N$-dialkylhydrazine 1, catalyst and solvent for the catalytic enantioselective version (Scheme 2, see ESIF).

Several alkald-derivated quaternary ammonium salts (bearing a free OH group), ($S$)-BINOL, ($S$)-BINOL-derived phosphoric acid and $N,N'$-bis[3,5-bis(trifluoromethyl)]phenyl thiourea (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$_2$O, toluene or CHCl$_3$ (40–50% conv. after 72 hours), but afforded 2 in racemic form, whereas ($S$)-BINOL and phosphoric acid derivatives were less active (22–30% conv., 72 h, racemic). Thiourea I, however, efficiently accelerated the model reactions with respect to the background reaction in several solvents (CHCl$_3$: 46–67%, 72 h; CH$_2$Cl$_2$: 58%, 72 h; toluene: 35–47%, 72 h; CH$_3$CN: 72%, 72 h), thereby opening opportunities for the development of an asymmetric catalytic version. Aliphatic $N,N$-dibenzylhydrazones 1B (slightly superior) and piperidin-1-yl derivatives 1A proved to be better substrates than other considered $N,N$-dialkylhydrazines such as pyrrolidine or $N,N$-dimethylamino derivatives 1C and 1D, respectively, while TMSCN provided higher reactivities over KCN or CH$_3$COCN. Finally, addition of 2–3 equivalents of PhOH as a protic additive to the reaction mixtures in toluene improved the catalytic efficiency, leading to the desired hydrazino nitriles 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 (1a=1B, R = i $Bu) and TMSCN–PhOH 3 : 2 in toluene \(0.1 \text{ M}\) at $0 \degree \text{C}\) as the model system and the results are presented in Table 1.

Initially we explored the behavior of bifunctional catalysts 3a and 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 3a or the hydroxyl group in 3b).\textsuperscript{22} Unfortunately, the reaction proceeded with low enantioselectivity after prolonged reaction times (entries 1 and

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**Scheme 1** Asymmetric catalytic Strecker-type reactions of hydrazones.

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**Scheme 2** Preliminary optimization of Strecker-type reactions of hydrazones \(1\) (the best choices are marked in blue).
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 tBuOH 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;‡ the assistance of the dialkylamino group N atom should not be ruled out, as related N-acyl hydrazones exhibited no reactivity.§

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

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>
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<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>
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<td>5</td>
<td>3e</td>
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<td>40</td>
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<tr>
<td>6</td>
<td>3f</td>
<td>3</td>
<td>71</td>
<td>40</td>
</tr>
<tr>
<td>7†</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>
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<tr>
<td>10‡</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>

†Unless otherwise stated, reactions were performed with 1a (0.1 mmol), TMSCN (0.3 mmol), 3 (20 mol%) and PhOH (0.2 mmol) in toluene (1 mL) at 0 °C. § Determined by 1H NMR. ‡ Determined by HPLC on chiral stationary phases. *Without PhOH. ‡ 10 mol% catalyst.

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. 23 Finally, Jacobsen-type

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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=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, concluding that the transformation proceeds via anion-binding catalysis.29 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 π–π 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</th>
<th>Yield (%)</th>
<th>ee (%)</th>
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</thead>
<tbody>
<tr>
<td>1</td>
<td>i-Bu, 1a</td>
<td>3</td>
<td>2a</td>
<td>93</td>
<td>72</td>
</tr>
<tr>
<td>2</td>
<td>i-Pr, 1b</td>
<td>3</td>
<td>2b</td>
<td>98</td>
<td>76</td>
</tr>
<tr>
<td>3</td>
<td>Et, 1c</td>
<td>3</td>
<td>2c</td>
<td>89</td>
<td>62</td>
</tr>
<tr>
<td>4</td>
<td>(CH₃)₂CH₂, 1d</td>
<td>3</td>
<td>2d</td>
<td>93</td>
<td>86</td>
</tr>
<tr>
<td>5</td>
<td>CH₂Ph, 1e</td>
<td>3</td>
<td>2e</td>
<td>91</td>
<td>82 (98)</td>
</tr>
<tr>
<td>6</td>
<td>CH₂CH₂Ph, 1f</td>
<td>3</td>
<td>2f</td>
<td>96</td>
<td>74 (98)</td>
</tr>
<tr>
<td>7</td>
<td>t-Bu, 1g</td>
<td>7</td>
<td>2g</td>
<td>50</td>
<td>68</td>
</tr>
<tr>
<td>8</td>
<td>n-Bu, 1h</td>
<td>3</td>
<td>2h</td>
<td>90</td>
<td>72</td>
</tr>
</tbody>
</table>

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*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. bIsolated yield after column chromatography. cDetermined by HPLC on chiral stationary phases. In parentheses, ee after a single crystallization. dReaction performed in trifluorotoluene.

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Scheme 3 Synthesis of acids 5 and 6a and imidazolidinones 7.

Scheme 4 Synthesis and X-ray structure of (S)-8. H atoms except H8 are omitted for clarity. Thermal ellipsoids are drawn at 50% probability.

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**Footnote:** Employing *in situ* generated acetic formic anhydride under solvent free conditions. R. Edwards, *J. Am. Chem. Soc.*, 1942, 64, 1583.
Supporting this hypothesis, substitution of the piperidino group of Scheme 4).

PhOH for the in situ 86% ee. The protocol requires a combination of TMSCN and or phosphomolibdic acid stains followed by heating. Optical rotations were measured using a Perkin-Elmer 341 MC polarimeter.

In summary, an enantioselective Strecker-type transformation of aliphatic N,N-dibenzylhydrazones 1 has been developed. The reaction can be efficiently catalyzed by a tert-leucine derived bifunctional amide-thiourea to afford the corresponding hydrazine 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 imidazolidinones 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.

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, h11 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-dibenzylhydrazones 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-Dibenzylhydrazinyl)-4-methylpentanenitrile (2a).

Colourless oil (93% yield); [α]D25 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), 2.60 (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, 121.4, 61.9, 50.6, 40.7, 24.8, 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–i-PrOH (98 : 2)]; flow rate 1.0 mL min−1; tminor = 10.3 min, tmajor = 9.4 min.

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

Colourless oil (98% yield); [α]D25 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 [C18H21N3] 293.1905; found: 293.1904. The enantiomeric excess was determined by HPLC using a Chiralpak AD-H column [hexane–i-PrOH (98 : 2)]; flow rate 1.0 mL min−1; tminor = 7.7 min, tmajor = 8.2 min.

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

Colourless oil (89% yield); [α]D25 −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 [C16H23N3] 279.1735; found: 279.1731. The enantiomeric excess was determined by HPLC using a Chiralpak AD-H column [hexane–i-PrOH (98 : 2)]; flow rate 1.0 mL min−1; tminor = 11.6 min, tmajor = 10.4 min.

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

White solid (93% yield); MP: 77–79 °C; [α]D25 −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 Stetter/formylation protocol

Mixed acetic formic anhydride, 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 Stetter 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]D 25 at 1.4 (c 0.7, 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, 1H), 4.24–3.97 (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 (dd, 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, 131.0, 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 [C32H26N2O3]2+ 536.2076; found: 536.2065. The enantiomeric excess was determined by HPLC using a Chiralpak OD column [hexane–i-ProH (98:2)]; flow rate 1 mL min−1; τmajor = 22.2 min, τminor = 25.7 min.

(S)-N’,N’-Dibenzyl-N-(1-cyano-2-methylpropyl)formo-hydrazide (4b). White solid (98% yield); MP: 110–112 °C; [α]D 25 at 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, 137.3, 136.9, 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, 29.3, 19.3, 18.8, 18.4, 18.1; HRMS (CI): calculated for [C34H25N3O3]2+ 332.1919; found: 332.1915. The enantiomeric excess was determined by HPLC using a Chiralpak OJ-H column [hexane–i-ProH (96:4)]; flow rate 1 mL min−1; τmajor = 35.7 min, τminor = 25.5 min.
(S)-2-(2,2-Dibenzyl-1-formylhydrazinyl)-4-methylpentanoic acid (5a). White solid (80% yield); MP: 148–150 °C; [α]D25 0.55 (c 1.0, CHCl3) (82% ee); mixture of rotamers: 1H NMR (300 MHz, CDCl3) δ 8.30 (s, 0.1H), 8.04 (s, 0.9H), 7.36–7.25 (m, 10H), 5.24 (s, 1H), 4.47–4.18 (m, 0.4H), 4.12–3.93 (m, 4.6H), 2.41–2.32 (m, 1H), 1.75–1.57 (m, 1H), 1.36–1.26 (m, 1H), 1.04 (d, J = 6.6 Hz, 2.7H), 0.95 (d, J = 6.6 Hz, 2.7H), 0.70 (d, J = 6.6 Hz, 0.3H), 0.63 (d, J = 6.6 Hz, 0.3H); 13C NMR (75 MHz, CDCl3) δ 174.4, 167.7, 163.1, 129.7, 129.4, 129.2, 128.8, 128.6, 128.3, 128.0, 59.7, 58.6, 38.8, 25.6, 23.4, 22.0; HRMS (FAB): calculated for [C21H26N2NaO3]+ 377.1841; found: 377.1849. The enantiomeric excess was determined by HPLC using a Chiralpak OJ-H column [hexane-i-PrOH (90:10)]; flow rate 1.0 mL min−1; τminor = 7.2 min, τmajor = 10.2 min. 

(S)-2-(2,2-Dibenzyl-1-formylhydrazinyl)-3-methylbutanoic acid (5b). White solid (66% yield); MP: 118–120 °C; [α]D25 0.47 (c 1.0, CHCl3) (99.8% ee); mixture of rotamers: 1H NMR (300 MHz, CDCl3) δ 8.23 (s, 1H), 7.43–7.24 (m, 10H), 5.17 (s, 1H), 4.10–3.83 (m, 4H), 3.55 (d, J = 11.5 Hz, 1H), 2.96–2.78 (m, 1H), 1.07 (d, J = 6.6 Hz, 3H), 0.90 (d, J = 6.6 Hz, 3H); 13C NMR (125 MHz, CDCl3) δ 174.5, 167.5, 163.6, 163.1, 129.3, 129.1, 129.0, 128.9, 128.5, 128.2, 127.9, 69.1, 59.5, 56.9, 27.2, 20.7, 19.7; HRMS (FAB): calculated for [C20H24N2NaO3]+ 363.1685; found: 363.1692. The enantiomeric excess was determined by HPLC using a Chiralpak AD-H column [hexane-i-PrOH (95:5)]; flow rate 1.0 mL min−1; τminor = 30.7 min, τmajor = 26.1 min. 

(S)-2-(2,2-Dibenzylhydrazinyl)-4-methylpentanoic acid (6a). Sulfuric acid (63% w/v, 17.5 mL) was added to a solution of 4a (168 mg, 0.5 mmol) in the minimal amount of CH2Cl2. 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 removed in vacuo and the crude acid 5a was treated with 6 M HClaq (15 mL) and stirred at 90 °C for 12 h. The solvent was removed in vacuo and a solution of crude acid 6a, re-dissolved in CH2Cl2, was treated with NaHCO3 sat. until pH ~ 8, and extracted with CH2Cl2 (2 × 10 mL) and Et2O (2 × 10 mL). The organic extracts were dried over Na2SO4 and the solvents were removed in vacuo. Crystallization from pentane afforded the corresponding acid 6a as a white solid (103 mg, 63%); MP: 140–142 °C; [α]D25 0.5 (c 0.5, CHCl3) (62% ee); 1H NMR (300 MHz, DMSO-d6) δ 7.35–7.21 (m, 10H), 3.83 (d, J = 13.0 Hz, 2H), 3.56 (d, J = 13.0 Hz, 2H), 3.14 (t, J = 6.9 Hz, 1H), 1.51–1.39 (m, 1H), 1.16 (t, J = 6.9 Hz, 2H), 0.71 (d, J = 6.7 Hz, 3H), 0.60 (d, J = 6.7 Hz, 3H); 13C NMR (75 MHz, DMSO-d6) δ 177.0, 139.3, 129.7, 128.6, 127.4, 61.5, 40.5, 24.6, 23.1, 22.6; HRMS (CI): calculated for [C20H24N2O2]+ 327.1526; found: 327.1526. The enantiomeric ratio was determined by HPLC using a Chiralpak AD-H column [hexane-i-PrOH (95:5)]; flow rate 1.0 mL min−1; τminor = 8.7 min, τmajor = 9.4 min.

General procedure for the transformation of 2 into imidazolidinones 7

A solution of the Strecker adduct 2 (0.5 mmol) in anhydrous Et2O (1.0 mL) was added to a suspension of LiAlH4 (2.1 mmol, 78 mg) in anhydrous Et2O (10.0 mL) at 0 °C. 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 (cylohexane–EtO2, 2:1) afforded the corresponding imidazolidinones 7.
The enantiomerich 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 \(^{-1}\).

\(\{S\}: t_R = 10.7\) min (47 mg, 45%). X-ray quality crystals were obtained by crystallization in hexane-\(\alpha\)-OEt at room temperature. MP: 172−174 °C. \([\delta]_{D}^{25} = -14.3\) (c 1.0, CHCl\(_3\)) (99.8% ee).

\(\{R\}: t_R = 21.3\) min (10 mg, 11%). \([\delta]_{D}^{25} +12.6\) (c 0.7, CHCl\(_3\)) (99.8% ee).

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**Notes and references**


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 P4_12_2, Z = 8, μ(MoKα) = 1.769 mm^-1, 96964 reflections measured, 7175 independent reflections (R_{int} = 0.0579). The final R_{w} values were 0.0314 (I > 2σ(I)). The final wR_{2} values were 0.0680 (I > 2σ(I)). The final R_{c} values were 0.0492 (all data). The final wR_{2} values were 0.0741 (all data). The goodness of fit on F^{2} was 1.008. Flack parameter = 0.004(5).

