

Asymmetric organocatalytic Strecker-type reactions of aliphatic *N,N*-dialkylhydrazones†Cite this: *Org. Biomol. Chem.*, 2013, **11**, 8247Aurora Martínez-Muñoz,^a David Monge,^{*a} Eloísa Martín-Zamora,^a Eugenia Marqués-López,^a Eleuterio Álvarez,^b Rosario Fernández^{*a} and José M. Lassaletta^{*b}

The enantioselective organocatalytic Strecker-type reaction of aliphatic *N,N*-dialkylhydrazones is presented. Using trimethylsilyl cyanide (TMS-CN) 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.

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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, anti-tumour 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

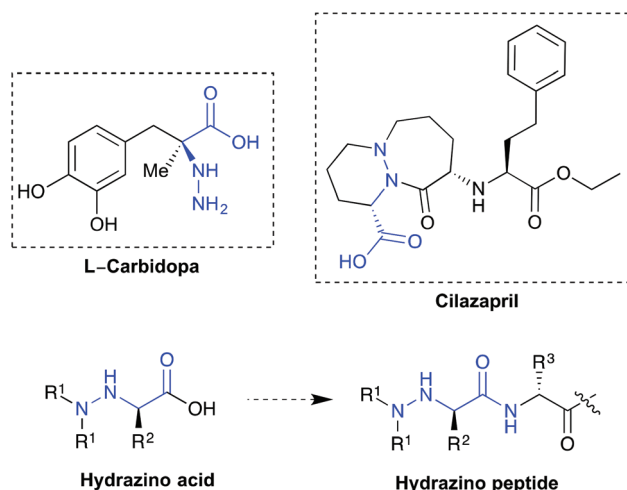


Fig. 1 Hydrazino acids in medicinal chemistry.

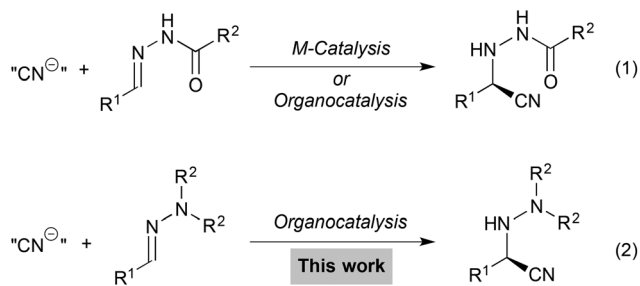
Existing routes to enantioenriched hydrazino acids⁷ rely generally on elaboration of amino acid derivatives,⁸ sporadic catalytic hydrogenation of hydrazones,⁹ and electrophilic amination of enolates with azodicarboxylates.¹⁰ In this context, the development of asymmetric catalytic versions of hydrazone 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

^aDepartamento de Química Orgánica, Universidad de Sevilla, C/ Prof. García González, 1, 41012 Sevilla, Spain. E-mail: dmonge@us.es, ffernand@us.es; Fax: +34 954624960; Tel: +34 954551518

^bInstituto de Investigaciones Químicas (CSIC-US), Américo Vespucio 49, E-41092 Sevilla, Spain. E-mail: jmlassa@iiq.csic.es; Fax: +34 954460565; Tel: +34 954489563

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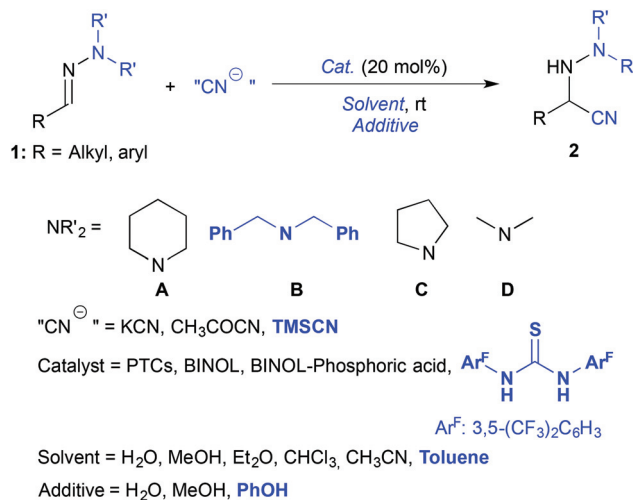
Scheme 1 Asymmetric catalytic Strecker-type reactions of hydrazones.

Tsogoeva reported an enantioselective organocatalytic hydrazone hydrocyanation by an *O*-silylated BINOL-phosphate.^{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.¹³ On the other hand, we have investigated the ambiphilic reactivity of aldehyde *N,N*-dialkylhydrazones.¹⁴ Their imine-type reactivity has been exploited in Mannich-type additions of ketene silyl acetals and thioacetals,¹⁵ in Staudinger-like cycloadditions¹⁶ and cyanosilylations^{13c} 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.¹⁷ The mild nature of H-bonding and Brønsted acid organocatalytic activations,¹⁸ however, appears to be more compatible with hydrazones, and applications have been developed in other contexts.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 (**1A**, R = *i*Bu) or *N,N*-dibenzyl (**1B**, R = *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 CHCl₃ (<15% conv.), while a polar protic solvent like MeOH afforded cleanly the corresponding hydrazino nitriles **rac-2** in excellent yields (90–95%) in short reaction times (<4 h),²⁰ suggesting that HCN, produced *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*-dialkylhydrazone **1**, catalyst and solvent for the catalytic enantioselective version (Scheme 2, see ESI†).

Several alkaloid-derived 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



Scheme 2 Preliminary optimization of Strecker-type reactions of hydrazones **1** (the best choices are marked in blue).

ability to establish H-bonding cooperative networks to activate reagents. Phase transfer catalysts (PTCs) showed a moderate catalytic activity in Et₂O, toluene or CHCl₃ (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 (CHCl₃: 46–67%, 72 h; CH₂Cl₂: 58%, 72 h; toluene: 35–47%, 72 h; CH₃CN: 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*-dialkylhydrazones such as pyrrolidine or *N,N*-dimethylamino derivatives **1C** and **1D**, respectively, while TMSCN provided higher reactivities over KCN or CH₃COCN. 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.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 M] at 0 °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**).²² Unfortunately, the reaction proceeded with low enantioselectivity after prolonged reaction times (entries 1 and

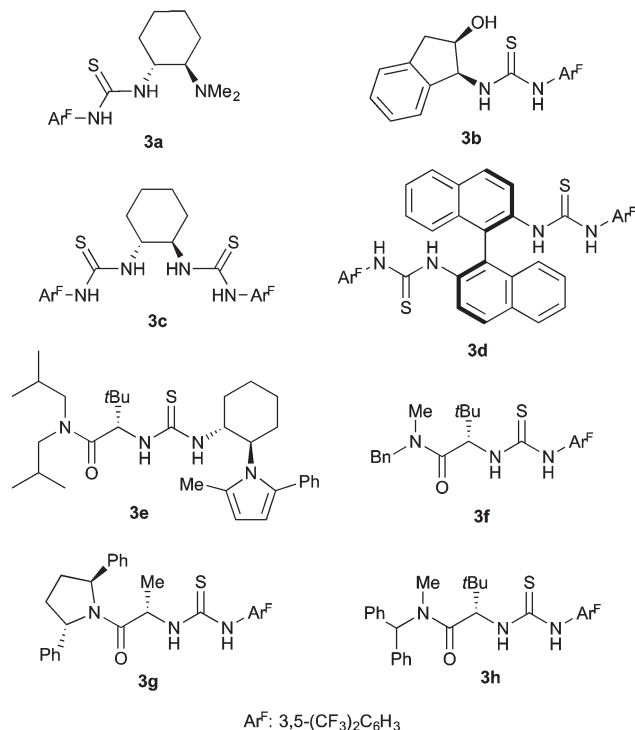


Fig. 2 Thiourea organocatalysts tested.

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

Entry	Catalyst	<i>t</i> (days)	Conv. ^b (%)	ee ^c
1	3a	7	48	10
2	3b	7	>95	16
3	3c	7	63	16
4	3d	1	>95	18
5	3e	7	40	40
6	3f	3	71	40
7 ^d	3f	7	76	46
8	3g	3	22	<i>rac</i>
9	3h	3	75	72
10 ^d	3h	7	79	44
11 ^e	3h	3	>95	72

^a 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. ^b Determined by ¹H NMR. ^c Determined by HPLC on chiral stationary phases. ^d Without PhOH. ^e 10 mol% catalyst.

2). Bis-thioureas **3c** 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

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 *i*PrOH (>95%, 66% ee), HFIP (>95%, 64% ee) or 1-naphthol (>95%, 54% ee) PhOH is also possible, whereas bulkier *t*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[‡]; the assistance of the dialkylamino group N atom should not be ruled out, as related *N*-acyl hydrazones exhibited no reactivity.§²⁵

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

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

§ Reactions performed with acyl hydrazones **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.

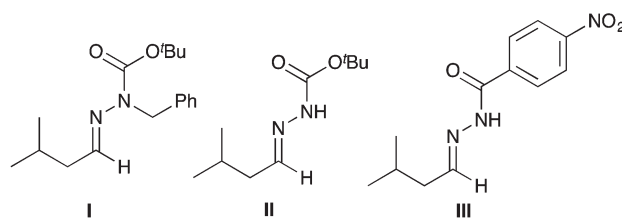


Table 2 Scope of the synthesis of enantioenriched hydrazino nitriles **2**^a

Entry	R	t (days)	2	Yield ^b (%)	ee ^c
1	i-Bu, 1a	3	2a	93	72
2	i-Pr, 1b	3	2b	98	76
3	Et, 1c	3	2c	89	62
4	(CH ₃) ₃ CH ₂ , 1d	3	2d	93	86
5	CH ₂ Ph, 1e	3	2e	91	82 (98)
6	CH ₂ CH ₂ Ph, 1f	3	2f	96	74 (98)
7	<i>t</i> -Bu, 1g	7	2g	40	68
8 ^d	<i>t</i> -Bu, 1g	4	2g	50	68
9	C ₆ H ₁₁ , 1h	3	2h	90	72

^a Unless otherwise stated, reactions were performed with **1** (0.5 mmol), TMSCN (1.5 mmol), **3h** (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.

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.

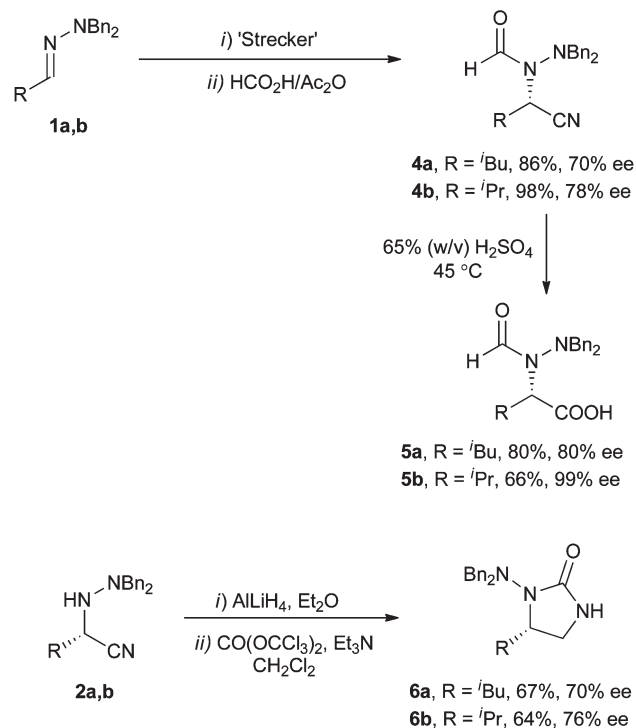
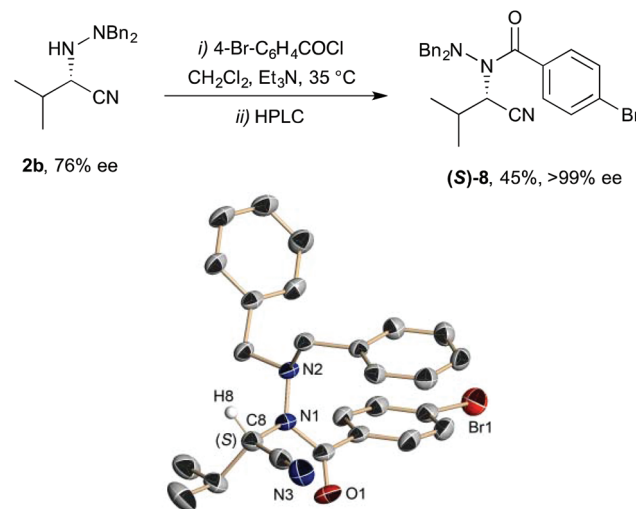
Importantly, single crystallizations made it possible to improve the enantioselectivities (**5a**: 82% ee; **5b**: >99% ee) while slightly compromising the chemical yields. Alternatively, hydrazino nitriles **2a,b** were subjected to reduction with lithium aluminum hydride and subsequent condensation 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,²⁶ often present in biologically active compounds.²⁷

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

¶ Employing *in situ* generated acetic formic anhydride under solvent free conditions. R. Edwards, *J. Am. Chem. Soc.*, 1942, **64**, 1583.

**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.

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 hydrazone–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 hydrazone cation might be additionally stabilized by π – π interactions between the

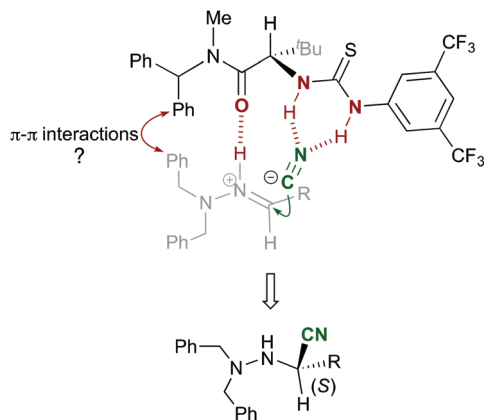


Fig. 3 Activation and stereochemical model.

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*-dibenzylhydrazones **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 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.

^{||}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*-dibenzylamino by the piperidino group of **1A**, (R = *i*-Bu) 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**, **h**³¹ 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–Et₂O, 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), 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, 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}; τ _{minor} = 10.3 min, τ _{major} = 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 [C₁₉H₂₃N₃]⁺ 293.1905; found: 293.1894. The enantiomeric excess was determined by HPLC using a Chiralpak AD-H column [hexane–*i*-PrOH (98:2)]; flow rate 1 mL min^{–1}; τ _{minor} = 7.7 min, τ _{major} = 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 [C₁₈H₂₁N₃]⁺ 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}; τ _{minor} = 11.6 min, τ _{major} = 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,

10H), 4.00 (d, $J = 12.9$ Hz, 2H), 3.67 (d, $J = 12.9$ Hz, 2H), 3.37 (dd, $J = 7.9, 4.6$ Hz, 1H), 2.73 (s, 1H), 1.66–1.59 (dd, $J = 14.0, 7.7$ Hz, 1H), 1.28–1.22 (dd, $J = 14.0, 5.8$ Hz, 1H), 0.78 (s, 9H); ^{13}C NMR (125 MHz, CDCl_3) δ 137.7, 129.7, 128.4, 127.6, 122.3, 62.1, 49.2, 45.6, 30.1, 29.5; HRMS (CI): calculated for $[\text{C}_{21}\text{H}_{27}\text{N}_3]^+$ 321.2205; found: 321.2197. The enantiomeric excess was determined by HPLC using a Chiralpak AD-H column [hexane-*i*-PrOH (99 : 1)]; flow rate 1 mL min^{-1} ; $\tau_{\text{minor}} = 13.9$ min, $\tau_{\text{major}} = 14.7$ min.

(S)-2-(2,2-Dibenzylhydrazinyl)-3-phenylpropanenitrile (2e). Yellow solid (91% yield); MP: 101–103 °C; $[\alpha]_{\text{D}}^{25} -31.2$ (c 0.5, CHCl_3) (98% ee after a single crystallization from pentane); ^1H NMR (300 MHz, CDCl_3) δ 7.32–7.25 (m, 13H), 7.08–7.05 (m, 2H), 3.87 (d, $J = 13.0$ Hz, 2H), 3.64 (d, $J = 13.0$ Hz, 2H), 3.62 (overlapped signal, 1H), 2.89 (s, 1H), 2.87–2.72 (m, 2H); ^{13}C NMR (125 MHz, CDCl_3) δ 137.4, 135.4, 129.7, 129.3, 128.9, 128.5, 127.6, 127.5, 120.5, 61.5, 53.2, 37.9; HRMS (CI): calculated for $[\text{C}_{23}\text{H}_{23}\text{N}_3]^+$ 341.1892; found: 341.1899. The enantiomeric excess was determined by HPLC using a Chiralpak OD column [hexane-*i*-PrOH (98 : 2)]; flow rate 1.0 mL min^{-1} ; $\tau_{\text{minor}} = 16.5$ min, $\tau_{\text{major}} = 15.0$ min.

(S)-2-(2,2-Dibenzylhydrazinyl)-4-phenylbutanenitrile (2f). White solid (96% yield); MP: 65–67 °C; $[\alpha]_{\text{D}}^{25} -7.2$ (c 0.3, CHCl_3) (98% ee after a single crystallization from pentane); ^1H NMR (500 MHz, CDCl_3) δ 7.28–7.15 (m, 12H), 7.12–7.09 (m, 1H), 6.94–6.93 (m, 2H), 3.80 (d, $J = 12.9$ Hz, 2H), 3.64 (d, $J = 12.9$ Hz, 2H), 3.33 (t, $J = 6.9$ Hz, 1H), 2.74 (s, 1H), 2.53–2.44 (m, 2H), 1.81–1.74 (m, 1H), 1.71–1.64 (m, 1H); ^{13}C NMR (125 MHz, CDCl_3) δ 140.2, 137.5, 129.8, 128.7, 128.5, 128.4, 127.6, 126.4, 120.8, 61.7, 51.2, 33.3, 31.6; HRMS (CI): calculated for $[\text{C}_{24}\text{H}_{25}\text{N}_3]^+$ 355.2048; found: 355.2052. 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} ; $\tau_{\text{minor}} = 16.8$ min, $\tau_{\text{major}} = 15.0$ min.

(S)-2-(2,2-Dibenzylhydrazinyl)-3,3-dimethylbutanenitrile (2g). Reaction was performed in trifluorotoluene. White solid (50% yield); MP: 78–80 °C; $[\alpha]_{\text{D}}^{25} -18.1$ (c 1.1, CHCl_3) (68% ee); ^1H NMR (300 MHz, CDCl_3) δ 7.43–7.27 (m, 10H), 4.04 (d, $J = 12.9$ Hz, 2H), 3.67 (d, $J = 12.9$ Hz, 2H), 3.19 (s, 1H), 2.81 (s, 1H), 0.88 (s, 9H); ^{13}C NMR (75 MHz, CDCl_3) δ 137.6, 129.8, 128.3, 127.5, 120.6, 63.1, 61.5, 34.0, 26.3; HRMS (CI): calculated for $[\text{C}_{20}\text{H}_{25}\text{N}_3]^+$ 307.2048; found: 307.2040. The enantiomeric excess was determined by HPLC using a Chiralpak AD-H column [hexane-*i*-PrOH (99 : 1)]; flow rate 1.0 mL min^{-1} ; $\tau_{\text{minor}} = 7.6$ min, $\tau_{\text{major}} = 8.7$ min.

(S)-2-Cyclohexyl-2-(2,2-dibenzylhydrazinyl)acetonitrile (2h). White solid (90% yield); MP: 63–65 °C; $[\alpha]_{\text{D}}^{25} -7.8$ (c 0.3, CHCl_3) (72% ee); ^1H NMR (300 MHz, CDCl_3) δ 7.39–7.27 (m, 10H), 3.93 (d, $J = 12.9$ Hz, 2H), 3.68 (d, $J = 12.9$ Hz, 2H), 3.27 (d, $J = 6.1$ Hz, 1H), 1.68–1.58 (m, 4H), 1.48–1.36 (m, 2H), 1.15–0.98 (m, 4H); ^{13}C NMR (75 MHz, CDCl_3) δ 137.6, 129.8, 128.4, 127.6, 120.3, 61.5, 57.9, 39.4, 29.7, 28.8, 26.1, 25.8, 25.7; HRMS (CI): calculated for $[\text{C}_{22}\text{H}_{27}\text{N}_3]^+$ 333.2205; found: 333.2208. 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} ; $\tau_{\text{minor}} = 9.3$ min, $\tau_{\text{major}} = 11.5$ min.

General procedure for the one pot Strecker/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 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 Na_2SO_4 and the solvents were removed *in vacuo*. Flash chromatography (cyclohexane- Et_2O , 4 : 1) afforded the corresponding formamide derivatives 4.

(S)-*N,N'*-Dibenzyl-*N*-(1-cyano-3-methylbutyl)formo-hydrazide (4a). Colourless oil (86% yield); $[\alpha]_{\text{D}}^{25} -7.4$ (c 1.0, CHCl_3) (70% ee); a mixture of rotamers: ^1H NMR (300 MHz, CDCl_3) 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 (d, $J = 6.6$ Hz, 0.4H), 0.61 (d, $J = 6.6$ Hz, 0.6H), 0.59–0.49 (m, 0.3H); ^{13}C NMR (125 MHz, CDCl_3) δ 163.8, 161.3, 137.5, 137.4, 135.7, 135.6, 130.1, 129.8, 129.7, 129.5, 129.0, 128.9, 128.8, 128.7, 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 $[\text{C}_{21}\text{H}_{26}\text{N}_3\text{O}]^+$ 336.2076; found: 336.2065. The enantiomeric excess was determined by HPLC using a Chiralpak OD column [hexane-*i*-PrOH (98 : 2)]; flow rate 1 mL min^{-1} ; $\tau_{\text{minor}} = 22.2$ min, $\tau_{\text{major}} = 25.7$ min.

(S)-*N,N'*-Dibenzyl-*N*-(1-cyano-2-methylpropyl)formo-hydrazide (4b). White solid (98% yield); MP: 110–112 °C; $[\alpha]_{\text{D}}^{25} -13.8$ (c 1.0, CHCl_3) (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); ^{13}C NMR (75 MHz, DMSO, 363 K) δ 165.2, 162.8, 137.6, 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, 56.6, 49.9, 29.4, 19.3, 18.8, 18.4, 18.1; HRMS (CI): calculated for $[\text{C}_{20}\text{H}_{24}\text{N}_3\text{O}]^+$ 322.1919; found: 322.1915. The enantiomeric excess was determined by HPLC using a Chiralpak OJ-H column [hexane-*i*-PrOH (96 : 4)]; flow rate 1 mL min^{-1} ; $\tau_{\text{minor}} = 25.5$ min, $\tau_{\text{major}} = 35.7$ 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 CH_2Cl_2 . The reaction was stirred at 45 °C for 24 h, followed by pouring into ice/water and extracted with Et_2O (3 × 15 mL). The organic extracts were dried over Na_2SO_4 and the solvents were removed *in vacuo*. Crystallization from pentane afforded the corresponding acids 5.

(S)-2-(2,2-Dibenzyl-1-formylhydrazinyl)-4-methylpentanoic acid (5a). White solid (80% yield); MP: 148–150 °C; $[\alpha]_{\text{D}}^{25} +55.1$ (*c* 1.0, CHCl₃) (82% ee); a 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, 136.1, 129.7, 129.4, 129.2, 128.8, 128.6, 128.3, 128.0, 59.7, 58.6, 58.5, 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; τ_{minor} = 7.2 min, τ_{major} = 10.2 min.

(S)-2-(2,2-Dibenzyl-1-formylhydrazinyl)-3-methylbutanoic acid (5b). White solid (66% yield); MP: 118–120 °C; $[\alpha]_{\text{D}}^{25} +42.7$ (*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, 136.5, 136.1, 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; τ_{minor} = 30.7 min, τ_{major} = 26.1 min.

(S)-2-(2,2-Dibenzylhydrazinyl)-4-methylpentanoic acid (6a). Sulfuric acid (65% 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 HCl_{aq} (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; $[\alpha]_{\text{D}}^{25} -3.6$ (*c* 0.5, CHCl₃) (62% ee); ¹H NMR (300 MHz, DMSO-*d*₆) 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-*d*₆) 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 [C₂₀H₂₇N₂O₂]⁺ 327.2073; found: 327.2081. 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; τ_{minor} = 8.7 min, τ_{major} = 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 (cyclohexane–Et₂O, 2 : 1) afforded the corresponding imidazolidinones **7**.

(S)-1-(Dibenzylamino)-5-isobutylimidazolidin-2-one (7a). White solid (67% yield); MP: 129–131 °C; $[\alpha]_{\text{D}}^{25} +17.2$ (*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 (CI): calculated for [C₂₁H₂₈N₃O]⁺ 338.2232; found: 338.2230. 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; τ_{minor} = 5.0 min, τ_{major} = 4.8 min.

(S)-1-(Dibenzylamino)-5-isopropylimidazolidin-2-one (7b). White solid (64% yield); MP: 98–100 °C; $[\alpha]_{\text{D}}^{25} -57.8$ (*c* 0.9, CHCl₃) (76% ee); ¹H NMR (300 MHz, CDCl₃) δ 7.43–7.32 (m, 10H), 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, 129.0, 128.6, 128.1, 127.9, 60.5, 59.6, 55.5, 43.8, 27.4, 18.4, 14.4; HRMS (CI): calculated for [C₂₀H₂₆N₃O]⁺ 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; τ_{minor} = 5.6 min, τ_{major} = 5.1 min.

Determination of absolute configuration (Scheme 4): synthesis of (S)-4-bromo-N-(1-cyano-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 333 K) 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),

2.67–2.55 (m, 1H), 1.21 (d, $J = 6.6$ Hz, 3H), 1.06 (d, $J = 6.6$ Hz, 3H); ^{13}C NMR (125 MHz, DMSO, 333 K) δ 171.6, 167.2, 137.1, 136.0, 135.4, 132.1, 131.7, 130.8, 129.9, 129.8, 129.6, 128.9, 128.3, 127.8, 123.6, 118.8, 59.6, 55.2, 29.6, 20.1, 19.8; HRMS (CI): calculated for $[\text{C}_{26}\text{H}_{26}\text{BrN}_3\text{O}]^+$ 476.1337; found: 476.1340. 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**)-**8**: $t_{\text{R}} = 10.7$ min (47 mg, 45%). X-ray quality crystals were obtained by crystallization in hexane-AcOEt at room temperature. MP: 172–174 °C. $[\alpha]_{\text{D}}^{25} -14.3$ (c 1.0, CHCl_3) (99.8% ee).

(**R**)-**8**: $t_{\text{R}} = 21.3$ min (10 mg, 11%). $[\alpha]_{\text{D}}^{25} +12.6$ (c 0.7, CHCl_3) (99.8% ee).

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