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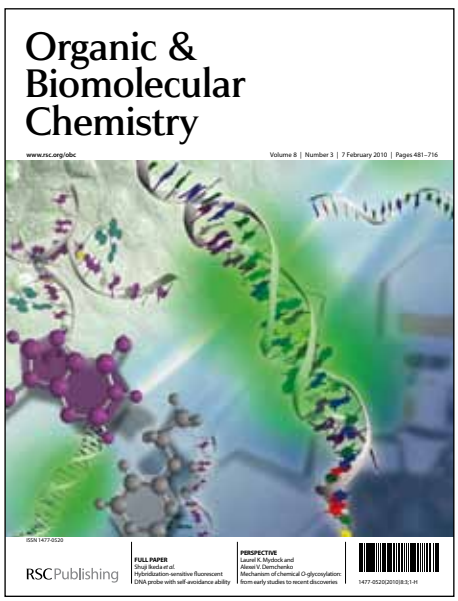

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ARTICLE TYPE

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 tranformations 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 esencially pure enantiomers.

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Introduction

Hydrazino acids are important bioactive molecules in medicinal chemistry (Figure 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]

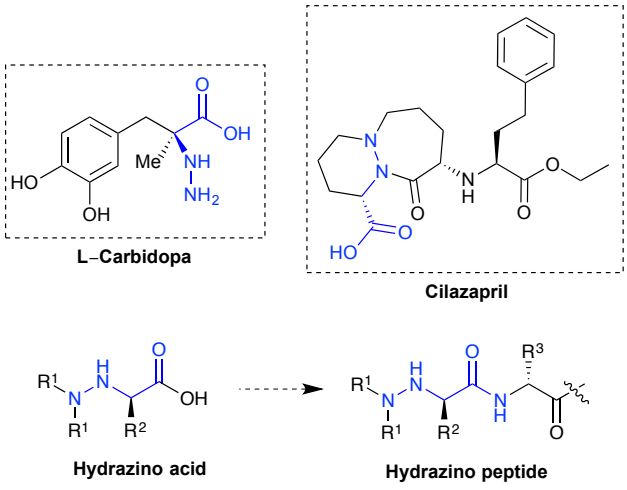
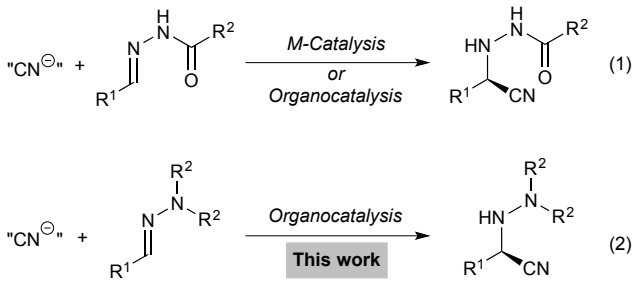


Fig. 1 Hydrazino acids in medicinal chemistry

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 great interest in recent years as valuable precursors of conformationally restricted,[5] protease–resistant peptidomimetics.[6]

Existing routes to enantioenriched hydrazino acids[7] 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 as 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 reported few inventions have relied on *N*-acylhydrazones as imine surrogates (Eq. 1, Scheme 1).[12]



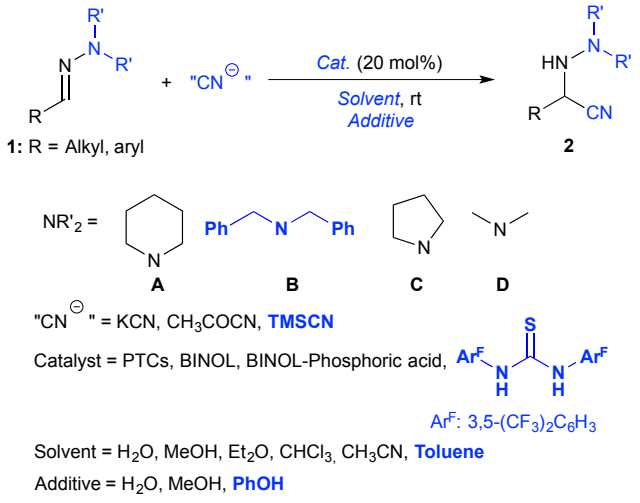
Scheme 1 Asymmetric catalytic Strecker-type reactions of hydrazones

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 a *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 (Eq. 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 on 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 cycloadditions[16] 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 the Strecker–type reactivity enploying 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 $CHCl_3$ (<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*, spontaneusly 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 Supplementary Information).



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

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 ability to establish H–bonding cooperative networks to activate reagents. Phase transfer catalysts (PTCs) showed a moderate catalytic activity in Et_2O, 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_2Cl_2: 58%, 72 h; toluene: 35–47%, 72 h; CH_3CN: 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 the higher reactivities over KCN or CH_3COCN. Finally, addition of 2–3 equivalents of PhOH as 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.

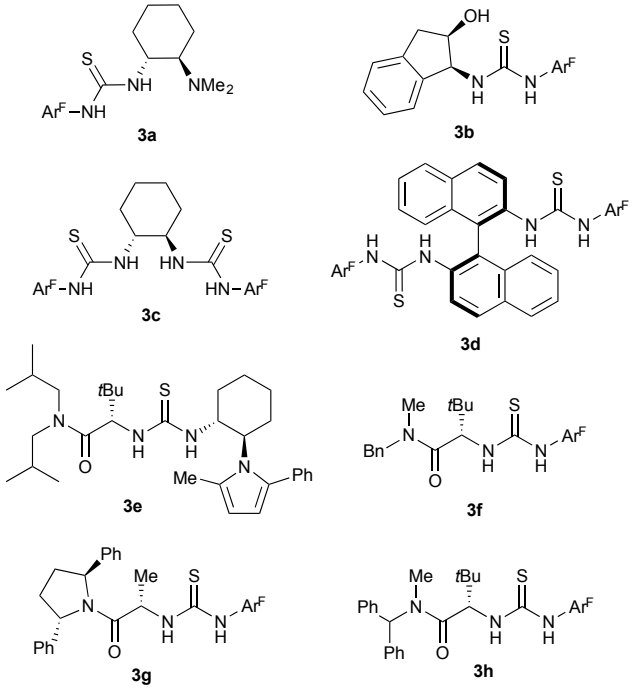
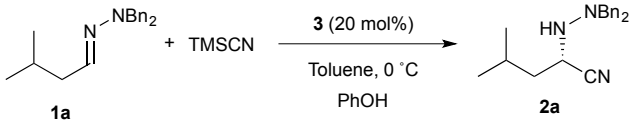


Fig. 2 Thiourea Organocatalysts tested

Previous studies have shown that chiral thiourea-based catalyst 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 (Figure 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 [0.1M] at 0 °C as the

model system and the results are collected in Table 1.

Table 1 Screening of catalysts for the enantioselective Strecker-type reaction of **1a**.[a]



1a **2a**

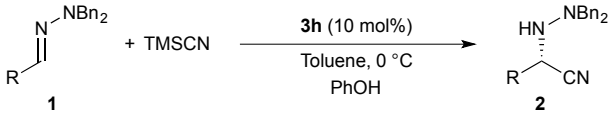
Entry	Catalyst	t (days)	Conv. (%)[b]	ee[c]
1	3a	7	48	10
2	3b	7	>95	16
3	3c	7	63	16
4	3d	1	>95	18
5	3e	7	40	40
6	3f	3	71	40
7[d]	3f	7	76	46
8	3g	3	22	*rac*
9	**3h**	**3**	**75**	**72**
10[d]	3h	7	79	44
11[e]	**3h**	**3**	**>95**	**72**

[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 ºC. [b] Determined by ^{1}H NMR. [c] Determined by HPLC on chiral stationary phases. [d] Without PhOH. [e] 10 mol% catalyst.

Initially we explored the behavior of bifunctional catalysts **3a** and **3b** for the simultaneous activation of the hydrazone (by the thiourea as an hydrogen-bond donor moiety) and the cyanide reagent (by the amino nitrogen in **3a** or hydroxyl group in **3b**).[22] Unfortunately, the reaction proceeded with low enantioselectivity after prolonged reaction times (entries 1,2). Bis–thioureas **3c** and **3d** also afforded product **2a** with poor enantiomeric ratios (entries 3,4). Notably, (*R*)–BINAM derived bis–thiourea **3d** proved to be the most active catalyst, as a significant 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 to the aromatic groups atached to both N atoms.[23] Finally, Jacobsen–type thiourea catalysts **3e-h** were tested (entries 5-6, 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 7,10) revealed the role of this additive as activator of TMSCN, affording similar conversions in prolonged reaction times (7 days). Noteworthy, the catalyst loading could be reduced to 10 mol% without compromising the selectivity nor the reactivity, as shown in entry 11. A further optimization was then performed to identify best solvent, reaction temperature, and protic additives (see Supplementary Information). From this study, reactions performed in toluene at 0 °C in the presence of PhOH (2 equivalents) afforded 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) in substitution of 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;[24] 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 3 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). Noteworthy, products **2e** and **2f** proved to be fairly crystalline, and this circumstance was exploited to obtain essentially pure enantiomers (99:1 ee) after a single crystallization.

Table 2 Scope of the synthesis of enantioenriched hydrazino nitriles **2**.[a]

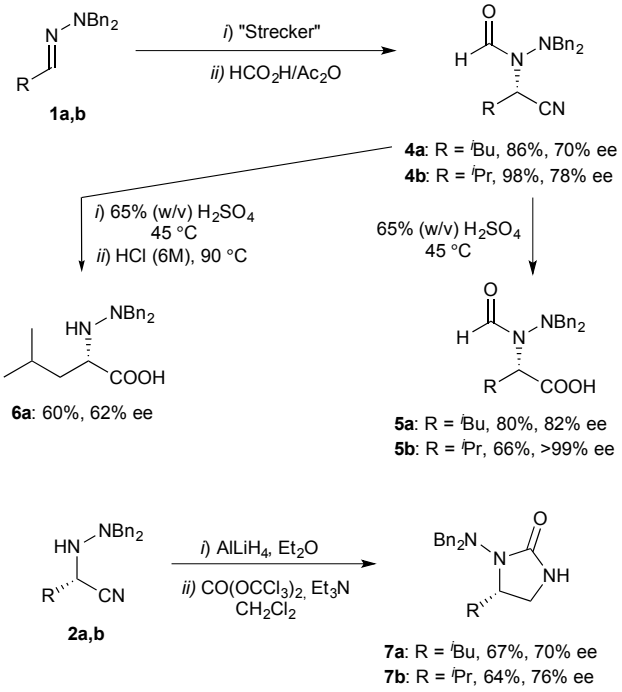


1 **2**

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	$(CH_3)_3CH_2$, **1d**	3	**2d**	93	86
5	CH_2Ph, **1e**	3	**2e**	91	82 (98)
6	CH_2CH_2Ph, **1f**	3	**2f**	96	74 (98)
7	*t*-Bu, **1g**	7	**2g**	40	68
8[d]	*t*-Bu, **1g**	4	**2g**	50	68
9	C_6H_{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 ºC. [b] Isolated yield after column chromatography. [c] Determined by HPLC on chiral stationary phases. In parenthesis, ee after a single crystallization. [d] Reaction performed in trifluorotoluene.

Furthermore, the cyano group in adducts **2** can be conveniently transformed into a variety of valuable functional groups. Attempts to hydrolize directly adducts **2** under acidic or basic conditions were unsuccessful as a result of a 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 excelent 86 and 98% yield, respectively (Scheme 3), and these products were selectively hydrolized 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 a slight racemization. Unfortunately, attempts to achieve a selective removal of the *N*-benzyl groups were unsuccessful.

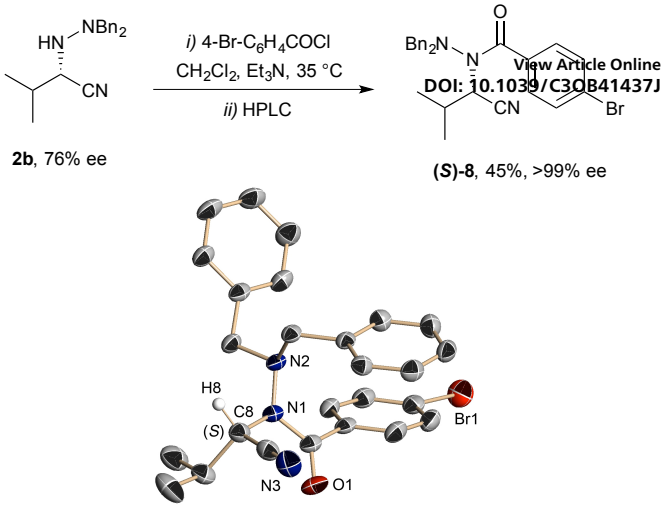


Scheme 3 Synthesis of acids **5**, **6a** and imidazolidinones **7**.

Importantly, single crystallizations made 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*)-**7** (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** (Figure 3).



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.

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 tranformation proceeds via anion-binding catalysis.[30] On this basis, a similar mode of activation is suggested in Figure 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 occurs where the preferred orientation of hydrazonium cation might be additionally stabilized by π-π interactions between benzhydryl moiety of optimum catalyst **3h** and benzyl groups of hydrazone **1**.[31]

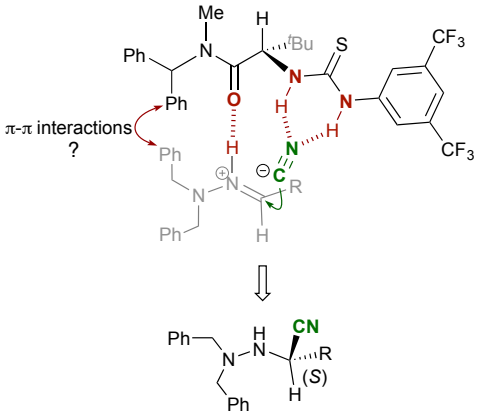


Figure 3 Activation and stereochemical model

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 cyanide source. The synthetic potential of

adducts **2** has been illustrated by transformations into protected hydrazino acids **5-6** and imidazolidinones **7**.

General methods.

^{1}H NMR spectra were recorded at 300 MHz or 500 MHz; ^{13}C 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 ^{1}H 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 on 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. Not commercially available catalysts **3c,d**,**g,h**[31] were synthesized according to literature. Synthesis and characterization data of hydrazones **1** are described in the Supplementary Information.

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/Et_2O, 6:1). Enantiomeric excesses were determined by HPLC analysis.

(*S*)-2-(2,2-Dibenzylhydrazinyl)-4-methylpentanenitrile (2a): Colourless oil (93% yield); $[\alpha]_D^{25}$ –8.7 (*c* 1.3, $CHCl_3$). (72% ee); ^{1}H NMR (300 MHz, $CDCl_3$) 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); ^{13}C NMR (125 MHz, $CDCl_3$) 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 $[C_{20}H_{25}N_3]^+$ 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; τ_{minor} = 10.3 min, τ_{major} = 9.4 min.

(*S*)-2-(2,2-Dibenzylhydrazinyl)-3-methylbutanenitrile (2b): Colourless oil (98% yield); $[\alpha]_D^{25}$ −14.5 (*c* 0.9, $CHCl_3$). (76% ee); ^{1}H NMR (500 MHz, $CDCl_3$) 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); ^{13}C NMR (125 MHz, $CDCl_3$) 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 $[C_{19}H_{23}N_3]^+$ 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; τ_{minor} = 7.7 min, τ_{major} = 8.2 min.

(*S*)-2-(2,2-Dibenzylhydrazinyl)butanenitrile (2c): Colourless oil (89% yield); $[\alpha]_D^{25}$ −16.6 (*c* 0.8, $CHCl_3$). (62% ee); ^{1}H NMR (300 MHz, $CDCl_3$) 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); ^{13}C NMR (125 MHz, $CDCl_3$) δ 137.5, 129.8, 128.5, 127.6, 121.0, 61.6, 53.4, 25.1, 10.0; HRMS (CI): calculated for $[C_{18}H_{21}N_3]^+$ 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; 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; $[\alpha]_D^{25}$ −23.1 (*c* 0.3, $CHCl_3$). (86% ee); ^{1}H NMR (300 MHz, $CDCl_3$) 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 $[C_{21}H_{27}N_3]^+$ 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; τ_{minor} = 13.9 min, τ_{major} = 14.7 min.

(*S*)-2-(2,2-Dibenzylhydrazinyl)-3-phenylpropanenitrile (2e): Yellow solid (91% yield); MP: 101-103 °C; $[\alpha]_D^{25}$ −31.2 (*c* 0.5, $CHCl_3$). (98% ee after a single crystallization from pentane); ^{1}H 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 (overlaped 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 $[C_{23}H_{23}N_3]^+$ 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; τ_{minor} = 16.5 min, τ_{major} = 15.0 min.

(*S*)-2-(2,2-Dibenzylhydrazinyl)-4-phenylbutanenitrile (2f): White solid (96% yield); MP: 65-67 °C; $[\alpha]_D^{25}$ −7.2 (*c* 0.3, $CHCl_3$). (98% ee after a single crystallization from pentane); ^{1}H 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 $[C_{24}H_{25}N_3]^+$ 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; τ_{minor} = 16.8 min, τ_{major} = 15.0 min.

(*S*)-2-(2,2-Dibenzylhydrazinyl)-3,3-dimethylbutanenitrile (2g): Reaction performed in trifluorotoluene. White solid (50% yield); MP: 78-80 °C; $[\alpha]_D^{25}$ –18.1 (*c* 1.1, $CHCl_3$). (68% ee); ^{1}H 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 $[C_{20}H_{25}N_3]^+$ 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; τ_{minor} = 7.6 min, τ_{major} = 8.7 min.

(*S*)-2-Cyclohexyl-2-(2,2-dibenzylhydrazinyl)acetonitrile (2h): White solid (90% yield); MP: 63-65 °C; $[\alpha]_D^{25}$ −7.8 (*c* 0.3, $CHCl_3$). (72% ee); ^{1}H 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 $[C_{22}H_{27}N_3]^+$ 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; τ_{minor} = 9.3 min, τ_{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 (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 x 10 mL). Combined organic extracts were washed with 10% aqueous solution of sodium bicarbonate (2 x 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)formohydrazide (4a): Colourless oil (86% yield); $[\alpha]_D^{25}$ −7.4 (*c* 1.0, $CHCl_3$). (70% ee); mixture of rotamers: ^{1}H 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 $[C_{21}H_{26}N_3O]^+$ 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; τ_{minor} = 22.2 min, τ_{major} = 25.7 min.

(*S*)-*N'*,*N'*-Dibenzyl-N-(1-cyano-2-methylpropyl)formohydrazide (4b): White solid (98% yield); MP: 110-112 °C; $[\alpha]_D^{25}$ −13.8 (*c* 1.0, $CHCl_3$). (76% ee); mixture of rotamers: ^{1}H NMR (300 MHz, DMSO, 363K) 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, 363K) 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 $[C_{20}H_{24}N_3O]^+$ 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; τ_{minor} = 25.5 min, τ_{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 ammount 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 x 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; $[\alpha]_D^{25}$ +55.1 (*c* 1.0, $CHCl_3$). (82% ee); mixture of rotamers: ^{1}H NMR (300 MHz, $CDCl_3$) 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); ^{13}C NMR (75 MHz, $CDCl_3$) 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 $[C_{21}H_{26}N_2NaO_3]^+$ 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; 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; $[\alpha]_D^{25}$ +42.7 (*c* 1.0, $CHCl_3$). (99.8% ee); mixture of rotamers: ^{1}H NMR (300 MHz, $CDCl_3$) 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); ^{13}C NMR (125 MHz, $CDCl_3$) 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 $[C_{20}H_{24}N_2NaO_3]^+$ 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; 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 ammount 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 x 15 mL). The organic extracts were removed *in-vacuo* and the crude acid **5a** was treated with 6M HCl_{aq} (15 mL) and stirred at 90 ºC for 12 h. The solvent was removed *in-vacuo* and a solution of crude acid **6a**, redisolved in CH_2Cl_2, was treated with $NaHCO_3$ sat. until pH ~ 8, and extracted with CH_2Cl_2 (2 x 10 mL) and Et_2O (2 x 10 mL). The organic extracts were dried over Na_2SO_4 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; $[\alpha]_D^{25}$ −3.6 (*c* 0.5, $CHCl_3$) (62% *ee*); ^{1}H 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); ^{13}C 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 $[C_{20}H_{27}N_2O_2]^+$ 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; τ_{minor} = 8.7 min, τ_{major} = 9.4 min.

General procedure for the transformation of 2 into imidazolidinones 7:

A solution of Strecker adduct **2** (0.5 mmol) in anhydrous Et_2O (1.0 mL) was added to a suspension of $LiALH_4$ (2.1 mmol, 78 mg) in anhydrous Et_2O (10.0 mL) at 0 ºC. The reaction mixture was allowed to warm to room temperature and stirred overnight. AcOEt (5 mL) and water (0.2 mL) were sequentially, dropwise added to the reaction 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 CH_2Cl_2 (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 CH_2Cl_2 (2 mL) was added dropwise and the mixture reaction was allowed to warm to room temperature and stirred overnight. The reaction was diluted with CH_2Cl_2 (2 mL), washed with water (5 mL), brine (5 mL), dried over Na_2SO_4 and the solvent was removed *in vacuo*. Flash chromatography (Cyclohexane/Et_2O, 2:1) afforded the corresponding imidazolidinones **6**.

(*S*)-1-(Dibenzylamino)-5-isobutylimidazolidin-2-one (7a): White solid (67% yield); MP: 129-131 °C; $[\alpha]_D^{25}$ +17.2 (*c* 0.2, $CHCl_3$). (70% ee). ^{1}H NMR (500 MHz, $CDCl_3$) 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); ^{13}C NMR (125 MHz, $CDCl_3$) 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 $[C_{21}H_{28}N_3O]^+$ 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; 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; $[\alpha]_D^{25}$ −57.8 (*c* 0.9, $CHCl_3$). (76% ee). ^{1}H NMR (300 MHz, $CDCl_3$) 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); ^{13}C NMR (75 MHz, $CDCl_3$) 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 $[C_{20}H_{26}N_3O]^+$ 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; τ_{minor} = 5.6 min, τ_{major} = 5.1 min.

Determination of absolute configuration (Scheme 5): Synthesis of (*S*)-4-bromo-*N*-(1-cyano-2-methylpropyl)-*N*-(1,3-diphenylpropan-2-yl)benzamide (8).

Et_3N (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 CH_2Cl_2 (2.5 mL). The reaction was stirred at reflux for 48 h, neutralized with a saturated solution of $NaHCO_3$ and extracted with dichloromethane (3 x 10 mL). Combined organic extracts were dried over Na_2SO_4 and the solvent removed *in-vacuo*. Flash chromatography (Cyclohexane/Et_2O, 6:1) afforded **8** as a yellow solid (73 mg, 70 %, 70% ee). ^{1}H NMR (300 MHz, DMSO 333K) 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, 333K) 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 $[C_{26}H_{26}BrN_3O]^+$ 476.1337; found: 476.1340. The enantioenriched mixture was resolved by semipreparative HPLC on a Chiralpak OJ-H column, [hexane/*i*-PrOH (80:20)], 6 mL/min. Analytical OJ-H, [hexane/*i*-PrOH (80:20)], 1 mL/min.

(*S*)-8: 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. $[\alpha]_D^{25}$ −14.3 (*c* 1.0, $CHCl_3$). (99.8% ee).

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

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Notes and references

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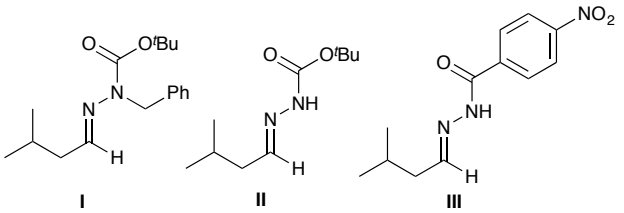
† Electronic Supplementary Information (ESI) available: experimental procedures, characterization data, NMR spectra for new compounds, HPLC traces and CIF data for **(*S*)-8**. CCDC 945611. See DOI: 10.1039/b000000x/.

£ 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 (0.15 mmol), **3h** (10 mol%) and PhOH (0.1 mmol) in toluene (1 mL) afforded no product after 4 days at rt.



I II III

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

∫ In the X-ray structure of compound **7** a π-π stabilizing interaction between one phenyl ring and 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**.

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