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Synthesis of enantiomerically pure ethylenediamines from chiral sulfinimines: a new twist to the Strecker reaction

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Abstract—Addition of various cyanide nucleophiles on chiral *t*-butylsulfinimine and *p*-tolylsulfinimine derivatives are described and demonstrated that aliphatic *t*-butylsulfinimines are excellent substrates for a new variant of the Strecker reaction where cyanide ions are delivered through ethylisopropoxyaluminum cyanide or trimethylsilylcyanide combined with a Lewis acid catalyst. The reaction proceeds with high yield and high diastereoselectivity, which can be further improved by additional crystallizations. © 2001 Elsevier Science Ltd. All rights reserved.

1. Introduction

The Strecker reaction[1] has been used for many years to synthesize aminonitriles and the corresponding aminoacids. In recent years, various enantioselective or diastereoselective versions of this reaction have been described in the literature,[2a–k] allowing the isolation of enantiopure compounds. In our search for new imidazoline derivatives of general formula **1** as antidepressants,[3] stereoselective synthesis (Fig. 1) of substituted ethylene diamine intermediates of type **2** was of interest. Ethylene diamines were usually obtained via the reduction of the corresponding aminonitriles **3**, conveniently prepared by the Strecker reaction on the aldehydes **4**.

Our strategy for chirality induction on the α carbon relied on the addition of cyanide nucleophiles on chiral imines obtained by condensation of the aldehyde with a chiral amine. In contrast to previous work,[4] preliminary experiments using enantiopure α-methylbenzylamine or

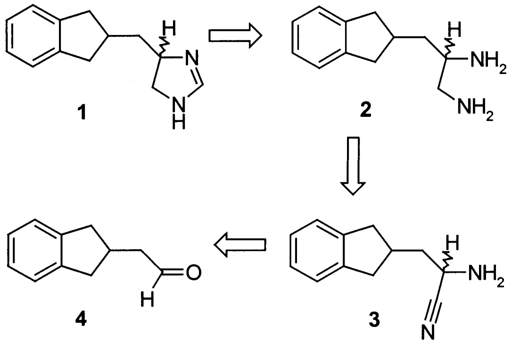
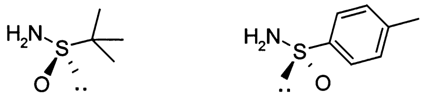
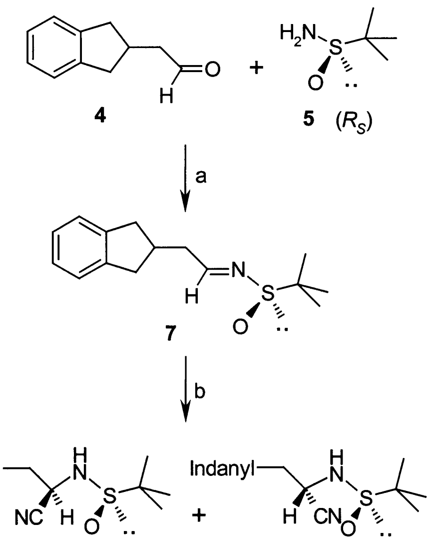


Figure 1.



5 (R_S) **6** (S_S)

Figure 2.



Scheme 1. *Reagents and conditions*: (a) Py·TsOH, MgSO$_4$, CH$_2$Cl$_2$, 25°C, 89%; (b) Et$_2$AlCN, *i*-PrOH, THF, 95% or TMSCN, CH$_2$Cl$_2$, 25°C, Lewis acid catalyst (see Table 2).

Keywords: amino nitriles; asymmetric induction; diamines; Strecker reaction.

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Table 1.

Solvent	T (°C)	Yield (%)[a]	Ratio **8a/8b**[b]
THF	25	95	97/3
THF	0	86	97/3
CH_2Cl_2	25	92	93/7
n-Heptane	25	93	96/4
Toluene	25	88	98/2

[a] Isolated yields.

[b] Determined by ^{1}H NMR and LC.

1-(naphthyl)ethylamine led to low diastereoselectivities (data not shown). We decided then to investigate the use of sulfinimines in a similar reaction. Chiral sulfinamides such as the *t*-butyl and the *p*-tolyl derivatives, **5** and **6**, respectively (Fig. 2), have been described as very potent chiral auxiliaries. The addition of hydrides[5–7] or alkyl residues[8,9] on the α carbon of sulfinimes generated from both **5** and **6** has been well documented, and the addition of diethylaluminumcyanide on *p*-tolylsulfinimine derivatives has been reported as well.[6,10–12] On the other hand, reports on the addition of various cyanide nucleophiles on chiral *t*-butylsulfinimine derivatives have been scarce. We report here the results of our investigations of this reaction.

2. Chemistry

Synthesis of *t*-butylsulfinimine **7** from aldehyde **4**[13] and *t*-butylsulfinamide **5**[14,15] took place in high yields, at room temperature in dichloromethane, in the presence of dry magnesium sulfate and a catalytic amount of pyridinium tosylate (Scheme 1).[14] This sulfinimine is remarkably stable and can be easily purified by silica gel chromatography. As could be expected, the (*E*) isomer only was formed, as indicated by the J_{15}N–^{1}H coupling constant value (3–4 Hz) measured in the NMR spectra.[16,17] In accordance with this spectroscopic result, the relative energy values of the two isomers calculated at the semiempirical level (PM3) indicated a higher stability for the (*E*) isomer. Two cyanide delivery agents were evaluated to prepare the cyanosulfinamide **8** with contrasting results: the ethylisopropoxyaluminumcyanide formed from diethylaluminumcyanide and *i*-propylalcohol,[18] and the trimethylsilylcyanide in combination with a Lewis acid catalyst.

In the former conditions, the reaction took place in high yield and high diastereoselectivity at room temperature in solvents of diverse polarity and chelating ability, such as THF, CH_2Cl_2, *n*-heptane and toluene (Table 1). A decrease of the temperature affected slightly the yield but increased significantly the reaction time (4–30 h) without improving the diastereoselectivity ratio (entry 2). The diastereoisomeric purity of the product **8a** could be further increased to 99/1 by crystallization from *n*-hexanes. The absolute configuration of the newly created chiral center was determined as (*R*), by single crystal X-ray diffraction.

In the second procedure, using TMSCN, the reaction did not proceed in the absence of a Lewis acid catalyst or below 10°C. The reaction was then performed using a large variety of Lewis acid catalysts, leading to the results summarized in

Table 2.

Entry	R–CN	Catalyst	Reaction time (h)	Yield (%)[a]	Ratio **8a/8b**[b]
1	TMS	ZnI_2[c]	24	74	24/76
2	TMS	ZnI_2	48	80	30/70
3	TMS	$ZnBr_2$	48	86	27/73
4	TMS	Ti(O-*i*-Pr)$_4$[c]	48	89	83/17
5	TMS	$TiCl_4$	48	61	52/48
6	TMS	$AlCl_3$[d]	24	20	57/43
7	TMS	$CeCl_3$[e]	48	3	85/15
8	TMS	$BF_3\cdot OEt_2$	48	72	32/68
9	TMS	$MgCl_2$	48	57	82/18
10	TMS	$MgBr_2\cdot OEt_2$	48	66	72/28
11	TMS	$SnCl_4$	48	74	35/65
12	TMS	$ZrBr_4$	24	89	81/19
13	TMS	Zr(O-*t*-Bu)$_4$	48	74	81/19
14	TMS	ZrI_4	20	94	58/42
15	TMS	Yb(OTf)$_3$	48	38	20/80
16	TMS	Sc(OTf)$_3$[c]	18	98	97/3
17	TMS	Y(OTf)$_3$	24	90	98/2
18	TMS	La(OTf)$_3$	48	48	98/2
19	TMS	Sm(OTf)$_3$	48	13	87/13
20	TMS	Sm(O-*i*-Pr)$_3$[c]	6	91	52/48
21	TMS	$SmCl_3$	48	27	92/8
22	TBS	ZnI_2	24	68	16/84
23	TBS	Sc(OTf)$_3$	48	<5	–
24	TBS	Yb(OTf)$_3$	48	<5	–
25	TBS	Ti(O-*i*-Pr)$_4$	48	<5	–

Conditions: The reaction was run with ca. 0.2 equiv. of catalyst at 25°C in CH_2Cl_2.

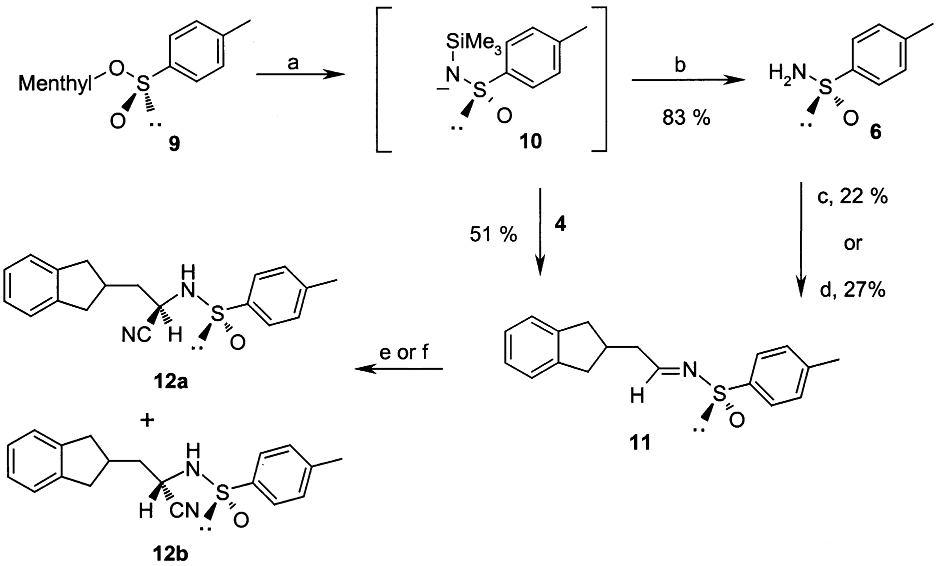
[a] Yields were measured by LC after filtration on silica gel to eliminate the catalyst and were in complete accordance with isolated yields. Unless otherwise noted, remaining residual starting material **7** and products **8a/8b** accounted for >90% of the starting sulfinimine **7**. The major side-product was identified as the cyanohydrine.

[b] Diastereoisomeric ratio was measured by LC.

[c] Performed twice to check the reproducibility.

[d] Degradation of the sulfinimine.

[e] The formation of a hydrated form of the catalyst might have precluded the reaction to work.



Scheme 2. *Reagents and conditions*: (a) LiHMDS, THF, −78°C; (b) NH_4Cl, 83%; (c) Py·TsOH, $MgSO_4$, CH_2Cl_2, 25°C; (d) $Ti(OEt)_4$, CH_2Cl_2, Δ; (e) Et_2AlCN, *i*-PrOH, THF, 94% or TMSCN, CH_2Cl_2, 25°C, Lewis acid catalyst (see Table 3).

Table 3.

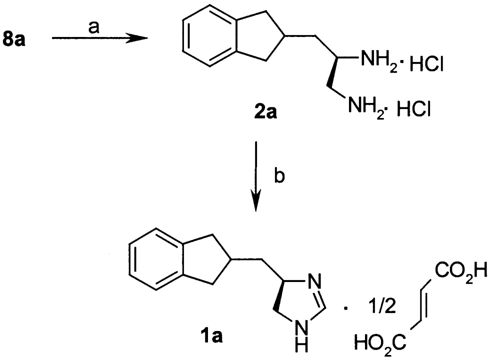
Entry	Catalyst	Reaction time (h)	Yield (%)[a]	Ratio **12a/12b**[b]
1	ZnI_2	24	<10	–
2	$Sc(OTf)_3$	36	75	17/83
3	Ti(O-*i*-Pr)$_4$	20	77	29/71
4	Sm(O-*i*-Pr)$_3$	4	70	14/86
5	$Yb(OTf)_3$	40	71	32/68

Conditions: the reaction was run with 2 equiv. of TMSCN, and ca. 0.2 equiv. of catalyst at 25°C in CH_2Cl_2.

[a] Yields were measured by LC on the reaction mixture after silica gel filtration to eliminate the catalyst.

[b] Diastereoisomeric ratio was measured by LC.

Table 2. The nature of the metal, as well as the salt form of the metal, have a profound influence on the yield and the diastereoselectivity of the reaction. Triflate salts $Sc(OTf)_3$, $Y(OTf)_3$, and $La(OTf)_3$ (entries 16–18) provided particularly efficient diastereoselectivity (>97/3), with the highest yield observed with $Sc(OTf)_3$. The most striking observation was the inversion of the diastereoselectivity obtained with ZnI_2, BF_3, $SnCl_4$ and $Yb(OTf)_3$ (entries 1, 8, 11 and 15). Indeed, while **8a** was the major product obtained with the diethylaluminumcyanide procedure, the catalysts cited above led to the second diastereoisomer **8b**. The effect of the salt form was best exemplified with Sm(III) salts where triflate and chloride (entries 19 and 21) gave low chemical yields and high diastereoselectivity, while the *i*-propoxide salt (entry 20) afforded high yield and low diastereoselectivity. Increasing the size of the cyanide agent using the *tert*-butyldimethylsilylcyanide instead of the trimethylsilylcyanide led to an increased diastereoisomeric ratio in the case of ZnI_2 (entry 22), but appeared detrimental with other catalysts (entries 23–25).



Scheme 3. *Reagents and conditions*: (a) (i) BH_3 DMS, THF, Δ; (ii) HCl, MeOH, Δ, 67%; (b) (i) HC(=NH)NH_2·AcOH, EtOH, 25°C; (ii) HO_2C–CH=CH–CO_2H, *i*-PrOH/Ether, 67%.

To access the enantiomeric form of the newly created chiral center, one can run the same reactions starting from the enantiomeric form of the sulfinamide **5**. In an attempt to investigate further these reactions, we have chosen the (S_S) *p*-tolylsulfinamide **6**, easily obtained by substitution of the menthyl sulfinate ester **9** with lithium bis(trimethylsilyl)amide and hydrolysis with NH_4Cl, according to a literature procedure (Scheme 2).[19] The condensation of **6** with our prototypical aldehyde **4** following the experimental procedure used with the *t*-butyl analog **5**, afforded the sulfinimine **11** (Scheme 2) with much lower yield (22%). Use of $Ti(OEt)_4$ resulted in a poor 27% yield also. Improved yields (51%) were obtained when **6** was not isolated, and the silylated intermediate anion **10** condensed directly with the aldehyde **4**.[19,20] Addition of ethyl-*i*-propoxyaluminumcyanide to the sulfinimine **11** led to the cyanosulfinamide in high diastereoselectivity (ratio **12a/12b**: 3/97) and high yield (95%). Crystallizations afforded the pure diastereoisomer **12b**. The TMSCN procedure was then investigated, and five Lewis acids catalysts were selected (Table 3), based on the results obtained with the *tert*-butylsulfinimine **7**. Yields were lower (<77%) and the diastereoselectivity never exceeded 14/86. Use of ZnI_2 never allowed an efficient catalysis of the reaction and resulted instead in degradation of the sulfinimine **11**.

To complete the evaluation of this synthetic route, two more steps were carried out: a reduction/deprotection sequence

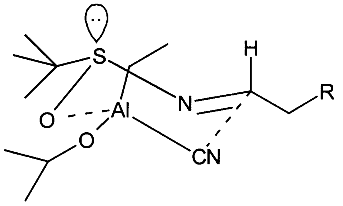


Figure 3.

and the cyclization of the resulting ethylene diamine **2** to the imidazoline **1** (Scheme 3). The first step proceeded smoothly by reacting the cyanosulfinamide **8a** with borane dimethylsulfide complex in THF under reflux.[21,22] Hydrolysis of the boride intermediate with a methanolic solution of hydrogen chloride led to the cleavage of the nitrogen–sulfur bond and afforded the ethylene diamine as its bis-hydrochloride salt. No racemization occurred during these steps. The freshly prepared free diamine was combined with formamidine acetate in ethanol, and the final imidazoline **1a** was isolated as the hemi-fumarate by crystallization from isopropanol/ether. A similar sequence afforded the pure enantiomer **1b** (ee>99/1) from the cyano-sulfinamide **12b**.

3. Discussion

Diastereoselective addition of nucleophiles to *tert*-butyl sulfinimines has been exemplified in the literature, but the addition of the cyanide nucleophiles to sulfinimines issued from aliphatic aldehydes has seldom been reported. In these studies, we have shown that delivering cyanide with ethyl-isopropoxyaluminumcyanide to chiral sulfinimes **7** and **11** afforded the cyanosulfinamide derivatives **8** and **12** with high yield and high diastereoselectivity. The high diastereo-selectivity is presumably linked to the existence of a very rigid transition state where the aluminum, the oxygen, the sulfur, the nitrogen and the two carbon atoms form a six membered ring (Fig. 3). Both the *tert*-butyl group and the aliphatic part of the sulfinimine **7** adopt an equatorial position, which increases the stability of the transition state. Because of the Al–O chelation, the cyano group is transferred on the same side than the oxygen atom, away from the sterically demanding *tert*-butyl group. The validity of the transition state hypothesis and the resulting absolute (*R*) stereochemistry at the α carbon of **8a** were confirmed by the X-ray diffraction data (Fig. 4). Although the aluminum atom has disappeared, the six membered transition state is still remnant on the structure of the crystallized cyano-sulfinamide product **8a**.

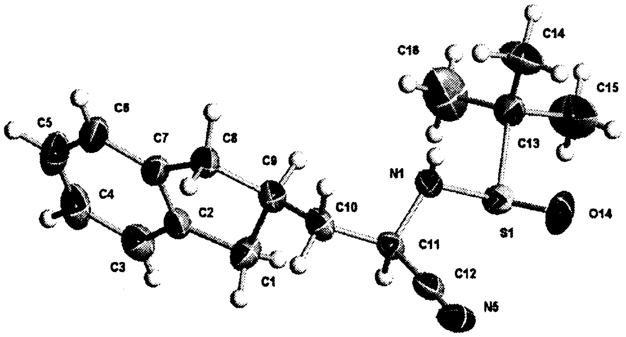


Figure 4.

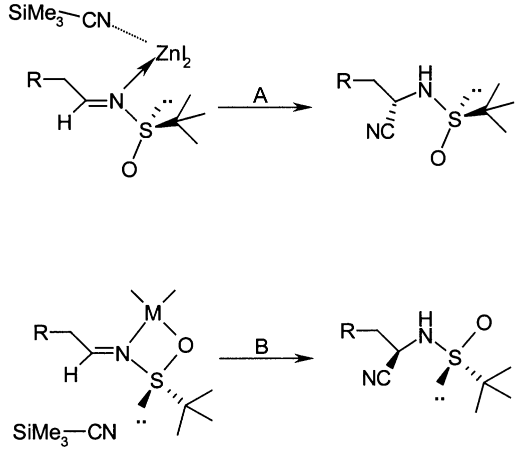


Figure 5.

In the case of the trimethylsilylcyanide addition catalysed by Lewis acids, no straightforward explanation is at hand and different mechanisms must compete in order to account for the contrasting results obtained. Among several possibilities, two major hypotheses seem relevant. In the first hypothesis, the metal is complexed by the imine nitrogen atom, activating the double bond and facilitating the delivery of the cyanide on the face away from the *t*-butyl group, as in the case of the Zn(II) catalysis (Fig. 5A). The diastereoisomeric excess and the result observed with the *tert*-butyldimethylsilylcyanide relative to the trimethylsilyl-cyanide (Table 2, entries 1 and 22) are compatible with a sterically induced diastereoselectivity. The transition state is indeed flexible, because of the possible rotation around the N–S bond. The second hypothesis relies on the chelation of the metal by both the nitrogen atom and the oxygen atom, resulting in a four membered transition state (Fig. 5B). Addition of the nucleophile occurs then on the less hindered face of the sulfinimine, away from the *tert*-butyl group. The rigid geometry of the transition state is compatible with the very high diastereoselectivity observed with some of the metals. The *p*-tolyl group of the sulfinimine **11** is not as bulky as the *tert*-butyl group, which might explain the poorer diastereoselectivity observed for **12** relative to **8**.

The relationship between the alternate mechanisms and the intrinsic nature of the metal is reinforced when the dia-stereoselectivity ratios are positionned in the place of the elements in the periodic table (Fig. 6). There is indeed a strong correlation between the position in the periodic table and the diastereoisomeric ratio. All three triflate salts of group IIIB metals (Sc, Y, La) yielded very high diastereo-selectivity (>97/3). From left to right, the ratio is inversed in a monotonous manner suggesting that the acidity or the basicity of the element induce the direction of the stereo-selectivity measured.

In conclusion, we have demonstrated that aliphatic *t*-butyl-sulfinimines are excellent substrates for a new variant of the Strecker reaction when cyanide ions are delivered through ethylisopropoxyaluminum cyanide or trimethylsilylcyanide

IIA	IIIB	IVB	IIB	IIIA	IVA
				$BF_3.OEt_2$ 32/68	
$MgCl_2$ 82/18				$AlCl_3$ 57/43	
	$Sc(OTf)_3$ 97/3	$Ti(O\text{-}i\text{-}Pr)_4$ 83/17	ZnI_2 25/75		
	$Y(OTf)_3$ 98/2	$Zr(O\text{-}t\text{-}Bu)_4$ 81/19			$SnCl_4$ 35/65
	$La(OTf)_3$ 98/2				

$La(OTf)_3$	$SmCl_3$	$Sm(OTf)_3$	$Sm(O\text{-}i\text{-}Pr)_3$	$Yb(OTf)_3$
98/2	98/2	87/13	52/48	20/80

Figure 6.

combined with a Lewis acid catalyst. The reaction proceeds with high yield and high diastereoselectivity, which can be further improved by additional crystallizations. Ensuing function transformations can be carried out to afford ethylene diamines with high enantiopurity. The *tert*-butyl sulfinamide has revealed more appropriate than its *p*-tolyl analog on aliphatic aldehydes. The scope of these reactions on aromatic aldehydes and ketones is under investigation.

4. Experimental

4.1. General

Reagents were commercially available and of synthetic grade. ^1H NMR spectra relative to TMS, were recorded on Bruker 200 or 400 MHz spectrometers. Infrared spectra were obtained as nujol emulsion, on a Bruker Fourier transform spectrometer. All new substances were homogeneous in TLC and exhibited spectroscopic data consistent with the assigned structures. Elemental analyses (C, H, N) were performed on a Carlo Erba 1108 instrument and are in agreement with the calculated values within the +/−0.4% range unless otherwise stated. Melting points were obtained on a Reichert hot stage microscope and are uncorrected. Optical rotations were measured on a Perkin–Elmer 241 Polarimeter. Silica gel 60, Merck 230–400 mesh, was used for both flash and medium pressure chromatography. TLC were performed on pre-coated 5×10 cm, Merck silica gel 60 F254 plates (layer thickness 0.25 mm). Liquid Chromatography analysis (LC) of the diastereoisomers were performed on a C_{18}, 3.5 μm, Kromasil column eluted with a gradient of $CH_3CN/H_2O/CH_3SO_3H$ from 25/1000/1 to 1000/25/1 at a flow rate of 0.2 mL min^{-1}, at 40°C and detection at 210 nm. The purity of the enantiomers (**1a** and **1b**) was determined by capillary electrophoresis on a HP 3DCE instrument equipped with a polyvinyl alcohol capillary eluted with tri-*O*-methyl-β-cyclodextrine in Tris buffer pH=2.5 and detection at 200 nm.

4.1.1. 5-Indan-2-ylmethyl-tert-butylsulfinamide (7). Prepared according to the literature procedure.[23] Colorless oil. ^1H NMR ($CDCl_3$, 300 MHz) δ 8.15 (t, 1H), 7.21 (m, 4H), 3.15 (m, 2H), 2.90 (m, 1H), 2.73 (m, 4H), 1.21 (s, 9H). IR (cm^{-1}) 1621, 1363, 1182, 1088. Anal. Calcd for $C_{15}H_{21}NOS$: C, 68.40; H, 8.04; N, 5.32; S, 12.17. Found: C, 68.67; H, 7.85; N, 5.13; S, 12.01.

4.1.2. Procedure using diethylaluminumcyanide. To a solution of Et_2AlCN (17.1 mmol, 1 M solution in toluene, 17.1 mL) in anhydrous THF (30 mL), *i*-PrOH (2.7 mL) was added under a nitrogen atmosphere. The mixture was stirred for 15 min at 25°C before transferring via a cannula to a dry ice cooled solution of sulfinimine **7** (11.4 mmol, 3.0 g) in anhydrous THF (70 mL). The reaction mixture was stirred at 25°C under an inert atmosphere and the reaction was monitored by TLC. After 2 h, the reaction mixture was cooled down to −78°C and a 10% aqueous $NaHCO_3$ solution (15 mL) was added. The suspension was filtered and the filtrate was extracted with EtOAc (3×100 mL). The combined organic phase was washed with brine, dried over $MgSO_4$, filtered and evaporated under reduced pressure. Silica gel column chromatography (cyclohexane/EtOAc 60:40) on the crude extract yielded the cyanosulfinamide **8a/8b** (2.98 g, 10.8 mmol) as a white powder in a 95% yield and a 95/5 diastereoisomeric ratio. Recrystallization twice from *n*-hexanes (50 mL)/toluene (24 mL) at −20°C afforded the cyanosulfinamide **8a** as a single diastereoisomer (ee≥99%) mp=109–110°C. $[\alpha]^{23}_D=-18°$ ($CHCl_3$, $c=11$ mg mL^{-1}). ^1H NMR ($CDCl_3$, 300 MHz) δ 7.20 (m, 4H), 4.25 (q, 1H), 3.6 (d, 1H), 3.15 (m, 2H), 2.70 (m, 3H), 2.15 (m, 2H), 1.25 (s, 9H). IR (Nujol, cm^{-1}) 3260, 2240, 1370, 1080. Anal. Calcd for $C_{16}H_{22}N_2OS$: C, 66.17; H, 7.63; N, 9.65; S, 11.04. Found C, 66.45; H, 7.56; N, 9.42; S, 11.08. X-Ray crystallography was performed on this material.

4.1.3. Procedure using TMSCN. To a solution of sulfinimine **7** (263 mg, 1 mmol) in anhydrous CH_2Cl_2 (10 mL), ZnI_2 (60 mg, 0.2 mmol) and then TMSCN (270 μL, 2 mmol) were added at 25°C. The reaction mixture was stirred under a nitrogen atmosphere at this temperature and the reaction was monitored by TLC. After 48 h, the solvent was evaporated under reduced pressure and the crude reaction mixture was separated by silica gel column chromatography to give 404 mg (73% yield) of a mixture of diastereoisomers **8a/8b** (ratio 25/75) as a yellowish oil.

4.1.4. Reduction with $BH_3{\cdot}Me_2S$. To a solution of sulfinamide **8a** (800 mg, 2.9 mmol) in THF (5 mL) at reflux, $BH_3{\cdot}Me2S$ (304 μL, 3.2 mmol) was added dropwise over a 10 min period. The reaction mixture was heated at reflux for 25 min. After cooling down to 25°C, a saturated methanolic HCl solution (15 mL) was added dropwise. The mixture was heated at reflux for 3 h to evaporate the solvent. This procedure was repeated twice, and the crude was then dissolved in MeOH (15 mL). The solvent was evaporated under reduced pressure and this was repeated twice. The product **2a** was finally obtained as a yellowish solid (870 mg, 92% purity). Washing with warm CH_3CN and recrystallization from MeOH afforded the bis hydrochloride salt of the diamine as a white solid, mp=219–220°C. ^1H NMR (DMSO-d_6, 300 MHz) δ 8.55 (m, 6H), 7.15 (m, 4H), 3.50 (m, 1H), 3.13 (m, 4H), 2.55 (m, 3H), 1.8 (m, 2H). IR (Nujol, cm^{-1}) 3200–2400. Enantiomeric ratio >95/5 (Chiral LC did not afford a more accurate measure of the ee).

4.1.5. 5-Indan-2-ylmethyl-4,5-dihydro-1*H*-imidazole; hemi-fumarate. The freshly prepared free base diamine was treated as previously reported.[24] White crystals, mp=202–204°C. ^{1}H NMR (DMSO-d_6, 300 MHz) δ 7.55 (s, 1H), 7.1 (m, 4H), 6.35 (s, 1H), 3.95 (m, 1H), 3.65 (m, 1H), 3.25 (m, 1H), 3.0 (m, 2H), 2.57 (m, 3H), 1.65 (m, 2H). IR (Nujol, cm^{-1}) 3400–1800, 1600, 1550. Anal. Calcd for $C_{13}H_{16}N_2$, $1/2C_4H_4O_4$: C, 69.75; H, 7.02; N, 10.84. Found C, 69.76; H, 6.92; N, 10.74. (ee≥99%).

Crystallographic data (excluding structure factors) for the structure in this paper have been deposited with the Cambridge Crystallographic Data Center as supplementary publication numbers CCDC 158084.

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