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An easy route to optically active 1-substituted-1-pyridyl-methylamines by diastereoselective reduction of enantiopure *N*-*tert*-butanesulfinyl ketimines

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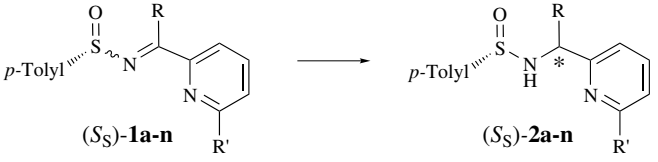
Abstract—The reduction of enantiopure *N*-*tert*-butanesulfinyl ketimines derived from pyridyl ketones afforded the related *N*-*tert*-butanesulfinyl amines with high yields and diastereoselectivities.

1. Introduction

Optically active 1-substituted-1-(pyridyl)methylamines have attracted much academic and commercial interest,[1] primarily due to their existence in naturally occurring compounds, such as tobacco alkaloids (nicotine, nornicotine, anabatine, etc.)[2] or as key fragments within potential drug candidates.[3] Moreover, they have a proven utility as ligands for metal complexes for asymmetric catalysis.[4] Among the approaches to the asymmetric syntheses of these compounds,[1] we have recently investigated the diastereoselective reduction of enantiopure *N*-*p*-toluenesulfinyl pyridyl ketimines with a variety of hydride transfer reagents obtaining 1-substituted-1-(pyridin-2-yl)methylamines with moderate to good diastereomeric excesses (Scheme 1).[5]

Since high diastereomeric excesses have been achieved only when the R substituent on the imine moiety is a sterically demanding group,[5b] or when the pyridine bears an



a: R = Me, R' = H up to 68% de
b: R = *i*-Pr, R' = H up to 94% de
c: R = *t*-Bu, R' = H up to 92% de
d: R = Ph, R' = H up to 34% de
e: R = 2-furyl, R' = H up to 42% de
f: R = 2-thienyl, R' = H up to 50% de

g: R = Me, R' = Me 96% de
h: R = Me, R' = Br 96% de
i: R = Me, R' = Ph 42% de
j: R = *t*-Bu, R' = Br 96% de
k: R = *t*-Bu, R' = Ph 98% de
l: R = Ph, R' = Me 84% de
m: R = Ph, R' = Br 76 % de
n: R = Ph, R' = Ph 86% de

Scheme 1.

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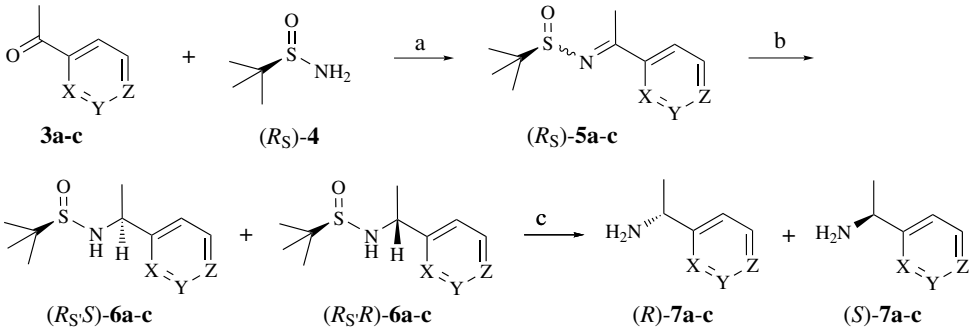
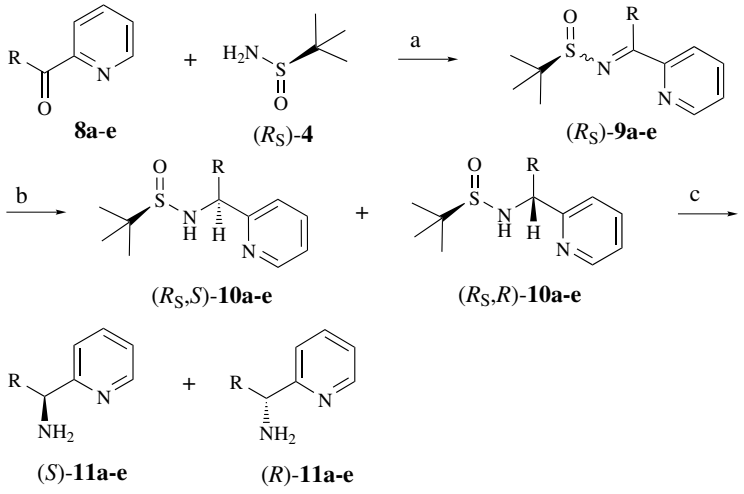


Scheme 2. Reagents and conditions: (a) $Ti(OEt)_4$, CH_2Cl_2, 40 °C, 14–60 h, 41–91%; (b) reduction (Table 1); (c) 6 M HCl, MeOH, rt, 3–6 h, 80–90%.



Scheme 3. Reagents and conditions: (a) $Ti(OEt)_4$, THF, 70 °C, 60–72 h, 14–68%; (b) Table 1; (c) 6 M, MeOH, rt, 3–6 h.

additional substituent at the 6-position,[5a] hoping to increase the stereoselectivity, we have decided to examine the reduction of ketimines having an *N*-*tert*-butanesulfinyl substituent.[6]

Herein, we report the results obtained in the reduction of a number of chiral *N*-*tert*-butanesulfinyl ketimines **5a**–**c** and **9a**–**e** derived from pyridyl ketones (Schemes 2 and 3).

2. Results and discussion

Starting our investigation, we examined the reduction of *N*-*tert*-butanesulfinyl ketimines **5** derived from the 2-, 3- and 4-acetylpyridines **3a**, **3b** and **3c**, respectively (Scheme 2). The ketimines (*R*$_S$)-**5a**–**c** were obtained in 43–91% yield by $Ti(OEt)_4$ mediated condensation of commercially available (*R*)-*tert*-butanesulfinamide (*R*$_S$)-**4** (1 equiv) with **3a**–**c** (1.1 equiv) in CH_2Cl_2 at 40 °C.[7] All imines were obtained as a single isomer, as determined from the ^{1}H NMR spectra. The reduction of (*R*$_S$)-**5a**–**c** with a number of hydride transfer reagents under a variety of conditions was examined (Table 1). The extent of the asymmetric induction was determined directly by ^{1}H NMR on the diastereoisomeric mixture of sulfinamides **6a**–**c**. The configuration of the new stereocentre in the reduction products was determined by converting an enriched mixture of the diastereoisomers of **6a**, **6b** and **6c** (6 M HCl, MeOH, rt, 3–6 h, 80–90%)[8] into the related known optically active amines **7a**, **7b** and **7c**, respectively, for which the correlation between the configuration and sign of the specific rotation has previously been established.[9]

Reductions were initially carried out using sodium borohydride ($NaBH_4$) which afforded good yields and low diastereoselectivities of the sulfinamides **6a**–**c**, but allowed us to unambiguously correlate in the ^{1}H NMR spectrum the signals of each proton to the related diastereomer. All other reducing reagents, namely tri-*sec*-butylborohydride (L-Selectride), diisobutylaluminium hydride (DIBAL) and borabicyclo[3.3.1]nonane (9-BBN) reduced the sulfinyl ketimines **5a**–**c** with high stereoselectivities (up to 98%

Table 1. Reduction of (R_S)-**5a–c**

Entry	Compound	Reducing agent/conditions	Reaction time (h)	Ratio[a] (R_S,R):(R_S,S)-**6**	Yield[b] (%)
1	**5a**	$NaBH_4$, MeOH, 25 °C[c]	1	32:68	93
2	**5a**	L-Selectride, THF, −78 °C[d]	6	1:99	31
3	**5a**	DIBAL, THF, −78 °C[e]	8	88:12	72
4	**5a**	9-BBN, THF, 0 °C[f]	22[g]	99:1	20[g]
5	**5a**	9-BBN, THF, 25 °C[e]	11	99:1	50
6	**5b**	$NaBH_4$, MeOH, 25 °C	1	30:70	94
7	**5b**	L-Selectride, THF, −78 °C	6	<5:>95	92
8	**5b**	DIBAL, THF, −78 °C	6	99:1	88
9	**5b**	9-BBN, THF, 0 °C[h]	30	99:1	55
10	**5b**	9-BBN, THF, 25 °C[h]	15	99:1	62
11	**5c**	$NaBH_4$, MeOH, 25 °C	1	30:70	93
12	**5c**	L-Selectride, THF, −78 °C	3	1:99	82
13	**5c**	DIBAL, THF, −78 °C	6	99:1	90
14	**5c**	9-BBN, THF, 0 °C[h]	20	99:1	52
15	**5c**	9-BBN, THF, 25 °C[h]	14	99:1	71

[a] Ratio of the crude reaction mixture determined by ^{1}H NMR.
[b] Isolated yields.
[c] Excess of the transfer reducing reagent was used.
[d] Imine/reducing transfer reagent ratio of 1/1.3.
[e] Imine/reducing transfer reagent ratio of 1/3.3.
[f] Imine/reducing transfer reagent ratio of 1/2.2.
[g] 50% Conversion and related yield.
[h] Imine/reducing transfer reagent ratio of 1/4.4.

de) affording sulfinamides **6a–c** with the same prevailing diastereomer, although the diastereoisomer composition of the amides was completely reversed when passing from L-Selectride to DIBAL and 9-BBN. Interestingly, it should be noted that it is possible to obtain the desired enantiopure or quasi-enantiopure diastereomer, **6a**, **6b** and **6c** by a proper choice of the reducing agent.

With these good results in hand, we carried out a deeper investigation for the application of this methodology to the synthesis of more complex 2-pyridyl systems. This stems from the fact that 1-susbstituted 1-(pyridyl-2-yl)methylamines are more interesting compounds from our point of view, namely for their use as ligands in metal complexes for asymmetric catalysis.[4a] For this purpose, a set of *N*-*tert*-butanesulfinyl ketimines (R_S)-**9a–e** were obtained by condensation of (R_S)-**4** (1 equiv) with a series of 2-pyridyl ketones **8a–e** (1.1 equiv) with varying steric and electronic demands about the carbonyl (Scheme 3). The condensation reactions were performed employing $Ti(OEt)_4$ (2 equiv) in THF at 70 °C to give ketimines **9a** (30%), **9b** (14%), **9c** (68%), **9d** (63%) and **9e** (50%) as a single isomer, as determined by ^{1}H NMR spectroscopy.

The reduction of (R_S)-**9a–e** was performed with four hydride transfer reagents under a variety of conditions (Table 2). The configurations of diastereomers **10a** and **10c** were attributed by correlation with the related known optically active amines **11a**[10] and **11c**,[11] respectively. In this way it has been possible to determine that in the ^{1}H NMR spectra, the resonances of the protons of the *t*-butyl group on the sulfur atom of the (R_S,R)-diastereomers of **5a** and **10a** (R = aliphatic groups) are shifted downfield with respect to those of the related (R_S,S)-diastereomers, whereas those of (R_S,R)-diastereomer **10c** (R = aromatic group) are shifted upfield with respect to those of the related (R_S,S)-diastereomer. By analogy, the configurations to the diastereomers of **10b**, **10d** and **10e** have been tentatively assigned. Yields and diastereoselectivities were greatly dependent on the nature of both the reducing agent and the substituent on the imine moiety. In all cases the addition of more than one equivalent of a reducing agent (up to 4.4 equiv) was required to drive the reduction to completion. Stereoselectivities were moderate to fairly good (53–76% de).

In the reduction of pyridylimines with alkyl groups **5a**, **9a** and **9b**, the diastereoselectivity was inversely proportional to the increase of the steric bulk of the substituent (**6a**: R = methyl, 98% de; **10a**: R = *iso*-propyl, 76% de; **10b**: R = *tert*-butyl, 74% de). As proof of that, L-Selectride reacted with **5a** at −78 °C to give very high stereoselectivity, but required a temperature of −40 °C to react with **9a** and failed to react also at this temperature with **9b**. On the other hand, the same reagent was the best stereoselective reducing agent with **9c**, **9d** and **9e** at −78 °C (R = phenyl, 2-furyl and 2-thienyl, respectively), though the sense of asymmetric induction was completely reversed in passing from **9d** to **9c** and **9e**. Therefore, under the same reaction conditions, the stereochemical result appears to be a compromise between the steric demand of the R-group on the imine moiety and that of the S-substituent.

3. Conclusion

In conclusion we have demonstrated that the reduction of *N*-*tert*-butanesulfinyl ketimines derived from pyridyl ketones affords the related *N*-*tert*-butanesulfinyl amines with moderate to high diastereoselectivities, giving the best stereochemical results with small substituents on the imine moiety (R = Me, Ph, etc.). Moreover, in the case of ketimines derived from isomeric acetylpyridines **5a–c** it is possible to obtain the enantiopure enantiomers of the corresponding 1-pyridylmetylamine simply by a proper

Table 2. Reduction of R_S-**9a–e**

Entry	Compound	Reducing agent/conditions	Reaction time (h)	Ratio[a] (R_SR):(R_SS)-**10**	Yield[b] (%)
1	**9a**	$NaBH_4$, MeOH, 25 °C[c]	1	40:60	90
2	**9a**	L-Selectride, THF, −78 °C[d]	24	No reaction	
3	**9a**	L-Selectride, THF, −40 °C[e]	8	12:88	69
4	**9a**	DIBAL, THF, −78 °C[f]	4	42:58	87
5	**9a**	9-BBN, THF, 0 °C[d]	4	34:66	67
6	**9b**	$NaBH_4$, MeOH, 25 °C[c]	1	1:1	94
7	**9b**	L-Selectride, THF, −40 °C[d]	24	No reaction	
8	**9b**	DIBAL, THF, −78 °C[d]	8	13:87	92
9	**9b**	9-BBN, THF, 0 °C[g]	11	35:65	50
10	**9c**	$NaBH_4$, MeOH, 25 °C[c]	1	32:68	95
11	**9c**	L-Selectride, THF, −78 °C[e]	12	19:81	50
12	**9c**	DIBAL, THF, −78 °C[g]	10	23:77	75
13	**9c**	9-BBN, THF, 0 °C[g]	21	48:52	50
14	**9d**	$NaBH_4$, MeOH, 25 °C[c]	1	55:45	91
15	**9d**	L-Selectride, THF, −78 °C[d]	5	77:23	27
16	**9d**	DIBAL, THF, −78 °C[d]	12	68:32	85
17	**9d**	9-BBN, THF, 0 °C[e]	12	25:75	77
18	**9e**	$NaBH_4$, MeOH, 25 °C[c]	1	56:44	90
19	**9e**	L-Selectride, THF, −78 °C[e]	8	15:85	30
20	**9e**	DIBAL, THF, −78 °C[f]	10	66:34	90
21	**9e**	9-BBN, THF, 0 °C[d]	10	1:1	75

[a] Ratio of the crude reaction mixture determined by ^{1}H NMR.
[b] Isolated yields.
[c] Excess of the transfer reducing reagent was used.
[d] Imine/reducing transfer reagent ratio of 1/2.2.
[e] Imine/reducing transfer reagent ratio of 1/4.4.
[f] Imine/reducing transfer reagent ratio of 1/1.1.
[g] Imine/reducing transfer reagent ratio of 1/3.3.

choice of the reducing agent. Since previous findings indicate that the reduction of the related *N*-*p*-toluenesulfinyl pyridyl ketimines gave the best results with large substituents (R = *tert*-butyl and *iso*-propyl),[5] it is possible to conclude that the (*S*)-*tert*-butanesulfinyl and (*S*)-*p*-tolylsulfinyl groups are complementary and can be chosen according to the desired pyridylamine.

4. Experimental

4.1. General methods

Melting points were determined on a Büchi 510 capillary apparatus and are uncorrected. The NMR spectra were obtained with a Varian VXR-300 spectrometer at 300 for ^{1}H and 75.4 MHz for ^{13}C. Chemical shifts are reported in ppm downfield from internal Me_4Si in $CDCl_3$. Optical rotations were measured with a Perkin–Elmer 241 polarimeter in a 1 dm tube. Elemental analyses were performed on a Perkin–Elmer 240 B analyser. Ethyl acetate and petroleum ether were distilled before use. THF was distilled from sodium–benzophenone ketyl and CH_2Cl_2 from P_2O_5. Both solvents were degassed thoroughly with dry nitrogen directly before use.

(*R*)-(+)-2-Methylpropane-2-sulfinamide **4**, 2-, 3- and 4-acetylpyridines **3a**, **3b** and **3c**, respectively, phenyl(pyridin-2-yl)methanone **8c** were purchased from Aldrich. 2-Methyl-1-(pyridin-2-yl)propan-1-one **8c**,[12] 2,2-dimethyl-1-(pyridin-2-yl)propan-1-one **8c**,[13] furan-2-yl(pyridin-2-yl)methanone **8c**[14] and pyridin-2-yl(thiophen-2-yl)methanone **8c**[15] were prepared according to reported procedures.

4.2. General procedure for the preparation of *N*-*tert*-butanesulfinyl ketimines 5a–c and 9a–e

A solution of the pyridyl ketone (0.55 mmol), (*R*)-(+)-2-methylpropane-2-sulfinamide (60.5 mg, 0.5 mmol) and $Ti(OEt)_4$ (0.228 g, 1.0 mmol) in anhydrous CH_2Cl_2 (2 mL) or THF (2 mL) was heated at 40 or 70 °C, respectively, for the proper time. After cooling, the solvent was removed under vacuum and the residue taken up in ethyl acetate (10 mL). This solution was vigorously stirred while a saturated solution of brine (2 mL) was slowly added. After 15 min, the mixture was filtered through a plug of Celite that was washed with ethyl acetate. The organic phase was separated and dried over Na_2SO_4. The solvent was evaporated and the residue purified by flash chromatography.

4.2.1. (R_S)-*N*-[1-(Pyridin-2-yl)ethylidene]-2-methylpropane-2-sulfinamide 5a. Reaction solvent: CH_2Cl_2; reaction time: 14 h; chromatographic eluent: petroleum ether/ethyl acetate = 1/1; 0.048 g (43%); yellow solid; mp 46–47 °C; $[\alpha]_D^{25} = -49.5$ (*c* 0.075, $CHCl_3$). ^{1}H NMR: δ 8.66 (d, 1H, $J = 5.1$ Hz), 8.14 (d, 1H, $J = 7.8$ Hz), 7.78 (dt, 1H, $J = 7.8$, 1.5 Hz), 7.41–7.36 (m, 1H), 2.87 (s, 3H), 1.34 (s, 9H). ^{13}C NMR: δ 183.6, 154.2, 147.7, 135.4, 122.6, 121.8, 57.5, 22.4, 19.3. Anal. Calcd for $C_{11}H_{16}N_2OS$: C, 58.90; H, 7.19; N, 12.49. Found: C, 59.05; H, 7.18; N, 12.51.

4.2.2. (R_S)-*N*-[1-(Pyridin-3-yl)ethylidene]-2-methylpropane-2-sulfinamide 5b. Reaction solvent: CH_2Cl_2; reaction time: 60 h; chromatographic eluent: petroleum ether/ethyl acetate = 2/8; 0.071 g (64%); yellow oil; $[\alpha]_D^{25} = +11.2$ (*c* 0.040, $CHCl_3$). ^{1}H NMR: δ 9.10 (d, 1H, $J = 1.8$, Hz), 8.71 (dd, 1H, $J = 4.8$, 1.8 Hz), 8.17 (d, 1H, $J = 8.1$ Hz), 7.39 (dd, 1H, $J = 8.1$, 4.8 Hz), 2.81 (s, 3H), 1.34 (s, 9H). ^{13}C NMR: δ 174.2, 152.1, 148.5, 134.3, 134.1, 123.3, 57.7, 22.4, 19.5. Anal. Calcd for $C_{11}H_{16}N_2OS$: C, 58.90; H, 7.19; N, 12.49. Found: C, 58.79; H, 7.20; N, 12.45.

4.2.3. (R_S)-*N*-[1-(Pyridin-4-yl)ethylidene]-2-methylpropane-2-sulfinamide 5c. Reaction solvent: CH_2Cl_2; reaction time: 40 h; chromatographic eluent: ethyl acetate; 0.102 g (91%); yellow oil; $[\alpha]_D^{25} = -20.1$ (*c* 0.141, $CHCl_3$). ^{1}H NMR: δ 8.74 (d, 2H, $J = 5.4$ Hz), 7.68 (d, 2H, $J = 6.0$ Hz), 2.78 (s, 3H), 1.34 (s, 9H). ^{13}C NMR: δ 173.9, 150.3, 145.2, 120.4, 58.0, 22.4, 19.1. Anal. Calcd for $C_{11}H_{16}N_2OS$: C, 58.90; H, 7.19; N, 12.49. Found: C, 58.77; H, 7.21; N, 12.53.

4.2.4. (R_S)-*N*-[2-Methyl-1-(pyridin-2-yl)propylidene]-2-methylpropane-2-sulfinamide 9a. Reaction solvent: THF; reaction time: 72 h; chromatographic eluent: petroleum ether/ethyl acetate = 1/1; 0.038 g (30%); yellow oil; $[\alpha]_D^{25} = -171.0$ (*c* 0.074, $CHCl_3$). ^{1}H NMR: δ 8.64 (d, 1H, $J = 4.8$ Hz), 7.74 (dt, 1H, $J = 7.8$, 1.5 Hz), 7.46 (br m, 1H), 7.31 (dd, 1H, $J = 7.8$, 4.8 Hz), 3.42–3.18 (br m, 1H), 1.25 (s, 15H). ^{13}C NMR: δ 185.1, 155.1, 148.4, 135.5, 123.6, 122.4, 56.5, 21.9, 21.7, 19.3. Anal. Calcd for $C_{13}H_{20}N_2OS$: C, 61.87; H, 7.99; N, 11.10. Found: C, 61.76; H, 7.93; N, 11.12.

4.2.5. (R_S)-*N*-[2,2-Dimethyl-1-(pyridin-2-yl)propylidene]-2-methylpropane-2-sulfinamide 9b. Reaction solvent: THF; reaction time: 72 h; chromatographic eluent: petroleum ether/ethyl acetate = 1/1; 0.019 g (14%); yellow-brown solid; mp 55–57 °C; $[\alpha]_D^{25} = -179.7$ (*c* 0.028, $CHCl_3$). ^{1}H NMR: δ 8.63 (d, 1H, $J = 4.8$ Hz), 7.71 (dt, 1H, $J = 7.8$, 1.5 Hz), 7.30–7.26 (m, 1H), 7.20 (d, 1H, $J = 7.8$ Hz), 1.26 (s, 9H), 1.22 (s, 9H). ^{13}C NMR: δ 187.7, 155.8, 148.7, 135.3, 123.0, 122.3, 56.7, 42.3, 28.1, 22.3. Anal. Calcd for $C_{14}H_{22}N_2OS$: C, 63.12; H, 8.32; N, 10.52. Found: C, 66.31; H, 8.35; N, 10.55.

4.2.6. (R_S)-*N*-[Phenyl(pyridin-2-yl)methylene]-2-methylpropane-2-sulfinamide 9c. Reaction solvent: THF; reaction time: 43 h; chromatographic eluent: petroleum ether/ethyl acetate = 1/1; 0.097 g (68%); yellow oil; $[\alpha]_D^{25} = -123.6$ (*c* 0.071, $CHCl_3$). ^{1}H NMR: δ 8.72 (br s, 1H), 7.80 (dt, 1H, $J = 7.8$, 1.8 Hz), 7.63 (br s, 2H), 7.52–7.48 (m, 5H), 1.33 (s, 9H). ^{13}C NMR: δ 154.8, 149.1, 137.1, 135.9, 132.0, 129.2, 128.2, 123.9, 57.7, 22.5. Anal. Calcd for $C_{16}H_{18}N_2OS$: C, 67.10; H, 6.33; N, 9.78. Found: C, 67.36; H, 6.35; N, 9.80.

4.2.7. (R_S)-*N*-[Furan-2-yl(pyridin-2-yl)methylene]-2-methylpropane-2-sulfinamide 9d. Reaction solvent: THF; reaction time: 60 h; chromatographic eluent: petroleum ether/ethyl acetate = 4/6; 0.087 g (63%); oil; $[\alpha]_D^{25} = -211.6$ (*c* 0.029, $CHCl_3$). ^{1}H NMR: δ 8.71 (d, 1H, $J = 4.5$ Hz), 7.81 (t, 1H, $J = 7.8$ Hz), 7.67 (s, 1H), 7.60 (br s, 1H), 7.42–7.48 (m, 1H), 6.79 (br s, 1H), 6.54 (s, 1H), 1.32 (s, 9H). ^{13}C NMR: δ 162.5, 148.9, 146.9, 136.0, 124.4, 123.9, 112.4, 57.8, 22.4. Anal. Calcd for $C_{14}H_{16}N_2O_2S$: C, 60.85; H, 5.84; N, 10.14. Found: C, 66.77; H, 5.87; N, 10.17.

4.2.8. (R_S)-*N*-[Pyridin-2-yl(thiophen-2-yl)methylene]-2-methylpropane-2-sulfinamide 9e. Reaction solvent: THF; reaction time: 60 h; chromatographic eluent: petroleum ether/ethyl acetate = 1/1; 0.073 g (50%); yellow oil; $[\alpha]_D^{25} = -83.5$ (*c* 0.074, $CHCl_3$). ^{1}H NMR: δ 8.72 (d, 1H, $J = 4.8$ Hz), 7.82 (dt, 1H, $J = 7.8$, 1.8 Hz), 7.63 (dd, 1H, $J = 4.8$, 1.2 Hz), 7.54 (d, 1H, $J = 7.8$ Hz), 7.40 (ddd, 1H, $J = 7.8$, 4.8 Hz, $J = 1.2$ Hz), 7.08 (br s, 1H), 7.04 (t, 1H, $J = 4.8$ Hz), 1.30 (s, 9H). ^{13}C NMR: δ 168.2, 153.8, 149.0, 135.9, 133.5, 133.0, 127.9, 124.1, 123.6, 57.7, 22.3. Anal. Calcd for $C_{14}H_{16}N_2OS_2$: C, 57.50; H, 5.51; N, 9.58. Found: C, 57.36; H, 5.53; N, 9.56.

4.3. Representative procedure for the reduction of imines with DIBAL

Diisobutylaluminium hydride (DIBAL) (0.45 mmol, 0.45 mL of a 1.0 M solution in THF) was added dropwise at −78 °C to a solution of the imine (0.20 mmol) in THF (2 mL). After the proper time, MeOH (1 mL) was added at −78 °C to the mixture, which was then warmed at room temperature and evaporated under reduced pressure. Aqueous 2 M NaOH (2 mL) was added to the residue and the crude mixture was extracted with ethyl acetate. The organic phase was separated, dried over Na_2SO_4, the solvent was evaporated and the residue was purified by flash chromatography.

4.4. Representative procedure for the reduction of imines with $NaBH_4$

Sodium borohydride ($NaBH_4$) (15.0 mg, 0.40 mmol) was added portionwise to a cooled (0 °C) solution of the imine (0.20 mmol) in MeOH (3 mL). After 1 h at 25 °C, the reaction was quenched with saturated aqueous ammonium chloride (4 mL). The crude mixture was extracted with ethyl acetate and the separated organic phase was dried over anhydrous Na_2SO_4. The solvent was evaporated under reduced pressure and the residue was purified by flash chromatography.

4.5. Representative procedure for the reduction of imines with L-Selectride

A solution of tri-*sec*-butylborohydride (L-Selectride) (0.20 mmol, 0.2 mL of a 1.0 M solution in THF) was added dropwise at −78 °C to a solution of the imine (0.20 mmol) in THF (2 mL). After the proper time, the reaction was quenched with saturated aqueous ammonium chloride (3 mL) and then extracted with ethyl acetate. The mixture was filtered through a Celite pad that was washed with ethyl acetate. The organic phase was separated, dried over Na_2SO_4, the solvent was evaporated and the residue purified by flash chromatography.

4.6. Representative procedure for the reduction of imines with 9-BBN

9-Borabicyclo[3.3.1]nonane (9-BBN) (0.90 mL of a 0.5 M solution in THF, 0.45 mmol) was added dropwise at 0 °C or room temperature to a solution of the imine (0.20 mmol) in THF (2 mL). After the proper time MeOH (1 mL) was added at the proper temperature and the mixture was stirred for a further 15 min. The solvent was evaporated under reduced pressure. Aqueous 2 M NaOH (2 mL) was added to the residue and the crude mixture was extracted with ethyl acetate. The organic phase was separated, dried over Na_2SO_4, the solvent was evaporated and the residue was purified by flash chromatography.

4.6.1. (R_S,*R*)-*N*-[1-(Pyridin-2-yl)ethyl]-2-methylpropane-2-sulfinamide (R_S,*R*)-6a. This compound was obtained as a sole diastereomer; yellow oil; $[\alpha]_D^{25} = -55.1$ (*c* 0.092, $CHCl_3$). ^{1}H NMR: δ 8.55 (d, 1H, $J = 4.8$ Hz), 7.67 (dt, 1H, $J = 7.8$, 1.5 Hz), 7.30 (d, 1H, $J = 7.8$ Hz), 7.20 (dd, 1H, $J = 4.8$, 1.8 Hz), 4.84 (d, 1H, $J = 4.8$ Hz), 4.65–4.55 (m, 1H), 1.51 (d, 3H, $J = 6.6$ Hz), 1.26 (s, 9H). ^{13}C NMR: δ 161.8, 149.0, 136.8, 122.3, 121.0, 55.6, 55.2, 23.3, 22.7. Anal. Calcd for $C_{11}H_{18}N_2OS$: C, 58.37; H, 8.02; N, 12.38. Found: C, 58.44; H, 8.05; N, 12.40.

4.6.2. (R_S,*S*)-*N*-[1-(Pyridin-2-yl)ethyl]-2-methylpropane-2-sulfinamide (R_S,*S*)-6a. This compound was obtained as a sole diastereomer; yellow oil; $[\alpha]_D^{25} = -41.3$ (*c* 0.052, $CHCl_3$). ^{1}H NMR: δ 8.57 (d, 1H, $J = 4.8$ Hz), 7.67 (dt, 1H, $J = 7.8$, 1.8 Hz), 7.30 (d, 1H, $J = 7.8$ Hz), 7.20 (dd, 1H, $J = 4.8$, 1.8 Hz), 4.75–4.55 (m, 1H), 4.00 (d, 1H, $J = 5.7$ Hz), 1.62 (d, 3H, $J = 6.6$ Hz), 1.21 (s, 9H). ^{13}C NMR: δ 162.2, 149.3, 136.7, 122.3, 121.0, 56.6, 55.9, 24.1, 22.5. Anal. Calcd for $C_{11}H_{18}N_2OS$: C, 58.37; H, 8.02; N, 12.38. Found: C, 58.31; H, 8.04; N, 12.35.

4.6.3. (R_S,*R*)-*N*-[1-(Pyridin-3-yl)ethyl]-2-methylpropane-2-sulfinamide (R_S,*R*)-6b. This compound was obtained as a sole diastereomer; red oil; $[\alpha]_D^{25} = -33.2$ (*c* 0.032, $CHCl_3$). ^{1}H NMR: δ 8.60 (d, 1H, $J = 2.1$ Hz), 8.55 (dd, 1H, $J = 4.8$, 2.1 Hz), 7.70 (dt, 1H, $J = 7.8$, 2.1 Hz), 7.30 (dd, 1H, $J = 7.8$, 4.8 Hz), 4.64–4.53 (m, 1H), 3.50 (s, 1H), 1.56 (d, 3H, $J = 6.6$ Hz), 1.24 (s, 9H). ^{13}C NMR: δ 149.2, 148.3, 139.3, 134.3, 123.6, 55.6, 51.9, 22.6, 22.5. Anal. Calcd for $C_{11}H_{18}N_2OS$: C, 58.37; H, 8.02; N, 12.38. Found: C, 58.47; H, 8.04; N, 12.39.

4.6.4. (R_S,*R*)- and (R_S,*S*)-*N*-[1-(Pyridin-3-yl)ethyl]-2-methylpropane-2-sulfinamide 6b. This compound was obtained as a mixture of diastereomers in which the (R_S,*S*)-diastereomer is prevailing; oil; ^{1}H NMR: δ 8.60 (d, 1H, $J = 2.1$ Hz, major isomer), 8.60 (d, 1H, $J = 2.1$ Hz, minor isomer), 8.55 (dd, 1H, $J = 4.8$, 1.5 Hz, major isomer), 8.55 (dd, 1H, $J = 4.8$, 1.5 Hz, minor isomer), 7.70 (dt, 1H, $J = 3.6$, 1.5 Hz, major isomer), 7.70 (dt, 1H, $J = 3.6$, 1.5 Hz, minor isomer), 7.30 (dd, 1H, $J = 7.8$, 4.8 Hz, major isomer), 7.30 (dd, 1H, $J = 7.8$, 4.8 Hz, minor isomer) 4.54–4.68 (m, 1H, major isomer), 4.54–4.68 (m, 1H, minor isomer), 3.50 (s, 1H, minor isomer), 3.39 (s, 1H, major isomer), 1.58 (d, 3H, $J = 6.6$ Hz, major isomer) 1.56 (d, 3H, $J = 6.6$ Hz, minor isomer), 1.24 (s, 9H, minor isomer), 1.21 (s, 9H, major isomer). Anal. Calcd for $C_{11}H_{18}N_2OS$: C, 58.37; H, 8.02; N, 12.38. Found: C, 58.53; H, 8.00; N, 12.36.

4.6.5. (R_S,*R*)-*N*-[1-(Pyridin-4-yl)ethyl]-2-methylpropane-2-sulfinamide (R_S,*R*)-6c. This compound was obtained as a only diastereomer; red oil; $[\alpha]_D^{25} = -32.4$ (*c* 0.094, $CHCl_3$). ^{1}H NMR: δ 8.58 (d, 2H, $J = 5.4$ Hz), 7.30 (d, 2H, $J = 5.4$ Hz), 4.58–4.47 (m, 1H), 3.68 (br s, 1H), 1.52 (d, 3H, $J = 6.6$ Hz), 1.25 (s, 9H). ^{13}C NMR: δ 152.7, 149.9, 121.5, 55.7, 53.3, 22.5, 22.4. Anal. Calcd for $C_{11}H_{18}N_2OS$: C, 58.37; H, 8.02; N, 12.38. Found: C, 58.43; H, 8.05; N, 12.36.

4.6.6. (R_S,*S*)-*N*-[1-(Pyridin-4-yl)ethyl]-2-methylpropane-2-sulfinamide (R_S,*S*)-6c. This compound was obtained as a sole diastereomer; red oil; $[\alpha]_D^{25} = -50.0$ (*c* 0.036, $CHCl_3$). ^{1}H NMR: δ 8.58 (d, 2H, $J = 6.0$ Hz), 7.28 (d, 2H, $J = 6.0$ Hz), 4.64–4.52 (m, 1H), 3.42 (d, 1H, $J = 3.3$ Hz) 1.54 (d, 3H, $J = 6.6$ Hz), 1.23 (s, 9H). ^{13}C NMR: δ 152.6, 149.9, 121.9, 55.9, 53.7, 24.6, 22.5. Anal. Calcd for $C_{11}H_{18}N_2OS$: C, 58.37; H, 8.02; N, 12.38. Found: C, 58.41; H, 8.02; N, 12.41.

4.6.7. (R_S,*R*)- and (R_S,*S*)-*N*-[2-Methyl-1-(pyridin-2-yl)-propyl]-2-methylpropane-2-sulfinamide 10a. This compound was obtained as a mixture of diastereomers with the (R_S,*S*)-diastereomer prevailing; chromatographic eluent: ethyl acetate; oil; ^{1}H NMR: δ 8.57 (dd, 1H, $J = 4.8$, 0.6 Hz, major isomer), 8.54 (dd, 1H, $J = 4.2$, 0.6 Hz, minor isomer), 7.68–7.59 (m, 1H, minor isomer), 7.68–7.59 (m, 1H, major isomer), 7.24–7.12 (m, 2H, minor isomer), 7.24–7.12 (m, 2H, major isomer), 5.11 (d, 1H, $J = 5.4$ Hz, minor isomer), 4.32 (d, 1H, $J = 4.8$ Hz, major isomer), 4.24 (t, 1H, $J = 4.8$ Hz, major isomer), 4.16 (t, 1H, $J = 4.8$ Hz, minor isomer), 2.19 (m, 1H, major isomer), 2.05 (m, 1H, minor isomer), 1.29 (s, 9H, minor isomer), 1.15 (s, 9H, major isomer), 0.99 (d, 6H, $J = 5.4$ Hz, minor isomer), 0.88 (d, 6H, $J = 5.1$ Hz, major isomer). Anal. Calcd for $C_{13}H_{22}N_2OS$: C, 61.38; H, 8.72; N, 11.01. Found: C, 61.44; H, 8.75; N, 10.99.

4.6.8. (R_S,*R*)- and (R_S,*S*)-*N*-[2,2-Dimethyl-1-(pyridin-2-yl)propyl]-2-methylpropane-2-sulfinamide 10b. This compound was obtained as a mixture of diastereomers with the (R_S,*S*)-diastereomer prevailing; chromatographic eluent: ethyl acetate; oil; ^{1}H NMR: δ 8.57 (d, 1H, $J = 4.2$ Hz, major isomer), 8.54 (d, 1H, $J = 4.8$ Hz, minor isomer), 7.68–7.55 (m, 1H, major isomer), 7.68–7.55 (m, 1H, minor isomer), 7.23–7.10 (m, 2H, major isomer), 7.23–7.10 (m, 2H, minor isomer), 5.33 (d, 1H, $J = 8.1$ Hz, minor isomer), 4.65 (d, 1H, $J = 6.6$ Hz, major isomer), 4.17 (d, 1H, $J = 6.6$ Hz, major isomer), 4.05 (d, 1H, $J = 8.1$ Hz, minor isomer), 1.29 (s, 9H, minor isomer), 1.09 (s, 9H, major isomer), 0.98 (s, 9H, minor isomer), 0.91 (s, 9H, major isomer). Anal. Calcd for $C_{14}H_{24}N_2OS$: C, 62.64; H, 9.01; N, 10.44. Found: C, 62.55; H, 9.04; N, 10.41.

4.6.9. (R_S,*R*)- and (R_S,*S*)-*N*-[Phenyl(pyridin-2-yl)methyl]-2-methylpropane-2-sulfinamide 10c. This compound was obtained as a mixture of diastereomers. The spectra data refer to the case in which the (R_S,*S*)-diastereomer is prevailing; chromatographic eluent: ethyl acetate; oil; ^{1}H NMR: δ

8.56 (d, 1H, $J = 4.2$ Hz, major isomer), 8.55 (d, 1H, $J = 4.8$ Hz, minor isomer), 7.64 (dt, 1H, $J = 7.5$, 1.5 Hz, minor isomer), 7.57 (dt, 1H, $J = 7.5$, 1.5 Hz, major isomer), 7.46–7.23 (m, 5H, major isomer), 7.46–7.23 (m, 5H, minor isomer), 7.41 (t, 1H, $J = 7.5$ Hz, minor isomer), 7.15 (ddd, 1H, $J = 7.5$, 6.0, 0.9 Hz, major isomer), 7.15 (ddd, 1H, $J = 7.5$, 6.0, 0.9 Hz, minor isomer), 7.05 (d, 1H, $J = 8.1$ Hz, major isomer), 5.77 (d, 1H, $J = 2.7$ Hz, major isomer), 5.71 (d, 1H, $J = 4.8$ Hz, minor isomer), 5.64 (d, 1H, $J = 3.0$ Hz, major isomer), 4.85 (d, 1H, $J = 4.8$ Hz, minor isomer), 1.27 (s, 9H, major isomer), 1.22 (s, 9H, minor isomer). Anal. Calcd for $C_{16}H_{20}N_2OS$: C, 66.63; H, 6.99; N, 9.71. Found: C, 66.54; H, 7.01; N, 9.74.

4.6.10. (R_S,*R*)- and (R_S,*S*)-*N*-[Furan-2-yl(pyridin-2-yl)methyl]-2-methylpropane-2-sulfinamide (10d). This compound was obtained as a mixture of diastereomers. The spectra data refer to the case in which the (R_S,*S*)-diastereomer is prevailing; chromatographic eluent: ethyl acetate; oil; ^{1}H NMR: δ 8.58 (ddd, 1H, $J = 4.8$, 1.8, 0.9 Hz, major isomer), 8.58 (ddd, 1H, $J = 4.8$, 1.8, 0.9 Hz, minor isomer), 7.69 (td, 1H, $J = 7.8$, 1.8 Hz, minor isomer) 7.66 (td, 1H, $J = 7.8$, 1.8 Hz, major isomer), 7.41 (d, 1H, $J = 7.8$ Hz, minor isomer), 7.38 (dd, 1H, $J = 1.8$, 0.6 Hz, major isomer) 7.26–7.18 (m, 2H, major isomer), 7.26–7.18 (m, 2H, minor isomer), 6.37–6.22 (m, 2H, major isomer), 6.37–6.22 (m, 3H, minor isomer), 5.72 (d, 1H, $J = 4.2$ Hz, major isomer), 5.53 (d, 1H, $J = 3.9$ Hz, major isomer), 4.85 (d, 1H, $J = 6.0$ Hz, minor isomer), 1.28 (s, 9H, major isomer), 1.22 (s, 9H, minor isomer). Anal. Calcd for $C_{14}H_{18}N_2O_2S$: C, 60.41; H, 6.52; N, 10.06. Found: C, 60.33; H, 6.44; N, 10.03.

4.6.11. (R_S,*R*)- and (R_S,*S*)-*N*-[Pyridin-2-yl(thiophen-2-yl)methyl]-2-methylpropane-2-sulfinamide (10e). This compound was obtained as a mixture of diastereomers. The spectra data refer to the case in which the (R_S,*S*)-diastereomer is prevailing; chromatographic eluent: ethyl acetate; oil; ^{1}H NMR: δ 8.58 (d, 1H, $J = 4.8$ Hz, major isomer), 8.58 (d, 1H, $J = 4.8$ Hz, minor isomer), 7.68 (dt, 1H, $J = 7.8$, 1.5 Hz, major isomer), 7.68 (dt, 1H, $J = 7.5$, 1.5 Hz, minor isomer), 7.73–7.52 (m, 1H, minor isomer), 7.42 (d, 1H, $J = 7.8$ Hz, major isomer), 7.28–7.16 (m, 2H, major isomer), 7.28–7.16 (m, 2H, minor isomer), 7.05–7.01 (m, 2H, major isomer) 7.00–6.90 (m, 1H, major isomer), 7.08–6.90 (m, 1H, minor isomer), 5.95 (d, 1H, $J = 5.4$ Hz, major isomer), 5.91 (d, 1H, $J = 3.9$ Hz, minor isomer), 5.75 (d, 1H, $J = 3.9$ Hz, minor isomer), 4.82 (d, 1H, $J = 5.4$ Hz, major isomer), 1.30 (s, 9H, minor isomer), 1.23 (s, 9H, major isomer). Anal. Calcd for $C_{14}H_{18}N_2OS_2$: C, 57.11; H, 6.16; N, 9.51. Found: C, 57.22; H, 6.18; N, 9.49.

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