Pergamon

Tetrahedron: *Asymmetry* 13 (2002) 303–310

TETRAHEDRON: *ASYMMETRY*

Asymmetric synthesis of diarylmethylamines by diastereoselective addition of organometallic reagents to chiral *N*-*tert*-butanesulfinimines: switchover of diastereofacial selectivity

Niklas Plobeck* and David Powell

Department of Chemistry, AstraZeneca R&D Montreal, 7171 Frederick-Banting Street, St-Laurent, Quebec, Canada H4S 1Z9

Received 8 February 2002; accepted 19 February 2002

Abstract—Diastereoselective addition of organometallic reagents to chiral *N*-*tert*-butanesulfinimines gave alkylated adducts in high yields and diastereoselectivities. Cleavage of the chiral auxiliary under mildly acidic conditions gave diarylmethylamines in high yield. A reversal in the diastereoselectivity was observed by using either phenylmagnesium bromide in toluene or phenyllithium in THF. The use of the same chiral auxiliary thus allowed the synthesis of both enantiomers of a number of diarylmethylamines.

1. Introduction

Diarylmethylamines are an important class of amines present in many structures showing biological activity and important as synthetic intermediates (Fig. 1).[1–3] There are relatively few reports on asymmetric synthesis of diarylmethylamines.[4,5] Recently, the *N*-*tert*-butanesulfinyl group has been demonstrated to be a useful readily available chiral auxiliary giving high asymmetric induction for nucleophilic addition to imines.[6] However, no examples of additions of aryl metal reagents to *N*-*tert*-butanesulfinylarylaldimines have been reported. Because of its favorable properties and the mild conditions for cleavage, we wanted to apply this chiral auxiliary to the asymmetric synthesis of diarylmethylamines.

Herein, we wish to report two sets of conditions for nucleophilic additions to chiral *N*-*tert*-butanesulfinylarylaldimines allowing the synthesis of both enantiomers of chiral diarylmethylamines in high yield and enantiomeric purity using the same chiral auxiliary (Scheme 1). A switchover of diastereofacial selectivity in the addition was observed depending on the reagent and solvent used.

2. Results and discussion

2.1. Preparation of *N*-*tert*-butanesulfinyl aldimines

Chiral *N*-*tert*-butanesulfinyl aldimines **3** were prepared in high yields by condensation of aldehydes with (*R*)-*tert*-butanesulfinamide **1** (Table 1).[7]

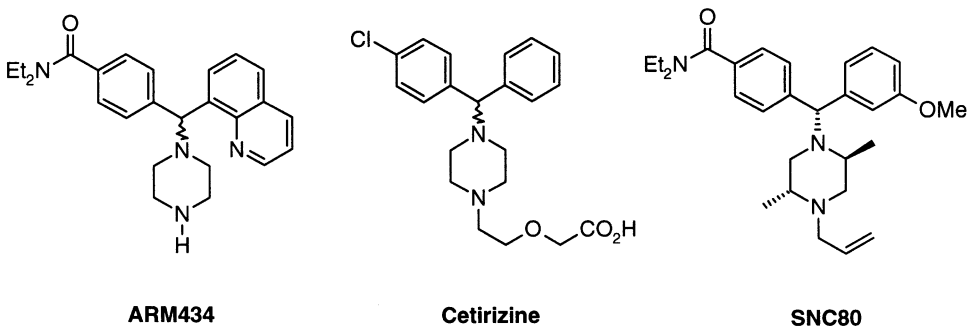
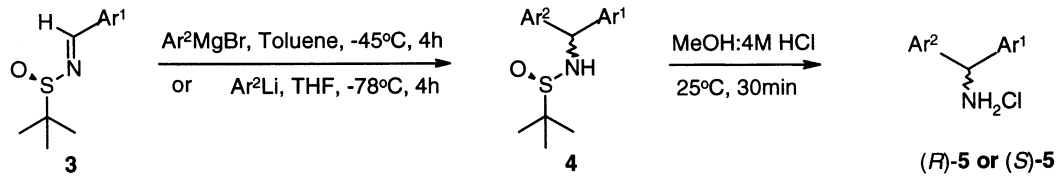


Figure 1.

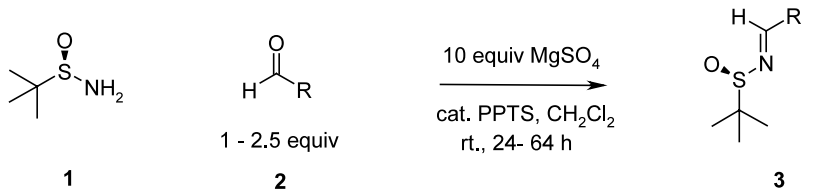
* Corresponding author. Fax: +1 (514) 832 3232; e-mail: niklas.plobeck@astrazeneca.com

0957-4166/02/$ - see front matter
PII: S0957-4166(02)00099-X



Scheme 1.

Table 1. Preparation of *N-tert*-butanesulfinyl aldimines **3a–g**



Aldimine	R	Yield (%)
3a	Phenyl	75
3b	1-Naphthyl	99
3c	4-Cl-Phenyl	99
3d	4-Br-Phenyl	81
3e	4-CF_3-Phenyl	53
3f	4-$(CH_3)_2$N-Phenyl	94
3g	3-Furanyl	88

2.2. Effects of solvent and organometallic reagent

The additions of PhLi and PhMgBr to the substrate **3c** were performed in different solvents (Table 2). The additions were completed at −78°C and the reactions were allowed to warm to 25°C over 4 h. The diastereomeric ratios were determined after cleavage of the chiral auxiliary by treatment with HCl in methanol. Phenyllithium gave a fast reaction in THF, occurring readily at −78°C to give a 27:73 diastereomeric ratio. The reaction in toluene was slower and gave a lower diastereomeric ratio. Addition of PhMgBr to **3c** in THF gave a very slow reaction (<5% conversion). Addition in CH_2Cl_2 as solvent has been reported to give the best diastereoselectivity for addition of many alkyl Grignard reagents,[6] and addition of PhMgBr to **3c** gave a good diastereomeric ratio (84:16) but was slow (15% conversion). Toluene was found to give a faster reaction and addition of PhMgBr occurred readily at −45°C to give complete conversion in less than 4 h with good diastereofacial selectivity (d.r. = 88:12). The presence of $AlMe_3$ as a Lewis acid additive to promote the reaction gave a small improvement in diastereoselectivity but the reaction was much slower.

An interesting switchover in diastereoselectivity was observed for the addition of PhMgBr compared to PhLi.

2.3. Diastereoselective addition to *N-tert*-butanesulfinimines

The most important results are shown in Table 3. Two sets of conditions were used for the diastereoselective addition of organometallic reagents to aldimines **3b–g** based on the initial results in Table 2. Addition of phenyllithium in THF at −78°C and phenylmagnesium bromide in toluene at −45°C was compared for the examples **3b–g**. Most of the examples investigated gave the corresponding *N-tert*-butanesulfinylamide **4** in high yield and high diastereoselectivity. The switchover of diastereofacial selectivity in the addition between PhMgBr and PhLi was observed in all cases except **3f**. The substrate **3f** containing a basic dimethylamino group was an exception, giving no reaction with PhMgBr and non-selective reaction with PhLi. The diastereomeric mixture of sulfinylamides **4** could in some cases be further purified by chromatography or recrystallization. In the case of **4b**, the diastereomeric ratio was increased from 86:14 to >99:1 by two recrystallizations.

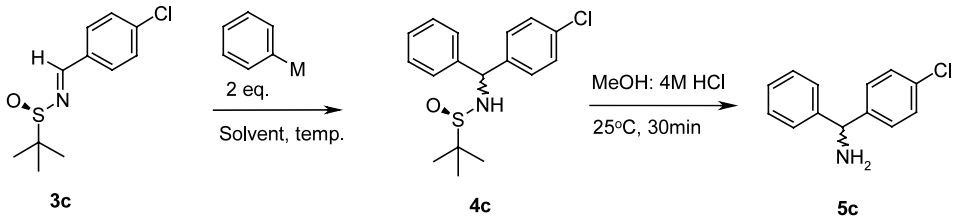
2.4. Effects of steric and electronic nature of reagent

The optimised reaction conditions were applied to different aryl Grignard reagents (Table 4). It was found that aryl Grignard reagents with electron-withdrawing or electron-donating groups could be added to aldimine **3a** in high yield and high diastereomeric ratio giving the same diastereomer in excess. 4-Fluorophenylmagnesium bromide reacted more slowly and gave a lower yield, whilst the sterically hindered mesityl Grignard reagent gave a good yield but reacted with slightly lower diastereoselectivity.

2.5. Mechanism and stereochemistry

Switchover of diastereofacial selectivity in the addition was observed between PhMgBr and PhLi in all cases except **3f** (Table 3). A similar switchover was observed

Table 2. Effect of solvent on diastereomeric ratio and % conversion[a]

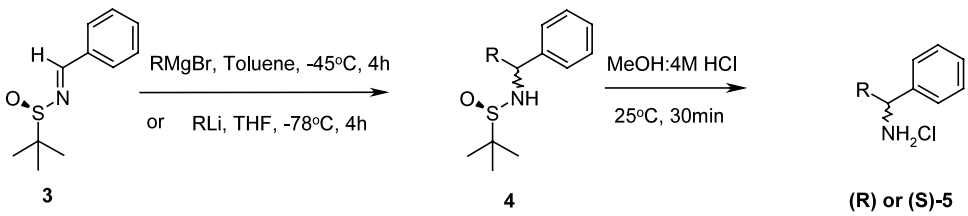


3c **4c** **5c**

M	Solvent	Temperature (°C)	**3c** to **4c** % conversion[b]	D.r.[c]
Li	THF	−78	85 (78)	27:73
Li	Toluene	−78 to +25	75	39:61
MgBr	THF	−78 to +25	<5	
MgBr	CH_2Cl_2	−78 to +25	15	84:16
MgBr	Toluene	−78 to −45	100 (86)	88:12
MgBr	Toluene + 1.1 equiv. $AlMe_3$	−78 to +25	20	91:9

[a] Addition of 1.8 M PhLi in cyclohexane/Et_2O or 3 M PhMgBr in Et_2O to 0.04 M **3c** in solvent.
[b] As determined by ^1H NMR, numbers in parenthesis indicate isolated yield after purification.
[c] Determined by chiral HPLC of the unpurified **5c** HCl salt.

Table 3. Addition of organometallic reagents to *N-tert*-butanesulfinimines **3b–g**



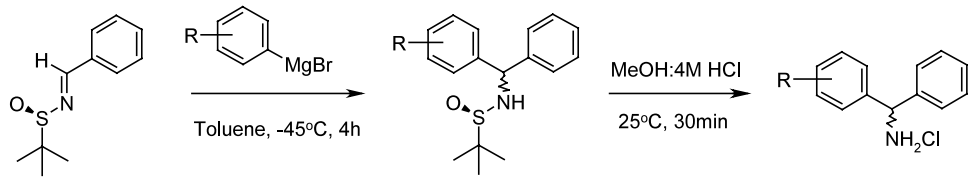
3 **4** **(R) or (S)-5**

Aldimine **3**	R	M	Sulfinylamide **4**		Amine **5**	
			Yield (%)[a]	D.r.[b]	Absolute config.	Yield (%)
b	1-Naphthyl	MgBr	88 (62)[c]	86:14 (99.5:0.5)[c]	*S*[d]	94
		Li	84	8:92	*R*[d]	94
c	4-Cl-Phenyl	MgBr	86	88:12	*S*[d]	97
		Li	78	27:73	*R*[d]	94
d	4-Br-Phenyl	MgBr	89	85:15	*S*[d]	80
		Li	85	13:87	*R*[d]	88
e	4-CF_3-Phenyl	MgBr	85	80:20	*S*[e]	71
		Li	92	8:92	*R*[e]	75
f	4-Me_2N-Phenyl	MgBr	N.r.	–	–	–
		Li	64	≈50:50[f]	–	–
g	3-Furanyl	MgBr	76	97:3	*S*[e]	81
		Li	64	29:71	*R*[e]	74

[a] Yields represent isolated yields after purification.
[b] Determined by chiral HPLC of the unpurified amine·HCl.
[c] After two recrystallizations from EtOAc:hexanes.
[d] Determined by comparison of the sign of optical rotation with known lit. compounds.
[e] Determined by analogy with results in entry b, c and d.
[f] Based on isolated yield of diastereomers.

in the related addition of ester enolates to chiral toluenesulfinimines[8] and also in some cases for addition to *tert*-butanesulfinimines.[6] In those cases the stereoselectivity of addition was explained by proposing a six-membered chelating transition state model in the case of the magnesium reagent addition and a non-chelation model for lithium reagent addition where steric hindrance factors determine the selectivity. In the three cases in our series where the absolute configurations of the product diarylmethylamines are known (**5b–d**), the observed stereoselectivity was the same as predicted by these models. For example, addition of phenyllithium and phenylmagnesium bromide to **3c** gave (*R*)-**5c** and (*S*)-**5c**, respectively (Scheme 2).

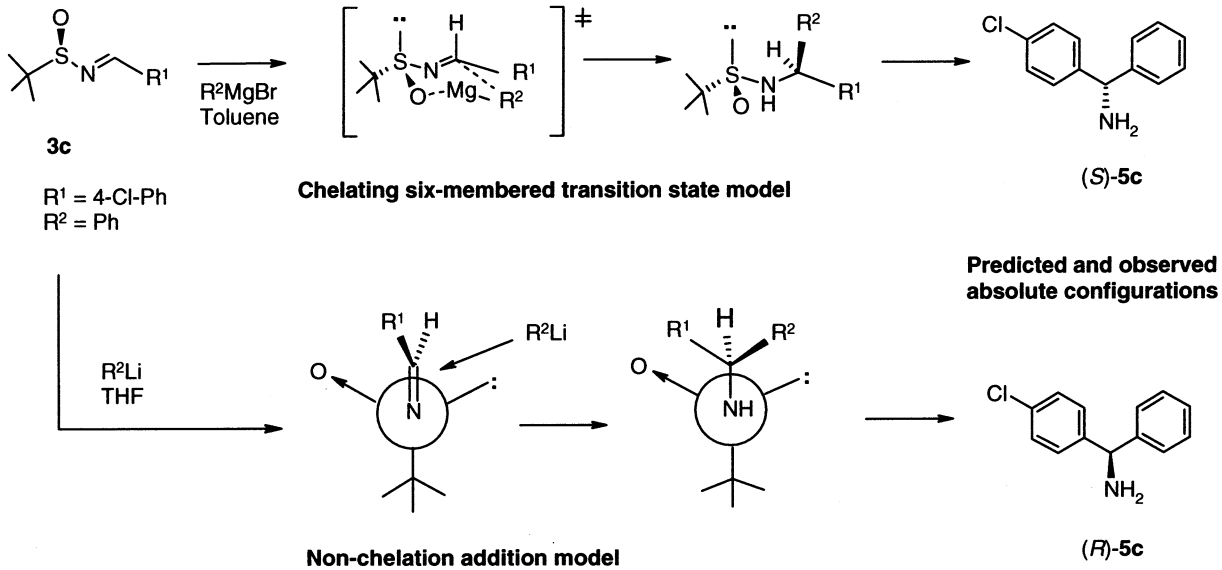
Table 4. Grignard additions to *N-tert*-butanesulfinyl aldimine **3a**



3a **4** **5**

Compound	R	Sulfinylamide **4**	D.r.[a]	Amine **5**
		Yield (%)		Yield (%)
c	4-Cl	89	93:7	94
i	4-Me	85	88:12	87
j	4-MeO	92	91:9	98
k	4-F	49	92:8	87
l	2,4,6-Me	76	73:27[b]	90

[a] Determined by chiral HPLC of the unpurified amine·HCl.
[b] Determined by ^{1}H NMR analysis of the (*R*)-MPA amide.



Scheme 2.

3. Conclusion

The practical and versatile asymmetric synthesis of diarylmethylamines reported here utilizes *N-tert*-butanesulfinimines **3**, which are easily accessible in large scale and high yield. Diastereoselective addition of organomagnesium or organolithium reagents to these *N-tert*-butanesulfinimines gives either diastereomer of *N-tert*-butanesulfinamides **4** in excess and in high yield by choice of reagent and solvent. The diastereomeric *N-tert*-butanesulfinamides can in some cases be further purified by chromatography or recrystallization to give enantiomerically pure diarylmethylamines after cleavage of the chiral auxiliary. The mild and rapid cleavage of the chiral auxiliary allows the recovery of the diarylmethylamines in high yield. The method thus requires only one enantiomer of the stoichiometric chiral auxiliary to access both enantiomers of the diarylmethylamine products **5**.

4. Experimental

4.1. Materials and methods

Purification by flash chromatography was carried out on silica gel 60 (70–230 mesh), eluting with gradients of EtOAc in hexane. Melting points were recorded on a Büchi 535 melting point apparatus and are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded on a Varian Unity Plus 400 MHz spectrometer. Spectra were recorded in $CDCl_3$ or CD_3OD and chemical shifts are given in ppm relative to TMS. IR spectra were recorded on a Perkin–

Elmer Paragon 1000 FT-IR spectrometer. Dry solvents with molecular sieves were obtained from Fluka.

4.2. Accurate mass determination by time-of-flight mass spectrometer

Time-of-flight mass spectrometer (LCT, Micromass Inc. England) and HPLC (HP1100, Hewlett Packard) were used for the accurate mass determination with instrument parameters of: ion mode: electrospray; desolvation temp.: 350°C; source temp.: 130°C; sample cone voltage: 30 V. Acquisition was carried out in the mass range 100–1000 Da, one spectrum per second at 5000 resolution. The sample was introduced into LCT mass spectrometer in loop injection mode with a HPLC flow of 0.4 mL/min. The mobile phase consisted of 50% water and 50% acetonitrile. Leucine-enkephalin (lock mass 556.2771 Da) was used as the reference standard (Sigma Ref. L-9133, 1 mg/mL in water). The sample was prepared with the analyte compound and the reference standard in methanol each 0.5 μg/μL. One microliter of the sample solution was injected into the LCT. The mass calibration was performed with polyethylene glycol (PEG) according to the LCT operator's manual.

4.3. Synthesis of *N*-*tert*-butanesulfinyl aldminines

The preparation of compounds **3a** and **3g** is described in a published procedure. Compounds **3b**–**f** were prepared analogously.[7]

4.3.1. (*R*)-(−)-2-Methyl-*N*-[(1*E*)-1-naphthalenylmethylene]-2-propanesulfinamide, 3b. Obtained in 99% yield as a yellow solid, mp = 52–54°C. IR (KBr) υ 3054, 2965, 1579, 1512, 1364, 1178, 1073 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 9.16 (1H, s), 9.02 (1H, d, J = 8.4 Hz), 8.04 (1H, d, J = 6.5 Hz), 8.00 (1H, d, J = 8.4 Hz), 7.91 (1H, d, J = 7.4 Hz), 7.66–7.55 (3H, m), 1.33 (9H, s). ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.44, 133.83, 133.24, 131.95, 131.16, 129.33, 128.79, 127.98, 126.44, 125.18, 124.31, 57.62, 22.58. HRMS calcd for $C_{15}H_{18}NSO$ (M+H), 260.1109; found 260.1101 (3.1 ppm).

4.3.2. (*R*)-(−)-*N*-[(1*E*)-(4-Chlorophenyl)methylene]-2-methyl-2-propanesulfinamide, 3c. Obtained in 99% yield as a white solid, mp = 41–42°C. IR (KBr) υ 2957, 1592, 1566, 1488, 1404, 1363, 1090 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 8.55 (1H, s), 7.79 (2H, d, J = 8.9 Hz), 7.45 (2H, d, J = 8.9 Hz), 1.27 (9H, s). ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.42, 138.57, 132.46, 130.47, 129.28, 57.85, 22.56. HRMS calcd for $C_{11}H_{15}NSOCl$ (M+H), 244.0563; found 244.0553 (4.1 ppm).

4.3.3. (*R*)-(−)-*N*-[(1*E*)-(4-Bromophenyl)methylene]-2-methyl-2-propanesulfinamide, 3d. Obtained in 82% yield as a yellow oil. IR (film) υ 3455, 1608, 1587, 1364, 1085 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 8.53 (1H, s), 7.72 (2H, d, J = 8.4 Hz), 7.62 (2H, d, J = 8.4 Hz), 1.25 (9H, s). ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.59, 132.87, 132.26, 130.62, 127.20, 57.89, 22.58. HRMS calcd for $C_{11}H_{15}NSOBr$ (M+H), 288.0057; found 288.0051 (2.1 ppm).

4.3.4. (*R*)-(−)-2-Methyl-*N*-[(1*E*)-[4-(trifluoromethyl)-phenyl]methylene]-2-propanesulfinamide, 3e. Obtained in 53% yield as a yellow oil. IR (film) υ 2964, 1607, 1574, 1324, 1169, 1131, 1088 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 8.64 (1H, s), 7.98 (2H, d, J = 7.9 Hz), 7.74 (2H, d, J = 7.9 Hz), 1.28 (9H, s). ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.46, 136.83, 133.83, 133.52, 129.51, 125.95, 125.92, 124.97, 58.13, 22.59. HRMS calcd for $C_{12}H_{15}NSOF_3$ (M+H), 278.0826; found 278.0815 (4.0 ppm).

4.3.5. (*R*)-(−)-*N*-[(1*E*)-[4-(Dimethylamino)phenyl]-methylene]-2-methyl-2-propanesulfinamide, 3f. Obtained in 94% yield as a light yellow solid, mp = 81–83°C. IR (KBr) υ 1610, 1583, 1548, 1362, 1179, 1083 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 8.43 (1H, s), 7.72 (2H, d, J = 8.9 Hz), 6.69 (2H, d, J = 8.9 Hz), 3.05 (6H, s), 1.24 (9H, s). ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.59, 152.96, 131.15, 122.31, 111.28, 57.25, 40.00, 22.43. HRMS calcd for $C_{13}H_{21}N_2SO$ (M+H), 253.1374; found 253.1362 (4.7 ppm).

4.3.6. (*R*)-(−)-*N*-[(1*E*)-3-Furanylmethylene]-2-methyl-2-propanesulfinamide, 3g. Obtained in 88% yield as a white solid, mp = 115–116°C. IR (KBr) υ 3111, 1609, 1147, 1070 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 8.55 (1H, s), 7.91 (1H, s), 7.49 (1H, s), 6.83 (1H, s), 1.24 (9H, s). ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.41, 147.65, 144.64, 124.26, 107.82, 57.43, 22.45. HRMS calcd for $C_9H_{14}NO_2S$ (M+H), 200.0745; found 200.0737 (4.0 ppm).

4.4. General procedure for the addition of Grignard reagents to *N*-*tert*-butanesulfinyl aldimines

A solution of the *N*-*tert*-butanesulfinyl aldimine **3** (0.2 mmol) in dry toluene (5 mL) at −45°C was treated with dropwise addition of Grignard reagent (0.4 mmol). The reaction mixture was stirred at −45°C for 4 h then quenched with sat. aq. NH_4Cl. Aqueous workup and concentration followed by column chromatography through silica gel gave the purified compound. The diastereomeric ratio was determined by HPLC analysis of the unpurified amine·HCl formed after cleavage of the sulfinyl group (Chiracel AD column, 97:3:0.1 hexanes/EtOH/DEA; 1.0 mL/min; 254 nm).

Compounds in Table 3.

4.4.1. (*R*)-2-Methyl-*N*-[(*S*)-1-naphthalenylphenylmethyl]-2-propanesulfinamide, 4b. This reaction was carried out on a 2 mmol scale. Obtained in 88% yield as a white solid, mp = 134–135°C. Recrystallization from EtOAc:hexanes provided the product in a diastereomeric ratio of 98:2 with 74% yield. A second recrystallization gave a d.r. of >99.5:0.5 and 62% yield. The diastereomeric ratio as determined by chiral HPLC was in agreement with that obtained by ^1H NMR analysis of the crude reaction mixture. IR (KBr) υ 3208, 2959, 1598, 1493, 1454, 1061, 923 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 8.00–7.22 (12H, m), 6.45 (1H, d, J = 2.8 Hz), 3.78 (1H, d, J = 2.8 Hz), 1.26 (9H, s). ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.98, 136.59, 133.90, 130.97, 128.82, 128.77, 127.88, 127.80, 126.20, 125.60,

125.11, 123.62, 58.90, 55.99, 22.69. HRMS calcd for $C_{21}H_{24}NSO$ (M+H), 338.1578; found, 338.1584 (−1.8 ppm).

4.4.2. (*R*)-*N*-[(*S*)-(4-Chlorophenyl)phenylmethyl]-2-methyl-2-propanesulfinamide, 4c. Obtained in 86% yield as an off-white solid, mp = 136–139°C. IR (KBr) υ 3443, 3212, 1601, 1490, 1454, 1364, 1059 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 7.37–7.26 (9H, m), 5.61 (1H, d, $J = 2.8$ Hz), 3.71 (1H, d, $J = 2.8$ Hz), 1.26 (9H, s). ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.13, 129.75, 133.46, 129.23, 128.97, 128.77, 128.03, 127.10, 61.39, 55.89, 22.64. HRMS calcd for $C_{17}H_{21}NSOCl$ (M+H), 321.1032; found 322.1019 (4.0 ppm).

4.4.3. (*R*)-*N*-[(*S*)-(4-Bromophenyl)phenylmethyl]-2-methyl-2-propanesulfinamide, 4d. Obtained in 89% yield as a white crystalline solid, mp = 136–137°C. IR (KBr) υ 3305, 3081, 2955, 1485, 1455, 1400, 1068, 1008 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 7.50–7.27 (9H, m), 5.60 (1H, d, $J = 2.8$ Hz), 3.73 (1H, bs), 1.25 (9H, s). ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.14, 141.40, 132.81, 130.68, 130.08, 129.14, 128.19, 122.70, 62.54, 57.00, 23.74.

4.4.4. (*R*)-2-Methyl-*N*-[(*S*)-phenyl[4-(trifluoromethyl)-phenyl]methyl]-2-propanesulfinamide, 4e. Obtained in 85% yield as a yellow oil. IR (neat) υ 3192, 2961, 1619, 1455, 1418, 1326, 1125, 1068 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 7.60–7.55 (4H, m), 7.36–7.25 (5H, m), 5.70 (1H, s), 3.76 (1H, s), 1.26 (9H, s). ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.29, 141.74, 129.08, 128.80, 128.23, 128.16, 127.82, 127.64, 127.18, 125.56, 61.62, 56.03, 22.63.

4.4.5. (*R*)-2-*N*-[(*S*)-(3-Furanyl)phenylmethyl]-2-methyl-2-propanesulfinamide, 4g. Obtained in 76% yield as a light yellow oil. IR (neat) υ 3196, 2978, 1503, 1474, 1455, 1364, 1157, 1058 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 7.40–7.28 (7H, m), 6.33 (1H, d, $J = 1.8$ Hz), 5.56 (1H, d, $J = 2.8$ Hz), 3.66 (1H, d, $J = 2.8$ Hz), 1.24 (9H, s). ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.46, 141.80, 140.51, 128.77, 127.95, 127.15, 126.34, 109.64, 55.72, 54.61, 22.58. HRMS calcd for $C_{15}H_{20}NO_2S$ (M+H), 278.1215; found 278.1216 (−0.4 ppm).

Compounds in Table 4.

4.4.6. (*R*)-*N*-[(*R*)-(4-Chlorophenyl)phenylmethyl]-2-methyl-2-propanesulfinamide, 4c. Obtained in 89% yield as an off-white solid, mp = 65–68°C. IR (KBr) υ 3446, 3194, 2959, 1490, 1455, 1364, 1089, 1060 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 7.38–7.26 (9H, m), 5.61 (1H, d, $J = 2.8$ Hz), 3.69 (1H, d, $J = 2.8$ Hz), 1.25 (9H, s). ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.10, 140.78, 133.60, 128.98, 128.67, 128.64, 127.85, 127.74, 61.61, 55.94, 22.61. HRMS calcd for $C_{17}H_{21}NSOCl$ (M+H), 321.1032; found 322.1020 (3.7 ppm).

4.4.7. (*R*)-2-Methyl-*N*-[(*R*)-(4-methylphenyl)phenylmethyl]-2-propanesulfinamide, 4i. Obtained in 85% yield as a off-white solid, mp = 59–61°C. IR (KBr) υ 3442, 2958, 1636, 1513, 1364, 1179, 1060 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 7.41–7.10 (9H, m), 5.61 (1H, d, $J = 2.8$ Hz), 3.68 (1H, d, $J = 2.8$ Hz), 2.30 (3H, s), 1.25 (9H, s). ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.39, 139.75, 137.51, 129.47, 128.49, 127.79, 127.52, 127.11, 61.84, 55.77, 22.64, 21.00. HRMS calcd for $C_{18}H_{24}NSO$ (M+H), 302.1578; found 302.1575 (1.0 ppm).

4.4.8. (*R*)-*N*-[(*R*)-(4-Methoxyphenyl)phenylmethyl]-2-methyl-2-propanesulfinamide, 4j. The diastereomeric ratio as determined by chiral HPLC was in agreement with that obtained from ^1H NMR analysis of the (*R*)-α-methoxyphenylacetic amide.[9] Obtained in 92% yield as a slight yellow oil. IR (film) υ 3444, 2958, 1511, 1455, 1252, 1057 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 7.41–7.27 (7H, m), 6.84 (2H, d, $J = 8.4$ Hz), 5.60 (1H, s), 3.76 (3H, s), 3.65 (1H, s), 1.25 (9H, s). ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.06, 141.51, 134.85, 128.47, 127.51, 114.13, 61.57, 55.79, 55.21, 22.66. HRMS calcd for $C_{18}H_{24}NSO_2$ (M+H), 318.1528; found 318.1515 (4.1 ppm).

4.4.9. (*R*)-*N*-[(*R*)-(4-Fluorophenyl)phenylmethyl]-2-methyl-2-propanesulfinamide, 4k. Obtained in 49% yield as an off-white solid, mp = 64–65°C. IR (KBr) υ 3448, 3202, 2960, 1603, 1509, 1455, 1223, 1059 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 7.40–7.26 (5H, m), 7.03–6.98 (2H, m), 5.63 (1H, d, $J = 2.8$ Hz), 3.67 (1H, d, $J = 2.8$ Hz), 1.26 (9H, s). ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.39, 160.95, 141.05, 138.44, 129.01, 128.93, 128.64, 127.74, 115.82, 115.61, 61.56, 55.90, 22.64. HRMS calcd for $C_{17}H_{21}NSOF$ (M+H), 306.1328; found 206.1319 (2.9 ppm).

4.4.10. (*R*)-2-Methyl-*N*-[(*R*)-phenyl(2,4,6-trimethylphenyl)methyl]-2-propanesulfinamide 4l. The diastereomeric ratio was determined by ^1H NMR analysis of the (*R*)-α-methoxyphenylacetamide derivative. Obtained in 76% yield as a slight yellow solid, mp = 60–63°C. IR (KBr) υ 3252, 2958, 1611, 1493, 1450, 1363, 1074 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 7.35–7.18 (5H, m), 6.84 (2H, s), 6.09 (1H, d, $J = 5.1$ Hz), 3.69 (1H, d, $J = 5.1$ Hz), 2.25 (9H, s), 1.32 (9H, s). ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.23, 137.33, 136.41, 136.21, 130.24, 128.15, 126.47, 126.28, 56.54, 22.82, 20.95. HRMS calcd for $C_{20}H_{28}NSO$ (M+H), 330.1891; found 330.1881 (3.0 ppm).

4.5. General procedure for the addition of lithium reagents to *N*-*tert*-butanesulfinyl aldimines

A solution of the *N*-*tert*-butanesulfinyl aldimine **3** (0.2 mmol) in dry THF (5 mL) at −78°C was treated with dropwise addition of the organolithium reagent (0.4 mmol). The reaction mixture was stirred at −78°C for 4 h then quenched with sat. aq. NH_4Cl. Aqueous workup and concentration followed by column chromatography through silica gel gave the purified compound. The diastereomeric ratio was determined by HPLC analysis of the unpurified amine hydrochloride formed after cleavage of the sulfinyl group (Chiracel AD column, 97:3:0.1 hexanes/EtOH/DEA; 1.0 mL/min; 215 nm).

4.5.1. (*R*)-2-Methyl-*N*-[(*R*)-1-naphthalenylphenylmethyl]-2-propanesulfinamide, 4b. Obtained in 84% yield as a light yellow oil. IR (film) υ 3441, 3205, 2959, 1510, 1474, 1455, 1364, 1058 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 8.32 (1H, d, $J=8.4$ Hz), 7.85 (1H, d, $J=7.4$ Hz), 7.79 (1H, dd, $J=6.5$ Hz, 2.8 Hz), 7.58–7.24 (9H, m), 6.45 (1H, d, $J=2.8$ Hz), 3.91 (1H, d, $J=2.8$ Hz), 1.23 (9H, s). ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.62, 137.57, 133.93, 130.49, 128.87, 128.65, 128.62, 128.47, 126.83, 125.87, 125.60, 125.23, 123.15, 57.61, 55.87, 22.61.

4.5.2. (*R*)-*N*-[(*R*)-(4-Chlorophenyl)phenylmethyl]-2-methyl-2-propanesulfinamide, 4c. Obtained in 78% yield as an off-white solid, mp = 77–80°C.

4.5.3. (*R*)-*N*-[(*R*)-(4-Bromophenyl)phenylmethyl]-2-methyl-2-propanesulfinamide, 4d. Obtained in 85% yield as a white solid, mp = 96–98°C. IR (KBr) υ 3442, 2959, 1634, 1486, 1403, 1364, 1058 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 7.45–7.24 (9H, m), 5.59 (1H, d, $J=2.8$ Hz), 3.71 (1H, d, $J=2.8$ Hz), 1.25 (9H, s). ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.60, 140.69, 131.90, 128.95, 128.65, 127.83, 127.72, 121.72, 61.64, 55.92, 22.59.

4.5.4. (*R*)-2-Methyl-*N*-[(*R*)-phenyl[4-(trifluoromethyl)-phenyl]methyl]-2-propanesulfinamide, 4e. Obtained in 92% yield as a yellow oil. IR (neat) υ 3191, 1619, 1474, 1455, 1325, 1165, 1068 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 7.59–7.28 (9H, m), 5.69 (1H, s), 3.79 (1H, s), 1.26 (9H, s). ^{13}C NMR (100 MHz, $CDCl_3$) δ 146.42, 140.39, 130.11, 129.80, 129.47, 128.77, 128.02, 127.79, 127.61, 125.79, 125.23, 61.90, 56.02, 22.58.

4.5.5. (*R*)-*N*-[[4-(Dimethylamino)phenyl]phenylmethyl]-2-methyl-2-propanesulfinamide, 4f. First diastereomer: obtained in 30% yield as a yellow solid. ^1H NMR (400 MHz, $CDCl_3$) δ 7.39–7.22 (7H, m), 6.68 (2H, d, $J=9.3$ Hz), 5.55 (1H, d, $J=2.8$ Hz), 3.69 (1H, d, $J=2.8$ Hz), 2.93 (6H, s), 1.25 (9H, s). Second diastereomer: obtained in 34% yield as a yellow solid. IR (KBr) υ 3215, 2956, 1614, 1522, 1060 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 7.43–7.19 (7H, m), 6.65 (2H, d, $J=8.4$ Hz), 5.57 (1H, d, $J=2.8$ Hz), 3.63 (1H, d, $J=2.8$ Hz), 2.90 (6H, s), 1.25 (9H, s). ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.01, 141.87, 130.42, 128.39, 128.20, 127.75, 127.29, 112.51, 61.54, 55.71, 40.44, 22.69.

4.5.6. (*R*)-2-*N*-[(*R*)-(3-Furanyl)phenylmethyl]-2-methyl-2-propanesulfinamide, 4g. Obtained in 64% yield as a light yellow oil. IR (neat) υ 3201, 2959, 1501, 1455, 1364, 1158, 1060 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 7.41–7.26 (7H, m), 6.39 (1H, s), 5.45 (1H, d, $J=3.2$ Hz), 3.65 (1H, d, $J=3.2$ Hz), 1.23 (9H, s). ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.64, 140.87, 140.08, 128.51, 127.79, 127.60, 127.18, 109.52, 55.03, 54.64, 22.53. HRMS calcd for $C_{15}H_{20}NO_2S$ (M+H), 278.1215; found 278.1203 (4.3 ppm).

4.6. General procedure for the cleavage of the sulfinyl chiral auxiliary

Compound **4** (0.12 mmol) was treated with a 1:1 mixture of MeOH and 4.0 M HCl in dioxane (2 mL) at room temperature for 1 h. The mixture was concentrated to dryness and precipitated with diethyl ether. The precipitate was collected by filtration and washed with diethyl ether to give the amine hydrochloride of sufficient purity such that no other purification was required.

4.6.1. (α^1S)-α-Phenyl-1-naphthalenemethanamine, 5b. Obtained in 94% yield as a white solid, mp = 245–250°C (dec.). IR (KBr) υ 3384, 2854, 2361, 1600, 1510, 1452 cm^{-1}. ^1H NMR (400 MHz, CD_3OD) δ 8.00–7.96 (3H, m), 7.70–7.64 (2H, m), 7.52–7.41 (7H, m), 6.45 (1H, s), 4.90 (5H, bs). ^{13}C NMR (100 MHz, CD_3OD) δ 138.32, 135.54, 133.55, 131.37, 130.72, 130.34, 130.11, 129.19, 128.10, 127.44, 126.16, 124.42, 124.13, 56.00. $[\alpha]_D^{23} = +0.22$ (c 0.9, MeOH). The amine hydrochloride was converted to the free amine by treatment with sodium carbonate. $[\alpha]_D^{23} = -17.8$ (c 0.6, $CHCl_3$). (lit.[10] $[\alpha]_D^{23} = +43.6$ (c 1.0, $CHCl_3$ for (R)).

4.6.2. (α^1R)-α-Phenyl-1-naphthalenemethanamine, 5b. Obtained in 94% yield as a white solid. $[\alpha]_D^{23} = -0.20$ (c 1.1, MeOH).

4.6.3. (α^1R)-4-Chloro-α-phenyl-benzenemethanamine, 5c. Obtained in 94% yield as a white solid, mp = 267–270°C. ^1H NMR (400 MHz, CD_3OD) δ 7.48–7.41 (9H, m), 5.87 (1H, s), 4.89 (3H, bs). ^{13}C NMR (100 MHz, CD_3OD) δ 138.13, 137.34, 136.01, 130.16, 128.32, 58.67. $[\alpha]_D^{23} = -0.33$ (c 1.0, MeOH). The amine hydrochloride was converted to the free amine by treatment with sodium carbonate. $[\alpha]_D^{23} = -1.0$ (c 1.0, EtOH). (lit.[5] $[\alpha]_D^{23} = +10.8$ (c 2.18, EtOH for (S)).

4.6.4. (α^1S)-4-Chloro-α-phenyl-benzenemethanamine, 5c. Obtained in 97% yield as a white solid. $[\alpha]_D^{23} = +0.30$ (c 1.0, MeOH).

4.6.5. (α^1S)-4-Bromo-α-phenyl-benzenemethanamine, 5d. Obtained in 80% yield as a white solid. ^1H NMR (400 MHz, CD_3OD) δ 7.63–7.61 (2H, m), 7.47–7.36 (7H, m), 5.68 (1H, s), 4.90 (3H, bs). $[\alpha]_D^{23} = +1.2$ (c 1.0, MeOH). (lit.[4] $[\alpha]_D^{23} = +2.3$ (c 1.0, MeOH for (S)).

4.6.6. (α^1R)-4-Bromo-α-phenyl-benzenemethanamine, 5d. Obtained in 88% yield as a white solid. $[\alpha]_D^{23} = -1.3$ (c 1.0, MeOH). (lit.[4] $[\alpha]_D^{23} = +2.3$ (c 1.0, MeOH for (S)).

4.6.7. (α^1R)-α-Phenyl-4-(trifluoromethyl)-benzenemethanamine, 5e. Obtained in 71% yield as a white solid. ^1H NMR (400 MHz, CD_3OD) δ 7.77 (2H, d, $J=7.9$ Hz), 7.65 (2H, d, $J=7.9$ Hz), 7.48–7.44 (5H, m), 5.81 (1H, s), 4.90 (3H, bs). $[\alpha]_D^{23} = +0.81$ (c 1.0, MeOH).

4.6.8. (α^1R)-α-Phenyl-4-(trifluoromethyl)-benzenemethanamine, 5e. Obtained in 75% yield as a white solid. $[\alpha]_D^{23} = -0.65$ (c 1.1, MeOH).

4.6.9. (α^3R)-α-Phenyl-3-furanmethanamine, 5g. Obtained in 81% yield as a white solid. ^1H NMR (400 MHz, CD_3OD) δ 7.59–7.43 (7H, m), 6.52 (1H, s), 5.59 (1H, s), 4.90 (3H, bs). ^{13}C NMR (100 MHz, CD_3OD) δ 145.82, 142.47, 137.90, 130.33, 128.37, 124.23, 110.19, 52.23. $[\alpha]_D^{23} = -0.42$ (c 2.0, MeOH).

4.6.10. (α^3R)-α-Phenyl-3-furanmethanamine, 5g. Obtained in 74% yield as a white solid. $[\alpha]_D^{23}=+0.17$ (*c* 1.3, MeOH).

4.6.11. (α^1R)-4-Methyl-α-phenyl-benzenemethanamine, 5i. Obtained in 87% yield as a white solid, mp = 256–259°C (dec.). ^{1}H NMR (400 MHz, CD_3OD) δ 7.47–7.39 (5H, m), 7.31–7.25 (4H, m), 5.60 (1H, s), 4.88 (3H, bs), 2.35 (3H, s). ^{13}C NMR (100 MHz, CD_3OD) δ 140.21, 138.72, 135.59, 130.83, 130.24, 129.95, 128.32, 59.20, 21.10. $[\alpha]_D^{23}=-0.16$ (*c* 1.0, EtOH).

4.6.12. (α^1R)-4-Methoxy-α-phenyl-benzenemethanamine, 5j. Obtained in 98% yield as a white solid, mp = 214–215°C (dec.). ^{1}H NMR (400 MHz, CD_3OD) δ 7.47–7.40 (5H, m), 7.33 (2H, d, $J=9.3$ Hz), 6.99 (2H, d, $J=9.3$ Hz), 5.60 (1H, s), 4.88 (3H, s), 3.80 (3H, bs). ^{13}C NMR (100 MHz, CD_3OD) δ 161.62, 138.80, 130.42, 130.23, 129.90, 128.14, 115.55, 58.95, 55.85. $[\alpha]_D^{23}=+0.28$ (*c* 1.5, MeOH).

4.6.13. (α^1R)-4-Fluoro-α-phenyl-benzenemethanamine, 5k. Obtained in 87% yield as a white solid. ^{1}H NMR (400 MHz, CD_3OD) δ 7.48–7.42 (7H, m), 7.22–7.18 (2H, m), 5.69 (1H, s), 4.89 (3H, bs). ^{13}C NMR (100 MHz, CD_3OD) δ 165.52, 163.06, 138.37, 134.70, 130.78, 130.70, 130.37, 130.11, 128.23, 117.19, 116.97, 58.66. $[\alpha]_D^{23}=+0.1$ (*c* 0.8, MeOH).

4.6.14. (α^1R)-2,4,6-Trimethyl-α-phenyl-benzenemethanamine, 5l. Obtained in 90% yield as a white solid. ^{1}H NMR (400 MHz, CD_3OD) δ 7.42–7.37 (3H, m), 7.20 (2H, d, $J=7.4$ Hz), 7.00 (2H, s), 6.06 (1H, s), 4.89 (3H, bs). ^{13}C NMR (100 MHz, CD_3OD) δ 140.54, 138.54, 137.80, 131.73, 131.34, 130.18, 129.28, 126.82, 54.08, 20.97, 20.87. $[\alpha]_D^{23}=+0.41$ (*c* 1.5, MeOH).

Acknowledgements

We thank Dr. William Brown and Dr. Christopher Walpole for valuable discussions and support and Mr. Edward Zhou for accurate mass determinations.

References

1. ARM434: Plobeck, N.; Delorme, D.; Wei, Z.-Y.; Yang, H.; Zhou, F.; Schwarz, P.; Gawell, L.; Gagnon, H.; Pelcman, B.; Schmidt, R.; Yue, S.-Y.; Walpole, C.; Brown, W.; Zhou, E.; Labarre, M.; Payza, K.; St-Onge, S.; Kamassah, A.; Morin, P.-E.; Projean, D.; Ducharme, J.; Roberts, E. *J. Med. Chem.* **2000**, *43*, 3878–3894.
2. SNC80: Calderon, S. N.; Rothman, R. B.; Porreca, F.; Flippen-Anderson, J. L.; McNutt, R. W.; Xu, H.; Smith, L. E.; Bilsky, E. J.; Davis, P.; Rice, K. C. *J. Med. Chem.* **1994**, *37*, 2125–2128.
3. Cetirizine: Opalka, C. J.; D'Ambra, T. E.; Faccone, J. J.; Bodson, G.; Cossement, E. *Synthesis* **1995**, 766–768.
4. Delorme, D.; Berthelette, C.; Lavoie, R.; Roberts, E. *Tetrahedron: Asymmetry* **1998**, *9*, 3963–3966 and references cited therein.
5. For a recent catalytic asymmetric synthesis of diarylmethylamines, see: Hayashi, T.; Ishigedani, M. *J. Am. Chem. Soc.* **2000**, *122*, 976–977.
6. Cogan, D. A.; Liu, G.; Ellman, J. A. *Tetrahedron* **1999**, *55*, 8883–8904 and references cited therein.
7. Liu, G.; Cogan, D. A.; Owens, T. D.; Tang, T. P.; Ellman, J. A. *J. Org. Chem.* **1999**, *64*, 1278–1284.
8. Fujisawa, T.; Kooriyama, Y.; Shimizu, M. *Tetrahedron Lett.* **1996**, *37*, 3881–3884.
9. López, B.; Quiñoá, E.; Riguera, R. *J. Am. Chem. Soc.* **1999**, *121*, 9724–9725.
10. Mokhallalati, M. K.; Pridgen, L. N. *Synth. Commun.* **1993**, *23*, 2055–2064.