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Asymmetric synthesis of diverse α,α-diarylmethylamines via aryl Grignard additions to chiral *N*-2,4,6-triisopropylbenzenesulfinylimines

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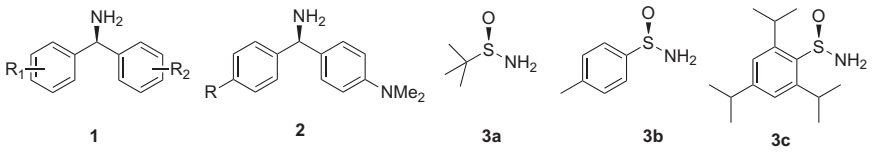
ABSTRACT

A mild method has been developed for the asymmetric synthesis of a variety of chiral diarylmethylamines via the addition of aryl Grignard reagents to chiral *N*-2,4,6-triisopropylbenzenesulfinylimines in high yields and high diastereoselectivities. Higher stereoselectivity was obtained for most of the examples studied when the reactions are performed at ambient temperature as compared to cryogenic conditions. *N*-2,4,6-Triisopropylbenzenesulfinamide was shown to be the optimal chiral auxiliary as it provided higher diastereoselectivities when compared to the more commonly employed *tert*-butanesulfinamide or *p*-toluenesulfinamide in the synthesis of diarylmethylamine synthons. A rationale for the improved selectivity derived from the triisopropylbenzyl auxiliary is presented.

1. Introduction

α,α-Diarylmethylamines **1** (Fig. 1) are components of many pharmaceutical and bioactive molecules.[1a–f,12] In the last decade, efforts have been devoted toward developing practical syntheses of these important synthons.[2–9] Methods for the synthesis of **1** via stereoselective addition of organometallic reagents to a suitable chiral imine species are reported including the catalytic asymmetric additions of arylboronic acids, aryl boroxines, or aryl titanium reagents to *N*-arylsulfonylimines, arylboronic acids to *N*-Boc imines,[8–11] phenylzinc reagents to masked *N*-formylimine,[12] and arylboronic acids[5,6,13] to chiral *N*-*tert*-butanesulfinyl or *N*-diphenylphosphinoyl imines with good to excellent stereoselectivity. However, few reports have addressed the asymmetric additions of aryl organometallic reagents to chiral sulfinylimines.[3,4]

The organometallic addition to chiral sulfinylimines would provide a direct and practical approach to chiral diarylmethylamines. We are interested in employing this chemistry in the synthesis of diarylmethylamines **2** that contain strong electron donating group. The synthesis of **2** via organometallic addition to *tert*-butanesulfinylarylaldimine was reported but the reaction was void of stereoselectivity.[4a] Additionally, few reports have studied the relationship between the structure of the chiral sulfinamides and the stereoselectivity of the corresponding organometallic addition. Recently, in the process development for the synthesis of (*S*)-cetirizene, we identified a hindered arenesulfinamide, 2,4,6-triisopropylbenzenesulfinamide (TIPPSA, **3c**) as the optimal chiral auxiliary in the synthesis of the key intermediate (*S*)-(4-chlorophenyl)phenylmethaneamine.[14,15] It was observed that the phenyl magnesium bromide addition to an aldimine derived from



1 2 3a 3b 3c

Fig. 1. Stuctures of diaryl methamines **1** and **2** and chiral benzenesulfinamides **3a**–**c**.

3c afforded the product in higher stereoselectivity than either *t*-BSA (**3a**) or *p*-TSA (**3b**). Herein we wish to report a detailed study on the application of TIPPSA in the synthesis of **2** with diverse functionalities under mild reaction conditions.

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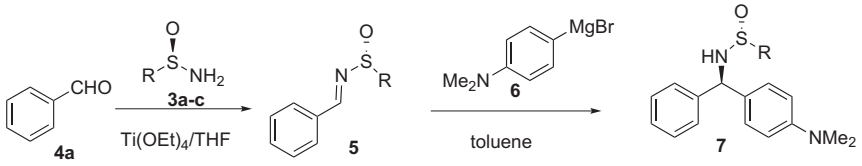
2. Results and discussions

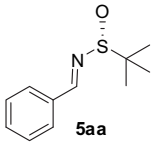
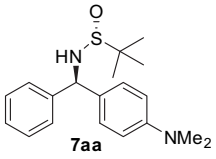
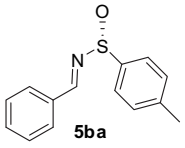
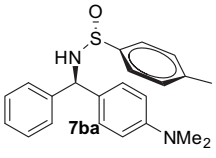
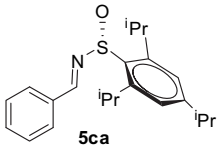
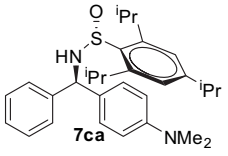
Chiral *tert*-butanesulfinamide (*t*-BSA) has been widely utilized as a chiral auxiliary in the synthesis of chiral amines through the addition of suitable nucleophiles to the corresponding chiral sulfinylimines.[16] Most notably, the bulky *tert*-butyl group of **3a** has been shown to offer improved facial discrimination because the bulky *tert*-butyl group maintains the desired conformation in the transition state for the nucleophilic addition.[20] However, studies have shown that in some cases the reactivity of the sulfinylimines was diminished due to the large size of *tert*-butyl moiety.[17] Recent reports have demonstrated that the use of 2,4,6-triisopropylbenzenesulfinamde (TIPPSA) overcame this limitation in the asymmetric process.[17–19] Since our first report on the synthesis of enantiopure TIPPSA,[3a] several reports have demonstrated that this chiral auxiliary not only allowed for retained reactivity but also provided the steric hindrance necessary for high stereoselectivity.[17–19] Therefore, the scope of the application of TIPPSA for the synthesis of diarylmethylamines with various functionalities was studied.

The effect of chiral sulfinamides on stereoselectivity was first studied in the synthesis of (4-*N*,*N*-dimethylaminophenyl)phenylmethaneamine **2a**. Recently, Plobeck and Powell[4a] studied the organometallic addition to the aldimine (**5aa**) derived from benzaldehyde and *t*-BSA and observed no reaction when the corresponding 4-(dimethylamino)phenyl magnesium bromide (**6**) was used. Therefore, our initial studies focused on the addition of **6** to aldimines **5aa**, **5ba**, and **5ca** that were prepared in excellent yield by the condensation of benzaldehyde with *t*-BSA, *p*-TSA, and TIPPSA in the presence of $Ti(OEt)_4$, respectively (Fig. 1).[3]

The reactions were first performed at −40 °C by the addition of 2 equiv of readily available Grignard **6** to an aldimine solution in toluene[15c] under an inert atmosphere (Table 1). The reactivity of the sulfinimines was similar, but the selectivity was proportional to the size of the substituent on the sulfinylimine. Using *t*-BSA as the auxiliary, the addition reaction was complete in about 30 min providing the desired product **7aa** in excellent yield and moderate selectivity (70% de). Reactions of the tolyl sulfinylimine **5ba** with **6** afforded the addition product in poor selectivity (16% de). However with TIPPSA as the auxiliary, the reaction was complete in 1 h and afforded the product **7ca** in good yield and 82% de.

Table 1
Results on the addition of **6** to aldimines **5aa**, **5ba**, and **5ca**



Imines **5**	Products **7**	Reaction temperature	
		−40 °C	rt
 **5aa**	 **7aa**	85:15 dr[a] 90% conversion[b] 30 min	84:16 dr 99% conversion 10 min
 **5ba**	 **7ba**	58:42 dr 88% conversion 1 h	65:35 dr 95% conversion 20 min
 **5ca**	 **7ca**	91:9 dr 95% conversion 1 h	91:9 dr 99% conversion 10 min

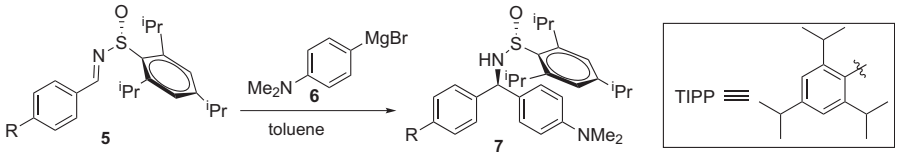
[a] Diastereomeric ratio (dr) based on ^{1}H NMR analysis of the benzylic proton and/or secondary amine proton of the crude product.
[b] Conversion is based on ^{1}H NMR analysis and verified by the isolated yields, which closely correlate with the reported conversions.

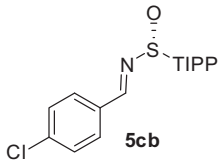
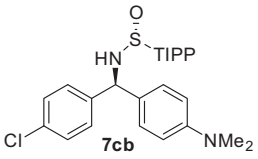
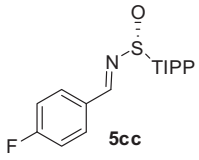
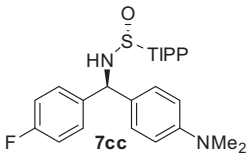
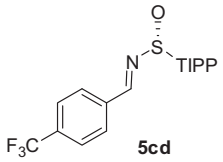
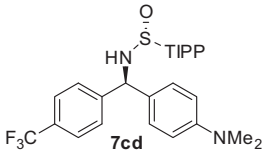
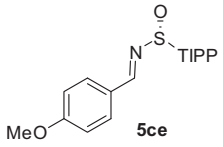
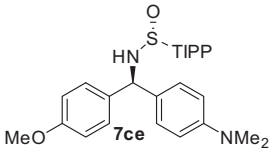
Due to the improved selectivity for the addition reactions with the TIPPSA as the chiral auxiliary, the synthesis of a variety of (4-*N*,*N*-dimethylaminophenyl)arylmethaneamines was studied. The reactions were first performed at −40 °C and it was observed that the electrophile had a noticeable effect on the reactivity and selectivity of the addition reactions. As mentioned above, that reaction of **6** with **5ca** at −40 °C proceeded to completion in about 1 h and provided the addition product **7ca** (91:9 dr). The corresponding additions of **6** to sulfinylimine **5cb**, **5cc**, and **5cd**, which contain the electron withdrawing chloride, fluoride, and trifluoromethyl functionality, respectively, was complete in less than 30 min and provided the addition products **7cb**, **7cc**, and **7cd** with drs of 86:14, 86:14, and 91:9, respectively. However, the reaction rate decreased dramatically for the reaction with *p*-methoxyphenyl sulfinylimine **5ce** in which only 83% conversion was observed after 20 h and afforded **7ce** (94:6 dr).

The temperature effect on the addition reactions was also investigated. Typically, lower reaction temperatures correspond to an increase in the stereoselectivity in a given asymmetric process. Interestingly, for the electron deficient aldimines an increase in

stereoselectivity was observed when the reactions were performed at ambient temperature as compared to −40 °C (Table 2). It should also be noted that with the electron donating *p*-methoxy aldimine **5ce** only a slight decrease in stereoselectivity was observed with the 40 °C increase in reaction temperature (−40 °C 88% de; rt 84% de). only 1.5 h. Similar results were observed using *p*-methoxylphenyl magnesium bromide. It was observed that, in most cases, the addition reaction to aryl sulfinylimines **5cc** or **5cd** that contain a strong electron withdrawing substituent is relatively faster and the stereoselectivity is moderate to good (72–88% de). Remarkably,

Table 2
Effects of temperature on the addition of Grignard reagent **6** to aldimines **5cb**–**ce**



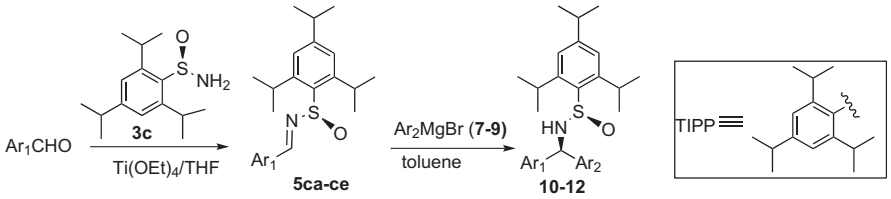
Imines **5**	Products **7**	Reaction temperature	
		−40 °C	rt
 **5cb**	 **7cb**	91:9 dr[a] 99% conversion[b] 45 min	93:7 dr 99% conversion 10 min
 **5cc**	 **7cc**	86:14dr 99% conversion 30 min	91:9 dr 99% conversion 10 min
 **5cd**	 **7cd**	86:14 dr 99% conversion 30 min	>95:5 dr 99% conversion 10 min
 **5ce**	 **7ce**	94:6 dr 83% conversion 20 h[c]	92:8 dr 99% conversion 10 min

[a] Diastereomeric ratio (dr) based on ^{1}H NMR analysis of the benzylic proton and/or secondary amine proton of the crude product. The 95:5 ratio indicates that the other diastereomer was not detected.
[b] Conversion is based on ^{1}H NMR analysis and verified by the isolated yields, which closely correlate to the reported conversions.
[c] The reaction was first conducted at −40 °C for about 4–6 h and then warmed slowly to rt and stirred for 15 h.

The scope of the TIPPSA chemistry was extended to the synthesis of a variety of diarylmethylamines with different aryl substituents. The addition reactions of Grignard reagents **7**–**9** to imines **5ca**–**ce** were first performed at −40 °C where the reaction time, conversion, and stereoselectivity were monitored (Table 3). It was observed that the nucleophilicity or electrophilicity of the reaction partners had a noticeable effect on the conversion. Slow reactions were observed for the addition of phenyl magnesium bromide **7** to **5cb** and **5ce** where the reaction was complete in 20 h. In contrast the reactions of **7** with **5cc** or **5cd**, which contained strong electron withdrawing F^- and CF_3^- groups was complete in the reaction of *p*-chlorophenyl magnesium bromide **9** with phenyl aldimine **5cc** was complete in 20 h but took 2 h with *p*-trifluoromethylphenyl aldimine **5cd** providing the desired product **12cc** and **12cd** in 82% de. This example highlights the impact of the substituent on the reactivity of the aldimines.

In order to make the asymmetric synthesis of the diarylmethylamines more practical, the corresponding organometallic additions were conducted at ambient temperatures (Table 3). A significant effect was observed for all of the reactions explored. First, the reaction rate was increased with complete conversions being obtained in 20–60 min. In the majority of examples surveyed we observed an

Table 3
Addition of Grignard reagents **7**–**9** to aldimines **5ca**–**ce** at −40 °C and rt in toluene for the synthesis of **10**–**12**



Imines **5**	Grignard			Reaction temperature
	7	**8**	**9**	
5ca		**11ca** 20 h,[c] 93:7,[b] 62%[a] 20 min, 94:6, 99%	**12ca** 20 h, 85:15, 90% 1 h, >95:5, 98%	−40 °C rt
5cb	**10cb** 20 h, 91:9, 86% 20 min, 93:7, 99%	**11cb** 20 h, 88:12, 65% 20 min, 92:8, 99%		−40 °C rt
5cc	**10cc** 1.5 h, 94:6, 90% 20 min, 95:5, 99%	**11cc** 1.5 h, 90:10, 98% 20 min, 93:7, 99%	**12cc** 20 h, 91:9, 92% 1 h, 91;9, 97%	−40 °C rt
5cd	**10cd** 1.5 h, 87:13, 97% 20 min,91:9, 99%	**11cd** 1.5 h, 87:13, 98% 20 min, 91:9, 99%	**12cd** 2 h, 91:9, 98% 1 h, 91:9, 99%	−40 °C rt
ce	**10ce** 20 h, >95:5, 56% 40 min,>95:5, 98%		**12ce** 20 h,>95:5, 87% 1 h, >95:5, 94%	−40 °C rt

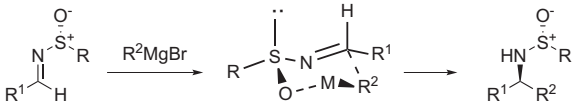
[a]Conversion is based on ^{1}H NMR analysis and verified by the isolated yields, which closely correlate to the reported conversions.
[b]Diastereomeric ratio (dr) determined by ^{1}H NMR analysis of the benzylic proton and/or secondary amine proton of the crude product. The 95:5 ratio indicates that the other diastereomer was not detected.
[c]The reaction was first conducted at −40 °C for about 4–6 h and then warmed slowly to rt and stirred for 15 h.

increase in stereoselectivity while performing the reactions at ambient temperatures as compared to cryogenic conditions. Selected examples include the selectivity for the reaction of phenyl Grignard reagent **7** with *p*-trifluoromethylphenyl sulfinylimine **5cd** in the synthesis of **10cd** increased from 74% de to 82% de and reaction of *p*-methoxyphenyl Grignard reagent **8** with **5cd** in the synthesis of **11cd** increased from 75% de to 82% de. More profoundly, the selectivity improved from 70% de to >90% de in the reaction of *p*-chlorophenyl magnesium bromide **9** with sulfinylimine **5ca**.

The opposite diastereomers can be readily accessed with improved selectivity by switching the nucleophile and electrophile components. It was observed that in each pair of the reactions the weaker nucleophile leads to a slightly improved stereoselectivity when the reaction was performed at ambient temperature. For example, the addition of phenyl magnesium bromide **7** to **5cb** provided **10cb** (93:7 dr) and the synthesis of the opposite diastereomer **12ca** by addition of *p*-chlorophenyl magnesium bromide **9** to **5ca** gave a dr >95:5. Similarly, addition of *p*-methoxylphenyl magnesium

bromide **8** to **5cb** provided **11cb** (92:8 dr), and the synthesis of the opposite diastereomer **12ce** by addition of *p*-chlorophenyl magnesium bromide **9** to **5ce** gave a dr >95:5.

Considering the improved selectivity of triisopropylbenzenesulfinylimines as compared to the *tert*-butanesulfinyl- and *p*-toluenesulfinylimines counterparts, a series of computations on these substrates were performed. Davis–Ellman proposes a chair-like transition state[20] (Scheme 1) to explain the origin of enantioselectivity in the organometallic addition to the sulfinylimines. The resulting stereoselectivity for the reaction will depend on the substrate and reaction conditions utilized. As for Grignard reagent additions, a six-membered ring transition state with Mg coordinated to the oxygen of the sulfinyl group was proposed. In this transition state, the bulky *tert*-butyl group is proposed to occupy the less hindered equatorial position thus directing the nucleophilic attack through the corresponding ring transition state. Reduced selectivity is observed once this six-membered ring transition state was interfered by coordinating solvents, such as Et_2O or THF. In conjunction with this model, in which the chiral substituent on the sulfinyl occupies the equatorial position, we can relate the enantiofacial control by the relative preference of each substitute to occupy the equatorial position of a cyclohexyl-ring system. This trend appears to hold true for the *p*-toluene, *tert*-butyl, and TIPP sulfinylimines (Table 4). The calculated energy difference between the equatorial and axial orientations for the *p*-toluene and *tert*-butyl (B3LYP 6-31*) substituents are 3.5 and 5.5 kcal/mol. These values are in close agreement with reported values of 2.9 for a phenyl substituent and >4.5 kcal/mol for the *tert*-butyl, respectively.[21] However for the TIPP group, due to the appended *ortho*-isopropyl functionalities on the benzene ring, the preference for equatorial orientation is greater at 14.6 kcal/mol (B3LYP 6-31*).[21,22] The high equatorial presence for the TIPP substituent can be attributed to the appended bulky *ortho iso*-propyl groups, which are drawn in close proximity to the ring system in the axial conformer. This effect is evident in the comparison of the de values in Table 4, which could suggest that the stereoselectivities are increased as the equatorial preference of the substituent was augmented.[23]



Scheme 1. Davis–Ellman's proposed model for the organometallic addition to chiral sulfinylimines.[21]

Table 4
Equatorial preferences (kcal/mol) of *tert*-butyl, *p*-toluene, and the TIPP groups

Substituent	B3LYP 6-31*	Literature	de[b]
	ΔG (kcal/mol)	ΔG (kcal/mol)[22]	
p-Toluene	3.5	2.9[a]	30%
tert-Butyl	5.5	>4.5	74%
TIPP	14.6	NA	86%

[a] Reported for the phenyl substituent.
[b] de of the corresponding reaction between the phenyl sulfinylimine and Grignard reagent **8**.[23]

3. Conclusion

A practical asymmetric methodology was developed for the synthesis of a variety of diarylmethanamines via the addition of aryl Grignard reagents to *N*-triisopropylbenzenesulfinylimines. Through the development of the chemistry with a focus on the effects of temperature, a mild and efficient process was identified. Higher conversions, reaction rates, and stereoselectivities were obtained in the synthesis of diarylmethylamines by conducting the reactions in toluene at ambient temperatures as compared to cryogenic conditions. The chiral auxiliary TIPPSA provides improved stereoselectivity as compared to *t*-BSA in the synthesis of diverse diary methylamines. Additionally, calculations were performed to determine the equatorial preference for the TIPP group in a cyclohexane ring system to be 14.6 kcal/mol and this is greater than the equatorial preference for the *tert*-butyl functionality. In accordance with the Davis–Ellman model for the organometallic addition to chiral sulfinylimines, the greater equatorial preference of the TIPP group accounts for the increased stereocontrol with this auxiliary.

4. Experimental

4.1. General information

^{1}H NMR and ^{13}C NMR spectra were recorded in deuteriochloroform on 400/500 MHz NMR spectrometers. Chemical shifts were reported in parts per million (ppm) from tetramethylsilane with the solvent resonance as the internal standard ($CDCl_3$: 7.26 ppm for ^{1}H NMR, 77.0 ppm for ^{13}C NMR; CD_3OD: 3.31 ppm for ^{1}H NMR). Abbreviations for signal coupling are as follows: s=singlet, d=doublet; t=triplet, q=quartet, dd=doublet of doublets, sep=septet m=multiplet. High resolution mass spectrum (ES, positive) was determined on a Thermo LTQ FT Ultra Mass Spectrometer. All materials were purchased from commercial suppliers and used without further purification unless otherwise noted.

4.2. Synthesis of sulfinylimines[3]

The characterization data of the following compounds **5aa**,[1,12] **5ba**,[1,12] and **5ca**[1,12] match that have been reported.

*4.2.1. (R_S)-N-(4-Chlorobenzylidene)-2,4,6-triisopropylbenzenesulfinamide, **5cb**.* ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.13 (d, J=6.8 Hz, 6H), 1.24 (d, J=6.9 Hz, 6H), 1.28 (d, J=6.8 Hz, 6H), 2.89 (sep, J=6.9 Hz, 1H), 3.82 (sep, J=6.8 Hz, 2H), 7.08 (s, 2H), 7.42 (d, J=8.5 Hz, 2H), 7.78 (d, J=8.5 Hz, 2H), 8.80 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 23.7, 23.7, 24.0, 24.3, 27.9, 34.4, 123.0, 129.3, 130.5, 132.8, 134.4, 138.5, 149.7, 152.9, 159.9; HRMS calculated for $C_{22}H_{29}NOSCl$ (M+1): 390.1658; found: 390.165 (0.357 ppm).

*4.2.2. (R_S)-N-(4-Fluorobenzylidene)-2,4,6-triisopropylbenzenesulfinamide, **5cc**.* ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.14 (d, J=6.8 Hz, 6H), 1.24 (d, J=6.9 Hz, 6H), 1.28 (d, J=6.8 Hz, 6H), 2.89 (sep, J=6.9 Hz, 1H), 3.84 (sep, J=6.8 Hz, 2H), 7.09 (s, 2H), 7.13 (t, J=8.6 Hz, 2H), 7.86 (dd, J=5.5, 8.8 Hz, 2H), 8.80 (s, 1H); ^{19}F NMR (376 MHz, $CDCl_3$) δ −106.05; ^{13}C NMR (100 MHz, $CDCl_3$) δ 23.7, 23.7, 24.0, 24.3, 27.9, 34.3, 116.1, 116.3, 122.9, 130.7, 130.8, 131.4, 131.5, 134.5, 149.7, 152.8, 159.8, 163.9, 166.5; HRMS calculated for $C_{22}H_{29}NOSF$ (M+1): 374.1954; found: 374.1949 (0.183 ppm).

*4.2.3. (R_S)-N-(4-Trifluoromethylbenzylidene)-2,4,6-triisopropylbenzenesulfinamide, **5cd**.* ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.14 (d, J=6.8 Hz, 6H), 1.25 (d, J=6.8 Hz, 6H), 1.30 (d, J=6.8 Hz, 6H), 2.90 (sep, J=6.9 Hz, 1H), 3.83 (sep, J=6.8 Hz, 2H), 7.10 (s, 2H), 7.71 (d, J=8.2 Hz, 2H), 7.97 (d, J=8.1 Hz, 2H), 8.90 (s, 1H); ^{19}F NMR (376 MHz, $CDCl_3$) δ −63.00; ^{13}C NMR (100 MHz, $CDCl_3$) δ 23.6, 23.7, 24.0, 24.3, 28.0, 34.4, 123.0, 125.9 (q), 129.5, 133.4, 133.8, 134.0, 137.1, 149.8, 153.0, 159.9; HRMS

calculated for $C_{23}H_{29}F_3NOS$ (M+1): 424.1922; found: 424.1918 (0.191 ppm).

4.2.4. (R_S)-N-(4-Methoxybenzylidene)-2,4,6-triisopropylbenzenesulfinamide, ***5ce***. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.15 (d, J=6.8 Hz, 6H), 1.24 (d, J=6.8 Hz, 6H), 1.29 (d, J=6.8 Hz, 6H), 2.89 (sep, J=6.9 Hz, 1H), 3.85 (s, 3H), 3.87 (sep, J=6.8 Hz, 2H), 6.94 (d, J=8.8 Hz, 2H), 7.08 (s, 2H), 7.80 (d, J=8.8 Hz, 2H), 8.76 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 23.7, 23.7, 24.0, 24.3, 27.9, 34.3, 55.4, 114.3, 122.8, 127.5, 131.2, 135.0, 149.6, 152.6, 160.3, 162.9; HRMS calculated for $C_{23}H_{32}NO_2S$ (M+1): 385.2154; found: 386.214 (0.316 ppm).

4.3. General procedure for the Grignard addition to sulfinylimines at ambient temperatures

To a stirred solution of sulfinylarylaldimine (2–3 mmol) in toluene (1.0 M) under an argon atmosphere at rt was added the Grignard reagent dropwise and the reaction was monitored by TLC. When completed, the reaction was quenched with and the product was extracted with EtOAc. The organic phase was separated and dried over (Na_2SO_4), concentrated, and analyzed by ^{1}H NMR. The products were then isolated by flash silica chromatography.

4.4. General procedure for the Grignard addition to sulfinylimines at −40 °C

To a stirred solution of sulfinylarylaldimine (2–3 mmol) in toluene (1.0 M) under an argon atmosphere at −40 °C (dry ice/CH_3CN) was added the Grignard reagent dropwise. The progress of the reactions was monitored by TLC analysis. If the reaction was not complete within 4–6 h, the reaction was allowed to warm to rt and stirred overnight. The reaction was then quenched with water and the mixture was extracted with EtOAc. The organic phase was separated, dried over Na_2SO_4, concentrated, and analyzed by ^{1}H NMR.

Compound **7ca**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.19 (d, J=6.9 Hz, 6H), 1.23 (d, J=6.7 Hz, 6H), 1.26 (d, J=6.7 Hz, 6H), 2.85 (s, 6H) 2.87 (sep, J=7.0 Hz, 1H), 2.90 (s, 6H), 3.95 (br s, 2H), 4.78 (major, d, J=1.9 Hz, 1H), 4.80 (minor, d, J=2.5 Hz, 0.10H), 5.69 (minor, 2.2 Hz, 0.10H), 5.71 (major, d, J=1.8 Hz, 1H), 6.62 (d, J=8.8 Hz, 2H), 7.07 (s, 2H), 7.19 (d, J=9.0 Hz, 2H), 7.31 (t, J=7.8 Hz, 2H), 7.46 (d, J=7.9 Hz, 2H); ^{13}C NMR (400 MHz) δ 23.8, 24.3, 24.5, 28.2, 34.4, 40.5, 61.7, 112.7, 123.1, 128.1, 128.2, 128.3, 128.5, 129.1, 130.3, 137.9, 141.3, 148.0, 150.1, 152.0; HRMS calculated for $C_{30}H_{41}N_2O_2S$ (M+1): 477.2940; found: 477.2936 (0.288 ppm).

Compound **7cb**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.19 (d, J=6.9 Hz, 6H), 1.24 (d, J=6.7 Hz, 6H), 1.26 (d, J=6.7 Hz, 6H), 2.87 (sep, J=7.0 Hz, 1H), 2.90 (s, 6H), 3.92 (br s, 2H), 4.72 (minor, d, J=2.9 Hz, 0.11H), 4.76 (major, d, J=1.8 Hz, 1H), 5.65 (minor, J=2.8 Hz, 0.09H), 5.69 (major, d, J=1.4 Hz, 1H), 6.62 (d, J=8.6 Hz, 2H), 7.07 (s, 2H), 7.16 (d, J=8.7 Hz, 2H), 7.30 (d, J=8.5 Hz, 2H), 7.42 (d, J=8.5 Hz, 2H); ^{13}C NMR (400 MHz) δ 23.8, 24.2, 24.5, 28.1, 34.3, 40.5, 60.8, 112.6, 123.2, 128.0, 128.6, 129.4, 129.6, 133.3, 137.6, 139.9, 148.0, 150.2, 152.2; HRMS calculated for $C_{30}H_{40}N_2OClS$ (M+1): 512.2550; found: 511.2546 (0.391 ppm).

Compound **7cc**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.19 (d, J=6.7 Hz, 6H), 1.23 (d, J=6.7 Hz, 6H), 1.26 (d, J=6.3 Hz, 6H), 2.87 (m, 1H), 2.89 (s, 6H), 3.92 (br s, 2H), 4.72 (minor, s, 0.09H), 4.76 (major, s, 1H), 5.66 (minor, s, 0.09H), 5.69 (major, s, 1H), 6.63 (d, J=8.6 Hz, 2H), 7.06 (s, 2H), 7.17 (d, J=8.4 Hz, 2H), 7.24 (m, 2H), 7.45 (m, 2H); ^{13}C NMR (400 MHz) δ 23.8, 24.2, 24.5, 28.1, 34.3, 40.4, 40.6, 60.9, 112.6, 112.7, 123.1, 128.0, 129.1, 129.6, 129.7, 129.9, 137.0, 137.6, 148.0, 150.1, 152.0; HRMS calculated for $C_{30}H_{39}FN_2OS$: 494.2467.

Compound **7cd**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.20 (d, J=6.8 Hz, 6H), 1.24 (d, J=6.8 Hz, 6H), 1.27 (d, J=6.5 Hz, 6H), 2.88 (sep, J=7.0 Hz, 1H), 2.88 (s, 6H), 3.92 (br s, 2H), 4.78 (minor, d, J=3.0 Hz, 0.12H), 4.79 (major, d, J=1.9 Hz, 1H), 5.72 (minor, J=2.8 Hz, 0.12H), 5.77 (major, d, J=1.5 Hz, 1H), 6.62 (d, J=8.7 Hz, 2H), 7.08 (s, 2H), 7.17 (d, J=9.0 Hz, 2H), 7.58–7.62 (m, 4H); ^{13}C NMR (400 MHz) δ 23.8, 24.2, 24.4, 28.2, 34.4, 40.4, 61.1, 112.6, 116.7, 123.2, 125.4–125.5 (m), 128.1, 128.3, 129.1, 137.5, 145.7, 148.0, 150.3, 152.2; HRMS calculated for $C_{31}H_{40}F_3N_2OS$ (M+1): 545.2813; found: 545.2809 (0.280 ppm).

Compound **7ce**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.20 (d, J=6.9 Hz, 6H), 1.23 (d, J=6.9 Hz, 6H), 1.26 (d, J=6.6 Hz, 6H), 2.86 (sep, J=7.0 Hz, 1H), 2.86 (s, 6H), 3.77 (s, 3H), 3.96 (br s, 2H), 4.74 (minor, d, J=2.9 Hz, 0.07H), 4.76 (major, d, J=1.8 Hz, 1H), 5.65 (minor, J=2.8 Hz, 0.07H), 5.67 (major, d, J=1.6 Hz, 1H), 6.62 (d, J=8.8 Hz, 2H), 6.73 (d, J=8.4 Hz, 2H), 6.86 (d, J=8.6 Hz, 2H), 7.06 (s, 2H), 7.40 (d, J=8.7, 2H); ^{13}C NMR (400 MHz) δ 23.8 (2C), 24.3 (2C), 24.5 (2C), 28.1 (2C), 34.4, 40.6 (2C), 55.3, 61.1, 112.6 (2C), 113.8, 123.1 (2C), 128.0 (2C), 129.1 (2C), 129.2 (2C), 130.6, 133.3, 137.9, 148.0 (2C), 150.1, 151.8, 159.1; HRMS calculated for $C_{31}H_{43}N_2O_2S$ (M+1): 507.3045; found: 507.3041 (0.301 ppm).

Compound **10cb**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.19 (d, J=6.8 Hz, 6H), 1.24 (d, J=6.8 Hz, 6H), 1.26 (d, J=6.5 Hz, 6H), 2.89 (sep, J=7.0 Hz, 1H), 3.92 (br s, 2H), 4.77 (minor, d, J=2.7 Hz), 4.80 (major, d, J=2.3 Hz, 1H), 5.75 (minor, d, J=2.9 Hz), 5.77 (major, d, J=2.3 Hz, 1H), 7.07 (s, 2H), 7.23–7.26 (m, 1H), 7.28–7.34 (m, 6H), 7.41–7.44 (m, 2H); ^{13}C NMR (400 MHz) δ 23.7, 23.8, 24.1, 24.4, 28.2, 34.3, 61.3, 123.2, 127.1, 128.0, 128.7, 129.0, 129.5, 133.7, 137.4, 139.2, 142.0, 148.0, 152.2; HRMS calculated for $C_{28}H_{35}NOSCl$ (M+1): 468.2128; found: 468.2123 (0.223 ppm).

Compound **10cc**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.19 (d, J=6.7 Hz, 6H), 1.24 (d, J=6.8 Hz, 6H), 1.25 (d, J=7.2 Hz, 6H), 2.88 (sep, J=7.1 Hz, 1H), 3.92 (br s, 2H), 4.76 (minor, d, J=2.2 Hz), 4.82 (major, d, J=1.8 Hz 1H), 5.76 (minor), 5.77 (major, d, J=1.6 Hz, 1H), 7.04 (t, J=8.5 Hz, 2H), 7.07 (s, 2H), 7.22–7.26 (m, 1H), 7.29–7.35 (m, 4H), 7.43–7.47 (m, 2H); ^{13}C NMR (400 MHz) δ 23.7, 23.8, 24.1, 24.4, 28.2, 34.3, 61.3, 115.4, 115.6, 123.2, 127.1, 128.0, 128.9, 129.7, 129.8, 136.3, 137.4, 142.2, 148.0, 152.2, 161.2, 163.6; HRMS calculated for $C_{28}H_{35}NOSF$ (M+1): 452.2423; found: 452.2419 (0.218 ppm).

Compound **10cd**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.19 (d, J=6.7 Hz, 6H), 1.24 (d, J=7.0 Hz, 6H), 1.26 (d, J=6.6 Hz, 6H), 2.88 (sep, J=6.9 Hz, 1H), 3.92 (br s, 2H), 4.81 (minor, d, J=3.3 Hz), 4.84 (major, d, J=2.4 Hz, 1H), 5.82 (minor, d, J=3.15 Hz), 5.85 (major, d, J=2.3 Hz, 1H), 7.08 (s, 2H), 7.24–7.27 (m, 1H), 7.29–7.35 (m, 4H), 7.62 (s, 4H); ^{13}C NMR (400 MHz) δ 23.7, 23.8, 24.1, 24.4, 28.2, 34.3, 61.5, 123.2, 125.5, 125.6, 125.9, 126.9, 127.2, 128.1, 128.2, 128.4, 129.1, 137.2, 141.6, 144.8, 148.0, 152.3; HRMS calculated for $C_{29}H_{35}NOF_3S$ (M+1): 502.2391; found: 502.2388 (0.382 ppm).

Compound **10ce**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.19 (d, J=6.8 Hz, 6H), 1.24 (d, J=6.9 Hz, 6H), 1.26 (d, J=6.5 Hz, 6H), 2.87 (sep, J=6.8 Hz, 1H), 3.70 (s, 3H), 3.92 (br s, 2H), 4.77 (minor, d, J=2.50 Hz, 0.04H), 4.81 (major, d, J=2.53 Hz, 1H), 5.74 (d, J=2.35 Hz, 1H), 6.88 (d, J=8.3 Hz, 2H), 7.07 (s, 2H), 7.20–7.24 (m, 1H), 7.29 (t, J=7.8 Hz, 2H), 7.35–7.4 (m, 4H); ^{13}C NMR (400 MHz) δ 23.7, 23.8, 24.1, 24.5, 28.1, 34.3, 55.3, 61.6, 114.0, 123.1, 127.1, 127.7, 128.8, 129.3, 132.5, 137.7, 142.7, 148.0, 152.0, 159.3; HRMS calculated for $C_{29}H_{38}NO_2S$ (M+1): 464.2623; found: 464.2619 (0.176 ppm).

Compound **11ca**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.19 (d, J=6.8 Hz, 6H), 1.24 (d, J=6.9 Hz, 6H), 1.26 (d, J=6.5 Hz, 6H), 2.87 (sep, J=6.8 Hz, 1H), 3.70 (s, 3H), 3.92 (br s, 2H), 4.77 (major, d, J=2.50 Hz 1H), 4.81 (minor, d, J=2.53 Hz), 5.74 (d, J=2.35 Hz, 1H), 6.82 (d, J=8.3 Hz, 2H), 7.07 (s, 2H), 7.25–7.30 (m, 3H), 7.34 (t, J=7.8 Hz, 2H), 7.46 (m, 2H); ^{13}C NMR (400 MHz) δ 23.7, 23.8, 24.1, 24.5, 28.1, 34.3, 55.3, 61.6, 113.9, 114.2, 123.1, 127.7, 128.0, 128.4, 128.5, 129.5, 134.7, 137.8, 141.0, 148.0 (2C), 152.0, 159.1; HRMS calculated for $C_{29}H_{38}NO_2S$ (M+1): 464.2623; found: 464.2619 (0.306 ppm).

Compound **11cb**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.19 (d, J=6.8 Hz, 6H), 1.24 (d, J=7.0 Hz, 6H), 1.26 (d, J=6.9 Hz, 6H), 2.88 (sep, J=7.0 Hz, 1H), 3.75 (s, 3H), 3.92 (br s, 2H), 4.76 (d, J=2.2 Hz, 1H), 5.70 (minor,

d, J=2.7 Hz), 5.72 (major, J=2.0 Hz, 1H), 6.83 (d, J=8.7 Hz, 2H), 7.07 (s, 2H), 7.24 (d, J=8.7 Hz, 2H), 7.32 (d, J=8.1 Hz, 2H), 7.41 (d, J=8.43 Hz, 2H); ^{13}C NMR (400 MHz) δ 23.7, 23.8, 24.2, 24.4, 28.1, 34.3, 55.3, 60.8, 114.3, 123.2, 128.4, 128.7, 129.3, 129.4, 133.5, 134.2, 137.5, 139.5, 148.0, 152.2, 159.3; HRMS calculated for $C_{29}H_{37}NO_2SCl$ (M+1): 498.2324; found: 498.2229 (0.109 ppm).

Compound **11cc**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.20 (d, J=6.9 Hz, 6H), 1.24 (d, J=7.0 Hz, 6H), 1.26 (d, J=6.9 Hz, 6H), 2.88 (sep, J=6.9 Hz, 1H), 3.75 (s, 3H), 3.92 (br s, 2H), 4.75 (minor, d, J=2.6 Hz, 0.08H), 4.77 (major, d, J=2.1 Hz, 1H), 5.72 (minor, d, J=2.7 Hz, 0.08H), 5.73 (major, 2.1 Hz, 1H), 6.83 (d, J=8.8 Hz, 2H), 7.03 (t, J=8.7 Hz, 2H), 7.07 (s, 2H), 7.26 (d, J=8.7 Hz, 2H), 7.42–7.47 (m, 2H); ^{13}C NMR (400 MHz) δ 23.8, 24.2, 24.4, 28.1, 34.3, 55.3, 60.8, 114.3, 115.3, 155.5, 123.2, 128.3, 129.6, 129.7, 134.4, 136.6 (d, J=3.2 Hz, 1C), 137.5, 148.0, 152.1, 159.2, 163.6; HRMS calculated for $C_{29}H_{37}NO_2SF$ (M+1): 482.2529; found: 482.2524 (0.091 ppm).

Compound **11cd**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.20 (d, J=7.0 Hz, 6H), 1.24 (d, J=6.9 Hz, 6H), 1.26 (d, J=6.6 Hz, 6H), 2.88 (sep, J=6.8 Hz, 1H), 3.75 (s, 3H), 3.92 (br s, 2H), 4.80 (d, J=2.2 Hz, 1H) 5.77 (minor, d, J=2.7 Hz, 0.11H), 5.81 (major, d, J=2.0 Hz, 1H), 6.84 (d, J=8.7 Hz, 2H), 7.08 (s, 2H), 7.25 (d, J=8.6 Hz, 2H), 7.61 (s, 4H); ^{13}C NMR (400 MHz) δ 23.7, 23.8, 24.1, 24.4, 28.2, 34.3, 55.3, 61.0, 114.4, 123.2, 125.5 (q, J=3.75 Hz), 127.1, 128.2, 128.9, 133.8, 137.4, 145.2, 148.0, 152.3, 159.4; HRMS calculated for $C_{30}H_{37}NO_2F_3S$ (M+1): 532.2497; found: 532.2493 (0.314 ppm).

Compound **12ca**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.19 (d, J=6.9 Hz, 6H), 1.24 (d, J=6.8 Hz, 6H), 1.26 (d, J=6.5 Hz, 6H), 2.87 (sep, J=6.8 Hz, 1H), 3.92 (br s, 2H), 4.78 (major, d, J=2.7 Hz, 1H), 4.81 (minor, d, J=2.3 Hz, 0.07H), 5.74 (major, d, J=2.7 Hz 1H), 5.77 (minor, d, J=2.3 Hz, 0.07H), 7.08 (s, 2H), 7.23–7.26 (m, 1H), 7.28–7.34 (m, 6H), 7.41–7.44 (m, 2H); ^{13}C NMR (400 MHz) δ 23.7, 23.8, 24.2, 24.4, 28.2, 34.3, 61.7, 123.2, 127.9, 128.1, 128.6, 128.7, 129.0, 133.6, 137.5, 140.3, 141.0, 148.0, 152.2; HRMS calculated for $C_{28}H_{35}ClNOS$ (M+1): 468.21218; found: 468.2124 (0.297 ppm).

Compound **12cc**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.20 (d, J=6.6 Hz, 6H), 1.24 (d, J=6.5 Hz, 6H), 1.25 (d, J=5.9 Hz, 6H), 2.88 (sep, J=6.9 Hz, 1H), 3.92 (br s, 2H), 4.75 (minor, d, J=2.2 Hz, 0.09H), 4.77 (major, d, J=1.9 Hz 1H), 5.74 (d, J=2.5 Hz, 1H), 7.04 (t, J=8.7 Hz, 2H), 7.08 (s, 2H), 7.28 (2, 4H), 7.38–7.43 (m, 2H); ^{13}C NMR (400 MHz) δ 23.7, 23.8, 24.1, 24.4, 28.1, 34.3, 60.9, 115.5, 115.7, 123.2, 128.5, 129.1, 129.6, 129.7, 133.8, 135.9, 136.0, 137.2, 140.7, 148.0, 152.3; HRMS calculated for $C_{28}H_{34}ClFNOS$ (M+1): 468.2034; found: 468.2030 (0.351 ppm).

Compound **12cd**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.20 (d, J=7.0 Hz, 6H), 1.24 (d, J=6.7 Hz, 6H), 1.26 (d, J=6.2 Hz, 6H), 2.89 (sep, J=6.8 Hz, 1H), 3.92 (br s, 2H), 4.80 (d, J=2.6 Hz, 1H), 5.81 (minor, d, J=2.8 Hz, INCON), 5.82 (major, d, J=2.7 Hz, 1H) 7.09 (s, 2H), 7.29 (s, 4H), 7.56–7.64 (m, 4H); ^{13}C NMR (400 MHz) δ 23.8 (2C), 24.1 (2C), 24.4 (2C), 28.1 (2C), 34.3, 54.6, 123.0 (4C), 127.1 (2C), 127.1, 128.5 (2C), 128.6, 128.7, 129.4, 131.1, 132.4, 138.0, 142.8, 147.7 (2C), 151.8; HRMS calculated for $C_{29}H_{34}F_3ClNOS$ (M+1): 536.2002; found: 536.1998 (0.325 ppm).

Compound **12ce**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.20 (d, J=6.9 Hz, 6H), 1.24 (d, J=6.6 Hz, 6H), 1.25 (d, J=5.4 Hz, 6H), 2.88 (sep, J=7.0 Hz, 1H), 3.80 (s, 3H), 3.92 (br s, 2H), 4.75 (d, J=1.9 Hz, 1H), 5.69 (major, d, J=2.4 Hz, 1H), 5.73 (minor, J=2.0 Hz), 6.88 (d, J=8.6 Hz, 2H), 7.07 (s, 2H), 7.25–7.35 (m, 6H); ^{13}C NMR (400 MHz) δ 23.7, 23.8, 24.2 (2C), 24.4 (2C), 28.1 (2C), 34.3, 55.3, 61.2, 114.1 (2C), 123.1 (2C), 128.5 (2C), 129.0 (2C), 129.2 (2C), 132.2, 133.5, 137.5, 141.2, 148.0 (2C), 152.1, 159.4; HRMS calculated for $C_{29}H_{37}ClNO_2S$ (M+1): 498.2234; found: 498.2230 (0.310 ppm).

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Supplementary data

Additional procedures, spectral data and characterizations (^{1}H and ^{13}C NMR), and HRMS of all new products. Supplementary data associated with this article can be found in online version at doi:10.1016/j.tet.2011.07.019.

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21. Calculations performed with the Spartan '08 program on a Windows XP PC employing the B3LYP 6-31* level of theory.
22. Several twist boat conformers were found at 7.5 kcal/mol higher than the equatorial conformation. In order to obtain a more direct comparison between the *tert*-butyl and TIPP substituents, the conformation of the cyclohexane ring was constrained to match the axial *tert*-butyl cyclohexane system before the conformation search.
23. The stereoselectivities for the addition of 4-methyoxyphenyl magnesium bromide **8** to **5aa**, **5ba**, and **5ca** are 84:16 dr, 62:28 dr, and 93:7 dr at −40 °C and 85:15 dr, 64:36 dr, and 94:6 dr at ambient temperature, respectively.