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Practical Asymmetric Synthesis of α-Branched 2-Piperazinylbenzylamines by 1,2-Additions of Organometallic Reagents to *N*-*tert*-Butanesulfinyl Imines

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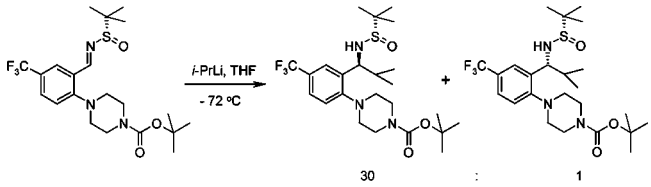

2-[4-(*tert*-Butoxycarbonyl)piperazinyl]benzylidene-*tert*-butanesulfinamides underwent nucleophilic 1,2-addition with different organometallic reagents to give highly diastereomerically enriched adducts. X-ray crystallography of the resulting α-branched *N*-Boc-2-piperazinylbenzyl-*tert*-butanesulfinamides confirms different mechanisms depending on the organometallic reagent used. Differential deprotection of the *N*-Boc and the *tert*-butanesulfinamides was investigated, and the dehydration byproducts have been identified and characterized. To avoid the formation of byproducts in the acidic deprotection step, the *N*-*tert*-butanesulfinamide group was converted to the corresponding *N*-*tert*-butanesulfonamide (Bus), which allowed for clean orthogonal deprotection. The efficient synthesis and deprotection of the *N*-Boc-2-piperazinylbenzyl-*tert*-butanesulfinamides herein described constitutes an attractive method for extensive structure−activity studies in the search for novel ligands of the human melanocortin 4 receptor.

Introduction

Benzylamines are ubiquitous structures in organic and medicinal chemistry. Many benzylamines are present in molecules that display important pharmacological activities.[1] During the course of a medicinal chemistry program aimed at discovering small molecule ligands of the human melanocortin type 4 receptor (MC4R), we found that various compounds possessing the 2-piperazinylbenzylamine core displayed excellent biological activities at that receptor.[2] To better explore and understand the structure−activity relationships (SAR) of this novel class of molecules, we needed to synthesize α-branched piperazinylbenzylamines in asymmetric fashion. The synthetic method of choice would have to satisfy a few requirements, including excellent enantio- or diastereoselectivity, predictability of the stereochemical outcome of the reaction, and employment of readily available starting materials. In addition, it would be desirable to find a method robust enough to allow for the kilogram preparation of intermediates during eventual preclinical studies.

Among the existing methods for the preparation of optically pure benzylamines bearing a stereogenic center at the α-position, those involving the nucleophilic addition of an organometallic reagent to a C=N imine bond, where a stereodirecting group originates on the nitrogen atom, stood out due to the operational simplicity and the availability of commercial starting materials.[3] The chiral

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(1) For a few examples see: (a) Tucci F. C.; Zhu Y.-F.; Struthers R. S.; Guo Z.; Gross T. D.; Rowbottom M. W.; Acevedo O.; Gao Y.; Saunders J.; Xie Q.; Reinhart G. J.; Liu X.-J.; Ling N.; Bonneville A. L. K.; Chen T.-K.; Bozigian H.; Chen C. *J. Med. Chem.* **2005**, *48*, 1169−1178. (b) Ekhato V.; Huang, Y. *J. Labelled Compd. Radiopharm.* **1997**, *39*, 1020−1038. (c) Macdonald, S. J. F.; Clarke, G. D. E.; Dowle, M. D.; Harrison, L. A.; Hodgson, S. T.; Inglis, G. G. A.; Johnson, M. R.; Shah, P.; Upton, R. J.; Walls, S. B. *J. Org. Chem.* **1999**, *64*, 5166−5175.

(2) Chen, C.; Pontillo, J.; Fleck, B. A.; Gao, Y.; Wen, J.; Tran, J. A.; Tucci, F. C.; Foster, A. C.; Saunders: J. *J. Med. Chem.* **2004**, *49*, 6821−6830.

(3) For reviews on asymmetric additions of organometallic reagents to C=N bonds see: (a) Bloch, R. *Chem. Rev.* **1998**, *98*, 1407−1438. (b) Kobayashi, S.; Ishitani, H. *Chem. Rev.* **1999**, *99*, 1069−1094. (c) Giuseppe Alvaro, G.; Savoia, D. *Synlett* **2002**, 651−673. (d) Enders, D.; Reinhold: U. *Tetrahedron: Asymmetry* **1997**, *8*, 1895−1946. (e) Weinreb, S. M.; Orr, R. K. *Synthesis* **2005** 1205−1227.

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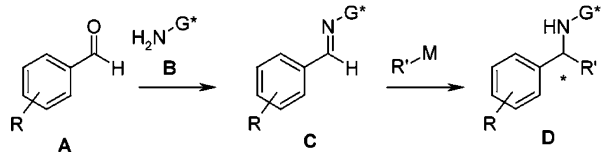
SCHEME 1



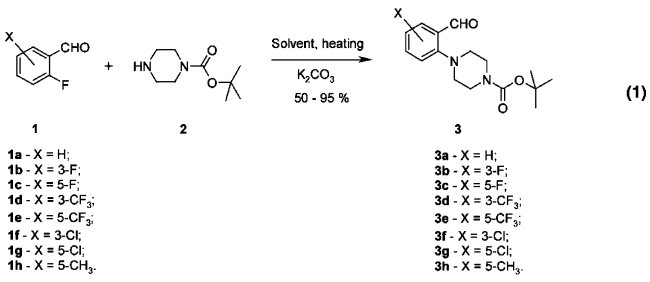
imine **C** is readily prepared from a condensation reaction of a benzaldehyde **A** and a chiral amine **B**, and after organometallic addition, the protected enantiopure benzylamine **D** is obtained. Depending on the nature of the stereodirecting group (**G**), it can also function as a protecting group for the newly formed benzylamine (Scheme 1).

Our group chose the addition of organometallic reagents to chiral *N*-sulfinyl imines developed by Davis and Ellman,[4] since it fulfilled all of the requirements mentioned earlier. Thus, the benzaldehyde of choice is condensed with either enantiomer of *N*-*tert*-butanesulfinamide (reagent **B**, Scheme 1) to yield the corresponding chiral *N*-sulfinyl aldimine (compound **C**, Scheme 1). This, in turn, reacts with an organometallic reagent (Grignard or alkyllithium) to produce the final compound (**D**, Scheme 1).

In this paper, we report our efforts on the application of the Ellman−Davis method to the asymmetric synthesis of 2-piperazinylbenzylamines bearing an α-substituent.

Results and Discussion

a. Preparation of 2-Piperazinylbenzaldehydes. The preparation of the starting materials in our synthetic sequence, the 2-piperazinylbenzaldehydes, was accomplished by the aromatic nucleophilic substitution (S_NAr) reaction between the appropriately substituted 2-fluorobenzaldehyde **1a**−**1h** and *N*-Boc-piperazine **2** (eq 1).[5]



(1)

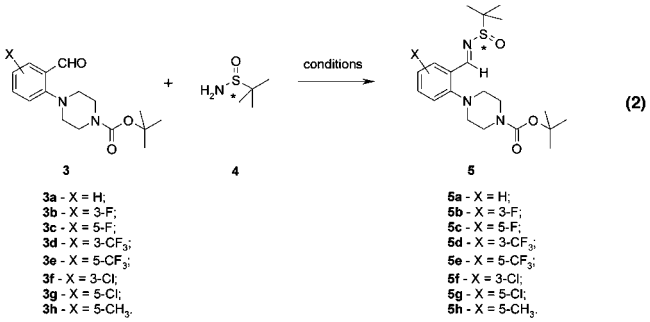
The results are summarized in Table 1. Most reactions were conducted in a similar manner as reported by Reinhoudt and co-workers, i.e., using DMF as the solvent and K_2CO_3 as the base, at high temperatures (110−150 °C).[5] For a few substrates, however, the reaction was sluggish under those conditions, and upon prolonged heating, in addition to starting materials, several byproducts resulting from decomposition of *N*-Boc-piperazine and DMF were observed. For instance, when 2,3-difluorobenzaldehyde (**1b**) was heated to 110 °C in the presence of 2 equiv of *N*-Boc-piperazine and K_2CO_3, in DMF, only 45% yield of product was observed, in conjunction with varying amounts of *N*,*N*-dimethylamino displacement of the fluorine at the 2-position (entry 2, Table 1). Changing the reaction solvent and temperature to refluxing 1,4-dioxane (101 °C) not only avoided the occurrence of the *N*,*N*-dimethylamino impurity but it also suppressed the decomposition of *N*-Boc-piperazine, allowing it to react with the substrate, albeit at a slower rate (entry 3, Table 1). The S_NAr of 2-fluoro-5-methylbenzaldehyde (**1h**) was very sluggish in DMF due to the presence of the deactivating methyl group at the 5-position (entry 11, Table 1). In this case, the reaction had to be conducted in dimethylacetamide (DMA) in order to allow a higher reaction temperature (155 °C). In most cases, the products were isolated after a standard workup, followed by recrystallization of the crude from a mixture of hexanes and EtOAc.

TABLE 1. Reaction Conditions for the Aromatic Nucleophlic Substitutions of Fluorobenzaldehydes 1 and *N*-Boc-piperazine 2

entry	reactant	product	conditions	yield (%)
1	**1a**	**3a**	DMF, 130 °C, 18 h	71[a,e]
2	**1b**	**3b**	DMF, 110 °C, 21 h	45[d]
3	**1b**	**3b**	1,4-dioxane, 101 °C, 48 h	75[b,e]
4	**1c**	**3c**	DMF, 140 °C, 18 h	32[c,d]
5	**1c**	**3c**	DMSO, 80 °C, 20 h	8[d]
6	**1d**	**3d**	DMF, 110 °C, 24 h	67[c,e]
7	**1e**	**3e**	DMF, 130 °C, 2 h	92[a,e]
8	**1e**	**3e**	DMSO, 80 °C, 24 h	64[d]
9	**1f**	**3f**	DMF, 110 °C, 12 h	20[a,e]
10	**1g**	**3g**	DMF, 100 °C, 16 h	13[c,d]
11	**1h**	**3h**	DMF, 130 °C, 36 h	20[e]
12	**1h**	**3h**	DMA, 155 °C, 22 h	61[b,d]

[a] Purification was conducted by trituration with hexanes. [b] Purification was conducted by crystallization from hexanes or a mixture of EtOAc and hexanes. [c] Purification was conducted by silica gel chromatography. [d] Two equivalents of *N*-Boc-piperazine was used. [e] One equivalent of *N*-Boc-piperazine were used.

b. Preparation of the *N*-Sulfinyl Imines. Benzaldehydes **3a**−**h** were then converted to the corresponding *N*-*tert*-butanesulfinyl imines by condensation with either enantiomer of *N*-*tert*-butanesulfinamide (eq 2).



(2)

Initially, several conditions were investigated, including the use of anhydrous $MgSO_4$, as suggested by earlier studies of Ellman and co-workers.[6] In their investigations, they found that in the case of aromatic aldehydes, an excess of the former was needed in order to drive the

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(6) Liu, G.; Cogan, D. A.; Owens, T. D.; Tang, T. P.; Ellman, J. A. *J. Org. Chem.* **1999**, *64*, 1278−1284 and references therein.

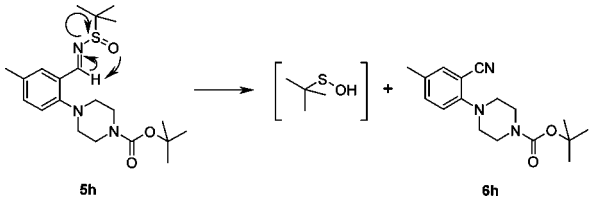
TABLE 2. Reaction between Benzaldehydes 3a−h and *N-tert*-Butanesulfinamides 4 under Various Conditions (eq 2)

entry	benzaldehyde	*n-tert*-butanesulfinamide	product	conditions	reagent	yield (%)[a]
1	**3a**	*Ss*-**4**	*Ss*-**5a**	THF, rt, 14 h	$Ti(OEt)_4$	73[c,d]
2	**3b**	*Ss*-**4**	*Ss*-**5b**	THF, rt, 16 h	$Ti(OEt)_4$	100[b]
3	**3b**	*Rs*-**4**	*Rs*-**5b**	THF, rt, 18 h	$Ti(OEt)_4$	90[c]
4	**3b**	*Ss*-**4**	*Ss*-**5b**	CH_2Cl_2, reflux, 48 h	Cs_2CO_3	91[c]
5	**3c**	*Ss*-**4**	*Ss*-**5c**	THF, rt, 16 h	$Ti(OEt)_4$	94[b]
6	**3c**	*Rs*-**4**	*Rs*-**5c**	THF, rt, 7 h	$Ti(OEt)_4$	100[b]
7	**3d**	*Ss*-**4**	*Ss*-**5d**	THF, rt, 16 h	$Ti(OEt)_4$	90[b]
8	**3e**	*Ss*-**4**	*Ss*-**5e**	THF, rt, 16 h	$Ti(OEt)_4$	100[b]
9	**3e**	*Ss*-**4**	*Ss*-**5e**	CH_2Cl_2, reflux, 24 h	Cs_2CO_3	88[c]
10	**3e**	*Ss*-**4**	*Ss*-**5e**	THF, rt, 24 h	−	−
11	**3e**	*Ss*-**4**	*Ss*-**5e**	CH_2Cl_2, rt, 24 h	$MgSO_4$	−
12	**3f**	*Ss*-**4**	*Ss*-**5f**	THF, rt, 24 h	$Ti(OEt)_4$	97[b]
13	**3f**	*Rs*-**4**	*Rs*-**5f**	THF, rt, 24 h	$Ti(OEt)_4$	100[b]
14	**3g**	*Ss*-**4**	*Ss*-**5g**	THF, rt, 16 h	$Ti(OEt)_4$	91[c,d]
15	**3h**	*Ss*-**4**	*Ss*-**5h**	THF, rt, 16 h	$Ti(OEt)_4$	99[c]
16	**3h**	*Ss*-**4**	*Ss*-**5h**	CH_2Cl_2, reflux, 48 h	Cs_2CO_3	9[e]

[a] Isolated yields of pure products. [b] Product triturated with hexanes. [c] Purification was performed by recrystallization from EtOAc or hexane/EtOAc mixtures. [d] Purification performed by silica gel chromatography. [e] Slow conversion. After prolonged heating decomposition was observed.

reaction to completion when $MgSO_4$ was used as the dehydrating agent.[6] In our efforts to identify an efficient synthetic route to the desired α-branched benzylamines, we purposely avoided reaction conditions that relied on the use of an excess of either reacting partner. In the absence of any catalyst, no reaction occurred between benzaldehyde **3e** and (*S*)-*N-tert*-butanesulfinamide *Ss*-**4** in THF (entry 10, Table 2). When the same benzaldehyde **3e** was allowed to react with an equimolar amount of sulfinamide *Ss*-**4**, in CH_2Cl_2 in the presence of anhydrous $MgSO_4$ at room temperature, very little product was observed, even after prolonged reaction times (>24 h) (entry 11, Table 2). The condensations proved more efficient by the use of 4 equiv of the powerful Lewis acid and dehydrating agent $Ti(OEt)_4$.[7] Thus, by performing the reaction in THF at ambient temperature, it was possible to accomplish the condensation between **3e** and *Ss*-**4** in quantitative yield (entry 8, Table 2). The same methodology was applied to other benzaldehydes **3a**−**h** with similar results. Both enantiomers of sulfinamide **4** participated in the condensation with similar efficiency (entries 3, 6, and 13, Table 2). The reactions were normally completed within 2 h at ambient temperature, and the workup consisted of pouring the entire reaction mixture onto a brine solution. The titanium oxide salts that formed were promptly removed by filtration through a pad of Celite, and the product could be obtained by washing the cake with an organic solvent such as EtOAc or CH_2Cl_2. After solvent removal, the resulting *N*-sulfinyl imines were of sufficient purity (>95% by HPLC) to be used in the next step without further purification. In several cases, however, the resulting imines were recrystallized from hexanes/EtOAc to achieve greater purity.

Despite the fact that $Ti(OEt)_4$ was a powerful catalyst for the condensation described above, its use in large-scale reactions generated large amounts of titanium oxides byproducts and required tedious vacuum filtration and washing of the cake with copious amounts of solvents. A recent report by Nakata's group described the use of Cs_2CO_3 as a catalyst for the condensation between aldehydes and sulfinamides.[8] When we applied this method to our system, we were delighted to find that for benzaldehydes activated by an electron-withdrawing group (**3b** and **3e**) the reactions proceeded to give the desired products in excellent yields (entries 4 and 9, Table 2). The conversions were typically 96% after 24 h of reflux in CH_2Cl_2, and the workup was greatly simplified by decantation of the solid Cs_2CO_3 and filtration. Upon concentration, the product was obtained in pure form after recrystallization from hexanes/EtOAc. Yields were greater than 85% in both cases. When benzaldehyde **3h**, containing an electron-donating methyl group at the 5-position, was reacted with (*S*)-*N-tert*-butanesulfinamide **4a** in refluxing CH_2Cl_2, in the presence of 1.05 equiv of Cs_2CO_3, a very slow conversion to the corresponding imine was observed (entry 16, Table 2). Upon prolonged heating, thermal decomposition of the imine via syn elimination to give the corresponding benzonitrile and the transient sulfenic acid was observed (eq 3). This is not unprecedented, since similar processes have been reported, first by Davis[9] and later by Ellman.[10]



5h **6h** (3)

The geometry of the *N-tert*-butanesulfinyl imines synthesized herein was determined by a combination of NMR spectroscopy and X-ray crystallography. In all cases, only one species was observed by ^1H and ^{13}C NMR spectroscopy. The X-ray crystal structures of *N*-sulfinyl imines *Ss*-**5b**, *Ss*-**5e**, and *Ss*-**5g** are shown in Figure 1 and confirm the presence of the *E* geometry only. The enan-

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(10) Mukade, T.; Dragoli, D. R.; Ellman, J. A. *J. Comb. Chem.* **2003**, *5*, 590−596.

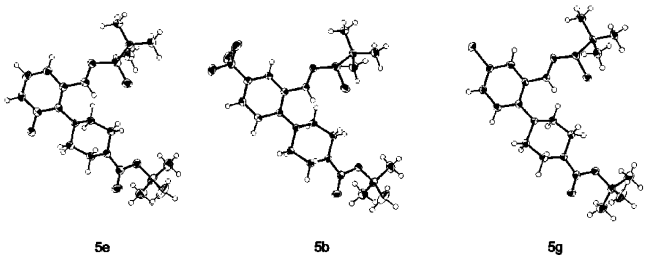
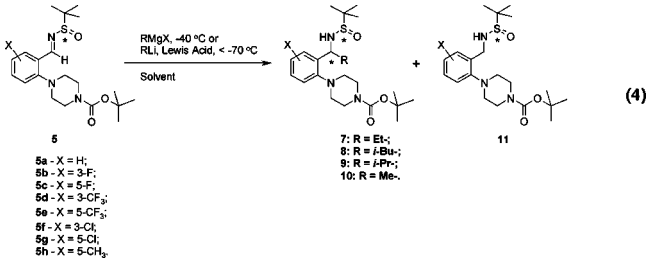


FIGURE 1. ORTEP representations of the X-ray structures of *N-tert*-butanesulfinyl imines *Ss*-**5b**, *Ss*-**5e**, and *Ss*-**5g**.

tiomeric purities of the products were maintained, according to chiral HPLC.

c. Asymmetric Addition of Organometallics across the C=N Imine Double Bond. The results of our investigations on the asymmetric additions of organolithium and organomagnesium reagents to *N-tert*-butanesulfinyl imines **5a**−**h** are summarized in Table 3. We started our studies by looking into the addition of Grignard reagents to *N-tert*-butanesulfinyl imine *Ss*-**5b**. Grignard reagents are easily prepared from alkyl or aryl halides or can be purchased from commercial sources. In contrast, only a few alkyl- and aryllithium reagents are available commercially, and they are much less trivial to prepare, especially in larger quantities. When a solution of EtMgBr was added slowly to compound *Rs*-**5b**, in CH_2Cl_2 at −40 °C, the starting material was completely consumed and a mixture of 1:10 of the *Rs,R*-**7b** and *Rs,S*-**7b**, respectively, resulted (eq 4). In addition,



(4)

ca. 8% of the reduction product **11b** was observed (entry 1, Table 3). Addition of *i*-BuMgBr under the same conditions, however, led to the production of **11b** as the major product, with little *Rs,S*-**8b** present (entry 2, Table 3). Other solvents were investigated, such as THF, toluene, and Et_2O, but none was able to suppress the formation of **11b**. In fact, in the cases of toluene and Et_2O, the conversions were poor, on the order of 20% or lower (entries 4 and 5, Table 3). The presence of a Lewis acid, such as Me_3Al, did not lead to any improvement when the solvent was toluene (entry 6, Table 3). At this point we turned our attention to alkyllithium reagents in an attempt to utilize some of the knowledge acquired by Ellman and co-workers on the use of Lewis acids to

TABLE 3. Organometallic Additions to *N-tert*-Butanesulfinyl Imines 5a-h

entry	substrate	reagent	Lewis acid	solvent	product(s)	ratio[a]	yield (%)[b]
1	*Rs*-**5b**	EtMgBr	−	CH_2Cl_2	*Rs,R*-**7b**/*Rs,S*-**7b**/**11b**	1:10:1	94[c]
2	*Rs*-**5b**	*i*-BuMgBr	−	CH_2Cl_2	*Rs,S*-**8b**/**11b**	1:10	93[c]
3	*Rs*-**5b**	*i*-BuMgBr	−	THF	*Rs,S*-**8b**/**11b**	6:5	95[c]
4	*Rs*-**5b**	*i*-BuMgBr	−	$PhCH_3$	*Rs,S*-**8b**/**11b**	1:5	N/A[d]
5	*Rs*-**5b**	*i*-BuMgBr	−	Et_2O	*Rs,S*-**8b**/**11b**	1:3	N/A[d]
6	*Rs*-**5b**	*i*-BuMgBr	Me_3Al	$PhCH_3$	*Rs,S*-**8b**/**11b**	1:5	N/A[d]
7	*Ss*-**5a**	*i*-BuLi	−	THF	*Ss,S*-**8a**/*Ss,R*-**8a**[g]	7:1	67[c]
8	*Ss*-**5a**	*i*-BuLi	Me_3Al	THF	*Ss,S*-**8a**/*Ss,R*-**8a**[g]	6:1	70[c]
9	*Ss*-**5b**	*i*-BuLi	−	THF	*Ss,S*-**8b**/*Ss,R*-**8b**[f]	7:1	58[c]
10	*Ss*-**5b**	*i*-BuLi	Me_3Al	THF	*Ss,S*-**8b**/*Ss,R*-**8b**	12:1	60[e]
11	*Rs*-**5b**	*i*-BuLi	Et_3Al	THF	*Rs,R*-**8b**/*Rs,S*-**8b**	5:1	70[c]
12	*Ss*-**5b**	*i*-BuLi	Oct_3Al	THF	*Ss,S*-**8b**/*Ss,R*-**8b**	6:1	70[c]
13	*Rs*-**5c**	*i*-BuLi	Me_3Al	THF	*Rs,R*-**8c**/*Rs,S*-**8c**[g]	13:1	87[c]
14	*Rs*-**5d**	*i*-BuLi	Me_3Al	THF	*Rs,R*-**8d**/*Rs,S*-**8d**[g]	10:1	90[c]
15	*Ss*-**5d**	*i*-BuLi	−	THF	*Ss,S*-**8d**/*Ss,R*-**8d**	7:1	67[c]
16	*Ss*-**5d**	*i*-BuLi	Me_3Al	THF	*Ss,S*-**8d**/*Ss,R*-**8d**[g]	10:1	90[c]
17	*Ss*-**5e**	*i*-BuLi	−	THF	*Ss,S*-**8e**/*Ss,R*-**8e**[g]	7:1	67[c]
18	*Ss*-**5e**	*i*-BuLi	Me_3Al	THF	*Ss,S*-**8e**/*Ss,R*-**8e**[g]	18:1	59[c]
19	*Ss*-**5g**	*i*-BuLi	Me_3Al	THF	*Ss,S*-**8g**/*Ss,R*-**8g**[g]	13:1	65[c]
20	*Ss*-**5h**	*i*-BuLi	−	THF	*Ss,S*-**8h**/*Ss,R*-**8h**[g]	7:1	61[c]
21	*Ss*-**5h**	*i*-BuLi	Me_3Al	THF	*Ss,S*-**8h**/*Ss,R*-**8h**[g]	12:1	79[c]
22	*Ss*-**5a**	*i*-PrLi	−	THF	*Ss,S*-**9a**/*Ss,R*-**9a**[g]	20:1	57[e]
23	*Ss*-**5a**	*i*-PrLi	Me_3Al	THF	*Ss,S*-**9a**/*Ss,R*-**9a**	11:1	52[e]
24	*Ss*-**5b**	*i*-PrLi	−	THF	*Ss,S*-**9b**/*Ss,R*-**9b**[f]	12:1	67[e]
25	*Ss*-**5b**	*i*-PrLi	Me_3Al	THF	*Ss,S*-**9b**/*Ss,R*-**9b**	12:1	67[e]
26	*Ss*-**5b**	*i*-PrLi	Oct_3Al	THF	*Ss,S*-**9b**/*Ss,R*-**9b**	6:1	50[e]
27	*Ss*-**5c**	*i*-PrLi	−	THF	*Ss,S*-**9c**/*Ss,R*-**9c**[g]	10:1	81[c]
28	*Ss*-**5e**	*i*-PrLi	−	THF	*Ss,S*-**9e**/*Ss,R*-**9e**[f]	30:1	59[e]
29	*Ss*-**5e**	*i*-PrLi	Me_3Al	THF	*Ss,S*-**9e**/*Ss,R*-**9e**	12:1	54[e]
30	*Ss*-**5g**	*i*-PrLi	−	THF	*Ss,S*-**9g**/*Ss,R*-**9g**[g]	20:1	82[c]
31	*Ss*-**5g**	*i*-PrLi	Me_3Al	THF	*Ss,S*-**9g**/*Ss,R*-**9g**	10:1	41[c]
32	*Ss*-**5h**	*i*-PrLi	Me_3Al	THF	*Ss,S*-**9h**/*Ss,R*-**9h**[f]	11:1	71[c]
33	*Rs*-**5c**	MeLi	−	THF	*Rs,R*-**10c**/*Rs,S*-**10c**[f]	2:1	68[c]
34	*Rs*-**5c**	MeLi	Me_3Al	THF	*Rs,R*-**10c**/*Rs,S*-**10c**	1.5:1	46[c]

[a] Ratios were determined by reverse phase HPLC/MS. [b] Yields refer to isolated amounts of the major diastereomer. [c] Purification performed by silica gel chromatography. [d] Conversions for these reactions were usually lower than 20%. [e] Major diastereomer purified by crystallization. [f] Configuration determined by X-ray crystallography. [g] Configurations were determined by correlation with similar compounds.

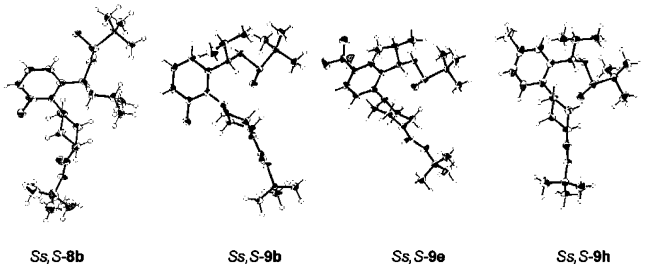


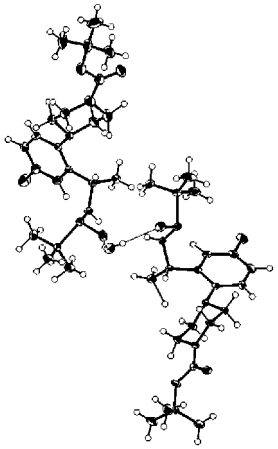
FIGURE 2. ORTEP representations of the X-ray structures of *N-tert*-butanesulfinamides *Ss,S*-**8b**, *Ss,S*-**9b**, *Ss,S*-**9e**, and *Ss,S*-**9h**.

improve reactivity and diastereoselectivity of the additions to *N-tert*-butanesulfinyl imines.[11]

Dropwise addition of *i*-BuLi to a chilled (−72 °C) solution of *Ss*-**5b** in THF, in the absence of any additives, resulted in the formation of products *Ss,S*-**8b** and *Ss,R*-**8b** in 7:1 ratio, respectively. Most importantly, no reduction product was observed. The major diastereomer *Ss,S*-**8b** was isolated in 58% after silica gel chromatography (entry 9, Table 3). When the reaction was conducted in the presence of 2 equiv of Me_3Al, the ratio of diastereomers was increased to 12:1, favoring compound *Ss,S*-**8b**. Alternatively to chromatography, the major product could be isolated in pure form and in good yield (60%) after recrystallization from hexanes/EtOAc (entry 10, Table 3). The stereochemical assignment was conducted by X-ray crystallography of *Ss,S*-**8b** (Figure 2). Interestingly, the stereochemical outcome of the *i*-BuLi reaction is the opposite of the *i*-BuMgBr one. We briefly investigated the nature of the aluminum Lewis acid. When bulkier Et_3Al and *n*-Oct_3Al were utilized in lieu of Me_3Al, the *i*-BuLi additions to either *Rs*-**5b** or *Ss*-**5b** gave approximately the same diastereomeric ratio (5−6:1), both inferior to that of Me_3Al. The sense of stereochemical induction followed the Me_3Al case, i.e., *Ss*-**5b** gave rise to a new stereocenter of *S*-configuration, whereas *Rs*-**5b** gave rise to an *R*-center (entries 11 and 12, Table 3).

Other substrates, when subjected to the Me_3Al-mediated additions of *i*-BuLi, gave good to excellent diastereoselectivities and good overall yields (entries 13, 14, 16, 18, 19 and 21, Table 3). We found that, in all cases, the diastereoselectivity is dependent on the rate and temperature at which the organolithium reagent is introduced. Higher selectivities are obtained when the internal reaction temperature remains below −70 °C. Lower selectivities resulted when the reactions were run in the absence of Me_3Al (entries 15, 17, and 20, Table 3).

Marked differences in selectivities were observed when *i*-PrLi was utilized instead. For instance, addition of *i*-PrLi to sulfinyl imine *Ss*-**5a**, in THF at −72 °C, resulted in an excellent 20:1 mixture of *Ss,S*-**9a** and *Ss,R*-**9a**, respectively (entry 22, Table 3). When the same addition was performed in the presence of 2 equiv of Me_3Al, the same sense of stereochemical induction was observed, albeit in an inferior 11:1 ratio (entry 23, Table 3). Similar results were obtained with the remaining substrates *Ss*-**5b**, *Ss*-**5c**, *Ss*-**5e**, *Ss*-**5g**, and *Ss*-**5h** (entries 24−32, Table 3). In those cases, the reactions conducted in the absence of any additives gave excellent diastereoselectivities that were at least equal to, if not better than, those of the Me_3Al-mediated additions. In all cases examined herein, where the (*S*)-*N-tert*-butanesulfinyl group was utilized as the chiral auxiliary, the newly created stereocenter in the major product had *S*-configuration, as ascertained by X-ray crystallography of compounds *Ss,S*-**9b**, *Ss,S*-**9e**, and *Ss,S*-**9h** (Figure 2). The stereochemistry of the other compounds obtained in this study were assigned by correlation with similar compounds, based on TLC and spectroscopic behavior. Similarly to the *i*-BuLi additions, use of bulkier *n*-Oct_3Al as the Lewis acid led to a decrease in diastereoselectivity (entry 26, Table 3).



Rs,S-**10c**

FIGURE 3. ORTEP representation of the X-ray structure of *N-tert*-butanesulfinamide *Rs,S*-**10c**. The unit cell consists of two molecules of *Rs,S*-**10c** hydrogen-bonded through a molecule of H_2O.

Finally, addition of MeLi to *Rs*-**5c**, in the presence of Me_3Al, gave a nonselective mixture of *Rs,R*-**10c** and *Rs,S*-**10c** in a 1.5:1 ratio, respectively (entry 34, Table 3). The same reaction, when preformed in the absence of Me_3Al, gave essentially the same ratio (entry 33, Table 3). The stereochemical assignment of the reaction products was based on the X-ray crystal structure of the minor isomer (Figure 3). We attribute the lack of selectivity in this particular reaction to the size of the alkyllithium reagent used, since the bulkier *i*-PrLi and *i*-BuLi, under similar conditions, gave much greater diastereomeric ratios.

d. Mechanistic Rationale. In view of our results described above, it is clear that there are two operating manifolds in the asymmetric addition of organometallics to the chiral *N-tert*-butanesulfinyl imines. When Grignard reagents are used, for instance, in the addition to *N-tert*-butanesulfinyl imine *Rs*-**5b**, a chelation-controlled model is valid, where Mg coordinates with the oxygen of the sulfinyl imine, leading to a six-membered transition state. This is in accordance to the model proposed by Ellman and co-workers.[10] In this case, both the bulky *tert*-butyl group and the aryl moiety adopt equatorial positions, allowing the delivery of the R group from the same face. The stereodirecting ability of this chelation-controlled model dictates that, when the sulfur configuration is *R* (*Rs*), the newly formed chiral center of the major product should have the *S* configuration (Figure 4). Given

(11) Cogan, D. A.; Liu, G.; Ellman, J. A. *Tetrahedron* **1999**, *55*, 8883−8904.

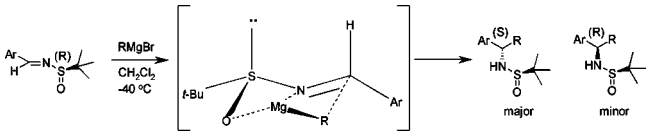


FIGURE 4. Model predictive of the "chelation-controlled" addition of Grignard reagents to *N-tert*-butanesulfinyl imines.

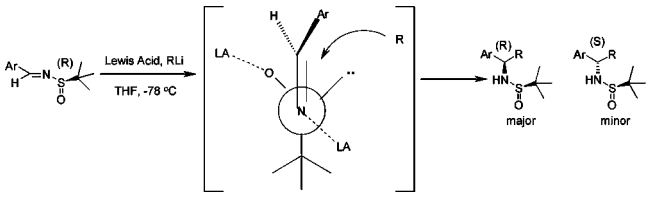


FIGURE 5. Model predictive of the "Yamamoto-type" addition of alkyllithium reagents to *N-tert*-butanesulfinyl imines.

the outcome of these reactions, having a large substituent, such as the *N*-Boc-piperazinyl group, ortho to the imine carbon apparently did not disturb this proposed transition state conformation.

In the case of addition of alkyllithiums to the *N-tert*-butanesulfinyl imines, either mediated by Me_3Al or uncatalyzed, a reversal in stereochemical outcome was observed. Thus, when *Ss*-**5b** was treated with *i*-BuLi/Me_3-Al in THF, great diastereofacial selection was observed for the newly formed stereocenter, which had predominantly the *S*-configuration. Alternatively, when *Rs*-**5b** was subjected to the same reaction conditions, the major product had *R*-configuration. The same trend was observed for all other examples.

The diastereofacial selectivity of the alkylithium additions can be rationalized by using a model similar to the one proposed by Plobeck and Powell,[12] where a nonchelated or "Yamamoto-type" transition state is involved.[13] In this model, the Lewis acid (LA) coordinates with the sulfinyl oxygen, leaving the opposite face of the complex open for nucleophilic attack. A second equivalent of LA most likely enhances the reactivity of the imine nitrogen, facilitating the addition (Figure 5).

In the absence of Me_3Al, however, the reaction outcomes are similar and appear more dependent on the size of the organolithium used. Thus, when MeLi was utilized, very little selectivity was observed (2:1). With larger *i*-BuLi, which contains one substituent on the α-carbon, higher de's were obtained (typically 7:1). When *i*-PrLi, containing a doubly-substituted α-position, was used, excellent degrees of selectivities were seen (>10:1). Examination of the X-ray strucutures of sulfinyl imines *Ss*-**5b**, *Ss*-**5e**, and *Ss*-**5g** suggest that the *N*-Boc-piperazinyl group at the ortho-position of the aryl ring may be shielding the *re* face of the C=N imine bond, and the incoming nucleophile would preferentially add to the *si* face (Figure 6). Bulkier organolithium reagents would be expected to yield greater selectivities in this case.

e. Orthogonal Deprotection. One of the attractive features of the use of *N-tert*-butanesulfinamide **4** as a chiral auxiliary for the preparation of benzylamines is the fact that, after formation of the new stereocenter, the sulfinyl group functions as an amine protecting group, which can be easily removed under mild acidic conditions.[10] Since it was practical to utilize a Boc protecting group on the arylpiperazine starting materials, it became paramount to find selective deprotection methods for both of these acid-labile protecting groups. Thus, when compound *Ss,S*-**9h** was treated with 1.2 equiv of HCl in MeOH at ambient temperature, clean removal of the *tert*-butanesulfinyl group was accomplished within 1 h. Conversely, when *Ss,S*-**9h** was exposed to ~25 equiv of trifluoroacetic acid in CH_2Cl_2 at 0.1 M concentration, the Boc group was selectively removed in 68% isolated yield to give compound **13h**. Approximately 5% of the double deprotection product **15h** was observed, along with 10% of the sulfenyl imine **14h** (Scheme 2). When larger amounts of TFA were used, more byproducts were observed. Either lowering the reaction temperature or reducing the amount of TFA slowed the reaction but did not avoid the formation of **14h** and **15h**. Similar results were obtained for other substrates.

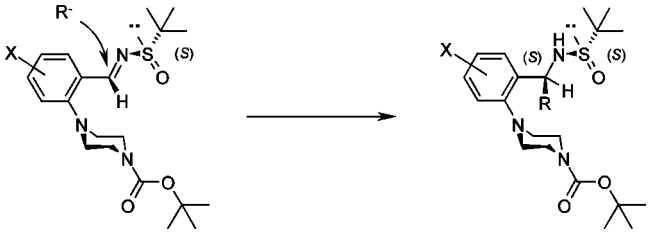
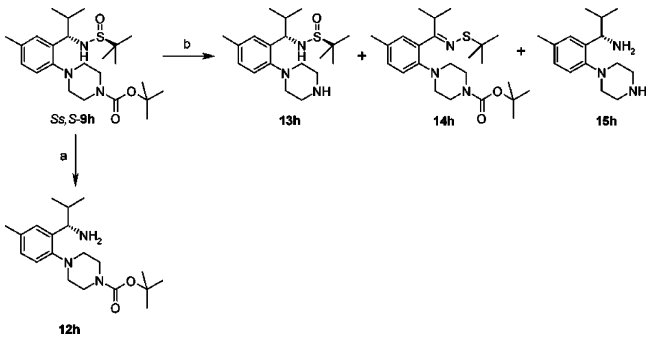


FIGURE 6. Model for "uncatalyzed" alkyllithium additions to *N-tert*-butanesulfinyl imines.

SCHEME 2[a]



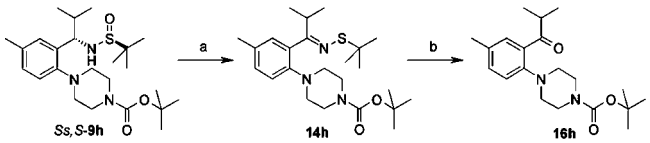
[a] Key: (a) HCl/dioxane (1.2 equiv), MeOH, rt, 1 h (95%); (b) TFA (3 equiv), CH_2Cl_2, rt, 1 h (68%)

We reasoned that sulfenyl imine **14h** is formed due to the possible presence of trace amounts of trifluoroacetic anhydride in commercial TFA. To confirm that assumption, *Ss,S*-**9h** was exposed to trifluoroacetic anhydride in CH_2Cl_2 at low temperature. After approximately 15 min, the starting material was consumed, leading to the exclusive formation of **14h**. This compound is sufficiently stable to allow for purification by silica gel chromatography and characterization. In addition, exposure of **14h** to methanolic acid led to the smooth conversion to ketone **16h** (Scheme 3). The acidic hydrolysis of sulfenyl imines to the corresponding carbonyl compounds is well-documented,[14] and the synthetic route described in Scheme 3 represents an attractive way to convert amines to

(12) Plobeck, N.; Powell, D. *Tetrahedron: Asymmetry* **2002**, *13*, 303−310.

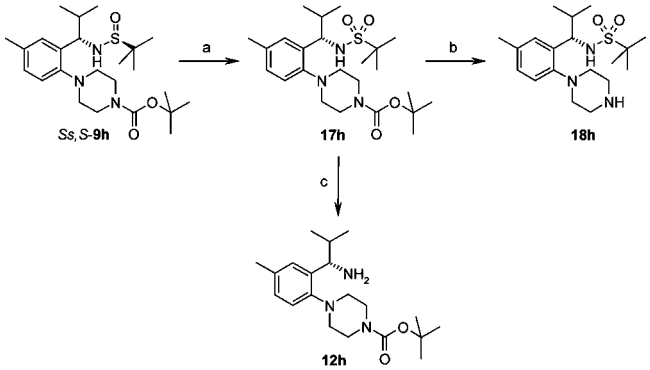
(13) (a) Yamamoto, Y.; Komatsu, T.; Maruyama, K. *J. Am. Chem. Soc.* **1984**, *106*, 5031−5033. (b) Yamamoto, Y.; Nishii, S.; Maruyama, K.; Komatsu, T.; Ito, W. *J. Am. Chem. Soc.* **1986**, *108*, 7778−7786. (c) Davis, F. A.; McCoull, W. *J. Org. Chem.* **1999**, *64*, 3396−3397.

SCHEME 3[a]



[a] Key: (a) trifluoroacetic anhydride, CH_2Cl_2, 0 °C (95%); (b) 0.1 N HCl(aq)., EtOH, rt, 1 h (85%)

SCHEME 4[a]



[a] Key: (a) *m*CPBA, CH_2Cl_2, rt, 1 h (95%); (b) TFA (3 equiv), CH_2Cl_2, rt, 1 h (95%); (c) anisole, trifluoromethanesulfonic acid, CH_2Cl_2, rt, 3 h (90%)

ketones and aldehydes. We are currently investigating the generality of this approach.

To avoid the formation of byproducts and to maximize the yields of the benzylamine deprotections, we decided to oxidize the *N-tert*-butylsulfinamide group to the corresponding sulfonamide, with the knowledge that the *N-tert*-butylsulfonamide (Bus) would tolerate TFA.[15] Other groups have also utilized a similar strategy.[16] Thus, compound *Ss,S*-**9h** was oxidized by *m*CPBA in CH_2Cl_2, at room temperature, in nearly quantitative yield. The resulting sulfonamide **17h**, when treated with TFA in CH_2Cl_2, was smoothly converted to the secondary amine **18h** in 95% yield. Alternatively, the sulfonamide group in **17h** could be selectively removed by treatment with trifluoromethane sulfonic acid in CH_2Cl_2, in the presence of 2 equiv of anisole, to give benzylamine **12h** (Scheme 4).

Conclusion

We have demonstrated the practical conversion of 2-fluorobenzaldehydes to protected chiral (arylpiperazinyl)benzylamines, which are key intermediates for the preparation of MC4R ligands. The synthetic route presented herein utilizes chiral *N-tert*-butanesulfinamide as both an activating agent for the addition or organometallics reagents to the C=N bond and a powerful stereodirecting group. The diastereoselectivities obtained are good to excellent, and in many cases the major product can be isolated in pure form by a simple recrystallization. The stereochemical assignments were effected via X-ray crystallography, and models predictive of the stereochemical outcome of the additions have been applied. In addition, the resulting products can be efficiently deprotected selectively to allow for further manipulations.

Experimental Section

General Procedure for the Preparation of 2-Piperazinylbenzaldehydes (3a−h, Table 1). A solution containing the corresponding 2-fluorobenzaldehyde, *N*-Boc-piperazine, and K_2CO_3 in either DMF, DMA, or 1,4-dioxane was heated to the temperatures and times listed in Table 1. After consumption of the starting material, the reaction mixture was cooled to room temperature and filtered, and the solids were rinsed EtOAc. The filtrate was concentrated in vacuo, and the residue was diluted with EtOAc and washed with 0.1 N HCl, saturated aqueous $NaHCO_3$ solution, and brine. The organic extracts were dried over anhydrous $MgSO_4$ and filtered, followed by concentration at reduced pressure. The residue was triturated with hexanes to afford the desired products as yellow solids, unless stated otherwise.

General Procedure for the Condensation Reaction between 2-Piperazinylbenzaldehydes 3a−h and *N-tert*-Butanesulfinamides 4, using $Ti(OEt)_4$ (Table 2). A solution containing the corresponding 2-piperazinylbenzaldehyde **3** and *N-tert*-butanesulfinamide **4** in THF was treated with $Ti(OEt)_4$ (tech. grade, Ti ~20%, contains excess ethanol) at ambient temperature. The resulting homogeneous mixture was stirred, under N_2, for the times indicated in Table 2. The reaction mixture was cautiously poured onto a saturated NaCl aqueous solution, with vigorous stirring. The resulting suspension was filtered through a pad of Celite and rinsed thoroughly with EtOAc and CH_2Cl_2, until no more product could be detected by TLC. The organic layer was separated, dried over anhydrous $MgSO_4$, and filtered. The solvents were removed in a rotary evaporator at reduced pressure. The resulting solids were either triturated or recrystallized from hexanes to give the final product in analytically pure form, unless otherwise stated.

General Procedure for the Condensation Reaction between 2-Piperazinylbenzaldehydes 3a−h and *N-tert*-Butanesulfinamides 4, using Cs_2CO_3 (Table 2). A solution of the corresponding 2-piperazinylbenzaldehyde **3** and *N-tert*-butanesulfinamide **4** in CH_2Cl_2 was treated with Cs_2CO_3. The resulting suspension was heated to reflux and the reaction progress was monitored by TLC and HPLC/MS. The reactions were allowed to proceed for the times indicated in Table 2 and then cooled to ambient temperature. The solids were removed by filtration, and the filtrate was concentrated in vacuum. The residue was purified by crystallization from EtOAc.

General Procedure for the Organolithium Additions to *N-tert*-Butanesulfinyl Imines 5 (Table 3). A round-bottom flask equipped with a magnetic stirring bar, thermometer, and an inert gas inlet was flame-dried under N_2. Upon cooling, the flask was charged with the corresponding *N-tert*-butanesulfinyl imine **5** and THF. The resulting solution was cooled to −72 °C (dry ice/acetone bath) and the desired organolithium reagent was introduced via syringe in a dropwise fashion, to keep the internal temperature below −68 °C. After the addition, the reaction was kept at low temperature for another hour and then quenched with saturated NH_4Cl aqueous. Upon warming to room temperature, the mixture was transferred to a separatory funnel and the reaction was partitioned between EtOAc and H_2O. The organic layer was separated, washed with brine, and dried over anhydrous $MgSO_4$. Filtration and concentration under vacuum gave a residue that was purified by silica gel chromatography or crystallization.

General Procedure for the Me_3Al-Mediated Organolithium Additions to *N-tert*-Butanesulfinyl Imines 5 (Table 3). A three-necked round-bottom flask equipped with a magnetic stirring bar, thermometer, a dropping funnel, and

(14) Davis, F. A.; Slegeir, W. A. R.; Evans, S.; Schwartz, A.; Goff, D. L.; Palmer, R. *J. Org. Chem.* **1973**, *38*, 2809−2813.
(15) Sun, P.; Weinreb, S. M.; Shang, M. *J. Org. Chem.* **1997**, *62*, 8604−8608.
(16) (a) Borg, G.; Chino, M.; Ellman, J. A. *Tetrahedron Lett.* **2001**, *42*, 1433−1436. (b) Kells, K. W.; Chong, J. M. *J. Am. Chem. Soc.* **2004**, *126*, 15666−15667.

an inert gas inlet was flame-dried under N_2. Upon cooling, the flask was charged with the corresponding *N-tert*-butanesulfinyl imine **5** and THF. The flask was cooled to −40 °C and then Me_3Al was introduced slowly. The reaction was stirred at that temperature for 20 min, and then cooled to −72 °C (dry ice/acetone bath). The desired organolithium reagent was added in a dropwise fashion at such a rate to keep the internal temperature below −68 °C. After the addition, the reaction was kept at low temperature for another hour and then quenched with a 5% aqueous HCl solution (60 mL) carefully at −72 °C. The reaction mixture was brought up slowly to room temperature to ensure the controlled release of methane gas. The mixture was transferred to a separatory funnel and the reaction was partitioned between EtOAc and H_2O. The organic layer was separated, washed with brine, and dried over anhydrous $MgSO_4$. Filtration and concentration under vacuum gave a residue that was purified by silica gel chromatography or crystallization.

Deprotection of Compound *Ss,S*-9h. Trifluoroacetic acid (2 mL) was added dropwise to a solution of *N-tert*-butanesulfinamide *Ss,S*-**9h** (451 mg, 1.00 mmol) in CH_2Cl_2 (10 mL). The reaction was monitored by TLC and HPLC/MS. After the disappearance of the starting material (1 h), the reaction mixture was slowly poured onto a 1:1 mixture of saturated $NaHCO_3$ and saturated Na_2CO_3 solutions (v/v, 20 mL). The products were extracted with CH_2Cl_2 (50 mL). The organic layer was separated, dried over anhydrous $MgSO_4$, and filtered. Evaporation gave the crude residue as a yellow foam. According to HPLC/MS, the crude product mixture consisted of ∼85% of amine **13h**, ∼10% of sulfenyl imine **14h**, and ∼5% of doubly deprotected amine **15h**. This was purified by silica gel chromatography, eluting with a 400:50:2 mixture of $CHCl_3$/MeOH/NH_4OH v/v, respectively. Pure **13h** was obtained as a white solid (238 mg, 0.68 mmol, 68%).

4-[2-((*S*)-1-Amino-2-methylpropyl)-4-methylphenyl]piperazine-1-carboxylic Acid *tert*-Butyl Ester (12h). To a methanol (100 mL) solution of *Ss,S*-**9h** (10.45 g, 23.13 mmol) at room temperature was added HCl (6.65 mL of a 4 N solution in 1,4-dioxane, 26.60 mmol) dropwise, and the mixture was stirred at room temperature until all starting material disappeared (∼80 min). The reaction was monitored by TLC and HPLC/MS, and no byproducts were found. MeOH and excess HCl were removed by rotary evaporator in vacuo to give the hydrochloride salt of amine **12h** as a white solid that was used in the next reaction without further purification. For characterization purposes, an analytically pure sample of this material was obtained after silica gel chromatography (5−10% MeOH/CH_2Cl_2, v/v) as a white foam.

Sulfenyl Imine (14h). To a CH_2Cl_2 (5 mL) solution of *Ss,S*-**9h** (130.6 mg, 289.1 μmol) at 0 °C, was added trifluoroacetic anhydride (48.3 μL, 347 μmol). The color of the resulting solution turned yellow almost immediately. The mixture was stirred at 0 °C until all starting material disappeared (∼10 min). The reaction was monitored by TLC and HPLC/MS. The mixture was diluted with 30 mL of EtOAc and washed with a saturated solution of $NaHCO_3$ (10 mL). The organic layer was separated and dried over Na_2SO_4. Solvents were removed by rotary evaporation to give crude **14h**, which was purified by silica gel chromatography, eluting with a 20% mixture of EtOAc in hexanes, v/v. The title compound **14h** was obtained as a white solid (112.0 mg, 89%).

4-(2-Isobutyryl-4-methylphenyl)piperazine-1-carboxylic Acid *tert*-Butyl Ester (16h). To a methanol (5 mL) solution of **14h** (12.6 mg, 29.1 μmol) at room temperature was added HCl (8.0 μL of a 4 N solution in 1,4-dioxane, 29.1 μmol) dropwise and the mixture was stirred at ambient temperature until all starting material disappeared (∼1 h). The reaction was monitored by TLC and HPLC/MS. MeOH was removed in a vacuum, to give ketone **16h** as a white solid that was purified by silica column chromatography (20% EtOAc/hexanes, v/v) to give a white foam (9.2 mg, 91%).

4-{4-Methyl-2-[(*S*)-2-methyl-1-(2-methylpropane-2-sulfonylamino)propyl]phenyl}piperazine-1-carboxylic Acid *tert*-Butyl Ester (17h). To a CH_2Cl_2 (5 mL) solution of *Ss,S*-**9h** (70.0 mg, 155 μmol) at room temperature was added *m*-CPBA (∼55%, 63.4 mg, 202 μmol) and the mixture was stirred at room temperature until all starting material disappeared (∼45 min). The reaction was monitored by TLC and HPLC/MS. The mixture was diluted with EtOAc (30 mL) and washed with an aqueous solution of $Na_2S_2O_3$ (200 mg) and Na_2CO_3 (2.0 g). The organic solution was dried over Na_2SO_4. Solvents were removed by evaporation in a vacuum to give sulfonamide **17h** as a white solid (72.0 mg, 100%).

2-Methylpropane-2-sulfonic Acid [(*S*)-2-Methyl-1-(5-methyl-2-piperazin-1-ylphenyl)propyl]amide (18h). To a CH_2Cl_2 (2.55 mL) solution of **17h** (38.7 mg, 82.8 μmol) at room temperature was added trifluoroacetic acid (0.45 mL, 6.0 mmol) and the mixture was stirred at room temperature until all starting material disappeared (∼45 min). The reaction was monitored by TLC and HPLC/MS. The mixture was basified with a saturated solution of $NaHCO_3$ (20 mL) extracted with EtOAc (30 mL). The organic layer was dried over Na_2SO_4, and the solvents were removed in vacuo to give amine **18h** as white foam, which was used in the next step without any further purification. For characterization purposes, an analytical sample of this material was obtained after silica gel chromatography (5−10% MeOH/CH_2Cl_2, v/v) as a white foam.

Acknowledgment. We thank Drs. Lev Zegelman, David Provencal, and Raymond S. Gross, for experimental assistance, and Dr. John Huffman of the Indiana University Molecular Structure Center, for assistance with the X-ray structural determinations.

Supporting Information Available: Experimental procedures, characterization data, and copies of ^{13}C NMR spectra for all compounds and X-ray crystallographic parameters (CIF files) for compounds *Ss*-**5b**, *Ss*-**5e**, *Ss*-**5g**, *Ss,S*-**8b**, *Ss,S*-**9b**, *Ss,S*-**9e**, *Ss,S*-**9h**, and *Rs,S*-**10c**. This material is available free of charge via the Internet at http://pubs.acs.org.

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