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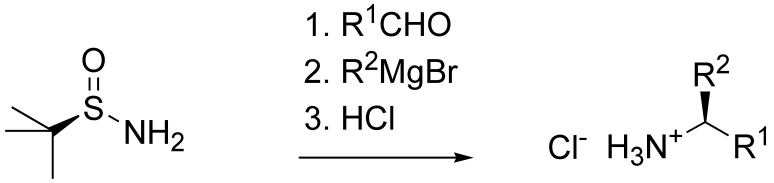

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Parallel Solution-Phase Asymmetric Synthesis of α-Branched Amines

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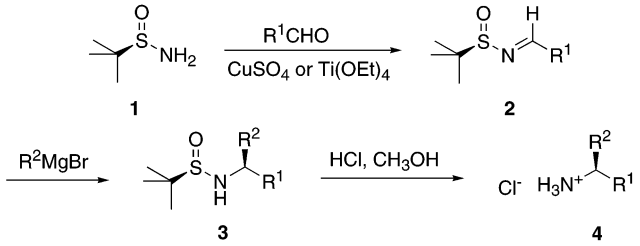
A general method is reported for the parallel solution-phase asymmetric synthesis of α-substituted amines based on the stereoselective addition of organomagnesium reagents to enantiomerically pure *tert*-butanesulfinyl imines. The sulfinyl imines are prepared in high yields by condensation of *tert*-butanesulfinamide with aldehydes, followed by quenching and removal of the titanium species with diatomaceous earth saturated with water. Addition of organomagnesium reagents then proceeds with high diastereoselectivities. After aqueous workup following the organometallic addition, liquid/liquid separation is readily accomplished using 1PS filter cartridges. Acidic alcoholysis of the resulting sulfinamide products, followed by acid/base extraction and isolation, affords the desired amine hydrochlorides. The effectiveness of this sequence of reaction and workup procedures was demonstrated by the parallel synthesis of 10 α-substituted amines in excellent overall yields (72−84%) and high enantiopurities (80−97% ee). Notably, all 10 amine hydrochlorides were obtained in analytically pure form without requiring chromatography or crystallization of any of the intermediates or products. Finally, reaction times can be reduced by the use of microwave irradiation in the sulfinyl imine condensation step. Sulfinyl group cleavage and concomitant resin capture using sulfonic acid resin can also be accomplished through the use of microwave irradiation.

The amine functionality is incorporated into >75% of all drugs and drug candidates.[1] Consequently, α-substituted amines are essential building blocks in many drug discovery efforts. However, with the exception of α-amino acids, relatively few chiral α-substituted amines can be purchased in enantioenriched form, and general methods for their asymmetric synthesis have only recently been reported.[2] For these reasons, enantioenriched α-substituted amines are rarely used as building bocks in the preparation of combinatorial libraries. As well, the synthesis of enantioenriched α-substituted amine building blocks can be a rate-limiting step in lead optimization efforts. In this paper, we report convenient parallel synthesis procedures for the solution-phase asymmetric synthesis of α-substituted amine building blocks for both combinatorial library production and medicinal chemistry efforts.

Results and Discussion

We have previously reported a general method for the asymmetric synthesis of α-substituted amines using *tert*-butanesulfinamide **1** as a chiral amine reagent (Scheme 1).[3] In this method, *tert*-butanesulfinamide is first condensed with aldehydes to give the *tert*-butanesulfinyl imines **2**. The diasteroeselective addition of organometallic reagents to the sulfinyl imines **2** provides the sulfinamide products **3**. Acidic alcoholysis followed by ether precipitation then affords the desired enantiomerically enriched amine hydrochlorides **4**. As described in the subsequent sections, each of these steps can be modified such that the parallel synthesis of analytically pure amines may be accomplished in high yields and with high enantiopurities.

Scheme 1. Asymmetric Synthesis of α-Branched Amines Using *tert*-Butanesulfinamide



Imine Formation Mediated by Titanium Tetraethoxide (Method A). We have previously established that both $CuSO_4$ and $Ti(OEt)_4$ may be used as a Lewis acid and water scavenger to condense *tert*-butanesulfinamide with aldehydes.[4] However, to maximize synthesis generality in our parallel synthesis efforts, we have chosen to employ $Ti(OEt)_4$, because it is the more effective reagent for providing good conversion for sterically hindered or electronically deactivated aldehydes.

In our initial studies, the crude product of the $Ti(OEt)_4$-mediated condensation reaction was directly submitted to the Grignard addition step (Scheme 1). Unfortunately, the titanium reagent and byproducts quenched the Grignard reagent, which necessitated that all titanium-derived materials be removed prior to Grignard reagent addition. Removal of titanium materials is most effectively accomplished by mixing the condensation reaction mixture with water-saturated diatomaceous earth in a commercially available syringe-styled cartridge. After straightforward filtration and washing, the very small quantity of residual titanium oxide powder can easily be removed by filtration through a silica gel plug (Scheme 2).

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Scheme 2. Parallel Synthesis of Sulfinyl Imines **2**

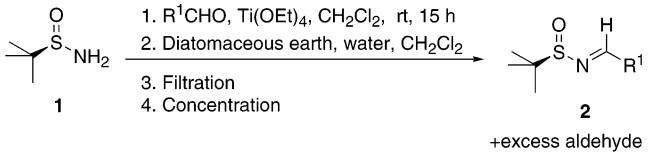
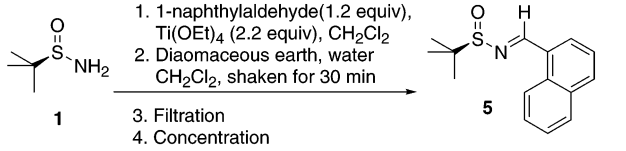


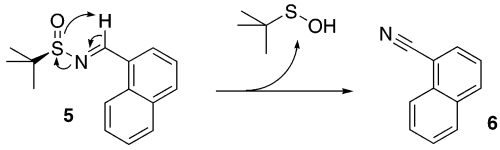
Table 1. Imine Formation Using a Microwave Reactor



entry	reaction conditions	yield (%)[a]
1	rt, 16 h	99
2	150 °C, 10 min	41
3	130 °C, 10 min	86
4	110 °C, 10 min	100
5	90 °C, 10 min	100

[a] Isolated yield based upon mass balance of purified material.

Scheme 3. Thermal Decomposition of *tert*-Butanesulfinyl Imine **5**



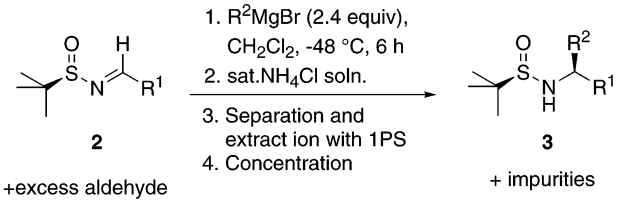
We have also explored using support-bound diethanolamine, which was recently reported to scavenge titanium reagents.[5] Although this support-bound reagent effectively removed all of the titanium-based material, a significant amount of the resin is required, because excess $Ti(OEt)_4$ is utilized in the condensation reaction.

Imine Formation Accelerated by Microwave Irradiation (Method B). Organic reactions accelerated by microwave irradiation are increasingly being used to enhance the rate of compound production by dramatically reducing reaction times.[6] The use of microwave irradiation therefore appeared to be applicable to the synthesis of sulfinyl imines. Using 1-naphthylaldehyde as a model substrate, condensation reactions mediated by $Ti(OEt)_4$ were carried out under microwave conditions using the Emrys Synthesizer (Personal Chemistry, Inc.).

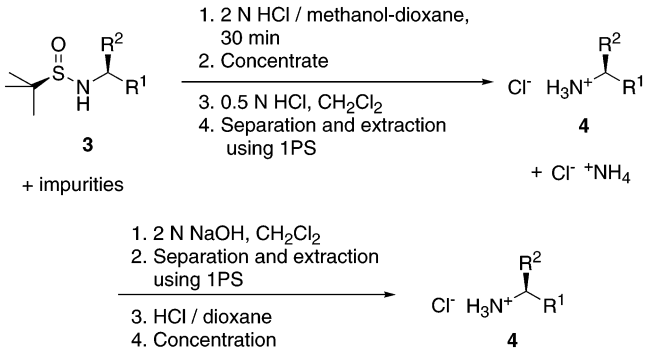
Isolated product yields were obtained for the condensation reactions under various irradiation conditions (Table 1). A low yield of sulfinyl imine **5** was observed at temperatures above 130 °C (entries 2 and 3), due to thermal decomposition of imine **5** to 1-naphthonitrile **6** (Scheme 3). An analogous thermal decomposition of toluenesulfinyl imines has been reported by Davis and co-workers.[7] Fortunately, imine **5** could be obtained in quantitative yield when microwave irradiation was performed for 10 min at temperatures between 90 and 110 °C (entries 4 and 5).

Nucleophilic Addition of Organomagnesium Reagents to *N*-Sulfinyl Imines. The nucleophilic addition of organomagnesium reagents to sulfinyl imines proceeded with high diastereoselectivity at − 48 °C. After allowing the reaction to proceed for 6 h at − 48 °C, the reaction temperature was slowly raised to room temperature to ensure complete reaction. Quenching of excess organomagnesium reagent was then performed by addition of saturated ammonium chloride. Phase separation was successfully achieved with 1PS filter cartridges, available from Whatman. Because only the organic solution can pass through these silicone-soaked filter cartridges, isolation of the desired organic phase was straightforward. Evaporation of the organic solvent afforded a crude mixture of desired sulfinamide **3**, the undesired alcohol derived from Grignard reaction of the small amount of excess aldehyde, and any residual *tert*-butanesulfinamide that resulted from the decomposition of unreacted sulfinyl imines.

Scheme 4. Reaction of Organomagnesium Reagents with Unpurified Sulfinyl Imine **2**



Scheme 5. Removal of the Sulfinyl Group to Provide Amine Hydrochloride **4**



Cleavage of the Sulfinyl Group and Isolation of the Amine Hydrochloride Products. Acidic alcoholysis of sulfinamides **3** occurs rapidly upon addition of a hydrogen chloride solution in methanol. We have previously isolated the pure amine hydrochloride products **4** by precipitation upon addition of ether. However, during the parallel synthesis sequence, impurities accumulate because purifications are not performed after either the condensation or the Grignard addition steps. In addition, amines that are large and nonpolar tend to precipitate as amine hydrochlorides in only modest yields. We therefore examined the separation of the desired amines from any neutral byproducts using acid/base extraction (Scheme 5). The crude reaction product obtained from the Grignard addition step was dissolved in methanol, and a dioxane solution of hydrogen chloride was added. After stirring for 30 min, the reaction solution was concentrated, and the residue was then dissolved in 1 N hydrochloric acid. The acidic solution was washed with dichloromethane to separate the neutral byproducts into the organic phase. The aqueous phase was then treated with 2 N sodium hydroxide solution to liberate the free amine, which was then extracted with dichloromethane. Any ammonia that might have been formed by decomposition of residual *tert*-butanesulfinamide would remain in the aqueous phase. Straightforward isolation of the organic phase containing the free amine was then

Table 2. Parallel Asymmetric Synthesis of α-Branched Amines **4** from *tert*-Butanesulfinamide **1**

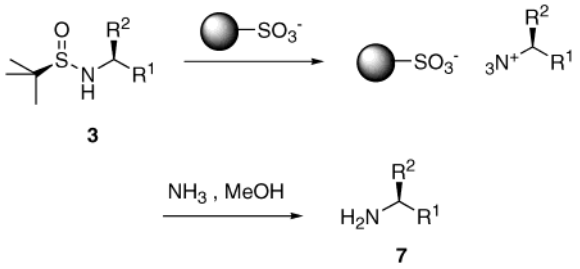
entry[a]	amine product	R_1CHO	R_2MgBr	overall yield (%)[b]	ee (%)[c]
1	**4a**	EtCHO	MeMgBr	76	83
2[d]	**4a**	EtCHO	MeMgBr	72	83
3	**4b**	EtCHO	PhMgBr	82	93
4	**4c**	*i*-PrCHO	MeMgBr	80	97
5	**4d**	*i*-PrCHO	EtMgBr	82	95
6	**4e**	*i*-PrCHO	PhMgBr	82	81
7	**4f**	PhCHO	MeMgBr	83	94
8	**4g**	BnCHO	MeMgBr	77	91
9[d]	**4g**	BnCHO	MeMgBr	76	90
10	**4h**	BnCHO	EtMgBr	81	87
11	**4i**	BnCHO	PhMgBr	63	93
12	**4j**	1-naphthCHO	MeMgBr	71	80
13[d]	**4j**	1-naphthCHO	MeMgBr	64	79

[a] Unless otherwise noted, the imine condensation step was performed at room temperature (method A). [b] Overall yield from *tert*-butanesulfinamide **1** based upon the mass balance of analytically pure material **4**. [c] Determined by GC analysis of the (+)- and (−)-MTPA derivatives. [d] Imine formation was carried out using microwave heating at 110 °C for 10 min (method B).

accomplished using a 1PS filter cartridge. A 2 M solution of HCl in dioxane was then added, and the mixture was concentrated to provide the pure amine hydrochloride, as determined by ^{1}H NMR and elemental analysis.

Parallel Asymmetric Synthesis of α-Branched Amines. The viability of the parallel synthesis procedure was demonstrated by the parallel asymmetric synthesis of 10 α-substituted amines using various combinations of aldehydes and Grignard reagents. As shown in Table 2, the desired amine hydrochloride products were obtained in very high overall yields from *tert*-butanesulfinamide **1** and with high enantiomeric purities. Notably, all 10 of the amine hydrochloride products were obtained in analytically pure form. As shown in entries 2, 9, and 13, when microwave-mediated imine synthesis was employed, the products were still obtained in analytically pure form and with comparable enantiomeric purity but in slightly reduced overall yields.

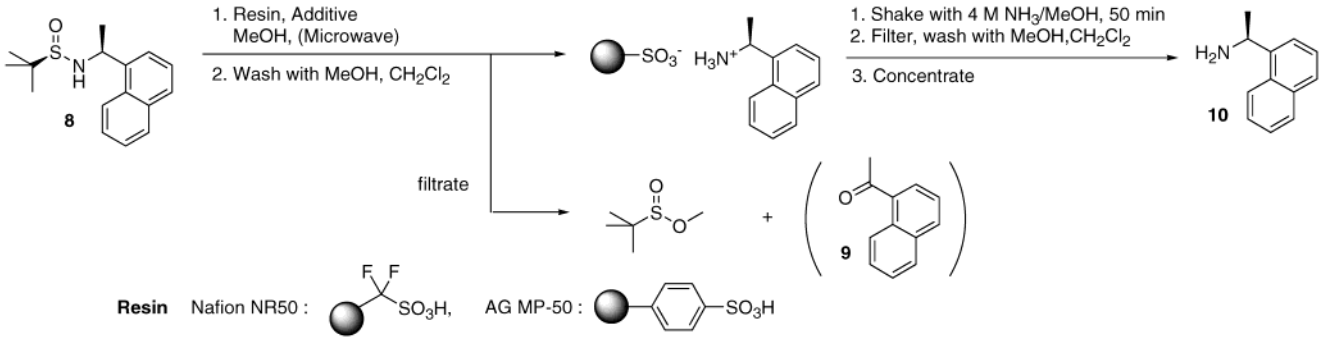
Scheme 6. Resin Capture of Product Amine



Microwave-Assisted Resin Capture of the Product Amines. Romo and co-workers reported a method in which *N*-Boc-protected amines are deprotected with concomitant resin capture by treatment with sulfonic acid resin.[8] The captured amines can be recovered by washing the resin with an alcoholic solution of ammonia. This report inspired us to explore sulfinyl group removal and amine capture using acidic ion-exchange resin.

At first, acidic alcoholysis of purified sulfinamide **8** was attempted using both macroporous sulfonic acid (AG MP-50) resin and highly acidic Nafion (NR50) resin; however, little sulfinyl group cleavage in methanol was observed for either reagent, even under refluxing conditions. In contrast, alcoholysis with Nafion at 130 °C for 10 min using a microwave reactor resulted in complete consumption of the substrate (entry 1, Table 3). Washing the resin with methanol and dichloromethane followed by elution with methanolic ammonia provided the product amine **10** in pure form but in only 69% yield. Interestingly, acetonaphthone **9** was isolated in 20% yield from the washing solution. Acetonaphthone **9** likely results from the thermal decomposition of sulfinamide **8** (Scheme 7). Indeed, Trost and Liu previously reported the thermal decomposition of sulfinamides as a method for the preparation of imines.[9] When the less acidic

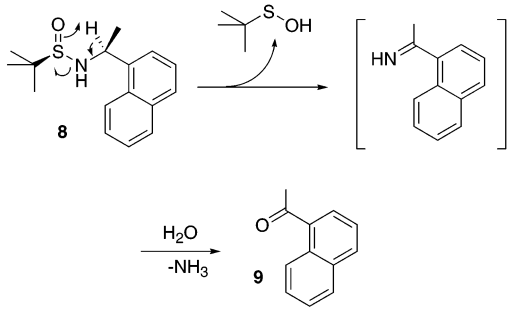
Table 3. Optimization of Resin Capture Assisted by Microwave Irradiation



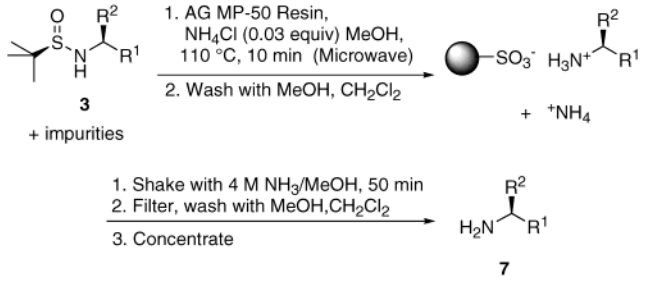
entry	resin	condition	additive	**9** (% yield)[a]	**10** (% yield)[a]
1	Nafion NR50 (3 equiv)	130 °C, 10 min	none	20	69
2	AG MP-50 (3 equiv)	130 °C, 3 × 10 min	none	16	69
3	Nafion NR50 (3 equiv)	130 °C, 10 min	PhSH	2	72
4	Nafion NR50 (3 equiv)	130 °C, 10 min	Bu_4NBr (1.5 equiv)	0	89[b]
5	Nafion NR50 (3 equiv)	130 °C, 10 min	NH_4Cl (1.5 equiv)	0	81[c]
6	Nafion NR50 (3 equiv)	110 °C, 10 min	NH_4Cl (0.1 equiv)	3	85
7	AG MP-50 (3 equiv)	110 °C, 10 min	NH_4Cl (0.1 equiv)	0	82
8	AG MP-50 (3 equiv)	110 °C, 10 min	NH_4Cl (0.03 equiv)	3	85

[a] Based upon the mass balance yield of analytically pure material. [b] Product was contaminated with additive. [c] A small amount of product was obtained from the filtrate.

Scheme 7. Thermal Decomposition of Sulfinamide **8**



Scheme 8. Microwave Assisted Resin Capture Using Crude Compounds



macroporous sulfonic acid resin was used, complete substrate consumption was accomplished by irradiating three times for 10 min at 130 °C (entry 2, Table 3). However, once again, significant quantities of the undesired side product **9** were produced.

Next, additives were screened to identify an additive that would catalyze the formation of the desired amine product without generating the ketone byproduct. Ammonium chloride was the most effective additive for this purpose (entries 5−8, Table 3). Presumably, the chloride ion attacks the electrophilic sulfur to catalyze the release the desired amine product. The procedure was most effective when only a catalytic amount of ammonium chloride was used (entries 7 and 8). The optimized reaction protocol to afford free amines is shown in Scheme 8. It should be noted that because this resin capture procedure provides the free amine, this procedure should only be applied to nonvolatile amines.

Asymmetric Synthesis of α-Branched Amines Using Microwave-Assisted Resin Capture. A series of chiral amines were synthesized by a reaction sequence incorporating two microwave reactions: (1) imine synthesis and (2) sulfinyl group removal and resin capture (Scheme 8). The observed overall yields of amines **4** from *tert*-butanesulfinamide **1** for entries 1−3 (Table 4) were slightly lower than obtained when sulfinyl group cleavage was accomplished with acidic methanol (entries 8, 11, and 12, respectively, Table 2). Nevertheless, a range of α-phenethylamine and diphenylmethylamine derivatives, which are frequently found in biologically active compounds, were prepared in analytically pure form, in good overall yields, and with high enantiomeric purity.

Conclusion

A general method has been developed for the parallel solution-phase asymmetric synthesis of α-substituted amines based on the stereoselective addition of organomagnesium reagents to enantiopure *tert*-butanesulfinyl imines. This sequence of reactions and workup procedures provides α-substituted amine hydrochlorides in excellent overall yields and with high enantiopurities. Significantly, the amine hydrochlorides are obtained in analytically pure form without requiring chromatography or crystallization of any of the intermediates or products. The developed parallel synthesis procedures provide an effective means to rapidly prepare enantiomerically enriched amines as building blocks for both combinatorial library production and medicinal chemistry efforts.

Table 4. Parallel Asymmetric Synthesis of Amines **4** from *tert*-Butanesulfinamide **1** Using Microwave-Assisted Resin Capture (Scheme 8)[a]

entry	amine product	R_1CHO	R_2MgBr	overall yield (%)[a]	ee (%)[b]
1	**4g**	BnCHO	MeMgBr	64	89
2	**4i**	BnCHO	PhMgBr	61	90
3	**4j**	1-naphthCHO	MeMgBr	65	87
4	**4k**	4-MeOPhCHO	MeMgBr	60	96
5	**4l**	4-MeOPhCHO	PhMgBr	62	90
6	**4m**	4-ClPhCHO	MeMgBr	68	92
7	**4n**	4-ClPhCHO	PhMgBr	69	84

[a] Overall yield from *tert*-butanesulfinamide **1** based upon the mass balance of analytically pure material **4**. [b] Determined by GC analysis of the (+)- and (−)-MTPA derivatives.

Experimental Section

General Methods. All aldehydes were obtained from commercial suppliers and were distilled before use. Titanium tetraethoxide containing 5−15% 2-propanol was purchased from Strem Chemicals (Newburyport, MA) and was used without further purification. Organomagnesium reagents in diethyl ether were purchased form Aldrich. Dichloromethane was distilled under nitrogen from calcium hydride. A 4 M solution of ammonia in methanol was prepared by dilution of a saturated ammonia solution obtained by bubbling ammonia gas into methanol. Sulfinamide **1** was prepared as previously described.[11] Syringe-styled polypropylene cartridges (12 mL, Catalog no. 2427, 6 mL, Catalog no. 2454) with 70 μm PE frits and PTFE stopcocks (Catalog no. 2406) were obtained from Applied Separations (Allentown, PA). Diatomaceous earth (Hydromatrix, Part no. 198003) was purchased from Varian Inc. The 1PS Filter Tubes (1PS filter media with polypropylene support and housing, 6 mL, Catalog no. 6987-0699) were obtained from Whatman Inc. (Clifton, NJ). Sulfonic acid resin (AG MP-50 resin, 100−200 mesh, Catalog no. 143-0841) was purchased from Bio-Rad Laboratories (Hercules, CA), and was activated by the procedure described by Romo et al.[8] Nafion resin (NR50, 10−35 mesh bead, Catalog no. 16889) was obtained from Lancaster. Microwave reactions were performed using the Emrys Synthesizer from Personal Chemistry Inc. (Foxboro, MA). NMR spectra were obtained with a Bruker AMX-300 spectrometer in CD_3OD unless otherwise noted. 1H NMR spectra are reported in parts per million using residual CHD_2-OD as an internal standard at 3.30 ppm. Gas chromatographic analysis was carried out using an Agilent Technologies 6890N instrument with an HP ultra II column at 20 psi and at a 0.8 mL flow rate.

General Procedure for the Synthesis of *tert*-Butanesulfinyl Imines 2 (Method A). To a solution of *tert*-butanesulfinamide **1** (0.121 g, 1.00 mmol) and aldehyde (1.2 mmol) in CH_2Cl_2 (2.5 mL) was added titanium tetraethoxide (purity: 85−95%, 0.46 mL, 2 mmol) under a nitrogen atmosphere. The mixture was stirred at room temperature for 15 h. Diatomaceous earth (8 mL) was placed in a polypropylene SPE cartridge (12 mL, with 70 μm PE frit) equipped with a PTFE stopcock and then was soaked with water (2.5 mL). The reaction mixture was then transferred to the SPE cartridge with rinsing with 5 mL of CH_2Cl_2, and the cartridge was plugged with a glass stopper coated with PTFE seal tape. The cartridge was shaken vigorously for 30 s so that the diatomaceous earth flowed freely in the cartridge. The mixture was shaken for 30 min with a wrist action shaker. During the mixing, the cartridge was shaken vigorously with hands at intervals to ensure effective mixing. The solid phase was filtered and washed with CH_2Cl_2until no product could be found in the elution. The filtrate was evaporated and filtered through a 0.5-cm plug of silica gel (Merck 60 230−400 mesh) in a glass pipet. The silica gel was washed with a small amount of a 9:1 CH_2Cl_2/Et_2O mixture. The product imine contaminated with excess aldehyde was obtained by evaporation of the solvent from the filtrate.

General Procedure for the Synthesis of *tert*-Butanesulfinyl Imines 2 (Method B). A Smith Process vial (2−5 mL) containing *tert*-butanesulfinamide **1** (0.121 g, 1.00 mmol), aldehyde (1.2 mmol), dichloromethane (dry, 2.5 mL), and titanium tetraethoxide (purity: 85−95%, 0.46 mL, 2 mmol) was heated to 110 °C in an Emrys Synthesizer. After heating for 10 min, the reaction mixture was transferred to the SPE cartridge (12 mL) containing diatomaceous earth (8 mL) and water (2.5 mL). The cartridge was treated in the same way as method A to afford the product imine contaminated with excess aldehyde.

General Procedure for Addition of Organomagnesium Reagents to *tert*-Butanesulfinyl Imines. The mixture obtained by method A or B was dissolved in CH_2Cl_2 (5 mL) and cooled to −48 °C. To this cooled mixture, the appropriate organomagnesium reagent in diethyl ether (3.0 M, 0.800 mL, 2.40 mmol) was added slowly dropwise. The reaction mixture was stirred at −48 °C for 6 h and then was allowed to gradually warm to room temperature. After stirring overnight, the reaction was quenched by the addition of saturated aqueous ammonium chloride solution (2 mL). After stirring vigorously for 10 min, the mixture was transferred to a 1PS filter cartridge equipped with a PTFE stopcock, and the organic phase was isolated. The aqueous phase was rinsed with dichloromethane (3 × 2 mL) and evaporated to afford the desired crude sulfinamide product **3**.

General Procedure for the Synthesis of α-Substituted Amine Hydrochlorides (Conventional Acid/Base Extraction Method). The mixture obtained by the general procedure for organomagnesium reagent addition was dissolved in methanol (2 mL). To this mixture was added 4 N hydrogen chloride in 1,4-dioxane (2 mL). The mixture was stirred for 30 min and then concentrated to dryness. The obtained mixture was distributed in 0.5 N hydrochloric acid (2 mL) and dichloromethane (2 mL) and was transferred to a 1PS filter cartridge (12 mL) equipped with a PTFE stopcock. The organic layer was removed, and the aqueous layer was washed with CH_2Cl_2 (3 × 2 mL). A 2 N sodium hydroxide solution (2 mL) was then added to the aqueous layer, and the resulting free amine was extracted with dichloromethane (3 × 2 mL). A 4 N solution of HCl in 1,4-dioxane (1 mL) was added to the latter combined dichloromethane extracts. The resulting solution was evaporated and dried under reduced pressure to afford analytically pure amine hydrochloride.

General Procedure for the Synthesis of α-Substituted Amine Hydrochlorides (Microwave-Assisted Resin Capture Procedure for Nonvolatile Amine Synthesis). To a Smith Process vial (2−5 mL) containing AG MP-50 resin (3.5 mequiv/g dry resin, 0.571 g, 2 equiv) and ammonium chloride (0.0016 g, 0.030 mmol, 0.03 equiv) was added a methanolic solution (4 mL) of the mixture obtained according to the general procedure for Grignard addition. The mixture was heated at 110 °C for 10 min using an Emrys Synthesizer. The resin was separated from the solution phase by filtering through an SPE cartridge (6 mL) equipped with a PTFE stopcock. The resulting resin was then washed with methanol (2 × 4 mL for 10 min) and CH_2Cl_2 (2 × 4 mL for 10 min). The resin was shaken with a 4 M ammonia methanol solution (4 mL) for 50 min. The methanol solution was filtered, and the resin was washed with methanol (3 × 3 mL for 10 min). The combined filtrate and methanol wash was evaporated, taken up in dichloromethane, and filtered through a plug of Celite. The Celite was washed with a small amount of CH_2Cl_2. A 4 N HCl solution in 1,4-dioxane (1 mL) was added to this filtrate. Concentration of this filtrate then afforded analytically pure amine hydrochloride.

General Procedure for the Determination of Enantiomeric Purity. The amine hydrochloride (2−3 mg) was separately derivatized with an excess of (*R*)- and (*S*)-α-methoxy-α-(trifluoromethyl)phenylacetyl (MTPA) chloride according to Mosher's procedure.[10] Ratios of the MTPA amide diastereomers were determined by gas chromatography (GC) analysis (see General Methods).

Product Characterization. (*S*)-2-Butanamine Hydrochloride (4a). Prepared according to the general procedure using propanaldeyde and methylmagnesium bromide. The enantiomeric ratio was determined by GC analysis of the MTPA derivatives (100−250 °C, 2°/min; (*R*)-MTPA derivative of (*R*)-amine r_t = 30.4 min, (*S*)-amine r_t = 31.1 min). ^{1}H NMR δ 0.99 (t, J = 7.5, 3H), 1.26 (d, J = 6.6, 3H), 1.47−1.75 (m, 2H), 3.10−3.23 (m, 1H). Anal. Calcd for $C_4H_{12}ClN$: C, 43.84; H, 11.04; N, 12.78. Found: C, 43.88; H, 11.34; N, 12.51.

(*R*)-1-Phenylpropamine Hydrochloride (4b). Prepared according to the general procedure using propionaldehyde and phenylmagnesium bromide. The enantiomeric ratio was determined by GC analysis of the MTPA derivatives (150−250 °C, 5°/min; (*R*)-MTPA derivative of (*R*)-amine r_t = 16.6 min, (*S*)-amine r_t = 16.9 min). ^{1}H NMR δ 0.87 (t, J = 7.4, 3H), 1.85−2.09 (m, 2H), 4.13 (dd, J = 9.2, 6, 1H), 7.36−7.48 (m, 5H). Anal. Calcd for $C_9H_{14}ClN$: C, 62.97; H, 8.22; N, 8.16. Found: C, 62.91; H, 8.38; N, 8.00.

(*S*)-3-Methyl-2-butanamine Hydrochloride (4c). Prepared according to the general procedure using isobutyraldehyde and methylmagnesium bromide. The enantiomeric ratio was determined by GC analysis of the MTPA derivatives (100−250 °C, 2°/min; (*R*)-MTPA derivative of (*R*)-amine r_t = 33.7 min, (*S*)-amine r_t = 34.7 min). ^{1}H NMR δ 0.98 (d, J = 7, 6H), 1.22 (d, J = 6.7, 3H), 1.75−1.92 (m, 1H), 3.03−3.14 (m, 1H). Anal. Calcd for $C_5H_{14}ClN$: C, 48.58; H, 11.41; N, 11.33, Found: C, 48.65; H, 11.72; N, 11.01.

(*S*)-2-Methyl-3-pentanamine hydrochloride (4d). Prepared according to the general procedure using isobutyraldehyde and ethylmagnesium bromide. The enantiomeric ratio was determined by GC analysis of the MTPA derivatives (100−250 °C, 2°/min; (*R*)-MTPA derivative of (*R*)-amine r_t = 38.1 min, (*S*)-amine r_t = 38.7 min). ^{1}H NMR δ 0.92−1.04 (m, 9H), 1.49−1.79 (m, 2H), 1.87−2.01 (m, 1H), 2.86−2.96 (m, 1H). Anal. Calcd for $C_6H_{16}ClN$: C, 52.35; H, 11.72; N, 10.18. Found: C, 52.22; H, 12.00; N, 10.08.

(*R*)- 1-Phenyl-2-methyl-1-propanamine Hydrochloride (4e). Prepared according to the general procedure using isobutyraldehyde and phenylmagnesium bromide. The enantiomeric ratio was determined by GC analysis of the MTPA derivatives (150−250 °C, 5°/min; (*R*)-MTPA derivative of (*R*)-amine r_t = 17.3 min, (*S*)-amine r_t = 17.5 min). ^{1}H NMR δ 0.78 (d, J = 6.7, 3H), 1.12 (d, J = 6.6, 3H), 2.09−2.24 (m, 1H), 3.9 (d, J = 9.2, 1H), 7.35−7.48 (m, 5H). Anal. Calcd for $C_{10}H_{16}ClN$: C, 64.68; H, 8.68; N, 7.54. Found: C, 64.56; H, 8.91; N, 7.37.

(*S*)-1-Phenylethanamine Hydrochloride (4f). Prepared according to the general procedure using benzaldehyde and methylmagnesium bromide. The enantiomeric ratio was determined by GC analysis of the MTPA derivatives (150−250 °C, 5°/min; (*R*)-MTPA derivative of (*R*)-amine r_t = 15.3 min, (*S*)-amine r_t = 15.9 min). ^{1}H NMR δ 1.61 (d, J = 6.9, 3H), 4.43 (q, J = 6.9, 1H), 7.35−7.46 (m, 5H). Anal. Calcd for $C_8H_{12}ClN$: C, 60.95; H, 7.67; N, 8.89. Found: C, 60.74; H, 7.97; N, 8.62.

(*S*)-1-Phenyl-2-propanamine Hydrochloride (4g). Prepared according to the general procedure using phenylacetaldehyde and methylmagnesium bromide. The enantiomeric ratio was determined by GC analysis of the MTPA derivatives (150−250 °C, 5°/min; (*R*)-MTPA derivative of (*R*)-amine r_t = 17.2 min, (*S*)-amine r_t = 17.7 min). ^{1}H NMR δ 1.22 (d, J = 6.6, 3H), 2.76 (dd, J = 13.5, 8.2, 1H), 2.95 (dd, J = 13.5, 6.2, 1H), 3.42−3.55 (m, 1H), 7.20−7.38 (m, 5H). Anal. Calcd for $C_9H_{14}ClN$: C, 62.97; H, 8.22; N, 8.16. Found: C, 62.90; H, 8.36; N, 7.92.

(*S*)-1-Phenyl-2-butanamine Hydrochloride (4h). Prepared according to the general procedure using phenylacetaldehyde and ethylmagnesium bromide. The enantiomeric ratio was determined by GC analysis of the MTPA derivatives (150−250 °C, 5°/min; (*R*)-MTPA derivative of (*R*)-amine r_t = 18.6 min, (*S*)-amine r_t = 19.0 min). ^{1}H NMR δ 1.01 (t, J = 7.5, 3H), 1.51−1.73 (m, 2H), 2.81−2.98 (m, 2H), 3.33−3.39 (m, 1H), 7.21−7.38 (m, 5H). Anal. Calcd for $C_{10}H_{16}ClN$: C, 64.68; H, 8.68; N, 7.54. Found: C, 64.29; H, 8.97; N, 7.44.

(*R*)-1,2-Diphenylethanamine Hydrochloride (4i). Prepared according to the general procedure using phenylacetaldehyde and phenylmagnesium bromide. The enantiomeric ratio was determined by GC analysis of the MTPA derivatives (100−300 °C, 5°/min; (*R*)-MTPA derivative of (*R*)-amine r_t = 35.6 min, (*S*)-amine r_t = 35.7 min). ^{1}H NMR δ 3.14−3.33 (m, 2H), 4.49 (dd, J = 8.9, 6.5, 1H), 7.05−7.12 (m, 2H), 7.15−7.26 (m, 3H), 7.30−7.43 (m, 5H). Anal. Calcd for $C_{14}H_{16}ClN$: C, 71.94; H, 6.90; N, 5.99. Found: C, 71.66; H, 7.26; N, 5.92.

(*S*)-(−)-1-(1-Naphthyl)ethanamine Hydrochloride (4j). Prepared according to the general procedure using 1-naphthaldeyde and methylmagnesium bromide. The enantiomeric ratio was determined by GC analysis of the MTPA derivatives (100−300 °C, 5°/min; (*R*)-MTPA derivative of (*R*)-amine r_t = 34.3 min, (*S*)-amine r_t = 34.9 min). ^{1}H NMR δ 1.74 (d, J = 6.8, 3H), 5.37 (q, J = 6.8, 1H), 7.52−7.67 (m, 4H), 7.91−7.78 (m, 2H), 8.12 (d, J = 8.5, 1H). Anal. Calcd for $C_{12}H_{14}ClN$: C, 69.39; H, 6.79; N, 6.74. Found: C, 69.21; H, 6.77; N, 6.56.

(*S*)-1-(4-Methoxyphenyl)ethylamine Hydrochloride (4k). Prepared according to the general procedure for microwave-assisted resin capture using 4-methoxybenzaldehyde and methylmagnesium bromide. The enantiomeric ratio was determined by GC analysis of the MTPA derivatives (100−300 °C, 5°/min; (*R*)-MTPA derivative of (*R*)-amine r_t = 29.6 min, (*S*)-amine r_t = 30.3 min). ^{1}H NMR δ 1.59 (d, J = 6.9, 3H), 3.78 (s, 3H), 4.38 (q, J = 6.9, 1H), 6.97 (dt, J = 8.8, 3.0, 2H), 7.36 (dt, J = 8.8, 3.0, 2H). Anal. Calcd for $C_9H_{14}ClNO$: C, 57.60; H, 7.52; N, 7.46. Found: C, 57.79; H, 7.70; N, 7.46.

(*S*)-(4-Methoxyphenyl)phenylmethylamine Hydrochloride (4l). Prepared according to the general procedure for microwave assisted resin capture using 4-methoxybenzaldehyde and phenylmagnesium bromide. The enantiomeric ratio was determined by GC analysis of the MTPA derivatives (100−300 °C, 5°/min; (*R*)-MTPA derivative of (*R*)-amine r_t = 38.0 min, (*S*)-amine r_t = 38.2 min). ^{1}H NMR δ 3.78 (s, 3H), 5.56 (s, 1H), 6.97 (dt, J = 8.8, 2.1, 2H), 7.29 (dt, J = 8.7, 2.1, 2H) 7.35−7.46 (m, 5H). Anal. Calcd for $C_{14}H_{16}ClNO$: C, 67.33; H, 6.46; N, 5.61. Found: C, 67.05; H, 6.75; N, 5.46.

(*S*)-1-(4-Chlorophenyl)ethylamine Hydrochloride (4m). Prepared according to the general procedure for microwave assisted resin capture using 4-chlorobenzaldehyde and methylmagnesium bromide. The enantiomeric ratio was determined by GC analysis of the MTPA derivatives (100−300 °C, 5°/min; (*R*)-MTPA derivative of (*R*)-amine r_t = 28.5 min, (*S*)-amine r_t = 29.3 min). ^{1}H NMR δ 1.6 (d, J = 6.9, 3H), 4.45 (q, J = 6.9, 1H), 7.40−7.49 (m, 4H). Anal. Calcd for $C_8H_{11}Cl_2N$: C, 50.02; H, 5.77; N, 7.29. Found: C, 50.30; H, 5.97; N, 7.21.

(*S*)-(4-chlorophenyl)phenylmethylamine Hydrochloride (4n). Prepared according to the general procedure for microwave assisted resin capture using 4-chlorobenzaldehyde and phenylmagnesium bromide. The enantiomeric ratio was determined by GC analysis of the MTPA derivatives (100−300 °C, 5°/min; (*R*)-MTPA derivative of (*R*)-amine r_t = 36.9

min, (*S*)-amine r_t = 37.2 min). ^{1}H NMR δ 5.65 (s, 1H), 7.33−7.49 (m, 9H). Anal. Calcd for $C_{13}H_{13}Cl_2N$: C, 61.43; H, 5.16; N, 5.51. Found: C, 61.37; H, 5.22; N, 5.44.

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