ARTICLE

OBC
www.rsc.org/obc

A rapid and general method for the asymmetric synthesis of 2-substituted pyrrolidines using *tert*-butanesulfinamide

Kristin M. Brinner† and Jonathan A. Ellman*

Center for New Directions in Organic Synthesis, Chemistry Department, University of California, Berkeley, CA 94720, USA.
E-mail: kristin_brinner@chiron.com, ellman@cchem.berkeley.edu; Fax: +1 510 642 8369; Tel: +1 510 642 4488

Received (Pittsburgh, PA, USA) 8th March 2005, Accepted 11th April 2005
First published as an Advance Article on the web 4th May 2005

A new method for the asymmetric synthesis of 2-substituted pyrrolidines in three steps from commercially available starting materials is described. Addition of the Grignard reagent prepared from 2-(2-bromoethyl)-1,3-dioxane to *N*-*tert*-butanesulfinyl aldimines proceeds in high yields and with good diastereoselectivities. The sulfinamide products are then cleanly converted into pyrrolidines in one step.

Introduction

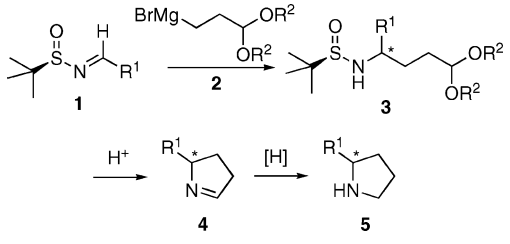
Pyrrolidines are an important class of biologically active compounds as they are found in a wide variety of natural products[1] and pharmaceuticals.[2] As a result, the synthesis of pyrrolidines has been an active area of research. Substituted pyrrolidines are accessed through a variety of routes. Cycloadditions have been exploited for the synthesis of highly functionalized pyrrolidines.[3] Intramolecular addition of nucleophiles into imines can also be used to construct pyrrolidines.[4] Additionally, nitroalkanes and azides have been used in a variety of routes.[5] 2-Alkylpyrrolidines were synthesized *via* asymmetric alkylation of a chiral formamidine derived from from L-valinol,[6] or preparation from 3-acylpropionic acids and phenylglycinol.[7] Finally, intramolecular nucleophilic addition of carbon- and nitrogen-based nucleophiles are utilized to afford variously substituted pyrrolidines.[8]

tert-Butanesulfinamide chemistry has been extensively exploited for the asymmetric synthesis of amines, including α-branched and α,α-dibranched amines,[9] β-amino acids,[10] β-amino alcohols[11] and 1,2-amino alcohols.[12] Here we report an efficient asymmetric synthesis of 2-substituted pyrrolidines **5** from simple, commercially available starting materials. This particular class of pyrrolidines is pharmaceutically relevant, as over 200 compounds containing this pharmacophore are currently in advanced biological testing.[13]

Results and discussion

Synthesis of pyrrolidines

We envisioned the synthesis of pyrrolidines starting with addition of Grignard reagent **2** to *N*-sulfinyl aldimines **1** (Scheme 1). Because the R^1 group of aldimine **1** becomes the 2-substituent in chiral pyrrolidine **5**, the commercial availability of over 3000 aldehydes allows for diverse inputs at this position. Additionally,



Scheme 1 Synthesis of pyrrolidines.

† Current address: Chiron Corporation, Emeryville, CA 94608, USA.

a variety of Grignard reagents **2a–d** (R^2 = -$(CH_2)_2$-, Me, Et, -$(CH_2)_3$-, respectively) with different acetal protecting groups should readily be accessible from commercially available alkyl bromides, allowing for optimization of yield and diastereoselectivity as necessary. Simultaneous cleavage of the acetal and sulfinamide protecting groups under acidic conditions would affect cyclization to form pyrrolines **4**, which would afford the final pyrrolidine product **5** upon reduction. Ideally, these two transformations could occur in one step, to rapidly access the pyrrolidine products.

N-Sulfinyl aldimines **1** were prepared by standard $Ti(OEt)_4$ condensation conditions.[14] Initial reaction of *N*-sulfinyl benzaldimine **1a** (R^1 = Ph) with Grignard reagent **2a** (R^2 = -$(CH_2)_2$-) at −48 °C afforded the desired sulfinamide product in good yield and diastereoselectivity (entry 1, Table 1). However, upon addition of this Grignard reagent to *N*-sulfinyl phenylacetaldimine **1b** (R^1 = Bn), a complex mixture of compounds was observed (entry 2). Because phenylacetaldimines are sensitive to competitive α-deprotonation, this result was not surprising. Reactions of this sort are typically carried out in non-coordinating solvents to increase the reactivity of the Grignard reagent towards addition rather than deprotonation. Unfortunately, no initiation of Grignard reagent **2a** (R^2 = -$(CH_2)_2$-) was observed in Et_2O, even when using highly activated Rieke magnesium.[15] Initial attempts to improve the addition of Grignard reagent **2a** (R^2 = -$(CH_2)_2$-) to aldimine **1b** (R^1 = Bn) in THF through the use of additives, including $AlMe_3$, $BF_3{\cdot}OEt_2$, $ZnCl_2$ and $MgBr_2$, also did not prove useful. Given these issues, the capacity of alternative Grignard precursors to initiate in Et_2O was next investigated. While Grignard reagents **2b** (R^2 = Me) and **2c** (R^2 = Et) did not form in Et_2O, 2-(2-bromoethyl)-1,3-dioxane successfully

Table 1 Synthesis of sulfinamide **3a**

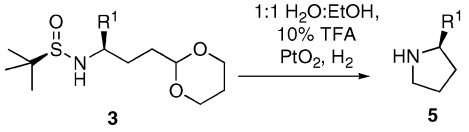
Entry	R^1	R^2	Solvent	Yield (%)[a]	dr
1	Ph	-$(CH_2)_2$-	THF	85	90 : 10[b]
2	Bn	-$(CH_2)_2$-	THF	—	—
3	Ph	-$(CH_2)_3$-	THF	95	90 : 10[b]
4	Bn	-$(CH_2)_3$-	Et_2O	82	88 : 12[b]
5	CH_2CH_2Ph	-$(CH_2)_3$-	THF	81	92 : 8[c]
6	*i*-Pr	-$(CH_2)_3$-	THF	Quant.	>90 : 10[d]

[a] Yield of purified material. [b] Determined by HPLC analysis of crude, filtered reaction material. [c] Determined by LCMS analysis of crude, filtered reaction material. [d] Determined by LCMS. The lack of any significant chromophores in this molecule made precise determination of dr difficult. The minor diastereomer was not observed in the NMR of the unpurified addition product.

DOI:10.1039/b502080h

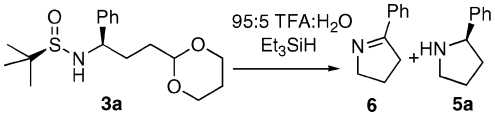
initiated in Et_2O. Grignard reagent **2d** (R^2 = -$(CH_2)_3$-) added cleanly to *N*-sulfinyl aldimines in both THF and Et_2O (entries 3–6). Additionally, Grignard reagent **2d** (R^2 = -$(CH_2)_3$-) formed much more cleanly than **2a** (R^2 = -$(CH_2)_2$-) in THF, which was plagued by the production of significant amounts of Wurtz coupled product, as well as a precedented cyclopropyl ether byproduct.[16]

With the desired sulfinamide intermediates **3** synthesized, conditions were developed to affect acidic deprotection and reduction to afford the final pyrrolidine products. Conversion of sulfinamides **3** to pyrrolidines **5** proceeded in good yield using 1 : 1 EtOH : H_2O, 10% TFA and 10 mol% PtO_2 under a H_2 atmosphere (eqn. 1).[17] However, it was difficult to remove all traces of platinum byproducts that visibly contaminated the pyrrolidine products. Aqueous workups, column chromatography and scavenging using sulfonic acid resin all failed to completely remove platinum from the pyrrolidines.



(1)

Because the presence of even trace amounts of platinum byproducts was undesirable, alternative acidic deprotection and reduction conditions were investigated. Reaction of sulfinamide **3a** (R^1 = Ph) in 95 : 5 TFA : H_2O with 10 eq. of Et_3SiH gave trace amounts of the desired pyrrolidine **5a** (entry 1, Table 2).[18] Surprisingly, pyrroline byproduct **6** was observed to form as the major product of this reaction (eqn. 2). This requires isomerization of imine **4a** to imine **6**. Resubjecting pyrroline **6** to the reaction conditions did not increase conversion to desired pyrrolidine **5a**. Apparently, once the imine double bond is in conjugation with the phenyl ring, Et_3SiH is not a strong enough reducing agent to affect conversion to **5a**. Varying the relative concentrations of sulfinamide **3a** and Et_3SiH in 95 : 5 TFA : H_2O, the ratio of TFA to H_2O or the use of other cosolvents did not resolve this issue.



(2)

In order to determine the potential role of the solvent in the isomerization, experiments were run where the sulfinamide was dissolved in 95 : 5 TFA : H_2O and the Et_3SiH was added after a set period of time. The unexpected results of this experiment revealed that waiting even 2 min between addition of TFA and Et_3SiH almost entirely eliminated the formation of **6** and after 10 min the formation of **6** was not observed (entries 3 and 4, Table 2). Using these optimized deprotection/reduction conditions, **5a–5d** were successfully synthesized (Table 3).[19]

Conversion of sulfinamides **3a** and **3b** to pyrrolidines **5a** and **5b** and comparison to literature optical rotation values revealed that the addition of Grignard **2d** proceeded with the opposite sense of induction typically observed for Grignard additions to sulfinyl aldimines. This reversal in selectivity has previously been observed when the sulfinyl aldimine bears a coordinating group.[21] Intramolecular chelation of the acetal could explain the reversal in diastereoselectivity.[22]

Table 2 Optimization of conditions for converting **3a** to pyrrolidine **5a**

Entry	Time/min[a]	Ratio **6** : **5a**[b]
1	0	94 : 6
2	2	8 : 92
3	10	0 : 100
4	30	0 : 100

[a] **3a** was dissolved in 95 : 5 TFA : H_2O, with time indicating the period of time between addition of TFA : H_2O and Et_3SiH. [b] Ratio determined by NMR after aqueous workup of crude reaction material.

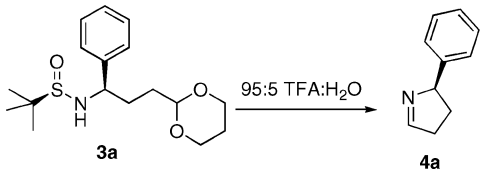
Table 3 Synthesis of pyrrolidines **5**

Entry	R	Compound	Yield (%)[a]
1	Ph	**5a**	92
2	Bn	**5b**	84
3	CH_2CH_2Ph	**5c**	63
4	*i*-Pr	**5d**	48

[a] Yield of purified HCl salt of pyrrolidine.[20]

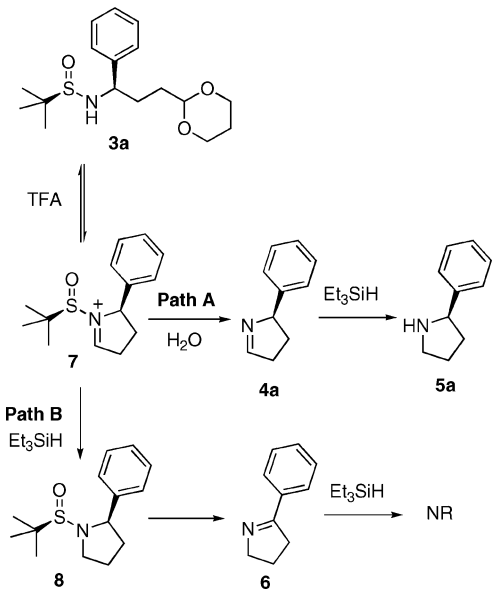
Mechanism of pyrroline formation

Pyrroline **6** was a surprising byproduct of the unoptimized reaction conditions for the deprotection and reduction of sulfinamide **3a**. We therefore investigated the mechanism of its formation. Formation of **4a** was monitored by NMR upon treatment of sulfinamide **3a** with 95 : 5 d_1TFA : D_2O. In less than 15 min, pyrroline **4a** was formed as the only product (eqn. 3).[23]



(3)

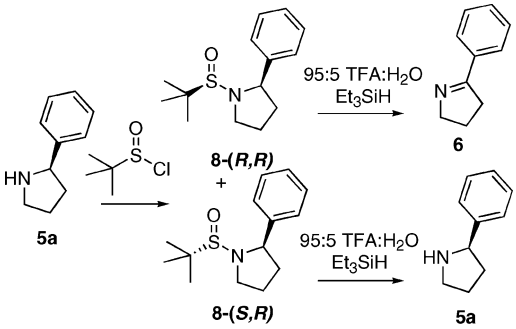
It has previously been observed that the deprotection of sulfinamides in 95 : 5 TFA : H_2O is not complete after even 24 h.[24] Rapid formation of **4a** suggests that sulfinamide **3a** is being activated in some manner to dramatically accelerate deprotection of the *N*-sulfinyl group. Therefore, the following mechanism is proposed (Scheme 2). TFA mediates the formation of transient *N*-sulfinyl pyrroline **7** through acidic cleavage of the acetal. There are then two likely pathways for the formation of pyrrolines **4a** and **6** from this intermediate. Firstly, water could cleave the sulfinyl group to afford pyrroline **4a** (pathway A). This was supported in the NMR experiments as sulfinamide **3a** rapidly converts to **4a** in 95 : 5 TFA : H_2O. Under the optimized stepwise conditions, pyrroline **4a** would then be reduced upon addition of Et_3SiH to afford the desired pyrrolidine **5a**. Alternatively, when Et_3SiH is present at the outset of the reaction, Et_3SiH could intercept and reduce the highly activated *N*-sulfinyl pyrroline **7** before it reacted with water, to afford *N*-sulfinyl pyrrolidine **8** (pathway B). Sulfinamide **8** could



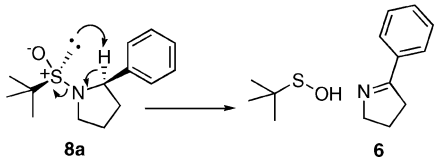
Scheme 2 Potential mechanism of formation of pyrroline **6**.

then form pyrroline **6** through an unknown reaction mechanism. This pyrroline is not reactive to Et_3SiH, as resubjecting pyrroline **6** to the reaction conditions does not affect any reduction to pyrrolidine **5a**.

Evidence for pathway B was supported by independent synthesis of **8** (Scheme 3). After separation, the diastereomers **8-(*R,R*)** and **8-(*S,R*)** were individually subjected to the 95 : 5 TFA : H_2O and Et_3SiH reaction conditions. While diastereomer **8-(*S,R*)** was converted to pyrrolidine **5a**, diastereomer **8-(*R,R*)** was converted to pyrroline **6**, presumably through a concerted elimination mechanism (eqn. 4).[25]



Scheme 3 Evidence for proposed mechanism of pyrroline formation **6**.



(4)

In conclusion, a rapid and general method for the asymmetric synthesis of 2-substituted pyrrolidines using *tert*-butanesulfinamide is described. The mechanism of formation of a surprising byproduct under unoptimized conditions for the deprotection and reduction step was also investigated. This byproduct could be completely eliminated by straightforward modification of the reaction conditions to provide pyrrolidines in three steps from commercially available aldehydes and 2-(2-bromoethyl)-1,3-dioxane.

Experimental

General details

Unless otherwise noted, all reagents were obtained from commercial suppliers and used without further purification. Tetrahydrofuran and diethyl ether were distilled from sodium/benzophenone ketyl, toluene from sodium and dichloromethane from CaH_2 immediately before use. All reactions were carried out in flame or oven dried glassware under a nitrogen atmosphere unless indicated otherwise. Chromatography was carried out using Merck 230–400 mesh silica gel. IR spectra were recorded on a Nicolet Avatar 370 DTGS spectrometer using single bounce HATR on a ZnSe crystal, only partial data is reported. HPLC analysis was performed on a HP HPLC. Data for ^{1}H NMR are reported as shift (ppm), multiplicity, coupling constant (Hz) and integration. Data for ^{13}C NMR are reported as chemical shift (ppm). Mass spectra were obtained from the University of California at the Berkeley Micro-Mass facility. *tert*-Butanesulfinamide and *tert*-butanesulfinyl imines (**1a-d**) were prepared as previously described.[14]

General procedure for addition of Grignard reagent 2 (R = -$(CH_2)_3$-) to *N-tert*-butanesulfinyl imines 1

(R^1 = Ph, CH_2CH_2Et, *i*-Pr). Freshly crushed magnesium turnings (15.0 eq.) were flame dried with catalytic amounts of I_2 in the reaction flask and subsequently suspended in THF (3.0 M). 2-(2-Bromoethyl)-1,3-dioxane (5.0 eq., 3.0 M in THF) was added dropwise. The reaction mixture was periodically cooled in a rt water bath to prevent refluxing. After addition of the 2-(2-bromoethyl)-1,3-dioxane solution was complete, the reaction mixture was stirred for 1 h. The solution was then transferred to a different flask to remove the remaining Mg and was cooled to −48 °C. Upon cooling, a small amount of precipitate may be observed. *N-tert*-Butanesulfinyl imines (1 M in THF) were added dropwise to the Grignard solution, the solution was stirred for 12 h at −48 °C and then was slowly warmed to rt. The reaction mixtures were then quenched with sat. $NH_4Cl_{(aq)}$ and extracted with EtOAc (× 3). The combined organic layers were dried (Na_2SO_4), concentrated and the products purified to diastereomeric purity by column chromatography (2 : 1 hexanes : EtOAc, to 100% EtOAc) to afford the sulfinamide products as colorless waxy solids. The diastereomeric ratio was determined by HPLC analysis of crude, filtered material.

From *N*-sulfinyl aldimine **1** (R^1 = Ph, 345 mg, 1.65 mmol), sulfinamide **3a** (R^1 = Ph, 507 mg, 1.56 mmol, 95%) was obtained. Mp 82–84 °C. IR 3303, 1136, 1053, 1002 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.21 (s, 9H), 1.26 (m, 1H), 1.31–1.55 (m, 2H), 1.80 (m, 1H), 2.10 (m, 2H), 3.42 (d, J = 3.9, 1H), 3.69 (m, 2H), 4.03 (m, 2H), 4.33 (m, 1H), 4.44 (t, J = 5.1, 1H), 7.25 (m, 5H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 22.6, 25.6, 30.8, 31.3, 55.6, 58.9, 66.7, 101.6, 127.1, 127.7, 128.6, 142.1. HPLC (Microsorb 100 Å SiO_2, 90 : 10 hexanes : EtOAc, 1 mL min^{-1}): major, 16.8 min; minor, 25.5 min, 90 : 10 dr. HRMS (FAB+) calcd for $C_{17}H_{28}N_1O_3S_1$ [M + H] 326.178990; found, 326.178991. $[\alpha]_D^{25}$ −46.7 (*c* 1.04, $CHCl_3$).

From *N*-sulfinyl aldimine **1** (R^1 = CH_2CH_2Ph, 390 mg, 1.65 mmol), sulfinamide **3c** (R^1 = CH_2CH_2Ph, 470 mg, 1.33 mmol, 81%) was obtained. Mp 60–61 °C. IR 3300, 1140, 1045, 1009 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.13 (s, 9H), 1.24 (m, 1H), 1.51–1.88 (m, 7H), 2.63 (t, J = 7.5, 2H), 3.17 (m, 1H), 3.26 (m, 1H), 3.63 (m, 2H), 3.99 (dd, J = 4.5, 11.5, 2H), 4.42 (m, 1H), 7.09–7.21 (m, 5H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 22.6, 25.6, 29.8, 31.1, 31.7, 37.9, 55.9, 56.3, 66.8, 101.9, 125.8, 128.3, 128.4, 141.5. LCMS (Eclipse XDB-C8, 5μm, 40 : 60 to 95 : 5 MeCN : H_2O, 0.1% TFA, 1 mL min^{-1}): major, 7.3 min; minor, 8.0 min, dr 92 : 8. HRMS (FAB+) calcd for $C_{19}H_{32}NO_3S$ [M + H] 354.209790; found, 354.210291. $[\alpha]_D^{25}$ −40.8 (*c* 1.06, $CHCl_3$).

From *N*-sulfinyl aldimine **1** (R^1 = *i*-Pr, 290 mg, 1.65 mmol), sulfinamide **3d** (R^1 = *i*-Pr, 500 mg, 1.65 mmol, quant.) was obtained. IR 3259, 1142, 1051, 999 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.77 (d, J = 6.5, 3H), 0.77 (d, J = 7.0, 3H), 1.17 (s, 9H), 1.27 (m, 1H), 1.30 (m, 1H), 1.41 (m, 1H), 1.59 (m, 1H), 1.82–1.92 (m, 2H), 2.88 (m, 1H), 3.15 (m, 2H), 3.58 (m, 2H), 3.92 (dd, J = 4.5, 11, 2H), 4.39 (t, J = 4.5, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 17.3, 18.4, 22.6, 25.6, 25.7, 31.7, 32.4, 56.0, 62.3, 66.7, 101.9. Dr >90 : 10. HRMS (FAB+) calcd for $C_{14}H_{30}NO_3S$ [M + H] 292.194830; found 292.194641. $[\alpha]_D^{25}$ −14.8 (*c* 1.00, $CHCl_3$).

Sulfinamide **3b** (R^1 = Bn). Freshly crushed magnesium turnings (1.2 g, 50 mmol, 30.0 eq.) were flame dried with catalytic amounts of I_2 in the reaction flask and subsequently were suspended in Et_2O (17 mL). 2-(2-Bromoethyl)-1,3-dioxane (2.3 mL, 17 mmol, 10.0 eq., in 5.5 mL of Et_2O) was added dropwise. The reaction mixture was periodically cooled in a rt water bath to prevent refluxing. After the addition of the solution of 2-(2-bromoethyl)-1,3-dioxane was complete, the reaction mixture was stirred for 1 h. The solution was transferred to a different flask to remove the remaining Mg and then was cooled to −48 °C. Upon cooling, a small amount of precipitate may be observed. *N-tert*-Butanesulfinyl imine **2** (R^1 = Bn, 368 mg, 1.65 mmol, in 1.7 mL of Et_2O) was added dropwise to the Grignard solution, the resulting solution was stirred for 12 h at −48 °C and then was slowly warmed to rt. The reaction mixture was quenched with sat. $NH_4Cl_{(aq)}$ and extracted with Et_2O (× 3). The combined organics were dried (Na_2SO_4), concentrated

and the product purified to diastereomeric purity by column chromatography (2 : 1 hexanes : EtOAc to 100% EtOAc) to afford **3b** (460 mg, 1.36 mmol, 82%) as a colorless, waxy solid. The diastereomeric ratio was determined by HPLC analysis of crude, filtered material. Mp 91–92 °C. IR 3139, 1140, 1049 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 1.11 (s, 9H), 1.16 (m, 1H), 1.41–1.63 (m, 4H), 1.88 (m, 1H), 2.83 (d, $J = 6.0$, 2H), 3.16 (d, $J = 7.8$, 1H), 3.39 (m, 1H), 3.59 (m, 2H), 3.92 (m, 2H), 4.36 (t, $J = 4.8$, 1H), 7.11 (m, 5H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 22.6, 25.7, 28.8, 31.5, 42.5, 55.9, 56.9, 66.8, 101.9, 126.5, 128.3, 130.0, 137.1. HPLC (SiO_2, 90 : 10 hexanes : EtOAc, 1 mL min^{-1}): major, 16.0 min; minor, 19.7 min, dr 88 : 12. HRMS (FAB+) calcd for $C_{18}H_{30}N_1O_3S_1$ [M + H] 340.194420; found 340.194641. $[\alpha]_D^{25}$ −27.6 (*c* 1.06, $CHCl_3$).

General procedure for the deprotection and reduction of 3a–3d to afford 5a–5d

N-*tert*-Butanesulfinamides **3a–3d** (1.0 eq.) were dissolved in 95 : 5 TFA : H_2O to a final concentration of 0.1 M. After stirring for 30 min, Et_3SiH (10.0 eq.) was added to the reaction solutions and the reaction mixtures were stirred vigorously for 24 h. The reaction mixtures were concentrated and the products were purified by column chromatography (20 : 1 : 0.1 to 10 : 1 : 0.5 CH_2Cl_2 : MeOH : NH_4OH) to afford the free amine products. After concentrating the column fractions, the products were resuspended in MeOH and concentrated again to ensure complete removal of all NH_3. Resuspension in CH_2Cl_2 followed by addition of 1 M HCl in Et_2O afforded the amine hydrocholorides as yellow oils. NMRs are reported for the free amine and purified yields and optical rotation are based on the HCl salt of the amine products, except where indicated otherwise.

From sulfinamide **3a** (91 mg, 0.28 mmol), (*R*)-2-phenylpyrrolidine·HCl (**5a**) (45 mg, 0.25 mmol, 88%) was obtained. IR 2957 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ 1.70 (m, 1H), 1.83–1.95 (m, 2H), 2.18 (m, 1H), 2.77 (s, br, 1H), 3.00 (m, 1H), 3.19 (m, 1H), 4.10 (t, $J = 7.5$, 1H), 7.22–7.35 (m, 5H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 25.4, 33.9, 46.6, 62.6, 126.5, 127.0, 128.4, 143.4. HRMS (FAB+) calcd for $C_{10}H_{14}N_1$ [M + H] 148.112850; found 148.112625. $[\alpha]_D^{25}$ −9.10 (*c* 1.00, MeOH), literature $[\alpha]_D$ −22.0 (*c* 2.0, MeOH).[7a]

To confirm optical purity, pyrrolidine **5a** (7 mg, 0.05 mmol) was dissolved in CH_2Cl_2 (0.5 mL). The solution was cooled to 0 °C and *i*-Pr_2EtN (0.02 mL, 0.1 mmol) was added to the solution, followed by either (*R*)-(+)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride (MTPA) or (*S*)-(+)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride (25 mg, 0.1 mmol). After stirring for 30 min at 0 °C, the solutions were warmed to rt, diluted with CH_2Cl_2 and washed with 1.0 M $NaHSO_{4(aq)}$. The organic layers were dried (Na_2SO_4) and concentrated to afford the MTPA amides. HPLC analysis (2.1 cm × 5 μM Hypersil Si column, detection at 210 nm, 1 mL min^{-1}, 98 : 2 hexanes : *i*PrOH) on the unpurified material established ≥99% enantiomeric excess, with the $t_R = 6.09$ min for the amide derived from the (*R*)-(+)-MTPA chloride and $t_R = 8.13$ min for the amide derived from the (*S*)-(−)-MTPA chloride.

From sulfinamide **3b** (74 mg, 0.22 mmol), (*R*)-2-benzylpyrrolidine·HCl (**5b**) (30 mg, 0.19 mmol, 84%) was obtained. IR 2923 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ 1.70 (m, 1H), 1.94 (m, 1H), 1.97 (m, 2H), 2.88 (m, 1H), 3.12 (m, 2H), 3.26 (m, 1H), 3.63 (m, 1H), 3.97 (s, br, 1H), 7.21 (m, 5H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 22.7, 29.5, 37.4, 44.9, 61.9, 126.9, 128.6, 128.6, 136.6. HRMS (FAB+) calcd for $C_{11}H_{16}N_1$ [M + H] 162.128140; found 162.128275. $[\alpha]_D^{25}$ −9.20 (*c* 1.00, MeOH), $[\alpha]_D^{25}$ −17.0 (*c* 1.00, 2 N HCl), literature $[\alpha]_D^{25}$ −15.1 (*c* 0.6, MeOH),[26] for enantiomer $[\alpha]_D^{25}$ (20.00 (*c* 0.3, MeOH).[7b]

From sulfinamide **3c** (84 mg, 0.24 mmol), (*R*)-2-phenethylpyrrolidine·HCl (**5c**) (33 mg, 0.15 mmol, 63%), was obtained. IR 2925 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 1.42 (m, 1H), 1.75–2.02 (m, 5H), 2.74 (m, 2H), 3.00 (m, 1H), 3.15 (m, 2H), 3.98 (s, br, 1H), 7.20–7.33 (m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.9, 31.5, 33.6, 37.1, 46.0, 59.0, 125.9, 128.4, 128.4, 141.8. HRMS (FAB+) calcd for $C_{12}H_{18}N$ [M + H] 176.144080; found 176.143925. $[\alpha]_D^{25}$ −100.9 (*c* 1.00, MeOH).

From sulfinamide **3d** (80 mg, 0.27 mmol), (*R*)-2-isopropylpyrrolidine·HCl (**5d**) (20 mg, 0.13 mmol, 48%), was obtained. IR 2964 cm^{-1}. NMR of HCl salt of pyrrolidine reported. ^1H NMR (400 MHz, MeOD) δ 1.05, (d, $J = 6.8$, 3H), 1.11 (d, $J = 6.8$, 3H), 1.72 (m, 1H), 1.95 (m, 3H), 2.05 (m, 1H), 3.19 (m, 1H), 3.34 (m, 2H). ^{13}C NMR (100 MHz, MeOD) δ 19.1, 19.6, 23.7, 28.9, 31.0, 45.4, 67.4. HRMS (FAB+) calcd for $C_7H_{15}N$ [M + H] 114.128290; found 114.128275. $[\alpha]_D^{25}$ −9.20 (*c* 1.00, MeOH).

Pyrroline **4a**. *N*-*tert*-Butanesulfinamide **3a** (11 mg, 0.033 mmol) was dissolved in 95 : 5 d_1TFA : D_2O and the reaction progress was monitored by ^1H and ^{13}C NMR. Complete conversion to pyrroline **4a** was observed at 15 min. Peaks corresponding to the cleaved diol protecting group and the *tert*-butanesulfinic acid are indicated separately. ^1H NMR (300 MHz, 95 : 5 d_1TFA : D_2O) δ 2.45 (m, 1H), 3.02 (m, 1H), 3.46–3.60 (m, 2H), 5.65 (m, 1H), 7.31 (m, 2H), 7.51 (m, 3H), 9.02 (m, 1H). ^{13}C NMR (125 MHz, 95 : 5 d_1TFA : D_2O) δ 37.4, 59.4, 73.9, 127.6, 131.4, 132.0, 136.1, 183.4. HRMS (FAB+) calcd for $C_{10}H_{12}N$ [M + H] 146.097310; found 146.096974. 1,3-Propanediol: ^1H NMR (500 MHz, 95 : 5 d_1TFA : D_2O) δ 2.34 (m, 2H), 4.61 (m, 4H). ^{13}C NMR (125 MHz, 95 : 5 d_1TFA : D_2O) δ 29.9, 66.6. *tert*-Butanesulfinic acid: ^1H NMR (500 MHz, 95 : 5 d_1TFA : D_2O) δ 1.2 (s, 1H). ^{13}C NMR (125 MHz, 95 : 5 d_1TFA : D_2O) δ 21.5, 28.2.

Compounds **8-(*R,R*)** and **8-(*R,S*)**. Pyrrolidine **5a** (140 mg, 0.11 mmol, 0.2 M) was dissolved in THF (4.0 mL) and *i*-Pr_2EtN (300 μL, 1.7 mmol, 2.2 eq.) was added. The resulting solution was added to a solution of THF (4.8 mL) containing DMAP (23 mg, 0.19 mmol, 0.2 eq.), *i*-Pr_2EtN (240 μL, 1.4 mmol, 1.5 eq.) and *tert*-butanesulfinyl chloride (0.47 mL, 2.0 M in toluene, 0.95 mmol, 1.2 eq.). The resulting solution was stirred at rt for 12 h. The reaction mixture was concentrated and the products purified by column chromatography (4 : 1 to 2 : 1 hexanes : EtOAc) to afford **8-(*R,R*)** (49 mg, 0.19 mmol, 25%) as a white solid and **8-(*R,S*)** (100 mg, 0.40 mmol, 50%) as a yellow oil. **8-(*R,R*)**: IR 1058 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ 1.10 (s, 9H), 1.77–1.90 (m, 3H), 2.13 (m, 1H), 3.57 (m, 1H), 3.67 (m, 1H), 5.06 (dd, $J = 2.5$, 8, 1H), 7.20–7.32 (m, 5H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 23.0, 24.1, 36.6, 54.9, 57.4, 88.7, 123.3, 126.3, 126.5, 144.6. HRMS (FAB+) calcd for $C_{14}H_{22}NOS$ [M + H] 252.141490; found, 252.142211. $[\alpha]_D^{25}$ +108.8 (1.00 *c*, $CHCl_3$). **8-(*R,S*)**: IR 1060 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 1.10 (s, 9H), 1.87 (m, 2H), 1.97 (m, 1H), 2.23 (m, 1H), 2.99 (m, 1H), 3.89 (m, 1H), 4.64 (m, 1H), 7.20–7.35 (m, 5H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 23.7, 26.3, 35.9, 42.0, 57.2, 69.2, 127.1, 127.1, 128.2, 143.2. HRMS (FAB+) calcd for $C_{14}H_{22}NOS$ [M + H] 252.141490; found 252.142211. $[\alpha]_D^{25}$ +93.6 (*c* 0.99, $CHCl_3$).

Pyrroline **6**. Et_3SiH (0.46 mL, 2.8 mmol, 10 eq.) in 95 : 5 TFA : H_2O (2.8 mL) was added to sulfinamide **3a** (92 mg, 0.28 mmol). The reaction mixture was stirred overnight, concentrated and the product purified by column chromatography (30 : 1 CH_2Cl_2 : MeOH, 0.1% NH_4OH). To remove traces of Et_3SiH, the product was dissolved in 1 M $HCl_{(aq)}$, washed with Et_2O, brought to basic pH with solid $NaHCO_3$ and extracted with CH_2Cl_2. The CH_2Cl_2 layer was dried (Na_2SO_4), acidified with 1 M HCl in Et_2O and concentrated to afford **6** (20 mg, 14 mmol, 50%) as a glassy, clear solid. Mp 73–74 °C. IR 1645 cm^{-1}. ^1H NMR (500 MHz, MeOD) δ 2.46 (m, 2H), 3.69 (m, 2H), 4.27 (m, 2H), 7.69 (m, 2H), 7.85 (m, 1H), 8.09 (m, 2H). ^{13}C NMR (125 MHz, MeOD) δ 19.5, 35.1, 53.6, 125.9, 129.5, 130.2, 136.2, 186.1. HRMS (FAB+) calcd for $C_{10}H_{12}N_1$ [M + H] 146.097170; found 146.096974.

Acknowledgements

This work was supported by the NSF-CHE-0139468 (J. A. E.). The Center for New Directions in Organic Synthesis is supported by Bristol-Myers-Squibb as a sponsoring member and Novartis as a supporting member.

References

1 For examples, see: (*a*) A. Elbein; R. I. Molyneux, in *Alkaloids, Chemical and Biological Perspectives*, ed. S. W. Pelletier, John Wiley, New York, 1990; (*b*) *The Alkaloids: Chemistry and Biology*, ed. G. A. Cordell, Academic Press, San Diego, 2000, vol 54.
2 (*a*) R. L. Elliot, H. Kopeka, N.-H. Lin, Y. He and D. S. Garvey, *Synthesis*, 1995, 772; (*b*) N.-H. Lin, G. M. Carrera, Jr. and D. J. Anderson, *J. Med. Chem.*, 1994, **37**, 3542.
3 (*a*) K. M. Belyk, C. D. Beguin, M. Palucki, N. Grinberg, J. DaSilva, D. Askin and N. Yasuda, *Tetrahedron Lett.*, 2004, **45**, 3265; (*b*) S. E. Denmark and L. R. Marcin, *J. Org. Chem.*, 1995, **60**, 3221.
4 (*a*) A. R. Katritzky, X.-L. Cui, B. Yang and P. J. Steel, *J. Org. Chem.*, 1999, **64**, 1979; (*b*) D. Duncan and T. Livinghouse, *J. Org. Chem.*, 2001, **66**, 5237.
5 (*a*) N. Halland, R. G. Hazell and K. A. Jorgensen, *J. Org. Chem.*, 2002, **67**, 8331; (*b*) D. S. Matteson and G. Y. Kim, *Org. Lett.*, 2002, **4**, 2153.
6 A. I. Meyers, D. A. Dickman and T. R. Bailey, *J. Am. Chem. Soc.*, 1985, **107**, 7974.
7 (*a*) A. I. Meyers and L. E. Burgess, *J. Org. Chem.*, 1991, **56**, 2294; (*b*) L. E. Burgess and A. I. Meyers, *J. Org. Chem.*, 1992, **57**, 1656.
8 (*a*) D. Diez, T. M. Beneitez, I. S. Marcos, N. M. Garrido, P. Basabe and J. G. Urones, *Synlett*, 2001, **5**, 655; (*b*) T. Akiyama, Y. Ishida and H. Kagoshima, *Tetrahedron Lett.*, 1999, **40**, 4219; (*c*) C. Serino, N. Stehle, Y. S. Park, S. Florio and P. Beak, *J. Org. Chem.*, 1999, 1160.
9 (*a*) D. A. Cogan and J. A. Ellman, *J. Am. Chem. Soc.*, 1999, **121**, 268; (*b*) D. A. Cogan, G. Liu and J. A. Ellman, *Tetrahedron*, 1999, **55**, 8883.
10 T. P. Tang and J. A. Ellman, *J. Org. Chem.*, 2002, **67**, 7819.
11 T. P. Tang, S. K. Volkman and J. A. Ellman, *J. Org. Chem.*, 2001, **66**, 8772.
12 T. Kochi, T. P. Tang and J. A. Ellman, *J. Am. Chem. Soc.*, 2003, **125**, 11276.
13 *MDL Drug Data Report*, MDL Information Systems, Inc., San Leandro, CA, 2001.
14 G. Liu, D. A. Cogan, T. D. Owens, T. P. Tang and J. A. Ellman, *J. Org. Chem.*, 1996, **64**, 1278.
15 R. D. Rieke, P. T. J. Li, T. P. Burns and S. T. Uhm, *J. Org. Chem.*, 1981, **46**, 4323.
16 (*a*) C. Feugeas, *Bull. Soc. Chim. Fr.*, 1963, 2568; (*b*) J. C. Towell, *J. Org. Chem.*, 1976, **41**, 560.
17 These conditions had previously been used to cyclize and reduce 4-aminobutyraldehyde dimethyl acetal derivatives to afford the pyrrolidine products. O. Poupardin, C. Greek and J. P. Genet, *Synlett*, 1998, 1279.
18 These conditions had previously been used to reduce a pyrroline to a pyrrolidine.S. Esslinger, J. Titus, H. P. Koch, R. J. Bridges and A. R. Chamberlin, *Bioorg. Med. Chem. Lett.*, 2002, **10**, 3509.
19 Low yield in the synthesis of **5d** is attributed to the relative volatility of this product.
20 To ensure that no epimerization of **3a** had occurred during conversion to **5a**, both (−)- and (+)-MTPA amides were prepared and analyzed by HPLC and ^{1}H NMR. Only one diastereomer was detected for each amide product. See Experimental for characterization.
21 T. P. Tang, S. K. Volkman and J. A. Ellman, *J. Org. Chem.*, 2001, **66**, 8772 and references therein.
22 F. A. Davis and W. McCoull, *J. Org. Chem.*, 1999, **64**, 3396.
23 Propane 1,4-diol and *tert*-butanesulfinic acid were also formed as the aldehyde and amine were deprotected in the course of this reaction.
24 Unpublished results.
25 (*a*) T. Mukade, D. R. Dragoli and J. A. Ellman, *J. Comb. Chem.*, 2003, **5**, 590; (*b*) F. A. Davis, A. J. Friedman and E. W. Kluger, *J. Am. Chem. Soc.*, 1974, **96**, 5000.
26 O. W. Gooding and R. P. Bansal, *Synth. Commun.*, 1995, **25**, 1155.