Design, Synthesis, and Utility of a Support-Bound *tert*-Butanesulfinamide

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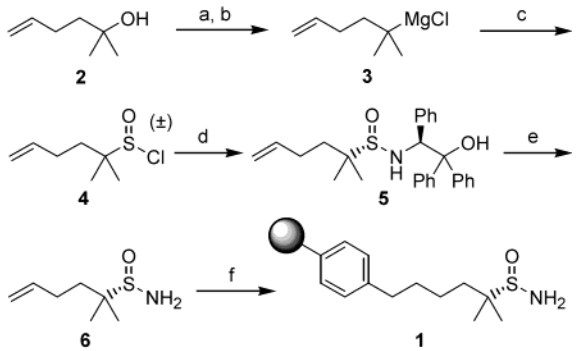
Amines are one of the most prevalent functionalities found in drugs. Not surprisingly, the synthesis of amine-containing compounds is a major focus of solid-phase synthesis, and a number of extensively utilized linkers have been developed for this purpose.[1] However, linkers for the *asymmetric* synthesis of amines have received only limited development despite their potential importance for the multistep asymmetric synthesis of drug leads and natural product-like compounds.[2] Herein, we report a novel and efficient synthesis of a support-bound *tert*-butanesulfinamide derivative **1** (SBS linker) and demonstrate the utility of this linker not only for the asymmetric synthesis of enantioenriched amines but also for the multistep asymmetric synthesis of pavine and isopavine alkaloids.

The versatility of *tert*-butanesulfinamide for the asymmetric synthesis of amines is well documented.[3] First, in contrast to most aldimines and ketimines, *tert*-butanesulfinyl imines are stable, isolable synthetic intermediates.[4] Second, addition of nucleophiles provides with high stereoselectivity α-branched and α,α-dibranched amines,[5] α-[6] and *β*-amino acids,[7] α-trifluoromethylamines,[8] and 1,2-amino alcohols.[9] Finally, the *tert*-butanesulfinyl group[7a] and the corresponding oxidation product, the *tert*-butanesulfonyl group,[10] serve as efficient acid-labile amine-protecting groups. To take advantage of all aspects of *tert*-butanesulfinamide chemistry we chose to link *tert*-butanesulfinamide to solid support using an all-carbon tether. This unreactive tether ensures that the support-bound derivative is compatible with a complete range of organometallic addition and acidic cleavage reaction conditions. We selected enantiomerically pure **6** as the key sulfinamide intermediate since we have previously demonstrated that alkene-appended functionality can be efficiently coupled to inexpensive bromopolystyrene by hydroboration followed by Suzuki cross-coupling.[11]

Beginning with tertiary alcohol **2**, chlorination in concentrated HCl was immediately followed by Grignard formation at 72 °C (Scheme 1). Sulfinyl chloride **4** is then prepared in a one-pot sequence by addition of Grignard **3** to sulfur dioxide condensed at −48 °C followed by chlorination with thionyl chloride.

Scheme 1[a]



[a] Reagents and conditions: (a) conc HCl; (b) Mg, THF, 72 °C; (c) SO_2, THF, −48 °C then $SOCl_2$; (d) cat. DMAP, *i*-Pr_2EtN, THF, −78 °C, (*S*)-2-amino-1,1,2-triphenylethanol; (e) Li, NH_3, NH_4Cl, THF, −48 °C; (f) bromopolystyrene, 5% $Pd(PPh_3)_4$, 2 M Na_2CO_3, 72 °C.

By taking advantage of the configurational lability of sulfinyl chlorides, we next developed a dynamic resolution process for the high-yield conversion of racemic **4** to enantiopure sulfinamide **6**. In particular, we extensively explored the addition of chiral alcohol and amine nucleophiles to provide a crystalline, diastereomerically pure sulfinyl intermediate that in a single step could be converted to **6**. Under optimal conditions (*S*)-2-amino-1,1,2-triphenylethanol[12] is added to sulfinyl chloride **4** with DMAP as a sulfinyl transfer catalyst *to provide a 16:1 diastereomeric ratio of sulfinamide products from which a single diastereomer* **5** *is isolated in 76% yield after recrystallization*. Without the DMAP additive only a 2:1 diastereomer ratio is observed. This result marks a dramatic advance in the dynamic resolution of sulfinyl halides with chiral amine nucleophiles.[13] In addition, the essential role of catalytic DMAP suggests that chiral sulfinyl transfer reagents might be developed for the catalytic asymmetric synthesis of sulfinyl compounds.

Diastereomerically pure **5** is readily converted to enantiomerically pure sulfinamide **6** in 65% yield by dissolving metal reduction. Hydroboration of **6** and Suzuki coupling with bromopolystyrene provides the SBS linker **1**.[14]

To correlate the solid- and solution-phase synthesis methods, the synthesis of chiral α-branched amines was first explored (Scheme 2). Condensation of aldehydes with **1** was efficiently accomplished with $Ti(OEt)_4$ as a Lewis acid and water scavenger.[15] Subsequent addition of ethylmagnesium bromide provided the desired α-branched amine products **7**. Cleavage from support to obtain amine hydrochlorides **8** was then achieved using HCl in a CH_2Cl_2/*n*BuOH solvent comixture for maximum swelling

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(14) Racemic support-bound sulfinamide **1** may also readily be accessed by addition of NH_4OH to **4** to provide racemic **6** in 71% yield.

(15) Condensation of ketones with **1** has been accomplished using $Ti(OEt)_4$ in THF at elevated temperatures.

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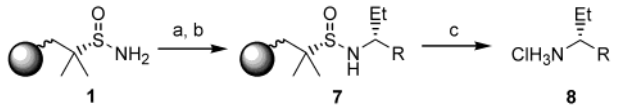
Scheme 2[a]



[a] Reagents and conditions: (a) RCHO, $Ti(OEt)_4$, THF; (b) EtMgBr, CH_2Cl_2, −48 °C; (c) 0.67 N HCl, 1:1 CH_2Cl_2/*n*BuOH.

Table 1. Solid-Phase Synthesis of α-Branched Amines

compound	R	% yield[a]	dr [b]
8a	*i*Pr	95	97:3 (97:3)
8b	Ph	95	88:12 (92:8)
8c	Bn	90	89:11 (92:8)
8d	*p*MeOPh	95	96:4 (99:1)

[a] Yields were determined via ^{1}H NMR integration against an internal standard. [b] Numbers in parentheses represent solution-phase results.

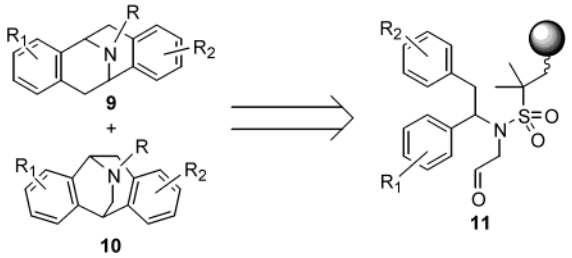


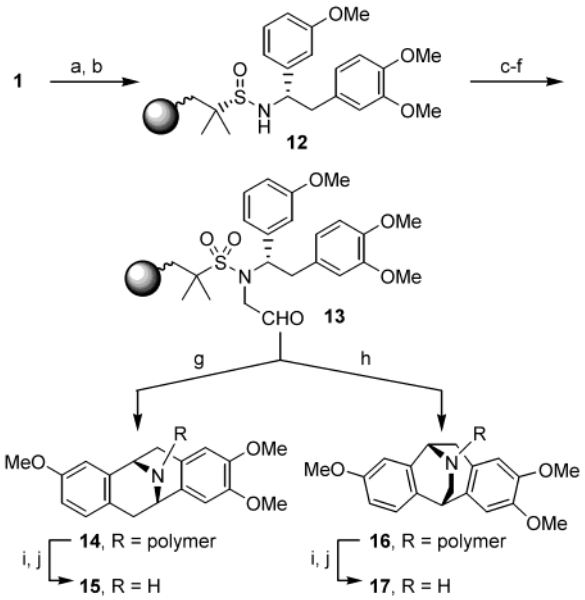
Figure 1. Pomeranz−Fritsch synthesis of pavine and isopavine alkaloids.

of the polystyrene support. Notably, amine hydrochlorides **8** were obtained in near quantitative overall yields in three steps based on the loading of brominated polystyrene. Furthermore, the % ee of the products was only slightly lower than that observed for the corresponding solution-phase synthesis (Table 1).

To demonstrate the utility and versatility of **1**, the syntheses of the pavine and isopavine classes of alkaloids, **9** and **10**, were undertaken (Figure 1). These alkaloids have important and diverse bioactivities. For example, pavine derivatives have been identified that inhibit TNF-α production[16] and isopavine derivatives are potent PCP receptor ligands.[17] We envisioned that diverse members of both alkaloid classes could potentially be accessed from the common intermediate **11** through modified Pomeranz−Fritsch conditions.[18] The α-branched amine present in **11** should be accessible by addition of aryl Grignard reagents to support-bound arylacetaldimines that may readily be accessed by condensation of arylacetaldehydes and **1**. Notably, due to competitive α-deprotonation, only one successful example of Grignard additions to arylacetaldimines has been reported.[5a]

The synthesis was initiated by condensation of 3,4-dimethoxyphenylacetaldehyde with **1** using excess $Ti(OEt)_4$ (Scheme 3). Addition of 3-methoxyphenylmagnesium bromide provided the desired amine **12**, which could be cleaved from support in 75% yield from bromopolystyrene. The sulfinyl nitrogen was then allylated by deprotonation with KO-*t*-Bu followed by addition of allyl bromide. The sulfinyl group was then oxidized to the sulfonamide with *m*-CPBA to provide a linker that is stable to subsequent acidic reaction conditions. Catalytic osmylation with excess *N*-methylmorpholine *N*-oxide in THF provided the 1,2-glycol, which was then cleaved with $Pb(OAc)_4$ in 10:1 CH_2Cl_2/acetic acid to give the aldehyde cyclization precursor **13**.

Scheme 3[a]



[a] Reagents and conditions: (a) 3,4-$(MeO)_2PhCH_2CHO$, $Ti(OEt)_4$, THF; (b) 3-MeOPhMgBr, CH_2Cl_2, −48 °C; (c) KO-*t*-Bu, NMP, allyl bromide; (d) *m*-CPBA, CH_2Cl_2/DMF; (e) 2.5% OsO_4/*t*-BuOH, NMO, THF; (f) $Pb(OAc)_4$, 10:1 CH_2Cl_2/AcOH; (g) dil HCl, CH_2Cl_2; (h) 3:1 CH_2Cl_2/HCO_2H; (i) 0.1 N TfOH, 1,4-dimethoxybenzene, CH_2Cl_2; (j) sulfonic acid resin then NH_3/MeOH.

In the presence of dilute HCl in CH_2Cl_2 aldehyde **13** was cyclized *with complete selectivity* to the pavine derivative **14**. Similarly, isopavine alkaloid **16** was obtained *with complete selectivity* through formic acid-mediated cyclization.[19] The final free amine derivatives **15** and **17** were obtained in high purity[20] without purification by cleavage from the solid phase using dilute triflic acid in CH_2Cl_2 followed by neutralization and scavenging with sulfonic acid resin.[21] Over the eight-step sequence, **15** and **17** were obtained in 86:14 enantiomeric ratios and 45 and 47% yields, respectively.

The efficient preparation of support-bound sulfinamide **1** was accomplished using a dynamic resolution methodology to access the key enantiomerically pure sulfinamide intermediate **6**. Using linker **1** chiral amines can be synthesized in near quantitative yields and in good enantiomeric purities. Finally, the synthesis of pavine and isopavine alkaloids demonstrates the utility of the linker for the multistep asymmetric synthesis of natural product-like compounds. Further applications of sulfinamide **1** will be reported in due course.

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Supporting Information Available: Synthetic procedures and characterization of new compounds (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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