# Chiral *N*-Acyl-*tert*-butanesulfinamides: The "Safety-Catch" Principle Applied to Diastereoselective Enolate Alkylations

Bradley J. Backes, Dean R. Dragoli, and Jonathan A. Ellman*,†

*Department of Chemistry, University of California, Berkeley, California 94720*

*Received February 12, 1999*

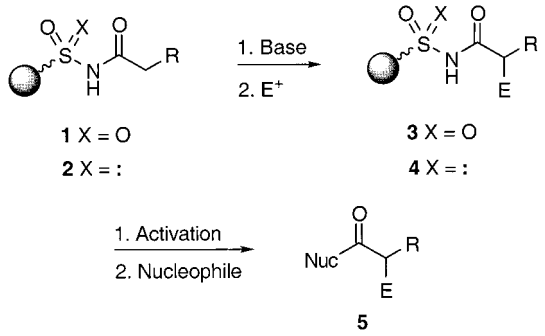
Diastereoselective enolate alkylation reactions of *N*-acylsulfinamides and conversion of the alkylation products to a variety of enantiopure products are reported. Several sulfinamides were prepared in solution followed by acylation to provide *N*-acylsulfinamides. The *N*-acylsulfinamides were then evaluated in diastereoselective enolate alkylation reactions. Of the sulfinamides evaluated, *tert*-butanesulfinamide provided the highest diastereoselectivity. To establish the potential utility of sulfinamides as versatile auxiliaries, methods were developed for (1) the racemization-free acylation of *tert*-butanesulfinamide to prepare optically pure *N*-acyl-*tert*-butanesulfinamides, (2) the diastereoselective *C*-alkylation of *N*-acyl-*tert*-butanesulfinamides, (3) the conversion of the *N*-acyl-*tert*-butanesulfinamides to the active ester equivalent by *N*-alkylation and *S*-oxidation, and (4) the cleavage of the *N*-alkyl-*N*-acyl-*tert*-butanesulfonamides to give chiral alcohol, ester, amide, and carboxylic acid target compounds. These studies provide the groundwork for the development of sulfinamides as dual chiral auxiliaries and linkers for the multistep solid-phase synthesis of enantioenriched compounds.

## Introduction

Previously we reported on the utility of *N*-acylsulfonamide **1** (Scheme 1) for solid-phase enolate alkylation reactions.[1,2] Treatment of **1** with >2 equiv of strong base provides an enolate that is stable indefinitely, even at room temperature, since decomposition by ketene formation or Claisen condensation would require that the high-energy sulfonamide dianion be the leaving group. Alkylation can therefore be performed even with unreactive alkylating agents such as 2-iodopropane to provide α-substituted products **3** in high yields. At the end of a synthesis sequence, target compounds **5** can be cleanly and rapidly obtained via activation by *N*-alkylation with diazomethane[1,3] or bromoacetonitrile[4] and release from the support by the addition of a variety of nucleophiles under mild conditions.

The solid-phase synthesis of enantioenriched compounds[5] has numerous applications for the identification of ligands to biological receptors[6] as well as ligands for asymmetric catalysis.[7] Unfortunately, while *N*-acylsulfonamide **1** is general for enolate alkylations, shows superior stability through multistep reaction sequences, and can be cleaved with a variety of nucleophiles after an activation step, the *N*-acylsulfonamide **1** is not chiral and consequently only racemic products result from the enolate alkylation step.

**Scheme 1**




One approach for the solid-phase synthesis of enantiomerically enriched compounds is the adaptation of known chiral auxiliaries to the support.[8] For asymmetric enolate alkylation reactions in solution, the *N*-acyloxazolidinones of Evans[9] and the pseudoephedrine tertiary amides of Myers[10] provide the gold standards in the field. Support-bound oxazolidinone-based auxiliaries have been developed,[11] and diastereoselective enolate alkylation has been demonstrated followed by hydrolytic cleavage from the support to provide enantioenriched α-alkylated carboxylic acids. However, this method is limited, since reaction with even modestly unreactive alkylating agents such as ethyl iodide requires higher reaction temperatures resulting in enolate decomposition via ketene formation.[12] In addition, it is often desirable to perform multiple steps on support-bound substrates to access useful classes of target compounds, and the use of basic

† Phone: 510-642-4488. Fax: 510-642-8369. E-mail: jellman@uclink.berkeley.edu.

(1) Backes, B. J.; Ellman J. A. *J. Am. Chem. Soc.* **1994**, *116*, 11171.
(2) For *N*-acylsulfonamide alkylation reactions in solution, see: (a) Belletire, J. L.; Spletzer, E. G. *Tetrahedron Lett.* **1986**, *27*, 131. (b) Belletire, J. L.; Mahmoodi, N. O. *Synth. Commun.* **1989**, *19*, 3371.
(3) Kenner, G. W.; McDermott, J. R.; Sheppard, R. C. *J. Chem. Soc., Chem. Commun.* **1971**, 636.
(4) Backes, B. J.; Virgilio, A. A.; Ellman J. A. *J. Am. Chem. Soc.* **1996**, *118*, 3055.
(5) For a seminal example, see: Worster, P. M.; McArthur, C. R.; Leznoff, C. C. *Angew. Chem., Int. Ed. Engl.* **1979**, *18*, 221.
(6) Bunin, B. A.; Plunkett, M. J.; Ellman, J. A. *Proc. Natl. Acad. Sci. U.S.A.* **1994**, *91*, 4708.
(7) Liu, G.; Ellman, J. A. *J. Org. Chem.* **1995**, *60*, 7712.
(8) Backes, B. J.; Ellman, J. A. *Curr. Opin. Chem. Biol.* **1997**, *1*, 86.
(9) Evans, D. A.; Ennis, M. D.; Mathre, D. J. *J. Am. Chem. Soc.* **1982**, *104*, 1734.
(10) Meyers, A. G.; Gleason, J. L.; Yoon, T.; Kung, D. W. *J. Am. Chem. Soc.* **1994**, *116*, 9361.
(11) Allin, S. M.; Shuttleworth, S. J. *Tetrahedron Lett.* **1996**, *37*, 8023.
(12) Rathke, M. W.; Woodbury, R. P.; Sullivan, D. F. *J. Org. Chem.* **1977**, *42*, 2038.

10.1021/jo990271w CCC: $18.00 
Published on Web 06/30/1999

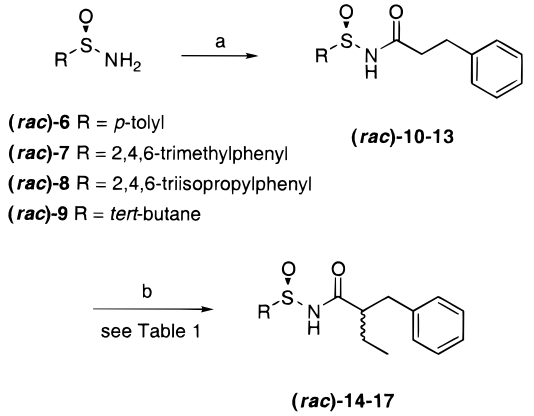
or strongly nucleophilic reaction conditions in subsequent steps is likely to result in decomposition of the *N*-acyloxazolidinone linkage. Tertiary amide auxiliaries, exemplified by the pseudoephedrine auxiliary of Myers, complement oxazolidinone systems since alkylation with unreactive alkylating agents provides high yields of products due to the stability of the tertiary amide carboxamide enolate. Indeed, Kurth has developed an amide-based dual chiral auxiliary and linker that provides good enolate alkylation diastereoselectivities with the release of the product from support facilitated by iodolactonization.[13] Unfortunately, direct cleavage of the amides generally requires harsh conditions,[14] compromising the utility of tertiary amide auxiliaries as general dual chiral auxiliaries and linkers.

We envisioned the sulfinamide functionality **2** as a dual chiral auxiliary and linker for asymmetric enolate alkylation reactions. Although the chemistry of *N*-acylsulfinamides has previously been little explored,[15] the sulfinamide could potentially provide several advantages over known auxiliary linker systems including enolate alkylation generality, linkage stability through multiple steps on solid support, and mild cleavage and functionalization after an activation step. Toward this end, several sulfinamides were prepared and their *N*-acylsulfinamide derivatives were evaluated in diastereoselective enolate alkylation reactions. These efforts led to the identification of *tert*-butanesulfinamide as a low molecular weight, optically and thermally stable chiral auxiliary[16] that provides promising diastereoselectivities. With a goal toward applying *N*-acylsulfinamides as dual auxiliaries and linkers for solid-phase synthesis, methods have been developed for (1) the racemization-free acylation of *tert*-butanesulfinamide to prepare optically pure *N*-acyl-*tert*-butanesulfinamides, (2) the diastereoselective *C*-alkylation of *N*-acyl-*tert*-butanesulfinamides, (3) activation by *N*-alkylation and *S*-oxidation of *N*-acyl-*tert*-butanesulfinamides to provide *N*-alkyl-*N*-acyl-*tert*-butanesulfonamides, and (4) the cleavage of *N*-alkyl-*N*-acyl-*tert*-butanesulfonamides to give chiral alcohol, ester, amide, and carboxylic acid products.

## Results and Discussion

**Sulfinamide and *N*-Acylsulfinamide Synthesis.** All of the sulfinamides evaluated are prepared easily in a few steps from commercially available materials. *p*-Toluenesulfinamide (**(*rac*)-6**, Scheme 2) is prepared efficiently in 63% yield from *p*-toluenesulfinic acid sodium salt by conversion to the sulfinyl chloride with oxalyl chloride followed by aminolysis with $NH_3$ in $Et_2O$. A two-step procedure is employed to prepare 2,4,6-trimethylphenylsulfinamide (**(*rac*)-7**) and 2,4,6-triisopropylsulfinamide (**(*rac*)-8**) from their requisite sulfonyl chlorides in 38% yield and 39% yield, respectively. Treatment of 2,4,6-trimethylphenylsulfonyl chloride and 2,4,6-triisopropylsulfonyl chloride with trimethyl phosphite, $Et_3N$, and EtOH in $CH_2Cl_2$ as solvent provides the respective ethyl sulfinate esters in high yield.[17] The sulfinate esters are displaced with lithium hexamethyldisilazide (LHMDS) in THF, followed by desilylation with KF on alumina,[18] to give **(*rac*)-7** and **(*rac*)-8**. *tert*-Butanesulfinyl chloride is prepared in nearly quantitative yield by oxidation of *tert*-butyl disulfide with $Cl_2$ in $H_2O$.[19] Treatment of *tert*-butanesulfinyl chloride with ammonium hydroxide then provides *tert*-butanesulfinamide (**(*rac*)-9**) in 98% yield. To prepare *N*-acylsulfinamides **(*rac*)-10**−**13**, sulfinamides **(*rac*)-6**−**9** are treated with 2−3 equiv of *n*-BuLi or NaH in THF, followed by the rapid addition of the symmetrical anhydride of hydrocinnamic acid.

**Scheme 2**




(a) 2.5-3.0 equiv *n*-BuLi or NaH, THF, -10 °C then $O(COCH_2CH_2Ph)_2$; (b) 2.5 equiv LTMP, THF, then EtI (Table 1).

**Table 1. *N*-Acylsulfinamide Enolate Alkylation Reactions (Scheme 2)**

| no. | substrate | diastereoselectivity[a] | yield, % |
|---|---|---|---|
| 1 | **(*rac*)-10**, R = *p*-tolyl | **(*rac*)-14** (74:26) | 88[b] |
| 2 | **(*rac*)-11**, R = 2,4,6-trimethylphenyl | **(*rac*)-15** (75:25) | 76[c] |
| 3 | **(*rac*)-12**, R = 2,4,6-triisopropylphenyl | **(*rac*)-16** (73:27) | 96[c] |
| 4 | **(*rac*)-13**, R = *tert*-butane | **(*rac*)-17** (84:16) | 93[b] |

[a] Diastereomeric ratios determined by reverse phase HPLC analysis of unpurified mixture. [b] Yield represents a mass balance of the isolated mixture of diastereomers. [c] Yield represents the conversion of starting material to diastereomeric products as determined by reverse phase HPLC analysis of unpurified mixture.

**Enolate Alkylation of *N*-Acylsulfinamides.** To effect *C*-alkylation, the *N*-acylsulfinamide is treated with 2.5 equiv of lithium 2,2,6,6-tetramethylpiperidide (LTMP) in THF at −78 °C and the solution temperature is raised to 0 °C to ensure complete deprotonation (Scheme 2, Table 1). After lowering the temperature to −78 °C, EtI is added, and the reaction mixture is allowed to reach ambient temperature over several hours, followed by quenching with a dilute solution of AcOH in THF. Alkylation of *N*-acyl-*p*-toluenesulfinamide **(*rac*)-10** pro-

(13) (a) Moon, H. S.; Schore, N. E.; Kurth, M. J. *J. Am. Chem. Soc.* **1992**, *57*, 6088. (b) Moon, H. S.; Schore, N. E.; Kurth, M. J. *Tetrahedron Lett.* **1994**, *35*, 8915.

(14) Myers and co-workers have developed specialized conditions to provide highly enantiomerically enriched carboxylic acid, alcohol, aldehyde, and ketone products upon pseudoephedrine auxiliary cleavage: Myers, A. G.; Yang, B. H.; Chen, H.; McKinstry, L.; Kopecky, D. J.; Gleason, J. L. *J. Am. Chem. Soc.* **1997**, *119*, 6496.

(15) *N*-Acylsulfinamides have found use as sulfur transfer reagents. For leading references, see: Garcia-Ruano, J. L.; Alonso, R.; Zarzuelo, M. M.; Noheda, P. *Tetrahedron: Asymmetry* **1995**, *6*, 1133.

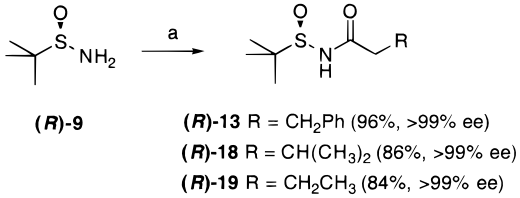
(16) We have since employed *tert*-butanesulfinimines for the asymmetric synthesis of the following. (a) α-Substituted amines: Liu, G.; Cogan, D. A.; Ellman, J. A. *J. Am. Chem. Soc.* **1997**, *119*, 9913. (b) α,α-Dibranched amines: Cogan, D. A.; Ellman, J. A. *J. Am. Chem. Soc.* **1999**, *121*, 268. (c) *β*-Substituted *β*-amino acids, *β*,*β*-disubstituted *β*-amino acids, and α,*β*-disubstituted *β*-amino acids: Tang, T. P.; Ellman, J. A. *J. Org. Chem.* **1999**, *64*, 12.

(17) Klunder, J. M.; Sharpless, K. B. *J. Org. Chem.* **1987**, *52*, 2598.

(18) Davis, F. A.; Reddy, R. E.; Szewczyk, J. M.; Portonovo, P. S. *Tetrahedron Lett.* **1993**, *34*, 6229.

(19) Netscher, T.; Prinzbach, H. *Synthesis* **1987**, 683.

**Scheme 3**




(a) 2.5 equiv KH, THF, - 10 °C then isobutyl carbonic mixed anhydride or symmetrical anhydride.

vides a 74:26 mixture of diastereomeric products **(*rac*)-14** in 88% yield.[20] It was thought that by increasing the steric bulk in the *ortho* positions, increased diastereofacial selectivity would be observed. In actuality, *ortho* substitution has little effect on the diastereoselectivity of this transformation as alkylation of **(*rac*)-11** and **(*rac*)-12** provides 75:25 and 73:27 mixtures of **(*rac*)-15** and **(*rac*)-16**, respectively. *tert*-Butanesulfinamide (**9**) proved to be the most promising auxiliary providing the highest diastereoselectivity in initial studies (84:16). *tert*-Butanesulfinamide is also appealing due to its low molecular weight, crystalline nature, and thermal stability, which led us to develop a highly efficient and economical catalytic synthesis of optically pure *tert*-butanesulfinamide.[21] We therefore decided to further explore enolate alkylation reactions and chemical transformations on *tert*-butanesulfinamide derivatives.

**Racemization-Free Acylation of (*R*)-*tert*-Butanesulfinamide.** In initial studies, (*R*)-*tert*-butanesulfinamide (**(*R*)-9**)[21] in THF at −10 °C was treated with 2.5 equiv of 95% NaH and added dropwise to symmetrical anhydrides in THF. Although this procedure results in good yields of *N*-acyl-*tert*-butanesulfinamide products, significant racemization is observed. For example, acylation with butyric anhydride results in a 90% yield of **(*R*)-19**, with >20% racemization. However, by inverting the order of addition, and employing KH as base, high yields of enantiopure *N*-acyl-*tert*-butanesulfinamides can be obtained (Scheme 3). Specifically, treatment of **(*R*)-9** in THF at −10 °C with 2.5 equiv of 25% KH in oil, followed by the slow addition of a mixed anhydride prepared from isobutyl chloroformate, 1-methylmorpholine (NMM), and either hydrocinnamic acid or valeric acid, provides enantiopure **(*R*)-13** (96%, >99% ee) and **(*R*)-18** (86%, >99% ee), respectively. Acylation employing butyric anhydride gives **(*R*)-19** in 84% yield (>99% ee). The chiral *N*-acyl-*tert*-butanesulfinamides **(*R*)-13**, **(*R*)-18**, and **(*R*)-19** are each crystalline with long shelf lives (>1 year).

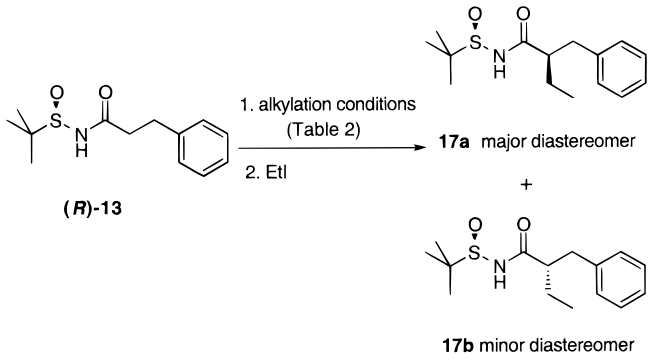
**Optimization of Diastereoselective Enolate Alkylation.** A wide range of alkylation conditions were screened in our attempts to improve the diastereoselectivity of the enolate alkylation reaction (Table 2). Alkylation of *N*-acyl-*tert*-butanesulfinamide **(*R*)-13** with EtI to provide **17a** and **17b** was utilized as our model system (Scheme 4). In a typical experiment, **(*R*)-13** is treated with base in solvent at −78 °C, and the solution temperature is raised to 0 °C to ensure complete deprotonation.

**Table 2. *N*-Acylsulfinamide Enolate Alkylation Optimization (Scheme 4)**

| no. | base | additive | solvent | temp (°C) | **17a**:**17b**[a] | yield, % |
|---|---|---|---|---|---|---|
| 1 | LDA | | THF | −78 to 0 | 80:20 | 90[b] |
| 2 | $LiNEt_2$ | | THF | −78 to 0 | 74:26 | 85[c] |
| 3 | KHMDS | | THF | −78 to 0 | – | NR |
| 4 | LTMP | | THF | −78 to 0 | 84:16 | 95[b] |
| 5 | LTMP | | THF | 0 | 84:16 | 92[c] |
| 6 | LTMP | | $Et_2O$ | −78 to 0 | 73:27 | 71[c] |
| 7 | LTMP | | toluene | −78 to 0 | 62:38 | 51[c] |
| 8 | LTMP | LiCl | THF | −78 to 0 | 80:20 | >95[c] |
| 9 | LTMP | HMPA | THF | −78 to 0 | 69:31 | 75[c] |
| 10 | LTMP | $MgCl_2$ | THF | −78 to 0 | 78:22 | 85[c] |
| 11 | LTMP | $MgBr_2$ | THF | −78 to 0 | 77:23 | 83[c] |
| 12 | KH/LTMP | | THF | −78 to 0 | 90:10 | 94[b] |
| 13 | NaH/LTMP | | THF | −78 to 0 | 83:17 | 80[c] |
| 14 | KO-*t*-Bu/LTMP | | THF | −78 to 0 | 84:16 | 86[c] |

[a] Diastereomeric ratio determined by reverse phase HPLC analysis of unpurified mixture. [b] Yield represents a mass balance of the isolated mixture of diastereomers. [c] Yield represents the conversion.

**Scheme 4**




After lowering the temperature to −78 °C, the lithium enolate is transmetalated, or an additive is introduced, followed by the addition of EtI. The reaction mixture is then allowed to reach ambient temperature over several hours and quenched with a dilute solution of AcOH in THF.

Several alkali metal amide bases were evaluated (Table 2, entries 1−4). The level of diastereoselectivity improves with the increase in steric bulk of the base, with LTMP providing higher diastereoselectivity (entry 4, 84:16) than lithium diisopropylamide (LDA) (entry 1, 80:20) or $LiNEt_2$ (entry 2, 74:16). These results may suggest that higher *E*/*Z* enolate ratios are obtained with greater steric bulk of the base. However, it is also possible that the amine base remains coordinated to the lithium counterion, thus providing increased diastereofacial selectivity. Deprotonation of the α-carbon employing the less basic potassium hexamethyldisilazide (KHMDS) does not occur (entry 4). Using LTMP as base, enolate formation and alkylation at 0 °C does not change the dr (entry 5, 84:16). The use of less polar solvents $Et_2O$ (entry 6) and toluene (entry 7) with LTMP as base gives reduced levels of diastereoselectivity and lower yields.

Addition of lithium chloride[22] or magnesium salts[23] has been shown to increase the diastereoselectivity for some asymmetric enolate alkylation reactions, and the addition

(20) LTMP provides higher conversions and diastereoselectivities than LDA in enolate alkylation reactions of these derivatives. For example, treatment of **(*rac*)-10** with 2.5 equiv of LDA followed by alkylation with EtI results in a 70:30 mixture of **(*rac*)-14**.

(21) Cogan, D. A.; Liu, G.; Kim, K.; Backes, B. J.; Ellman, J. A. *J. Am. Chem. Soc.* **1998**, *120*, 8011.

(22) Myers, A. G.; Gleason, J. L.; Yoon, T.; Kung, D. W. *J. Am. Chem. Soc.* **1997**, *119*, 6656.

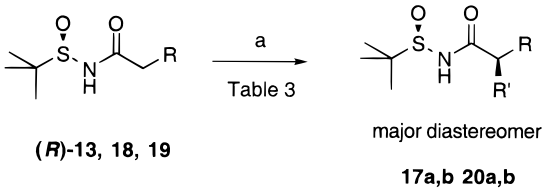
(23) (a) Larcheveque, M.; Ignatova, E.; Cuvigny, T. *Tetrahedron Lett.* **1978**, *41*, 3961. (b) Larcheveque, M.; Ignatova, E.; Cuvigny, T. *J. Organomet. Chem.* **1979**, *177*, 5.

**Table 3. Alkylation of *N*-Acyl-*tert*-butanesulfinamides (Scheme 5)**

| substrate | R′X | major diastereomer | ds[a] | yield, %[b] |
|---|---|---|---|---|
| **13**, R = $CH_2Ph$ | EtI | **17a** | 90:10 | 83 |
| **13**, R = $CH_2Ph$ | *i*-PrI | **20a** | 90:10 | 82 |
| **18**, R = $CH_2CH_3$ | BnBr | **17b** | 14:86 | 72 |
| **19**, R = $CH(CH_3)_2$ | BnBr | **20b** | 17:83 | 72 |

[a] Diastereomeric ratio determined by reverse phase HPLC analysis of unpurified mixture. [b] Yield represents a mass balance of the isolated major diastereomer.

**Scheme 5**



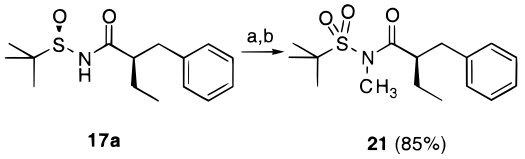

(a) i. 1.5 equiv KH, THF, 0 °C ii. 1.5 equiv LTMP, THF -78 °C iii. 1.5 equiv alkylating agent (Table 3).

of HMPA can improve *E*/*Z* enolate ratios[24] resulting in increased diastereoselectivities. Therefore, the use of additives in either the alkylation step or in the enolate formation step was next investigated. Addition of LiCl (entry 8) before enolate formation provides a lower dr (entry 8, 80:20) as does the addition of HMPA (entry 9, 69:31). Transmetalation of the lithium enolate with $Mg^{2+}$ employing $MgCl_2$ (entry 10) or $MgBr_2$ (entry 11) also results in lower yields and lower diastereoselectivity. Interestingly, the addition of 1.5 equiv of KH to ionize the *N*-acylsulfinamide followed by enolate formation with 1.5 equiv of LTMP results in a modest increase in the dr (entry 12, 90:10). The use of NaH in the same manner does not improve the result (entry 13, 83:17). It appears that the use of a "mixed Li/K salt" is necessary for improved diastereoselctivity. It is surprising that addition of KO-*t*-Bu followed by addition of LTMP does not provide the same dr (entry 14, 85:15).

The sense of asymmetric induction in the alkylation step (Scheme 4) has been determined unequivocally by chemical correlation of cleavage products obtained after activation (vide infra). We currently do not have a working model that rationalizes the observed sense of induction.

**Enolate Alkylation Reactions of *N*-Acyl-*tert*-butanesulfinamides.** To establish the generality of our enolate alkylation conditions, *N*-acyl-*tert*-butanesulfinamides **(*R*)-13**, **(*R*)-18**, and **(*R*)-19** were alkylated with unreactive and reactive alkylating agents employing the best reaction conditions from Table 2 (Table 3, Scheme 5). *N*-Acyl-*tert*-butanesulfinamides in THF are treated with 1.5 equiv of KH at 0 °C followed by enolate formation with LTMP at −78 °C. The reaction mixture is then allowed to come to 0 °C to ensure complete deprotonation, and enolate alkylation is performed at −78 to 0 °C over 4 h. Alkylation of **(*R*)-13** with EtI, as reported in Table 2, provides a 90:10 mixture of diastereomers. The isomers are easily separated by employing column chromatography to provide an 83% yield of the major diastereomer **17a**. Alkylation of **(*R*)-13** with *i*-PrI proceeds with 90:10 dr, and the major isomer **20a** is obtained in 82% yield after medium-pressure liquid chromatography (MPLC) separation. Alkylation of butyric acid derivative **(*R*)-19** with BnBr provides slightly lower levels of diastereoselection (16:84) with MPLC separation providing major diastereomer **17b** in 72% yield. Alkylation of valeric acid derivative **(*R*)-18** with BnBr provides slightly lower levels of diastereoselection (17:83) as well, with MPLC separation giving major diastereomer **20b** in 72% yield. It should be noted that the use of KH to ionize the *N*-acylsulfinamide nitrogen provides a modest increase in dr for all of the cases listed in Table 3. For example, treatment of **(*R*)-18** with LTMP and alkylation with BnBr gives a 20:80 ratio of **17a** and **17b**.

**Scheme 6**




(a) TMG, MeI, DMF, 0 °C; (b) catalytic $RuCl_3$, $NaIO_4$, $CH_2Cl_2$, $CH_3CN$, $H_2O$, 0 °C.

**Activation and Cleavage.** To provide a derivative suitable for nucleophilic cleavage, **17a** is alkylated by employing MeI and 1,1,3,3-tetramethylguanidine (TMG), with DMF as solvent to give *N*-methyl-*N*-acyl-*tert*-butanesulfinamide. Oxidation with $RuCl_3$ and $NaIO_4$[25] is performed after an extractive isolation to give **21** in 84% yield for the two-step process (Scheme 6). *N*-Methyl-*N*-acylsulfonamides are versatile derivatives for cleavage.[26] Attempts to forego the oxidation step and directly employ the *N*-methyl-*N*-acyl-*tert*-butanesulfinamide intermediates in cleavage reactions were not successful. These intermediates either do not react with the nucleophiles or under forcing conditions undergo decomposition. It is also plausible to perform the activation sequence by employing the oxidative step followed by *N*-alkylation. However, mixtures of *N*- and *O*-alkylated products (90:10) are obtained when alkylation of *N*-acyl-*tert*-butanesulfonamides is performed.[27]

*N*-Methyl-*N*-acyl-*tert*-butanesulfonamide **21** can be cleaved with several nucleophiles to give high yields of a variety of products without racemization. Treatment of **21** with LiOOH in a THF/$H_2O$ mixture[28] provides carboxylic acid **22** in high yield with no racemization observed. Cleavage with BnOLi in THF gives the benzyl ester **23** in 97% yield (>99:1). To obtain amides, **21** is treated with benzylamine in dioxane under refluxing conditions to give **24** in 92% yield with no racemization observed. Alcohol **25** is obtained in 97% yield (>99:1) by reduction with LAH in THF.

Transformation of *N*-methyl-*N*-acyl-*tert*-butanesulfinamides to carboxylic acid derivatives allows for straightforward determination of the sense of induction in the enolate alkylation step by chemical correlation. Saponification after activation of the major diastereomer **17a** (Scheme 4) provides the carboxylic acid product **22**

(24) Ireland, R. E.; Wipf, P.; Armstrong, J. D. *J. Org. Chem.* **1991**, *56*, 650.

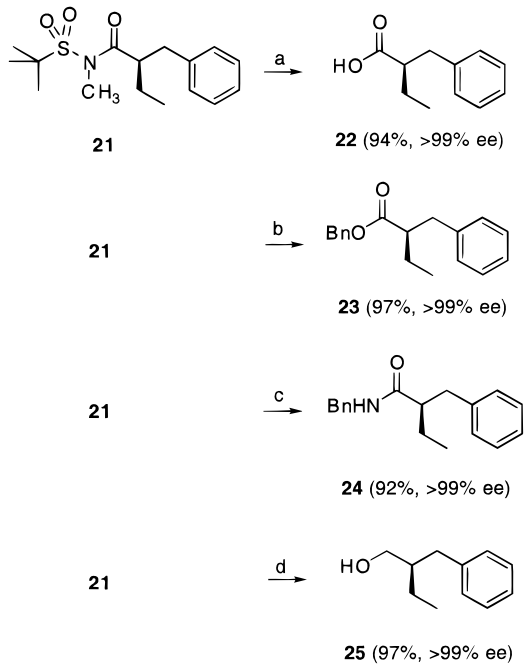
(25) Gao, Y.; Sharpless, K. B. *J. Am. Chem. Soc.* **1988**, *110*, 7738.

(26) Nagashima, H.; Ozaki, N.; Washiyama, M.; Itoh, K. *Tetrahedron Lett.* **1985**, *26*, 657.

(27) In initial studies towards the *N*-alkylation of *N*-acyl-*tert*-butanesulfinamides or *N*-acyl-*tert*-butanesulfonamides employing iodoacetonitrile (ref 4), unwanted *S*- and *O*-alkylation are also observed.

(28) Evans, D. A.; Britton, T. C.; Ellman, J. A. *Tetrahedron Lett.* **1987**, *28*, 6141.

**Scheme 7**




(a) LiOH, $H_2O_2$, THF/$H_2O$, 0 °C; (b) BnOH, *n*-BuLi, THF, 0 °C; (c) $BnNH_2$, dioxane, 90 °C; (d) LAH, THF, -78 °C to 0 °C.

(Scheme 7). Comparison to **22** prepared employing known methods[29] unambiguously established the relative stereochemistry of the major isomer **17a**.

## Conclusion

*tert*-Butanesulfinamide (**(*R*)-9**) is a low molecular weight, optically and thermally stable chiral auxiliary for which we have recently reported an efficient preparation from inexpensive starting materials.[21] Highly stable *N*-acyl-*tert*-butanesulfinamide derivatives can be prepared from **9** in high yields without racemization. Diastereoselective alkylations can be performed with both reactive (BnBr) and unreactive (*i*-PrI) alkylating agents. Activation by *N*-alkylation and *S*-oxidation of the *N*-acyl-*tert*-butanesulfinamides provides *N*-methyl-*N*-acyl-*tert*-butanesulfonamide derivatives that can be reacted with nucleophiles to provide a variety of enantiopure products upon cleavage. We are currently developing a chiral *tert*-butanesulfinamide handle for solid-phase synthesis.[30] While the diastereoselectivity currently observed for enolate alkylation reactions of *N*-acyl-*tert*-butanesulfinamides is moderate, adaptation to support will simplify the parallel optimization of this transformation.[31] *N*-Acylsulfinamides will also be evaluated as substrates for other asymmetric transformations.

(29) The *N*-acyloxazolidinone asymmetric enolate alkylation chemistry of Evans (ref 9) was used to prepare **22**.

(30) A support-bound *tert*-butanesulfinamide chiral auxiliary and linker will be useful for the preparation of other classes of compounds. For example, sulfinimines are versatile chiral nitrogen intermediates in asymmetric synthesis (see ref 16 and Davis, F. A.; Portonovo, P. S.; Reddy, R. E.; Reddy, G. V.; Szewczyk, J. M.; Zhou, P. *Phosphorus, Silicon Relat. Elem.* **1997**, *120&121*, 291).

(31) Bray, A. M.; Chiefari, D. S.; Valerio, R. M.; Maeji, N. J. *Tetrahedron Lett.* **1995**, *36*, 5081.

## Experimental Section

**General Methods.** Unless otherwise noted, materials were obtained from commercial suppliers and used without further purification. Tetrahydrofuran (THF) was distilled under $N_2$ from sodium benzophenone ketyl prior to use, and $CH_2Cl_2$ was distilled under $N_2$ from $CaH_2$. Chromatography was carried out using Merck 60 230−240 mesh silica gel according to the procedure of Still.[32] Thin-layer chromatography was carried out on Merck 60 F254 250-$\mu$m silica gel plates. IR spectra were recorded using KBr pellets or NaCl plates, and only partial data are reported. $^1$H and $^{13}$C NMR spectra were acquired in $CDCl_3$, unless otherwise stated. NMR chemical shifts are reported in ppm downfield from an internal solvent peak, or TMS, and *J* values are in hertz. All HPLC assays were performed utilizing a Rainin Dynamax Microsorb C18 reverse phase analytical column or a Diacel chiral phase column.

**Mixed Carbonic Anhydride Method for (*R*)-*tert*-Butanesulfinamide Acylation.** To a 1 L three-neck round-bottom flask fitted with a mechanical stirrer were added 35% KH in oil (24 g, 150 mmol) and THF (250 mL). The flask was cooled to −10 °C with an NaCl/ice bath, and **(*R*)-9** (6.0 g, 49 mmol) was added in several portions with venting. To a second 500 mL round-bottom flask were added the carboxylic acid (54 mmol), *N*-methylmorpholine (5.9 mL, 54 mmol), and THF (220 mL). The flask was cooled to −20 °C, and isobutyl chloroformate (7.0 mL, 54 mmol) was added dropwise over 5 min. After stirring an additional 5 min, the contents of the flask were filter cannulated to the sulfinamide-containing flask dropwise over the course of 35 min. After addition, the amine hydrochloride salts remaining in the flask were washed with cold THF (30 mL), and the solution was filter cannulated to the first flask as before. Aqueous 1 M $K_2CO_3$ (50 mL) was added dropwise (carefully!) to quench the remaining KH and electrophile. The contents of the flask were concentrated, acidified with 1 M HCl, and extracted with $CH_2Cl_2$ (3 × 200 mL). The organic layers were combined, washed with 0.1 M $NaHSO_4$ (3 × 300 mL), saturated $NaHCO_3$ (3 × 300 mL), and brine (3 × 300 mL), and dried ($Na_2SO_4$).

**(*R*)-*N*-Hydrocinnamoyl-*tert*-butanesulfinamide (13).** Acylation of 6.0 g (49 mmol) of **(*R*)-9** with hydrocinnamic acid (8.1 g, 54 mmol) afforded 12 g (96%) of **(*R*)-13** as a colorless solid after purification on silica gel (40:60 EtOAc/hexanes). The enantiomeric purity was determined to be >99:1 by HPLC analysis on a chiral phase (Diacel Chiralcel OD column, 90:10 hexane/EtOH, 1 mL/min, 232 nm; **(*S*)-13**, $t_R$ = 7.9 min; **(*R*)-13**, $t_R$ = 13.5 min). The material could be recrystallized from ethyl ether−hexane mixtures: mp 102−104 °C; $[\alpha]^{23}_D$ −29.1 (*c* 1.00, $CH_2Cl_2$); IR 1701, 1420, 1062 cm$^{-1}$; $^1$H NMR (400 MHz) $\delta$ 1.16 (s, 9), 2.69−2.75 (m, 2), 2.97 (t, 2, *J* = 7.5), 7.20 (d, 2, *J* = 6.9), 7.23−7.30 (m, 3), 7.47 (s, 1); $^{13}$C NMR (101 MHz) $\delta$ 21.9, 30.9, 37.7, 57.2, 126.4, 128.4, 128.6, 140.1, 173.4. Anal. Calcd for $C_{13}H_{19}NO_2S$: C, 61.63; H, 7.56; N, 5.53. Found: C, 61.67; H, 7.65; N, 5.63.

**(*R*)-*N*-Isovaleroyl-*tert*-butanesulfinamide (18).** Acylation of 6.0 g (49 mmol) of **(*R*)-9** with isovaleric acid (5.5 g, 54 mmol) afforded 9.0 g (86%) of **(*R*)-18** as a colorless solid after purification on silica gel (50:50 to 70:30 EtOAc/hexanes). The enantiomeric purity was determined to be >99:1 by HPLC analysis on a chiral phase (Diacel AS column, 95:5 hexane/*i*-PrOH, 1 mL/min, 232 nm; **(*S*)-18**, $t_R$= 15.3 min; **(*R*)-18**, $t_R$ = 18.8 min). The material could be recrystallized from ethyl ether−acetone mixtures: mp 121−123 °C; $[\alpha]^{23}_D$ = −23.6 (*c* 1.00, $CH_2Cl_2$); IR 1693, 1465, 1060 cm$^{-1}$; $^1$H NMR (300 MHz) $\delta$ 0.92−0.96 (m, 6), 1.23 (s, 9), 2.06−2.10 (m, 1), 2.11−2.15 (m, 2), 8.32 (bs, 1); $^{13}$C NMR (101 MHz) $\delta$ 22.1, 22.3, 25.8, 45.3, 57.1, 174.0. Anal. Calcd for $C_9H_{16}NO_2S$: C, 52.60; H, 9.33; N, 6.82. Found: C, 52.87; H, 9.07; N, 6.81.

**Symmetrical Anhydride Method for (*R*)-*tert*-Butanesulfinamide Acylation.** To a 1 L three-neck round-bottom flask fitted with a mechanical stirrer were added 35% KH in oil (24 g, 150 mmol) and THF (250 mL). The flask was cooled to 0 °C with an ice bath, and **(*R*)-9** (6.0 g, 49 mmol) was added

(32) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.

in several portions with venting. To a second 250 mL round-bottom flask were added the symmetrical anhydride (52 mmol) and THF (100 mL). The contents of the flask were cannulated to the sulfinamide-containing flask dropwise over the course of 35 min. Aqueous $K_2CO_3$ (50 mL, 1 M) was then added dropwise (carefully!) to quench the remaining KH and electrophile. The contents of the flask were concentrated, acidified with 1 M HCl, and extracted with $CH_2Cl_2$ (3 × 200 mL). The organic layers were combined, washed with saturated $NaHCO_3$ (3 × 300 mL), and dried ($Na_2SO_4$).

**(*R*)-*N*-Butanoyl-*tert*-butanesulfinamide (19).** Acylation of 6.0 g (49 mmol) of **(*R*)-9** with butanoic anhydride (8.1 g, 52 mmol) afforded 7.9 g (84%) of **(*R*)-19** as a colorless solid after purification on silica gel (50:50 to 70:30 EtOAc/hexanes). The enantiomeric purity was determined to be >99:1 by HPLC analysis on a chiral phase (Diacel AS column, 90:10 hexane/EtOH, 1 mL/min, 232 nm; **(*S*)-19**, $t_R$ = 6.9 min; **(*R*)-19**, $t_R$ = 9.2 min). The material could be recrystallized from ethyl ether−hexane mixtures: mp 53−54 °C; $[\alpha]^{23}_D$ −24.2 (*c* 1.00, $CH_2Cl_2$); IR 3169, 2964, 1701, 1676 $cm^{-1}$; $^1H$ NMR (300 MHz) $\delta$ 0.95 (t, 3, *J* = 7.4), 1.25 (s, 9), 1.61−1.69 (m, 2), 2.31−2.40 (m, 2), 7.89 (bs, 1); $^{13}C$ NMR (101 MHz) $\delta$ 13.7, 18.6, 22.1, 38.1, 57.1, 174.7. Anal. Calcd for $C_8H_{17}NO_2S$: C, 50.23; H, 8.89; N, 7.34. Found: C, 50.30; H, 8.89; N, 7.34.

**Enolate Alkylation Optimization.** For alkylation experiments (Table 2), the procedure to *C*-alkylate **(*rac*)-10**−**13** was followed by employing the base (entries 1−4) or solvent (entries 6−7) listed. For entry 5, enolate formation and alkylation were performed at 0 °C. For entries 8−9, 2.5 equiv of the additive listed was introduced before enolate formation. For entries 10−11, 2.5 equiv of the additive listed was introduced after enolate formation and before enolate alkylation. The general alkylation procedure employing KH/LTMP (entry 12) is given in the following sections. For entries 13−14, NaH or KO-*t*-Bu (2.5 equiv LTMP) was substituted for KH. Diastereoselectivity was determined employing an HPLC assay (10−100% MeOH/$H_2O$−0.1% TFA, 254 nm, 60 min, 1 mL/min: **17a**, $t_R$ = 47.5 min; **17b**, $t_R$ = 44.6 min). Yields were determined by HPLC conversion of starting material to diastereomeric products or by a mass balance recovery of the diastereomeric mixture after column chromatography. **(*R,R*)-*N*-2-Phenylmethylbutanoyl-*tert*-butanesulfinamide (17a).** The diastereomerically pure material obtained from purification on silica gel could be recrystallized from ethyl ether−hexane mixtures: mp 106−108 °C; $[\alpha]^{23}_D$ −14.0 (*c* 1.00, $CH_2Cl_2$); IR 3166, 1698, 1062 $cm^{-1}$; $^1H$ NMR (400 MHz) $\delta$ 0.95−0.99 (m, 12), 1.55−1.61 (m, 1), 1.72−1.80 (m, 1), 2.55−2.60 (m, 1), 2.80 (d, 2, *J* = 6.1), 7.15−7.21 (m, 2), 7.23−7.27 (m, 3), 7.43 (s, 1); $^{13}C$ NMR (101 MHz) $\delta$ 11.8, 21.5, 25.6, 38.6, 51.0, 57.2, 126.3, 128.4, 129.0, 139.1, 175.8. Anal. Calcd for $C_{15}H_{23}NO_2S$: C, 64.00; H, 8.20; N, 4.98. Found: C, 64.10; H, 8.21; N, 5.01. **(*S,R*)-*N*-2-Phenylmethylbutanoyl-*tert*-butanesulfinamide (17b).** The diastereomerically pure material obtained from purification on silica gel could be recrystallized from ethyl ether−hexane mixtures: mp 103−105 °C; $[\alpha]^{23}_D$ +28.1 (*c* 1.00, $CH_2Cl_2$); IR 3176, 1706, 1059 $cm^{-1}$; $^1H$ NMR (400 MHz) $\delta$ 0.94 (bt, 3), 1.12 (s, 9), 1.55−1.61 (m, 1), 1.71−1.78 (m, 1), 2.50−2.60 (m, 1), 2.80 (dd, 1, *J* = 6.3, *J* = 13.6), 2.94 (dd, 1, *J* = 8.4, *J* = 13.6), 7.15−7.26 (m, 6); $^{13}C$ NMR (101 MHz) $\delta$ 11.8, 22.0, 25.1, 38.0, 50.7, 57.5, 126.5, 128.6, 129.2, 139.2, 176.4. Anal. Calcd for $C_{15}H_{23}NO_2S$: C, 64.00; H, 8.20; N, 4.98. Found: C, 64.08; H, 8.15; N, 5.20.

**General Conditions for Enolate Alkylation.** To a 25 mL round-bottom were added an *N*-acylsulfinamide (3.95 mmol) and THF (4 mL). The flask was cooled to 0 °C with an ice bath, and 35% KH in oil (677 mL, 5.95 mmol) was added slowly. After stirring for 1 h, the mixture was cooled to −78 °C with a dry ice/acetone bath. To a second flask were added TMP (1.1 mL, 6.5 mmol) and THF (3 mL). The flask was cooled to −78 °C, and 2.1 M *n*-BuLi (2.8 mL, 5.95 mmol) was added dropwise. The mixture was warmed to 0 °C for 1 h and cooled to −78 °C whereupon the contents were transferred via cannula to the first flask. After stirring for 30 min, the mixture was warmed to 0 °C for 1 h and again cooled to −78 °C whereupon alkylating agent (5.95 mmol) was added. After 1 h, the dry ice/acetone bath was removed and the mixture was allowed to come to room temperature over 4 h. A dilute solution of AcOH in THF was added, and the mixture was concentrated, diluted with $CH_2Cl_2$ (100 mL), washed with 0.1 M $NaHSO_4$ (3 × 100 mL), saturated $NaHCO_3$ (3 × 100 mL), and brine (3 × 100 mL), dried ($Na_2SO_4$), and concentrated.

**(*R,R*)-*N*-2-Phenylmethylbutanoyl-*tert*-butanesulfinamide (17a).** Alkylation of 0.93 g (3.7 mmol) of **(*R*)-13** with iodoethane (450 $\mu$L, 5.6 mmol) afforded 0.84 g (83%) of **17a** as a colorless solid after purification on silica gel (5 cm × 20 cm eluting with 90:10 to 50:50 hexanes/EtOAc). The diastereomeric ratio was determined to be 90:10 by reverse phase HPLC analysis (10:90−100% MeOH/$H_2O$−1% TFA, 60 min, 1 mL/min, 254 nm; **17a**, $t_R$ = 47.5 min; **17b**, $t_R$ = 44.6 min). The material could be recrystallized from ethyl ether−hexane mixtures: mp 105−107 °C. Spectral data matched those listed previously.

**(*R,R*)-*N*-2-Phenylmethyl-3-methylbutanoyl-*tert*-butanesulfinamide (20a).** Alkylation of 0.25 g (1.0 mmol) of **(*R*)-13** with 2-iodopropane (150 $\mu$L, 1.5 mmol) afforded 0.24 g (82%) of **20a** as a colorless solid after purification on silica gel (2 × 15 cm, 15:85 to 40:60 EtOAc/hexanes). The diastereomeric ratio was determined to be 90:10 by reverse phase HPLC analysis (10:90 to 35:65% MeOH/$H_2O$−1% TFA, 254 nm, 60 min, 1 mL/min; **20a**, $t_R$ = 40.3 min; **20b**, $t_R$ = 41.9 min). The material could be recrystallized from ethyl ether−hexane mixtures: mp 124−126 °C; $[\alpha]^{23}_D$ −32 (*c* 1.00, $CH_2Cl_2$); IR 3259, 1675, 1049 $cm^{-1}$; $^1H$ NMR (300 MHz) $\delta$ 0.90 (s, 9), 1.06 (d, 3, *J* = 7.0), 1.08 (d, 3, *J* = 7.0), 2.00−2.07 (m, 1), 2.27−2.32 (m, 1), 2.77 (dd, 1, *J* = 11.4, *J* = 13.3), 2.92 (dd, 1, *J* = 4.0, *J* = 13.3), 6.72 (bs, 1), 7.14−7.26 (m, 5); $^{13}C$ NMR (101 MHz) $\delta$ 20.2, 21.1, 21.7, 31.2, 36.1, 56.5, 57.4, 126.4, 128.6, 129.2, 139.7, 175.7. Anal. Calcd for $C_{16}H_{25}NO_2S$: C, 65.00; H, 8.53; N, 4.74. Found: C, 64.90; H, 8.45; N, 5.10.

**(*S,R*)-*N*-2-Phenylmethylbutanoyl-*tert*-butanesulfinamide (17b).** Alkylation of 0.88 g (4.6 mmol) of **(*R*)-18** with benzyl bromide (820 $\mu$L, 6.9 mmol) afforded 0.93 g (72%) of **17b** as a colorless solid after MPLC purification on silica gel (10:90 to 50:50 EtOAc/hexanes, linear gradient). The diastereomeric ratio was determined to be 14:86 by reverse phase HPLC analysis. The material could be recrystallized from ethyl ether−hexane mixtures: mp 103−105 °C. Spectral data matched those listed previously.

**(*S,R*)-*N*-2-Phenylmethyl-3-methylbutanoyl-*tert*-butanesulfinamide (20b).** Alkylation of 0.80 g (4.0 mmol) of **(*R*)-19** with benzyl bromide (717 $\mu$L, 6.0 mmol) afforded 0.85 g (72%) of **20b** as a colorless solid after MPLC purification on silica gel gel (10:90 to 40:60 EtOAc/hexanes, linear gradient). The diastereomeric ratio was determined to be 17:83 by reverse phase HPLC analysis. The material could be recrystallized from ethyl ether−hexane mixtures: mp 119−122 °C; $[\alpha]^{23}_D$ +21 (*c* 1.00, $CH_2Cl_2$); IR 3152, 2955, 1695 1060 $cm^{-1}$; $^1H$ NMR (300 MHz) $\delta$ 1.05−1.24 (m, 15), 1.95−2.01 (m, 1), 2.30−2.45 (m, 1), 2.89−2.91(m, 2), 7.18−7.26 (m, 6); $^{13}C$ NMR (101 MHz) $\delta$ 20.4, 22.0, 24.1, 30.8, 35.4, 56.0, 57.3, 126.5, 128.7, 129.1, 139.6, 175.5. Anal. Calcd for $C_{16}H_{25}NO_2S$: C, 65.00; H, 8.53; N, 4.74. Found: C, 65.09; H, 8.48; N, 4.69.

**(*R*)-*N,N*-Methyl-2-phenylmethylbutanoyl-*tert*-butanesulfonamide (21).** To a 25 mL round-bottom flask were added **17a** (1.85 g, 6.58 mmol), DMF (6.6 mL), and TMG (1.07 mL, 8.55 mmol). The mixture was cooled to 0 °C with an ice bath whereupon MeI (615 $\mu$L, 9.87 mmol) was added. After stirring 30 min, the reaction mixture was diluted with EtOAc (50 mL) and washed with 0.1 M $NaHSO_4$ (3 × 50 mL) and brine (3 × 50 mL). The organic layer was added to a 100 mL round-bottom flask and concentrated. To the flask were added $CH_3CN$ (20 mL), $CH_2Cl_2$ (20 mL), $H_2O$ (30 mL), and $NaIO_4$ (2.26 g, 9.90 mmol). The reaction mixture was cooled to 0 °C with an ice bath, and a catalytic amount of $RuCl_3$ (10 mg) was added. After stirring for 1 h, $CH_2Cl_2$ (20 mL) was added, and the mixture was washed with brine (3 × 50 mL), dried ($Na_2SO_4$), and concentrated. Purification on silica gel (5 × 15 cm, 20:80 EtOAc/hexane) provided 1.72 g (85%) of **21** as a colorless oil. The enantiomeric purity was determined to be >99:1 by HPLC analysis on a chiral phase (Diacel OJ column, 97:3 hexane/IPA, 1 mL/min, 254 nm; **(*S*)-21**, $t_R$ = 9.6 min; **(*R*)-21**,

$t_R$ = 10.7 min): $[\alpha]^{23}_D$ −34.1 (*c* 1.00, $CH_2Cl_2$); IR 2976, 1686, 1129 $cm^{-1}$; $^1H$ NMR (300 MHz) $\delta$ 0.93 (t, 3, *J* = 7.5), 1.27 (s, 9), 1.51−1.60 (m, 1), 1.72−1.79 (m, 1), 2.68 (dd, 1, *J* = 6.4, *J* = 13.2), 3.10 (dd, 1, *J* = 7.8, *J* = 13.2), 3.18 (s, 3), 3.44−3.53 (m, 1), 7.19−7.27 (m, 5); $^{13}C$ NMR (101 MHz) $\delta$ 11.7, 24.7, 26.3, 36.2, 38.5, 49.2, 63.9, 126.4, 128.4, 129.4, 139.8, 177.5. Anal. Calcd for $C_{14}H_{25}NO_3S$: C, 61.70; H, 8.09; N, 4.50. Found: C, 61.55; H, 8.05; N, 4.59.

**(*R*)-2-Phenylmethylbutyric acid (22).** To a 50 mL round-bottom flask were added **21** (311 mg, 1.00 mmol), $H_2O$ (4 mL), and THF (12 mL). After cooling to 0 °C with an ice bath, 30% $H_2O_2$ (1.13 mL, 10 mmol) and LiOH (105 mg, 2.5 mmol) were added. The reaction mixture was strirred overnight and allowed to come to room temperature. The flask was then cooled to 0 °C using an ice bath, and $NaHSO_3$ (1.5 g, 12 mmol) in $H_2O$ (3 mL) was added slowly. The reaction mixture was concentrated, diluted with $CH_2Cl_2$ (20 mL), washed with 0.1 M $NaHSO_4$ (3 × 20 mL), and brine (3 × 20 mL), dried ($Na_2SO_4$), and concentrated. Purification on silica gel (3 × 15 cm, 15:85 EtOAc/hexane) provided 168 mg (94%) of **22** as a colorless oil. The enantiomeric purity was determined to be >99:1 by HPLC analysis on a chiral phase after conversion to the methyl ester by employing $CH_2N_2$ (Diacel AS column, 90:10 hexane/EtOH, 1 mL/min, 254 nm; **(*R*)-22**, $t_R$ = 7.9 min; **(*S*)-22**, $t_R$ = 10.2 min): $[\alpha]^{23}_D$ −40.0 (*c* 1.00, $CH_2Cl_2$); IR 3028, 1708 $cm^{-1}$; $^1H$ NMR (400 MHz) $\delta$ 0.98 (t, 3, *J* = 7.5), 1.58−1.74 (m, 2), 2.60−2.67 (m, 1), 2.77 (dd, 1, *J* = 7.0, *J* = 13.7), 2.99 (dd, 1, *J* = 7.8, *J* = 13.7), 7.19−7.31 (m, 5), 10.02 (bs, 1); $^{13}C$ NMR (101 MHz) $\delta$ 11.6, 24.7, 37.7, 48.9, 126.4, 128.5, 128.9, 139.2, 182.1. Anal. Calcd for $C_{11}H_{14}O_2$: C, 74.10; H, 7.92. Found: C, 74.08; H, 8.05.

**(*R*)-Benzyl-2-phenylmethylbutyrate (23).** To a 10 mL round-bottom flask were added BnOH (206 $\mu$L) and THF (4 mL). The flask was cooled to −78 °C with a dry ice/acetone bath, and 2.5 M *n*-BuLi in hexanes (600 $\mu$L, 1.5 mmol) was added dropwise via syringe. To a second 25 mL flask were added **21** (311 mg, 1.00 mmol) and THF (4 mL), and the flask was cooled to 0 °C with an ice bath. The BnOLi solution was then added to the second flask dropwise via cannula. After stirring the reaction mixture for 4 h, 3 M $NH_4Cl$ (3 mL) was added, and the reaction mixture was concentrated, diluted with $CH_2Cl_2$ (20 mL), washed with 0.1 M $NaHSO_4$ (3 × 20 mL) and brine (3 × 20 mL), dried ($Na_2SO_4$), and concentrated again. Purification on silica gel (3 × 15 cm, 10:90 EtOAc/hexane) provided 260 mg (97%) of **23** as a colorless oil. The enantiomeric purity was determined to be >99:1 by HPLC analysis on a chiral phase (Diacel OJ column, 97:3 hexane/IPA, 1 mL/min, 254 nm; **(*R*)-23**, $t_R$ = 8.2 min; **(*S*)-23**, $t_R$ = 11.7 min); $[\alpha]^{23}_D$ −55.0 (*c* 1.00, $CH_2Cl_2$); IR 2962, 1733 $cm^{-1}$; $^1H$ NMR (300 MHz) $\delta$ 0.99 (t, 3, *J* = 7.4), 1.61−1.81 (m, 2), 2.56−2.75 (m, 1), 2.86 (dd, 1, *J* = 6.4, *J* = 13.5), 3.10 (dd, 1, *J* = 8.6, *J* = 13.5), 5.11 (s, 2), 7.19−7.40 (m, 10); $^{13}C$ NMR (101 MHz) $\delta$ 11.9, 25.4, 38.4, 49.4, 66.1, 126.4, 128.2, 128.3, 128.5, 128.6, 129.1, 136.2, 139.5, 175.5. Anal. Calcd for $C_{18}H_{20}O_2$: C, 80.50; H, 7.51. Found: C, 80.28; H, 7.25.

**(*R*)-*N*-Benzyl-2-phenylmethylbutyramide (24).** To a 10 mL round-bottom flask fitted with a reflux condenser were added **21** (311 mg, 1.00 mmol), benzylamine (210 $\mu$L, 2.0 mmol), and dioxane (2.6 mL), and the reaction solution was heated at reflux overnight. The reaction mixture was diluted with $CH_2Cl_2$ (20 mL), washed with 0.1 M $NaHSO_4$ (3 × 20 mL) and brine (3 × 20 mL), dried ($Na_2SO_4$), and concentrated. Purification on silica gel (3 × 15 cm, 10:90 EtOAc/hexane) provided 246 mg (92%) of **24** as a colorless solid. The enantiomeric purity was determined to be >99:1 by HPLC analysis on a chiral phase (Diacel OJ column, 90:10 hexane/IPA, 1 mL/min, 254 nm; **(*S*)-24**, $t_R$ = 9.4 min; **(*R*)-24**, $t_R$ = 12.1 min): mp 85−87 °C; $[\alpha]^{23}_D$ −51.0 (*c* 1.00, $CH_2Cl_2$); IR 3305, 1643 $cm^{-1}$; $^1H$ NMR (300 MHz) $\delta$ 0.94 (t, 3, *J* = 7.4), 1.42−1.59 (m, 1), 1.71−1.85 (m, 1), 2.18−2.22 (m, 1), 2.75 (dd, 1, *J* = 5.4, *J* = 13.4), 2.93 (dd, 1, *J* = 9.7, *J* = 13.4), 4.25 (dd, 1, *J* = 7.3, *J* = 14.8), 4.38 (dd, 1, *J* = 6.0, *J* = 14.8), 5.53 (bs, 1), 6.95−6.99 (m, 2), 7.14−7.28 (m, 8); $^{13}C$ NMR (101 MHz) $\delta$ 12.3, 26.1, 39.3, 43.4, 52.3, 126.3, 127.3, 127.7, 128.5, 128.6, 129.1, 138.3, 140.1, 174.8. Anal. Calcd for $C_{18}H_{21}NO_2$: C, 80.80; H, 7.92; N, 5.24. Found: C, 80.38; H, 8.02; N, 5.30.

**(*R*)-2-Phenylmethylbutanol (25).** To a 10 mL round-bottom flask were added **21** (311 mg, 1.00 mmol) and THF (2 mL), and the flask was cooled to −78 °C with a dry ice/acetone bath. A 1 M solution of LAH in THF (1.1 mL, 1.1 mmol) was added dropwise over a 10 min period. After stirring for 1 h, the reaction mixture was warmed to 0 °C, and 10% $NH_4Cl$ (1 mL) was added. The resulting precipitate was washed with several portions of THF (1 mL). The organic layer was concentrated, diluted with $CH_2Cl_2$ (20 mL), washed with 0.1 M $NaHSO_4$ (3 × 20 mL) and brine (3 × 20 mL), dried ($Na_2SO_4$), and concentrated. Purification on silica gel (3 × 15 cm, 10:90 EtOAc/hexane) provided 159 mg (97%) of **25** as a colorless oil. The enantiomeric purity was determined to be >99:1 by HPLC analysis on a chiral phase (Diacel OJ column, 97:3 hexane/EtOH, 1 mL/min, 254 nm; **(*R*)-25**, $t_R$ = 10.4 min; **(*S*)-25**, $t_R$ = 11.5 min): $[\alpha]^{23}_D$ −5.0 (*c* 1.00, $CH_2Cl_2$); IR 3328, 2965 $cm^{-1}$; $^1H$ NMR (300 MHz) $\delta$ 0.96 (t, 3, *J* = 7.5), 1.33−1.51 (m, 2), 1.71−1.79 (m, 1), 2.1 (s, 1), 2.62 (dd, 1, *J* = 6.8, *J* = 13.6), 3.10 (dd, 1, *J* = 5.5, *J* = 13.6), 3.54 (d, 2, *J* = 5.4), 7.18−7.33 (m, 5); $^{13}C$ NMR (101 MHz) $\delta$ 11.5, 23.5, 37.4, 44.3, 64.6, 126.0, 128.5, 129.3, 141.0. Anal. Calcd for $C_{11}H_{16}O$: C, 80.40; H, 9.82. Found: C, 80.28; H, 9.67.

**Acknowledgment.** Support from the NSF is gratefully acknowledged. B.J.B. thanks the NSF and Abbott Laboratories for a graduate fellowship.

**Supporting Information Available:** Synthesis and characterization of compounds **6**−**9** (Scheme 2) and **10**−**17** (Scheme 2, Table 1). This material is available free of charge via the Internet at http://pubs.acs.org.

JO990271W