JOC Notes

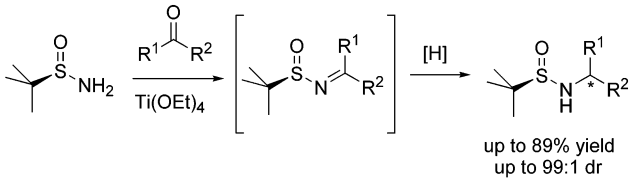
One-Pot Asymmetric Synthesis of Either Diastereomer of *tert*-Butanesulfinyl-protected Amines from Ketones

Jessica Tanuwidjaja, Hillary M. Peltier, and Jonathan A. Ellman*

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

jellman@berkeley.edu

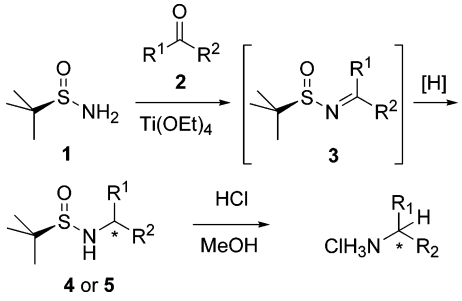
Received August 8, 2006



A one-pot method for the asymmetric synthesis of *tert*-butanesulfinyl-protected amines is described. Condensation of aryl alkyl and dialkyl ketones with *tert*-butanesulfinamide followed by in situ reduction with the appropriate reagent provides either diastereomer of the sulfinamide products in good yields and with diastereomeric ratios of up to 99:1.

A previous study by the Ellman group showed that *tert*-butanesulfinyl-protected amines can be prepared in a one-pot procedure (Scheme 1).[1] The sulfinyl group can then easily be cleaved under mildly acidic conditions to obtain the amine product as its hydrochloride salt. *tert*-Butanesulfinamide (**1**)[2] was condensed with a variety of ketones **2** using $Ti(OEt)_4$ as a Lewis acid and water scavenger. The *N*-sulfinyl imine intermediates **3** were then reduced in situ using $NaBH_4$ to afford sulfinamides in 66−86% yield and with diastereomeric ratios from 90:10 to 97:3. This procedure gives predominantly the (R_S,*R*) diastereomer **4** of the sulfinamide product (Table 1). Surprisingly, in subsequent work it was observed that different reducing agents such as Superhydride or L-Selectride gave the opposite sense of induction to provide sulfinamide diastereomers **5**.[3] The different sense of induction provided by these reagents presents the opportunity to prepare both amine stereoisomers from the same sulfinamide reagent. Herein, we report the scope

SCHEME 1



of asymmetric reductive amination using L-Selectride to provide (R_S,*S*) diastereomer **5** as the major product in good yield and with good to excellent diastereoselectivity. This method provides a synthetically useful procedure for the preparation of enantioenriched amines[4,5] and complements past studies.[1,3,6] In addition, the scope of the one-pot $NaBH_4$ reduction method was expanded to include biologically relevant cyclic substrates. After this work had been completed, researchers at Amgen reported a study on the reduction of both cyclic and acyclic *N*-*tert*-butanesulfinyl imines with both $NaBH_4$ in wet THF and L-Selectride in dry THF and invoked a cyclic versus an acyclic transition state, respectively, to explain the opposing stereochemical outcomes.[7] The imine reduction results reported by Amgen are generally consistent with the one-pot reductive amination results reported here with all significant differences being noted.

Our investigation began with L-selectride-mediated reductive amination of the aryl alkyl ketone acetophenone (**2a**). The sulfinamide product **5a** was obtained in 89% yield and with a diastereomeric ratio of 97:3 (Table 1, entry 2).[8] Dialkyl ketones **2b**−**e** also afforded sulfinamide products in good yields and with good to excellent selectivities. However, to obtain good yields for the reductive amination of aliphatic ketones, it is important that the condensation step is performed under conditions that are not more forcing than is necessary. For example, in the reductive amination of ketone **2c**, a 76% yield

(1) Borg, G.; Cogan, D. A; Ellman, J. A. *Tetrahedron Lett.* **1999**, *40*, 6709.

(2) (a) For a review on applications of *tert*-butanesulfinamide, see: Ellman, J. A.; Owens, T. D.; Tang, T. P. *Acc. Chem. Res.* **2002**, *35*, 984. (b) For a recent general review on the synthesis and applications of sulfinamides, see: Senanayake, C. H.; Krishnamurthy, D.; Lu, Z.-H.; Zhengxu, H.; Gallou, I. *Aldrichimica Acta* **2005**, *38*, 93. (c) For a recent review on additions to arenesulfinyl imines, see: Zhou, P.; Chen, B.-C.; Davis, F. A. *Tetrahedon* **2004**, *60*, 8003.

(3) (a) Kochi, T.; Tang, T. P.; Ellman, J. A. *J. Am. Chem. Soc.* **2003**, *125*, 11276. (b) Peltier, H. M.; Ellman, J. A. *J. Org. Chem.* **2005**, *70*, 7342.

(4) For leading references on asymmetric reductions of preformed, isolated imines, see: (a) Nolin, K. A.; Ahn, R. W.; Toste, F. D. *J. Am. Chem. Soc.* **2005**, *127*, 12462. (b) Yang, Q.; Shang, G.; Gao, W.; Deng, J.; Zhang, X. *Angew. Chem., Int. Ed.* **2006**, *45*, 3832. (c) Storer, R. I.; Carrera, D. E.; Ni, Y.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2006**, *128*, 84. (d) Hoffmann, S.; Seayad, A. M.; List, N. *Angew. Chem., Int. Ed.* **2005**, *44*, 7424. (e) Blaser, H.-U.; Malan, C.; Pugin, B.; Spindler, F.; Steiner, H.; Studer, M. *Adv. Synth. Catal.* **2003**, *345*, 103. (f) Uematsu, N.; Fujii, A.; Hashiguchi, S.; Ikariya, T.; Noyori, R. *J. Am. Chem. Soc.* **1996**, *118*, 4916. (g) Cobley, C. J.; Henschke, J. P. *Adv. Synth. Catal.* **2003**, *345*, 195. (h) Hansen, M. C.; Buchwald, S. L. *Org. Lett.* **2000**, *2*, 713. (i) Qin, J.; Friestad, G. K. *Tetrahedron* **2003**, *59*, 6393.

(5) For the only alternative asymmetric reductive amination method, see: Nugent, T. C.; Wakchaure, V. N.; Ghosh, A. K.; Mohanty, R. R. *Org. Lett.* **2005**, *7*, 4967.

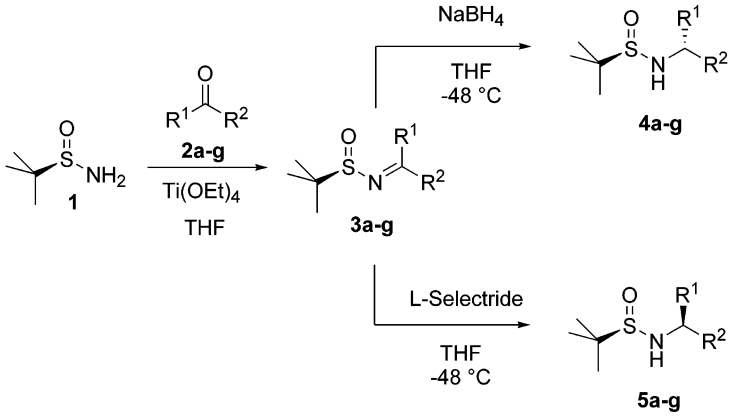
(6) For diethylzinc reduction of preformed *N*-sulfinyl imines catalyzed by $Ni(acac)_2$, see: Xiao, X.; Wang, H.; Huang, Z.; Yang, J.; Bian, X.; Qin, Y. *Org. Lett.* **2006**, *8*, 139.

(7) Colyer, J. T.; Anderson, N. G.; Tedrow, J. S.; Soukup, T. S.; Faul, M. M. *J. Org. Chem.* **2006**, *71*, 6859.

(8) Researchers at Amgen reported a 92:8 dr for L-Selectride reduction of the isolated *N*-*tert*-butanesulfinyl imine prepared from acetophenone.[7]

10.1021/jo0616512 CCC: $37.00
Published on Web 12/22/2006

TABLE 1. Reductive Amination of Acyclic Ketones



entry[a]	ketone	R^1	R^2	temp (°C)/ time (h)[b]	reductant	product	yield[c] (%)	dr[d]
1[e]	**2a**	Me	Ph		$NaBH_4$	**4a**	78	96:4[f]
2	**2a**	Me	Ph	75/15	L-Selectride	**5a**	89	97:3[f]
3[e]	**2b**	Me	*n*Bu		$NaBH_4$	**4b**	82	83:17
4	**2b**	Me	*n*Bu	60/10	L-Selectride	**5b**	72	86:14
5[e]	**2c**	Me	*i*Pr		$NaBH_4$	**4c**	66	97:3
6	**2c**	Me	*i*Pr	60/15	L-Selectride	**5c**	76	96:4
7	**2c**	Me	*i*Pr	75/15	L-Selectride	**5c**	33	96:4
8	**2d**	Me	*t*Bu	75/19	$NaBH_4$	**4d**	62	99:1
9	**2d**	Me	*t*Bu	75/19	L-Selectride	**5d**	83	96:4
10[e]	**2e**	Me	*i*Bu		$NaBH_4$	**4e**	74	92:8
11	**2e**	Me	*i*Bu	60/10	L-Selectride	**5e**	70	96:4
12[g]	**2a**	Me	Ph	75/15	$NaBH_4$	**4a**	93	96:4

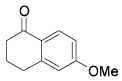
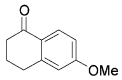
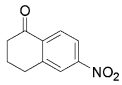
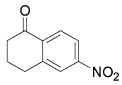
[a] All reactions were performed on a 0.5−1.0 mmol scale unless otherwise indicated. All reductions were performed at −48 °C. [b] Temperature and time for condensation to go to completion. [c] Yields of analytically pure material after chromatography. [d] Unless otherwise noted, diastereomeric ratios were determined by GC analysis of (*R*)- and (*S*)-MTPA derivatives formed after cleavage of the sulfinyl group. [e] Previously published result.[1] [f] Diastereomeric ratio determined by HPLC analysis of the crude sulfinamide product. [g] Reaction performed on a 10-g (45 mmol) scale.

of sulfinamide **5c** was obtained upon imine reduction when the condensation step was performed at 60 °C for 15 h (entry 6). In contrast, when the condensation step was performed under more forcing conditions (75 °C for 15 h), **5c** was obtained in a significantly lower overall yield (entry 7). For dialkyl ketone substrates, the highest diastereomeric ratios were obtained for α-branched ketones **2c** and **2d** (entries 6 and 9),[9] although a *β*-branched ketone also gave product with high selectivity (entry 11). Presumably, substitution at the α- and *β*-positions of dialkyl ketones provides additional steric discrimination leading to higher selectivity than for unbranched dialkyl ketones (entry 4). This trend was also observed for the previously reported method using $NaBH_4$ as the reducing agent (entries 3, 5, 8, and 10). In the study by Amgen, a pronounced scale dependence was observed for the reduction of *N*-*tert*-butanesulfinyl imines with $NaBH_4$ in wet THF, with considerable reduction in dr being observed at 20 mmol versus 0.2 mmol scale.[7] We therefore chose to evaluate scale dependence for our one-pot reductive amination procedure when using $NaBH_4$ as the reductant. As shown in entry 12, when the $NaBH_4$-mediated reductive amination was performed on a 10-g scale (45 mmol), no drop in yield or dr was observed, thereby clearly demonstrating that the one-pot $NaBH_4$ reductive amination procedure does not show scale dependence.

The scope of the one-pot condensation and reduction procedures was explored further by employing cyclic ketones **2f**−**j** (Table 2). Reductive amination of ketone **2f** with either $NaBH_4$ or L-Selectride provided sulfinamides **4f** and **5f** with excellent diastereomeric ratios of 99:1 and >98:2, respectively (entries 1 and 2). However, the yields for these transformations are modest due to competing side reactions that occur during the imine condensation step. Reductive amination of the six-membered ring system **2g** proceeded in dramatically increased yields (entries 3 and 4). Using $NaBH_4$ resulted in amine **4g** in 80% yield and with 84:16 dr. When L-Selectride was used as the reductant, **5g** was obtained in 83% yield and with 99:1 dr. To explore the electronic effects of various substituents on the aryl ring, the reductive amination conditions were applied to both electron-rich and electron-poor six-membered ring systems **2h**,**i**, respectively. Use of $NaBH_4$ resulted in amine **4h** in 89% yield and with 91:9 dr (entry 5). Amine **5h** was obtained in 80% yield and with 97:3 dr when L-Selectride was employed as the reducing agent (entry 6). Amines **4i** and **5i** were also produced in good yield with use of either $NaBH_4$ or L-Selectride, 73 and 72%, and with high selectivity, 90:10 and 98:2 dr, respectively (entries 7 and 8). Notably, entries 5−8 demonstrate that the one-pot reductive amination conditions are general for six-membered ring substrates with electron-donating or electron-withdrawing substituents. When the method was applied to the seven-membered ring system **2j**, depending on the conditions utilized, the amines were produced either in good yield or with good selectivity, but not both. Specifically, use of $NaBH_4$ produced **4j** in quantitative yield, but with a diastereoselectivity

(9) Researchers at Amgen reported a much lower dr for L-Selectride reduction of the isolated *N*-*tert*-butanesulfinyl imine prepared from methyl *tert*-butyl ketone (88:12).[7] In our hands, L-Selectride reduction of this isolated imine gave 96:4 dr, which is the same dr observed for the one-pot reductive amination sequence (Table 1, entry 9).

TABLE 2. Reductive Amination of Cyclic Ketones

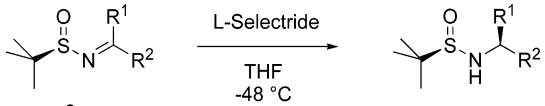
entry	ketone	structure	temp (°C) /time (h)[a]	reductant	product	yield[b] (%)	dr[c]
1	**2f**		75 / 4.5	$NaBH_4$	**4f**	28	99:1
2	**2f**		75 / 4.5	L-Selectride	**5f**	27	>98:2
3	**2g**		75 / 7.5	$NaBH_4$	**4g**	80	84:16
4	**2g**		75 / 7.5	L-Selectride	**5g**	83	99:1
5	**2h**		75 / 48	$NaBH_4$	**4h**	89	91:9[d]
6	**2h**		75 / 48	L-Selectride	**5h**	80	97:3[d]
7	**2i**		75 / 14	$NaBH_4$	**4i**	73	90:10[d]
8	**2i**		75 / 14	L-Selectride	**5i**	72[e]	98:2[d]
9	**2j**		75 / 17	$NaBH_4$	**4j**	100	58:42[d]
10	**2j**		75 / 17	L-Selectride	**5j**	49	88:12[d]

[a] Temperature and time for condensation to go to completion. [b] Yields of analytically pure material after chromatography. [c] Diastereomeric ratios were determined by GC analysis of (*R*)- and (*S*)-MTPA derivatives formed after cleavage of the sulfinyl group. [d] Diastereomeric ratio determined by HPLC analysis of the crude sulfinamide product. [e] Because L-Selectride efficiently reduces nitro groups, only 1.1 equiv of L-Selectride was used, and the reaction was quenched at −78 °C.

of 58:42 (entry 9). Use of L-Selectride produced **5j** in 49% yield and with 88:12 dr (entry 10). The generally successful reductive amination of these cyclic substrates is significant because the amine products are prevalent substructures in drugs and drug candidates.[10]

$Ti(OEt)_4$ serves as both a desiccant and a Lewis acid for the imine synthesis step.[11] When using $NaBH_4$ as the reducing agent, the yield and diastereoselectivity of the reduction are also improved by employing $Ti(OEt)_4$ as an additive.[1] However, when using L-Selectride as the reducing agent, $Ti(OEt)_4$ has minimal effect on the yield or the selectivity of the reduction step (Table 3).[12] Reduction of *N*-sulfinyl imines **3a** and **3c** in the absence of $Ti(OEt)_4$ gave sulfinamides **5a** and **5c** with comparable yields and diastereomeric ratios as those obtained in the one-pot condensation and reduction procedure (Table 3, entries 1 and 3).

TABLE 3. Effect of $Ti(OEt)_4$ on L-Selectride Reductions



3a,c **5a,c**

entry	additive	ketone	R^1	R^2	product	yield	dr
1	none	**3a**	Me	Ph	**5a**	82	96:4[a]
2	$Ti(OEt)_4$	**3a**	Me	Ph	**5a**	89	97:3
3	none	**3c**	Me	*i*Pr	**5c**	86	95:5[b]
4	$Ti(OEt)_4$	**3c**	Me	*i*Pr	**5c**	76	96:4

[a] Diastereomeric ratio determined by HPLC analysis of the crude sulfinamide product. [b] Diastereomeric ratio determined by GC analysis of (*R*)- and (*S*)-MTPA derivatives formed after cleavage of the sulfinyl group.

In conclusion, an efficient one-pot procedure for the asymmetric reductive amination of ketones is reported. The sulfin-

(10) For examples, see: (a) Uiterweerd, P. G. H.; van der Sluis, M.; Kaptein, B.; de Lange, B.; Kellogg, R. M.; Broxterman, Q. B. *Tetrahedron: Asymmetry* **2003**, *14*, 3479. (b) Rover, S.; Adam, G.; Cesura, A. M.; Galley, G.; Jenck, F.; Monsma, F. J., Jr.; Wichmann, J.; Dautzenberg, F. M. *J. Med. Chem.* **2000**, *43*, 1329. (c) Coe, B. K.; Weissman, A.; Welch, W. M.; Broune, R. G. *J. Pharmacol. Exp. Ther.* **1983**, *226*, 686. (d) Welch, W. M.; Kraska, A. R.; Sarges, R.; Coe, K. B. *J. Med. Chem.* **1984**, *27*, 1508. (e) Hurd, Y. L.; Ungerstedt, U. *Eur. J. Pharmacol.* **1989**, *166*, 251.

(11) Liu, G.; Cogan, D. A.; Owens, T. D.; Tang, T. P.; Ellman, J. A. *J. Org. Chem.* **1999**, *64*, 1278.

(12) In the L-Selectride-mediated reduction of isolated *N-tert*-butanesulfinyl imines, Amgen also observed that $Ti(OEt)_4$ as an additive had minimal effect on reaction dr.[7]

amide products are easily accessed in good yields and with good to excellent diastereoselectivities of up to 99:1. This method complements previously described asymmetric reductions of *N*-sulfinyl ketimines and expands the scope of these methods. The procedure provides facile and efficient access to either stereoisomer of the sulfinamide product from a common *N*-sulfinyl imine intermediate simply by appropriate choice of the reductant. Considering the convenience and generality of the method and the abundance of natural products and biologically active molecules that contain the amine functionality, this method should find wide use in both academics and industry.

Experimental Section

General Procedure A for L-Selectride Reductions. Ketone was added to a solution of (*R*)-**1** and $Ti(OEt)_4$ in THF at room temperature (rt). The reaction mixture was heated to the temperature indicated in Table 1, and the reaction conversion was followed by TLC. Once the reaction was determined to be complete by TLC, the mixture was cooled to room temperature and then to −48 °C. L-Selectride (1 M solution in THF) was added dropwise. The reaction mixture was allowed to warm to rt. Once the reduction was determined to be complete by TLC, the reaction mixture was cooled to 0 °C and MeOH was added dropwise until gas evolution was no longer observed. The crude reaction mixture was poured into an equal volume of brine while being rapidly stirred. The resulting suspension was filtered through a plug of celite, and the filter cake was washed with EtOAc. The filtrate was washed with brine, and the brine layer was extracted with EtOAc (3×). The combined organic portions were dried (Na_2SO_4), filtered, and concentrated. Sulfinamides **5a**−**j** were purified by silica gel chromatography (hexanes/EtOAc).

General Procedure B for $NaBH_4$ Reductions. Ketone was added to a solution of (*R*)-**1** and $Ti(OEt)_4$ in THF at rt. The reaction mixture was heated to the temperature indicated in Table 1, and the reaction conversion was followed by TLC. Once the reaction was determined to be complete by TLC, the mixture was cooled to room temperature and then to −48 °C. The reaction mixture was added dropwise via cannula to a −48 °C suspension of $NaBH_4$ in a minimum amount of THF. The vessel was then rinsed with THF (2×). The reaction mixture was allowed to warm to rt. Once the reduction was determined to be complete by TLC, the reaction mixture was cooled to 0 °C and MeOH was added dropwise until gas evolution was no longer observed. The crude reaction mixture was poured into an equal volume of brine while being rapidly stirred. The resulting suspension was filtered through a plug of celite, and the filter cake was washed with EtOAc. The filtrate was washed with brine, and the brine layer was extracted with EtOAc (3×). The combined organic portions were dried (Na_2SO_4), filtered, and concentrated. Sulfinamides **4d** and **4f**−**j** were purified by silica gel chromatography (hexanes/EtOAc).

(*R*$_S$,*S*)-*N*-(1,2-Dimethylpropyl)-2-methylpropylsulfinamide (5c). General procedure A was followed with a 0.5 M solution of (*R*)-**1** (63.3 mg, 0.523 mmol, 1 equiv), $Ti(OEt)_4$ (0.254 mL, 1.05 mmol, 2 equiv), 3-methyl-2-butanone (0.0672 mL, 0.628 mmol, 1.2 equiv), and L-Selectride (1.46 mL, 1.46 mmol, 3 equiv). Chromatography (60:40 EtOAc/hexanes) afforded 76.4 mg (76%) of **5c** as a pale yellow oil. The diastereomeric ratio was determined by GC analysis of (*R*)- and (*S*)-MTPA derivatives of the amine hydrochloride salts of crude **5c** (Ultra II column, 100−250 °C, 2 °C/min, 20 psi; (*R*)-MTPA derivative of **4c** t_R = 29.7 min (minor diastereomer), **5c** t_R = 30.4 min (major diastereomer). ^{1}H NMR (400 MHz) δ 0.77 (d, 3H, J = 6.0 Hz), 0.79 (d, 3H, J = 6.8 Hz), 1.11 (d, 3H, J = 6.8 Hz), 1.11 (s, 9H), 1.57−1.65 (m, 1H), 2.76 (br d, 1H, J = 7.2 Hz), 3.05−3.15 (m, 1H); ^{13}C (100 MHz) δ 18.1, 18.2, 19.7, 22.7, 33.8, 55.8, 57.7. All analytical data agree with the literature data.[1]

(*R*$_S$,*R*)-*N*-(1,2,2-Trimethylpropyl)-2-methylpropylsulfinamide (4d). General procedure B was followed with a 0.5 M solution of (*R*)-**1** (118 mg, 0.974 mmol, 1 equiv), $Ti(OEt)_4$ (0.472 mL, 1.95 mmol, 2 equiv), pinacolone (0.150 mL, 1.17 mmol, 1.2 equiv), and $NaBH_4$ (147 mg, 3.90 mmol, 4 equiv). Chromatography (60:40 EtOAc/hexanes) afforded 124 mg (62%) of **4d** as a white crystalline solid. The diastereomeric ratio was determined by GC analysis of (*R*)- and (*S*)-MTPA derivatives of the amine hydrochloride salts of crude **4d** (Ultra II column, 100−250 °C, 2 °C/min, 20 psi; (*R*)-MTPA derivative of **4d** t_R = 31.8 min (major diastereomer), **5d** t_R = 32.8 min (minor diastereomer). mp 55−58 °C; $[\alpha]^{23}{}_D$ −2.3° (*c* 1.0, MeOH, for amine hydrochloride); IR 1057, 1364, 1474, 1653, 2870, 2958, 3251 cm^{-1}; ^{1}H NMR (400 MHz) δ 0.88 (s, 9H), 1.09 (d, 3H, J = 6.8 Hz), 1.16 (s, 9H), 3.05−3.11 (m, 1H), 3.21 (br s, 1H); ^{13}C (100 MHz) δ 16.0, 22.8, 26.3, 34.5, 55.5, 59.0; MS (FAB): *m*/*z* $[M + H]^+$ 206. Anal. Calcd for $C_{10}H_{23}NOS$: C, 58.49; H, 11.29; N, 6.82. Found: C, 58.14; H, 11.39; N, 7.00.

(*R*$_S$,*S*)-*N*-(1,2,2-Trimethylpropyl)-2-methylpropylsulfinamide (5d). General procedure A was followed with a 0.5 M solution of (*R*)-**1** (59.0 mg, 0.487 mmol, 1 equiv), $Ti(OEt)_4$ (0.236 mL, 0.974 mmol, 2 equiv), pinacolone (0.0745 mL, 0.584 mmol, 1.2 equiv), and L-Selectride (1.46 mL, 1.46 mmol, 3 equiv). Chromatography (60:40 EtOAc/hexanes) afforded 83.0 mg (83%) of **5d** as a white crystalline solid. The diastereomeric ratio was determined by GC analysis of (*R*)- and (*S*)-MTPA derivatives of the amine hydrochloride salts of crude **5d** (Ultra II column, 100−250 °C, 2 °C/min, 20 psi; (*R*)-MTPA derivative of **4d** t_R = 31.8 min (minor diastereomer), **5d** t_R = 32.8 min (major diastereomer). mp 72−75 °C; $[\alpha]^{23}{}_D$ +2.3° (*c* 1.0, MeOH); IR 1016, 1055, 1377, 1652, 2958, 2978, 3128, 3249 cm^{-1}; ^{1}H NMR (400 MHz) δ 0.89 (s, 9H), 1.23 (s, 9H), 1.25 (d, 3H, J = 6.8 Hz), 2.76 (br d, 1H, J = 9.2 Hz), 3.02−3.09 (m, 1H); ^{13}C (100 MHz) δ 18.9, 23.0, 26.4, 35.5, 56.4, 62.3; MS (FAB): *m*/*z* $[M + H]^+$ 206. Anal. Calcd for $C_{10}H_{23}NOS$: C, 58.49; H, 11.29; N, 6.82. Found: C, 58.71; H, 11.56; N, 6.81.

Acknowledgment. This work was supported by the National Science Foundation (CHE-0446173). J.T. thanks the Department of Chemistry at the University of California at Berkeley for a Summer Research Award, and H.M.P. thanks Eli Lilly for a graduate student fellowship.

Supporting Information Available: Full experimental details, spectral data, and characterization for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

JO0616512