A Lewis Acid Promoted Asymmetric Umpolung Reaction with Chiral *N*-Sulfinyl Imines as the Electrophiles

Xin Xu,[a] Jun-ying Liu,[a] Dian-jun Chen,[a] Cody Timmons,[a] and Guigen Li*[a]

Keywords: Amino ketones / Asymmetric synthesis / 1,3-Dithianes / *N*-Sulfinyl imines / Umpolung

An new asymmetric umpolung reaction has been developed by reacting *N*-sulfinyl imines with 2-lithio-2-phenyl-1,3-dithiane. The reaction was conducted at between –20 and –25 °C in THF in the presence of Et_2AlCl as the Lewis acid promoter. Excellent diastereoselectivities (up to >95 % *de*) and chemical yields (64–95 %) have been achieved for nine substrates with all individual isomers separated and characterized. The absolute structure of the chiral products has been unambiguously determined by synthetic conversions to a known sample. 2-Lithio-2-phenyl-1,3-dithiane was found to be much less reactive than its 2-methyl counterpart, which was reported very recently. All individual isomers have been readily separated by column chromatography. The absolute structure of the chiral products has been unambiguously determined by conversion into a known compound. This method provides an easy access to enantiomerically pure α-amino ketones.

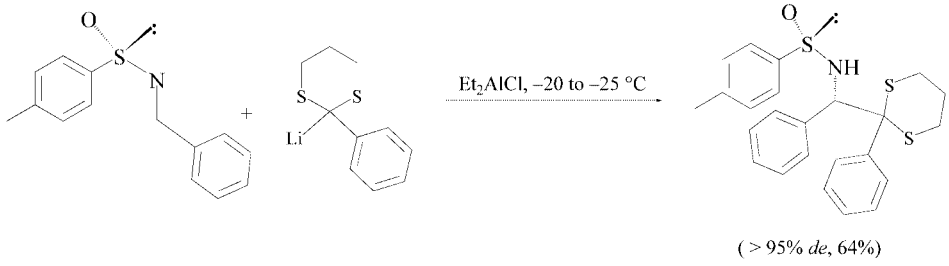
Introduction

The umpolung reaction is a very useful synthetic tool in organic chemistry and has been widely applied for numerous transformations by temporarily reversing the characteristic reactivity of carbonyl groups.[1–4] This reaction is often conducted by allowing dithiane anions derived from aldehydes to react with various electrophiles.[2] Although the racemic umpolung reaction has become classic and well-known, there has been little work on the asymmetric umpolung reaction documented so far.[1b,4]

A few years ago, we reported several asymmetric carbon–carbon bond formations with *N*-sulfinyl imines[6,7] as the electrophiles and lithium (α-carbalkoxyvinyl)cuprates.[8] These reactions resulted in β-branched Morita–Baylis–Hillman ester adducts[9] functionalized with an array of multifunctional groups that can serve as versatile building blocks for organic synthesis. We later envisioned that *N*-sulfinyl imines could be utilized as the electrophilic component in a reaction with dithiane anions to give the corresponding *N*-sulfinyl-α-amino-1,3-dithianes, which are the direct precursors to α-amino ketones.[10] In this paper, we report our preliminary results on this asymmetric reaction, which is exemplified in Scheme 1.[11]

Results and Discussion

At the beginning, the reaction of *N*-sulfinyl imine with 2-lithio-2-phenyl-1,3-dithiane (entry 1 of Table 1) was performed at –78 °C in THF, but only a very small amount of the product was observed after the reaction was performed for more than 10 hours. The reaction temperature was then



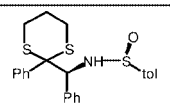
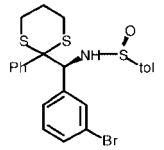
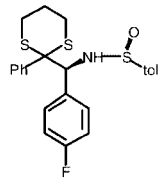
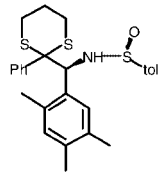
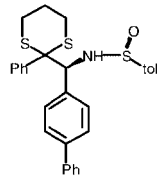
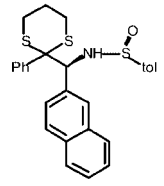
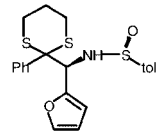
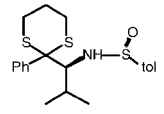
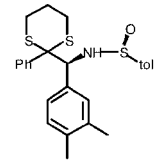
Scheme 1.

increased to between –20 and –25 °C; no obvious improvement was observed. Since Et_2AlCl has been successfully utilized to promote our previous *N*-sulfinyl imine-based asymmetric C–C bond formations,[8] it was thus examined for

[a] Department of Chemistry and Biochemistry, Texas Tech University,
Lubbock, TX 79409-1061, USA
E-mail: guigen.li@ttu.edu

 DOI: 10.1002/ejoc.200400775

Table 1. The results of asymmetric umpolung reaction promoted by Et_2AlCl.[a]

Entry	Product	% *de*	% Yield[b]	$[\alpha]_D^{25}$ [c]	m.p. [°C]
1	 **1**	> 95 %	64 %	+95.0 (*c* = 0.06)	75–77
2	 **2**	> 95 %	95 %	+15.6 (*c* = 4.4)	110–112
3	 **3**	89 %	95 %	+62.7 (*c* = 1.6)	134–136
4	 **4**	85 %	90 %	+61.5 (*c* = 1.0) (+101.0, *c* = 0.3)	73–75 (173–175)
5	 **5**	75 %	82 %	+40.3 (*c* = 0.33) (+11.4, *c* = 0.14)	129–131 (89–91)
6	 **6**	32 %	68 %	+29.5 (*c* = 1.1) (+21.3, *c* = 0.54)	82–84 (96–98)
7	 **7**	31 %	76 %	+76.1 (*c* = 0.44) (+34.3, *c* = 1.5)	50–52 (90–92)
8	 **8**	52 %	76 %	+64.4 (*c* = 0.86) (+72.2, *c* = 0.36)	131–132 (142–144)
9	 **9**	50 %	86 %	+95.7 (*c* = 0.23) (+38.1, *c* = 0.16)	103–105 (164–166)

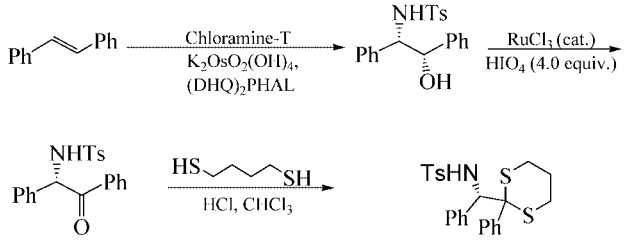
[a] All experiments were performed during 19 hours. [b] Yield after column chromatography. [c] Optical rotation and melting point data for minor isomers are given in parentheses. CH_2Cl_2 was used as the solvent for the measurements of optical rotations.

the present reaction. It was found that *N*-sulfinyl imine was consumed with 19 hours and the reaction provided a good yield (64%) with excellent diastereoselectivity (>95%).

The *N*-sulfinyl imine starting materials employed in this reaction were prepared according to a literature procedure in which the Andersen reagent was treated with LiHMDS, followed by treatment with aldehydes.[6] Meanwhile, 2-phenyl-1,3-dithiane was synthesized by reacting benzaldehyde with 1,3-dithiol in the presence of hydrogen chloride in $CHCl_3$,[2] followed by deprotonation with *n*BuLi at –20 °C.

The 2-lithio-2-phenyl-1,3-dithiane used in our reaction showed much lower reactivity toward *N*-sulfinyl imines than 2-lithio-2-methyl-1,3-dithiane as reported by Davis.[12] The former did not give any of the desired product at –78 °C, whereas the latter reacted with *N*-sulfinyl imines at this temperature completely within 20 minutes. We believe that the stabilization effect of the phenyl ring on the anion is responsible for the lower reactivity of 2-lithio-2-phenyl-1,3-dithiane.

The absolute structure was determined by converting an authentic sample, synthesized by a Sharpless asymmetric aminohydroxylation (AA) reaction,[13] into product **1** in Table 1 (Scheme 2). In this procedure, the AA-derived *N*-tosyl-1,2-amino alcohol was first oxidized to the corresponding *N*-tosyl-α-amino ketone.[14] This ketone was then protected to give the α-amino dithioketal. Chiral HPLC analysis proved that the resulting α-amino dithioketal is identical to the minor isomer of product **1** after oxidation of the sulfinyl group to a sulfonyl group [chiralcel-OD-H, *i*PrOH/hexane (1:19), 1.0 mL/min, 22.05 min, (S_S,*R*)-(–)-isomer]. It should be mentioned that this determination procedure itself can serve as an effective approach to α-amino ketones, although it sacrifices one chiral center and requires an additional step should carbonyl protection be required for further transformations.



Scheme 2.

As shown in Table 1, 2-lithio-2-phenyl-1,3-dithiane reacted very well with all aldehydes examined under the new conditions. The first four substrates (entries 1–4 of Table 1) gave good to excellent diastereoselectivity and high yields. For all aldehydes, chemical yields are very good, although diastereoselectivity is low for the rest of the substrates. The low diastereoselectivities could potentially be the result of the high reactivity associated the use of such a strong Lewis acid promoter. However, both isomers of the product can be cleanly separated by column chromatography. The optical rotations of all major and minor isomers were measured and found to be positive; this indicates that the optical rotation is determined by the *N*-sulfinyl group instead of the newly created chiral center of each product. Davis and coworkers have also noted similar positive optical rota-

tion data,[12] although none of their products are the same as ours.

To understand the asymmetric induction pattern of this reaction, a straightforward hypothesis of a chair-like transition state is proposed in Figure 1, which is similar to that suggested by Davis (Figure 1).[12] 2-Lithio-2-phenyl-1,3-dithiane approaches the electrophilic carbon center of the sulfonyl imine from the less-hindered side of the stereogenic sulfur center, which is the side that contains the lone pair of electrons. In this model, the two lone-pairs of electrons are both coordinated by Lewis acidic centers (Li and Al, respectively). The phenyl group of 2-lithio-2-phenyl-1,3-dithiane and that of *N*-sulfinyl imine are arranged in *gauche* positions.

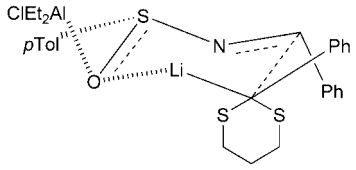


Figure 1. Model of asymmetric induction.

Even though this model can be reasonably used to explain the resulting stereochemistry of this reaction, a possible open-chain model cannot be excluded.[15]

Conclusion

In summary, an asymmetric umpolung reaction has been developed by reacting *N*-sulfinyl imines with 2-lithio-2-phenyl-1,3-dithiane in the presence of Et_2AlCl as the promoter. 2-Lithio-2-phenyl-1,3-dithiane was found to be much less reactive than its 2-methyl counterpart. All individual isomers have been readily separated by column chromatography. The absolute structure of the chiral products has been unambiguously determined by conversion into a known compound. This method provides an easy access to enantiomerically pure α-amino ketones.

Experimental Section

General Information: All reactions were conducted under nitrogen atmosphere in oven-dried glassware with magnetic stirring. THF was dried by freshly distilling from sodium and benzophenone under nitrogen protection. *n*BuLi (in hexane) and Et_2AlCl (in hexane) were purchased from commercial sources and were used without purification. Their stoichiometries were calculated based on the reported purities from the manufacturers. Flash chromatography was performed on E. Merck silica gel 60 (230–400 mesh). NMR spectra were recorded at 300 MHz for ^1H NMR and 125 MHz for ^{13}C NMR spectroscopy. $CDCl_3$ was the only solvent used for the NMR analysis, with TMS as the internal standard. High-resolution mass spectral analysis was conducted by the Scripps Research Institute.

Typical Procedure for the Asymmetric Umpolung Reaction Represented by Entry 1 of Table 1: Under an N_2 atmosphere, a dry flask was loaded with 2-phenyl-1,3-dithiane (60 mg, 0.3 mmol) and dry THF (1.5 mL). The solution was cooled to between –20 and –25 °C and *n*BuLi (0.19 mL, 0.31 mmol in hexane) was then added. The reaction mixture was stirred for 1 h at this temperature. A solution of *N*-sulfinyl phenylimine in THF (47.4 mg, 0.195 mmol, 1.0 mL) was then added, followed by dropwise addition of Et_2AlCl (0.15 mL, 0.15 mmol, 1.0 M in hexane). After the addition was complete, stirring was continued for 19 h at the same temperature. The reaction was quenched with 3 mL of saturated NH_4Cl. The mixture was extracted with EtOAc (3 × 5 mL). The organic extracts were washed with brine and dried with Na_2SO_4. After removal of the solvents, the crude product was purified by column chromatography (hexane/EtOAc, 4:1) to give (S_S,*S*)-*N*-[phenyl(2-phenyl-1,3-dithian-2-yl)methyl]-*p*-toluenesulfinamide (**1**) (55 mg, 64%, only one isomer) as a white solid. M.p. 75–77 °C. $[\alpha]_D^{25}$ = +95.0 (*c* = 0.06, CH_2Cl_2). IR (deposit from CH_2Cl_2 solution on a NaCl plate): $\tilde{\nu}$ = 3258, 3056, 2923, 1093 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ = 7.58–7.55 (m, 2 H), 7.39–7.35 (m, 2 H), 7.19–7.15 (m, 3 H), 6.97–6.91 (m, 3 H), 6.86–6.81 (m, 2 H), 6.46–6.43 (m, 2 H), 5.15 (d, *J* = 6.9 Hz, 1 H), 4.69 (d, *J* = 6.9 Hz, 1 H), 2.67–2.49 (m, 4 H), 2.19 (s, 3 H), 1.84–1.81 (m, 2 H) ppm. ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 140.9, 140.8, 137.4, 137.0, 130.6, 129.0, 128.8, 128.2, 127.5, 127.2, 126.7, 125.8, 65.3, 65.1, 27.4, 27.2, 24.6, 21.2 ppm. HRMS [M + H^+]: *m*/*z* = 440.1165; calcd. for $C_{24}H_{26}NOS_3$ 440.1171.

(S_S,*S*)-*N*-[3-Bromophenyl(2-phenyl-1,3-dithian-2-yl)methyl]-*p*-toluenesulfinamide (2): White solid, 74 mg (95%, only one isomer). M.p. 110–112 °C. $[\alpha]_D^{25}$ = +15.6 (*c* = 4.4, CH_2Cl_2). IR (deposit from CH_2Cl_2 solution on a NaCl plate): $\tilde{\nu}$ = 3293, 3055, 2906, 1092 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ = 7.62–7.59 (m, 2 H), 7.35–7.32 (m, 2 H), 7.27–7.22 (m, 3 H), 7.10–7.06 (m, 1 H), 6.95–6.92 (m, 2 H), 6.72–6.67 (m, 1 H), 6.49–6.48 (m, 1 H), 6.40 (m, 1 H), 5.47 (d, *J* = 5.4 Hz, 1 H), 4.64 (d, *J* = 5.4 Hz, 1 H), 2.71–2.63 (m, 4 H), 2.22 (s, 3 H), 1.90 (m, 2 H) ppm. ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 141.0, 139.8, 139.3, 137.3, 132.2, 130.2, 129.8, 128.7, 128.4, 127.9, 127.8, 127.7, 125.6, 120.6, 64.9, 62.4, 27.5, 27.1, 24.5, 21.1 ppm.

(S_S,*S*)-*N*-[4-Fluorophenyl(2-phenyl-1,3-dithian-2-yl)methyl]-*p*-toluenesulfinamide (3): Yield: 95%. M.p. 134–136 °C. $[\alpha]_D^{25}$ = +62.7 (*c* = 1.6, CH_2Cl_2). IR (deposit from CH_2Cl_2 solution on a NaCl plate): $\tilde{\nu}$ = 3295, 3054, 2907, 1093 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ = 7.63–7.60 (m, 2 H), 7.40–7.38 (m, 2 H), 7.27–7.21 (m, 3 H), 7.00–6.97 (m, 2 H), 6.60–6.54 (m, 2 H), 6.48–6.43 (m, 2 H), 5.35 (d, *J* = 6.2 Hz, 1 H), 4.72 (d, *J* = 6.2 Hz, 1 H), 2.72–2.58 (m, 4 H), 2.24 (s, 3 H), 1.92–1.88 (m, 2 H) ppm. ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 162.9, 160.9, 140.9, 140.4, 137.4, 132.9, 132.8, 130.6, 130.6, 130.4, 128.8, 128.3, 127.6, 125.7, 113.5, 113.3, 65.2, 63.5, 27.5, 27.1, 24.5, 21.1 ppm.

(S_S,*S*)-*N*-[(2-Phenyl-1,3-dithian-2-yl)(3,4,6-trimethylphenyl)methyl]-*p*-toluenesulfinamide (4): Yield: 90%. Major isomer, white solid, 60 mg, m.p. 73–75 °C. $[\alpha]_D^{25}$ = +61.5 (*c* = 1.0, CH_2Cl_2). IR (deposit from CH_2Cl_2 solution on a NaCl plate): $\tilde{\nu}$ = 3308, 3053, 2919, 1094 cm^{-1}. ^1H NMR ($CDCl_3$, 500 MHz): δ = 7.77–7.73 (m, 2 H), 7.53–7.48 (m, 2 H), 7.30–7.24 (m, 3 H), 7.09–7.05 (m, 2 H), 6.58 (s, 1 H), 6.15 (s, 1 H), 5.10 (d, *J* = 7.2 Hz, 1 H), 4.78 (d, *J* = 7.2 Hz, 1 H), 2.71–2.52 (m, 4 H), 2.31 (s, 3 H), 2.08 (s, 3 H), 1.95 (s, 3 H), 1.95–1.87 (m, 2 H), 1.85 (s, 3 H) ppm. ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 141.3, 140.8, 136.9, 135.6, 134.1, 133.1, 132.4, 131.4, 130.8, 130.2, 128.8, 128.0, 127.5, 125.7, 65.9, 60.6, 31.5, 27.3, 27.2, 24.7, 21.2, 19.3, 19.1 ppm. HRMS [MH^+]: *m*/*z* = 482.1646; calcd. for $C_{27}H_{32}NOS_3$ 482.164.

(S_S,*R*)-Isomer: Minor isomer, white solid, 5 mg, m.p. 173–175 °C (dec.). $[\alpha]_D^{25}$ = +101.0 (*c* = 0.3, CH_2Cl_2). IR (deposit from CH_2Cl_2 solution on a NaCl plate): $\tilde{\nu}$ = 3257, 3050, 2920, 1093 cm^{-1}. ^1H NMR ($CDCl_3$, 500 MHz): δ = 7.71–7.68 (m, 2 H), 7.56–7.52 (m, 2 H), 7.31–7.25 (m, 5 H), 6.90 (s, 1 H), 6.75 (s, 1 H), 5.11 (d, *J* = 3.5 Hz, 1 H), 5.02 (d, *J* = 3.5 Hz, 1 H), 2.76–2.48 (m, 4 H), 2.42

(s, 3 H), 2.18 (s, 3 H), 2.15 (s, 3 H), 1.90 (s, 3 H), 1.90–1.78 (m, 2 H) ppm. ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 142.5, 141.1, 137.3, 136.4, 135.6, 132.7, 131.2, 131.2, 131.1, 131.0, 129.5, 128.1, 127.5, 125.7, 65.5, 61.4, 27.7, 27.0, 24.5, 21.4, 19.5, 19.4, 19.1 ppm. HRMS [MH$^+$]: *m*/*z* = 482.1638; calcd. for $C_{27}H_{32}NOS_3$ 482.164.

(S_S,*S*)-*N*-[Biphenyl(2-phenyl-1,3-dithian-2-yl)methyl]-*p*-toluenesulfinamide (5): Yield: 82%. Major isomer, white solid, 55 mg; m.p. 129–131 °C. $[\alpha]_D^{25}$ = +40.3 (*c* = 0.33, CH_2Cl_2). IR (deposit from CH_2Cl_2 solution on a NaCl plate): $\tilde{\nu}$ = 3299, 3054, 2906, 1093 cm^{-1}. ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 7.69–7.66 (m, 2 H), 7.49–7.23 (m, 10 H), 7.14 (d, *J* = 8.1 Hz, 2 H), 7.00 (d, *J* = 8.1 Hz, 2 H), 6.58 (d, *J* = 8.1 Hz, 2 H), 5.26 (d, *J* = 6.8 Hz, 1 H), 4.82 (d, *J* = 6.8 Hz, 1 H), 2.78–2.58 (m, 4 H), 2.22 (s, 3 H), 1.95–1.87 (m, 2 H) ppm. ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 140.9, 140.8, 140.7, 140.0, 137.4, 136.1, 130.6, 129.5, 128.9, 128.6, 128.3, 127.6, 127.1, 126.9, 125.8, 125.4, 65.2, 64.6, 27.5, 27.3, 24.6, 21.2 ppm.

(S_S,*R*)-Isomer: Minor isomer white solid, 8.0 mg; m.p. 89–91 °C. $[\alpha]_D^{25}$ = +11.4 (*c* = 0.14, CH_2Cl_2). IR (deposit from CH_2Cl_2 solution on a NaCl plate): $\tilde{\nu}$ = 3257, 3050, 2920, 1093 cm^{-1}. ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 7.64–7.61 (m, 4 H), 7.58–7.55 (m, 2 H), 7.43–7.38 (m, 4 H), 7.35–7.32 (m, 3 H), 7.27–7.24 (m, 3 H), 7.01 (d, *J* = 8.5 Hz, 2 H), 5.35 (d, *J* = 2.5 Hz, 1 H), 4.86 (d, *J* = 2.5 Hz, 1 H), 2.76–2.60 (m, 4 H), 2.44 (s, 3 H), 1.90–1.85 (m, 2 H) ppm. ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 142.3, 141.4, 140.9, 140.6, 137.7, 134.6, 130.3, 130.2, 129.6, 128.7, 128.3, 127.7, 127.3, 127.0, 125.8, 125.6, 66.6, 64.7, 27.7, 27.0, 24.4, 21.4 ppm.

(S_S,*S*)-*N*-[2-Naphthyl(2-phenyl-1,3-dithian-2-yl)methyl]-*p*-toluenesulfinamide (6): Yield: 68%. Major isomer, white solid, 33 mg; m.p. 82–84 °C. $[\alpha]_D^{25}$ = +29.5 (*c* = 1.1, CH_2Cl_2). IR (deposit from CH_2Cl_2 solution on a NaCl plate): $\tilde{\nu}$ = 3297, 3054, 2919, 1094 cm^{-1}. ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 7.66–7.63 (m, 3 H), 7.46–7.43 (m, 1 H), 7.40–7.34 (m, 5 H), 7.22–7.20 (m, 3 H), 6.88–6.80 (m, 3 H), 6.67–6.64 (m, 1 H), 5.35 (d, *J* = 6.5 Hz, 1 H), 4.93 (d, *J* = 6.5 Hz, 1 H), 2.71–2.66 (m, 4 H), 2.00 (s, 3 H), 1.91 (m, 2 H) ppm. ^{13}C NMR ($CDCl_3$, 125 MHz): δ141.0, 140.5, 137.4, 134.5, 132.5, 132.1, 130.6, 128.8, 128.7, 128.3, 127.9, 127.6, 127.3, 126.6, 126.1, 125.7, 125.6, 125.5, 65.2, 64.6, 27.5, 27.3, 24.7, 20.9 ppm. HRMS [MH$^+$]: *m*/*z* = 490.1326; calcd. for $C_{28}H_{28}NOS_3$ 490.1327.

(S_S,*R*)-Isomer: Minor isomer, white solid, 17 mg; m.p. 96–98 °C. $[\alpha]_D^{25}$ = +21.3 (*c* = 0.54, CH_2Cl_2). IR (deposit from CH_2Cl_2 solution on a NaCl plate): $\tilde{\nu}$ = 3259, 3054, 2908, 1093 cm^{-1}. ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 7.79–7.75 (m, 2 H), 7.67–7.60 (m, 4 H), 7.45–7.22 (m, 9 H), 7.09–7.05 (m, 1 H), 5.36 (d, *J* = 2.7 Hz, 1 H), 4.99 (d, *J* = 2.7 Hz, 1 H), 2.73–2.61 (m, 4 H), 2.44 (s, 3 H), 1.88 (m, 2 H) ppm. ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 142.3, 141.4, 137.7, 133.2, 133.0, 132.4, 130.3, 129.9, 129.2, 128.3, 128.2, 127.7, 127.5, 127.2, 126.5, 126.1, 125.8, 125.5, 67.0, 64.8, 27.7, 27.0, 24.5, 21.4 ppm. HRMS [MH$^+$]: *m*/*z* = 490.1332; calcd. for $C_{28}H_{28}NOS_3$ 490.1327.

(S_S,*S*)-*N*-[2-Furyl-(2-phenyl-1,3-dithian-2-yl)methyl]-*p*-toluenesulfinamide (7): Yield: 76%. Major isomer, white solid, 32 mg; m.p. 50–52 °C. $[\alpha]_D^{25}$ = +76.1 (*c* = 0.44, CH_2Cl_2). IR (deposit from CH_2Cl_2 solution on a NaCl plate): $\tilde{\nu}$ = 3307, 3054, 2907, 1095 cm^{-1}. ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 7.72–7.69 (m, 2 H), 7.59–7.54 (m, 2 H), 7.26–7.16 (m, 5 H), 7.08 (dd, *J* = 0.8, 1.8 Hz, 1 H), 6.08 (dd, *J* = 1.8, 3.4 Hz, 1 H), 5.79 (dd, *J* = 0.8, 3.4 Hz, 1 H), 4.92 (d, *J* = 8.4 Hz, 1 H), 4.86 (d, *J* = 8.4 Hz, 1 H), 2.70–2.64 (m, 4 H), 2.33 (s, 3 H), 1.94–1.83 (m, 2 H) ppm. ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 149.8, 141.7, 141.6, 141.1, 137.6, 130.1, 129.2, 128.3, 127.6, 125.7, 110.0, 109.6, 64.7, 60.8, 27.5, 27.5, 24.6, 21.3 ppm. HRMS [MH$^+$]: *m*/*z* = 430.0961; calcd. for $C_{22}H_{24}NO_2S_3$ 430.0964.

(S_S,*R*)-Isomer: Minor isomer, white solid, 17 mg; m.p. 90–92 °C. $[\alpha]_D^{25}$ = +34.3 (*c* = 1.5, CH_2Cl_2). IR (deposit from CH_2Cl_2 solution on a NaCl plate): $\tilde{\nu}$ = 3257, 3055, 2907, 1094 cm^{-1}. ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 7.71–7.67 (m, 2 H), 7.54–7.51 (m, 2 H), 7.31–7.24 (m, 6 H), 6.25 (dd, *J* = 1.8, 3.3 Hz, 1 H), 6.05 (dd, *J* = 0.5, 3.3 Hz, 1 H), 5.00 (d, *J* = 5.3 Hz, 1 H), 4.75 (d, *J* = 5.3 Hz, 1 H), 2.66–2.60 (m, 4 H), 2.40 (s, 3 H), 1.85–1.82 (m, 2 H) ppm. ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 149.4, 142.2, 141.5, 141.4, 137.9, 129.9, 129.6, 128.4, 127.7, 125.9, 110.7, 110.2, 63.8, 60.7, 27.6, 27.3, 24.4, 21.4 ppm.

(S_S,*S*)-*N*-[2-Methyl-1-(2-phenyl-1,3-dithian-2-yl)propyl]-*p*-toluenesulfinamide (8): Yield 76%. Major isomer, white solid, 35 mg; m.p. 131–132 °C. $[\alpha]_D^{25}$ = +64.4 (*c* = 0.86, CH_2Cl_2). IR (deposit from CH_2Cl_2 solution on a NaCl plate): $\tilde{\nu}$ = 3344, 3055, 2959, 2906, 1092 cm^{-1}. ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 7.96–7.90 (m, 4 H), 7.39–7.26 (m, 5 H), 3.98 (d, *J* = 10.8 Hz, 1 H), 3.78 (dd, *J* = 1.0, 10.8 Hz, 1 H), 2.75–2.61 (m, 4 H), 2.44 (s, 3 H), 2.28–2.19 (m, 1 H), 1.95 (m, 2 H), 1.08 (d, *J* = 6.9 Hz, 3 H), 0.25 (d, *J* = 6.9 Hz, 3 H) ppm. ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 143.6, 141.3, 138.1, 130.0, 129.4, 128.7, 127.5, 126.1, 71.5, 66.2, 27.5, 27.3, 27.2, 25.0, 22.8, 21.4, 17.3 ppm.

(S_S,*R*)-Isomer: Minor isomer, white solid, 11 mg; m.p. 142–144 °C. $[\alpha]_D^{25}$ = +72.2 (*c* = 0.36, CH_2Cl_2). IR (deposit from CH_2Cl_2 solution on a NaCl plate): $\tilde{\nu}$ = 3356, 2958, 2925, 1092 cm^{-1}. ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 7.95–7.93 (m, 2 H), 7.69–7.66 (m, 2 H), 7.41–7.37 (m, 2 H), 7.31–7.28 (m, 3 H), 4.67 (d, *J* = 7.5 Hz, 1 H), 3.57 (dd, *J* = 1.5, 7.5 Hz, 1 H), 2.75–2.61 (m, 3 H), 2.58–2.52 (m, 1 H), 2.43 (s, 3 H), 2.00–1.94 (m, 1 H), 1.87–1.81 (m, 2 H), 0.88 (d, *J* = 7.5 Hz, 3 H), 0.68 (d, *J* = 7.5 Hz, 3 H) ppm. ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 142.5, 141.1, 139.3, 129.9, 129.5, 128.8, 127.4, 125.8, 68.9, 65.0, 28.7, 27.5, 27.4, 24.4, 23.4, 21.4, 17.9 ppm.

(S_S,*S*)-*N*-[3,4-Dimethylphenyl(2-phenyl-1,3-dithian-2-yl)methyl]-*p*-toluenesulfinamide (9): Yield: 86%. Major isomer, white solid, 41 mg; m.p. 103–105 °C. $[\alpha]_D^{25}$ = +95.7 (*c* = 0.23, CH_2Cl_2). IR (deposit from CH_2Cl_2 solution on a NaCl plate): $\tilde{\nu}$ = 3320, 3053, 2919, 1094 cm^{-1}. ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 7.71–7.67 (m, 2 H), 7.56–7.53 (m, 2 H), 7.28–7.25 (m, 3 H), 7.12–7.09 (m, 2 H), 6.78 (d, *J* = 7.9 Hz, 1 H), 6.36 (dd, *J* = 1.8, 7.9 Hz, 1 H), 6.26–6.22 (m, 1 H), 4.88–4.80 (m, 2 H), 2.71–2.52 (m, 4 H), 2.32 (s, 3 H), 2.12 (s, 3 H), 2.00 (s, 3 H), 1.97–1.86 (m, 2 H) ppm. ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 141.6, 140.9, 137.1, 135.8, 134.9, 134.3, 130.9, 130.3, 128.9, 128.3, 128.1, 127.5, 126.3, 125.7, 66.4, 65.1, 27.4, 27.3, 24.7, 21.2, 19.5, 19.4 ppm.

(S_S,*R*)-Isomer: Minor isomer, white solid, 15 mg; m.p. 164–166 °C. $[\alpha]_D^{25}$ = +38.1 (*c* = 0.16, CH_2Cl_2). IR (deposit from CH_2Cl_2 solution on a NaCl plate): $\tilde{\nu}$ = 3260, 3054, 2921, 1093 cm^{-1}. ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 7.64–7.57 (m, 4 H), 7.33–7.25 (m, 6 H), 6.95 (d, *J* = 7.8 Hz, 1 H), 6.77–6.74 (m, 1 H), 5.17 (d, *J* = 2.7 Hz, 1 H), 4.77 (d, *J* = 2.7 Hz, 1 H), 2.78–2.55 (m, 4 H), 2.43 (s, 3 H), 2.20 (s, 3 H), 2.10 (s, 3 H), 1.94–1.80 (m, 2 H) ppm. ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 142.5, 141.2, 137.8, 136.6, 135.2, 132.6, 131.4, 130.4, 129.6, 128.5, 128.1, 127.6, 127.2, 125.6, 66.6, 64.6, 27.6, 27.1, 24.5, 21.4, 19.7, 19.6 ppm.

Acknowledgments

We gratefully acknowledge financial support from NIH (CA, 99995-1) and the Robert A. Welch Foundation (grant no. D-1361). The contents of this article are solely the responsibility of the authors and do not necessarily represent the official views of the National Cancer Institute.

[1] D. Seebach, *Angew. Chem. Int. Ed.* **1979**, *18*, 239; b) D. Enders, J. P. Shilvock, *Chem. Soc. Rev.* **2000**, *29*, 359; c) T. Schrader, *Chem. Eur. J.* **1997**, *3*, 1273.

[2] a) D. Seebach, N. R. Jones, E. J. Corey, *J. Org. Chem.* **1968**, *33*, 300; b) B. T. Grobel, D. Seebach, *Synthesis* **1977**, 357.

[3] a) E. L. Eliel, S. Morris-Natschke, *J. Am. Chem. Soc.* **1984**, *106*, 2943; b) J. E. Lynch, E. L. Eliel, *J. Am. Chem. Soc.* **1984**, *106*, 2937.

[4] a) For a leading review, see: A. B. Smith, C. M. Adams, *Acc. Chem. Res.* **2004**, *37*, 365; b) V. K. Aggarwal, A. Thomas, S. T. Schade, *Tetrahedron* **1997**, *53*, 16 213; c) K. Afarinkia, A. Faller, A. J. Twist, *Synthesis* **2003**, 357.

[5] For recent applications of 1,3-dithianes in organic synthesis see: a) A. B. Smith, S. M. Pitram, A. M. Boldi, M. J. Gaunt, C. Sfouggatakis, W. H. Moser, *J. Am. Chem. Soc.* **2003**, *125*, 14 435; b) M. J. Gaunt, H. F. Sneddon, P. R. Hewitt, P. Orsini, D. F. Hook, S. V. Ley, *Org. Biomol. Chem.* **2003**, *1*, 15; c) E. Tyrell, G. A. Skinner, J. Janes, G. Milsom, *Synlett* **2002**, *7*, 1073.

[6] a) F. A. Davis, P. Zhou, B.-C. Chen, *Chem. Soc. Rev.* **1998**, *27*, 13; b) F. A. Davis, Y. Zhang, Y. Andemichael, T. Fang, D. L. Fanelli, H. Zhang, *J. Org. Chem.* **1999**, *64*, 1403; c) Y. W. Hong, M. H. Xu, G. Q. Lin, *Org. Lett.* **2004**, *6*, 3953.

[7] a) J. A. Ellman, T. D. Owens, T. P. Tang, *Acc. Chem. Res.* **2002**, *35*, 984; b) T. Kochi, T. Mukade, J. A. Ellman, *J. Synth. Org. Chem.* **2004**, *62*, 128.

[8] a) G. Li, H.-X. Wei, B. R. Whittlesey, N. N. Batrice, *J. Org. Chem.* **1999**, *64*, 1061; b) H.-X. Wei, J. D. Hook, K. A. Fitzgerald, G. Li, *Tetrahedron: Asymmetry* **1999**, *10*, 661.

[9] a) D. Basavaiah, A. J. Rao, T. Satyanarayana, *Chem. Rev.* **2003**, *103*, 2811; b) E. Ciganek, *Org. React.* **1997**, *51*, 201; c) For a review regarding β-branched Baylis–Hillman adduct synthesis see: G. Li, J. Hook, H.-X. Wei, in *Recent Research Developments in Organic and Bioorganic Chemistry*, Transworld Research Network, **2001**, vol. 4, p. 49.

[10] For the previous synthesis of α-amino-ketones and their chiral counterparts see: a) M. T. Reetz, *Angew. Chem. Int. Ed. Engl.* **1991**, *30*, 1513; b) F. J. Sardina, H. Rapoport, *Chem. Rev.* **1996**, *96*, 1825; c) J. Jurczak, A. Golebiowski, *Chem. Rev.* **1989**, *89*, 149.

[11] a) A. G. Myers, T. Yoon, *Tetrahedron Lett.* **1995**, *36*, 9429; b) M. R. Paleo, M. I. Calaza, F. J. Sardina, *J. Org. Chem.* **1997**, *62*, 6862; c) A. Padwa, M. Dharan, J. Smolanoff, S. I. Wetmore, *J. Am. Chem. Soc.* **1973**, *95*, 1954.

[12] During the preparation of this manuscript a paper appeared in which the more-reactive 2-lithio-2-alkyl-1,3-dithiane was used as the nucleophile at –78 °C without the use of a Lewis acid promoter (three examples): F. A. Davis, T. Ramachandar, H. Liu, *Org. Lett.* **2004**, *6*, 3393.

[13] a) G. Li, H.-T. Chang, K. B. Sharpless, *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 451; b) G. Li, K. B. Sharpless, *Acta Chem. Scand.* **1996**, *50*, 649; c) G. Li, H. H. Angert, K. B. Sharpless, *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 2813.

[14] a) P. H. J. Carlsen, T. Katsuki, S. V. Martin, K. B. Sharpless, *J. Org. Chem.* **1981**, *46*, 3936; b) S. V. Martin, M. T. Nunez, *J. Org. Chem.* **1990**, *55*, 1928.

[15] a) D. A. Evans, J. Bartrolli, T. L. Shih, *J. Am. Chem. Soc.* **1981**, *103*, 2127; b) M. A. Walker, C. H. Heathcock, *J. Org. Chem.* **1991**, *56*, 5747.

Received: October 28, 2004

