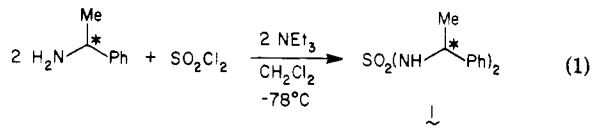
Communications

threo-*N*,*N*'-Bis(α-methylbenzyl)sulfamide: A Readily Available Chiral Ligand for Asymmetric Lithium Aluminum Hydride Reductions[1]

Summary: Prochiral ketones were asymmetrically reduced at −20 °C with a reagent prepared by the reaction of lithium aluminum hydride with the title compound and *N*-benzylmethylamine.

Sir: The advantages of chiral bidentate ligands with C_2 symmetry for metal-mediated chiral recognition, as first delineated by Kagan in 1972 for asymmetric hydrogenation,[2-4] have since been demonstrated in other asymmetric processes.[5-7] Chiral ligands with C_2 symmetry have generally been prepared by derivation of tartaric acid or by resolution. An alternative process is to couple two chiral molecules of C_1 symmetry in such a way as to produce a molecule of C_2 symmetry.[8-10] We report here the facile preparation of *threo*-*N*,*N*'-bis(α-methylbenzyl)sulfamide (1) from α-methylbenzylamine and its application with lithium aluminum hydride in the asymmetric reduction of a variety of prochiral ketones.[11]

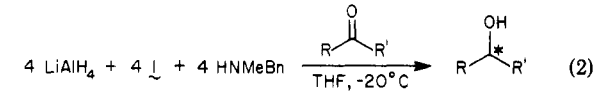
Condensation of either (*R*)- or (*S*)-α-methylbenzylamine with sulfuryl chloride cleanly produced *R*,*R* and *S*,*S* sulfamide 1 in 89% yield (eq 1). A 0.5-mol scale was easily



(1)

accommodated (vide infra). Dichloromethane proved a superior solvent to petroleum ether, which had been used in previous *N*,*N*'-dialkylsulfamide preparations.[12]

Partial decomposition of lithium aluminum hydride with 1 equiv of sulfamide 1 and 1 equiv of *N*-benzylmethylamine in tetrahydrofuran produced a reagent effective in the asymmetric reduction of prochiral ketones (eq 2).



(2)

Conditions were optimized by using *n*-butyl 2-naphthyl ketone (2) as a substrate due to ready measurement of the resulting enantiomeric excess by chiral stationary-phase HPLC.[13] *N*-Benzylmethylamine as an additive was found superior to ethanol[14] and a variety of secondary amines[15] with respect to the enantioselectivity and reactivity of the resulting reagent. Ethanol gave a moderately selective reagent for the reduction of acetophenone (75% ee) but worked poorly with 2 (23% ee). Other secondary amines gave between 36% ee (diisopropylamine) and 87% ee (pyrrolidine) with 2. The use of amines may result in the formation of alane type species via the alane extraction mechanism of Ashby.[16]

Table I

substrate	reaction time,[a] h	isolated yield, %	% ee (confign)
n-butyl 2-naphthyl ketone (2)	1	80	87[b] (*R*[c])
acetophenone	1	50	81[d] (*R*[d])
9-anthryl trifluoromethyl ketone	18	97	55[b] (*S*[b])
2-octanone	1	57	29[e] (*R*[f])
cyclohexyl methyl ketone	1	71	71[g] (*R*[f])
1-adamantyl methyl ketone	18	85	48[g] (*R*[h])
n-butyl cyclohexyl ketone	18	97	9[i] (*R*[f])
n-butyl t-butyl ketone	21	99	1[j] (*R*[f])

[a] Reactions performed by using (*S*,*S*)-1 at −20 °C under conditions described in the general experimental procedure. [b] Reference 13. [c] Absolute configuration assigned according to Pirkle's chiral recognition model.[13] [d] Kasai, M.; Froussios, C.; Ziffer, H. *J. Org. Chem.* **1983**, *48*, 459. [e] Hill, R. K. *J. Am. Chem. Soc.* **1958**, *80*, 1611. [f] Jacques, J.; Gros, C.; Bourcier, S.; Brienne, M. J.; Toullec, J. In "Stereochemistry"; Kagan, H. B., Ed.; Georg Thieme Publishers: Stuttgart, 1977; Vol. IV, Chapter 3. [g] Dale, J. A.; Mosher, H. S. *J. Am. Chem. Soc.* **1973**, *95*, 512. [h] Absolute configuration assigned according to Mosher's model.[g] [i] Burrows, E. P.; Welch, F. J.; Mosher, H. S. *J. Am. Chem. Soc.* **1960**, *82*, 880. [j] Foley, W. M.; Welch, F. J.; La Combe, E. M.; Mosher, H. S. *Ibid.* **1959**, *81*, 2779.

Aging the reagent beyond the 1 h at room temperature used in the general procedure (vide infra), either for 16 h at room temperature or for 80 min at reflux, produced only a slightly less selective and less active species. The reduction showed a dependence on the form of $LiAlH_4$ used to prepare the reagent. Homogeneous solutions of $LiAlH_4$ gave a less selective reagent for 2 (54% ee) as did impure solid sources (76% ee).

Initially, very low reaction temperatures were studied. Ketone 2 was reduced with 89% ee upon reaction at −100 °C to −55 °C over 48 h. Interestingly, aliquots showed that the enantiomeric excess increased as the reaction proceeded. Reaction at −20 °C gave 87% ee with a 1-h reaction time. Due to the operational simplicity of the latter conditions with only a slight loss in selectivity, −20 °C was chosen for subsequent reactions with other substrates (Table I).

Examination of Table I reveals that although aryl alkyl ketones were reduced with greater selectivity, fully saturated dialkyl ketones could also be asymmetrically reduced. Systems with this capability have only been found recently,[17-19] and the reduction of cyclohexyl methyl ketone

(1) Presented at the 187th National Meeting of the American Chemical Society, St. Louis, MO, April 12, 1984. A preliminary account of this work was presented at the 28th National Organic Chemistry Symposium, Bozeman, MT, June 23, 1983.

(2) Although the importance of "bifunctional" chiral ligands was noted as early as 1953,[3] the importance of symmetry was not specifically cited until 1972.[4]

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(14) Noyori, R.; Tomino, I.; Tanimoto, Y. *J. Am. Chem. Soc.* **1979**, *101*, 3129.

(15) Achiral amine additives have also been used with *N*-methylephedrine: Terashima, S.; Tanno, N.; Koga, K. *Tetrahedron Lett.* **1980**, *21*, 2753.

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with 71% ee compares favorably with known methods for the reduction of secondary alkyl methyl ketones, especially considering that sulfamide 1 is very readily available in both enantiomeric forms[20] and that extremely low temperatures or high pressures are not required.

All of the substrates in Table I were reduced according to the following general procedure. A solution of 1.218 g (4.00 mmol) (*S,S*)-1 in 11 mL of THF (distilled from sodium benzophenone ketyl) was added dropwise over 12 min to 151.8 mg (4.00 mmol) of $LiAlH_4$ powder (transferred from a fresh bottle under nitrogen) stirred in 25 mL of THF at ca. 0 °C under nitrogen in a dry 100-mL flask. Stirring was continued for 15 min at room temperature before addition of a solution of 516 μL (485 mg, 4.00 mmol) of *N*-benzylmethylamine (distilled from CaH_2) in 11 mL of THF over 2 min. The resulting cloudy solution was stirred at room temperature for 1 h and cooled to ca. −20 °C (dry ice/CCl_4 bath). A solution of 1.00 mmol of ketone in 7 mL of THF was then cooled to ca. −20 °C and added dropwise via cannula over 2 min to the stirred reagent. After the indicated reaction time at −20 °C (for overnight reactions, the flask was transferred to a freezer), the reaction mixture was added via cannula over 10 min to a stirred ice-cold mixture of 12 mL of ether and 12 mL of 3.6 M H_2SO_4. The resulting cloudy grey aqueous phase was separated and extracted with ether (3 × 15 mL). The clear organic phase was combined with the ether extracts and washed with brine (2 × 15 mL), dried ($MgSO_4$), and concentrated to a clear oil. Trituration in ca. 40 mL of hexane (or pentane for more volatile substrates) precipitated (*S,S*)-1 (85–95% recovery, homogeneous by TLC).[21] Concentration of the filtrate and flash chromatography yielded the pure alcohols which were examined for enantiomeric excess.

Preparation of (*S,S*)-1. An oven-dried, nitrogen-purged, 2-L three-necked flask equipped with a mechanical stirrer and 250-mL addition funnel was cooled to ca. −78 °C (dry ice/acetone bath) and charged with 360 mL of dichloromethane (dried over 4A molecular sieves), 139 mL (101 g, 1.00 mol) of triethylamine (distilled from CaH_2), and 129 mL (121 g, 1.00 mol) of (*S*)-(−)-α-methylbenzylamine (Hexcel, distilled from CaH_2, $[\alpha]^{20}_D$ −40.5° (neat)). Subsequently, 40.2 mL (67.5 g, 0.50 mol) of sulfuryl chloride (freshly distilled) in 155 mL of dichloromethane were added dropwise with rapid stirring over a 2-h period, causing white solids to precipitate. The reaction mixture was stirred at −78 °C for 15 min and then allowed to warm to ca. 5 °C. Addition of 250 mL of water produced two clear phases: the aqueous phase was washed with dichloromethane (100 mL) and the combined organic phases were washed with water (3 × 250 mL), dried (Na_2SO_4), and filtered through a 1.5-cm pad of Florisil. Concentration in vacuo afforded 148.3 g of white solid. Two recrystallizations from ether–dichloromethane (3:1)/hexane (equal volume) yielded 135.8 g (89%) of white crystalline solid: mp 98–99 °C; $[\alpha]^{20}_D$ −80.1° (*c* 2.18, EtOH); IR (Nujol) 3315, 1320, 1150, 975, 700 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.22 (m, 10), 4.41 (m, 4), 1.47 (d, 6, J = 7 Hz); ^{13}C NMR ($CDCl_3$) δ 142.65, 128.60, 127.51, 126.07, 50.75, 20.64. Anal. Calcd for $C_{16}H_{20}N_2O_2S$: C, 63.13; H, 6.62; N, 9.20; S, 10.53. Found: C, 63.30; H, 6.79; N, 9.18; S, 10.80. The enantiomeric sulfamide, (*R,R*)-1, was prepared similarly from (*R*)-(+)-α-methylbenzylamine.

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(20) (*R,R*)-1 and (*S,S*)-1 are now available from Aldrich.
(21) For 2,2,2-trifluoro-1-(9-anthryl)ethanol, which is insoluble in hexane, the sulfamide was recovered by flash chromatography.

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Registry No. (*R,R*)-1, 91410-68-3; (*S,S*)-1, 27304-75-2; 2, 33489-63-3; (*R*)-$CH_3(CH_2)_5CH(OH)CH_3$, 5978-70-1; $LiAlH_4$, 16853-85-3; (*R*)-$PhCH(NH_2)CH_3$, 3886-69-9; (*S*)-$PhCH(NH_2)CH_3$, 2627-86-3; $PhC(O)CH_3$, 98-86-2; $CH_3(CH_2)_5C(O)CH_3$, 111-13-7; *n*-BuC(O)-*t*-Bu, 19078-97-8; (*R*)-α-butyl-1-naphthalenemethanol, 91464-57-2; (*R*)-α-methylbenzenemethanol, 1517-69-7; (*S*)-α-(trifluoromethyl)-9-anthracenemethanol, 60646-30-2; (*R*)-α-methylcyclohexanemethanol, 3113-99-3; (*R*)-α-methyl-1-adamantanemethanol, 91410-69-4; (*R*)-α-butylcyclohexanemethanol, 63126-49-8; (*R*)-2,2-dimethyl-3-heptanol, 51716-29-1; 9-anthryl trifluoromethyl ketone, 53531-31-0; cyclohexyl methyl ketone, 823-76-7; 1-adamantyl methyl ketone, 1660-04-4; *n*-butyl cyclohexyl ketone, 5445-35-2.

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Photochemical Dimerization and Cross Cycloaddition of 2-Naphthalenecarbonitrile

Summary: A new photodimer from 2-naphthalenecarbonitrile (2-NN) and a cross cycloadduct between 2-NN and naphthalene are described, showing that addition involving unsubstituted naphthalene rings is possible. Intermediacy of singlet exciplexes is suggested.

Sir: While the photodimerization of anthracene is one of the oldest known photochemical reactions[1] and has been extensively investigated,[2] the photodimerization of naphthalene derivatives is limited in scope. Naphthalene itself does not photodimerize and, with the exception of a 1,8-disubstituted derivative[3] and some intramolecular examples,[4] the reported dimerizations are restricted to some 2-alkoxynaphthalenes,[5] esters, and other functional derivatives of 2-naphthalenecarboxylic acid.[3,6] (in the latter case, cage dimers are invariably obtained probably through a second photochemical step). Sasse recognized that the dimerization is regioselective, in that bonding occurs only between substituted rings in head-to-tail orientation.[5,6]

2-Naphthalenecarbonitrile (2-NN) was reported to form a photodimer. On the basis of the NMR spectrum, Zweig assigned the structures 1 or 2 to this product.[7] Sasse later observed that the reported spectroscopic data were similar to those of the cage dimers he had obtained from the naphthalene carboxy esters and suggested that the 2-NN photodimer has indeed structure 3. As the photochemistry of aromatic nitriles is of current interest both

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