In fact, we found that under the typical Mukaiyama reaction conditions, $TiCl_4$ in dichloromethane solution at −78 °C (procedure C),[8] the condensation of 1 with 6 occurred, leading again to the furan derivatives 7 in appreciable yields (Table II). The conversion presumably involved the fast formation of intermediate adduct C by chemoselective attack on the acetal function and then slower cyclization to furan 7.

Besides the satisfactory degree of applicability of the above approach, it has to be noted that the formation of the same furan **7d** through both procedure B and C (entries d and g, Table II) disclosed a previously unknown synthetic equivalence between 2-methyl-2,5-dihydro-2,5-dimethoxyfuran (**5**) (R = Me) and 4,5,5-trimethoxypentan-2-one.

Experimental Section

Ethyl 2-(Methoxyphenylmethyl)-3-oxobutanoate (3d): Procedure A. To a stirred solution of ethyl 3-oxobutanoate (5.0 mmol) and benzaldehyde dimethyl acetal (8.0 mmol) in dry dichloromethane (40 mL) was added dropwise a solution of trimethylsilyl trifluoromethanesulfonate (8.0 mmol) in dry dichloromethane (10 mL) under a nitrogen atmosphere at −78 °C (−25 °C for entries g and h, Table I) over a period of 5 min. The reaction was monitored by TLC and continued until the disappearance of the 1,3-dicarbonyl compound. Then, diethyl ether (200 mL) was added, and the solution was washed with cold water (3 × 15 mL) and dried over anhydrous sodium sulfate. After the removal of the solvent in vacuo, the resulting crude product was purified by column chromatography on silica gel. Elution with 9/1 *n*-pentane/diethyl ether afforded **3d** (97% yield) as an unseparable mixture of 1/1 erythro and threo stereoisomers. ^1H NMR (CCl_4): δ 7.30 (s, 5 H), 4.80 and 4.77 (2 d, 1 H, J = 10 Hz), 3.7–4.2 (m, 3 H), 3.20, 3.14, and 3.10 (3 s, 3 H), 2.35 and 1.90 (2 s, 3 H), 1.30, 1.28, and 1.00 (3 t, 3 H, J = 7 Hz). IR (1% CCl_4, ν_{max}, cm^{-1}): 3097, 3076, 3040, 1760, 1725, 1622, 1458, 1110, 702. MS, m/z 250 (M^+). Anal. Calcd for $C_{14}H_{18}O_4$: C, 67.18; H, 7.25. Found: C, 67.09; H, 7.30.

Ethyl 2-(5-Methyl-2-furyl)-3-oxobutanoate (7d): Procedure B. To a stirred solution of ethyl 3-oxobutanoate (6.0 mmol) and 2-methyl-2,5-dihydro-2,5-dimethoxyfuran[9] (**5**, R = Me) (6.0 mmol) in a 1/1 (v/v) mixture of dry CH_2Cl_2/Et_2O (50 mL) was added $ZnCl_2$ (6.0 mmol) under a nitrogen atmosphere at room temperature over a period of 30 min. After 48 h, diethyl ether (200 mL) was added, and the resulting solution was submitted to the same workup as in procedure A. Pure **7d** (65% yield) was isolated as rather dense oil (n^{19} 1.4905) through silica gel chromatography by elution with 9/1 *n*-pentane/Et_2O. ^1H NMR (CCl_4): δ 13.23 (s, 1 H), 5.91 (d, 1 H, J = 3 Hz), 5.71 (d, 1 H, J = 3 Hz), 4.15 (q, 2 H, J = 7 Hz), 2.25 (s, 3 H), 1.94 (s, 3 H), 1.23 (t, 3 H, J = 7 Hz). IR (1% CCl_4, ν_{max}, cm^{-1}): 1730, 1710 (br), 1650, 1600, 1270, 1230. MS: m/z 210 (M^+). Anal. Calcd for $C_{11}H_{14}O_4$: C, 62.85; H, 6.71. Found: C, 62.98; H, 6.77.

Ethyl 2-(5-Methyl-2-furyl)-3-oxobutanoate (7d): Procedure C. To a stirred solution of ethyl 3-oxobutanoate (6.0 mmol) and 4,5,5-trimethoxypentan-2-one (**6**) (6.6 mmol), prepared according the procedure reported in ref 10, in dry dichloromethane (40 mL) was added dropwise a solution of titanium tetrachloride (6.6 mmol) in dry dichloromethane (10 mL) under a nitrogen atmosphere at −78 °C over a period of 5 min. After the disappearance of 1,3-dicarbonyl compound (2 h), the mixture was stirred at room temperature for 24 h to complete the furanization process. Then, diethyl ether (200 mL) was added, and the resulting solution was submitted to the same workup as in procedure A, and chromatographic purification afforded pure **7d** (60% yield).

Supplementary Material Available: Analytical and spectral data for adducts 3 and furans 7 (2 pages). Ordering information is given on any current masthead page.

(8) In this case both procedure A and B proved to be uneffective leading essentially to the recovery of the starting materials.
(9) Levisalles J. *Bull. Soc. Chim. Fr.* **1957**, 997.
(10) Scettri, A. *Tetrahedron* **1985**, *41*, 5141.

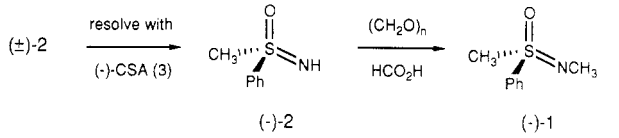
Preparation of (+)- and (−)-*N*,*S*-Dimethyl-*S*-phenylsulfoximine via an Improved Resolution. Accurate Determination of Very High Enantiomeric Purities by On-Column GC Analysis of Diastereomeric Derivatives

Christopher S. Shiner* and Andrew H. Berks

Department of Chemistry and Biochemistry, University of Colorado, Boulder, Colorado 80309-0215

Received June 14, 1988

(+)- and (−)-*N*,*S*-Dimethyl-*S*-phenylsulfoximine (**1**) have been employed in asymmetric syntheses, resolutions, and mechanistic studies.[1,2] The nonracemic sulfoximines are readily available via resolution of *S*-methyl-*S*-phenylsulfoximine (**2**) with (+)- or (−)-10-camphorsulfonic acid (**3**), followed by N-methylation.[3-5] However, the reported



procedure apparently has often furnished material of only 90–99% ee.[6] We recently employed the sulfoximine method for resolution of camphenilone (**4**),[7,8] and after considerable experimentation the published resolution afforded **1** of 98–99% ee. Herein we report that recrystallization of the camphorsulfonate salts **5** and *ent*-**5** furnished both antipodes of **2** and ultimately of **1** in greater than 99.9% enantiomeric purity. On-column capillary GC analysis of the camphanyl derivative of **2** comprised an accurate and convenient method for ee determination. An improved procedure facilitated the N-methylation of **2**, and the use of silver nitrate impregnated silica gel for chromatography further enhanced the camphenilone resolution.

The enantiomeric purities of sulfoximines **1** and **2** have previously been evaluated via polarimetry, an inherently imprecise and unreliable technique.[9] Racemic **2** and **1** have also been resolved by analytical HPLC on a chiral stationary phase.[10] We determined the ee of **2** or the de of derived camphorsulfonate salts (e.g., **5**) via N-acylation with commercially available (−)-camphanic acid chloride

(1) Reviews: (a) Johnson, C. R. *Aldrichimica Acta* **1985**, *18*, 3–10. (b) Johnson, C. R.; Barbachyn, M. R.; Meanwell, N. A.; Stark, C. J., Jr.; Zeller, J. R. *Phosphorus and Sulfur* **1985**, *24*, 151–163.
(2) Sulfoximine-mediated resolution of ketones: (a) Johnson, C. R.; Zeller, J. R. *Tetrahedron* **1984**, *40*, 1225–1233. (b) Johnson, C. R.; Zeller, J. R. *J. Am. Chem. Soc.* **1982**, *104*, 4021–4023.
(3) Johnson, C. R.; Schroeck, C. W. *J. Am. Chem. Soc.* **1973**, *95*, 7418–7423 and references cited therein.
(4) The chemistry of sulfoximine-mediated ketone resolution can be employed in conjunction with homochiral ketones for resolution of 1 (ref 1b).
(5) Sulfoximines have also been resolved via chromatography on chiral stationary phases: Allenmark, S.; Nielsen, L.; Pirkle, W. H. *Acta Chem. Scand., Ser. B* **1983**, *B37*, 325–328. See also ref 10.
(6) See, for example: (a) Reference 2. (b) Zimmerman, H. E.; Solomon, R. D. *J. Am. Chem. Soc.* **1986**, *108*, 6276–6289.
(7) Shiner, C. S.; Berks, A. H.; Fisher, A. M. *J. Am. Chem. Soc.* **1988**, *110*, 957–958.
(8) Resolution of camphenilone via the sulfoximine method has been described previously (ref 2b).
(9) For discussion see, for example: Rosen, T.; Watanabe, M.; Heathcock, C. H. *J. Org. Chem.* **1984**, *49*, 3657–3659. Review of polarimetry: Lyle, G. G.; Lyle, R. E. In *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic: New York, 1983; Vol. 1, Chapter 2.
(10) Wainer, I. W.; Alembik, M. C.; Johnson, C. R. *J. Chromatogr.* **1986**, *361*, 374–378. The accuracy of this method for determination of high enantiomeric purities was not investigated. Although this approach obviates the derivatization of **2**, the sulfoximine must be isolated from the camphorsulfonate salt prior to the analysis, and a special HPLC column is required.

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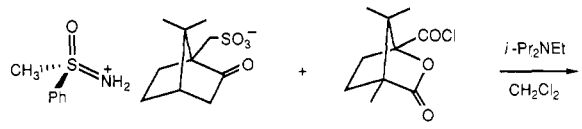
(6) and diisopropylethylamine, followed by capillary GC analysis of the resulting diastereomers (e.g., 7).[11] Routine



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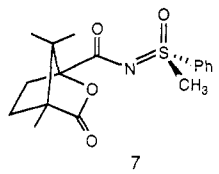

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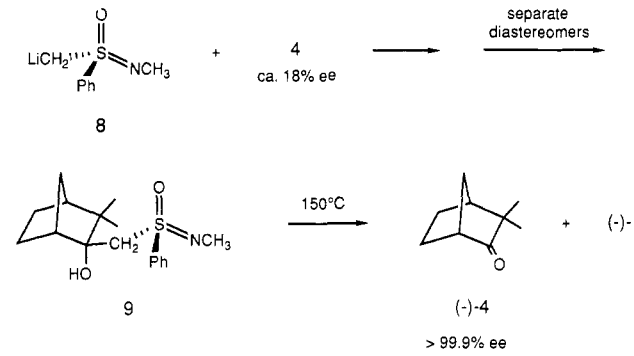
analyses were expedited by the direct derivatization of the salts, without prior isolation of the free base. Quantitation of the resolved, derivatized sulfoximines by GC required optimization of the chromatographic conditions and integration parameters, as described in the Experimental Section. In conventional split-mode vaporizing injection,[12] discrimination against the major component resulted in peak area ratios that were somewhat too low. However, on-column injection[13] did permit the accurate determination of diastereomer ratios exceeding 2000:1, the value corresponding to 99.9% ee or de. Although extensively documented in the analytical chemistry literature, on-column capillary GC apparently has not been widely employed for the quantitation of diastereomer mixtures in synthesis.

This convenient analytical scheme enormously facilitated our investigation of the resolution of **2**. Following the published procedure,[3] treatment of (±)-**2**[14] with (−)-10-camphorsulfonic acid (**3**) in hot acetone afforded salt **5** of 98–99% de. Optimal results were obtained by using spectrophotometric or HPLC grade acetone[15] and freshly recrystallized **3**. As reported earlier,[3] isolation of **2** at this stage and repetition of the resolution procedure did not enhance the diastereomeric purity of the salt.

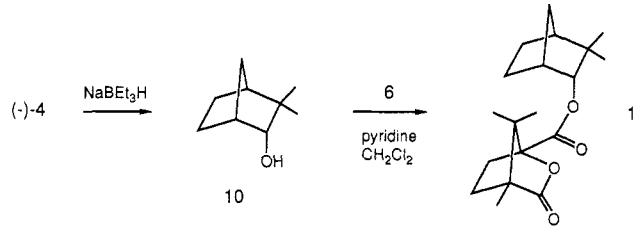
Two recrystallizations of salt **5** from dry acetonitrile then furnished material of greater than 99.9% de, as indicated by derivatization and GC analysis, in 60–65% overall yield. A third recrystallization effected further enhancement of the de, although minute peaks with the retention time of the minor diastereomer could still be detected. The resolution of (±)-**2** with (+)-**3** proceeded analogously in all respects. Acetonitrile proved to the ineffective as solvent for the formation and initial purification of the salt.

After the liberation of (−)-**2** from **5** via the published procedure,[3] the sulfoximine was subjected to Eschweiler–Clarke N-methylation. Complete conversion to (−)-**1** occurred smoothly upon treatment of (−)-**2** with paraformaldehyde in 98% formic acid,[16] in contrast with the more sluggish reaction employing 37% aqueous formaldehyde as described previously.[17]

We employed sulfoximine (−)-**1**[18] for the resolution of camphenilone (**4**),[19] optimizing this process with respect to the enantiomeric purity of the product. Generation[2] of the *C*-lithio sulfoximine derivative **8** and exo addition to **4**[20] of ca. 18% ee afforded two diastereomeric alcohols which were cleanly separated by flash chromatography on silver nitrate impregnated silica gel. Thermolysis[2] of the major diastereomer **9** then furnished (−)-**4**[21] in 73% yield after careful purification. The enantiomeric composition



of the ketone was established[19] by reduction with sodium triethylborohydride, followed by derivatization of the known[22] endo alcohol **10** with camphanic acid chloride (**6**).



Capillary GC analysis with on-column injection[13] indicated that the diastereomeric purity of the ester **11**[11] was greater than 99.9% de. This result also affirms that N-methylation of **2** and C-lithiation of **1** proceed without detectable racemization.

Experimental Section

Materials. (−)-Camphanic acid chloride (**6**) was purchased from Aldrich or Fluka and used without purification. Camphene was purchased from Fluka. Diisopropylethylamine and pyridine were distilled from calcium hydride under argon and stored over activated 3A molecular sieves. Acetonitrile, ethyl acetate, methanol, and methylene chloride were HPLC or spectrophotometric grade. Acetonitrile was stored over activated 3A molecular sieves.

(11) Camphanate esters have been employed previously in capillary GC determinations of alcohol enantiomeric purities: Oppolzer, W.; Chapuis, C.; Dupuis, D.; Guo, M. *Helv. Chim. Acta* **1985**, *68*, 2100–2114.

(12) Limitations of vaporizing injectors in capillary GC have been discussed; see, for example: Grob, K., Jr.; Neukom, H. P. *HRC CC, J. High Resolut. Chromatogr. Chromatogr. Commun.* **1979**, *2*, 15–21.

(13) On-column injection generally affords increased accuracy and precision in quantitative analyses: Grob, K. *On-Column Injection in Capillary Gas Chromatography: Basic Technique, Retention Gaps, Solvent Effects*; Dr. Alfred Hüthig Verlag: Heidelberg, 1987. See also: Grob, K. *HRC CC, J. High Resolut. Chromatogr. Chromatogr. Commun.* **1978**, *1*, 263–267. Jenkins, R.; Jennings, W. *Ibid.* **1983**, *6*, 228–231. Grob, K., Jr.; Neukom, H. P. *J. Chromatogr.* **1980**, *189*, 109–117.

(14) Johnson, C. R.; Haake, M.; Schroeck, C. W. *J. Am. Chem. Soc.* **1970**, *92*, 6594–6598. Preparation of (±)-methyl phenyl sulfoxide, the precursor of (±)-**2**: Johnson, C. R.; Keiser, J. E. *Organic Syntheses*; Wiley: New York, 1973; Collect. Vol. 5, pp 791–793.

(15) Acetone is notoriously difficult to purify and dry: Burfield, D. R.; Smithers, R. H. *J. Org. Chem.* **1978**, *43*, 3966–3968.

(16) These conditions have been employed for N-methylation of other sulfoximines: Schmidbaur, H.; Kammel, G. *Chem. Ber.* **1971**, *104*, 3234–3240.

(17) Johnson, C. R.; Schroeck, C. W.; Shanklin, J. R. *J. Am. Chem. Soc.* **1973**, *95*, 7424–7431.

(18) Absolute configuration of **1**: Jonsson, E. U.; Johnson, C. R. *J. Am. Chem. Soc.* **1971**, *93*, 5308–5309.

(19) Experimental procedures are provided as supplementary material.

(20) Prepared by ozonolysis of camphene: Bailey, P. S. *Chem. Ber.* **1955**, *88*, 795–801. We employed dimethyl sulfide for reduction: Pappas, J. J.; Keaveney, W. P.; Gancher, E.; Berger, M. *Tetrahedron Lett.* **1966**, 4273–4278.

(21) Absolute configurations of camphene and camphenilone: Buchbauer, G.; Koch, H. *Chem. Ber.* **1978**, *111*, 2533–2535. Midgley, J. M.; Whalley, W. B.; Buchbauer, G.; Hana, G. W.; Koch, H.; Roberts, P. J.; Ferguson, G. *J. Chem. Soc., Perkin Trans. 1* **1978**, 1312–1315.

(22) Prepared previously by $LiAlH_4$ reduction of camphenilone: Yates, P.; Hambly, G. F. *Can. J. Chem.* **1979**, *57*, 1656–1667 and references cited therein. We found that $NaBEt_3H$ furnished crude alcohol of higher purity, as indicated by capillary GC analysis.

Resolution of *S*-Methyl-*S*-phenylsulfoximine (2). A hot solution of (−)-**3** (15.7 g, 68 mmol, recrystallized[19] from ethyl acetate) in 100 mL of acetone (HPLC or spectrophotometric grade, from a new bottle, 1.5 mL/mmol) was carefully added with swirling to a hot solution of (±)-**2**[14] (10.0 g, 64.5 mmol) in 195 mL of acetone (3.0 mL/mmol) in a 500-mL Erlenmeyer flask. Because a vigorous reaction occurs on mixing, the clear, boiling solutions were removed from the hot plate immediately prior to the addition. Solvent was evaporated on a hot plate under a stream of argon until crystals formed, usually after 1–2 min, and the mixture was allowed to cool. After 2 h, the crystals were filtered, washed with acetone, and suction-filtered to dryness, furnishing 10.4 g of **5** as white needles (26.9 mmol, 83% yield), mp 182–183 °C. Derivatization and GC analysis (vide infra) indicated that the isomeric purity of this salt was 98.8% de. For recrystallization, 10.4 g (26.9 mmol) of **5** was dissolved in 250 mL of hot, dry acetonitrile (24 mL/g). After hot filtration, the solution was slowly cooled to room temperature under argon. Further cooling at −20 °C for 12 h enhanced the yield without compromising diastereomeric purity. After filtration, the crystals were washed with acetonitrile and suction-filtered to dryness, furnishing 9.2 g of **5** (23.7 mmol, 73% yield overall), mp 182–183 °C, 99.7% de by derivatization and GC analysis. This material was recrystallized as above from 220 mL of acetonitrile to afford 8.3 g of **5** (21.4 mmol, 66% yield overall): mp 182–183 °C; $[\alpha]^{25}_D$ −43.2° (*c* 3.60, MeOH), −28.8° (*c* 7.57, H_2O). After derivatization, GC analysis indicated that the diastereomer ratio was 3550:1, greater than 99.9% de. A third recrystallization gave salt of higher de, but analysis still revealed traces of material with the retention time of the minor *N*-acyl diastereomer.

The above procedure was also employed for resolution of (±)-**2** with (+)-**3**, which gave analogous results in all respects. The following data were obtained for the enantiomer of **5**: mp 182–183 °C (lit.[23] mp 180–181 °C); $[\alpha]^{25}_D$ +43.5° (*c* 3.13, MeOH), +29.0° (*c* 6.81, H_2O) (lit.[23] $[\alpha]^{20}_D$ +28° (*c* 1, H_2O)).

Via the published procedure,[3] the salt **5** afforded (−)-**2** in 96% yield. For the preparation of **1**, resolved **2** normally was used without purification. A sample of (−)-**2** was subjected to bulb-to-bulb distillation (bath temperature 132–140 °C, 1 mmHg), affording a low-melting white solid: mp 32–34 °C (lit.[3] mp for (+)-**2** 31–33 °C); $[\alpha]^{25}_D$ −17.9° (*c* 2.62, MeOH).[24]

Derivatization of 5 or 2 with Camphanic Acid Chloride. A solution of **5** (6 mg, 0.016 mmol) or **2** (3 mg, 0.019 mmol), (−)-camphanic acid chloride (**6**, 7 mg, 0.032 mmol), and diisopropylethylamine (14 μL, 0.010 g, 0.080 mmol) in methylene chloride (0.4 mL) was stirred for 0.5 h. A 0.1-mL aliquot then was diluted with 1 mL of water and extracted with three 0.3-mL portions of ethyl acetate. The combined extracts were analyzed by capillary GC as described below. Derivatization and analysis of the enantiomeric salt prepared from (±)-**2** and (+)-**3** proceeded analogously. As expected, variation in the scale of the derivatization reaction did not influence the diastereomer ratios.

For characterization of *N*-acylsulfoximine **7**, a sample was prepared by treatment of 0.105 g of **5** with 0.100 g of **6** and 0.18 g of diisopropylethylamine in 4 mL of methylene chloride. After workup, an intensely yellow-colored impurity was separated by chromatography of the oily crude product on 3 g of silica, eluting with methylene chloride/methanol/triethylamine (100:4:1). After concentration, the product was dissolved in methylene chloride, and the solution was filtered. Removal of solvent, addition and evaporation of two portions of hexanes, and final concentration at 0.1 mmHg and 25 °C for 24 h gave 87 mg of analytically pure **7** (95% yield) as a pale yellow solid: ^{1}H NMR (250.1 MHz, $CDCl_3$) δ 0.96 (s, 3 H), 1.01 (s, 3 H), 1.04 (s, 3 H), 1.53–1.66 (m, 1 H), 1.77–2.00 (m, 2 H), 2.32–2.47 (m, 1 H), 3.34 (s, 3 H), 7.51–7.70 (m, 3 H), 7.90–7.98 (m, 2 H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 9.6, 16.8, 16.9, 29.2, 30.8, 44.5, 54.0, 55.1, 93.6, 127.0, 129.7, 133.9, 138.5, 175.5, 178.8; IR ($CDCl_3$) 2950 (m), 1777 (s), 1636 (s), 1230 (s), 1115 cm^{-1} (s); mass spectrum (CI+, isobutane), *m/z* (relative intensity) 336 ($(M + 1)^+$, 25), 257 (10), 182 (28), 130 (60), 85 (60), 71 (100); high-resolution mass spectrum (CI+, isobutane) calcd for $C_{17}H_{22}NO_4S$ ($(M + 1)^+$) 336.1269, found 336.1258; $[\alpha]^{25}_D$ −34.9° (*c* 2.29, CH_2Cl_2). Anal. Calcd for $C_{17}H_{21}NO_4S$: C, 60.86; H, 6.32; N, 4.18; S, 9.56. Found: C, 60.95; H, 6.35; N, 4.10; S, 9.37.

A 174-mg sample of **7** was dissolved in 5 mL of hot 3:1 ethyl acetate/hexanes with the aid of a few drops of methylene chloride. Hot filtration, followed by cooling to room temperature and then to −20 °C, afforded opaque straw-colored prisms: mp 147–148 °C.

The enantiomeric purity of (−)-camphanic acid chloride (**6**) was checked by reaction with (−)-menthol, whereupon the minor ester diastereomer could not be detected by capillary GC analysis with on-column injection. The analysis was carried out as described below, with an initial oven temperature of 100 °C maintained for 30 s followed by heating to 220 °C at 25 °C/min and then to 250 °C at 2 °C/min. Derivatization of the racemate and GC analysis established that the retention times of the esters of (+)- and (−)-menthol were 14.62 and 15.02 min, respectively.

Quantitative GC Analysis of Diastereomeric Sulfoximine Derivatives. A Hewlett-Packard 5890A gas chromatograph with vaporizing and on-column injectors and a flame ionization detector was employed in conjunction with an HP 3390A digital integrator. An HP Ultra 2 column (cross-linked 5% phenyl methyl silicone gum phase, similar to SE-54), 25 m × 0.32 mm with 0.52 μm film thickness, was used for all analyses with hydrogen as carrier gas. To optimize integration of very small peaks, integrator attenuation and threshold values of 1 and 0, respectively, were specified. A 2 cm/min chart speed facilitated visual inspection of the base line and of integration tick marks.

In initial studies the vaporizing injector was employed with a straight tube glass insert, an injection port temperature of 250 °C, and a split ratio of 15:1. With a temperature program increasing from 245 to 270 °C at 2 °C/min followed by isothermal elution, the retention times of **7** and the diastereomer incorporating the (+)-enantiomer of **2** were 11.56 and 11.20 min, respectively. In a control experiment, nearly identical peak areas for the diastereomers were obtained in acylation and GC analysis of racemic **2**. To assess the accuracy of this technique for analysis of diastereomer ratios ≥ 2000:1, we injected 2-μL portions of six solutions containing 0.0023–6.8 mg/mL of **7** and a fixed amount of an internal standard, generating peak areas for **7** of 5300–(2.03 × 10^7) counts. Injection port discrimination resulted in a nonlinear calibration curve for **7**, with decreasing peak area/mass ratios for increasingly concentrated samples.[12] Furthermore, routine maintenance (e.g., cleaning of the injection port) caused significant variations in the diastereomer peak area ratios. Although the on-column technique afforded clearly superior results (vide infra), the vaporizing injection analyses were not uninformative. Diastereomer ratios determined by vaporizing injection were always at least 15% lower than the ratios measured for the same samples with the on-column technique. Thus, the former values constituted lower limits for actual diastereomeric purities and could be employed in monitoring preparative resolution experiments.

For on-column injections,[13] we utilized the HP duckbill-type inlet, which is configured so that samples are transferred to the column within the column oven. A Hamilton 10-μL syringe and an HP fused-silica needle (part number 19091-63000) were used with toluene as injection solvent. An initial oven temperature of 100 °C was maintained for 30 s followed by heating to 230 °C at 25 °C/min and then to 261 °C at 2 °C/min. To minimize the effects of accumulating nonvolatile residues, 6-in. lengths of the column were cut off at ca. 50-injection intervals. Representative retention times for **7** and the diastereomer incorporating the (+)-enantiomer of **2** were 18.21 and 17.86 min, respectively. Base-line resolution was obtained in analyses of **5** or (−)-**2**, wherein **7** was the predominant diastereomer. As the minor diastereomer in analyses of the (+)-sulfoximine, **7** eluted on the tail of the major peak. Despite greater uncertainties in quantitating the minor isomer, the latter mixtures afforded peak area ratios comparable to those obtained for analogous samples in the (−)-sulfoximine series. As before, GC analysis of the diastereomer mixture derived from racemic **2** gave nearly identical peak areas. A linear cali-

(23) Fusco, R.; Tenconi, F. *Chim. Ind. (Milan)* **1965**, *47*, 61–62; *Chem. Abstr.* **1965**, *62*, 10357*h*.

(24) Optical rotations in acetone have been reported for (+)-**2** ($[\alpha]_D$ +36.5° (*c* 1.2)) (ref 3) and (+)-**1** ($[\alpha]^{25}_D$ +183.2° (*c* 1.7)) (ref 17). Prior to development of the GC method for analysis of **5** and **2**, we found that methanol was superior to acetone as solvent for optical rotation measurements (cf. ref 15). In early experiments, we measured rotations in acetone at concentrations similar to those cited previously; resolved samples of **2** and **1** gave average $[\alpha]^{25}_D$ values of ±36.8° and ±184.1°, respectively.

bration curve was obtained for 1-μL injections of seven solutions containing 0.0748–299 ng/μL of **7** and a fixed amount of an internal standard, with peak areas for **7** of 70 100 ± 2400 (3.4%) counts/ng. This range permits quantitation of diastereomer ratios of 4000:1. At higher concentrations of **7**, column overloading caused severe deterioration of the base line, whereas smaller quantities gave irreproducible integrations. By proper adjustment of sample concentrations, diastereomer ratios exceeding 2000:1, the value corresponding to 99.9% de, could easily by demonstrated.

(*R*)-(−)-*N*,*S*-Dimethyl-*S*-phenylsulfoximine (1). A mixture of (−)-**2** (0.516 g, 3.33 mmol), 98% formic acid (10 mL), and paraformaldehyde (0.20 g, 6.67 mmol) was heated under argon at 100 °C in an oil bath. Complete reaction, as indicated by GC analysis, required 36 h. After concentration almost to dryness on a hot plate under a stream of argon, the residue was dissolved in 20 mL of 2 M H_2SO_4, and the solution was washed with two 10-mL portions of methylene chloride. The aqueous phase was then basified with 2 M NaOH and extracted with three 20-mL portions of methylene chloride. The latter extracts were dried over $MgSO_4$, filtered, and evaporated, affording 0.510 g of (−)-**1** (3.02 mmol, 91% yield) as a faintly straw-colored oil. This material was greater than 99% homogeneous by capillary GC analysis, and used without purification as described previously:[17] ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 28.8, 44.1, 127.9, 128.7, 132.1, 138.5; mass spectrum (70 eV), *m*/*z* (relative intensity) 171 (2), 170 (5), 169 (M^+, 45), 154 (95), 141 (18), 125 (38), 106 (100), 77 (98). ^1H NMR and IR data were identical with those reported previously for racemic material.[14] A sample of (−)-**1** was subjected to bulb-to-bulb distillation (bath temperature 120–125 °C, 1 mmHg), affording a colorless oil: $[\alpha]^{25}_D$ −135.9° (*c* 4.60, MeOH).[24]

Acknowledgment. We gratefully acknowledge financial support provided by the National Institutes of Health. We also thank Dr. Robert M. Barkley for valuable discussions of quantitative GC analyses.

Registry No. (−)-**1**, 80482-67-3; (±)-**2**, 81162-81-4; (−)-**2**, 60933-65-5; (+)-**2**, 33903-50-3; (−)-**3**, 35963-20-3; (+)-**3**, 3144-16-9; (±)-**4**, 52363-25-4; (−)-**4**, 50896-19-0; (−)-**5**, 116724-94-8; (+)-**5**, 7044-59-9; **6**, 39637-74-6; **7** (isomer 1), 116724-95-9; **7** (isomer 2), 116836-64-7; **8**, 50635-99-9; **9**, 116724-96-0; (−)-**10**, 79896-06-3; **11**, 116724-97-1.

Supplementary Material Available: Experimental procedures for camphenilone resolution and ee determination and for purification of 10-camphorsulfonic acid (2 pages). Ordering information is given on any current masthead page.

Aromatic Bromination Using BrF with No Friedel–Crafts Catalyst

Shlomo Rozen,*[†] Michael Brand,[†] and Rami Lidor[‡]

School of Chemistry, Raymond and Beverly Sackler Faculty of Exact Sciences, Tel-Aviv University, Tel-Aviv 69978, and Bromine Compounds Ltd., Beer Sheva, Israel

Received May 6, 1988

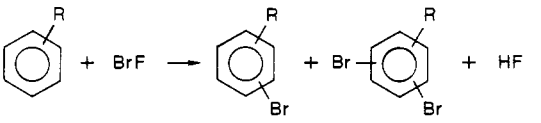
The use of elemental fluorine in organic synthesis has not yet achieved the stage of being a standard procedure, but on the other hand it is not the frightening proposition it used to be until recently. It can serve as a source for fluorine radicals,[1] electrophilic fluorine,[2] and nucleophilic fluorine generated in situ.[3] But elemental fluorine is more than that. Recently, we have shown that it can serve as a vehicle for performing difficult chemical transformations for the preparation of fluorine-free compounds. Thus, for example, one can perform epoxidations,[4] hydroxylation of heterocycles,[5] bromination and chlorination of pyridine derivatives,[6] iodinations,[7] and more. In this study, we report the use of BrF as an electrophilic aromatic bromination agent.

Brominations with bromine of activated rings occur readily, but rings bearing deactivating substituents require large amounts of Friedel–Crafts catalysts, which present both disposal as well as safety problems. The high reaction temperatures required, the yields of which often do not exceed 70–80%, and the loss of one bromine atom through the inevitable generation of HBr are all additional problems. These limitations are magnified when dibromination is the goal of the reaction.

The main role of any catalyst in aromatic electrophilic bromination is to polarize the reagent in such a way that the bromine atom will be as positive as possible, usually using metals with empty low energy D orbitals. Many other sources for positive bromine, such as NaOBr, are not very soluble in organic solvents and therefore of little use. We have searched for a simple and yet soluble molecule in which the bromine is highly polarized by being attached to a strongly electronegative moiety. Since fluorine is the most electronegative element, BrF seemed to be an ideal candidate.

Bromine monofluoride has been the subject of several studies conducted by inorganic chemists. It could not be obtained in a pure form, but Naumann successfully isolated and fully characterized its complex with pyridine.[9] A mixture of Br_2 and BrF_3 has also been used on several occasions for adding the elements of Br and F to various olefins.[10] We adopted a different approach. Passing fluorine through a cold suspension of bromine in trichlorofluoromethane resulted in the formation of BrF but, because of its tendency to disproportionate to BrF_3 and Br_2, we did not attempt purification or isolation but used it directly for organic synthesis. Thus, BrF adds to many types of double bonds[8] as well as acetylenes[3a] to produce the corresponding adducts in good yields.

We report here the use of BrF for electrophilic bromination and dibromination of a broad spectrum of aromatic compounds.[11] The method is general, addition of catalyst is not required,[12] and it offers excellent yields, short reaction times, and very mild conditions, thus reducing or completely eliminating most of the problems associated with present methods.



[†] School of Chemistry.
[‡] Bromine Compounds, Ltd.

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0022-3263/88/1953-5545$01.50/0