(36/100), 222 (8), 208 (27), 201 (84), 173 (34), 145 (45), and 129 (27); UV (MeOH) 244 (ε 9700), 344 (5900), 394 (2600); IR (KBr) 3360, 3050, 1670, 1600, 1420, 1340, 1320, 1200, 1135, 835, 804, and 720 cm^{-1}; ^1H and ^{13}C NMR, Table I.

Isobatzelline D (7): a reddish brown solid; HREIMS M^+ 279.0230 (calcd for $C_{12}H_{10}N_3OS^{35}Cl$, Δ mmu 0.3); LREIMS 281/279 (38/100), 266/264 (25/72), 246 (18), 232 (23), 220 (11), 196 (11), 186 (7), 173 (9), 159 (6); IR (KBr) 3450, 3310, 2930, 1640, 1560, 1545, 1485, 1440, 1400, 1340, 1320, 1290, 1250, 1145, 1080, and 960 cm^{-1}; UV (MeOH) 239 (ε 33 900), 263 (25 000), and 439 nm (25 200); ^1H and ^{13}C NMR, Table I.

Catalytic Hydrogenation of 4 to Product 8. A suspension of 25 mg of isobatzelline A (4) and 10 mg of 10% Pd/C in 10 mL of MeOH was agitated under 30 psig hydrogen atmosphere at room temperature for 16 h. After removal of the catalyst and the solvent, the reddish brown solid was separated on a Hibar NH_2 HPLC column to give 6 mg (34%) of 8, as a greenish brown solid: mp dec >200 °C; HRFABMS MH^+ 202.0994 (calcd for $C_{11}H_{12}ON_3$, Δ 1.4 mmu); LREIMS 201 (100), 174 (34), 145 (16), 119 (11), 105 (29), 91 (39), and 77 (17); UV (MeOH) 244 (ε 14 200), 346 (8500), and 392 nm (4000); IR (KBr) 3400, 2930, 1660, 1605, 1430, 1360, 1350, 1320, 1255, 1205, 1100, 835, and 800 cm^{-1}; ^1H NMR (1:2 $CDCl_3$-CD_3OD) δ 2.86 (2 H, t, J = 7.6 Hz), 3.82 (2 H, t, J = 7.6 Hz), 3.94 (3 H, s), 5.63 (1 H, s), and 7.00 (1 H, s); ^{13}C NMR (CD_3OD) δ 19.5, 36.5, 43.9, 87.9, 119.8, 123.9, 125.1, 131.9, 158.0, 159.6, and 169.6.

Conversion of 4 to 1. An aqueous $NaNO_2$ solution (100 mg in 5 mL) was added dropwise into an ice-chilled solution containing 20 mg of 4 in glacial acetic acid (2 mL) and dioxane (1 mL). After stirring at 0 °C for 2 h, 3 mL of 1 N HCl was added, and the solution was stirred at room temperature overnight and then extracted with $CHCl_3$-MeOH (1:1, 10 mL × 2). The extract was fractionated on a Superco LC-NH_2 cartridge with 1% MeOH-$CHCl_3$ and subsequently purified on a HPLC LiChrosorb-NH_2 column with 3% MeOH-$CHCl_3$ to give 1 (4 mg, 20%), along with 4 (2 mg).

Conversion of 4 to 7. A solution of 10 mg of 4 in 5 mL of dioxane was stirred with 10 mg of DDQ at room temperature overnight. The resulting product was purified by HPLC (LiChrosorb NH_2, 3% MeOH-$CHCl_3$) to give 6 mg (60%) of 7.

Conversion of 5 and 6 to 8. Isobatzellines B (5, 15 mg) and C (6, 30 mg) were reduced to 8 (8 mg (65%) and 19 mg (74%), respectively) under the conditions already described above for the conversion of 4 to 8.

Acknowledgment. We thank Dr. S. Pomponi and Ms. C. Diaz for sponge taxonomy and Dr. K. L. Rinehart, Jr., University of Illinois at Urbana-Champaign, for mass spectra. This is Harbor Branch contribution No. 766.

Supplementary Material Available: ^{13}C NMR spectra for compounds 4-8 (5 pages). Ordering information is given on any current masthead page.

Transalkylation Reactions of 4,4'-(1-Methylethylidene)bisphenol with Diphenyl Ether

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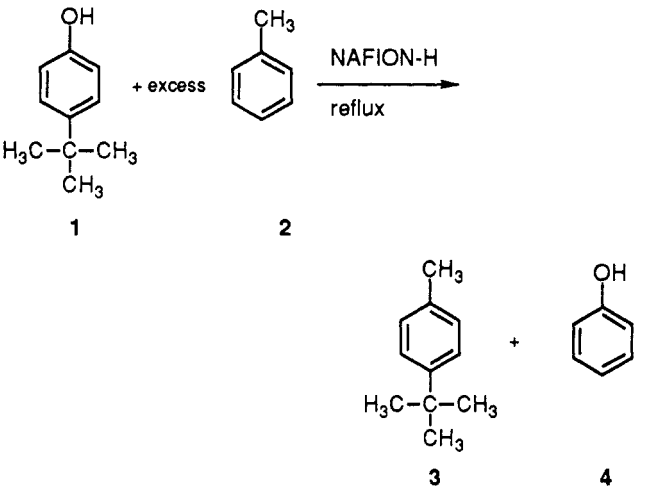
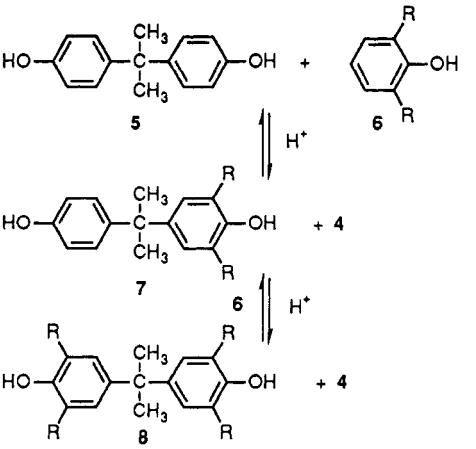
Olah and others[1-3] have recently described the use of Nafion-H resins as catalysts in the de-*tert*-butylation of aromatic compounds. Phenol and biphenols containing *tert*-butyl groups, in the presence of Nafion, undergo an almost quantitative transalkylation reaction with toluene, or biphenyl, to yield the unsubstituted phenol or biphenol along with 4-*tert*-butyltoluene or 4-*tert*-butylbiphenyl as coproducts. For example, 4-*tert*-butylphenol (1) and toluene (2) yield phenol (4; 96%) and 4-*tert*-butyltoluene (3; 96%) as products (Scheme I).

Transalkylation reactions between phenols and bisphenols have been reported previously.[4-6] Mark[5] found that bisphenols such as 4,4'-(1-methylethylidene)bisphenol

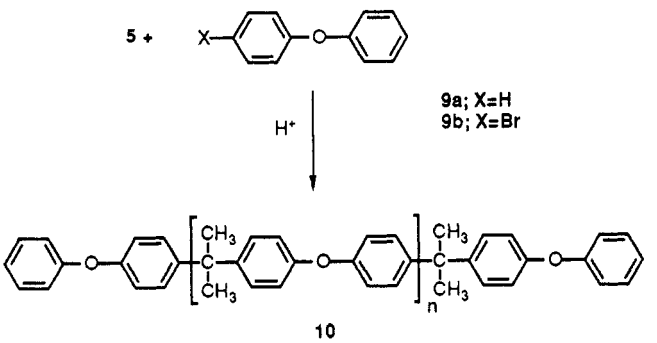
Scheme I



Scheme II



Scheme III



(1) Olah, G. A.; Surya, G. K.; Prakash, G. K.; Iyer, P. S.; Tashiro, M.; Yamamoto, T. *J. Org. Chem.* **1987**, *52*, 1881.
(2) Tashio, M. *Synthesis* **1979**, 921.
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(5) Mark, V., U.S. Patent 4,560,808, Dec. 24, 1985; *Chem. Abstr.* **1986**, *104*, 225358p.
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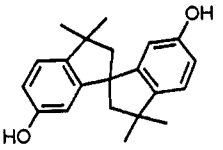
(BPA, **5**) in the presence of a large excess of another phenol (**6**; R = alkyl) and methanesulfonic acid as catalyst could be transformed into the other bisphenol (**8**) by a transalkylation reaction (Scheme II). The unsymmetrically substituted bisphenol **7** is an intermediate in the reaction and a large excess of the second phenol **6** is used in order to drive the reaction to completion.

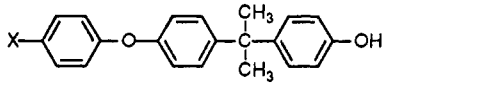
It appeared possible that a transalkylation reaction of **5** with an aromatic substrate such as diphenyl ether (**9a**; X = H) might yield a polymer (**10**) and phenol as products (Scheme III).

We have found, however, that when **5** is reacted with a large excess of **9a** in the presence of Nafion at 100 °C, only 6,6′-dihydroxy-3,3,3′,3′-tetramethyl-1,1′-spirobiindan (**11**) is produced. When the reaction was attempted with

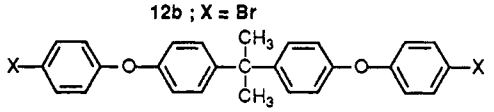


11

methanesulfonic acid as catalyst at 65 °C, **11** was again formed. This product has been prepared previously by heating **5** with hydrobromic acid.[7] Recent U.S. patents also describe the preparation of **11** from **5** in the presence of Nafion[8] and methanesulfonic acid[9] at elevated temperatures. We have found that if the reaction is performed at room temperature with methanesulfonic acid as catalyst, transalkylated products are formed. The monotransalkylated (**12a**; X = H) or the ditransalkylated (**13a**; X =



12a ; X = H
12b ; X = Br

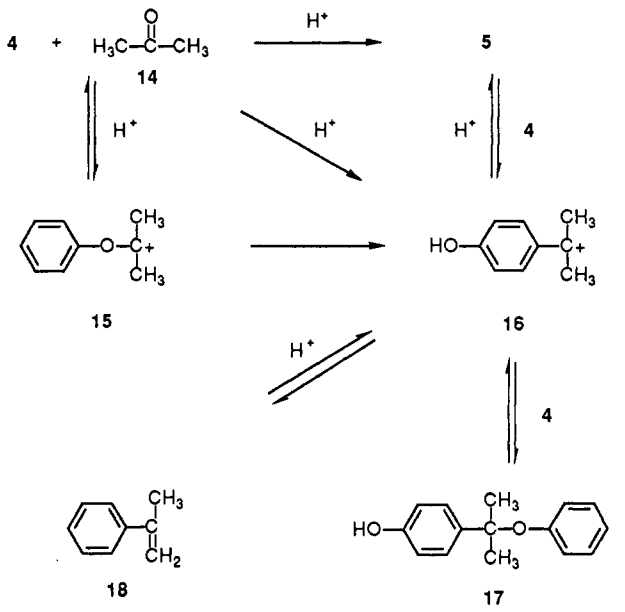


13a ; X = H
13b ; X = Br

H) products can be selectively synthesized by changing the acid concentration, **13a** being formed at higher concentrations of the acid. The reaction is slow under these conditions and does not proceed further to give any significant amount of higher oligomers. Increasing the temperature gives **11** as the major product. Similar results were obtained with other acids. We have found that bromodiphenyl ether (**9b**; X = Br) is considerably less reactive than **9a** under these conditions and undergoes only very low conversions to the monotransalkylated product (**12b**; X = Br). This decrease in reactivity of **9b** is consistent with recent results on the bromination of **9a** with a mild brominating agent, (bromomethyl)methylsulfonium bromide, which yields **9b** with high selectivity.[10] When the temperature of the reaction is raised in an attempt to speed up the reaction and to produce the disubstituted product, e.g., **13b**, the major product of the reaction is **11**.

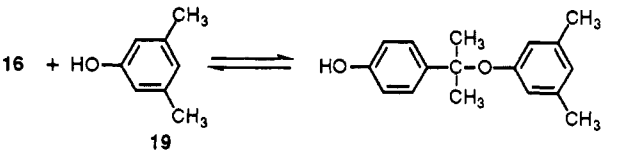
BPA (**5**) is manufactured by the direct condensation of acetone (**14**) with a large excess of phenol (**4**) in the

Scheme IV



presence of an acid catalyst, preferably an ion exchange resin (Scheme IV).[11] The reaction is not quantitative enough to use as a polymer-forming reaction directly since polyalkylation reactions and indan-forming reactions act as terminating reactions especially when the stoichiometry approaches 1:1 in the reaction. The excess phenol probably minimizes the formation of oligomeric species by lowering the concentration of the intermediate carbocation **16** and the alkene **18** in the reaction mixture since it is these intermediates that probably go on to react further to yield indan and spirobiindan products.

By carrying out the reaction in the presence of a substituted phenol that could react with the carbocation **16** in an O-alkylation reaction but because of steric reasons would be unable to be C-alkylated, we felt the problem might be resolved. Therefore, **9a** was reacted with **5** in the presence of a large excess of 3,5-dimethylphenol (**19**). A clean reaction occurred, yielding **13a** as the final product with **12a** as the intermediate product. Small amounts of



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higher oligomers (e.g., **10**; n = 1, Scheme III) were also formed. Under these conditions reaction of **5** with **9b** gives the dimer **13b** as product and none of the spirobiindan **11** is formed!

We next attempted to react acetone directly with diphenyl ether in the presence of a large excess of **19**. Reaction does occur but a complex mixture of products is obtained. When a small amount of phenol is added to the reaction mixture, a clean reaction occurs, giving a product mixture comparable to that obtained in the reaction of **5** with diphenyl ether. Apparently it is necessary to have the carbocation **16** as an intermediate that then alkylates **9a** to give **12a**. A carbocation is not available from **19** by reaction with **14** because of steric hindrance. Acid cleavage of **12a** would yield the carbocation **20**, which would then alkylate **9a** to give **13a**.

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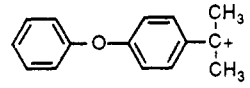

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Experimental Section

General Methods. Melting points were measured on a Fisher-Johns melting point apparatus and are uncorrected. Flash chromatography was done on silica gel 60 (32–63 μm) from BDH. ^{1}H NMR spectra were obtained in chloroform-*d* solution at 200 MHz or 300 MHz on a Varian XL-200 or XL-300 FT NMR spectrometer. ^{13}C NMR spectra were obtained at 75.5 MHz on a Varian XL-300 FT NMR spectrometer and are reported in ppm from tetramethylsilane on the δ scale. Low- and high-resolution mass spectra (MS and HRMS) were obtained on a Du Pont 21-492B instrument. HPLC analyses were done on a Milton Ray HPLC instrument, using a Spherisorb ODS2 reverse-phase column (250 × 4.6 mm, 5 μm) and methanol as an eluent at flow rate of 1.0 mL per minute; a UV detector was set at 254-nm wavelength. Microanalyses were done at Guelph Chemical Laboratories Ltd., Ontario, Canada, and Galbraith Laboratories, Inc., TN.

The Claisen's alkali was prepared as follows: dissolve 35 g of potassium hydroxide in 25 mL of water, cool the solution, add 100 mL of methanol, and cool the solution. 4,4'-(1-Methylethylidene)bisphenol (BPA) was obtained from the General Electric Company.

Reaction of Diphenyl Ether (9a) with BPA (5). To a suspension of **5** (5.708 g, 25 mmol) and **9a** (34.042 g, 200 mmol) in chloroform (5 mL), at room temperature, was added methanesulfonic acid (3.0 mL) dropwise. After being stirred for 36 h, the reaction mixture was diluted with chloroform (500 mL) and then washed with aqueous sodium hydroxide solution (1 N, 4 × 150 mL). The organic phase was dried over anhydrous sodium sulfate and the solvent was removed at reduced pressure. The residue was diluted with petroleum ether (300 mL) and extracted with Claisen's alkali (2 × 75 mL). The combined alkaline extracts were diluted with water (100 mL), cooled to 0 °C, and acidified carefully with concentrated hydrochloric acid to pH 1–2. The acidified mixture was then extracted with ether (3 × 150 mL) and the ether phase was dried over anhydrous sodium sulfate. Removal of the solvent in vacuo and purification of the residue by flash chromatography (15% ethyl acetate in hexanes) gave the desired phenol **12a** as a solid: 6.10 g (80.2%). Further purification by flash chromatography (20% ethyl acetate in hexanes) and then by recrystallization from 1,2-dichloroethane gave an analytical sample as colorless crystals: mp 76–78 °C; ^{1}H NMR (200 MHz) δ 1.65 (s, 6 H, 2 CH_3), 4.70 (s, 1 H, OH), 6.74 (dd, 2 H, J = 2.2, 6.6 Hz, Ar H), 6.90 (dd, 2 H, J = 2.2, 6.6 Hz, Ar H), 6.98–7.03 (m, 2 H, Ar H), 7.07–7.20 (m, 5 H, Ar H), 7.28–7.36 (M, 2 H, Ar H); ^{13}C NMR δ 31.07, 41.91, 114.77, 118.28, 118.76, 123.06, 127.97, 128.02, 129.68, 143.02, 145.87, 153.36, 154.87, 157.38; MS (EI, m/z, relative intensity) 304 ($M^{+\bullet}$, 44), 289 ($M^{+\bullet}$ – CH_3, 100).

Anal. Calcd for $C_{21}H_{20}O_2 \cdot {}^1/_2ClCH_2CH_2Cl$: C, 74.67; H, 6.27. Found: C, 75.01; H, 6.33.

Reaction of 5 with 9a at 80–90 °C. A suspension of **5** (517 mg, 2.5 mmol) and **9a** (1.28 g, 7.50 mmol) was stirred in the presence of either Amberlyst-15 (342 mg) or methanesulfonic acid (0.2 mL) at 80–90 °C. After a few hours, a red solution was obtained and the reaction was followed over 18 h by TLC. After 4–5 h phenol and **11** were the main products. After 18 h the BPA was gone and **11** was the principal product. Compound **11**: mp 218–219 °C. (lit.[8] mp 215–217 °C); ^{1}H NMR (200 MHz) δ 1.30 and 1.36 (2 s, 12 H, CH_3), 2.18 (d, 2 H, J = 11.1 Hz, CH_2), 2.33 (2 d, 4 H, J = 11.1 Hz, CH_2), 4.29 (s, 2 H, OH), 6.15 (d, 2 H, J = 2.2 Hz, $C_{7,7'}$-H), 6.68 (dd, 2 H, J = 2.2 Hz, J = 8.2 Hz, $C_{5,5'}$-H), 7.01 (d, 2 H, J = 8.2 Hz, $C_{4,4'}$-H).

Reaction of 9a with 5 in the Presence of 3,5-Dimethylphenol. A mixture of **5** (4.564 g, 0.020 mol) and **9a** (34.04 g, 0.200 mol) was dissolved in 3,5-dimethylphenol (24.43 g, 0.200 mol) at 65–68 °C and methanesulfonic acid (4.0 mL) was added. After being stirred for 2–3 days, the reaction mixture was cooled to room temperature and diluted with ether (150 mL). The diluted reaction mixture was washed with 10% sodium hydroxide solution (6 × 50 mL), water (2 × 50 mL), and brine (50 mL). After drying over anhydrous sodium sulfate, the solvent was distilled in vacuo and excess **9a** was removed by vacuum distillation. The residue was then purified by flash chromatography (petroleum ether, then 10% ethyl acetate in hexanes) to give the phenol **12a** (404 mg, 6.65%), the ether **13a** (5.40 g, 71.05%) and the trimer (**10**; n = 1; 549 mg, 9.31%) in 87% total yield. Further purification of **13a** by flash chromatography (twice, petroleum ether in hexanes 1:10) followed by vacuum distillation and recrystallization from ethanol gave colorless crystals. This material was >99% pure by HPLC and had mp 45–46 °C. This compound has been reported previously to have mp 62–63 °C.[12]

Compound **13a**: ^{1}H NMR (300 MHz) δ 1.67 (s, 6 H, 2CH_3), 6.93 (d, 4 H), 7.02 (dd, 4 H, J = 1.2, 8.7 Hz), 7.10 (t, 2 H, J = 7.8 Hz), 7.21 (d, 4 H, J = 9.0 Hz), 7.33 (dd, 4 H, J = 7.2, 8.4 Hz); ^{13}C NMR δ 31.08, 42.14, 118.31, 118.83, 123.12, 128.06, 129.71, 145.57, 155.03, 157.37; MS (EI, m/z, relative intensity) 380 ($M^{+\bullet}$, 67.8), 365 ($M^{+\bullet}$ – CH_3, 100); HRMS (EI, m/z) for $C_{27}H_{24}O_2$ ($M^{+\bullet}$) calcd 380.1776, found 380.1768.

Trimer **10** (n = 1): syrup; ^{1}H NMR (300 MHz) δ 1.68 (s, 6 H, 2CH_3), 1.69 (s, 6 H, 2CH_3), 6.91 (2 d, 8 H), 7.02 (dd, 4 H), 7.09 (2 t, 2 H), 7.20 (2 d, 8 H), 7.28–7.36 (m, 4 H).

Reaction of 9a with Acetone in the Presence of 3,5-Dimethylphenol. At 55–60 °C methanesulfonic acid (2.0 mL) was added to a solution of acetone (580 mg, 10 mmol), **9a** (17.02 g, 0.100 mol), thiosalicyclic acid (100 mg), and 3,5-dimethylphenol (12.22 g, 0.100 mol). The resulting red solution was stirred at 55–60 °C for 2–4 days and the reaction was monitored by HPLC. Among other unidentified products, the ether **13a** was formed in about 34% yield by HPLC.

Reaction of 9a with Acetone in the Presence of Phenol and 3,5-Dimethylphenol. At 62–65 °C, methanesulfonic acid (1.0 mL) was added to a solution of acetone (290 mg, 5.00 mmol), **9a** (8.51 g, 50.0 mmol), phenol (940 mg, 10.0 mmol), 3,5-dimethylphenol (6.11 g, 50.0 mmol), and a catalytic amount of 1,3-propanedithiol (two drops). The resulting dark red solution was stirred at 62–65 °C for 4 days, at which time the ratios of the products **12a**, **13a**, and trimer **10** (n = 1) were determined by HPLC to be 1:12.8:1.5. Another 5 mmol of acetone (290 mg) was added to the reaction mixture, with the option of workup instead at this stage, and the reaction was continued for another 4 days. The reaction mixture was then cooled to room temperature and diluted with ether (100 mL). The ether phase was washed with potassium hydroxide solution (1.5 N, 2 × 50 mL) and dried over anhydrous sodium sulfate. The solvent was removed at reduced pressure and the residue was heated to 120–160 °C at 0.1 mmHg using a Kugelrohr distillation apparatus until no more diphenyl ether could be distilled off. The crude products were taken up in 15% ethyl acetate–hexanes and purified on a short dry column, eluting with 10% ethyl acetate–hexanes. After removal of solvent at reduced pressure, the residue weighed 3.02 g and contained mainly the products **12a** (11.7%), **13a** (60.8%), trimer **10** (n = 1, 10.0%), and **9a** in the ratio of 4.34:22.61:1.00:5.51 by HPLC. The total yield based on acetone (10 mmol, 580 mg) was 82.5%.

Reaction of 9b with 5. To a suspension of **5** (5.71 g, 5.00 mmol) and **9b** (37.37 g, 0.150 mol) in chloroform (5 mL) was added methanesulfonic acid (2.5 mL). The red suspension was stirred at room temperature for 18 h and at 40 °C for another 14 h. TLC indicated the formation of **11** as a side product and a considerable amount of unreacted **5** remained. The reaction mixture was diluted with methylene chloride (100 mL) and washed with sodium hydroxide solution (1 N, 5 × 35 mL) and water (30 mL). After drying, evaporating solvents, and purification by chromatography, the desired phenol **12b** was obtained as white crystals in very low yield (<10%): mp 143.5–144.5 °C; ^{1}H NMR (200 MHz) δ 1.66 (s, 6 H, 2CH_3), 5.01 (br s, 1 H, OH), 6.76 (d, J = 8.6 Hz, 2 H), 6.89 (d, J = 9.0 Hz, 2 H), 6.90 (d, J = 8.8 Hz, 2 H), 7.12 (d, J = 8.8 Hz, 2 H), 7.21 (d, J = 8.4 Hz, 2 H), 7.42 (d, J = 9.0 Hz, 2 H); ^{13}C NMR δ 31.05, 41.95, 114.81, 115.41, 118.44, 120.30, 127.96, 128.16, 132.61, 142.91, 146.44, 153.37, 154.34, 156.70; MS (EI, m/z, relative intensity) 384 ($M^{+\bullet}$ + 2, 7.0), 383 ($M^{+\bullet}$ + 2 – $H^\bullet$, 43.9), 382 ($M^{+\bullet}$, 7.3), 381 ($M^{+\bullet}$ – $H^\bullet$, 44.5), 369 ($M^{+\bullet}$ + 2 – CH_3, 100), 367 ($M^{+\bullet}$ – $^\bullet CH_3$, 39.3), 289 ($M^{+\bullet}$ – $^\bullet CMe_2PhOH$, 32.2); HRMS (EI, m/z) for $C_{21}H_{19}BrO_2$ ($M^{+\bullet}$) calcd 382.0569, found 382.0571.

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Reaction of 9b with 5 in the Presence of 3,5-Dimethylphenol. A mixture of **5** (1.14 g, 5.00 mmol) and **9b** (12.46 g, 50.00 mmol) was dissolved in 3,5-dimethylphenol (6.11 g, 50.0 mmol) at 62–65 °C and methanesulfonic acid (1.0 mL) was then added. The resulting red solution was stirred at 65 °C for 2–4 days and the reaction was followed by HPLC. The reaction flask was cooled to room temperature and ether (100 mL) was added. The solution was washed with sodium hydroxide solution (1 N, 10 × 20 mL) until no more 3,5-dimethylphenol could be detected by TLC. The ether was distilled and the residue was diluted with petroleum ether (60 mL), which was then extracted with Claisen's alkali (2 × 30 mL). The combined basic extracts were acidified with concentrated hydrogen chloride solution to pH 1 and the acidified mixture was extracted with ether (3 × 75 mL). The combined ether extracts were washed with water (50 mL) and dried over anhydrous sodium sulfate. Removal of solvent and flash chromatography of the residue (10% ethyl acetate in hexanes) gave the desired phenol **12b** as white crystals: 410 mg (21.5%).

After being washed with Claisen's alkali, the petroleum ether phase containing compound **13b** was concentrated in vacuo and excess bromodiphenyl ether was removed by distillation at reduced pressure. The residue was purified by chromatography (petroleum ether, then 2.5% ethyl acetate in hexanes) and afforded the dibromide **13b** as a syrup: 550 mg (20.5%); ^{1}H NMR (200 MHz) δ 1.67 (s, 6 H, $2CH_3$), 6.88 (d, 4 H, J = 9.0 Hz, Ar H meta to Br), 6.90 (d, 4 H, J = 8.8 Hz, Ar H meta to $C(Me)_2$), 7.20 (d, 4 H, J = 8.8 Hz, Ar H ortho to $C(Me)_2$), 7.41 (d, 4 H, J = 9.0 Hz, Ar H ortho to Br); ^{13}C NMR δ 31.03, 42.20, 115.49, 118.45, 120.37, 128.17, 132.63, 145.98, 154.52, 156.62.

Reaction of 9b with Acetone in the Presence of Phenol and 3,5-Dimethylphenol. Methanesulfonic acid (1.0 mL) was added to a solution of acetone (290 mg, 5.00 mmol), phenol (940 mg, 10.0 mmol), **9b** (12.46 g, 50.00 mmol), 3,5-dimethylphenol (6.109 g, 50 mmol), and a catalytic amount of propanedithiol at 63 °C. The resulting red solution was stirred at 63 °C overnight (~18 h), and another 1 mL of methanesulfonic acid was added into the reaction mixture. The reaction was continued for another 18–24 h. The reaction mixture was then cooled to room temperature and diluted with ether (100 mL). After washing with concentrated sodium bicarbonate solution the ether was first removed by normal distillation and the crude reaction mixture was distilled by using a Kugelrohr distillation apparatus at reduced pressure to remove phenol, 3,5-dimethylphenol, and excess **9b**. The residue weighed 1.60 g and contained the desired phenol **12b** (6.8%) and the dibromide **13b** (48.0%), determined by HPLC.

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Registry No. **5**, 80-05-7; **9a**, 101-84-8; **9b**, 101-55-3; **10** (n = 1), 127619-34-5; **11**, 1568-80-5; **12a**, 127619-35-6; **12b**, 98771-03-0; **13a**, 14984-19-1; **13b**, 101191-93-9; 3,5-dimethylphenol, 108-68-9; acetone, 67-64-1; phenol, 108-95-2.

Remarkable Dependency of Diastereoselectivity on the Selection of Hydride Sources and Lewis Acids in the Reduction of 2-(Trifluoromethyl)propiophenone

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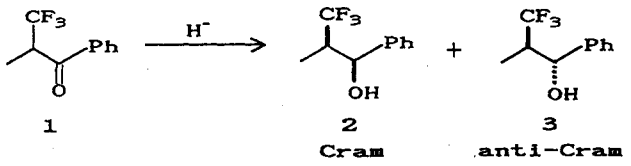
Diastereoselective reduction in acyclic systems has been a subject of great interest. In recent decades considerable progress has been made in controlling the stereochemistry of newly formed chiral centers by the aid of interactions between polar neighboring groups and Lewis acids.[1] Among the polar groups, trifluoromethyl has especially attracted interest, since stereoselective synthesis of organofluorine compounds has been of great importance from a biological point of view.[2] However, to our knowledge, there is only one example concerning trifluoromethyl group induced stereoselective synthesis.[3] In order to reveal effects between the trifluoromethyl group and Lewis acids, the reduction of 2-(trifluoromethyl)propiophenone (1) in the presence of various Lewis acids was studied. This report describes a remarkable dependency of diastereoselectivity on the selection of hydride sources and Lewis acids in the reduction of 1 and the first demonstration of strong coordination of a trifluoromethyl group to aluminum (Scheme I).

Scheme I



1 2 Cram 3 anti-Cram

Table I. Reduction of 1 without Added Lewis Acid

entry	reducing agent	solvent	temp (°C)	Cram:anti-Cram[a]	yield (%)
1	$NaBH_4$	EtOH	0–rt[b]	86:14	56
2	$LiAlH_4$	Et_2O	0–rt	84:16	63
3	Red-Al	Et_2O	0–rt	78:22	78
4	DIBAL-H	Et_2O	0–rt	84:16	72
5	$(CH_3)_2SBH_3$	Et_2O	0–rt	78:22	75
6	$LiEt_3BH$	Et_2O	0–rt	95:5	84
7	K^sBu_3BH	Et_2O	−78–rt	99:1	41

[a] Isomeric ratio was determined by HPLC. [b] rt = room temperature.

Initially, the reduction of 1 was examined by using a variety of reducing agents without added Lewis acid, which demonstrated that the reactions always produced the Cram isomer[4] predominantly, as shown in Table I. With K^sBu_3BH (entry 7), extremely high selectivity was observed; however, the yield of the desired product was low and 2-methylpropiophenone was formed in 17% yield as a byproduct. This may arise via elimination of HF followed by addition caused by the strong basicity of K^sBu_3BH. The above observation suggests that the reduction proceeded on the basis of Felkin–Anh's model, where the trifluoromethyl group has the greater effective bulkiness compared to the methyl group.[5] Thus, the metal-assisted cyclic conformation expected by coordination of fluorine atom to the metal may play no important role under the above conditions.[6]

(1) Review: (a) Eliel, E. L. In *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic Press: New York, 1983; Vol. 2, Chapter 5. (b) Nogradi, M. In *Stereoselective Synthesis*; VCH, Weinheim, 1987; pp 131–148.

(2) Filler, R.; Kobayashi, Y. In *Biomedicinal Aspects of Fluorine Chemistry*; Kodansha and Elsevier Biomedical: Amsterdam, 1982.

(3) Morizawa, Y.; Yasuda, A.; Uchida, K. *Tetrahedron Lett.* **1986**, *27*, 1833.

(4) The relative configurations of newly formed stereocenters were determined as follows. Protection of the hydroxyl group in **2** as a acetate followed by oxidation ($RuCl_3$–$NaIO_4$) led to the carboxylic acid. Deprotection followed by esterification with Na_2CO_3–EtI–HMPA system gave the ethyl 2-hydroxy-3-(trifluoromethyl)butanoate. The identity of this compound was confirmed by ^{1}H NMR comparison with the authentic data (ref 3).

(5) The trifluoromethyl group with steric bulk is comparable to that of the isopropyl group. Bott, G.; Field, L. D.; Sternhell, S. *J. Am. Chem. Soc.* **1980**, *102*, 5618.

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