temperature. The THF solvent was evaporated to half volume, and the reaction mixture was cooled overnight at −10 °C to precipitate the 2-MeIm byproduct. The filtrate was evaporated to yield crude PTC, which upon crystallization from *n*-hexane yielded 2.78 g (91%) of PTC, mp 83–84 °C.

General Procedure for the Preparation of Symmetrical Ureas. The known symmetrical ureas[17] listed below were prepared in yields listed in Table I by adding the amine (11–15 mmol, 22 mmol for $C_6H_5NH_2$) to a solution of PTC (5 mmol) in THF or EtOAc (10–15 mL) and stirring at room temperature for 3–10 h. Except for **2d**, the precipitated products were isolated by suction filtration of the reaction suspension followed by crystallization from the indicated solvents.

***N,N'*-Dicyclohexylurea (2a)**: crystallized from $CHCl_3$, mp 231–232 °C (lit. mp 232–233 °C). In an alternative aqueous preparation, $C_6H_{11}NH_2$ (1.48 g, 15 mmol) was added to a suspension of PTC (0.765 g, 5 mmol) in water (50 mL) for an overnight reaction at room temperature. Filtration of the precipitate followed by crystallization from $CHCl_3$ yielded 1.14 g, mp 231–232 °C.

***N,N'*-Diphenylurea (2b)**: crystallized from EtOAc, mp 238–239 °C (lit. mp 238 °C). ***N,N'*-Dibenzylurea (2c)**: crystallized from ethanol, mp 168–169 °C (lit. mp 168 °C). ***N,N'*-Diallylurea (2d).** This product was isolated by addition of *n*-hexane to the reaction solution and filtration of the resultant suspension, mp 92–94 °C (lit. mp 91–93 °C). ***N*-Phenyl-*N'*-allylurea (2e)** (in situ). A solution of PTC (1.53 g, 10 mmol) in THF (15 mL) was treated with aniline (0.93 g, 10 mmol) in *n*-hexane (200 mL) dropwise for 30 min at room temperature without observed precipitation. To this solution was added allylamine (0.57 g, 10 mmol), and the product precipitated immediately.[30] After stirring for 15 min, the urea was filtered and crystallized from benzene, affording 1.42 g, mp 115–116 °C (lit. mp 115–116 °C).

General Procedure for the Preparation of Secondary Carbamates 3a–b. Dropwise addition of the primary amine (10 mmol) either neat or in *n*-C_6H_{14} (150 mL) to a stirred solution of PTC (11 mmol) in THF (15 mL) and *n*-C_6H_{14} (40 mL) for 45–60 min at 0 to −10 °C precipitates the product. It is isolated by filtration and crystallization from the indicated solvent in the yields listed in Table II.

2-Thioxopyrid-3-yl cyclohexylcarbamate (3a): crystallized from C_6H_6; mp 145–146 °C; IR 3310 (NH), 1700–1720 cm^{-1} (C=O). Anal. Calcd for $C_{12}H_{16}N_2O_2S$: C, 57.12; H, 6.40; N, 11.10; S, 12.70. Found: C, 57.35; H, 6.54; N, 11.09; S, 12.50. **2-Thioxopyrid-3-yl allylcarbamate (3b)**: crystallized from $CHCl_3$; mp 110–111 °C; IR 3280 (NH), 1700 cm^{-1} (C=O). Anal. Calcd for $C_9H_{10}N_2O_2S$: C, 51.41; H, 4.80; N, 13.31; S, 15.25. Found: C, 51.58; H, 4.74; N, 13.10; S, 15.08.

General Procedure for the Preparation of Tertiary Carbamates 3c–d. A solution of PTC (10 mmol) in THF (25 mL) is mixed with the secondary amine (10 mmol), and the solution is stirred for 2–3 h at room temperature. The carbamate is isolated by solvent evaporation and crystallization from EtOAc.

2-Thioxopyrid-3-yl Piperidinylcarbamate (3c): mp 117–118 °C; IR 1715 cm^{-1} (C=O); GCMS *m/z* 238; ^{13}C NMR 171.9, 151.8, 129.9, 113.2, 133.9 (py C2–C6), 151.6 (C=O), 45.9, 45.4, 25.5, 24.2 ppm (pip C_α–C_γ). **2-Thioxopyrid-3-yl pyrrolidinylcarbamate (3d)**: mp 135–137 °C; IR 3320 (NH), 1720 cm^{-1} (C=O); MS *m/z* 224; ^{13}C NMR 171.8, 151.6, 130.1, 113.3, 133.9 (py C2–C6), 151.6 (C=O), 46.6, 46.5, 25.6, 24.9 ppm (pyrr C_α–C_β).

Acknowledgment. Carbon-13 NMR spectra were obtained at the NMR facilities of the Francis Bitter National Magnet Laboratory, Massachusetts Institute of Technology. The NMR facility is supported by Grant 00995 from the Division of Research of the National Institutes of Health and by the National Science Foundation under Contract C-76D. Assistance provided by Dr. David Ruben is appreciated.

(30) Since the *N*-allyl 2-thioxopyrid-3-yl carbamate (**3b**) was isolated in 75% yield, the sequence of amine addition may be reversed in this case.

Enantioselective Reduction of Aryl Trifluoromethyl Ketones with BINAL-H. A Preparation of 2,2,2-Trifluoro-1-(9-anthryl)ethanol

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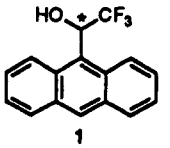
In connection with a study on the enantioselective synthesis of γ-lactones,[1] we required 2,2,2-trifluoro-1-(9-anthryl)ethanol [(*R*)- or (*S*)-**1**] for determination of optical purity by ^1H NMR spectroscopy.[2] Owing to the relatively high cost of this reagent[3] and the necessity of a severalfold (typically 3 mol equiv) excess of it to produce nonequivalence, we sought an alternative and economical route to this compound.



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One possible route to **1** is the asymmetric reduction of 9-anthryl trifluoromethyl ketone (**2a**). In 1977, Pirkle reported the asymmetric reduction of **2a** with a reducing agent derived from lithium aluminum hydride and a chiral oxazoline, providing (*R*)-**1** in 51% ee.[2] Since that time, however, numerous asymmetric reducing agents have been developed,[4] and it was our expectation that one could be found to reduce **2a** with much better selectivity. Furthermore, we were interested in the effect of the trifluoromethyl group on the enantioselectivity of some asymmetric reductions since, in contrast to the voluminous literature on the reduction of alkyl aryl ketones, there were very few reports of the asymmetric reduction of trifluoromethyl ketones.[5-7]

A brief survey of the reagents most commonly used for the asymmetric reduction of alkyl aryl ketones revealed that Noyori's BINAL-H reagent[8] reduces **2a** and other "hindered" aryl trifluoromethyl ketones in good to excellent enantioselectivities.[9] Other asymmetric reducing agents were ineffectual. For example, reduction of **2a** with Itsuno's reagent[10a] [derived from BH_3 and (*S*)-2-amino-3-

(1) Chong, J. M.; Mar, E. K. *Tetrahedron Lett.* **1990**, *31*, 1981.
(2) Pirkle, W. H.; Sikkenga, D. L.; Pavlin, M. S. *J. Org. Chem.* **1977**, *42*, 384.
(3) The price of (*R*)- or (*S*)-**1** is $24.30/100 mg (Aldrich).
(4) For a comparison of various asymmetric reducing agents for the reduction of different classes of ketones, see: Brown, H. C.; Park, W. S.; Cho, B. T.; Ramachandran, P. V. *J. Org. Chem.* **1987**, *52*, 5406.
(5) (a) BINAL-H reduction of fluoroalkyl alkynyl ketones: Hanzawa, Y.; Kawagoe, K.; Kobayashi, Y. *Chem. Pharm. Bull.* **1987**, *35*, 2609. (b) Yeast reduction of aryl trifluoromethyl ketones: Bucciarelli, M.; Forni, A.; Moretti, I.; Torre, G. *Synthesis* **1983**, 897.
(6) There are several scattered reports on the asymmetric reduction of 2,2,2-trifluoroacetophenone. Enantioselectivities ranged from 0.7 to 77% ee. (a) Brown, H. C.; Pai, G. G. *J. Org. Chem.* **1985**, *50*, 1384. (b) Midland, M. M.; Kazubski, A. *J. Org. Chem.* **1982**, *47*, 2495. (c) Baba, N.; Matsumura, Y.; Sugimoto, T. *Tetrahedron Lett.* **1978**, 4281. (d) Nasipuri, D.; Bhattacharya, P. K. *J. Chem. Soc., Perkin Trans. 1* **1977**, 576. (e) Morrison, J. D.; Tomaszewski, J. E.; Mosher, H. S.; Dale, J.; Miller, D.; Elsenbaumer, R. L. *J. Am. Chem. Soc.* **1977**, *99*, 3167. (f) Seebach, D.; Daum, H. *Chem. Ber.* **1974**, *107*, 1748.
(7) After this work was completed, Corey reported the reduction of **2a** with a modified "CBS" reducing agent consisting of a chiral *B*-*n*-butyloxazaborolidine as catalyst and catecholborane. (*R*)-**1** was obtained in 94% ee and >95% yield. Corey, E. J.; Bakshi, R. K. *Tetrahedron Lett.* **1990**, *31*, 611.
(8) Noyori, R.; Tomino, I.; Tanimoto, Y.; Nishizawa, M. *J. Am. Chem. Soc.* **1984**, *106*, 6709.
(9) For all reductions described in this work, the BINAL-H reagent with EtOH as coligand was used.

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methyl-1,1-diphenylbutan-1-ol] gave a 75% yield of (*R*)-1 of 13% ee, Corey's "CBS" reagent[10b] [consisting of a chiral *B*-methyloxazaborolidine as catalyst and BH_3] gave only 16% yield of (*R*)-1 of 18% ee, while Brown's chlorodiisopinocampheylborane[10c] was very slow (<10% reaction after 20 h at room temperature) at reducing **2a**.

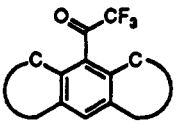
Following Noyori's procedure, 2.6 equiv of (*S*)-BINAL-H was allowed to react with ketone **2a** at −60 °C. Although the reduction was extremely slow, requiring 3 days to reach 51% conversion, we were gratified to find trifluoromethylcarbinol **3a** was obtained in 93% ee (entry 1, Table I). The absolute configuration of **3a** was determined to be *R* based on the sign of the optical rotation. Since (*S*)-BINAL-H reduces alkyl aryl ketones to give the corresponding (*S*)-alcohol, and taking into consideration the higher atomic number of fluorine over carbon, (*S*)-BINAL-H operates on **2a** with the same sense of asymmetric induction as predicted by Noyori's transition-state model (with the 9-anthryl group acting as the unsaturated group). This was not found to be the case, however, for the BINAL-H reduction of alkynyl trifluoromethyl ketones as reported by Kobayashi et al.[5a] They found that the (*R*)-alcohol was produced with (*R*)-BINAL-H, albeit in only 21% ee for their one reported example.

As Pirkle had reported that (*R*)-1 of 51% ee could be recrystallized several times to near optical purity,[2] we felt that the enantioselectivity of the BINAL-H reduction of **2a** could be compromised to a certain extent in favor of improving the yield (while decreasing the reaction time). Thus, reductions of **2a** at higher temperatures were carried out. Performing the reaction at −20 °C did give higher yields, and, unexpectedly, similar enantioselectivities (entry 2). In fact, the (*S*)-BINAL-H reductions of **2a** at 0 °C and 25 °C also gave good ee's (entries 3 and 4). Hence, it seems that the enantioselectivity of these reactions varies only slightly with temperature. Noyori has also reported this slight "temperature-independent" phenomenon in the reduction of acetophenone using BINAL-H with MeOH (but not EtOH) as coligand.[8,11]

The enantioselectivity is, however, sensitive to the amount of BINAL-H reagent used. The ee is maintained in the 84–91% range when the number of equivalents of BINAL-H reagent is reduced to 2.1; further lowering to 1.6 and 1.2 equiv proved detrimental, giving alcohol **3a** in 75% and 56% ee, respectively (entries 4, 6–8). However, the need to use >2 equiv of BINAL-H is not an important (economic) restriction on its use since the 1,1′-bi-2-naphthol may be quantitatively recovered by simple base extraction with no detectable racemization.

In a preparative experiment, **2a** (4.7 mmol) was treated with 2.1 equiv of (*R*)-BINAL-H (−20 °C, 24 h) to afford (*S*)-1 in 89% yield and 91% ee (entry 5). Two recrystallizations from high-boiling petroleum ether improved the enantiomeric purity to 99%.[12]

We next examined the BINAL-H reduction of other aryl trifluoromethyl ketones (entries 9–22, Table I). Ketones **2b** and **2d**, structurally related to **2a** in terms of steric hindrance around the carbonyl functionality (i.e. each has two ortho substituents), were reduced with (*S*)-BINAL-H at −60 °C to give the corresponding (*R*)-carbinols with 93% and 97% ee, respectively (entries 9 and 13). Once again, reduction of the same ketones at 0 °C gave only slightly lower enantioselectivities (entries 10 and 14). However, reduction of ketones **2c** and **2e**, which have only one ortho substituent, proceeded in only 70% and 74% ee, respectively (entries 11 and 15). The nonhindered trifluoromethyl ketones **2f–h** were reduced with very low (1–27% ee) levels of asymmetric induction (entries 17–22). Thus, it appears that substitution at the ortho positions is very important in these reductions with BINAL-H, and substitution at *both* positions ortho to the trifluoromethyl ketone (as in general structure **4**) is critical in obtaining good enantioselectivities (>90% ee).



4

It is interesting to note that good (>90% ee) selectivities are observed in the BINAL-H reduction of simple unsubstituted alkyl aryl ketones such as acetophenone.[8] By comparison, 2,2,2-trifluoroacetophenone is reduced with only 27% ee. It thus appears that for the BINAL-H reduction of aryl trifluoromethyl ketones, ortho substituents on the aryl portion are required to override the apparently larger effective size of a trifluoromethyl group compared to an alkyl group. This larger effective size is likely due to electronic effects since pivalophenone (where the alkyl group is a *tert*-butyl group) is reduced with 44% ee under comparable conditions.[8,13]

Although alcohols **3b**, **3d**, and **3e** have not been previously reported, we were fairly certain of the assignment of the absolute configuration (*R*). These alcohols have the same sign of rotation and exhibit similar HPLC behavior on a chiral Pirkle covalent leucine column (elutes second) as (*R*)-**3a**, (*R*)-**3c**, and (*R*)-**3f** (whose absolute configurations have been established[12]). Nevertheless, we utilized Trost's method for determination of absolute configuration of secondary alcohols by ^1H NMR analysis of their *O*-methylmandelate esters to confirm our assignments.[14] In this model, the group in close proximity to the mandelate phenyl moiety is expected to be shifted upfield, when the ester is viewed in an extended Newman projection.

Thus, the (*S*)-*O*-methylmandelate esters of **3d** and **3e** were prepared and their ^1H NMR spectra were analyzed. The 4-methyl group of the ester of **3d** appears at δ 2.21 (major diastereomer) and δ 2.25 (minor diastereomer) while the 2-methyl group of the ester of **3e** appears at δ 2.39 (major diastereomer) and δ 2.43 (minor diastereomer). In both of these esters, the major diastereomers have upfield chemical shifts which correspond to structure **5a** and not **5b**, thereby confirming that the alcohols are indeed of the *R* configuration.

In summary, the BINAL-H reduction of hindered aryl trifluoromethyl ketones occurs with good enantioselectivities, predictable stereochemistry, and with high tolerance to the reaction temperature. This chemistry may be used

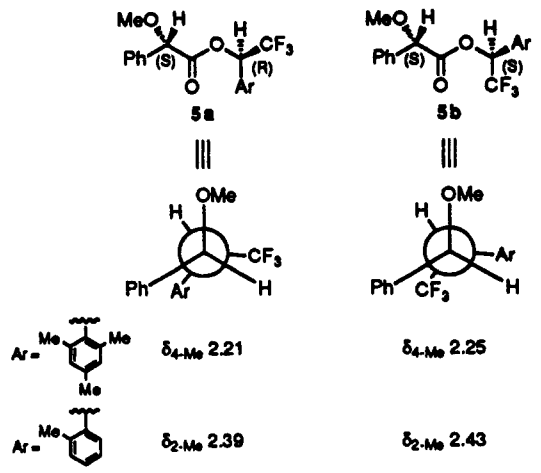
(10) (a) Itsuno, S; Ito, K.; Hirao, A.; Nakahama, S. *J. Chem. Soc., Chem. Commun.* **1983**, 469. (b) Corey, E. J.; Bakshi, R. K.; Shibata, S.; Chen, C.-P.; Singh, V. K. *J. Am. Chem. Soc.* **1987**, *109*, 7925. (c) Brown, H. C.; Chandrasekharan, J.; Ramachandran, P. V. *J. Org. Chem.* **1988**, *50*, 5446.

(11) We ruled out the possibility that the trifluoromethyl group was causing this slight temperature-independent asymmetric reduction. (*S*)-BINAL-H (2.1 equiv) reduction of 9-acetylanthracene at −60 °C and 0 °C gave the corresponding (*S*)-alcohol in 95% ee (2% yield, 72 h) and 93% ee [$[\alpha]^{25}_D$ −17° (*c* 0.48, $CHCl_3$), 46% yield, 24 h], respectively. In each case, the remainder of the material was recovered starting ketone.

(12) Determined by HPLC on a Pirkle covalent leucine column. Pirkle, W. H.; Finn, J. M. *J. Org. Chem.* **1981**, *46*, 2935. Structure 1 in Table I of this reference is ambiguous. The lower hydrogen in the structure should be replaced by a hydroxyl group.

(13) In other systems, it has been estimated that trifluoromethyl and isopropyl groups are sterically comparable in size. See ref 5a and Bott, G.; Field, L. D.; Sternhell, S. *J. Am. Chem. Soc.* **1980**, *102*, 5618.

(14) Trost, B. M.; Belletire, J. L.; Godleski, S.; McDougal, P. G.; Balkovec, J. M.; Baldwin, J. J.; Christy, M. E.; Ponticello, G. S.; Varga, S. L.; Springer, J. P. *J. Org. Chem.* **1986**, *51*, 2370.



to prepare Pirkle's chiral solvating agent, 2,2,2-trifluoro-1-(9-anthryl)ethanol.

Experimental Section

General. All reactions were carried out with dry glassware under an atmosphere of argon unless otherwise noted. Common reagents were purified by procedures noted previously.[24] Optically pure (*R*)- and (*S*)-(−)-1,1′-bi-2-naphthol were obtained by enzymatic resolution according to the procedure of Kazlauskas.[15] 9-Bromoanthracene was prepared in 90% yield from anthracene and NBS in DMF following Mitchell's procedure.[16] Spectral data were recorded using common analytical instruments.[24] The enantiomeric excesses of the trifluoromethyl carbinols were determined on a Pirkle covalent leucine column (5 μm, 250 mm × 4.6 mm i.d., Regis Chemicals Ltd.) with hexane/*i*-PrOH, 90:10 (v/v), as eluant for alcohols **3a–b** and hexane/*i*-PrOH, 98:2 (v/v), for alcohols **3c–g**, a flow rate of 0.6 mL/min, and detection at 254 nm. The ee of **3h** was determined by GC analysis [7% DB-1701 column (30 m × 0.25 mm), 180 °C isothermal] of the derived (+)-MTPA ester.[17]

Preparation of Aryl Trifluoromethyl Ketones. Following the procedure of Creary,[18] an ether solution (0 °C) of the aryllithium (1 equiv, prepared from the corresponding aryl bromide and *n*-BuLi[19]) was added to a −78 °C ether solution of ethyl trifluoroacetate (1.5 equiv). The reaction was then allowed to warm to room temperature, stirred for 30–60 min, and quenched with saturated NH_4Cl solution. Standard extractive workup followed by column chromatography and/or Kugelrohr distillation provided ketones **2a**,[20] **2b**, **2c**, **2d**, **2e**, **2f**, **2g**, and **2h**[21] in 74, 78, 82, 42, 42, 64, 63, and 60% yields, respectively. Spectral data for compounds that are unknown or not previously well-characterized are described below.

1-(2-Methylnaphthyl) trifluoromethyl ketone (2b): bp 85–100 °C (air bath temperature, 0.3 Torr); IR (film) 3056, 1739, 1209, 1177, 1155, 1080, 815 cm^{-1}; ^1H NMR (200 MHz) δ 7.90–7.80 (m, 2 H), 7.66–7.47 (m, 3 H), 7.31 (d, 1 H, *J* = 8.5 Hz), 2.49 (s, 3 H); ^{13}C NMR (63 MHz) δ 190.9 (q, *J* = 37 Hz), 134.0, 131.4, 130.9, 130.2, 129.9, 128.4, 128.1, 127.6, 126.0, 123.5, 115.9 (q, *J* = 293 Hz), 19.4; MS *m/z* (relative intensity) 238 (58, M^+), 169 (100), 141 (59), 115 (27). Anal. Calcd. for $C_{13}H_9F_3O$: C, 65.55; H, 3.81. Found: C, 65.29; H, 4.02.

1-Naphthyl trifluoromethyl ketone (2c): bp 80–100 °C (air bath temperature, 0.3 Torr) [lit.[5b] bp 93 °C (1.5 Torr)]; IR (film) 3053, 1708, 1202, 1146, 1067, 918, 777 cm^{-1}; ^1H NMR (200 MHz) δ 8.86–8.78 (m, 1 H), 8.22–8.10 (m, 2 H), 7.94–7.88 (m, 1 H), 7.72–7.51 (m, 3 H); ^{13}C NMR (63 MHz) δ 182.3 (q, *J* = 34 Hz), 136.0, 133.8, 131.5 (q, *J* = 4 Hz), 131.0, 129.3, 128.8, 126.9, 126.1, 125.0, 123.9, 116.7 (q, *J* = 293 Hz); MS *m/z* (relative intensity) 224 (72, M^+), 155 (100), 127 (97). Anal. Calcd for $C_{12}H_7F_3O$: C, 64.29; H, 3.15. Found: C, 64.21; H, 3.33.

2′,4′,6′-Trimethyl-2,2,2-trifluoroacetophenone (2d): bp 70–80 °C (air bath temperature, 20 Torr); IR (film) 2927, 1739, 1611, 1199, 1152, 911 cm^{-1}; ^1H NMR (200 MHz) δ 6.90 (s, 2 H), 2.27 (s, 3 H), 2.20 (s, 6 H); ^{13}C NMR (50 MHz) δ 191.3 (q, *J* = 37 Hz), 140.9, 135.0, 131.6, 128.7, 115.7 (q, *J* = 293 Hz), 20.9, 19.0; MS *m/z* (relative intensity) 216 (29, M^+), 147 (100), 119 (43). Anal. Calcd for $C_{11}H_{11}F_3O$: C, 61.11; H, 5.13. Found: C, 61.01; H, 5.33.

2′-Methyl-2,2,2-trifluoroacetophenone (2e): bp 60–72 °C (air bath temperature, 20 Torr); IR (film) 3069, 2975, 1712, 1185, 1145, 934, 738 cm^{-1}; ^1H NMR (200 MHz) δ 7.90–7.84 (m, 1 H), 7.54–7.45 (m, 1 H), 7.35–7.27 (m, 2 H), 2.55 (s, 3 H); ^{13}C NMR (50 MHz) δ 182.3 (q, *J* = 34 Hz), 142.3, 134.0, 132.6, 130.4 (q, *J* = 4 Hz), 129.2, 125.9, 116.5 (q, *J* = 293 Hz); MS *m/z* (relative intensity) 188 (37, M^+), 119 (100), 91 (89), 65 (20). Anal. Calcd for $C_9H_7F_3O$: C, 57.45; H, 3.75. Found: C, 57.51; H, 3.90.

4′-Methoxy-2,2,2-trifluoroacetophenone (2g): bp 45–75 °C (air bath temperature, 0.3 Torr) [lit.[22] bp 72–73 °C (2 Torr)]; IR (film) 3017, 2941, 2845, 1705, 1602, 1273, 1203, 1166, 940 cm^{-1}; ^1H NMR (200 MHz) δ 8.05 and 6.99 (AA′XX′ system, 4 H, J_{AX} = 9.1 Hz), 3.91 (s, 3 H); ^{13}C NMR (50 MHz) δ 178.9 (q, *J* = 34 Hz), 165.4, 132.7 (q, *J* = 2 Hz), 122.7, 116.9 (q, *J* = 291 Hz), 114.4, 55.6; MS *m/z* (relative intensity) 204 (51, M^+), 135 (100), 107 (7.8), 92 (11). Anal. Calcd for $C_9H_7F_3O_2$: C, 52.95; H, 3.46. Found: C, 53.09; H, 3.41.

4′-Fluoro-2,2,2-trifluoroacetophenone (2h): bp 40–75 °C (air bath temperature, 20 Torr) [lit.[22] bp 66–67 °C (34 Torr)]; IR (film) 3079, 1719, 1601, 1187, 1161, 943 cm^{-1}; ^1H NMR (200 MHz) δ 8.12 and 7.23 (AA′XX′ system, 4 H, J_{AX} = 8.2 Hz); ^{13}C NMR (50 MHz) δ 179.0 (q, *J* = 35 Hz), 167.1 (d, *J* = 260 Hz), 133.1 (dq, *J* = 10, 2 Hz), 126.4 (d, *J* = 3 Hz), 116.6 (q, *J* = 291 Hz), 116.5 (d, *J* = 22 Hz); MS *m/z* (relative intensity) 192 (11, M^+), 123 (100), 95 (55). Anal. Calcd for $C_8H_4F_4O$: C, 50.02; H, 2.10. Found: C, 49.87; H, 2.37.

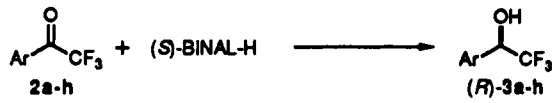
BINAL-H Reduction of Aryl Trifluoromethyl Ketones. A representative procedure for the reduction of **2a** with (*R*)-BINAL-H is given below, followed by spectral data of trifluoromethyl carbinols that are unknown or not previously well-characterized.[23]

(*S*)-2,2,2-Trifluoro-1-(9-anthryl)ethanol [(*S*)-1 or (*S*)-3a]. To a solution of (*R*)-BINAL-H[24] (10 mmol) in THF (total volume of 66 mL) at −20 °C was added a solution of **2a** (1.30 g, 4.73 mmol) in THF (15 mL). The temperature was maintained at −20 °C for 24 h using a Neslab CC-60IIA CryoCool immersion cooler. The reaction was quenched with MeOH (2 mL), warmed to room temperature, and diluted with Et_2O (250 mL). The reaction mixture was washed with 1 N HCl (50 mL) and cold (0 °C) 1 N NaOH (2 × 100 mL). The organic layer was dried, concentrated under reduced pressure, and chromatographed on silica gel (70 g, petroleum ether–ether, 4:1, crude product loaded with minimum amount of CH_2Cl_2) to give 1.16 g of (*S*)-1 (89% yield, 91% ee by HPLC). The spectral data were identical with those previously described by Pirkle.[2] Two recrystallizations of this material from high-boiling petroleum ether provided 0.67 g (51% yield) of (*S*)-1: mp 135–136 °C [lit.[25] mp 132–135 °C]; 99% ee by HPLC; $[\alpha]^{25}_D$ +31° (*c* 1.015, $CHCl_3$) [lit.[25] $[\alpha]^{25}_D$ +29° (*c* 6.3, $CHCl_3$)].

The NaOH washes obtained from the above workup were acidified with 1 N HCl and extracted with Et_2O (3 × 100 mL).

(15) Kazlauskas, R. J. *J. Am. Chem. Soc.* **1989**, *111*, 4953.
(16) Mitchell, R. H.; Lai, Y.-H.; Williams, R. V. *J. Org. Chem.* **1979**, *44*, 4733.
(17) Dale, J. A.; Dull, D. L.; Mosher, H. S. *J. Org. Chem.* **1969**, *34*, 2543.
(18) Creary, X. *J. Org. Chem.* **1987**, *52*, 5026.
(19) Mesityllithium was generated from mesityl bromide and *t*-BuLi; commercially purchased phenylmagnesium bromide was used to prepare **2f**.
(20) Compound **2a** is commercially available but is expensive [$62.60/5 g (Aldrich)]. An alternate route is through treatment of anthracene with trifluoroacetic anhydride at high pressure.[2]
(21) The initial product was the diethyl ketal adduct. Hydrolysis with silica gel/10% H_2SO_4/CH_2Cl_2 (Huet, F.; Lechevallier, A.; Pellet, M.; Conia, J. M. *Synthesis* **1978**, 63) gave **2h**.
(22) Herkes, F. E.; Burton, D. J. *J. Org. Chem.* **1967**, *32*, 1311.
(23) For **3c**, see: Pirkle, W. H.; Hoekstra, M. S. *J. Org. Chem.* **1974**, *39*, 3904. For **3f**, see: Feigl, D. M.; Mosher, H. S. *J. Org. Chem.* **1968**, *33*, 4242.
(24) We have been using a slightly modified procedure for preparing the BINAL-H reagent. See: Chong, J. M.; Mar, E. K. *Tetrahedron* **1989**, *45*, 7709.
(25) *Aldrich Catalog/Handbook of Fine Chemicals*; Aldrich Chemical Co.: Milwaukee, WI, 1990; p 1281.

Table I. Enantioselective Reduction of Aryl Trifluoromethyl Ketones with (*S*)-BINAL-H



2a-h (*R*)-3a-h

entry	Ar	equiv of (*S*)-BINAL-H[a]	temp (°C)	time (h)	yield[b] (%)	ee[c,d] (%)
1	a: 9-anthryl	2.6	-60	72	51	93
2		2.6	-20	22	90	98
3		2.6	0	14	100	92
4		2.6	25	1	93	84
5		2.1[e]	-20	24	89	91[f]
6		2.1	25	3	99	84
7		1.6	25	3	82	75
8		1.2	25	20	97	56
9	b: 2-methyl-1-naphthyl	2.5	-60	24	85	93
10		2.5	0	3	100	85
11	c: 1-naphthyl	2.4	-60	24	93	70
12		2.3	0	3	97	65
13	d: 2,4,6-trimethylphenyl	2.3	-60	24	69	97[g]
14		2.2	0	24	94	87[g]
15	e: 2-methylphenyl	2.2	-60	24	81	74[g]
16		2.2	0	22	91	62[g]
17	f: phenyl	2.2	-60	4	97	27
18		2.2	0	4	98	23
19	g: 4-methoxyphenyl	2.0	-60	3	99	6[h]
20		2.0	0	3	98	1[h]
21	h: 4-fluorophenyl	2.1	-60	3	87	9[h,i]
22		2.2	0	3	94	14[h,i]

[a] Unless otherwise stated, 1.0 mmol of (*S*)-BINAL-H was used in each case. [b] Isolated yields. In each case, the yield based on recovered starting material was >95%. [c] Determined by HPLC analysis on a Pirkle covalent leucine column.[12] [d] Unless otherwise stated, the alcohols are of *R* configuration on the basis of the sign of the optical rotation and on the basis of the order of elution (second) on a Pirkle covalent leucine column.[12] [e] 10 mmol of (*R*)-BINAL-H was used. [f] (*S*)-Alcohol was obtained. [g] *R* configuration was corroborated by ^{1}H NMR analysis of the derived (*S*)-*O*-methylmandelate ester.[14] See text. [h] Unknown configuration. [i] Determined by GC analysis of the derived (+)-MTPA ester.

After the organic layer was dried and concentrated under reduced pressure, 2.8 g of (*R*)-binaphthol was obtained (99% recovery). HPLC analysis (same operating conditions as for alcohols **3a-b**) showed the material to be essentially 100% ee.

(*R*)-2,2,2-Trifluoro-1-(2-methylnaphthyl)ethanol [(*R*)-3b]: mp 73-74 °C; IR ($CHCl_3$) 3581, 3220 (br), 3041, 3003, 2949, 1502, 1262, 1166, 1119, 1034 cm^{-1}; ^{1}H NMR (250 MHz) δ 8.60 (br s, 1 H), 7.70 (dd, 1 H, J = 7.6, 1.6 Hz), 7.64 (d, 1 H, J = 8.4 Hz), 7.44-7.31 (m, 2 H), 7.16 (d, 1 H, J = 8.4 Hz), 5.70 (br s, 1 H), 3.07 (br s, 1 H), 2.40 (br s, 3 H); ^{13}C NMR (63 MHz) δ 136.5 (br), 133.1 (br), 131.9, 130.0, 129.3 (br), 128.5 (2 C), 126.2, 125.5 (q, J = 284 Hz), 125.0 (2 C), 70.8 (br q, J = 33 Hz), 21.0; MS m/z (relative intensity) 240 (96, M$^+$), 222 (2.5), 171 (100), 143 (62), 128 (58); 93% ee by HPLC; $[\alpha]^{25}_D$ -36° (c 0.634, $CHCl_3$). Anal. Calcd for $C_{13}H_{11}F_3O$: C, 65.00; H, 4.62. Found: C, 65.00; H, 4.73.

(*R*)-2,2,2-Trifluoro-1-(2,4,6-trimethylphenyl)ethanol [(*R*)-3d]: IR (film) 3479 (br), 2959, 1611, 1269, 1166, 1128, 849, 697 cm^{-1}; ^{1}H (250 MHz) δ 6.85 (s, 2 H), 5.47 (br q, 1 H, J = 8.0 Hz), 2.72 (br s, 1 H), 2.40 (br s, 6 H), 2.25 (s, 3 H); ^{13}C (63 MHz) δ 138.6, 138.0, 130.5 (br), 126.8, 125.5 (q, J = 283 Hz), 70.4 (q, J = 32 Hz), 20.7 (2 C); MS m/z (relative intensity) 218 (60, M$^+$), 200 (12), 149 (100), 121 (24), 105 (18); 97% ee by HPLC; $[\alpha]^{25}_D$ -30° (c 0.544, $CHCl_3$). Anal. Calcd for $C_{11}H_{13}F_3O$: C, 60.55; H, 6.00. Found: C, 60.58; H, 6.01.

(*R*)-2,2,2-Trifluoro-1-(2-methylphenyl)ethanol [(*R*)-3e]: IR (film) 3399 (br), 3031, 2935, 1266, 1172, 1134, 759, 729 cm^{-1}; ^{1}H NMR (250 MHz) δ 7.52 (br d, 1 H, J = 6.7 Hz), 7.26-7.12 (m, 3 H), 5.20 (q, 1 H, J = 6.6 Hz), 3.37 (br s, 1 H), 2.29 (s, 3 H); ^{13}C NMR (63 MHz) δ 136.5, 132.6, 130.6, 129.2, 127.0, 126.3, 124.7 (q, J = 283 Hz), 68.8 (q, J = 32 Hz), 19.1; MS m/z (relative intensity) 190 (68, M$^+$), 172 (25), 121 (100); 74% ee by HPLC; $[\alpha]^{25}_D$ -26° (c 0.664, $CHCl_3$). Anal. Calcd for $C_9H_9F_3O$: C, 56.85; H, 4.77. Found: C, 56.81; H, 5.01.

2,2,2-Trifluoro-1-(4-methoxyphenyl)ethanol (3g): IR (film) 3433 (br), 2940, 2842, 1611, 1514, 1251, 1170, 1128, 820 cm^{-1}; ^{1}H NMR (200 MHz) δ 7.33 and 6.87 (AA'XX' system, 4 H, J_{AX} = 8.8 Hz), 4.86 (dq, 1 H, J = 6.8, 4.6 Hz), 3.75 (s, 3 H), 3.55 (d, 1 H, J = 4.6 Hz); ^{13}C NMR (63 MHz) δ 160.3, 128.8, 126.4, 124.4 (q, J = 282 Hz), 114.0, 72.4 (q, J = 32 Hz), 55.2; MS m/z (relative intensity) 206 (62, M$^+$), 170 (8.2), 137 (100), 109 (12), 94 (6.5). Anal. Calcd for $C_9H_9F_3O_2$: C, 52.43; H, 4.40. Found: C, 52.44; H, 4.58.

2,2,2-Trifluoro-1-(4-fluorophenyl)ethanol (3h): IR (film) 3408 (br), 1608, 1512, 1271, 1230, 1175, 1129, 822 cm^{-1}; ^{1}H NMR (250 MHz) δ 7.41 and 7.06 (AA'XX' system, 4 H, J_{AX} = 8.6 Hz), 4.94 (dq, 1 H, J = 6.6, 3.9 Hz), 3.54 (d, 1 H, J = 3.9 Hz); ^{13}C NMR (63 MHz) δ 163.4 (d, J = 248 Hz), 129.9, 129.3 (d, J = 8 Hz), 124.2 (q, J = 281 Hz), 115.6 (d, J = 22 Hz), 72.2 (q, J = 32 Hz); MS m/z (relative intensity) 194 (37, M$^+$), 158 (2.7), 125 (100), 97 (36); 14% ee by GC; $[\alpha]^{25}_D$ +1.4 (±0.9)° (c 0.193, $CHCl_3$). Anal. Calcd for $C_8H_6F_4O$: C, 49.50; H, 3.12. Found: C, 49.49; H, 3.15.

Preparation of (*S*)-*O*-Methylmandelate Esters for Determination of the Absolute Configurations of 3d and 3e. To a CH_2Cl_2 solution of the trifluoromethyl carbinol (1 equiv) was added HOBT (1 equiv), (*S*)-*O*-methylmandelic acid (1 equiv), DCC (1.4 equiv), and DMAP (1 equiv). After stirring for 1 h at room temperature, the reaction mixture was concentrated under reduced pressure and chromatographed on silica gel (petroleum ether-ether, 20:1), affording the (*S*)-*O*-methylmandelate ester.

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Annulation of Heterocycles via Intramolecular Nitrile Oxide-Heterocycle Cycloaddition Reaction[1]

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In recent years the INOC (intramolecular nitrile oxide-olefin cycloaddition) reaction has received a great deal

