The IR spectrum of the $CHCl_3$-soluble fraction showed complete absence of ester carbonyl.

Evaporation of the $CHCl_3$ solution and repeated treatment with Et_2O gave a soluble fraction which on reduction in volume and standing at room temperature gave colorless prisms of diketopiperazine 8; this plus additional material from the mother liquor and from later fractions (see below) amounted to 0.31 g (28% from **3c**). An analytical sample recrystallized from benzene had mp 139.5–141 °C (sublimes about 130 °C) and $[\alpha]^{23}_D$ −10° (*c* 0.5, $CHCl_3$).

Anal. Calcd for $C_9H_{16}N_2O_2$: C, 58.67; H, 8.75; N, 15.21. Found: C, 58.79; H, 8.68; N, 15.22.

The ether-insoluble material was further fractionated by extraction with cyclohexane and with water (from $CHCl_3$ solution). The cyclohexane fractions contained slightly impure compound **9** as an oil, characterized by IR and NMR spectra and by conversion to a *p*-bromophenyl carbamate, the latter being purified by preparative-layer chromatography on SiO_2 (EtOAc, two passes) for analysis (glass).

Anal. Calcd for $C_{16}H_{22}BrN_3O_2$: C, 52.18; H, 6.02; Br, 21.70; N, 11.41. Found: C, 52.27; H, 6.11; Br, 21.58; N, 11.30.

A sample of **7**·2HBr on neutralization with aqueous hydrazine cyclized to an oil that was spectrally (IR, NMR) identical with **9** obtained in the solvent fractionation.

The water-soluble fraction contained **5c** plus a small amount of **8** (by NMR); integration of the NMR spectrum gave the yield of **5c**. The bis(*p*-bromophenyl carbamate) of **5c** had: mp 122 °C, 136–152 °C (dimorphic) (EtOAc); $[\alpha]^{24}_D$ −14° (*c* 1, MeOH).

Anal. Calcd for $C_{23}H_{28}Br_2N_4O_4$: C, 47.27; H, 4.83; Br, 27.35; N, 9.59. Found: C, 47.28; H, 4.88; Br, 27.29; N, 9.49.

A small additional amount of **8** was recovered from the insoluble material remaining from the cyclohexane and water extractions.

Acknowledgments. This work was done under contracts N01-CM-33728 and -43761 from the Division of Cancer Treatment, National Cancer Institute, National Institutes of Health, DHEW. We thank Professor Richard Hiskey for comments on the manuscript.

Registry No.—**1**, 41927-14-4, **2**·HBr, 63714-68-1; **3a**, 63714-61-4; **3b**, 63714-62-5; **3c**, 60457-02-5; **4a**·HBr, 63714-63-6; **4b**·HBr, 63714-64-7; **5a**, 63714-65-8; **5a**·HBr, 63714-69-2; **5b**·HBr, 63714-66-9; **5c**, 63714-70-5; **5c** bis(*p*-bromophenyl carbamate), 63714-73-8; **6**·2HBr, 63743-86-2; **7**·2HBr, 63714-67-0; **8**, 60421-32-1; **9**, 63714-71-6; **9** *p*-bromophenyl carbamate, 63714-72-7; BH_3, 13283-31-3; THF, 109-99-9.

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Asymmetric Synthesis in Optically Active 2-Methyltetrahydrofuran

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Received September 14, 1976

Several examples have been reported for successful asymmetric syntheses effected through the use of chiral media.[1] In these cases, the enantiomeric enrichment ordinarily has not been large and this is particularly true for additions and reductions employing Grignard reagents (values range as high as 18% but are generally less than 5%). For these reactions, chiral dialkyl ethers and amines commonly have been used. It has been recognized that the asymmetric bias should increase the more intimate the involvement of the solvent in the reaction transition state. Thus, the omission of the use of chiral derivatives of tetrahydrofuran is notable in view of the known greater ability of Grignard reagents to associate more effectively with tetrahydrofuran than to noncyclic ethers.[2] We wish to report our examination of the use of optically active 2-methyltetrahydrofuran (2-MeTHF) as a chiral solvent for a number of reactions involving Grignard reagents.

Experimental Section

Analytical gas chromatography was obtained using an F and M Model 720 instrument with twin 5 ft columns (10% DEGS on Diatoport S). Preparative chromatography was performed on an Aerograph Autoprep Model 700 using a 20 ft × ⅜ in. column (20% DEGS on Chromosorb W). NMR spectra were recorded using a Varian Model A-60 spectrometer. Optical rotations were measured using a Rudolph Model 62 polarimeter with a sodium lamp source. Fractional distillation employed a 20 × 300 mm column having approximately 30 theoretical plates and packed with stainless steel Helipak.

Optically Active 2-Methyltetrahydrofuran (2-MeTHF). Following reported procedures, optically active 2-MeTHF was prepared from racemic tetrahydrofurfuryl alcohol. The alcohol was resolved via the phthalate half-ester using brucine.[3] The recovered optically active alcohol was converted to the tosyl ester and reduced to 2-MeTHF with lithium aluminum hydride.[4] All conversions were 88–95% and the physical properties of the intermediates corresponded to literature values. The initially prepared 2-MeTHF, as well as that later recovered from reactions, was collected in an ethyl ether extract which was concentrated and fractionally distilled (bp 78–80 °C). The lower and and higher boiling fractions yielded additional product by preparative GC. Repeated isolation of the optically active solvent in this manner caused no racemization and routinely provided enantiomer samples for the several experiments having specific rotations of $[\alpha]_D^{20}$ +27.01° and $[\alpha]_D^{20}$ −27.47° (neat).[5]

All reactions described below were first run in racemic solvent to develop procedures before using the optically active solvent. Since the 2-MeTHF forms peroxides readily, it was always distilled from lithium aluminum hydride and in a nitrogen atmosphere immediately prior to use. A nitrogen atmosphere was employed in all reactions.

After a reaction was completed, in each case the product was hydrolyzed by the careful addition of 10 mL of 5% sulfuric acid solution. The organic layer was isolated and washed with 5% sodium bisulfite and 5% sodium bicarbonate solutions. After it was dried with anhydrous magnesium sulfate, it was distilled to recover the reaction solvent and then the product was isolated by either vacuum distillation or preparative gas chromatography. The aqueous layer and all subsequent aqueous washings were extracted continuously for 24 h with ethyl ether to recover additional solvent as described above.

Formation of (+)-1-Phenylethanol. Phenylmagnesium bromide was prepared from 0.610 g (0.0251 mol) of magnesium with 3.93 g (0.025 mol) of bromobenzene in 17.1 g (20 mL) of (+)2-MeTHF ($[\alpha]_D^{20}$ +27.01°). To this solution maintained at −10 °C there was added in 30 min 1.50 g (0.034 mol) of freshly distilled acetaldehyde dissolved in 10 mL of pentane. After hydrolysis a 49% yield (preparative GC) of 1-phenylethanol was obtained: $[\alpha]_D^{20}$ +0.93° (neat, 1-1); optical purity 2.15%. The retention time was identical with that for authentic 1-phenylethanol. Downer and Kenyon[6] report a specific rotation $[\alpha]_D^{17}$ −43.3 (neat) for the pure levo enantiomer. Also, this optically active alcohol was obtained from racemic 1-phenylethanol by resolution according to the method of Downer and Kenyon.[6] When this sample was subjected to the same preparative GC conditions, no loss in activity was noted. Repetition of this experiment without the use of pentane where pure acetaldehyde was added directly to the Grignard reagent during 30 min provided 1-phenylethanol having 1.6% optical purity.

Formation of (+)-*tert*-Butylphenylcarbinol. a. In 2-MeTHF. Phenylmagnesium bromide was prepared from 0.489 g (0.0201 mol) of magnesium and 3.14 g (0.02 mol) of bromobenzene in 8.55 g (10 mL) of (+)2-MeTHF. A solution containing 2.58 g (0.03 mol) of freshly distilled pivaldehyde in 10 mL of pentane was added with stirring in 90 min with the reaction temperature maintained at −10 °C. The reaction mixture was hydrolyzed at once and yielded (by distillation) 1.8 g (57%) of the carbinol: bp 68–75 °C (1 mm); mp 53–54 °C; $[\alpha]_D^{20}$

+2.82° (c 10.87, benzene), optical purity 11% (lit.[7] mp 54–54.5 °C, $[\alpha]_D^{22}$ +25.9° (c 2.24, benzene)). The carbinol was both recrystallized from ether–pentane and sublimed under reduced pressure, but neither process resulted in a product of higher rotation. The structure of the product was confirmed by NMR spectra (four singlet signals). This preparation of *tert*-butylphenylcarbinol was repeated with levo 2-MeTHF ([α] −22.40, optical purity 81.5%) and using the same amounts of reactants indicated above. In this case, pure pivaldehyde was added to refluxing (85 °C) Grignard reagent mixture. A 78% yield of levo product distilled at 70–72 °C (1.4 mm). The specific rotation was $[\alpha]_D^{20}$ −1.52° (c 25, benzene). This corresponds to an optical purity of 5.87% and stereoselectivity of 7.2%.

b. In Ethyl Ether–2-MeTHF (1:1). Phenylmagnesium bromide was prepared from 0.510 g (0.021 mol) of magnesium and 3.14 g (0.02 mol) of bromobenzene in 3.75 g (0.05 mol) of ethyl ether. After the reaction was complete, 4.31 g (0.05 mol) of (+)2-MeTHF was added and the mixture was stirred for 30 min to equilibrate the solvated 2-MeTHF. Pivaldehyde (2.15 g, 0.025 mol) was added as in part a. After hydrolysis and isolation as above, 1.9 g (58%) of *tert*-butylphenylcarbinol was obtained. This product was racemic and provided an NMR spectrum identical with that of the authentic carbinol.

c. In Ethyl Ether–2-MeTHF with Excess 2-MeTHF (Solvent Exchange). Phenylmagnesium bromide was prepared as in part b except using 7 g (0.1 mol) of ethyl ether. When the Grignard reagent formation was complete, the solvent was removed at reflux with a stream of dry nitrogen. Finally the reagent was pumped at 1 mm to leave a viscous residue. After 7.0 g of 2-MeTHF was added, the mixture was stirred 30 min to attain solvent equilibration. Pivaldehyde (2.15 g, 0.025 mol) was added and the reaction and product isolation were completed as above. The *tert*-butylphenylcarbinol (2.1 g, 64%) was optically active: $[\alpha]_D^{19}$ +0.15°, optical purity 0.6%.

Asymmetric Reduction of Isobutyrophenone. Isobutylmagnesium chloride was prepared by the reaction of magnesium (0.0563 g, 0.024 mol) with isobutyl chloride (1.85 g, 0.02 mol) in 8.55 g (10 mL) of (+)2-MeTHF at reflux. The reaction was difficult to start and was assisted by the addition of a trace of bromobenzene. The isobutylmagnesium chloride solution was cooled to 20 °C and a solution of 2.52 g (0.017 mol) of isobutyrophenone in 10 mL of pentane was added during 2 h. The reaction mixture was hydrolyzed immediately and after the usual workup 2.20 g (86%) of 2-methyl-1-phenylpropanol was isolated by distillation: bp 57–62 °C (0.5 mm); $[\alpha]_D^{22}$ +1.59° (c 10.09, ether); optical purity 3.3%. Levene and Mikeska[8] report $[\alpha]_D^{20}$ +47.7° (c 6.997, ether) for a pure enantiomer. The reaction mixture was shown by GC to contain no unreacted ketone and the NMR spectra of the product was consistent with the indicated structure. The reaction was repeated with the temperature maintained at −10 °C during the addition of the isobutyrophenone. In this case the optical purity of the product was 2.1%.

Kinetic Resolution of 2-Bromo-1-phenylpropane. Magnesium (0.365 g, 0.015 mol) and 2-bromo-1-phenylpropane (5.97 g, 0.03 mol) were reacted in 5.4 g of (+)2-MeTHF and 5 mL of pentane. After the reaction started the reaction flask was cooled in an ice–water bath. During 2 h most of the magnesium dissolved. The reaction mixture was hydrolyzed and the unreacted 2-bromo-1-phenylpropane was isolated and purified by preparative GC and finally vacuum distilled: bp 47–50 °C (0.3 mm); $[\alpha]_D^{20}$ −0.5 °C (c 8.01, ethanol), optical purity 2.1% (lit.[9] $[\alpha]_D^{20}$ −22.96° (c 4.964, ethanol)).

Discussion and Results

Each type of reaction examined produced optically active products when active 2-MeTHF was used as solvent (2.1 to 11% optical purity). Each example was chosen so that steric factors would be as significant as possible in the developing diasteromeric reaction transition states leading to chiral products. Nevertheless, the extent of enantiomeric enrichment was not superior to that reported earlier with Grignard reagents in chiral ethers. For example, the reaction of phenylmagnesium bromide with pivaldehyde in (+)2-MeTHF provided *tert*-butylphenylcarbinol in 11% optical purity. For a comparison, the reaction of the same Grignard with 2-butanone (which has a carbonyl group with less difference in steric requirement for it's attached groups than that in pivaldehyde) in (+)-2,3-dimethoxybutane gave methylethylphenylcarbinol in about 18% optical purity.[10]

Optically active *tert*-butylphenylcarbinol was prepared by addition of pivaldehyde to phenylmagnesium bromide at −10 and 85 °C with the greater stereoselectivity at the lower temperature. At the concentration used with this Grignard reagent a viscous unstirrable mixture developed at −30 °C and precluded lower temperature experiments.

The attempts to achieve asymmetric synthesis from the Grignard reagent first prepared in ethyl ether and followed by an equal molar amount of (+)-2-methyltetrahydrofuran added before reaction with pivaldehyde or solvent exchange with (+)2-MeTHF effected before reaction with the aldehyde, resulted in lower enantiomeric enrichment in the carbinol product. This suggests that the 2-methyltetrahydrofuran may be less competitive in solvating the Grignard reagent than expected. A thermodynamic measure of the basicity of 2-methyltetrahydrofuran compared to tetrahydrofuran relative to an acid having steric requirements comparable to the magnesium atom site in the Grignard reagent would be desirable.

Other reactions in 2-MeTHF including Grignard reduction and kinetic resolution also gave products having observable but low enantiomeric enrichment.

Registry No.—(+)2-MeTHF, 63798-12-9; (−)2-MeTHF, 63798-13-0; acetaldehyde, 75-07-0; (+)-1-phenylethanol, 15157-69-7; phenyl bromide, 108-86-1; (+)-*tert*-butylphenylcarbinol, 23439-91-0; pivaldehyde, 630-19-3; (−)-*tert*-butylphenylcarbinol, 24867-90-1; (±)-*tert*-butylphenylcarbinol, 57377-60-3; isobutyl chloride, 513-36-0; isobutyophenone, 611-70-1; (+)-2-methyl-1-phenylpropanol, 14898-86-3; (±)-2-bromo-1-phenylpropane, 14367-52-3; (−)-2-bromo-1-phenylpropane, 63798-14-1.

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Cycloadditions of 2,5-Dimethyl-3,4-diphenylcyclopentadienone to Cyclooctene, Cyclooctadienes, and the 76 °C Melting Dimer of Cyclooctatetraene

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The cycloaddition reactions of the potent electron-deficient diene, 2,5-dimethyl-3,4-diphenycyclopentadienone (1) to a remarkable variety of alkenes have been reported. These adducts have been used in the synthesis of novel substances,[2] and the structures of the Diels–Alder adducts have given some insight into the origins of cycloaddition stereoselectivity.[3,4] We wish to report facile and remarkably stereoselective cycloadditions of 1 to cyclooctenes and cyclooctadienes and to show that attempted cycloadditions to cyclooctatetraene give mainly cycloadducts of 1 to a cyclooctatetraene dimer.

Heating the dimer of 1 with cyclooctene at 90 °C for 1 day gave a product which appeared, by NMR, to be a 96:4 mixture of 1:1 adducts. The bridged carbonyl at 5.69 μm established the Diels–Alder nature of the adduct. Recrystallization from methanol gave a pure adduct **3a**, mp 171–172 °C, which had a methyl singlet at 1.25 ppm in the NMR spectrum ($CDCl_3$).