with titanium, the availability of organoaluminum reagents, and the possible control of regioselectivity through a variety of available titanium compounds indicate that titanium–organoaluminum systems offer synthetic promise for the alkylation of γ and δ alkynols. Furthermore, the deuterium incorporation mentioned indicates the possibility of additional functional conversions of the reaction intermediates.

Experimental Section

Materials. All alkynols were purchased from Farchan Division, Story Chemical Corp., and were dried over 3-A Molecular Sieves. Methylene chloride was distilled from P_2O_5 under nitrogen. Liquid materials were transferred under N_2 or argon using syringe techniques. Cp_2TiCl_2 was purchased from Strem Chemicals, Inc., and used without further purification.

Alkylation Procedure. Reactions were carried out in glassware which had been dried at 110 °C, assembled while hot, and flushed with argon while cooling. In a typical reaction 50 mmol of 2 M $Al(C_2H_5)_2Cl$ solution in methylene chloride was transferred to a 250-mL three-necked round-bottom flask equipped with a gas inlet, magnetic stirrer, and 50-mL dropping funnel. Additional solvent was added to dilute the organoaluminum reagent to 0.75 M. The alkynol (20 mmol) was added to the dropping funnel with a syringe (weighed before and after) along with 25 mL of methylene chloride. The $Al(C_2H_5)_2Cl$ solution was cooled to 0 °C, and the alkynol was added dropwise to form the mixed ethylchloroalkynoxyaluminum system (solution I).

A second 250-mL flask equipped as described above was charged with the appropriate amount of Cp_2TiCl_2 followed by 50 mL of methylene chloride and cooled to the desired temperature. Solution I was transferred to the dropping funnel with a syringe and added dropwise. The reactions were terminated by addition of 8 mL of methanol followed by 50 mL of a 5% H_2SO_4 solution saturated with sodium chloride. The resulting mixture was stirred over an oxygen atmosphere for 1 h, filtered, and then extracted with 5 50-mL portions of diethyl ether. The ether extract was dried over $MgSO_4$ and filtered. The product solutions were then reduced in volume, filtered, and analyzed by GLC.

Gas Chromatographic Analyses. All yields were determined by GLC (Hewlett-Packard 5750) using an 8 ft × 1/8 in. XE-60 column and are corrected for response factors. Samples were isolated for spectral investigations by preparative GLC using 0.25 in. Carbowax 20M and SE-30 columns.

Spectra. NMR spectra were run on a Perkin-Elmer R-20 B spectrometer. IR spectra were taken with a Perkin-Elmer 457 spectrophotometer.

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Registry No.—Cp_2TiCl_2, 1271-19-8; $Al(C_2H_5)_2Cl$, 96-10-6.

References and Notes

(1) R. A. Coleman, C. M. O'Doherty, H. E. Tweedy, T. V. Harris, and D. W. Thompson, *J. Organomet. Chem.*, **129**, 69 (1977).
(2) H. E. Tweedy, R. A. Coleman, and D. W. Thompson, *J. Organomet. Chem.*, in press.
(3) J. C. W. Chien, Ed., "Coordination Polymerization", Academic Press, New York, N.Y., 1975.
(4) R. E. Ireland, "Organic Synthesis", Prentice-Hall, Englewood Cliffs, N.J., 1969, p 3.
(5) M. Schlösser, *Angew. Chem., Inter. Ed., Engl.*, **13**, 701 (1974).

Selective Reduction of Some *N*-Formyl Dipeptide Esters with Borane–Tetrahydrofuran

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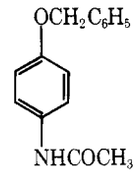
In recent years there have been reported a number of examples of selective reduction of carbonyl groups in polyfunctional molecules by borane–tetrahydrofuran (BH_3·THF).[1-4] We describe here some results that we obtained while investigating the reduction products of peptide derivatives as compounds of possible biological interest.

The *N*-formyl dipeptide esters **3a–c**, prepared by the EEDQ coupling method,[5] were reduced for 1.5 h at reflux temperature in tetrahydrofuran with limited amounts of borane. To avoid the drastic workup conditions (refluxing methanolic HCl) recommended by Kornet et al.[1] for borane reductions of acylamino esters, we tried HBr in acetic acid for this purpose. When reduction of the amide **1** was followed by addition of HBr–HOAc to the reaction mixture, a 90% yield of analytically pure *N*-ethyl-4-benzyloxyaniline (**2**·HBr) was



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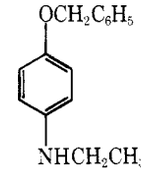

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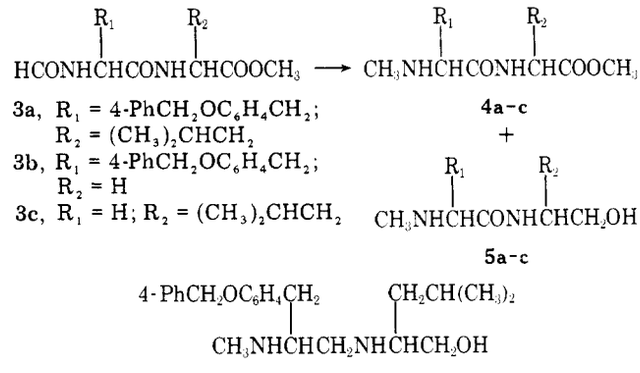
obtained directly. We therefore adopted this procedure for all of our reductions and have found it useful whenever a mild or nonaqueous workup is desirable.[6]

Reduction of *N*-formyl-*O*-benzyl-L-tyrosyl-L-leucine methyl ester (**3a**) with different amounts of BH_3·THF gave as principal isolated products (by crystallization) the *N*-methyl dipeptide ester **4a** and the (*N*-methylaminoacyl)amino alcohol **5a**; these and subsequent *N*-methylated products were easily recognized by the NMR singlet at δ 2.5–3.1. The results (Table I) show that the *N*-formyl group in **3a** is reduced more easily than the peptide or ester functions (runs 1 and 2). An increase in the hydride ion–substrate ratio leads to larger amounts of direduction product **5a** at the expense of mono-



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reduction product **4a** (run 3); however, with further increases in hydride, separation of products by crystallization becomes more difficult, and interpretation of the results is correspondingly less certain. Possibly under these conditions some

Table I. BH_3 Reduction of Formyl Dipeptide Ester 3a

Run	Mequiv of hydride ion mmol of substrate	Products,[a] % yield 4a·HBr[b]	5a·HBr[c,d]	6·2HBr[e]
1	4	40	6	
2	5	53	9	
3	6	20	27	
4	7	1	15	9
5	11			34

[a] Satisfactory analytical data (±0.3% for C, H, N, Br) were reported for all new compounds listed in the table. [b] Mp 166–176 °C (MeOH–Et_2O); $[\alpha]^{26}_D$ −30° (*c* 1, DMF). [c] Mp 218–222 °C (MeOH–Et_2O); $[\alpha]^{26}_D$ −27° (*c* 1, DMF). [d] Microanalysis obtained on free base: mp 128–129 °C (EtOAc); $[\alpha]^{23}_D$ −60° (*c* 0.8, $CHCl_3$). [e] Mp 166–170 °C (MeOH–Et_2O); $[\alpha]_D$ +29° (*c* 0.5, $CHCl_3$).

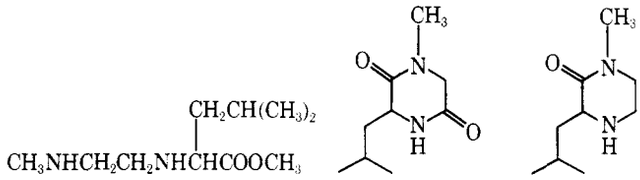
Table II. BH_3 Reduction[a] of Formyl Dipeptide Esters 3a–c

Run	Substrate[b]	Products[b] (% yield)
1[c]	**3a**[d]	**4a**·HBr (53), **5a**·HBr (9)
2	**3b**[e]	**4b**·HBr[f] (52), **5b**·HBr[g] (1)
3	**3c**[h]	**4c**[i] (28, 38),[j] **5c**[k] (28, 40),[j] **7**·2HBr[l] (19, 16)[j,m]

[a] 5 mequiv of hydride per mmol of dipeptide. [b] Satisfactory analytical data (±0.2% for C, H, N, Br) were reported for all new compounds listed in the table except as noted. [c] Data from Table I, run 2. [d] Mp 110–112 °C (C_6H_6–Et_2O); $[\alpha]^{26}_D$ +13° (*c* 1, C_6H_6). [e] Mp 120–120.5 °C (EtOAc); $[\alpha]^{26}_D$ +11° (*c* 1, $CHCl_3$). [f] See Experimental Section. [g] Mp 152–157 °C ($CHCl_3$–Et_2O); $[\alpha]^{23}_D$ −3° (*c* 0.5, DMF). [h] Mp 78.5–80.5 °C (EtOAc); $[\alpha]^{23}_D$ +8° (*c* 1, $CHCl_3$). [i] Estimated and microanalyzed as neutralization product **8**; see text and Experimental Section. [j] Second figure estimated from NMR spectrum of crude neutralization product (see Experimental Section). [k] Microanalysis on bis(*p*-bromophenyl carbamate). [l] Mp 148–153 °C (MeOH–Et_2O); $[\alpha]^{23}_D$ +16° (*c* 0.6, MeOH). [m] Includes product isolated as **7**·2HBr and that estimated as **9** (see text and Experimental Section).

racemization occurred, complicating the isolation of products. At the highest hydride–substrate ratios, fully reduced diamino alcohol **6** could be isolated (runs 4 and 5).

Since the use of 5 mequiv of hydride per mol of peptide gave the highest yield of monoreduction product **4a**, the same ratio was used to reduce peptide esters **3b** and **3c** (Table II). As only a small amount of a single crystalline product (identified as diamino ester **7**·2HBr) was obtained on reduction and workup of **3c**, the products and yields were determined indirectly. Neutralization of the noncrystalline portion of the reaction product from run 3 gave *N*-sarcosylleucinol (**5c**), diketopiperazine **8**, and ketopiperazine **9**. That **8** and **9** arose by cyclization of reduction products **4c** and **7**, respectively, was indicated by disappearance of the strong methyl ester IR (1740 cm^{-1}) and NMR (δ 3.77) peaks upon neutralization. Moreover, the roughly 2:3 ratio of ester to *N*-methyl peaks in the NMR spectrum before neutralization accounted for all of the reduction product subsequently estimated as **8** and **9**; thus **9** probably was not formed by reduction of **8**. Yields for run 3 (Table II) were also estimated from the NMR spectrum of the crude neutralization product and showed the same trend as the isolated yields.



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When *N*-methyl dipeptide ester **4a** was subjected to the standard reduction conditions and workup, 69% of unchanged starting material was recovered as well as about 1% of **5a**. Chromatography of the mother liquor gave, in addition to small amounts of unidentified materials, a substance whose IR spectrum showed only ester carbonyl absorption and which was probably *N*-(2-methylamino-3-(4-benzyloxyphenyl)-propyl)leucine methyl ester dihydrobromide (8%). As in the previous examples, the amount of material unaccounted for does not permit conclusions on the extent of racemization. However, exposure of **4a** to BH_3·THF at room temperature for 1.5 h followed by HBr–HOAc workup gave a 95% recovery of crystalline **4a** of unchanged optical rotation; thus little if any racemization is due to the workup procedure.

Discussion

Tyrosylglycine derivative **3b** (run 2, Table II) showed the same preference for reduction at the formyl group as did the tyrosylleucine derivative **3a**. However, reduction of the glycylleucine derivative **3c** was much less selective; substantial reduction of ester and peptide carbonyl groups occurred. A similar loss of selectivity was noted by Roeske et al. in a report[4] that appeared during the preparation of this manuscript. These workers found that reduction of Boc-Gly-Leu-OMe and Cbz-Gly-Leu-OMe with BH_3·THF at −20 °C gave 26–30% of the peptide bond reduction products and 40–42% recovered starting materials, while reduction of Cbz-Leu-Leu-OMe gave 7% of the peptide bond reduction product and 79% recovered starting material. Although no comment was made on the difference in reducibility a strong steric influence is consistent with our results and with those of Brown and Heim.[7]

We conclude that BH_3·THF reduction of formamide groups in structures containing both ester and secondary amide functions can be selective and preparatively useful. However, with peptide substrates, racemization may be extensive enough to preclude the use of this reaction to modify the structures of larger peptides and proteins.[8–10]

Experimental Section

Borane in tetrahydrofuran (1 M) was obtained from Ventron Corp. Melting points (Kofler hot stage) are uncorrected. Satisfactory IR and NMR spectra were obtained for all compounds. Microanalyses were performed by Galbraith Laboratories. Optical rotations were determined on a Perkin-Elmer Model 141 polarimeter.

Borane Reductions. General Procedure. The procedure for reduction of *N*-formyl-*O*-benzyl-L-tyrosylglycine methyl ester (**3b**) is typical. To 10.0 mL (30 mequiv) of 1 M BH_3·THF, stirred magnetically at 0 °C under N_2, was added over 5–10 min a solution–suspension of 22.2 g (6.00 mmol) of **3b** in 20 mL of dry THF. The clear solution was then heated at reflux for 1.5 h and allowed to cool. Saturated HBr in HOAc (6 mL, 30 mequiv) was added, dropwise at first (H_2!), and stirring was continued for about 1.5 h. The resulting solution was partially concentrated in vacuo and reconcentrated with toluene to remove some of the acetic acid. The colorless residue was treated with THF–$CHCl_3$ to provide a crystalline white solid (1.66 g); an additional 0.15 g was obtained on evaporation of the mother liquor and treatment with $CHCl_3$–Et_2O. Total crude **4b**·HBr: 1.83 g (70%); $[\alpha]^{28}_D$ +4° (*c* 1, DMF). Recrystallization of **4b**·HBr from MeOH–Et_2O gave three crops totaling 1.36 g (52%); all three crops had identical spectra and optical rotations: $[\alpha]^{27}_D$ +46° (*c* 1, MeOH); mp 195–198 °C.

In the case of **3a** and **3c**, the residue from concentration of the reaction mixture was diluted with a large volume of ether and the resulting semisolid was triturated with several portions of ether before attempting recrystallization from MeOH–Et_2O.

Reduction of 4-Benzyloxyacetanilide (1). A 2.41-g sample (10.0 mmol) of **1** was reduced as above using 30 mequiv of BH_3. After addition of HBr–HOAc (7 mL) and stirring for 30 min, addition of seed crystals (obtained by diluting a drop of the reaction mixture with ether) induced crystallization. The slurry was stirred for 1 h, then filtered quickly and washed immediately with THF and with ether to give 2.12 g of **2**·HBr (69%): mp 142–144 °C with resolidification; remelts 160–162 °C.

Anal. Calcd for $C_{15}H_{17}NO$·HBr: C, 58.45; H, 5.88; Br, 25.92; N, 4.54. Found: C, 58.31; H, 5.83; Br, 25.94; N, 4.49.

A second crop, 0.45 g (15%), obtained by dilution of the filtrate with ether, had mp 142–144 °C and remelts 159–161 °C.

Anal. Found: C, 58.28; H, 5.92; Br, 26.08; N, 4.46.

A third crop (0.18g, 6%) had mp 142–144 °C and remelts 161.5–162.5 °C. Total yield, 2.75 g (90%).

Estimation of Products from Reduction of 3c. The ether-triturated product from reduction of 6.00 mmol of **3c** failed to crystallize from MeOH–Et_2O. Crystallization from $CHCl_3$–Et_2O gave white crystals of **7**·2HBr; physical data appear in footnotes to Table II.

The filtrate of **7**·2HBr failed to yield other crystalline products. After evaporation the residue in 3 mL of MeOH was treated with 11 mmol of 85% aqueous hydrazine for 23 h at 40 °C. Evaporation and treatment with 2-PrOH gave a crystalline precipitate of hydrazine hydrobromide. Filtration, evaporation of the filtrate, and extraction of the residue with $CHCl_3$ left a small additional amount of the salt.

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.

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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.

References and Notes

(1) M. J. Kornet, P. A. Thio, and S. I. Tan, *J. Org. Chem.*, **33**, 3637 (1968).
(2) N. M. Yoon, C. S. Pak, H. C. Brown, S. Krishnamurthy, and T. P. Stocky, *J. Org. Chem.*, **38**, 2786 (1973).
(3) P. L. Russ and E. A. Caress, *J. Org. Chem.*, **41**, 149 (1976).
(4) R. W. Roeske, F. L. Weitl, K. U. Prasad, and R. M. Thompson, *J. Org. Chem.*, **41**, 1260 (1976).
(5) B. Belleau and G. Malek, *J. Am. Chem. Soc.*, **90**, 1651 (1968).
(6) When the reduction product contains a B–O bond, as in reduction of an ester, treatment with methanol (e.g., recrystallization from a methanolic solvent) may also be required. For another example of the method published recently by one of us (P.L.R.), see ref 3.
(7) H. C. Brown and P. Heim, *J. Org. Chem.*, **38**, 912 (1973).
(8) J. R. McDermott and N. L. Benoiton, *Can. J. Chem.*, **51**, 2555 (1973).
(9) For protein modification via reductive alkylation, see M. Friedman, L. D. Williams, and M. S. Masri, *Int. J. Pept. Protein Res.*, **6**, 183, (1974).
(10) A procedure for the reduction of protein carboxyl groups with BH_3·THF has been developed: M. Z. Atassi and A. F. Rosenthal, *Biochem. J.*, **111**, 593 (1969).

Asymmetric Synthesis in Optically Active 2-Methyltetrahydrofuran

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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; $[\alpha]_D^{20}$