for 1 h. Progress of the reaction was monitored by TLC using hexane–ethyl acetate (1:1) as mobile phase. A solution of the reaction mixture in ether (40 mL) was washed successively with water (2 × 10 mL), saturated sodium bicarbonate (2 × 20 mL), 2 N sodium hydroxide (2 × 20 mL), and water (2 × 20 mL). Evaporation (reduced pressure) of the ether afforded benzyl bromide **4b** as a thermally unstable viscous oil, homogeneous by TLC, (0.8 g, 65%) [attempted purification by high vacuum distillation (160 °C; 10^{-4} mmHg) failed due to thermal decomposition]: IR (neat) ν_{max} 2956, 2931, 1512, 1291, 1272, 1256, 1140, 989, 848, 783 cm^{-1}; ^1H NMR 0.16 (s, 6 H, 2 × CH_3), 1.00 (s, 9 H, 3 × CH_3), 3.80 (s, 3 H, OCH_3), 4.44 (s, 2 H, CH_2), 6.7–7.0 (3 H, Ar H) ppm; EI mass spectrum, *m/e* 332, 330 (M^+), 315, 313, 275, 273, 251, 229, 214, 179, 149, 73 (base).

5-[(*tert*-Butyldimethylsilyl)oxy]-(±)-combretastatin (1b). Lithium sand (96.6 mg) in anhydrous tetrahydrofuran (10 mL) was treated under argon with ultrasound (bath, 150 W).[8] A mixture of benzyl bromide **4b** (0.76 g, 2.3 mmol) and 3,4,5-trimethoxybenzaldehyde (0.29 g, 1.5 mmol in 20 mL of tetrahydrofuran) was added (dropwise) followed by a small piece of sodium. Treatment of the reaction mixture with ultrasound was continued for 3 h. Progress of the reaction was monitored by TLC (1:1 hexane–ethyl acetate) by following disappearance of the benzyl bromide. The aldehyde and product showed the same R_f value. Excess lithium was removed by filtration (Celite), and the filtrate solvent was evaporated under reduced pressure. The residue was chromatographed on a column of silica gel (75 g) with a gradient of hexane–ethyl acetate (9:1 → 7:3) to give protected (±)-combretastatin **5** (0.40 g, 60%) as a very viscous oil: IR (neat) ν_{max} 3500, 2954, 2934, 1593, 1511, 1463, 1422, 1272, 1230, 1128, 840 cm^{-1}; ^1H NMR 0.14 (s, 6 H, 2 × CH_3), 1.00 (s, 9 H, 3 × CH_3), 2.90 (distorted d, 2 H, J = 6 Hz, CH_2), 3.78 (s, 3 H, OCH_3), 3.84 (s, 9 H, 3 × OCH_3), 4.85 (t, 1 H, J = 7.0 Hz, C*H*OH), 6.58 (s, 2 H, Ar H), 6.66–6.86 (3 H, Ar H).

Anal. Calcd for $C_{24}H_{36}O_6Si$: C, 64.25; H, 8.09. Found: C, 64.55; H, 8.25.

Racemic Combretastatin (1a). To a solution of silyl ether **1b** (0.23 g) in dry tetrahydrofuran (5 mL, stirred under argon) was added (dropwise) a 1 M tetrahydrofuran solution of tetrabutylammonium fluoride (2 mL, 2 mmol). After addition, a yellow color appeared immediately and reaction was complete within 10 min (indicated by TLC using 35:65 hexane–ethyl acetate). The reaction mixture was extracted with ether (25 mL) and the ethereal solution washed with water (2 × 10 mL). Evaporation of the ether yielded pure (±)-combretastatin (0.16 g, 93%) as an amorphous solid: mp 103–105 °C; IR (thin film) ν_{max} 3450, 2937, 1592, 1510, 1462, 1457, 1419, 1274, 1234, 1125, 650 cm^{-1}; ^1H NMR 2.85 (distorted AB system, 2 H CH_2), 3.78 (s, 12 H, 4 × OCH_3), 4.66 (dd, 1 H, J = 9, 5 Hz, -C*H*OH), 6.45 (s, 2 H), 6.52–6.75 (3 H, Ar H).

Anal. Calcd for $C_{18}H_{22}O_6$: C, 64.66; H, 6.63. Found: C, 64.67; H, 6.65.

Natural (−)-Combretastatin (1a). A semipreparative HPLC column was prepared by using the chiral adsorbent, Pirkle prep-10-DNBPG (D) [*N*-(3,5-dinitrobenzoyl)-D-phenylglycine bonded to silica, 10μm, irregular, supplied by Regis Chemical Co.], and slurry-packed (acetone–chloroform, 1:1) under high pressure (3000–6000 psi) in a stainless steel column (10 mm × 50 cm). The protected racemic combretastatin (**1b**) was found to have almost base-line resolution on a similar analytical column (4.6 mm × 25 cm, 5μm, supplied by Regis). Therefore, **1b** (700 mg) was dissolved in hexane–isopropyl alcohol (9:1, 5 mL) and applied to the semipreparative column in 0.5-mL aliquots. The resolution was performed by using hexane–isopropyl alcohol (9:1) as mobile phase at a flow rate of 2.5 mL per min. All the fractions were subjected to analytical HPLC and the enantiomerically pure early fractions from all ten aliquots were combined to yield the pure (−) enantiomer (83.1 mg, 24%): $[\alpha]^{25}_D$ −33.33°. The pure enantiomer was deprotected as with the racemic material to afford natural combretastatin (**1a**) displaying $[\alpha]^{25}_D$ −7.8 (*c* 0.51, $CHCl_3$), identical with the natural product $[\alpha]^{25}_D$ −8.5 (*c* 1.41, $CHCl_3$).[1b]

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Registry No. (−)-**1a**, 82855-09-2; (±)-**1a**, 89064-44-8; (±)-**1b**, 97315-17-8; (−)-**1b**, 97315-21-4; **3a**, 621-59-0; **3b**, 97315-18-9; **4a**, 97315-19-0; **4b**, 97315-20-3; 3,4,5-trimethoxybenzaldehyde, 86-81-7.

Palladium-Catalyzed Reaction of Organoalanes and Organozincs with α,β-Unsaturated Acetals and Ortho Esters as Conjugate Addition Equivalents[1]

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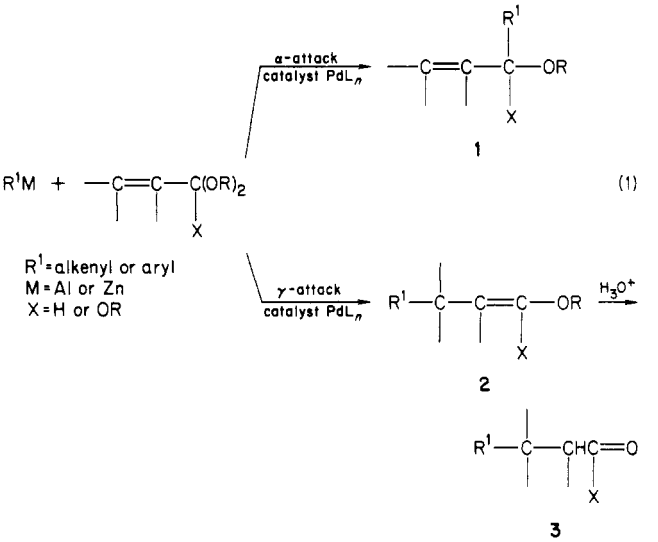
We have recently developed a Pd-catalyzed allylation of organoalanes and organozincs that proceeds with retention of regio- and stereochemistry of the allylic group.[3] Of particular interest is the fact that a wide variety of allylic electrophiles, such as those containing halogens, OAc, $OAlR_2$, $OPO(OR)_2$, and even $OSiR_3$, participate in the reaction.[3b] This finding prompted us to investigate the Pd-catalyzed reaction of organoalanes and organozincs with α,β-unsaturated acetals and ortho esters. In principle, the reaction may involve allylation in the α- and/or γ-position (eq 1). Since the products of γ-attack can be



hydrolyzed to give **3**, the overall transformation via γ-attack is equivalent to conjugate addition to α,β-unsaturated aldehydes or esters. Since conjugate addition of organometals to α,β-unsaturated aldehydes and esters, especially those that are β-unsubstituted, is prone to competitive polymerization of the α,β-unsaturated carbonyl derivatives

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Table I. Palladium-Catalyzed Reaction of Organometals with Allylic Acetals and Ortho Esters

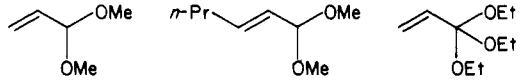
organometal	allylic reagent	product	yield, % isolated	yield, % GLC
(*E*)-*n*-pent(Me)C=CHAlMe$_2$[a]	4	(4*E*)-*n*-pent(Me)C=CHCH$_2$CH=CHOMe[a,b]	69	92
(*E*)-*n*-pentCH=CHAl(Bu-*i*)$_2$[a]	4	(4*E*)-*n*-pentCH=CHCH$_2$CH=CHOMe[a,b]	54	62
PhZnCl	4	PhCH$_2$CH=CHOMe[b]	70	73
PhZnCl	5	Ph(*n*-Pr)CHCH=CHOMe[b]	44	50
(*E*)-*n*-pent(Me)C=CHAlMe$_2$[a]	6	(4*E*)-*n*-pent(Me)C=CH(CH$_2$)$_2$COOEt[a]		35[c]
(*E*)-*n*-pent(Me)C=CHAlMe$_2$[a]	6	(4*E*)-*n*-pent(Me)C=CH(CH$_2$)$_2$COOEt[a]	50[d]	60[d]
PhZnCl	6	Ph(CH$_2$)$_2$COOEt		55[c]
PhZnCl	6	Ph(CH$_2$)$_2$COOEt	74[e]	77[e]

[a] ≥98% *E*. Pent = pentyl. [b] The vinyl ethes are ca 2:1 mixtures of the *E* and *Z* isomers. [c] The reaction was run in THF for 24 h at room temperature. [d] Zinc chloride (1 equiv) and HMPA (1.5 equiv) were added. [e] HMPA (1.5 equiv) was added.

and 1,2-addition,[4] successful preparation of **3** via **2** would provide an attractive alternative.

Uncatalyzed reactions of the Grignard reagents with α,β-unsaturated aldehydes and ortho esters have been reported to give mixtures of **1** and **2**. This reaction can be catalyzed by $TiCl_4$ to give regioselectively **1**,[5] while the Cu-catalyzed reaction of the Grignard reagents gives **2**.[6] With Ni complexes as catalysts, the reaction can lead to double carbon–carbon bond formation.[7]

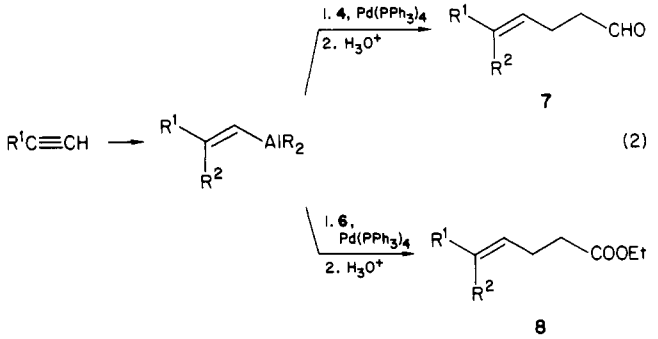
We have found that the reaction of alkenylalanes and phenylzinc chloride with acrolein dimethyl acetal (**4**) in THF in the presence of 5 mol % of $Pd(PPh_3)_4$ proceeds exclusively via γ-attack to give **2** (X = H) in good yields.



4 **5** **6**

Although the reaction of phenylzinc chloride with **5** proceeds similarly, the product yield is only modest. The corresponding reaction of phenylzinc chloride with ethyl orthoacrylate (**6**) is sluggish. However, addition of HMPA (1.5 equiv) accelerates the rate of reaction and significantly increases the product yield. In the reaction of alkenylalanes with **6**, $ZnCl_2$[8] (1 equiv) as well as HMPA (1.5 equiv) must be added for satisfactory results.

The experimental results are summarized in Table I, and the following observations and comments are worth noting. First, the observed regiochemistry, i.e., exclusive γ-attack, is in sharp contrast with that observed earlier with allyl derivatives having one heteroatom substituent.[3] However, it resembles that observed in the Cu-promoted allylation of the Grignard reagents.[6] No products corresponding to α-attack and disubstitution were detected by either GLC or ^{1}H NMR in the reactions of **4** and **5**. Although no product of α-attack was detected in the reactions of **6** either, minor amounts ($^1/_4$–$^1/_3$ of the major products in GLC peak area) of unidentified byproducts, the GLC retention time of which corresponded to the products of disubstitution, were present. It is possible that these byproducts have arisen via α-attack. Second, the reactions herein described proceed with ≥98% retention of the alkenyl group of an alkenylalane. Third, in the reaction of acetals **4** and **5**, the alkenyl ethers are formed as ca. 2:1 mixtures of *E* and *Z* isomers. Alkenyl ethers are known to be readily convertible to aldehydes **3** (X = H) in high yields by acid hydrolysis,[6] as indicated by conversion of (4*E*)-5-methyl-1-methoxy-1,4-decadiene into (4*E*)-5-methyl-4-decenal in 85% yield. Fourth, in the allylation reaction with **6**, the presumed initial products, i.e., ketene acetals, are not isolated but directly converted into β-substituted propionic esters by treatment with 3 N HCl. Fifth, since stereodefined alkenylalanes are readily obtainable via hydroalumination[9] or carboalumination[9,10] of alkynes, an efficient and selective synthesis of compounds represented by **7** and **8** from alkynes is now feasible (eq 2).



Experimental Section

All organometallic reactions were carried out under an atmosphere of nitrogen. Tetrakis(triphenylphosphine)palladium was prepared according to a literature procedure.[11] Ethyl orthoacrylate was prepared from commercially available ethyl orthopropionate by sequential bromination and dehydrobromination following a known procedure.[12] Purification of THF and HMPA was carried out by distillation from Na and benzophenone and from calcium hydride, respectively. Zinc chloride was dried by heating for 2–3 h at 90–110 °C (0.05 mm). All other reagents were purchased from commercial sources and used without purification.

(4*E*)-5-Methyl-1-methoxy-1,4-decadiene. To a solution of dichlorobis(η^5-cyclopentadienyl)zirconium (0.29 g, 1 mmol) in 10 mL of 1,2-dichloroethane were added sequentially 1-heptyne (0.38 g, 5 mmol) and trimethylalane (0.68 g, 0.95 mL, 10 mmol) at 0 °C.[13] The mixture was stirred at room temperature for 9 h and then slowly added to a mixture of acrolein dimethyl acetal (0.76 g, 7.5 mmol) and tetrakis(triphenylphosphine)palladium (0.28 g, 0.25 mmol) in 10 mL of THF at 0 °C. The reaction mixture was stirred overnight at room temperature and then slowly added to an ice-cold aqueous NH_4Cl solution. At 0 °C, 3 N HCl was then added until the solid aluminum residue dissolved. The layers were separated, and the aqueous layer was extracted with ether. The combined organic layers were washed successively with aqueous $NaHCO_3$ and brine, dried over $MgSO_4$, and concentrated. The

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residue was passed through a Florisil (60–200 mesh) column using 20% ether–hexane as eluent to remove Pd-containing compounds, if any. The product obtained after evaporation of the solvents was purified by chromatography on a silica gel column (60–200 mesh) using 2% ether–hexane as eluent. Concentration under reduced pressure afforded 0.63 g (3.45 mmol, 69% yield) of the title compound: IR (neat) 2230 (s), 1651 (m), 1207 (m) cm^{-1}; ^1H NMR ($CDCl_3$, Me_4Si) δ 0.8–1.0 (distorted t, 3 H), 1.1–1.5 (m, 6 H), 1.6 (s, 3 H), 1.8–2.1 (m, 2 H), 2.5–2.9 (m, 2 H), 3.50 (s, 3 H), 3.58 (s, 3 H), 4.2–4.5 (m, 1 H), 4.55–4.85 (m, 1 H), 5.0–5.25 (t, J = 7 Hz, 1 H), 5.85 (d, J = 6 Hz, 1 H, for the 1*Z*,4*E* isomer), 6.32 (d, J = 12.5 Hz, 1 H, for the 1*E*,4*E* isomer); MS (CI), m/e 182 ($M^{+\cdot}$). Anal. Calcd for $C_{12}H_{22}O$: C, 79.05; H, 12.17. Found: C, 78.78; H, 12.34. The ratio of the *E* and *Z* isomers calculated by the ratio of the areas of the doublets at 6.32 and 5.85 ppm was 67:33. The GLC yield of this compound estimated against *n*-hexadecane as an internal standard was 92%.

(*E*)-5-Methyl-4-decenal. This compound was prepared in 85% yield by treating (4*E*)-5-methyl-1-methoxy-1,4-decadiene with dilute HCl in acetone–H_2O (4:1) for 4 h at refluxing temperature: IR (neat) 2718 (m), 1725 (s) cm^{-1}; ^1H NMR ($CDCl_3$, Me_4Si) δ 0.90 (t, 3 H), 1.1–1.5 (m, 6 H), 1.60 (s, 3 H), 1.7–2.1 (m, 2 H), 2.1–2.5 (m, 4 H), 5.0–5.3 (m, 1 H), 9.72 (s, 1 H); ^{13}C NMR ($CDCl_3$, Me_4Si) δ 13.00, 14.91, 19.89, 21.55, 26.59, 30.51, 38.63, 43.02, 120.82, 136.29, 201.54.

1-Methoxy-3-phenylpropene. To 1.67 mL (5 mmol) of phenylmagnesium bromide (3 M in diethyl ether) was added a solution of zinc chloride (0.68 g, 5 mmol) in 10 mL of THF at 0 °C. The mixture was stirred at room temperature for 0.5 h and then added to a mixture of acrolein dimethyl acetal (0.51 g, 0.6 mL, 5 mmol) and $Pd(PPh_3)_4$ (0.28 g, 0.25 mmol) in 10 mL of THF. The reaction mixture was worked up in a manner similar to that described above and purified by chromatography on a silica gel column (60–200 mesh) using 0.5% ether–hexane as the eluent. Concentration provided 0.52 g (3.5 mmol, 70% yield) of the title compound: IR (neat) 1651 (s), 1598 (w), 1210 (s) cm^{-1}; ^1H NMR ($CDCl_3$, Me_4Si) δ 3.2 (d, J = 9 Hz, 2 H), 3.42 (s, 3 H), 3.52 (s, 3 H), 4.4–4.6 (m, 1 H), 4.7–5.0 (m, 1 H), 5.8–5.9 (d, J = 6 Hz, 1 H, for the *Z* isomer), 6.35 (d, J = 12.5 Hz, 1 H, for the *Z* isomer), 7.0–7.3 (br s, 5 H); MS (CI), m/e 148 ($M^{+\cdot}$). The ratio of the *E* and *Z* isomers determined by the areas of the doublets for the corresponding 1-alkenyl protons was 71:29. The major resonances observed in the ^{13}C NMR ($CDCl_3$, Me_4Si) were at δ 34.07, 55.76, 101.91, 125.72, 125.97, 128.32 (2), and 148.18. Minor resonances were observed at δ 30.21, 59.43; 105.58, 141.71, and 146.67.

1-Methoxy-3-phenyl-1-hexene. This compound was prepared in 44% isolated yield by the reaction of phenylzinc chloride with the dimethyl acetal of (*E*)-2-hexenal in the presence of 5 mol % of $Pd(PPh_3)_4$ in a manner analogous to that described for the preparation of 1-methoxy-3-phenylpropene: IR (neat) 1648 (s), 1601 (w), 1204 (s) cm^{-1}; ^1H NMR ($CDCl_3$, Me_4Si) δ 0.75–1.1 (distorted t, 3 H), 1.0–1.85 (m, 4 H), 3.0–3.3 (m, 1 H), 3.42 (s, 3 H), 3.49 (s, 3 H), 4.4–4.6 (m, 1 H), 4.75–5.0 (m, 1 H), 5.88 (d, J = 6 Hz, 1 H, for the *Z* isomer), 6.32 (d, J = 12.5 Hz, 1 H, for the *E* isomer), 7.1–7.4 (m, 5 H); MS (CI), m/e 190 ($M^{+\cdot}$). Ratio of the *E* and *Z* isomers determined by the ratio of the areas of the doublets at 6.32 and 5.88 ppm was 76:24.

Ethyl 3-Phenylpropanoate. To 3.3 mL (10 mmol) of phenylmagnesium bromide (3 M in diethyl ether) was added a solution of zinc chloride (1.36 g, 10 mmol) in 30 mL of THF at 0 °C. The mixture was stirred at room temperature for 0.5 h and then added to a mixture of ethyl orthoacrylate (2.6 g, 15 mmol) and $Pd(PPh_3)_4$ (0.57 g, 0.5 mmol) in 30 mL of THF. To this was added HMPA (2.68 g, 2.6 mL, 15 mmol), and the reaction mixture was stirred at room temperature for 12 h and poured onto ice-cold 3 N HCl. The aqueous layer was extracted with ether. The combined organic layers were washed successively with aqueous $NaHCO_3$ and water, dried over $MgSO_4$, concentrated, and then passed through a Florisil (60–200 mesh) column using 30% ether–hexane as eluent. Evaporation of solvents followed by distillation provided 1.32 g (7.4 mmol, 74% yield) of the title compound: bp 130–133 °C (17 mm); IR (neat) 1730 (s) cm^{-1}; ^1H NMR ($CDCl_3$, Me_4Si) δ 1.16 (t, J = 7 Hz, 3 H), 2.4–2.7 (m, 2 H), 2.75–3.0 (m, 2 H), 4.05 (q, J = 7 Hz, 2 H), 7.05–7.3 (m, 5 H).

Ethyl (*E*)-5-Methyl-4-decenoate. To a solution of zirconocene dichloride (0.12 g, 0.4 mmol) in 8 mL of dry 1,2-dichloroethane was added 1-heptyne (0.19 g, 2 mmol).[13] The mixture was cooled to 0 °C and trimethylalane (0.29 g, 0.38 mL, 4 mmol) was added dropwise. The reaction mixture was stirred overnight at room temperature, and then a solution of anhydrous $ZnCl_2$ (0.27 g, 2 mmol) was added to it. The mixture thus obtained was then added to a mixture of ethyl orthoacrylate (0.52 g, 3 mmol), $Pd(PPh_3)_4$ (0.12 g, 0.1 mmol), and HMPA (0.54 g, 0.5 mL, 3 mmol). After being stirred at room temperature for 6 h, the reaction mixture was slowly poured onto a 1:1 mixture of ice-cold aqueous NH_4Cl and 3 N HCl. The mixture was stirred at room temperature for 1 h, and the layers were separated. The aqueous layer was extracted with ether, and the combined organic layers were washed successively with $NaHCO_3$ and water, dried over $MgSO_4$, and concentrated. The product was passed through a Florisil (60–200 mesh) column (60:40 hexane:ether) to remove palladium residues, if any, and the solvents were evaporated. Distillation provided 0.21 g (1 mmol, 50% yield) of the title compound: bp 75–79 °C (0.3 mm); IR (neat) 1728 (s) cm^{-1}; ^1H NMR ($CDCl_3$, Me_4Si) δ 0.75–1.0 (distorted t, 3 H), 1.1–1.5 (m, 9 H), 1.60 (s, 3 H), 1.7–2.5 (m, 6 H), 3.95–4.25 (q, J = 7 Hz, 2 H), 4.9–5.2 (m, 1 H). Anal. Calcd for $C_{13}H_{24}O_2$: C, 73.54; H, 11.39. Found: C, 73.46; H, 11.52. The GLC yield of the compound estimated against *n*-nonane used as an internal standard was 60%. The GLC trace of the reaction product before purification also showed the formation of another unidentified product, the retention time of which corresponded to the product of disubstitution.

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Registry No. **4**, 6044-68-4; **5**, 18318-83-7; **6**, 42216-96-6; (1*E*,4*E*)-$CH_3(CH_2)_4C(CH_3)$=$CHCH_2CH$=$CHOMe$, 97614-16-9; (1*Z*,4*E*)-$CH_3(CH_2)_4C(CH_3)$=$CHCH_2CH$=$CHOMe$, 97614-17-0; $(C_5H_5)_2ZrCl_2$, 1291-32-3; $(PPh_3)_4Pd$, 14221-01-3; (*E*)-$CH_3(CH_2)_4C(CH_3)$=$CH(CH_2)_2CHO$, 97614-18-1; (*E*)-$PhCH_2CH$=$CHOMe$, 60053-38-5; (*Z*)-$PhCH_2CH$=$CHOMe$, 60053-39-6; PhZnCl, 28557-00-8; (*E*)-$CH_3(CH_2)_2CH(Ph)CH$=$CHOMe$, 97614-19-2; (*Z*)-$CH_3(CH_2)_2CH(Ph)CH$=$CHOMe$, 97614-20-5; $Ph(CH_2)_2C(U)OEt$, 2021-28-5; (*E*)-$CH_3(CH_2)_4C(CH_3)$=$CH(CH_2)_2C(O)OEt$, 97614-21-6; ethyl orthopropionate, 115-80-0; 1-heptyne, 628-71-7; trimethylalane, 75-24-1.

Mild Hydrogen-Transfer Reductions Using Sodium Hypophosphite

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Phosphinic acid and sodium hypophosphite (NaH_2PO_2) are known to be effective reagents for the transfer hydrogenation of certain functional groups in the presence of an appropriate catalyst. In this way various olefins,[1] alkynes,[2] nitriles,[3] nitroaromatics,[4] and 1,4-benzoquinones[5] have been reduced under relatively mild reaction conditions. However, the reduction of other functional groups such as ketones, aldehydes, azides, epoxides, *N*-oxides, and the hydrogenolysis of halides or of benzylic protecting

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