Furfural. From excess acetic anhydride and 1.20 g (12.5 mmol) of furfural as usual was obtained 1.5 g (60%) of colorless liquid which solidified to a white crystalline solid, pure by GC: bp 120–125 °C (15 mm) [lit.[3] bp 132–136 °C (18 mm)]; IR (Nujol) 1755, 1500, 1470, 1245, 1205, 1075, 1060, 1015, 965, 935, 925, 902, 880, 830, 750 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.70 (s, 1 H), 7.45 (br s, 1 H), 6.45 (m, 2 H), 2.1 (s, 6 H); ^{13}C NMR ($CDCl_3$) δ 168.374, 148.113, 143.678, 110.461, 109.703, 83.591, 20.586; GC/MS (EI), m/e (relative intensity) 198 (P, 3), 155 (11), 139 (6), 113 (3), 97 (60), 95 (59), 69 (3), 43 (100), 39 (27).

Cinnamaldehyde. Cinnamaldehyde (1.80 g, 13.6 mmol) and excess acetic anhydride as usual gave 1.95 g (60%) of a white solid which was recrystallized from ether–hexane: mp 84–86 °C (lit.[3] mp 84–87 °C); IR (NaCl) 1755, 1660, 1615, 1490, 1470, 1245, 1195, 1120, 1060, 1005, 940, 748, 690 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.1–7.6 (m, 6 H), 6.87 (d, J = 16 Hz, 1 H), 5.93 (dd, J = 16, 7 Hz, 1 H), 2.1 (s, 6 H); ^{13}C NMR ($CDCl_3$) δ 168.591, 135.598, 135.219, 128.826, 128.664, 127.039, 121.838, 89.767, 20.857; GC/MS (EI) m/e (relative intensity) 234 (P, 1), 192 (1), 174 (1), 133 (25), 131 (56), 115 (7), 104 (12), 77 (12), 55 (11), 43 (100).

3-Phenylpropionaldehyde. From 1.50 g (11.2 mmol) of the aldehyde and excess acetic anhydride according to the usual procedure was obtained 2.36 g (89.3%) of colorless liquid, pure by GC: bp 185–190 °C (0.7 mm); IR (NaCl) 3020, 2930, 1755, 1600, 1500, 1460, 1245, 1205, 1105, 1010, 945, 745, 695 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.22 (s, 5 H), 6.85 (t, J = 6 Hz, 1 H), 2.7 (m, 2 H), 2.2 (m, 2 H), 2.1 (s, 6 H); ^{13}C NMR ($CDCl_3$) δ 168.753, 140.636, 128.501, 128.285, 126.118, 90.146, 34.671, 29.687, 20.532; GC/MS (EI), m/e (relative intensity) 176 (P – HOAc, 6), 134 (22), 116 (32), 105 (31), 91 (28), 78 (11), 65 (8), 43 (100); GC/MS (CI), m/e (relative intensity) 237 (P + 1, 1), 195 (1), 176 (1), 163 (1), 145 (4), 117 (100), 103 (5), 89 (5), 61 (15).

3-Nitrobenzaldehyde. The aldehyde (1.00 g, 6.62 mmol) was combined with excess acetic anhydride and run in the usual way to yield 1.55 g (92.5%) of a white solid, pure by GC: mp 64–66 °C; IR (Nujol) 1755, 1535, 1455, 1232, 1200, 1090, 1055, 1010, 985, 905, 815, 735 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.73 (s, 1 H), 7.4–8.5 (m, 4 H), 2.12 (s, 6 H); ^{13}C NMR ($CDCl_3$) δ 168.645, 148.438, 137.765, 132.944, 129.910, 124.547, 121.892, 88.412, 20.694; GC/MS (EI) m/e (relative intensity) 210 (P – acetyl, 2), 194 (3), 150 (18), 134 (21), 105 (10), 77 (12), 51 (13), 43 (100); GC/MS (CI), m/e (relative intensity) 294 (P + 41, 1), 282 (P + 29, 7), 224 (1), 212 (2), 194 (33), 180 (4), 164 (5), 152 (75), 136 (5), 122 (10), 103 (45), 89 (13), 61 (100).

4-Tolualdehyde. 4-Tolualdehyde (2.00 g, 16.6 mmol) was allowed to react with excess acetic anhydride in the usual way to give 3.45 g (93%) of GC-pure white solid: mp 78–80 °C (lit.[3] mp 68–70 °C); IR (Nujol) 1765, 1750, 1230, 1205, 1070, 1005, 960, 930, 815 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.10 (s, 6 H), 2.35 (s, 3 H), 7.30 (AB q, J_{AB} = 8 Hz, J_{AA} = 14 Hz, 4 H), 7.63 (s 1 H); ^{13}C NMR ($CDCl_3$) δ 20.748, 21.182, 89.821, 126.605, 129.260, 132.835, 139.661, 168.645; GC/MS (EI), m/e (relative intensity) 222 (P, 0.5), 179 (2), 163 (2), 121 (22), 119 (39), 91 (20), 43 (100).

4-Cyanobenzaldehyde. The aldehyde (0.50 g, 3.44 mmol) was allowed to react in the usual way to give 0.72 g (84.7%) of white solid pure by GC: mp 98–102 °C; IR (Nujol) 2190, 1750, 1450, 1235, 1195, 1065, 1010, 960, 830 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.67 (s, 4 H), 7.32 (s, 1 H), 2.15 (s, 6 H); ^{13}C NMR ($CDCl_3$) 168.536, 140.311, 132.456, 127.580, 118.154, 113.658, 88.575, 20.694; GC/MS (EI) m/e (relative intensity) 234 (P + 1, 1), 190 (5), 173 (2), 130 (37), 102 (14), 76 (5), 51 (7), 43 (100); GC/MS (CI), m/e (relative intensity) 274 (P + 41, 5), 262 (P + 29, 11), 234 (P + 1, 100), 219 (1), 190 (2), 174 (13), 160 (10), 145 (4), 132 (96), 118 (2), 103 (18), 89 (15), 69 (8), 61 (50).

Hexanal. The usual procedure gave a colorless liquid pure by GC: bp 128–129 °C (2 mm); IR (NaCl) 2950, 2860, 1750, 1460, 1370, 1230, 1110, 1090, 1040, 990, 950 cm^{-1}; ^1H NMR (CCl_4) δ 6.65 (t, J = 5 Hz, 1 H), 2.1 (s, 6 H), 1.2–1.8 (m, 8 H), 0.9 (t, J = 5 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 169.078, 90.742, 33.263, 31.475, 23.132, 22.536, 20.694, 13.922; GC/MS (CI), m/e (relative intensity) 243 (P + 41, 1), 203 (P + 1, 2), 161 (9), 143 (100), 131 (6), 103 (23), 89 (21), 83 (34), 61 (30).

Acrolein. The usual procedure gave a colorless liquid, pure by GC: bp 98–105 °C (2 mm); IR (NaCl) 3080, 2980, 2930, 1750, 1425, 1360, 1230, 1200, 1120, 1000 cm^{-1}; ^1H NMR (CCl_4) δ 2.1 (s, 6 H), 5.2–6.3 (m, 3 H), 7.03 (d, J = 5 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 168.536, 131.535, 120.321, 89.171, 20.694; GC/MS (CI), m/e (relative intensity) 159 (P + 1, 1), 145 (11), 117 (5), 103 (23), 99 (100), 89 (20), 61 (14), 57 (24).

Reaction of Benzaldehyde with Acetic Propionic Anhydride. Acetic propionic anhydride (prepared from acetyl chloride, triethylamine, and propionic acid) and benzaldehyde were allowed to react in the usual way to give a product which was analyzed by GC/MS as a 1:2:1 ratio of three components: A, 25% α,α-diacetoxytoluene; **B**, 50% α-acetoxy-α-propionoxytoluene; **C**, 25% α,α-dipropionoxytoluene. The mass spectra (EI) were as follows. A: m/e (relative intensity) 208 (P, 1), 165 (4), 149 (3), 123 (2), 105 (40), 77 (27), 60 (3), 51 (17), 43 (100). B: m/e (relative intensity) 222 (P, 1), 179 (2), 165 (4), 149 (3), 105 (48), 77 (32), 57 (57), 51 (22), 43 (100). C: m/e (relative intensity) 236 (P, 1), 179 (4), 163 (3), 105 (37), 77 (26), 57 (100), 51 (18).

Acknowledgment. It is a pleasure to thank Professor Charles A. Root for supplying superbly reactive anhydrous ferric chloride.[13] In addition, these studies would have been much more tedious without the assistance of Robert Zimmermann (JEOL FX-90Q) and Jim Spriggle (Finnigan 4021 GC/MS).

Registry No. Benzaldehyde, 100-52-7; propionaldehyde, 123-38-6; furfural, 98-01-1; cinnamaldehyde, 104-55-2; 3-phenylpropionaldehyde, 104-53-0; 3-nitrobenzaldehyde, 99-61-6; 4-tolualdehyde, 104-87-0; 4-cyanobenzaldehyde, 105-07-7; hexanal, 66-25-1; 3,4-dimethyl-2-pentenal, 57398-52-4; acrolein, 107-02-8; α,α-diacetoxytoluene, 581-55-5; 1,1-propanediol diacetate, 33931-80-5; 2-furanylmethanediol diacetate, 613-75-2; 3-phenyl-2-propene-1,1-diol diacetate, 64847-78-5; 3-phenyl-1,1-propanediol diacetate, 85337-09-3; (3-nitrophenyl)methanediol diacetate, 29949-19-7; (4-methylphenyl)methanediol diacetate, 2929-93-3; (4-cyanophenyl)methanediol diacetate, 36735-42-9; 1,1-hexanediol diacetate, 64847-81-0; 3,4-dimethylpent-2-ene-1,1-diol diacetate, 85337-10-6; 2-propene-1,1-diol diacetate, 869-29-4; acetic anhydride, 108-24-7; acetic propionic anhydride, 13080-96-1; α-acetoxy-α-propionoxytoluene, 85337-11-7; α,α-dipropionoxytoluene, 55696-47-4; ferric chloride, 7705-08-0.

Synthesis of Functionalized Aliphatic Aldehydes via a Copper-Catalyzed Grignard Coupling Reaction

Robert A. Volkmann,* Jeffery T. Davis, and Clifford N. Meltz

Central Research, Pfizer Inc., Groton, Connecticut 06340

Received November 29, 1982

Aldehydo esters have found widespread use in the preparation of prostaglandins,[1] leukotrienes,[2] insect pheromones,[3] and a variety of other natural products.[4] A number of procedures are available for their synthesis.[5] Those most commonly employed involve the ozonolysis of

(1) Reuter, J. M.; Salomon, R. G. *J. Org. Chem.* **1978**, *43*, 4247.
(2) (a) Gleason, J. G.; Bryan, D. B.; Kinzig, C. M. *Tetrahedron Lett.* **1980**, *21*, 1129. (b) Rokach, J.; Girard, Y.; Guindon, Y.; Atkinson, J. G.; Larue, M.; Young, R. N.; Masson, P.; Holme, G. *Ibid.* **1980**, *21*, 1485.
(3) Bestmann, H. J.; Koschatzky, K. H.; Schätzke, W.; Süss, J.; Vostrowsky, O. *Liebigs Ann. Chem.* **1981**, 1705.
(4) (a) McLamore, W. M.; Celmer, W. D.; Bogert, V. V.; Pennington, F. C.; Sobin, B. A.; Solomons, I. A. *J. Am. Chem. Soc.* **1953**, *75*, 105. (b) Marx, M.; Marti, F.; Reisdorff, J.; Sandmeier, R.; Clark, S. *Ibid.* **1977**, *99*, 6754. (c) Nicolaou, K. C.; Seitz, S. P.; Pavia, M. R.; Petasis, N. A. *J. Org. Chem.* **1979**, *44*, 4011.
(5) (a) Meyers, A. I.; Nabeya, A.; Adickes, H. W.; Politzer, I. R.; Malone, G. R.; Kovelesky, A. C.; Nolen, R. L.; Portnoy, R. C. *J. Org. Chem.* **1973**, *38*, 36. (b) Taub, D.; Hoffsommer, R. D.; Kuo, C. H.; Slates, H. L.; Zelawski, Z. S.; Wendler, N. L. *Tetrahedron* **1973**, *29*, 1447. (c) Finke, R. G.; Sorrell, T. N. *Org. Synth.* **1980**, *59*, 102. (d) Schreiber, S. L.; Claus, R. E.; Reagan, J. *Tetrahedron Lett.* **1982**, *23*, 3867.

0022-3263/83/1948-1767$01.50/0

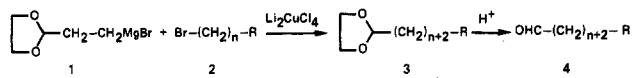
Table I

reactn	alkyl halide	Grignard, equiv	coupling yield, % (bp of acetal, °C)	aldehyde[a,b]	hydrolysis yield, % (bp of aldehyde, °C)
1	$Br(CH_2)_4CH_3$	1.1	88 (60-65/0.1 mm)	$OHC(CH_2)_6CH_3$	46 (44/0.9 mm)[c]
2	$Br(CH_2)_4OCH_3$	1.38	49 (87-92/0.1 mm)	$OHC(CH_2)_6OCH_3$	80 (48-52/0.05 mm)[15]
3	$Br(CH_2)_5Cl$	1.1	89 (82-83/0.1 mm)	$OHC(CH_2)_7Cl$	72 (62-65/0.1 mm)[16,d]
4	$Br(CH_2)_4CN$	1.4	81 (106-109/0.1 mm)	$OHC(CH_2)_6CN$	85 (77-81/0.05 mm)[17]
5	$Br(CH_2)_2CO_2Et$	1.25	28 (89-92/0.1 mm)	$OHC(CH_2)_4CO_2Et$	80 (50-51/0.1 mm)[18]
6	$Br(CH_2)_3CO_2Et$	1.2	66 (95-97/0.1 mm)	$OHC(CH_2)_5CO_2Et$	85 (58-62/0.1 mm)[19]
7	$Br(CH_2)_4CO_2Et$	1.33	77 (104-105/0.1 mm)	$OHC(CH_2)_6CO_2Et$	86 (67-73/0.05 mm)[5]
8	$Br(CH_2)_7CO_2Et$	1.5	74 (135-140/0.1 mm)	$OHC(CH_2)_9CO_2Et$	80 (101-104/0.05 mm)[e,f]

[a] All products gave satisfactory IR and ^1H NMR spectra and had boiling points in agreement with known compounds. [b] All yields are based on distilled products that were >95% pure by ^1H NMR. [c] Since the starting acetal also steam distills under these conditions, the hydrolysis procedure was modified (the acetal was heated to reflux in aqueous benzoic acid for 24 h). [d] The hydrolysis took ca. 5 h. [e] The hydrolysis took ca. 14 h. [f] 60-MHz NMR ($CDCl_3$) δ 1.0-1.9 (m, 17 H), 2.05-2.55 (m, 4 H), 4.05 (q, 2 H), 9.74 (t, 1 H). Treatment with 2,4-dinitrophenylhydrazine gave the 2,4-DNP as a yellow solid, mp 58-60 °C (ethanol/H_2O). Anal. Calcd for $C_{19}H_{28}N_4O_6$: C, 55.87; H, 6.86; N, 13.72. Found: C, 55.69; H, 6.74; N, 13.64.

alkoxycycloalkenes[6] and the Rosemund reduction of ester-containing acyl halides.[7] Our work with aldehydo esters prompted us to investigate other synthetic routes to these molecules. To this end, we have found an efficient alternative involving readily available starting materials that not only permits their synthesis but also the preparation of other functionalized aliphatic aldehydes.

In the presence of various metal catalysts, Grignard reagents cross-couple with a variety of aliphatic and aromatic halides.[8] We reasoned that the coupling of a Grignard reagent bearing a masked aldehyde moiety with (carboethoxy)alkyl halides could provide a convenient avenue for aldehydo ester synthesis. We selected the readily available Grignard reagent (1) derived from 2-(2-



bromoethyl)-1,3-dioxolane that has been used by Büchi[9] and and others[10] in carbonyl addition reactions for our coupling studies. Since we were aware of the reported instability of Grignard reagents derived from β-halo acetals (ketals)[11] especially at warm temperatures, we assumed that very mild conditions would have to be employed in order that ester attack and α-deprotonation be minimized.

Treatment of 1 with a variety of alkyl halides 2 in THF at −10 °C in the presence of dilithium tetrachlorocuprate[12] (0.05 equiv) afforded the desired coupling products 3 in good yield. In the case of alkyl halides possessing no acidic protons, only a slight excess of Grignard reagent was required. However, in the coupling reactions involving bromo alkyl esters and nitriles, ca. 1.2–1.5 equiv of 1 were used. We typically monitored the coupling reaction by ^1H NMR and looked for the disappearance of alkyl halide starting material. While a competitive ester (nitrile) deprotonation does appear to occur (reactions 4–8, Table I), unacceptable yields were only observed with the coupling of ethyl 3-bromopropionate (reaction 5). In the reaction of 1 with 1-bromo-5-chloropentane (reaction 3), only bromide coupling occurred. The cross-coupling reaction appears quite general for aliphatic primary bromides. Preliminary indications suggest the coupling of 1 with secondary bromides[13] and aryl iodides is not useful.

In the case of the acetal esters (reactions 5–8), a method was required for a high-yield selective hydrolysis of the acetal moiety. In most instances, existing literature procedures were either ineffective or nonselective. We found however that this hydrolysis could best be achieved via a continuous steam distillation[14] of these acetals (using a liquid–liquid continuous extractor) from an aqueous benzoic acid solution. Our intention with these conditions was to remove aldehyde as it is formed in order to minimize its exposure to aqueous acid and, at the same time, push the equilibrium toward acetal hydrolysis. In general, if the acetal intermediates 3 are distilled after the coupling reaction, the crude hydrolysis products 4 are pure enough to use directly in subsequent reactions. The coupling/hydrolysis procedure has been carried out on a mole scale and does not appear to be scale dependent.

Experimental Section[20]

General Procedure. A. Grignard Coupling. To a 1.6 M solution of alkyl halide in anhydrous tetrahydrofuran containing 0.1 equiv of lithium chloride and 0.05 equiv of copper (II) chloride was added dropwise 1.1–1.5 equiv of a tetrahydrofuran solution of Grignard 1[21] (after 1 equiv of Grignard 1 was added, an aliquot was removed, subjected to workup conditions, and analyzed by ^1H NMR). The reaction temperature was maintained at ca. −10 °C with external cooling. In general, Grignard solution was added

(6) Schmidt, U.; Grafen, P. *Justus Liebigs Ann. Chem.* **1962**, *656*, 97.
(7) Burgstahler, A. W.; Weigel, L. O.; Shaefer, C. G. *Synthesis* **1976**, 767.
(8) (a) Bergbreiter, D. E.; Whitesides, G. M. *J. Org. Chem.* **1975**, *40*, 779. (b) Fouquct, G.; Schlosser, M. *Angew. Chem., Int. Ed. Engl.* **1974**, *13*, 82.
(9) Büchi, G.; Wüest, H. *J. Org. Chem.* **1969**, *34*, 1122.
(10) (a) Loozen, H. J. J. *J. Org. Chem.* **1975**, *40*, 520. (b) Roush, W. R.; Gillis, H. R.; Ko, A. I. *J. Am. Chem. Soc.* **1982**, *104*, 2269.
(11) See: Stowell, J. C. *J. Org. Chem.* **1976**, *41*, 560. Greater stability for these Grignard reagents can be obtained if the corresponding six-membered acetals are used.
(12) (a) Tamura, M.; Kochi, J. *Synthesis* **1971**, 303. (b) Baer, T. A.; Carney, R. L. *Tetrahedron Lett.* **1976**, 4697.
(13) Alkyl and aryl iodides appear superior to the corresponding bromides in cross-coupling reactions. See: Nunomoto, S.; Kawakami, Y.; Yamashita, Y. *Bull. Chem. Soc. Jpn.* **1981**, *54*, 2831. We have not investigated the coupling of 1 with secondary iodides.
(14) This technique was reported earlier by J. C. Stowell (ref 11). By substituting benzoic acid for oxalic acid, we effectively reduced the amount of ester hydrolysis.
(15) Ströbele, R. German Patent 821 202, 1951.
(16) Epsztein, R.; Holand, S.; Marszak, I. *C. R. Held. Seances Acad. Sci.* **1961**, *252*, 1803.
(17) Ohno, M.; Naruse, N.; Torimitsu, S.; Teresawa, I. *J. Am. Chem. Soc.* **1966**, *88*, 3168.
(18) Brown, G. B.; Armstrong, M. D.; Moyer, A. W.; Anslow, W. P.; Baker, B. R.; Querry, M. V.; Bernstein, S.; Safir, S. R. *J. Org. Chem.* **1947**, *12*, 160.
(19) Bestmann, H. J.; Koschatzky, K. H.; Vostrowsky, O. *Chem. Ber.* **1979**, *112*, 1923.
(20) Melting points were determined with a Thomas-Hoover capillary apparatus and are uncorrected. Infrared spectra were recorded by using Perkin-Elmer Model 21 and Model 727B spectrometers. NMR spectra were obtained with a Varian EM 360 60-MHz spectrometer with Me_4Si as an internal standard. Microanalyses were performed by the Pfizer Analytical Department.
(21) Grignard 1 was generated by using the procedure of Büchi (ref 9). Grignard concentrations were determined by the method of Watson and Eastham: Watson, S. C.; Eastham, J. F. *J. Organomet. Chem.* **1967**, *9*, 165.

until the alkyl halide was consumed (the addition of 1 in the coupling of 0.05–0.15 mol of alkyl halide takes ca. 1.5 h). The reaction mixture was poured into a separatory funnel containing saturated ammonium chloride and diethyl ether. The ethereal layer was separated, and the aqueous layer was again extracted with diethyl ether. The ethereal solutions were combined, washed with brine, and dried over magnesium sulfate. Filtration, evaporation of volatiles, and distillation provided the desired acetals.

B. Acetal Hydrolysis. The reaction flask was equipped with a liquid–liquid continuous extractor that was designed to return the bottom aqueous layer to the reaction flask. The upper layer in the continuous extractor consisted of an organic solvent such as hexane or ethyl acetate. For small-scale reactions (<20 mmol), a Dean–Stark trap[11] was modified to serve as the extractor. A 0.45 M solution of acetal in water containing benzoic acid (0.1 equiv) was heated to reflux with stirring for 1.25 h,[22] during which time the product, in most cases, steam distilled into the trap. After cooling, the contents of the trap and reaction flask were combined and extracted with ethyl acetate (2×). The combined organic extracts were washed with aqueous sodium bicarbonate followed by brine and dried over magnesium sulfate. Filtration, evaporation of volatiles, and distillation gave the desired aldehydes.

Registry No. **2** (n = 4; R = CH_3), 110-53-2; **2** (n = 4; R = OCH_3), 4457-67-4; **2** (n = 5; R = Cl), 54512-75-3; **2** (n = 4; R = CN), 5414-21-1; **2** (n = 2; R = CO_2Et), 539-74-2; **2** (n = 3; R = CO_2Et), 2969-81-5; **2** (n = 4; R = CO_2Et), 14660-52-7; **2** (n = 7; R = CO_2Et), 29823-21-0; **3** (n = 4; R = CH_3), 4359-57-3; **3** (n = 4; R = OCH_3), 85318-81-6; **3** (n = 5; R = Cl), 85318-82-7; **3** (n = 4; R = CN), 13050-10-7; **3** (n = 2; R = CO_2Et), 56741-64-1; **3** (n = 3; R = CO_2Et), 85318-83-8; **3** (n = 4; R = CO_2Et), 85318-84-9; **3** (n = 7; R = CO_2Et), 85318-85-0; **4** (n = 4; R = CH_3), 124-13-0; **4** (n = 4; R = OCH_3), 85318-86-1; **4** (n = 5; R = Cl), 72359-96-7; **4** (n = 4; R = CN), 13050-09-4; **4** (n = 2; R = CO_2Et), 27983-42-2; **4** (n = 3; R = CO_2Et), 3990-05-4; **4** (n = 4; R = CO_2Et), 1540-83-6; **4** (n = 7; R = CO_2Et), 85318-87-2; Li_2CuCl_4, 15489-27-7; 2-(2-bromoethyl)-1,3-dioxolane, 18742-02-4.

(22) In general, aldehydes that steam distill are formed in ca. 1–2 h. The generation of aldehydes that do not steam distill is much slower. The period required for each acetal hydrolysis is shown in Table I.

Communications

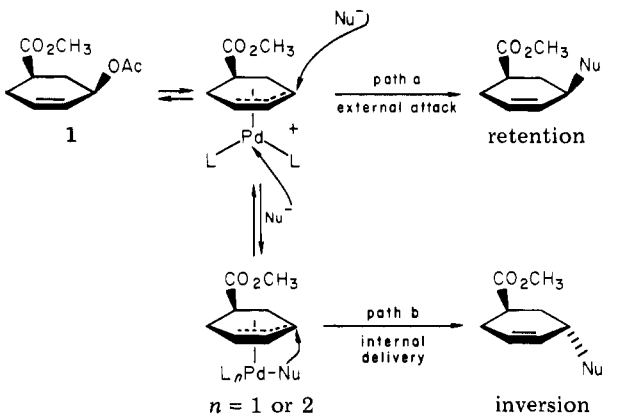
Regioselectivity in Organo-Transition-Metal Chemistry. A New Indicator Substrate for Classification of Nucleophiles

Summary: A new model for the characterization of nucleophiles is proposed, based on the regioselectivity of the reaction of a given nucleophile with 3-acetoxy-3-cyano-1-phenylpropene (14) in the presence of Pd(0) catalyst. A general correlation between regioselectivity using this indicator substrate and literature data on stereospecificity of nucleophilic substitution in other model compounds is apparent.

Sir: The characterization of nucleophilic reactivity is, in general, a difficult task. While there have been significant advances in the classification both of leaving groups[1a] and of nucleophiles,[1b] much work remains to be done, especially with respect to the latter. There is a growing need for a reliable criterion for predicting nucleophilic reactivities, especially with respect to electrophilic transition-metal complexes. It would allow one to employ transition metals in organic synthesis in a more rational manner to provide high degrees of chemoselectivity, regioselectivity, and stereochemical control. These benefits are probably best exemplified by palladium-catalyzed nucleophilic allylic substitution reactions that have been extensively used in organic synthesis for obtaining carbon–carbon or carbon–heteroatom bonds.[2]

Nucleophiles can be qualitatively classified via the mechanism by which they attack (π-allyl)palladium species. The two distinct mechanistic pathways are shown in Scheme I. Path a (usually attributed to "soft" nucleophiles[3]) involves external attack at carbon, resulting in retention of its configuration, while path b (usually

Scheme I



(1) (a) Stirling, C. J. M. *Acc. Chem. Res.* **1980**, *12*, 198. (b) Hirsch, J. A. "Concepts in Theoretical Organic Chemistry"; Allyn and Bacon: Boston, 1974; Chapter 8, (Nucleophilic Character).

(2) (a) Trost, B. M. *Acc. Chem. Res.* **1980**, *13*, 385. (b) Trost, B. M.; Verhoeven, T. R. In "Comprehensive Organometallic Chemistry"; Pergamon Press: Oxford, England, 1982, Vol. 8, pp, 799–938. (c) Tsuji, J. "Organic Synthesis with Palladium Compounds"; Springer: New York, 1980.

(3) (a) Pearson, R. G. "Symmetry Rules for Chemical Reactions"; Wiley: New York, 1976. (b) Ho, T.-L. *Chem. Rev.* **1975**, *75*, 1.

(4) (a) Trost, B. M.; Verhoeven, T. R. *J. Org. Chem.* **1976**, *41*, 3215. (b) Trost, B. M.; Verhoeven, T. R. *J. Am. Chem. Soc.* **1980**, *102*, 4730.

(5) Fiaud, J. C.; Malleron, J. L. *Tetrahedron Lett.* **1980**, 4437.

(6) Fiaud, J. C.; Malleron, J. L. *J. Chem. Soc., Chem. Commun.* **1981**, 1159.

(7) Trost, B. M.; Keinan, E. *Tetrahedron Lett.* **1980**, 2591.

(8) Trost, B. M.; Rivers, G. T., unpublished results. See: Trost, B. M.; Keinan, E. *Tetrahedron Lett.* **1980**, 2595.

(9) Trost, B. M.; Keinan, E. *J. Am. Chem. Soc.* **1978**, *100*, 7779.

(10) (a) Trost, B. M.; Verhoeven, T. R.; Fortunak, J. M. *Tetrahedron Lett.* **1979**, 2301. (b) See also: Backvall, J. E.; Nordberg, R. E.; Bjorkaman, E. E.; Moberg, C. *J. Chem. Soc., Chem. Commun.* **1980**, 943. (c) Backvall, J. E.; Nordberg, R. E. *J. Am. Chem. Soc.* **1981**, *103*, 4959.

(11) Matsushita, H.; Negishi, E. *J. Chem. Soc., Chem. Commun.* **1982**, 160.

(12) Hayashi, Y.; Riediker, M.; Temple, J. S.; Schwartz, J. *Tetrahedron Lett.* **1981**, 2629.

(13) Kumada, M. 10th International Conference on Organometallic Chemistry, Toronto, Canada, Aug 1981.

(14) Gendreau, Y.; Normant, J. F. *Tetrahedron* **1979**, *25*, 1517.

(15) Consiglio, G.; Morandini, F.; Piccolo, O. *J. Am. Chem. Soc.* **1981**, *103*, 1846.

0022-3263/83/1948-1769$01.50/0