Synthesis of Lactones by the Palladium-Catalyzed Carbonylation of Halo Alcohols

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Abstract: The synthesis of lactones in high yields by the palladium-catalyzed carbonylation reaction of halo alcohols can be effected under mild conditions (1-4 atm CO, 25-60 °C) with a high turnover of palladium. Benzyl, allyl, aryl, and vinyl halides containing primary, secondary, or tertiary alcohol groups are readily converted to a variety of lactones, including phthalides and butenolides, by this simple procedure.

Introduction

Lactones containing both saturated and unsaturated five, and larger, rings occur widely in nature.[1,2] Many of these naturally occurring compounds, as well as some of their synthetically produced derivatives, exhibit a broad spectrum of biological activity, possessing fungicidal, herbicidal, antibiotic, antitumor, and antihelminthic properties.[3-8] They also have been employed in the treatment of arthritis and allergies and are believed to function in plant and insect defense mechanisms.[9-13] In addition, they contribute to the taste and essence of many foods and beverages.[14,15] Their use as reactive intermediates in organic synthesis and the ability of certain members to undergo ring opening to yield polyesters have also lent importance to the synthesis of this class of compounds.[16-20]

This paper reports a new palladium(0)-catalyzed synthesis of β-lactones, $\Delta^{\alpha,\beta}$-butenolides, and phthalide derivatives by the carbonylation of halo alcohols. The synthesis is based on the knowledge that carboxylic esters can be obtained from the palladium-catalyzed carbonylation of organic halides in an alcohol solvent.[21-23] The catalytic sequence requires the oxidative addition of the organic halide to palladium(0), "insertion" of carbon monoxide into the palladium-carbon σ bond, and reductive elimination induced by the alcohol function. The presence of base is necessary to keep the catalyst active, which allows a high turnover of palladium to be obtained, by absorbing the hydrogen halide produced in the reaction. It may also activate the hydroxyl group for attack on the acyl complex.[22]

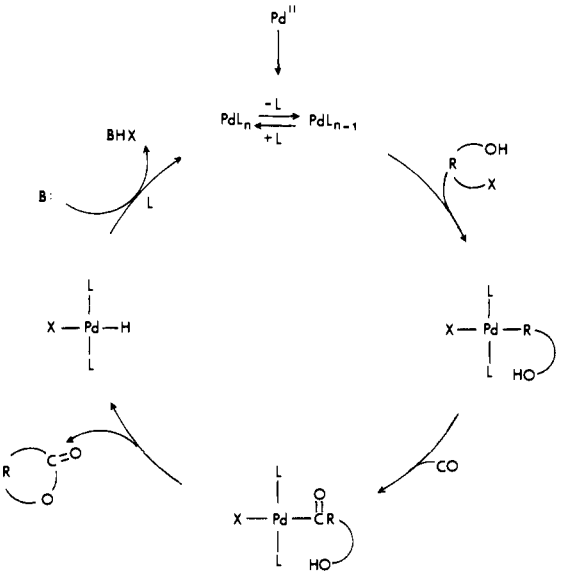
Results and Discussion

In this work we have extended the reaction sequence to the synthesis of lactones from halo alcohols as illustrated in Scheme I.

Several aspects of the catalytic cycle deserve comment. First, all four-coordinate palladium(0) complexes are coordinatively saturated and are required to undergo ligand dissociation before oxidative addition can occur.[24] Second, the stereochemistry of oxidative addition has been determined in a number of cases. With benzyl halides, it occurs predominantly with inversion of configuration at carbon.[25] With vinyl halides, retention of geometry has been observed.[26] In addition, insertion of carbon monoxide has been shown to occur with retention of configuration at carbon.[27] While these facts were first determined to help elucidate the mechanistic aspects of the oxidative addition reaction, in this case they are significant because inversion of configuration with benzyl halides would allow the synthesis of optically active lactones, and retention of configuration with vinyl halides is mandatory in the systems described, since only the *Z* isomer can be converted to the lactone.

A preliminary investigation of the carbonylation of simple organic halides was undertaken to determine whether carbonylation could be carried out under mild conditions with high turnover of palladium and good conversion to product. Reactions with iodobenzene and benzyl bromide (Table I) showed that both compounds could be converted to the corresponding methyl esters in methanol under milder conditions and with higher turnover than had been previously reported.[21-23]

Scheme I



Subsequently, a number of halo alcohols were converted to the corresponding lactones. A summary of these results is presented in Tables II and III.

Benzylic and Allylic Halides. *o*-Bromomethylbenzyl alcohol (**1**) was converted to 3-isochromanone (**2**) (Table I). The yield of product was particularly dependent on the reaction solvent. Either tetrahydrofuran (THF) or benzene afforded the highest yield of lactone from the carbonylation of **1**. Polar solvents such as *N,N*-dimethylformamide (DMF) and *N*-methylpyrrolidone (NMP) led to an increase in the yield of side products (which were not identified) at the expense of the lactone.

By contrast, the optimum conversion of 2-bromo-2-phenylethanol (**3**) to tropic acid β-lactone (**4**) was realized in DMF or NMP. The use of THF or benzene in this case led to the generation of large amounts of styrene oxide at the expense of lactone formation. The formation of styrene oxide was independent of the palladium-catalyzed reaction and occurred readily by stirring with potassium carbonate in THF.

Surprisingly, carbonylation of the allylic halide *cis*-4-chlorobut-2-en-1-ol (**5**) also produced a β-lactone (**6**) rather than the expected δ-lactone (**7**). The carbonylation of **5** with cobalt carbonyls, however, has been previously reported to produce **7**.

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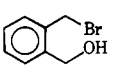
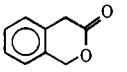
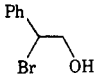
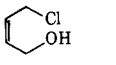
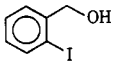
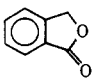
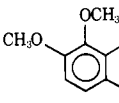
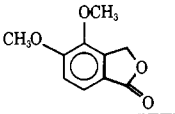
Table I. Carbonylation of Organic Halides[a]

halide	catalyst (mol %)	P_{CO}, atm	temp, °C	product	yield, % (time, h)	turnover
PhI	$Pd(diphos)(PPh_3)_2$ (0.20)[b]	3	55	$PhCO_2CH_3$	95[c]	475
PhI	$Pd(diphos)(PPh_3)_2$ (0.02)	3	55	$PhCO_2CH_3$	82 (14.5)	4100
$PhCH_2Br$	$PdCl_2(PPh_3)_2$ (0.20)	1	25	$PhCH_2CO_2CH_3$	71 (24)	355

[a] MeOH solvent, K_2CO_3 base. [b] diphos = $Ph_2PCH_2CH_2PPh_2$. [c] GC yield; isolated yield, 82%.

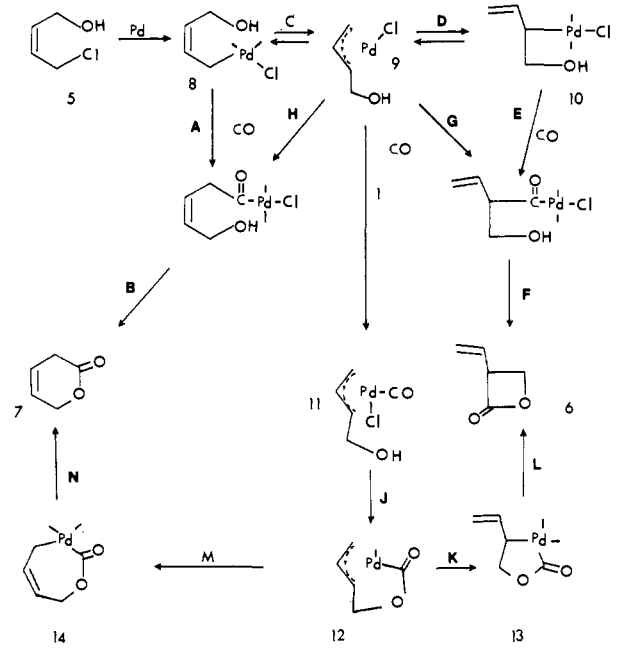
Table II. Palladium-Catalyzed Synthesis of Various Lactones

halo alcohol		reaction conditions: solvent	P_{CO}	Pd, mol %[a]	temp, °C	time, h	product		yield, %	turnover
	(1)	THF	1	1.6	25	24		(2)[d]	71	44
	(3)	DMF	1	1.6	25	24		(4)[e]	63	39
	(5)[c]	THF	1	4.0[b]	25	72		(6)[f]	52	13
	(15)	DMF DMF	1 1	0.82 0.33	60 55	72 72		(16)[g]	100 88	122 268
	(18)	DMF	4	2.0	50	60		(20)[h]	78	39

[a] Based on halo alcohol. [b] $Pd(CO)(PPh_3)_3$ catalyst. [c] Colonge, J.; Poilane, G. P. *Bull. Soc. Chim. Fr.* **1955**, 953. [d] Murahashi, S. *Sci. Pap. Inst. Phys. Chem. Res. (Jpn.)* **1936**, *30*, 180. Swan, J. *J. Chem. Soc.* **1949**, 1720. Markgraf, J. H.; Bosta, S. J. *Synth. Commun.* **1972**, *2*, 139. [e] Testa, E.; Fontanella, L.; Christiani, G. F.; Mariani, L. *Justus Liebigs Ann. Chem.* **1961**, *639*, 166, report ν(CO) 1825 cm^{-1}. Anal. Calcd for $C_9H_8O_2$: C, 72.97; H, 5.40. Found: C, 72.94; H, 5.48. ^1H NMR ($CDCl_3$): δ 7.3 (s, 5 H, ArH), 5.6 (d of d, 1 H), 4.2 (d of d, 1 H, J = 8 Hz). ^{13}C NMR ($CDCl_3$): 154.53 s (CO), 135.58 s, 129.39 d, 128.91 d, 128.62 d (aromatic), 77.81 d (CH), 70.99 t (OCH_2) ppm. [f] IR: 1820 (CO), 1660 (C=C) cm^{-1}. ^1H NMR ($CDCl_3$): δ 6.2–4.8 (m, 4 H, OCH and vinyl H), 4.5 (d of d, 1 H), 4.1 (d of d, 1 H, aliphatic H, J = 8, 8 Hz). ^{13}C NMR ($CDCl_3$): 154.66 s (CO), 132.06 d (C=*C*H), 120.82 t (C=*C*H_2), 77.30 d (CH), 69.07 t (OCH_2) ppm. Mass spectrum: parent ion at m/e 98. Anal. Calcd for $C_5H_6O_2$: C, 61.21; H, 6.16. Found: C, 60.57; H, 6.22. [g] Brown, H. C.; Kim, S. C.; Krishnamurthy, S. *J. Org. Chem.* **1980**, *45*, 1. [h] Reference 33.

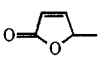
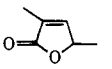
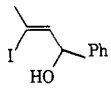
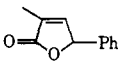
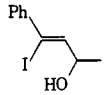
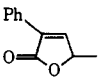
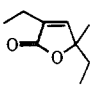
A plausible mechanism for this is illustrated in Scheme II. The first step may involve the oxidative addition of 4-chlorobut-2-en-1-ol (**5**) to palladium yielding the σ-bonded complex **8**. Since the reaction sequence AB would appear to offer a facile route to **7**, the absence of **7** indicates either that step C must be very fast or that the allylic complex **9** is formed directly from **5** and palladium(0).

Scheme II



From **9**, pathway DEF would lead to the observed product. However, it is difficult to explain why this pathway would be favored exclusively over an alternative route such as CAB, since carbon monoxide insertion into primary carbon–palladium σ bonds is favored over secondary, and lactone formation proceeds through a six- as opposed to a four-membered cyclic transition state. The predominance of DEF could be explained, however, if the equilibrium mixture of **8**, **9**, and **10** were shifted far to the right. The carbonylation of the π-allyl complex as opposed to the σ complexes might be a more reasonable alternative. A path such as GF would lead to the correct product, and would be favored over a path such as HB since H requires conversion of the stable syn-π-allyl complex to an acyl complex containing a *Z* double bond. Steps IJ, which involve hydroxyl attack on a coordinated molecule of carbon monoxide (**11** → **12**) (as opposed to insertion of carbon monoxide into a metal–carbon σ bond), provide an alternate mechanism for carbonylation. In this case, exclusive formation of the β-lactone would be expected since it proceeds through a five-membered cyclic intermediate (**13**) via KL as opposed to the seven-membered intermediate **14** via MN. In keeping with this proposed mechanism (path CIJKL), it is known that many allyl compounds, including allyl halides, react with palladium yielding π-allyl complexes.[29] In addition, attack on coordinated carbon monoxide by hydroxide and other nucleophiles is known to occur readily,[29,30] and in particular was proposed in the

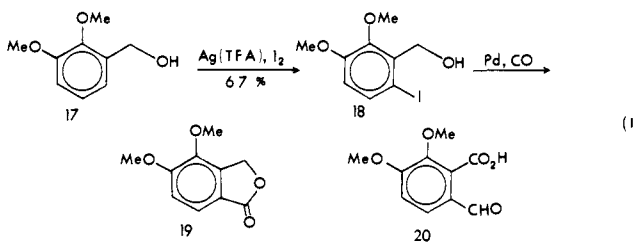
Table III. Palladium-Catalyzed Synthesis of $\Delta^{\alpha,\beta}$-Butenolides[a]

iodide	reaction conditions: P_{CO}	Pd, mol %[a]	temp, °C	time, h	product	yield, %	turnover
 (**21a**)	1	1.6	25	72	 (**22a**)[b]	76	48
 (**21b**)	3	0.40	35	72	 (**22b**)[c]	95	237
 (**21c**)	1	0.82	25	72	 (**22c**)[d]	100	122
 (**21d**)	2	0.82	35	48	 (**22d**)[e]	99	121
 (**21e**)	5	3.6	25	72	 (**22e**)[e]	46	13
 (**21f**)	5	8.3	25	24	 (**22f**)[e]	69	8
 (**21g**)	3	0.70	35	72	 (**22g**)[f]	84	120

[a] Based on halo alcohol. [b] Freeman, R. *Mol. Phys.* **1962**, *5*, 499. [c] Srinivasan, R.; Hiroaka, H. *Tetrahedron Lett.* **1969**, 2767. [d] Inayana, S.; Kawanata, T. *Chem. Pharm. Bull.* **1973**, *21*, 461. [e] Hussain, S. A. M. T.; Ollis, W. D.; Smith, C.; Stoddart, J. F. *J. Chem. Soc., Perkin Trans. 1* **1975**, 1480. [f] Anal. Calcd for $C_9H_{14}O_2$: C, 70.13; H, 9.09. Found: C, 69.57; H, 9.46. IR: 1770 (CO) cm^{-1}. ^1H NMR ($CDCl_3$): δ 6.8 (t, 1 H, C = CH, J = 2 Hz), 2.3 (q of d, 2 H, CH_2, J = 2, 7 Hz), 1.7 (q, 2 H, CH_2, J = 7 Hz), 1.4 (s, 3 H, CH_3), 1.1 (t, 3 H, CH_3, J = 7 Hz), 0.9 (t, 3 H, CH_3, J = 7 Hz). ^{13}C NMR ($CDCl_3$): 172.59 s (CO), 151.65 d (C = *C*H), 134.52 s (C = *C*C), 86.50 s (OC), 31.50 t (CH_2), 23.91 q (CH_3), 18.69 t (CH_2), 12.06 q (CH_3), 8.07 q (CH_3) ppm. Mass spectrum: parent ion at m/e 154.

palladium(II)-catalyzed conversion of homopropargyl alcohols to α-methylene-γ-butyrolactones.[31]

Aryl Halides. *o*-Iodobenzyl alcohol (**15**) was converted to phthalide **16** in good yields under mild conditions. The palladium-catalyzed carbonylation of *o*-bromobenzyl alcohol was reported[32] to give only low yields of phthalide **16,** acceptable yields (81%) were obtained only with a 30-fold amount of triphenylphosphine at 130 °C. This same reaction sequence affords the valuable pseudomeconin (**19**) in two steps starting from 2,3-dimethoxybenzyl alcohol (**17**) (eq 1). Previously re-



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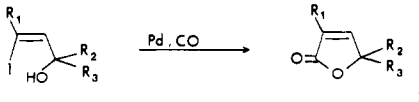
ported syntheses of **19** have involved four or five steps starting from opianic acid (**20**).[17,33]

Vinyl Halides. $\Delta^{\alpha,\beta}$-Butenolides (**24**) were readily synthesized under mild conditions by the carbonylation of *Z* vinyl iodides (**21**) (eq 2). The iodide precursors to 3- and 3,5-sub-



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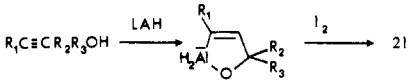
stituted butenolides were conveniently prepared from acetylenic alcohols by their reaction with lithium aluminum hydride followed by iodination of the organoaluminum intermediate (**23**) (eq 3).[34] A different procedure was used to prepare the precursors to 3-unsubstituted butenolides since treatment of the required terminal acetylenic alcohols with $LiAlH_4$ and



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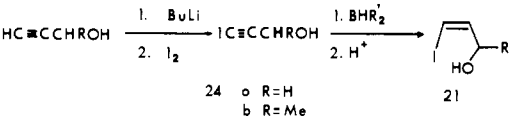
iodine yielded iodo alkynes and diiodo derivatives. Terminal acetylenic alcohols were converted to the *Z* iodides by conversion to the iodo alkyne **24** followed by hydroboration and hydrolysis (eq 4).[35] The synthesis of *Z* vinyl iodides is summarized in Table IV.



(4

With either hydrogen or an alkyl substituent at R_1 or R_2, excellent yields of butenolides were obtained as the only products with primary, secondary, or tertiary *Z* vinyl iodo alcohols. With a phenyl group at R_1 or R_2, the yields of product were somewhat lower and other unidentified side products were formed as well. This may be due to a combination of electronic and steric effects contributed by the phenyl group. In **21f** the polarization of the double bond may be such that it makes oxidative addition more difficult. In **21e** the increased steric hindrance along with the decreased basicity of the hydroxyl group may combine to make the ring-closure step more difficult.

Of the many reported syntheses of $\Delta^{\alpha,\beta}$-butenolides, relatively few have been applied to the synthesis of alkyl- or phenyl-substituted 3 or 3,5 derivatives.[16] In many cases the palladium-catalyzed reaction gives equivalent or better yields, often with a savings in the number of synthetic steps required.

Catalyst. A number of palladium triphenylphosphine complexes have been used as catalysts for the carbonylation

Table IV. Synthesis of *Z* Vinyl Iodides

iodide	yield %	IR cm^{-1} OH	IR cm^{-1} C=C	^1H NMR, δ =CH	OCH_2	OH	CH_3		
21a	*a*	3360	1615	6.3 (m, 2 H)	4.1 (d, 2 H, *J* = 5 Hz	3.7 (s, 1 H)			
21b	61	3350	1615	6.1 (m, 2 H)	4.4 (p of d, 1 H, *J* = 2, 5 Hz)	2.9 (s, 1 H)	1.3 (d, 3 H, *J* = 5 Hz)		
21c	71	3350	1655	5.7 (t of q, 1 H, *J* = 2, 6 Hz)	4.1 (d of q, 2 H, *J* = 2, 6 Hz)	3.1 (s, 1 H)	2.6 (q, 3 H, *J* = 2 Hz)		
21d	83	3360	1660	5.5 (d of q, 1 H, *J* = 2, 7 Hz)	4.3 (p, 1 H, *J* = 7 Hz)	3.1 (s, 1 H)	2.4 (d, 3 H, *J* = 2 Hz, $=CCH_3$	1.3 (d, 3H, *J* = 7 Hz, $-C-CH_3$)	
21e	65	3500	1660	5.7 (d of q, 1 H, *J* = 2, 8 Hz)	5.3 (d, 1 H, *J* = 8 Hz)		2.5 (d, 3 H, *J* = 2 Hz)		7.6-7.2 (m, 5 H, C_6H_5)
21f	78	3350	1625	6.0 (d, 1 H, *J* = 7 Hz)	4.6 (p, 1 H, *J* = 7 Hz)	2.2 (s, 1 H)	1.4 (d, 3 H, *J* = 7 Hz)		7.6-7.1 (m, 5 H, C_6H_5
21g	47	3340	1630	5.8 (t, 1 H, *J* = 2 Hz)			1.3 (s, 3 H) 1.0 (t, 3 H, *J* = 7 Hz) 0.9 (t, 3 H, *J* = 7 Hz)		2.5 (q of d, 2 H, CH_2, *J* = 2, 7 Hz) 1.7 (q of d, 2 H, CH_2, *J* = 2, 7 Hz)

[a] Not determined owing to loss of product during workup.

of organic halides.[21-23] Bis(triphenylphosphine)palladium(II) chloride (**25**) was the catalyst used most often in this study. It is conveniently handled, and can be readily reduced to palladium(0) in situ. It also keeps the concentration of triphenylphosphine in solution to a minimum, which is advantageous since free triphenylphosphine is known to retard the rate of oxidative addition. It is worth noting that the use of palladium complexes containing phosphines which are more powerful donors (such as triethylphosphine) is not possible owing to the formation of inert palladium phosphine carbonyls.[36]

A surprising difference between the carbonylation of organic halides and halo alcohols was observed using bis(triphenylphosphine)bis(diphenylphosphinoethane)palladium(0) (**26**) [diphos = bis(diphenylphosphinoethane)] as the catalyst and deserves comment. Organic halides were readily converted to the corresponding esters in good yields with high turnover using **26** (Table I). By contrast, the conversion of *o*-iodobenzyl alcohol (**15**) to phthalide **16** via **26** was sluggish. Furthermore, **26** proved completely ineffective in the conversion of *o*-bromomethylbenzyl alcohol (**1**) to 3-isochromanone (**2**), or of 2-bromo-2-phenylethanol (**3**) to tropic acid β-lactone (**4**). However, bis(triphenylphosphine)palladium(II) chloride (**25**) could

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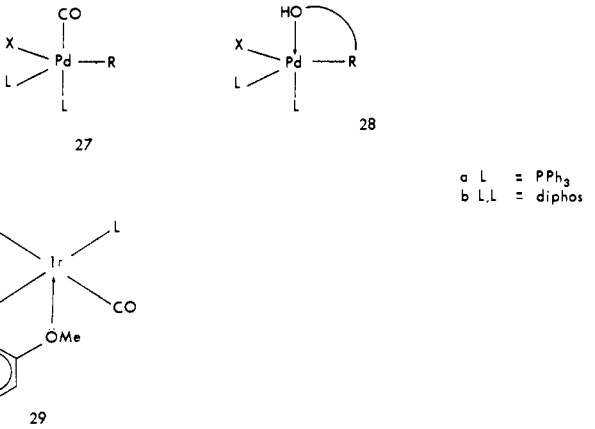
be used to convert either organic halides or halo alcohols to the corresponding esters or lactones. A plausible explanation for this is as follows.

Insertion of carbon monoxide into the palladium-carbon bond requires prior coordination of carbon monoxide, and a five-coordinate intermediate such as **27** has been proposed.[37] However, when R contains a hydroxyl group (**28**), the necessary fifth coordination site may be blocked. In **28a** dissociation of triphenylphosphine could free a coordination site, whereas in **28b** dissociation of diphos is far less likely. Although a hydroxyl group is not a good ligand for palladium, the close proximity in which it is held to palladium could greatly enhance its coordinative ability. This is supported by the fact that the iridium complex **29** containing dimethyl(*o*-anisyl)phosphine was reported to undergo oxidative addition to alkyl halides 100 times as fast as similar complexes containing *m*- or *p*-dimethyl(anisyl)phosphine.[38] The greater reactivity of **29** was attributed to increased nucleophilicity of the metal center via



interaction of the *o*-methoxyl group.

Conclusion

Of the many recently published lactone syntheses involving transition metals, some involve the use of toxic metal carbonyls such as nickel tetracarbonyl,[39] others require stoichiometric amounts of heavy metals as in the palladium(II)-catalyzed carbonylation of vinyl mercurials,[40] while still others are specific for only one type of lactone.[41] The palladium(0)-catalyzed carbonylation of halo alcohols, on the other hand, requires only a small amount of palladium, and can be used to synthesize a variety of different lactones. In addition the necessary halo alcohols can be synthesized from readily available starting materials in one or two steps. This technique should prove adaptable to the synthesis of many other lactones as well.

Experimental Section

All carbonylations were performed using deaerated anhydrous solvents and care was taken to exclude oxygen from all parts of the system. All palladium complexes were prepared according to published procedures.[21,25,42]

Procedure for the Carbonylation of Iodobenzene. Under an argon atmosphere, 54.1 mg (0.0527 mmol) of bis(triphenylphosphine)bis(diphenylphosphinoethane)palladium(0)[42] and 7.25 g (52.5 mmol) of anhydrous potassium carbonate were added to a carbonylation apparatus and purged several times with carbon monoxide. By means of a syringe, 12 mL of methanol and 5.35 g (26.2 mmol) of iodobenzene were added to the flask. The vessel was then filled with 3 atm of carbon monoxide and heated with stirring at 55 °C. As the pressure dropped more carbon monoxide was added to keep the pressure at 3

atm. Small aliquots were periodically withdrawn and analyzed via GC (20% FFAP on Chromosorb W, 160 °C) to determine the extent of the reaction. When the reaction was shown to be complete, the reaction mixture was filtered, and the solid residue was washed several times with diethyl ether. The filtrate was dried over magnesium sulfate, the ether was removed in vacuo, and the residue was distilled under reduced pressure to give 2.92 g (21.5 mmol, 82%) of methyl benzoate. Identification was confirmed by comparison of the GC retention time and the NMR spectrum with those of an authentic sample.

Procedure for the Carbonylation of Benzyl Bromide. By a procedure similar to that described for iodobenzene, 0.0100 g (0.0143 mmol) of bis(triphenylphosphine)palladium(II) chloride[42] and 0.990 g (7.17 mmol) of potassium carbonate were added to a flask containing a serum cap. The flask was evacuated and then filled with carbon monoxide. By means of a syringe, 5 mL of THF, 1 mL of methanol, and 1.21 g (7.08 mmol) of benzyl bromide were added to the flask and the mixture was stirred under carbon monoxide for 24 h. At the end of this time the mixture was filtered, the solvents were removed in vacuo, and the residue was distilled to give 0.750 g (5.00 mmol, 71%) of methyl phenylacetate. Identification was confirmed by comparison of the GC retention time and NMR spectrum with those of an authentic sample.

***o*-Bromomethylbenzyl Alcohol (1).** To a rapidly stirred solution of 2.62 g (19.0 mmol) of α,α'-dihydroxy-*o*-xylene and 30 mL of anhydrous *N,N*-dimethylformamide (DMF) at 0 °C was added 2.03 g (9.35 mmol) of bromomethylenedimethylammonium bromide[43] in small batches via a solid addition tube. After the addition was complete, the mixture was stirred overnight at 45 °C. The DMF was distilled under reduced pressure, the residue was taken up in diethyl ether, and the ether extract was washed several times with water and then dried over magnesium sulfate. Removal of the ether in vacuo gave an off-white solid which was recrystallized from hexane yielding 1.04 g (5.16 mmol, 55%) of *o*-bromomethylbenzyl alcohol as fine, white needles: mp 55 °C; IR (KBr) 3450 (OH) cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.3–7.0 (m, 4 H, ArH), 4.8 (s, 2 H, OCH_2), 4.6 (s, 2 H, $BrCH_2$), 1.7 (s, 1 H, OH). Anal. Calcd for C_8H_9BrO: C, 47.76; H, 4.47. Found: C, 47.54; H, 4.36.

2-Bromo-2-phenylethanol (3). Hydrogen bromide was slowly bubbled through a solution of 6.02 g (50.0 mmol) of styrene oxide in 50 mL of chloroform at −15 °C. After 2 h the flask was capped and placed in a freezer overnight. The chloroform was then removed in vacuo and the residue was taken up in diethyl ether. After washing with water, 10% aqueous hydrochloric acid, a saturated sodium bicarbonate solution, and again with water, the ether extract was dried over magnesium sulfate. The ether was removed in vacuo and the residue was recrystallized from hexane to yield 5.80 g (28.8 mmol, 58%) of 2-bromo-2-phenylethanol as white crystals:[44] mp 38 °C; IR (KBr) 3400 (OH) cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.1–7.5 (m, 5 H, ArH), 4.9 (t, 1 H, BrCH), 3.9 (d, 2 H, OCH_2), 2.1 (s, 1 H, OH). Anal. Calcd for C_9H_8BrO: C, 47.76; H, 4.47. Found: C, 47.50; H, 4.39.

Dehydrobromination of the above compound yielded phenylacetaldehyde, thus eliminating the possibility that it was the isomeric 2-bromo-1-phenylethanol, which is known to yield acetophenone upon dehydrobromination.[44]

2,3-Dimethoxy-5-iodobenzyl Alcohol (18). This reaction was carried out as reported for the synthesis of 1,2-dimethoxy-4-iodobenzene.[45] To a mixture of 5.52 g (25.0 mmol) of silver trifluoroacetate and 4.20 g (25.0 mmol) of 2,3-dimethoxybenzyl alcohol in 40 mL of chloroform was added, dropwise, a solution of 6.35 g (25.0 mmol) of iodine in 200 mL of chloroform. The mixture was stirred overnight, after which it was filtered. The filtrate was washed with saturated solutions of sodium bicarbonate and sodium chloride, and then dried over magnesium sulfate. Removal of the chloroform in vacuo yielded a yellow oil which was taken up in diethyl ether. Addition of hexane precipitated 4.95 g (16.8 mmol, 67%) of 2,3-dimethoxy-5-iodobenzyl alcohol as white crystals: mp 69–70 °C; IR (KBr) 3400 (OH) cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.4 (d, 1 H, ArH, J = 8 Hz), 6.6 (d, 1 H, ArH, J = 8 Hz), 4.7 (s, 2 H, $ArCH_2O$), 3.8 (d, 6 H, $ArOCH_3$), 2.2 (s, OH). Anal. Calcd for $C_9H_{11}IO_3$: C, 36.73; H, 3.74. Found: C, 36.65; H, 3.56.

Synthesis of Iodoalkynols and *Z* Vinyl Iodides. To a stirred solution of 104 mmol of the alkynol in 200 mL of THF at −78 °C was slowly added 82.0 mL (209 mmol) of a 2.55 M solution of *n*-butyllithium in hexane. After the addition was complete, stirring was continued for another 25 min. To the solution was then added 26.7 g (105 mmol) of iodine in THF. The mixture was allowed to warm to ambient temperature and then poured onto a mixture of ice and dilute hydrochloric acid. After separation of the organic from the aqueous layer, the THF was removed in vacuo, and the residue was taken up in diethyl ether. The ether extract was then washed with aqueous solutions of sodium bisulfite and sodium bicarbonate and with water and then dried over magnesium sulfate. The ether was then removed in vacuo yielding the iodo alkynol as an oil. Distillation under reduced pressure resulted in decomposition (yield 3-iodopropynol 82%): IR 3350 (OH), 2190 (C≡C) cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.4 (bd, 2 H, C≡CCH_2), 1.8 (bt, 1 H, OH). Yield 4-iodobut-3-yn-2-ol 64%: IR 3350 (OH), 2180 (C≡C)cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.5 (q, 1 H, OCH, J = 7 Hz), 3.2 (s, 1 H, OH), 1.4 (d, 3 H, CCH_3, J = 7 Hz).

A solution of 20.0 mmol of the iodo alkynol in 10 mL of THF was added dropwise to a stirred solution of 40.0 mmol of disiamylborane in THF at 0 °C.[35] After the addition was complete, the mixture was allowed to warm to room temperature and stirring was continued for 1 h. The mixture was then washed with 10% sodium hydroxide, saturated sodium bicarbonate, and saturated sodium chloride solutions. Removal of the borane side products was effected by oxidation with sodium hydroxide and hydrogen peroxide.[46] After removal of the solvents in vacuo, the residue was taken up in diethyl ether, washed several times with water, and dried over magnesium sulfate. After filtration, the ether was removed in vacuo and distillation of the residue in a Kugelrohr apparatus under reduced pressure yielded the *Z* vinyl iodides as light yellow oils (Table IV). The vinyl iodides were not sufficiently stable at ambient temperatures to obtain elemental analyses.

Conversion of Internal Acetylenic Alcohols to *Z* Vinyl Iodides, General Method.[34] To a cooled, stirred solution of 2.16 g (40.0 mmol) of sodium methoxide and 19.5 mmol of the acetylenic alcohol (all of which were obtained from the Farchan Division, Story Chemical Co.) in 30 mL of tetrahydrofuran (THF) was added 40 mL of a 0.5 M solution of lithium aluminum hydride in THF. After stirring from 1 to 24 h, the solution was brought to 0 °C and 10 mL of ethyl acetate was added to destroy the excess $LiAlH_4$. After stirring at 0 °C for 20 min the mixture was cooled to −78 °C and 9.00 g (35.4 mmol) of iodine in 50 mL of THF was slowly added. After the addition was complete, the mixture was allowed to warm to room temperature and placed in a separatory funnel with 150 mL of diethyl ether, 100 mL of water, and enough hydrochloric acid to dissolve the suspended solids. The ether layer was then washed with saturated bicarbonate solution and water and then dried over magnesium sulfate. Removal of the solvent in vacuo yielded the *Z* vinyl iodides, all of which are unstable at ambient temperature. The iodides were either stored in a freezer or carbonylated directly. No formation of the *E* isomer was observed by NMR (Table IV).

General Procedure for the Carbonylation of Halo Alcohols (Table II). A mixture of 0.0328–0.0410 mmol of bis(triphenylphosphine)-palladium(II) chloride,[21] 2.00–12.50 mmol of the halo alcohol, and 2.00–12.50 mmol of potassium carbonate in a flask stoppered with a serum cap was evacuated and then filled with carbon monoxide. By means of a syringe, 10 mL of THF or DMF followed by 1 drop of hydrazine were added and the mixture was stirred under 1 atm of carbon monoxide for 24 h. The mixture was filtered, and, when THF was the solvent, it was removed in vacuo, the residue was distilled under reduced pressure, and the distillate was recrystallized. When DMF was the solvent, at the end of the reaction, the mixture was either fractionally distilled (tropic acid β-lactone, **4**) or ether was added and the mixture was extracted with water. The ether layer was dried and the product either was distilled after removal of the ether (lactones **4** and **6**) or recrystallized (lactones **16** and **20**).

General Procedure for the Carbonylation of Vinyl Iodides (Table III). To a mixture of 0.04 mmol of bis(triphenylphosphine)palladium(II) chloride[21] and 10 mmol of anhydrous potassium carbonate in a carbonylation flask fitted with a rubber septum (purged with carbon monoxide) were added 10 mL of THF and 10 mmol of iodo alcohol followed by 2 drops of hydrazine via a syringe. The mixture was stirred under 1–3 atm carbon monoxide for 24–72 h at 25–35 °C. Diethyl ether (40 mL) was then added and the mixture was filtered. The lactones were isolated by removal of the solvent and purified by distillation.

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Anomalous Equilibrium and Kinetic α-Deuterium Secondary Isotope Effects Accompanying Hydride Transfer from Reduced Nicotinamide Adenine Dinucleotide

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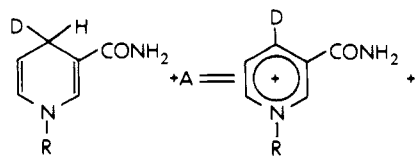
Abstract: The kinetic α-deuterium secondary isotope effect on the second-order rate constant has been measured for the nonenzymatic direct hydride transfer reduction of 4-cyano-2,6-dinitrobenzenesulfonate by NADH (deuterium substitution of the hydrogen bonded to the 4 carbon of NADH which is not transferred to the acceptor). Values of 1.156 ± 0.018 and 1.1454 ± 0.0093 were obtained using direct and intramolecular competition methods, respectively. The corresponding (enzyme catalyzed) equilibrium isotope effects were found to be 1.013 ± 0.020 and 1.0347 ± 0.0087 as determined by direct and intermolecular competition methods, respectively. Thus, the value of the kinetic effect is significantly greater than that on the equilibrium. It is suggested that this may arise either from participation of the α hydrogen in a hyperconjugative stabilization of an early transition state or from its participation in the reaction coordinate motion of a nonlinear activated complex. The values of the equilibrium effect allow calculation of a fractionation factor (relative to acetylene) for hydrogen bonded to the 4 carbon of NAD^+ of 1.448 ± 0.028 or 1.418 ± 0.020. This is larger than expected based on comparison with hydrogen bound to sp^2 carbon in propene (1.336) or benzene (1.368) but is consistent with the decreased aromatic character of pyridinium vibrational spectra. The lack of a significant inverse value for the equilibrium α-deuterium effect suggests complications in the interpretation of reported kinetic secondary effects of 0.85 and 1.2 for the forward ($sp^3 \rightarrow sp^2$) and reverse ($sp^2 \rightarrow sp^3$) rate constants for the nonenzymatic transhydrogenation of *N*-benzyl-1,4-dihydronicotinamide and its nicotinamide salt.

An understanding of the chemistry of enzyme cofactors should lead to a greater understanding of the possible roles these substances play in biological processes. Thus, nonenzymatic reductions of specific acceptors by dihydronicotinamides have been studied as models for the chemical mechanisms of the NAD^+-dependent dehydrogenases. Particular interest has been focused on the question whether the formal hydride transfer in these reactions (eq 1) takes place in a single kinetic



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event (as a hydride ion transfer) or whether various one-electron intermediates are present. Multistep mechanisms have been proposed. These include electron transfer followed by atom transfer; electron transfer and proton transfer, followed by another electron transfer, and so on. The principal evidence for such decoupled mechanisms has been the observation[1] that, if a simple bimolecular mechanism were followed, then large inverse secondary α-deuterium isotope effects would be required to explain the kinetic data reported for several dihydronicotinamide reactions. Since the α hydrogen is bonded to a carbon which undergoes a sp^3 to sp^2 hybridization change in the course of the reaction, the secondary isotope effect was expected to have a value greater than one. It was initially proposed that the inverse effect was only apparent and was the

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