Table I. Proton and Carbon NMR Chemical Shift Assignments for 3a Recorded at 300.068/75.459 MHz for $^1H/^{13}C$ ($CDCl_3$ Solvent)

position	δ ^1H (ppm)	δ ^{13}C (ppm)	position	δ ^1H (ppm)	δ ^{13}C (ppm)
1		53.59	7	5.08	126.66
2	5.55	139.40	8	4.25	65.96
3	5.75	132.45	8a	2.24	48.17
4	2.72	44.72	9	0.98, 1.17	56.84
4a	2.70	46.61	1-CH_3	1.34	20.12
5	4.01	67.81	6-CH_3	1.55	18.51
6		136.54			

affording a colorless oil, which soldified upon standing overnight in a refrigerator. Recrystallization of the resulting solid from acetone afforded pure **2** (120 mg, 60%) as a colorless microcrystalline solid: mp 58–59 °C; IR (KBr) 2990 (s), 1720 (vs), 1170 (s), 1010 (s), 850 cm^{-1} (m); ^1H NMR ($CDCl_3$) δ 1.70 (m, 6 H), 1.87 (m, 2 H), 2.42 (m, 2 H), 2.72 (m, 4 H); ^{13}C NMR ($CDCl_3$) δ 15.48 (q), 15.87 (q), 41.88 (d), 43.52 (d), 46.11 (t), 46.37 (s), 47.74 (d), 50.92 (d), 52.22 (s), 55.61 (d), 59.96 (d), 211.3 (s), 212.7 (s); mass spectrum (70 eV), *m/e* (relative intensity) 202 (molecular ion, 71.8), 174 (37.5), 159 (49.2), 121 (100.0), 91 (48.3), 80 (72.9), 77 (41.6), 39 (66.9).

Anal. Calcd for $C_{13}H_{14}O_2$: C, 77.20; H, 6.98. Found: C, 76.95; H, 7.00.

1,6-Dimethyl-1α,4α,4aα,5α,8β,8aα-hexahydro-1,4-methanonaphthalene-5,8-diol (3a). Sodium borohydride reduction of **1a** (200 mg, 1.0 mmol) was performed in the presence of cerous chloride by using a previously published procedure.[8] Crude diol **3a** (180 mg, 90%) was thereby obtained. Recrystallization of this material from acetone afforded pure **3a** (180 mg, 90%) as a colorless microcrystalline solid: mp 129–130 °C; IR (KBr) 3500 (vs), 3010 (w), 1610 (s), 1410 (s), 1320 (s), 1110 cm^{-1} (s); mass spectrum (70 eV), *m/e* (relative intensity) (no molecular ion), 109 (17.0), 97 (18.5), 80 (100.0), 79 (43.0), 77 (19.4), 53 (10.2), 39 (19.2); ^1H and ^{13}C NMR data for **3a** are given in Table I.

Anal. Calcd for $C_{13}H_{18}O_2$: C, 75.69; H, 8.77. Found: C, 75.45; H, 9.01.

Acknowledgment. Financial support of this study by the Air Force Office of Scientific Research (Grant AFOSR-84-0085), the Robert A. Welch Foundation (Grant E-792 to G.E.M. and Grant B-963 to A.P.M.), the National Institutes of Health Biomedical Research Program, and the University of North Texas Faculty Research Committee is gratefully acknowledged.

Palladium(0)-Catalyzed Cyclization Followed by Allylation of Allylic Alkynoates and the Related System

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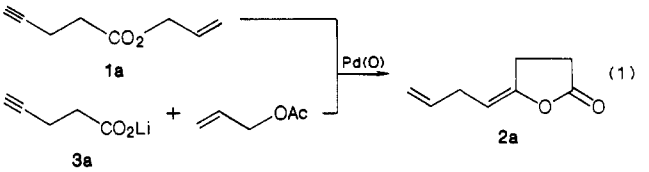
Intramolecular cyclization of alkynoic acids catalyzed by mercury(II)[1] and palladium(II) salts[2] provides a convenient method of preparing synthetically and biologically important unsaturated lactones. The development of the cyclization coupled with a carbon–carbon bond-forming reaction which gives a substituted unsaturated lactone may be expected to enhance remarkably the usefulness of this methodology. Very recently it has been reported that the alkenylpalladium chloride intermediates generated by the $PdCl_2$-catalyzed intramolecular cyclization of lithium alkynoates are trapped by allylic chlorides to give the allyl-substituted unsaturated lactones. Use of a large amount of allylic chlorides (20 equiv), however, is required for the trapping.[3] Here we have studied another approach to the synthesis of substituted unsaturated lactones, i.e., the palladium(0)-catalyzed cyclization followed by allylation of allylic alkynoates and a related system of lithium alkynoates and allylic acetates (for example, eq 1). This approach is featured with the use of an equimolar amount of alkynoate and allylic moieties, respectively.



When allyl 4-pentynoate (**1a**) was heated at 100 °C in acetonitrile in the presence of a palladium(0) complex catalyst (5.0 mol %) generated from $Pd_2(dba)_3{\cdot}CHCl_3$ and trimethylolpropane phosphite, (*E*)-4,7-octadien-4-olide (**2a**) was obtained in a good yield (Table I). Interestingly the formation of the lactone is highly dependent upon the ligand and the solvent. Trimethylolpropane phosphite was the best ligand. Triisopropyl phosphite was similarly effective. On the other hand, trimethyl and triphenyl phosphites were not effective. Triphenylphosphine showed a medium effect. Acetonitrile or a mixed solvent containing acetonitrile was a good solvent for the synthesis of **2a**. No formation of the lactone was observed in benzene or THF although the starting substrate **1a** was consumed.

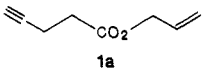
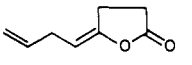
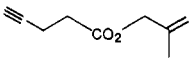
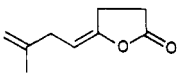
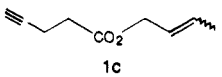
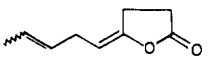
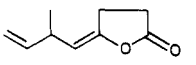
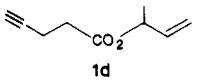
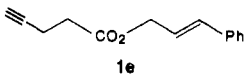
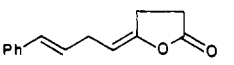
Various allylic 4-pentynoates could be used for the reaction. Methallyl and cinnamyl esters gave the unsaturated lactones in good yields. In the latter case, diisopropyl phenylphosphonite was an effective ligand. One feature of the reaction is the regio- and stereoselective cyclization of the alkynoate moiety to produce the γ-(*E*)-alkylidene-γ-butyrolactone exclusively. The 4*E* stereochemistry of the products **2a**, **2b**, **2c**, **2c′**, and **2e** was assigned on the basis of the ^1H NMR chemical shifts of the C-5 olefinic protons δ 5.25, 5.29, 5.24, 5.12, and 5.34, respectively. The literature values[3] of the C-5 olefinic protons of (*E*)- and (*Z*)-**2a** are δ 5.28 and 4.64, respectively, which are compatible with the calculated values.[4] The stereochemistry of the allylic moiety in **2c** and **2e** was predominantly to exclusively *E*. The regioselectivity of the carbon–carbon bond formation toward the allylic moiety depends on its structure. In contrast to the regioselective reaction of the cinnamyl group, the carbon–carbon bond-forming reaction of 2-butenyl 4-pentynoate (**1c**) took place nonregioselectively to give two isomeric γ-(*E*)-alkylidene-γ-butyrolactones, i.e., (4*E*)-7-nonadien-4-olide (**2c**) (7*E* isomer/7*Z* isomer = 9.7) and (*E*)-6-methyl-4,7-octadien-4-olide (**2c′**). It is worth noting that isomeric 1-methyl-2-propenyl 4-pentynoate (**1d**) gave the almost same result as **1c**. This finding suggests the participation of the alkenyl(π-allyl)-palladium complex in the allylation step.

On the basis of two features of the reaction, i.e., the stereoselective cyclization of the alkynoate moiety and the intermediacy of the (π-allyl)palladium complex, the rea-

(1) (a) Yamamoto, M. *J. Chem. Soc., Chem. Commun.* **1978**, 649. (b) Kraft, G. A.; Katzenellenbogen, J. A. *J. Am. Chem. Soc.* **1981**, *103*, 5459.
(2) Lambert, C.; Utimoto, K.; Nozaki, H. *Tetrahedron Lett.* **1984**, *25*, 5323.
(3) Yanagihara, N.; Lambert, C.; Iritani, K.; Utimoto, K.; Nozaki, H. *J. Am. Chem. Soc.* **1986**, *108*, 2753. Under the ultrasound irradiation, the reaction can be done by the use of 1.5–2.5 equiv of allylic chlorides.
(4) Pascal, C.; Meier, J.; Simon, W. *Helv. Chim. Acta* **1966**, *49*, 164.

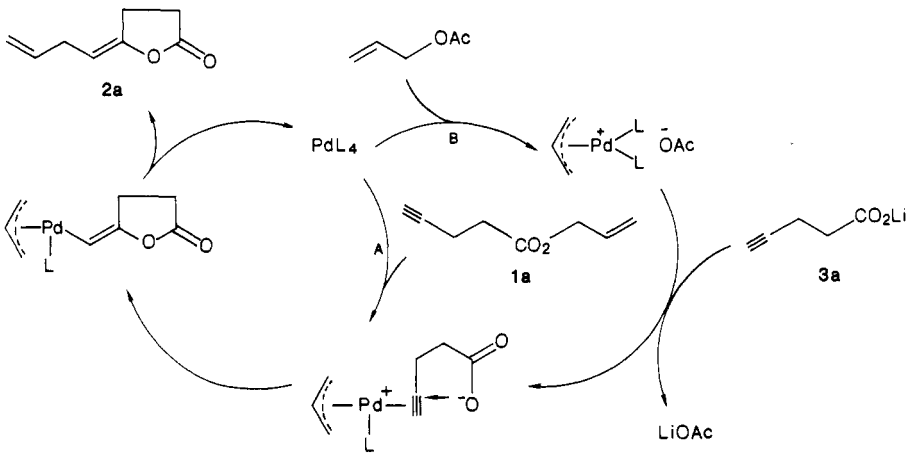
0022-3263/88/1953-2650$01.50/0

Table I. Palladium(0)-Catalyzed Synthesis of γ-(*E*)-Alkylidene-γ-butyrolactones from Allylic Alkynoates[a]

allylic alkynoate	ligand	solvent (mL)	γ-(*E*)-alkylidene-γ-butyrolactone	yield (%)[e]
 1a	$P(OCH_2)_3CEt$	MeCN (5)	 2a	86 (73)[f]
		MeCN (2.5)–C_6H_6 (2.5)		78
		MeCN (2.5)–C_6H_6 (2.5)		69[d]
	$P(OPr\text{-}i)_3$	MeCN (5)		76
		MeCN (3.3)–THF (1.7)		66
		THF (5)		0[h]
		C_6H_6 (5)		0[h]
	$P(OMe)_3$	MeCN (2.5)–C_6H_6 (2.5)		3[i]
	$P(OPh)_3$	MeCN (2.5)–C_6H_6 (2.5)		14[i]
	$P(Bu\text{-}n)_3$	MeCN (2.5)–C_6H_6 (2.5)		1[i]
	PPh_3	MeCN (2.5)–C_6H_6 (2.5)		30
	$Ph_2PCH_2CH_2PPh_2$	MeCN (2.5)–C_6H_6 (2.5)		0[h]
 1b	$P(OCH_2)_3CEt$	MeCN (4)–THF (1)	 2b	80[b] (65)[f]
 1c	$P(OCH_2)_3CEt$	MeCN (4)–THF (1)	 2c	32[b,j] (*Z*:*E* = 3:29)[g]
			 2c′	24[b]
 1d	$P(OCH_2)_3CEt$	MeCN (4)–THF (1)	2c	33[b,j] (*Z*:*E* = 3:30)[g]
			2c′	25[b]
 1e	$P(OCH_2)_3CEt$	MeCN (5)	 2e	72[c]
	$PhP(OPr\text{-}i)_2$	MeCN (5)		92[c]

[a] Allylic alkynoate, 0.30 mmol; $Pd_2(dba)_3{\cdot}CHCl_3$, 0.0075 mmol; ligand/Pd = 4 except $Ph_2PCH_2CH_2PPh_2$/Pd = 2; temperature, 100 °C; time, 2 h. [b] Temperature, 120 °C. [c] Time, 3 h. [d] Ligand/Pd = 2. [e] Yield was determined by GC. [f] The value in parentheses is isolated yield by PLC in the reaction using 1.50 mmol of allylic alkynoate. [g] The ratio was determined by GC. [h] Any major product was not detected by GC although allyl 4-pentynoate was consumed. [i] Allyl 4-pentynoate remained almost unreacted. [j] 4-Penten-4-olide was produced in ca. 40% yield.

Scheme I

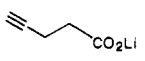
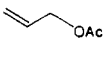
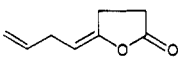
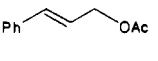
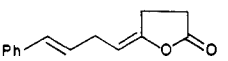
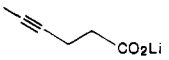
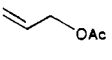
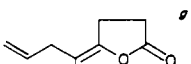
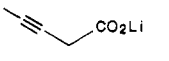
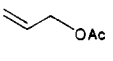
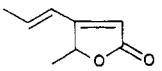


sonable reaction path of the palladium(0)-catalyzed reaction of **1a** as a representative is depicted in Scheme I (route A), where a novel catalytic species of a (π-allyl)palladium cation activating the carbon–carbon triple bond is involved.[5] Oxidative addition of the palladium(0) complex to **1a** generates a (π-allyl)palladium cation and an alkynoate gegenanion. The (π-allyl)palladium cation activates the carbon–carbon triple bond toward the intramolecular nucleophilic attack of the carboxylate anion from the opposite side of the palladium atom to form an (*E*)-alkenyl(π-allyl)palladium intermediate. Subsequent coupling of the π-allyl and alkenyl groups[6] gives **2a** and regenerates the palladium(0) complex. Thus the present palladium(0)-catalyzed reaction may be mechanistically discriminated from the recently reported $PdCl_2$-catalyzed cyclization–allylation reaction of lithium alkynoates and allylic chlorides[3] where the palladium atom preserves a divalent

(5) Stoichiometric cyclization of allyl 4-pentenoate effected by the palladium(0) complex has been reported: Tsuda, T.; Chujo, Y.; Saegusa, T. *Synth. Commun.* **1981**, *11*, 775.

(6) Matsushita, H.; Negishi, E. *J. Am. Chem. Soc.* **1981**, *103*, 2882.

Table II. Palladium(0)-Catalyzed Synthesis of Unsaturated Lactones from Lithium Alkynoates and Allylic Acetates[a]

lithium alkynoate	allylic acetate	ligand	unsaturated lactones	yield (%)[d]
 **3a**		$P(OCH_2)_3CEt$	 **2a**	79[b]
		$P(OCH_2)_3CEt$ $PhP(OPr\text{-}i)_2$	 **2e**	84[e] (59)[f] 88
 **3b**		$P(OCH_2)_3CEt$ $P(OCH_2)_3CEt$ PPh_3	 **4b**	65[c] 56[c,e] (38)[f] 44[c]
 **3c**		$P(OPr\text{-}i)_3$ $PhP(OPr\text{-}i)_2$ PPh_3 $MePPh_2$	 **4c**	7 19 41 8

[a] Lithium alkynoate, 0.30 mmol; lithium alkynoate:allylic acetate:$Pd_2(dba)_3{\cdot}CHCl_3$:ligand= 1:1:0.025:0.2; solvent, MeCN (3 mL)–THF (2 mL); temperature, 100 °C; time; 3 h. [b] Time, 4 h. [c] Temperature, 120 °C. [d] Yield was determined by GC. [e] The palladium(0) catalyst was prepared by the reaction of $Pd(OAc)_2$ (5.0 mol %) and 2 equiv of *n*-BuLi in the presence of the ligand. [f] The value in parentheses is isolated yield by PLC in the reaction using 1.50–2.00 mmol of lithium alkynoate and the $Pd(OAc)_2$–2*n*-BuLi catalyst. [g] The product is a single stereoisomer which was tentatively assigned as trans based upon mechanistic consideration of the formation of γ-(*E*)-alkylidene-γ-butyrolactones unsubstituted at the C-1 of the alkylidene group.

oxidation state throughout the reaction and the alkenylpalladium chloride intermediates react with a large excess of allylic chlorides (20 equiv) regioselectively at the γ-position in an S_N2' fashion.

Instead of the allylic alkynoate, use of an equimolar mixture[7] of lithium alkynoate and allylic acetate effected the same reaction. This finding is readily understandable by the assumed reaction path (route B) in Scheme I. Exchange of the carboxylate moieties between lithium alkynoate and the (π-allyl)palladium acetate complex generates the key intermediate of the (π-allyl)palladium alkynoate complex. The results are summarized in Table II. In addition to lithium 4-pentynoate, lithium 4-hexynoate and 3-pentynoate could be used as an alkynoic acid component. In the latter case, the triphenylphosphine ligand gave a good result to produce a conjugated γ-lactone by the secondary isomerization.

Interestingly the palladium(0) complex effected the cyclization of the free alkynoic acid, i.e., 4-pentynoic acid, in the presence of the trimethylolpropane phosphite ligand in MeCN to produce 4-penten-4-olide in excellent yield. Use of the triphenylphosphine ligand or the benzene and THF solvents decreased the yield of 4-penten-4-olide.

Experimental Section

IR spectra were determined on a Hitachi 260-50 grating spectrophotometer. ^1H NMR spectra (400 MHz) were recorded on a JEOL JNM-JX-400 instrument. All chemical shifts are reported in δ downfield from internal tetramethylsilane. Coupling constants (*J*) are reported in hertz. Mass spectra were obtained on a JEOL DX-300 instrument. Gas chromatographic analyses (GC) were made on a Shimadzu 4CPT instrument. GC quantitative analyses of reaction products were made with internal standards with calibration based upon authentic samples employing a 20% silicone DC 550 on Celite 545 column. Preparative layer chromatography (PLC) was performed on a silica gel plate (20 × 20 × 0.2 cm).

Tetrahydrofuran (THF) was distilled from $LiAlH_4$ under nitrogen. Acetonitrile and benzene were distilled from CaH_2 under nitrogen. Allylic 4-pentynoates **1a–e** were prepared by the reaction of 4-pentynoyl chloride and allylic alcohols. 4-Pentynoyl chloride was obtained from commercially available 4-pentynoic acid and thionyl chloride. 4-Hexynoic acid and 3-pentynoic acid were prepared according to the published method.[8] Lithium alkynoates were prepared by the reaction of alkynoic acids and *n*-butyllithium in THF. Allylic acetates were commercial reagents. $Pd_2(dba)_3{\cdot}CHCl_3$ was prepared by the reported procedure.[9] $Pd(OAc)_2$ was a commercial reagent. Phosphorus ligands were commercial reagents and were distilled under nitrogen after drying over $CaSO_4$ (Drierite) except PPh_3, $MePPh_2$, and $Ph_2PCH_2CH_2PPh_2$ which were used without further purification.

Palladium(0)-Catalyzed Reaction of Allyl 4-Pentynoate (1a). The reaction was carried out under nitrogen. To an 80-mL glass tube were added $Pd_2(dba)_3{\cdot}CHCl_3$ (0.0388 g, 0.0375 mmol), MeCN (25 mL), $P(OCH_2)_3CEt$–benzene solution (0.300 mmol), and **1a** (0.217 mL, 1.50 mmol) in this order. The glass tube was sealed by flame and was heated at 100 °C for 2 h. The reaction mixture was concentrated to give the residue which was purified twice by PLC (ether:hexane = 1:2 v/v) to give the product **2a** (0.151 g, 73%): IR (neat, cm^{-1}) 1790, 1700, 1120, 910; ^1H NMR 2.65–2.75 (m, 4 H), 2.84 (t, *J* = 8.0, 2 H), 5.02 (d, *J* = 10.1, 1 H), 5.07 (d, *J* = 17.1, 1 H), 5.25 (t, *J* = 7.9, 1 H), 5.80 (ddt, *J* = 17.1, 10.1, 6.0, 1 H); MS, *m/e* (relative intensity) 138 (M^+, 26), 95 (100), 83 (45), 56 (53), 55 (51), 54 (41); HRMS, *m/e* 138.0659, calcd for $C_8H_{10}O_2$ 138.0681. The experiment determining the GC yield of **2a** was carried out similarly by using **1a** (0.30 mmol), $Pd_2(dba)_3{\cdot}CHCl_3$ (0.0075 mmol), the phosphorus ligand (0.060 mmol), and the solvent (5 mL).

The reactions of **1b–e** were carried out as described above and the products **2b–e** were identified as follows. Product **2b** (PLC, benzene:ether = 6:1 v/v): IR (neat, cm^{-1}) 3080, 1800, 1695, 1300, 1120, 910; ^1H NMR 1.74 (s, 3 H), 2.63–2.71 (m, 4 H), 2.84 (t, *J* = 8.6, 2 H), 4.73 (br s, 1 H), 4.75 (br s, 1 H), 5.29 (t, *J* = 8.1, 1 H); MS, *m/e* 152 (M^+, 91), 124 (59), 110 (51), 109 (90), 95 (99), 81 (52), 68 (52), 56 (73), 55 (100), 43 (74); HRMS, *m/e* 152.0816, calcd for $C_9H_{12}O_2$ 152.0837. The products **2c** and **2c'** were separated by PLC (C_6H_6:Et_2O = 6:1 v/v). Analysis of ^1H NMR spectra of **2c** consisting of (*E*)-**2c** and (*Z*)-**2c** gave the following ^1H NMR data of the major component of (*E*)-**2c**. They were not separable by PLC (C_6H_6:Et_2O = 6:1 v/v), but were separated by GC. GC–mass spectroscopy of the mixture gave the following mass spectrum data of (*E*)-**2c**. Product (*E*)-**2c**: IR (neat, cm^{-1}) 3020, 1800, 1695, 1300, 1120, 970, 905; ^1H NMR 1.68 (d, *J* = 6.1, 3 H), 2.64 (t, *J* = 7.0, 2 H), 2.67 (t, *J* = 8.5, 2 H), 2.83 (t, *J* = 8.5, 2 H), 5.24 (t, *J* = 7.9, 1 H), 5.41 (dt, *J* = 15.3, 5.9, 1 H), 5.50 (dq, *J* = 15.2, 6.0, 1 H); MS, *m/e* (relative intensity) 152 (M^+, 83), 124 (53), 110 (46), 95 (100), 81 (47), 68 (54), 56 (70), 42 (98); HRMS, *m/e*

(7) Without the palladium(0) catalyst, no reaction took place between lithium 4-pentynoate and allyl acetate in MeCN–THF at 100 °C.

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152.0828, calcd for $C_9H_{12}O_2$ 152.0837. In the ^1H NMR spectrum of **2c**, the two absorptions of 5.36 (dt, J = 11, 7) and 5.54 (dq, J = 11, 7) may be assigned to the two olefinic protons of the disubstituted olefinic moiety of the minor component (*Z*)-**2c** although they are not clearly separated from those of (*E*)-**2c**. Product **2c'**: IR (neat, cm^{-1}) 3090, 1800, 1700, 1640, 1300, 1120, 1005, 910, 850; ^1H NMR 1.14 (d, J = 7.0, 3 H), 2.69 (t, J = 8.5, 2 H), 2.82–2.94 (m, 3 H), 4.97 (d, J = 10.1, 1 H), 5.02 (d, J = 17.1, 1 H), 5.12 (d, J = 9.9, 1 H); MS, m/e (relative intensity) 152 (M^+, 19), 129 (47), 101 (100), 69 (47), 55 (41); HRMS, m/e 152.0816, calcd for $C_9H_{12}O_2$ 152.0837. Product **2e** (PLC, ether:hexane = 6:5 v/v): IR (neat, cm^{-1}) 3025, 1790, 1690, 1590, 1490, 1300, 1100, 960, 830, 740, 680; ^1H NMR 2.65–2.72 (m, 4 H), 2.84 (t, J = 7.3, 2 H), 5.34 (tt, J = 8.0, 2.3, 1 H), 6.18 (dt, J = 15.8, 6.2, 1 H), 6.42 (d, J = 15.7, 1 H), 7.15–7.40 (m, 5 H); MS, m/e (relative intensity) 214 (M^+, 100), 130 (33), 129 (34), 95 (41), 91 (49); HRMS, m/e 214.0972, calcd for $C_{14}H_{14}O_2$ 214.0994.

Palladium(0)-Catalyzed Reaction of Lithium 4-Hexynoate (3b) and Allyl Acetate. The reaction was carried out under nitrogen. The palladium(0) catalyst solution was prepared separately by the reaction of *n*-BuLi hexane solution (0.15 mmol) and $Pd(OAc)_2$ (0.017 g, 0.075 mmol) in THF (8 mL) containing $P(OCH_2)_3CEt$ (0.086 mL, 0.30 mmol) at room temperature for 15 min. To a stirred suspension of **3b** (0.177 g, 1.50 mmol) in MeCN (12 mL) in an 80-mL glass tube was added the above-prepared palladium(0) catalyst solution followed by allyl acetate (0.162 mL, 1.50 mmol). The glass tube was sealed by flame and was heated at 120 °C for 3 h under magnetic stirring. The reaction mixture was concentrated to give the residue which was purified twice by PLC (ether:hexane = 1:1 v/v) to give **4b** (0.087 g, 38%): IR (neat, cm^{-1}) 3075, 1790, 1700, 1640, 1300, 1120, 990, 910; ^1H NMR 1.71 (s, 3 H), 2.64–2.70 (m, 4 H), 2.82 (t, J = 8.2, 2 H), 5.02–5.09 (m, 2 H), 5.73 (ddt, J = 17.0, 10.1, 6.5, 1 H); MS, m/e (relative intensity) 152 (M^+, 100), 137 (19), 124 (23), 110 (39), 109 (82), 97 (77), 95 (54), 68 (47), 56 (50), 43 (32); HRMS, m/e 152.0809, calcd for $C_9H_{12}O_2$ 152.0837.

The reaction of lithium 4-pentynoate (**3a**) and cinnamyl acetate was carried out as described above. The product **4c** was identified as follows. Product **4c**: IR (neat, cm^{-1}) 1750, 1650, 1310, 1180, 960; ^1H NMR 1.45 (d, J = 6.6, 3 H), 3.02 (dd, J = 17.2, 7.0, 1 H), 3.16 (dd, J = 17.3, 6.5, 1 H), 4.97 (q, J = 6.8, 1 H), 5.22 (dq, J = 16.8, 1.3, 1 H), 5.24 (dq, J = 10.3, 1.2, 1H), 5.81 (s, 1 H), 5.84 (ddt, J = 17.4, 10.3, 6.6, 1 H); MS, m/e (relative intensity) 138 (M^+, 23), 95 (100), 67 (27), 68 (27), 43 (22); HRMS, m/e 138.0696, calcd for $C_8H_{10}O_2$ 138.0681.

A New Synthesis of 4-Substituted Isoquinolines

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Although 4-substituted isoquinolines are relatively rare in nature, considerable interest in the syntheses of these molecules has been generated by reports of their significant pharmacological activity.[1-4] In particular, analogues of papaverine in which the benzyl substituent is transposed from C-1 to C-4 have been attractive as synthetic targets. A strategy that has proven very effective introduces the C-4 substituent by the reaction of a 1,2-dihydroisoquinoline, which behaves as an enamine, with an aldehyde or alkyl halide.[5] Appropriate 1,2-dihydroisoquinolines can be generated in situ from 1,2,3,4-tetrahydroisoquinolines,[6] the Bobbit modification[7,8] of the Pomerantz–Fritsch reaction, or the $LiAlH_4$ reduction of isoquinoline and its salts;[9-11] but none of these appears to be as effective as the boron-activated enamine **3**, prepared by the reduction of isoquinoline (**1**) with sodium triethylborohydride (**2**). The reactions of **3** with aryl aldehydes produce superior yields of **6** (R = Ar) and can be carried out as "one-pot" operations. Aliphatic aldehydes can also be used, but the yields of **6** (R = alkyl, H) are not as high.

Scheme I

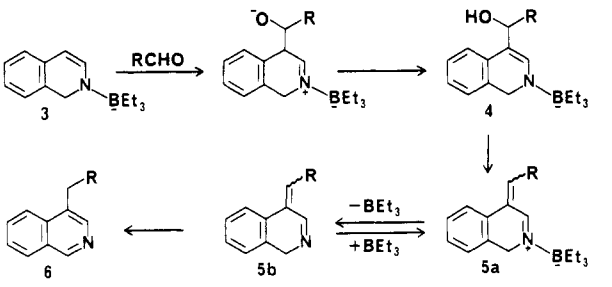
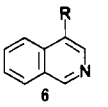
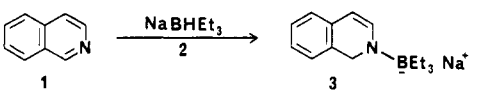


Table I. Yields and Physical Constants for Compounds 6



compd	R	% yield	mp, °C	bp, °C (mmHg)
6a	benzyl	65	117.5–118.5	
6b	2-furylmethyl	60	53.0–53.5	
6c	3,4-dimethoxybenzyl	58	83.5–84.0	
6d	4-quinolylmethyl	65	181.0–182.0	
6e	methyl	25		54–55 (0.03)
6f	*n*-propyl	28		60–61 (0.025)
6g	β-phenethyl	38		120–122 (0.03)



The formation of **3** can be followed by the disappearance of the doublet for **2** at δ −12.6 in the ^{11}B NMR spectrum and the appearance of a broad singlet for **3** at δ −6.1 as isoquinoline is added to a sample tube containing **2** (1 M in THF). The reaction is virtually instantaneous at room temperature and provides a solution of **3** that can be used directly.

Presumably, the overall mechanistic pathway leading to **6** involves electrophilic attack of the aldehyde at C-4 followed by proton transfer, conjugate loss of hydroxide, and rearomatization (Scheme I). However, it does not appear that these processes are complete prior to quenching since the workup procedure affects product

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