

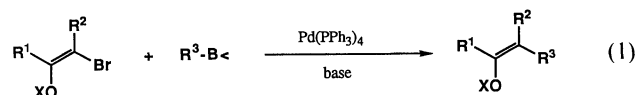
The Palladium-Catalyzed Cross-Coupling Reaction of Enol Acetates of α -Bromo Ketones with 1-Alkenyl-, Aryl-, or Alkylboron Compounds; A Facile Synthesis of Ketones and Their Enol Acetates

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Synopsis. The synthesis of stereodefined enol acetates of ketones is readily accomplished by palladium-catalyzed cross-coupling reaction between alkyl-, aryl-, or 1-alkenylboron reagents with enol acetates of α -bromo ketones. Hydroboration of alkene with 9-BBN, followed by coupling with (Z)-2-ethoxy-1-bromoethene gives the enol ether of aldehyde. These enol acetates and ethers are readily deprotected to give corresponding ketones and aldehydes in high yields.

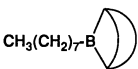
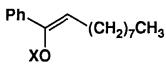
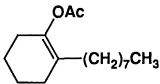
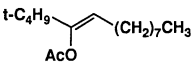
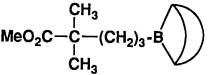
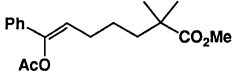
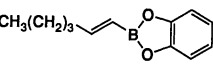
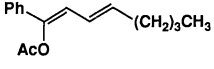
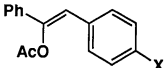
Our recent success in achieving the coupling of 1-alkenyl or aryl halides with 9-alkyl-9-borabicyclo[3.3.1]nonane (9-R-9-BBN),¹⁾ 1-alkenylboronic acids or their esters,²⁾ and arylboronic acids³⁾ in the presence of palladium catalyst and base encouraged us to explore the possibilities of achieving a similar alkylation of α -acetoxy- or α -alkoxy- β -bromoalkenes **1** (Eq. 1). The reaction provides enol acetate or ether derivatives **2** which can serve as dienophiles of cycloaddition⁴⁾ or as precursors of the ketones by deprotection of acetoxy group with bases. Although the synthesis of ketones via the base induced alkylation of α -bromo ketones^{5a,5b)} or α -diazo ketones^{5c)} with organoboranes have been reported, the present procedure provides an alternative feasible synthetic route to such ketone and their enol

**1a**: R¹ = Ph, R² = H, X = SiMe₃**1b**: R¹ = Ph, R² = H, X = Me**1c**: R¹ = Ph, R² = H, X = Ac**1d**: R¹, R² = -(CH₂)₄-, X = Ac**1e**: R¹ = Bu^t, R² = H, X = Ac**1f**: R¹ = Prⁱ, R² = H, X = Ac**2**

acetate derivatives.

Although the coupling⁶⁾ of Grignard reagents with trimethylsilyl enol ethers of α -bromo aldehydes or α -bromo ketones have been successfully utilized for the synthesis of aldehydes or ketones, the reaction of 9-octyl-9-BBN with **1a** in dioxane at 60 °C in the presence of 3 equivs of powdered K₃PO₄ and 3 mol% of Pd(PPh₃)₄ results in a complex mixture of products which includes the corresponding coupling product **2** (R¹=Ph, R²=H, R³=C₈H₁₇, X=SiMe₃) (30–40%), acetophenone, and hexadecane (Entry 1 in Table 1). The result indicates that the cross-coupling to give **2** is

Table 1. Syntheses of Enol Acetates and Ethers (Eq. 1)^{a)}

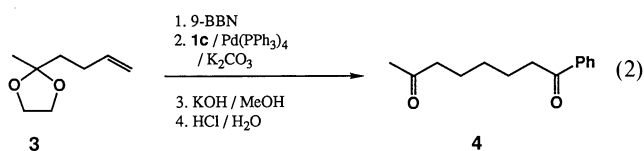
Entry	1	Boron reagent	Product	Yield/% ^{b)}
1	1a			X=SiMe ₃ 30–40
2	1b			X=Me 83
3	1c			X=Ac (89)
4	1d			(63) ^{c)}
5	1e			(58)
6	1c			(93)
7	1c			(80)
8	1c	PhB(OH) ₂		X=H (79)
9	1c	<i>p</i> -MePhB(OH) ₂		X=Me 80
10	1c	<i>p</i> -MeOPhB(OH) ₂		X=OMe 73

a) All reactions were carried out in dioxane at 60 °C for 16 h (Entries 1–6) or 80 °C for 5 h (Entries 7–10) in the presence of K₂CO₃ (3 equivs) (Entries 3–6) or K₃PO₄ (3 equivs) (Entries 1, 2, and 7–10) and Pd(PPh₃)₄ (3 mol%) unless otherwise noted. b) GLC yields based on **1** employed and isolated yields are in parentheses. c) The reaction was conducted for 46 h.

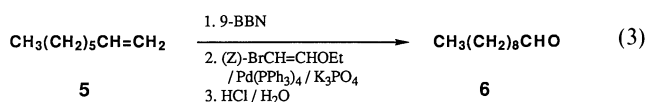
presumably competing with the formation of palladium enolate species⁷⁾ of acetophenone which leads to acetophenone and dimerization product by the reaction with 9-octyl-9-BBN. Fortunately, the clean couplings are readily achieved by utilizing methyl enol ether **1b** or enol acetate **1c** of α -bromoacetophenone, particularly the latter bromide works well with representative organo-boron reagents. Oxidative addition⁸⁾ of 1-halo-1-alkene to palladium(0) complex is retarded by electron-donating substituents, and electron-withdrawing groups reverse the effect on the rate. Transfer^{1,9)} of organic group from boron to palladium(II) halide which is usually rate-determining step in the reaction with less nucleophilic organometallics such as tin and boron compounds is also retarded by electron-donating groups. Thus, the acetate of bromoacetophenone **1c** provides a higher yield of coupling product over methyl ether derivative **1b** (Entries 2 and 3). Several other enol acetates are readily prepared by a similar hydroboration-coupling sequence (Entries 4–6). A catechol ester of 1-hexenylboronic acid or arylboronic acids couple with **1c** in dioxane at 80 °C in the presence of K_3PO_4 (3 equivs) and $Pd(PPh_3)_4$ (3 mol%) (Entries 7–10).

The introduction of a phenyl group α to carbonyl is a useful step in the synthesis¹⁰⁾ of a variety of biologically interesting compounds. The present procedure appears to provide such a method for the arylation of α -bromo ketone (Entries 8–10). The coupling of **1c** with phenylboronic acid under the above conditions, followed by treatment of the reaction mixture with 1 M KOH (1 M=1 mol dm⁻³) in methanol, gives benzyl phenyl ketone in 70% yield.

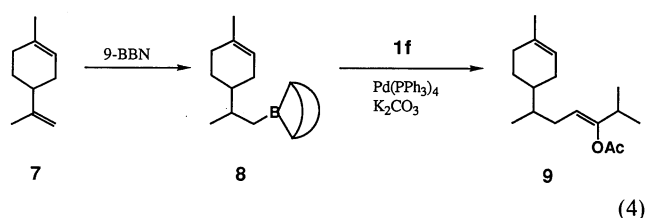
The procedure can be readily extended to the syntheses of ketones and aldehydes from alkenes via hydroboration. The hydroboration of **3** with 9-BBN is followed by the coupling with **1c** in dioxane at 60 °C in the presence of K_2CO_3 (3 equivs) and $Pd(PPh_3)_4$ (3 mol%). The treatment of the resulting mixture with 1 M KOH in methanol, and then aqueous HCl gives the diketone **4** in a 78% yield (Eq. 2). Analogously, a



sequence of hydroboration of alkenes with 9-BBN, the coupling with (Z)-2-ethoxy-1-bromoethene, and finally the deprotection with acid provides a method for synthesis of aldehydes from alkenes with two more carbon atoms homologation. Thus, decanal **6** is obtained from 1-octene in a yield of 62% (Eq. 3).



The utility of present coupling reaction is demonstrated by the extension of diterpene to sesquiterpene using limonene as an example (Eq. 4). Brown's



hydroboration reaction is quite chemoselective, thus a selective monohydroboration of less hindered terminal double bond of limonene **7** is readily achieved by the use of one equiv of 9-BBN with **7**. Upon treatment with (Z)-2-acetoxy-1-bromo-3-methyl-1-butene **1f**, which is prepared from methyl isobutyrate by Kowalski's (dibromomethyl)lithium method,¹¹⁾ affords the desired enol acetate **9** in a yield of 67%.

Experimental

¹H NMR spectrometer (90 MHz) are recorded in δ values using tetramethylsilane as an internal standard. Mass spectra were taken on a JEOL JMS-D300 for a high-resolution analysis and Finnigan ITD 800.

Material and Reagents. Tetrahydrofuran (THF) and dioxane were dried and distilled before use. 9-Borabicyclo[3.3.1]nonane (9-BBN) in THF from Aldrich Chemical Co. was used directly. $Pd(PPh_3)_4$ and K_3PO_4 were commercial products. Phenylboronic acid,¹²⁾ 4-methylphenylboronic acid,¹²⁾ 4-methoxyphenylboronic acid,¹²⁾ (E)-1-hexenyl-1,3,2-benzodioxaborole¹³⁾ were prepared by the known procedures. Trimethylsilyl enol ether **1a**¹⁴⁾ and methyl enol ether **1b**¹⁵⁾ of α -bromoacetophenone were synthesized by bromination-dehydrobromination of corresponding enol ethers of acetophenone. Enol acetates¹⁶⁾ of α -bromoacetophenone **1c**, α -bromocyclohexanone **1d**, *t*-butyl bromomethyl ketone **1e** were prepared by treatment of lithium enolates of α -bromo ketones with acetic anhydride. The reaction of methyl isobutyrate with dibromomethyl lithium, followed by acetic anhydride by the method¹¹⁾ of Kowalski provided **1f**.

General Procedure for the Cross-Coupling Reaction of 9-Alkyl-9-BBN Derivatives (Entries 1–6 in Table 1). A 25 ml two-necked round-bottom flask equipped with a reflux condenser, a septum inlet, and a magnetic stirring bar was flushed with nitrogen, and charged with a 0.5 M (1 M=1 mol dm⁻³) solution of 9-BBN in THF (1.1 mmol) through the septum inlet with a syringe. Alkene (1.1 mmol) was added slowly at 0 °C, and then the reaction mixture was gradually warmed up to room temperature. After stirring for 2 h at room temperature, dioxane (4 ml), $Pd(PPh_3)_4$ (0.03 mmol), K_3PO_4 (3 mmol) for entries 1 and 2 or K_2CO_3 (3 mmol) for Entries 3–6, and **1** (1.0 mmol) were added. The mixture was stirred for 16 h at 60 °C in an oil bath. Water (20 ml) was added and stirred for 30 min in air. The product was extracted with benzene, washed with brine, and finally dried over $MgSO_4$. Chromatography over silica gel with hexane-ethyl acetate gave the ketone.

The following compounds were prepared by these procedure.

(Z)-1-Acetoxy-1-phenyl-1-decene: IR (film) 1768, 1209, 760, and 694 cm⁻¹; ¹H NMR ($CDCl_3$) δ =7.25–7.45 (m, 5H), 5.81 (t, 1H, J =7.2 Hz), 2.28 (s, 3H), 2.11 (m, 2H), 1.20–1.50 (m, 12H), and 0.88 (t, 3H, J =5.1 Hz); MS m/z (rel intensity) 105 (41), 120 (53), 133 (100), 232 (57), 233 (14), and 274 (7); MS, Found: m/z (M^+) 274.1917. Calcd for $C_{18}H_{24}O_2$: M , 274.1933.

1-Acetoxy-2-octylcyclohexene: IR (film) 1758 and 1703 cm⁻¹; ¹H NMR ($CDCl_3$) δ =2.11 (s, 3H), 1.50–2.20 (m, 10H),

1.20—1.40 (m, 12H), and 0.92 (t, 3H, $J=5.3$ Hz); MS m/z (rel intensity) 43 (100), 98 (89), 252 (1); MS, Found: m/z (M^+) 252.2025. Calcd for $C_{16}H_{28}O_2$: M , 252.2089.

(Z)-3-Acetoxy-2,2-dimethyl-3-dodecene: IR(film) 1770 and 1690 cm^{-1} ; 1H NMR ($CDCl_3$) $\delta=5.07$ (t, 1H, $J=6.8$ Hz), 2.17 (s, 3H), 1.60—1.90 (m, 2H), 1.15—1.40 (m, 12H), 1.06 (s, 9H), and 0.88 (t, 3H, $J=5.3$ Hz); MS m/z (rel intensity) 43 (100), 57 (37), 155 (68), and 254 (0.8); MS, Found: m/z (M^+) 254.2220. Calcd for $C_{16}H_{30}O_2$: M , 254.2246.

Methyl (6Z)-7-acetoxy-7-phenyl-2,2-dimethyl-6-heptenoate: IR (film) 1762 and 1728 cm^{-1} ; 1H NMR ($CDCl_3$) $\delta=7.15$ —7.40 (m, 5H), 5.78 (t, 1H, $J=7.3$ Hz), 3.66 (s, 3H), 2.28 (s, 3H), 1.90—2.30 (m, 2H), 1.30—1.60 (m, 4H) and 1.17 (s, 6H); MS m/z (rel intensity) 105 (92), 133 (100), 230 (36), 262 (44) and 304 (6); MS, Found: m/z (M^+) 304.1682. Calcd for $C_{18}H_{24}O_4$: M , 304.1675.

The Cross Coupling of Arylboronic Acids or (E)-1-Hexenyl-1,3,2-benzodioxaborole (Entries 7—10 in Table 1). To the flask was added $Pd(PPh_3)_4$ (0.03 mmol), K_3PO_4 (3 mmol), an arylboronic acid (1.1 mmol) and flushed with nitrogen. A solution of enol acetate of α -bromo ketone (1 mmol) in dioxane (4 ml) was added, and then the mixture was stirred for 5 h at 80 °C. The product was isolated by the same procedure as shown in the above reaction. The coupling with (E)-1-hexenyl-1,3,2-benzodioxaborole followed the same procedure.

(1Z,3E)-1-Acetoxy-1-phenyl-1,3-octadiene: IR (film) 1707, 1201, 1185, 1040, 1024, 970, 760 cm^{-1} ; 1H NMR ($CDCl_3$) $\delta=7.25$ —7.50 (m, 5H), 6.42 (dd, 1H, $J=9.3$ and 16.3 Hz), 6.08 (d, 1H, $J=9.3$ Hz), 5.88 (dt, 1H, $J=16.3$ and 6.0 Hz), 2.33 (s, 3H), 2.00—2.30 (m, 2H), 1.20—1.50 (m, 4H), and 0.91 (t, 3H, $J=6.3$ Hz); MS m/z (rel intensity) 43 (100), 77 (63), 105 (69), 159 (87), 202 (76), and 244 (16); MS, Found: m/z (M^+) 244.1437. Calcd for $C_{16}H_{20}O_2$: M , 252.115.

(Z)-1-Acetoxy-1,2-diphenylethene: IR (Nujol) 1760, 1642, and 763 cm^{-1} ; 1H NMR ($CDCl_3$) $\delta=7.30$ —7.90 (m, 10H), 6.69 (s, 1H), and 2.30 (s, 3H); MS m/z (rel intensity) 105 (46), 196 (100), and 238 (9); MS, Found: m/z (M^+) 238.1023. Calcd for $C_{16}H_{14}O_2$: M , 238.0994.

(Z)-1-Acetoxy-1-phenyl-2-(4-methylphenyl)ethene: IR (Nujol) 1770, 1650, and 758 cm^{-1} ; 1H NMR ($CDCl_3$) $\delta=7.10$ —7.60 (m, 9H), 6.67 (s, 1H), 2.35 (s, 3H), and 2.30 (s, 3H); MS m/z (rel intensity) 105 (62), 210 (100), and 252 (8); MS, Found: m/z (M^+) 252.1170. Calcd for $C_{17}H_{16}O_2$: M , 252.1150.

(Z)-1-Acetoxy-1-phenyl-2-(4-methoxyphenyl)ethene: IR (Nujol) 1760 and 1643 cm^{-1} ; 1H NMR ($CDCl_3$) $\delta=7.20$ —7.60 (m, 7H), 6.70—7.00 (m, 2H), 6.64 (s, 1H), 3.82 (s, 3H), and 2.31 (s, 3H); MS m/z (rel intensity) 105 (57), 121 (65), 226 (100), and 268 (17); MS, Found: m/z (M^+) 268.1076. Calcd for $C_{17}H_{16}O_3$: M , 268.1099.

(3Z)-3-Acetoxy-2-methyl-6-(4-methyl-3-cyclohexenyl)-3-heptene 9: To a solution of limonene (1.0 mmol) in THF (0.5 ml) was added a solution of 9-BBN in THF (0.5 M, 1.1 mmol) at 0 °C. The mixture was warmed up slowly to room temperature, and then stirred for 5 h. Dioxane (8 ml), K_2CO_3 (0.4 g), $Pd(PPh_3)_4$ (0.03 mmol), and (Z)-2-acetoxy-1-bromo-3-methyl-1-butene **1f** (1.1 mmol) were added successively, and the mixture was stirred for 18 h at 60—70 °C. Isolation by chromatography over silica gel with hexane/ether 20/1 gavel **9** in a yield of 67%.

9: IR (film) 1760 and 1682 cm^{-1} ; 1H NMR ($CDCl_3$) $\delta=5.37$ (broad s, 1H), 4.98 (t, 1H, $J=7.6$ Hz), 2.83 (7 lines, 1H, $J=6.6$ Hz), 2.13 (s, 3H), 1.64 (s, 3H), 1.64 (s, 3H), 1.10—2.00 (m, 10H), 1.00 (d, 6H, $J=6.6$ Hz), and 0.90 (d, 3H, $J=6.6$ Hz); MS m/z (rel intensity) 43 (100), 81 (47), 119 (79), 161 (40), 264 (6); MS Found: m/z (M^+) 264.2074. Calcd for $C_{17}H_{28}O_2$: M , 264.2089.

Homologated Aldehyde for Ketones (4 and 6): A mixture of K_3PO_4 (3 mmol), $Pd(PPh_3)_4$ (0.03 mmol), 9-octyl-9-BBN (1 mmol), (Z)-2-ethoxy-1-bromoethene (1.2 mmol) in dioxane (6 ml) and H_2O (1 ml) was stirred for 5 h at 80 °C. The reaction mixture was acidified by aqueous 3 M HCl solution (2 mL), and stirred for 1 h at room temperature. Decanal **6** was isolated by chromatography over silica gel with hexane/ether=5/1 in a yield of 62%.

To a solution of 9-BBN in THF (1.1 mmol) was added ethylene acetal of 5-hexen-2-one **3** (1.0 mmol), and the mixture was stirred for 3 h at room temperature. Dioxane (6 ml), K_2CO_3 (3 mmol), $Pd(PPh_3)_4$ (0.03 mmol), and 2-acetoxy-1-bromo-2-phenylethene **1c** (1 mmol) were added to the above borane solution. After stirring for 16 h at 60 °C, the mixture was treated with 1 M KOH solution in methanol (3.5 mmol) for 1.5 h, followed by aqueous 3 M HCl (7 ml) for 1 h at room temperature. 1-Phenyl-1,7-octanedione **4** was isolated by column chromatography in a yield of 78%.

4: IR (film) 1760, 1741, 1649, and 1632 cm^{-1} ; 1H NMR ($CDCl_3$) $\delta=7.80$ —8.00 (m, 2H), 7.30—7.60 (m, 3H), 2.97 (t, 2H, $J=6.6$ Hz), 2.45 (t, 2H, $J=6.6$ Hz), 2.13 (s, 3H), and 1.20—1.90 (m, 6H); MS, Found: m/z (M^+) 218.1309. Calcd for $C_{14}H_{18}O_2$: M , 218.1307.

References

- 1) N. Miyaura, T. Ishiyama, H. Sasaki, M. Ishikawa, M. Satoh, and A. Suzuki, *J. Am. Chem. Soc.*, **111**, 314 (1989).
- 2) N. Miyaura, K. Yamada, H. Sugimoto, and A. Suzuki, *J. Am. Chem. Soc.*, **107**, 972 (1985).
- 3) N. Miyaura, T. Yanagi, and A. Suzuki, *Synth. Commun.*, **1981**, 11, 513.
- 4) E. Ciganek, *Org. React.*, **32**, 1 (1984).
- 5) a) H. C. Brown, M. M. Rogic, and M. W. Rathke, *J. Am. Chem. Soc.*, **90**, 6218 (1968); b) H. C. Brown, H. Nambu, and M. M. Rogic, *ibid.*, **91**, 6852 (1969); c) J. Hooz and S. Linke, *J. Am. Chem. Soc.*, **90**, 5936 (1968).
- 6) a) K. Tamao, M. Zembayashi, and M. Kumada, *Chem. Lett.*, **1976**, 1237 and 1239.
- 7) Y. Ito, T. Nirao, and T. Saegusa, *J. Org. Chem.*, **43**, 1011 (1978).
- 8) J. K. Stille and K. S. Y. Lau, *Acc. Chem. Revs.*, **10**, 434 (1977); J. K. Stille "Oxidative Addition and Reductive Elimination," in "The Chemistry of Metal-Carbon Bond and Cleavage of Metal-Carbon Bonds," ed by F. R. Hartly and S. Patai, John Wiley & Sons Ltd., New York (1985), Vol. 2, Chap. 9, p. 625.
- 9) J. K. Stille, *Angew. Chem., Int. Ed. Engl.*, **25**, 508 (1986), and Refs. 1 and 2.
- 10) M. W. Rathke and D. Vogiazoglou, *J. Org. Chem.*, **52**, 3697 (1987); I. Kuwajima and H. Urabe, *J. Am. Chem. Soc.*, **104**, 6831 (1982), and references cited therein.
- 11) C. J. Kowalski and M. S. Haque, *J. Org. Chem.*, **50**, 5140 (1985).
- 12) F. R. Bean and J. R. Johnson, *J. Am. Chem. Soc.*, **54**, 4415 (1932).
- 13) N. Miyaura and A. Suzuki, *Org. Synth.*, **68**, 130 (1988).
- 14) M. Zembayashi, K. Tamao, and M. Kumada, *Synthesis*, **1977**, 422.
- 15) A stereoselective synthesis of **1b** from 1-ethoxy-1-phenylethene was achieved in a yield of 65% by similar method⁶ for the preparation of (Z)-2-ethoxy-1-bromoethene.
- 16) G. C. Joshi, W. D. Chambers, and E. W. Warnhoff, *Tetrahedron Lett.*, **1967**, 3613; C. J. Kowalski, X. Creary, A. J. Rollin, and M. C. Burke, *J. Org. Chem.*, **43**, 2601 (1978); C. J. Kowalski, A. E. Weber, and K. W. Fields, *ibid.*, **47**, 5088 (1982).