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Palladium-Catalyzed Carbonylative Cross-Coupling Reaction of 1-Halo-1-alkenes with 9-Alkyl-9-BBN Derivatives. A Direct Synthesis of α,β-Unsaturated Ketones

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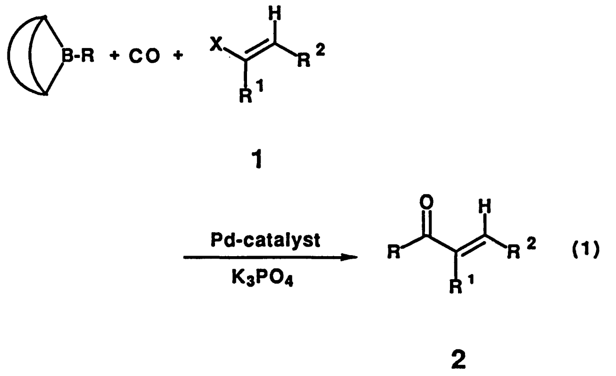
Synopsis. The synthesis of α,β-unsaturated ketones by means of the palladium-catalyzed cross-coupling reaction between 9-alkyl-9-borabicyclo[3.3.1]nonanes (9-R-9-BBN) and 1-halo-1-alkenes under carbon monoxide atmosphere is described.

Carbonylative cross-coupling of organic halides with organometallic compounds, such as organotin,[1] boron,[2] aluminum,[3] and zinc[4] compounds has been extensively studied and reported to provide a good method for the synthesis of unsymmetrical ketones. Among a variety of organometallic reagents, organoboron compounds were first examined by Kojima and his co-workers[2a] for the synthesis of alkyl aryl ketones. Due to the low nucleophilicity of alkyl group on boron, the transmetallation between organoboranes and acylpalladium(II) species generated in catalytic cycles is anticipated to be a step of retarding for the coupling of organoboron compounds. They found that bis(acetylacetonato)zinc(II) accelerates the transmetallation and the palladium-catalyzed carbonylative coupling of organoboranes with aryl and benzyl halides to give the corresponding ketones. However, when we applied the procedure in the reaction with 1-halo-1-alkenes, it was found that no expected α,β-unsaturated ketones are obtained. Thus, we have reinvestigated such a carbonylative cross-coupling reaction of organoboranes, and observed that the cross-coupling reaction of 9-R-9-BBN, with carbon monoxide and 1-iodo-1-alkenes is effectively induced with K_3PO_4 at room temperature in the presence of Pd-catalyst (Eq. 1). The reactions with aryl or benzyl halides proceed nicely under similar conditions to give the corresponding products, respectively.



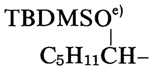
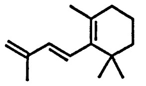
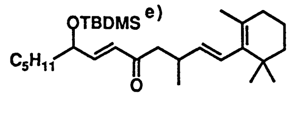
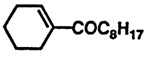
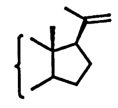
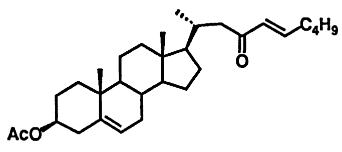
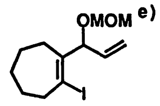
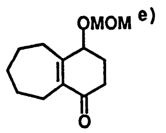
The effects of such conditions on the reaction of 9-octyl-9-BBN with (*E*)-1-hexenyl, phenyl, and benzyl halides are listed in Table 1. The addition of bis(acetylacetonato)zinc(II) never accelerates the reaction with 1-iodo-1-alkene (Entry 1). When we use K_3PO_4 as a base, 1-iodo-1-hexene is effectively carbonylated and couples with 9-octyl-9-BBN in the presence of 5 mol% of $Pd(PPh_3)_4$ to give (*E*)-5-pentadecen-7-one in almost quantitative yields (Entries 2—4). Both $Pd(PPh_3)_4$ and $PdCl_2(PPh_3)_2$ are effective as catalysts for the present carbonylative coupling reaction (Entries 4 and 5). However, dichloro[1,1′-bis(diphenylphosphino)ferrocene]palladium(II), $PdCl_2$(dppf), gives a lower yield of ketone (Entry 6) whereas this catalyst has been reported to be a good catalyst for the carbonylative coupling reaction of aryl triflates[1e] with organostannanes. The carbonylation of 1-bromo-1-octene gives a mixture of products, (*E*)-7-heptadecen-9-one and (*E*)-7-hexa-

Table 1. Carbonylative Cross-Coupling Reaction of 9-Octyl-9-BBN with Organic Halides[a)]

Entry	Organic halide	Catalyst	Solvent	Additive	CO/atm	Temp/°C	Yield[b)]/%
1	(*E*)-$C_4H_9CH{=}CHI$	$Pd(PPh_3)_4$	HMPA/THF[e)] =1/4	$Zn(acac)_2$	1	50	0
2	(*E*)-$C_4H_9CH{=}CHI$	$Pd(PPh_3)_4$	Dioxane	K_3PO_4	1	25	98
3	(*E*)-$C_4H_9CH{=}CHI$	$Pd(PPh_3)_4$	Dioxane	K_3PO_4	3	25	92
4	(*E*)-$C_4H_9CH{=}CHI$	$Pd(PPh_3)_4$	Benzene	K_3PO_4	1	25	99
5	(*E*)-$C_4H_9CH{=}CHI$	$PdCl_2(PPh_3)_2$	Benzene	K_3PO_4	1	25	98
6	(*E*)-$C_4H_9CH{=}CHI$	$PdCl_2$(dppf)	Dioxane	K_3PO_4	1	25	51
7	(*E*)-$C_6H_{13}CH{=}CHBr$	$Pd(PPh_3)_4$	Dioxane	K_3PO_4	3	65	31[c)]
8	(*E*)-$C_6H_{13}CH{=}CHBr$	$Pd(PPh_3)_4$	Dioxane	K_3PO_4/KI[d)]	1	25	69
9	PhI	$PdCl_2(PPh_3)_2$	Benzene	K_3PO_4	1	25	(82)
10	PhI	$Pd(PPh_3)_4$	Dioxane	K_3PO_4	1	25	51
11	$PhCH_2Br$	$PdCl_2(PPh_3)_2$	Benzene	K_3PO_4	1	25	(72)

a) All reactions were carried out in 6 ml of solvent for 5 h using catalyst (5 mol%), organic halides (1 mmol), 9-octyl-9-BBN (1.1 mmol), and $Zn(acac)_2$ (1.1 mmol) or K_3PO_4 (3 mmol). b) GLPC yields based on organic halides and isolated yields were in parentheses. c) (*E*)-7-Hexadecene (16%) was also obtained. d) 3 equiv of KI. e) HMPA; hexamethylphosphoric triamide, THF; tetrahydrofuran.

Table 2. Carbonylative Cross-Coupling Reaction of 9-Alkyl-9-BBN with Alkenyl Iodides[a)]

Organic halide 1		Alkene	Product	Method[b)]	Yield[c)]/%
R^1	R^2				
H	C_4H_9	1-Octene	(*E*)-$C_4H_9CH=CHCOC_8H_{17}$	A	99
H	*t*-C_4H_9	$CH_2=CH(CH_2)_8CO_2Me$	(*E*)-*t*-$C_4H_9CH=CHCO(CH_2)_{10}CO_2Me$	B	(78)
H	Ph	$CH_2=CH(CH_2)_8CN$	(*E*)-$PhCH=CHCO(CH_2)_{10}CN$	B	(68)
H	 $\overset{\mathrm{TBDMSO^{e)}}}{C_5H_{11}CH-}$			B	(53)
$-(CH_2)_4-$		1-Octene		B	90
H	C_4H_9			A	(48)
				A[d)]	(74)

a) The 9-alkyl-9-BBN derivatives obtained by hydroboration of alkenes (1.1 equiv) with 9-BBN (1.1 equiv) were directly used for the next coupling reaction with haloalkenes (1.1 equiv). b) Method A: The reaction was conducted in benzene at room temperature for 5 h under 1 atm CO in the presence of K_3PO_4 (3 equiv) and $Pd(PPh_3)_4$ (5 mol%); Method B: The same conditions with A, except in dioxane under 3 atm CO. c) GLC yields based on organic iodides and isolated yields are in parentheses. d) $PdCl_2(PPh_3)_2$ (5 mol%) was used as a catalyst. e) TBDMS; *t*-butyldimethylsilyl, MOM; methoxymethyl.

decene, in a ratio of 2:1 even under 3 atmospheric pressure of carbon monoxide (Entry 7), the yield of which can be improved to 69% by running the reaction in the presence of powdered potassium iodide (Entry 8). Iodobenzene and benzyl bromide are also carbonylated and coupled with 9-octyl-9-BBN in good yields under the same reaction conditions (Entries 9 and 11).

In Table 2, the representative results obtained by a sequence of hydroboration of alkenes, followed by coupling with 1-iodo-1-alkenes under carbon monoxide atmosphere in the presence of $Pd(PPh_3)_4$ (5 mol%) and K_3PO_4 (3 equiv) are summarized. In Method A, the reaction is carried out under relatively mild conditions by using 1 atm of carbon monoxide at room temperature, whereas Method B is performed under 3 atm of carbon monoxide. Although the carbonylative coupling proceeds especially smoothly when iodoalkenes substituted with alkyls are used, the presence of electron-withdrawing substituents[5)] leads to a mixture of carbonylated and uncarbonylated coupling products. For example, the carbonylation of 3-iodo-2-cyclohexenone and 1-iodo-1-octen-3-one mainly gives direct coupling products without the CO insertion, together with small amounts of the desired α,β-unsaturated ketones.

As shown in the last column of Table 2, the hydroboration-carbonylative coupling sequence can be readily extended to intramolecular reaction to afford cyclic ketones.

The reaction may proceed by a pathway similar to that of the palladium-catalyzed carbonylative coupling reaction of organometallics[1–4)] which involves (a) oxidative addition of haloalkene to Pd(0) complex, (b) insertion of carbon monoxide to give acylpalladium(II) halide, (c) transfer of alkyl group on boron to acylpalladium(II) halide with the aid of K_3PO_4, and (d) reductive elimination to ketone. Although the carbonylation[6)] of 9-alkyl-9-BBN with carbon monoxide to provide ketones is known, we have not observed any evidence that acylboron species are participated in a catalytic cycle.

In a course of our study on the palladium-catalyzed reaction[7a)] of organoboranes, we reported the direct coupling reactions of aryl,[7b)] 1-alkenyl,[7a,c)] and alkylboron[7d)] compounds with organic halides. The present reaction can make it possible for the extension of such coupling reactions to the synthesis of ketones.

Experimental

IR spectra were recorded on a Hitachi Perkin–Elmer Model 125 spectrometer. ^1H NMR spectra were obtained with a Hitachi-R-90H Fourier transform NMR spectrometer (90 MHz) and 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. GLC analyses were performed on a Hitachi 163 instrument using Silicone OV-17 on Uniport B (2 m).

Material and Reagents. Benzene 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 $PdCl_2(PPh_3)_2$ were commercial products. $PdCl_2(dppf)$ was prepared by the reported procedure.[8)] (*E*)-

1-Iodo-1-hexene,[9] (*E*)-1-bromo-1-octene,[10] (*E*)-3,3-dimethyl-1-iodo-1-butene,[9] (*E*)-β-iodostyrene,[9] 1-iodocyclohexene,[11] and (*E*)-3-(*t*-butyldimethylsiloxy)-1-iodo-1-octene[12] were prepared by reported procedures. 1-(2,6,6-Trimethyl-1-cyclohexenyl)-3-methyl-1,3-butadiene[13] and 3β-acetoxy-20-methylene-5-pregnene[14] were prepared from the corresponding ketones by Wittig olefination. 1-Iodo-2-(1-methoxymethoxy-2-propenyl)-1-cycloheptene was prepared[7d] as follows. Treatment of 2-chloro-1-cycloheptenecarbaldehyde obtained by Vilsmeier reaction of cycloheptanone with NaI in acetonitrile in the presence of 1 equivalent of chlorotrimethylsilane at room temperature for 24 h gave 2-iodo-1-cycloheptenecarbaldehyde in a yield of 54% (bp 95—100 °C/0.1 mmHg; 1 mmHg=133.322 Pa). This was treated with vinylmagnesium bromide (1 equiv) in THF, followed by the reaction with chloromethyl methyl ether (1.2 equiv) to afford the compound in an 83% yield.

General Procedure for the Carbonylative Cross-Coupling Reaction. A 50 ml pressure bottle equipped with a magnetic stirring bar was charged with an alkene (1.1 mmol) in THF (0.5 ml). A 0.5 M (1M=1 mol dm^{-3}) solution of 9-BBN in THF (1.1 mmol) was added slowly at 0 °C, and then the reaction mixture was warmed up slowly to room temperature. After stirring for 5 h, dioxane or benzene (6 ml), $Pd(PPh_3)_4$ (5 mol%), K_3PO_4 (3 mmol), and iodoalkene (1 mmol) were added. The flask was flushed with carbon monoxide (1 or 3 atmospheric pressure) and the mixture was stirred for 5 h at room temperature. Water (20 ml) was added and stirred for 30 min. 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 ketones were obtained by this procedure.

(*E*)-5-Pentadecen-7-one: n_D 1.4531; IR (film) 1700, 1680, 1635, 1470, and 985 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ=0.92 (t, 6H, J=6.0 Hz), 1.28 (m, 16H), 2.22 (dt, 2H, J=7.2 Hz), 2.52 (t, 2H, J=7.4 Hz), 6.08 (d, 1H, J=15.6 Hz), and 6.82 (dt, 1H, J=15.8 and 6.6 Hz); MS m/z (rel intensity) 28 (27), 41 (53), 55 (97), 111 (53), 126 (22), 167 (13), and 225 (100); High resolution MS, Found: m/z, 224.2163. Calcd for $C_{15}H_{28}O$: M, 224.2140.

Methyl (*E*)-15,15-Dimethyl-12-oxo-13-hexadecenoate: n_D 1.4853; IR (film) 1740, 1700, 1680, 1625, 1460, 1440, 1360, 1165, and 980 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ=1.09 (s, 9H), 1.28 (m, 16H), 2.30 (t, 2H, J=7.2 Hz), 2.53 (t, 2H, J=7.2 Hz), 3.66 (s, 3H), 6.00 (d, 1H, J=16.0 Hz), and 6.81 (d, 1H, J=16.0 Hz); MS m/z (rel intensity) 41 (47), 55 (52), 111 (100), 126 (26), 221 (11), 253 (20), 279 (25), and 311 (33); High resolution MS, Found: m/z, 310.2510. Calcd for $C_{19}H_{34}O_3$: M, 310.2508.

(*E*)-12-Oxo-14-phenyl-13-tetradecenonitrile: Mp 64 °C; IR (Nujol) 2250, 1695, 1610, 1580, 1470, 1380, and 1080 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ=1.31 (m, 16H), 2.32 (t, 2H, J=6.6 Hz), 2.66 (t, 2H, J=6.9 Hz), 6.72 (d, 1H, J=16.3 Hz), and 7.49 (m, 6H); MS m/z (rel intensity) 41 (13), 55 (10), 77 (18), 103 (35), 131 (100), 146 (79), 159 (7), 188 (3), and 297 (4); High resolution MS, Found: m/z, 297.2083. Calcd for $C_{20}H_{27}ON$: M, 297.2093.

(1*E*,6*E*)-8-(*t*-Butyldimethylsiloxy)-3-methyl-1-(2,6,6-trimethyl-1-cyclohexenyl)-1,6-tridecadien-5-one: n_D 1.4805; IR (film) 1705, 1685, 1640, 1470, 1365, 1260, 1100, 980, 840, and 780 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ=−0.03 (s, 6H) , 0.88 (s, 18H), 1.04 (d, 3H, J=6.4 Hz), 1.23 (m, 8H), 1.44 (m, 4H), 1.58 (s, 3H), 1.91 (m, 2H), 2.56 (s, 2H), 2.73 (m, 1H), 4.25 (m, 1H), 5.24 (dd, 1H, J=15.8 and 7.0 Hz), 5.81 (d, 1H, J=16.0 Hz), 6.19 (d, 1H, J=15.8 Hz), and 6.73 (dd, 1H, J=15.8 and 4.8 Hz); MS m/z (rel intensity) 73 (74), 95 (37), 107 (34), 121 (45), 161 (31), 177 (73), 215 (46), 269 (25), 337 (10), 403 (8), and 460 (26); High resolution MS, Found: m/z 460.3731. Calcd for $C_{29}H_{52}O_2Si$: M, 460.3736.

1-(1-Cyclohexenyl)nonan-1-one: n_D 1.4777; IR (film) 1670, 1640, 1460, 1440, 1385, 1205, and 1185 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ=0.88 (t, 3H, J=5.6 Hz), 1.28 (m, 12H), 1.62 (m, 4H), 2.23 (m, 4H), 2.61 (t, 2H, J=6.7 Hz), and 6.87 (s, 1H); MS m/z (rel intensity) 29 (22), 41 (47), 53 (22), 81 (74), 109 (100), 124 (57), and 222 (89); High resolution MS, Found: m/z 222.1974. Calcd for $C_{15}H_{26}O$: M, 222.1948.

Steroid: Mp 83 °C; IR (Nujol) 1745, 1715, 1690, 1640, 1260, and 1055 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ=0.73 (s, 3H), 0.94 (d, 3H, J=4.6 Hz), 0.96 (t, 3H, J=4.8 Hz), 1.02 (s, 3H), 2.02 (s, 3H), 0.9—2.5 (m, 29H), 4.3—4.8 (m, 1H), 5.35 (d, 1H, J=4.1 Hz), 6.01 (d, 1H, J=15.8 Hz), and 6.75 (dt, 1H, J=15.8 and 6.8 Hz); MS m/z (rel intensity) 43 (65), 55 (100), 81 (50), 105 (38), 145 (29), 161 (23), 282 (86), 390 (4), 434 (2), and 469 (2); High resolution MS, Found: m/z, 468.3623. Calcd for $C_{31}H_{48}O_3$: M, 468.3604.

11-(Methoxymethoxy)bicyclo[5.4.0]undec-1(7)-en-8-one: n_D 1.5045; IR (film) 1660, 1440, 1280, 1140, 1080, 1020, 910, 870, and 840 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ=1.60 (m, 8H), 2.10 (m, 2H), 2.47 (m, 4H), 3.43 (s, 3H), 4.18 (m, 1H), 4.67 (d, 1H, J=6.8 Hz), and 4.81 (d, 1H, J=7.0 Hz); MS m/z (rel intensity) 45 (100), 79 (12), 91 (9), 120 (5), 133 (5), 163 (13), and 224 (3); High resolution MS, Found: m/z, 224.1402. Calcd for $C_{13}H_{20}O_3$: M, 224.1413.

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