Synthesis of Substituted 5-(3-Oxobutyl)pyrimidines via Palladium-Catalyzed Coupling Reactions of Iodopyrimidines with Methyl Vinyl Ketone

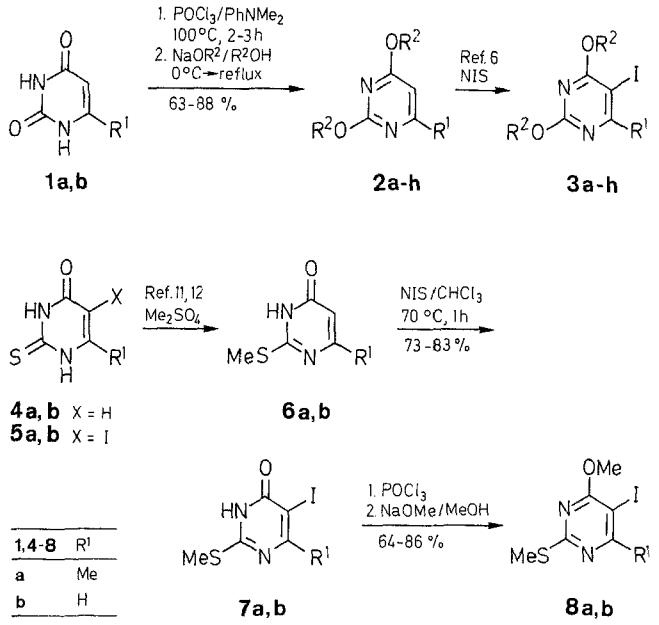
Akimori Wada,* Hirofumi Yasuda, Shōichi Kanatomo

School of Pharmacy, Hokuriku University, Ho-3, Kanagawa-machi, Kanazawa 920-11, Japan

The reactions of several substituted halopyrimidines with methyl vinyl ketone in the presence of palladium diacetate–triphenylphosphine complex in triethylamine are investigated. In the reactions of bromopyrimidines, the usual olefinic substituted products are obtained. But on using iodopyrimidines, the addition of pyrimidine to the carbon–carbon double bond of methyl vinyl ketone occurs to afford substituted 5-(3-oxobutyl)pyrimidines. Possible mechanisms are presented.

The palladium-catalyzed coupling reaction of aryl halides with olefins has found wide application in organic synthesis.[1] Although various types of olefins were used in this reaction, there are a few reports[2–4] dealing with α,β-unsaturated ketones as the olefin because of the low yields.[5] In connection with our studies[6] on the olefinic substitution reactions of halopyrimidines, we investigated the reactions of iodoyrimidines with methyl vinyl ketone. A novel reaction was found, in which formally the pyrimidines added to the carbon–carbon double bond of the methyl vinyl ketone to afford 5-(3-oxobutyl)pyrimidines. In spite of extensive studies on the reactions of aryl halides with olefins, this is the first report of the conjugate addition-type reaction of arylhalide using palladium catalysis.[7]

2,4-Dialkoxy-6-methylpyrimidines **2a–h** were prepared from uracils **1a, b** by chlorination with phosphoryl chloride followed by treatment with the corresponding sodium alkoxide.[8] Iodination of **2** were carried out by *N*-iodosuccinimide (NIS)[6] prepared by reaction of *N*-chlorosuccinimide with sodium iodide.[9] As the yields of the iodination of the 2-methylthio analogs of **2**[10] by the above method were very low (< 10%), another method suitable for large scale reaction was investigated. An attempt to iodinate of thiouracil **(4a)** leading to **5a** was not successful, since only a tar product was obtained. However, the reaction of 2-methylthiouracil **(6a)**[11] with *N*-iodosuccinimide proceeded smoothly to afford an iodo derivative **7a** in 83% yield. The conversion of **7a** into **8a** was achieved by the usual way[8] in 86% yield. Similarly, **7b** was obtained from **6b**[12] in 73% yield and was converted into **8b** in 64% yield (Scheme **A**, Table 1).



1,4-8	R^1
a	Me
b	H

2, 3	R^1	R^2	2, 3	R^1	R^2
a	Me	Me	e	Me	*n*-Bu
b	Me	Et	f	Me	*s*-Bu
c	Me	*n*-Pr	g	Me	$MeOCH_2CH_2$
d	Me	*i*-Pr	h	H	Me

Scheme A

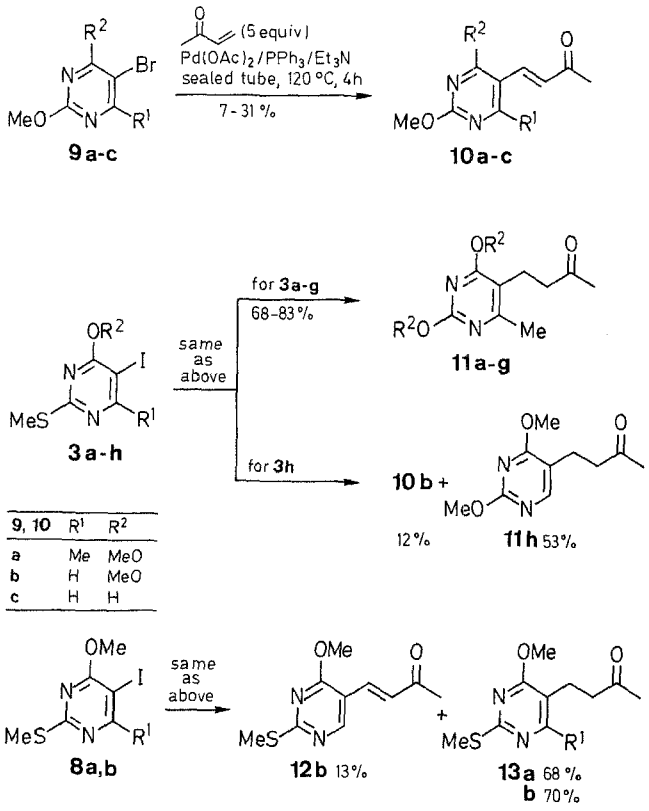
Coupling reactions of halopyrimidines with methyl vinyl ketone were achieved with a mixture containing the appropriate halopyrimidine **(3, 8, 9)**, triethylamine, and 5 equivalents of methyl vinyl ketone in the presence of a catalytic amount of the palladium diacetate–triphenylphosphine complex. The reaction mixture was heated at 120°C for 4 h in a sealed tube. Bromopyridines **9a–c**[14–16] afforded 5-(3-oxo-1-butenyl)pyrimidines **10a–c**, respectively by the normal arylation with the recovery of starting material. Although the yields of **10** were low, yield of product obtained from **9** increased in accordance with less steric hindrance.[6]

In contrast to these examples, the iodopyrimidine **(3a)** gave a pale yellow compound **(11a)** as the sole product in 83% yield. The structure of **10a** was clearly indicated to be 2,4-dimethoxy-6-methyl-5-(3-oxobutyl)pyrimidine by IR, ^{1}H-NMR and mass spectra data. This structure was confirmed by the transformation of **10a** into **11a** by hydrogenation over palladium on carbon. Likewise, 2,4,6-trisubstituted 5-iodopyrimidines **3b–g** and **8a** gave the corresponding saturated products **11b–g** and **13a**, respectively, in good yields. Two products were obtained from the 6-demethylated pyrimidines **3h** and **8b**. The major products **11h** and **13b** were saturated compounds and the minor products **10b** and **12b** were the corresponding unsaturated ketones (Scheme **B**, Table 2 and 3). These findings indicate that steric and electronic factors play important roles in these coupling reactions.

Table 1. 2,4-Dialkoxypyrimidines **2** and 2,4-Dialkoxy-5-iodopyrimidines **3**

Product	Yield[a] (%)	mp (°C) (solvent)[b] or bp (°C)/Torr	Molecular Formula[c] or Lit. mp	IR ($CHCl_3$) ν (cm^{-1})	^{1}H-NMR ($CDCl_3$/TMS) δ, J (Hz)
2a	76	66–68 (PE[d])	69–70[8]		
2b	77	142–143/70	$C_9H_{14}N_2O_2$ (182.2)	1595; 1570	1.41 (t, 3H, J = 7); 1.45 (t, 3H, J = 7); 2.4 (s, 3H); 4.32 (q, 4H, J = 7); 4.48 (q, 2H, J = 7); 6.30 (s, 1H)
2c	74	165–170/7	$C_{11}H_{18}N_2O_2$ (210.3)	1595; 1570	1.04 (t, 3H, J = 7); 1.07 (t, 3H, J = 7); 1.6–2.1 (m, 4H); 2.41 (s, 3H); 4.42 (t, 4H, J = 7); 6.40 (s, 1H)
2d	76	105–110/9	$C_{11}H_{18}N_2O_2$ (210.3)	1595; 1565	1.31 (d, 6H, J = 7); 1.36 (d, 6H, J = 7); 2.3 (s, 3H); 5.0–5.5 (m, 2H); 6.05 (s, 1H)
2e	78	160–165/6	$C_{13}H_{22}N_2O_2$ (238.3)	1595; 1565	0.98 (t, 6H, J = 7); 1.2–2.0 (m, 8H); 2.35 (s, 3H); 4.33 (t, 4H, J = 6.5); 6.16 (s, 1H)
2f	88	175–180/5	$C_{13}H_{22}N_2O_2$ (233.3)	1595; 1565	0.98 (t, 3H, J = 7); 1.03 (t, 3H, J = 7); 1.34 (d, 3H, J = 7); 1.37 (d, 3H, J = 7); 1.5–2.0 (m, 4H); 2.39 (s, 3H); 5.1–5.5 (m, 2H); 6.28 (s, 1H)
2g	63	170–175/11	$C_{13}H_{18}N_2O_4$ (242.3)	1600; 1570	2.32 (s, 3H); 3.40 (s, 6H); 3.69 (t, 2H, J = 5.5); 3.74 (t, 2H, J = 5.5); 4.32 (t, 2H, J = 5.5); 4.34 (t, 2H, J = 5.5); 6.23 (s, 1H)
2h	77	95–98/22	202 (760)[13]		
3a	80	83–84 (PE)	82–84[6]		
3b	74	47–48 (PE)	$C_9H_{13}IN_2O_2$ (308.1)	1560; 1540	1.40 (t, 3H, J = 7); 1.43 (t, 3H, J = 7); 2.5 (s, 3H); 4.32 (q, 2H, J = 7); 4.39 (q, 2H, J = 7)
3c	74	140–145/6	$C_{11}H_{17}IN_2O_2$ (336.2)	1560; 1540	1.02 (t, 3H, J = 7); 1.05 (t, 3H, J = 7); 1.6–2.0 (m, 4H); 2.56 (s, 3H); 4.24 (t, 2H, J = 7); 4.32 (t, 2H, J = 7)
3d	82	135–140/7	$C_{11}H_{17}IN_2O_2$ (336.2)	1560; 1540	1.40 (d, 12H, J = 7); 2.60 (s, 3H); 5.6–5.4 (m, 2H)
3e	87	135–140/9	$C_{13}H_{21}IN_2O_2$ (364.2)	1565; 1545	1.00 (t, 6H, J = 7); 1.5–2.1 (m, 8H); 2.60 (s, 3H); 4.31 (t, 2H, J = 7); 4.37 (t, 2H, J = 7)
3f	61	135–140/7	$C_{13}H_{21}IN_2O_2$ (364.2)	1565; 1545	1.01 (t, 6H, J = 7); 1.38 (d, 3H, J = 7); 1.4 (d, 3H, J = 7); 1.6–2.1 (m, 4H); 2.65 (s, 3H); 5.0–5.6 (m, 2H)
3g	86	135–140/6	$C_{11}H_{17}IN_2O_4$ (368.2)	1570; 1545	2.57 (s, 3H); 3.41 (s, 3H); 3.44 (s, 3H); 3.72 (t, 2H, J = 6); 3.76 (t, 2H, J = 6); 4.45 (t, 2H, J = 6); 4.48 (t, 2H, J = 6)
3h	35	63–64 (PE)	$C_6H_7IN_2O_2$ (266.0)	1550	4.02 (s, 3H); 4.09 (s, 3H); 8.57 (s, 1H)

[a] Yield of isolated pure product.
[b] Uncorrected.
[c] Satisfactory microanalyses obtained: C ±0.23, H ±0.26, N ±0.27.
[d] PE = petroleum ether.



For R^1 and R^2 in **11a–h**, see compounds **2** and **3**.
For R^1 in **13a, b**, see compound **8**.

Scheme **B**

One possible pathway to the saturated products **11** is reduction of the usual aryl substituted olefins **10**. However, the reduction of the carbon–carbon double bond of **10a** did not occur under the reaction conditions used: **10a** was recovered unchanged.

Applying an arylation mechanism proposed by Heck (Scheme **C**),[17] there are two possible routes for the formation of saturated ketones, homolytic fission[18] of initialy formed σ-complex **14** followed by hydrogen abstraction of radical **15** from triethylamine or excess methyl vinyl ketone (Scheme **D**, path a), or heterolytic fission[19] of **14** to give carbanion **16**, and

Table 2. Yields of the Products Formed in the Coupling Reactions of Halopyrimidines **3**, **8**, and **9** with Methyl Vinyl Ketone

Educt	Product	Yield[a] (%)	Product	Yield[a] (%)
3a	–	–	**11a**	83
3b	–	–	**11b**	68
3c	–	–	**11c**	79
3d	–	–	**11d**	81
3e	–	–	**11e**	80
3f	–	–	**11f**	77
3g	–	–	**11g**	74
3h	**10b**	12	**11h**	53
8a	–	–	**13a**	68
8b	**12b**	13	**13b**	70
9a[14]	**10a**	7	–	–
9b[15]	**10b**	24	–	–
9c[16]	**10c**	31	–	–

[a] Yield of isolated pure product.

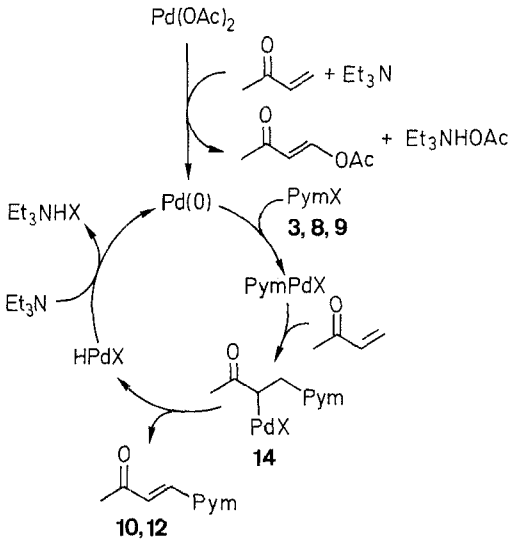
Table 3. Physical and Spectral Data of **10–13**

Product	mp (°C) (solvent)[a] or bp (°C) / Torr	Molecular Formula[b]	IR ($CHCl_3$) ν (cm^{-1})	^{1}H-NMR ($CDCl_3$/TMS) δ, J (Hz)
10a	95–97 ($CHCl_3$/hexane)	$C_{11}H_{14}N_2O_3$ (222.1)	1685; 1575; 1550	2.33 (s, 3H); 2.52 (s, 3H); 3.96 (s, 3H); 4.02 (s, 3H); 6.82 (d, 1H, J = 16); 7.51 (d, 1H, J = 16)
10b	81–83 ($CHCl_3$/hexane)	$C_{10}H_{12}N_2O_2$ (192.2)	1680; 1595; 1555	2.30 (s, 3H); 3.92 (s, 3H); 3.99 (s, 3H); 6.64 (d, 1H, J = 16); 7.25 (d, 1H, J = 16); 8.18 (s, 1H)
10c	74–75 ($CHCl_3$/hexane)	$C_9H_{10}N_2O_2$ (178.2)	1680; 1595; 1550	2.40 (s, 3H); 4.09 (s, 3H); 6.79 (d, 1H, J = 16); 7.46 (d, 1H, J = 16); 8.74 (s, 2H)
12b	89–91 ($CHCl_3$/hexane)	$C_{10}H_{12}N_2O_2S$ (224.3)	1675; 1575; 1540	2.35 (s, 3H); 2.56 (s, 3H); 4.04 (s, 3H); 6.83 (d, 1H, J = 15); 7.42 (d, 1H, J = 15), 8.39 (s, 1H)
11a	130–135/7	$C_{11}H_{16}N_2O_3$ (224.3)	1715; 1575	2.24 (s, 3H); 2.48 (s, 3H); 2.4–3.2 (m, 4H); 4.08 (s, 3H); 4.11 (s, 3H)
11b	130–135/11	$C_{13}H_{20}N_2O_3$ (252.1)	1720; 1580	1.38 (t, 6H, J = 6); 2.15 (s, 3H); 2.35 (s, 3H); 2.4–3.2 (m, 4H); 4.27 (q, 2H, J = 6); 4.39 (q, 2H, J = 6)
11c	135–140/18	$C_{15}H_{24}N_2O_3$ (280.2)	1710; 1570	1.05 (t, 3H, J = 7); 1.17 (t, 3H, J = 7); 1.4–2.0 (m, 4H); 2.15 (s, 3H); 2.37 (s, 3H); 2.4–3.0 (m, 4H); 4.24 (t, 2H, J = 6); 4.31 (t, 2H, J = 6)
11d	140–145/14	$C_{15}H_{24}N_2O_3$ (280.2)	1710; 1570	1.30 (d, 12H, J = 6); 2.10 (s, 3H); 2.30 (s, 3H); 2.4–2.8 (m, 2H); 4.8–5.4 (m, 2H)
11e	160–165/14	$C_{17}H_{28}N_2O_3$ (308.2)	1715; 1575	0.96 (t, 6H, J = 7); 1.2–1.9 (m, 8H); 2.11 (s, 3H); 2.33 (s, 3H); 2.4–2.9 (m, 4H); 4.22 (t, 2H, J = 7); H 4.32 (t, 2H, J = 7)
11f	160–165/12	$C_{17}H_{28}N_2O_3$ (308.2)	1715; 1575	0.97 (t, 6H, J = 7); 1.36 (d, 6H, J = 7); 1.4–2.2 (m, 4H); 2.18 (s, 3H); 2.37 (s, 3H); 3.5–3.9 (m, 4H); 4.8–5.4 (m, 2H)
11g	170–175/17	$C_{15}H_{24}N_2O_5$ (312.4)	1715; 1575	2.13 (s, 3H); 2.37 (s, 3H); 2.5–2.8 (m, 4H); 3.39 (s, 6H); 3.5–3.9 (m, 4H); 4.41 (t, 2H, J = 6); 4.44 (t, 2H, J = 6)
11h	115–120/6	$C_{10}H_{14}N_2O_3$ (210.2)	1715; 1575	2.17 (s, 3H); 2.74 (s, 4H); 3.99 (s, 3H); 4.02 (s, 3H); 8.07 (s, 1H)
13a	155–160/14	$C_{11}H_{16}N_2O_2S$ (240.3)	1715; 1565	2.18 (s, 3H); 2.40 (s, 3H); 2.52 (s, 3H); 2.5–2.9 (m, 4H); 3.98 (s, 3H)
13b	135–140/7	$C_{10}H_{14}N_2O_2S$ (226.3)	1715; 1575	2.16 (s, 3H); 2.56 (s, 3H); 2.76 (s, 4H); 4.06 (s, 3H); 8.24 (s, 1H)

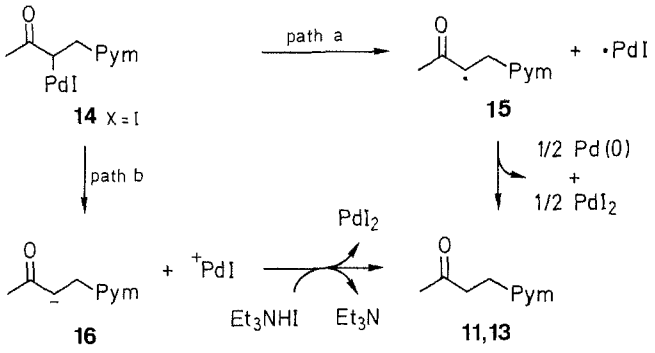
[a] Uncorrectred.

[b] Satisfactory microanalyses obtained: C ±0.32, H ±0.25, N ±0.28.

subsequent protonation by the tertiary ammonium salt produced in the catalytic cycle (path b). Since we could not obtained definite evidence, further mechanistic investigations are in progress.



Scheme **C**



Scheme **D**

The novel conjugate addition type reaction of 5-iodopyrimidines to the methyl vinyl ketone described here should provide a facile route to β-pyrimidine-substituted ketones.

IR absorption spectra were recorded on a Hitachi 270 spectrometer, and ^{1}H-NMR spectra on a JEOL JNM-MH-100 spectrometer (with TMS as an internal standard). Mass spectra were obtained with a JEOL JMS-100 instrument.

2,4-Dialkoxypyrimidines 2; General Procedure:
A mixture of uracil **1a** or **1b** (50 mmol), *N,N*-dimethylaniline (12 g, 100 mmol), and phosphoryl chloride (20 mL) is heated at 100 °C for 2–3 h. After removed excess $POCl_3$ under reduced pressure, the residue is poured into ice-water (200 mL), and then extracted with ether (3 × 150 mL). The combined extract is washed with brine (150 mL) and then dried (Na_2SO_4). The extract is concentrated to 50 mL, and then added to the appropriate alcohol (200 mL) solution containing the corresponding sodium alkoxide (100 mmol) at 0 °C. The reaction mixture is stirred for an additional 2 h, and then heated under reflux for 3 h. After cooling, the solvent is removed under reduced pressure, and the residue is poured into water (150 mL) and then extracted with ether (3 × 150 mL). The combined extract is washed with brine (150 mL) and then dried (Na_2SO_4). The solvent is removed under reduced pressure, and the residue is purified by recrystallization or distillation to give the alkoxypyrimidines **2** (Table 1).

5-Iodo-2,4-dialkoxypyrimidines 3; General Procedure:
Compounds **3b–h** were prepared according to the method previously described[6] for **3a** (Table 1).

5-Iodo-4-methoxy-6-methyl-2-methylthiopyrimidine (8a):
5-Iodo-4-hydroxy-6-methyl-2-methylthiopyrimidine (**7a**): A solution of 4-hydroxy-6-methyl-2-methylthiopyrimidine (**6a**,[11] 5.0 g, 32 mmol) and *N*-iodosuccinimide [prepared from *N*-chlorosuccinimide (4.7 g, 35 mmol) and NaI (5.1 g, 35 mmol)] in $CHCl_3$ (40 mL) is heated at 70 °C for 1 h. After cooling, the solvent is removed under reduced pressure. Water (30 mL) is added to this residue, and the precipitated crystals are collected. The crystals are washed with water until the color of iodine disappeared, and then dried with P_2O_5 in desiccator to afford **7a**; yield: 7.5 g (83%); mp 186–188 °C.

^{1}H-NMR (DMSO-d_6): δ = 2.43 (s, 3H); 2.45 (s, 3H), NH is absence.

5-Iodo-4-methoxy-6-methyl-2-methylthiopyrimidine (**8a**): The 5-iodopyrimidine **7a** (5.1 g, 17 mmol) is chlorinated with $POCl_3$ and then treated with NaOMe/MeOH by the usual method[8] to afford **8a**; yield: 4.3 g (86%); mp 72–73 °C (petroleum ether).

$C_7H_9IN_2OS$	calc.	C 28.39	H 3.06	N 9.46
(296.1)	found	28.59	2.96	9.47

IR ($CHCl_3$): $\nu = 1540\ cm^{-1}$.

^{1}H-NMR ($CDCl_3$): δ = 2.53 (s, 3H); 2.58 (s, 3H); 4.03 (s, 3H).

MS (70 eV): $m/z = 296\ (M^+)$.

5-Iodo-4-methoxy-2-methylthiopyrimidine (8b):
5-Iodo-4-hydroxy-2-methylthiopyrimidine (**7b**): Compound **7b** is obtained from 4-hydroxy-2-methylthiopyrimidine (**6b**,[12] 4 g, 28 mmol) by the same manner described above to give **7b**; yield: 5.5 g (73%); mp 189–191 °C.

5-Iodo-4-methoxy-2-methylthiopyrimidine (**8b**): The treatment[8] of **7b** with $POCl_3$ and then with NaOMe/MeOH afforded **8b**; yield: 3.7 g (64%); mp 85–87 °C (petroleum ether).

$C_6H_7IN_2OS$	calc.	C 25.54	H 2.50	N 9.93
(282.1)	found	25.52	2.50	9.96

IR ($CHCl_3$): $\nu = 1530\ cm^{-1}$.

^{1}H-NMR ($CDCl_3$): δ = 2.44 (s, 3H), 3.93 (s, 3H); 8.31 (s, 1H).

MS (70 eV): $m/z = 282\ (M^+)$.

Coupling Reaction of Halopyrimidines 3, 8, and 9 with Methyl Vinyl Ketone; General Procedure:
A mixture of **3, 8** or **9** (5 mmol), methyl vinyl ketone (25 mmol), Et_3N (10 mmol), palladium(0) diacetate (40 mg, 0.17 mmol), and PPh_3 (80 mg, 0.31 mmol) is heated in a sealed tube at 120 °C for 4 h. After cooling, excess methyl vinyl ketone is removed under reduced pressure, and the residue is purified by column chromatography on silica gel (CH_2Cl_2/*n*-hexane, 2:1, or CH_2Cl_2/EtOAc, 9:1) to give **10–13** (Table 2 and 3).

Hydrogenation of 10a into 11a:
Palladium on carbon (80 mg) is added to a solution of **10a** (60 mg, 0.27 mmol) in MeOH (50 mL), and the resulting mixture is hydrogenated at room temperature and 1 atm H_2. When the absorption of H_2 is completed, the catalyst is filtered off, and MeOH is removed under reduced pressure. The residue is purified by column chromatography on silica gel (CH_2Cl_2/EtOAc, 9:1) to afford **11a**; yield: 50 mg (83%). This was identical in all respects with the sample obtained above.

Received: 30 March 1988; revised: 7 June 1988

(1) For reviews, see: Heck, R.F. *Palladium Reagents in Organic Synthesis*, Academic Press, Orlando, FL, 1985, p. 179.
Heck, R.F. *Org. React.* **1982**, *27*, 345.
Heck, R.F. *Acc. Chem. Res.* **1979**, *12*, 146.
(2) Zebovitz, T.C., Heck, R.F. *J. Org. Chem.* **1979**, *42*, 3907.
(3) Kasahara, A., Izumi, T., Maemura, M. *Bull. Chem. Soc. Jpn.* **1977**, *50*, 1021.
(4) Jeffery, T. *J. Chem. Soc. Chem. Commun.* **1984**, 1287.
(5) α,β-Unsaturated ketone has been used in Heck type reactions involving substrates other than aryl halide; see:
Kjonass, R.A. *J. Org. Chem.* **1986**, *51*, 3708, and references cited therein.
(6) Wada, A., Yamamoto, J., Hase, T., Nagai, S., Kanatomo, S. *Synthesis* **1986**, 555.

(7) Related conjugate addition reactions of arylmercurials and -stannanes have been reported:
Cacchi, S., Misiti, D., Palmieri, G. *J. Org. Chem.* **1982**, *47*, 2995.
Cacchi, S., Misiti, D., Palmieri, G. *Tetrahedron* **1981**, *37*, 2941.
Cacchi, S., La Torre, F., Misiti, D. *Tetrahedron Lett.* **1979**, 4591.
(8) Gabriel, S., Colman, J. *Ber. Dtsch. Chem. Ges.* **1899**, *32*, 2921.
(9) Vanker, Y.D., Kumaravel, G. *Tetrahedron Lett.* **1984**, *25*, 233.
(10) McOmie, J.F.W., Sayer, E.R., Chesterfield, J. *J. Chem. Soc.* **1957**, 1830.
(11) Nishiwaki, T. *Tetrahedron* **1966**, *22*, 2401.
(12) Vonbruggen, H., Strehlke, P. *Chem. Ber.* **1973**, *106*, 3039.
(13) Hilbert, G.E., Johnson, T.B. *J. Am. Chem. Soc.* **1930**, *32*, 2001.
(14) Nishiwaki, T. *Tetrahedron* **1967**, *23*, 2657.
(15) Hilbert, G.E., Jansen, E.F. *J. Am. Chem. Soc.* **1934**, *56*, 134.
(16) Brown, D.J. *Aust. J. Chem.* **1964**, *17*, 802.
(17) Heck, R.F. *J. Am. Chem. Soc.* **1969**, *91*, 6707.
(18) Maitlis, P.M. *The Organic Chemistry of Palladium*, Academic Press, Orlando, FL, 1971, Vol. 1, p. 66.
(19) Yamamura, K. *J. Org. Chem.* **1978**, *43*, 724.