

Phosphine ligands and nitrogen bases in the solvent-free Heck reaction of butenone with aryl iodides. A highly selective synthesis of benzalacetones

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Dedicated to Professor Keiichiro Fukumoto on the occasion of his 70th birthday

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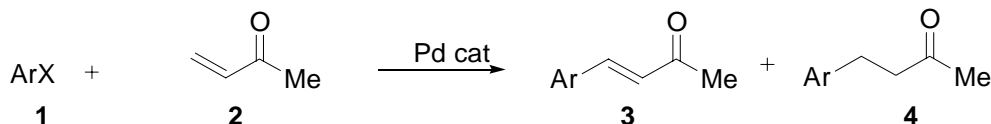
Abstract

The solvent-free palladium-catalyzed reaction of butenone with aryl iodides has been studied. Phosphine ligands have been found to affect the vinylic substitution to hydroarylation (conjugate addition type) ratio. The nature of the nitrogen base also plays a role in controlling the product selectivity. In the presence of Pd(OAc)₂, tris-(2,4,6-trimethoxyphenyl)phosphine and proton sponge the reaction affords exclusively vinylic substitution products usually in high to excellent yield.

Keywords: Palladium, Heck reaction, hydroarylation, conjugate addition, benzalacetones

Introduction

The palladium-catalyzed Heck reaction of α,β -enones with aryl halides represents a very useful procedure for the preparation of vinylic substitution products. With butenone as the starting olefin, it provides an easy access to benzalacetones **3**, useful reaction intermediates¹ as well as biologically active compounds.²



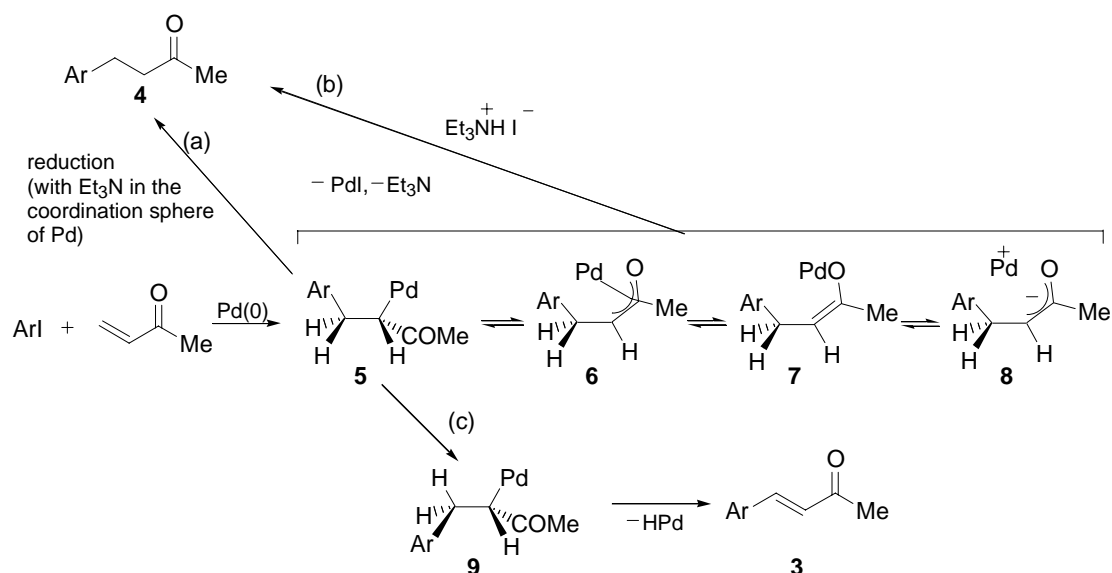
Scheme 1

However, depending on the reaction conditions, minor amounts of hydroarylation (conjugate addition-type)³ derivatives **4** can be formed, making it difficult to isolate pure vinylic substitution products. For example, the reaction of butenone (3 equiv.)⁴ with iodobenzene in the presence of Pd(OAc)₂, Et₃N in DMF at 80 °C for 24 h afforded benzalacetone and 4-phenyl-2-butanone in 84% yield as an approx. 96:4 mixture. The addition of PPh₃ led to the isolation of β-aryl derivatives in 87% yield, as an approx. 88:12 vinylic substitution (*vs*):hydroarylation (*h*) mixture. We were intrigued by the observed phosphine effect on the reaction outcome, and found it to be of interest to investigate the reaction further. Particularly, because of our interest in environmentally friendly processes,^{3n,5} we decided to investigate the palladium-catalyzed reaction of butenone with aryl iodides under solvent-free conditions.⁶ We now report the results of this study.

Results and Discussion

We initially attempted the reaction of butenone with PhI at 80 °C, in the presence of Et₃N and catalytic amounts of Pd(OAc)₂ in the absence of phosphine ligands. Analysis of the reaction mixture after 14 h revealed the formation of benzalacetone in 56% yield along with 4-phenyl-2-butanone (18%). Keeping phenyl iodide as the phenyl donor and Et₃N as the base, we then explored the effect of phosphine ligands. As shown in Table 1, phosphine ligands were found to influence the vinylic substitution to hydroarylation ratio. In particular, their presence usually influences the *vs*:*h* ratio so as to increase the amount of the hydroarylation product compared the reaction without phosphine ligands (Table 1, entries 2–6).

A possible explanation for the formation of **4** (Scheme 2a; the ligands are not represented for the sake of simplicity) considers the reduction of the carbopalladation adduct **5** by Et₃N. The ability of Et₃N to reduce σ-organopalladium adducts has already been observed by us^{3a,n,7c} and others.^{3e,3l,7a,b} Stokker^{3e} showed that α-deuterated hydroarylation products could be obtained when a cyclic α,β-unsaturated lactone was treated with phenyl iodide in the presence of perdeuterated triethylamine and catalytic amounts of Pd(PPh₃)₄.



Scheme 2

The phosphine's effect on the product selectivity and the ability of Et₃N to reduce σ -organopalladium complexes may suggest that both the phosphine ligand and Et₃N can coordinate to the palladium atom in the σ -alkylpalladium intermediate **5** (the latter via displacement of iodide anions or phosphine ligands⁸). In the absence of phosphines, *i.e.*, when **5** should contain only Et₃N in the coordination sphere of palladium, the vinylic substitution path is envisioned to be favored (Table 1, entry 1) by the low energy requirements for reaching the syn-planar arrangement of the C-H bond and the adjoining C-Pd bond, as shown in **9** (Scheme 2c). In the presence of phosphines — when the reaction is likely to involve at least one phosphine ligand linked to the palladium atom of **5** — the steric congestion associated with attaining this alignment could increase the energy requirements of the transition state and consequently favor the competing reduction path. For example, with PPh₃ the *vs:h* ratio is 54:46 (Table 1, entry 2).

An alternative, or competing, mechanism (Scheme 2b) for the substitution of the C-H bond for the C-Pd bond that does not involve the reduction of the carbopalladation adduct **5** considers the protonation of the anionic fragment of **5**. Triethylammonium iodide might be involved in this step. The role of acids in favoring the hydroarylation path has been already observed.³¹ In this case, the palladium carbon-bound enolate complex **5** might be in equilibrium with its synthetic equivalents **6-8**. Et₃N could act as a reducing agent in the regeneration of Pd(0) species from the Pd(II) species derived from the protonation of the Pd(II)-enolate intermediate(s).⁹

Table 1. Palladium-catalyzed reaction of phenyl iodide with butenone^a

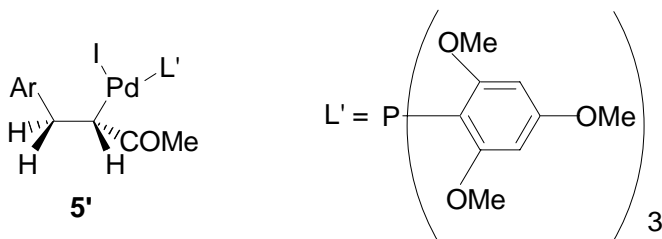
Entry	Base	Catalyst	Total yield (%) ^b	Yield (%)		<i>vs:h</i> ^c
				3a	4a	
1	Et ₃ N	Pd(OAc) ₂	73	56	18	77:23

Entry	Base	Catalyst	Total yield (%) ^b	Yield (%)		<i>vs:h</i> ^c
				3a	4a	
2	Et ₃ N	Pd(OAc) ₂ /PPh ₃	80	43	37	54:46
3	Et ₃ N	Pd(PPh ₃) ₄	63	29	34	46:54
4	Et ₃ N	Pd(OAc) ₂ /P(2-tol) ₃	78	42	35	55:45
5	Et ₃ N	Pd(OAc) ₂ /P(4-MeOC ₆ H ₄) ₃	79	47	32	60:40
6	Et ₃ N	Pd(OAc) ₂ /P(4-Cl-C ₆ H ₄) ₃	56	22	34	40:60
7	Et ₃ N	Pd(OAc) ₂ /tdmpp ^d	61	43	18	70:30
8	Et ₃ N	Pd(OAc) ₂ /ttmpp ^e	79	70	9	89:11
9	Proton sponge ^{f,g}	Pd(OAc) ₂ /ttmpp ^e	90	>89	traces	>99:1
10	Proton sponge ^{f,g}	Pd(OAc) ₂	11	10	1	96:4
11	Proton sponge ^{f,g}	Pd(OAc) ₂ (PPh ₃) ₂	30	29	1	97:3

^a Reactions were carried out at 80 °C for 14 h, using 0.200 g (0.98 mmol) of PhI and the following molar ratios: PhI:butenone:base:Pd:ligand (when added) = 1:3:3:0.05:0.1. ^b Calculated on the isolated products. ^c Calculated by ¹H NMR analysis of the isolated *vs:h* mixtures. ^d Tris-(2,6-dimethoxyphenyl)-phosphine. ^e Tris-(2,4,6-trimethoxyphenyl)phosphine. ^f 1,8-bis-(dimethylamino)naphthalene. ^g PhI: proton sponge = 1:1.

Whatever the real nature of the reaction intermediates may be, it remains that in the presence of a variety of phosphine ligands the reaction of phenyl iodide with butenone gives a greater proportion of the hydroarylation product than it does when phosphine ligands are omitted. Notably, only upon going to the electron-rich sterically encumbered ligand tris-(2,4,6-trimethoxyphenyl)phosphine (ttmpp) does the vinylic substitution product form in yield significantly higher than in the absence of phosphines (Table 1, entry 8).

A working hypothesis accounting for the beneficial effect of ttmpp considers coordinatively unsaturated palladium species¹⁰ such as **5'** (that do not readily proceed along the reduction path) as the main σ -alkylpalladium intermediates. Their formation might be favored by the steric congestion around the bonding face of the ligand and by its high basicity.¹¹ The electron-donating ability of the ligand could stabilize palladium in its 2⁺ oxidation state even when the Pd-P bond length presumably increases because of the ligand size.¹²



tris(2,4,6-trimethoxyphenyl)phosphine (ttmpp)

We next turned our attention to the amine base. Surmising that the employment of a more hindered amine could hamper its coordination to palladium and further improve the selectivity for vinylic substitution *vs* reduction (Scheme 2a), we subjected butenone and phenyl iodide to ttmp, Pd(OAc)₂ and the sterically demanding proton-sponge [1,8-bis-(dimethylamino)naphthalene]. We were pleased to find that, under these conditions, **4a** could be isolated as almost the only β-phenyl product, in excellent yield (Table 1, entry 9). High vinylic substitution to hydroarylation ratios were also obtained when the reaction was run in the presence of proton sponge, but omitting the ligand or substituting PPh₃ for ttmp (Table 1, entries 10 and 11), but the yields were low. Both ttmp and proton sponge are required to give the best results. Clearly, proton sponge is also a stronger base than triethylamine and this could favor the vinylic substitution path by preventing protonation of palladium-enolate intermediates (Scheme 2b). However, we have not made any attempt to clear this point up.

Using the ttmp/proton sponge combination, the study was extended to include other aryl iodides. The preparative results are summarized in Table 2.

A number of aryl iodides containing electron-donating and electron-withdrawing substituents gave the corresponding vinylic substitution products in high- to excellent yield. Only 2-iodoanisole produced the Heck derivative in low yield (Table 2, entry 5), presumably because of the higher energy requirements for the rotation around the C_α-C_β bond of the corresponding carbopalladation adduct (owing to the *ortho* substituent).

In conclusion, we have demonstrated that under the best conditions developed so far [Pd(OAc)₂, ttmp, proton sponge, 80 °C], benzalacetones containing a number of functional groups can be prepared in good to excellent yield from aryl iodides and butenone under solvent-free conditions. The observation that phosphine ligands and nitrogen bases can influence the reaction course in this process, and that it is possible to take advantage of their properties to develop a highly selective reaction, suggests an exploration of their employment in other synthetic applications.

Table 2. Palladium-catalyzed reaction of aryl iodides **1** with butenone^a

Entry	Aryl iodide 1		Yield ^b of 3 (%)
1	PhI	a	89
2	4-Me-C ₆ H ₄ -I	b	80
3	3-Me-C ₆ H ₄ -I	c	67
4	4-MeO-C ₆ H ₄ -I	d	82
5	3-MeO-C ₆ H ₄ -I	e	87
6	2-MeO-C ₆ H ₄ -I	f	32 ^c
7	4-Me-3-O ₂ N-C ₆ H ₄ -I	g	98
8	4-Cl-C ₆ H ₄ -I	h	98
9	3-CF ₃ -C ₆ H ₄ -I	i	96
10	4-MeCO-C ₆ H ₄ -I	j	85

^a Reactions were carried out at 80 °C for 14 h, using 1 equiv. of **1**, 3 equiv. of butenone, 1.1 equiv. of proton sponge, 0.05 equiv. of Pd(OAc)₂, and 0.1 equiv. of ttmpp. ^b Yields are given for isolated products. ^c 2-Iodoanisole was recovered in 64% yield.

Experimental Section

General Procedures. Melting points were determined with a Büchi apparatus and are uncorrected. All of the starting materials, catalyst, ligands, bases, and solvents are commercially available and were used as purchased, without further purification. Reaction products were purified on axially compressed columns (packed with SiO₂ 25–40 nm, Macherey Nagel) connected to a Gilson solvent delivery system and to a Gilson refractive index detector. *n*-Hexane/EtOAc mixtures were used for elution. ¹H NMR spectra (CDCl₃; TMS as internal standard) were recorded at 200 MHz. ¹³C NMR spectra were recorded at 50.3 MHz. IR spectra were recorded in KBr dispersions unless otherwise stated.

Typical procedure for the palladium-catalyzed vinylic substitution of butenone (**3g**)

A 5 mL Supelco vial equipped with a triangular magnetic bar was charged with 4-methyl-3-nitrophenyl iodide (0.263 g, 1 mmol), butenone (0.245 mL, 3 mmol), proton sponge (0.235 g, 1.1 mmol), Pd(OAc)₂ (0.011 g, 0.05 mmol) and ttmpp (0.053 g, 0.10 mmol). The vial was sealed and heated at 80 °C for 14 h. After this time, the reaction mixture was diluted with diethyl ether, the organic layer washed with 0.1M HCl, saturated NaHCO₃, saturated NaCl, dried over Na₂SO₄ and concentrated under reduced pressure. The residue was chromatographed on silica gel eluting with a *n*-hexane/EtOAc 85/15 (*v/v*) mixture to afford 0.200 g (98% yield) of **3g** as a yellow solid: mp 87–88 °C; IR 1674, 1525, 1348, 979, 819 cm⁻¹; ¹H NMR δ 8.04 (d, *J* = 1.5 Hz, 1H), 7.59 (dd, *J* = 8.2 Hz, *J* = 1.5 Hz, 1H), 7.41 (d, *J* = 16.2 Hz, 1H), 7.31 (d, *J* = 8.2 Hz, 1H), 6.68 (d, *J* = 16.2 Hz, 1H), 2.53 (s, 3H), 2.32 (s, 3H); ¹³C NMR δ 197.8, 149.4, 140.3, 135.5, 133.7, 133.5, 131.9, 128.5, 124.0, 27.8, 20.5; MS *m/e* (relative intensity) 205 (M⁺, 26), 190 (100), 160 (11), 144 (24), 143 (27). Anal. Calcd for C₁₁H₁₁NO₃: C, 64.37; H, 5.41; N, 6.83. Found: C, 64.43; H, 5.42; N, 6.85%.

3a. (pale yellow solid) mp 38–39; lit.¹³ mp 36–39 °C.

3b. pale yellow oil; IR (Nujol) 1669, 1257, 803 cm⁻¹; ¹H NMR δ 7.48 (d, *J* = 16.2 Hz, 1 H), 7.46 (d, *J* = 8.2 Hz, 2 H), 7.22 (d, *J* = 8.2 Hz, 2 H), 6.70 (d, *J* = 16.2 Hz, 1 H), 2.39 (s, 6 H); ¹³C NMR δ 198.4, 143.4, 140.9, 131.4, 129.5, 128.1, 126.0, 27.2, 21.3; MS *m/e* (relative intensity) 160 (M⁺, 22), 145 (100), 117 (50). Anal. Calcd for C₁₁H₁₂O: C, 82.45; H, 7.55. Found: C, 82.53; H, 7.54%.

3c. pale yellow oil; IR (Nujol) 1672, 1257, 778, 691 cm⁻¹; ¹H NMR δ 7.40 (d, *J* = 16.2 Hz, 1H), 7.28–7.02 (m, 4H), 6.59 (d, *J* = 16.2 Hz, 1H), 2.55 (s, 6H); ¹³C NMR δ 198.3, 143.6, 138.5, 134.2, 131.3, 128.8, 128.7, 126.8, 125.4, 27.3, 21.2; MS *m/e* (relative intensity) 160 (M⁺, 7), 145 (100), 115 (44). Anal. Calcd for C₁₁H₁₂O: C, 82.45; H, 7.55. Found: C, 82.38; H, 7.56%.

3d. (pale yellow solid) mp 68–69 °C; lit.¹³ mp 70–72 °C.

3e. pale yellow oil; lit.¹⁴ bp 110–115 °C (0.030 Torr); IR (Nujol) 1673, 125, 782, 732, 689 cm⁻¹; ¹H NMR δ 7.45 (d, *J* = 16.3 Hz, 1H), 7.29 (t, *J* = 7.8 Hz, 1H), 7.16–7.00 (m, 2H), 6.93 (dt, *J* = 8.2 Hz, *J* = 0.7 Hz, 1H), 6.67 (d, *J* = 16.3 Hz, 1H), 3.80 (s, 3H), 2.36 (s, 3H); ¹³C NMR δ 198.3, 159.7, 143.2, 135.5, 129.7, 127.1, 120.8, 116.1, 112.8, 55.0, 27.2; MS *m/e* (relative intensity) 176 (M⁺, 64), 161 (100), 133 (52), 118 (50). Anal. Calcd for C₁₁H₁₂O₂: C, 74.96; H, 6.87. Found: C, 75.04; H, 6.88%.

3f. (pale yellow solid) mp 45–46 °C; IR 1669, 1248, 754 cm⁻¹; ¹H NMR δ 7.88 (d, *J* = 16.5 Hz, 1 H), 7.52 (dd, *J* = 7.6 Hz, *J* = 1.5 Hz, 1 H), 7.35 (td, *J* = 7.0 Hz, *J* = 1.5 Hz, 1 H), 7.01–6.82 (m, 2 H), 6.74 (d, *J* = 16.5 Hz, 1 H), 3.87 (s, 3 H), 2.38 (s, 3 H); ¹³C NMR δ 199.2, 158.2, 138.8, 131.9, 128.3, 127.7, 123.2, 120.8, 111.1, 55.5, 27.1; MS *m/e* (relative intensity) 176 (M⁺, 13), 161 (55), 145 (100), 118 (27). Anal. Calcd for C₁₁H₁₂O₂: C, 74.96; H, 6.87. Found: C, 74.88; H, 6.86%.

3h. (pale yellow solid) mp 54–55 °C; lit.¹³ mp 54–55 °C.

3i. pale yellow oil; lit.¹⁵ b.p. 90–92 °C (0.2 Torr); IR 1676, 1334, 799, 697 cm⁻¹; ¹H NMR δ 7.82 (m, 5 H), 6.75 (d, *J* = 16.2 Hz, 1 H), 2.38 (s, 3 H); ¹³C NMR δ 197.8, 141.2, 135.2, 131.2 (q, *J* = 32.4 Hz), 131.1, 129.4, 128.4, 126.6 (q, *J* = 3.6 Hz), 124.6 (q, *J* = 3.9 Hz), 123.7 (q, *J* = 271.0 Hz), 27.5; MS *m/e* (relative intensity) 214 (M⁺, 20), 199 (81), 171 (35), 161 (100), 145 (40). Anal. Calcd for C₁₁H₉F₃O: C, 61.68; H, 4.24. Found: C, 61.74; H, 4.25%.

3j. (pale yellow solid) mp 105–106 °C; IR 1678, 1660, 1263, 817 cm⁻¹; ¹H NMR δ 7.88 (d, *J* = 8.3 Hz, 2 H), 7.53 (d, *J* = 8.3 Hz, 2 H), 7.44 (d, *J* = 16.2 Hz, 1 H), 6.69 (d, *J* = 16.2 Hz, 1 H), 2.52 (s, 3 H), 2.31 (s, 3 H); ¹³C NMR δ 197.9, 197.1, 141.5, 138.6, 137.9, 128.9, 128.7, 128.2, 27.6, 26.6a; MS *m/e* (relative intensity) 188 (M⁺, 100), 173 (73), 145 (86), 131 (48), 115 (28). Anal. Calcd for C₁₂H₁₂O₂: C, 76.56; H, 6.43. Found: C, 76.64 H, 6.42%.

Acknowledgments

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References and Notes

1. For recent references, see: (a) Alexakis, A.; March, S. *J. Org. Chem.* **2002**, *67*, 8753. (b) Park, M. Y.; Yang, S. G.; Kim, Y. H. *Heteroatom Chem.* **2002**, *13*, 431. (c) Andriamialisoa, Z.; Valla, A.; Cartier, D.; Labia, R. *Helv. Chim. Acta* **2002**, *85*, 2926. (d) Shen, Y.; Feng, X.; Zhang, G.; Jiang, Y. *Synlett* **2002**, 1353. (e) Deng, Guisheng; T., X.; Qu, Z.; Wang, J. *Angew. Chem., Internat. Ed.* **2002**, *41*, 2773. (f) Mizutani, H.; Degrado, S. J.; Hoveyda, A.

- H. *J. Am. Chem. Soc.* **2002**, *124*, 779. (g) Oi, S.; Honma, Y.; Inoue, Y. *Org. Lett.* **2002**, *4*, 667. (h) Wang, Z.; Fetterly, B.; Verkade, J. G. *J. Organomet. Chem.* **2002**, *646*, 161.
- See, for example: (a) Yamagami C.; Motohashi N.; Akamatsu M. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 2281. (b) Yamagami, C.; Kishida, N.; Ka, S.; Horiuchi, M.; Motohashi, N. *Chem. Pharm. Bull.* **1998**, *46*, 274. (c) Motohashi, N.; Yamagami, C.; Tokuda, H.; Okuda, Y.; Ichiishi, E.; Mukainaka, T.; Nishino, H.; Saito, Y. *Mut. Res.* **2000**, *464*, 247. (d) Motohashi, N.; Ashihara, Y.; Yamagami, C.; Saito, Y. *Mut. Res.* **2001**, *474*, 113. (e) Yamagami, C.; Motohashi, N. *Eur. J. Med. Chem.* **2002**, *37*, 127.
 - (a) Cacchi, S.; Arcadi, A. *J. Org. Chem.* **1983**, *48*, 4236. (b) Cacchi, S.; F. La Torre, G. Palmieri *J. Organomet. Chem.* **1984**, *268*, C48. (c) Cacchi, S.; G. Palmieri *Synlett* **1984**, 575. (d) Arcadi, A.; Marinelli, F.; Cacchi, S. *J. Organomet. Chem.* **1986**, *312*, C27. (e) Stokker, G. E. *Tetrahedron Lett.* **1987**, *28*, 3179. (f) Wada, A.; Yasuda, H.; Kanatomo, S. *Synthesis* **1988**, 771. (g) Wolff, S.; Hoffmann, H. M. R. *Synthesis* **1988** 760. (h) Hoffmann, M. H. R.; Schmidt, B.; Wolff, S. *Tetrahedron* **1989**, *45*, 6113. (i) Amorese, A.; Arcadi, A.; Bernocchi, E.; Cacchi, S.; Cerrini, S.; Fedeli, W.; Ortar, G. *Tetrahedron* **1989**, *45*, 813. (j) Konopelski, J. P.; Chu, K. S.; Negrete, G. R. *J. Org. Chem.* **1991**, *56*, 1355. (k) Wada, A.; Ohki, K.; Nagai, S.; Kanatomo, S. *J. Heterocyclic Chem.* **1991**, *28*, 509. (l) Friestad, G. K.; Braunchaud, B. P. *Tetrahedron Lett.* **1995**, *36*, 7047. (m) Hagiwara, H.; Eda, Y.; Morohashi, K.; Suzuki, T.; Ando, M.; Ito, N. *Tetrahedron Lett.* **1998**, *39*, 4055. (n) Cacchi, S.; Fabrizi, G.; Gasparrini, F.; Pace, P.; Villani, C. *Synlett* **2000**, 650.
 - Decreasing the excess of butenone leads to the formation of significant amounts of 3,3-diphenylbutan-2-one, most probably derived from the palladium-catalyzed hydroarylation of the vinylic substitution product **3a** formed initially. For example, subjecting phenyl iodide to 1.5 equiv. of butenone in the presence of Pd(PPh₃)₄ under our usual conditions produced **3a**, **4a** and 3,3-diphenyl-2-butanone in 13, 21 and 30% yield, respectively.
 - (a) Cacchi, S.; G. Fabrizi, Gasparrini, F.; Pace, P.; Villani, C. *Synlett* **1999**, 345. (b) Battistuzzi, G.; Cacchi, S.; Fabrizi, G. *Synlett* **2002**, 439. (c) Cacchi, S.; Fabrizi, G.; Goggiamani, A.; Moreno-Manás, Vallribera, A. *Tetrahedron Lett.* **2002**, *43*, 5537.
 - For reviews on solvent-free reactions, see: (a) Dittmer, D. C. *Chem. Ind.* **1997**, 779. (b) Metzger, J. O. *Angew. Chem., Internat. Ed.* **1998**, *37*, 2975. (c) Loupy, A.; Petit, Alain; H., J.; Texier-Boullet, F.; Jacquault, P.; Mathe, D. *Synthesis* **1998**, 1213. (d) Tanaka, K.; Toda, F. *Chem. Rev.* **2000**, *100*, 1025. (e) Diaz-Ortiz, A.; de la Hoz, A.; Langa, F. *Green Chem.* **2000**, *2*, 165. (f) Varma, R. S. *Pure Appl. Chem.* **2001**, *73*, 193.
 - (a) Cabri, W.; Candiani, I.; De Bernardis, S.; Francalanci, F.; Penco, S. *J. Org. Chem.* **1991**, *56*, 5796. (b) Laschat, S.; Narjes, F.; Overman, L.E. *Tetrahedron* **1994**, *50*, 347. (c) Arcadi, A.; Cacchi, S.; Fabrizi, G.; Marinelli, F.; Pace, P. *Tetrahedron* **1996**, *52*, 6983.
 - For some examples of phosphine displacement by amines in palladium complexes, see: (a) Widenhofer, R. A.; Buchwald, S. L. *Organometallics* **1996**, *15*, 3534. (b) Khong, H. A.; Widenhofer, R. A. *Organometallics* **1997**, *36*, 2610.

9. For some leading references on palladium enolates, see: (a) Ito, Y.; Hirao, T.; Saegusa, T. *J. Org. Chem.* **1978**, *43*, 1011. (b) Minami, I.; Nisar, M.; Yuhara, M.; Shimizu, I.; Tsuji, J. *Synthesis* **1987**, 992. (c) Nokami, J.; Mandai, T.; Watanabe, H.; Ohyama, H.; Tsuji, J. *J. Am. Chem. Soc.* **1989**, *111*, 4126. (d) Burkhardt, E. R.; Bergman, R. G.; Heathcock, C. H. *Organometallics* **1990**, *9*, 30. (e) Ogoshi, S.; Morimoto, T.; Nishio, K.-I.; Ohe, K.; Murai, S. *J. Org. Chem.* **1993**, *58*, 9. (f) Soeoka, M.; Tokunoh, R.; Miyazaki, F.; Hagiwara, E.; Shibasaki, M. *Synlett* **1997**, 463. (g) Garg, N.; Larhed, M.; Hallberg, A. *J. Org. Chem.* **1998**, *63*, 4158. (h) Shim, J.-G.; Nakamura, H.; Yamamoto, Y. *J. Org. Chem.* **1998**, *63*, 8470. (i) Kawatsura, M.; Hartwig, J. F. *J. Am. Chem. Soc.* **1999**, *121*, 1473. (j) Albéniz, A. C.; Catalina, N. M.; Espinet, P.; Redón, R. *Organometallics* **1999**, *18*, 5571. (k) Lei, A.; Zhang, X. *Tetrahedron Lett.* **2002**, *43*, 2525.
10. A sterically demanding ligand such as P(2-tol)₃ has been reported to create coordinatively unsaturated palladium species: Paul, F.; Patt, J.; Hartwig, J.F. *Organometallics* **1995**, *14*, 3030.
11. Wada, M.; Higashizaki, S. *J. Chem. Soc. Chem. Comm.* **1984**, 482.
12. Tolman, C.A. *Chem. Rev.* **1977**, *77*, 313.
13. Elias, G.; Rao, M. *Eur. J. Med. Chem.* **1988**, *23*, 379.
14. Evans, D. A.; Gauchet-Prunet, J. A.; Carreira, E. M.; Charette, A. B. *J. Org. Chem.* **1991**, *56*, 741.
15. Edwards, M. L.; Ritter, H. W.; Stemerick, D. M.; Stewart, K. T. *J. Med. Chem.* **1983**, *26*, 431.