

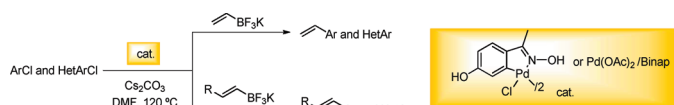
General Reaction Conditions for the Palladium-Catalyzed Vinylation of Aryl Chlorides with Potassium Alkenyltrifluoroborates

Emilio Alacid and Carmen Nájera*

Departamento de Química Orgánica, Facultad de Ciencias, and Instituto de Síntesis Orgánica (ISO),
Universidad de Alicante, Apdo. 99, 03080-Alicante, Spain

cnajera@ua.es

Received July 31, 2009



Activated and deactivated aryl and heteroaryl chlorides are efficiently cross-coupled with potassium vinyl- and alkenyltrifluoroborates using 4-hydroxyacetophenone oxime derived palladacycle as precatalyst in 1 to 3 mol % Pd loading, Binap as ligand, and Cs₂CO₃ as base in DMF at 120 °C. The reactions can also be performed using Pd(OAc)₂ as Pd(0) source, although with lower efficiency. Bidentate ligands such as Binap and dppp can be used, the former being the best choice. Only in the case of deactivated aryl chlorides should the reaction temperature be increased to 160 °C to achieve good yields. The corresponding cross-coupled compounds, such as styrenes, stilbenes, and alkenylarenes, are obtained in good yields and with high regio- and diastereoselectivity.

Introduction

During the last 10 years, considerable progress has been achieved in the palladium-catalyzed cross-coupling reactions of activated and deactivated aryl chlorides with organoboron compounds leading to biaryls.¹ However, alkenylation reactions devoted to the synthesis of styrenes, stilbenes, alkenylarenes, and related alkenylheterocycles using aryl and heteroaryl chlorides remain challenging.² Few examples have been described using bulky N-heterocyclic carbenes³ or an electron-rich ferrocenylphosphine⁴ as ligands for the reaction of alkenylboronic acids with aryl chlorides to afford stilbenes and alkenylarenes. When simple vinylations are

intended, the trivinylboroxine–pyridine complex must be used exclusively reacting with aryl iodides and bromides, due to its rather low reactivity and stability.⁵ Potassium organotrifluoroborates have emerged as an excellent alternative to boronic acids and boronate esters due to their stability and versatility in cross-coupling reactions.⁶ Several types of potassium organotrifluoroborates such as aryl,⁷ cycloalkyl,⁸ dialkylaminomethyl,⁹ and alkoxyethyl¹⁰ derivatives have been successfully employed for the coupling of aryl and heteroaryl chlorides. However, attempted cross-coupling

*To whom correspondence should be addressed. Fax: +34 965903549. E-mail: cnajera@ua.es.

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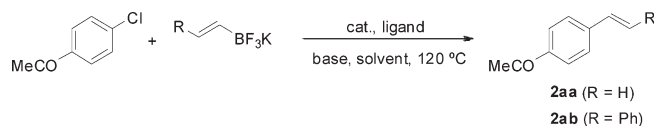
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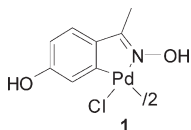
TABLE 1. Reaction Conditions Optimization for Cross-Coupling of 4-Chloroacetophenone with Potassium Vinyl- and Styryltrifluoroborates^a

entry	R	cat. (mol % Pd)	ligand (mol %)	base	solvent	time	no.	yield (%) ^b
1	H	1 (2)		K ₂ CO ₃	H ₂ O ^c	30 min ^d	2aa	25
2	H	1 (2)		K ₂ CO ₃	H ₂ O ^c	14 h	2aa	10
3	H	1 (3)	(<i>S</i>)-Binap (6)	K ₂ CO ₃	H ₂ O ^c	30 min ^d	2aa	45
4	H	1 (3)	(<i>S</i>)-Binap (6)	Cs ₂ CO ₃	H ₂ O ^c	30 min ^d	2aa	57
5	H	1 (3)	Ph ₃ P (9)	Cs ₂ CO ₃	DMF	30 min ^d	2aa	62 ^e
6	H	1 (3)	(<i>S</i>)-Binap (6)	Cs ₂ CO ₃	DMF	30 min ^d	2aa	74 ^f
7	H	1 (3)	(<i>S</i>)-Binap (6)	Cs ₂ CO ₃	DMF	18 h	2aa	99 (89)
8	H	1 (3)	Ph ₃ P (9)	Cs ₂ CO ₃	DMF	18 h	2aa	81 (68)
9	H	1 (3)	XantPhos (6)	Cs ₂ CO ₃	DMF	18 h	2aa	0
10	H	1 (3)	Ruphos (6)	Cs ₂ CO ₃	DMF	18 h	2aa	0
11	H	1 (3)	dppf (6)	Cs ₂ CO ₃	DMF	18 h	2aa	0
12	H	1 (3)	dppp (6)	Cs ₂ CO ₃	DMF	18 h	2aa	93
13	H	Pd(OAc) ₂ (3)	(<i>S</i>)-Binap (6)	Cs ₂ CO ₃	DMF	18 h	2aa	96
14	H	PdCl ₂ (3)	(<i>S</i>)-Binap (6)	Cs ₂ CO ₃	DMF	18 h	2aa	85
15	H	1 (1)	(<i>S</i>)-Binap (2)	Cs ₂ CO ₃	DMF	18 h	2aa	80 ^g
16	H	1 (1)	dppp (2)	Cs ₂ CO ₃	DMF	20 h	2aa	66
17	H	Pd(OAc) ₂ (1)	(<i>S</i>)-Binap (2)	Cs ₂ CO ₃	DMF	18 h	2aa	57 ^h
18	H	PdCl ₂ (1)	(<i>S</i>)-Binap (2)	Cs ₂ CO ₃	DMF	18 h	2aa	29 ⁱ
19	Ph	1 (3)	(<i>S</i>)-Binap (6)	Cs ₂ CO ₃	DMF	16 h	2ab	91
20	Ph	Pd(OAc) ₂ (3)	(<i>S</i>)-Binap (6)	Cs ₂ CO ₃	DMF	18 h	2ab	99
21	Ph	PdCl ₂ (3)	(<i>S</i>)-Binap (6)	Cs ₂ CO ₃	DMF	18 h	2ab	92
22	Ph	1 (1)	(<i>S</i>)-Binap (6)	Cs ₂ CO ₃	DMF	18 h	2ab	86
23	Ph	Pd(OAc) ₂ (1)	(<i>S</i>)-Binap (6)	Cs ₂ CO ₃	DMF	18 h	2ab	42

^aReaction conditions: 4-chloroacetophenone (32 μ L, 0.25 mmol), CH₂=CHBF₃K (40 mg, 0.3 mmol), cat. (see column), ligand (see column), base (0.75 mmol) and solvent (1 mL) at 120 °C under Ar. ^bIsolated yield of the crude product determined by ¹H NMR. In parentheses, yield after flash chromatography. ^cTBAB (0.25 mmol) was added. ^dHeating in a microwave reactor (30 W, 14.5 psi) with air stream cooling. ^e3% of 4,4'-bisacetylstilbene was obtained. ^f2% of 4,4'-bisacetylstilbene was also obtained. ^g3% of 4,4'-bisacetylstilbene and 2% of acetophenone were obtained. ^h2% of 4,4'-bisacetylstilbene and 4% of acetophenone were obtained. ⁱ1% of 4,4'-bisacetylstilbene and 6% of acetophenone were obtained.

of potassium vinyltrifluoroborate with aryl chlorides only succeeded with 4-chloroacetophenone using the combination PdCl₂ (2 mol %) and RuPhos (6 mol %) as catalyst, Cs₂CO₃ as base in THF/H₂O (9:1) at 85 °C during 22 h.¹¹ Under these conditions, the corresponding 4-acetylstyrene was obtained in 65% yield and the formation of the homo-coupled 4,4'-bisacetylstilbene and Heck's product 4,4'-bisacetylstilbene was also observed.

Recently, we have described the cross-coupling of potassium vinyl- and alkenyltrifluoroborates with aryl and heteroaryl bromides using 1 mol % Pd loading of 4-hydroxyacetophenone oxime derived palladacycle or Pd(OAc)₂ as precatalysts, K₂CO₃ as base, and TBAB as additive under water reflux to afford styrenes, stilbenoids, and alkenylarenes.¹² However, these phosphine-free reaction conditions failed with aryl chlorides. We report here the first alkenylation reaction of aryl and heteroaryl chlorides with potassium vinyl and alkenyltrifluoroborates using palladacycle **1** and (*S*)-Binap as catalysts in organic solvents.

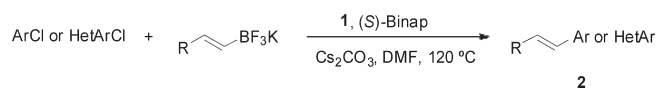


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Results and Discussion











Initial studies were performed with 4-chloroacetophenone and potassium vinyltrifluoroborate using 1 mol % of complex **1** as catalyst (Table 1). Using the same reaction conditions as those previously reported for aryl bromides,¹² K₂CO₃ as base and tetra-*n*-butylammonium bromide (TBAB) in refluxing water under conventional or microwave heating, very low yields of the coupling product **2aa** were obtained (Table 1, entries 1 and 2). A higher yield (up to 57%) was observed after addition of 6 mol % of a bidentate phosphane, such as (*S*)-Binap (6 mol %) and **1** (3 mol % Pd) as catalysts and K₂CO₃ or Cs₂CO₃ as base (Table 1, entries 3 and 4), although the reaction failed under MW heating when aqueous THF¹⁰ or dioxane was used as solvents. The rest of the experiments were performed using Cs₂CO₃ (3 equiv) as base. When DMF was used as solvent in the presence of triphenylphosphane and (*S*)-Binap, 62 and 74% yields of **2aa** were obtained, respectively (Table 1, entries 5 and 6), whereas quantitative crude yields were obtained using (*S*)-Binap under conventional heating after 18 h reaction time (Table 1, entry 7). The same reaction was performed with racemic Binap, affording product **2aa** in 97% crude yield.¹³ When the reaction was performed with 2 mol % of a complex generated by a 1:1 palladacycle/Binap mixture, the reaction afforded product **2aa** in only 41% yield. A lower crude yield (81%) was observed when triphenylphosphane

(13) The use of (*S*)-Binap instead of racemic Binap was due its availability in large quantities in our lab.

TABLE 2. Cross-Coupling of Aryl and Heteroaryl Chlorides with Potassium Alkenyltrifluoroborates^a

entry	organic chloride	R	cat.	Pd/ ligand (mol %)	time	product no.	yield (%) ^b
1		H	1	2/4	18 h		2aa 82 (96)
2			Pd(OAc) ₂	3/6	18 h		2aa 83 (95)
3		Ph	1	3/6	16 h		2ab 85 (91)
4			Pd(OAc) ₂	3/6	18 h		2ab 86 (98)
5		<i>n</i> -C ₈ H ₁₇	1	3/6	18 h		2ac 80 (93 ^c)
6			Pd(OAc) ₂	3/6	18 h		2ac 70 (82 ^c)
7		H	1	2/4	18 h		2ba 85 (97)
8		Ph	1	3/6	16 h		2bb 83 (90)
9		H	1	3/6	20 h		2ca 90 (98)
10		Ph	1	3/6	20 h		2cb 91 (95)
11		<i>n</i> -C ₈ H ₁₇	1	3/6	18 h		2cc 77 (98)
12		H	1	3/6	20 h		2da 81 (93)
13		Ph	1	3/6	20 h		2db 89 (97 ^d)
14		<i>n</i> -C ₈ H ₁₇	1	3/6	24 h		2dc 71 (85 ^e)
15		H	1	3/6	24 h ^f		2ea 83 (91 ^g)
16			Pd(OAc) ₂	3/6	24 h ^f		2ea 54 (76 ^h)
17		Ph	1	3/6	24 h ^f		2eb 82 (89 ^g)
18		<i>n</i> -C ₈ H ₁₇	1	3/6	24 h ^f		2ec 76 (87 ^g)
19		H	1	3/6	24 h		2fa 59 (72)
20		Ph	1	3/6	24 h		2fb 70 (87)
21		<i>n</i> -C ₈ H ₁₇	1	3/6	24 h ^f		2fc 52 (63)
22		H	1	3/6	24 h ^f		2ga 75 (88 ^h)
23		Ph	1	3/6	24 h ^f		2gb 86 (92)

TABLE 2. Continued

entry	organic chloride	R	cat.	Pd/ ligand (mol %)	time	product no.	yield (%) ^b
24		H	1	3/6	20 h		2ha 52 (67)
25		Ph	1	3/6	24 h		2hb 63 (72)
26		<i>n</i> -C ₈ H ₁₇	1	3/6	24 h		2hc 56 (82)
27		H	1	3/6	24 h		2ia 61 (88)
28		Ph	1	3/6	24 h		2ib 84 (91)
29		H	1	3/6	24 h		2ja 64 (81)
30		Ph	1	3/6	34 h		2jb 77 (88)

^aReaction conditions: organic chloride (0.25 mmol), alkenylBF₃K (0.3 mmol), Cs₂CO₃ (249 mg, 0.75 mmol), complex **1** (see column), and DMF (1 mL) at 120 °C under Ar. ^bIsolated yield after flash chromatography. In parentheses, yield determined by ¹H NMR of the crude product. ^c3% of regioisomeric 2-(4-acetylphenyl)dec-1-ene (**3ac**) was obtained. ^d5% of 2-(1-naphthyl)styrene was obtained. ^e3% of 2-(1-naphthyl)dec-1-ene (**3db**) was obtained. ^fAt 160 °C. ^g4% of 4,4'-dimethoxystilbene was obtained. ^h2% of anisole was obtained. ⁱ8% of 2-(4-methoxyphenyl)styrene (**3eb**) was obtained. ^j7% of 2-(4-methoxyphenyl)dec-1-ene (**3ec**) was obtained. ^k6% of 2,2'-dichlorostilbene was obtained.

was used instead of Binap under conventional thermal conditions (Table 1, entry 8). In both cases, product **2aa** was isolated in 89 and 68% yield after purification (Table 1, compare entries 7 and 8). The role of Binap seems to be important as stabilizer of the in situ generated Pd(0) atoms, whereas the palladacycle is less prone to generate Pd(0) when coordinated by the ligand.

On the other hand, this coupling failed in the presence of phosphanes such as XantPhos, Ruphos, and dppf (Table 1, entries 9–11), with dppp affording slightly lower yield than Binap (Table 1, entry 12), whereas Pd(OAc)₂ and PdCl₂ gave 96 and 85% yields, respectively (Table 1, entries 13 and 14). When the Pd loading using palladacycle **1** was decreased to 1 mol % and (*S*)-Binap or dppp to 2 mol %, yields of 80 and 66% for product **2aa**, respectively, were obtained, corroborating that Binap is a better bidentate ligand than dppp (Table 1, entries 15 and 16). In the case of Pd(OAc)₂ or PdCl₂ (1 mol %) and (*S*)-Binap (2 mol %) as ligand, product **2aa** was obtained in much lower 57 and 29% yields, respectively (Table 1, entries 17 and 18). Potassium (*E*)-styryltrifluoroborate was cross-coupled with 4-chloroacetophenone using palladacycle **1**, Pd(OAc)₂, or PdCl₂ with a 3 mol % Pd loading, affording stereoselectively (*E*)-4-acetylstilbene (**2ab**) in high yields (>91%) (Table 1, entries 19–21). However, a much lower yield was obtained when the Pd loading was 1 mol % using Pd(OAc)₂ than complex **1** (Table 1, compare entries 22 and 23).

Different activated and deactivated aryl chlorides and heterocyclic chlorides were cross-coupled with potassium vinyl and alkenyltrifluoroborates using these optimized reaction conditions: palladacycle **1** or Pd(OAc)₂ and (*S*)-Binap (1:2) as a catalytic mixture and Cs₂CO₃ as base under Ar, DMF as solvent and conventional heating at 120 °C

(Table 2). In the case of the coupling of 4-chloroacetophenone and potassium vinyltrifluoroborate, a 2 mol % Pd loading was used, affording **2aa** in 82% isolated yield (Table 2, entry 1), the loading of Pd(OAc)₂ being increased to 3 mol % in order to achieve similar yields (Table 2, entry 2). In the case of potassium (*E*)-styryl- and (*E*)-dec-1-enyltrifluoroborate (3 mol % of Pd), products **2ab** and **2ac** were regio- and stereoselectively obtained, respectively, either with palladacycle **1** or with Pd(OAc)₂ (Table 2, entries 3 or 4 and 5 or 6). 4-Benzoylchlorobenzene gave styrene **2ba** and stilbene **2bb** in high yields using similar conditions than with 4-chloroacetophenone (Table 2, entries 7 and 8). After the coupling of 4-chlorobenzonitrile and 1-naphthyl chloride, the corresponding styrenes **2ca** and **2da**, stilbenes **2cb** and **2db**, and dec-1-enylbenzenes **2cc** and **2dc**, respectively, were obtained in good yields under the same reaction conditions (Table 2, entries 9–14). In several cases, deactivated 4-chloroanisole, 3,5-dimethoxychlorobenzene, and 2-chlorotoluene needed to be heated at 160 °C in order to achieve higher yields than when working at 120 °C (Table 2, entries 15–23). In the vinylation of 4-chloroanisole with potassium vinyltrifluoroborate, the use of Pd(OAc)₂ provided lower yield than when using complex **1** (Table 2, compare entries 15 and 16). When potassium styryl- or dec-1-enyltrifluoroborates were used as nucleophilic partners, less than 8% of the regioisomeric products **3** was also obtained (Table 2, entries 5, 6, 13, 14, 17, and 18). In the cross-coupling of 4-chloroanisole and 2-chlorotoluene with vinyltrifluoroborate, less than 6% of the Heck products, 4,4'-dimethoxy- and 4,4'-dimethylstilbene, respectively, was obtained (Table 2, entries 15 and 22).

Heteroaryl chlorides were also used as coupling partners with the corresponding potassium alkenyltrifluoroborates.

Thus, 3-chloropyridine was alkenylated with potassium vinyl, (*E*)-styryl, and (*E*)-dec-1-enyltrifluoroborates to provide products **2ha**, **2hb**, and **2hc**, respectively, in moderate yields (Table 2, entries 24–26). 4-Chloro-2-methylquinoline gave good yields of the corresponding vinyl and styryl derivatives **2ia** and **2ib** (Table 2, entries 27 and 28). Under the same reaction conditions, 5-chlorofurfural was cross-coupled with potassium vinyl- and (*E*)-styryltrifluoroborate giving products **2ja** and **2jb** in good yields (Table 2, entries 29 and 30).

Conclusions

It can be concluded that the oxime-derived palladacycle **1** or Pd(OAc)₂ can be very efficient precatalysts for the cross-coupling reaction of potassium vinyl and alkenyltrifluoroborates with a wide range of aryl and heteroaryl chlorides when Binap is added as a ligand. These types of cross-coupling must be performed in the presence of Cs₂CO₃ as base and in DMF as solvent at temperatures of 120 or 160 °C and with less than 3 mol % Pd loading.

Experimental Section

General Procedure for the Cross-Coupling of Potassium Alkenyltrifluoroborates with Organic Chlorides [4-Vinylacetophenone (2aa**) as Example].** A glass tube was charged with palladium catalyst (2 mol % of Pd), (*S*)-Binap (6.2 mg, 4 mol %), potassium vinyltrifluoroborate (40 mg, 0.3 mmol), and Cs₂CO₃ (249 mg, 0.75 mmol) and sealed with a septum. The mixture was purged by alternating five cycles of evacuation and inert gas introduction, and then, not dry *N,N*-dimethylformamide (1 mL) and 4-chloroacetophenone (0.032 mL, 0.25 mmol) were added and the mixture heated at 120 °C (bath temperature). When the reaction was stopped and cooled at room temperature, the mixture was diluted with 10 mL of water and the product was extracted in diethyl ether (2 × 15 mL). The combined organic layers were washed with water (4 × 15 mL) and dried over anhydrous MgSO₄. The solvent was removed under slight vacuum, and the product was purified by flash chromatography in pentane/diethyl ether 95:5 obtaining 30 mg of 4-vinylacetophenone (82% yield).

4'-Vinylacetophenone (2aa**):** Oil; *R*_f 0.45 (hexane/ethyl acetate 10:1); IR (film) ν 3029, 2926, 1683, 1611, 1265 cm⁻¹; ¹H NMR (CDCl₃, 300 MHz) δ 7.93 (d, 2H, *J* = 8.4 Hz), 7.49 (d, 2H, *J* = 8.2 Hz), 6.76 (dd, 1H, *J* = 17.6 and 10.9 Hz), 5.90 (d, 1H, *J* = 17.6 Hz), 5.41 (d, 1H, *J* = 10.9 Hz), 2.59 (s, 3H); ¹³C NMR (CDCl₃, 75 MHz) δ 197.7, 142.2, 136.4, 136.0, 128.8,

128.6, 126.4, 116.8, 26.7; MS *m/z* 146 (M⁺, 42), 131 (100), 103 (64).

General Procedure for the Cross-Coupling of Potassium Styryltrifluoroborate with Organic Chlorides [4-Acetylstilbene (2ab**) as Example].** A glass tube was charged with palladium catalyst (3 mol % of Pd), (*S*)-Binap (9.3 mg, 6 mol %), potassium (*E*)-styryltrifluoroborate (60 mg, 0.3 mmol), and Cs₂CO₃ (249 mg, 0.75 mmol) and sealed with a septum. The mixture was purged by alternating five cycles of evacuation and inert gas introduction, and then, *N,N*-dimethylformamide not dry (1 mL) and 4-chloroacetophenone (0.032 mL, 0.25 mmol) were added, heating the mixture at 120 °C (bath temperature). When the reaction was stopped and cooled at room temperature, the mixture was diluted with 10 mL of water and the product was extracted in diethyl ether (2 × 15 mL). The combined organic layers were washed with water (4 × 15 mL) and dried over anhydrous MgSO₄. The solvent was removed under vacuum, and the product was purified by flash chromatography in hexane/ethyl acetate 95:5 to afford 47 mg of 4-acetylstilbene (85% yield).

(*E*)-4-Acetylstilbene (2ab**):** Colorless solid; *R*_f 0.20 (hexane/ethyl acetate 9:1); mp 139–141 °C; IR (KBr) ν 3010, 2945, 2895, 1707, 1603, 1518, 1366, 1355, 1261, 1184 cm⁻¹; ¹H NMR (CDCl₃, 300 MHz) δ 7.95 (d, 2H, *J* = 8.5 Hz), 7.58 (d, 2H, *J* = 8.3 Hz), 7.56–7.53 (m, 2H), 7.41–7.38 (m, 2H), 7.33–7.30 (m, 1H), 7.23 (d, 2H, *J* = 16.3 Hz), 7.12 (d, 2H, *J* = 16.3 Hz), 2.60 (s, 3H); ¹³C NMR (CDCl₃, 75 MHz) δ 197.6, 142.1, 136.8, 136.1, 131.6, 129.0, 128.9, 128.4, 127.6, 126.9, 126.6, 26.7; MS *m/z* 223 (M⁺ + 1, 11), 222 (M⁺, 65), 208 (17), 207 (100), 179 (22), 178 (66), 177 (10), 176 (13).

Most of the compounds are all known, and some of them are commercially available (a list of which can be found in the Supporting Information).

Acknowledgment. Dedicated to Professor Benito Alcaide on occasion of his 60th birthday. This work was financially supported by the Ministerio de Educación y Ciencia (MEC) of Spain (Grants CTQ2004-00808/BQU, CTQ2007-62771/BQU, and Consolider INGENIO 2010, CSD200700006), the Generalitat Valenciana (PROMETEO/2009/039), and the University of Alicante. E.A. thanks the MEC for a predoctoral fellowship. We thank Medalchemistry S. L. for a generous gift of (*S*)-Binap.

Supporting Information Available: Physical and spectral data, as well as the ¹H NMR and ¹³C NMR spectra of known compounds are included. This material is available free of charge via the Internet at <http://pubs.acs.org>.