JOC Article

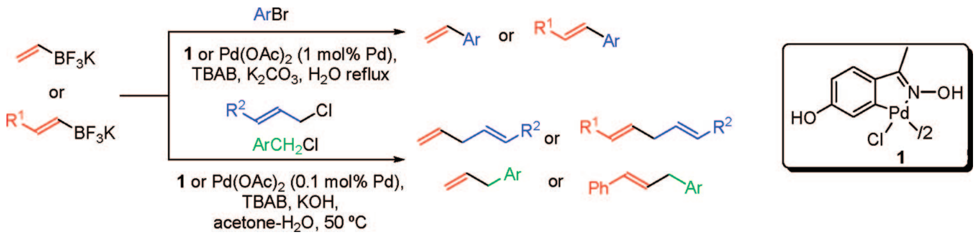
Palladium-Catalyzed Cross-Coupling Reactions of Potassium Alkenyltrifluoroborates with Organic Halides in Aqueous Media[†]

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 October 21, 2008



Potassium vinyl and alkenyltrifluoroborates are cross-coupled with aryl and heteroaryl bromides using 1 mol % Pd loading of 4-hydroxyacetophenone oxime derived palladacycle or $Pd(OAc)_2$ as precatalysts, K_2CO_3 as base, and TBAB as additive and water reflux under conventional or microwave heating to afford styrenes, stilbenoids, and alkenylbenzenes. These borates can be cross-coupled diastereoselectively with allyl and benzyl chlorides using KOH as base in acetone−water (3:2) at 50 °C and 0.1 mol % Pd loading, giving the corresponding 1,4-dienes and allylarenes, respectively. These simple phosphine-free reaction conditions allow the palladium recycling from the aqueous phase during up to five runs by extractive separation of the products, which contain 58−105 ppm of Pd.

Introduction

Palladium-catalyzed vinylation of aromatic halides is an important strategy for the synthesis of styrenes[1] and stilbenes.[2] The Heck reaction using ethylene (or its equivalents) and styrenes allows the preparation of this type of compound.[3] A second approach involves the cross-coupling reaction of aryl halides with alkenylmetals, such as organomagnesium,[4] organotin,[5] organosilane,[6] and organoboron[7] derivatives. The Suzuki−Miyaura reaction of organoboron compounds is nowadays the most widely used cross-coupling reaction because of its low toxicity as well as the possibility of being carried out in water or aqueous solvents. Several types of alkenylboron derivatives, such as boronic acids or anhydrides,[8] related esters,[9] and trifluoroborates[10] have been coupled with aryl iodides, bromides, and triflates. In recent years, potassium organotrifluoroborates have become very useful organoboron reagents in cross-coupling reactions.[11] They are crystalline compounds

---

[†] Dedicated to Professor Ryoji Noyori on occasion of his 70th birthday.

(1) For reviews about applications of styrenes, see: (a) Agbossou, F.; Carpentier, J.-F.; Mortreux, A. *Chem. Rev.* **1995**, *95*, 2485–2506. (b) *Modern Styrenic Polymers: Polystyrenes and Styrenic Copolymers*; Scheirs, J., Priddy, D. B., Eds.; John Wiley: Chichester, 2003. (c) De Meijere, A.; von Zezchwitz, P.; Bräse, S. *Acc. Chem. Res.* **2005**, *38*, 413–422. (d) *Palladium-Catalyzed Coupling Reactions for Industrial Fine Chemical Syntheses*; John Wiley & Sons: Hoboken, 2002; Vol. 1.

(2) Stilbenoids are very important compounds exhibiting many biological activities: Ferré-Filmon, K.; Delaude, L.; Demonceau, A.; Noels, A. F. *Coord. Chem. Rev.* **2004**, *248*, 2323–2336.

(3) For recent reviews, see: (a) Alonso, F.; Beletskaya, I. P.; Yus, M. *Tetrahedron* **2005**, *61*, 11711–11835. (b) Polshettiwar, V.; Molnár, A. *Tetrahedron* **2007**, *63*, 6949–6976.

(4) Bumagin, N. A.; Luzikova, E. V. *J. Organomet. Chem.* **1997**, *532*, 271–273.

(5) (a) McKean, D. R.; Parrinello, G.; Renaldo, A. F.; Stille, J. K. *J. Org. Chem.* **1987**, *52*, 422–424. (b) Grasa, G. A.; Nolan, S. P. *Org. Lett.* **2001**, *3*, 119–122. (c) Littke, A. F.; Schwartz, L.; Fu, G. C. *J. Am. Chem. Soc.* **2002**, *124*, 6343–6348.

(6) For recent publications, see: (a) Alacid, E.; Nájera, C. *J. Org. Chem.* **2008**, *73*, 2315–2322. (b) Denmark, S. E.; Butler, C. R. *J. Am. Chem. Soc.* **2008**, *130*, 3690–3704. (c) Gordillo, A.; de Jesús, E.; López-Mardomingo, C. *Chem. Commun.* **2007**, 4056–4058. (d) Nakao, Y.; Imanaka, H.; Chen, J.; Yada, A.; Hiyama, T. *J. Organomet. Chem.* **2007**, *692*, 585–603.

(7) For recent reviews, see: (a) Alonso, F.; Beletskaya, I. P.; Yus, M. *Tetrahedron* **2008**, *64*, 3047–3101. (b) Yin, L.; Liebscher, J. *Chem. Rev.* **2007**, *107*, 133–173. (c) Corbet, J. P.; Mignani, G. *Chem. Rev.* **2006**, *106*, 2651–2710. (d) *Boronic Acids*; Hall, D. G., Ed., Wiley-VCH: Weinheim, 2005. (e) Leadbeater, N. E. *Chem. Commun.* **2005**, 2881–2902.

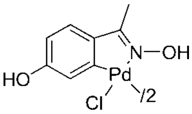
(8) (a) Kerins, F.; O'Shea, D. F. *J. Org. Chem.* **2002**, *67*, 4968–4971. (b) Peyroux, E.; Berthiol, F.; Doucet, H.; Santelli, M. *Eur. J. Org. Chem.* **2004**, 1075–1082. (c) Barder, T. E.; Walker, S. D.; Martinelli, J. R.; Buchwald, S. L. *J. Am. Chem. Soc.* **2005**, *127*, 4685–4696. (d) Mantel, M. L. H.; Sobjerg, L. S.; Huynh, T. H. V.; Ebran, J.-P.; Lindhart, A. T.; Nielsen, N. C.; Skrydstrup, T. *J. Org. Chem.* **2008**, *73*, 3570–3573.

(9) (a) Stewart, S. K.; Whiting, A. *J. Organomet. Chem.* **1994**, *482*, 293–300. (b) Lightfoot, A. P.; Twiddle, S. J. R.; Whiting, A. *Synlett* **2005**, 529–531.

10.1021/jo802356n CCC: $40.75

more stable to air and moisture than boronic acids. Alkenyltrifluoroborates can be prepared by reaction of alkenylboron compounds with KHF_2 starting from organolithium and magnesium compounds[10d] and also by hydroboration of alkynylpinacolborates,[12] nowadays some of them being commercially available. The typical cross-coupling conditions for the synthesis of styryl and other alkenylborates from aryl iodides, bromides, and triflates used $PdCl_2$ (2 mol %), a phosphine (6 mol %) such as PPh_3 or bis(diphenylphosphino)ferrocene (dppf), and an amine as base in aqueous isopropanol.[10f,k] Similar reaction conditions have been used for the reaction between allyl chlorides and styryltrifluoroborates at 100 °C under microwave (MW) heating.[13] For the preparation of styrenes, potassium vinyltrifluoroborate has been coupled with aryl and heteroaryl bromides and triflates in THF−H_2O (9:1) at 85 °C using Cs_2CO_3 as base during 22 h.[10e,f,i†]

The only report about the use of neat water as solvent was the cross-coupling of potassium (*E*)-styryltrifluoroborate with aryl bromides under MW heating (150 °C) using Na_2CO_3 as base, tetra-*n*-butylammonium (TBAB) as additive, and ultralow Pd loading.[10h] However, under these reaction conditions isomerization of the C−C double bond occurred, affording a ca. 5:1 *trans*/*cis* mixture of stilbenes. We have recently described the first cross-coupling of potassium aryltrifluoroborates with aryl chlorides under water reflux using 4-hydroxyacetophenone oxime derived palladacycle **1** as precatalyst, K_2CO_3 as base, and TBAB as additive.[14] The same palladacycle was able to catalyze the coupling with allyl and benzyl chlorides using KOH as base in acetone−H_2O as solvent at 50 °C.[14] We describe here that these reaction conditions can also be used for the cross-coupling of aryl bromides and allyl and benzyl chlorides with potassium vinyl- and alkenyltrifluoroborates in the synthesis of styrenes, stilbenes, alkenylbenzenes, allyl benzenes, and 1,4-dienes. Attempts for easy product separation and also Pd recycling experiments under these reaction conditions would be considered.



1

Results and Discussion

The reaction of aryl bromides with potassium vinyl-, styryl-, and dec-1-enyltrifluoroborates (1.5 equiv) was performed under water reflux using TBAB (1 equiv)[15] and 3 and 2 equiv of K_2CO_3, respectively (Table 1). Initial studies on the reaction of 4-bromoacetophenone with 1.5 equiv of potassium vinyltrifluoroborate gave product **2aa** in 93% crude yield (Table 1, entry 1). However, when 1.01 equiv of potassium vinyltrifluoroborate was used, 72% yield of **2aa** was obtained together with 15% of 4,4′-diacetylstilbene (Table 1, entry 2). The vinylation of 4-bromoacetophenone performed under conventional thermal (in a pressure tube) or MW conditions showed that palladacycle **1** afforded 4-acetylstyrene (**2aa**) in higher yields and lower reaction times than $Pd(OAc)_2$ (Table 1, compare entries 1 with 3 and 4 with 5). Parallel studies were performed with potassium (*E*)-styryltrifluoroborate using 2 equiv of K_2CO_3, providing regio- and stereoselectively stilbene (*E*)-**2ba** in higher yields using palladacycle **1** than $Pd(OAc)_2$ (Table 1, compare entries 6 with 7 and 8 with 9). However, when potassium (*Z*)-styryltrifluoroborate[12] was cross-coupled with 4-bromoacetophenone, a lower stereoselectivity than in the case of the *E*-isomer was obtained, affording product **2ba** in a 80:20 *Z*/*E* ratio (Table 1, entries 10 and 11). In case of the cross-coupling of potassium (*E*)-dec-1-enyltrifluoroborate with 4-bromoacetophenone, (*E*)-dec-1-enylbenzene **2ca** was isolated in a regio- and stereoselective manner with high yields under conventional or MW heating (Table 1, entries 12 and 13).

Vinylation reactions of alkenyltrifluoroborates with deactivated aryl bromides, such as 2-bromotoluene, 1-bromonaphthalene, 4-bromoanisole, and 6-methoxy-2-bromonaphthalene, were carried out using palladacycle **1** as precatalyst under conventional and MW heating, providing styrenes **2ab**−**ae**, stilbenes **2bb**−**2be**, and (*E*)-1-(dec-1-enyl)-4-methoxybenzene (**2cd**) in good yields but with longer reaction times than previous mentioned examples (Table 1, entries 14−31). Only in the case of the preparation of styrenes **2ac** and **2ad** under MW conditions was the formation of the Heck products 1,2-di(1-naphthyl)ethylene (21%) and 4,4′-dimethoxystilbene (11%) observed (Table 1, entries 19 and 23). The alkenylation of 4-bromoanisole with potassium (*E*)-styryl and (*E*)-dec-1-enyltrifluoroborates afforded mainly stilbene **2bd** and 1-decenyl-4-methoxybenzene **2 cd**, as well as the corresponding regioisomeric compounds resulting from the arylation at the α-position (Table 1, entries 24−27). 6-Methoxy-2-bromonaphthalene reacted with vinyltrifluoroborate to provide in good yield 6-methoxy-2-vinylnaphthalene (**2ae**), a precursor of the antiinflamatory naproxene (Table 1, entries 28 and 29). When the cross-coupling was performed with (*E*)-styryltrifluoroborate, the corresponding stilbene **2be** was obtained regio- and stereoselectively (Table 1, entries 30 and 31).

These aqueous conditions were tolerated by easily hydrolizable aryl bromides such as ethyl 4-bromobenzoate and 4-bromobenzonitrile (Table 1, entries 32−35). Both electrophiles were cross-coupled with potassium vinyltrifluoroborate under conventional thermal conditions using palladacycle **1** as precatalyst, affording styrenes **2af** and **2ag**, respectively, in good yields (Table 1, entries 32 and 34). Under the same reaction conditions potassium (*E*)-styryltrifluoroborate gave steroselectively the corresponding stilbenes **2bf** and **2bg** in 81% and 84% yield, respectively (Table 1, entries 33 and 35).

Heterocyclic bromides, such as 5-bromothiophene-2-carboxaldehyde and 3-bromopyridine, afforded the corresponding vinyl

---

(10) (a) Puentener, K.; Scalone, M.;Hoffmann-La Roche AG, Patent 1057831, 2000; CAN 134:17683. (b) Darses, S.; Genêt, J.-P.; Brayer, J.-L.; Demoute, J.-P. *Tetrahedron Lett.* **1997**, *38*, 4393–4396. (c) Darses, S.; Michaud, G.; Genêt, J.-P. *Tetrahedron Lett.* **1998**, *39*, 5045–5048. (d) Darses, S.; Michaud, G.; Genêt, J.-P. *Eur. J. Org. Chem.* **1999**, 1875–1883. (e) Molander, G. A.; Rivero, M. R. *Org. Lett.* **2002**, *4*, 107–109. (f) Molander, G. A.; Bernardi, C. R. *J. Org. Chem.* **2002**, *67*, 8424–8429. (g) Molander, G. A.; Felix, L. A. *J. Org. Chem.* **2005**, *70*, 3950–3956. (h) Arvela, R. K.; Leadbeater, N. E.; Mack, T. L.; Kormos, C. M. *Tetrahedron Lett.* **2006**, *47*, 217–220. (i) Kabalka, G. W.; Al-Masum, M.; Mereddy, A. R.; Dadush, E. *Tetrahedron Lett.* **2006**, *47*, 1133–1136. (j) Carter, R. R.; Wyatt, J. K. *Tetrahedron Lett.* **2006**, *47*, 6091–6094. (k) Molander, G. A.; Brown, A. R. *J. Org. Chem.* **2006**, *71*, 9681–9686. (l) Joucha, L.; Cusati, G.; Pinel, C.; Djakovitch, L. *Tetrahedron Lett.* **2008**, *49*, 4738–4741.

(11) For reviews, see: (a) Darses, S.; Genêt, J.-P. *Chem. Rev.* **2008**, *108*, 288–325. (b) Doucet, H. *Eur. J. Org. Chem.* **2008**, 2013–2030. (c) Molander, G. A.; Ellis, N. *Acc. Chem. Res.* **2007**, *40*, 275–286. (d) Stefani, H. A.; Cella, R.; Vieira, A. S. *Tetrahedron* **2007**, *63*, 3623–3658. (e) Molander, G. A.; Figueroa, R. *Aldrichimica Acta* **2005**, *38*, 49–56. (f) Darses, S.; Genêt, J.-P. *Eur. J. Org. Chem.* **2003**, 4313–4327.

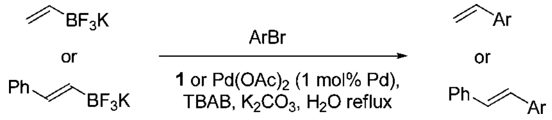
(12) Molander, G. A.; Ellis, N. M. *J. Org. Chem.* **2008**, *73*, 6841–6844.

(13) Kabalka, G. W.; Dadush, E.; Al-Masum, M. *Tetrahedron Lett.* **2006**, *47*, 7459–7461.

(14) Alacid, E.; Nájera, C. *Org. Lett.* **2008**, *10*, 5011–5014.

(15) TBAB can act as phase-transfer catalyst and also can stabilize palladium nanoparticles, avoiding aggregation: Reetz, M. T.; Westermann, E. *Angew. Chem., Int. Ed.* **2000**, *39*, 165–168.

TABLE 1. Alkenylation of Aryl and Heteroaryl Bromides with Potassium Vinyl and Alkenyltrifluoroborates for the Synthesis of Styrenes, Stilbenoids, and Alkenylbenzenes[a]



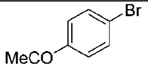
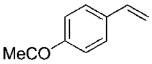
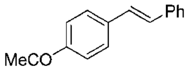
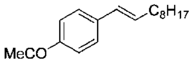
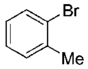
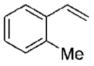
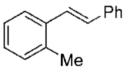
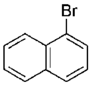
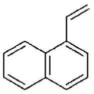
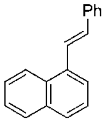
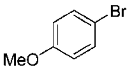
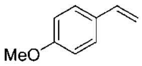
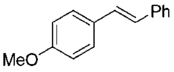
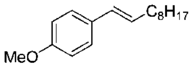
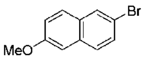
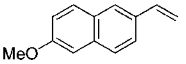
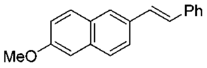
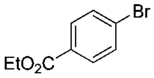
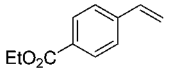
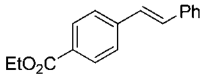
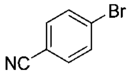
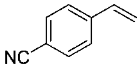
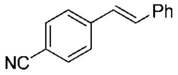
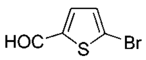
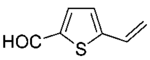
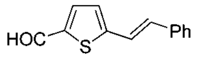
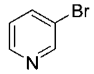
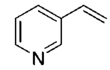
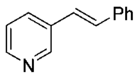
entry	ArBr/HetArBr	$RCH=CHBF_3K$	cat.	t	product	no.	yield (%)[b]
1		$CH_2=CHBF_3K^c$	**1**	2 h		**2aa**	(93)
2		$CH_2=CHBF_3K^{c,d}$	**1**	3 h		**2aa**	$(72)^e$
3		$CH_2=CHBF_3K^c$	$Pd(OAc)_2$	20 h		**2aa**	(82)
4			**1**	20 min[f]		**2aa**	92 (98)
5			$Pd(OAc)_2$	20 min[f]		**2aa**	(89)
6		(E)-$PhCH=CHBF_3K^g$	**1**	3 h		**2ba**	91 (98)
7			$Pd(OAc)_2$	24 h		**2ba**	(88)
8			**1**	20 min[f]		**2ba**	93 (99)
9			$Pd(OAc)_2$	20 min[f]		**2ba**	(92)
10		(Z)-$PhCH=CHBF_3K^g$	**1**	14 h		**2ba**[h]	55 (82)
11			$Pd(OAc)_2$	14 h		**2ba**[h]	(79)
12		(E)-$C_8H_{17}CH=CHBF_3^g$	**1**	3 h		**2ca**	93 (98)
13			**1**	20 min[f]		**2ca**	89 (95)
14		$CH_2=CHBF_3K^c$	**1**	14 h		**2ab**	65 (81)
15			**1**	30 min[f]		**2ab**	68 (89)
16		(E)-$PhCH=CHBF_3K^g$	**1**	14 h		**2bb**	88 (91)
17			**1**	20 min[i]		**2bb**	92 (99)
18		$CH_2=CHBF_3K^c$	**1**	10 h		**2ac**	74 (82)
19			**1**	20 min[f]		**2ac**	$(78)^j$
20		(E)-$PhCH=CHBF_3K^g$	**1**	14 h		**2bc**	83 (90)
21			**1**	20 min[f]		**2bc**	90 (98)
22		$CH_2=CHBF_3K^c$	**1**	24 h		**2ad**	67 (76)
23			**1**	20 min[f]		**2ad**	63 (75^k)
24		(E)-$PhCH=CHBF_3K^g$	**1**	14 h		**2bd**	78 (99^l)
25			**1**	20 min[f]		**2bd**	(75^m)
26		(E)-$C_8H_{17}CH=CHBF_3^g$	**1**	22 h		**2cd**	81 (98^n)
27			**1**	20 min[f]		**2cd**	$(91)^o$
28		$CH_2=CHBF_3K^c$	**1**	14 h		**2ae**	57 (76)

TABLE 1. Continued

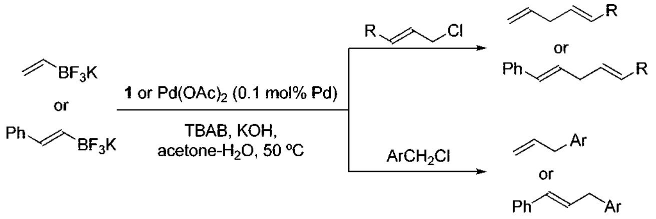
entry	ArBr/HetArBr	RCH=CHBF$_3$K	cat.	t	product	no.	yield (%)^b
29			**1**	30 min^f		**2ae**	68 (81)
30		(E)-PhCH=CHBF$_3$K^g	**1**	14 h		**2be**	72 (85)
31			**1**	20 min^f		**2be**	(79)
32		CH$_2$=CHBF$_3$K^c	**1**	8 h		**2af**	71 (84^p)
33		(E)-PhCH=CHBF$_3$K^g	**1**	8 h		**2bf**	81 (91)
34		CH$_2$=CHBF$_3$K^c	**1**	14 h		**2ag**	82 (94^q)
35		(E)-PhCH=CHBF$_3$K^g	**1**	14 h		**2bg**	84 (93)
36		CH$_2$=CHBF$_3$K^c	**1**	14 h		**2ah**	75 (84)
37			**1**	20 min^f		**2ah**	86 (99)
38		(E)-PhCH=CHBF$_3$K^g	**1**	16 h		**2bh**	80 (92)
39			**1**	20 min^i		**2bh**	82 (99)
40		CH$_2$=CHBF$_3$K^c	**1**	14 h		**2ai**	52 (75)
41			**1**	30 min^f		**2ai**	81 (92)
42		(E)-PhCH=CHBF$_3$K^g	**1**	14 h		**2bi**	79 (83)
43			**1**	20 min^i		**2bi**	86 (92)

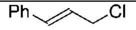
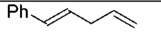
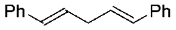
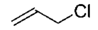
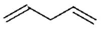
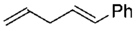
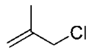
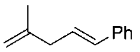
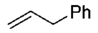
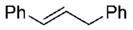
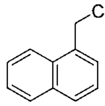
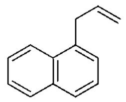
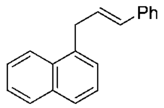
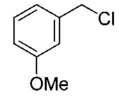
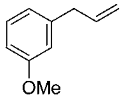
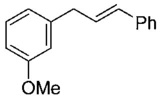
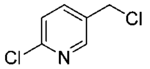
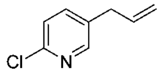
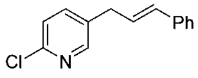
[a] Reactions were performed with ArBr or HetArBr (0.3 mmol), RCH=CHBF$_3$K (0.45 mmol), **1** or Pd(OAc)$_2$ (1 mol % Pd), K$_2$CO$_3$ (0.6 or 0.9 mmol), and TBAB (97 mg, 0.3 mmol) in H$_2$O (1 mL) in a pressure tube at 120 °C bath temperature. [b] Isolated yield after flash chromatography. In parenthesis, yield of the crude product determined by ^{1}H NMR. [c] 3 equiv of K$_2$CO$_3$. [d] 1.01 equiv of potassium vinyltrifluoroborate was used. [e] 15% of 4,4′-diacetylstilbene was also obtained. [f] Under microwave heating (40 W, 120 °C, 3−5 bar). [g] 2 equiv of K$_2$CO$_3$. [h] As 80:20 *Z*/*E* stereoisomer ratio. [i] Under microwave heating (30 W, 100 °C, 1−3 bar). [j] 21% of 1,2-di(1-naphthyl)ethylene was also obtained. [k] 11% of 4,4′-dimethoxystilbene was also obtained. [l] 3% of regioisomer 1-(4-methoxyphenyl)-1-phenylethylene was also obtained. [m] 10% of regioisomer 1-(4-methoxyphenyl)-1-phenylethylene was also obtained. [n] 12% of regioisomer 1-(4-methoxyphenyl)-1-octylethylene was also obtained. [o] 10% of regioisomer 1-(4-methoxyphenyl)-1-octylethylene was also obtained. [p] 2% of 4,4′-di(ethoxycarbonyl)stilbene was also obtained. [q] 3% of 4,4′-dicyanostilbene was also obtained.

derivatives **2ah** and **2ai** in good yields when reacted with potassium vinyltrifluoroborate (Table 1, entries 36, 37 and 40, 41, respectively), whereas compounds **2bh** and **2bi** were stereoselectively obtained using potassium (*E*)-styryltrifluoroborate (Table 1, entries 38, 39 and 42, 43, respectively). Although the cross-coupling of aryl chlorides with potassium aryltrifluoroborates could be achieved under these reactions conditions,[14] the less reactive potassium alkenyltrifluoroborates could not be cross-coupled with aryl chlorides.

Next, the cross-coupling of potassium vinyltrifluoroborates with representative allyl and benzyl chlorides was studied using K$_2$CO$_3$ as base and TBAB as additive in refluxing water. However, under these reactions conditions the cross-couplings with cinammyl and benzyl chloride failed. In the case of cinnamyl chloride a complex mixture of products was observed. For benzyl chloride the corresponding benzyl alcohol was exclusively obtained. When KOH was used as base and TBAB as additive in acetone−H$_2$O (3:2) at 50 °C, allyl and benzyl chlorides could be successfully cross-coupled with potassium alkenyltrifluoroborates (Table 2). In these processes only 0.1 mol % Pd loading was necessary to achieve cross-coupled products in good yields. In general, conventional thermal conditions afforded higher yields than MW heating. Thus, initial studies for the coupling with cinnamyl chloride in the presence of palladacycle **1** afforded 1,4-dienes **3aa** and **3ba** in higher yields than when using Pd(OAc)$_2$ (Table 2, entries 1−4). Therefore, palladacycle **1** was used as precatalyst when performing other couplings. Allyl chloride gave 1,4-dienes **3ab** and **3bb** in good yields, although volatile 1,4-pentadiene (**3ab**) was obtained in 61% yield after distillation (Table 2, entries 5 and

TABLE 2. Alkenylation of Allyl and Benzyl Chlorides with Potassium Vinyl and Styryltrifluoroborates for the Synthesis of 1,4-Dienes and Allylbenzenes[a]



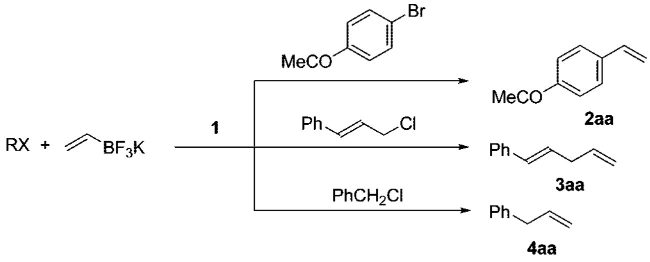
entry	allylCl/BnCl	RCH=CHBF3K	cat.	t	product	no.	yield (%)[b]
1		CH_2=$CHBF_3K$	**1**	14 h		**3aa**	84 (94)
2			$Pd(OAc)_2$	14 h		**3aa**	(66)
3		(*E*)-PhCH=$CHBF_3K$	**1**	14 h		**3ba**	68 (96)
4			$Pd(OAc)_2$	14 h		**3ba**	(93)
5		CH_2=$CHBF_3K$	**1**	14 h		**3ab**	61[c]
6		(*E*)-PhCH=$CHBF_3K$	**1**	14 h		**3bb**	79 (99)
7		(*E*)-PhCH=$CHBF_3K$	**1**	14 h		**3bc**	77 (87)
8	$PhCH_2Cl$	CH_2=$CHBF_3K$	**1**	14 h		**4aa**	75 (88)
9			$Pd(OAc)_2$	14 h		**4aa**	(51)
10		(*E*)-PhCH=$CHBF_3K$	**1**	14 h		**4ba**	85 (96)
11			$Pd(OAc)_2$	14 h		**4ba**	(78)
12		CH_2=$CHBF_3K$	**1**	8 h		**4ab**	83 (94)
13		(*E*)-PhCH=$CHBF_3K$	**1**	6 h		**4bb**	87 (96)
14		CH_2=$CHBF_3K$	**1**[d]	14 h		**4ac**	59 (75[e])
15		(*E*)-PhCH=$CHBF_3K$	**1**	8 h		**4bc**	89 (97)
16		CH_2=$CHBF_3K$	**1**[f]	14 h		**4ad**	81 (97[g])
17		(*E*)-PhCH=$CHBF_3K$	**1**	14 h		**4bd**	81 (96)

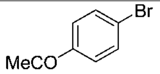
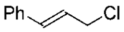
[a] Reactions were performed with allyl or benzyl chloride (1 mmol), RCH=$CHBF_3K$ (1.5 mmol), **1** or $Pd(OAc)_2$ (0.1 mol % Pd), KOH (112 mg, 2 mmol), and TBAB (192 mg, 0.5 mmol) in acetone−H_2O (3:2, 5 mL) at 50 °C bath temperature. [b] Isolated yield after flash chromatography. In parenthesis, yield of the crude product determined by ^{1}H NMR. [c] Isolated by distillation at 30 °C. [d] 1 mol % Pd loading was used. [e] 9% of the regioisomer 3-(prop-1-enyl)anisole was also obtained. [f] 0.5 mol % Pd loading was used. [g] 1% of the regioisomer 2-chloro-4-(prop-1-enyl)pyridine was also obtained.

6). Methallyl chloride was coupled with potassium (*E*)-styryltrifluoroborate, providing 4-methyl-1-phenylpenta-1,4-diene (**3bc**) in good yield (Table 2, entry 7). Dienes **3ba**−**bc** were stereoselectively obtained with *E*-configuration.

Using the former reaction conditions, benzyl chlorides have been cross-coupled with potassium alkenyltrifluoroborates for the first time, affording allylbezenes **4** in good yields. Palladacycle **1** showed again higher efficiency than $Pd(OAc)_2$ in the reaction of benzyl chloride with vinyl and styryltrifluoroborates (Table 2, entries 8−11). 1-(Chloromethyl)naphthalene, 3-(chloromethyl)anisole, and 2-chloro-4-(chloromethyl)pyridine afforded allylic products **4ab**, **4ac**, and **4ad**

TABLE 3. Recycling Experiments of the Palladium-Catalyzed Suzuki−Miyaura Reaction of Potassium Vinyltrifluoroborate with 4-Bromoacetophenone and Cinnamyl and Benzyl Chloride



entry	run	RX	**1** (mol% Pd)	method[a]	t	**no.**	yield (%)[b]	Pd leaching (ppm)[c]
1	1		1	A	2 h	**2aa**	95	90.6
2	2			A	2 h	**2aa**	91	87.1
3	3			A	2.5 h	**2aa**	87	58.4
4	4			A	4 h	**2aa**	83	79.6
5	5			A	14 h	**2aa**	76	103.1
6	6			A	24 h	**2aa**	37	86.2
7	1		0.5	B	1.5 h	**3aa**	91	79.7
8	2			B	2.5 h	**3aa**	93	91.2
9	3			B	5 h	**3aa**	81	65.4
10	4			B	10 h	**3aa**	78	68.2
11	5			B	24 h	**3aa**	80	51.6
12	6			B	24 h	**3aa**	44	64.3
13	1	$PhCH_2Cl$	0.5	B	4.5 h	**4aa**	86	104.8
14	2			B	10 h	**4aa**	79	96.3
15	3			B	24 h	**4aa**	75	109.5
16	4			B	24 h	**4aa**	47	88.3

[a] Method A: 4-bromoacetophenone (0.5 mmol), $CH_2{=}CHBF_3K$ (100 mg, 0.75 mmol), **1** (1 mol % Pd), K_2CO_3 (207 mg, 1.5 mmol), and TBAB (162 mg, 0.5 mmol) in H_2O (1 mL) in a pressure tube at 120 °C bath temperature. Method B: allyl or benzyl chloride (0.5 mmol), $CH_2{=}CHBF_3K$ (100 mg, 0.75 mmol), **1** (0.5 mol % Pd), KOH (56 mg, 1 mmol), and TBAB (81 mg, 0.25 mmol) in acetone−H_2O (3:2, 2.5 mL) at 50 °C bath temperature. [b] Isolated crude yield after flash chromatography. In parenthesis, yield of the crude product determined by ^1H NMR. [c] Determined in the crude product by ICP-OES.

in good yields, the Pd loading being increased to 0.5 mol % in the last example (Table 2, entries 12, 14, and 16). Products **4ba**−**4bd**, resulting from the cross-coupling of benzylic chlorides with potassium styryltrifluoroborate, were obtained with retention of the C−C double bond configuration (Table 2, entries 10, 11, 13, 15, and 17). In all of these vinylation reactions with allyl and benzyl chlorides, no isomerization of the double bond along the chain was observed, except in the case of the reaction of potassium vinyltrifluoroborates with 3-(chloromethyl)anisole and 2-chloro-4-(chloromethyl)pyridine (Table 2, entries 14 and 16).

Recycling experiments were carried out for the cross-coupling of 4-bromoacetophenone and potassium vinyltrifluoroborate under conventional thermal conditions using method A (Table 3, entries 1−6). After the reaction was finished, the product was extracted with ethyl acetate, and reagents were added again to the aqueous phase except palladacycle **1**. Four more runs were performed in 2, 2.5, 4, and 14 h, yielding product **2aa** in 91%, 87%, 83%, and 76%. In the sixth cycle, the yield decreased to 37% after 24 h reaction time. ICP-OES analyses of the obtained crude products indicated relatively low levels of Pd in the range of 86.2−103.1 ppm.

Method B was used in the presence of palladacycle **1** (0.5 mol % Pd) in the case of the recycling experiments for the vinylation of cinnamyl and benzyl chloride (Table 3). The cross-coupling of potassium vinyltrifluoroborate and cinnamyl chloride was performed efficiently during 5 runs, giving product **3aa** in 91%, 93%, 81%, 78%, and 80% yield in 1.5, 2.5, 5, 10, and 24 h, respectively (Table 3, entries 7−12). However, lower efficiency was observed in the case of benzyl chloride. Thus, product **4aa** was obtained in 86%, 79%, and 75% yield in 4.5, 10, and 24 h, yield decreasing to 47% in the fourth cycle. Leaching analyses indicated 51.5−109.5 ppm of Pd in the crude products.

Conclusions

The reaction conditions found for the Suzuki−Miyaura reaction between aryl bromides and potassium alkenyltrifluoroborates, aqueous potassium carbonate, and TBAB as additive under conventional or microwave heating at 120 °C are appropriate for the preparation of styrenes, unsymmetrical stilbenes, and alkenylbenzenes. Ligand-less Pd(OAc)$_2$ or the 4-hydroxyacetophenone oxime derived palladacycle, which are efficient source of Pd nanoparticles, act as precatalyst using 1 mol % Pd loading. In the case of potassium styryl- and dec-1-enyltrifluoroborates the reaction was faster than with vinyltrifluoroborate. The cross-coupling of allyl and benzyl chlorides was performed using KOH in aqueous acetone at 50 °C, affording 1,4-dienes and allylbenzenes, respectively. For the vinylation reactions, the palladacycle was a better precatalyst than Pd(OAc)$_2$, and a lower Pd loading (0.1 mol % Pd) can be used. Cross-couplings with alkenyltrifluoroborates took place in a stereoselective manner without isomerization of the C−C double bond. In addition, both reaction conditions allow the separation of the products by extractive workup and the recovery of Pd in the aqueous basic layer.

Experimental Section

General Procedure for the Cross-Coupling of Aromatic Bromides with Potassium Alkenyltrifluoroborates [2-Methoxy-6-vinylnaphthalene (2ae) as Example]. A pressure glass vessel (10 mL) sealed with a septum was charged with the aryl bromide (0.3 mmol), tetra-*n*-butylammonium bromide (97 mg, 0.3 mmol), potassium alkenyltrifluoroborate (0.45 mmol), and catalyst (1 mol % Pd) in water (1 mL). The mixture was stirred and heated at 120 °C (bath temperature), and the reaction was monitored by GC until completion. When the reaction was performed in a microwave reactor, the mixture was stirred and heated at 30−40 W, 1−5 bar, 100−120 °C, 20−30 min, and 40 psi of air stream cooling. Then, the crude reaction was cooled at room temperature, the product was extracted with diethyl ether (3 × 15 mL), and the combined organic layers were washed with water (3 × 15 mL) and dried over magnesium sulfate. The solvent was removed under vacuum, and the products were purified by flash chromatography on silica gel. For recycling experiments, the product was extracted in situ with ethyl acetate (6 × 5 mL), and the combined organic layers were washed with water (3 × 15 mL) and dried over magnesium sulfate. The aqueous phase in the vessel reaction was recharged with all reagents except the catalyst.

2-Methoxy-6-vinylnaphthalene.[6a] White solid; mp 91−93 °C; R_f 0.60 (hexane/diethyl ether 10/1); IR (KBr) $\nu = 3054, 2838, 1633, 1597, 1482, 1258$ cm^{-1}; ^{1}H NMR (CDCl$_3$, 300 MHz) δ 7.72−7.68 (m, 3H), 7.62 (d, 1H, $J = 8.5$ Hz), 7.14 (d, 2H, $J = 8.1$ Hz), 6.89 (dd, 1H, $J = 17.6$ and 10.9 Hz), 5.85 (d, 1H, $J = 17.6$ Hz), 5.29 (d, 1H, $J = 10.9$ Hz); ^{13}C NMR (CDCl$_3$, 75 MHz) δ 157.7, 136.9, 134.2, 132.9, 129.5, 128.8, 126.9, 126.1, 123.7, 118.9, 113.0, 105.7, 55.2; MS *m/z* 184 (M$^+$, 100), 169 (17), 141 (50), 115 (19).

The following compounds are commercially available: 4-vinylacetophenone (**2aa**), (*E*)-4-styrylacetophenone (**2ba**), 2-methylstyrene (**2ab**), (*E*)-2-methylstilbene (**2bb**), 1-vinylnaphthalene (**2ac**), (*E*)-4-styrylnaphthalene (**2bc**), 4-methoxystyrene (**2ad**), (*E*)-4-methoxystilbene (**2bd**), 2-methoxy-6-vinylnaphthalene (**2ae**), ethyl 4-vinylbenzoate (**2af**), 4,4′-di(ethoxycarbonyl)stilbene (**2bf**), 4-vinylbenzonitrile (**2ag**), 4,4′-dicyanostilbene (**2bg**), 3-vinylpyridine (**2ai**), and (*E*)-3-styrylpyridine (**2bi**). Compounds (*E*)-4-(decen-1-yl)acetophenone (**2ca**),[16] (*E*)-1-(decen-1-yl)-4-methoxybenzene (**2cd**),[16] (*E*)-5-styrylthiophene-2-carbaldehyde (**2bh**),[17] and (*E*)-2-methoxy-6-styrylnaphthalene (**2be**)[18] have been previously reported.

General Procedure for the Cross-Coupling of Allyl and Benzyl Chlorides with Potassium Alkenyltrifluoroborates [(*E*)-1-Phenylpenta-1,4-diene (3aa) as Example]. A 1 M solution of KOH (2 mL, 2 mmol) was added to a solution of allyl/benzyl chloride (1 mmol), tetrabutylammonium bromide (322 mg, 1 mmol), potassium alkenyltrifluoroborate (1.5 mmol), and catalyst (0.292 mg, 0.1 mol % Pd) in acetone (3 mL) in a round-bottom flask. The mixture was stirred and heated at 50 °C, and the reaction was monitored by GC until completion. Then, the crude reaction was cooled at room temperature, the product was extracted with diethyl ether (3 × 15 mL), and the combined organic layers were washed with water (3 × 15 mL) and dried over magnesium sulfate. The solvent was removed under slight vacuum, and the products were purified by flash chromatography on silica gel. For recycling experiments the product was extracted in situ with ethyl acetate (6 × 5 mL), and the combined organic layers were washed with water (3 × 15 mL) and dried over magnesium sulfate. The aqueous phase in the vessel reaction was recharged with 3 mL of acetone and all reagents except the catalyst.

(*E*)-1-Phenylpenta-1,4-diene (3aa). Colorless oil; $R_f = 0.57$ (hexane); IR (film) $\nu = 3047, 1636, 1423, 1275$ cm^{-1}; H NMR (CDCl$_3$, 300 MHz) δ 7.36−7.16 (m, 5H), 6.41 8d, 1H, $J = 15.7$ Hz), 6.22 (dt, 1H, $J = 15.8$ and 6.5 Hz), 5.97−5.83 (m, 1H), 5.14−5.03 (m, 2H), 2.98−2.93 (m, 2H); ^{13}C NMR (CDCl$_3$, 75 MHz) δ 137.7, 136.6, 131.0, 128.6, 128.3, 127.1, 126.2, 115.8, 37.1; MS *m/z* 145 (M$^+$ + 1, 5), 144 (M$^+$, 39), 143 (M$^+$ − 1, 23), 129 (100), 128 (58), 115 (37), 91 (15).

The compounds 1-phenyl-1,4-pentadiene (**3aa**), 1,4-pentadiene (**3ab**), allylbenzene (**4aa**), 1-allylnaphthalene (**4ab**), and 2-allylanisole (**4ac**) are commercially available. The compounds (*E*)-1,3-diphenylpropene (**4ba**),[19] (1*E*,4*E*)-1,5-diphenyl-1,4-pentadiene (**3ba**),[20] and (*E*)-3-(1-naphthyl)-1-phenylpropene (**4bb**)[21] have been previously reported.

Acknowledgment. This work was financially supported by the Dirección General de Investigación from the Ministerio de Educación y Ciencia (MEC) of Spain (Grants CTQ2004-00808/BQU, CTQ2007-62771/BQU, and Consolider INGENIO 2010, CSD200700006), the Generalitat Valenciana (GV05/157), and the University of Alicante. E.A. thanks the MEC for a predoctoral fellowship.

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

JO802356N

---

(16) Santelli, M.; Doucet, H.; Berthiol, F.; Fall, Y. *Synthesis* **2007**, 1683–1696.

(17) Nam, H.; Buu-Höi, N. G.; Xuong, D. *J. Chem. Soc.* **1954**, 1690–1696.

(18) Geissler, H.; Gross, P.;Aventis Research and Technologies GmbH and Co. KG, Germany, Patent 9819813402, 1999; CAN 131:257324.

(19) Bokadia, M. M.; Brown, B. R.; Cobern, D.; Roberts, A.; Somerfield, G. A. *J. Chem. Soc.* **1962**, 1658–1666.

(20) Tsukamoto, H.; Sato, M.; Kondo, Y. *Chem. Commun.* **2004**, 1200–1201.

(21) Tsukamoto, H.; Uchiyama, T.; Suzuki, T.; Kondo, Y. *Org. Biomol. Chem.* **2008**, *6*, 3005–3013.