A Novel Palladium Catalyst for Cross-Coupling of Allyl Acetates with Arylboronic Acids

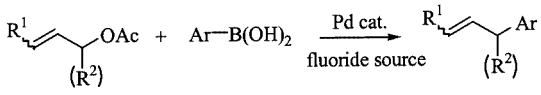
Didier Bouyssi,[a] Vincent Gerusz,*[b][‡] and Geneviève Balme*[a]

Keywords: Palladium / Catalysis / Allylation / Boronic acids / Cross-coupling

The palladium-catalyzed coupling reactions of various arylboronic acids and allylic acetates take place readily under mild conditions. The choice of ligand in the palladium catalyst and the solvent are critical to the yields of coupled products.

Introduction

Over the past twenty years, the palladium-catalyzed coupling of aryl-, vinyl- and alkylboronic acids with aryl and vinyl bromides, iodides and triflates (Suzuki coupling)[1] has gained in popularity due to the broad functional group tolerance, the availability of boronic acid substrates and the lack of toxic by-products. On the other hand, palladium(0) complexes have been shown to catalyze a wide variety of synthetically useful substitutions of allylic substrates with stabilized carbon nucleophiles.[2] Rather surprisingly, however, few studies[3] on the use of boronic acids as nucleophiles in these palladium-catalyzed allylic reactions have been reported so far. The first reported low yields (12%),[3a] along with the concern that acetate and phosphane ligands could slow down the crucial transmetallation step,[4] might explain this slow development. However, two recent articles initiated a breakthrough in this field. The first one by Moreno-Mañas' group[3b] reported the coupling of arylboronic acids with allyl bromides under basic conditions in refluxing benzene (58−91% yield), while the second one by Hayashi and co-workers[3c] described the reaction of phenylboronic acid with allylic acetates under basic conditions in water at room temperature using a resin-supported palladium catalyst (45−99% yield).[5] Due to the ready availability of allylic alcohols, we decided to focus our study on allylic acetates (Scheme 1).



Scheme 1

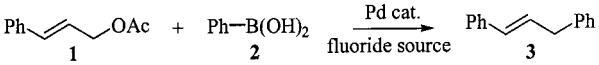
We would now like to report a novel palladium catalyst system which can efficiently cross-couple allylic acetates with a variety of arylboronic acids at room temperature under neutral conditions.

Results and Discussion

We first investigated various experimental conditions to carry out the model reaction of cinnamyl acetate (**1**) with phenylboronic acid (**2**). Since our main objective was to perform the reaction under the mildest possible conditions, we decided to avoid the use of a base, instead we resorted to a fluoride source to activate the boronic acid reagent as already reported for the Suzuki coupling.[6] The fluoride source indeed proved necessary as stirring equivalent molar amounts of **1** and **2** with 5 mol % of $[Pd_2(dba)_3]$ in refluxing THF for 4 h under argon led to complete recovery of the starting material, whereas using CsF or KF allowed the reaction to occur with excellent regio- and stereoselectivity yielding 1,3-diphenyl-(*E*)-propene (**3**) as the exclusive cross-coupling product (Table 1). The use of cesium as a counterion was more beneficial than potassium (entries 1 and 2; 9 and 4). However, increasing the amount of KF to 2.6 equivalents led to an increase of yields matching the ones obtained with more expensive CsF (entries 4,6 and 9; 5 and 10). $[PdCl_2(TFP)_2]$[7] proved to be the best catalyst (entries 4,3,7 and 8; 5 and 6; 1 and 9) while methanol was found to

[a] Laboratoire de Chimie Organique 1, CNRS UMR 5622, Université Claude Bernard, Lyon I, CPE,
43, Bd du 11 Novembre 1918, 69622 Villeurbanne, France
Fax: (internat.) +33-(0)47/2431-214
E-mail: balme@univ-lyon1.fr
[b] Aventis Cropscience,
14 /20 rue Baizet, 69623 Lyon, France
[‡] Current address: Bio Numerik Pharmaceuticals Inc.,
8122 Datapoint Drive Suite 400, San Antonio, Texas 78229, USA

Table 1. Optimization of reaction conditions



Entry	Catalyst[a]	$PhB(OH)_2$ (equiv.)	Fluoride source (equiv.)	Solvent [temp. (°C)]	Yield (%)[b] time (h)
1	$[Pd_2dba_3]$	1.1	CsF (1.1)	THF (60 °C)	52 (4 h)
2	$[Pd_2dba_3]$	1.1	KF (1.1)	THF (60 °C)	low (10 h)
3	$[Pd(OAc)_2]$	1.1	KF (2.2)	THF (60 °C)	low (4 h)
4	$[PdCl_2(TFP)_2]$	1.1	KF (2.2)	THF (room temp.)	52 (22 h)
5	$[PdCl_2(PPh_3)_2]$	1.3	KF (2.6)	THF (room temp.)	72 (22 h)
6	$[PdCl_2(TFP)_2]$	1.3	KF (2.6)	THF (room temp.)	76 (22 h)
7	$[PdCl_2(o\text{-tol})_2]$	1.1	KF (2.2)	THF (room temp.)	52 (24 h)
8	$[PdCl_2(PhCN)_2]$	1.1	KF (2.2)	THF (60 °C)	< 5 (7 h)
9	$[PdCl_2(TFP)_2]$	1.3	CsF (1.3)	THF (room temp.)	75 (8 h)
10	$[PdCl_2(PPh_3)_2]$	1.1	CsF (2.2)	THF (room temp.)	74 (16 h)
11	$[PdCl_2(TFP)_2]$	1.3	KF (2.6)	acetone (room temp.)	75 (19 h)[c]
12	$[PdCl_2(TFP)_2]$ (1.25%)	1.3	KF (2.6)	MeOH (room temp.)	87 (4 h)
13	$[Pd(OAc)_2]$	1.3	KF (2.6)	MeOH (room temp.)	low (24 h)
14	$[PdCl_2(TFP)_2]$(0.7%)	1.3	KF (2.6)	MeOH (room temp.)	98 (3 h)
15	$[PdCl_2(TFP)_2]$ (0.1%)	1.3	KF (2.6)	MeOH (room temp.)	86 (24 h)

[a] All reactions were performed with 2.5 mol % of catalyst except when mentioned otherwise. [b] Isolated yield. [c] Accompanied by 15% of allyl acetate dimerization product.[8]

be the solvent of choice (entries 6,11 and 14). Interestingly the catalyst concentration could be lowered to 0.1 mol % with increased reaction times and slightly decreasing yields (entries 14 and 15).

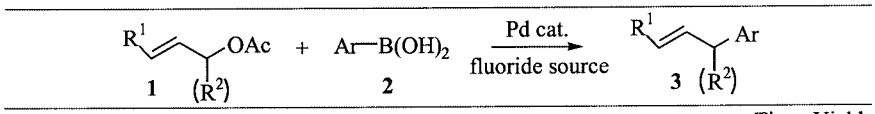
The best experimental conditions (entry 14, Table 1) were then applied to the cross-coupling reaction of different boronic acids and various allyl acetates (Table 2). Again, the reaction displayed excellent regio- and stereoselectivity since only one coupling product of exclusive (*E*) double bond geometry was observed, in which the aromatic moiety of the boronic acid reagent had displaced the less hindered site of the putative π-allyl complex intermediate[9] (entries 1−9 and 14). Electron-rich boronic acids (entries 6,9 and 11) and, more remarkably, sterically hindered substrates (entry 7) as well as electron-deficient aromatic rings (entries 2,3,4,5, 10 and 13) are well tolerated. In the case of 2-furylboronic acid (entry 8) the reaction was too slow or did not proceed in methanol, yielding instead (3-methoxy-1-propenyl)benzene.[10] However, switching to THF as solvent solved this problem, allowing the heterocyclic boronic acid to form in the desired fashion (entry 9). Finally, the reaction was extended to cyclic and acyclic secondary allyl acetates. (entries 12, 13 and 14)

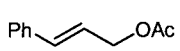
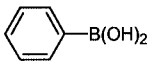
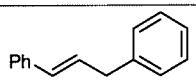
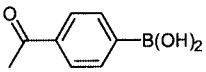
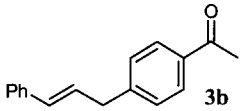
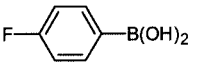
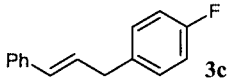
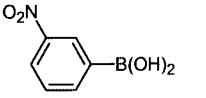
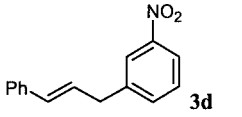
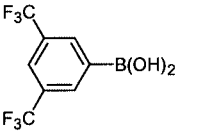
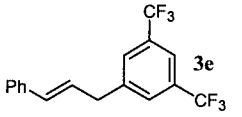
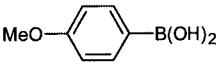
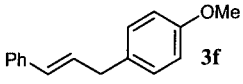
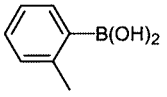
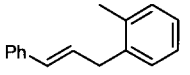
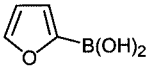
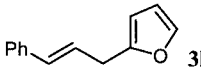
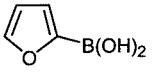
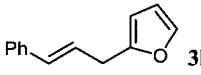
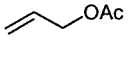
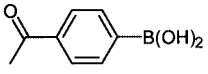
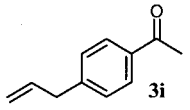
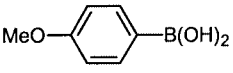
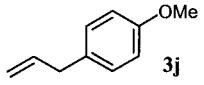
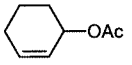
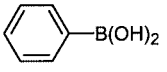
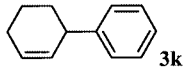
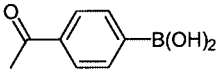
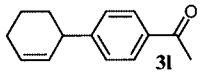
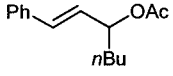
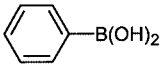
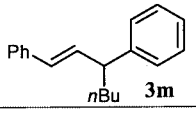
In summary, we have devised a novel catalyst system generally applicable to cross-coupling of a wide variety of boronic acids and allylic acetates under extremely mild, neutral conditions.

Experimental Section

General Remarks: Unless otherwise noted, all reactions were carried out under a nitrogen atmosphere using standard syringe, cannula, and septum techniques. Commercially available reagents were used as purchased. Tetrahydrofuran was dried by distillation over sodium/benzophenone ketyl. Other solvents were commercial anhydrous grades and were used without further drying. Thin-layer chromatography was carried out on Merck silica 60/F-254 aluminium-backed plates. Flash chromatography was performed using Merck silica gel 60 (40−63 μm). NMR spectra were recorded in $CDCl_3$. Chemical shifts (δ) are quoted in parts per million and coupling constants in Hz. Melting points were measured with a Büchi apparatus and are uncorrected.

Table 2. Cross-coupling of allyl acetates with arylboronic acids



Entry	Allyl acetate	Boronic acid	Product	Time (h)	Yield (%)[a]
1			 **3a**	3	98
2	"		 **3b**	21	89
3	"		 **3c**	4	77
4	"		 **3d**	6	85
5	"		 **3e**	20	66[b]
6	"		 **3f**	10	79
7	"		 **3g**	22	99
8	"		 **3h**	20	0[c]
9	"		 **3h**	20	67[d]
10			 **3i**	10	90
11	"		 **3j**	20	65
12			 **3k**	24	78
13	"		 **3l**	24	53
14			 **3m**	22	59

[a] All reactions were run at room temperature in MeOH using 0.7 mol % of $[PdCl_2(TFP)_2]$ as catalyst. [b] The reaction was carried out at 40 °C. [c] The isolated product resulted from attack of MeOH onto π-allyl palladium complex. [d] THF was used instead of MeOH.

General Procedure for the Reaction of Boronic Acids and Allylic Acetates: The allylic acetate (1 mmol) and $[PdCl_2(TFP)_2]$ (0.007 mmol) were added successively to a solution of KF (2.6 mmol) and boronic acid (1.3 mmol) in 5 mL of MeOH. The resulting mixture was stirred for the appropriate time (see Table 2) until completion (TLC monitoring). The reaction was then quenched with water and extracted with diethyl ether. The organic layer was washed with brine, dried over $MgSO_4$ and concentrated

in vacuo. The residue was purified by column chromatography on silica gel with diethyl ether/petroleum ether as the eluent to afford the coupling product.

The ^1H and ^{13}C NMR spectra of compounds **3a**,[3b] **3c**,[11a] **3f**,[3b] **3g**,[11b] **3h**,[11c] **3i**,[11d] **3j**,[11e] **3k**[11f] were as previously reported.

3-(4-Acetylphenyl)-1-phenyl-1-propene (3b): Colorless oil (210 mg, 89%) (diethyl ether/petroleum ether, 4:1). IR (NaCl): $\tilde{\nu}$ = 3080 cm^{-1}, 3026, 2918, 2918, 1682, 1605, 1571, 1411, 1356, 1266, 965, 828, 749, 694. ^1H NMR (300 MHz, $CDCl_3$): δ = 2.62 (s, 3 H), 3.63 (d, *J* = 6.8 Hz, 2 H), 6.37 (dt, *J* = 15.8, 6.8 Hz, 1 H), 6.51 (d, *J* = 15.8 Hz, 1 H), 7.22−7.43 (m, 7 H), 7.95 (d, *J* = 8.3 Hz, 2 H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 26.6, 39.3, 126.2, 127.4, 127.9, 128.6, 128.7, 128.9, 131.9, 135.4, 137.2, 145.9, 197.8. CI-HRMS (for [MH^+]) calcd. for $C_{17}H_{16}O$: 237.12794; found 237.12744.

3-(3-Nitrophenyl)-1-phenyl-1-propene (3d): White solid (203 mg, 85%) (diethyl ether/petroleum ether, 9:1), m.p. 50−51 °C. IR (KBr): $\tilde{\nu}$ = 3025 cm^{-1}, 2907, 1560, 1534, 1347, 971, 746, 734, 694, 686. ^1H NMR ($CDCl_3$, 300 MHz): δ = 3.68 (d, *J* = 6.8 Hz, 2 H), 6.35 (dt, *J* = 15.8, 6.8 Hz, 1 H), 6.53 (d, *J* = 15.8 Hz, 1 H), 7.24−7.42 (m, 5 H), 7.50 (dd, *J* = 7.8, 7.8 Hz, 1 H), 7.61 (d, *J* = 7.5 Hz, 1 H), 8.12 (m, 2 H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 39.3, 121.9, 123.9, 126.6, 127.6, 128.0, 129.0, 129.8, 132.9, 135.3, 137.3, 142.7, 148.8. EI-HRMS calcd. for $C_{15}H_{13}NO_2$: 239.0946; found 239.0948.

3-(3,5-Ditrifluoromethylphenyl)-1-phenyl-1-propene (3e): White solid (166 mg, 66%) (petroleum ether), m.p. 64.5−65.5 °C. IR (KBr): $\tilde{\nu}$ = 3022 cm^{-1}, 1622, 1376, 1277, 1170, 1116, 971, 889, 757. ^1H NMR (300 MHz, $CDCl_3$): δ = 3.71 (d, *J* = 6.8 Hz, 2 H), 6.35 (dd, *J* = 15.8, 6.8 Hz, 1 H), 6.53 (d, *J* = 15.8 Hz, 1 H), 7.27−7.46 (m, 5 H), 7.75 (s, 2 H), 7.81 (s, 1 H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 39.3, 120.8 (q, *J* = 3.7 Hz), 123.8 (q, *J* = 273 Hz), 126.7, 127.0, 128.1, 129.1 (q, *J* = 1.3 Hz), 132.2 (q, *J* = 3 3.0 Hz), 133.3, 137.2, 143.1. EI-HRMS calcd. for $C_{17}H_{12}F_6$: 330.08453; found 330.08452.

3-(4-Acetylphenyl)cyclohexene (3l): Colorless oil (106 mg, 53%) (diethyl ether/petroleum ether, 9:1). IR (NaCl): $\tilde{\nu}$ = 3019 cm^{-1}, 2929, 2857, 1682, 1605, 1357, 1267, 956, 828. ^1H NMR (300 MHz, $CDCl_3$): δ = 1.5−1.8 (m, 3 H), 2.0−2.1 (m, 3 H), 2.6 (s, 3 H), 3.45−3.5 (m, 1 H), 5.7 (dd, *J* = 10.2, 2.1 Hz, 1 H), 5.9−6.0 (m, 1 H), 7.3 (d, *J* = 8.3 Hz, 2 H), 7.9 (d, *J* = 8.3 Hz, 2 H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 21.1, 25.0, 26.7, 32.4, 42.0, 128.0, 128.6, 129.1, 129.2, 135.3, 152.2, 198.0. CI-HRMS (for [MH^+]) calcd. for $C_{14}H_{16}O$: 201.12794; found 201.12777.

1,3-Diphenyl-1-heptene (3m): Colorless liquid (147 mg, 59%). (petroleum ether). IR (NaCl): $\tilde{\nu}$ = 3024 cm^{-1}, 2927, 1646, 1599, 1493, 1682, 1605, 1451, 1465, 1377, 962, 743, 698. ^1H NMR (300 MHz, $CDCl_3$): δ = 1.0 (t, *J* = 7.0 Hz, 3 H), 1.30−1.45 (m, 4 H), 1.9−1.95 (m, 2 H), 3.50−3.55 (m, 1 H), 6.40−6.55 (m, 2 H), 7.25−7.45 (m, 10 H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 14.5, 23.2, 30.3, 36.1, 49.7, 126.6, 126.65, 127.5, 128.1, 128.9, 129.7, 135.0, 138.1, 145.2. CI-HRMS (for [MH^+]) calcd. for $C_{19}H_{22}$: 251.17997; found 251.17995.

Acknowledgments

The authors wish to thank Dr. Jean-Pierre Vors from Aventis Cropscience Lyon for his interest in this work.

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Received January 18, 2002
[O02025]