γ-Selective Cross-coupling of Potassium Allyltrifluoroborates with Aryl and 1-Alkenyl Bromides Catalyzed by a Pd(OAc)$_2$/D-t-BPF Complex

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Cross-coupling reactions of [RCH=CHCH$_2$BF$_3$]K with aryl or 1-alkenyl bromides occurred at the γ-carbon of an allylborane moiety with perfect regioselectivities (>99%) in the presence of a palladium/D-t-BPF complex and K$_2$CO$_3$ in refluxing THF.

Transition metal-catalyzed cross-coupling reactions have proved to be one of the most powerful methods for selective C–C bond formation.[1] Among the possible combinations of electrophiles and nucleophiles, coupling reactions of allylic metals with aryl, alkenyl, and allyl electrophiles or their reversed combination provide an important class of compounds due to the frequent occurrence of these fragments in natural products.[1c] Although there have been few attempts at employing allylboron compounds for this purpose,[2,3] no systematic study on selective coupling at the α- or γ-carbon of allylic boron reagents. Perfect control of the coupling position by phosphine ligands was first achieved by Hiyama et al. by using allyltrifluorosilanes.[4] They found that palladium-catalyzed coupling selectively occurs at the γ-carbon when using PPh$_3$ or bisphosphines possessing a large bite angle such as dppb, and the reaction proceeds at the α-carbon with bisphosphines possessing a relatively small angle such as dppp.[4c] Such an effect of phosphine ligands was also demonstrated by Tsuji in the regioselective Stille coupling of aryl halides with Me$_3$SiCH$_2$CH=CHCH$_2$SnBu$_3$ at the α- or γ-carbon.[5]

In this paper, we report γ-selective cross-coupling reactions of potassium allyltrifluoroborates with aryl and 1-alkenyl bromides (Scheme 1). Air- and water-stable allylborates 1, synthesized by treatment of allylboronic acids or esters with KHF$_2$, were advantageous over triallylboranes, allylboronic acids or esters in preparation and handling of pure and water-stable crystalline materials.[6] Although these K$^+$ salts are highly insoluble in common organic solvents, the reaction smoothly proceeded at refluxing temperature of THF in the presence of K$_2$CO$_3$ and a palladium catalyst prepared in situ from Pd(OAc)$_2$ and 1,1′-bis(di-t-butylphosphino)ferrocene (D-t-BPF).[7]

The yields and regioselectivities of the coupling position were highly sensitive to phosphine ligands employed for palladium acetate in the cross-coupling reaction between 4-bromoanisole and potassium crotyltrifluoroborate (1b) (Table 1). Since the reaction was very slow in the absence of a base, it was carried out in a basic solution as was previously reported in related palladium-catalyzed cross-coupling reactions of potassium aryl- and 1-alkenyltrifluoroborates.[6d] The use of K$_2$CO$_3$ (3 equiv.) gave the best results, but stronger bases, K$_3$PO$_4$ and KOH, resulted in yields of 9 and 30%, respectively. Dppm and dppe possessing a relatively small bite angle gave a mixture of two isomers (Entries 1 and 2), but bisphosphines that have a bite angle larger than dppf yielded a γ-coupling product 3 as the sole product (Entries 3–7). However, these catalysts suffered from low yields of the coupling products mainly due to formation of anisole via base-assisted β-hydride elimination from σ-allylpalladium(II) intermediate 5, which was generated by transmetalation between an oxidative adduct R^{2}PdX·L$_2$ and 1b by an S$_E$2′ mechanism (eq 2).[8] Among the ligands screened for optimization of the catalyst, D-t-BPF was found to be the best ligand to achieve high yields and high γ-selectivities for 4-bromoanisole (Entry 8).
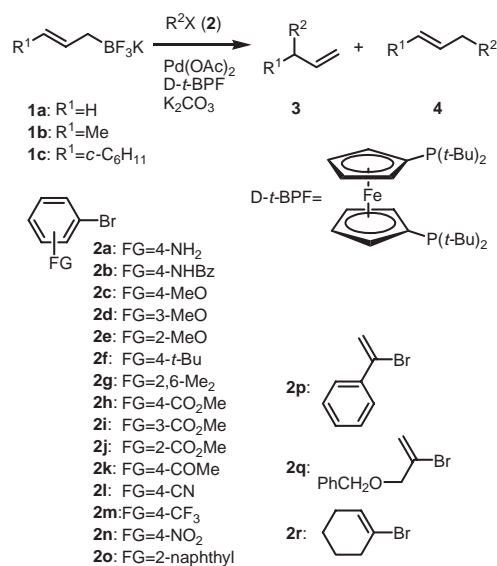
Scheme 1. γ-Selective cross-coupling of 1 giving 3.

Table 1. Effect of ligands[a]

| Entry	Ligand	Yield/%[b]	3/4
1	dppm	35	78/22
2	dppe	17	37/63
3	dppp	37	>99/1
4	dppf	68	>99/1
5	DPEphos	21	>99/1
6	Xantphos	10	>99/1
7	DBFphos	10	>99/1
8	D-t-BPF	(87)	>99/1
9[c]	D-t-BPF	(85)	>99/1
10	PPh$_3$[d]	42	78/22

[a]All reactions were carried out at reflux in THF–H$_2$O (10/1) for 20 h in the presence of Pd(OAc)$_2$ (3 mol %), a ligand (3 mol %), 4-bromoanisole (0.5 mmol), 1b (0.75 mmol), and K$_2$CO$_3$ (1.5 mmol) unless otherwise noted. [b]NMR yields and isolated yield are shown in parentheses. [c]The reaction was conducted in dry THF. [d]Pd(PPh$_3$)$_4$ (3 mol %) was used.

Table 2. γ-Selective cross-coupling of **1**[a]

Entry	**1**	**2**	Yield/%[b]	**3/4**
1	**1a**	**2i**	38	—
2	**1b**	**2a**	80	>99/1
3	**1b**	**2b**	96	>99/1
4	**1b**	**2c**	90	>99/1
5	**1b**	**2d**	85	>99/1
6	**1b**	**2e**	84	>99/1
7	**1b**	**2f**	88	98/2
8	**1b**	**2g**	87	>99/1
9	**1b**	**2h**	92	>99/1
10	**1b**	**2i**	92	>99/1
11	**1b**	**2j**	92	>99/1
12	**1b**	**2l**	77	>99/1
13	**1b**	**2m**	83	>99/1
14	**1b**	**2n**	80	>99/1
15	**1b**	**2o**	93	>99/1
16	**1b**	**2p**	75	>99/1
17	**1b**	**2q**	66	>99/1
18	**1b**	**2r**	65	>99/1
19	**1c**[c]	**2i**	98	>99/1

[a]All reactions were carried out at reflux in THF for 22 h in the presence of $Pd(OAc)_2$ (3 mol %), D-t-BPF (3.6 mol %), bromoarene (1 mmol), **1** (2.5 mmol), and K_2CO_3 (3 mmol). [b]Isolated yield by chromatography. [c]A mixture of $E/Z = 80/20$.


$$(1)$$

$$(2)$$
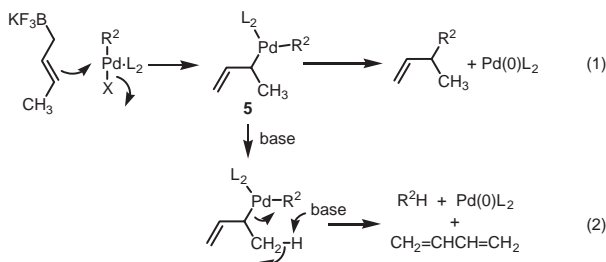
This catalyst worked well in aqueous K_2CO_3, but a heterogeneous system using K_2CO_3 and **1b**, both suspended in dry THF, was a better system (Entry 9). By using such a heterogeneous system that minimizes contact between the base and **5** (eq 2), the formation of anisole was reduced to a negligible amount. The bulkiness and strong electron-donating property of the di-t-butylphosphino group in D-t-BPF may serve to accelerate both oxidative addition of organic halides and reductive elimination from **5** without rearrangement to π-allylpalladium(II) or σ-allylpalladium(II) species bounded to the terminal carbon.[7] On the other hand, $Pd(PPh_3)_4$, a γ-selective catalyst for allyltrifluorosilanes,[4a,4b] resulted in 42% yield due to the formation of anisole (Entry 10).

The cross-couplings of potassium allyltrifluoroborates (**1**, 2.5 equiv.) and aryl or 1-alkenyl bromides in the presence of $Pd(OAc)_2$/D-t-BPF (3 mol %) and K_2CO_3 in anhydrous THF are summarized in Table 2. Potassium allyltrifluoroborate (**1a**) unexpectedly resulted in a low yield (Entry 1), but (E)-crotylborate (**1b**, Entries 2–18) and (E)-3-cyclohexyl-2-propenylborate (**1c**, Entry 19) afforded the corresponding γ-coupling products **3** with high regioselectivities (>99%) for representative aryl bromides (Entries 2–15).

The reaction proceeded smoothly at reflux in THF even for

electron-rich bromoarenes possessing a 4-NH_2 group and 4-NHBz group (Entries 2 and 3) and tolerated amino, ester, cyano, and nitro groups. It was also interesting that the steric hindrance of ortho-substituents did not affect the yields and regioselectivities (Entries 6, 8, and 11). Coupling with bromoalkenes resulted in lower yields than those in the case of coupling with bromoarenes, but the reactions again provided γ-coupling products with perfect regioselectivities (Entries 16–18).

Tetracoordinated allylborates such as **1b** are inert to carbonyl compounds, but their decomposition into tricoordinated allylboron species may allow their addition to aldehydes or ketones as was previously reported in BF_3-catalyzed allylboration of aldehydes with **1b**.[6a–6c] The coupling reaction of 4-bromoacetophenone (**2k**) with **1b** (3 equivalents) was faster than addition to the carbonyl group (eq 3, Entry 1). The allylboration product **7** was only obtained under forced conditions using 5 equiv. of **1b** for 22 h (Entry 2).

$$(3)$$
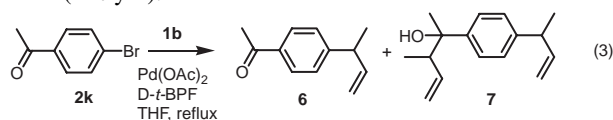
Entry	**1b/2k**	Time/h	Yield **6**/%	Yield **7**/%
1	3	3.5	94	0
2	5	22	55	45

The γ-coupling products thus synthesized are synthetically equivalent to 2-arylpropionic acids via oxidative cleavage of the C=C bond as is shown in the synthesis of ibuprofen (eq 4).[4a]

$$(4)$$
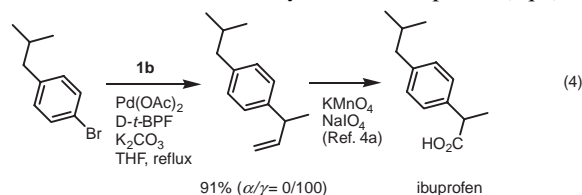
References

1 a) *Metal-Catalyzed Cross-Coupling Reactions*, 2nd ed., ed. by A. de Meijere, F. Diederich, Wiley-VHC, Weinheim, **2004**. b) *Cross-Coupling Reactions. A Practical Guide*, ed. by N. Miyaura, Springer, Berlin, **2002**. c) *Handbook of Organopalladium Chemistry for Organic Synthesis*, ed. by E.-I. Negishi, John Wiley & Sons, New York, **2002**. d) *Metal-Catalyzed Cross-Coupling Reactions*, ed. by F. Diederich, P. J. Stang, Wiley-VHC, Weinheim, **1998**.

2 a) V. N. Kalinin, F. S. Denisov, Y. N. Bubnov, *Mendeleev Commun.* **1996**, *6*, 206. b) E. G. Occhiato, A. Trabocchi, A. Guarna, *J. Org. Chem.* **2001**, *66*, 2459. c) S. Kotha, M. Behera, V. R. Shah, *Synlett* **2005**, 1877.

3 A. Fürstner, G. Seidel, *Synlett* **1998**, 161.

4 a) Y. Hatanaka, Y. Ebina, T. Hiyama, *J. Am. Chem. Soc.* **1991**, *113*, 7075. b) Y. Hatanaka, K.-i. Goda, T. Hiyama, *Tetrahedron Lett.* **1994**, *35*, 1279. c) Y. Hatanaka, K.-i. Goda, T. Hiyama, *Tetrahedron Lett.* **1994**, *35*, 6511.

5 Y. Obora, Y. Tsuji, M. Kobayashi, T. Kawamura, *J. Org. Chem.* **1995**, *60*, 4647.

6 a) R. A. Batey, A. N. Thadani, D. V. Smil, *Tetrahedron Lett.* **1999**, *40*, 4289. b) R. A. Batey, A. N. Thadani, D. V. Smil, *Synthesis* **2000**, 990. c) A. N. Thadani, R. A. Batey, *Org. Lett.* **2002**, *4*, 3827. d) S. Darses, J.-P. Genet, *Eur. J. Org. Chem.* **2003**, *2003*, 4313.

7 a) G. Mann, Q. Shelby, A. H. Roy, J. F. Hartwig, *Organometallics* **2003**, *22*, 2775. b) T. Itoh, K. Sato, T. Mase, *Adv. Synth. Catal.* **2004**, *346*, 1859. c) T. Itoh, T. Mase, *Tetrahedron Lett.* **2005**, *46*, 3573.

8 J. Tsuji, S. Imamura, *Bull. Chem. Soc. Jpn.* **1967**, *40*, 197.