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Remarkable regioselectivity in microwave-enhanced palladium-catalyzed allylation reaction involving allyltrifluoroborates and aryl halides

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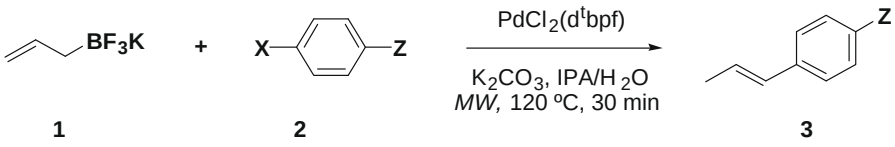
ABSTRACT

An unprecedented cross-coupling reaction of potassium allyltrifluoroborates and aryl halides to the corresponding *trans*-β-methylstyrenes in the presence of $PdCl_2(d^tbpf)$ catalyst under microwave heating was developed.

Potassium organotrifluoroborates have already been shown to be an indispensable class of transformative organic reagents for wide range of cross-coupling reactions.[1] The possible combinations of electrophiles and nucleophiles in cross-coupling reactions of allylic metals with aryl, alkenyl, and allyl electrophiles, or their reversed combination, are important due to the frequent occurrence of these fragments in natural products.[2] In light of their low toxicity and operational simplicity, we have attempted to use potassium allyltrifluoroborates as allylating agents and discovered a new palladium catalyst system for microwave-enhanced coupling of potassium allyltrifluoroborates and aryl halides with remarkable regioselectivity (Eq. (1)).



1 2 3 (1)

Following the recent application of potassium organotrifluoroborates in organic transformations, further advances of this field especially with microwave irradiation in water has recently been made.[3] We focused on the development of a new catalyst system for allylation reactions that involve potassium allyltrifluoroborates, organic halides as electrophiles, water as a solvent, and microwave activation. Except for a few recent reports attempts to use allylboron reagents (especially potassium allyltrifluoroborates) as coupling partners with dihalo compounds have been largely unknown.[4] Another significant advantage of using potassium allyltrifluoroborate is that it is stable and can be readily prepared compared to the corresponding allylboronic esters. Allylboronic esters are not common in Suzuki coupling reactions because of their sensitivity and reactivity. In preliminary observation, when potassium allyltrifluoroborate was treated with 4-bromoiodobenzene in the presence of a palladium catalyst in isopropanol/water (IPA/water) under microwave irradiation, an interesting coupling product was obtained (Scheme 1).

To obtain an efficient catalyst for homoallylation reactions using potassium allyltrifluoroborates and aryl halides, we introduced various palladium salts such as $Pd(OAc)_2$, $PdCl_2(dppf)CH_2Cl_2$, $Pd_2(dba)_3CHCl_3$, $PdCl_2(dphos)_2$, $Pd(dba)_2$, $PdCl_2(d^tbpf)$, and $Pd(Ph_3P)_4$ and ligands such as dppb, dppf, Ph_3P, and dppe. Bases such as KF, Cs_2CO_3, K_2CO_3, KOH, and $^iPr_2NEt$; solvents such as water, IPA/water, and THF/water were investigated using both microwave heating and conventional heating. Reactions investigated are summarized in Scheme 2. In method A, a 1 to 2 ratio of potassium

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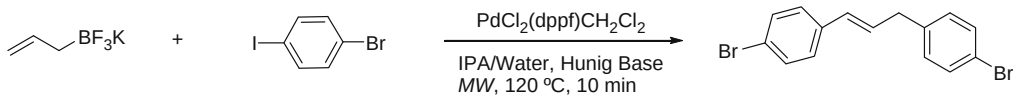
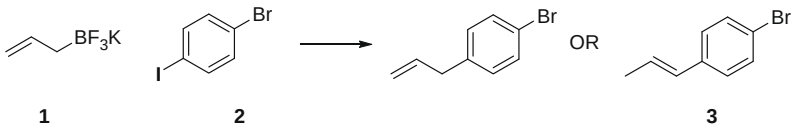


Scheme 1.



Method

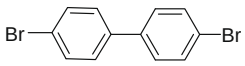
Method A 1 to 2 (.25 mmol: .5 mmol)
$PdCl_2(dppf)CH_2Cl_2$ 5 mole %
K_2CO_3 1.0 mmol
IPA/H_2O 2.5 mL
120 ºC, 2 days

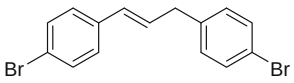
Method B 1 to 2 (.5 mmol: .5 mmol)
$PdCl_2(dppf)CH_2Cl_2$ 5 mole %
K_2CO_3 1.0 mmol
IPA/H_2O 2.5 mL
MW, 120 ºC, 20 min

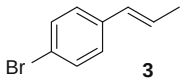
Method C 1 to 2 (.625 mmol: .25 mmol)
$PdCl_2(d^tbpf)$ 3 mole %
K_2CO_3 1.0 mmol
IPA/H_2O 2.5 mL
MW, 120 ºC, 20 min

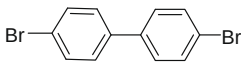
Method C in conventional heating
for overnight

Observed by GC-MS









Scheme 2.

Table 1
$PdCl_2(d^tbpf)$-catalyzed cross-coupling reaction of allyltrifluoroborate **1** and aryl halides **2**[a]

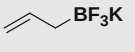
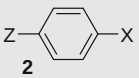
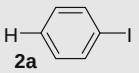
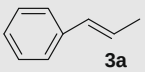
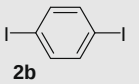
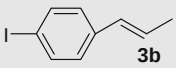
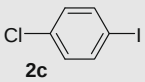
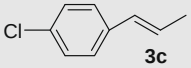
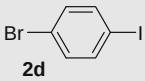
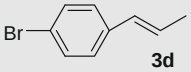
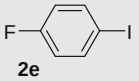
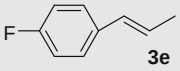
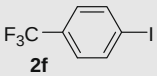
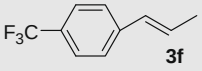
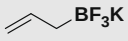
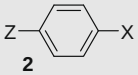
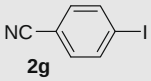
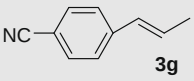
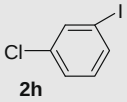
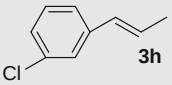
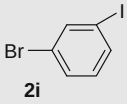
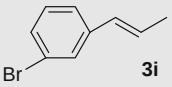
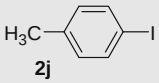
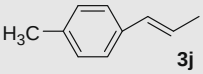
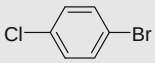
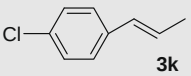
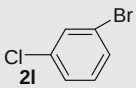
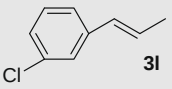
Entry	 1	 2	Product **3**	Reaction time (h)	Yield (%)
1	**1**	 **2a**	 **3a**	35	77
2	**1**	 **2b**	 **3b**	50	95
3	**1**	 **2c**	 **3c**	40	79
4	**1**	 **2d**	 **3d**	30	95
5	**1**	 **2e**	 **3e**	30	85
6	**1**	 **2f**	 **3f**	50	77

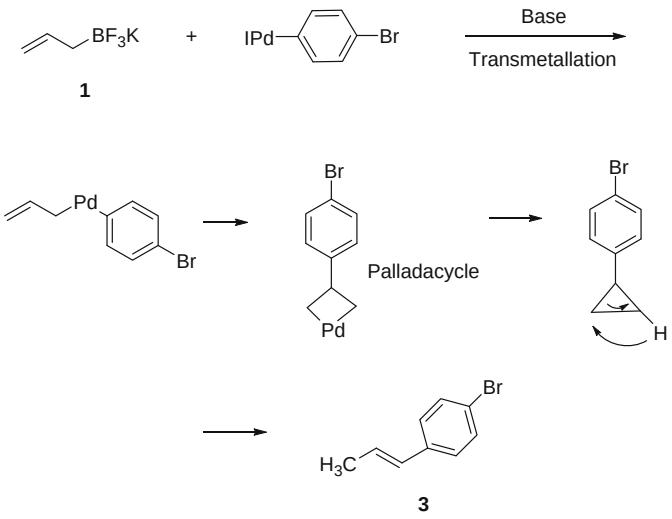
Table 1 (*continued*)

Entry	 1	 2	Product **3**	Reaction time (h)	Yield (%)
7	**1**	 **2g**	 **3g**	30	81
8	**1**	 **2h**	 **3h**	45	84
9	**1**	 **2i**	 **3i**	40	71
10	**1**	 **2j**	 **3j**	20	95
11	**1**	 **2k**	 **3k**	20	94[b]
12	**1**	 **2l**	 **3l**	30	71[b]

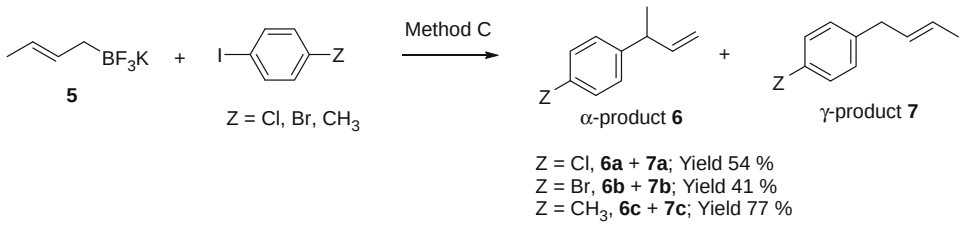
[a] All reactions were run at least two times. In all cases minor products were the corresponding α-methyl styrenes **4** or *exo*-products.
[b] Mixture of γ- and β-products. The products were purified by silica gel chromatography.

allyltrifluoroborate **1** and 4-bromoiodobenzene **2d** along with 5 mol % of $PdCl_2(dppf)CH_2Cl_2$ and 4 equiv of K_2CO_3 were added in 1 M solution of isopropanol–water and refluxed for overnight. The reaction progress was monitored by GC–MS. No allylation was observed but the homo-coupling product 4,4′-dibromo biphenyl, along with starting dihalo compounds, was observed. In method B, changing the proportion of potassium allyltrifluoroborate **1** and 4-bromoiodobenzene **2d** to 1:1 along with same loading of catalyst and base in isopropanol–water and the reaction mixture irradiated under microwave heating system generated the allylated product along with the double addition product shown previously, in Scheme 1. The reproducibility of this reaction was not reliable. Switching to a new palladium salt $PdCl_2(d^tbpf)$ in method C led to new catalyst system that performed in a selective monoallylation fashion. The combination of $PdCl_2(d^tbpf)$ catalyst, 4-bromoiodobenzene, K_2CO_3, and water–isopropanol under microwave irradiation for 30 min produced allyl coupling products with remarkable regioselectivity (Scheme 2). The potassium allyltrifluoroborate was prepared using the known method[5] and was then treated with various dihalides such as 1,4-diiodobenzene **2b**, 4-chloroiodobenzene **2c**, 4-bromoiodobenzene **2d**, and 4-fluoroiodobenzene **2e** (Table 1, entries 2–5) applying method C. In all cases, allylation reactions took place at the *central* carbon, β-carbon selectivity. When iodobenzene **2a** was employed the same selectivity was observed (Table 1, entry 1). When the catalyst was used in excess the starting material disappeared rapidly but the homo-coupled product predominated.

To observe the effect of substituents on the aromatic rings, functional groups attached to the aryl rings, such as CF_3, CN, and CH_3, were introduced by following the reaction conditions described in method C. Reactions furnished successful cross-coupling allylation products **3f**, **3g**, and **3j** with β-carbon selectivity (Table 1, entries 6, 7, and 10). 3-Chloroiodobenzene **2h** and 3-bromoiodobenzene **2i**, also gave the corresponding *trans*-β-methylstyrenes **3h** and **3i**, respectively (Table 1, entries 8 and 9).[6] 4-Chlrobromobenzene, **2k** and 3-chlorobromobenzene, **2l** also underwent the coupling reaction but selectivity was poor. γ- or terminal carbon addition products predominated along with β- or central carbon addition products (Table 1, entries 11 and 12). The ratio was γ:β (3:2). It was noted that GC–MS analysis showed complete conversion to the product but when the reaction mixture was subjected to silica gel chromatography, some of the products were lost. Product volatility could be the cause of the loss. The highlighted part of this new transformation is regioselectivity. The generally accepted mechanism for this type of reaction involves nucleophilic attack on a cationic π-allylpalladium complex at the terminal or γ-carbon, in some cases at the α-carbon.[4] Louis Hegedus's pioneering report on the carbanion attacking the *central* carbon of the π-allyl complex greatly supports the present observation.[7] A reasonable mechanism for cyclopropanation involves direct nucleophilic attack on



Scheme 3.



Scheme 4.

the central carbon of the π-allyl system to form palladacyclobutane, followed by reductive elimination to produce the cyclopropane which presumably isomerizes to *trans*-β-methylstyrene (Scheme 3).[8,9]

Interestingly, when same reaction condition (method C) was applied to potassium crotyltrifluoroborates and aryl halides, coupling products with α-selectivity were predominated along with trace amount of γ-adduct (Scheme 4).

In conclusion, our efforts demonstrate a facile and simplified coupling reaction of potassium allyltrifluoroborates and aryl halides with remarkable regioselectivity. Further use of these developments in synthetic organic chemistry is in progress.

Acknowledgments

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6. The ratio of the central carbon selectivity with *endo*-products $ArCH{=}CHCH_3$ **3a–3j**, and *exo*-products $ArC(CH_3){=}CH_2$ **4a–4j** was 5:1. In case of 4-methyliodobenzene, **2j**, the ratio was 3:2 (Table 1, entry 10). The *endo*- and *exo*-products were unable to be separated by chromatography. For simplification, *exo*-products were not shown.
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8. *The following procedure is representative*: Potassium allyltrifluoroborate **1** (93.0 mg, 0.625 mmol), 4-bromoiodobenzene **2d** (71.0 mg, 0.25 mmol), K_2CO_3 (104.0 mg, 0.75 mmol), and $PdCl_2(d^tbpf)$ (0.0075 mmol, 3 mol %) were placed in an argon-flushed pyrex tube. The pyrex tube was capped with a rubber septum, flushed with argon, and was added 2.5 mL of isopropanol/water (2:1). The resulting mixture in pyrex tube was placed in a CEM microwave unit and allowed to irradiate at 120 °C for 30 min. After standard work-up by adding ammonium chloride and ethyl ether, the ether layer was separated. The reaction mixture was adsorbed in silica gel and transferred into the column and was subjected to silica gel chromatography using hexane as an eluent. The pure product 4-bromo-*trans*-β-methylstyrene, **3d** was isolated in 95% yield (Table 1, entry 4) ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.22(m, 4H, –4-Br–C_6H_4), 6.26(d, J = 16.8 Hz, 1H), 6.24(dq, J = 15.8 Hz, 6.3 Hz, 1H) 1.80(d, J = 5.7 Hz, 3H). LRMS Calcd for C_9H_9Br M^+ 197. Found: 197.
9. *Analytical data for β-methylstyrenes*: Compound **3a** ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.30 (m, 4H, –C_6H_5), 6.42 (d, J = 15.9 Hz, 1H), 6.25 (dq, J = 15.9 Hz, 6.3 Hz, 1H) 1.89 (d, J = 6.3 Hz, 3H). LRMS: Calcd for C_9H_{10} M^+ 118. Found: 118; Compound **3b** ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.48 (m, 4H, –4-I–C_6H_4), 6.32 (d, J = 15.9 Hz, 1H), 6.24 (m, 1H) 1.86 (d, J = 4.8 Hz, 3H). LRMS: Calcd for C_9H_9I M^+ 244. Found: 244; Compound **3c** ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.24 (m, 4H, –4-Cl–C_6H_4), 6.27 (d, J = 15.3 Hz, 1H), 6.14 (dq, J = 15.3 Hz, 6.3 Hz, 1H) 1.81 (d, J = 6.3 Hz, 3H). LRMS: Calcd for C_9H_9Cl $(M+2)^+$ 154. Found: 154; Compound **3e** ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.20 (m, 4H, –4-F–C_6H_4), 6.37 (d, J = 15.6 Hz, 1H), 6.15 (dq, J = 16.2 Hz, 6.9 Hz, 1H) 1.87 (d, J = 6.3 Hz, 3H). LRMS: Calcd for C_9H_9F M^+ 136. Found: 136; Compound **3f** ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.42 (m, 4H, –4-CF_3–C_6H_4), 6.44 (d, J = 15.9 Hz, 1H), 6.36 (m, 1H) 1.93 (d, J = 5.4 Hz, 3H). ^{19}F NMR ($CDCl_3$, 282.3 MHz): δ −62.786. LRMS: Calcd for $C_{10}H_9F_3$ M^+ 186. Found: 186; Compound **3g** ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.36 (m, 4H, –4-CN–C_6H_4), 6.3 (m, 1H), 6.32 (m, 1H) 1.85(d, J = 3.6 Hz, 3H. Calcd for $C_{10}H_9N$ M^+ 143. Found: 143; Compound **3h** ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.24 (m, 4H, –3-Cl–C_6H_4), 6.35 (d, J = 16.8 Hz, 1H), 6.25 (m, 1H) 1.89 (d, J = 5.4 Hz, 3H). Calcd for C_9H_9Cl M^+ 152. Found: 152; Compound **3i** ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.37 (m, 4H, –3-Br–C_6H_4), 6.33(d, J = 15.9 Hz, 1H), 6.24 (dq, J = 15.9 Hz, 6.0 Hz, 1H), 1.89 (d, J = 5.1 Hz, 3H). Calcd for C_9H_9Br M^+ 198. Found: 198; Compound **3j** ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.10 (m, 4H, –4-Me–C_6H_4), 6.29 (d, J = 5.6 Hz, 1H), 6.10 (dq, J = 14.1 Hz, 6.6 Hz, 1H) 1.81 (d, J = 6.6 Hz, 3H). Calcd for $C_{10}H_{12}$ M^+ 132. Found: 132; Compound **3k** ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.20 (m, 4H, –4-Cl–C_6H_4), 6.31 (d, J = 15.9 Hz, 1H), 5.84 (m, 1H) 1.81 (d, J = 6.3 Hz, 3H). Calcd for C_9H_9Cl M^+ 152. Found: 152; Compound **3l** ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.26 (m, 4H, –3-Cl–C_6H_4), 6.35 (d, J = 17.0 Hz, 1H), 6.29 (m, 1H) 1.81 (d, J = 6.3 Hz, 3H). Calcd for C_9H_9Cl M^+ 152. Found: 152.