

Asymmetric Cross-coupling of Potassium 2-Butenyltrifluoroborates with Aryl and 1-Alkenyl Bromides Catalyzed by a Pd(OAc)₂/Josiphos Complex

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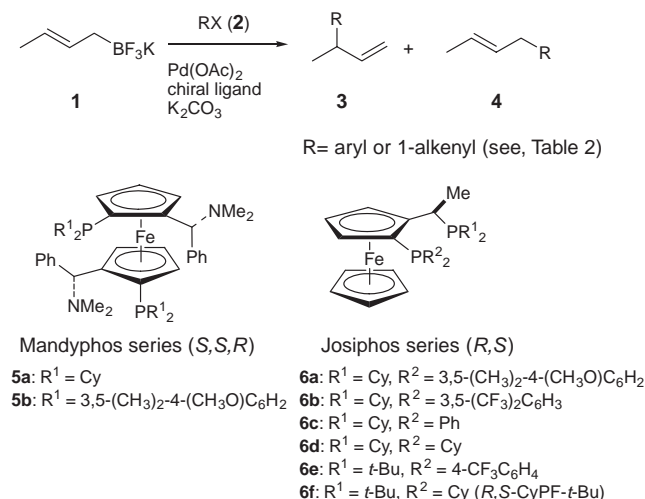
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The asymmetric cross-coupling reaction of [CH₃CH=CHCH₂BF₃]K with aryl or 1-alkenyl bromides selectively occurred at the γ -carbon of 2-butenylborane moiety with regioselectivities in a range of 84–99%. The enantioselectivities were in a range of 77–90%ee when a palladium/CyPF-*t*-Bu complex was used at 80 °C in the presence of K₂CO₃ (3 equiv.) in H₂O–MeOH (9/1).

Transition metal-catalyzed allylic substitutions with nucleophiles, especially their asymmetric reactions using chiral catalysts, provide an important class of compounds due to the frequent occurrence of allylic fragments in natural products or in synthetic intermediates.^{1,2} A number of efficient chiral catalysts have been developed for those purposes and have considerably expanded the scope of enantioselective C–C and C–heteroatom bond formation.^{3–5} The cross-coupling reaction between allylic metal reagents and electrophiles is another practical protocol for allylation of organic halides or triflates. Thus, there are excellent precedents achieved by palladium-catalyzed coupling reactions of boron, silicon, and tin compounds. Among studies using allylic metal reagents as the coupling partners, perfect control of the coupling position with phosphine ligands was first achieved by Hiyama, Hatanaka, and co-workers by using allyltrifluoro silanes.⁶

We recently reported that allylation of aryl and 1-alkenyl halides with [RCH=CHCH₂BF₃]K (R = Me, Ph) selectively occurs at the γ -carbon when a bulky and donating 1,1'-bis(di-*t*-butylphosphino)ferrocene (D-*t*-BPF) was used as a ligand of

a palladium catalyst.⁷ However, asymmetric version of these couplings remained unexplored. We report here the first attempts at asymmetric coupling of an allylic boron reagent via the γ -selective cross-coupling of potassium (*E*)-2-butenyltrifluoroborate (**1**) with aryl or 1-alkenyl bromides catalyzed by a palladium-Josiphos (**6f**, CyPF-*t*-Bu) complex (Scheme 1). The regioselectivities of the coupling position and enantioselectivities were highly sensitive to phosphine ligands employed for palladium acetate in the reaction between methyl 4-bromobenzoate and **1** (Entries 1–8 in Table 1). Since the reaction was very slow in the absence of a base as was previously reported in related palladium-catalyzed coupling reactions of potassium organotrifluoroborates,⁸ K₂CO₃ (3 equiv.) was used as a suspension in THF or a solution in aqueous THF or MeOH. Among ligands screened for optimization of the catalyst, *R,S*-CyPF-*t*-Bu (**6f**) was found to be the best ligand to achieve 63%ee with 92% γ -selectivity in refluxing THF (Entry 8), whereas other derivatives in Josiphos series (**6a–6e**) were not effective (4–44%ee, Entries 3–7). On the other hand, an analogous ferrocenyl ligand of Mandyphos (**5a** and **5b**) resulted in the formation of a γ -coupling product (31 and 46%ee). Allyltrifluoroborates (**1**), synthesized by treatment of allylboronic acids or esters with KHF₂, are highly insoluble in common organic solvents. Thus, addition of water to THF or MeOH significantly improved the yields and enantioselectivities owing to the high solubility of **1** in aqueous solvents (Entries 9–12). The reaction also took place in water (Entry 13, 86%, 81%ee), though the use of an organic solvent was essential



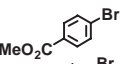

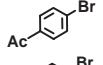
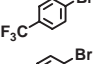
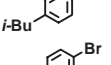

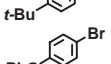
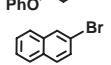


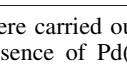
Scheme 1. Asymmetric coupling giving **3**.

Table 1. Effects of ligands and solvents^a

Entry	Ligand	Solvent	Yield/% ^b	3/4	%ee of 3 ^c
1	5a	THF	98	93/7	31
2	5b	THF	84	96/4	46
3	6a	THF	63	21/79	4
4	6b	THF	64	14/86	5
5	6c	THF	57	83/17	44 (R)
6	6d	THF	73	99/1	10 (R)
7	6e	THF	54	83/17	26 (R)
8	6f	THF	96	92/8	63 (R)
9	6f	THF–H ₂ O (9/1)	66	92/8	70 (R)
10	6f	THF–H ₂ O (1/4)	93	95/5	82 (R)
11	6f	MeOH–H ₂ O (1/1)	62	91/9	80 (R)
12	6f	MeOH–H ₂ O (1/9)	93	93/7	82 (R)
13	6f	H ₂ O	86	93/7	81 (R)

^aAll reactions were carried out at 80 °C for 22 h in the presence of Pd(OAc)₂ (3 mol %), chiral ligand (3.6 mol %), methyl 4-bromobenzoate (1 mmol), **1** (2.5 mmol), and K₂CO₃ (3 mmol). ^bIsolated yield by chromatography. ^cEnantiomer excess was determined by a chiral stationary column.

Table 2. Asymmetric cross-coupling giving **3**^a

Entry	2	Yield/% ^b	3/4	%ee of 3 ^c
1	2a 	93	93/7	82
2	2b 	85	89/11	79
3	2c 	97 ^d	91/9	80
4	2d 	70	90/10	90
5	2e 	86	84/16	80 (<i>R</i>) ^e
6	2f 	95	89/11	85
7	2g 	86	84/16	86
8	2h 	99	84/16	79
9	2i 	90	88/12	83 (<i>R</i>) ^e
10	2j 	47	>99/1	82
11	2k 	76	>99/1	77

^aAll reactions were carried out at 80 °C for 22 h in H₂O/MeOH (9/1) in the presence of Pd(OAc)₂ (3 mol %), CyPF-*t*-Bu (**5a**, 3.6 mol %), bromoarene or bromoalkene (1 mmol), **1a** (2.5 mmol), and K₂CO₃ (3 mmol). ^bIsolated yield by chromatography. ^cEnantiomer excess was determined by a chiral stationary column. ^d**1a**: 2.0 mmol, time: 4.5 h. ^eConfiguration determined by Ref. 5b.

to dissolve the bromide substrates. The absolute configuration of methyl 4-(1-methylallyl)benzoate thus obtained by a series of Josiphos ligands (Entries 3–13) was established to be *R* ($[\alpha]_D^{22} -12.7$ (*c* 0.58, CHCl₃)) by the specific rotation reported for (*S*)-isomer ($[\alpha]_D +12$ (*c* 0.9, CHCl₃)^{3d}) and retention times of two enantiomers in HPLC analysis.

Under these conditions⁹ optimized for methyl 4-bromobenzoate, the representative aryl bromides possessing a donation or withdrawing substituent resulted in 79–90%ee with γ -selectivities in a range of 84–91% (Table 2, Entries 3–9).¹⁰ Among the bromoarenes employed, 4-bromoanisole exceptionally predominated the formation of a α -coupling product (**4**) (75%, **3/4** = 45/55) for an unknown reason. Aryl bromides possessing a meta-substituent (Entry 2) gave comparable results to those having a para-substituent, but ortho derivatives such as methyl 2-bromobenzoate (81%, **3/4** = 28/72) and 2-bromoanisole (79%, **3/4** = 28/72) resulted in very low enantioselectivities (less than 10%). Two alkenyl bromides achieved perfect γ -selectivities without any difficulty with enantioselectivities comparable to those of aryl bromides (Entries 10 and 11).

In conclusion, CyPF-*t*-Bu in Josiphos series was found to be an excellent ligand for asymmetric coupling of **1** with aryl or 1-alkenyl bromides with high γ -selectivities. Although there is a precedent for X-ray structure of Pd(Ph)(Br)(CyPF-*t*-Bu), kinetic study suggested the formation of a cationic palladium(II) intermediate such as [Pd(Ph)(CyPF-*t*-Bu)]⁺ before transmetalation with **1**. Mechanisms of transmetalation and enantioselection will be reported elsewhere.

References and Notes

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- 9 General procedure for asymmetric γ -selective coupling reaction (Table 2): A flask charged with potassium 2-butenyl-trifluoroborate (2.5 mmol), Pd(OAc)₂ (3 mol %), CyPF-*t*-Bu (3.6 mol %) and K₂CO₃ (3.0 mmol) was flushed with nitrogen. H₂O/MeOH (9/1, 5 mL) and bromoarene (1.0 mmol) were then added. The resulting mixture was stirred at 80 °C for 22 h. Isolated yields determined by chromatography on silica gel are shown in Table 2. Enantiomer excess was determined by a chiral stationary column.
- 10 Specific rotations $[\alpha]_D^{23}$ were **3b**: -4.33 (*c* 0.44, CHCl₃), **3c**: -11.8 (*c* 0.59, benzene), **3d**: -6.65 (*c* 0.81, benzene), **3e**: -6.05 (*c* 1.03, CHCl₃), **3f**: -15.27 (*c* 0.67, benzene), **3g**: -9.49 (*c* 0.57, benzene), **3h**: -9.46 (*c* 0.56, benzene), **3i**: -10.18 (*c* 0.46, benzene), **3j**: -3.64 (*c* 0.68, benzene), **3k**: -1.58 (*c* 0.41, benzene).