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Selected Papers

Mechanistic Study of the Palladium-Catalyzed Stereoselective Cross-Coupling Reaction of 1,1-Dibromo-3,3,3-trifluoro-2-tosyloxypropene

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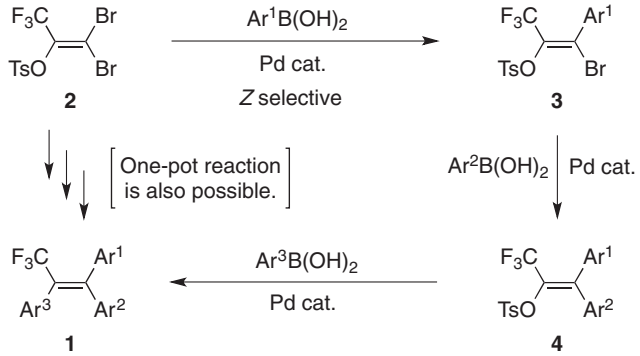
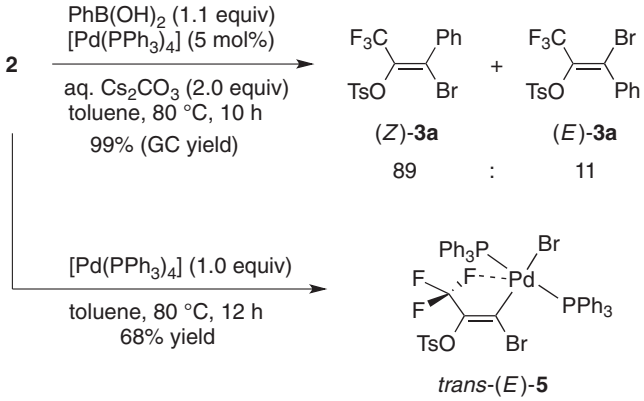
We prepared a Pd complex by the oxidative addition of 1,1-dibromo-3,3,3-trifluoro-2-tosyloxypropene to [Pd(PPh$_3$)$_4$]. The atomic distance between Pd and F in the complex was 2.95 Å, which was shorter than the sum of the van der Waals radii, suggesting that Pd–F interaction played an important role in determining the stereochemical outcome of the Pd-catalyzed cross-coupling reaction of the propene.



Scheme 1. Palladium-catalyzed threefold cross-coupling reaction of **2** with arylboronic acids.



Scheme 2. Pd-Catalyzed coupling reaction of **2** with PhB(OH)$_2$ and isolation of the oxidative adduct **5**.

Incorporation of fluorine atom(s) into biologically active substances and functional materials serves as a versatile molecular modification strategy to attain superior and unique biological activities and material properties.[1] Hence, it is crucial to develop synthetic reactions/methodologies for organofluorine compounds, which proceed with high efficiency and selectivity to give the target fluorinated molecules with the desired stereochemistry. Moreover, the elucidation of factors that govern the stereoselectivity of designed reactions is very important to construct new principles for the stereocontrol of synthetic reactions. We have recently established a highly versatile synthetic route to CF$_3$-substituted triarylethenes **1**; the route involves palladium-catalyzed threefold sequential cross-coupling reaction of 1,1-dibromo-3,3,3-trifluoro-2-tosyloxypropene (**2**) with arylboronic acids (Scheme 1).[2] Using this approach, any stereoisomers of **1** can be arbitrarily synthesized in a stereochemically pure form simply by changing the order in which the arylboronic acids are used. The one-pot preparation of **1** was also demonstrated. The success of the sequential cross-coupling approach was attributed to the high *Z*-selectivity of the first coupling. Since the presence of a CF$_3$ group was essential for attaining *Z* selectivity,[2] we surmised that electronic interaction between fluorine and palladium might be involved. To verify this hypothesis, we isolated the oxidative adduct of **2** to [Pd(PPh$_3$)$_4$] and monitored the oxidative addition process by ^{19}F and ^{31}P NMR. Reported herein are the details of the mechanistic studies.

The stereoselectivity of **3** was almost constant (*Z*/*E* = ca. 9:1), regardless of the electronic or steric nature of the substituents on the organoboronic acids.[2] For example, **2** reacted with PhB(OH)$_2$ in the presence of [Pd(PPh$_3$)$_4$] (5 mol %) and aq. Cs$_2$CO$_3$ (two molar equivalents) in toluene at 80 °C to give **3a** with a *Z*/*E* ratio of 89:11 (Scheme 2). Then, when a toluene solution of **2** and a stoichiometric amount of [Pd(PPh$_3$)$_4$] were heated at 80 °C, the oxidative adduct *trans*-(*E*)-**5** (*trans* implies the relative configuration of two PPh$_3$ with regard to a Pd; (*E*) expresses the configuration of the ethenyl moiety) was isolated in 68% yield as colorless prisms by recrystallization from EtOH/CH$_2$Cl$_2$. The complex *trans*-(*E*)-**5** was fully characterized by ^{1}H, ^{13}C, ^{19}F, and ^{31}P NMR, IR, mass spectrometry, and elemental analysis. Moreover, the structure of *trans*-(*E*)-**5** was unambiguously confirmed by single-crystal X-ray analysis (Figure 1).[3] The palladium atom adopted a square-planar geometry; the bond angles are 91.47(2)° for Br(1)–Pd–P(1), 88.46(2)° for Br(1)–Pd–P(2), 91.43(16)° for P(1)–Pd–C(1), and 88.53(16)° for P(2)–Pd–C(1). The bond lengths of Br(1)–Pd (2.4805(4) Å), P(1)–Pd (2.3600(0) Å), P(2)–Pd (2.3369(7) Å), and C(1)–Pd (1.978(7) Å) are nearly the same as those reported for the oxidative adduct of Br$_2$C=CH(ferrocenyl) to Pd(0).[4] Note that the atomic distance between F(1) and Pd is 2.959 Å, which is shorter than the sum (3.10 Å) of the van der Waals radii (1.47 Å for F and 1.63 Å for Pd),[5] indicating that F–Pd interaction might be operating to some extent in the complex-

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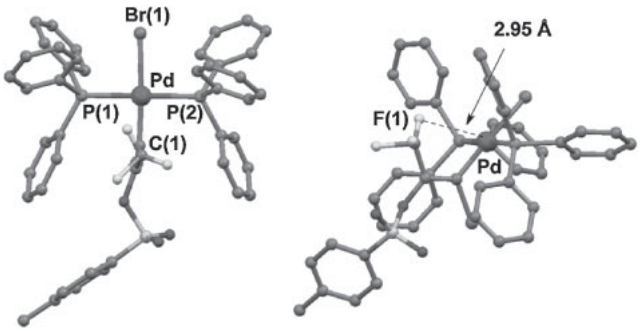
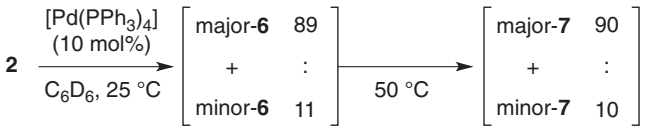


Figure 1. Molecular structure of *trans*-(*E*)-**5**.



Scheme 3. NMR monitoring of a mixture of **2** and $[Pd(PPh_3)_4]$.

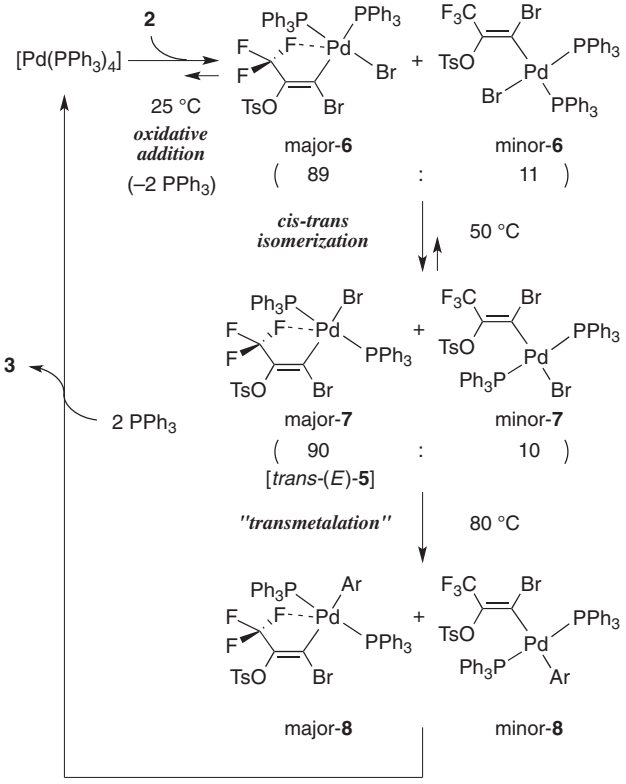
Table 1. NMR Data of Oxidative Adducts **6** and **7**

	Chemical shift/ppm	
	Major-**6**	Minor-**6**
^{19}F	−59.4 (d, $J = 5.5$ Hz)	−59.2 (s)
^{31}P	20.2 (d, $J = 29.6$ Hz)	19.6 (d, $J = 26.0$ Hz)
	28.1 (dq, $J = 29.6$, 5.5 Hz)	29.6 (d, $J = 26.0$ Hz)
	Major-**7**	Minor-**7**
^{19}F	−61.5 (t, $J = 5.6$ Hz)	−59.9 (s)
^{31}P	22.6 (q, $J = 5.6$ Hz)	23.3 (s)

ation.[6a] Such a short F–Pd contact has previously been observed with $[\{Pd(\mu_2\text{-}SC_6F_5)(\mu_2\text{-}(Ph_2P)_2CH_2)Pd\}(\mu_2\text{-}SC_6F_5)]_4(Et_2O)_2$ (2.945 Å)[6b] and $[Pd\{2,4,6\text{-}(CF_3)_3C_6H_2\}_2]$ (2.897 Å).[6c]

The isolated complex *trans*-(*E*)-**5** was confirmed to catalyze the cross-coupling of **2** with $PhB(OH)_2$, giving rise to **3a** in 50% yield with the same stereochemical outcome as that obtained with the aid of $[Pd(PPh_3)_4]$. This result clearly indicates that *trans*-(*E*)-**5** is involved in the catalytic cycle of the coupling reaction.

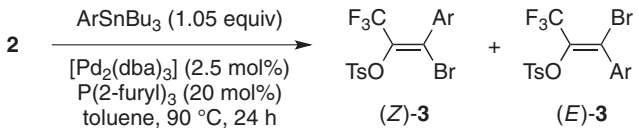
To gain further insight into the oxidative addition step, the reaction was monitored by ^{19}F and ^{31}P NMR (Scheme 3). The chemical shifts and coupling constants observed in the monitoring are summarized in Table 1. When **2** and $[Pd(PPh_3)_4]$ (10 mol %) were mixed in C_6D_6 at 25 °C, the resonance at 16.9 ppm in the ^{31}P NMR spectrum, which corresponded to $[Pd(PPh_3)_4]$, completely disappeared within 15 min. In turn, one major pair of resonances appeared at 20.2 and 28.1 ppm, and one minor pair at 19.6 and 29.6 ppm in the ^{31}P NMR spectrum, together with a resonance of free PPh_3 (−4.2 ppm). The ^{19}F NMR spectrum also showed two new resonances at −59.4 and −59.2 ppm with a ratio of 89:11, which was the same as that estimated from the ^{31}P NMR spectrum. These results indicated that two species (major-**6** and minor-**6**) formed in a ratio of 89:11 by mixing of **2** and $[Pd(PPh_3)_4]$. Heating the mixture at 50 °C for 3 h resulted in complete disappearance of **6** and the generation of two species (major-**7** and minor-**7**) in a ratio of 90:10.[7] On the basis of the ^{19}F and ^{31}P NMR data, major-**7** was



Scheme 4. Proposed catalytic cycle.

definitely assigned as *trans*-(*E*)-**5**. Each ^{31}P NMR spectrum of major- and minor-**7** showed only one signal, respectively. This observation indicates that the two PPh_3 groups in **7** are magnetically equivalent; in other words, the configuration of the two PPh_3 groups with regard to the Pd center is *trans*, which is consistent with the structure of *trans*-(*E*)-**5** disclosed by the X-ray analysis. Spin–spin coupling between fluorine and phosphine was observed with major-**7** (*trans*-(*E*)-**5**) but not with minor-**7**, suggesting that the distances between the CF_3 group and two PPh_3 groups of minor-**7** were long enough not to interact with each other. Hence, the stereochemistry of minor-**7** could be assigned as *trans*-(*Z*) (the structure is shown in Scheme 4). The initially observed **6** can be assigned similarly. Thus, the appearance of two signals of ^{31}P NMR in major- and minor-**6**, and their respective coupling constants of 29.6 and 26.0 Hz, indicate that the two PPh_3 groups in each **6** are magnetically nonequivalent and coordinated to Pd in a *cis* fashion. The presence of P–F coupling in major-**6** and its absence in minor-**6** are evidence that the configurations of the ethenyl moieties are *E* and *Z*, respectively.

Based on the experimental results, we proposed a catalytic cycle of the cross-coupling reaction of **2**, shown in Scheme 4. The oxidative addition of **2** to $[Pd(PPh_3)_4]$ proceeds smoothly at room temperature, giving rise to oxidative adduct **6** with high *E*-selectivity. The subsequent *cis–trans* isomerization at a Pd center should give **7**. Considering the observed short contact of F and Pd atoms of major-**7** (*trans*-(*E*)-**5**), the thermodynamic preference of major-**7** to minor-**7** is rationalized by the F–Pd coordination, which allows Pd to fulfill the 18-electron rule. As the *E*/*Z* ratios of **6** and **7** are almost constant, the *cis* configuration of the CF_3 and Pd moieties of major-**6** may also



Ar	3	Yield/%	(*Z*)-3	:	(*E*)-3
4-$Me_2NC_6H_4$	**3b**	76	90	:	10
4-$OHCC_6H_4$	**3c**	93	88	:	12
2-furyl	**3d**	84	87	:	13
2-thienyl	**3e**	87	93	:	7

Scheme 5. (*Z*)-Selective Pd-catalyzed coupling reaction of **2** with organotin reagents.

be attributed to F–Pd coordination. Transmetalation of **7** with arylboronic acids would give alkenyl(aryl)palladium complexes **8**, which then undergo *cis–trans* isomerization and subsequent reductive elimination, producing monocoupled products **3** with a *Z*/*E* ratio of approximately 9:1. Considering that heating at 80 °C, which was higher than the temperatures of the oxidative addition (25 °C) and *cis–trans* isomerization (50 °C), was essential to perform the coupling reaction smoothly, the rate-determining step should be transmetalation or reductive elimination.

Supposing that this mechanism, in which the stereoselectivity is determined before transmetalation, is valid, it is expected that the coupling reaction of **2** with organometallic reagents other than boron would also proceed with similar stereoselectivity. This is the case with organotin reagents. The results are shown in Scheme 5. A catalyst system consisting of $[Pd_2(dba)_3]$/P(2-furyl)$_3$ was effective in performing coupling reaction of **2** with arylstannanes, giving rise to **3** in high yields with high selectivity (ca. 9:1). These results clearly prove the validity of the proposed mechanism.

In summary, we have demonstrated that high *Z*-selectivity of the Pd-catalyzed coupling reaction of **2** originates from F–Pd interaction in the oxidative adducts. The present study sheds light on F–Pd interaction as a tool for stereocontrol in synthetic reactions.

Experimental

Preparation of *trans*-(*E*)-5. A vial tube (5 mL) equipped with a magnetic stirring bar was charged with **2** (85 mg, 0.20 mmol) and $[Pd(PPh_3)_4]$ (0.23 g, 0.20 mmol) under an argon atmosphere. Toluene (2 mL) was added to the mixture at room temperature. The resulting solution was heated on a hot plate at 80 °C for 12 h. The reaction mixture was allowed to cool down to room temperature, diluted with hexane (3 mL), filtered, and concentrated. Recrystallization of the crude product from CH_2Cl_2/EtOH gave *trans*-(*E*)-**5** as colorless prisms (0.14 g, 68%). Mp: 225.1–225.9 °C (dec.) ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.40 (s, 3H), 7.19 (d, $J = 8.4$ Hz, 2H), 7.35–7.42 (m, 18H), 7.53 (d, $J = 8.4$ Hz, 2H), 7.64–7.69 (m, 12H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.7, 119.6 (q, $J = 272.2$ Hz), 127.6, 128.0 (t, $J = 5.3$ Hz), 128.8, 130.2, 130.3 (t, $J = 24.4$ Hz), 131.2 (q, $J = 29.7$ Hz), 134.3, 134.8 (t, $J = 6.1$ Hz), 144.2, 146.5 (q, $J = 6.8$ Hz); ^{19}F NMR (282 MHz, $CDCl_3$): δ −61.5 (t, $J = 5.6$ Hz); ^{31}P NMR (121 MHz, $CDCl_3$): δ 22.6 (q, $J = 5.6$ Hz). IR (KBr): ν 3055, 1596, 1573, 1481, 1434, 1363, 1280, 1195, 1170, 1128, 1095, 1041, 889, 744, 692, 655, 563, 520, 495 cm^{-1}. MS (FAB): *m*/*z* (%) 976 (15, $[M^+ - Br + H] + 2$), 975 (20, $[M^+ - Br] + 2$), 974 (15, $[M^+ - Br + H]$), 973 (20, $[M^+ - Br]$), 449 (100). Anal. Calcd for $C_{46}H_{37}Br_2F_3O_3P_2PdS$: C, 52.37; H, 3.53%. Found: C, 52.21; H, 3.64%.

General Procedure for Coupling Reaction of 2 with Organotin Reagents. A Schlenk tube (20 mL) equipped with a magnetic stirring bar was charged with $[Pd_2(dba)_3]$ (11 mg, 13 μmol), P(2-furyl)$_3$ (24 mg, 0.1 mmol), and **2** (0.21 g, 0.50 mmol). The tube was then capped with a rubber septum, evacuated for 5 min, and purged with argon. The evacuation and purge operations were repeated twice. Toluene (5 mL) was added to the mixture at room temperature. The solution was stirred at room temperature for 5 min and degassed by three freeze–thaw operations before the addition of arylstannane (0.53 mmol). The resulting mixture was heated at 90 °C for 24 h. After the mixture was allowed to cool to room temperature, 1 M aq. KF (5 mL) was added. The resulting mixture was stirred for 1 h at room temperature. The organic layer was extracted with AcOEt (15 mL × 3). The combined organic layer was washed with 1 M aq. KF (15 mL) and saturated aq. NaCl (15 mL), dried over anhydrous $MgSO_4$, and then concentrated in vacuo. The residue was purified by column chromatography on silica gel containing 5 wt% of finely ground KF, followed by recrystallization.[8]

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Supporting Information

Crystallographic data of *trans*-(*E*)-**5** and characterization data for coupling products **3b**–**3e**. This material is available free of charge on the web at http://www.csj.jp/journals/bcsj/.

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3 Crystallographic data for compound *trans*-(*E*)-**5** have been deposited with Cambridge Crystallographic Data Centre: Deposition number CCDC-837537. Copies of the data can be obtained free of charge via http://www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge, CB2 1EZ, U.K.; Fax: +44 1223 336033; e-mail: deposit@ccdc.cam.ac.uk).

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7 This conversion was very sluggish at room temperature, as evidenced by the fact that almost no change was observed in the ^{19}F and ^{31}P NMR spectra after 4 h.

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