

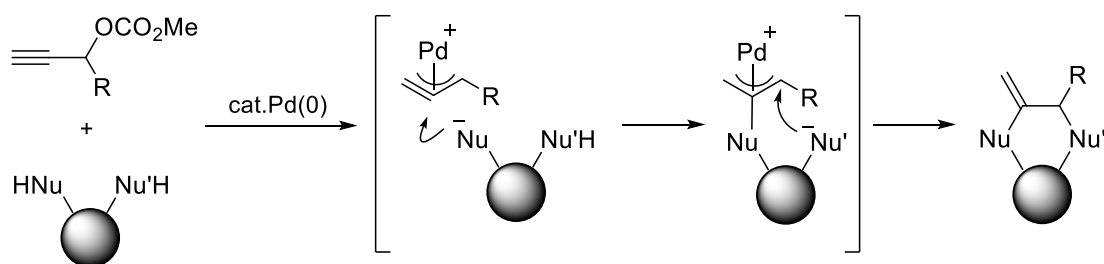
## SYNTHESIS OF DIHYDROBENZO[1,4]OXAZINES BY PALLADIUM-CATALYZED CYCLIZATION OF *N*-SUBSTITUTED 2-AMINOPHENOLS WITH PROPARGYLIC CARBONATES

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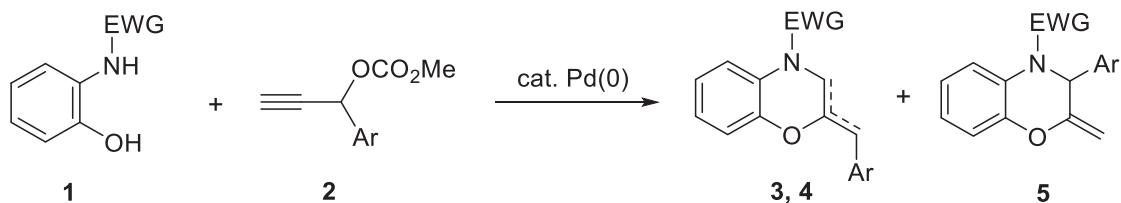
**Abstract** – The reaction of *N*-substituted 2-aminophenols with propargylic carbonates in the presence of a palladium-catalyst is described. The functionalized dihydrobenzo[1,4]oxazines were synthesized.

The palladium-catalyzed reaction of soft nucleophiles with propargylic compounds is one of the most successful palladium-catalyzed reaction developed to date.<sup>1</sup> For example, a substrate having two nucleophilic moieties within the molecule reacted with propargylic carbonate in the presence of palladium to generate the  $\pi$ -allylpalladium intermediate, which further reacted with the other nucleophilic part intramolecularly to afford the cyclized product (Scheme 1).<sup>2,3</sup> While our studies on the palladium-catalyzed reaction of bis-nucleophiles with propargylic compounds,<sup>3</sup> we focused on the nucleophilic activity of aminophenols having an electron-withdrawing substituent on the amino group. By introducing a nucleophilic oxygen and a nitrogen moiety within the substrates, we thought that dihydrobenzo[1,4]oxazines, common structures in many biologically active compounds,<sup>4</sup> could be constructed.<sup>5</sup> Herein, we describe the palladium-catalyzed reaction of *N*-substituted 2-aminophenols **1** with propargylic carbonates **2**, in which the dihydrobenzo[1,4]oxazines **3–5** have been constructed (Scheme 2).



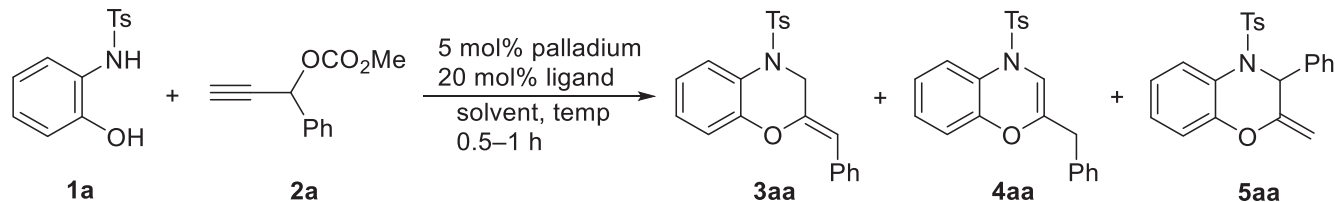
Scheme 1

‡ This paper is dedicated to Professor Kaoru Fuji on the occasion of his 80th birthday.



The examinations were started using *N*-tosyl-substituted 2-aminophenol **1a** and phenyl-substituted propargylic carbonate **2a** (Table 1). When **1a** and **2a** were treated with 5 mol% [(allyl)PdCl]<sub>2</sub>, 20 mol% DPPE in DMF at 120 °C, the expected dihydrobenzo[1,4]oxazine **3aa**, the olefinic isomer **4aa** and the regioisomer **5aa** were produced in a 10 : 2 : 5 ratio and 26% total yields (entry 1). Further attempts revealed that the presence of the monodentate ligand PPh<sub>3</sub> increased the yields (entries 2–4). Thus, the reaction with Pd(PPh<sub>3</sub>)<sub>4</sub> as the palladium catalyst was successful and afforded the products in 68% yields (entry 4). After several attempts (entries 5–7), we found that the products **3aa**, **4aa** and **5aa** were produced in a 10 : 4 : 3 ratio in 69% yields when the reaction was carried out in DMF at 80 °C (entry 7).

**Table 1.** Initial attempts using **1a** and **2a**

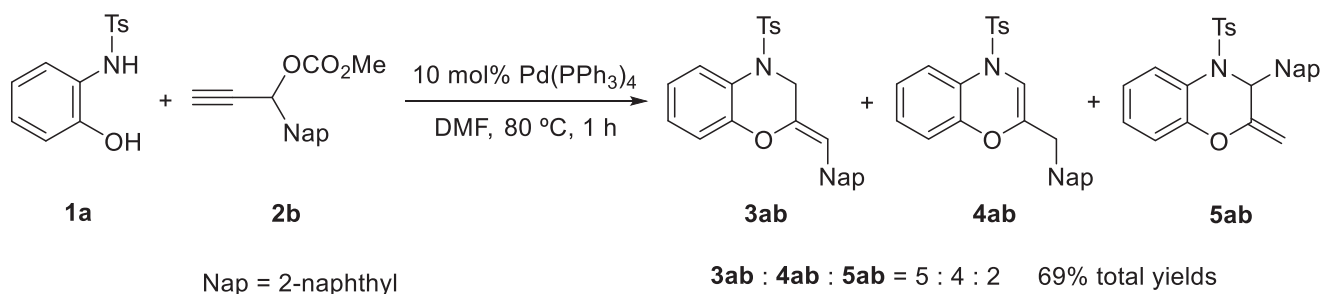


Entry	Palladium	Ligand	Solvent	Temp (°C)	3aa : 4aa :		Yields
					5aa		
1	[(allyl)PdCl] <sub>2</sub>	DPPE	DMF	120	10 : 2 : 5		26%
2	[(allyl)PdCl] <sub>2</sub>	BINAP	DMF	120	<b>3aa</b> only		35%
3	[(allyl)PdCl] <sub>2</sub>	PPh <sub>3</sub>	DMF	120	10 : 3 : 2		38%
4 <sup>a</sup>	Pd(PPh <sub>3</sub> ) <sub>4</sub>	–	DMF	120	5 : 3 : 1		68%
5 <sup>a</sup>	Pd(PPh <sub>3</sub> ) <sub>4</sub>	–	DMSO	120	10 : 2 : 3		46%
6 <sup>a</sup>	Pd(PPh <sub>3</sub> ) <sub>4</sub>	–	toluene	reflux	10 : 2 : 5		16%
7 <sup>a</sup>	Pd(PPh <sub>3</sub> ) <sub>4</sub>	–	DMF	80	10 : 4 : 3		69%

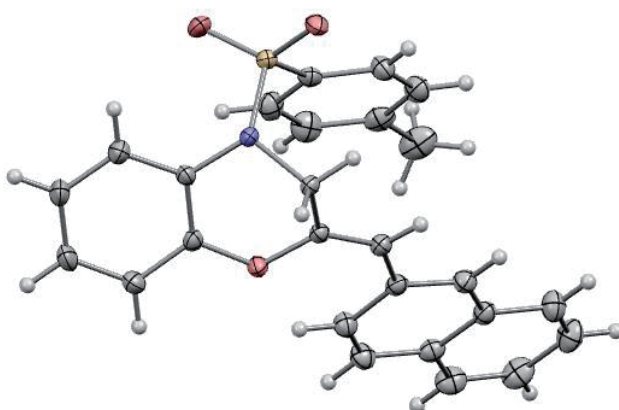
<sup>a</sup>10 mol% palladium was used.

Having identified a useful set of reaction conditions,<sup>6</sup> we next examined the reaction of naphthyl-substituted propargylic carbonate **2b** with **1a** (Scheme 3). The reaction successfully proceeded

to afford the corresponding dihydrobenzo[1,4]oxazine **3ab**, **4ab** and **5ab** in a 5 : 4 : 2 ratio and 69% total yields. The structure of the resulting product **3ab** was confirmed by an X-ray crystallographic analysis (Figure 1).<sup>7</sup>



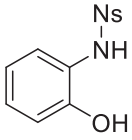
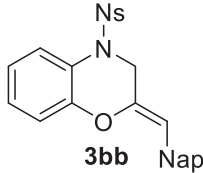
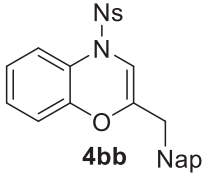
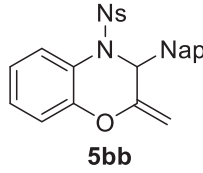
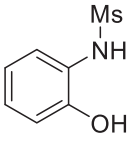
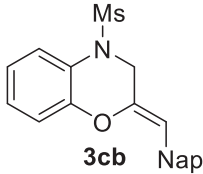
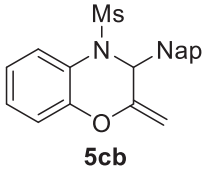
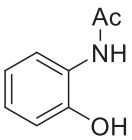
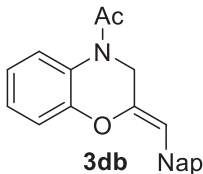
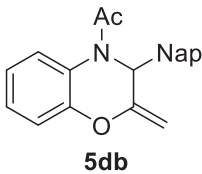
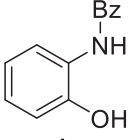
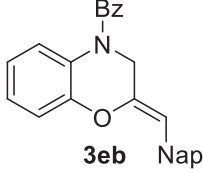
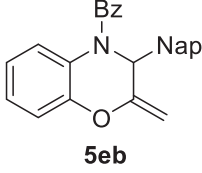
**Scheme 3**



**Figure 1.** ORTEP drawing of **3ab**

A study using various *N*-substituted 2-aminophenols **1b–1e** with **2b** was shown in Table 2. When a 2-nitrobenzenesulfonyl-substituted substrate **1b** was exposed to the optimal conditions, the dihydrobenzo[1,4]oxazines **3bb**, **4bb** and **5bb** were obtained in a 5 : 2 : 1 ratio and 70% total yields. The reaction using **1c** which contains a methanesulfonyl group proceeded to give the cyclized product **3cb** and **5cb** in a 2 : 1 ratio and 76% yields. Substrates **1d** and **1e** having an acetyl and a benzoyl group on the amino moiety reacted without problems to afford the corresponding products **3db** and **5db** (5 : 1), **3eb** and **5eb** (3 : 1), respectively.

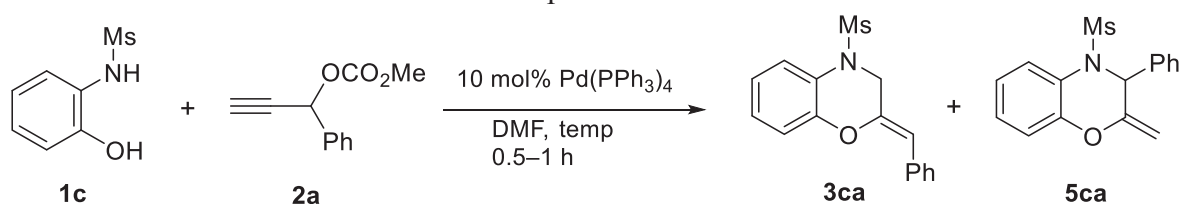
**Table 2.** Examination using various *N*-substituted 2-aminophenols **1b–1e** with **2b**

Substrate <b>1</b>	Products <sup>2)</sup>	Yields ( <b>3</b> : <b>4</b> : <b>5</b> )
 <b>1b</b>	 <b>3bb</b> +  <b>4bb</b> +  <b>5bb</b>	70% (5 : 2 : 1)
 <b>1c</b>	 <b>3cb</b> +  <b>5cb</b>	76% (2 : 0 : 1)
 <b>1d</b>	 <b>3db</b> +  <b>5db</b>	95% (5 : 0 : 1)
 <b>1e</b>	 <b>3eb</b> +  <b>5eb</b>	69% (3 : 0 : 1)

<sup>1)</sup> Reactions were carried out with **2b** in the presence of 10 mol% Pd(PPh<sub>3</sub>)<sub>4</sub> in DMF at 80 °C.

<sup>2)</sup> Nap = 2-naphthyl

Next we evaluated the reactivity of the 2-aminophenol **1c** with **2a** under the various temperature (Table 3). When **1c** and **2a** were reacted with 10 mol% of Pd(PPh<sub>3</sub>)<sub>4</sub> in DMF at 120 °C, the corresponding product **3ca** and its regioisomer **5ca** in a 3 : 1 ratio and 64% total yields (entry 1). It is interesting to note that the regioselectivity of the reaction is altered depending on the reaction temperature. Against the reactions at 120 °C and 80 °C afforded the **3ca** as a major product (entries 1 and 2), the same amount of the regioisomer **5ca** was produced together with **3ca** when the reaction was carried out at 60 °C (entry 3). Furthermore, **5ca** was predominantly obtained in the reaction at 25 °C (**3ca** : **5ca** = 1 : 1.5, 66% yields, entry 4).

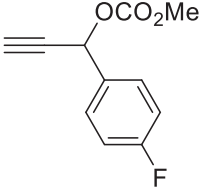
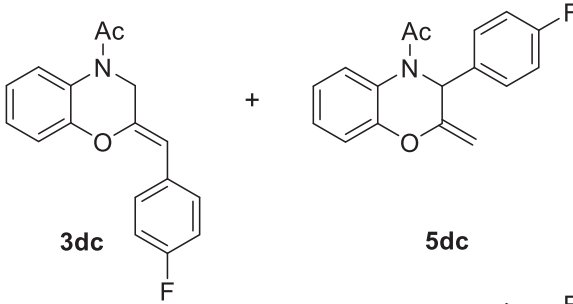
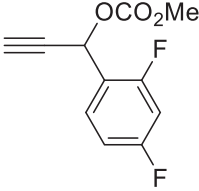
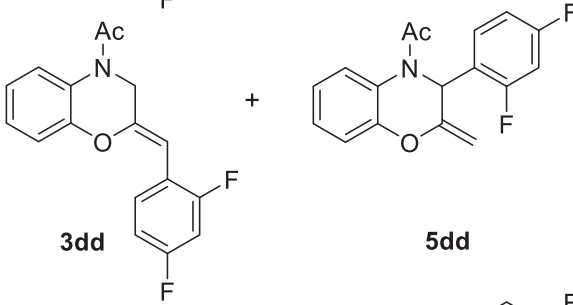
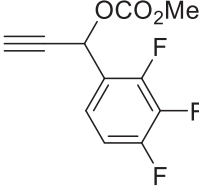
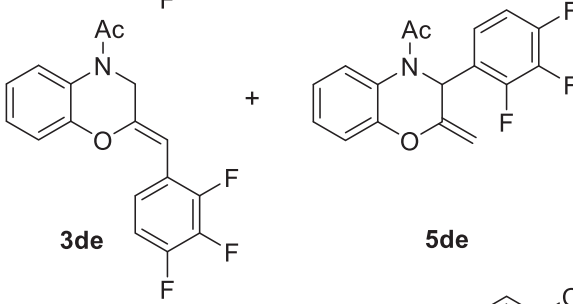
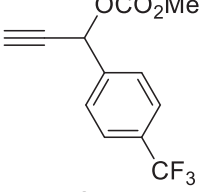
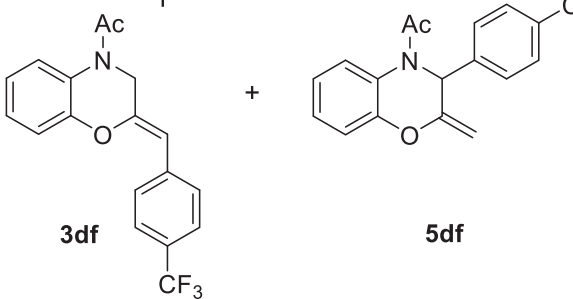
**Table 3.** Examination under various reaction temperature

Entry	Temp (°C)	<b>3ca</b> : <b>5ca</b>	Yields
1	120	3 : 1	64%
2	80	2 : 1	56%
3	60	1 : 1	68%
4	25	1 : 1.5	66%

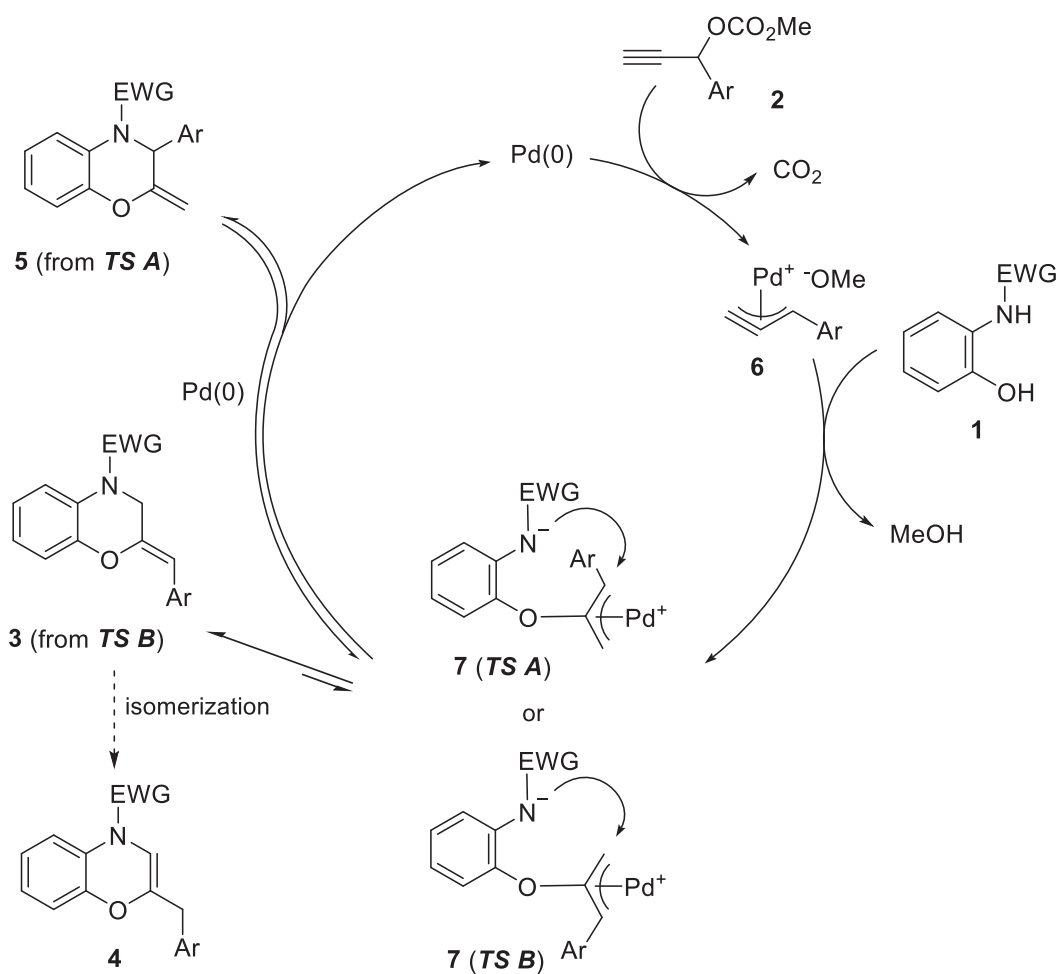
Table 4 shows the examinations using various propargylic carbonates **2c–2f**, having a fluorine substituent on the phenyl group, with **1d**. In the reaction conditions at 80 °C, the substrate **2c** containing a 4-fluorophenyl group successfully reacted to produce the 4-fluorophenyl-substituted dihydrobenzo[1,4]oxazine **3dc** and **5dc** in a 3 : 1 ratio and 67% total yields. Similarly, the corresponding products **3dd** and **5dd**, **3de** and **5de** were obtained in good yields from the reactions using difluoro- and trifluorophenyl-substituted substrates **2d** and **2e**, respectively. The reaction of the substrate **2f**, which has a trifluoromethyl group, also afforded the cyclized product **3df** and **5df** in a 2 : 1 ratio and 68% total yields.

A plausible mechanism for the production of the dihydrobenzo[1,4]oxazines is shown in Scheme 4. By reacting with palladium, the propargylic carbonate **2** is transformed to the  $\pi$ -propargylpalladium complex **6**, which reacts with aminophenol **1** to lead to the  $\pi$ -allylpalladium intermediate **7**. The intermediate **7** is further subjected to intramolecular attack of the amide anion to produce the cyclized product **3** and **5**. The part of the resulting **3** was further isomerized in situ to the olefinic isomer **4**. The observed regioselectivity depending on the reaction temperature in Table 3 is likely the result of kinetic and thermodynamic control in the cyclization process.<sup>3g,8</sup> In the reaction at low temperature, it is expected that the cyclization occurs via **TS A**<sup>9</sup> leading to **5** as the kinetic product. On the other hand, there would be equilibrium between the products and  $\pi$ -allylpalladium intermediate **7** in situ at the high temperature. As a result, this reversible process furnished the thermodynamically more stable product **3** via **TS B**.

**Table 4.** Examination using various F-substituted propargylic carbonates **2c–2f** with **1d**.

Substrate <b>2</b>	Products	Yields ( <b>3</b> : <b>5</b> )
 <b>2c</b>		67% (3 : 1)
 <b>2d</b>		65% (2 : 1)
 <b>2e</b>		83% (7 : 1)
 <b>2f</b>		68% (2 : 1)

<sup>1)</sup> Reactions were carried out with **1d** in the presence of 10 mol% Pd(PPh<sub>3</sub>)<sub>4</sub> in DMF at 80 °C.



**Scheme 4**

In conclusion, we have developed a methodology for the synthesis of dihydrobenzo[1,4]oxazines by a palladium-catalyzed cyclization of *N*-substituted 2-aminophenols with propargylic carbonates. The reaction afforded a variety of functionalized dihydrobenzo[1,4]oxazine, and the process provided an efficient and convenient protocol for the preparation of these derivatives.

#### ACKNOWLEDGEMENT

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5. Related reactions about the syntheses of 1,4-benzodioxines and piperadines were reported. See ref. 2d–g, 2n and 2p.
6. General procedure for the synthesis of dihydrobenzo[1,4]oxazines. Reaction of **1d** and **2f** (Table 4).



To a stirred solution of propargylic carbonate **2f** (30.0 mg, 116  $\mu\text{mol}$ ) in DMF (0.6 mL) were added 2-aminophenol **1d** (21.1 mg, 139  $\mu\text{mol}$ ),  $\text{Pd}(\text{PPh}_3)_4$  (13.4 mg, 11.6  $\mu\text{mol}$ ) at rt, and stirring was continued for 30 min at 80  $^\circ\text{C}$ . After filtration of the reaction mixture using small amount of silica gel followed by concentration, the residue was chromatographed on silica gel with hexane-AcOEt (3:1 v/v) as eluent to give the dihydrobenzo[1,4]oxazine **3df** (17.7 mg, 53.1  $\mu\text{mol}$ , 46%) and **5df** (8.8 mg, 26.4  $\mu\text{mol}$ , 22%) as colorless oil, respectively. **3df**: IR (ATR): 1666, 1615, 1494, 1319  $\text{cm}^{-1}$ ;  $^1\text{H-NMR}$  (500 MHz,  $\text{CDCl}_3$ )  $\delta$  1.92 (3H, s), 4.82 (2H, s), 6.66 (1H, s), 6.94 (1H, d,  $J = 8.0$  Hz), 7.01 (1H, t,  $J = 8.0$  Hz), 7.12 (1H, t,  $J = 8.0$  Hz), 7.53 (2H, d,  $J = 8.5$  Hz), 7.63 (2H, d,  $J = 8.5$  Hz), 7.90 (1H, d,  $J = 8.0$  Hz);  $^{13}\text{C-NMR}$  (125 MHz,  $\text{CDCl}_3$ )  $\delta$  22.4 ( $\text{CH}_3$ ), 70.8 ( $\text{CH}_2$ ), 117.1 (CH), 120.9 (CH), 123.6 (Cq, q,  $J_{\text{C-F}} = 273$  Hz), 124.5 (CH), 125.3 (CH), 126.1 (CH, q,  $J_{\text{C-F}} = 4$  Hz), 126.4 (Cq), 126.5 (CH), 128.9 (CH), 130.7 (Cq, q,  $J_{\text{C-F}} = 33$  Hz), 132.8 (Cq), 137.4 (Cq), 146.9 (Cq), 168.1 (Cq); HRMS (EI)  $m/z$  calcd for  $\text{C}_{18}\text{H}_{14}\text{F}_3\text{NO}_2$   $[\text{M}]^+$  333.0977, found 333.0972. **5df**: IR (ATR): 1663, 1588, 1490, 1322  $\text{cm}^{-1}$ ;  $^1\text{H-NMR}$  (500 MHz,  $\text{CDCl}_3$ )  $\delta$  1.96 (3H, s), 5.37 (1H, s), 5.38 (1H, s), 5.89 (1H, s), 6.99 (1H, t,  $J = 8.0$  Hz), 7.02 (1H, d,  $J = 8.0$  Hz), 7.13 (1H, t,  $J = 8.0$  Hz), 7.48 (2H, d,  $J = 8.5$  Hz), 7.64 (2H, d,  $J = 8.5$  Hz), 7.80 (1H, d,  $J = 8.0$  Hz);  $^{13}\text{C-NMR}$  (125 MHz,  $\text{CDCl}_3$ )  $\delta$  22.1 ( $\text{CH}_3$ ), 80.0 (CH), 114.0 ( $\text{CH}_2$ ), 116.7 (CH), 120.9 (CH), 123.8 (CH), 124.1 (Cq, q,  $J_{\text{C-F}} = 273$  Hz), 125.7 (CH, q,  $J_{\text{C-F}} = 4$  Hz), 126.2 (CH), 126.5 (Cq), 126.7 (CH), 130.9 (Cq, q,  $J_{\text{C-F}} = 33$  Hz), 140.5 (Cq), 141.7 (Cq), 146.2 (Cq), 168.3 (Cq); HRMS (EI)  $m/z$  calcd for  $\text{C}_{18}\text{H}_{14}\text{F}_3\text{NO}_2$   $[\text{M}]^+$  333.0977, found 333.0984.

7. CCDC 1936606 **3ab** contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via [www.ccdc.cam.ac.uk/data\\_request/cif](http://www.ccdc.cam.ac.uk/data_request/cif).
8. Other examples about the regio- or stereochemical control depending on the reaction temperature, see: (a) M. A. Blaskovich and R. W. Rickards, *Tetrahedron Lett.*, 1998, **39**, 3617; (b) Y. Arai, J. Nakazaki, and H. Segawa, *Tetrahedron Lett.*, 2008, **49**, 5810; (c) F. Alonso, S. G. Davies, A. S. Elend, and A. D. Smith, *Org. Biomol. Chem.*, 2009, **7**, 518.
9. It is known that the intramolecular nucleophilic attack to the  $\pi$ -allylpalladium predominantly occurs at the more substituted carbon, see ref. 1 and 3.