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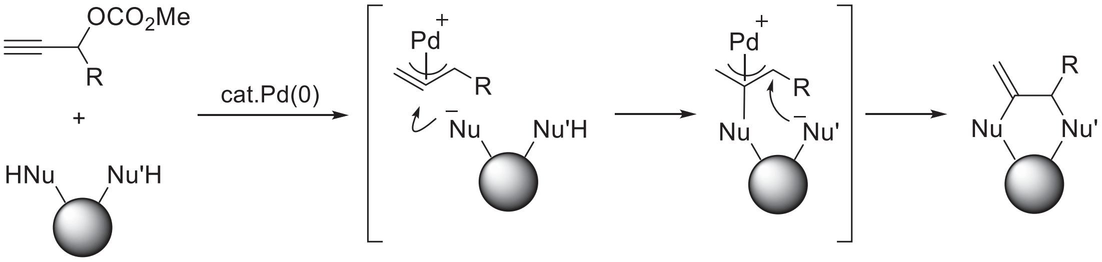
SYNTHESIS OF DIHYDROBENZO[1,4]OXAZINES BY PALLADIUM-CATALYZED CYCLIZATION OF *N*-SUBSTITUTED 2-AMINOPHENOLS WITH PROPARGYLIC CARBONATES

Masahiro Yoshida,* Shunya Mori, Kenji Matsumoto, and Tsukasa Hirokane

Faculty of Pharmaceutical Sciences, Tokushima Bunri University, Nishihama, Yamashiro-cho, Tokushima, 770-8514, Japan. E-mail: yoshida@ph.bunri-u.ac.jp

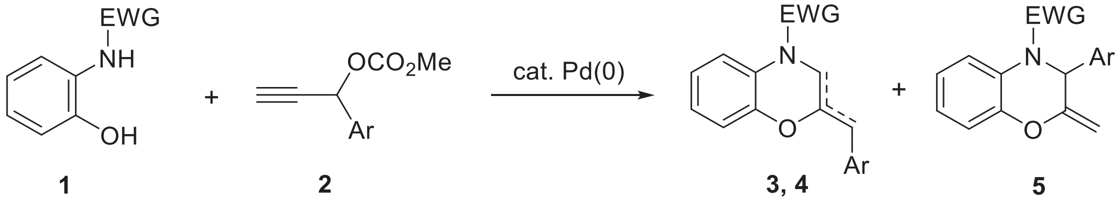
Abstract – The reaction of *N*-substituted 2-aminophenols with propargylic carbonates in the presence of a palladium-catalyst is described. The functionalized dihydrobenzo[1,4]oxazines were synthesized.

The palladium-catalyzed reaction of soft nucleophiles with propargylic compounds is one of the most successful palladium-catalyzed reaction developed to date.[1] For example, a substrate having two nucleophilic moieties within the molecule reacted with propargylic carbonate in the presence of palladium to generate the π-allylpalladium intermediate, which further reacted with the other nucleophilic part intramolecularly to afford the cyclized product (Scheme 1).[2,3] While our studies on the palladium-catalyzed reaction of bis-nucleophiles with propargylic compounds,[3] 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,[4] could be constructed.[5] 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

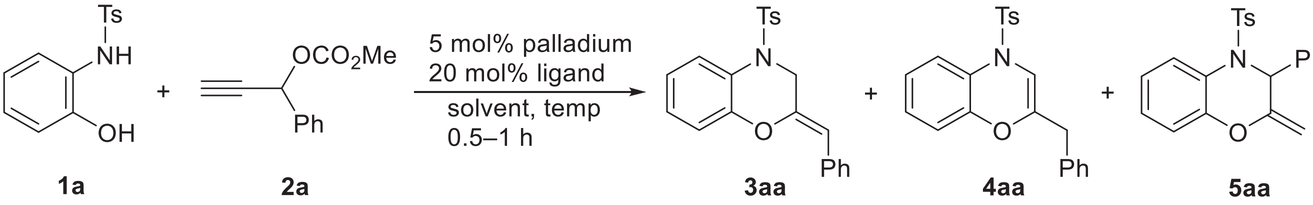
‡ This paper is dedicated to Professor Kaoru Fuji on the occasion of his 80th birthday.



Scheme 2

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]$_2$, 20 mol% DPPE in DMF at 120 ºC, 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$_3$ increased the yields (entries 2–4). Thus, the reaction with Pd(PPh$_3$)$_4$ 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 ºC (entry 7).

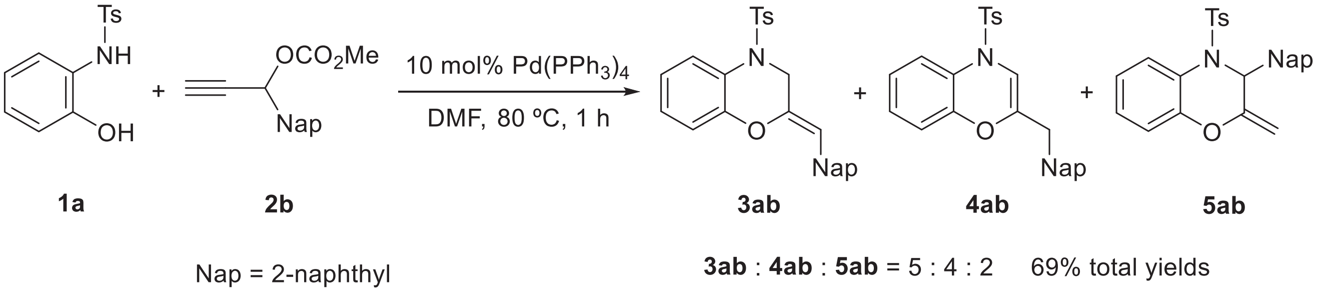
Table 1. Initial attempts using **1a** and **2a**



Entry	Palladium	Ligand	Solvent	Temp (ºC)	**3aa** : **4aa** : **5aa**	Yields
1	[(allyl)PdCl]$_2$	DPPE	DMF	120	10 : 2 : 5	26%
2	[(allyl)PdCl]$_2$	BINAP	DMF	120	**3aa** only	35%
3	[(allyl)PdCl]$_2$	PPh$_3$	DMF	120	10 : 3 : 2	38%
4[a]	Pd(PPh$_3$)$_4$	–	DMF	120	5 : 3 : 1	68%
5[a]	Pd(PPh$_3$)$_4$	–	DMSO	120	10 : 2 : 3	46%
6[a]	Pd(PPh$_3$)$_4$	–	toluene	reflux	10 : 2 : 5	16%
7[a]	Pd(PPh$_3$)$_4$	–	DMF	80	10 : 4 : 3	69%

[a] 10 mol% palladium was used.

Having identified a useful set of reaction conditions,[6] 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).[7]



Scheme 3

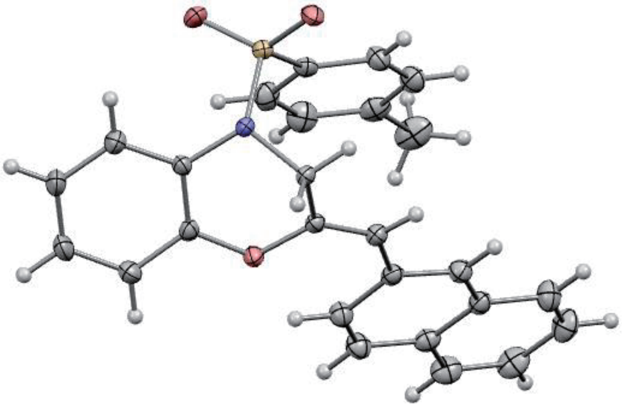
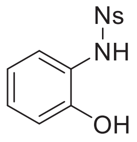
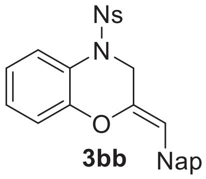
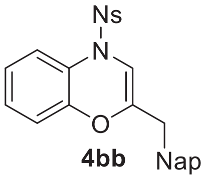
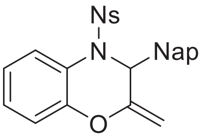
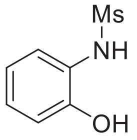
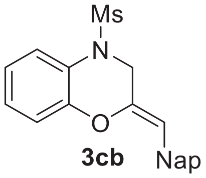
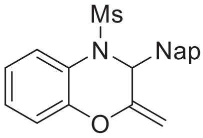
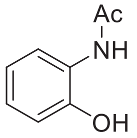
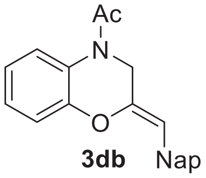
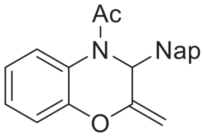
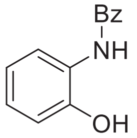
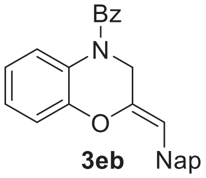
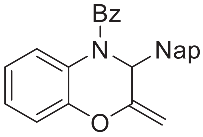


Figure 1. ORTEP drawing of **3ab**

A study using various *N*-substituted 2-aminophenols **1b–1e** with **2b** was shown in Table 2. When a 2-nitorobenzenesulfonyl-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.

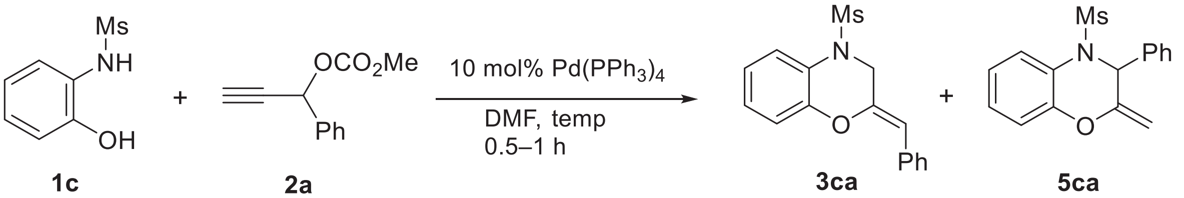
Table 2. Examination using various *N*-substituted 2-aminophenols **1b–1e** with **2b**

Substrate **1**	Products[2)]	Yields (**3** : **4** : **5**)
 **1b**	 **3bb** +  **4bb** +  **5bb**	70% (5 : 2 : 1)
 **1c**	 **3cb** +  **5cb**	76% (2 : 0 : 1)
 **1d**	 **3db** +  **5db**	95% (5 : 0 : 1)
 **1e**	 **3eb** +  **5eb**	69% (3 : 0 : 1)

[1)] Reactions were carried out with **2b** in the presence of 10 mol% Pd(PPh_3)$_4$ in DMF at 80 ºC.
[2)] 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_3)$_4$ in DMF at 120 ºC, 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 ºC and 80 ºC 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 ºC (entry 3). Furthermore, **5ca** was predominantly obtained in the reaction at 25 ºC (**3ca** : **5ca** = 1 : 1.5, 66% yields, entry 4).

Table 3. Examination under various reaction temperature

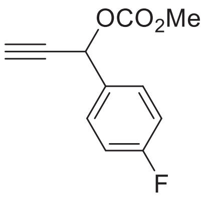
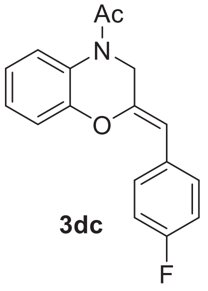
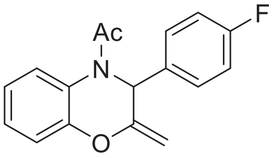
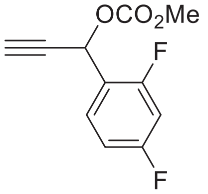
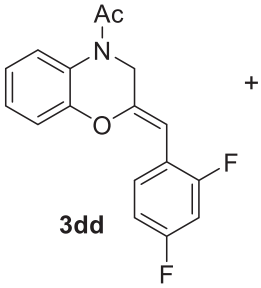
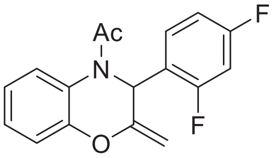
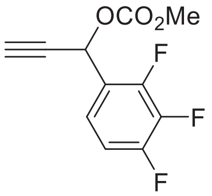
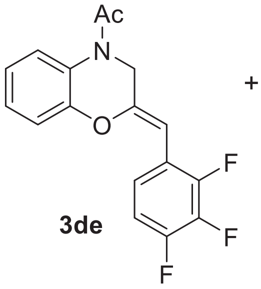
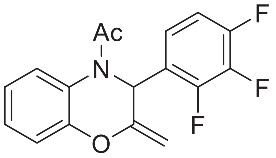
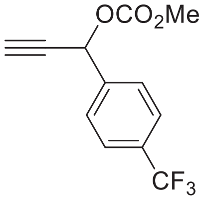
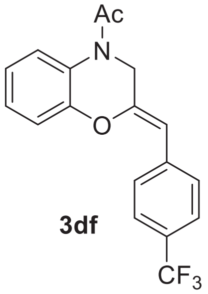
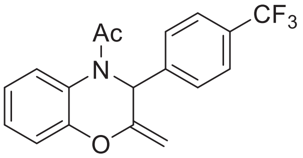


Entry	Temp (ºC)	**3ca** : **5ca**	Yields
1	120	3 : 1	64%
2	80	2 : 1	56%
3	60	1 : 1	68%
4	25	1 : 1.5	66%

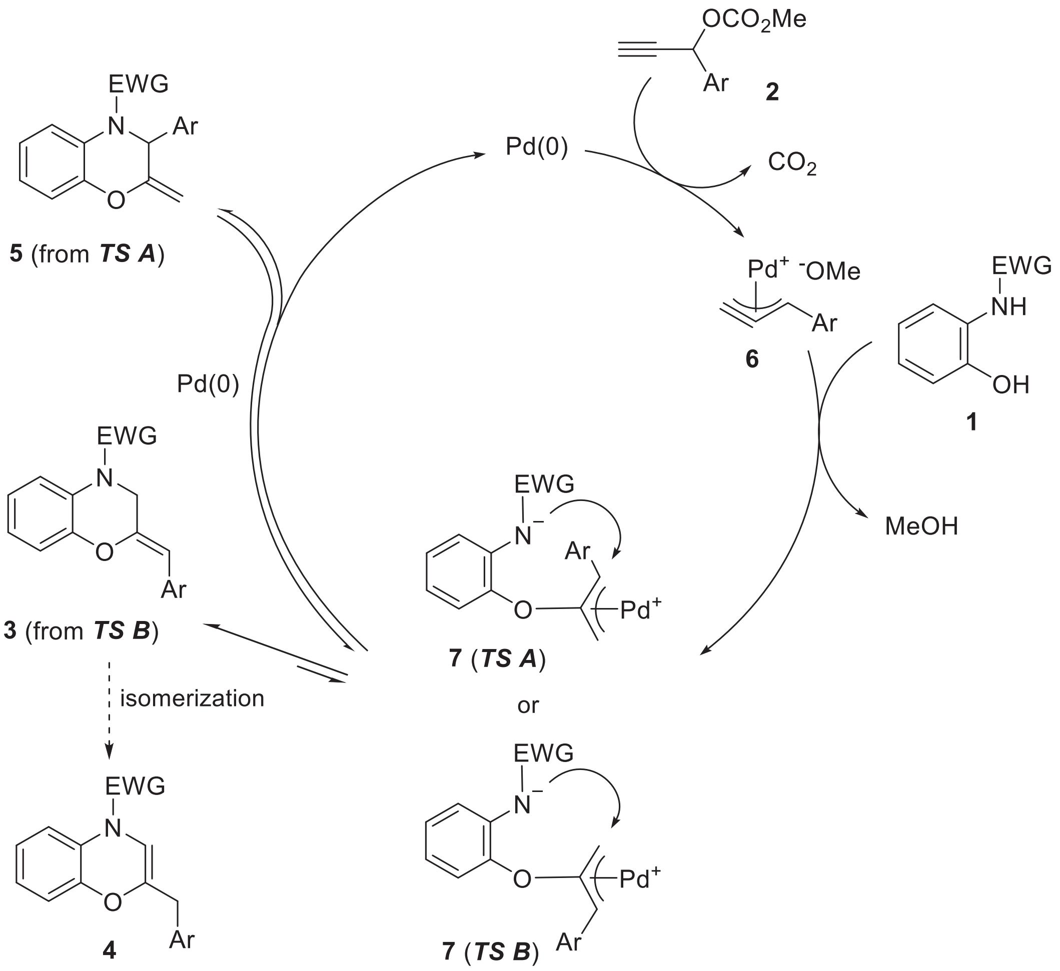
Table 4 shows the examinations using various propargylic carbonates **2c**–**2f**, having a fluorine substituent on the phenyl group, with **1d**. In the reaction conditions at 80 ºC, the substrate **2c** containing a 4-fluorophenyl group successfully reacted to produce the 4-fluorophenyl-substituted 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 π-propargylpalladium complex **6**, which reacts with aminophenol **1** to lead to the π-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.[3g,8] In the reaction at low temperature, it is expected that the cyclization occurs via **TS A**[9] leading to **5** as the kinetic product. On the other hand, there would be equilibrium between the products and π-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 **2**	Products	Yields (**3** : **5**)
 **2c**	 **3dc** +  **5dc**	67% (3 : 1)
 **2d**	 **3dd** +  **5dd**	65% (2 : 1)
 **2e**	 **3de** +  **5de**	83% (7 : 1)
 **2f**	 **3df** +  **5df**	68% (2 : 1)

[1] Reactions were carried out with **1d** in the presence of 10 mol% Pd(PPh_3)$_4$ in DMF at 80 ºC.



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 μmol) in DMF (0.6 mL) were added 2-aminophenol **1d** (21.1 mg, 139 μmol), Pd(PPh$_3$)$_4$ (13.4 mg, 11.6 μmol) at rt, and stirring was continued for 30 min at 80 °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 μmol, 46%) and **5df** (8.8 mg, 26.4 μmol, 22%) as colorless oil, respectively. **3df:** IR (ATR): 1666, 1615, 1494, 1319 cm^{-1}; ^{1}H-NMR (500 MHz, CDCl$_3$) δ 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}C-NMR (125 MHz, CDCl$_3$) δ 22.4 (CH$_3$), 70.8 (CH$_2$), 117.1 (CH), 120.9 (CH), 123.6 (Cq, q, $J_{C\text{-}F}$ = 273 Hz), 124.5 (CH), 125.3 (CH), 126.1 (CH, q, $J_{C\text{-}F}$ = 4 Hz), 126.4 (Cq), 126.5 (CH), 128.9 (CH), 130.7 (Cq, q, $J_{C\text{-}F}$ = 33 Hz), 132.8 (Cq), 137.4 (Cq), 146.9 (Cq), 168.1 (Cq); HRMS (EI) *m/z* calcd for $C_{18}H_{14}F_3NO_2$ [M]$^+$ 333.0977, found 333.0972. **5df:** IR (ATR): 1663,1588, 1490, 1322 cm^{-1}; ^{1}H-NMR (500 MHz, CDCl$_3$) δ 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}C-NMR (125 MHz, CDCl$_3$) δ 22.1 (CH$_3$), 80.0 (CH), 114.0 (CH$_2$), 116.7 (CH), 120.9 (CH), 123.8 (CH), 124.1 (Cq, q, $J_{C\text{-}F}$ = 273 Hz), 125.7 (CH, q, $J_{C\text{-}F}$ = 4 Hz), 126.2 (CH), 126.5 (Cq), 126.7 (CH), 130.9 (Cq, q, $J_{C\text{-}F}$ = 33 Hz), 140.5 (Cq), 141.7 (Cq), 146.2 (Cq), 168.3 (Cq); HRMS (EI) *m/z* calcd for $C_{18}H_{14}F_3NO_2$ [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.
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 π-allylpalladium predominantly occurs at the more substituted carbon, see refs. 1 and 3.