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Palladium-catalyzed oxyarylation of olefins using silver carbonate as the base. Probing the mechanism by electrospray ionization mass spectrometry

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ABSTRACT

The $Pd(OAc)_2$-catalyzed oxyarylation of electron-rich (**8** and **12**) and electron-poor (**10**) olefins by *ortho*-iodophenols (**3a**–**d**) was studied using Ag_2CO_3 as the base, in acetone, and in the presence and absence of PPh_3. The corresponding adducts of oxyarylation were obtained in moderate yields. The reaction mechanism was examined by electrospray ionization mass spectrometry (ESI-MS). Cationic arylpalladium intermediate (**14**), formed by the oxidative insertion of Pd(0) into **3a**, and the cationic palladacycles (**15**), obtained by reaction of **14** with olefins **8** and **12**, were intercepted by ESI-MS and characterized by ESI-MS/MS.

1. Introduction

The Heck reaction is one of the most versatile and industrially important palladium-catalyzed carbon-carbon reactions [1,2]. Therefore, this reaction mechanism and several variants have been extensively investigated [3]. Less attention has been given, however, to the oxyarylation (*oxa*-Heck) reaction, and only a few protocols for this interesting transformation have been reported [4–17]. In the first examples of oxyarylation reported by Horino and Inoue [4,5], *cis*-olefins (**1**) were allowed to react with phenylmercury chlorides (**2**, R = HgCl), in the presence of stoichiometric amounts of $PdCl_2$ in acetone–water, yielding stereoselectively compounds of type *trans*-**5** (Fig. 1). A few years latter, they [6] described the same protocol for an intramolecular version, using *ortho*-hydroxyphenylmercury chlorides (**3**, R = HgCl) instead of **2**. Those reactions were, in contrast, found to be *cis*-stereoselective, leading to compounds of type **6**. This approach was also used to prepare several naturally occurring pterocarpans, coumestans and derivatives [13–16]. The reaction of *ortho*-hydroxybenzylmercury chlorides (**4**, R = HgCl) with olefins also showed to be *cis*-stereoselective, leading to compounds type **7** [16].

Catalytic versions of oxyarylations were also reported, using substoichiometric amounts of $Pd(OAc)_2$ and *ortho*-iodophenols (**3**, R = I) to replace the *ortho*-mercuryphenols (**3**, R = HgCl) as the source of organopalladium intermediates [7–12].

We describe herein the $Pd(OAc)_2$-catalyzed oxyarylation of electron-rich (**8** and **12**) and electron-poor (**10**) olefins by *ortho*-iodophenols (**3a**–**d**) using Ag_2CO_3 as the base, in acetone, and in the presence and absence of PPh_3. To investigate the reaction mechanism, the cationic arylpalladium intermediates were intercepted by ESI-MS and characterized by ESI-MS/MS.

2. Results and discussion

Scheme 1 shows the reactions of olefins **8**, **10** and **12** with *ortho*-iodophenols (**3a**–**d**), and Table 1 summarizes major conditions and yields. Using 10 mol% $Pd(OAc)_2$, 20 mol% PPh_3 in acetone or DMF and Na_2CO_3 as the base, none of the desired adducts were formed (data not shown) [9]. However, when Ag_2CO_3 was used as the base in acetone at reflux, and in the presence of PPh_3, reasonable yields of **9a**, **11a** and **13a** were obtained (entries 1, 3 and 5). These

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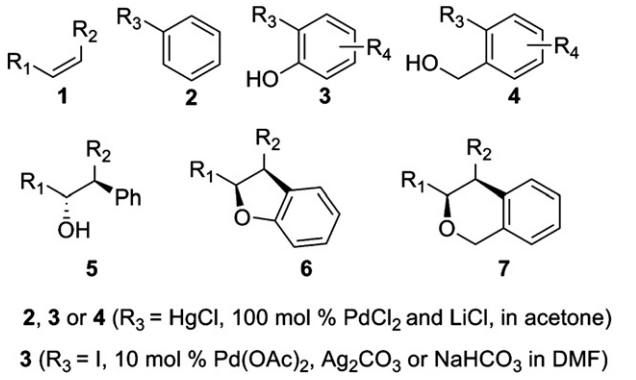
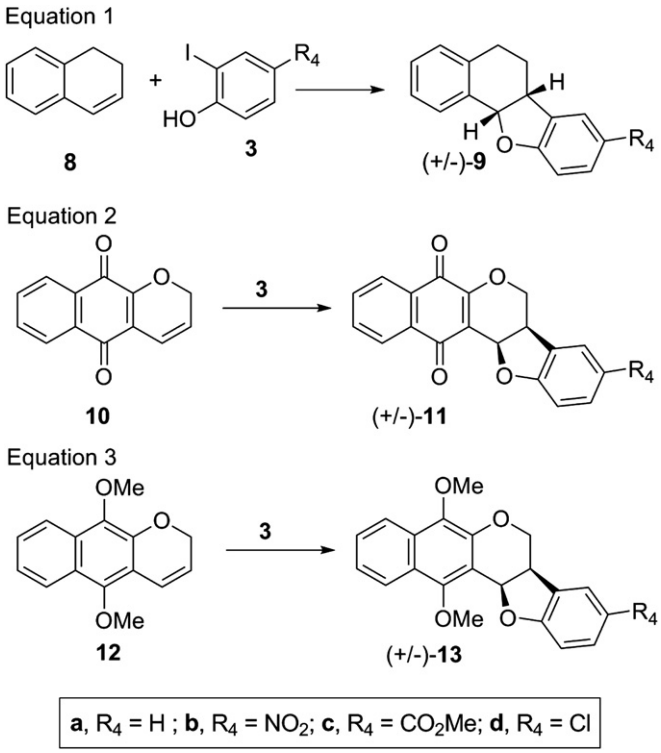


Fig. 1. Olefins (**1**), organopalladium species (**2**, **3** and **4**), reaction conditions and the corresponding products of oxyarylation (**5**, **6** and **7**).

reactions were also successfully carried out essentially in the same yields in the absence of PPh_3 (entries 2, 4 and 6). Since PPh_3 failed to improve the yields, we decided to use phosphine free experiments in the reactions of **8**, **10** and **12** with *ortho*-iodophenols **3b**, **3c** and **3d.** When **3b** was allowed to react with these olefins, adducts **9b**, **11b** and **13b** were respectively obtained in 10–50% yields (entries 7–9), whereas *ortho*-iodophenol **3c** led to products **9c**, **11c** and **13c** in 32–52% yields (entries 10–12). Only olefin **8** was allowed to react with *ortho*-iodophenol **3d**, and the adduct **9d** was obtained in a 68% yield.

Considering that electron-rich olefins react faster than electron-poor olefins under conditions favoring the cationic mechanism [17–19], competitive experiments were performed for the reaction of select olefin pairs (1 equiv. of each) with **3a** (1 equiv.) in the presence of Ag_2CO_3 as the base (Table 2). Olefin **8** was more reactive than **10**, and adduct **9a** was the main product formed in this experiment (entry 1). Olefin **12** was also more reactive than **10**, and adduct **13a** was the main product formed under the same conditions (entry 2). These results are in agreement with HOMO values (Table 3) since this orbital in **10** is lower in energy than those of **8** and **12**. However, **8** was slightly more reactive than **12**, in spite of the fact that the HOMO value in **12** is higher in energy. Steric hindrance between the methoxy group near the double bound in **12** and the incoming arylpalladium intermediate may be responsible for the lower reactivity of this olefin.



Scheme 1. Oxyarylation of olefins **8**, **10** and **12** by *ortho*-iodophenol **3a**–**d**.

Table 1
Yields and major conditions for the reactions outlined in Scheme 2 and performed in acetone, in the presence of 10 mol% of $Pd(OAc)_2$ and 3 equiv. of Ag_2CO_3 under reflux.

Entry	Olefin	3	Adduct	PPh_3	Yield (%)
1	**8**	**a**	**9a**	0.2 equiv.	45
2	**8**	**a**	**9a**	–	50
3	**10**	**a**	**11a**	0.2 equiv.	36
4	**10**	**a**	**11a**	–	40
5	**12**	**a**	**13a**	0.2 equiv.	50
6	**12**	**a**	**13a**	–	45
7	**8**	**b**	**9b**	–	50
8	**10**	**b**	**11b**	–	<10
9	**12**	**b**	**13b**	–	26
10	**8**	**c**	**9c**	–	52
11	**10**	**c**	**11c**	–	35
12	**12**	**c**	**13c**	–	43
13	**8**	**d**	**9d**	–	68

Table 2
Competitive experiments of selected olefins toward **3a**: 1 equiv. of each olefin, 1 equiv. of **3a**, 20 mol% $Pd(OAc)_2$, 20 mol% of PPh_3, 3 equiv. of Ag_2CO_3, acetone and reflux.

Entry	Olefin	Olefin	Products[c]
1[a]	**8**	**10**	**9** (45%) + **11** (4%)
2[a]	**12**	**10**	**13** (41%) + **11** (3%)
3[b]	**8**	**12**	**9** (25%) + **13** (15%)

[a] Reflux for 20 h.
[b] Reflux for 8 h.
[c] Product distribution measured by GC.

Table 3
HOMO values of olefins **8**, **10** and **12**.

Entry	Olefin/HOMO	HOMO (eV)
1	**8**	−7.95
2	**10**	−8.64
3	**12**	−7.43

HOMO in eV (*ab initio* HF 3-21G (*)).

To gain mechanistic information, we monitored the reaction of **8**, **10** and **12** with **3a** via direct infusion ESI-MS and its tandem version (ESI-MS/MS) in the positive ion mode hoping to intercept and characterized key cationic intermediates. ESI-MS has been recently incorporated in the set of techniques that are suitable for mechanistic studies in organic and inorganic chemistry, owing to its outstanding ability to "fish", with high sensitivity, speed and gentleness, ionic or ionized intermediates directly from reaction solutions in the gas phase [20]. Owing to these characteristics, ESI-MS is able to provide continuous snapshots of the changing composition of reaction solutions [21–28].

2.1. Oxa-Heck Pd(II) intermediates

We first studied the reaction of **3a** with **8** in acetone and in the presence of 10 mol% of $Pd(OAc)_2$, 20 mol% of PPh_3 and 3 equiv. of Ag_2CO_3, in acetone. Interestingly, ESI-MS provides the first mechanistic data for this reaction by intercepting the cationic Pd(II) species **14a** of *m*/*z* 723, formed in the oxidative addition step of Pd

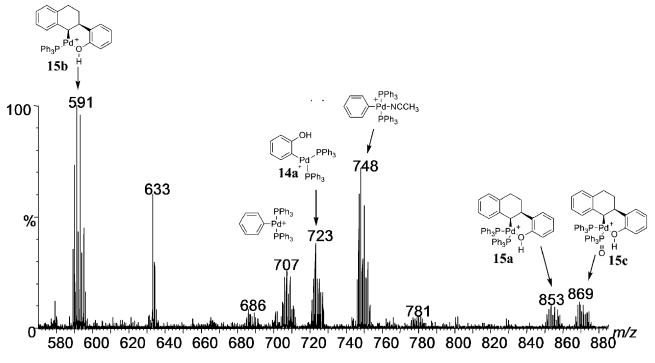


Fig. 2. ESI(+)-MS of the reaction solution of **8** with **3a** in the presence of $Pd(OAc)_2$, Ag_2CO_3 and PPh_3 in acetone after dilution with MeCN.

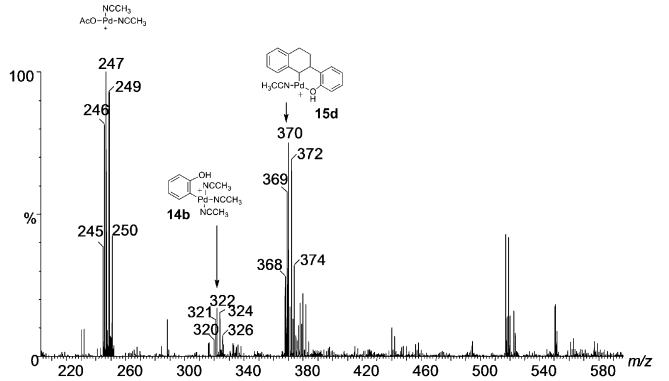


Fig. 4. ESI(+)-MS from the reaction solution of **8** with **3a** in the presence of $Pd(OAc)_2$ and Ag_2CO_3 in acetone after dilution with MeCN.

(0) to **3a**, and the cationic species **15a**, **15b** and **15e** originated by the carbopalladation of **8** by **14a** (Figs. 2 and 3). Intermediates **15** are the cationic versions of those proposed by Larock and others [29–34]. Cation **15c** is probably formed by oxidation of **15a** by air, since its formation is less important in reactions carried out under nitrogen. The ion of *m*/*z* 707 is formed due to aryl exchange, a successful feature in Heck reactions using a triphenylphosphine as a ligand. Aryl exchange is a typical process that occurs when aromatic halides are substituted by electron donor groups. The ion of *m*/*z* 748 is the adduct of acetonitrile from that *m*/*z* 707. Acetonitrile was used as solvent to dilute the reaction solution for ESI-MS analysis. These intermediates were subjected to collision-induced dissocition (CID), and Fig. S40 (Appendix) shows the resulting ESI (+)-MS/MS. In this spectrum, the ion of *m*/*z* 748 is shown to undergo loss of acetonitrile to form a fragment of *m*/*z* 707 ($^{+}PPh_4$), by a rearrangement that eliminates $PdPPh_3$. The intervention of cationic Pd intermediates in Heck reaction using ArI as a substrate has been suggested when halides scavengers, such as Ag_2CO_3, are present [17–19]. For the Heck-Matsuda reaction, in which diazonium salts are used as substrates instead of aryl iodides, ESI-MS and ESI-MS/MS have detected and characterized major cationic Pd intermediates [28]. For oxyarylation reactions, however, the intervention of cationic Pd intermediates is demonstrated herein for the first time.

When this reaction was monitored by ESI-MS in the absence of PPh_3, two new key species were intercepted a) the cationic palladium species **14b** (*m*/*z* 322) formed in the oxidative addition step of Pd(0) to **3a**, and b) **15d** (*m*/*z* 370) formed by carbopalladation of **8**. These cationic species were intercepted as adducts of acetonitrile, the solvent used to dilute the samples (Fig. 4).

When the reaction of **12** was monitored by ESI-MS in the absence of PPh_3, another key cationic palladium species of *m*/*z* 480 (**16a**), analogous to **15d**, was detected and further characterized by ESI-MS/MS (Fig. 5). As expected, this acetonitrile adduct of *m*/*z* 480 dissociated upon CID by acetonitrile loss forming **16b** of *m*/*z* 439. A structurally diagnostic loss of phenol occurred, forming **16c** of *m*/*z* 345. ESI-MS failed to intercept, however, possible Pd cationic intermediates resulting from the carbopalladation of **10**, perhaps due to their high reactivity and, therefore, too short-lived nature.

2.2. Mechanistic proposals

As Fig. 1 shows, the intermolecular oxyarylation of olefins leads to *trans*-adducts of type **5**, whereas in intramolecular versions, *cis*-adducts of type **6** and type **7** are obtained. Under the conditions favoring the neutral mechanism, **5** can be formed from an open intermediate $\mathbf{I_1}$ by stereoselective nucleophilic substitution at the C–Pd bond by water. However, in the intramolecular reactions carried out under the same conditions, *trans*-adducts would be expected if open intermediates operate. The *cis*-selectivity observed in these cases (adducts of type **6** and **7**) can be attributed to the intervention of palladacyclic intermediates, such as $\mathbf{I_2}$ and $\mathbf{I_3}$ (Fig. 6) [9,29–34]. Our results are in agreement with these proposals, once similar cationic intermediates ($\mathbf{I_4}$) were successfully intercepted by ESI-MS in the presence of Ag_2CO_3 and characterized by ESI-MS/MS.

Using the ESI-MS data and the **8** → **9a** transformation as an example, Scheme 2 presents a mechanistic rationalization for Pd-catalyzed oxyarylation in the presence and absence of PPh_3. The first step is the oxidative addition of Pd(0) to **3a** leading to the cationic arylpalladium species **14a** or **14b**, which are formed

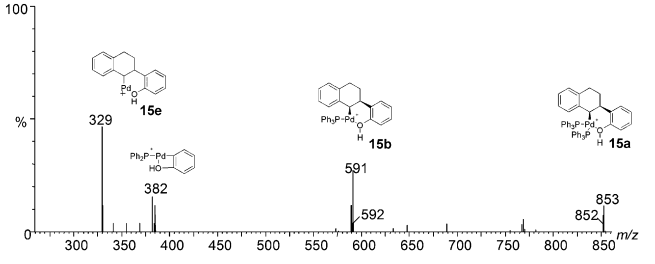


Fig. 3. ESI(+)-MS/MS of **15a** "fished" from the reaction solution containing **8**, **3**, $Pd(OAc)_2$, PPh_3 and Ag_2CO_3 in acetone after dilution with MeCN.

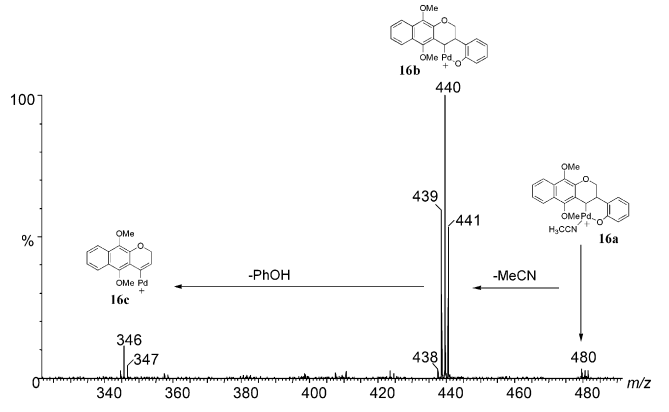


Fig. 5. ESI(+)-MS/MS of **16a** "fished" from the reaction mixture of **12** with **3a** in the presence of $Pd(OAc)_2$ and Ag_2CO_3 in acetone after dilution with MeCN.

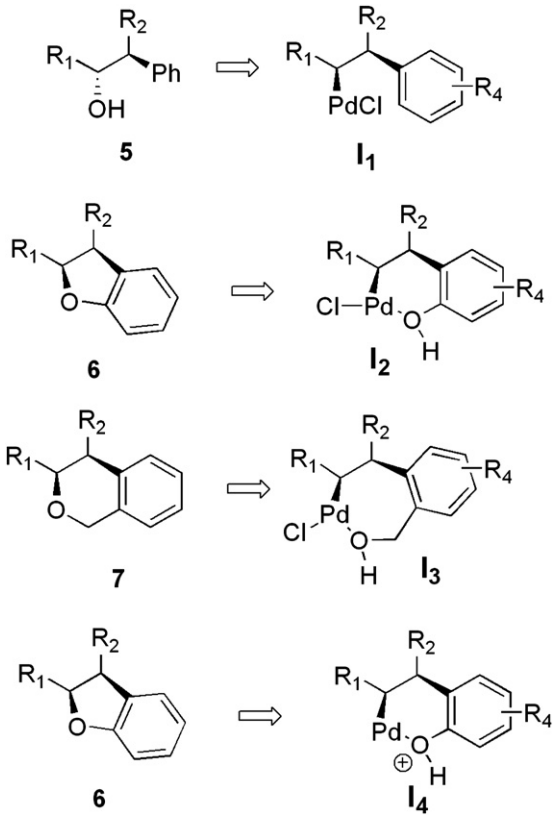


Fig. 6. Palladacycles proposed to explain the *cis* stereochemistry.

in the presence or absence of PPh_3, respectively. These intermediates undergo in turn regioselective carbopalladation of the double bond of the olefin **8**, yielding the cyclic Pd cationic intermediates **15b**, **15d** or **15e**, respectively. As for styrenes, the regioselectivity of this step seems to be controlled mainly by steric factors, since it is independent of the nature of the olefin [35]. The anti β-elimination of PdH is disfavored in **15** which allows for a reductive elimination of the Pd and the formation of the ether linkage [36] producing the adduct of oxyarylation **9a** and regenerating the Pd(0) catalyst.

3. Conclusions

The oxyarylation of electron-rich and electron-poor olefins by *ortho*-iodophenol and derivatives was accomplished in the presence of Ag_2CO_3 in acetone under reflux. These conditions favor the cationic mechanism and, accordingly, major cationic palladium intermediates were, for the first time, intercepted by ESI-MS and characterized by ESI-MS/MS.

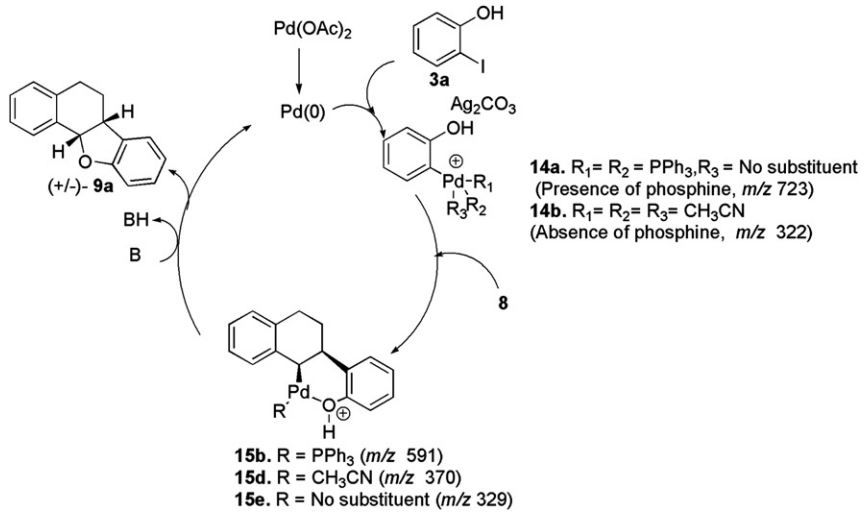
4. Experimental

4.1. General procedure of ESI-MS and ESI-MS/MS

ESI-MS and ESI-MS/MS. All experiments were performed on a hybrid quadrupole time-of- flight mass spectrometer (Q-TOF, Waters). For typical electrospray ionization (ESI) conditions, the Teflon-sealed microsyringe was placed in a pump that delivered the reagent solution into the ESI source at a flow rate of 10 μL min^{-1}. ESI and the mass spectrometer were operated in the positive ion mode. The main conditions were capillary voltage, 3500 eV; cone voltage, 35 eV; source temperature, 100 °C; desolvation temperature, 100 °C. The cationic species were subjected to collision-induced dissociation (CID) with argon by using collision energies ranging from 5 to 45 eV.

4.2. Procedure for oxyarylation of olefin 8 in acetone

To a stirred solution of **9** (0.5 mmol, 65 mg) in acetone (10 ml), *ortho*-iodophenol (**3a**, 0.5 mmol, 110 mg), silver carbonate (1.5 mmol, 413 mg) and 11.2 mg of $Pd(OAc)_2$ (0.05 mmol, 10 moL %) were added. The reaction mixture was refluxed for 24 h and filtered in celite with ethyl acetate. The organic layer was washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by flash column chromatography on silica (AcOEt/Hex 5:95) to give 55 mg (0.25 mmol) of **9a** in a 50% yield as a white amorphous solid. When **3b** (0.5 mmol, 110 mg), **3c** (0.5 mmol, 110 mg) and **3d** were used instead of **3a**, **9b** was obtained in a 50% yield (67 mg, 0.25 mmol) as a yellow solid, **9c** was obtained in a 52% yield (73 mg, 0.26 mmol) as a yellowish solid and **9d** as a white solid in 68% yield (75.5 mg, 0.34 mmol).



Scheme 2. Proposed mechanism for the palladium-catalyzed oxyarylation reaction of **8** by **3a** with key intermediates intercepted by ESI-MS and characterized by ESI-MS/MS.

4.3. Procedure for oxyarylation of olefin **10** in acetone

To a stirred solution of **10** (0.5 mmol, 106 mg) in acetone (10 ml), *ortho*-iodophenol (0.5 mmol, 110 mg), silver carbonate (1.5 mmol, 413 mg) and 11.2 mg of $Pd(OAc)_2$ (0.05 mmol, 10 mol%) were added. The reaction mixture was refluxed for 24 h and filtered in celite with ethyl acetate. The organic layer was washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude product **11a** was purified by flash column chromatography on silica (AcOEt/Hex 10:90) to give 62.3 mg (0.21 mmol) of **11a** in a 41% yield as a yellow solid. When **3b** (0.5 mmol, 110 mg) and **3c** (0.5 mmol, 110 mg) were used instead of **3a**, **11b** was obtained in less than a 10% yield (13.0 mg, 0.04 mmol) as a yellow solid after purification by column chromatography on silica (AcOEt/Hex 20:80), and **11c** was obtained in a 35% yield (63.3 mg, 0.17 mmol) as white solid after purification by column chromatography on silica (AcOEt/Hex 20:80).

4.4. Procedure for oxyarylation of olefin **12** in acetone

To a stirred solution of **12** (0.5 mmol, 121 mg) in acetone (10 ml), *ortho*-iodophenol (0.5 mmol, 110 mg), silver carbonate (1.5 mmol, 413 mg) and 11.2 mg of $Pd(OAc)_2$ (0.05 mmol, 10 mol%) were added. The reaction mixture was refluxed for 24 h and filtered in celite with ethyl acetate. The organic layer was washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude product **13a** was purified by flash column chromatography on silica (AcOEt/Hex 5:95) to give 83.5 mg (0.25 mmol) of **13a** in a 50% yield as a green oil. When **3b** (0.5 mmol, 110 mg) and **3c** (0.5 mmol, 110 mg) were used instead of **3a**, **13b** was obtained in a 26% yield as a yellow solid (49.5 mg, 0.13 mmol) after purification by column chromatography on silica (AcOEt/Hex 10:90) and **13c** was obtained in a 43% yield (84 mg, 0.21 mmol) as a white solid after purification by column chromatography on silica (AcOEt/Hex 10:90).

4.5. Substance ***9a***

Flash chromatography eluent: AcOEt–Hex 5:95; mp 40 °C; ^{1}H NMR (200 MHz, $CDCl_3$), δ (ppm): 7.56–7.52 (1H, m), 7.27–7.20 (2H, m), 7.14–7.08 (2H, m), 6.91–6.76 (3H, m), 5.63 (1H, d, $J = 8.0$ Hz), 3.71–3.70 (1H, m), 2.75–2.54 (2H, m), 2.96–2.11 (1H, m), 1.87–1.71 (1H, m); ^{13}C NMR (50 MHz, $CDCl_3$), δ (ppm): 159.3(C), 138.8(C), 133.3(C), 131.2(C), 130.1(CH), 128.3(CH), 128.2(CH), 126.6(CH), 124.3 (CH), 120.5(CH), 110.7(CH), 109.5(CH), 81.7(CH), 40.9(CH), 27.9 (CH_2), 27.5(CH_2); MS: m/z [M^+] 222; HRMS: $[M+H]^+$ m/z calculated for $C_{16}H_{14}O$ 222.1123, $[M+H]^+$ m/z found: 222.1223.

4.6. Substance ***9b***

Flash chromatography eluent: AcOEt–Hex 5:95; mp 126 °C; ^{1}H NMR (400 MHz, $CDCl_3$), δ (ppm): 8.40 (1H, d, $J = 1.6$ Hz), 8.11 (1H, dd, $J = 8.8$ Hz and $J = 2.7$ Hz), 7.55–7.52 (1H, m), 7.34–7.28 (2H, m), 7.19–7.16 (1H, m), 6.80 (1H, d, $J = 8.6$ Hz), 5.8 (1H, d, $J = 8.6$ Hz), 3.85–3.80 (1H, m), 2.71–2.62 (2H, m), 2.18–2.11 (1H, m), 1.92–1.84 (1H, m); ^{13}C NMR (50 MHz, $CDCl_3$), δ (ppm): 164.91(C), 138.6(C), 132.8(C), 131.9(C), 130.1(CH), 128.8(CH), 128.6(CH), 126.9(CH), 126.0 (CH), 120.9(CH), 109.4(CH), 84.3 (CH), 40.3(CH), 27.9(CH_2), 27.1 (CH_2); MS: m/z [M^+] 267; HRMS: $[M+H]^+$ m/z calculated for $C_{16}H_{13}NO_3$ 268.0974, $[M+H]^+$ m/z found: 222.1030.

4.7. Substance ***9c***

Flash chromatography eluent: AcOEt–Hex 3:97; mp 89 °C; ^{1}H NMR (200 MHz, $CDCl_3$), δ (ppm): 7.94 (1H, bs), 7.87 (1H, dd, $J = 8.3$ Hz and $J = 1.9$ Hz), 7.55–7.50 (1H, m), 7.29–7.26 (2H, m), 7.16–7.12 (1H, m), 6.76 (1H, d, $J = 8.3$ Hz), 5.76 (1H, d, $J = 8.8$ Hz), 3.88 (3H, s), 3.82–3.68 (1H, m); 2.68–2.62 (2H, m), 2.16–2.01 (1H, m), 1.92–1.76 (1H, m); ^{13}C NMR (50 MHz, $CDCl_3$), δ (ppm): 166.8(C), 163.5(C), 138.7(C), 132.6 (C), 131.6(C), 131.2(CH), 130.1(CH), 128.4 (CH), 126.7(CH), 126.2(CH), 122.7(C), 109.1(CH), 83.1(CH), 51.7(CH_3), 40.3(CH), 27.9(CH_2), 27.2(CH_2); MS: m/z [M^+] 280; HRMS: $[M+H]^+$ m/z calculated for $C_{18}H_{16}O_3$ 281.1178, $[M+H]^+$ m/z found: 281.1293.

4.8. Substance ***9d***

Flash chromatography eluent: AcOEt–Hex 3:97; mp 54 °C; ^{1}H NMR (200 MHz, $CDCl_3$), σ (ppm): 7.17 (1H, d, $J = 1.6$ Hz), 7.06 (1H, dd, $J = 8.4$ Hz and $J = 2.1$ Hz), 7.52–7.50 (1H, m), 7.30–7.23 (2H, m), 7.15–7.13 (1H, m), 6.70 (1H, d, $J = 8.2$ Hz), 5.68 (1H, d, $J = 8.6$ Hz), 3.69–3.64 (1H, m), 2.74–2.59 (2H, m), 2.08–2.00 (1H, m), 1.84–1.76 (1H, m); ^{13}C NMR (50 MHz, $CDCl_3$), σ (ppm): 157.96 (C), 138.58 (C), 133.21 (C), 132.83 (C), 130.04 (CH), 128.39 (CH), 128.35 (CH), 128.06 (CH), 126.66 (CH), 125.02 (C), 124.42 (CH), 110.39 (CH), 82.37 (CH), 41.04(CH), 27.7(CH_2), 27.3 (CH_2); MS: m/z [M^+] 256.

4.9. Substance ***11a***

Flash chromatography eluent: AcOEt–Hex 10:90; mp 145 °C; ^{1}H NMR (200 MHz, $CDCl_3$), δ (ppm): 8.21–8.10 (2H, m); 7.78–7.68 (2H, m); 7.30–7.18 (2H, m); 6.98–6.91 (2H, m); 5.66 (1H, d, $J = 6.7$ Hz); 4.59 (1H, dd, $J = 11.1$ and 5.0 Hz); 3.81 (1H, t (or dd), $J = 11.1$ Hz); 3.64–3.53 (1H, m); ^{13}C NMR (50 MHz, $CDCl_3$) δ (ppm): 183.2(C); 179.3(C); 158.7(C); 157.0(C); 134.5(CH); 133.4(CH); 131.8(C); 130.6 (C); 129.6(CH); 126.5(CH); 126.4(CH); 125.1(C); 124.5(CH); 121.2 (CH); 118.2(C); 110.8(CH); 72.3 (CH); 67.1(CH_2); 38.4(CH); HRMS: $[M+H]^+$ m/z calculated for $C_{19}H_{12}O_4$: 335.1283, $[M+H]^+$ m/z found: 335.0999.

4.10. Substance ***11b***

Flash chromatography eluent: AcOEt–Hex 20:80; mp 250 °C; ^{1}H NMR (400 MHz, $CDCl_3$), δ (ppm): 8.24–8.16 (4H, m); 7.86–7.77 (2H, m); 7.02 (1H, d, $J = 8.6$ Hz); 5.90 (1H, d, $J = 6.3$ Hz); 4.67 (1H, d, $J = 4.1$ and 10.9 Hz); 3.90 (1H, t, $J = 10.8$ Hz); 3.78–3.75 (1H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 179.0(C); (there is one carbonyl signal absent); 164.2(C); 157.4(C); 142.6(C); 134.9(CH); 133.9(CH); 131.8(C); 130.7 (C); 127.2(CH); 126.8(CH); 126.8(CH); 121.2(CH); 117.3(C); 110.9(CH); 74.8(CH); 66.6(CH_2); 38.1(CH); HRMS: $[M+H]^+$ m/z calculated for $C_{19}H_{11}NO_6$: 363.0869, $[M+H]^+$ m/z found: 363.0900.

4.11. Substance ***11c***

Flash chromatography eluent: AcOEt–Hex 20:80; mp 241 °C; ^{1}H NMR (400 MHz, $CDCl_3$), δ (ppm): 8.21–8.13 (2H, m); 7.99 (1H, s); 7.97 (1H, d, $J = 8.6$ Hz); 7.82–7.73 (2H, m); 6.95 (1H, d, $J = 8,3$ Hz); 5.77 (1H, d, $J = 6,8$ Hz); 4.61 (1H, dd, $J = 5.1$ and 11.3 Hz); 3.89 (3H, s); 3.82 (1H, t, $J = 11.0$ Hz); 3.68–3.63 (1H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 183.2(C); 179.1(C); 166.4(C); 162.7(C); 157.2(C); 134.7(CH); 133.6(CH); 132.5(CH); 131.8(C); 130.6(C); 126.6(CH); 126.6(CH); 126.6(CH); 126.4(CH); 125.6(C); 123.6(C); 117.6(C); 110.5(CH); 73.5(CH); 66.8(CH_2); 51.9(CH_3); 37.9 (CH); HRMS: $[M+H]^+$ m/z calculated for $C_{21}H_{14}O_6$: 393.1338, $[M+H]^+$ m/z found: 393.1329.

4.12. Substance ***13a***

Flash chromatography eluent: AcOEt–Hex 5:95; ^{1}H NMR ($CDCl_3$, 400 MHz):δ (ppm): 8.13–8.06 (2H, m); 7.54–7.39 (2H, m);

7.34–7.20 (2H, m); 6.97–6.87 (2H, m); 5.98 (1H, d, $J = 6.9$ Hz); 4.39 (1H, dd, $J = 11.0$ and 4.8 Hz), 4.17 (3H, s); 3.98–3.82 (4H, m); 3.74–3.63 (1H, m). ^{13}C NMR ($CDCl_3$, 100 MHz): δ (ppm): 159.6(C); 153.4(C); 144.4(C); 138.8(C); 129.7(C); 129.2(CH); 127.1(C); 126.9 (CH); 124.5(CH); 124.1(CH); 123,5(C); 122.5(CH); 121.7(CH); 120.9 (CH); 114.8(C); 110.2(CH); 75.0(CH_3); 66.8(CH_2); 61.2(CH_3); 40.3 (CH). MS: m/z [M^+] 334; HRMS: $[M+H]^+$ m/z calculated for $C_{21}H_{20}O_4$, 305.0814 $[M+H]^+$ m/z found: 305.0890.

4.13. **13.** *Substance* ***13b***

Flash chromatography eluent: AcOEt–Hex 10:90; mp 210 °C; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 8.30$–8.06 (4H, m), 7.52 (1H, t, $J = 7.7$ Hz); 7.44 (1H t, $J = 8.1$ Hz); 6.88 (1H, d, $J = 8.8$ Hz); 6.27 (1H, d, $J = 7.8$ Hz); 4.39 (1H, dd, $J = 4.7$ and 11.3 Hz); 4.16 (3H, s); 4.04 (1H, dd, $J = 8.2$ and 11.2 Hz); 3.95 (3H, s); 3.91–3.88 (1H, m); ^{13}C NMR (100 MHz, $CDCl_3$), δ (ppm): 164.7(C); 153.1(C); 144.0(C); 142.1(C); 138.8(C) 129.7(C); 128.4(C); 127.3(CH); 126.6(CH); 124.5(CH); 123.4 (C); 122.4(CH); 121.7(CH); 121.0(CH); 113.4(C); 109.8(CH); 77.2(CH); 66.6(CH_2); 64.0(CH_3); 61.9 (CH_3); 39.7(CH); HRMS: $[M+H]^+$ m/z calculated for $C_{21}H_{19}NO_6$, 350.0665, $[M+H]^+$ m/z found: 350.0623.

4.14. *Substance* ***13c***

Flash chromatography eluent: AcOEt–Hex 10:90; mp 145 °C; ^1H NMR (400 MHz, $CDCl_3$):$\delta = 8.12$–8.01 (2H, m); 8.02 (1H, s); 7.96 (1H, d, $J = 8.4$ Hz); 7.51 (1H, t, $J = 7.2$ Hz); 7.42 (1H, t, $J = 7.8$ Hz); 6.88 (1H, d, $J = 8.4$ Hz); 4.39 (1H, dd, $J = 11.2$ e 4.8 Hz); 4.17 (3H, s); 3.95 (3H, s); 3.90–3.87 (4H, m); 3.81–3.76 (1H, m); ^{13}C NMR (100 MHz, $CDCl_3$), δ (ppm): 166.8 (C); 163.6(C); 153.3(C); 144.3(C); 138.8(C); 132.2 (CH); 129.7(C); 127.5(C); 127.3(CH); 126.6(CH); 124.4(CH); 123.5(C); 123.3 (C); 122.5(CH); 121.7(CH); 114.12(C); 109.9(CH); 76.2(CH); 66.7(CH_2); 64.1(CH_3); 61.5 (CH_3); 52.0(CH_3); 39.8(CH); HRMS: $[M+H]^+$ m/z calculated for $C_{23}H_{22}O_6$, 363.0869, $[M+H]^+$ m/z found: 363.0900.

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Appendix. Supplementary material

Experimental procedure and spectroscopy data. This material is available free of charge via the Internet at http://pubs.acs.org. Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.jorganchem.2010.05.014.

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