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Palladium-catalyzed oxidative arylation of trisubstituted olefin: an efficient synthesis of 3-(disubstituted)alkylidene-oxindoles

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ABSTRACT

A palladium-catalyzed oxidative arylation of 3-(monosubstituted)alkylidene-oxindoles with arenes afforded 3-(disubstituted)alkylidene-oxindoles in good to moderate yields.

The palladium-catalyzed Mizoroki–Heck arylation of olefins with aryl halides has become a well-established synthetic method for C–C bond-formation.[1] However, the normal intermolecular Heck reaction did not work well for the synthesis of tetrasubstituted olefins due to the reluctance of trisubstituted olefins to participate in the carbopalladation process.[1] Increased steric crowdedness during the insertion of ArPdL species to the hindered olefin might be an important reason for the failure. As a powerful variant of the Heck reaction, a palladium(II)-catalyzed oxidative arylation of olefins with arenes has attracted much attention.[2] The oxidative cross-coupling between olefins and arenes, commonly known as the Fujiwara–Moritani reaction or simply dehydrogenative Heck reaction, circumvents the use of preformed or less readily accessible aryl halides. However, the reaction also did not work well for the synthesis of highly-substituted olefins.[2] Thus, the stereo- and regioselective synthesis of highly-substituted olefins is very challenging, and a very limited number of papers have been reported.[3]

The synthesis of 3-alkylidene-oxindoles has been extensively studied due to their diverse biological importance.[4–7] These compounds could be synthesized by many ways including the Knoevenagel type condensation reaction between oxindole and carbonyl compounds; however, the yield of product was low to moderate in most cases even under drastic conditions.[4a,h,5b–d] Thus, as an alternative method, 3-(disubstituted)alkylidene-oxindoles have been prepared most frequently by a palladium-catalyzed cyclization of *N*-arylpropiolamide derivatives, as shown in Scheme 1.[6,7] Zhu and co-workers have reported the synthesis of 3-(diarylmethylenyl)oxindole by a palladium-catalyzed domino carbopalladation/C–H activation/C–C bond-forming process.[6a] Li and co-workers have extended the scope of this reaction to a direct use of arenes instead of aryl halides.[6d] Other research groups including Player,[6h] Takemoto,[6i–k] and Hayashi[7b] have also used similar approaches involving the use of *N*-arylpropiolamide derivatives. However, a palladium-catalyzed arylation of 3-(monosubstituted)alkylidene-oxindole derivatives has not been reported. During the course of our recent studies on the Pd-catalyzed oxidative arylation of electron-deficient trisubstituted alkenes,[8] we found that the use of an electrophilic $ArPd^+$ intermediate, generated under the influence of AgOAc/PivOH, and the assistance of a chelation in the alkylpalladium intermediate were crucial for the successful arylation. We thought that the trisubstituted alkenyl moiety of 3-(monosubstituted)alkylidene-oxindoles could fulfill such requirements, and we decided to examine their arylation, as shown in Scheme 1.

At the outset of our study, we selected (*E*)-ethyl 2-(1-methyl-2-oxoindolin-3-ylidene)acetate (**1a**) as a model compound and examined a palladium-catalyzed phenylation with iodobenzene, as shown in Table 1. The reaction of **1a** and iodobenzene in the presence of $Pd(OAc)_2/PPh_3/Et_3N$ in DMF (entry 1) afforded very low yield (15%) of product (**2a**:**3a** = 3:1). The yield was not improved by modifying the reaction conditions including base and solvent (entries 2–4). The yield of product increased to 65% under the conditions of Chen and co-workers employing AgOAc in acetic acid (entry 5);[1b] however, the yield was not still satisfactory. Thus

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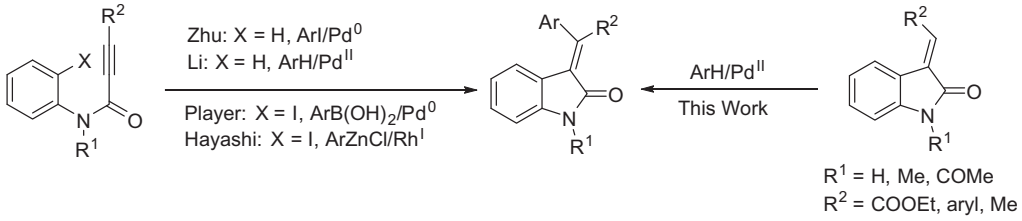
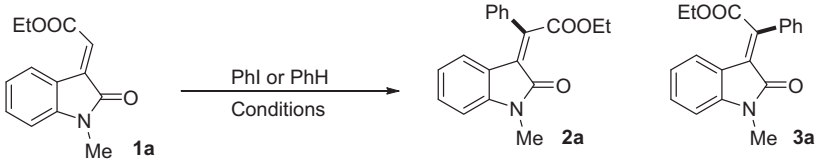


Scheme 1.

Table 1
Optimization of phenylation of **1a**



Entry	Conditions[a]	**2a**+**3a**[b] (%)
1	PhI (2.0 equiv), $Pd(OAc)_2$ (5 mol %), PPh_3 (10 mol %), Et_3N (2.0 equiv), DMF, 100 °C, 5 h	15[c]
2	PhI (2.0 equiv), $Pd(OAc)_2$ (5 mol %), PPh_3 (10 mol %), K_2CO_3 (2.0 equiv), DMF, 100 °C, 10 h	45
3	PhI (2.0 equiv), $Pd(OAc)_2$ (5 mol %), PPh_3 (10 mol %), K_2CO_3 (2.0 equiv), CH_3CN, reflux, 36 h	30[d]
4	PhI (2.0 equiv), $Pd(OAc)_2$ (5 mol %), TBAC (1.0 equiv), K_2CO_3 (2.0 equiv), DMF, 100 °C, 5 h	o[c]
5	PhI (2.0 equiv), $Pd(OAc)_2$ (5 mol %), AgOAc (1.1 equiv), AcOH (50 equiv), reflux, 5 h	65
6	Benzene (60 equiv), Pd(OAc)2 (5 mol %), AgOAc (2.5 equiv), PivOH (6.0 equiv), reflux, 36 h	34[e]
7	**Benzene** (**60** equiv), **$Pd(OAc)_2$** (**5** mol %), **AgOAc** (**4.5** equiv), **PivOH** (**6.0** equiv), **reflux**, **24 h**	**92**[f]
8	Benzene (60 equiv), $Pd(OAc)_2$ (10 mol %), AgOAc (3.5 equiv), PivOH (6.0 equiv), reflux, 24 h	89
9	Benzene (60 equiv), $Pd(OAc)_2$ (10 mol %), AgOAc (2.5 equiv), PivOH (6.0 equiv), reflux, 28 h	78
10	Benzene (60 equiv), $Pd(TFA)_2$ (5 mol %), AgOAc (2.5 equiv), PivOH (6.0 equiv), reflux, 36 h	72

[a] Substrate **1a** (0.5 mmol) was used.
[b] Isolated yield and the ratio of **2a**/**3a** is 3:1 ~ 4:1 (based on ^1H NMR).
[c] Severe decomposition.
[d] **1a** was recovered in 38%.
[e] **1a** was recovered in 48%.
[f] Isolated yield of **2a** (74%) and **3a** (18%).

we examined Pd(II)-catalyzed oxidative phenylation conditions with benzene in the presence of AgOAc and PivOH (entries 6–10).[8] Most of the entries afforded good yields of products; however, an excess use of AgOAc and/or the use of 10 mol % of $Pd(OAc)_2$ were crucial in order to obtain satisfactory yields of products.

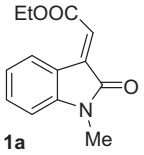
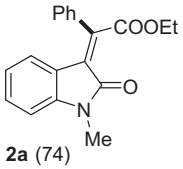
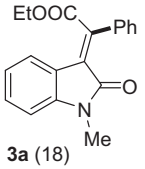
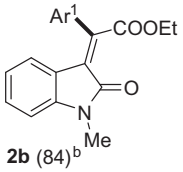
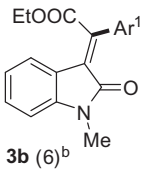
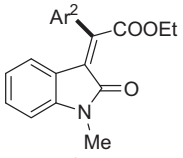
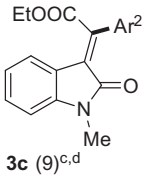
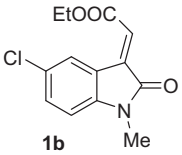
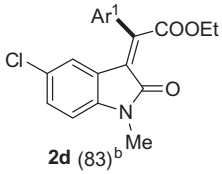
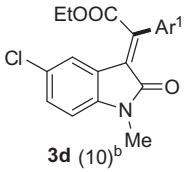
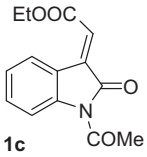
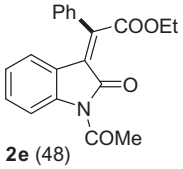
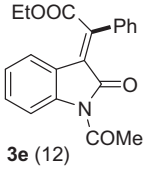
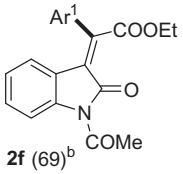
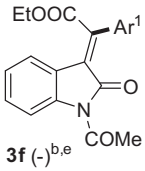
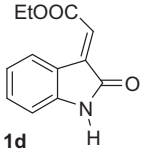
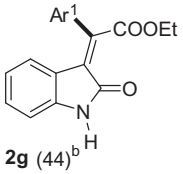
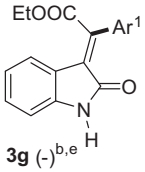
Although an excess amount of AgOAc was required, we selected the condition of entry 7 as an optimum one and examined the arylation of **1a**–**d**,[9] as shown in Table 2. The reaction of **1a** and *p*-xylene afforded **2b** as a major product in high yield (84%) along with a low yield (6%) of **3b** (entry 2). The reaction of **1a** and *o*-xylene produced **2c** (78%) and **3c** (9%) in good combined yield (entry 3); however, a trace amount of the corresponding regioisomer (2,3-dimethylphenyl derivative) was formed together. The reactions of 5-chloro derivative **1b** (entry 4), *N*-acetyl derivative **1c** (entries 5 and 6), and even NH derivative **1d** (entry 7) afforded the corresponding products in good to moderate yields (44–93%).[10]

The mechanism for the formation of **2a** and **3a** could be proposed, as shown in Scheme 2. The formation of the major product **2a** might follow a typical Heck mechanism, that is a syn-carbopalladation of **1a** with PhPd(OPiv) to form a C-Pd intermediate **I**, rotation around the C-C single bond, and a syn β-H elimination process. The minor compound **3a** could be formed from another C-Pd intermediate **III** that might be formed by an epimerization process via an *O*-Pd intermediate **II**. Such a stereomutation has been frequently observed in many examples[11] and caused the formation of a mixture of stereoisomers (vide infra). The stereochemistry of the major isomer was confirmed, **2d** as an example (shown in Scheme 2), by NOE experiments.

In order to examine the scope of the arylation reaction we tried the arylation of 3-arylidene and 3-alkylidene-oxindoles **1e**–**i**,[9,5e] and the results are summarized in Table 3. As shown in Table 3, the reactions of 3-arylidene-oxindoles **1e**–**h** (entries 1–4) required a longer reaction time and afforded lower yields of 3-(diarylmethylenyl)oxindoles than the ethoxycarbonylmethylene derivatives **1a**–**d**. It is interesting to note that aryl–aryl coupling products **4h** and **4i** were formed in low yields (entries 1 and 2). The plausible mechanism for the formation of **4h** is shown in Scheme 3 (vide infra). The corresponding aryl–aryl coupling products were also formed at the right position on TLC in other entries (entries 3 and 4); however, they could not be isolated in pure states because the corresponding cis/trans isomers showed very close mobility on TLC. In the reactions of **1g** and **1h** (entries 3 and 4), the minor isomers **3j** and **3k** were formed in an increased amount than the ethoxycarbonylmethylene derivatives **1a**–**d** (Table 2) presumably due to a partial double bond isomerization of starting material to the *Z*-isomer under the reaction conditions.[6g] The reaction of ethylidene derivative **1i** (entry 5) showed very close reactivity to that of **1a**.

The mechanism for the formation of 3-fluoren-9-ylidene-oxindole derivatives **4h** and **4i** could be proposed with **4h** as an example, as shown in Scheme 3. The carbopalladation of **1e** with PhPd(OPiv) produced an alkylpalladium intermediate **IV**. As reported by many research groups,[12] 1,4-palladium migration from alkyl to aryl moiety produced an arylpalladium intermediate **V**. A subsequent aryl–aryl coupling of **V** to form **VI** and the following Pd(II)-mediated dehydrogenation[13] via **VII** furnished the product **4h**. An oxidation of Pd(0) to Pd(II) by AgOAc might carry out the

Table 2
Pd-catalyzed oxidative arylation of **1a–d**[a]

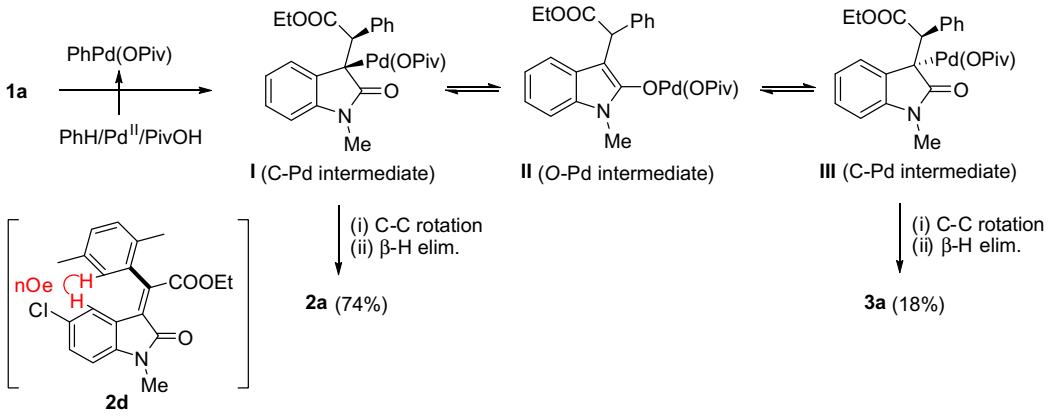
Entry	Substrate	Conditions	Product (%)	
1	 **1a**	Benzene reflux, 24 h	 **2a** (74)	 **3a** (18)
2	**1a**	*p*-Xylene 110 °C, 20 h	 **2b** (84)[b]	 **3b** (6)[b]
3	**1a**	*o*-Xylene 110 °C, 12 h	 **2c** (78)[c]	 **3c** (9)[c,d]
4	 **1b**	*p*-Xylene 110 °C, 12 h	 **2d** (83)[b]	 **3d** (10)[b]
5	 **1c**	Benzene reflux, 20 h	 **2e** (48)	 **3e** (12)
6	**1c**	*p*-Xylene 110 °C, 12 h	 **2f** (69)[b]	 **3f** (-)[b,e]
7	 **1d**	*p*-Xylene 110 °C, 20 h	 **2g** (44)[b]	 **3g** (-)[b,e]

[a] **1a–d** (0.5 mmol), arene (60 equiv), $Pd(OAc)_2$ (5 mol %), AgOAc (4.5 equiv), PivOH (6.0 equiv).
[b] Ar^1 is 2,5-dimethylphenyl.
[c] Ar^2 is 3,4-dimethylphenyl.
[d] A trace amount (<5%) of regioisomer (Ar^2 = 2,3-dimethylphenyl) was contaminated.
[e] Failed to isolate.

catalytic cycle. The reaction of **2h** under the same reaction conditions did not produce **4h** at all. The result supports the involvement of a palladium migration mechanism.

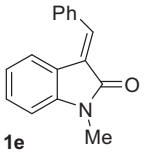
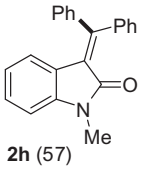
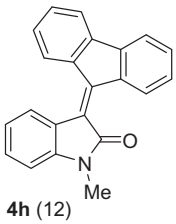
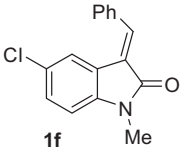
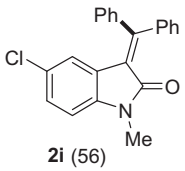
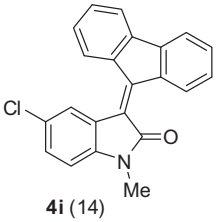
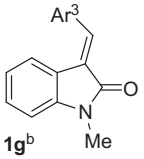
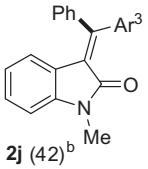
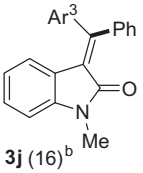
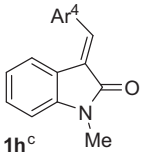
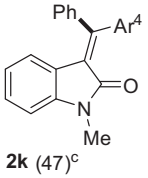
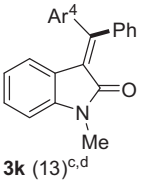
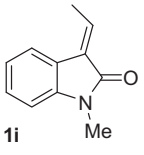
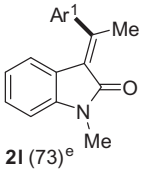
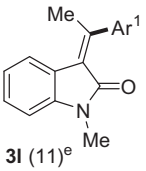
The importance of a carbonyl group at the 2-position of oxindoles **1a–i** was demonstrated by the following comparison experiments with **1j**[9g] and **1k**[9e] (Scheme 4). The reaction of **1j** and benzene under the same conditions did not produce **2m** in any trace amount. The starting material **1j** was recovered in 61% yield after 40 h. To the contrary, the reaction of **1k** afforded **2n** (82%) and **4n** (6%) in good combined yield. The results stated that the carbonyl group at the 2-position of **1a–i** and **1k** might facilitate both coordination and insertion of ArPdL species to the C=C double bond,[8] as shown in Scheme 4.

In summary, an efficient synthesis of 3-(disubstituted) alkylidene-oxindoles was carried out in good to moderate yields by a palladium-catalyzed oxidative arylation of 3-(monosubstituted)alkylidene-oxindoles with arenes. The carbonyl group at the 2-position of oxindoles might facilitate both coordination and insertion of arylpalladium species to the trisubstituted C=C double bond.

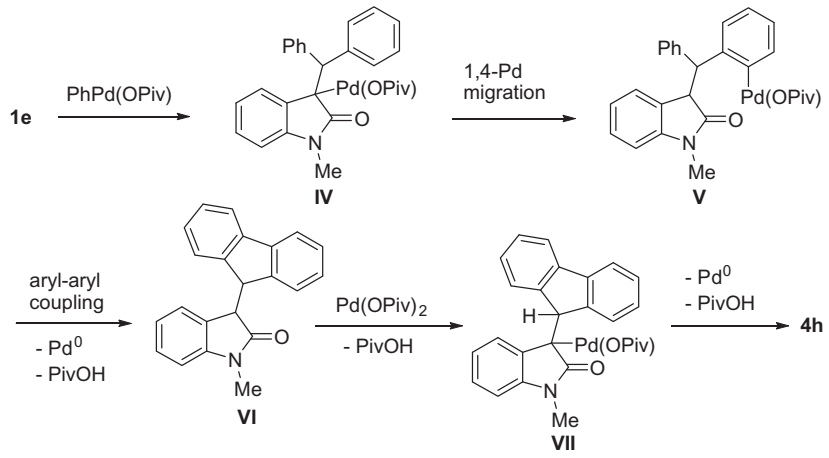


Scheme 2.

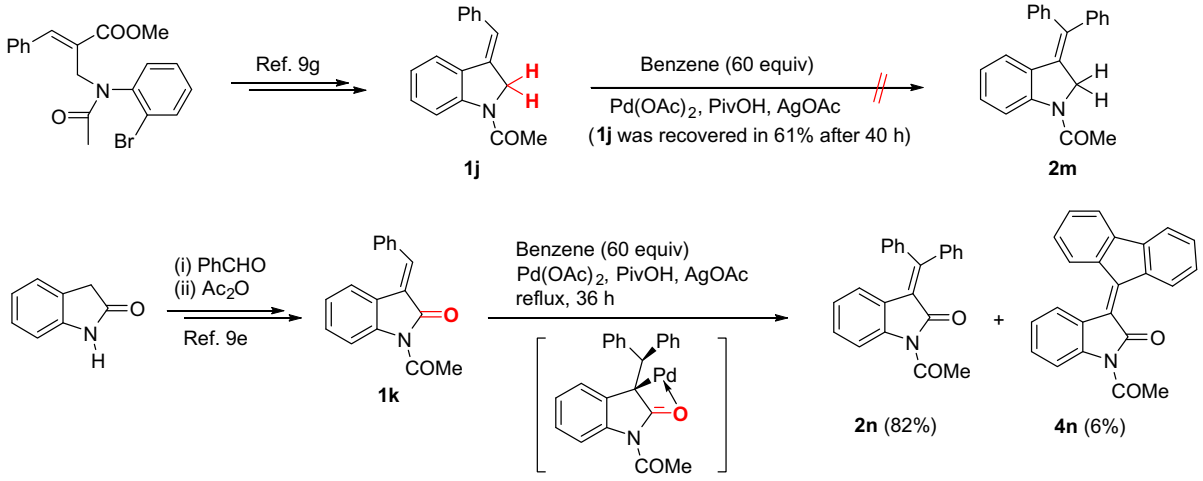
Table 3
Pd-catalyzed oxidative arylation of **1e–i**[a]

Entry	Substrate	Conditions	Product (%)	
1	 **1e**	Benzene reflux, 36 h	 **2h** (57)	 **4h** (12)
2	 **1f**	Benzene reflux, 45 h	 **2i** (56)	 **4i** (14)
3	 **1g**[b]	Benzene reflux, 45 h	 **2j** (42)[b]	 **3j** (16)[b]
4	 **1h**[c]	Benzene reflux, 45 h	 **2k** (47)[c]	 **3k** (13)[c,d]
5	 **1i**	*p*-Xylene 110 °C, 12 h	 **2l** (73)[e]	 **3l** (11)[e]

[a] **1e–h** (0.5 mmol), arene (60 equiv), $Pd(OAc)_2$ (5 mol %), AgOAc (4.5 equiv), PivOH (6.0 equiv).
[b] Ar^3 is 4-chlorophenyl.
[c] Ar^4 is 4-methoxyphenyl.
[d] A trace amount (ca. 5%) of remaining **1h** was contaminated.
[e] Ar^1 is 2,5-dimethylphenyl.



Scheme 3.



Scheme 4.

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Compound ***1f***: pale yellow solid, mp 140–142 °C; IR (KBr) 1703, 1608, 1482, 1270 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 3.15 (s, 3H), 6.62 (d, J = 8.4 Hz, 1H), 7.11 (dd, J = 8.4 and 2.1 Hz, 1H), 7.31–7.43 (m, 3H), 7.45–7.54 (m, 3H), 7.78 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 26.25, 108.96, 122.42, 122.76, 126.28, 127.09, 128.80, 129.21, 129.33, 129.99, 134.39, 138.80, 142.66, 168.04; ESIMS m/z 270 $[M+H]^+$, 272 $[M+H+2]^+$. Anal. Calcd for $C_{16}H_{12}ClNO$: C, 71.25; H, 4.48; N, 5.19. Found: C, 71.41; H, 4.33; N, 5.08.
10. *Typical procedure for the synthesis of* ***2a*** *and* ***3a***: A stirred mixture of **1a** (116 mg, 0.5 mmol), $Pd(OAc)_2$ (5.6 mg, 5 mol %), AgOAc (377 mg, 2.25 mmol), and PivOH (307 mg, 3.0 mmol) in benzene (2.7 mL, 60 equiv) was heated to reflux for 24 h under N_2 balloon atmosphere. After the aqueous extractive workup and column chromatographic purification process (hexanes/Et_2O, 2:1) compounds **2a** (114 mg, 74%) and **3a** (28 mg, 18%) were obtained as pale yellow oils. Other compounds were synthesized similarly, and the selected spectroscopic data of **2a**, **3a**, **2e**, **3e**, **2g**, **2h**, **4h**, **2l**, **3l**, and **4n** are as follows.
Compound ***2a***: 74%; pale yellow oil; IR (film) 1712, 1609, 1470, 1256, 1230 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.28 (t, J = 7.2 Hz, 3H), 3.15 (s, 3H), 4.32 (q, J = 7.2 Hz, 2H), 6.62–6.74 (m, 3H), 7.11–7.18 (m, 1H), 7.37–7.45 (m, 3H), 7.45–7.52 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 13.90, 25.91, 61.94, 108.15, 120.54, 121.83, 123.36, 125.42, 127.91, 129.05, 129.75, 130.32, 133.66, 141.47, 144.39, 166.18, 168.03; ESIMS m/z 308 $[M+H]^+$. Anal. Calcd for $C_{19}H_{17}NO_3$: C, 74.25; H, 5.58; N, 4.56. Found: C, 74.51; H, 5.63; N, 4.36.
Compound ***3a***: 18%; pale yellow oil; IR (film) 1713, 1607, 1470, 1262 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.28 (t, J = 7.2 Hz, 3H), 3.08 (s, 3H), 4.34 (q, J = 7.2 Hz, 2H), 6.73 (d, J = 7.8 Hz, 1H), 6.94 (td, J = 7.8 and 1.2 Hz, 1H), 7.25 (td, J = 7.8 and 1.2 Hz, 1H), 7.29 (d, J = 7.8 Hz, 1H), 7.32–7.38 (m, 3H), 7.40–7.48 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 13.95, 25.83, 62.15, 108.16, 120.60, 122.16, 122.76, 124.85, 128.14, 128.53, 129.36, 130.43, 133.23, 141.26, 143.79, 165.97, 167.70; ESIMS m/z 308 $[M+H]^+$. Anal. Calcd for $C_{19}H_{17}NO_3$: C, 74.25; H, 5.58; N, 4.56. Found: C, 74.21; H, 5.75; N, 4.48.
Compound ***2e***: 48%; pale yellow solid, mp 142–144 °C; IR (KBr) 1730, 1600, 1461, 1277, 1241 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.28 (t, J = 7.2 Hz, 3H), 2.65 (s, 3H), 4.33 (q, J = 7.2 Hz, 2H), 6.70–6.85 (m, 2H), 7.17–7.24 (m, 1H), 7.38–7.51 (m, 5H), 8.18 (d, J = 8.4 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 13.86, 26.80, 62.10, 116.63, 121.08, 122.93, 124.29, 124.50, 127.65, 129.30, 130.14, 130.77, 133.27, 140.63, 143.04, 166.53, 167.73, 170.59; ESIMS m/z 336 $[M+H]^+$. Anal. Calcd for $C_{20}H_{17}NO_4$: C, 71.63; H, 5.11; N, 4.18. Found: C, 71.87; H, 5.36; N, 4.03.
Compound ***3e***: 12%; pale yellow solid, mp 154–156 °C; IR (KBr) 1723, 1600, 1463, 1285, 1241 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.28 (t, J = 7.2 Hz, 3H), 2.51 (s, 3H), 4.35 (q, J = 7.2 Hz, 2H), 7.11 (td, J = 7.8 and 1.2 Hz, 1H), 7.27–7.47 (m, 7H), 8.23 (d, J = 8.1 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 13.91, 26.95, 62.43, 116.70, 121.24, 122.11, 123.43, 124.88, 128.30, 128.40, 129.75, 130.84, 133.09, 139.91, 142.83, 166.15, 167.35, 170.73; ESIMS m/z 336 $[M+H]^+$. Anal. Calcd for $C_{20}H_{17}NO_4$: C, 71.63; H, 5.11; N, 4.18. Found: C, 71.92; H, 5.47; N, 4.16.
Compound ***2g***: 44%; pale yellow oil; IR (film) 3271, 1728, 1615, 1467, 1241 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.30 (t, J = 7.2 Hz, 3H), 2.22 (s, 3H), 2.27 (s, 3H), 4.30 (q, J = 7.2 Hz, 2H), 6.15 (d, J = 7.8 Hz, 1H), 6.62 (td, J = 7.8 and 1.2 Hz, 1H), 6.75 (d, J = 7.8 Hz, 1H), 7.04–7.17 (m, 4H), 8.91 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 13.92, 18.94, 20.91, 61.80, 110.02, 121.64, 122.22, 123.60, 126.78, 127.56, 130.06, 130.28, 130.59, 132.78, 133.11, 136.32, 141.34, 141.80, 167.86, 167.92; ESIMS m/z 322 $[M+H]^+$. Anal. Calcd for $C_{20}H_{19}NO_3$: C, 74.75; H, 5.96; N, 4.36. Found: C, 74.58; H, 6.12; N, 4.19.
Compound ***2h***:[6e,7b] 57%; pale yellow solid, mp 160–162 °C; IR (KBr) 1701, 1607, 1470, 1258 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 3.11 (s, 3H), 6.34 (d, J = 7.5 Hz, 1H), 6.59 (td, J = 7.5 and 1.2 Hz, 1H), 6.67 (d, J = 7.5 Hz, 1H), 7.08 (td, J = 7.5 and 1.2 Hz, 1H), 7.18–7.40 (m, 10H); ESIMS m/z 312 $[M+H]^+$.
Compound ***4h***: 12%; reddish solid, mp 156–158 °C; IR (KBr) 1691, 1606, 1471, 1261 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 3.25 (s, 3H), 6.76 (d, J = 7.8 Hz, 1H), 6.89 (td, J = 7.8 and 1.2 Hz, 1H), 7.08 (td, J = 7.8 and 1.2 Hz, 1H), 7.14–7.33 (m, 4H), 7.47–7.55 (m, 2H), 8.06 (d, J = 7.8 Hz, 1H), 8.31 (d, J = 7.8 Hz, 1H), 9.03 (dd, J = 7.8 and 1.2 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 26.10, 108.25, 119.31, 119.97, 121.25, 122.82, 125.11, 126.56, 126.94, 127.46, 128.10, 129.16, 130.22, 131.18, 131.23, 137.48, 137.84, 141.51, 143.11, 144.07, 148.87, 167.64; ESIMS m/z 310 $[M+1]^+$. Anal. Calcd for $C_{22}H_{15}NO$: C, 85.41; H, 4.89; N, 4.53. Found: C, 85.23; H, 5.02; N, 4.37.
Compound ***2l***: 73%; pale yellow oil; IR (film) 1700, 1607, 1470, 1254 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.02 (s, 3H), 2.25 (s, 3H), 2.67 (s, 3H), 3.19 (s, 3H), 5.83 (d, J = 7.8 Hz, 1H), 6.56 (td, J = 7.8 and 1.2 Hz, 1H), 6.66 (d, J = 7.8 Hz, 1H), 6.79 (s, 1H), 7.00–7.14 (m, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 18.32, 20.91, 21.97, 25.59, 107.26, 121.68, 122.32, 122.69, 123.46, 126.15, 127.94, 128.70, 129.98, 130.53, 136.29, 142.06, 142.09, 154.75, 167.96; ESIMS m/z 278 $[M+H]^+$. Anal. Calcd for $C_{19}H_{19}NO$: C, 82.28; H, 6.90; N, 5.05. Found: C, 82.34; H, 6.68; N, 4.94.
Compound ***3l***: 11%; pale yellow oil; IR (film) 1709, 1607, 1469, 1255 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.08 (s, 3H), 2.25 (s, 3H), 2.48 (s, 3H), 3.06 (s, 3H), 6.72–6.80 (m, 2H), 6.94–7.10 (m, 3H), 7.23 (td, J = 7.8 and 1.2 Hz, 1H), 7.60 (d, J = 7.8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 18.88, 21.09, 24.61, 25.58, 107.68, 121.61, 123.09, 123.74, 123.98, 126.18, 128.11, 128.37, 129.83, 130.10, 135.15, 142.90, 143.36, 152.84, 166.02; ESIMS m/z 278 $[M+H]^+$. Anal. Calcd for $C_{19}H_{19}NO$: C, 82.28; H, 6.90; N, 5.05. Found: C, 82.41; H, 7.05; N, 5.12.
Compound ***4n***: 6%; reddish solid; mp 212–214 °C (dec.); IR (KBr) 1717, 1598, 1460, 1276 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.72 (s, 3H), 7.00–7.12 (m, 2H), 7.14–7.38 (m, 4H), 7.40–7.54 (m, 2H), 8.10 (d, J = 8.1 Hz, 1H), 8.23 (d, J = 8.1 Hz, 1H), 8.28 (d, J = 7.8 Hz, 1H), 8.69 (d, J = 7.8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 27.09, 116.71, 119.64, 120.15, 124.02, 124.05, 124.70, 125.75, 126.08, 127.29, 128.18, 129.36, 130.61, 131.82, 132.00, 137.17, 137.42, 139.96, 142.08, 143.12, 150.56, 167.28, 171.05; ESIMS m/z 338 $[M+H]^+$. Anal. Calcd for $C_{23}H_{15}NO_2$: C, 81.88; H, 4.48; N, 4.15. Found: C, 81.74; H, 4.66; N, 4.01.
11. For the stereo-mutation via an *O*-Pd intermediate, see: (a) Ikeda, M.; El Bialy, S. A. A.; Yakura, T. *Heterocycles* **1999**, *51*, 1957–1970. and further references cited therein; (b) Cropper, E. L.; White, A. J. P.; Ford, A.; Hii, K. K. *J. Org. Chem.* **2006**, *71*, 1732–1735. When we subjected the reaction mixture of **1a** for a longer time (48 h) the ratio between **2a** and **3a** was not changed. In addition, we could not observe the formation of **3a** in any trace amount when we subjected **2a** to the palladium-catalyzed arylation reaction conditions. The results stated that the possibility for the Pd-catalyzed isomerization between **2a** and **3a** would be low.
12. For the alkyl to aryl 1,4-palladium migration, see: (a) Huang, Q.; Fazio, A.; Dai, G.; Campo, M. A.; Larock, R. C. *J. Am. Chem. Soc.* **2004**, *126*, 7460–7461; (b) Wang, L.; Pan, Y.; Jiang, X.; Hu, H. *Tetrahedron Lett.* **2000**, *41*, 725–727; (c) Ma, S.; Gu, Z. *Angew. Chem., Int. Ed.* **2005**, *44*, 7512–7517. and further references cited therein.
13. For Pd(II)-catalyzed oxidation of α,β-position of carbonyl compounds, see: (a) Muzart, J. *Eur. J. Org. Chem.* **2010**, 3779–3790. and further references cited therein; (b) Giri, R.; Maugel, N.; Foxman, B. M.; Yu, J.-Q. *Organometallics* **2008**, *27*, 1667–1670.