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Palladium-catalyzed arylation of methyl 2-(acetoxymethyl)acrylate: a convenient synthesis of rearranged Morita–Baylis–Hillman acetates

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ABSTRACT

Palladium-catalyzed arylation of methyl 2-(acetoxymethyl)acrylate with aryl iodides afforded the primary acetates of Morita–Baylis–Hillman adducts in good yields with high stereoselectivity under mild conditions (50 °C).

Very recently, a palladium-catalyzed chelation-assisted arylation of allyl acetate has been examined extensively to provide cinnamyl acetate via the selective β-H elimination process[1,2] instead of β-acetoxy elimination.[3] As shown in Scheme 1, many research groups have reported the arylation of allyl acetate with various arene sources;[1,2] however, there is no precedent reports on the arylation of allyl acetate bearing an ester group at the 2-position via the selective β-H elimination process, to the best of our knowledge.[3e–g]

During the studies on the palladium-catalyzed oxidative arylation of alkenes with arenes,[4] we presumed that the primary acetate of Morita–Baylis–Hillman (MBH) adduct **2a** could be synthesized efficiently via a Pd-catalyzed chelation-assisted arylation of methyl 2-(acetoxymethyl)acrylate (**1a**),[5,6] as shown in Scheme 1. The primary acetate **2a** has been prepared most frequently via the rearrangement of an acetoxy group from the corresponding secondary MBH acetate,[7] and this compound has been widely used in organic synthesis.[7i–k]

The starting material **1a** was prepared by the acetylation of the MBH adduct between formaldehyde and methyl acrylate as reported.[5] At the outset of our experiment, we examined the reaction of **1a** and benzene under the conditions of Jiao[1b] and Liu.[1a] However, the results of both conditions were disappointing. Compound **2a** was obtained in very low yields, 20% and 9% respectively, as shown in Table 1 (entries 1 and 2). Thus, we examined the reaction of **1a** and benzene in the presence of $Pd(TFA)_2$/AgOAc (2.5 equiv)/PivOH (entry 3).[4a–e] The yield of **2a** increased dramatically to 87%. Under the condition, a diphenyl compound **3a** was not formed even in the presence of an excess amount of AgOAc (6.0 equiv) after 48 h. Although compound **2a** was produced as an *E*/*Z* mixture (12:1), we examined the reaction with other arenes such as *p*-xylene, *o*-dichlorobenzene, *m*-dichlorobenzene, and *m*-xylene. The reaction of **1a** and *p*-xylene (entry 4) afforded **2b** in high yield (89%). However, a regioisomeric problem was observed when we used *o*-dichlorobenzene and *m*-dichlorobenzene (entries 5 and 6), although the combined yields of products were high (90–92%). When we used *m*-xylene (entry 7), an inseparable regioisomeric mixture was obtained in moderate yield (62%). The problematic regioselectivity in combination with unsatisfactory stereoselectivity reduced the synthetic applicability of this method.

Thus, we decided to examine the reaction of **1a** and iodobenzene, and the results of optimization of reaction conditions are summarized in Table 2. When we examined the conditions of Jiao employing an excess amount (2.0 equiv) of allyl acetate,[2a] compound **2a** was obtained in 80% (entry 1) with a similar stereoselectivity (*E*/*Z* = 10:1). However, compound **1a** is a valuable starting material as compared to simple allyl acetate, thus we examined the reaction with an equimolar amount of **1a** in the presence of 2.0 equiv of iodobenzene (entry 2). Then, the yield of **2a** decreased to 35%, and the results stated that both compound **1a** and allyl acetate might be destroyed to some extent under the reaction conditions. The yield of **2a** was not improved by using an excess amount of Ag_2CO_3 (entry 3). In these respects, we have to consider other reaction conditions. Literature survey suggested that the condition

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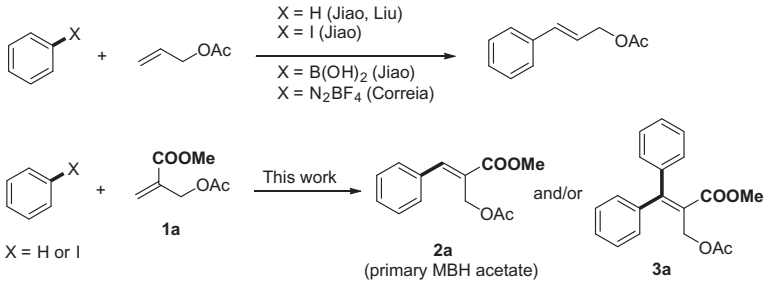
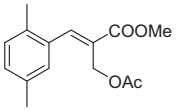
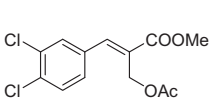
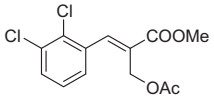
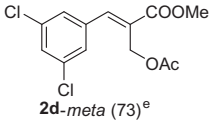
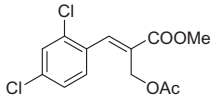
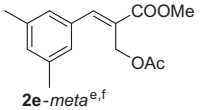
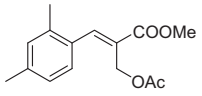


Scheme 1.

Table 1
Pd-catalyzed oxidative arylation of compound **1a**[a]

Entry	Conditions	Product[b] (%)	
1	$Pd(OAc)_2$ (5 mol%), Ag_2CO_3 (0.6 equiv), $CH_3(CH_2)_3COOH$ (16 equiv) BQ (2.0 equiv), benzene (100 equiv), reflux, 36 h	**2a** (20)	
2	$Pd(OAc)_2$ (10 mol %), AgOAc (2.0 equiv), DMSO (3.0 equiv) benzene (60 equiv), reflux, 12 h	**2a** (9)	
3	$Pd(TFA)_2$ (5 mol %), AgOAc (2.5 equiv), PivOH (6.0 equiv) benzene (60 equiv), reflux, 12 h	**2a** (87)[c]	
4	$Pd(TFA)_2$ (5 mol %), AgOAc (2.5 equiv), PivOH (6.0 equiv) *p*-xylene (60 equiv), 110 °C, 12 h	 **2b** (89)[d]	
5	$Pd(TFA)_2$ (5 mol %), AgOAc (2.5 equiv), PivOH (6.0 equiv) *o*-dichlorobenzene (60 equiv), 110 °C, 12 h	 **2c**-*meta* (52)[e]	 **2c**-*ortho* (40)[e]
6	$Pd(TFA)_2$ (5 mol %), AgOAc (2.5 equiv), PivOH (6.0 equiv) *m*-dichlorobenzene (60 equiv), 110 °C, 12 h	 **2d**-*meta* (73)[e]	 **2d**-*ortho* (17)[e]
7	$Pd(TFA)_2$ (5 mol %), AgOAc (2.5 equiv), PivOH (6.0 equiv) *m*-xylene (60 equiv), 110 °C, 12 h	 **2e**-*meta*[e,f]	 **2e**-*ortho*[e,f]

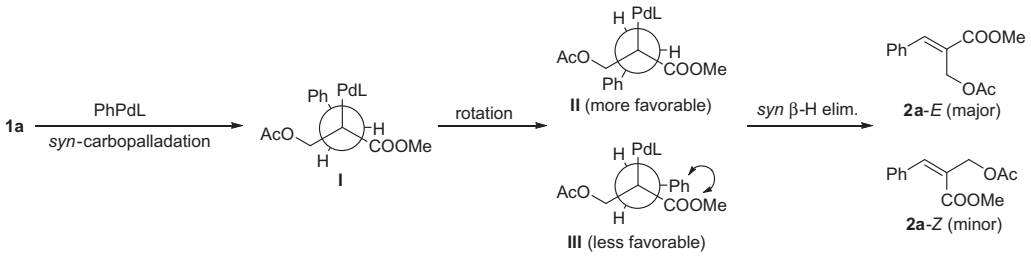
[a] Substrate **1a** (0.5 mmol).
[b] Isolated yield.
[c] *E*/*Z* ratio = 12:1.
[d] *E*/*Z* ratio = 11:1.
[e] Variable amount of *Z* isomer (ca. 5–10%) was contaminated.
[f] An inseparable mixture of **2e**-*meta* and **2e**-*ortho* (1:1) was obtained in 62% yield.

Table 2
Optimization of Pd-catalyzed arylation of **1a** with iodobenzene

Entry	Conditions	Product (%)
1	**1a** (2.0 equiv), PhI (1.0 equiv), $Pd(OAc)_2$ (5 mol %) Ag_2CO_3 (0.6 equiv), benzene, O_2 balloon, reflux, 10 h	**2a** (80) + **3a** (0)
2	**1a** (1.0 equiv), PhI (2.0 equiv), $Pd(OAc)_2$ (5 mol %) Ag_2CO_3 (0.6 equiv), benzene, O_2 balloon, reflux, 12 h	**2a** (35) + **3a** (0)
3	**1a** (1.0 equiv), PhI (2.0 equiv), $Pd(OAc)_2$ (5 mol %) Ag_2CO_3 (3.0 equiv), benzene, O_2 balloon, reflux, 12 h	**2a** (23) + **3a** (20)
4	**1a** (1.0 equiv), PhI (1.1 equiv), $Pd(OAc)_2$ (5 mol %) AgOAc (1.1 equiv), AcOH (50 equiv), reflux, 1 h	**2a** (82)[a] + **3a** (9)
5[b]	**1a** (1.0 equiv), PhI (2.1 equiv), $Pd(OAc)_2$ (5 mol %) AgOAc (3.0 equiv), AcOH (50 equiv), reflux, 3 h	**2a** (<5) + **3a** (81)
6[c]	**1a** (1.0 equiv), PhI (1.1 equiv), $Pd(OAc)_2$ (5 mol %) AgOAc (1.1 equiv), AcOH (50 equiv), 50 °C, 5 h	**2a** (86)[d] + **3a** (0)
7	**1a** (1.0 equiv), PhI (1.1 equiv), $Pd(OAc)_2$ (5 mol %) AgOAc (1.1 equiv), AcOH (50 equiv), 25 °C, 6 h	**2a** (68)[d] + **3a** (0)

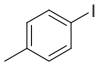
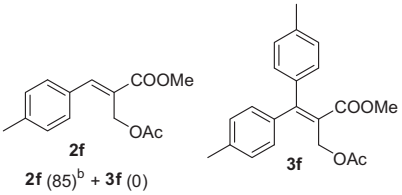
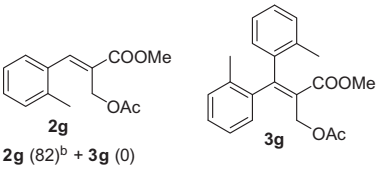
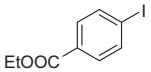
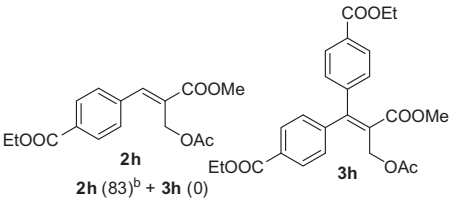
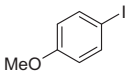
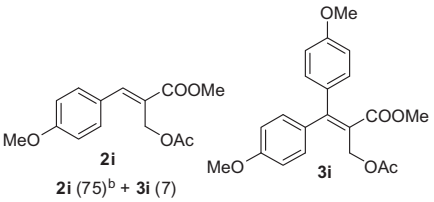
[a] *E*/*Z* = 13:1 (based on ^{1}H NMR spectrum).
[b] Selected as condition B.
[c] Selected as condition A.
[d] *E*/*Z* >32:1 (based on ^{1}H NMR spectrum).

of Chen could be a choice.[8,4a] According to Chen's condition, the reaction of **1a** and iodobenzene was examined in the presence of $Pd(OAc)_2$/AgOAc/AcOH (entry 4), and compound **2a** was obtained in good yield (82%). It is interesting to note that diaryl compound **3a** could be synthesized in high yield (81%) by increasing the amount of iodobenzene and AgOAc (entry 5).[9,10] However, the moderate stereoselectivity (*E*/*Z* = 13:1) was still a problem, although we could increase the yield of **2a** up to 82% (entry 4).



Scheme 2.

Table 3
Pd-catalyzed mono- and diarylation of **1a**

Entry	Iodoarene	Conditions[a]/time (h)	Products (%)
1		A/5 B/3	**2a** (86) [b] + **3a** (0) **2a** (<5) + **3a** (81)
2		A/12 B/5	 **2f** **3f** **2f** (85)[b] + **3f** (0) **2f** (6) + **3f** (82)
3		A/12 B/10	 **2g** **3g** **2g** (82)[b] + **3g** (0) **2g** (38) + **3g** (0)
4		A/12 B/6	 **2h** **3h** **2h** (83)[b] + **3h** (0) **2h** (5) + **3h** (79)
5		A/9 B/4	 **2i** **3i** **2i** (75)[b] + **3i** (7) **2i** (4) + **3i** (72)

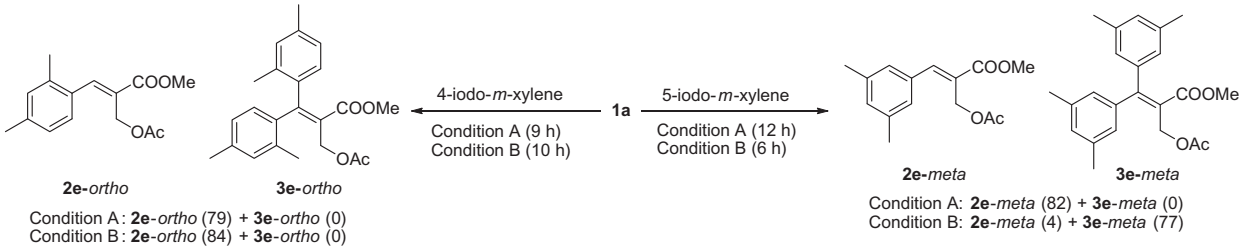
[a] Condition A: substrate **1a** (0.5 mmol), iodoarene (1.1 equiv), $Pd(OAc)_2$ (5 mol %), AgOAc (1.1 equiv), AcOH (50 equiv), 50 °C; Condition B: substrate **1a** (0.5 mmol), iodoarene (2.1 equiv), $Pd(OAc)_2$ (5 mol %), AgOAc (3.0 equiv), AcOH (50 equiv), reflux.

[b] Compounds **2a** and **2f–i** have their stereoisomers in small amounts, respectively, and the *E*/*Z* ratio was determined based on ^{1}H NMR spectrum (**2a** and **2f–h**: >32:1; **2i**: 12:1).

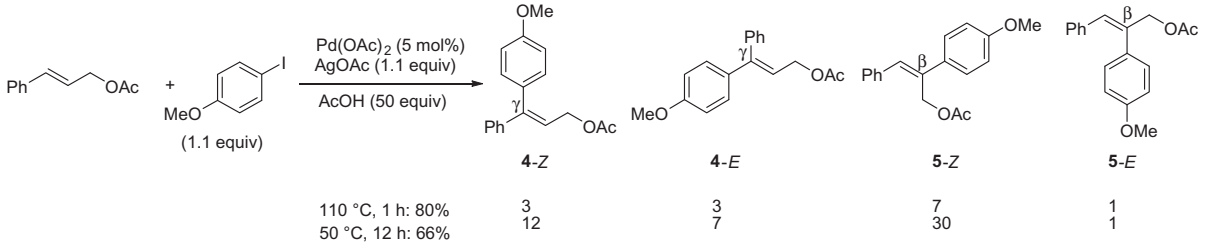
The stereoselectivity has to be improved in order to be practically useful. Thus we examined the reaction at lower temperature (entries 6 and 7). To our delight, the reaction proceeded at 50 °C (entry 6) to give **2a** in high yield (86%), and the *E*/*Z* selectivity increased to >32:1 at the temperature.[10] To our surprise, the reaction produced **2a** even at room temperature (25 °C); however, the yield was moderate (68%) as shown in entry 7.

The *E*/*Z* selectivity might be originated from the relative energy difference between the two conformers **II** and **III**, as shown in Scheme 2. The formation of **2a**-*E* as a major product could be explained as follows. *Syn*-carbopalladation of a phenylpalladium species onto the C=C double bond of **1a** to form the alkylpalladium intermediate **I**. A subsequent rotation around the C–C single bond and *syn* β-H elimination would produce **2a**. The conformer **III** is less favorable than **II** due to the presence of a steric hindrance between the phenyl group and COOMe. In order to check the size effect of acetoxymethyl group of **1a** on the stereoselectivity, we examined the reaction of 2-(benzoyloxymethyl)acrylate and iodobenzene under the optimized conditions (vide supra, 50 °C, 4 h). However, the stereoselectivity (*E*/*Z* = 24:1, 81%) of the corresponding product decreased a little as compared to that of **1a** (*E*/*Z* >32:1).

Encouraged by the results, we carried out the arylation of **1a** with various iodoarenes, and the results are summarized in Table 3. The reactions were carried out under the condition A (entry 6 in



Scheme 3.



Scheme 4.

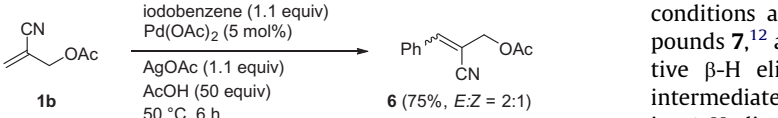
Table 2) and the condition B (entry 5 in Table 2) with some representative iodoarenes. As shown in Table 3, rearranged MBH acetates **2f**–**i** were obtained in good yields (75–85%) under the condition A. The stereochemistry of the MBH acetates **2f**–**h** was exclusively *E* (*E*/*Z* >32:1). For the *p*-methoxy derivative **2i**, the stereoselectivity was somewhat low (*E*/*Z* = 12:1) than other entries. It is interesting to note that the diaryl derivative **3i** was formed even at 50 °C, albeit in low yield (7%). In contrast, diarylated MBH acetates **3f**, **3h**, and **3i** were produced as major products (72–82%) under the condition B. However, compound **3g** was not formed presumably due to the steric hindrance between *ortho*-tolyl moieties.[2b,4d,i,8a,9a] In order to examine the feasibility for the synthesis of a differently-substituted diarylated product, we carried out the reaction of **2f** and *p*-methoxyiodobenzene (condition B, reflux, 7 h). The second arylation proceeded to give the corresponding diarylated product in good yield (70%); however, an inseparable mixture of *E*/*Z* (1:1) was produced presumably due to epimerization of the alkylpalladium intermediate.

In order to show the feasibility for the synthesis of **2e**-*meta* and **2e**-*ortho* (vide supra, entry 7 in Table 1), the reactions of **1a** and the corresponding iodoarenes were examined, as shown in Scheme 3. Both compounds **2e**-*ortho* and **2e**-*meta* were obtained in high yields with high stereoselectivity (*E*/*Z* = 33:1) under the condition A. Diarylated compound **3e**-*meta* was obtained in good yield (77%) under the condition B, whereas the reaction of 4-iodo-*m*-xylene did not produce **3e**-*ortho* due to steric reason as in the case of 2-iodotoluene (entry 3 in Table 3).

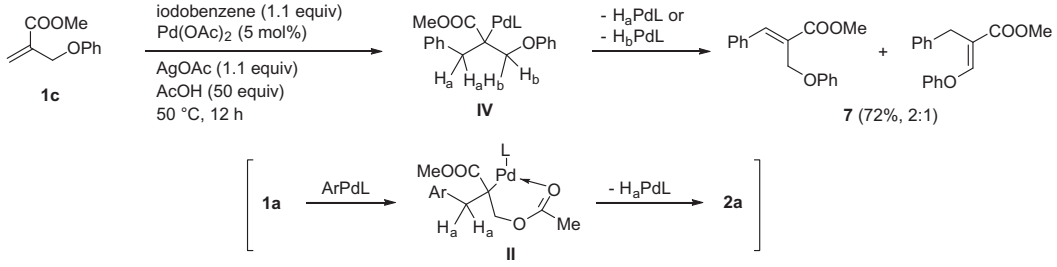
Nobody has reported the arylation of simple cinnamyl acetate, although there have been reported numerous papers on the arylation of allyl acetate.[1,2] Thus, we examined the reaction of cinnamyl acetate and *p*-methoxyiodobenzene, as shown in Scheme 4. The reaction provided four compounds. Both γ-aryl compounds (**4**-*Z* and **4**-*E*) and β-aryl compounds (**5**-*Z* and **5**-*E*) were formed together and isolated as a mixture.[11] At 110 °C, the ratio between γ-aryl and β-aryl was 3:4 while 19:31 at 50 °C. It is interesting to note that the *Z*/*E* ratio increased a little by lowering the reaction temperature.

As a next experiment, we examined the phenylation of nitrile derivative **1b**, as shown in Scheme 5. Although the phenylation reaction proceeded similarly to afford **6**[7a,g] in moderate yield (75%); however, the stereochemistry was not controlled even at 50 °C (6 h). The reason might be the small energy difference between the corresponding alkylpalladium intermediates **II** and **III** (vide supra, Scheme 2).

The reaction of phenyl allyl ether **1c** under the same reaction conditions afforded an inseparable mixture of phenylated compounds **7**,[12] as shown in Scheme 6. As compared to the regioselective β-H elimination in the case of **1a** to form **2a** via the intermediate **II** that was stabilized by chelation,[13] the corresponding β-H elimination of intermediate **IV** can happen with either H_a or H_b.



Scheme 5.



Scheme 6.

In summary, the primary acetates of Morita–Baylis–Hillman adducts were synthesized via a palladium-catalyzed arylation of methyl 2-(acetoxymethyl)acrylate with aryl iodides in good yield in a highly stereoselective manner under mild conditions (50 °C).

Acknowledgments

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10. *Typical procedure for the synthesis of* ***2a***: A mixture of **1a** (79 mg, 0.5 mmol), iodobenzene (112 mg, 1.1 equiv), $Pd(OAc)_2$ (6 mg, 5 mol%), AgOAc (92 mg, 1.1 equiv), and AcOH (1.5 g, 50 equiv) was heated to 50 °C for 5 h. After the aqueous extractive workup and column chromatographic purification process (hexanes/Et_2O, 20:1), the product **2a** was isolated as a colorless oil, 101 mg (86%). Other compounds were synthesized similarly, and the selected spectroscopic data of unknown compounds **2b**, **2e**-*meta*, **2e**-*ortho*, **2h**, **3a**, **3e**-*meta*, **3f**, and **3i** are as follows.
Compound ***2b***: 89%; colorless oil; IR (film) 1741, 1721, 1234 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.06 (s, 3H), 2.25 (s, 3H), 2.30 (s, 3H), 3.85 (s, 3H), 4.84 (s, 2H), 6.98 (s, 1H), 7.01–7.14 (m, 2H), 8.04 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 19.33, 20.79, 20.91, 52.13, 59.42, 127.17, 129.20, 129.95, 130.01, 133.31, 133.80, 135.21, 144.92, 167.05, 170.46; ESIMS *m/z* 285 $[M+Na]^+$. Anal. Calcd for $C_{15}H_{18}O_4$: C, 68.68; H, 6.92. Found: C, 68.53; H, 7.03.
Compound ***2e****-meta*: 82%; colorless oil; IR (film) 1742, 1718, 1234 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.03 (s, 3H), 2.25 (s, 6H), 3.76 (s, 3H), 4.88 (s, 2H), 6.91 (s, 2H), 6.94 (s, 1H), 7.86 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 20.83, 21.20, 52.15, 59.37, 126.13, 127.17, 131.23, 134.03, 138.13, 145.86, 167.35, 170.60; ESIMS *m/z* 285 $[M+Na]^+$. Anal. Calcd for $C_{15}H_{18}O_4$: C, 68.68; H, 6.92. Found: C, 68.85; H, 6.97.
Compound ***2e****-ortho*: 79%; colorless oil; IR (film) 1742, 1720, 1240 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.00 (s, 3H), 2.20 (s, 3H), 2.25 (s, 3H), 3.77 (s, 3H), 4.77 (s, 2H), 6.94 (d, *J* = 7.8 Hz, 1H), 6.96 (s, 1H), 7.01 (d, *J* = 7.8 Hz, 1H), 7.97 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 19.18, 20.87, 21.16, 52.13, 59.53, 126.60, 126.71, 128.66, 130.55, 131.02, 137.04, 139.48, 144.71, 167.20, 170.59; ESIMS *m/z* 285 $[M+Na]^+$. Anal. Calcd for $C_{15}H_{18}O_4$: C, 68.68; H, 6.92. Found: C, 68.59; H, 6.77.
Compound ***2h***: 83%; colorless oil; IR (film) 1742, 1721, 1243 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.40 (t, *J* = 7.2 Hz, 3H), 2.10 (s, 3H), 3.86 (s, 3H), 4.39 (q, *J* = 7.2 Hz, 2H), 4.92 (s, 2H), 7.44 (d, *J* = 8.4 Hz, 2H), 7.99 (s, 1H), 8.08 (d, *J* = 8.4 Hz, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 14.25, 20.85, 52.41, 59.00, 61.19, 128.42, 129.18, 129.80, 131.11, 138.41, 144.08, 165.86, 166.88, 170.50; ESIMS *m/z* 329 $[M+Na]^+$. Anal. Calcd for $C_{16}H_{18}O_6$: C, 62.74; H, 5.92. Found: C, 62.92; H, 5.69.
Compound ***3a***: 81%; colorless oil; IR (film) 1741, 1720, 1231 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.09 (s, 3H), 3.51 (s, 3H), 4.82 (s, 2H), 7.11–7.16 (m, 2H), 7.17–7.23 (m, 2H), 7.27–7.31 (m, 3H), 7.32–7.37 (m, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 20.88, 51.77, 64.11, 126.54, 128.01, 128.30, 128.36, 128.56, 128.70, 129.30, 139.49, 141.27, 153.27, 169.39, 170.56; ESIMS *m/z* 333 $[M+Na]^+$. Anal. Calcd for $C_{19}H_{18}O_4$: C, 73.53; H, 5.85. Found: C, 73.32; H, 5.96.
Compound ***3e****-meta*: 77%; colorless oil; IR (film) 1742, 1717, 1230 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.01 (s, 3H), 2.19 (s, 6H), 2.20 (s, 6H), 3.44 (s, 3H), 4.70 (s, 2H), 6.68 (s, 2H), 6.73 (s, 2H), 6.86 (s, 1H), 6.89 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 20.90, 21.18, 21.24, 51.71, 64.26, 125.95, 126.24, 126.94, 130.07, 130.27, 137.38, 137.67, 139.44, 141.18, 154.12, 169.73, 170.54; ESIMS *m/z* 389 $[M+Na]^+$. Anal. Calcd for $C_{23}H_{26}O_4$: C, 75.38; H, 7.15. Found: C, 75.16; H, 7.18.
Compound ***3f***: 82%; pale yellow oil; IR (film) 1742, 1718, 1231 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.01 (s, 3H), 2.26 (s, 3H), 2.27 (s, 3H), 3.46 (s, 3H), 4.74 (s, 2H), 6.89–6.95 (m, 2H), 6.96–7.10 (m, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 20.91, 21.20, 21.23, 51.73, 64.48, 125.40, 128.66, 128.68, 128.92, 129.38, 136.89, 138.29, 138.57, 138.70, 153.78, 169.69, 170.61; ESIMS *m/z* 361 $[M+Na]^+$. Anal. Calcd for $C_{21}H_{22}O_4$: C, 74.54; H, 6.55. Found: C, 74.51; H, 6.81.
Compound ***3i***: 72%; colorless oil; IR (film) 1739, 1716, 1605, 1512, 1249 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.03 (s, 3H), 3.47 (s, 3H), 3.73 (s, 3H), 3.74 (s, 3H), 4.76 (s, 2H), 6.74 (d, *J* = 9.0 Hz, 2H), 6.78 (d, *J* = 9.0 Hz, 2H), 6.98 (d, *J* = 9.0 Hz, 2H), 7.05 (d, *J* = 9.0 Hz, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 20.97, 51.74, 55.17, 55.24, 64.84, 113.34, 113.58, 124.31, 130.40, 131.17, 132.23, 134.03, 153.50, 159.82, 160.07, 170.01, 170.70; ESIMS *m/z* 393 $[M+Na]^+$. Anal. Calcd for $C_{21}H_{22}O_6$: C, 68.10; H, 5.99. Found: C, 68.42; H, 5.73.
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13. The β-H elimination with the ring proton is somewhat difficult because *syn*-periplanarity between the C–H and C–Pd bonds would be difficult, as noted in our previous paper.[4a]