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An expedient synthesis of 3-arylmethylbutenolides from α-methylene-γ-butyrolactones: a useful synthetic application of palladium-catalyzed chelation-controlled oxidative arylation protocol

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ABSTRACT

A palladium-catalyzed chelation-controlled oxidative arylation of α-methylene-γ-butyrolactones with arenes provided 3-arylmethylbutenolides as major products along with a low yield of α-arylidene-γ-butyrolactones. The selectivity might be due to a chelation between the palladium center and a directing group at the γ-position of α-methylene-γ-butyrolactones.

A palladium-catalyzed chelation-controlled arylation of olefins has been studied extensively for the purpose of stereo- and regiocontrol, and multiple arylations.[1,2] Various functional groups such as ester, ketone, amide, imide, and amines have been known to act as a directing group (DG), which stabilizes the palladium intermediate by chelation.[1,2] Most of the arylation reactions involved the use of aryl halides, arylboronic acids, and arenediazonium salts as an aryl source.[2] Recently, Pd-catalyzed oxidative Heck reactions of allyl esters have been reported with arenes and heteroarenes.[1] Very recently, we also reported an efficient palladium-catalyzed oxidative Heck type arylation of α-substituted methyl cinnamates.[1f]

Diversely substituted butenolides have been found in numerous natural products[3] and used for the synthesis of many biologically important compounds.[3–5] Thus, the synthesis of butenolides from α-methylene-γ-butyrolactones has been known as one of the important approaches to these compounds. Arcadi et al. reported a Pd-catalyzed arylation of α-methylene-γ-butyrolactones with aryl iodides; however, they obtained a mixture of arylidene lactone **A** and butenolide **B**, as shown in Scheme 1.[6a,b] The selectivity between **A** and **B** was dependent both on the reaction conditions and aryl iodides. Later, Colby and co-workers reported a selective synthesis of arylidene lactone derivative **A**, and they confirmed the stereochemistry of the arylidene moiety as *E*-form by chemical shift of the vinyl proton and X-ray crystal structure.[6c] However, there is no method for the selective synthesis of butenolide **B** to date. Based on the recent publications on palladium-catalyzed chelation-controlled arylations of olefins,[1,2] we presumed that such a chelation-controlled oxidative arylation protocol could be applied efficiently for the synthesis of 3-arylmethylbutenolides from α-methylene-γ-butyrolactones bearing a directing group (DG) such as an ester or ketone at the γ-position, as shown in Scheme 1.

As a starting material we selected α-methylene-γ-butyrolactone **1a**, which could be prepared readily by an indium-mediated Barbier type reaction between the Morita–Baylis–Hillman (MBH) bromide and methyl pyruvate.[7a] With this lactone **1a**, we examined the phenylation in the presence of $Pd(OAc)_2$, AgOAc, and pivalic acid in benzene,[1f,8a–c] as shown in Scheme 2. Carbopalladation of the C=C double bond of **1a** to an initially formed phenylpalladium species PhPd(OPiv) might generate an intermediate **I**. The carbopalladation might proceed stereoselectively to the same side of a directing group (–COOMe) due to a chelation-assisted stabilization effect of the intermediate **I**. In addition, the proton at the 4-position of the lactone ring is positioned in a syn-relationship with the palladium center, and a subsequent β-H elimination proceeded in this direction to produce 3-benzylbutenolide **2a** as a major product (77%).[9] A low yield (19%) of benzylidene lactone **3a** was formed by β-H elimination with the hydrogen at the benzyl moiety. The stereochemistry of a benzylidene moiety of **3a** would be *E*-form based on the chemical shift of a vinyl proton (δ = 7.77 ppm).[6c] Compound **3a** could be converted quantitatively into **2a** by treatment with DBU (0.3 equiv) in refluxing toluene (3 h), whereas the reaction of **3a** and AgOAc (1.0 equiv) in benzene

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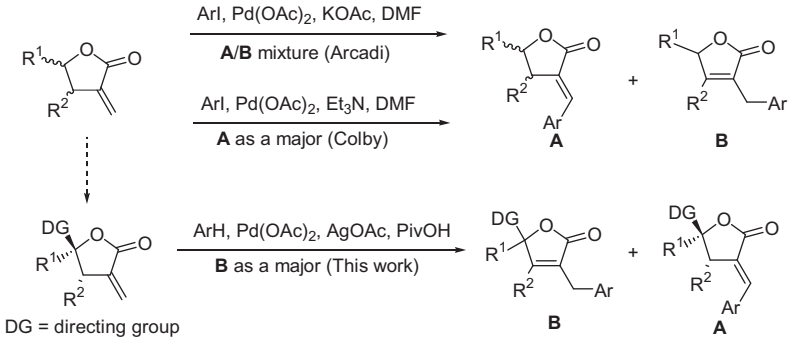
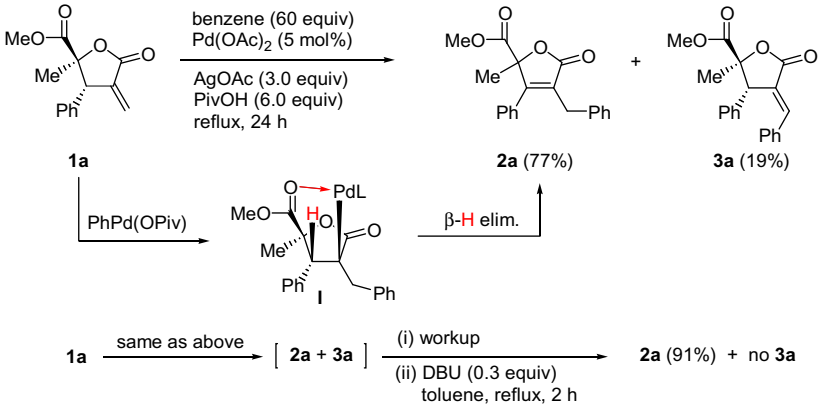


Scheme 1.



Scheme 2.

(reflux, 48 h) did not produce **2a** at all. In addition, the ratio between **2a** and **3a** (ca. 4:1) was not changed much when the palladium-catalyzed phenylation of **1a** was carried out for a long time (48 h). The results stated that **2a** must be formed directly by the Pd-catalyzed phenylation of **1a**. Actually, benzylbutenolide **2a** could be prepared in high yield (91%) by treatment of the crude reaction mixture of **2a** and **3a** with DBU, after a simple aqueous workup, as also shown in Scheme 2.

Encouraged by the successful results we examined arylations of **1a** with various arenes, and the results are summarized in Table 1.[10] The reactions of **1a** with *o*-xylene, *p*-xylene, *m*-xylene, and *o*-dichlorobenzene produced similar results (entries 2–5). In all entries, 3-arylmethylbutenolides **2b**–**e** were formed as major products (51–73%) along with arylidene lactones **3b**–**e** as minor products (16–22%). No regioisomeric products were observed when we used *o*-xylene and *o*-dichlorobenzene. When we used *m*-xylene (entry 4), *meta* and *ortho*-isomers were formed together (vide infra). Actually, the regioisomers could not be separated, and compounds **2d** (*meta*-**2d**/*ortho*-**2d** = 4:1) and **3d** (*meta*-**3d**/*ortho*-**3d** = 2:1) were isolated in 73% and 20%, respectively, as their regioisomeric mixtures.

In order to confirm the generality, similar lactone derivatives **1b**–**d** were prepared according to the reported methods[7a,b] and examined the oxidative arylation, as shown in Table 2. The reactions of acetyl derivative **1b** with benzene or *p*-xylene showed similar results (entries 1 and 2) with that of the ester derivative **1a**. The reaction of 4-unsubstituted lactone **1c** produced **2h** in moderate yield (45%). However, isolation of the corresponding benzylidene lactone **3h** failed due to the presence of some side product near the spot on TLC (entry 3). The reactions of a pentacyclic lactone **1d**,[7b] under the same reaction conditions with benzene or *p*-xylene, produced butenolide derivatives **2i** and **2j**, respectively, in good yields (entries 4 and 5). The corresponding lactone derivatives **3i** and **3j** were not observed.

Table 1
Pd-catalyzed arylation of **1a**

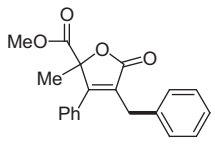
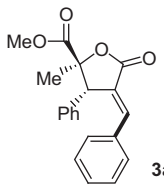
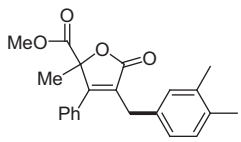
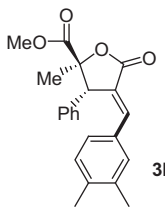
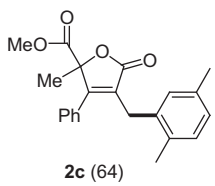
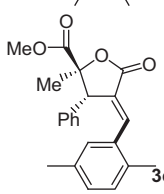
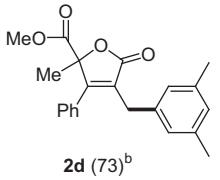
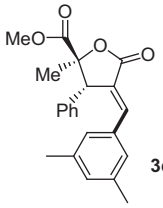
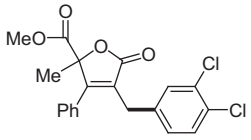
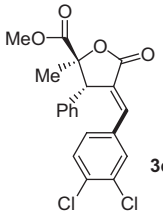
Entry	Conditions[a]	Products (%)	
1	Benzene reflux, 24 h	 **2a** (77)	 **3a** (19)
2	*o*-Xylene 100 °C, 24 h	 **2b** (70)	 **3b** (21)
3	*p*-Xylene 100 °C, 24 h	 **2c** (64)	 **3c** (22)

Table 1 (*continued*)

Entry	Conditions[a]	Products (%)	
4	*m*-Xylene 100 °C, 24 h	 **2d** (73)[b]	 **3d** (20)[c]
5	*o*-Dichlorobenzene 100 °C, 24 h	 **2e** (51)	 **3e** (16)

[a] Conditions: Substrate **1a** (0.5 mmol), $Pd(OAc)_2$ (5 mol %), AgOAc (3.0 equiv), PivOH (6.0 equiv), arene (60 equiv).

[b] *meta* (3,5-Dimethylphenyl)/*ortho* (2,4-dimethylphenyl) = 4:1.

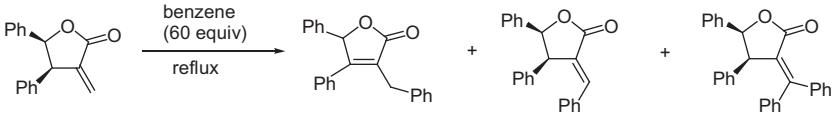
[c] *meta* (3,5-Dimethylphenyl)/*ortho* (2,4-dimethylphenyl) = 2:1.

In order to clarify the chelation effect on the selective formation of butenolides in the reactions of **1a**–**d**, we examined the reaction of 4,5-diphenyl lactone **1e**.[5a] The lactone **1e** has no suitable directing group, and we expected that the ratio between butenolide and benzylidene lactone might be changed. Actually, the reaction of **1e** produced three compounds, **2k**, **3k,** and **4**, as shown in Scheme 3. As expected, butenolide **2k** was produced as a minor product (17%) under the typical reaction conditions, while the yield of a benzylidene lactone **3k** increased to 32%. Without a directing group the carbopalladation of **1e** proceeded non-stereoselectively, as also shown in Scheme 3, and produced a mixture of **2k** and **3k**. It is interesting to note that a diarylated lactone **4** was obtained together in 37% in the reaction. The second phenylation of **3k** to **4** might occur because the benzylidene moiety of **3k** is sterically less crowded than that of **3a**. Reducing the amount of AgOAc (2.0 equiv) decreased the yield of **4**, while the yield increased to 63% by using an excess amount of AgOAc. The result using $Pd(TFA)_2$ was similar to that of $Pd(OAc)_2$.

Thus a plausible reaction mechanism could be suggested, as shown in Figure 1, with **1a** as a typical example. An arylpalladium intermediate could be generated from arene and $Pd(OPiv)_2$ most likely via an electrophilic palladation (S_EAr) process.[8b,11a–e] The regioselective formations of **2b**–**e**, **2g,** and **2j** suggested the involvement of an electrophilic palladation process. However, a partial contribution of a concerted metalation-deprotonation (CMD) process cannot be ruled out completely at this stage.[8a,i,11f,g] As described above, a subsequent carbopalladation of **1a** to form the intermediate **I**, and the following β-H elimination produced **2a**–**e** as major products. The reduced Pd^0 was oxidized to Pd^{II} by AgOAc, and the Pd^{II} carries out the catalytic cycle.

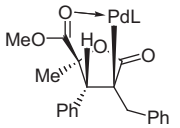
In order to compare the reactivity, the reaction of **1a** was examined with iodobenzene instead of benzene, as shown in Scheme 4. Literature survey suggested two plausible reaction conditions for the arylation of **1a** with aryl iodides. Chen and co-workers carried out the Pd-catalyzed arylation of cinnamates under the influence of AgOAc in acetic acid.[12] Fabrizi and co-workers performed the arylation of β-arylacrylamides in the presence of Et_3N.[13] The reaction in the presence of $Pd(OAc)_2$ and AgOAc in AcOH (Chen's condition) afforded the products **2a** and **3a** in high yield (93%) in short time (2 h). However, compounds **2a** (47%) and **3a** (46%) were isolated in almost equal amounts.[14] Interestingly, a mixture of products was formed when the reaction of **1a** was carried out under Fabrizi's condition employing excess amounts of Et_3N.[13] The compounds **2a** and **5** were isolated as a mixture in low yield (30%), along with a mixture of double bond-isomerized compounds **6** and **7** (34% as a 1:1 mixture). Compounds **5** and **7** might be produced by in-situ generated triethylamine hydroiodide-mediated demethoxycarbonylation of **2a** and **6**, respectively.[15]

In summary, a palladium-catalyzed chelation-controlled oxidative arylation of α-methylene-γ-butyrolactones with arenes was carried out to obtain 3-arylmethylbutenolides as major products. The selective formation of a butenolide might be the result of a chelation between the palladium center and a directing group.

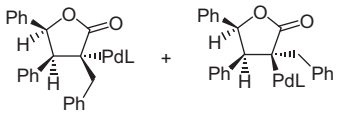


1e **2k** **3k** **4**

Conditions	2k	3k	4
$Pd(OAc)_2$ (5 mol%), AgOAc (3.0 equiv), PivOH (6.0 equiv), 24 h	17	32	37
$Pd(OAc)_2$ (5 mol%), AgOAc (2.0 equiv), PivOH (6.0 equiv), 24 h	18	60	10
$Pd(OAc)_2$ (10 mol%), AgOAc (6.0 equiv), PivOH (6.0 equiv), 24 h	13	0	63
$Pd(TFA)_2$ (5 mol%), AgOAc (2.0 equiv), PivOH (6.0 equiv), 10 h	23	43	15



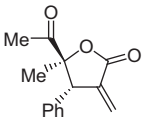
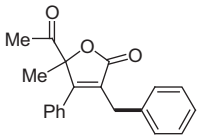
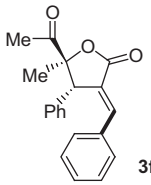
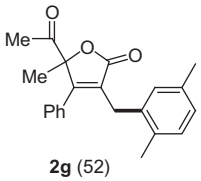
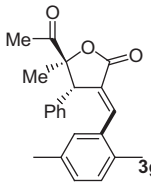
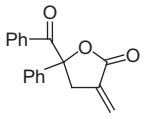
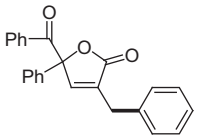
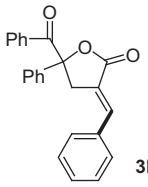
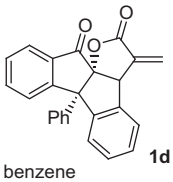
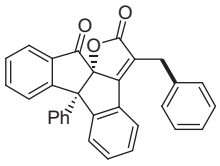
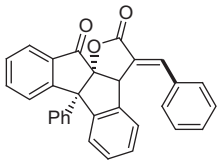
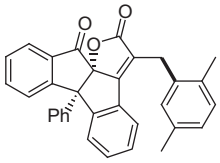
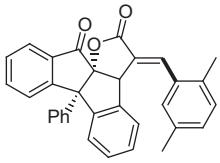
stereoselective carbopalladation of **1a** leading to selective formation of **2a** (Scheme 2)



non-stereoselective carbopalladation of **1e** leading to a mixture of **2k** and **3k**

Scheme 3.

Table 2
Pd-catalyzed arylation of **1b–d**

Entry	Substrate/conditions[a]	Products (%)	
1	 **1b** benzene reflux, 24 h	 **2f** (75)	 **3f** (16)
2	**1b** *p*-Xylene 100 °C, 24 h	 **2g** (52)	 **3g** (18)
3	 **1c** benzene reflux, 24 h	 **2h** (45)	 **3h**[b]
4	 **1d** benzene reflux, 24 h	 **2i** (95)	 **3i**[c]
5	**1d** *p*-Xylene 100 °C, 24 h	 **2j** (80)	 **3j**[c]

[a] Conditions: Substrate **1** (0.5 mmol), $Pd(OAc)_2$ (5 mol %), AgOAc (3.0 equiv), PivOH (6.0 equiv), arene (60 equiv).
[b] Observed in a trace amount on TLC, but failed to isolate.
[c] Not formed.

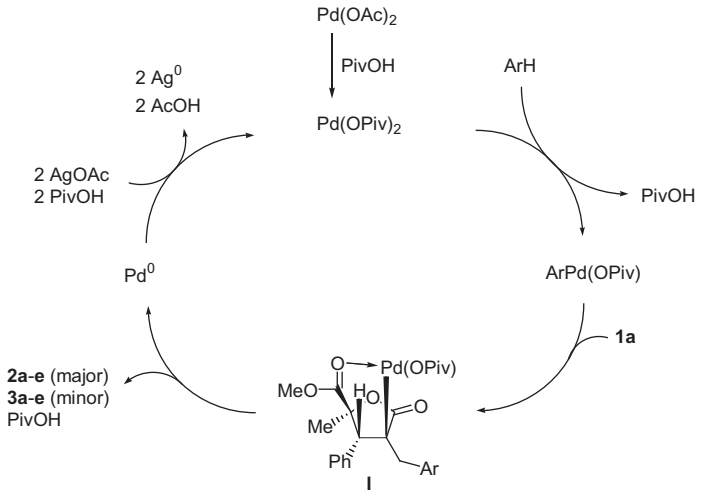
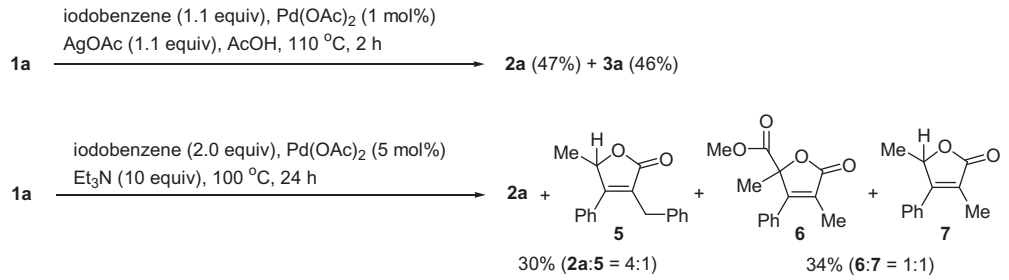


Figure 1. A plausible catalytic cycle.



Scheme 4.

Acknowledgments

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References and notes

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9. *Typical procedure for the synthesis of **2a** and **3a***: A stirred mixture of **1a** (123 mg, 0.5 mmol), $Pd(OAc)_2$ (5.7 mg, 5 mol %), AgOAc (251 mg, 1.5 mmol), and PivOH (307 mg, 3.0 mmol) in benzene (235 mg, 30 mmol) was heated to reflux under nitrogen atmosphere for 24 h. After cooling to room temperature, the reaction mixture was filtered over a pad of Celite and washed with CH_2Cl_2 (100 mL). The filtrates were washed with a saturated solution of $NaHCO_3$ (20 mL × 3), and the organic layer was dried over $MgSO_4$. After removal of solvent and column chromatographic purification process (hexanes/CH_2Cl_2, 1:1) **2a** was isolated as a white solid (124 mg, 77%) along with **3a** as a white solid (31 mg, 19%). Other compounds were synthesized similarly, and the selected spectroscopic data of **2a**, **2b**, **2f**, **2i**, **2j**, **3a**, **3b** and **3f** are as follows.
*Compound **2a***: 77%; white solid, mp 83–84 °C; IR (KBr) 1769, 1747, 1261, 1127, 1056 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.70 (s, 3H), 3.62 (d, J = 15.0 Hz, 1H), 3.73 (d, J = 15.0 Hz, 1H), 3.77 (s, 3H), 7.08–7.28 (m, 7H), 7.36–7.45 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.58, 30.15, 53.29, 86.74, 126.55, 127.59, 128.30, 128.56, 128.84, 128.95, 129.82, 130.28, 137.35, 161.23, 168.70, 172.56; ESIMS m/z 345 $[M+Na]^+$. Anal. Calcd for $C_{20}H_{18}O_4$: C, 74.52; H, 5.63. Found: C, 74.77; H, 5.49.
*Compound **2b***: 70%; colorless oil; IR (film) 1771, 1749, 1262, 1128, 1059 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.70 (s, 3H), 2.20 (s, 6H), 3.54 (d, J = 15.0 Hz, 1H), 3.67 (d, J = 15.0 Hz, 1H), 3.78 (s, 3H), 6.84 (d, J = 7.5 Hz, 1H), 6.91 (s, 1H), 7.00 (d, J = 7.5 Hz, 1H), 7.10–7.14 (m, 2H), 7.39–7.44 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.30, 19.78, 20.61, 29.66, 53.28, 86.64, 125.49, 127.64, 128.89, 128.98, 129.64, 129.76, 130.32, 134.59, 134.71, 136.65, 160.89, 168.78, 172.63 (one carbon was overlapped); ESIMS m/z 351 $[M+H]^+$. Anal. Calcd for $C_{22}H_{22}O_4$: C, 75.41; H, 6.33. Found: C, 75.64; H, 6.58.
*Compound **2f***: 75%; colorless oil; IR (film) 1766, 1726, 1054 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.59 (s, 3H), 2.15 (s, 3H), 3.65 (d, J = 14.7 Hz, 1H), 3.71 (d, J = 14.7 Hz, 1H), 7.04–7.28 (m, 7H), 7.35–7.45 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.78, 23.72, 30.33, 92.12, 126.71, 127.60, 128.32, 128.66, 128.94, 129.50, 129.89, 130.13, 137.31, 161.21, 172.97, 202.86; ESIMS m/z 307 $[M+H]^+$. Anal. Calcd for $C_{20}H_{18}O_3$: C, 78.41; H, 5.92. Found: C, 78.16; H, 6.11.
*Compound **2i***: 95%; white solid, mp 85–86 °C; IR (KBr) 1769, 1726, 1678, cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 3.83 (d, J = 16.0 Hz, 1H), 3.99 (d, J = 16.0 Hz, 1H), 6.83–6.85 (m, 2H), 7.02 (d, J = 8.0 Hz, 1H), 7.20–7.90 (m, 10H), 7.37 (t, J = 7.5 Hz, 1H), 7.50 (t, J = 8.0 Hz, 1H), 7.61 (d, J = 8.0 Hz, 1H), 7.76 (t,

J = 7.5 Hz, 1H), 7.81 (d, J = 7.5 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 30.74, 63.73, 96.98, 125.01, 125.31, 125.32, 125.52, 126.70, 127.03, 128.01, 128.45, 128.59, 128.69, 128.90, 128.95, 129.33, 130.60, 131.93, 133.47, 136.58, 137.01, 137.36, 151.12, 157.82, 159.33, 174.50, 196.87; ESIMS m/z 441 $[M+H]^+$. Anal. Calcd for $C_{31}H_{20}O_3$: C, 84.53; H, 4.58. Found: C, 84.74; H, 4.82.

Compound ***2j***: 80%; white solid, mp 165–167 °C; IR (KBr) 1768, 1727, 1602 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.19 (s, 3H), 2.29 (s, 3H), 3.75 (d, J = 17.1 Hz, 1H), 3.90 (d, J = 17.1 Hz, 1H), 6.43 (d, J = 7.5 Hz, 1H), 6.87–7.06 (m, 5H), 7.11 (t, J = 7.5 Hz, 1H), 7.22–7.35 (m, 5H), 7.49 (t, J = 7.8 Hz, 1H), 7.57 (d, J = 7.8 Hz, 1H), 7.73 (t, J = 7.5 Hz, 1H), 7.80 (d, J = 7.5 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.07, 20.93, 29.60, 63.52, 97.17, 124.48, 125.29, 125.46, 125.96, 126.87, 127.69, 128.01, 128.46, 128.74, 129.07, 129.28, 130.17, 130.32, 130.49, 131.66, 133.36, 133.90, 135.17, 135.64, 136.80, 136.96, 150.98, 158.15, 158.74, 174.60, 197.08; ESIMS m/z 469 $[M+H]^+$. Anal. Calcd for $C_{33}H_{24}O_3$: C, 84.59; H, 5.16. Found: C, 84.23; H, 5.37.

Compound ***3a***: 19%; white solid, mp 84–86 °C; IR (KBr) 1762, 1646, 1450, 1230 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.22 (s, 3H), 3.80 (s, 3H), 4.64 (d, J = 1.8 Hz, 1H), 7.18–7.40 (m, 10H), 7.77 (d, J = 1.8 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.81, 52.44, 53.33, 84.80, 126.84, 128.23, 128.71 (2C), 129.17, 130.26, 130.67, 133.42, 136.63, 139.50, 171.26, 173.12; ESIMS m/z 345 $[M+Na]^+$. Anal. Calcd for $C_{20}H_{18}O_4$: C, 74.52; H, 5.63. Found: C, 74.75; H, 5.61.

Compound ***3b***: 21%; white solid, mp 126–127 °C; IR (KBr) 1760, 1644, 1454, 1226 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.22 (s, 3H), 2.12 (s, 3H), 2.20 (s, 3H), 3.79 (s, 3H), 4.63 (d, J = 1.8 Hz, 1H), 7.01–7.09 (m, 3H), 7.18–7.39 (m, 5H), 7.72 (d, J = 1.8 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.62, 19.75, 20.86, 52.59, 53.31, 84.66, 125.27, 128.13, 128.52, 128.74, 129.10, 130.00, 131.05, 131.95, 136.95, 136.99, 139.74, 139.77, 171.55, 173.27; ESIMS m/z 351 $[M+H]^+$. Anal. Calcd for $C_{22}H_{22}O_4$: C, 75.41; H, 6.33. Found: C, 75.74; H, 6.55.

Compound ***3f***: 16%; white solid, mp 112–113 °C; IR (KBr) 1758, 1721, 1644, 1200 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.08 (s, 3H), 2.34 (s, 3H), 4.82 (d, J = 1.8 Hz, 1H), 7.20–7.36 (m, 10H), 7.76 (d, J = 1.8 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.01, 25.81, 50.38, 90.25, 126.69, 127.97, 128.68, 129.10, 130.42, 130.84, 133.17, 136.90, 140.08, 171.10, 209.63 (one carbon was overlapped); ESIMS m/z 307 $[M+H]^+$. Anal. Calcd for $C_{20}H_{18}O_3$: C, 78.41; H, 5.92. Found: C, 78.73; H, 5.76.

10. The optimization of reaction conditions was briefly examined. The use of $Cu(OAc)_2$ or $K_2S_2O_8$ as an oxidant was not effective, whereas Ag_2CO_3 showed a similar reactivity to that of AgOAc. The amount of arenes could be reduced to 40 equiv; however, we used 60 equiv of arenes for the convenience of reaction. The reaction of **1a** with commercial $Pd(OPiv)_2$ (benzene/AgOAc/PivOH, reflux, 24 h) showed very similar results (**2a**: 75%, **3a**: 15%). For the preparation of $Pd(OPiv)_2$ from $Pd(OAc)_2$ and PivOH in toluene, see: Ragaini, F.; Gasperini, M.; Cenini, S.; Arnera, L.; Caselli, A.; Macchi, P.; Casati, N. *Chem. Eur. J.* **2009**, *15*, 8064–8077.
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12. For the Pd-catalyzed Heck reaction with aryl iodide under the influence of AgOAc/AcOH, see: Xu, D.; Lu, C.; Chen, W. *Tetrahedron* **2012**, *68*, 1466–1474.
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14. The reason for the disruption of selectivity under Chen's condition is not clear at this stage. The compounds **2a** and **3a** were formed even at lower temperature (80 °C); however, the ratio between **2a** and **3a** was almost same with that of 110 °C.
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