Tetrahedron Letters 53 (2012) 5088–5093

Contents lists available at SciVerse ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Palladium-catalyzed arylation of α,β-unsaturated Weinreb amides

Ko Hoon Kim [a], Sangku Lee [b], Se Hee Kim [a], Cheol Hee Lim [a], Jae Nyoung Kim [a,*]

[a] Department of Chemistry and Institute of Basic Science, Chonnam National University, Gwangju 500-757, Republic of Korea
[b] Immune Modulator Research Center, KRIBB, Daejeon 305-806, Republic of Korea

ARTICLE INFO

Article history:
Received 5 June 2012
Revised 27 June 2012
Accepted 6 July 2012
Available online 20 July 2012

Keywords:
Palladium
Weinreb amides
Arylation
Chelation

ABSTRACT

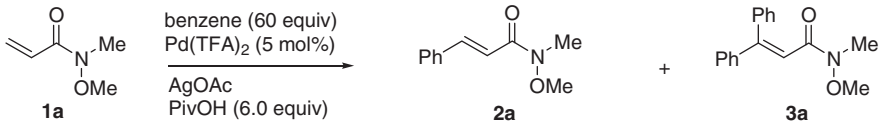
Palladium-catalyzed arylation of α,β-unsaturated Weinreb amides has been examined to obtain β-aryl-α,β-unsaturated Weinreb amides. The chelation between the palladium center of an alkylpalladium intermediate and Weinreb amide moiety facilitated both coordination and insertion steps.

Weinreb amides (*N*-methoxy-*N*-methyl amides) have been widely used as versatile synthetic intermediates in organic synthesis since their original discovery by Nahm and Weinreb.[1] Weinreb amides could react with Grignard reagents, organolithium reagents, and $LiAlH_4$ to afford ketones or aldehydes in high yield via stable metal-chelated intermediates. Among the Weinreb amides, α,β-unsaturated analogs have received much attention because of their synthetic applications in organic synthesis[2] and their interesting biological activity.[3]

Thus, there have been reported numerous approaches for the synthesis of α,β-unsaturated Weinreb amides.[4–7] The principal approach is the formation of an amide bond between α,β-unsaturated carboxylic acids and *N,O*-dimethylhydroxylamine.[4] The second method used Horner–Wadsworth–Emmons and Wittig type reactions.[5] Third approach involved the Julia and Julia-Kocienski olefination protocols.[6] Besides these methods, a cross-metathesis reaction between Weinreb acrylamide and olefin,[7a] and a gold-catalyzed reaction of vinylidenecyclopropanes and *N,O*-dimethylhydroxylamine have also been reported.[7b]

Although a palladium-catalyzed arylation of Weinreb acrylamide could produce β-aryl-α,β-unsaturated Weinreb amide, there is only one report involving a palladium-catalyzed reaction between alkenylboronic acids and *N*-methyl-*N*-methoxycarbamoyl chloride,[8] to the best of our knowledge. In these respects, we decided to examine a palladium-catalyzed direct oxidative arylation[9] of α,β-unsaturated Weinreb amides with arenes.

During our recent studies, we observed that the condition employing $Pd(TFA)_2$ in the presence of AgOAc and pivalic acid (PivOH) was effective for the palladium-catalyzed oxidative arylations of various carbon–carbon double bonds.[10] Thus, we examined the phenylation of Weinreb acrylamide **1a**[2h] in benzene under the above mentioned reaction conditions. To our delight, a Weinreb cinnamamide **2a**[4a,8] was obtained in good yield (88%), as shown in Scheme 1. When we used a limited amount of AgOAc (2.0 equiv), a diphenyl derivative **3a** was not formed at all. When we used excess amounts of AgOAc (5.0 equiv), compound **3a** was obtained as a major product (69%) along with a low yield of **2a** (7%).



AgOAc (2.0 equiv), reflux, 5 h: **2a** (88%) and no **3a**
AgOAc (5.0 equiv), reflux, 24 h: **2a** (7%) and **3a** (69%)

Scheme 1.

* Corresponding author. Tel.: +82 62 530 3381; fax: +82 62 530 3389.
E-mail address: kimjn@chonnam.ac.kr (J.N. Kim).

0040-4039/$ - see front matter © 2012 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.tetlet.2012.07.023

Table 1
Optimization of reaction conditions for the conversion of **2a** into **3a**[a]

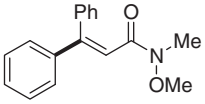
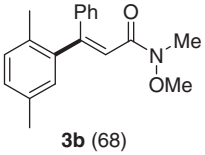
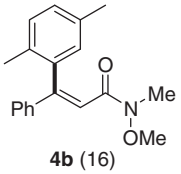
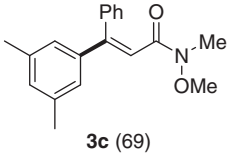
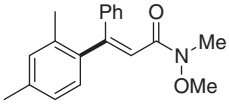
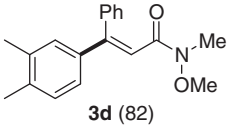
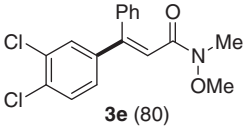
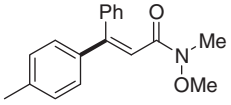
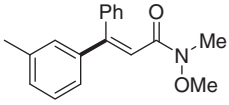
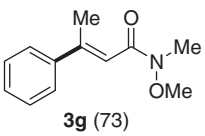
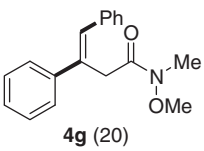
Entry	Pd catalyst[b]	Oxidant (equiv)	Additive[c]	Yield (%)
1	$Pd(TFA)_2$	AgOAc (2.0)	PivOH	71
2	$Pd(TFA)_2$	AgOAc (2.5)	PivOH	82
3	$Pd(TFA)_2$	AgOAc (3.0)	PivOH	87
4	$Pd(TFA)_2$	AgOAc (4.0)	PivOH	90
5	$Pd(TFA)_2$	AgOAc (3.0)	AcOH	51
6	$Pd(TFA)_2$	AgOAc (3.0)	No	28
7	$Pd(OAc)_2$	AgOAc (3.0)	PivOH	80
8	$Pd(TFA)_2$	$Cu(OAc)_2$ (3.0)	PivOH	<5
9	$Pd(TFA)_2$	Ag_2CO_3 (3.0)	PivOH	15
10	$Pd(TFA)_2$	$K_2S_2O_8$ (3.0)	PivOH	<5

[a] Substrate **2a** (0.5 mmol), benzene (60 equiv), reflux, 20 h.
[b] 5 mol %.
[c] 6.0 equiv.

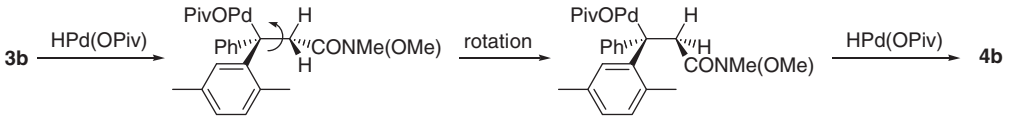
Encouraged by the facile phenylation of **2a** to **3a**, we decided to develop an efficient protocol for the palladium-catalyzed synthesis of β,β-disubstituted α,β-unsaturated Weinreb amides.[2,3] In order to further optimize the reaction conditions, we examined the conversion of **2a** into **3a** with benzene under various conditions, as shown in Table 1. As for the phenylation of **2a**, initially we used 2.0 equiv of AgOAc (entry 1) and obtained compound **3a** in 71%; however, a small amount of **2a** remained even after 20 h. The yield of **3a** increased using excess amounts of AgOAc (entries 2–4). The use of AcOH in place of PivOH was less effective (entry 5). Without an acid additive (entry 6) the yield decreased dramatically. The use of $Pd(OAc)_2$ was less effective slightly than $Pd(TFA)_2$ (entry 7). The use of other oxidants such as $Cu(OAc)_2$, Ag_2CO_3, and $K_2S_2O_8$ was not effective (entries 8–10).

Although the yield of **3a** was slightly higher with 4.0 equiv of AgOAc (entry 4), we selected the condition employing 3.0 equiv of AgOAc (entry 3), and examined the arylation of **2a** with various arenes, as summarized in Table 2.[11] The reaction with *p*-xylene afforded **3b** in moderate yield (68%) along with its stereoisomer **4b** (16%). The stereoisomer **4b** might be formed via a double bond isomerization process catalyzed by HPd(OPiv) species,[12] as shown in Scheme 2. The reaction with *m*-xylene afforded the desired compound **3c** in a similar yield (69%) along with a low yield of regioisomer **4c** (entry 3).[9l] When we used *o*-xylene compound **3d** was isolated in 82% yield, and we did not observe the formation of the corresponding stereo- and regioisomer in this case (entry 4).[10c,e,i] The situation was same with *o*-dichlorobenzene, and compound **3e** was obtained in good yield (entry 5).[10c,e,i] However, a

Table 2
Pd-catalyzed arylation of **2a**[a]

Entry	Arene	Product (%)	
1	Benzene	 **3a** (87)	
2	*p*-Xylene	 **3b** (68)	 **4b** (16)
3	*m*-Xylene	 **3c** (69)	 **4c** (18)
4	*o*-Xylene	 **3d** (82)	
5	*o*-Dichlorobenzene	 **3e** (80)	
6	Toluene	 **3f** 1:1 mixture (71%)	 **4f**
7[b]	Benzene	 **3g** (73)	 **4g** (20)

[a] Conditions: compound **2a** (0.5 mmol), arene (60 equiv), $Pd(TFA)_2$ (5 mol %), AgOAc (3.0 equiv), PivOH (6.0 equiv), reflux for benzene and 110 °C for other arenes, 20 h.
[b] Instead of **2a**, *trans* MeCH = CH-CONMe(OMe) (**2b**) was used as a substrate.

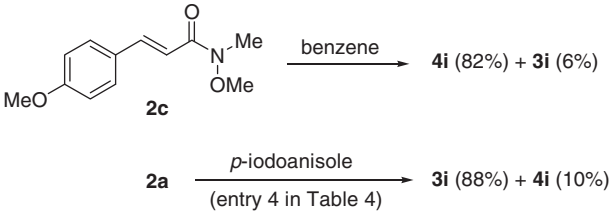


Scheme 2.

Table 3
Optimization of reaction conditions for the conversion of **2a** into **3a**[a]

Entry	Conditions	Yield (%)
1	AgOAc (1.1 equiv), AcOH (30 equiv), 100 °C, 2 h	77
2	Et_3N (10 equiv), 100 °C, 16 h	94
3[b]	Et_3N (10 equiv), 100 °C, 24 h	<5

[a] Conditions: compound **2a** (0.5 mmol), iodobenzene (2.0 equiv), $Pd(OAc)_2$ (5 mol %).
[b] Bromobenzene (2.0 equiv) was used.



Scheme 3.

Table 4
Pd-catalyzed arylation of **2a** with iodoarenes[a]

Entry	Iodoarene/time	Product (%)	
1	Iodobenzene 16 h	**3a** (94)	
2	*p*-Iodotoluene 24 h	**3f** (80)	**4f'** (8)
3	*o*-Iodotoluene 36 h	**3h** (72)	**4h** (3)
4	*p*-Iodoanisole 12 h	**3i** (88)	**4i** (10)
5	Ethyl 4-iodobenzoate 24 h	**3j** (89)	**4j** (3)
6	5-Iodo-*m*-xylene 24 h	**3c** (90)	**4c'**[b]

[a] Conditions: compound **2a** (0.5 mmol), iodoarene (2.0 equiv), $Pd(OAc)_2$ (5 mol %), Et_3N (10.0 equiv), 100 °C.
[b] Trace amount of **4c'** was observed but failed to isolate.

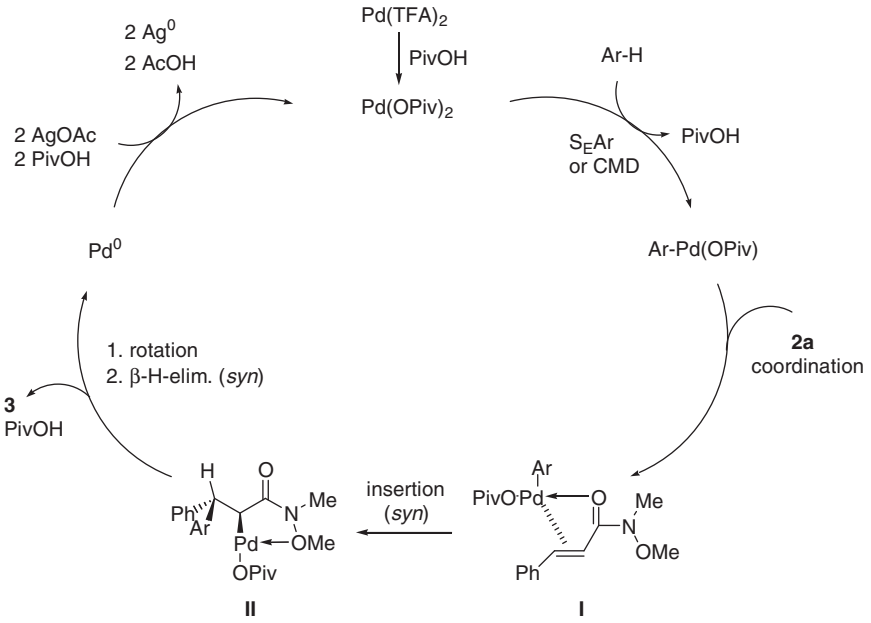


Figure 1. Catalytic cycle of arylation of **2a** with arene.

couple of products were produced in the reaction with toluene (entry 6). As expected, *para*- and *meta*-isomers **3f** and **4f** were isolated as a mixture (1:1) in 71% yield; however, a mixture of the *ortho* isomer and the corresponding stereoisomers of **3f** and **4f** were separated altogether in a low yield (ca. 17%).[9f–h] The reaction of Weinreb amide of *trans*-crotonic acid **2b**[2i] gave the corresponding product **3g** in good yield (entry 7). Interestingly, compound **4g** was obtained together, albeit in low yield (20%). Compound **4g** might be formed via the oxidative phenylation at the γ-position of **3g**,[13] and a following 1,3-hydrogen shift.[13b] Currently, further studies on the arylation at the allylic position are underway.

The results in Table 2 stated that the reactions with benzene or disubstituted arenes provided the corresponding stereo-defined β,β-diaryl-α,β-unsaturated Weinreb amides **3a–e** in good yields, while the reaction with mono-substituted arene such as toluene gave a mixture of products. Thus, we decided to develop a complementary method involving the use of an aryl halide in order to prohibit the regioisomeric problem. The literature survey suggested two plausible reaction conditions for the arylation of **2a** with aryl iodides. Chen and co-workers carried out the Pd-catalyzed arylation of cinnamates under the influence of AgOAc in acetic acid.[14] Fabrizi and co-workers performed the arylation of β-arylacrylamides in the presence of Et_3N.[15] Thus a brief optimization of the reaction condition was performed using iodobenzene, as shown in Table 3. The reaction of **2a** and iodobenzene under Chen's condition afforded **3a** in 77% yield in short time. The yield of **3a** increased to 94% when the reaction was carried out under Fabrizi's condition employing excess amounts of Et_3N. Bromobenzene showed a sluggish reactivity (entry 3) under the condition.

Thus we selected the Fabrizi's condition as an optimum one (entry 2 in Table 3) and examined the arylation of **2a** with some typical iodoarenes.[11] As shown in Table 4, the reaction with *p*-iodotoluene (entry 2) gave **3f** in good yield (80%) along with its stereoisomer **4f'** in low yield (8%). The reactions with *o*-iodotoluene (entry 3), *p*-iodoanisole (entry 4), ethyl 4-iodobenzoate (entry 5), and 5-iodo-*m*-xylene (entry 6) showed similar results, and the products **3h–j** and **3c** were obtained in good yields (72–90%) along with their stereoisomers **4h–j** (3–10%) as minor products. The yields of products were somewhat higher when we used iodoarenes (Table 4) instead of arenes (Table 2), although the corresponding stereoisomers were formed in most entries.[15] As an example, compound **3c** was obtained in 69% using *m*-xylene (entry 3 in Table 2) while the yield increased to 90% (entry 6 in Table 4) by using 5-iodo-*m*-xylene.

The minor stereoisomer, **4i** as an example, could be synthesized as a major product, as shown in Scheme 3. Palladium-catalyzed phenylation of the methoxy derivative **2c**[2i] produced **4i** as a major product (82%) along with a trace amount of **3i** (6%), while the reaction of **2a** with *p*-iodoanisole gave **3i** as a major product (entry 4 in Table 4).

Based on the experimental results, the mechanism for the Pd^{II}-catalyzed arylation of **2a** with arenes could be proposed, as shown in Figure 1. An arylpalladium intermediate ArPd(OPiv) might be generated from arene and $Pd(OPiv)_2$ either via an electrophilic palladation (S_EAr)[10a–c,g,k] or a concerted metalation-deprotonation (CMD) mechanism.[10a–c,h,i,l] The arylpalladium intermediate underwent the typical oxidative Heck catalytic process. It is interesting to note that the presence of a methoxy group in the Weinreb amide moiety could enhance the rate of the coordination/insertion process due to the possible chelation between the Pd center and the methoxy group in the alkylpalladium intermediate **II**.[14b,16,17] Subsequent rotation around the C–C bond and β-H elimination process furnished the arylated product **3**. When we used an aryl iodide, the mechanism might be similar with the proposed one by Fabrizi;[15a] that is a sequential generation of Pd^0 from $Pd(OAc)_2$ and Et_3N, an oxidative addition of ArI to Pd^0 to generate ArPdI, and the ArPdI species carrying out the normal Heck type catalytic cycle.

In summary, an efficient synthetic protocol of β,β-diaryl-α,β-unsaturated Weinreb amides has been developed. The synthesis was carried out via a palladium-catalyzed oxidative arylation of β-aryl-α,β-unsaturated Weinreb amides with arenes or a Heck type arylation with iodoarenes.

Acknowledgments

This research was supported by the Basic Science Research Program through the National Research Foundation of Korea (NRF) funded by the Ministry of Education, Science, and Technology (2012R1A1B3000541). Spectroscopic data were obtained from the Korea Basic Science Institute, Gwangju branch.

References and notes

1. Nahm, S.; Weinreb, S. M. *Tetrahedron Lett.* **1981**, *22*, 3815–3818.
2. For the synthetic applications of α,β-unsaturated Weinreb amides, see: (a) Marrec, O.; Borrini, J.; Billard, T.; Langlois, B. R. *Synlett* **2009**, 1241–1244; (b) Bennani, Y. L.; Sharpless, K. B. *Tetrahedron Lett.* **1993**, *34*, 2079–2082; (c) Rodriques, K. E. *Tetrahedron Lett.* **1991**, *32*, 1275–1278; (d) Nuzillard, J.-M.; Boumendjel, A.; Massiot, G. *Tetrahedron Lett.* **1989**, *30*, 3779–3780; (e) Evans, D. A.; Kaldor, S. W.; Jones, T. K.; Clardy, J.; Stout, T. J. *J. Am. Chem. Soc.* **1990**, *112*, 7001–7031; (f) Davies, S. G.; Iwamoto, K.; Smethurst, C. A. P.; Smith, A. D.; Rodriguez-Solla, H. *Synlett* **2002**, 1146–1148; (g) Burke, A. J.; Davies, S. G.; Garner, A. C.; McCarthy, T. D.; Roberts, P. M.; Smith, A. D.; Rodriguez-Solla, H.; Vickers, R. L. *Org. Biomol. Chem.* **2004**, *2*, 1387–1394; (h) Corminboeuf, O.; Renaud, P. *Org. Lett.* **2002**, *4*, 1735–1738; (i) Shintani, R.; Kimura, T.; Hayashi, T. *Chem. Commun.* **2005**, 3213–3214.
3. (a) For the biological activity of α,β-unsaturated Weinreb amides, see: Li, Z.; Liu, C.; Liu, W. USP 6020,332, 2000 (*Chem. Abstr.* **2000**, *132*, 118764).; (b) Li, Z.; Liu, C.; Liu, W. CN 1167568, 1997 (*Chem. Abstr.* **2000**, *132*, 60481).; (c) Li, Z.; Liu, C.; Liu, W. EP 860438A1, 1998 (*Chem. Abstr.* **1998**, *129*, 189128).; (d) Jan, V.; Gunther, H.; Peter, B.; Burkhard, S. EP 601477A1, 1994 (*Chem. Abstr.* **1994**, *121*, 108248).
4. For the synthesis of Weinreb amides from carboxylic acids including α,β-unsaturated derivatives, see: (a) Niu, T.; Zhang, W.; Huang, D.; Xu, C.; Wang, H.; Hu, Y. *Org. Lett.* **2009**, *11*, 4474–4477; (b) Kumar, A.; Akula, H. K.; Lakshman, M. K. *Eur. J. Org. Chem.* **2010**, 2709–2715; (c) Kim, J.-G.; Jang, D. O. *Bull. Korean Chem. Soc.* **2010**, *31*, 171–173; (d) Hioki, K.; Kobayashi, H.; Ohkihara, R.; Tani, S.; Kunishima, M. *Chem. Pharm. Bull.* **2004**, *52*, 470–472; (e) Williams, J. M.; Jobson, R. B.; Yasuda, N.; Marchesini, G.; Dolling, U.-H.; Grabowski, E. J. J. *Tetrahedron Lett.* **1995**, *36*, 5461–5464.
5. For the synthesis of α,β-unsaturated Weinreb amides via Horner–Wadsworth–Emmons and Wittig type reactions, see: (a) Ando, K. *Synlett* **2001**, 1272–1274; (b) Ando, K.; Nagaya, S.; Tarumi, Y. *Tetrahedron Lett.* **2009**, *50*, 5689–5691; (c) Kojima, S.; Hidaka, T.; Yamakawa, A. *Chem. Lett.* **2005**, *34*, 470–471; (d) Kojima, S.; Hidaka, T.; Ohba, Y. *Heteroatom Chem.* **2004**, *15*, 515–523; (e) Fortin, S.; Dupont, F.; Deslongchamps, P. *J. Org. Chem.* **2002**, *67*, 5437–5439; (f) Piva, O.; Comesse, S. *Eur. J. Org. Chem.* **2000**, 2417–2424; (g) Blackburn, L.; Kanno, H.; Taylor, R. J. K. *Tetrahedron Lett.* **2003**, *44*, 115–118; (h) Fang, F.; Li, Y.; Tian, S.-K. *Eur. J. Org. Chem.* **2011**, 1084–1091.
6. For the synthesis of α,β-unsaturated Weinreb amides via the Julia and Julia-Kocienski olefination protocols, see: (a) Manjunath, B. N.; Sane, N. P.; Aidhen, I. S. *Eur. J. Org. Chem.* **2006**, 2851–2855; (b) Alonso, D. A.; Fuensanta, M.; Gomez-Bengoa, E.; Najera, C. *Adv. Synth. Catal.* **2008**, *350*, 1823–1829; (c) Alonso, D. A.; Fuensanta, M.; Gomez-Bengoa, E.; Najera, C. *Eur. J. Org. Chem.* **2008**, 2915–2922; (d) Ghosh, A. K.; Banerjee, S.; Sinha, S.; Kang, S. B.; Zajc, B. *J. Org. Chem.* **2009**, *74*, 3689–3697; (e) Beney, C.; Boumendjel, A.; Mariotte, A.-M. *Tetrahedron Lett.* **1988**, *39*, 5779–5780.
7. For the other synthesis of α,β-unsaturated Weinreb amides, see: (a) Vedrenne, E.; Dupont, H.; Oualef, S.; Elkaim, L.; Grimaud, L. *Synlett* **2005**, 670–672; (b) Lu, B.-L.; Shi, M. *Chem. Eur. J.* **2011**, *17*, 9070–9075.
8. Krishnamoorthy, R.; Lam, S. Q.; Manley, C. M.; Herr, R. J. *J. Org. Chem.* **2010**, *75*, 1251–1258.
9. For selected oxidative Heck arylation with arenes, see: (a) Bras, J. L.; Muzart, J. *Chem. Rev.* **2011**, *111*, 1170–1214; (b) Yeung, C. S.; Dong, V. M. *Chem. Rev.* **2011**, *111*, 1215–1292; (c) Rossi, R.; Bellina, F.; Lessi, M. *Synthesis* **2010**, 4131–4153; (d) Karimi, B.; Behzadnia, H.; Elhamifar, D.; Akhavan, P. F.; Esfahani, F. K.; Zamani, A. *Synthesis* **2010**, 1399–1427; (e) Zhang, Y.-H.; Shi, B.-F.; Yu, J.-Q. *J. Am. Chem. Soc.* **2009**, *131*, 5072–5074; (f) Yokota, T.; Tani, M.; Sakaguchi, S.; Ishii, Y. *J. Am. Chem. Soc.* **2003**, *125*, 1476–1477; (g) Jia, C.; Lu, W.; Kitamura, T.; Fujiwara, Y. *Org. Lett.* **1999**, *1*, 2097–2100; (h) Kubota, A.; Emmert, M. H.; Sanford, M. S. *Org. Lett.* **2012**, *14*, 1760–1763; (i) Nishikata, T.; Lipshutz, B. H. *Org. Lett.* **2010**, *12*, 1972–1975; (j) Pan, D.; Yu, M.; Chen, W.; Jiao, N. *Chem. Asian J.* **2010**, *5*, 1090–1093; (k) Li, Z.; Zhang, Y.; Liu, Z.-Q. *Org. Lett.* **2012**, *14*, 74–77; (l) Shang, X.; Xiong, Y.; Zhang, Y.; Zhang, L.; Liu, Z. *Synlett* **2012**, 259–262; (m) Zhang, Y.; Li, Z.; Liu, Z.-Q. *Org. Lett.* **2012**, *14*, 226–229.
10. For our recent papers, see: (a) Kim, K. H.; Lee, H. S.; Kim, J. N. *Tetrahedron Lett.* **2011**, *52*, 6228–6233; (b) Kim, K. H.; Lee, H. S.; Kim, S. H.; Kim, J. N. *Tetrahedron Lett.* **2012**, *53*, 1323–1327; (c) Kim, K. H.; Lee, H. S.; Kim, S. H.; Kim, J. N. *Tetrahedron Lett.* **2012**, *53*, 2761–2764. and further references cited therein; The condition employing PivOH as a proton shuttle during the aryl C–H bond activation was originally developed by Fagnou and applied extensively for the C–H bond activation of arenes, see: (d) Lafrance, M.; Fagnou, K. *J. Am. Chem. Soc.* **2006**, *128*, 16496–16497; (e) Stuart, D. R.; Villemure, E.; Fagnou, K. *J. Am. Chem. Soc.* **2007**, *129*, 12072–12073; (f) Stuart, D. R.; Fagnou, K. *Science* **2007**, *316*, 1172–1175; (g) Liegault, B.; Lee, D.; Huestis, M. P.; Stuart, D. R.; Fagnou, K. *J. Org. Chem.* **2008**, *73*, 5022–5028; (h) Gorelsky, S. I.; Lapointe, D.; Fagnou, K. *J. Org. Chem.* **2012**, *77*, 658–668; (i) Potavathri, S.; Pereira, K. C.; Gorelsky, S. I.; Pike, A.; LeBris, A. P.; DeBoef, B. *J. Am. Chem. Soc.* **2010**, *132*, 14676–14681; (j) Potavathri, S.; Kantak, A.; DeBoef, B. *Chem. Commun.* **2011**, *47*, 4679–4681; (k) Miyasaka, M.; Hirano, K.; Satoh, T.; Miura, M. *J. Org. Chem.* **2010**, *75*, 5421–5424; (l) Baghbanzadeh, M.; Pilger, C.; Kappe, C. O. *J. Org. Chem.* **2011**, *76*, 8138–8142.
11. *Typical procedure for the synthesis of **3a** with benzene*: A stirred solution of **2a** (96 mg, 0.5 mmol), $Pd(TFA)_2$ (8.3 mg, 5 mol %), AgOAc (252 mg, 1.5 mmol), and PivOH (308 mg, 3.0 mmol) in benzene (2.7 mL, 30 mmol) was heated to reflux under nitrogen atmosphere for 20 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 the removal of solvent and column chromatographic purification process (hexanes/EtOAc, 5:1) compound **3a** was isolated as a pale yellow solid, 117 mg (87%). Other compounds were synthesized similarly, and the selected spectroscopic data of compounds **3a**–**e**, **4b**, and **4g** are as follows.
Compound 3a: 87%; pale yellow solid, mp 76–77 °C; IR (KBr) 1654, 1616, 1380, 1178 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 3.15 (s, 3H), 3.70 (s, 3H), 6.70 (br s, 1H), 7.21–7.27 (m, 2H), 7.28–7.38 (m, 8H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 32.31, 61.60, 117.38, 127.85, 128.00, 128.18, 128.20, 128.75, 129.17, 139.10, 141.56, 153.10, 167.24; ESIMS *m/z* 268 $[M+1]^+$. Anal. Calcd for $C_{17}H_{17}NO_2$: C, 76.38; H, 6.41; N, 5.24. Found: C, 76.69; H, 6.56; N, 5.11.*Compound 3b*: 68%; pale yellow oil; IR (film) 1654, 1617, 1378, 1178 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.02 (s, 3H), 2.33 (s, 3H), 3.19 (s, 3H), 3.67 (s, 3H), 6.29 (br s, 1H), 7.01–7.09 (m, 3H), 7.20–7.30 (m, 5H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 19.78, 20.84, 32.40, 61.69, 120.32, 127.88, 128.08, 128.72, 128.76, 130.30, 130.39, 132.91, 135.08, 138.99, 142.04, 152.16, 167.99; ESIMS *m/z* 296 $[M+1]^+$. Anal. Calcd for $C_{19}H_{21}NO_2$: C, 77.26; H, 7.17; N, 4.74. Found: C, 77.17; H, 7.34; N, 4.61.
Compound 3c: 69%; pale yellow oil; IR (film) 1655, 1614, 1597, 1376, 1176 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.28 (s, 6H), 3.14 (s, 3H), 3.70 (s, 3H), 6.65 (br s, 1H), 6.80–7.02 (m, 3H), 7.18–7.28 (m, 2H), 7.29–7.38 (m, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 21.22, 32.36, 61.61, 117.26, 126.12, 127.85, 127.96, 129.20, 130.54, 137.76, 139.37, 141.58, 153.70, 167.41; ESIMS *m/z* 296 $[M+1]^+$. Anal. Calcd for $C_{19}H_{21}NO_2$: C, 77.26; H, 7.17; N, 4.74. Found: C, 77.57; H, 7.40; N, 4.83.
Compound 3d: 82%; pale yellow oil; IR (film) 1654, 1610, 1376, 1175 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.15 (s, 3H), 2.19 (s, 3H), 3.06 (s, 3H), 3.62 (s, 3H), 6.60 (br s, 1H), 6.86–7.06 (m, 3H), 7.10–7.19 (m, 2H), 7.20–7.31 (m, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 19.52, 19.78, 32.35, 61.65, 116.51, 125.85, 127.85, 127.94, 129.22, 129.36, 129.56, 136.48, 137.70, 139.16, 139.41, 153.50, 167.35; ESIMS *m/z* 296 $[M+1]^+$. Anal. Calcd for $C_{19}H_{21}NO_2$: C, 77.26; H, 7.17; N, 4.74. Found: C, 77.32; H, 7.02; N, 4.63.
Compound 3e: 80%; pale yellow oil; IR (film) 1653, 1616, 1468, 1370, 1130 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 3.15 (s, 3H), 3.71 (s, 3H), 6.67 (br s, 1H), 7.13 (dd, *J* = 8.4 and 2.1 Hz, 1H), 7.17–7.24 (m, 2H), 7.33–7.42 (m, 5H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 32.26, 61.82, 118.91, 127.46, 128.19, 128.52, 129.12, 129.91, 130.23, 132.58, 132.90, 138.06, 141.60, 150.46, 166.76; ESIMS *m/z* 336 $[M+1]^+$, 338 $[M+3]^+$. Anal. Calcd for $C_{17}H_{15}Cl_2NO_2$: C, 60.73; H, 4.50; N, 4.17. Found: C, 60.86; H, 4.85; N, 4.14.
Compound 4b: 16%; pale yellow solid, mp 116–117 °C; IR (KBr) 1658, 1614, 1376, 1176 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.05 (s, 3H), 2.30 (s, 3H), 3.15 (s, 3H), 3.73 (s, 3H), 6.88 (br s, 1H), 6.92 (br s, 1H), 7.02–7.12 (m, 2H), 7.26–7.36 (m, 5H); ESIMS *m/z* 296 $[M+1]^+$.
Compound 4g: 20%; white solid, mp 110–111 °C; IR (KBr) 1663, 1598, 1380, 1174 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 3.09 (s, 3H), 3.54 (s, 3H), 3.76 (s, 2H), 6.98 (s, 1H), 7.15–7.23 (m, 2H), 7.24–7.33 (m, 6H), 7.40–7.46 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 32.43, 34.40, 61.20, 126.28, 127.01, 127.40, 128.30, 128.42, 128.72, 131.30, 135.46, 137.74, 142.25, 172.36; ESIMS *m/z* 282 $[M+1]^+$. Anal. Calcd for $C_{18}H_{19}NO_2$: C, 76.84; H, 6.81; N, 4.98. Found: C, 76.69; H, 6.92; N, 4.83.
*Typical procedure for the synthesis of **3a** with iodobenzene*: A stirred solution of **2a** (96 mg, 0.5 mmol), iodobenzene (205 mg, 1.0 mmol), and $Pd(OAc)_2$ (5.6 mg, 5 mol %) in triethylamine (0.7 mL, 5.0 mmol) was heated to 100 °C for 16 h under nitrogen atmosphere. After the aqueous extractive workup and column chromatographic purification process (hexanes/EtOAc, 5:1) compound **3a** was obtained as a pale yellow solid, 126 mg (94%). Other compounds were synthesized similarly, and the spectroscopic data of compounds **3f**, **3h**–**j**, and **4i** are as follows.
Compound 3f: 80%; colorless oil; IR (film) 1653, 1609, 1378, 1178, 1114 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.28 (s, 3H), 3.06 (s, 3H), 3.62 (s, 3H), 6.61 (br s, 1H), 7.02–7.08 (m, 2H), 7.09–7.19 (m, 4H), 7.23–7.30 (m, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 21.15, 32.31, 61.65, 116.45, 127.85, 127.96, 128.16, 128.96, 129.18, 138.66, 138.96, 139.31, 153.42, 167.40; ESIMS *m/z* 282 $[M+1]^+$. Anal. Calcd for $C_{18}H_{19}NO_2$: C, 76.84; H, 6.81; N, 4.98. Found: C, 77.04; H, 7.06; N, 4.77.
Compound 3h: 72%; pale yellow oil; IR (film) 1654, 1619, 1379, 1178, 1115 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.07 (s, 3H), 3.19 (s, 3H), 3.66 (s, 3H), 6.30 (br s, 1H), 7.12–7.31 (m, 9H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 20.25, 32.28, 61.65, 120.48, 125.63, 127.85, 127.95, 128.07, 128.71, 129.62, 130.46, 136.06, 138.89, 142.15, 151.86, 167.91; ESIMS *m/z* 282 $[M+1]^+$. Anal. Calcd for $C_{18}H_{19}NO_2$: C, 76.84; H, 6.81; N, 4.98. Found: C, 76.91; H, 6.96; N, 4.69.
Compound 3i: 88%; pale yellow oil; IR (film) 1653, 1603, 1510, 1379, 1248, 1179, 1031 cm^{-1}; ^1H NMR (DMSO-d_6, 300 MHz) δ 3.05 (s, 3H), 3.67 (s, 3H), 3.76 (s, 3H), 6.63 (br s, 1H), 6.93 (d, *J* = 9.0 Hz, 2H), 7.08–7.15 (m, 2H), 7.20 (d, *J* = 9.0 Hz, 2H), 7.29–7.40 (m, 3H); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 32.18, 55.21, 61.15, 113.90, 116.96, 127.72, 127.85, 129.05, 129.24, 133.20, 139.25, 150.29, 159.87, 166.55; ESIMS *m/z* 298 $[M+1]^+$. Anal. Calcd for $C_{18}H_{19}NO_3$: C, 72.71; H, 6.44; N, 4.71. Found: C, 72.98; H, 6.71; N, 4.74.
Compound 3j: 89%; pale yellow oil; IR (film) 1715, 1654, 1608, 1274, 1102 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.32 (t, *J* = 7.0 Hz, 3H), 3.11 (s, 3H), 3.66 (s, 3H), 4.31 (q, *J* = 7.0 Hz, 2H), 6.69 (br s, 1H), 7.12–7.18 (m, 2H), 7.26–7.29 (m, 3H), 7.30 (d, *J* = 8.0 Hz, 2H), 7.93 (d, *J* = 8.0 Hz, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 14.25, 32.20, 61.02, 61.81, 119.14, 128.05, 128.17, 128.27, 129.15, 129.47, 130.51, 138.55, 145.92, 151.88, 166.09, 167.01; ESIMS *m/z* 340 $[M+1]^+$. Anal. Calcd for $C_{20}H_{21}NO_4$: C, 70.78; H, 6.24; N, 4.13. Found: C, 70.86; H, 6.44; N, 4.04.
Compound 4i: 82%; pale yellow oil; IR (film) 1651, 1573, 1510, 1378, '1247, 1175 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 3.10 (s, 3H), 3.64 (s, 3H), 3.74 (s, 3H), 6.54 (br s, 1H), 6.80 (d, *J* = 8.5 Hz, 2H), 7.07–7.13 (m, 2H), 7.21–7.31 (m, 5H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 32.47, 55.10, 61.78, 113.29, 116.74, 128.19, 128.46, 128.76,

130.81, 131.26, 142.09, 153.05, 159.51, 167,51; ESIMS *m*/*z* 298 $[M+1]^+$. Anal. Calcd for $C_{18}H_{19}NO_3$: C, 72.71; H, 6.44; N, 4.71. Found: C, 72.65; H, 6.76; N, 4.59.

12. For the isomerization of double bond catalyzed by XPdH species, see: (a) Calo, V.; Nacci, A.; Monopoli, A.; Laera, S.; Cioffi, N. *J. Org. Chem.* **2003**, *68*, 2929–2933; (b) Huang, Q.; Larock, R. C. *J. Org. Chem.* **2003**, *68*, 7342–7349; (c) Nasveschuk, C. G.; Frein, J. D.; Jui, N. T.; Rovis, T. *Org. Lett.* **2007**, *9*, 5099–5102; (d) Narhi, K.; Franzen, J.; Backvall, J.-E. *Chem. Eur. J.* **2005**, *11*, 6937–6943; (e) Yip, K.-T.; Zhu, N.-Y.; Yang, D. *Org. Lett.* **2009**, *11*, 1911–1914; (f) Dankwardt, J. W.; Flippin, L. A. *J. Org. Chem.* **1995**, *60*, 2312–2313.
13. For the Pd-catalyzed γ-arylation of α,β-unsaturated carbonyl compounds, see: (a) Terao, Y.; Satoh, T.; Miura, M.; Nomura, M. *Tetrahedron Lett.* **1998**, *39*, 6203–6206; (b) Yu, M.; Xie, Y.; Li, J.; Zhang, Y. *Adv. Synth. Catal.* **2011**, *353*, 2933–2938; (c) Hyde, A. M.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2008**, *47*, 177–180.
14. For the selected examples on Pd-catalyzed Heck reaction with aryl iodide under the influence of AgOAc/AcOH, see (a) Xu, D.; Lu, C.; Chen, W. *Tetrahedron* **2012**, *68*, 1466–1474; (b) Guo, H.-M.; Rao, W.-H.; Niu, H.-Y.; Jiang, L.-L.; Liang, L.; Zhang, Y.; Qu, G.-R. *RSC Adv.* **2011**, *1*, 961–963.
15. (a) Bernini, R.; Cacchi, S.; De Salve, I.; Fabrizi, G. *Synlett* **2006**, 2947–2952; (b) Battistuzzi, G.; Bernini, R.; Cacchi, S.; De Salve, I.; Fabrizi, G. *Adv. Synth. Catal.* **2007**, *349*, 297–302.
16. For some selected Pd-catalyzed, chelation-assisted arylation of olefins with arenes, see: (a) Pan, D.; Jiao, N. *Synlett* **2010**, 1577–1588; (b) Pan, D.; Chen, A.; Su, Y.; Zhou, W.; Li, S.; Jia, W.; Xiao, J.; Liu, Q.; Zhang, L.; Jiao, N. *Angew. Chem., Int. Ed.* **2008**, *47*, 4729–4732; (c) Su, Y.; Jiao, N. *Org. Lett.* **2009**, *11*, 2980–2983; (d) Nilsson, P.; Larhed, M.; Hallberg, A. *J. Am. Chem. Soc.* **2003**, *125*, 3430–3431; (e) Prediger, P.; Barbosa, L. F.; Genisson, Y.; Correia, C. R. D. *J. Org. Chem.* **2011**, *76*, 7737–7749; (f) Delcamp, J. H.; Brucks, A. P.; White, M. C. *J. Am. Chem. Soc.* **2008**, *130*, 11270–11271; (g) Llamas, T.; Arrayas, R. G.; Carretero, J. C. *Adv. Synth. Catal.* **2004**, *346*, 1651–1654; (h) Yahiaoui, S.; Fardost, A.; Trejos, A.; Larhed, M. *J. Org. Chem.* **2011**, *76*, 2433–2438; (i) Datta, G. K.; Larhed, M. *Org. Biomol. Chem.* **2008**, *6*, 674–676; (j) Trejos, A.; Fardost, A.; Yahiaoui, S.; Larhed, M. *Chem. Commun.* **2009**, 7587–7589; (k) Skold, C.; Kleimark, J.; Trejos, A.; Odell, L. R.; Nilsson Lill, S. O.; Norrby, P.-O.; Larhed, M. *Chem. Eur. J.* **2012**, *18*, 4714–4722.
17. In order to clarify the chelation effect of a methoxy group in the Weinreb amide, we examined the control experiments with ethyl cinnamate and *N*,*N*-dimethylcinnamide under the same reaction conditions with a limited amount of AgOAc (2.0 equiv). The reaction of a mixture of **2a** and ethyl cinnamate (1:1) with benzene produced **3a** (52%) and ethyl 3,3-diphenylacrylate (28%) along with recovered **2a** (40%) and ethyl cinnamate (66%). The result stated that Weinreb amide **2a** is more reactive than ethyl cinnamate in about 1.9 times. The reaction of benzene with a 1:1 mixture of **2a** and *N*,*N*-dimethylcinnamide produced **3a** (20%) and *N*,*N*-dimethyl-3,3-diphenyl acrylamide (66%) along with recovered **2a** (68%) and *N*,*N*-dimethylcinnamide (23%). The result indicated that *N*,*N*-dimethylcinnamide is more reactive than **2a** in about 3.3 times. The high reactivity of *N*,*N*-dimethylcinnamide might be due to the rich electron density at the oxygen atom of the *N*,*N*-dimethylamide moiety which helps the coordination of PhPd(OPiv) to form the corresponding intermediate I (Fig. 1), as noted by Fabrizi. [15a] Further studies are currently in progress.