DOI: 10.1002/adsc.201100373

Palladium-Catalyzed Regioselective γ-Mono- and Diarylation of Acrylamide Derivatives with Aryl Halides

Ming Yu,[a] Yongju Xie,[a] Jinheng Li,[b,*] and Yuhong Zhang[a,c,*]

[a] Department of Chemistry, Zhejiang University, Hangzhou 310027, People's Republic of China
Fax: (+86)-571-8795-3244; e-mail: yhzhang@zju.edu.cn
[b] College of Chemistry and Chemical Engineering, Hunan University, Changsha 410082, People's Republic of China
Fax: (+86)-577-8836-8607; e-mail: jhli@hunnu.edu.cn
[c] State Key Laboratory of Applied Organic Chemistry, Lanzhou University, Lanzhou 730000, People's Republic of China

Received: May 12, 2011; Published online: November 7, 2011

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/adcs.201100373.

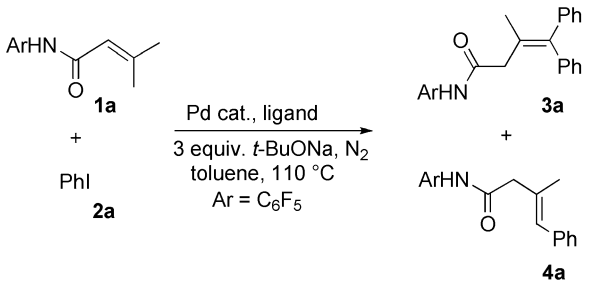
Abstract: Palladium-catalyzed direct mono- and diarylations involving C(sp^3)–H cleavage at the γ-position of acrylamides are described. The monoarylation products can be obtained with *ortho*-substituted aryl halides. Single crystal X-ray diffraction has shown that the double bond has shifted towards the introduced aryl group to afford the γ-arylated β,γ-unsaturated amide products. A second arylation occurs when less sterically hindered aryl halides are employed. This chemistry offers a novel disconnection for the synthesis of γ-arylated compounds.

Keywords: acrylamides; allylic compounds; amides; γ-arylation; aryl halides; C–C bond formation; palladium catalysis

The transition metal-catalyzed coupling of enolates with aryl and vinyl electrophiles has attracted significant research efforts due to its importance in organic synthesis and the chemical industry.[1] In particular, the palladium-catalyzed direct α-arylation of ketones and related carbonyl functional groups has emerged as a powerful and versatile tool for the generation of α-aryl ketones from ketones and aryl halides *via* an enolate mechanism.[2] Recently, some examples of the β-arylation reaction of ketones and related carbonyl functional groups were reported.[3] However, the extension of this reaction to α,β-unsaturated carbonyl compounds by the dienolate mechanism has been much less developed.[4] A key factor that contributes to the difficulty of developing such a process is the poor regioselectivity: there is the potential for the generation of α-, β-, and γ-regioisomeric products.[5] In addition, the reactivity of the dienolate is reduced compared to that of the enolate for it is less nucleophilic than the enolate. In fact, the γ-arylation of α,β-unsaturated ketones and related carbonyl functional groups is still rare.[6] To overcome these problems, activated α,β-unsaturated esters instead of simple α,β-unsaturated esters have been employed for the preparation of γ-arylated α,β-unsaturated esters.[7] Herein, we report the new Pd(0)-catalyzed intermolecular arylation of acrylamide derivatives with aryl iodides and aryl bromides. It is found that arylation at the γ-position to the C–H bond of the acrylamides can be smoothly achieved and the subsequent double bond shift leads to the formation of β,γ-unsaturated amide products. The α- and/or β-regioisomeric arylation products are not detected in this transformation. This chemistry will offer a novel disconnection for the synthesis of arylated compounds.

Initially, we examined the reaction of substrate **1a** and iodobenzene **2a** in the presence of 10 mol% $Pd(OAc)_2$ and 3 equiv. *t*-BuONa at 110 °C for 1 h, which afforded arylated product **3a** in 9% yield (Table 1). The result of heteronuclear multiple-bond coherence (HMBC) experiments of the product demonstrated that the CH_2 groups had correlations with carbonyl groups, revealing that double bond was shifted towards the aryl group. The most valuable information regarding the constitution of the arylated product was unambiguously established by X-ray analysis of the related derivative **4e** (CCDC 825218) (Figure 1), which clearly indicated the double bond shift towards the aryl group to give the β,γ-unsaturated amides. The 1,3-hydrogen shift in the absence of aryl iodide was not observed under the reaction conditions, showing that the 1,3-hydrogen shift took place after the arylation. The effects of palladium catalysts and phosphine ligands toward the reaction were examined (Table 1). The ligand has a significant impact on the reactivity. The reaction of substrate **1a** with iodobenzene **2a** in the absence of the ligand or in the

Table 1. The effect of palladium-catalysts and ligands.[a]



Entry	Catalyst	Ligand	Yield of **3a** [%][b]
1	$Pd(OAc)_2$	–	9
2	$Pd(OAc)_2$	dppb	trace
3	$Pd(OAc)_2$	PCy_3	trace
4	$Pd(OAc)_2$	xantphos	22
5	$Pd(Ph_3P)_4$	–	14
6	$Pd(OAc)_2$	Ph_3P	40 (24)[c,d]
7	$Pd(OAc)_2$	Ph_3P	66
8	$Pd(Ph_3P)_2Cl_2$	–	65[c]
9	$PdCl_2$	Ph_3P	32 (29)[d]

[a] *Conditions:* **1a** (79.5 mg, 0.3 mmol), iodobenzene (244.8 mg, 1.2 mmol), 10 mol% Pd catalyst, 20 mol% ligand, 3 equiv. *t*-BuONa (0.9 mmol, 86.4 mg), 2 mL toluene under a nitrogen atmosphere at 110 °C for 1 h.

[b] Isolated yield of **3a** and **4a**.

[c] Run at 80 °C for 12 h.

[d] The yield of single arylated **4a** is given in the parenthesis.

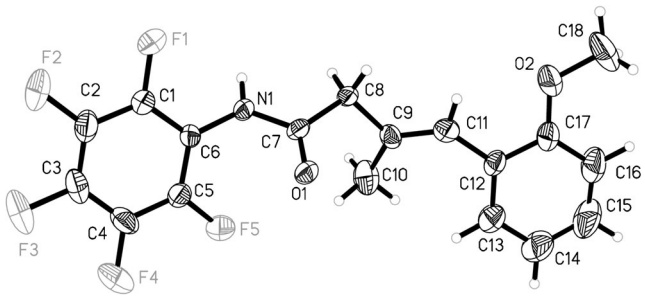


Figure 1. The X-ray crystal structure of product **4e**.

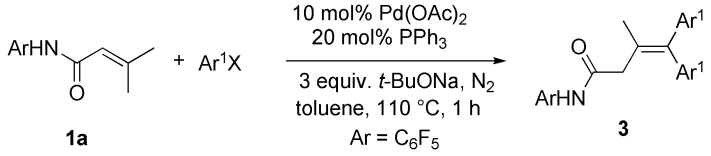
presence of alkylphosphine ligands such as dppb and PCy_3 showed poor reactivity (Table 1, entries 1–3). Better results were obtained with xantphos and the use of $Pd(PPh_3)_4$ delivered a 14% yield (Table 1, entries 4 and 5). The combination of 10 mol% $Pd(OAc)_2$ and 20 mol% PPh_3 afforded the diarylated product **3a** in 40% yield and the single arylated product in 24% yield at 80 °C for 12 h (Table 1, entry 6). The reaction efficiency was enhanced markedly when the temperature was increased to 110 °C to give a 66% yield after 1 h (Table 1, entry 7). Good results were also obtained by the use of $Pd(PPh_3)Cl_2$ to give a 65% yield at 80 °C for 12 h (Table 1, entry 8). In this case, however, the higher temperature did not favor the reaction. The combination of 10 mol% $PdCl_2$ and 20 mol% PPh_3 resulted in a mixture of **3a** and the single arylated product (Table 1, entry 9). The choice of palladium catalyst was important: $Pd(OAc)_2$ provided a superior result in comparison with $Pd(dba)_2$ or $Pd(CH_3CN)_2Cl_2$. There was no reaction when EtONa or Cs_2CO_3 was used as base (see Supporting Information).

We next examined the generality of this new tandem arylation reaction. The reaction was found to be chemoselective, and its wide scope is evident from the results summarized in Table 2. Both aryl iodides and aryl bromides reacted smoothly with **1a** to afford the diarylated β,γ-unsaturated amides. The electron-rich aryl iodides participated in the reaction to give the corresponding arylated products in good yields (Table 2, entries 1, 4, 6, and 10). Gratifyingly, aryl bromides showed almost the similar reactivity as aryl iodides to give the diarylated products in high efficiency (Table 2, entries 2–11). 4-Bromobiphenyl and 4-bromo-4′-methylbiphenyl underwent the reaction smoothly to afford the corresponding products in good yields (Table, 2, entries 12 and 13). It should be noted that electron-deficient aryl halides showed equally good reactivity as electron-rich aryl halides (Table 2, entries 14 and 15). The chemoselectivity of the reaction is noteworthy, as the presence of two halides (bromide and chloride) on the aromatic ring furnishes the β,γ-unsaturated amide **3j** as the sole reaction product. In addition, although the *N*-arylation and β-arylation (Heck reaction) could theoretically proceed under these conditions, the exclusive formation of products **3** was observed.

Interestingly, substrates containing *ortho*-substituents in the aryl halides participate in the reaction to give the corresponding single arylated β,γ-unsaturated amides (Table 3, entries 1–6). The X-ray diffraction analysis of the single crystal of product **4e** (CCDC 825218) indicated that the double bond in the acrylamides was shifted towards the aryl group and the amide was in the *trans*-position with regard to the aryl group to give an *E*-isomer (Figure 1). The results suggest that the direct arylation is predominantly controlled by steric factors in these systems and the second arylation failed to occur.

On the basis of the known chemistry of dienolates[6] and previous work on the Pd-catalyzed C–H bond activation,[8] we suggest two possible pathways (Path **A** and Path **B**) to account for the present arylation process (Scheme 1). In Path **A**, the Pd(0) initially undergoes the oxidative addition with aryl iodide to form intermediate **I**, which reacts with dienolate **II** to afford the intermediate **IV** and **VII**. The subsequent reductive elimination results in the arylated product **VIII**, which undergoes the 1,3-hydrogen shift to give the final γ-arylated product. Path **B** involves the formation of imine intermediate **V**, which results in the

Table 2. Direct diarylation of acrylamide derivatives.[a]



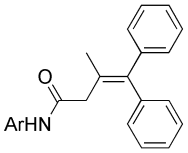
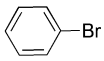
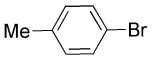
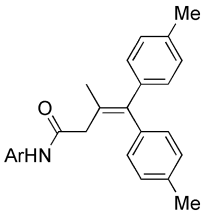
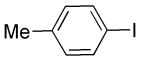
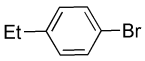
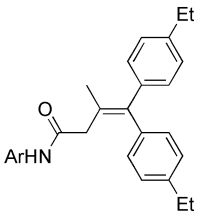
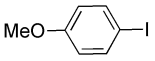
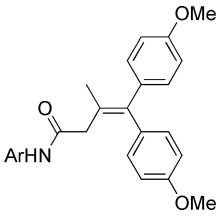
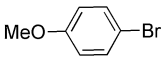
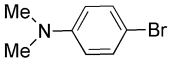
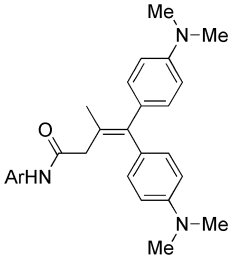
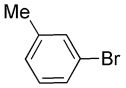
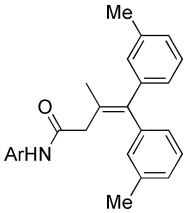
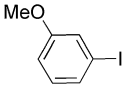
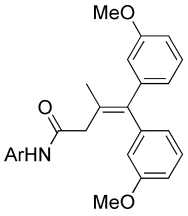
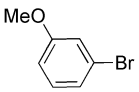
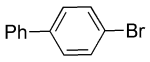
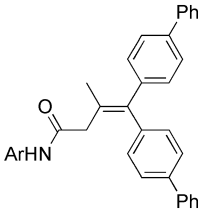
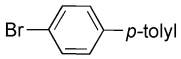
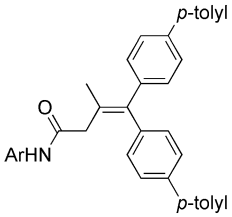
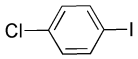
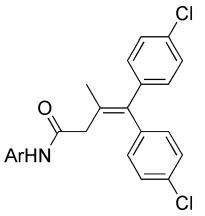
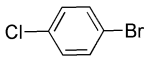
Entry	Ar^1-X	**3**	Yield[b] [%] (Product No.)
1			66 (**3a**)
2			48 (**3a**)
3			56 (**3b**)
4			64 (**3b**)
5			62 (**3c**)
6			56 (**3d**)
7			64 (**3d**)
8			55 (**3e**)
9			61 (**3f**)
10			56 (**3g**)
11			63 (**3g**)

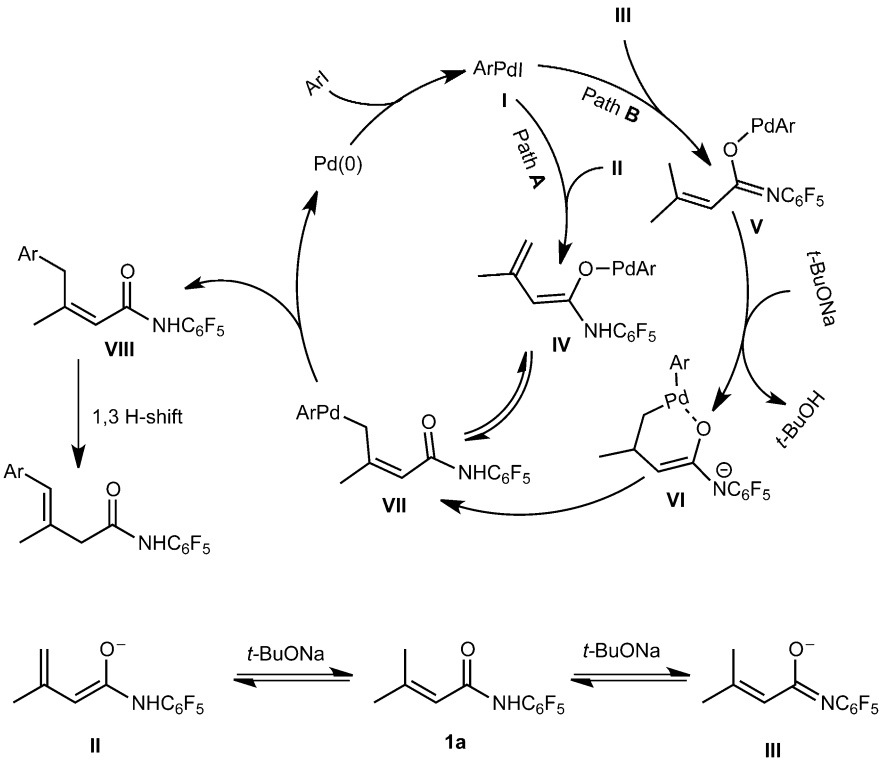
Table 2. (Continued)

Entry	Ar^1-X	3	Yield[b] [%] (Product No.)
12			71(**3h**)[c]
13			61 (**3i**)[c]
14			61 (**3j**)
15			63 (**3j**)

[a] *Conditions:* **1a** (79.5 mg, 0.3 mmol), aryl halide (1.2 mmol), 10 mol% $Pd(OAc)_2$ (6.7 mg, 0.03 mmol), 20 mol% PPh_3 (0.06 mmol, 15.7 mg), 3 equiv. *t*-BuONa (0.9 mmol, 86.4 mg), toluene (2 mL), 110 °C under N_2 for 1 h.

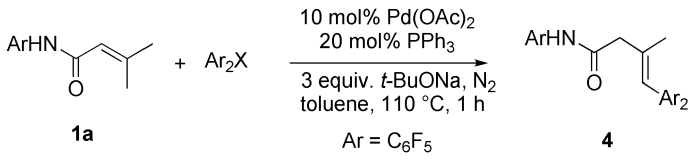
[b] Isolated yields.

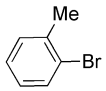
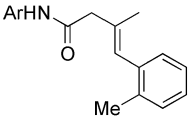
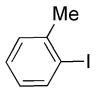
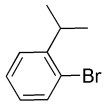
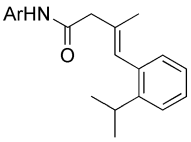
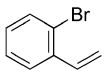
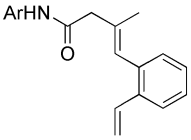
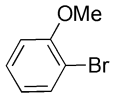
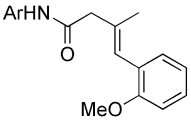
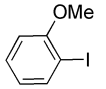
[c] The reaction was performed at 80 °C under N_2 for 12 h in the presence of 10 mol% $Pd(Ph_3P)_2Cl_2$ (0.03 mmol, 21.1 mg).



Scheme 1. The possible mechanism.

Table 3. Direct single arylation of acrylamide derivatives.[a]



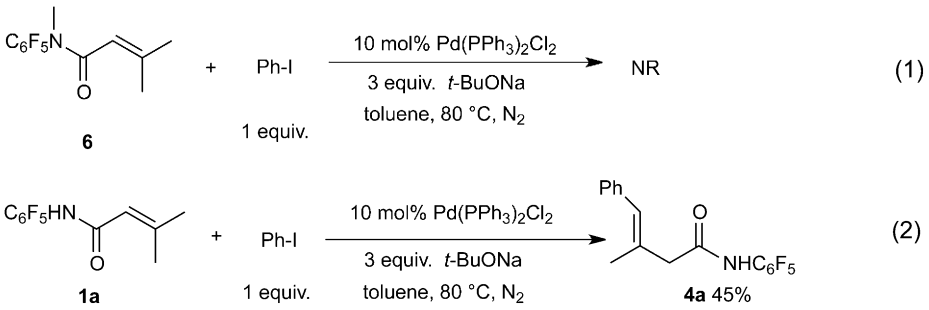
Entry	Ar^2-X	4	Yield[b] [%] (Product No.)
1			42 (**4b**)[c]
2			37(**4b**)[c]
3			70 (**4c**)
4			68 (**4d**)
5			65 (**4e**)[c,d]
6			61 (**4e**)[c]

[a] *Conditions:* **1a** (79.5 mg, 0.3 mmol), aryl halide (1.2 mmol), 10 mol% $Pd(OAc)_2$ (6.7 mg, 0.03 mmol), 20 mol% PPh_3 (0.06 mmol, 15.7 mg), 3 equiv. *t*-BuONa (86.4 mg, 0.9 mmol), toluene (2 mL), 110 °C under N_2 for 1 h.
[b] Isolated yields.
[c] The reaction was performed at 80 °C under N_2 for 12 h in the presence of 10 mol% $Pd(Ph_3P)_2Cl_2$ (0.03 mmol, 21.1 mg).
[d] **1a** (0.36 mmol), aryl bromide (0.3 mmol).

intermediate **VI** after the allylic hydrogen was abstracted by the base. The intramolecular anion exchange generates the same intermediate **VII**, which goes on to the product.

In an effort to gain more evidence about the mechanism, control experiments were performed to study the catalytic pathways (Scheme 2). Treatment of iodobenzene with (*E*)-*N*-perfluorophenylbut-2-enamide **6** failed to give the desired γ-arylated product under the identical conditions. This result shows that an acidic N–H bond in the amide directing group is essential for the reactivity. While this result is consistent with the mechanism illustrated in Path **B**, we still cannot rule out the mechanism shown in Path **A**.

In summary, we have developed a new method for achieving palladium-catalyzed direct mono- and di-



Scheme 2. Control experiments.

arylation of acrylamide derivatives at the γ-position with aryl halides. The monoarylation products can be achieved when *ortho*-substituted aryl halides are used. A 1,3-hydrogen shift towards the introduced aryl group occurred in the reaction, which led to the formation of the β,γ-unsaturated amides. The N–H bond of amides is crucial to the success of the reaction and this chemistry is compatible with a wide range of aryl iodides and bromides. Further studies to clarify the detailed mechanism and synthetic applications of this transformation are currently in progress.

Experimental Section

Typical Procedure for 3a

A mixture of 3-methyl-*N*-(perfluorophenyl) but-2-enamide **1a** (79.5 mg, 0.3 mmol), iodobenzene (244.8 mg, 1.2 mmol), Pd $(OAc)_2$ (6.7 mg, 0.03 mmol), PPh_3 (15.7 mg, 0.06 mmol) and *t*-BuONa (86.4 mg, 0.9 mmol) in toluene (2 mL) was stirred at room temperature under N_2 for 5 min, and then at 110 °C for 1 h. Afterward, the reaction mixture was allowed to cool to room temperature and filtered through a pad of celite. The solvent was evaporated under reduced pressure and the residue was subjected to flash column chromatography (sila gel, ethyl acetate/petroleum ether = 1:10, v/v) to obtain the desired products in 66% yield.

Acknowledgements

Funding from National Basic Research Program of China (No. 2011CB936003) and NSFC(No. 20872126, No. 2107216) is highly acknowledged.

References

[1] a) C. C. C. Johansson, T. J. Colacot, *Angew. Chem.* **2010**, *122*, 686; b) F. Bellina, R. Rossi, *Chem. Rev.* **2010**, *110*, 1082; c) F. Bellina, R. Rossi, *Angew. Chem.* **2010**, *122*, 686; *Angew. Chem. Int. Ed.* **2010**, *49*, 676; G. N. Varseev, M. E. Maier, *Org. Lett.* **2005**, *7*, 3881; d) A. Deagostino, C. Prandi, P. Venturello, *Org. Lett.* **2003**, *5*, 3815.

[2] For representative examples of α-arylation reactions, see: a) M. Palucki, S. L. Buchwald, *J. Am. Chem. Soc.* **1997**, *119*, 11108; b) D. C. Culkin, J. F. Hartwig, *Acc. Chem. Res.* **2003**, *36*, 234; c) F. Bellina, R. Rossi, *Chem. Rev.* **2010**, *110*, 1082; d) C.-K. Mai, M. F. Sammons, T. Sammakia, *Org. Lett.* **2010**, 12, 2306; e) J. M. Um, O. Gutierrez, F. Schoenebeck, K. N. Houk, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2010**, *132*, 6001.

[3] For representative examples of β-arylation reactions, see: a) A. Renaudat, L. Jean-Gerard, R. Jazzar, C. E. Kefalidis, E. Clot, O. Baudoin, *Angew. Chem.* **2010**, *122*, 7419; *Angew. Chem. Int. Ed.* **2010**, *49*, 7261; b) D. Shabashov, O. Daugulis, *J. Am. Chem. Soc.* **2010**, *132*, 3965.

[4] For representative examples of γ-arylation reactions of α,β-unsaturated carbonyl compounds see: a) G. Varseev, M. Maier, *Org. Lett.* **2005**, *7*, 3881; b) Y. Yamamoto, S. Hatsuya, J. Yamada, *J. Chem. Soc. Chem. Commun.* **1988**, 86; c) Y. Yamamoto, S. Hatsuya, J. Yamada, *J. Org. Chem.* **1990**, *55*, 3118; d) Y. Terao, T. Satoh, M. Miura, M. Nomura, *Bull. Chem. Soc. Jpn.* **1999**, *72*, 2345; e) T. Wang, J. Cook, *Org. Lett.* **2000**, *2*, 2057; f) A. M. Hyde, S. L. Buchwald, *Org. Lett.* **2009**, *11*, 2663.

[5] Y. Terao, Y. Kametani, H. Wakui, T. Satoh, M. Miura, M. Nomura, *Tetrahedron* **2001**, *57*, 5967.

[6] a) A. M. Hyde, S. L. Buchwald, *Angew. Chem.* **2008**, *120*, 183; *Angew. Chem. Int. Ed.* **2008**, *47*, 177; b) Y. Terao, T. Satoh, M. Miura, M. Nomura, *Tetrahedron Lett.* **1998**, *39*, 6203.

[7] D. S. Huang, J. F. Hartwig, *Angew. Chem.* **2010**, *122*, 5893; *Angew. Chem. Int. Ed.* **2010**, *49*, 5757.

[8] M. Wasa, K. M. Engle, J.-Q. Yu, *J. Am. Chem. Soc.* **2009**, *131*, 9886.

