DOI: 10.1002/ejoc.201000492

Palladium-Catalyzed C–C Coupling/C–H Activation: Formation of Isoindolinone-Fused Heterocyclic Compounds

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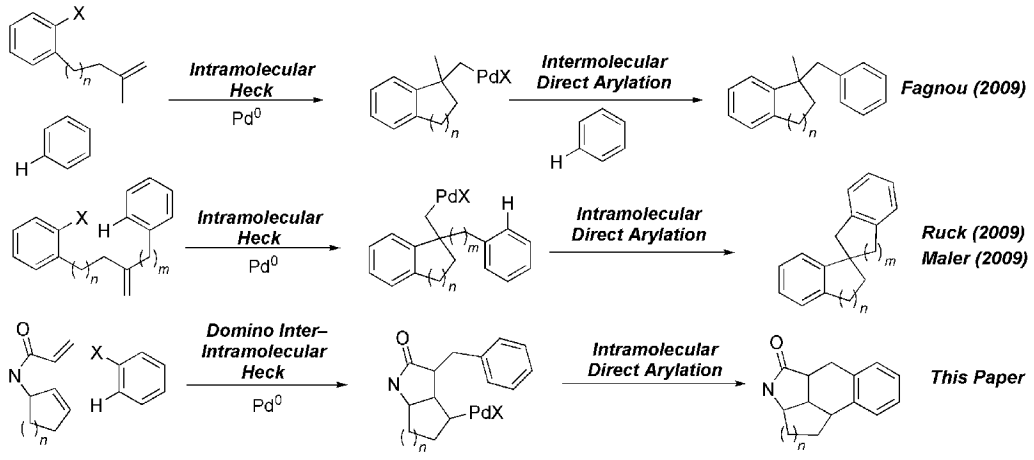
Keywords: Cyclization / Domino reactions / Fused-ring systems / Palladium / Isomerization

Inactivated dienes containing a cycloalkenyl moiety with aryl halides were used in a palladium-catalyzed reaction to give different kinds of rare, fused isoindolinone heterocyclic compounds through highly regioselective C–C coupling/C–H functionalization in a one-step domino reaction. Different dienes and aryl halides were shown to be very active in this reaction. Substituents on the aryl halides were ethoxycarbonyl, methoxycarbonyl, sulfonyl, formacyl, keto, cyano, acetyl, and naphthalene. The C–H functionalization and allyl isomerization occurred simultaneously when 1-iodobenzene or aryl halides were treated with substrates having allyl moieties on the protecting group. The generality of this process makes the reaction highly valuable due to the synthetic and medicinal importance of these kinds of fused heterocycles.

Introduction

Isoindolinone is an important heterocyclic scaffold. The use of isoindolinone derivatives in the areas of medicine, food, catalyst, dye, refineries, and electronics is well established.[1] Thus, the synthesis of the isoindolinone core and its derivatives have been an attractive goal in organic chemistry.[2] In recent years, there have been several developments in chemistry associated with isoindolinones.[3] To develop easy and practical approaches to a variety of isoindolinone derivatives decorated with useful pharmacophores, researchers have made use of new catalysts, mediums, or physical conditions in several well-established synthetic methodologies.[4,5] Furthermore, an array of new and innovative strategies from novel substrates have been developed that has made the synthesis of the isoindolinone core a much simpler process compared to earlier processes.[6–8] Because palladium-catalyzed cross-coupling in heterocyclic synthesis is indisputable, the electrophilic cyclization of *o*-alkynylanilines has proven to be a powerful tool in the construction of indoles.[9] Yasuhara and Sakamoto developed a palladium-catalyzed cascade sequence involving initial aminopalladation followed by a Heck reaction.[10] In this process, *o*-



Scheme 1. Formation isoindolinone by domino Heck–direct arylation involving alkylpalladium(II) intermediates.

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Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/ejoc.201000492.

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alkynylaniline derivatives were treated with alkenes containing electron-withdrawing groups to obtain 2-substituted 3-alkenylindoles.[11] Recently, Lu et al. reported the palladium(II)-catalyzed reaction of *o*-alkynylaniline derivatives and α,β-unsaturated carbonyl compounds, which was used to obtain 2-substituted 3-alkylindoles.[12] In this case, the reaction was performed in the presence of LiBr, which prevented the final β-hydride elimination reaction. In particular, the Pd-catalyzed olefination of aryl C–H bonds has the potential to emerge as a powerful platform for more direct access to the isoindole cores of complex molecules.[13–15] The first examples of a successful, convenient Heck–intramolecular direct arylation, involving alkylpalladium(II) intermediates and C–H functionalization, have recently been reported (Scheme 1).[16]

Results and Discussion

In recent years, we have created an efficient method of constructing five-membered heterocycles and tri- and tetracyclic heterocycles from 1,6-dienes or 1,6-enynes and aryl halides.[17] As part of our ongoing studies in this field, we report herein an efficient domino cyclization method for the preparation of different isoindolinones through carbopalladation and subsequent regioselective functionalization of the inactivated C–H bond. A survey of the reaction conditions was performed by using *N*-(cyclohex-2-enyl)-*N*-phenylacrylamide (**a**) and ethyl 4-bromobenzoate for the test experiment (Scheme 1, Table 1). The reaction of **a** with ethyl 4-bromobenzoate in *N*,*N*-dimethylformamide (DMF) in the presence of a catalytic amount of $Pd(OAc)_2$ produced ethyl 5-oxo-4-phenyl-0,1,2,3,3a,4,5,5a,6,10b-decahydronaphtho-[3,2,1-*cd*]indole-9-carboxylate **aa** in 53% yield after 24 h at 150 °C. There was also side product **i** with 15% yield, but the starting material was not completely converted. By controlling the experimental conditions, we discovered: (1) When the reaction time was prolonged from 24 to 36 h, the starting materials were completely converted into the product and the yield of **aa** increased to 70% (Table 1, Entries 1 and 2). However, there was no obvious increase in the yield of **aa** after prolonging the time from 36 to 54 h (Table 1, Entries 2 and 3). (2) When the temperature was decreased 140 °C, the amount of side product **i** formed increased (Table 1, Entry 4). When the temperature was increased to 170 °C, no results were obtained, except for one type of polymer (Table 1, Entry 5). (3) The Ag_2O additive prompted the conversion of the substrates (the substrate was completely converted in 24 h). However, the yield of **aa**

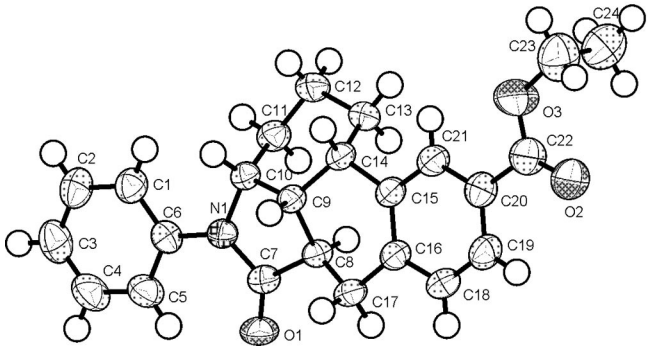
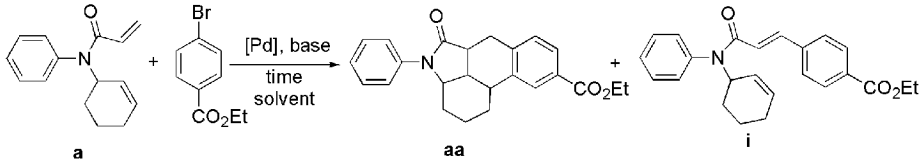


Figure 1. ORTEP plot of **aa** showing ellipsoids at the 30% probability level. Selected bond lengths [Å] and angles [°]: C9–C10 1.384(2), C9–C22 1.400(3), C10–C11 1.427(4), C11–C20 1.425(4), C20–C21 1.430(4), C21–C22 1.380(4), C9–C10–C30 120.9(2), C11–C10–C30 121.0(2), C20–C21–C24 124.6(2), C22–C21–C24 116.6(2).

Table 1. Palladium-catalyzed one-pot reaction for the synthesis of isoindolinone **aa**.[a]



Entry	[Pd] (mol-%)	Base (equiv.)	Solvent	*t* [h]	*T* [°C][b]	Yield [%]	
						aa	**i**
1	$Pd(OAc)_2/PPh_3$ (1:2)	$(nBu)_3N$ (2)	DMF	24	150	53	15
2	*$Pd(OAc)_2/PPh_3$ (2:4)*	*$(nBu)_3N$ (2)*	*DMF*	*36*	*150*	*70*	*20*
3	$Pd(OAc)_2/PPh_3$ (2:4)	$(nBu)_3N$ (2)	DMF	54	150	71	20
4	$Pd(OAc)_2/PPh_3$ (2:4)	$(nBu)_3N$ (2)	DMF	36	140	10	80
5	$Pd(OAc)_2/PPh_3$ (2:4)	$(nBu)_3N$ (2)	DMF	36	170	none	none
6	$Pd(OAc)_2/PPh_3$ (2:4)[c]	$(nBu)_3N$ (2)	DMF	36	150	60	10
7	$Pd(PPh_3)_4$ (2)	$(nBu)_3N$ (2)	DMF	36	150	69	20
8	$PdCl_2$ (2)	$(nBu)_3N$ (2)	DMF	36	150	40	58
9	$Pd(OAc)_2$ (2)[d]	$(nBu)_3N$ (2)	DMF	36	150	65	15
10	$Pd(OAc)_2$ (2)	$(nBu)_3N$ (2)	MeCN	36	150	30	60
11	$Pd(OAc)_2$ (2)	$(nBu)_3N$ (2)	toluene	36	150	40	50
12	$Pd(OAc)_2$ (2)	K_2CO_3 (2)	DMF	36	150	50	30

[a] All reactions were carried out under an atmosphere of argon by using **a** (1.0 equiv.), ethyl 4-bromobenzoate (1.2 equiv.), $Pd(OAc)_2$ (5 mol-%), Ph_3P (2 equiv.), base, and solvent (10 mL) at the indicated temperature. [b] Isolated yield. [c] Additive Ag_2O. [d] Additive Ag_2CO_3.

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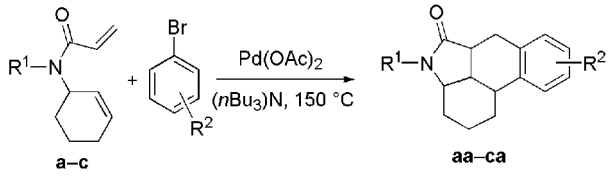
decreased, because it caused more kinds of side products (Table 1, Entry 6). (4) Other palladium catalysts, solvents, bases, and additives were used (Table 1, Entries 7–12). The structure of **aa** as the tricyclic product was obtained through X-ray diffraction analysis (Figure 1). The following standard reaction conditions were selected to carry out the following studies: 1,6-dienes (1 equiv.) reacted with different aryl halides (1.2 equiv.) in the presence of a palladium(II) catalyst (2 mol-%) and Ph_3P (4 mol-%) with $(n\text{Bu})_3N$ (2 equiv.) as an additive in DMF at 150 °C.

Domino Cyclization of Aryl Bromides with *N*-(Cyclohex-2-enyl)-*N*-acrylamide

The purpose of this study was to develop palladium-catalyzed processes to obtain directly physiologically active substances in a single operation and to provide a direct, efficient, and economic methodology for the construction of more stereocenters in nonracemic heterocycles. Illustrative examples intended to investigate the scope of this domino reaction are shown in Table 2 and Scheme 2. The reactions of a range of substituted aryl halides with *N*-(cyclohex-2-enyl)-*N*-phenylacrylamide (**a**), *N*-(cyclohex-2-enyl)-*N*-*p*-tolylacrylamide (**b**), and *N*-(cyclohex-2-enyl)-*N*-(naphthalen-1-yl)acrylamide (**c**) were examined. A variety of dienes and substituted aryl bromides were found to be compatible with this palladium-catalyzed domino reaction. A range of 1,2,3,3a,4,5a,6,10b-octahydronaphtho[3,2,1-*cd*]indol-5(4*H*)-one compounds were readily isolated in good to excellent yields when aryl halides with a variety of substituted groups were employed, except in the case of **ca**. The substituted groups could be ethoxycarbonyl, methoxycarbonyl, keto, naphthalenyl, sulfonyl, cyano, acetyl, or formacyl groups. By using 4-bromobenzonitrile and 1-(4-bromophenyl)ethanone with substrates **a** and **b**, the reaction allowed substitution with hydronaphtho[3,2,1-*cd*]indol-5-ones in yields beyond 70% (**aa, ad**, **ae**, **af**, **bb**, and **be**). The yield of compound **ag** was the highest at 82% (Table 2, Entry 7). The output of the reaction of substrate **a** was close to that of substrate **b**. These results demonstrated the wide application of the direct functionalization of molecular scaffolds in the synthesis of isoindolinone.

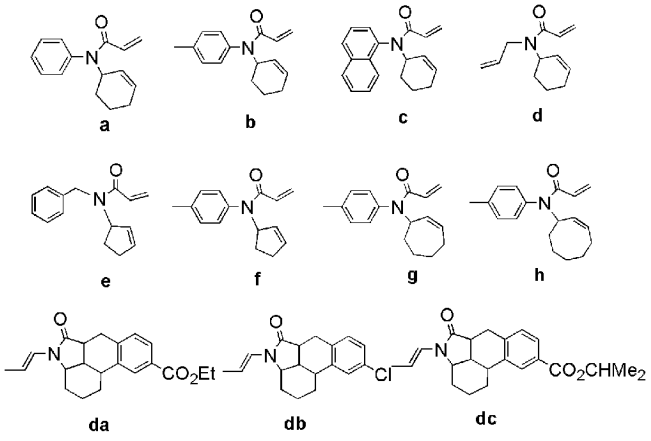
Table 2. Palladium-catalyzed domino reaction of aryl halides with **a**.[a]



a–c **aa–ca**

Entry	R^1	R^2	Product	Yield [%][b]
1	Ph (**a**)	*p*-$COOC_2H_5$	**aa**	70
2	Ph (**a**)	*p*-$COOCH_3$	**ab**	68
3	Ph (**a**)	*p*-CHO	**ac**	65
4	Ph (**a**)	*p*-$COCH_3$	**ad**	71
5	Ph (**a**)	*p*-CN	**ae**	70
6	Ph (**a**)	*p*-SO_2CH_3	**af**	70
7	Ph (**a**)	α-naphthalenyl	**ag**	82
8	*p*-MeC_6H_4 (**b**)	*p*-CHO	**ba**	65
9	*p*-MeC_6H_4 (**b**)	*p*-$COCH_3$	**bb**	70
10	*p*-MeC_6H_4 (**b**)	α-naphthalenyl	**bc**	64
11	*p*-MeC_6H_4 (**b**)	*p*-$COOCH_3$	**bd**	66
12	*p*-MeC_6H_4 (**b**)	*p*-SO_2CH_3	**be**	70
13	α-naphthalenyl (**c**)	α-naphthalenyl	**ca**	60

[a] General conditions: 1,6-diene (1.0 equiv.), $R^nC_6H_4Br$ (1.2 equiv.), $Pd(OAc)_2$ (2 mol-%), PPh_3 (4 mol-%), $(n\text{Bu})_3N$ (2 equiv.), DMF (10 mL), 150 °C. [b] Isolated yield after flash column chromatography.



Scheme 2.

Domino Reaction of Different 1,6-Dienes with Aryl Halides

To further broaden the scope of this reaction, we tested reactions of substituted aryl halides with *N*-allyl-*N*-(cyclohex-2-enyl)acrylamide (**d**), *N*-benzyl-*N*-(cyclopent-2-enyl)-acrylamide (**e**), *N*-(cyclopent-2-enyl)-*N*-*p*-tolylacrylamide (**f**), *N*-(cyclohept-2-enyl)-*N*-*p*-tolylacrylamide (**g**), and *N*-(cyclooct-2-enyl)-*N*-*p*-tolylacrylamide (**h**) under the aforementioned conditions. The reactions also proceeded smoothly. Similarly, except for the highest yield of **fa** at 85% and the lowest yield of **hc** at 52%, the majority of the yields of the products were around 60–80% (Table 3). When aryl halides with both C–Br and C–Cl bonds on the benzene ring were treated under the outlined conditions, the C–Br bond coupled selectively with the 1,6-dienes (Table 2, Entry 9; Table 3, Entry 13). However, the desired 4-allyl-1,2,3,3a,4,5a,6,10b-octahydronaphtho[3,2,1-*cd*]indol-5(4*H*)-ones were not isolated. When *N*-allyl-*N*-(cyclohex-2-enyl)-acrylamide (**d**) was treated with ethyl 4-bromobenzoate, 1-bromo-4-chlorobenzene, isopropyl 4-bromobenzoate, and 1-iodonaphthalene a series of allyl isomerization 4-allyl-octahydronaphthoindolones were obtained in good yields (Table 3, Entries 12–16). The structure of exceptional product **dc** was proven by X-ray diffraction analysis (Figure 2) and resulted from allyl isomerization. These results demonstrated that C–H functionalization and allyl isomerization could occur simultaneously when the protecting group was allyl on substrate **d**. However, the mechanism for this kind of reaction could not be defined (Scheme 2).[18]

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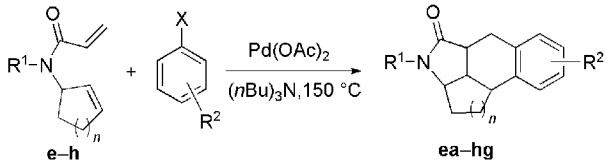
Table 3. Palladium-catalyzed domino reaction of aryl halides with **a**, **d**–**h**.[a]



Entry	R^1	$R^2C_6H_4X$	Product	Yield [%][b]
1	$PhCH_2$ (n = 1, **e**)	α-naphthalenyl bromide	**ea**	80
2	p-MeC_6H_4 (n = 1, **f**)	α-naphthalenyl bromide	**fa**	85
3	p-MeC_6H_4 (n = 3, **g**)	p-$EtO_2CC_6H_4Br$	**ga**	60
4	p-MeC_6H_4 (n = 3, **g**)	p-$OHCC_6H_4Br$	**gb**	65
5	p-MeC_6H_4 (n = 4, **h**)	p-$EtO_2CC_6H_4Br$	**ha**	70
6	p-MeC_6H_4 (n = 4, **h**)	p-$MeO_2CC_6H_4Br$	**hb**	60
7	p-MeC_6H_4 (n = 4, **h**)	p-NCC_6H_4Br	**hc**	52
8	p-MeC_6H_4 (n = 4, **h**)	α-naphthalenyl bromide	**hd**	80
9	p-MeC_6H_4 (n = 4, **h**)	p-$MeO_2SC_6H_4Br$	**he**	65
10	p-MeC_6H_4 (n = 4, **h**)	p-$MeOCC_6H_4Br$	**hf**	66
11	p-MeC_6H_4 (n = 4, **h**)	p-$OHCC_6H_4Br$	**hg**	64
12	allyl (n = 2, **d**)	p-$EtO_2CC_6H_4Br$	**da**	55
13	allyl (n = 2, **d**)	p-ClC_6H_4Br	**db**	62
14	allyl (n = 2, **d**)	p-$Me_2CHO_2CC_6H_4Br$	**dc**	76
15	allyl (n = 2, **d**)	p-$Me_2CHO_2CC_6H_4I$	**dc**	71
16	Ph (n = 2, **a**)	α-naphthalenyl iodide	**ag**	77

[a] General conditions: 1,6-diene (1.0 equiv.), $R^2C_6H_4X$ (X = Br; I) (1.2 equiv.), $Pd(OAc)_2$ (2 mol-%), PPh_3 (4 mol-%), $(nBu)_3N$ (2 equiv.), DMF (10 mL), 150 °C. [b] Isolated yield after flash column chromatography.

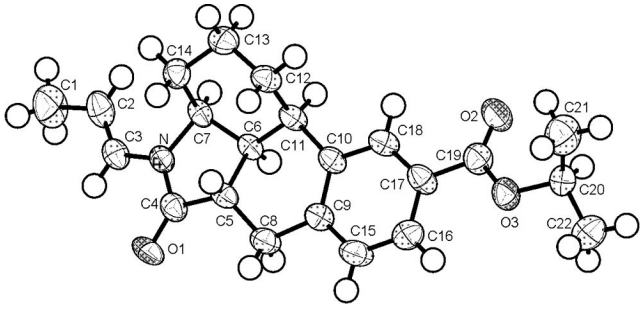
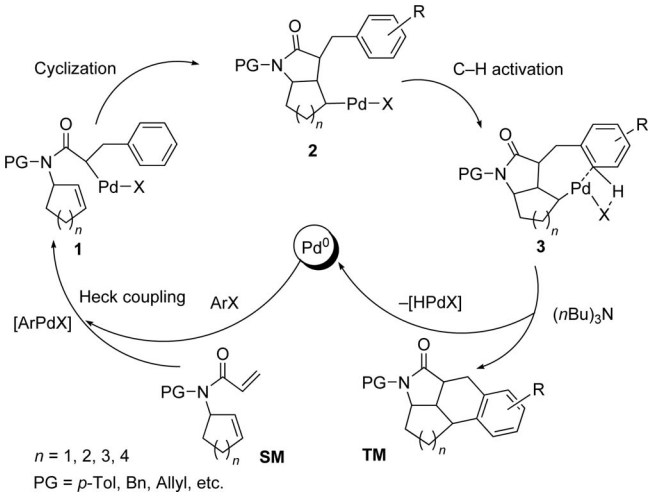


Figure 2. ORTEP plot of **dc** showing ellipsoids at the 30% probability level. Selected bond lengths [Å] and angles [°]: C9–C10 1.384(2), C9–C22 1.400(3), C10–C11 1.427(4), C11–C20 1.425(4), C20–C21 1.430(4), C21–C22 1.380(4), C9–C10–C30 120.9(2), C11–C10–C30 121.0(2), C20–C21–C24 124.6(2), C22–C21–C24 116.6(2).

All the resulting tri- and tetracyclic compounds were confirmed through 1D (^1H, ^{13}C) and 2D (COSY) NMR spectroscopic analysis and either elemental or HRMS analysis. Representative compounds **aa** and **dc** were additionally characterized by X-ray crystallography (Figures 1 and 2). Further details can be found in the Supporting Information (see also the Experimental section). The X-ray crystal structures proved the stereochemistry.

Mechanism

On the basis of the above observations, plausible mechanisms for the catalytic cycle pathways for the formation of fused polycyclic compounds are proposed in Scheme 3. Selective insertion of arylpalladium(II) halide into the allyl moiety of the starting material (**SM**) produces intermediate **1**, which then reacts with the carbon–carbon double bond through carbopalladation to afford **2**. σ-Bond metathesis[19] onto the different C–H bonds in **3** via intermediate **2** then generates the target molecular structure (**TM**) of the final products. Thus, C–H bond functionalization could be controlled by selecting differently substituted aromatic halides.



Scheme 3. Proposed mechanistic pathways.

Conclusions

In summary, we have developed an efficient method for the synthesis of isoindolinone derivatives through domino cyclization of 1,6-dienes with aryl halides in the presence of a $Pd(OAc)_2/PPh_3/(nBu)_3N$ catalyst with good yields under mild conditions. The catalyst system tolerates a wide range of dienes and aryl halides. The electronic properties of the substituted groups on the aryl halides have a great influence on the regioselectivity of the C–H functionalization reaction. C–H functionalization and allyl isomerization could simultaneously occur when 1-iodobenzene or aryl halides were treated with substrates having allyl moieties as protecting group. Further studies on the domino reaction for the synthesis of more complex products and their biological activity are now in progress in our laboratory.

Experimental Section

General: All the catalytic reactions were performed under an argon atmosphere by using an oven-dried Schlenk flask. The chemicals were purchased from Alfa Aesar and Acros Chemicals. All solvents and materials were predried, redistilled, or recrystallized before use. ^1H NMR (300 MHz) and ^{13}C NMR (75.5 MHz) spectra were recorded with a Bruker Avance 300 spectrometer with $CDCl_3$ as the solvent. Chemical shifts are reported in ppm by assigning TMS resonance in the ^1H NMR spectra as δ = 0.00 ppm and $CDCl_3$ resonance in the ^{13}C spectra as δ = 77.0 ppm. All coupling constants (J values) were reported in Hz. Column chromatography was

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performed on silica gel (300–400 mesh). Melting points were determined using a Gallenkamp melting point apparatus. The FTIR spectra were recorded as KBr pellets in the 4000–400 cm^{-1} range by using a Nicolet 5DX spectrometer. Mass spectra were performed with a Micromass GCT-MS. 2D NMR and HRMS spectroscopy were performed at the State-Authorized Analytical Center at the University of Science and Technology of China. X-ray crystallographic diffraction data of **aa**, **dc**, **ag**, **ac**, **ea**, and **ha** were collected at room temperature with a Bruker SMART Apex CCD diffractometer with Mo-K_α radiation (λ = 0.71073 Å) with a graphite monochromator by using the ω-scan mode. Data reductions and absorption corrections were performed with SAINT and SADABS software, respectively.[20] The structure was solved by direct methods and refined on F^2 by full-matrix least-squares by using SHELXTL.[21] All non-hydrogen atoms were treated anisotropically. The positions of hydrogen atoms were generated geometrically.

Synthesis: A typical procedure for the palladium-catalyzed tandem reaction of 1,6-dienes that contain acryl groups with aryl halides: substrate **a** (1.14 g, 5 mmol) and ethyl 4-bromobenzoate (1.37 g, 6 mmol), $Pd(OAc)_2$ (22.5 mg, 0.1 mmol), and PPh_3 (52.4 mg, 0.2 mmol) were added to a degassed solution of $(n\mathrm{Bu})_3\mathrm{N}$ (2.3 mL, 10 mmol) in DMF (10 mL). After the mixture was stirred for 30 min at room temperature, it was then heated at 150 °C for 36 h, and was then quenched with water and extracted with EtOAc (3 × 5 mL). The combined organic layer was washed with hydrochloric acid (5%), sodium carbonate (5%), and saturated sodium chloride solution. After separation, the organic layer was dried with $MgSO_4$ and then concentrated. The residue was purified by flash chromatography column (petroleum ether/EtOAc, 4:1) to give the corresponding isoindolinone.

X-ray Crystallographic Analysis: CCDC-766080 (for **aa**), -766081 (for **dc**), -766082 (for **ag**), -766083 (for **ac**), -766084 (for **ea**), and -766085 (for **ha**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre at www.ccdc.cam.ac.uk/data_request/cif.

Supporting Information (see footnote on the first page of this article): Characterization data for fused isoindolinones; X-ray structures of **aa**, **dc**, **ag**, **ac**, **ea**, **ha**; 2D NMR spectra of **ae**, **bb**, **dc**; ^{1}H NMR and ^{13}C NMR spectra of new compounds.

Acknowledgments

This research was partly supported by the National Science Foundation of China (20872002, 20572001) and the Education Department of Anhui Province. The authors are grateful to Prof. J. Hu and Prof. H. Zhang for their assistance in running NMR spectra and X-ray diffraction analyses.

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Received: April 11, 2010
Published Online: July 2, 2010

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