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Synthesis of Isoquinolinones via Regioselective Palladium-Catalyzed C–H Activation/Annulation

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Abstract: The isoquinoline motif and its derivatives are of significant interest due to their important biological activities. The effective synthesis of substituted isoquinoline compounds has historically been a significant challenge. A new palladium-catalyzed C–H activation/annulation of *N*-methoxy benzamides and 2,3-allenoic acid esters is described. For the first time, 2,3-allenoic acid esters are employed for the syntheses of 3,4-substituted hydroisoquinolones, the heteroannulation of allenes proceeded smoothly and afforded the products with good yields and excellent regioselectivity.

Keywords: transition-metal catalyst; C–H activation; C–H functionalization; 2,3-allenoic acid esters; hydroisoquinolinones; palladium-catalyzed annulation

1. Introduction

Isoquinoline and its derivatives form the cores of numerous natural products and they are the central components of many pharmaceutical agents [1–4]. Due to their unique DNA binding properties, isoquinolines and their derivatives show a wide range of biological activities, such as in vasodilatation [5–7], as well as for its antibacterial [3,8,9], anti-malarial [10], anti-HIV [11,12] and anti-tumor properties [13–15].

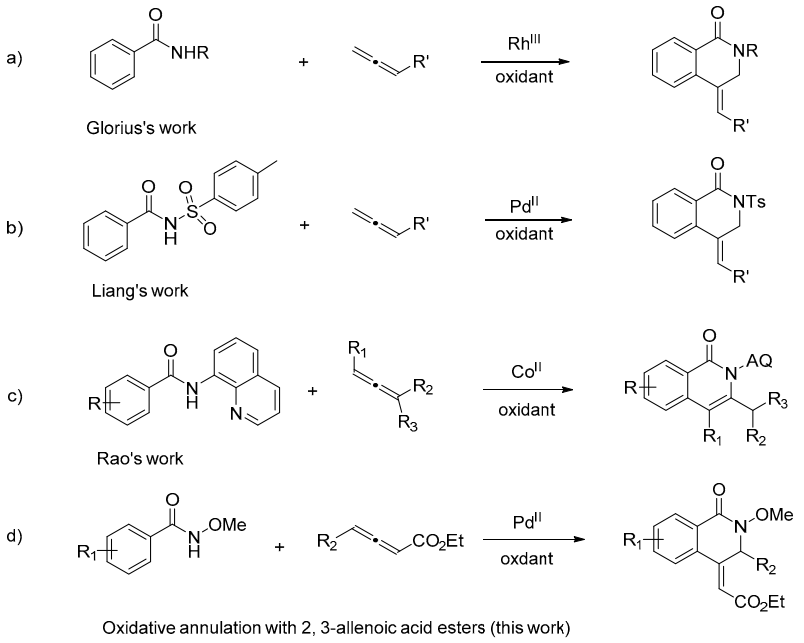
Isoquinolines possess diverse substitution patterns, and their synthesis has been the focus of many studies. Traditionally *ortho*-difunctionalized benzene starting materials are required for the construction of the heterocylic ring system [16,17]. A more general and efficient approach involves annulation of mono-functionalized arene with conventional synthetic methods, such as rearrangement [17,18], Fridel-Crafts reaction and *ortho*-lithiation, etc. [19,20].

Over the past decade, transition-metal-catalyzed direct C–H functionalization/annulation has established itself as a sustainable and more efficient strategy for constructing a range of valuable heterocylic products [21–24]. These transformations, which involve a metal-promoted activation of "inert" C–H bonds and cycloadditions of unsaturated substrates, allow the formation of cyclic products from readily available precursors in a rapid and atom-economical manner. Palladium [25,26], rhodium [27,28], and ruthenium [29,30] are among the most frequently used transition-metal catalysts for this activation/annulation; the applications of first-row transition metals, such as cobalt [31] and copper [32], have also been reported in these processes.

The interactions between catalyst and directing group promote the desired C–H activation and also control the selectivity. The coordination of the metal center to the heteroatom-containing functional group—such as benzamides [33–36], aryl imines [37], and anilides [38–40]—directs and facilitates selective cleavage of Csp^2-H bond to form the metallacycle. Migratory insertion of an alkene or alkyne forms the advanced intermediates, which undergo the subsequent reductive elimination to afford the heterocylic product. This approach is characterized by the incorporation of the directing group into the final heterocylic product structure. These reactions offer predictable site selectivity,

and are often broadly applicable and high-yielding [41–44]. Various heterocyclic scaffolds have been successfully constructed using this strategy, including isoindolinone [44,45], phenanthridinone [46], isoquinolines [45], and spiroindenes [47], etc.

For the synthesis of isoquinoline compounds, alkenes and alkynes have already been used to intercept the aryl metal species in the abovementioned transition-metal catalyzed oxidative annulation [44,47,48]. For example, Wang reported Rh(III)-catalyzed C–H allylation/Pd-catalyzed *N*-allyation to synthesize vinyl substituted dihydroisoquinolinones [49]. Marsden developed a Rh(III)-catalyzed C–H activation/annulation with vinyl esters as an acetylene equivalent [50]. In 2016, Niu developed a Co-catalyzed decarboxylative C–H activation/annulation cascade to get access to isoquinolines and isoindolinones [45]. In contrast, transition-metal catalyzed oxidative C–H coupling reactions between arene and allene remain relatively unexplored, although allenes have been widely applied in transition-metal catalyzed reactions [51–54]. The initial effort in this area, reported by Ma [55], resulted in a direct allenylation reaction with *N*-methoxybenzamide. In 2012, Glorius and co-workers [56] reported the synthesis of hydroisoquinolinones from the first carbometalation reaction of allenes; however, the applicable substrates were limited to alkyl substituted allenes (Scheme 1a). In 2014, the synthesis of 3,4-dihydroisoquinolin-1(2H)-ones was successfully achieved by Liang [57], using strong NH acidic *N*-benzoylsulfonamide to react with allenes in a palladium-catalyzed activation/annulation (Scheme 1b). Very recently, Rao (Scheme 1c) [58,59] and Volla [31] found that cobalt catalysts could effectively promote C–H activation of benzamide, aryl sulfonamides and facilitate the subsequent annulation with allenes to produce isoquinolinones and sultams respectively.



Scheme 1. Syntheses of isoquinolinone via metal-catalyzed oxidative annulation of allenes.

Our continuing efforts in metal-catalyzed C–H activation/cyclization reactions and their applications in the synthesis of natural products and the active pharmaceutical ingredients prompted us to explore and develop a facile method for the synthesis of isoquinoline. Herein, we report a protocol for palladium-catalyzed C–H activation/annulation between *N*-methoxybenzamide and 2,3-allenoic acid ester to afford a range of hydroisoquinolinones with the suitable functional groups for further structural elaborations (Scheme 1d).

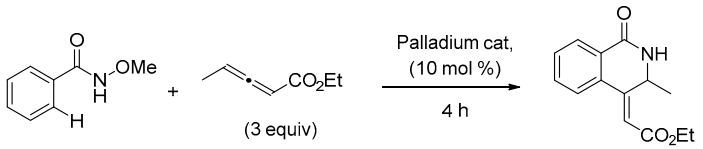
2. Results and Discussion

At the outset of this work, the reaction between *N*-methoxybenzamide **1a** and 2,3-allenoic acid esters **2a** was initially examined under the reaction conditions reported by Glorius in their work [56], which used [{RhCp*Cl_2}$_2$] as catalyst and CsOAc as additive. However, no desired product was observed when the reaction was performed in methanol at room temperature. Raising the reaction temperature did not improve the reaction. The result was not completely unexpected, considering the electron-poor nature of the 2,3-allenoic acid ester as starting material.

Disappointed by this result, we turned our attention from rhodium to palladium, which is well known for its different activity and selectivity as a catalyst [22]. To our delight, treatment of *N*-methoxybenzamide **1a** and 2,3-allenoic acid esters **2a** with $Pd(OAc)_2$ (10 mol%), Ag_2CO_3 (2 equiv.), in toluene at 100 °C afforded 3,4-dihydroisoquinolin-1(2H)-ones **3a** in an encouraging yield of 45% (Table 1, entry 1). Only one isomer of the shown structure was isolated, indicting a highly regioselective reaction. The yields could be further improved by testing other palladium catalysts (entries 2 and 3), $Pd(CH_3CN)_2Cl_2$ provided the highest yield of **3a** and was selected for further experimentation.

We also examined various oxidants, and found that the presence of silver salts is crucial to the reaction; only trace product could be detected when $Cu(OAc)_2$ or O_2 was employed (entries 6 and 7), and the best yield was obtained when Ag_2CO_3 (2 equiv.) was used. It was found that this annulation needed to be conducted at elevated temperature, as no reaction occurred when the temperature was below 65 °C; however, when the temperature was over 100 °C, the starting materials started decomposing due to their thermal instabilities. For this reason, an excess amount of 2,3-allenoic acid esters (3 equiv.) was required for the total consumption of *N*-methoxybenzamide. The optimal temperature was found to be 85 °C, as the reaction was able to give a good yield while also completing in a relatively short period of time (4 h).

Table 1. Selected results for the optimization of the reaction conditions for oxidative annulation.[1]



1a **2a** **3a**

Entry	Catalyst (10 mol%)	Oxidant (equiv.)	Temp (°C)	Additive (equiv.)	Solvent	Yield (%) [2]
1	$Pd(OAc)_2$	Ag_2CO_3 (2)	100	-	toluene	45
2	$Pd(TFA)_2$	Ag_2CO_3 (2)	100	-	toluene	43
3	$Pd(CH_3CN)_2Cl_2$	Ag_2CO_3 (2)	100	-	toluene	65
4	$Pd(CH_3CN)_2Cl_2$	Ag_2O (2)	100	-	toluene	30
5	$Pd(CH_3CN)_2Cl_2$	AgOAc (2)	100	-	toluene	35
6	$Pd(CH_3CN)_2Cl_2$	$Cu(OAc)_2$ (2)	100	-	toluene	trace
7	$Pd(CH_3CN)_2Cl_2$	O_2 (1 atm)	100	-	toluene	trace
8	$Pd(CH_3CN)_2Cl_2$	Ag_2CO_3 (2)	65	-	toluene	10
9	$Pd(CH_3CN)_2Cl_2$	Ag_2CO_3 (2)	75	-	toluene	35
10	$Pd(CH_3CN)_2Cl_2$	Ag_2CO_3 (2)	85	-	toluene	73
11	$Pd(CH_3CN)_2Cl_2$	Ag_2CO_3 (2)	85	K_2CO_3 (2)	toluene	70
12	$Pd(CH_3CN)_2Cl_2$	Ag_2CO_3 (2)	85	Cs_2CO_3 (2)	toluene	63
13	$Pd(CH_3CN)_2Cl_2$	Ag_2CO_3 (2)	85	DIPEA (2)	toluene	85
14	$Pd(CH_3CN)_2Cl_2$	Ag_2CO_3 (2)	85	DBU (2)	toluene	15
15	$Pd(CH_3CN)_2Cl_2$	Ag_2CO_3 (2)	reflux	DIPEA (2)	THF	none
16	$Pd(CH_3CN)_2Cl_2$	Ag_2CO_3 (2)	85	DIPEA (2)	$ClCH_2CH_2Cl$	20
17	$Pd(CH_3CN)_2Cl_2$	Ag_2CO_3 (2)	85	DIPEA (2)	DMF	none

[1] Reaction conditions: **1a** (0.5 mmol), **2a** (3 equiv.), catalyst (10 mol%), additive (2 equiv.), oxidant (2 equiv.) in specific solvent was heated at the temperature indicated. [2] Yield of isolated compounds.

Further optimization revealed that the presence of base did help to improve the yields, even though it was not essential. Among a variety of bases evaluated, inorganic bases generally facilitated the transformation, and the organic base DIPEA (*N*,*N*-diisopropylethylamine) showed the best efficiency. In contrast, the yield became very poor when DBU was present (entries 11–14). Next, common solvents, such as THF, DMF, and 1,2-dichloroethane, were screened. Toluene proved to

be the best choice, while the reactions in other solvents were less effective ($ClCH_2CH_2Cl$) or totally ineffective (DMF, THF) (entries 15–17).

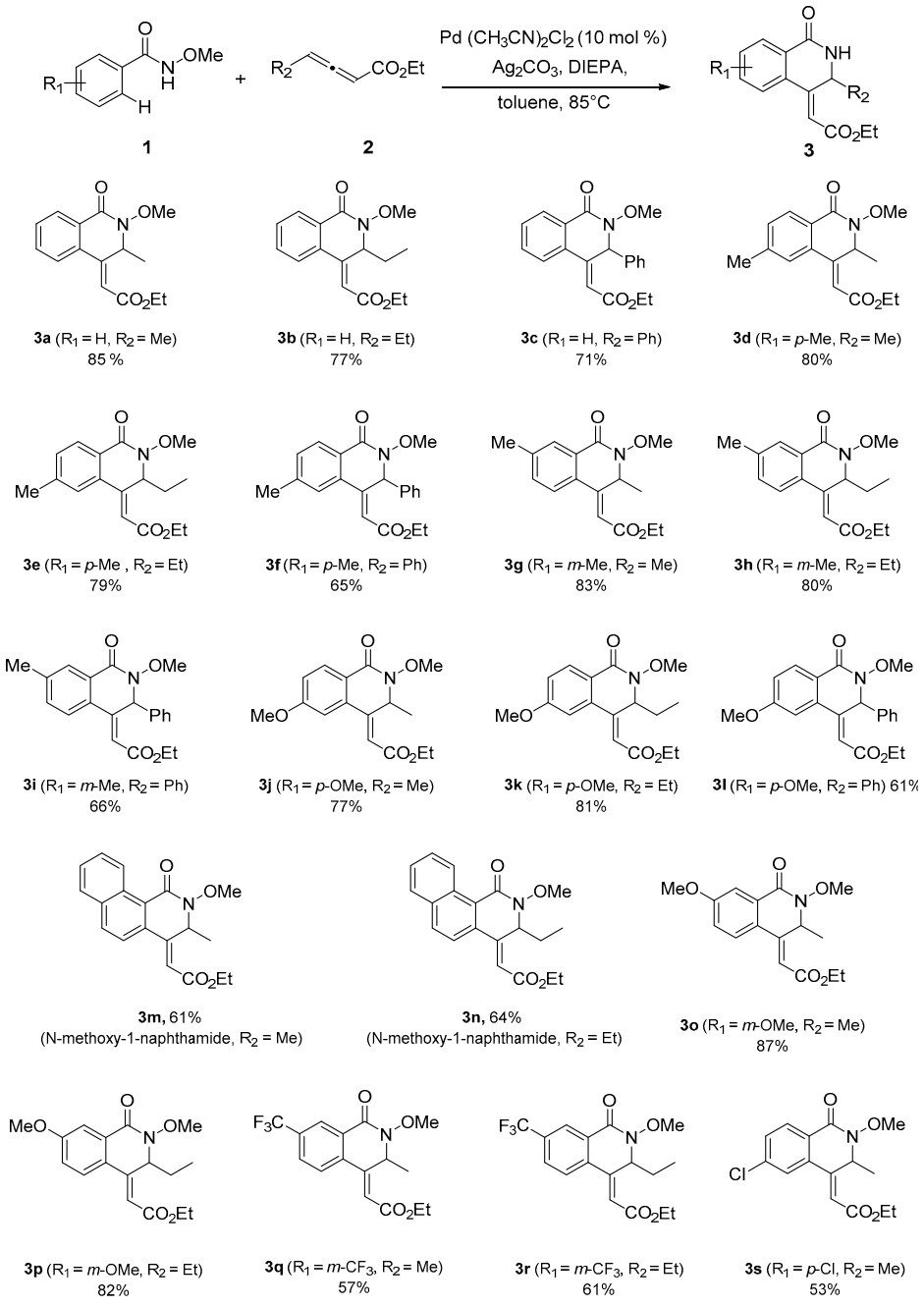
An assessment of the reaction scope was conducted under the optimized conditions, first by varying the substituents on the *N*-methoxybenzamide (Scheme 2). These experiments revealed that the electronic effects of substituents had a dramatic influence on the outcomes of this reaction. *N*-methoxybenzamide bearing electron-donating group, such as –OMe, and alkyl group at the 3-, and 4-positions all reacted smoothly to afford the corresponding hydroisoquinolinones in good yields (**3d**–**3p**, 61–87%). Impressively, *N*-methoxy-1-naphthamide was also a feasible substrate, and product **3m** was isolated with a modest yield of 61%. However, no reaction took place with *N*-methoxy-2-naphthamide. The presence of electron-withdrawing substituents such as trifluoromethyl, halogen, nitro, acetyl on the phenyl ring reduced the reactivities of these substrates significantly. CF_3- and Cl-substituted *N*-methoxybenzamides reacted with 2,3-allenoic acid esters to afford hydroisoquinolinones in relatively poor yields (**3q**–**3s**, 53–61%); no products could be isolated from the reactions when *para*-F-, *para*-NO_2-, *meta*-NO_2-, *para*-CH_3CO-substituted substrates were used. This observation was remarkably different from the previous reports by other researchers [46,50,60], where rhodium was adopted as catalyst for the annulations, which indicates the limitation of this reaction.

The substrate scope was further extended to substituted allenoic acid esters, containing functional groups such as methyl, ethyl and phenyl, formation of a variety of 3,4-dihydroisoquinolin-1(2H)-ones was smoothly achieved in good yields from 53% to 87% (Scheme 2).

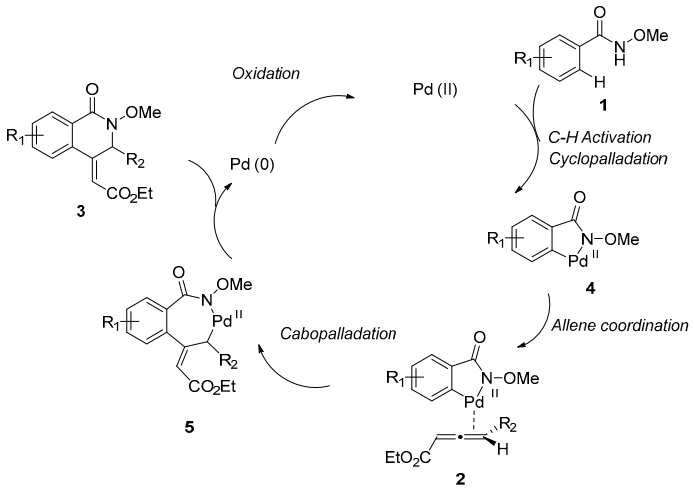
The ethyl 4-phenylbuta-2,3-dienoate, with the more sterically hindered phenyl group, afforded the products in relatively poorer yields. Importantly, the exocyclic double bond and the presence of an ester functional group in the molecules will allow for further elaboration of the products to generate more valuable skeletons for preparations of drug and biologically active compounds.

For this palladium-catalyzed C–H activation/annulation, the C–H bond activation site is decided by the relative steric repulsion between the substituents and the metal catalyst. If a *meta* substituent is present, the *ortho* position of directing group, which is opposite to the substituent, is preferred. The structure of **3** was determined and confirmed by 2D NMR experiment (NOESY) (**3g**) and X-ray analysis (**3i**) (see Supplementary Materials). Consistent with what is reported in the literature [56], the reaction was highly regioselective with regard to the insertion of allene into the palladium complex. The nucleophilic addition or reductive elimination occurred at C4 of 2,3-allenoic acid esters. While this feature likely rises from the steric hindrance of the palladium complex, the observed selectivity may also be preferred from the extra stabilities obtained from the conjugation with the ester functional group.

Based on literature precedents and experimental data, a plausible mechanism to account for the present reaction producing 3,4-dihydroisoquinolin-1(2H)-ones **3** is proposed in Scheme 3. The catalytic cycle is probably initiated by the coordination of palladium (II) with the *N*-methoxybenzamide **1**, followed by *N*-metalation and subsequent C–H activation, assisted by the presence of DIPEA to form a five-membered cyclopalladation intermediate **4**. The coordination and insertion of allene allenoic acid ester **2** leads to intermediate **5**, which undergoes reductive elimination to give the product **3** and Pd (0) species. Pd (II) is regenerated by the oxidation of Pd (0) with silver carbonate and close the catalytic cycles. Insertion of allene occurs when a C–C bond is formed with the central carbon atom of the allene moiety, the regioselectivity of the annulation is controlled by the steric effect of substituent groups on allenoic acid ester and influenced by the thermodynamic stability of the final products. The attack from the sterically less hindered face of the allene may be the explanation for the formation of the product with Z exocyclic double bond.



Scheme 2. Synthesis of isoquinolinone via palladium-catalyzed C–H activation annulation. [a] Reaction conditions: *N*-methoxybenzamide (0.50 mmol), 2,3-allenoic acid esters (3 equiv.), Ag_2CO_3 (2 equiv.), DIPEA (2 equiv.), $Pd(CH_3CN)_2Cl_2$ (10 mol%) in toluene (10 mL) was heated at 85 °C for 4 h. [b] Isolated yield.



Scheme 3. Plausible mechanism of palladium-catalyzed C–H activation/annulation.

3. Experimental Details

3.1. General Procedure for the Synthesis of N-Methoxybenzamide from Acid Chloride

The synthesis followed a procedure reported by Booker-Milburn et al. [61]. Methoxylamine hydrochloride (840 mg, 10 mmol) and potassium carbonate (2.76 g, 20 mmol) were dissolved in a mixture of water (25 mL) and EtOAc (50 mL), and cooled to 0 °C upon which acyl chloride (10 mmol) was added dropwise. The reaction was then allowed to warm to r.t. and stirred for between 5 h and overnight. The product was isolated by diluting the mixture with EtOAc/H_2O and separating the layers. The organic phase was then washed with brine and dried over $MgSO_4$, filtered and concentrated to give the product which was then recrystallized (EtOAc/Hex) to give the target compound.

3.2. General Procedure for the Synthesis of N-Methoxybenzamide from Acid

To a solution of substituted benzoic acid (10 mmol) in CH_2Cl_2 (30 mL) was added a few drops of DMF, followed by slow addition of oxalyl chloride (1.7 mL, 20 mmol) at room temperature. The reaction was stirred overnight. The reaction mixture was evaporated under reduced pressure to give crude acyl chloride, which was used directly without further purification. Methoxylamine hydrochloride (840 mg, 10 mmol) and potassium carbonate (2.76 g, 20 mmol) were dissolved in a mixture of water (25 mL) and EtOAc (50 mL), and cooled to 0 °C; acyl chloride (10 mmol), which was prepared as described above, was added dropwise. The reaction was then allowed to warm to r.t. and stirred for between 5 h and overnight. The product was isolated by diluting the mixture with EtOAc/H_2O and separating the layers. The organic phase was then washed with brine and dried over $MgSO_4$, filtered and concentrated to give the product which was then recrystallized (EtOAc/Hex) to give the target compound.

3.3. General Procedure for the Synthesis of 2,3-Allenoic Acid Esters

The synthesis followed a procedure reported by Kwon et al. [62]. Et_3N (63 mmol, 1.1 equiv.) was added to a stirred solution of (carbethoxymethylene)triphenylphosphorane (57.5 mmol, 1 equiv.) in CH_2Cl_2 (200 mL). After stirring for 10 min, the required acyl chloride (57.5 mmol, 1 equiv.) was added dropwise over 30 min at room temperature. After stirring overnight, the resulting mixture was poured unto a funnel packed with silica gel and was washed with CH_2Cl_2 several times. The combined filtrate was carefully concentrated, and the resulting crude oil was purified by flash column chromatography (hexane/EtOAc, 20:1) to provide the 4-substituted 2,3-allenoic acid esters.

3.4. General Procedure for Pd-Catalyzed Oxidative Annulation with 2,3-Allenoic Acid Esters

An oven-dried round-bottom flask (25 mL) was charged with *N*-methoxybenzamide (0.50 mmol), 2,3-allenoic acid esters (1.5 mmol, 3 equiv.), silver(I) carbonate (0.275 g, 1 mmol, 2 equiv.), *N*,*N*-diisopropylethylamine (DIPEA) (0.174 mL, 1 mmol, 10 mol%), Bis(acetonitrile)dichloropalladium (II) (13.0 mg, 0.05 mmol) in 5 mL toluene. The mixture was heated at 85 °C for 4 h under the atmosphere of air, then allowed to cool down. The reaction mixture was diluted with EtOAc (10 mL) and filtered through a Celite® pad, the filtrate was washed with water (10 mL). The aqueous layer was extracted with EtOAc (2 × 10 mL), and the combined organic layers were dried with anhydrous $MgSO_4$, then filtered and concentrated under reduced pressure. The crude product was purified by flash column chromatograph, eluted with n-hexane/EtOAc (10:1) to give the final product.

4. Conclusions

In conclusion, a palladium-catalyzed C–H activation/annulation of *N*-methoxybenzamides with 2,3-allenoic acid esters has been established. The strategy was able to proceed with high regioselectivity, and afforded various substituted 3,4-dihydroisoquinolin-1(2H)-ones in good yields under relatively mild conditions. This method is complementary to previously reported methods based on the use of rhodium catalysts and alkyl-substituted allenes substrates. Further application of this methodology in natural product synthesis is in progress, and the bioactivity data of the synthesized compounds will be reported in due course.

Supplementary Materials: The following are available online at www.mdpi.com/2073-4344/7/11/320/s1, Experimental procedure and spectral data for final products.

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Author Contributions: Y.L. conceived and designed the experiments; W.Q. and Y.H. performed the experiments; Y.W. analyzed the data; Y.L. wrote the paper.

Conflicts of Interest: The authors declare no conflict of interest.

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