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Multicomponent Synthesis of Isoindolinone Frameworks *via* Rh(III)-Catalysed in situ Directing Group Assisted Tandem Oxidative Olefination/Michael Addition

Liang Wang,[a]* Xi Liu,[a] Jian-biao Liu,[b] Jun Shen,[a] Qun Chen[a] and Ming-yang He[a]*

Abstract: A Rh(III)-catalysed three-component synthesis of isoindolinone frameworks via direct assembly of benzoyl chlorides, *o*-aminophenols and activated alkenes has been developed. The process involves in situ generation of *o*-aminophenol (OAP)-based bidentate directing group (DG), Rh(III)-catalysed tandem *ortho* C−H olefination and subsequent cyclization *via* aza-Michael addition. This protocol exhibits good chemoselectivity and functional group tolerance. Computational studies showed that the presence of hydroxyl group on the *N*-aryl ring could enhance the chemoselectivity of the reaction.

Isoindolinone derivatives are important heterocyclic compounds owing to their ubiquitous structures in natural products and pharmaceuticals.[1] For example, Taliscanine, Nuevamine and Pazinaclone have shown a wide range of biological properties including antihypertensive, antipsychotic, anti-inflammatory, and antiviral activities (Figure 1). Particularly, some biologically active compounds with general formula **I** possess anxiolytic and sedative activity. Thus, the development of efficient methodologies to access such heterocyclic scaffolds is of great importance.

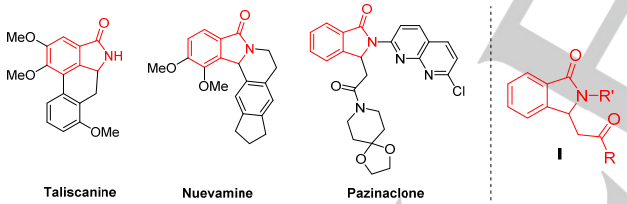
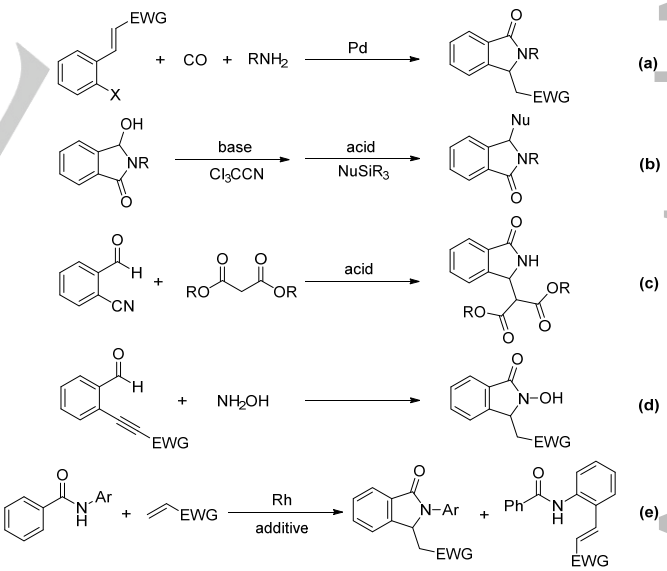


Figure 1. Selected biologically active isoindolinones.

Literatures on existing approaches toward the synthesis of compond **I** include palladium-catalysed three-component carbonylation/amination/Michael addition process (Scheme 1, **a**),[2] hydroxyl group activation followed by nucleophilic displacement (Scheme 1, **b**),[3] base-catalysed tandem aldol/cyclization reaction (Scheme 1, **c**),[4] intramolecular aza-conjugate addition (Scheme 1, **d**),[5] and tandem C-H olefination/Michael addition (Scheme 1, **e**).[6] While acknowledging these pioneering work in this field, the reported procedures **a~d** always suffered from the use of toxic reagents, tedious synthetic routes, or harsh reaction conditions. In most cases, the starting materials were not readily available. By contrast, route **e** which involved the direct C-H olefination followed by intramolecular *aza*-Michael addition should be a good alternative.[7] However, there are still some challenges to be addressed. Firstly, cumbersome operations are usually required for installation or removal of the DGs. Secondly, limited variability of the introduced DGs also remain as issues requiring further improvement. Finally, the C-H activation of *N*-aryl benzamides may be complicated since both arene C-H bonds on the *C*-aryl ring and *N*-aryl ring could be cleavaged.[6d,8]



Scheme 1. Synthetic approaches for preparation of isoindolinone **I.**

In past decades, some strategies including traceless DG,[9] deciduous DG,[10] transient DG,[11] and *in situ* DG[12] have been conceived and accomplished to address above issues. Especially, domino C-H activation reactions *via* in situ generation of a DG made these processes more simple and atom-efficient. Just recently, Wan and co-workers reported a three-component synthesis of *o*-arylated benzamides by utilizing *o*-aminophenol as the DG.[13] Such bidentate DG

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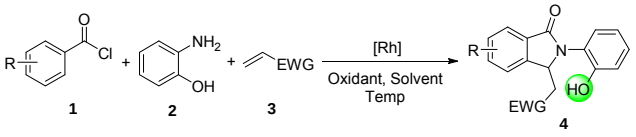
precursors features not only in the easy availability and low cost, but also in the direct utility without any prior elaboration. More importantly, easy variation of the hydroxyl group in the target products can be realized.

Inspired by these contributions, we envisioned that the direct assemblies of benzoyl chlorides, *o*-aminophenol activated alkenes may provide a step economical approach to access diverse isoindolinone **I**. In addition, the hydroxyl group on the *N*-aryl ring may enhance the regioselectivity of the reaction through coordination with the metal catalyst. Notably, further structural modification of the products can be achieved through the chemical modification of the hydroxyl group. Herein, in continuation of our interest in C-H activations,[14] we disclosed our recent findings in the Rh(III)-catalysed multicomponent synthesis of isoindolinone frameworks (Scheme 2).

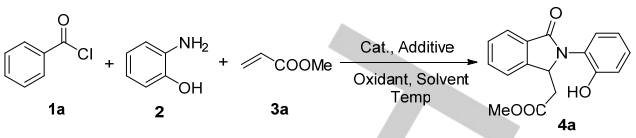


Scheme 2. Rh(III)-catalysed multicomponent synthesis of isoindolinones.

Initially, benzoyl chloride (**1a**), OAP (**2**) and methyl acrylate (**3a**) were selected as the model substrates to optimize the reaction conditions (Table 1). As shown from the results, tentative reaction in toluene led to the failure of the reaction (entry 1). Low yields were obtained in solvents such as *N,N*-dimethylformamide (DMF), dimethyl sulfoxide (DMSO), dioxane, and 1,2-dichloroethane (DCE) (15~41%, entries 2~5). Encouragingly, switching the solvent to acetonitrile provided the desired product **4a** in 69% yield (entry 6). Different oxidants were then examined and $Cu(OAc)_2•H_2O$ turned out to be the optimal (85% yield, entry 7). It was worth noting that the employment of additive such as $AgSbF_6$ and $AgBF_4$ gave inferior yeilds and C-H olefination on *N*-aryl ring was also observed. Substitution of $Cu(OAc)_2•H_2O$ with $Cu(OTf)_2$ gave only trace amount of the product, indicating that OAc might be necessary for the reaction. Other oxidants including $Cu(OTf)_2$, Ag_2O, $K_2S_2O_8$ and oxygen gave rather poor yields (entries 8~11). Further investigation in screening the base additives using K_2CO_3, Cs_2CO_3, $NaHCO_3$, NaOH and Et_3N proved that K_2CO_3 was the best choice (entries 12~15). Among the surveyed catalysts, $Pd(OAc)_2$ and $[RuCl_2(p\text{-Cymene})]_2$ were not effetive for this transforamtion, while only 32% yield of the corresponding product was obtained in the presence of $[\{Rh(cod)Cl\}_2]$ (entries 16~18). Finally, results showed that only moderate yield was obtained at 80 °C, and no obvious change in the yield was observed when the reaction was carried out at a higher temperature (entry 19).

With the optimized conditions in hand, a series of benzoyl chlorides were employed to explore the generality of this protocol (Table 2). Generally, most of the investigated benzoyl chlorides coupled with OAP (**2**) and methyl acrylate

Table 1. Optimization of reaction conditions.[a]



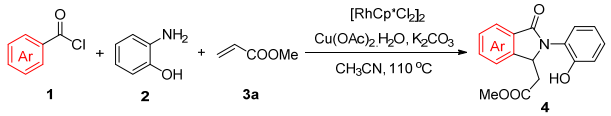
Entry	Catalyst	Base	Oxidant	Solvent	Yield(%)[b]
1	$[RhCp^*Cl_2]_2$	K_2CO_3	Ag_2CO_3	toluene	n.r.
2	$[RhCp^*Cl_2]_2$	K_2CO_3	Ag_2CO_3	DMF	15
3	$[RhCp^*Cl_2]_2$	K_2CO_3	Ag_2CO_3	DMSO	17
4	$[RhCp^*Cl_2]_2$	K_2CO_3	Ag_2CO_3	dioxane	29
5	$[RhCp^*Cl_2]_2$	K_2CO_3	Ag_2CO_3	DCE	41
6	$[RhCp^*Cl_2]_2$	K_2CO_3	Ag_2CO_3	CH_3CN	69
7	$[RhCp^*Cl_2]_2$	K_2CO_3	$Cu(OAc)_2•H_2O$	CH_3CN	85, 57[c], 22[d]
8	$[RhCp^*Cl_2]_2$	K_2CO_3	$Cu(OTf)_2$	CH_3CN	trace
9	$[RhCp^*Cl_2]_2$	K_2CO_3	Ag_2O	CH_3CN	21
10	$[RhCp^*Cl_2]_2$	K_2CO_3	$K_2S_2O_8$	CH_3CN	n.r.
11	$[RhCp^*Cl_2]_2$	K_2CO_3	O_2	CH_3CN	n.r.
12	$[RhCp^*Cl_2]_2$	Cs_2CO_3	$Cu(OAc)_2•H_2O$	CH_3CN	79
13	$[RhCp^*Cl_2]_2$	$NaHCO_3$	$Cu(OAc)_2•H_2O$	CH_3CN	14
14	$[RhCp^*Cl_2]_2$	NaOH	$Cu(OAc)_2•H_2O$	CH_3CN	23
15	$[RhCp^*Cl_2]_2$	Et_3N	$Cu(OAc)_2•H_2O$	CH_3CN	26
16	$Pd(OAc)_2$	K_2CO_3	$Cu(OAc)_2•H_2O$	CH_3CN	n.r.
17	$[\{Rh(cod)Cl\}_2]$	K_2CO_3	$Cu(OAc)_2•H_2O$	CH_3CN	32
18	$[RuCl_2(p\text{-Cymene})]_2$	K_2CO_3	$Cu(OAc)_2•H_2O$	CH_3CN	trace
19	$[RhCp^*Cl_2]_2$	K_2CO_3	$Cu(OAc)_2•H_2O$	CH_3CN	45[e], 81[f]

[a] Reaction conditions: mixture of **1a** (0.3 mmol), **2a** (0.3 mmol) and base (0.9 mmol) in solvent (2 mL) was stirred for 2 h; then **3a** (0.45 mmol), catalyst (5 mol%), and oxidant (0.6 mmol, 2 equiv.) were added, and the reaction mixture was further stirred overnight at 110 °C. [b] Isolated yields. [c] $AgSbF_6$ (20 mol%) as the additive. [d] $AgBF_4$ (20 mol%) as the additive. [e] Reaction at 80 °C. [f] Reaction at 120 °C

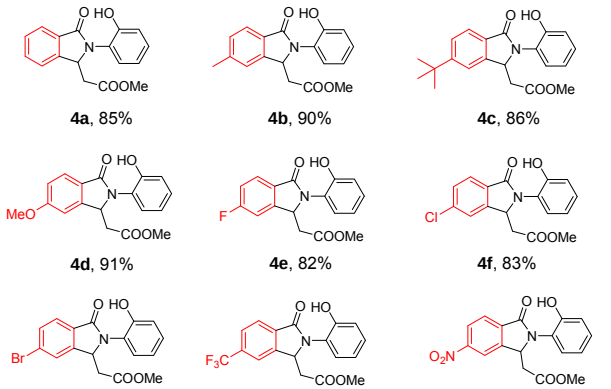
(**3a**) smoothly to provide the corresponding products in good yields (80~91%). Functional groups such as methyl, *tert*-butyl, methoxyl, fluoro, chloro, bromo, and trifluoromethyl survived the reactions well to afford the desired products in excellent yields. Notably, the C-halo bonds in the products **4e~4g** were not affected and no Heck coupling byproducts were detected, enabling the further functionalization of the initial products. However, *p*-nitrobenzoyl chloride was not compatible for this reaction system, and some unknown byproducts were detected. The steric hindrance showed negligible influence on the reaction, and substrate **1j** successfully delivered product **4j** in 88% yield. Interestingly, evaluation on the substrates **1k** and

1l showed that these reactions occurred selectively at the less hindered site. By contrast, extension of this protocol to heteroaryl benzoyl chlorides turned out to be unsuccessful under the standard conditions. No reaction occurred when **1m** was employed as the substrate and only olefinated product was obtained for substrate **1n** (**4n**, 47%).

Table 2. Reaction scope for benzoyl chlorides.[a]



1 2 3a 4

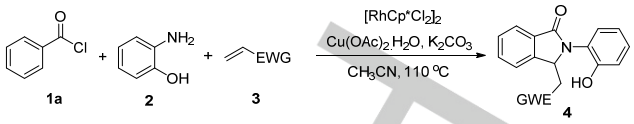


[a] Reaction conditions: mixture of **1** (0.3 mmol), **2a** (0.3 mmol) and K_2CO_3 (0.9 mmol) in CH_3CN (2 mL) was stirred for 2 h; then **3a** (0.45 mmol), $[RhCp^*Cl_2]_2$ (5 mol%), $Cu(OAc)_2$•H_2O (0.6 mmol, 2 equiv.) and CH_3CN (1 mL) were added, and the reaction mixture was further stirred overnight at 110 °C; isolated yields.

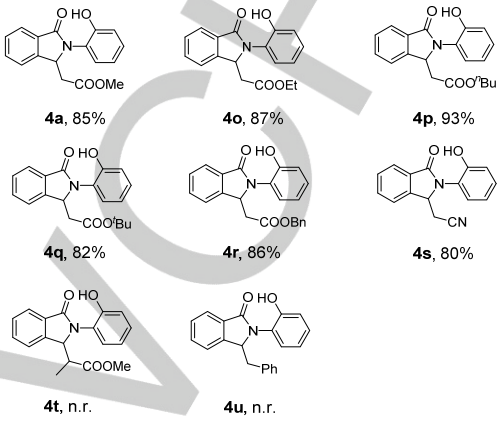
A series of alkenes were then examined and the results were summarized in Table 3. Olefins including methyl acrylate, methyl methacrylate, ethyl acrylate, *n*-butyl acrylate, *tert*-butyl acrylate and benzyl acrylate readily participated in this reaction, affording the corresponding products in good to excellent yields (80~93%). It was worth noting that reaction of acrylonitrile also proceeded smoothly to give the corresponding product **4s** in 80% yield, which enabled the further modification of isoindolinone frameworks. We also tried the reaction of methyl methacrylate, however, no desired product **4t** was observed, probably due to the steric effect. Finally, electron-neutral olefin such as styrene was checked and no reaction was observed.

Some control experiments were then conducted to get some insight into the reaction mechanism (Scheme 2).

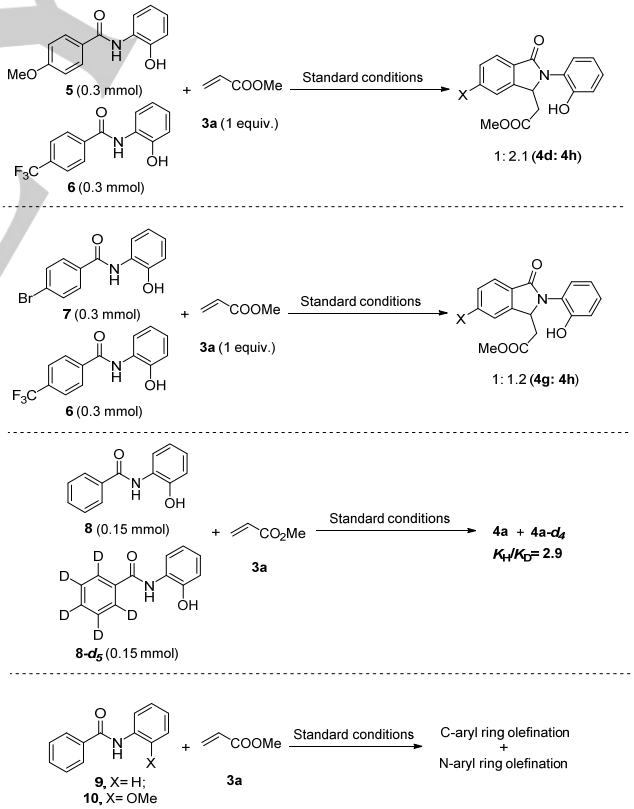
Table 3. Reaction scope for alkenes.[a]



1a 2 3 4



[a] Reaction conditions: mixture of **1a** (0.3 mmol), **2a** (0.3 mmol) and K_2CO_3 (0.9 mmol) in CH_3CN (2 mL) was stirred for 2 h; then **3** (0.45 mmol), $[RhCp^*Cl_2]_2$ (5 mol%), $Cu(OAc)_2$•H_2O (0.6 mmol, 2 equiv.) and CH_3CN (1 mL) were added, and the reaction mixture was further stirred overnight at 110 °C; isolated yields.



Scheme 2. Control experiment and isotope effect experiment.

Initially, competition reactions were performed with a series of benzamides. When an equimolar amount of substrate **5** and **6** were subjected to the standard reaction conditions with a single equivalent of **3a**, the reaction favored the formation of product **4h** which was derived from the more electron-deficient benzamide. However, when such competition experiment was conducted between substrate **7** and **6**, the products were formed in nearly equal amounts. These results suggested that the Michael reaction could not be the turnover limiting step for the catalytic cycle. Moreover, when a 1:1 mixture of **8** and ***d*$_5$-8** was subjected to the reaction, a significant kinetic isotope effect (k_H/k_D = 2.9) was observed (See Supporting information). This indicated that the C–H bond cleavage was involved in the rate-determining step. Finally, in order to better explain the good chemoselectivity of this reaction, substrates **9** and **10** were prepared and coupled with methyl acrylate **3a**. Although these reactions could provided the target products, considerable C-H olefination byproducts on the *N*-aryl ring of the benzamides were also detected, indicating that the presence of hydroxyl group on the *N*-aryl ring greatly enhance the chemoselectivity of the reaction.

In addition, a computational study was performed (Figure 1, also see Supporting information). As shown in Figure 1, among the three possible intermediates, the intermediate **b** is 4.1 and 7.7 kcal/mol more stable respectively than intermediates **a** and **c**, which should be attributed to the significant C-H/π interactions between Cp* ring and the phenyl rings.[15] The function of hydroxyl group on the *N*-aryl ring was speculated to stabilize the intermediate during the *N*-metalation process (See intermediate **A** in Scheme 3).

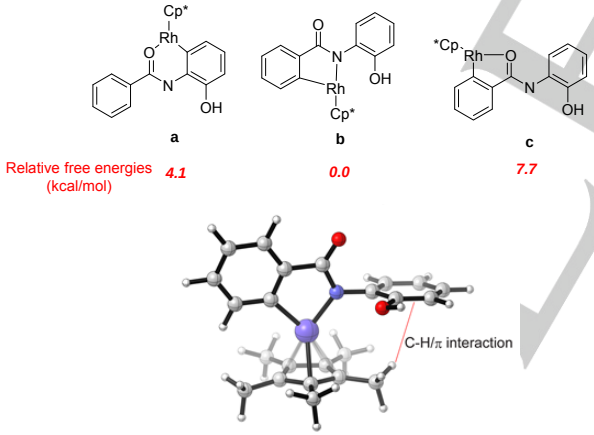
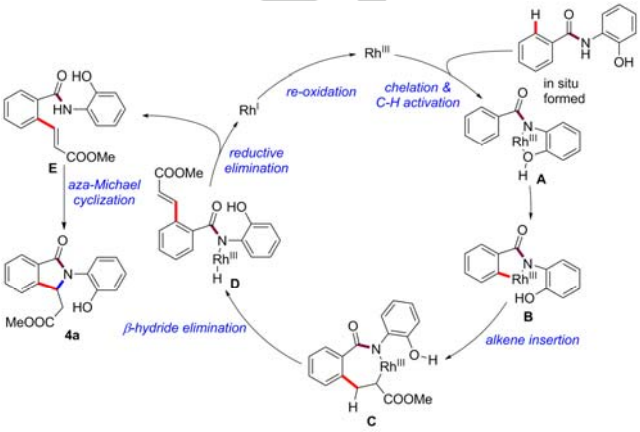


Figure 1. Possible structures of intermediates.

In light of these experiments, a plausible catalytic cycle was proposed (Scheme 3). Initially, the rhodium dimer precatalyst exchange ligands to form an acetate-ligated species with the copper acetate,[8a] which coordinates with in situ formed *N*-aryl benzamide to initiate *N*-metalation. A stable 5-membered rhodacycle **A** is formed with the assistance of hydroxyl group. A chemoselective C-H activation then occurs to generate 5-membered rhodacycle **B**. Then, insertion of an alkene leads to seven-membered rhodacycle **C**. Subsequent *β*-H elimination releases intermediate **D**, which undergoes intramolecular *aza*-Michael addition to generate the final product **4a**. The Rh^I cation is oxidized back to Rh^{III} by copper acetate to complete the catalytic cycle.



Scheme 3. Proposed mechanism.

In summary, a Rh(III)-catalysed three-component synthesis of isoindolinone frameworks via direct assembly of benzoyl chlorides, *o*-aminophenols and activated alkenes has been developed. A series of benzoyl chlorides and activated alkenes were well tolerated, affording the corresponding products in good to excellent yields. In most cases, excellent chemoselectivity was observed. It was assumed that the in situ generated *o*-aminophenol (OAP)-based bidentate directing group could stabilize the intermediate during the *N*-metalation and C-H activation process, which was consistent with the computational study. Notably, potential application of the target compounds was also exciting. The –OH group could be readily transformed to other functional groups via conventional organic reactions.

Experimental Section

General procedure for the synthesis of compound 4

In a 10 mL reaction vial equipped with a stir bar was charged with **1** (0.3 mmol), **2a** (0.3 mmol) and K_2CO_3 (0.9 mmol) and CH_3CN (2 mL). The mixture was stirred for 2 h. After that, **3** (0.45 mmol), $[RhCp^*Cl_2]_2$ (5 mol%), $Cu(OAc)_2•H_2O$ (0.6 mmol, 2 equiv.) and CH_3CN (1 mL) were added, and the reaction mixture was further stirred overnight at 110 °C. After reaction, the mixture was cooled to room temperature and 10 mL water was added. After extraction with ethyl acetate (3 × 10 mL), the combined organic phase was dried over Na_2SO_4, and the solvent was removed under reduced pressure. The residue was purified by silica gel chromatography to afford the desired product **4**.

Selected characterization data

4a: Light yellow solid; ^1H NMR (300 MHz, $CDCl_3$) δ 8.33 (s, 1H), 7.91 (dd, *J* = 4.5, 4.0 Hz, 1H), 7.65 – 7.58 (m, 1H), 7.58 – 7.49 (m, 2H), 7.25

– 7.15 (m, 2H), 7.09 (dd, *J* = 8.1, 1.4 Hz, 1H), 7.00 – 6.95 (m, 1H), 5.65 (dd, *J* = 8.4, 4.2 Hz, 1H), 3.59 (s, 3H), 2.84 (dd, *J* = 16.2, 4.3 Hz, 1H), 2.52 (dd, *J* = 16.2, 8.4 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.6, 168.2, 152.2, 145.2, 132.6, 130.7, 129.0, 128.7, 124.8, 124.3, 124.1, 122.6, 120.9, 120.2, 58.7, 52.0, 36.9. HRMS (ESI): Calcd for $C_{17}H_{15}NNaO_4$ $(M + Na)^+$ 320.0893, found 320.0899.

Acknowledgements

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Keywords: Isoindolinones • C-H activation • Rh(III) catalysis • Multicomponent synthesis • Chemoselectivity

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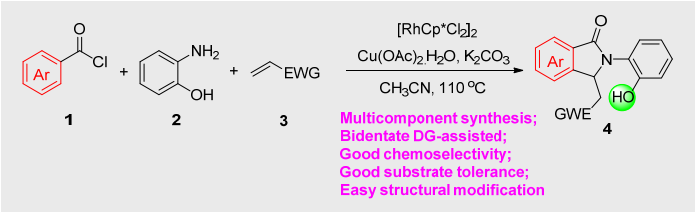

A Rh(III)-catalysed three-component, chemoselective synthesis of isoindolinone frameworks via direct assemblies of benzoyl chlorides, *o*-aminophenols and activated alkenes has been developed.

Liang Wang,[a] Xi Liu,[a] Jian-biao Liu,[b] Jun Shen,[a] Qun Chen[a] and Ming-yang He[a]**

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Multicomponent Synthesis of Isoindolinone Frameworks *via* Rh(III)-Catalysed in situ Directing Group Assisted Tandem Oxidative Olefination/Michael Addition