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Palladium-Catalyzed 5-*exo-dig* Cyclization Cascade, Sequential Amination/Etherification for Stereoselective Construction of 3-Methyleneindolinones

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Abstract. An cascade intramolecular 5-*exo-dig* cyclization of *N*-(2-iodophenyl)propiolamides and sequential amination/etherification (with *N*-hydroxybenzamides, phenyl hydroxycarbamate) protocol for the synthesis of amino- and phenoxy-substituted 3-methyleneindolinones using unexpensive $Pd(PPh_3)_4$ as catalyst has been developed. The protocol enables the assembly of structurally important oxindole cores featuring moderate functional group tolerance (particularly the halo group), affording a broad spectrum of products with diverse substituents in good to excellent yields.

Keywords: 3-Methyleneindolinones; Amination; Cyclization; *N*-(2-iodophenyl)propiolamides; *N*-hydroxybenzamides

Introduction

The oxindole skeleton is a structural motif not only in natural products[1] but also in several other fields such as medicinal,[2] agricultural,[3] and dye chemistry.[4] Especially, 3-methyleneindolinone derivatives are among the most important structural classes of 2-indolinones, which are present in numerous naturally occurring substances and biologically active compounds,[5] such as AMPK activator,[6] and to synthesize TMC-95A[7] and anti-cancer drugs.[8] Importantly, they are used as anticancer drugs, especially for breast cancer, due to tamoxifen-like activity, antirheumatic effects, etc.[9] For instance, Alkaloids isatinone A and B, which were isolated from ethanolic extracts of the herb Isatis costata, have significant antifungal activity.[10] Despite their wide importance, 3-methyleneindolinone exists as a pair of stereoisomers (*E*/*Z*), and highly stereoselective synthesis of (*E*)- and (*Z*)-3-methyleneindolinone derivatives still remains to be a formidable challenge.

Recently, *N*-arylpropiolamides have received significant attention in the formation of oxindole skeleton owing to their easy availability, cost effectiveness, and versatility in the synthesis of a wide variety of nitrogen based heterocycles.[11] In this regard, considerable efforts have been devoted to development of efficient protocols for the stereoselective synthesis of highly substituted 3-methyleneindolinones.[12] For example, palladium-catalyzed cascade intramolecular 5-*exo-dig*/Suzuki coupling of *N*-arylpropiolamides with arylboronic, aryl iodides and aryliodonium salts for the construction of all-carbon tetrasubstituted olefin containing oxindoles has been developed in recent years (Scheme 1a, eq 1).[13] Sekar and Müller also recently reported an improved procedure for the preparation of 3-allylidene-2(3*H*)-benzofuranones and 3-arylpropynylidene indolones *via* intramolecular 5-*exo-dig* of *N*-halophenylalkynylamides followed by subsequent Heck and Sonogashira coupling in the presence of palladium catalyst (Scheme 1a, eqs 2, 3).[14] In 2010, Müller and co-workers demonstrated a consecutive three-component cyclocarbopalladation, Sonogashira coupling, Michael addition of *N*-(2-iodophenyl)propiolamides, terminal alkynes, and amines giving 4-aminoprop-3-enylidene indolones which displayed intense solid-state fluorescence with large Stokes shifts (Scheme 1b).[15] Subsequently, Müller group and Tang group synthesized a series of 3-piperazinyl propenylidene indolone merocyanines and poly(indolone)s with good Aggregation Induced Emission (AIE) properties through similar procedure, respectively.[16] Indeed, palladium-catalyzed cross-coupling reaction is a well-established strategy to construct C-N bond for increasing molecular complexity and functional group,[17] yet there have no successful examples reported to-date regarding the synthesis of hetero-substituted 3-methyleneindolinone derivatives. In connection with our recent interests in *N*-hydroxybenzamides as amination substrates,[18] We herein report a palladium-catalyzed cascade reaction between *N*-(2-iodophenyl)propiolamides and *N*-hydroxybenzamides, phenyl hydroxycarbamate (Scheme 1c). This process

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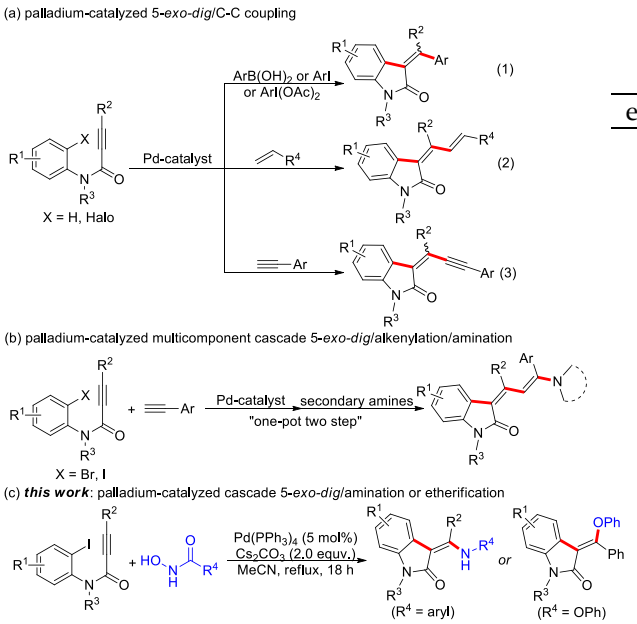
proceeds *via* the intramolecular 5-*exo-dig* cyclization of *N*-(2-iodophenyl)propiolamides in the presence of $Pd(PPh_3)_4$ and then continues the direct amination/etherification for stereoselective construction of amino- and phenoxy-substituted 3-methyleneindolinones.

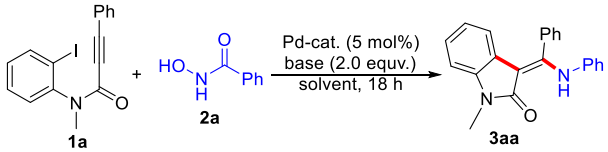


Scheme 1. Pd-catalyzed cascade 5-*exo-dig*/coupling reaction of *N*-(2-iodophenyl)propiolamides.

Results and Discussion

We commenced our investigation using *N*-(2-iodophenyl)-*N*-methyl-3-phenylpropiolamide **1a** with *N*-hydroxybenzamide **2a** in the presence of 5 mol% $Pd(PPh_3)_4$ and Cs_2CO_3 as a base in acetonitrile at reflux for 18 h. To our delight, the reaction resulted in the formation of 5-*exo-dig* cyclized/aminated product **3aa** as the major product in 92% yield. Unfortunately, substituting $Pd(PPh_3)_4$ with other palladium catalysts, including $Pd(OAc)_2$, $PdCl_2$, $PdBr_2$, $Pd(PPh_3)_2Cl_2$, and $Pd_2(dba)_3$, could not improve the yield at all (Table 1, entries 2-6). It is worth noting that no reaction occurred in the absence of a catalyst (Table 1, entry 7), suggesting the crucial role of the Pd-catalyst. Further screening of different bases suggested that Cs_2CO_3 gave the highest yield (Table 1, entries 13). A brief screening of solvents confirmed that acetonitrile gives the highest yields, whereas nitromethane, 1,2-dichloroehtane (1,2-DCE), tetrahydrofuran (THF), toluene, chlorobenzene, dimethylformamide (DMF), and dimethylsulfoxide (DMSO) were failed miserably to give the desired product (Table 1, entries 14-20). A lower reaction temperature (50 °C or 70 °C) gave only a moderate yield (53% and 68% respectively, Table 1, entries 21, 22). Similarly, decreasing the catalyst/base loading and reaction time reduced the reaction yields (Table 1, entries 23, 25, 27), while increasing the catalyst/base loading and reaction time could not improve the yield (Table 1, entries 24, 26, 28). Conclusively, 5 mol% $Pd(PPh_3)_4$ and 2 equiv of Cs_2CO_3 in acetonitrile at reflux gave the best output with (*Z*)-stereoselectivity.

Table 1. Optimization of the Reaction Conditions.[a] T



entry	catalyst	base	solvent	temp./°C	yield/%[b]
1[c]	$Pd(OAc)_2$	NaOAc	toluene	100	68
1	$Pd(PPh_3)_4$	Cs_2CO_3	MeCN	reflux	92
2	$Pd(OAc)_2$	Cs_2CO_3	MeCN	reflux	64
3	$PdCl_2$	Cs_2CO_3	MeCN	reflux	3[illegible]
4	$PdBr_2$	Cs_2CO_3	MeCN	reflux	37
5	$Pd(PPh_3)_2Cl_2$	Cs_2CO_3	MeCN	reflux	57
6	$Pd_2(dba)_3$	Cs_2CO_3	MeCN	reflux	34
7	-	Cs_2CO_3	MeCN	reflux	0
8	$Pd(PPh_3)_4$	Na_2CO_3	MeCN	reflux	57
9	$Pd(PPh_3)_4$	K_2CO_3	MeCN	reflux	54
10	$Pd(PPh_3)_4$	$Ag2CO3$	MeCN	reflux	39
11	$Pd(PPh_3)_4$	CsOAc	MeCN	reflux	72
12	$Pd(PPh_3)_4$	AgOAc	MeCN	reflux	59
13	$Pd(PPh_3)_4$	NaOAc	MeCN	reflux	64
14	$Pd(PPh_3)_4$	Cs_2CO_3	$MeNO_2$	90	34
15	$Pd(PPh_3)_4$	Cs_2CO_3	DCE	reflux	27
16	$Pd(PPh_3)_4$	Cs_2CO_3	THF	reflux	trace
17	$Pd(PPh_3)_4$	Cs_2CO_3	toluene	90	64
18	$Pd(PPh_3)_4$	Cs_2CO_3	PhCl	90	51
19	$Pd(PPh_3)_4$	Cs_2CO_3	DMF	90	trace
20	$Pd(PPh_3)_4$	Cs_2CO_3	DMSO	90	trace
21	$Pd(PPh_3)_4$	Cs_2CO_3	MeCN	50	53
22	$Pd(PPh_3)_4$	Cs_2CO_3	MeCN	70	68
23[c]	$Pd(PPh_3)_4$	Cs_2CO_3	MeCN	reflux	48
24[d]	$Pd(PPh_3)_4$	Cs_2CO_3	MeCN	reflux	82
25[e]	$Pd(PPh_3)_4$	Cs_2CO_3	MeCN	reflux	6[illegible]
26[f]	$Pd(PPh_3)_4$	Cs_2CO_3	MeCN	reflux	86
27[g]	$Pd(PPh_3)_4$	Cs_2CO_3	MeCN	reflux	57
28[h]	$Pd(PPh_3)_4$	Cs_2CO_3	MeCN	reflux	92

[a]Reaction condition: *N*-(2-iodophenyl)-*N*-methyl-3-phenylpropiolamide **1a** (0.25 mmol), *N*-hydroxybenzamide **2a** (0.25 mmol), solvent (3 mL), and catalyst (5.0 mol%) for 18 h. [b]Isolated yields. [c]2.5 mol% of catalyst was used. [d]10 mol% of catalyst was used. [e]1.0 equivalent of base was used. [f]4.0 equivalent of base was used. [g]reaction time for 12 h. [h]reaction time for 24 h.

With the optimal reaction conditions in hand, we investigated the substrate scope concerning various *N*-(2-iodophenyl)propiolamides **1** firstly. We were pleased to find that a wide range of *N*-(2-iodophenyl)propiolamides **1** could readily react with *N*-hydroxybenzamide **2a** to afford the corresponding products **3aa**-**3oa** in 77-95% yields (Table 2). In detail, electron-donating substituents (e.g. –Me and –OMe) and moderate electron-withdrawing groups

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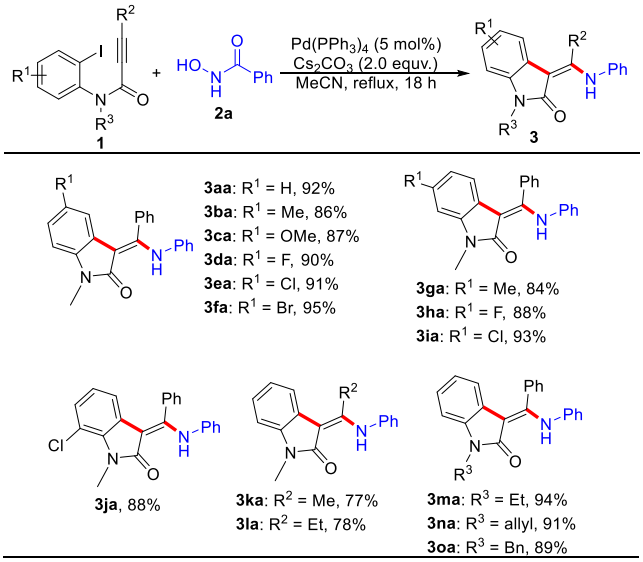
(e.g. –F, –Cl, and –Br) present at the *para*-, *meta*-, and *ortho*-position of aniline yielded the corresponding (*Z*)-3-(arylaminomethylene)indolin-2-ones **3aa**-**3ja** in good to excellent yields (84-95%). Interestingly, the reaction of the alkynyl moiety bearing an alkyl groups (e.g. –Me and –Et) also reacted to give the desired products **3ka** and **3la** in 77% and 78% yields, respectively. Meanwhile, the effect of various *N*-protecting groups, including ethyl, allyl and benzyl, on *N*-(2-iodophenyl)propiolamides **1** was also investigated, delightfully, all of the protected substrates reacted efficiently under the standard reaction conditions to give the respective products **3ma**, **3na**, and **3oa** in 94%, 91%, and 89% yields, respectively.

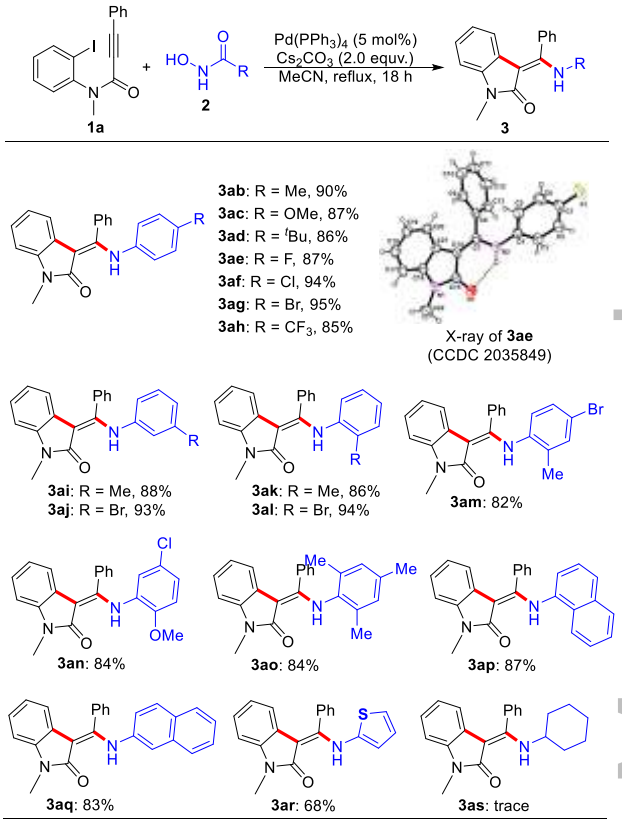
Table 2. Substrate scope of *N*-(2-iodophenyl)propiolamides.[a,b]



[a] Reaction conditions: *N*-(2-iodophenyl)propiolamides **1** (0.25 mmol), *N*-hydroxybenzamide **2a** (0.25 mmol), $Pd(PPh_3)_4$ (5 mmol%), Cs_2CO_3 (2.0 equiv) and MeCN (3 mL) under reflux for 18 h. [b] Isolated yield.

Subsequently, a variety of *N*-hydroxybenzamides **2** was investigated to extend substrate diversity **2** (Table 3). It was found that a wide range of *N*-hydroxybenzamides bearing different substituents on the benzene ring could be smoothly processed to afford the desired products **3ab**-**3al** in 85%-95% yields. The reaction efficiency was less affected by the variations of the electronic properties (e.g. –Me, –OMe, –^{t}Bu, and halo) or the position of substituents (*para*-, *meta*-, and *ortho*-) on the benzene ring, indicating that the transformation exhibits good tolerance of functional groups and steric hindrance. Interestingly, the electron-deficient substrates containing a strong electron-withdrawing group like –CF_3 also reacted to give the desired products **3ah** in 85% yield. Encouragingly, disubstituted, trisubstituted *N*-hydroxybenzamides, *N*-hydroxylnaphthamides and *N*-hydroxythiophene-3-carboxamide were also compatible with this transformation, affording the corresponding products **3am**-**3ar** in 68%-87% yields. However, the reaction of the alkyl-substituted *N*-hydroxyformamide was found to be inferior (Scheme 3, compound **3as**). Additionally, the *Z*-stereoconformation of compound **3ae** was confirmed by X-ray analysis.

Table 3. Substrate scope of *N*-hydroxybenzamides.[a,b]



[a] Reaction conditions: *N*-(2-iodophenyl)-*N*-methyl-3-phenylpropiolamide **1a** (0.25 mmol), *N*-hydroxybenzamides **2** (0.25 mmol), $Pd(PPh_3)_4$ (5 mmol%), Cs_2CO_3 (2.0 equiv) and MeCN (3 mL) under reflux for 18 h. [b] Isolated yield.

Furthermore, to verify whether this transformation is suitable for other class of *N*-hydroxyformamide, we extended this protocol to phenyl hydroxycarbamate **4** under the standard conditions (Table 4). Surprisingly, an exclusively *E*-stereoisomer product was isolated with the absolute configuration of the isolated product were also confirmed by X-ray crystallographic analysis (compound **5f**). As further demonstration of the substrate scope of this transformation showed that the reaction of substrate **4** with various *N*-(2-iodophenyl)propiolamides **1** under the standard conditions smoothly furnished the corresponding products **5a**-**5i** in 76%-94% yields. Of note, substituted aromatic rings of different electronic properties were readily tolerated as well as *N*-protected groups.

Table 4. Synthesis of 3-(phenoxy(phenyl)methylene)indolin-2-ones using phenyl hydroxycarbamate.[a,b]

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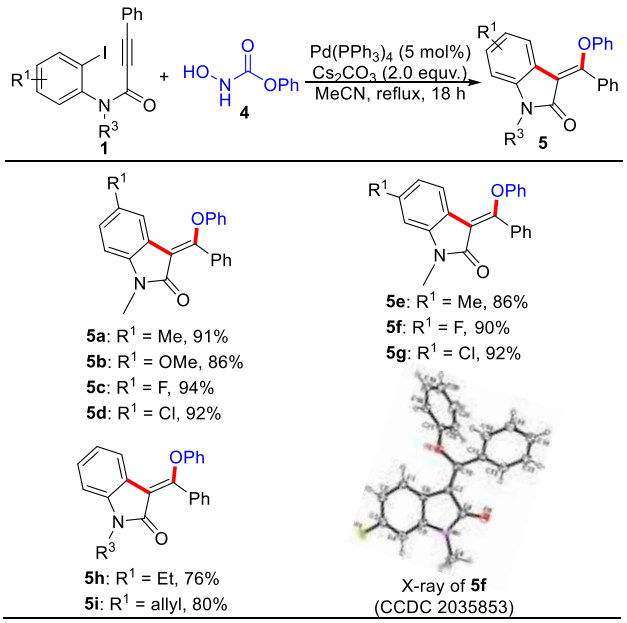
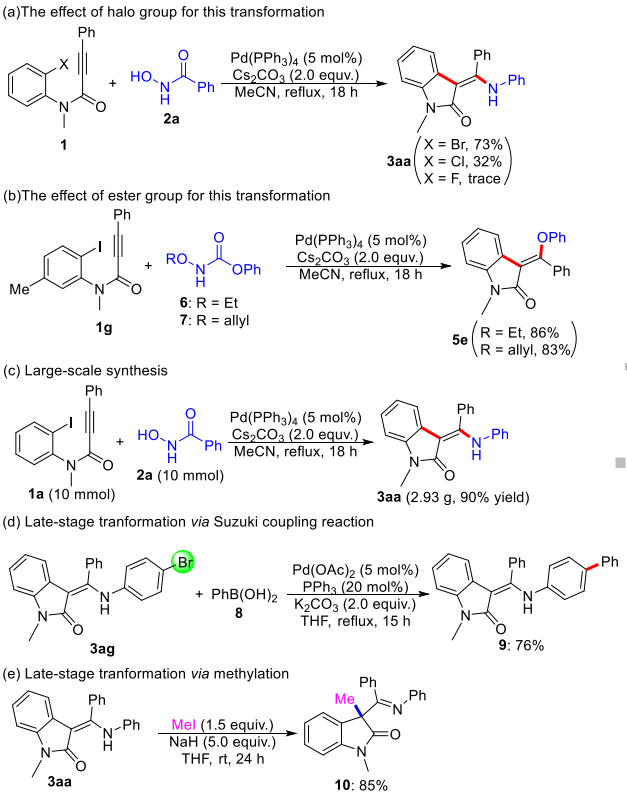


[a] Reaction conditions: *N*-(2-iodophenyl)propiolamides **1** (0.25 mmol), phenyl hydroxycarbamate **4** (0.25 mmol), $Pd(PPh_3)_4$ (5 mmol%), Cs_2CO_3 (2.0 equiv) and MeCN (3 mL) under reflux for 18 h. [b] Isolated yield.

In addition, the effect of halogen substituent (e.g. fluoro, chloro, and bromo) of *N*-(2-iodophenyl)propiolamide **1** on the fate of the reaction was investigated (Scheme 2a). The reaction of fluoro-substituted substrate was unsuccessful in this transformation, whereas the reaction of chloro- and bromo-substituted substrate gave a poor yield of the desired product. Simultaneously, the effect of substitution on phenyl hydroxycarbamate, such as phenyl ethoxycarbamate **6** and phenyl (allyloxy)carbamate **7**, was also examined (Scheme 2b). Gratifyingly, the *O*-substituted phenyl hydroxycarbamate **6** and **7** reacted smoothly with *N*-(2-iodophenyl)propiolamides **1g** without compromising the optimized reaction conditions to afford their corresponding product **5e** in 86% and 83% yield, respectively. Moreover, the scalability of the reaction was investigated with the large-scale (10 mmol) reaction of *N*-(2-iodophenyl)-*N*-methyl-3-phenylpropiolamide **1a** with *N*-hydroxybenzamide **2a** under the optimized reaction conditions that gave the corresponding product **3aa** in 90% yield without any significant loss in the optimized reaction yields (Scheme 2c). Notably, further synthetic transformations of the obtained products were also explored. The synthesized product **3ag** readily undergoes the Suzuki coupling reaction to yield the corresponding product **9** in 76% yield (Scheme 2d), illustrating that compounds containing halgen substituents could be further functionalized by a C-C coupling reaction for further π-expansion of the 3-alkylideneoxindole skeleton. To our delight, the treatment of 3-alkylideneoxindole **3aa** with iodomethane in the presence of sodium hydride led to the corresponding product **10** of 3-methylation (Scheme 2e), thus providing a synthetic approach for the C3-selective functionalization of the oxindole framework.



Scheme 2. Further Studies.

To further probe the mechanisms for this transformation, some control experiments were designed and investigated (Scheme 3). When aniline and isocyanatobenzene were employed under standard conditions, respectively. The same product was obtained in 85% yield using isocyanatobenzene as substrate (Scheme 3b) while no reaction occurred using aniline (Scheme 3a). In addition, *O*-benzoyl-substituted substrate **11** also could generate the corresponding product **3aa** in 72% yield (Scheme 3c). These results implied isocyanatobenzene is a possible intermediate. Compared to aromatic alkyne substituents, only a trace amount of the desired product **3aa** was produced (detected by TLC) when *N*-(2-iodophenyl)-*N*-methylpropiolamide used as substrate under the standard conditions (Scheme 3d). Moreover, *N*-(2-iodophenyl)-*N*-methylcinnamamide generated the intramolecular annulation product **15** in 45% yield, could not undergo the cascade intramolecular 5-*exo*-*dig*/amination process (Scheme 3e). For the etherification, phenol was employed as a substrate to react with *N*-(2-iodo-5-methylphenyl)-*N*-methyl-3-phenylpropiolamide **1g** under the same condition, and the desired product **5e** was observed in 86% yield (Scheme 3f). These facts demonstrated that *N*-hydroxybenzamide would generate isocyanatobenzene as the key intermediate *via* proton migration and Lossen rearrangement process in the presence of Cs_2CO_3 as base.[19]

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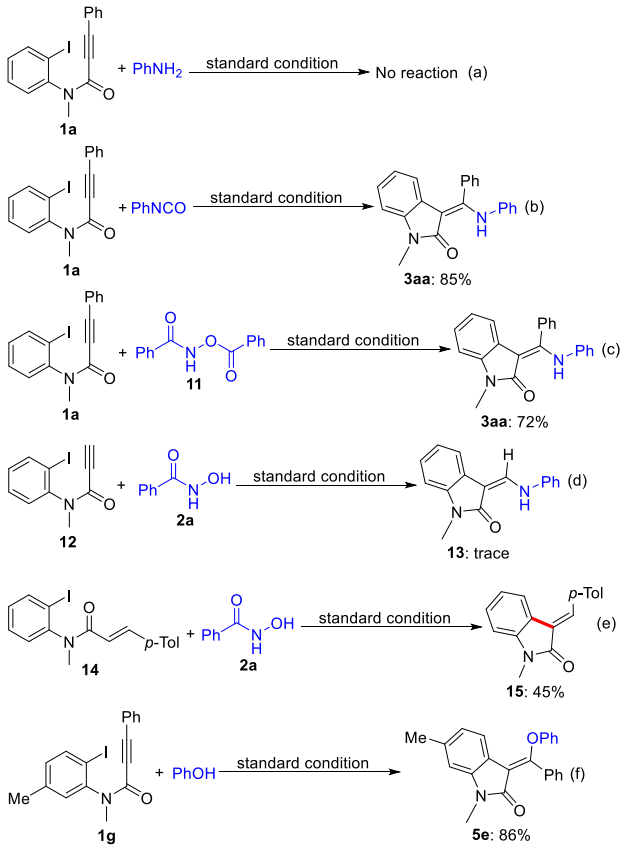
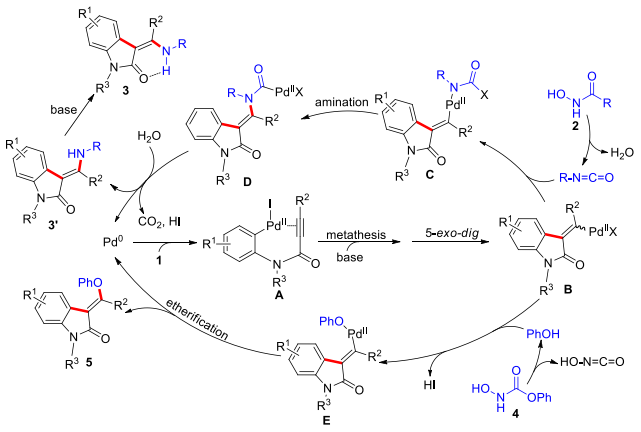


Scheme 3. Control experiments.

Driven by the above experimental results and literature precedents,[20,21] a plausible reaction pathway was proposed as shown in Scheme 4. Initially, the oxidative addition of *N*-(2-iodophenyl)propiolamides **1** by the ligated Pd(0) species that subsequently coordinate with the triple bond of propiolamide generates arylpalladium species **A**, which undergoes cascade metathetic displacement of iodide by carbonate and intramolecular 5-*exo*-*dig* annulation to form intermediate **B** (*via syn*-carbopalladation and subsequent *E*,*Z*-equilibration). Then intermediate **B** could be trapped by isocyanatobenzene derived from *N*-hydroxybenzamides **2** to give intermediate **C**, which provides intermediate **D** by amination of vinyl palladium species. Finally, the reductive elimination and decarboxylation of intermediate **D** furnishes the intermediate **3′** and regenerates Pd(0), which continues to participate in the next cycle. The compound **3′** quickly converts to the final compound **3** with an intramolecular hydrogen bond to make the (*Z*)-stereoisomer more stable *via* base-catalyzed isomerization of vinylogous amide. On the other hand, the intermediate would prior to react with highly active phenol derived from phenyl hydroxycarbamate **4** to furnish the corresponding product **5** through the etherification of intermediate **E**.



Scheme 4. Proposed Mechanism.

Conclusion

In conclusion, we have established a versatile protocol for the synthesis of structurally diverse 3-methyleneindolinones through Pd(0)-catalyzed cascade reaction of readily available N-(2-iodophenyl)propiolamides with N-hydroxybenzamides and phenyl hydroxycarbamate. This highly efficient and stereoselectivity strategy constructs two new chemical bonds and one new five-membered ring through sequential intramolecular 5-exo-dig annulation and amination/etherification process. A wide range of novel 3-alkylideneoxindoles were obtained with good functional group tolerance to show the broadness of the reaction. Moreover, gram-scale synthesis and easily transformation through cross-coupling and methylation showed the practical utility of this protocol.

Experimental Section

General procedure for the synthesis of amino-substituted 3-methyleneindolinones 3. The mixture of alkynamide **1** (0.25 mmol), *N*-hydroxyamide **2** (0.25 mmol), $Pd(PPh_3)_4$ (5 mol%), Cs_2CO_3 (2.0 equiv.) and MeCN (3 mL) were successively added to a Schlenk reaction tube. The reaction mixture was stirred vigorously at reflux in oil bath with stirring 18 hours. After the reaction mixture was cooled to room temperature, extracted with CH_2Cl_2 (3 × 10 mL), and washed with brine. The organic layers were combined, dried over Na_2SO_4, filtered, and then evaporated under vacuum. The residue was purified using flash column chromatography with a silica gel (200-300 mesh), using ethyl acetate and petroleum ether as the elution solvent to give desired product **3**.

General procedure for the synthesis of phenoxy-substituted 3-methyleneindolinones 5. The mixture of alkynamide **1** (0.25 mmol), phenyl hydroxycarbamate **4** (0.25 mmol), $Pd(PPh_3)_4$ (5 mol%), Cs_2CO_3 (2.0 equiv.) and MeCN (3 mL) were successively added to a Schlenk reaction tube. The reaction mixture was stirred vigorously at reflux in oil bath with stirring 18 hours. After the reaction mixture was cooled to room temperature, extracted with CH_2Cl_2 (3 × 10 mL), and washed with brine. The organic layers were combined, dried over Na_2SO_4, filtered, and then evaporated under vacuum. The residue

was purified using flash column chromatography with a silica gel (200-300 mesh), using ethyl acetate and petroleum ether as the elution solvent to give desired product **5**.

X-Ray Diffraction Studies of 3ae and 5f

Crystallographic data for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-2035849 for **3ae** and CCDC-2035853 for **5f** and cif file details are provided in the Supporting Information. Copies of the data are available free of charge on application to CCDC. [E-mail: deposit@ccdc.cam.ac.uk]

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