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Palladium-Catalyzed Ligand-Free Double Cyclization Reactions for the Synthesis of 3-(1′-Indolyl)-phthalides

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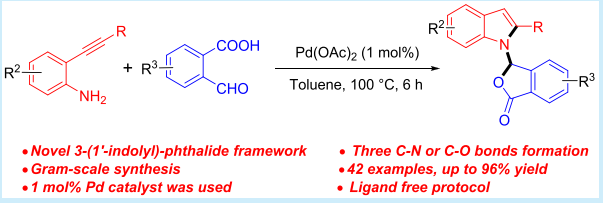
ABSTRACT: Indole and phthalide are privileged heterocyclic scaffolds in numerous natural products and bioactive molecules. The synthesis and biological evaluation of the compounds combining these two scaffolds have rarely been reported. Herein, we repot the first palladium-catalyzed ligand-free double cyclization reactions that enable efficient synthesis of 3-(1′-indolyl)-phthalides (42 examples, up to 96% yield) under mild conditions. Notably, only 1.0 mol % of catalyst loading is used, suggesting high efficiency. Late-stage elaborations give highly functionalized analogues.



The privileged heterocyclic indole and phthalide scaffolds widely exist in natural products (NPs) and pharmaceuticals, and such compounds have proven to possess a wide variety of pharmacological properties, such as anti-inflammatory, anticancer, and antinociception.[1−5] Representative indole-containing examples are Hippadine (lycorine-type alkaloids found in the bulbs),[6] Psilocin (a substituted tryptamine alkaloid with serotonergic psychedelic activity),[7] and (−)-Aurantioclavine (isolated from *Penicillium aurantiovirens* and as an intermediate for the synthesis of polycyclic alkaloids of the communesin family)[8] (Figure 1A). In addition,

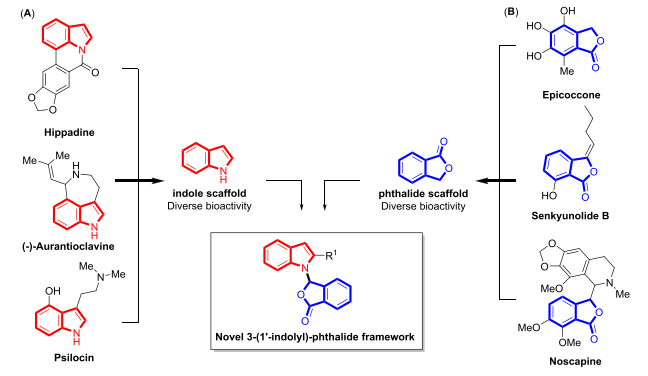


Figure 1. Design of structurally rare 3-(1′-indolyl)-phthalides. (A) Indole-containing NPs. (B) Phthalide-containing NPs.

phthalide fragments are also prevalent in natural products and biologically active compounds,[4] such as Noscapine (a benzylisoquinoline alkaloid isolated from plants of the poppy family),[9] Epicoccone (a subgroup of polyphenols isolated from *Aspergillus flavipes* with free radical scavenging activity),[10] and Senkyunolide B (one of the flavor constituents of celery oil with potent spasmolysis of smooth muscle)[11] (Figure 1B). Due to their diverse and interesting biological profiles of indoles and phthalides, compounds combining the indole and phthalide moieties may have potential biological activities. Very recently, Hasbullah et al. preliminarily revealed that the phthalide-fused indoles were cytotoxic against HL-60 and HepG2 cells.[12] Of note, the syntheses of compounds containing indole and phthalide moieties have not been extensively explored, and very few approaches have been documented in the literature, thus limiting further biological evaluation of such compounds. In 1960, Johnson et al. achieved the first synthesis of substituted 3-(indolyl)-phthalides from 2-formylbenzoic acid and indole substrates; the types of products depended on the substitution pattern of indole substrates; and the reactions were performed at high temperatures (up to 270 °C) (Scheme 1A).[13] Until recently, another two groups independently reported the synthesis of 3-(indolyl)-phthalides under microwave or aqueous conditions (Scheme 1B).[12,14]

Evidently, these approaches relied on indole substrates, and the appendage diversity of the products only depends on the substituents attached to the indole core. Therefore, the efficient syntheses of compounds containing indole and phthalide moieties are greatly needed. We believe that use of different starting materials could achieve the diversity of this focused library. Herein, we reported the first Pd-catalyzed ligand-free double cyclization reactions for the synthesis of new 3-(1′-indolyl)-phthalides from 2-formylbenzoic acid and 2-ethynylaniline, in which one C−O bond, two C−N bonds, one indole, and one phthalide were formed simultaneously

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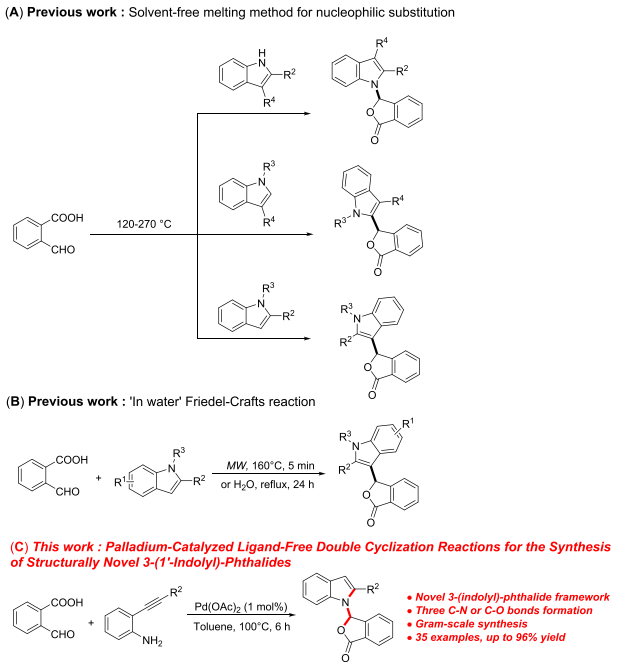
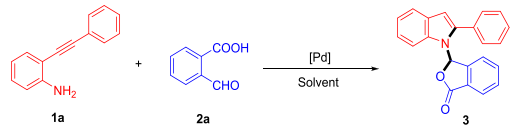
Scheme 1. Previously Reported Approaches for the Construction of 3-(Indolyl)-phthalides and the Approach Presented in This Work



(Scheme 1C). Compared to previously reported methods, this protocol generated a series of 3-(indolyl)-phthalide derivatives in excellent yields (42 examples, up to 96% yield). This protocol was ligand-free and could be performed on a gram scale. Notably, only 1.0 mol % of catalyst loading was used in these reactions, indicating high efficiency and practicality.

Initially, 2-ethynylaniline **1a** (1.0 mmol) and 2-formylbenzoic acid **2a** (1.0 mmol) were used as model substrates to examine the scope of this transformation in the presence of 10 mol % of $Pd(OAc)_2$ (Table 1). Compound **3** was obtained in 34% yield when the reaction was performed in DMF (Table 1, entry 1). Encouraged by this result, we further examined the reactivity in other solvents (Table 1, entries 2−6). To our delight, compound **3** was generated in 73% yield when the reaction was carried out in toluene (Table 1, entry 6). Other solvents such as MeCN, DMSO, MeOH, and H_2O turned out to be less efficient, and compound **3** was afforded in relatively lower yields (Table 1, entries 2−5). Next, we examined the effects of different ratios of substrates on the reactivity (Table 1, entries 7−9). Compound **3** was obtained in 93% and 94% yield, respectively, when 1.5 and 3.0 equiv of **2a** was used (Table 1, entries 7 and 8), about 20% higher than that when 1.0 equiv of **2a** was used (Table 1, entry 6). Besides, compound **3** was afforded in only 58% yield when 1.5 equiv of **1a** was utilized (Table 1, entry 9). Intriguingly, when 1 mol % of catalyst ($Pd(OAc)_2$) loading was employed, the desired product **3** was obtained in 92% yield, comparable to that in the presence of 10 mol % of $Pd(OAc)_2$ (Table 1, entry 10). Other palladium catalysts such as $Pd(acac)_2$, $Pd(PPh_3)_4$, $PdCl_2(PPh_3)_2$, $PdCl_2(dppf)$, and $Pd_2(dba)_3$ were less efficient and delivered the desired compound in <50% yield (Table 1, entries 11−15). Unfortunately, when the reactions were conducted at lower temperatures, the product **3** was afforded in 46% and 63% yield, respectively (Table 1, entries 16 and 17). According to the above optimizations, the optimal reaction condition was 2-ethynylaniline (1.0 mmol), 2-formylbenzoic acid (1.5 mmol), $Pd(OAc)_2$ (1.0 mol %), and toluene (1 mL), at 100 °C for 6 h (Table 1, entry 10).

Table 1. Optimization of the Reaction Conditions[a]



1a 2a 3

entry	catalyst	solvent	T (°C)	ratio (**1a**:**2a**)	**3** (%)[b]
1	$Pd(OAc)_2$	DMF	100	1:1	34
2	$Pd(OAc)_2$	MeCN	80	1:1	52
3	$Pd(OAc)_2$	DMSO	100	1:1	53
4	$Pd(OAc)_2$	MeOH	60	1:1	55
5	$Pd(OAc)_2$	H_2O	100	1:1	13
6	$Pd(OAc)_2$	toluene	100	1:1	73
7	$Pd(OAc)_2$	toluene	100	1:1.5	93
8	$Pd(OAc)_2$	toluene	100	1:3	94
9	$Pd(OAc)_2$	toluene	100	1.5:1	58[c]
10	$Pd(OAc)_2$	toluene	100	1:1.5	92[d] (90[e])
11	$Pd(acac)_2$	toluene	100	1:1.5	42[c]
12	$Pd(PPh_3)_4$	toluene	100	1:1.5	39[c]
13	$PdCl_2(PPh_3)_2$	toluene	100	1:1.5	22[c]
14	$PdCl_2(dppf)$	toluene	100	1:1.5	48[c]
15	$Pd_2(dba)_3$	toluene	100	1:1.5	29[c]
16	$Pd(OAc)_2$	toluene	rt	1:1.5	46[c]
17	$Pd(OAc)_2$	toluene	60	1:1.5	63[c]

[a]Reaction conditions: **1a** (1 mmol), **2a** (1 mmol), palladium catalyst (10 mol %), solvent (1 mL), 6 h. [b]NMR yields determined by ^1H NMR using the triphenylmethane as an internal standard. [c]1.5 mmol of **1a** was used. [d]1.0 mol % of catalyst was used. [e]Isolated yield.

With the optimized reaction conditions in hand, we next examined the scope of 2-ethynylanilines and 2-formylbenzoic acids (Scheme 2). As shown in Scheme 2, compounds **3**−**31** were obtained in moderate to excellent yields (66−96%) regardless of their substitution patterns and electronic nature, and various R^1 substitutions attached to the phenyl ring were well tolerated in these reactions. When R^1 was halogen, the corresponding products **4**−**9** were generated in good yields (79−92%), which could be used for further functionalization. Delightfully, both electron-deficient (substituted with $-CF_3$, $-CN$, $-OCF_3$, $-NO_2$, $-COMe$, $-COOMe$) and electron-rich (substituted with alkyl, $-OMe$, $-OEt$, $-Ph$) 2-ethynylanilines proceeded well under the optmized conditions and furnished the compounds **10**−**27** in moderate to excellent yields (66−96%). Interestingly, compounds **28**−**31** bearing the alkyl groups were also formed in moderate yields (71−79%). For 5-chloro-2-formylbenzoic acid, its corresponding product **32** was obtained in 83% yield, comparable to that of compound **3**. For anilines bearing additional substituents, the corresponding products **33**−**44** were formed in moderate to good yields (66−91%). Finally, 2-ethynylaniline **1a** (5 mmol) and 2-formylbenzoic acid **2a** (7.5 mmol) were employed to examine the scability. To our delight, the desired product **3** was formed in 85% yield under the standard reaction conditions. Among these 3-(indolyl)-phthalides, X-ray crystallographic study was performed and further confirmed the structure of compound **3** (CCDC number: 1886364). It is worth noting that only 3-(1′-indolyl)-phthalides were afforded exclusively under the optimal conditions, and the 3-(3′-indolyl)-phthalides were not observed in these reactions.

To showcase the synthetic utilities, compound **3** was used for late-stage diversification (Scheme 3). As shown in Scheme

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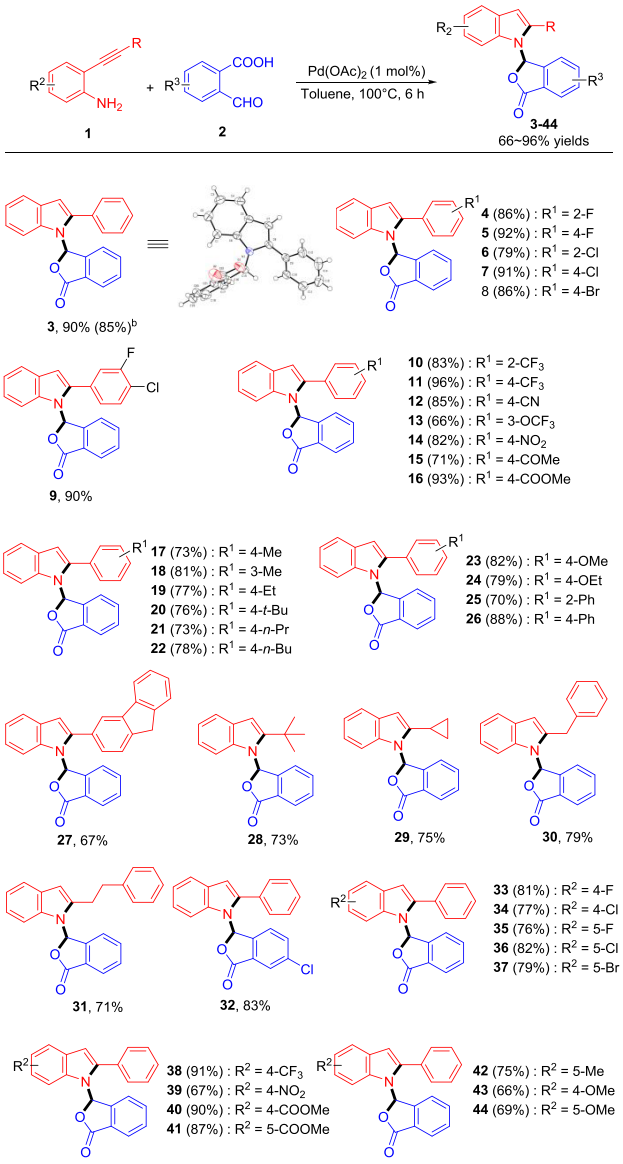
Org. Lett. XXXX, XXX, XXX−XXX

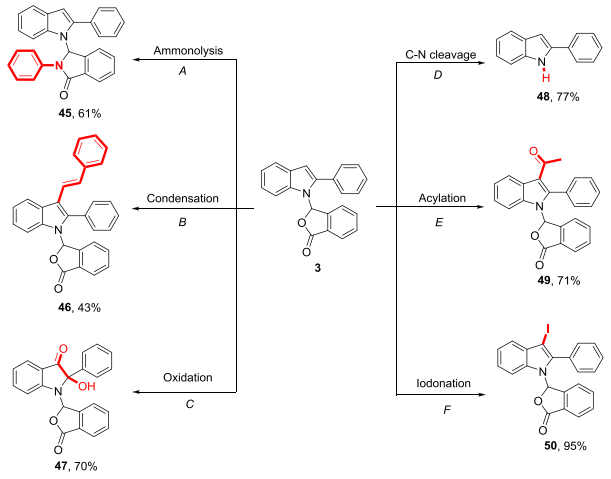
Scheme 2. Scope of 2-Ethynylanilines[a]



[a]Conditions: **1** (1 mmol), **2** (1.5 mmol), $Pd(OAc)_2$ (1 mol %), toluene (1 mL), 100 °C, 6 h. [b]**1a** (5 mmol), **2a** (7.5 mmol), $Pd(OAc)_2$ (1 mol %), toluene (10 mL), 100 °C, 6 h.

3A, compound **3** reacted smoothly with aniline, giving compound **45** in 61% yield. In the presence of $FeCl_3{\cdot}6H_2O$, dehydration reaction between compound **3** and 2-phenylacetaldehyde afforded alkenylated compound **46** in 43% yield (Scheme 3B). Oxidation of compound **3** with $RuCl_3{\cdot}3H_2O$ yielded compound **47** in 70% yield (Scheme 3C). Treatment of **3** with *t*-BuOK led to the C−N bond cleavage, yielding compound **48** in 76% yield (Scheme 3D). We proposed that the phthalide ring could be used as a new protecting group for indole substrates and could be removed under mild conditions. Friedel−Crafts acetylation of compound **3** with acetyl chloride with the assistance of Et_2AlCl gave the acylated compound **49** in 71% yield, and the acetyl group could be used for further transformations (Scheme 3E). Iodination reaction of **3** with NaI yielded the C-3 iodinated product **50** in quantitative yield (Scheme 3F), which could be employed for building 3-(indolyl)-phthalide collections. Presented here are just a few

Scheme 3. Late-Stage Elaborations[a]

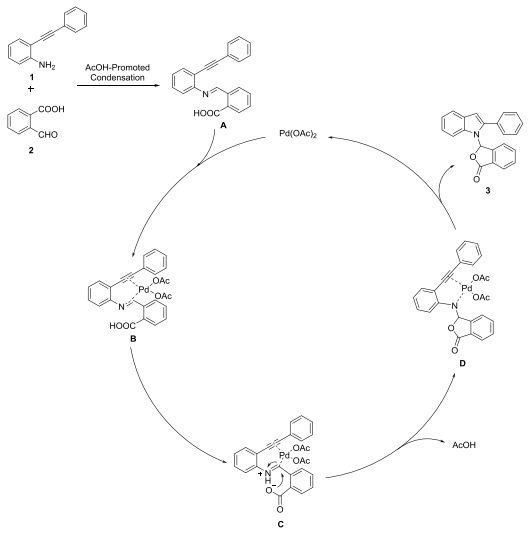


[a](A) Aniline (1 equiv), AcOH. (B) 2-Phenylacetaldehyde (1.1 equiv), FeCl3·6H_2O (2.5 mol %), EtOH (2.2 equiv), DCM. (C) $NaIO_4$ (1 equiv), $RuCl_3{\cdot}3H_2O$ (5 mol %), MeCN. (D) *t*-BuOK (1 equiv), THF. (E) Et_2AlCl (1.5 equiv), acetyl chloride (1.2 equiv), DCM. (F) NaI (1 equiv), $PhI(OAc)_2$, MeCN:H_2O (1:1).

examples regarding the late-stage elaboration of 3-(1′-indolyl)-phthalides. Conceivably, more transformations could happen starting from 3-(1′-indolyl)-phthalides, generating a diverse compound library for biological testing.

Based on these results, the proposed mechanism for the synthesis of 3-(1′-indolyl)-phthalides is depicted in Scheme 4.

Scheme 4. Proposed Reaction Mechanism for the Formation of 3-(1′-Indolyl)-phthalides



Initially, the intermediate **A**, generated *in situ* from substrates **1a** and **2a** through the condensation reaction, coordinated with $Pd(OAc)_2$ to form complex **B**. Protonation exchange gave the activated imine **C**, which promoted further intramolecular cyclization and transmetalation to generate the complex **D**. Further 5-endo N-cyclization transformation of complex **D** afforded the product **3** and released the palladium catalyst. Through the palladium-catalyzed cascade reactions, the new 3-(1′-indolyl)-phthalide framework was efficiently constructed, in which one C−O bond and two C−N bonds were formed

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simultaneously. Another possible pathway was that 2-ethynylaniline first generated the 2-aryl indole under the optimized reaction conditions, and the NH group of the 2-aryl indole attacked the aldehyde group of 2-formylbenzoic acid, followed by intramolecular dehydration reaction, finally yielding the desirable products. To prove this possible pathway, we tested the reactivity between 2-aryl indole and 2-formylbenzoic acid under the optimized conditions. However, no desirable product was formed, thus excluding this possibility.

In conclusion, we have developed the first palladium-catalyzed ligand-free double cyclization reactions that enable efficient synthesis of structurally novel and biologically interesting 3-(1′-indolyl)-phthalides (42 examples, up to 96% yield) under mild conditions, regardless of their attached substituents. Of note, only 1.0 mol % of catalyst loading was used in these reactions, and high reactivity (85% yield) was also observed when the reaction was performed on a gram scale (5.0 mmol). Through the palladium-catalyzed cascade reactions, the 3-(1′-indolyl)-phthalide framework was efficiently accessed, in which one C−O bond and two C−N bonds were formed simultaneously. Late-stage elaborations based on the 3-(1′-indolyl)-phthalide scaffold were carried out, giving highly functionalized analogues, which could be potentially used for construction of a diverse compound library. Relative to previous methods, the protocol presented here has several advantages such as mild reaction conditions, low catalyst loading, and ligand free and more importantly achieves greater appendage diversity.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.9b04241.

Experimental procedures, characterization data, and ^{1}H NMR and ^{13}C NMR spectra for new compounds (PDF)

Accession Codes

CCDC 1886364 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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