Regioselective Synthesis of Substituted Imidate *N*-[1-Methyleneisobenzofuran-3(1*H*)-ylidene]benzenamines via Palladium-Catalyzed Tandem Heteroannulation of *o*-(1-Alkynyl)benzamides with Iodobenzene

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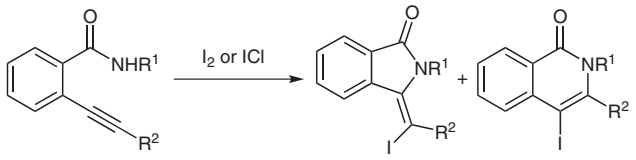
Abstract: A variety of substituted imidate *N*-[1-methyleneisobenzofuran-3(1*H*)-ylidene]benzenamines have been prepared in good to excellent yields by the palladium-catalyzed tandem heteroannulation of *o*-(1-alkynyl)benzamides with iodobenzene. The products obtained from this process were unusual substituted *N*-[isobenzofuran-3(1*H*)-ylidene]benzenamines. The tandem cyclization of readily available *o*-(1-alkynyl)benzamides and aryl iodides provided a powerful tool for the preparation of functionally substituted *N*-[isobenzofuran-3(1*H*)-ylidene]benzenamine compounds.

Keywords: isobenzofuran, *o*-(1-alkynyl)benzamide, iodobenzene, tandem, palladium catalysis

Carbocycles and heterocycles are basic skeletons of many biologically active natural products. Because tandem reactions allow a considerable increase in the molecular complexity in a single operation, they have received considerable attention in the design and synthesis of complex biologically active compounds and natural products.[1] During the past decades, palladium-catalyzed domino cyclization reactions have emerged as a powerful tool to construct complex carbocyclic and heterocyclic molecules.[2] Among them, the palladium-catalyzed cyclization of alkynes is particularly effective for the synthesis of a wide variety of carbocycles and heterocycles.[3] Their popularity stems in part from their tolerance of many functional groups such as carbonyl and hydroxy groups, which allows them to be employed in the synthesis of highly complex molecules and industrial chemical processes.[4] The key step in these reactions is the addition of arylpalladium halide to the triple bond which affords an intermediate that can participate in a wide variety of useful synthetic processes.

The substituted isobenzofurans (IBF) are integral parts of numerous natural products and are extremely important in medicinal chemistry.[5] Among these isobenzofuran derivatives, 3-substituted isobenzofuran-1(3*H*)-ones are vital heterocyclic motifs in many bioactive compounds such as isocoumarins, anthraquinones, anthracyclines, and several alkaloids.[6] For example, 3-alkylidene isobenzofuran-1(3*H*)-one derivatives are reported to possess antispasmodic, herbicidal, and insecticidal properties.[7] On the other hand, imidates, which are also called imidoates and orimido esters, are esters of the hypothetical imidic acids.[8] They are very useful synthetic building blocks[9] and important pharmacophores.[10] In view of their potential usefulness in synthetic and medicinal chemistry, many efficient methodologies have been developed for the construction of imidate framework by the following reactions: 1) the Pinner reaction,[11] one of the most popular methods in which nitriles and alcohols are condensed to various imidates in the presence of hydrogen chloride or hydrogen bromide; 2) the reaction of amines with orthoesters;[12] 3) the modified Staudinger ligation;[13] 4) some other methods including the base-catalyzed reaction of nitriles with alcohols,[14] the Cu(I)-catalyzed three-component coupling of terminal alkyne, sulfonyl azide, and alcohol,[15] the palladium-catalyzed insertion of isonitrile into *ortho*-bromoarylalcohol,[16] and the three-component coupling reaction of aryne, isonitrile, and aldehyde.[17]



Scheme 1 Larock developed nitrogen-participated cyclization

Very recently, Larock reported a method of regio- and stereoselective synthesis of isoindolin-1-ones by the electrophilic cyclization of *o*-(1-alkynyl)benzamides with ICl, I_2, and NBS[18] (Scheme 1). Compared to Larock's nitrogen-participated result, when similar alkynyl carboxamides were employed as substrates, electrophilic oxygen-participated cyclization gave exclusively pyran derivatives in our experiments (Scheme 2).[19] Thus, it indicates that the relative nucleophilicity of nitrogen and oxygen atoms of the amide group is a crucial factor in determining the reaction result in these processes. In addition, it has been reported that vinylic, aryl, and alkynylpalladium complexes promoted tandem cyclizations of alkynes possessing nucleophilic center to form various carbo- and heterocycles by in situ coupling/cyclization reactions.[2,3] Pursuing our interest in constructing carbocycles and heterocycles,[19] we investigated the palladium-catalyzed annulation of *o*-(1-alkynyl)benzamides initiated by the addition of

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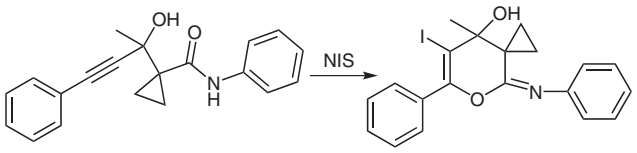
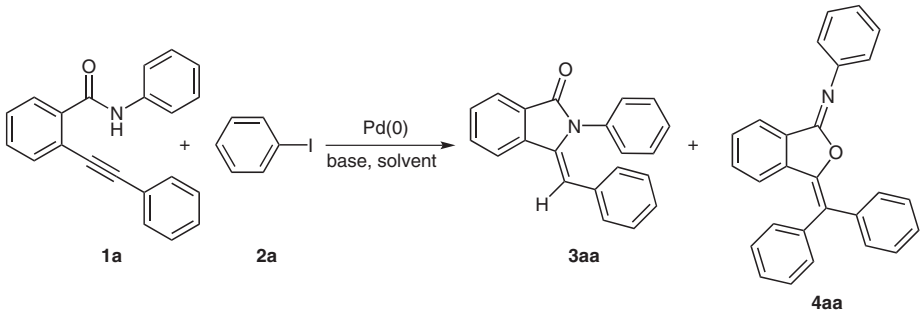
arylpalladium halide to the triple bond. Unexpectedly, this chemistry produces five-membered cyclic imidate *N*-[isobenzofuran-3(1*H*)-ylidene]benzenamine in moderate to excellent yields with good regio- and stereoselectivity. Herein, we wish to report the successful synthesis of substituted [isobenzofuran-3(1*H*)-ylidene]benzenamine compounds by the palladium-catalyzed tandem reactions.



Scheme 2 We reported oxygen-participated cyclization

In the preliminary study, we started our investigations of reaction conditions by using *o*-(1-alkynyl)benzamide **1a** (0.5 mmol), 1.2 equivalents of iodobenzene, 5 mol% of $Pd_2(dba)_3$ as the catalyst, and 2.0 equivalents of K_2CO_3 in DMF as the solvent at 80 °C under argon atmosphere. The intramolecular addition product isoindolinone **3aa** was isolated as the only product (Table 1, entry 1). Further study revealed that if K_2CO_3 or Cs_2CO_3 was used as base, and DMSO, DMF, or THF was used as the solvent, and the same product isoindolinone **3aa** was still isolated exclusively (Table 1, entries 1–4). Iodobenzene failed to participate in the above process, and the expected tandem reaction of *o*-(1-alkynyl)benzamide **1a** with iodobenzene was proved to be not successful. Based on the result obtained, we envisioned that the base might play undesirable role in the present reaction. Thus, we attempted to introduce weaker base to the reaction system. To our delight, when Et_3N was employed as the base, a new compound, in addition to isoindolinone **3aa**, was isolated as the minor product. By NMR and mass spectroscopic analyses, the new product was identified as the unusual five-membered ring imidate *N*-[isobenzofuran-3(1*H*)-ylidene]benzenamine **4aa**. Although Larock reported the electrophilic cyclization of *o*-(1-alkynyl)benzamides to synthesize isoindolinones by nucleophilic attack of the nitrogen of the amide group on the activated carbon–carbon triple bond.[18] However, the present reaction gave isobenzofuran derivative by nucleophilic attack of the oxygen of the amide group, which was apparently different with Larock's work. Stimulated by the unexpected result, we further investigated the effects of solvents, bases, and catalysts in this reaction. The use of alternative bases in the reaction gave greatly altered selectivity. For example, stronger bases such as K_2CO_3, Cs_2CO_3, and Et_3N mainly gave isoindolinone (Table 1, entries 1–5); weak inorganic bases $NaHCO_3$, NaOAc, and NaOAc·$3H_2O$ also resulted in a mixture of the above two products in prolong time (Table 1, entries 6–8); using organic bases such as pyridine and 2,6-lutidine finally suppressed isoindolinone product and slowly gave the desired compound **4aa** after 20 hours (Table 1, entries 9–13). With regard to the reaction solvent, generally, more polar solvents tended to reduce product selectivity, and less polar solvents generally required longer reaction time. None of those tested, however, were efficient or produced better results than in MeCN. In addition, $Pd(PPh_3)_4$ was further proven to be the best catalyst for the present conversion. Thus, the palladium-catalyzed tandem heteroannulation of *o*-(1-alkynyl)benzamides **1** with organic halides **2** was conducted under the optimum conditions of $Pd(PPh_3)_4$ as the catalyst, 2,6-lutidine as the base in refluxing MeCN.[20]

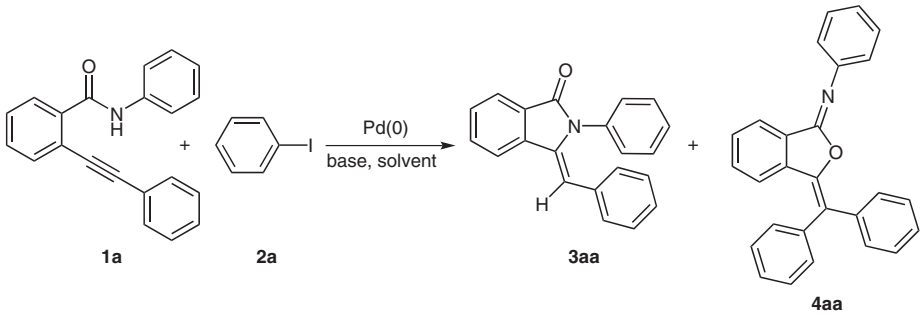
Table 1 Optimization of the Pd-Catalyzed Cyclization of *o*-(1-Alkynyl)benzamide **1a** with Iodobenzene **2a**[a]



1a **2a** **3aa** **4aa**

Entry	Catalysts	Base	Solvent	Yield (%)[b]
1	$Pd_2(dba)_3$	K_2CO_3	DMF	0 (65)
2	$Pd_2(dba)_3$	K_2CO_3	DMSO	0 (67)
3	$Pd_2(dba)_3$	Cs_2CO_3	DMSO	0 (71)
4	$Pd_2(dba)_3$	K_2CO_3	THF	0 (68)
5	$Pd_2(dba)_3$	Et_3N	THF	27 (56)
6	$Pd_2(dba)_3$	$NaHCO_3$	THF	15 (68)

Table 1 Optimization of the Pd-Catalyzed Cyclization of *o*-(1-Alkynyl)benzamide **1a** with Iodobenzene **2a**[a] (continued)



1a **2a** **3aa** **4aa**

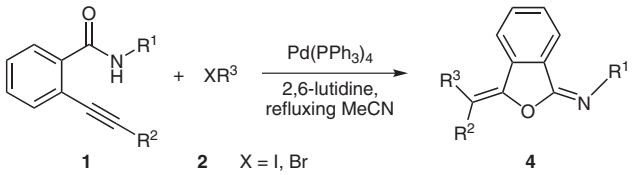
Entry	Catalysts	Base	Solvent	Yield (%)[b]
7	$Pd_2(dba)_3$	NaOAc	THF	25 (60)
8	$Pd_2(dba)_3$	NaOAc×3H_2O	THF	23 (58)
9	$Pd_2(dba)_3$	pyridine	THF	56 (0)
10	$Pd_2(dba)_3$	2,6-lutidine	THF	63 (0)
11	$Pd_2(dba)_3$	2,6-lutidine	MeCN	70 (0)
12	$Pd_2(dba)_3$×$CHCl_3$	2,6-lutidine	MeCN	68 (0)
13	Pd/C	2,6-lutidine	MeCN	49 (0)
14	$Pd(OAc)_2$/Ph_3P	2,6-lutidine	MeCN	no reaction
15	$Pd(PPh_3)_4$	2,6-lutidine	MeCN	73 (0)
16	$Pd(PPh_3)_4$	2,6-lutidine	toluene	34 (0)

[a] Reactions were carried out on a 0.5 mmol scale in 3.0 mL of solvent under argon atmosphere with 1.0 equiv of **1a**, 1.2 equiv of iodobenzene, 2.0 equiv of base, and 0.05 equiv of catalyst at 80 °C for the appropriate time (TLC analysis).
[b] The numbers in parentheses are the isolated yields of isoindolinone **3aa**.

With the optimized reaction conditions in hand, the reactions of *o*-(1-alkynyl)benzamide **1** with a wide variety of aryl halids **2** were examined and afforded the cyclic imidates **4** in moderate to excellent yields. As shown in Table 2, the nature of the substituents attached to aromatic halide, and the amide nitrogen had a major impact on the success of the reaction. Difference in the rates of reaction or the yields was observed for substrates bearing different functional groups. First, we proceeded to elucidate the scope of the reaction by examining the effect of various substituents on the aniline ring. The tandem reaction of *N*-phenylcarboxamide **1a** generated the corresponding cyclic imidate in 73% yield for 20 hours (Table 2, entry 1). Generally, introduction of electron-donating group such as methyl or methoxy groups on the aniline ring significantly enhanced the reactivity. Higher yields were obtained in shorter reaction time (Table 2, entries 2, 3, 6). In contrast, lower yields were observed but in good regioselectivity for weak electron-withdrawing Cl and Br groups (Table 2, entries 4, 5, 7). However, the electron-withdrawing NO_2 group attached to the aniline nitrogen afforded intramolecular cyclization product, and isoindolinone **3** was obtained as the exclusive product. The isoindolinone derivative **3** was formed by nucleophilic nitrogen attack of the carbon–carbon triple bond activated by Pd(0) catalyst prior to tandem cyclization. When benzamides bearing *n*-butyl and benzyl groups on the nitrogen were employed as substrates, the tandem reaction afforded the best result, and the desired cyclic imidates **4ha** and **4ia** was obtained 91% and 94% yields, respectively (Table 2, entries 8 and 9). The effect of substitution on the aromatic ring of iodobenzene was also examined based on the reactions of **1a** with a variety of substituted iodobenzenes under the optimal reaction conditions. All the tested reactions afforded the corresponding substituted *N*-[1-(diphenylmethylene)isobenzofuran-3(1*H*)-ylidene]benzenamine **4** in moderate to excellent yields. In contrast, weakly electron-donating 1-iodo-4-methylbenzene gave exclusively the desired product **4ab** in good yield and in good regioselectivity and stereoselectivity (Table 2, entry 10). However, the cyclization of *N*-phenyl-2-(2-phenylethynyl)benzamide **1a** with the stronger electron-donating 1-iodo-4-methoxybenzene exhibited poor reactivity, and the corresponding product **4ac** was isolated in 57% yield after prolonged reaction time. In addition to ^{1}H NMR and ^{13}C NMR spectroscopic data, the formation of *N*-{(*E*)-1-[(4-methoxyphenyl)(phenyl)methylene]isobenzofuran-3(1*H*)-ylidene}benzenamine (*E*)-**4ac** was also confirmed by the corresponding X-ray crystallographic data (Figure 1).[21] On the whole, introducing an electron-withdrawing group on the aromatic ring of iodobenzene substantially improved the yield of the reaction. For example, 1-chloro-4-

iodobenzene bearing an electron-withdrawing Cl group in the *para* position usually produced better results (Table 2, entry 12). When bromobenzene was employed as the substrate, the reaction gave isoindolinone **3** as the major product, and the expected product was isolated in only 27% yield (Table 2, entry 13). However, when chlorobenzene was used as the reactant, no desired product was observed.

Table 2 Pd-Catalyzed Tandem Cyclization of *o*-(1-Alkynyl)benzamide **1** with Aryl Halides **2**[a]



1 **2** **4**

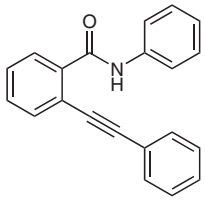
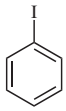
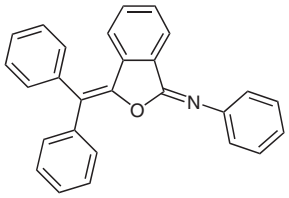
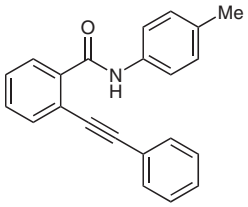
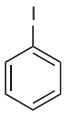
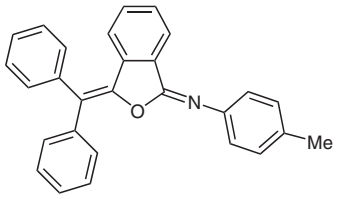
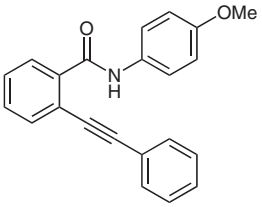
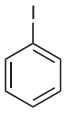
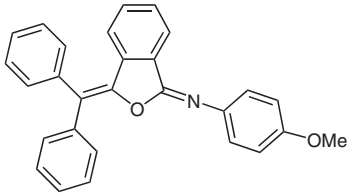
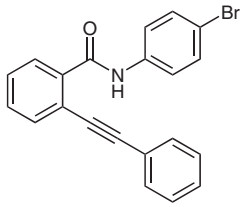
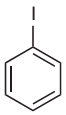
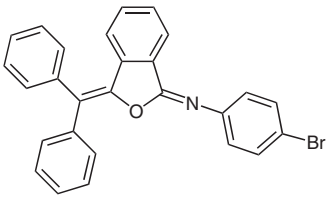
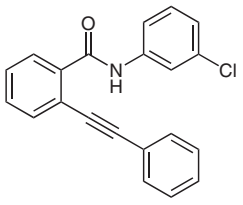
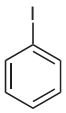
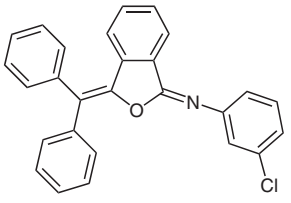
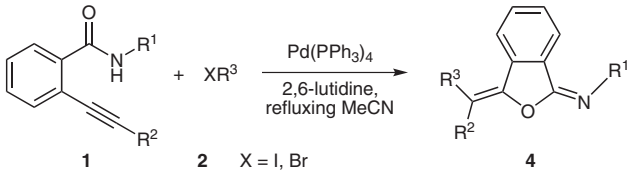
Entry	Substrate **1**	Substrate **2**	Product	Time (h)	Yield (%)[b]
1	 **1a**	 **2a**	 **4aa**	20	73
2	 **1b**	 **2a**	 **4ba**	16	78
3	 **1c**	 **2a**	 **4ca**	16	86
4	 **1d**	 **2a**	 **4da**	24	69
5	 **1e**	 **2a**	 **4ea**	24	66

Table 2 Pd-Catalyzed Tandem Cyclization of *o*-(1-Alkynyl)benzamide **1** with Aryl Halides **2**[a] (continued)



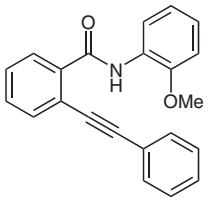
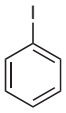
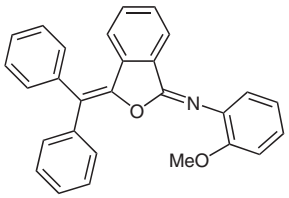
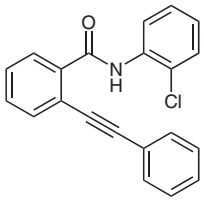
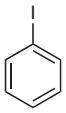
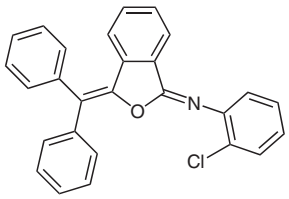
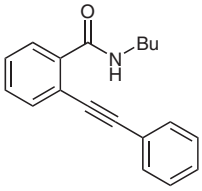
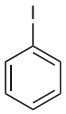
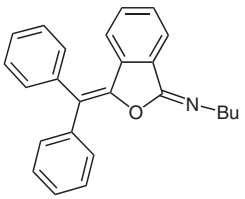
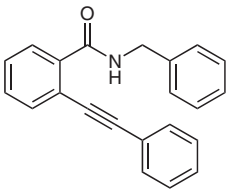
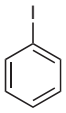
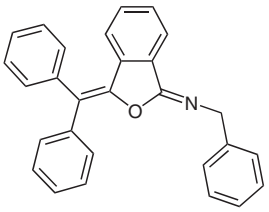
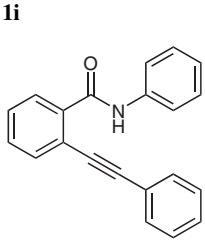
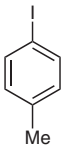
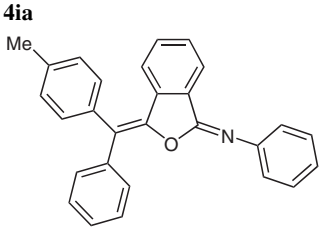
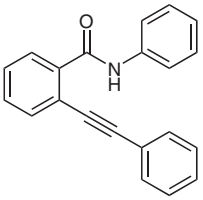
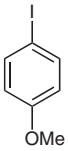
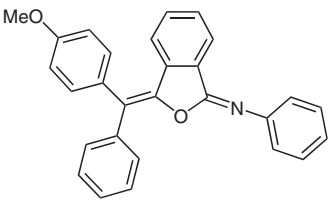
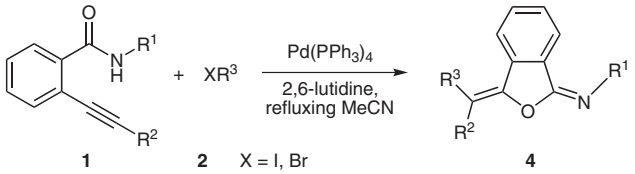
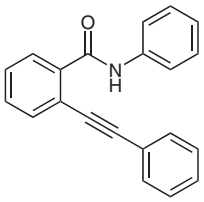
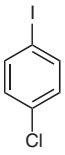
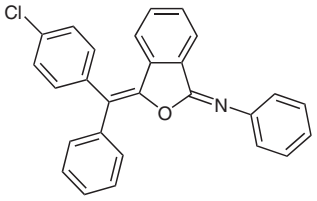
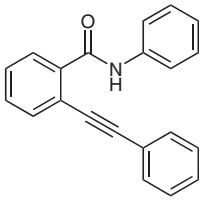
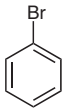
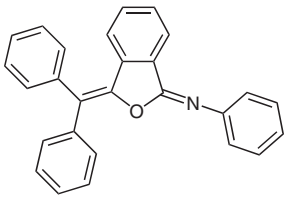
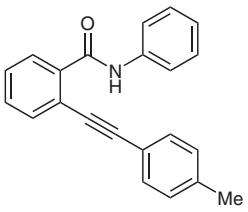
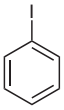
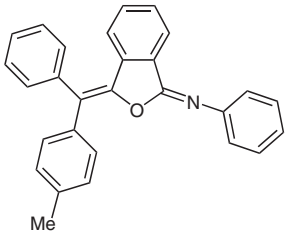
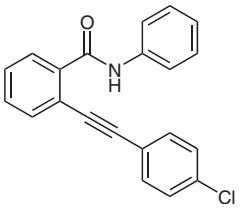
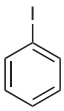
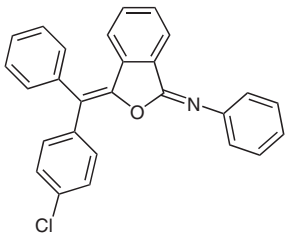
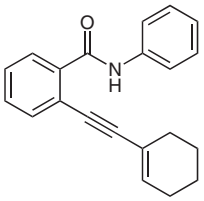
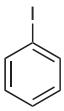
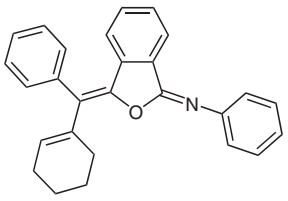
Entry	Substrate **1**	Substrate **2**	Product	Time (h)	Yield (%)[b]
6	 **1f**	 **2a**	 **4fa**	16	80
7	 **1g**	 **2a**	 **4ga**	24	61
8	 **1h**	 **2a**	 **4ha**	16	91
9	 **1i**	 **2a**	 **4ia**	16	94
10	 **1a**	 **2b**	 **4ab**	20	71
11	 **1a**	 **2c**	 **4ac**	30	57

Table 2 Pd-Catalyzed Tandem Cyclization of *o*-(1-Alkynyl)benzamide **1** with Aryl Halides **2**[a] (continued)



Entry	Substrate **1**	Substrate **2**	Product	Time (h)	Yield (%)[b]
12	 **1a**	 **2d**	 **4ad**	16	91
13	 **1a**	 **2e**	 **4ae**	30	37
14	 **1j**	 **2a**	 **4ja**	20	79
15	 **1k**	 **2a**	 **4ka**	20	83
16	 **1l**	 **2a**	 **4la**	20	75

[a] Reactions were carried out in 3.0 mL of refluxing MeCN under argon atmosphere with 0.50 mmol **1**, 0.60 mmol aryl halides, 2.0 equiv of 2,6-lutidine, and 0.05 equiv of $Pd(PPh_3)_4$ for an appropriate time.
[b] Isolated yields.

Finally, using *N*-phenylcarboxamides and iodobenzene as the model substrates, we also briefly investigated the effect of various substituents on the remote end of the alkyne moiety in the present cyclization process. *o*-(1-Alkynyl)benzamides bearing with an electron-withdrawing group or an electron-donating group on the benzene ring were employed in the reaction, and the corresponding products were isolated in good yields (Table 2, entries 14 and 15). Cyclohexenyl- and phenyl-substituted alkynes exhibited the similar reactivity (Table 2, entry 1 vs. 16).

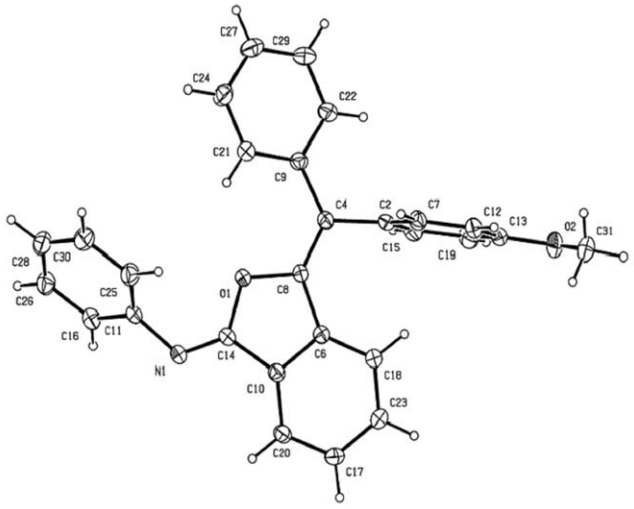
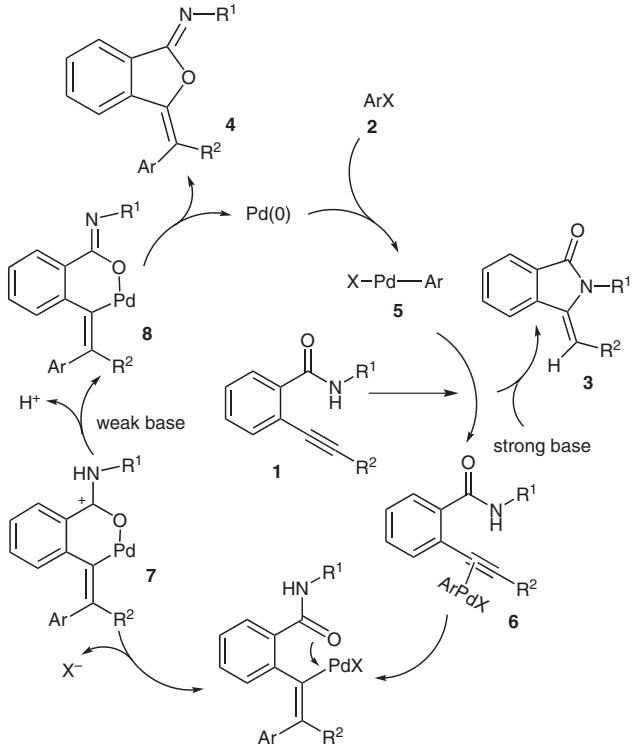


Figure 1 Structure of cyclic imidate (*E*)-**4ac**

Disappointingly, TMS-substituted alkyne afforded none of the desired product, possibly due to steric hindrance to cyclization by the bulky TMS group that blocked the incoming oxygen nucleophile. Unfortunately, when the reaction of terminal alkyne was investigated, a mixture of unidentified products was obtained.



Scheme 3

On the basis of the above results obtained, a plausible mechanism accounting for the formation of the substituted *N*-[isobenzofuran-3(1*H*)ylidene]benzenamine is depicted in Scheme 3. The process was assumed to consist of the following key steps: 1) oxidative addition of the organic halide to Pd(0) catalyst to form palladium(II) intermediate **5**; 2) coordination of the resulting palladium intermediate **5** to triple bond of alkyne to generate important complex **6**;[22] 3) intramolecular nucleophilic attack of the oxygen of the carboxamides group on the vinylic palladium intermediate to afford a six-membered metallocycle intermediate **7** including the carbocation; 4) deprotonation of intermediate **7** promoted by the weak base nucleophile in the reaction mixture to form an enamine intermediate **8**; 5) reductive elimination of the intermediate **8** to afford the expected product **4** and regeneration of the Pd(0) catalyst. In the presence of a stronger base, we assumed that *o*-(1-alkynyl)benzamide **1** underwent intramolecular nucleophilic attack of the nitrogen of the amide group on the carbon–carbon triple bond, followed by deprotonation to directly afford the cyclized products. As we observed, stronger base favored the intramolecular reaction. In this case, the organic halide cannot participate in the above reaction. Therefore, the isoindolinone (phthalimidine) **3** as was isolated as the major product.

In conclusion, an efficient, regioselective, palladium-catalyzed synthesis of substituted *N*-[isobenzofuran-3(1*H*)-ylidene]benzenamine (cyclic imidate) using *o*-(1-alkynyl)benzamides **1** with iodobenzene has been developed. A variety of iodobenzenes undergo this process to give the unexpected products **4** in good yields and in good regio- and stereoselectivity. The tandem cyclization of readily available *o*-(1-alkynyl)benzamides afforded a rapid increase in molecular complexity and provided a powerful tool for the preparation of a wide range of functionally substituted *N*-[isobenzofuran-3(1*H*)-ylidene]benzenamines. Our further studies will focus on the development of more tandem reaction of *o*-(1-alkynyl)benzamide to form other heterocyclic compounds.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

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(20) **General Procedure for the Preparation of *N*-[Isobenzofuran-1 (3*H*)-ylidene]benzenamine Compounds**
To a solution of *o*-(1-alkynyl)benzamides **1** (0.50 mmol) in MeCN (3.0 mL) was added 2,6-lutidine (1.00 mmol). The mixture was stirred for 10 min and $Pd(PPh_3)_4$ (5 mol%) and organic halides (0.60 mmol) were added. The resulting mixture was then heated under an argon atmosphere at refluxing temperature. When the reaction was considered complete, as determined by TLC analysis, the reaction mixture was cooled to r.t., quenched with a sat. aq solution of NH_4Cl, and extracted with EtOAc. The combined organic extracts were washed with H_2O and sat. brine. The organic layers were dried over Na_2SO_4 and filtered. The solvents were evaporated under reduced pressure. The residue was purified by chromatography on silica gel to afford the corresponding *N*-[1-(diphenylmethylene)isobenzofuran-3 (1*H*)-ylidene]benzenamine. Thus, starting with **1a** (149 mg, 0.5 mmol) and iodobenzene **2a** (122 mg, 0.6mmol), a yellowish solid product **4aa** (273 mg, 73%) was isolated; mp 173–175 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.24 (d, *J* = 8.0 Hz, 1 H), 7.14–7.29 (m, 5 H), 7.35–7.41 (m, 5 H), 7.48–7.52 (m, 7 H), 8.00 (d, *J* = 7.6 Hz, 1 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 120.77, 123.27, 123.42, 124.02, 124.76, 127.50, 127.86, 128.38, 128.59, 129.24, 129.26, 129.86, 130.66, 130.82, 131.68, 136.67, 137.80, 137.90, 145.64, 145.77, 153.98. IR (neat): 3052, 2923, 1681, 1013, 755, 693 cm^{-1}. Anal. Calcd for $C_{27}H_{19}NO$: C, 86.84; H, 5.13; N, 3.75; O, 4.28. Found: C, 86.70; H, 5.06; N, 3.73; O, 4.35.

(21) The atomic coordinates for **4ac** have been deposited at the Cambridge Crystallographic Data Centre (deposition number: CCDC 800275). The coordinates can be obtained on request from the Director Cambridge Crystallographic Data Centre. Postal Address: 12 Union Road, Cambridge CB2 1EZ, UK; Email: deposit@ccdc.cam.ac.uk; fax: +44 (1223) 336033; tel.: +44 (1223)762910.

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