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Palladium/Copper-Catalyzed Denitrogenative Alkylidenation and *ortho*-Alkynylation Reaction of 1,2,3-Benzotriazin-4(3*H*)-ones

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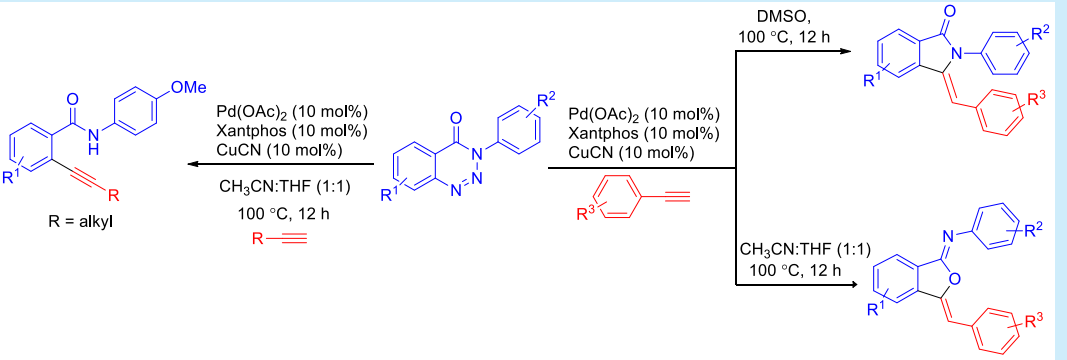
Supporting Information



ABSTRACT: An efficient palladium-catalyzed approach to access various functionalized (*Z*)-3-benzylidene-isoindoline-1-ones and (*Z*)-3-benzylidene(imino)isobenzofuranones via a denitrogenative tandem alkynylation/cyclization reaction of 1,2,3-benzotriazin-4(3*H*)-ones with aromatic terminal alkynes is described. Furthermore, a denitrogenative *ortho*-alkynylation reaction of 1,2,3-benzotriazinones with aliphatic terminal alkynes is also developed. The reaction proceeds through a five-membered azapalladacyclic intermediate with the extrusion of a nitrogen molecule. The significance of the reaction is also demonstrated by a one-pot synthesis of (*Z*)-3-benzylideneisobenzofuran-1(3*H*)-one derivatives in good to high yields.

Transition-metal-catalyzed denitrogenative transannulation reactions of 1,2,3-triazoles such as pyridotriazoles, *N*-sulfonyl-1,2,3-triazoles, 1,2,3-benzotriazones, and *N*-aroylbenzotriozoles have emerged as a powerful method in the preparation of various *N*-heterocycles relevant to natural products and pharmaceuticals.[1,2] In this context, the research groups of Murakami,[3] Liu,[4] and Cheng[5] studied a variety of transannulation reactions of 1,2,3-benzotriazinones with various π-components such as alkynes, alkenes, allenes, isocyanides, and benzynes to prepare functionalized isoquinolones and isoindolinone derivatives in a highly effective manner. Mechanistically, the reaction proceeds through a five-membered aza-metallacycle intermediate, which is in sharp contrast to other 1,2,3-triazoles that proceed via a metallocarbene intermediate,[1] and extrude only molecular nitrogen as effluent which is eco-friendly in nature. Recently, a visible-light-promoted regioselective denitrogenative insertion of terminal alkynes into 1,2,3-benzotriazinones to synthesize substituted isoquinolones was also described by Yu and Wang.[6] Despite these significant contributions on annulation reactions, denitrogenative cross-coupling reactions involving 1,2,3-benzotriazones are scarcely studied and relatively unknown.

Very recently, our group[7a] and Cheng et al.[7b] independently reported a nickel-catalyzed denitrogenative biaryl synthesis using 1,2,3-benzotriazinones and organoboronic acids. Encouraged by this result, we continued our interest in search of new coupling reactions of 1,2,3-benzotriazinones. Herein, we report a Pd/Cu-catalyzed denitrogenative tandem alkynylation/cyclization reaction of 1,2,3-benzotriazinones with aromatic terminal alkynes to synthesize highly stereoselective (*Z*)-3-aryl(alkyl)idene isoindolin-1-one and (*Z*)-3-benzylidene-(imino)isobenzofuranone derivatives. As compared to isoquinolone synthesis, isoindolinones from 1,2,3-benzotriazinones are less commonly studied and notably by employing terminal alkynes as the coupling partner with 1,2,3-benzotriazinones are yet to be developed (Figure 1). In addition to this cyclization reaction, a method is also developed with aliphatic terminal alkynes to access *ortho*-alkynylated benzamides in good yields (Figure 1).

3-Substituted isoindolin-1-ones are one of the important heterocyclic compounds which are present in numerous drugs, natural products, and materials.[8] Particularly, 3-arylmethylene isoindolin-1-one has been recognized as a vital scaffold not only because of its remarkable biological activities but also as a useful intermediate for the synthesis of various alkaloids.[9] The literature report reveals that transition-metal-catalyzed tandem alkynylation/cyclization reaction was perhaps one of the most

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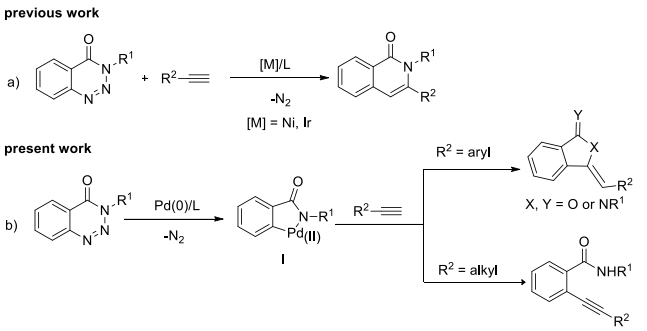


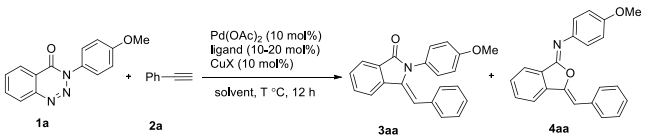
Figure 1. Metal-catalyzed denitrogenative reactions of 1,2,3-benzotriazinones with terminal alkynes.

frequently utilized strategies to synthesize 3-arylmethylene isoindolin-1-one derivatives in a highly stereoselective manner.[10] In 2000, Kundu and his co-workers reported a palladium-catalyzed stereoselective synthesis of (*Z*)-3-aryl-(alkyl)idene isoindolin-1-ones using *ortho*-halo benzamides and terminal alkynes as substrates.[10a] Since then, more efficient catalyst systems involving palladium[10b−d] and copper[10e−i] were developed to improve its scope and versatility. To avoid the use of *ortho*-halo benzamides in the reaction, the directing group assisted C−H activation strategy has been developed as an excellent alternative for the synthesis of isoindolinone derivatives.[11] However, to perform these transformations, special directing groups such as 2-aminoquinoline,[11a−c] pyridine oxides,[11d] and 2-aminophenyl-1*H*-pyrazole[11e] and, in most cases, a higher reaction temperature are always necessary. Despite these notable efforts, the development of mild, efficient, and environmentally friendly strategies toward the synthesis of isoindolinone molecules is still in high demand.

The reaction of 1,2,3-benzotriazin-4-(3*H*)-one (**1a**) with phenyl acetylene (**2a**) in the presence of $Pd(OAc)_2$ (10 mol %) as the catalyst, Xantphos (20 mol %) as the ligand, and CuCN (10 mol %) as an additive in DMSO at 100 °C for 12 h under a nitrogen atmosphere afforded (*Z*)-3-benzylidene-isoindoline-1-one (**3aa**) in 92% isolated yield (Table 1, entry 1). The reaction is highly stereoselective, where the desired product formed as a Z-isomer. Control experiments revealed that, in the absence of a palladium catalyst, no reaction occurred. Changing the ligand from Xantphos to other phosphine ligands such as PPh_3, dppe, and dppp, the desired product was obtained only in 38−52% yield. Nitrogen ligands such as 2,2′-bipyridine and 1,10-phenanthroline are not compatible with the present catalytic reaction. Other copper(I) salts like CuI and CuBr were also active but furnished the product **3aa** in 48 and 10% yields, respectively. However, in the absence of copper salt, the reaction yielded the desired product in a very low yield (entry 16). The choice of solvent is essential in obtaining the desired product in high yield. Of all of the solvents that we screened, DMSO appeared to be the best, and other common solvents such as DMF, 1,2-dichloroethane (DCE), and toluene were relatively less effective. Finally, decreasing the reaction temperature lowered the product yield to 85%. As shown in Table 1, (*Z*)-*N*-((*Z*)-3-benzylideneisobenzofuran-1(3*H*)-ylidene)-4-methoxyaniline (**4aa**) was observed as the competitive side product; however, when the reaction was carried out in CH_3CN solvent, **4aa** was obtained as a primary product in 75% yield (entry 13).

Under optimized reaction conditions, we have investigated the scope of the cyclization reaction with a range of 1,2,3-benzotriazinones (**1b−h**). As shown in Scheme 1, the reaction is compatible with *N*-aryl-substituted 1,2,3-benzotriazinones affording the corresponding products **3ba−ea** in good to high

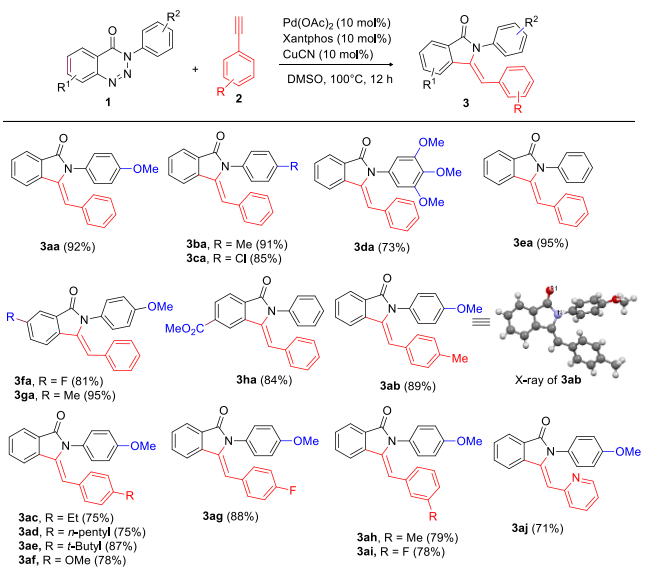
Table 1. Optimization of Reaction Conditions[a]



				yield[b] (%)	
entry	ligand	copper salts	solvent	**3aa**	**4aa**
1	Xantphos	CuCN	DMSO	97 (92)[c]	3
2	PPh_3	CuCN	DMSO	52	9
3	dppe	CuCN	DMSO	40	14
4	dppp	CuCN	DMSO	38	10
5	phen[e]	CuCN	DMSO		
6	bpy[f]	CuCN	DMSO		
7	Xantphos	CuI	DMSO	48	40
8	Xantphos	CuBr	DMSO	10	5
9	Xantphos	CuCN	DMF	74	7
10	Xantphos	CuCN	NMP	49	3
11	Xantphos	CuCN	DCE		
12	Xantphos	CuCN	toluene	9	
13	Xantphos	CuCN	CH_3CN	13	75
14[d]	Xantphos	CuCN	DMSO	86	2
15[g]	Xantphos	CuCN	DMSO	85	3
16	Xantphos		DMSO	5	

[a]All of the reactions were carried out using 1,2,3-benzotriazin-4-(3*H*)-one (**1a**) (0.40 mmol), phenyl acetylene (**2a**) (0.60 mmol), $Pd(OAc)_2$ (0.04 mmol), ligand (0.04−0.08 mmol), additive (0.04 mmol), and solvent (dry), 2 mL at the mentioned temperature for 12 h under N_2. [b]GC yields. [c]Isolated yield. [d]The reaction was carried out at 80 °C. [e]phen = 1,10-phenanthroline. [f]bpy = 2,2′-bipyridine. [g]The reaction was carried out at 80 °C for 24 h.

Scheme 1. Synthesis of (*Z*)-3-Benzylidene-isoindoline-1-ones[a,b]



[a]All of the reactions were carried out using 1,2,3-benzotriazin-4-(3*H*)-ones **1** (0.40 mmol), aromatic terminal alkynes **2** (0.60 mmol), $Pd(OAc)_2$ (0.04 mmol), Xantphos (0.04 mmol), and CuCN (0.04 mmol) for 12 h. [b]Isolated yields.

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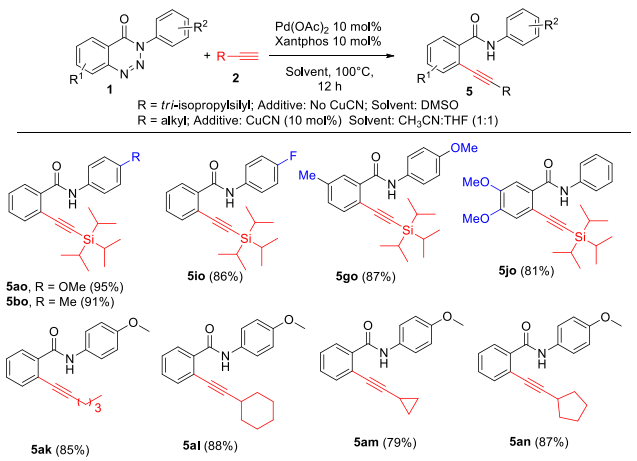
yields. On the other hand, reactions involving *N*-alkyl-substituted 1,2,3-benzotriazinones were unsuccessful. Benzotriazinones having fluoro (**1f**), methyl (**1g**), and carbonyl (**1h**) substituents on the benzene ring also participated in the reaction, giving the desired products **3fa**–**ha** in 81, 95, and 84% yields, respectively. Similarly, the reaction of **1a** with a variety of terminal alkynes (**2b**–**j**) afforded the desired (*Z*)-3-aryl methylene isoindolin-1-ones in good to high yields. For instance, substituted phenyl acetylenes (**2b**–**i**) containing electron donating and neutral groups both at the *para*- and *meta*-positions gave the corresponding products **3ab**–**ai** in 75–89% yields. Single-crystal X-ray analysis of **3ab** further confirms the structure and the stereoselectivity.[12] Heteroaromatic alkyne, 2-ethynylpyridine (**2j**), also furnished the product **3aj** in 71% yield. Unfortunately, aliphatic alkynes such as 1-hexyne (**2k**), ethynylcyclohexane (**2l**), ethynylcyclopropane (**2m**), and ethynylcyclopentane (**2n**) failed to deliver the desired product **3**. However, *tri*-isopropyl silylacetylene (**2o**) underwent a coupling reaction smoothly with **1a** even in the absence of CuCN to give *ortho*-alkynlated benzamides **5ao** in 95% yield. In a similar fashion, **2o** also underwent coupling with **1b**, **1g**, **1i**, and **1j** to give the desired products in 81–97% yields (Scheme 2), albeit TMS acetylene failed to participate in the reaction.

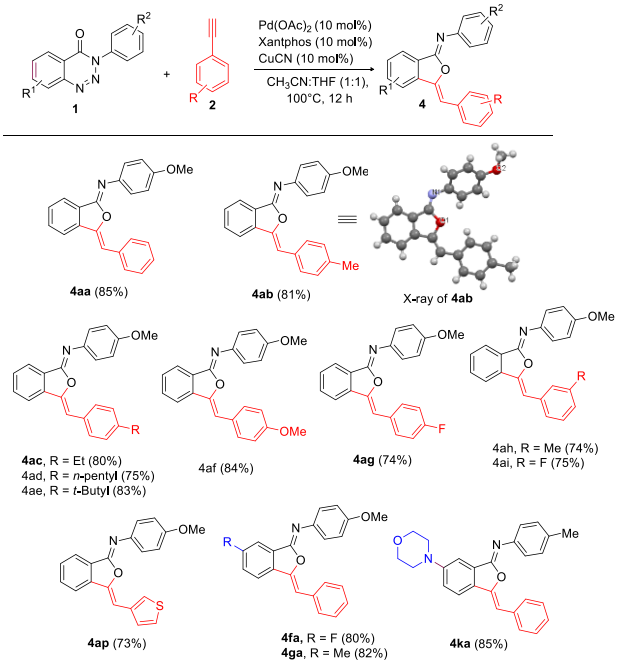
Scheme 2. Synthesis of *ortho*-Alkynylated Benzamides[a,b]



[a]All of the reactions were carried out using 1,2,3-benzotriazin-4-(3*H*)-ones **1** (0.40 mmol), terminal alkynes **2k**–**o** (0.60 mmol), $Pd(OAc)_2$ (0.04 mmol), and Xantphos (0.04 mmol) for 12 h. [b]Isolated yields.

Excited by the formation of substituted alkynes **5ao**–**jo**, we next turned our attention to find a suitable reaction condition for the *ortho*-alkynylation reaction of **1** with other aliphatic alkynes **2k**–**n** (see the Supporting Information). Interestingly, by changing the solvent from DMSO to a binary solvent comprised of CH_3CN and THF in a ratio of 1:1, the desired *ortho*-alkynylated products **5ak**–**an** were obtained in good to high yields (Scheme 2). To our surprise, when the reaction was carried out with phenylacetylene (**2a**) under similar reaction conditions, (*Z*)-3-benzylidine (imino)isobenzofuranone (**4aa**) was selectively obtained in 85% isolated yield. This result is highly interesting because, in the reported tandem alkynylation/cyclization reactions, the examples are limited only to the preparation of isoindolin-1-one derivatives, whereas the synthesis of (*Z*)-3-(imino)isobenzofuranones[13] has yet to be explored. Thus, we also studied the scope of the (imino)-isobenzofuranone synthesis with other benzotriazinones **1** and substituted terminal alkynes **2**. Aromatic alkynes bearing methyl- (**2b**), ethyl- (**2c**), *n*-pentyl- (**2d**), *t*-butyl- (**2e**), methoxy- (**2f**), and fluoro- (**2g**) substituents at the *para*-position underwent a cyclization reaction, giving **4ab**–**ag** in good yields. *meta*-Substituted aromatic terminal alkynes **2h** and **2i** also gave **4ah** and **4ai** in 74 and 75% yield, respectively. Pleasingly, 3-ethynyl thiophene (**2p**) also furnished the desired products in good yields. Correspondingly, **1f**, **1g**, and **1k** also successfully participated in the reaction, giving **4fa**, **4ga**, and **4ka** in 80, 82, and 85% yields, respectively. It is important to mention that *ortho*-substituted aromatic terminal alkynes are not suitable for the present denitrogenative tandem alkynylation/cyclization reaction. Moreover, in all of the reactions, as shown in Scheme 3, isoindoline-1-ones **3** were observed in 5–15% yield.

Scheme 3. Synthesis of (*Z*)-3-Benzylidine (Imino)isobenzofuranones[a,b]



[a]All of the reactions were carried out using 1,2,3-benzotriazin-4-(3*H*)-ones **1** (0.40 mmol), aromatic terminal alkynes **2** (0.60 mmol), $Pd(OAc)_2$ (0.04 mmol), Xantphos (0.04 mmol), and CuCN (0.04 mmol) for 12 h. [b]Isolated yields.

A gram scale reaction of **1a** with **2a** was performed. Gratifyingly, the reaction proceeded smoothly in the presence of 5 mol % $Pd(OAc)_2$ and afforded **3a** in a 90% yield. Subsequently, the significance of the present catalytic reaction is also demonstrated by achieving a one-pot synthesis of biologically relevant (*Z*)-3-benzylideneisobenzofuran-1(3*H*)-one derivatives[14] **6a**–**d** from **1a** and **2a** via a tandem alkynylation/cyclization and hydrolysis process (Scheme 4a). In addition, a Pd/C-catalyzed reduction reaction of **3** and **4** was also carried out in acetic acid at rt for 2 h to obtain 3-benzylated isoindolinones[15] **7a**–**b** and *ortho*-alkylated benzamides **8a**–**b** in good to high yields (Scheme 4c).

To understand the role of CuCN in the tandem alkynylation/cyclization process, we have performed a controlled experiment by treating *N*-(4-methoxyphenyl)-2-

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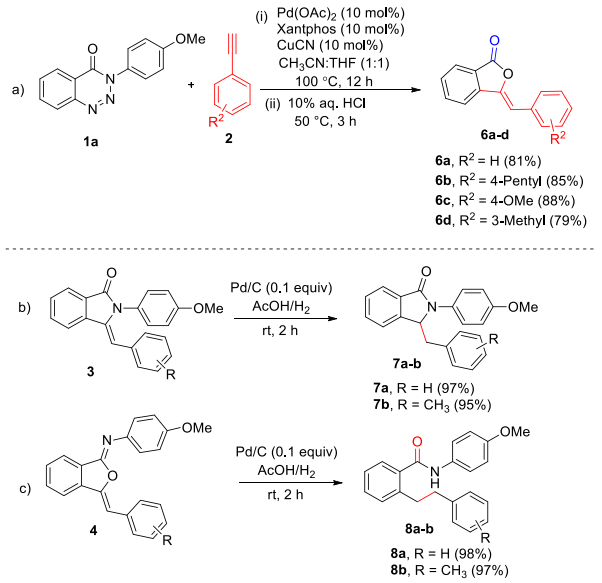
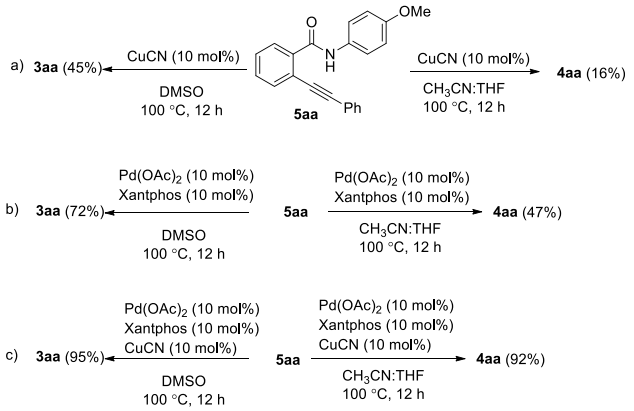
Scheme 4. Synthetic Applications



(phenylethynyl)benzamide (**5aa**) in the presence of CuCN (10 mol %) in DMSO solvent at 100 °C (Scheme 5). After 12

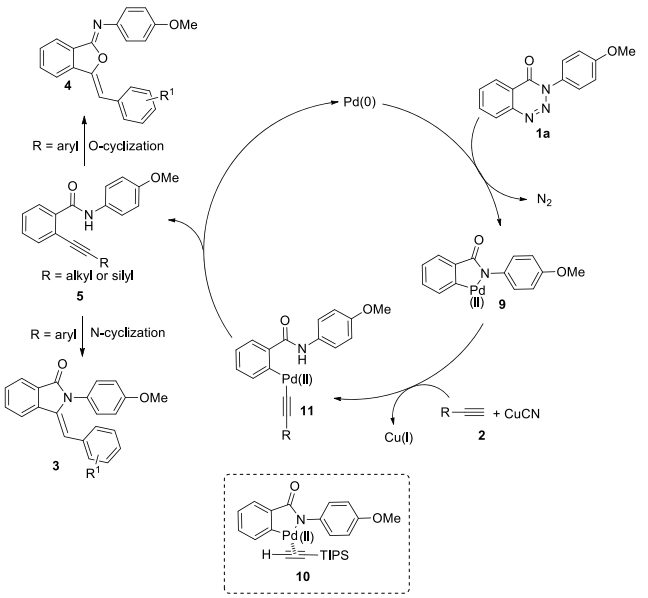
Scheme 5. Mechanistic Studies



h, the reaction afforded **3aa** only in 45% yield[10e] due to poor conversion of **5aa**. When the same reaction was carried out with $Pd(OAc)_2$ (10 mol %) and Xantphos (10 mol %), the desired product **3aa** was obtained in 72% yield. The yield of **3aa** was improved to 95% when **5aa** was treated in the presence of both $Pd(OAc)_2$ and CuCN. Similarly, cyclomerization of **5aa** also yielded **4aa**[16] in high yield by changing the solvent from DMSO to the binary solvent comprising CH_3CN and THF. These results show that both palladium and copper are necessary for the cyclomerization process to obtain **3aa** and **4aa** in high yield. Moreover, it also appears that CuCN played a vital role not only in the transmetalation step to obtain **11** but also in the cycloisomerization process in improving the product yields of **3** and **4**.

A plausible catalytic reaction mechanism is proposed, as shown in Scheme 6. Oxidative addition of palladium(0) to 1,2,3-benzotriazin-4(3*H*)-ones affords five-membered aza-nickelacyclic intermediate **9**.[3d] The reaction of **9** with terminal alkyne **2** in the presence of CuCN affords intermediate **11**. On the other hand, the reaction of TIPS acetylenes proceeds through an intermediate **10** which then reacts with base

Scheme 6. Proposed Mechanism



(OAc$^-$) to give intermediate **11**. Subsequent reductive elimination of **11** affords **5** and regenerates the Pd(0) for the further catalytic cycle. If the alkyne is aromatic, the resultant **5** may undergo facile *N*- and *O*-cyclization under the suitable standard reaction conditions to give **3** and **4**, respectively. In the case of nonaryl acetylenes, the cyclization of **5** is not favorable under our present reaction conditions possibly due to the poor coordination of alkyne to metal complex because of the bulkier TIPS substituent. Similarly, the presence of an aliphatic moiety at another end of acetylene also might have left alkyne **5** less activated for the cyclization. This was further confirmed by the results shown in Schemes 1 and 3.

The exact reasons for the chemoselective *O*- versus *N*-cyclization reaction by changing the solvents are unclear at the moment. However, we assume that the metalation of amide oxygen[16a,17] and the change in solvent polarity might have favored the *O*-cyclization reaction leading to 3-(imino)-isobenzofuranones. During the course of studies, we did not observe any isoquinolinone derivatives, which is in contrast to the previously reported nickel-catalyzed reaction[3a] with the same set of starting materials. This is probably due to the slow reactivity of azapalladacycle **9** toward alkyne insertion. Moreover, the generation of copper acetylides during the reaction might have led to the facile formation of intermediate **11**.

In conclusion, we have successfully developed the first denitrogenative alkylidenation reaction of 1,2,3-benzotriazin-4(3*H*)-ones with aromatic terminal alkynes using a palladium complex as the catalyst. By fine-tuning the solvents, we can selectively prepare (*Z*)-3-benzylidene-isoindoline-1-ones and (*Z*)-3-(imino)isobenzofuranones in good to high yields. Furthermore, synthetically useful *ortho*-alkynylated benzamides were also synthesized in good to high yields using aliphatic alkynes as a coupling partner. The significance of the reaction is also demonstrated by a one-pot synthesis of (*Z*)-3-benzylideneisobenzofuran-1(3*H*)-one derivatives in good to high yields.

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■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.9b04297.

Experimental procedures and characterization of all products (PDF)

Accession Codes

CCDC 1963275−1963276 contain 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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