Palladium-Catalyzed Synthesis of Isoquinolinones via Sequential Cyclization and N–O Bond Cleavage of *N*-Methoxy-*o*-alkynylbenzamides

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Abstract: A palladium-catalyzed controlled 6-*endo*-*dig* cyclization process has been developed for the chemoselective synthesis of isoquinolin-1-ones from *N*-alkoxy-*o*-alkynylbenzamides. The mechanism and scope of the reaction have also been investigated. Deuterium-labeling studies were used to confirm the intramolecular 1,5-hydrogen shift as a key step in the transformation.

Key words: alkynes, regioselectivity, palladium, cyclization, amides

Isoquinolinones, which are also known as 1-oxo-1,2-dihydroisoquinolines, are one of the key structural units found in plant alkaloid derivatives.[1] These structures can also be found in synthetic molecules that possess a range of biological activities.[2] Isoquinolinone itself has been used as a basic building block for the synthesis of more complex isoquinolinone ring systems.[3] The development of practical synthetic strategies for the construction of isoquinolinone systems has been extensively explored by a number of material, organic, and pharmaceutical chemists because of the widespread occurrence and utility of this structural motif. Of these methods, the use of an intramolecular reaction is one of the most convenient tools for the preparation of substituted isoquinolinone derivatives.[4] To date, several methods have been developed for the construction of the isoquinolinone framework involving the cyclization reaction of benzamide derivatives.[5] The cyclization of *o*-alkynylbenzamides in particular represents a straightforward and powerful strategy for the direct synthesis of isoquinolinones. Although a variety of different methods has been reported for the intramolecular annulation of *o*-alkynylbenzamide using either a base,[6] electrophile,[7] or transition-metal catalyst,[6,8] these methods often suffers from a lack of regioselectivity because of competitive cyclization processes that can occur through either the *5*-*exo* or *6*-*endo* cyclization modes. Moreover, the oxygen and nitrogen atoms of the amide moieties involved in these methods can both behave as nucleophiles, leading to a lack of chemoselectivity in the cyclized products. The development of a method providing exclusive control over chemo- and regioselective outcomes of the reaction is therefore both desirable and challenging.

During the course of our ongoing investigations based on the reactivity of the nitrogen–oxygen bond,[9] we recently found that the intramolecular cyclization of Weinreb amides bearing an alkyne moiety proceeded predominantly via the O-nucleophilic attack of the carbonyl group in the presence of $CuCl_2$/NCS to form isobenzofuran-1-ones.[10] Interestingly, however, much less is known about influencing the chemoselective nucleophilic attack of the amide nitrogen over the carbonyl oxygen in Weinreb amides.[11] It was envisaged that the coordination of a palladium catalyst to both the *N*-alkoxyamide and alkyne would lead to the formation of a product resulting from the opposing chemo- and regioselectivities. Herein, we report the development of a method for the palladium-catalyzed cyclization of *N*-alkoxy-*o*-alkynylbenzamides to afford isoquinolin-1-ones exclusively.

Our study towards the development of a method for the palladium-catalyzed intramolecular addition of Weinreb amides to alkynes started with an investigation of the reaction of *N*-methoxy-*N*-methyl-2-(2-phenylethynyl)-benzamide (**1a**) with $PdCl_2(PPh_3)_2$ (Table 1).

The treatment of **1a** with 20 mol% of $PdCl_2(PPh_3)_2$ in refluxing 1,2-dichloroethane for 24 hours led to the formation of the cyclized product *N*-methylisoquinolin-1-one **2a** via cyclization, elimination of the methoxy group, and protonation at the 4-position, albeit in low yield (Table 1, entry 1).[11,12] The survey of catalysts revealed that $PdCl_2(PPh_3)_2$ is a superior catalyst over the other catalysts such as $PdBr_2(PPh_3)_2$, $Pd(OAc)_2$, $Pd(PPh_3)_4$, $FeCl_3$, $FeCl_2$, $ZnCl_2$, $Zn(OTf)_2$, $InCl_3$, $PtCl_2$, and $AuCl_3$. To allow for the reaction to be conducted at a higher temperature, toluene and chlorobenzene were investigated as the reaction solvent. Unfortunately, however, the use of these solvents resulted only in a reduction in the chemical yield (Table 1, entries 2 and 3). It is noteworthy that the addition of benzoquinone to the catalytic reaction led to a significant improvement in the chemical yield (Table 1, entry 4).[13] A control reaction performed in the absence of the palladium catalyst did not provide any of the desired product, confirming the critical role of the palladium catalyst in the reaction (Table 1, entry 5). It was envisaged that the yield of **2a** could be improved by the addition of a protic additive. With this in mind, the reaction was conducted in the presence of isopropyl alcohol and pleasingly provided the desired product in an 81% yield (Table 1, entry 6). Moreover, the reaction was found to be tolerant to an atmosphere of molecular oxygen, with these conditions providing a slightly enhanced yield of **2a** (Table 1, entry 7). Although a reduction in the catalyst loading to 10 mol% was tolerated (Table 1, entry 8), further reduction of the

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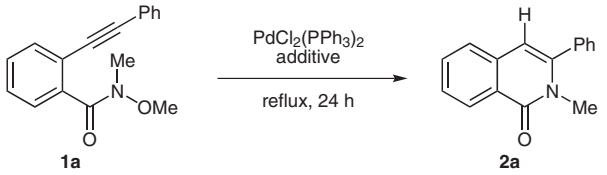
Table 1 Optimization Studies for the Palladium-Catalyzed Cyclization of **1a**[a]



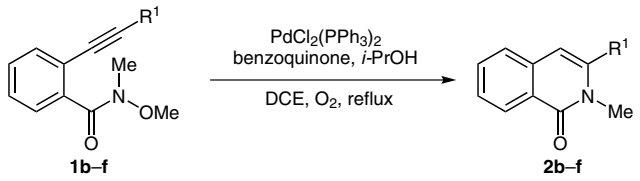
Entry	$PdCl_2(PPh_3)_2$ (mol%)	Solvent	Additive (equiv)	Yield (%)[b]
1	20	DCE	–	28
2	20	toluene	–	23
3	20	PhCl	–	16
4	20	DCE	benzoquinone (5)	66
5	–	DCE	benzoquinone (5)	–
6	20	DCE	benzoquinone (5), *i*-PrOH (3)	81
7[c]	20	DCE	benzoquinone (5), *i*-PrOH (3)	85
8[c]	10	DCE	benzoquinone (5), *i*-PrOH (3)	81
9[c,d]	5	DCE	benzoquinone (5), *i*-PrOH (3)	66

[a] Reaction conditions: **1a** (0.2 mmol) in DCE (0.05 M) under an Ar atmosphere.
[b] Isolated yield.
[c] Reaction was carried out under an O_2 atmosphere.
[d] Reaction was conducted over 48 h.

catalyst loading to 5 mol% had an adverse impact on the yield of the product **2a** (Table 1, entry 9).

With our optimized conditions in hand,[14] we proceeded to investigate the scope of this Weinreb amide cyclization reaction by varying the nature of the substituent on the triple-bond terminus (Table 2).

Table 2 Palladium-Catalyzed Cyclization of Substrate **1** with the Acetylene Units[a]

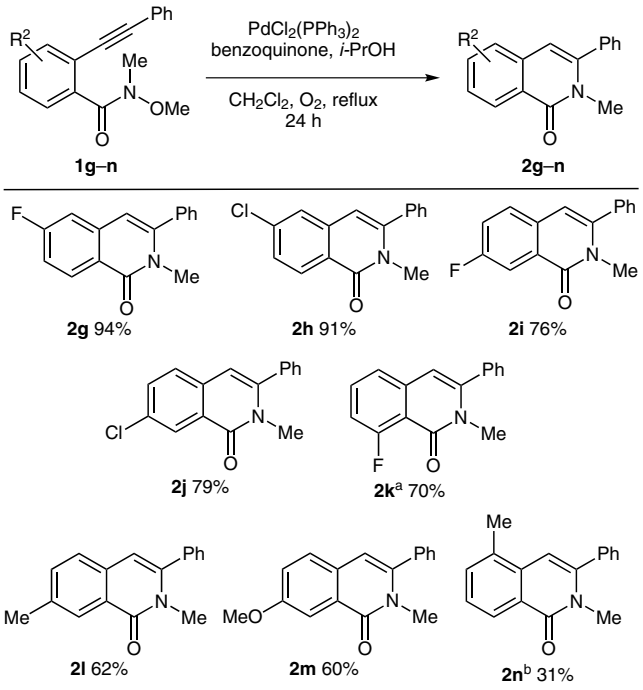


Entry	Substrate **1**	Product **2**	Yield (%)[b]
1	**1b** R^1 = 4-FC_6H_4	**2b**	89
2	**1c** R^1 = 4-MeC_6H_4	**2c**	54
3	**1d** R^1 = 4-$MeOC_6H_4$	**2d**	62
4	**1e** R^1 = *n*-Bu	**2e**	46
5[c]	**1f** R^1 = cyclohexyl	**2f**	45

[a] Conditions: **1b–f** (0.2 mmol), $PdCl_2(PPh_3)_2$ (0.2 equiv), benzoquinone (5 equiv), *i*-PrOH (3 equiv) in DCE (0.05 M) under an O_2 atmosphere.
[b] Isolated yield.
[c] Chlorobenzene was used as the solvent.

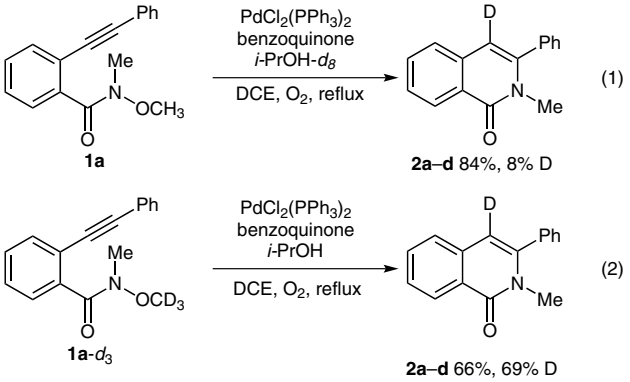
The cyclization reaction of Weinreb amide **1b** bearing a *p*-fluorophenyl group gave the desired isoquinolinone **2b** in 89% yield, whereas the introduction of an electron-donating group to the phenyl ring led to a decrease in the yield of the reaction (Table 2, entries 1–3). Although aliphatic substituents were well tolerated under the optimized conditions, a higher temperature was needed in the case of the cyclohexyl substituent likely because of steric hindrance (Table 2, entries 4 and 5).

Further examination of a variety of different substituents on the benzene ring demonstrated the scope and feasibility of this reaction for the construction of isoquinolinone derivatives (Scheme 1). This new Pd(II)-catalyzed cyclization protocol was also tolerant of substrates bearing halogen groups on the benzene ring. For example, substrates bearing fluoro and chloro groups on the benzene ring at positions *para* and *meta* to the carbonyl group were well tolerated, providing the cyclized products **2g–j**, respectively, in isolated yields of 76–94%. Similarly, the application of a substrate bearing a fluoro group *ortho* to the carbonyl group produced **2k** in 70% yield, albeit following an extended reaction time. When substrates containing electron-rich aromatic rings were subjected to the cyclization conditions, the desired isoquinolinones **2l–n** were obtained in relatively lower yields, indicating the preference of the reaction for electron-deficient ring systems.



Scheme 1 Palladium-catalyzed cyclization: scope of the substituent on the aromatic ring. *Reagents and conditions*: [a] The reactions was conducted over 48 h; [b] Chlorobenzene was used as the solvent.

To elucidate the mechanism of the reaction, deuterium-labeling experiments were performed as shown in Scheme 2. Surprisingly, when the reaction of **1a** was conducted with deuterated isopropyl alcohol, the product **2a**-*d* was isolated containing only 8% of deuterium at the 4-position (Scheme 2, eq. 1). To determine the source of the hydrogen atom at the 4-position, compound **1a**-d_3 containing a deuterium-labeled methoxy group was subjected to the palladium-catalyzed cyclization reaction in the presence of isopropyl alcohol (Scheme 2, eq. 2). This reaction resulted in 69% deuterium incorporation at the 4-position of the isoquinolinone **2a**-*d*, indicating that the hydrogen atom at the 4-position was derived predominantly from an intramolecular hydrogen shift from the methoxy group.



Scheme 2 Labeling experiments

Based on the experimental results, we have proposed the following plausible mechanism for the transformation. Alkyne activation of the *N*-methoxy-*N*-methyl-2-(2-phenylethynyl)benzamide (**1a**) by the palladium catalyst leads to the π complex **A** (Scheme 3). Subsequent intramolecular nucleophilic attack of the nitrogen atom of the Weinreb amide onto the triple bond occurs in the 6-*endo*-*dig* mode to generate intermediate **B**, which undergoes a 1,5-hydorgen shift to generate **C** with the concomitant formation of formaldehyde. Liberation of the catalyst then provides isoquinolinone **2a**. Alternatively, chloride anion mediated N–O bond cleavage would lead to the generation of vinylpalladium intermediate **D**, which would subsequently undergo protodepalladation to form **2a** as a minor pathway. Although the roles of benzoquinone and molecular oxygen are unclear, benzoquinone would act as ligand for the palladium catalyst.[13]

In summary, we have successfully developed a new method for the synthesis of isoquinolin-1-ones involving the palladium-catalyzed cyclization of the Weinreb amide derivatives of *o*-alkynyl benzoic acids via an N–O bond cleavage and 1,5-hydrogen shift mechanism. Mechanistic studies indicated that an intramolecular rearrangement of the hydrogen atom takes place. Further mechanistic study and substrate scope are in progress in our laboratory. The present reaction highlights the utility of Weinreb amides as nucleophiles.

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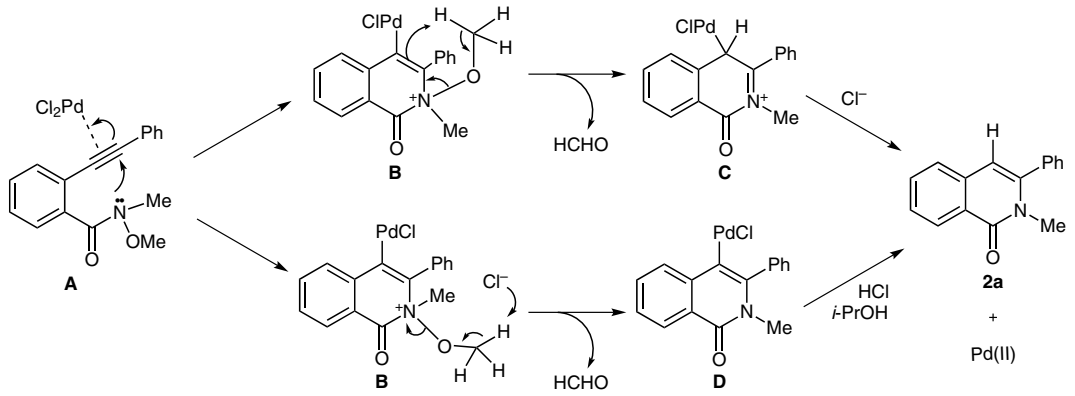

Scheme 3 Proposed mechanism for the cyclization of the 2-alkynylbenzamides

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(14) **General Procedure for the Palladium-Catalyzed Synthesis of Isoquinolinone**

To a solution of *N*-alkoxy-*o*-alkynylbenzamide **1** (0.20 mmol) in DCE (4 mL) was added *i*-PrOH (0.6 mmol), *p*-benzoquinone (1.0 mmol), and $PdCl_2(PPh_3)_2$ (0.04 mmol) under O_2 atmosphere. After being refluxed for 24 h, the reaction mixture was concentrated in vacuo. The residue was purified by flash column chromatography on silica gel eluting with EtOAc–hexane (1:3) and/or toluene–Et_2O (3:1). Representative spectroscopic data of selected products are as follows.

2-Methyl-3-phenylisoquinolin-1(2*H*)-one (2a)

Yellow solid; mp 66–67 °C (EtOAc–hexane; lit.[5f] 63 °C). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.45 (br d, *J* = 7.5 Hz, 1 H), 7.64 (br t, *J* = 8.1 Hz, 1 H), 7.51–7.39 (m, 7 H), 6.46 (s, 1 H), 3.44 (s, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 163.3, 143.8, 136.3, 136.1, 132.2, 128.8, 128.7, 128.5, 127.7, 126.5, 125.7, 124.7, 107.5, 34.1. IR (KBr): ν_{max} = 1652, 1619 cm^{-1}. ESI-HRMS: *m/z* calcd for $C_{16}H_{13}NO$ $[M + H]^+$: 236.1069; found: 236.1066.

3-(4-Fluorophenyl)-2-methylisoquinolin-1(2*H*)-one (2b)

Yellow solid; mp 135–137 °C (EtOAc–hexane). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.44 (d, *J* = 7.8 Hz, 1 H), 7.64 (t, *J* = 7.8 Hz, 1 H), 7.51–7.45 (m, 2 H), 7.42–7.37 (m, 2 H), 7.17 (t, *J* = 8.4 Hz, 2 H), 6.44 (s, 1 H), 3.41 (s, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 164.6, 163.3, 161.3, 142.7, 136.2, 132.3, 132.2, 130.7, 130.6, 127.8, 126.7, 125.8, 124.9, 115.9, 115.6, 107.7, 34.1. IR (KBr): ν_{max} = 1650, 1619 cm^{-1}. ESI-HRMS: *m/z* calcd for $C_{16}H_{13}ONF$ $[M + H]^+$: 254.0976; found: 254.0967.

7-Chloro-2-methyl-3-phenylisoquinolin-1(2*H*)-one (2h)

White solid; mp 148–150 °C (EtOAc–hexane). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.37 (d, *J* = 8.4 Hz, 1 H), 7.49–7.45 (m, 4 H), 7.42–7.37 (m, 3 H), 6.36 (s, 1 H), 3.40 (s, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 162.8, 145.4, 138.6, 137.6, 135.8, 129.7, 129.2, 128.7, 128.6, 127.1, 124.9, 123.2, 106.4, 34.1. IR (KBr): ν_{max} = 1649, 1624 cm^{-1}. ESI-HRMS: *m/z* calcd for $C_{16}H_{13}ONCl$ $[M + H]^+$: 270.0680; found: 270.0673.

