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Phosphine-Triggered Selectivity Switch in Silver-Catalyzed *o*-Alkynylbenzohydroxamic Acid Cycloisomerizations

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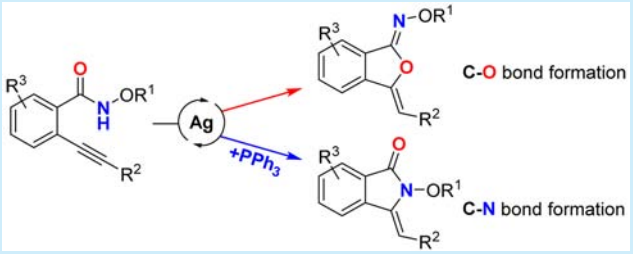
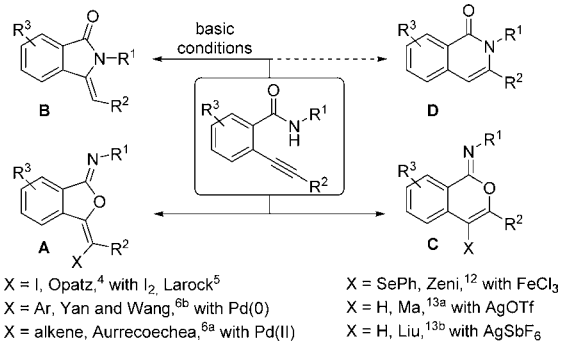
Supporting Information

ABSTRACT: A silver-catalyzed cycloisomerization reaction of a series of *o*-alkynylbenzohydroxamic acids is reported. Several 5-*exo*-*dig* and 6-*endo*-*dig* modes of cyclization were observed with the nitrogen or oxygen atoms of the amide group acting as nucleophiles. The selectivity was strongly dependent on the silver salt used and on the presence of triphenylphosphine as an additive. Indeed, while the use of Ag_2O at room temperature allowed the isolation of isobenzofuran-1-one oximes (7 compounds, 48−92% yield), $[Ag(Im)]_n$ with the concomitant addition of 2 equiv of PPh_3 led to a switch in selectivity and to a family of isoindolin-1-ones (10 compounds, 59−87%).



Isoindolinones and isobenzofuranones are important heterocycles in organic chemistry since numerous drugs, natural products, and materials feature these skeletons.[1] Isoindolinones are also central cores in the structure of pigments.[2] Although numerous methodologies have been developed for the synthesis of such skeletons,[3] a convenient approach is the cycloisomerization of *o*-alkynylbenzamides which could lead to either structure through *N*- or *O*-cyclization mode. Despite the four possible isomers expected from this reaction (Scheme 1), most conditions studied were found to be quite selective. As an example, Opatz clearly demonstrated that iodonium-mediated reactions led to iminoisobenzofurans[4] **A** rather than isoindolin-1-ones **B** as initially mistakenly reported by Larock.[5] Functionalized iminoisobenzofurans **A** could also be produced using palladium(0) or palladium(II) catalysts.[6] Similarly, Zhu showed a synergistic effect between Pd and Cu in performing a cyclizative dimerization.[7] In the presence of $CuCl_2$ and *N*-chlorosuccinimide (NCS), Miyata and co-workers described the cyclization of Weinreb amides into isobenzofuranones **A** with loss of the nitrogen-containing moiety.[8] The preparation of isobenzofuranones **A** was reported to be possible using basic[9] as well as metal-catalyzed conditions in the presence of base.[10] More recently, hypervalent iodine derivatives allowed for a cascade reaction leading to tetracyclic structures via an *N*-5-*exo*-*dig* cyclization.[11] Iminoisocoumarin derivatives **C**, resulting from a *O*-6-*endo*-*dig* cyclization, were selectively obtained using $FeCl_3$ with diaryl diselenides[12] or in the presence of a catalytic amount of silver salts.[13]

Scheme 1. Cyclizations of *o*-Alkynylbenzamides[4−13]



This latest report attracted our attention, as our group had previously developed silver-catalyzed cycloisomerization reactions.[14] In particular, we previously shed light on an unprecedented counteranion effect affecting the regioselectivity in the acetalization/cycloisomerization reaction. π-Acidic silver salts (AgOTf, $AgPF_6$, $AgSbF_6$, $AgNO_3$) led to pyranoquinoline cores through a 6-*endo*-*dig* cyclization, while more basic salts (AgO, Ag_2O, Ag_2CO_3) furnished furoquinolines via a 5-*exo*-*dig* cyclization.[14h,i] Moreover, a nitrogen effect led to the development of a methodology involving an air-stable silver imidazolate polymer, $[Ag(Im)]_n$, selectively yielding furoqui-

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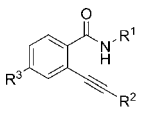
nolines.[14c,d] As a continuing study, we wanted to assess if a similar regioselectivity control could be observed in the cycloisomerization of *o*-alkynylbenzamides. Additionally, we envisioned that the use of hydroxamic acids instead of simple amides might result in a *N*-cyclization process, thanks to the enhanced nucleophilicity of the nitrogen due to the α effect of the σ-bonded heteroatoms.

We started our investigation with substrate **1a** (Figure 1), featuring a benzyl-protected hydroxamic acid and a methyl



1a, R^1 = OBn, R^2 = CH_2OMe, R^3 = H
1e, R^2 = Ph
1f, R^2 = CH_2OH
1g, R^2 = $CH_2(CH_3)OH$
1h, R^2 = C_4H_9
1i, R^2 = $Si(CH_3)_3$
1k, R^2 = 3-(OCH_3)Ph

1b, R^1 = OMe, R^2 = CH_2OMe, R^3 = H
1c, R^1 = OPiv, R^2 = CH_2OMe
1d, R^1 = Bn, R^2 = CH_2OMe

1j, R^1 = OBn, R^2 = CH_2OMe, R^3 = NO_2

Figure 1. Structures of substrates **1a**−**k**.

propargyl ether group. From this substrate, four different products were expected, **2a**−**5a** (Figure 2), resulting from a 5-*exo-dig* or 6-*endo-dig* cyclization, each mode of cyclization involving either the nitrogen or oxygen atom of the amide as the nucleophile. A shortened optimization is presented in Figure 2 (see the Supporting Information for complete details). When **1a** was stirred in ethanol (0.2 M) without silver, we observed only a 15% conversion to the derivatives **2a** and **4a** after 48 h. As we had previously observed an effect, depending on the silver salt used, on the regioselectivity of the acetalization/cycloisomerization reaction,[14h] various silver sources were screened. Notably, the best solvent for good selectivity was found to be ethanol (among toluene, DCE, DMF, TFE and EtOH). We were pleased to see that silver oxide was able to promote the cyclization in only 3 h at room temperature, generating **2a** as the major product. The use of silver carbonate and silver imidazolate also resulted in **2a** as the major product. Surprisingly, with silver imidazolate as a catalyst, product **3a**, resulting from an *N*-cyclization, was also observed. Finally, silver nitrate and silver triflate led to an increase of the product ratio in favor of **4a**, obtained through a *O-6-endo-dig* cyclization process. This modulation by the nature of the silver salts agrees with the trend discussed above governing the acetalization/cycloisomerization reaction.[14h,i] As we wanted to demonstrate the potential of the silver imidazolate polymer as an air- and light-stable precatalyst, 5 mol % of PPh_3 was concomitantly added in order to depolymerize the silver source and thus accelerate the reaction.[14d,15]

To our surprise, the main observation was an unexpected slight switch of the selectivity in favor of the *N*-5-*exo-dig* product **3a** (**2a**/**3a** 79:20). Further increasing the amount of triphenylphosphine in the reaction mixture to 1 equiv resulted in a 45:55 ratio of **2a** to **3a**. Addition of more than 1 equiv of phosphine at 0.2 M was found to be detrimental to the reaction, leading to incomplete conversion to product. Finally, the concentration also had an interesting effect on the selectivity. Indeed, when the reaction was performed at 0.01 M instead of 0.2 M with 1 equiv of PPh_3, the ratio changed to 32:68 ratio of **2a** to **3a**. The effects of variations in temperature on the reaction outcome were also examined. While decreasing the temperature to −50 °C led to an inversion of selectivity in favor of **2a**, running the reaction at 70 °C led to 80:20 selectivity in favor of **3a**.

These results may be due to the increased quantity of phosphine solubilized in the reaction mixture at higher temperature and dilution. Interestingly, the same inversion of selectivity was observed when silver oxide, carbonate, nitrate and triflate were used together with PPh_3. However, it was surprising that silver nitrate and triflate, which catalyzed the conversion of **1a** into **2a** and **4a** when used alone, did not lead to **5a**, resulting from a *N-6-endo-dig* process, but primarily to formation of **2a** and **3a** when used with PPh_3 (see the SI). Though P(*p*-Tol)$_3$ and P(*n*-Bu)$_3$ phosphines have similar steric hindrance to PPh_3, they did not lead to improved selectivity.

Also, much more hindered P(*o*-Tol)$_3$ (Tolman cone angle, θ = 195° versus 145° for PPh_3)[16] and the less basic P(OPh)$_3$ did not favor the formation of **3a**. Finally, introduction of an amine (DABCO or Et_3N) in place of triphenylphosphine did not lead to the same change in selectivity (**2a**/**3a** ≈ 90:10). It is important to add that, in the absence of silver, PPh_3 was not able to promote the reaction.

Having selective conditions in hand to obtain isoindolin-1-one and isobenzofuran-1-one oximes, we studied the silver-catalyzed cycloisomerization using substrates **1a**−**k** (Figure 1).

Initially, we considered cycloisomerization to furnish isobenzofuran-1-one oximes in the presence of silver(I) oxide (Scheme 2). Thus, the protection of the hydroxamic acid

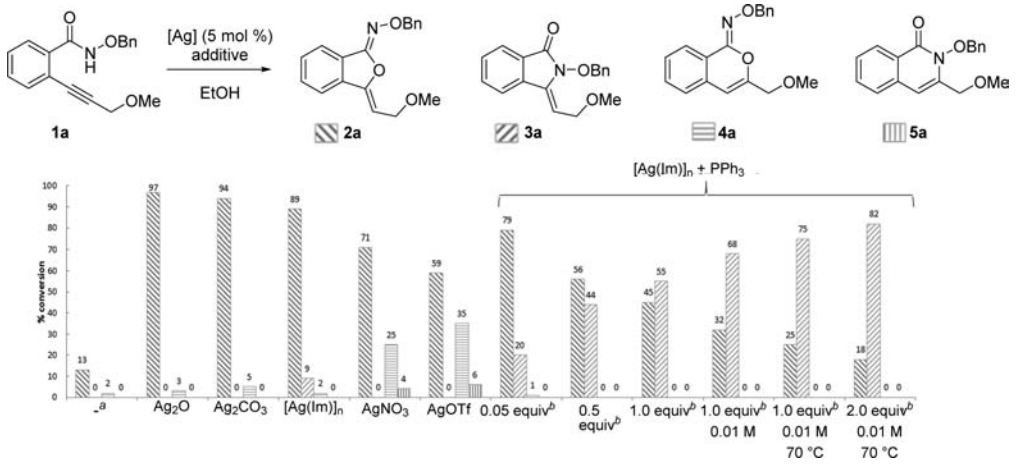


Figure 2. Optimization for the synthesis of isobenzofuran-1-one oximes **3a**. Reaction conditions: substrate (0.1 mmol) at 0.2 M in EtOH (0.5 mL), silver catalyst (0.005 mmol), rt; (a) conversion after 48 h at rt; (b) equivalents of PPh_3 as an additive.

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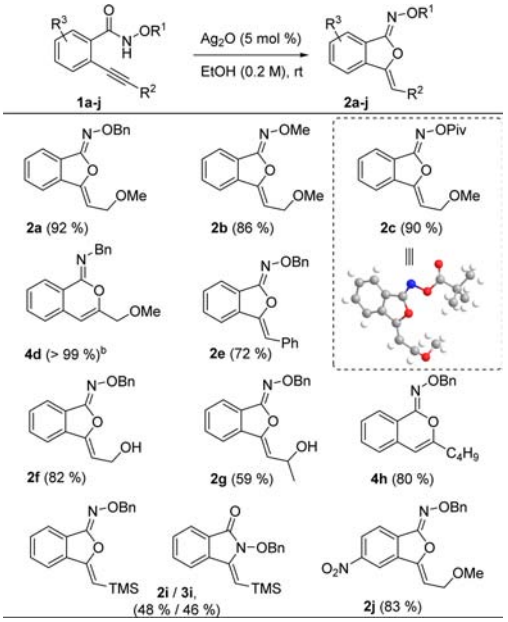
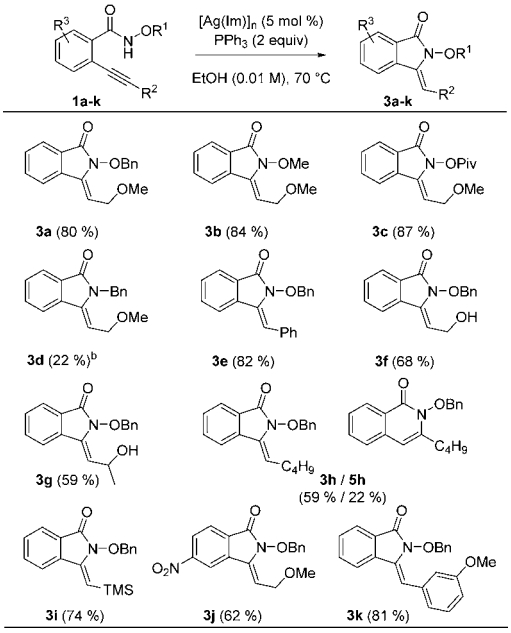
Scheme 2. Synthesis of Isobenzofuran-1-one Oximes[a]



[a]Reaction conditions: **1a–j** (0.2 mmol), Ag_2O (0.01 mmol), EtOH (1 mL), rt, 3–4 h; isolated yields are given. [b]Conversion is given; cyclized compound could not be isolated.

Scheme 3. Synthesis of Isoindolin-1-ones[a]



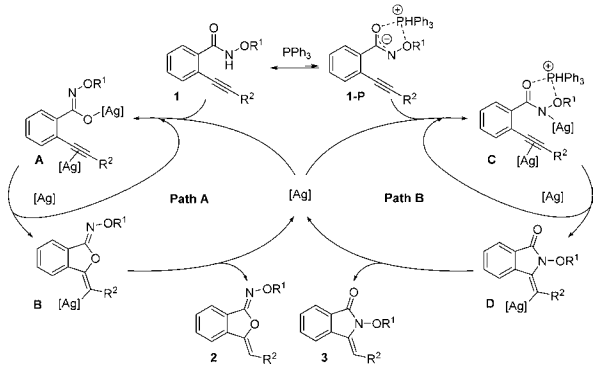
[a]Reaction conditions: **1a–k** (0.2 mmol), $[Ag(Im)]_n$ (0.01 mmol), PPh_3 (0.4 mmol), EtOH (20 mL), 70 °C, 1 h; isolated yields are given. [b]Conversion is given; cyclized compound was not isolated.

hydroxyl group was first evaluated. Replacing the benzyl ether with a methyl or a pivaloyl group did not have a significant impact on the outcome of the reaction, as **2b** and **2c** were isolated in 86% and 90% yield, respectively. Pleasingly, the compound **2c** was isolated in crystalline form and thus was unambiguously confirmed as the isobenzofuran-1-one oxime. When the *N*-benzylbenzamide **1d** was used in place of hydroxamic acid **1a**, cyclization occurred in favor of **4d**, resulting from a 6-*endo-dig* process. This result is in agreement with the previous report of Ma and co-workers,[13a] but in our hands, the iminoisocoumarin **4d** was unstable during its isolation on silica gel and afforded the corresponding isocoumarin derivative. We next evaluated the influence of the alkyne on the cyclization. Substrates **1e–g**, featuring a phenylacetylene, a propargyl alcohol, and a 2-methylpropargyl alcohol, respectively, were efficiently converted to the expected **2e–g** via a 5-*exo-dig* process in yields ranging from 59% to 82%. On the other hand, when a butyl group was introduced, the silver-catalyzed cycloisomerization selectively yielded isocoumarin oxime **4h** (80%). In contrast to **4d**, which featured an imino group, the oxime **4h** was stable on silica gel. Interestingly, with a terminal trimethylsilyl (TMS) group, the selectivity for the 5-*exo-dig* process was still observed, but compounds **2i** and **3i**, resulting from *O*- and *N*-cyclizations respectively, were separated and isolated in similar yields (48% and 46%). Finally, the presence of a nitro group in a *meta* position with respect to the alkynyl substituent of **1j** did not affect the reaction, and isobenzofuranone oxime **2j** was obtained in an 83% yield.

Substrates **1a–k** (Figure 1) were then subjected to $[Ag(Im)]_n/PPh_3$ conditions to generate isoindolin-1-ones **3a–k** (Scheme 3). Hydroxamic acids **1a–c** featuring OBn, OMe, and OPiv groups, respectively, gave corresponding **3a–c** in yields up to 87%. Importantly, **1d**, which contained an *N*-benzyl group, did not react to completion with only 22% conversion. This significant difference in reactivity between the amide **1d** and the hydroxamic acid **1a**, as well as in selectivity for the silver(I) oxide cyclization (Scheme 3), highlighted the importance of the hydroxamic acid moiety in our methodology. Compounds **3e–g**, featuring a phenyl, a methylhydroxyl, and a 2-propylhydroxyl group were isolated in yields ranging from 59% to 82%. Interestingly, **1h** was cyclized to **3h** in 59% yield, with concomitant formation of **5h** in 22% yield. It is important to note that compound **5h**, resulting from a *N*-6-*endo-dig* process, was rarely observed in previous studies.[17] While the reaction was not selective with Ag_2O, TMS-containing **3i** was selectively formed in 74% yield in the presence of $[Ag(Im)]_n/PPh_3$. Finally, **3j** and **3k** exhibiting a nitrophenyl substitution or a *m*-methoxyphenyl one were isolated in 62% and 81% yield, respectively.

A tentative mechanism may be proposed on the basis of our previous results[14d,h,i] and others.[18] Indeed, knowing the exact structure of **2c** (X-ray), we could argue that the formation of compounds **2a–j** proceeded through silver-catalyzed *anti*-addition of the amido group to the alkynyl moiety (path A, Scheme 4). Thus, silver ions could coordinate separately to the

Scheme 4. Tentative Mechanisms for Silver-Catalyzed Cycloisomerization Reactions



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alkynyl bond and to the oxygen on the amide (A) to selectively furnish *O*-5-*exo*-*dig* products.[18] This activation mode is preferred to a combined amido-[Ag]-alkyne chelation[18] that would produce a *syn* addition on the alkyne, consequently leading to **2** after a *cis*−*trans* isomerization step. Similarly, compounds **3a**−**k** are obtained through a closely related mechanism (path B). In this case, PPh_3 (pK_a 7.6)[19] slowly deprotonates the hydroxamic acid derivatives **1** ($pK_a \approx 14$)[20] and interacts with the oxygens of substrates **1-P**, thus preventing them from reacting. An *N*−Ag interaction in **C** then affords the cyclized intermediate **D**, which is converted into **3** upon protonolysis or protodemetalation.

In conclusion, we have developed two silver-catalyzed methodologies allowing for the selective formation of either isobenzofuran-1-one oximes (Ag_2O) or isoindolin-1-ones ($[Ag(Im)]_n/PPh_3$) starting from an identical *o*-alkynylbenzohydroxamic acid derivative. The importance of the use of *O*-protected hydroxamic acid substrates rather than amides as internal nucleophiles was highlighted by the lack of reactivity of amide-containing compounds or instability of the resulting products. Triphenylphosphine played a crucial role in the selectivity switch from *O* to *N*-cyclization, and its precise mode of action will be further investigated.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b02235.

Experimental procedures, characterization data, and ^1H and ^{13}CNMR spectra (PDF)
X-ray data for **2c** (CIF)

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Notes

The authors declare no competing financial interest.

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