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Communication

Oxoarylation of ynamides with *N*-aryl hydroxamic acids

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ABSTRACT

Ynamides are electron-rich alkynes with unique reactivities and act as flexible building blocks in organic synthesis. Therefore, the investigation for transformation of ynamides with exceptional selectivity and efficiency is attractive and interesting. Herein, we report an oxoarylation of ynamides with *N*-aryl hydroxamic acids. In the presence of catalytic $Cu(OTf)_2$, both the terminal and internal ynamides could undergo an addition/[3,3] sigmatropic rearrangement cascade with *N*-aryl hydroxamic acids to achieve oxoarylation, along with providing selective entry to (ortho-amino)arylacetamides and oxindoles. Moreover, deuterium-labelling reaction and gram-scale reaction were conducted to probe the mechanism and showcase the scalability.

Ynamide is a type of *N*-substituted electron rich alkynes which exhibits unique chemical properties and serves as flexible synthons in organic synthesis [1]. Therefore, the development of divergent transformations for ynamides has gained considerable attention [2]. In typical, their oxofunctionalization was widely investigated since this process could deliver privileged functionalized amides. For example, Liu and Ye reported that the oxofunctionalization of ynamides could be achieved upon transition-metal-catalysis with pyridine-*N*-oxide [3]. Meanwhile, the addition reaction of ynamides with carboxylic acids could trigger oxofunctionalization [4]. This has been successfully applied in racemization-free ligation of amides, peptides and macrocyclic esters by Zhao and coworkers [5]. Besides, an oxoallylation of ynamide with allyl alcohol has been nicely established by Ye, and this process could produce privileged medium-sized lactams in an efficient manner [6]. Liu reported a $PtCl_2$-catalyzed oxoarylation of terminal ynamides with nitrones [7], while the internal ynamides could not achieve oxoarylation in this process [8]. Therefore, the investigation of oxoarylation for both terminal and internal ynamides toward privileged molecules construction remains challenging and important.

N-Aryl hydroxamic acids exist extensively in naturally occurring secondary metabolites and these compounds exhibit weak acidities [9]. They are known to be used as metal-chelating agents in biological investigation and directing group in metal-catalyzed tansformation [10–12]. In typical, Maulide reported a sigmatropic rearrangement of hydroxamic acid, and this process involved an addition reaction between hydroxamic acid and the *in situ* generated electrophilic enolonium-like intermediate [13]. Moreover, they also tested the addition reaction of hydroxamic acid with oxazolidinone-derived ynamide to give an oxoarylation product in 30% yield upon treatment with triflimide. This indicated that the oxoarylation of ynamides with hydroxamic acids would be promising. In continuation of our interests in ynamides [14], we hypothesized that the utilization of transition-metal-catalyst might promote their oxoarylation process in an efficient manner. Herein, we would like to report a $Cu(OTf)_2$-catalyzed oxoarylation of ynamides with hydroxamic acids for facile and selective entry to (*ortho*-aminoaryl)amides and oxindoles.

We commenced our study by investigating *N*-sulfonyl ynamide **1a** and *N*-benzoyl-*N*-phenylhydroxylamine **2a**. Initially, we conducted the reaction in DCE at 45 °C without any catalyst and there was no new product detected (Table 1, entry 1). When $AuCl(PPh_3)$/$AgNTf_2$ was used as catalyst (5 mol%), and gratifyingly, a new product **3a** was observed and isolated in 75% yield (entry 2). The standard analysis including ^1H NMR, ^{13}C NMR and HRMS showed that **3a** was an (*ortho*-aminoaryl)amide compound. This indicated an oxoarylation occurrence. Variations of the catalysts to IPrAuCl/$AgNTf_2$ and XPhosAuCl/$AgNTf_2$ would decrease the yield to 49% and 52% respectively (entries 3 and 4). The next survey of catalysts showed that $Cu(OTf)_2$ could deliver **3a** in a comparable 75% yield (entry 5), while the use of AgOTf and $Sc(OTf)_3$ would lead to lower yields (entries 6 and 7). To our surprise, the utilization of $Zn(OTf)_2$ would only give trace product (entry 8). When $PtCl_2$ was used, the hydrolyzation rather than oxoarylation was observed (entry 9). On the other hand, either increasing the temperature to 60 °C with

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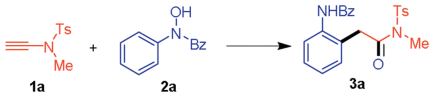
Table 1
Reaction conditions.[a]



Entry	Catalyst	Solvent	Temp. (°C)	Yield (%)[b]
1	–	DCE	45	–
2[c]	$AuCl(PPh_3)$/$AgNTf_2$	DCE	45	75
3[c]	IPrAuCl/$AgNTf_2$	DCE	45	49
4[c]	XPhosAuCl/$AgNTf_2$	DCE	45	52
5	$Cu(OTf)_2$	DCE	45	75
6	AgOTf	DCE	45	61
7	$Sc(OTf)_3$	DCE	45	50
8	$Zn(OTf)_2$	DCE	45	trace
9	$PtCl_2$	DCE	45	–
10	$Cu(OTf)_2$	DCE	60	65
11	$Cu(OTf)_2$	DCM	45	56
12	$Cu(OTf)_2$	THF	45	trace
13	$Cu(OTf)_2$	Toluene	45	trace
14	$Cu(OTf)_2$	CH_3CN	45	trace

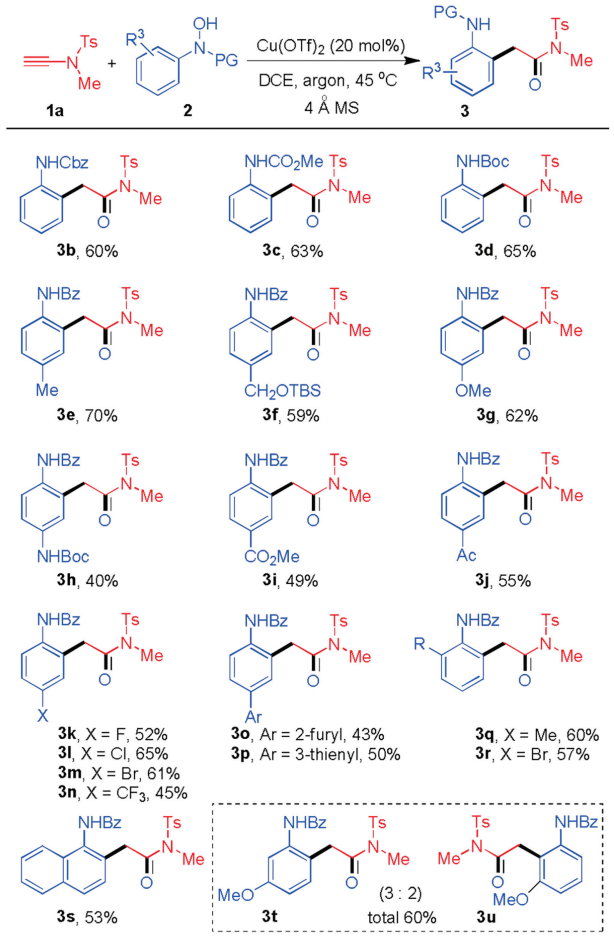
[a] Reaction conditions: **1a** (0.2 mmol), **2a** (0.3 mmol), 4 Å MS (50 mg), catalyst (20 mol%), solvent (2 mL), argon, 2 h.
[b] Yield refers to isolated product.
[c] 5 mol% catalyst was used.

$Cu(OTf)_2$ catalyst or changing the solvent to DCM at 45 °C would decrease the yield (entries 10 and 11). Moreover, the survey of solvents showed that THF, toluene and CH_3CN would shut down the reactivity to deliver trace product (entries 12–14).

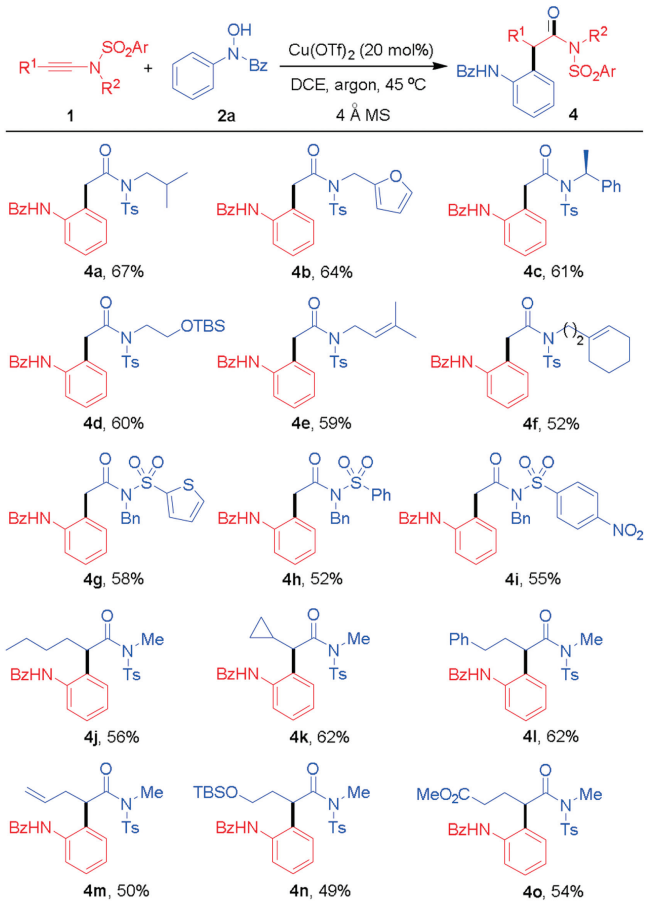
With the optimized reaction condition in hand, we next tested the substrate scope (Scheme 1). As shown in Scheme 1, the *N*-protecting groups of hydroxamic acids varied from benzoyl to Cbz, ester and Boc, and these hydroxamic acids could serve as oxoarylation source for ynamide **1a** to give the products in good yields (**3b**-**3d**). Meanwhile, many functional groups substituted on the aromatic ring of *N*-aryl hydroxamic acids were tested. For example, the *para*-substituted *N*-aryl hydroxamic acids could well engage in this cascade process to deliver the corresponding (*ortho*-aminoaryl)amides in good yields (**3e**-**3j**). The functionalities including methyl, hydroxymethyl, methoxy, *N*-Boc amine, ester, ketone, were well tolerated in this process and also offered ample opportunities for further derivatization. Moreover, the structure of **3e** was confirmed by X-ray analysis (CCDC: 2021769). On the other hand, the halogen substitutions like fluoro, chloro, bromo, and CF_3, were compatible in this reaction (**3k**-**3n**). The heterocyclic substitutions like furan and thiophene could also perform well in this process (**3o** and **3p**). Meanwhile, the *ortho*-substituted *N*-aryl hydroxamic acids were employed in this oxoarylation to furnish the products smoothly (**3q** and **3r**). When the *N*-(naphthalen-1-yl)hydroxamic acid **1s** was used, the regioselective (naphthalen-1-amino-2-yl)amide **3s** could be formed exclusively. When the *meta*-substituted *N*-aryl hydroxamic acid **2t** was subjected, the process would deliver a mixture of oxoarylation products **3t** and **3u** (total 60% yield). The ratio of **3t** and **3u** was 3:2, probably because the process would favor the less steric transition state and the corresponding product **3t** was the major isomer.

Meanwhile, the generality of ynamides were also explored. As shown in Scheme 2, the terminal ynamides with *N*-substitutions like isobutyl, furan-2-methyl, (*S*)-1-phenylethyl, could well engage in this process (**4a**-**4c**). And the functionalities like hydroxy, prenyl, cyclohexenyl, were tolerated (**4d**-**4f**) and also offer considerable potential for late-stage transformation. On the other hand, the sulfonyl substitutions were investigated while thiophene, phenyl and 4-nitrophenyl were found compatible (**4g**-**4i**). Furthermore, the internal ynamides were next subject to this oxoarylation process. As shown in Scheme 2, the substitutions like butyl, cyclopropyl, phenylethyl, allyl, hydroxy, ester, were well applicable to yield the functionalized products smoothly (**4j**-**4o**). The aryl substituted ynamides diverged from the reactivity pattern and were observed with hydrolyzation products. Therefore, this process represents a general oxoarylation for both terminal and internal ynamides, and provides a distinct approach to (*ortho*-aminoaryl)amides.

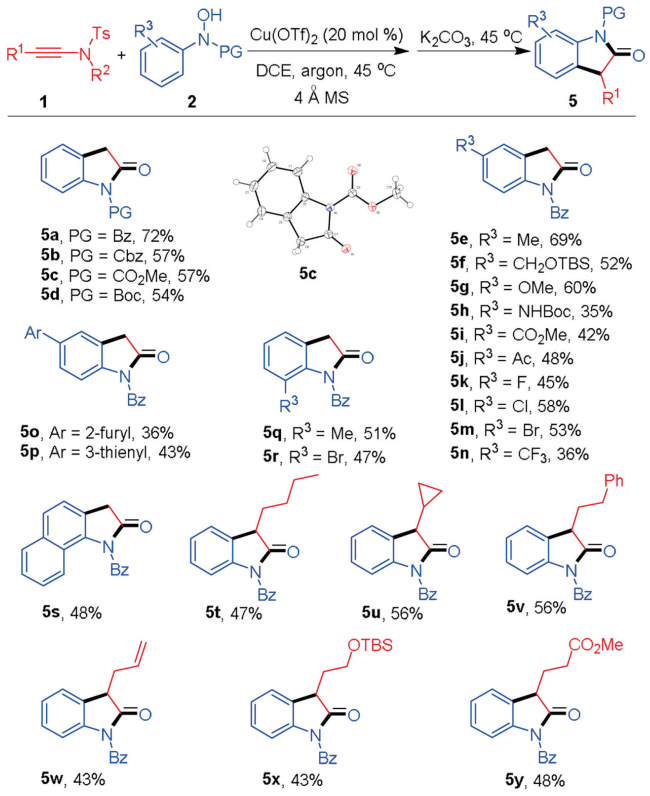
Considering that the moiety of *N*-tosyl of amides **3** and **4** could act as leaving group in intramolecular cyclization, we envisioned that treatment of **3** and **4** with base might enable a lactamization. Upon completion of the $Cu(OTf)_2$-catalyzed oxoarylation of ynamide **1a** and hydroxamic acid **2a**, we treated the reaction solution with K_2CO_3 at 45 °C. To our delight, we indeed found the consumption of (*ortho*-aminoaryl)amides and a new product **5a** was isolated in 72% yield. The standard analysis showed that **5a** was an oxindole compound. We next investigated the scope of this oxoarylation/lactamization process in a one-pot manner. As shown in Scheme 3, a variety of ynamides and hydroxamic acids were subject to this reaction. Besides benzoyl groups, differential protecting groups of hydroxamic acids including Cbz, ester and Boc, were all amenable to this process to deliver the *N*-protected oxindoles in good yields (**5b**-**5d**). The structure of **5c** was confirmed by X-ray analysis (CCDC: 2021773). The *para*-substitutions of hydroxamic acids with methyl, hydroxymethyl, methoxy, amino, ester, ketone, fluoro, chloro, bromo, trifluoromethyl, furan,



Scheme 1. Substrate scope of hydroxamic acid. Reaction conditions: **1a** (0.2 mmol), **2** (0.3 mmol), 4 Å MS (50 mg), $Cu(OTf)_2$ (20 mol%), DCE (2 mL), 45 °C, argon, 2 h. Yields refer to isolated products.



Scheme 2. Substrate scope of ynamides. Reaction conditions: **1** (0.2 mmol), **2a** (0.3 mmol), 4 Å MS (50 mg), $Cu(OTf)_2$ (20 mol%), DCE (2 mL), 45 °C, argon, 2 h. Yields refer to isolated products.



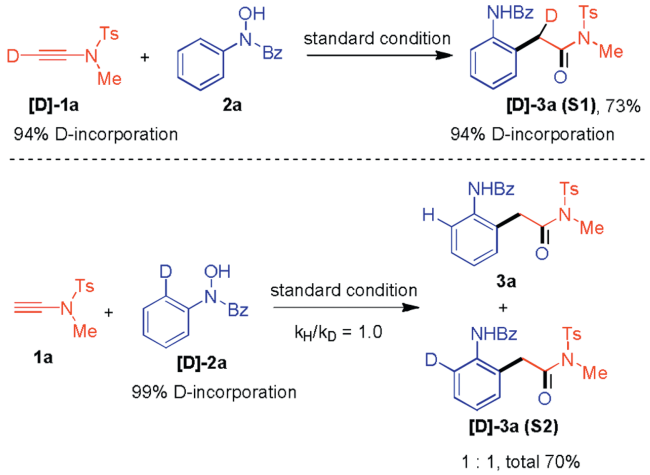
Scheme 3. Scope of oxoarylation/lactamization. Reaction conditions: **1** (0.2 mmol), **2** (0.3 mmol), 4 Å MS (50 mg), $Cu(OTf)_2$ (20 mol%), DCE (2 mL), 45 °C, argon, 2 h, then K_2CO_3 (0.4 mmol), 45 °C, 2 h. Yields refer to isolated products.

thiophene, were well tolerated in this one-pot process (**5e**-**5p**). Moreover, this process could also produce the 7-substituted and naphthalene-containing oxindoles in moderate yields (**5q**-**5s**), which were difficult to be synthesized in conventional methods. Meanwhile, when the internal ynamides were used, this process could deliver the corresponding oxindole products (**5t**-**5y**) rapidly. Considering the wealth of oxindoles in medicinal chemistry [15,16], this method provides a direct approach to these molecules in an efficient way.

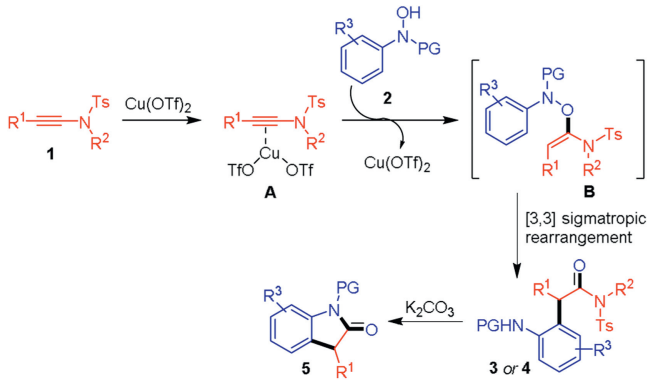
In order to probe the mechanism, a deuterium-labelling reaction was conducted (Scheme 4). The [D]-**1a** was prepared and subject to reaction with **2a**, and [D]-**3a** was obtained in 73% yield and deuterium is incorporated in the α-position of amide. Additionally, the [D]-**2a** was prepared and subject to an intramolecular competition experiment to probe the C–H functionalization event. The result showed that a primary kinetic isotope effect was not observed. This suggests that C–H functionalization is not the rate-determining step of this oxoarylation process.

Based on these results, a plausible reaction mechanism was proposed (Scheme 5). Initially, the ynamides was activated by Cu $(OTf)_2$, which could be attacked by *N*-aryl hydroxamic acid to deliver intermdiate **B**. The following rapid [3,3] sigmatropic rearrangement would deliver (*ortho*-aminoaryl)amide (**3** and **4**) to constitute the oxoarylation of ynamides. Upon treatment with K_2CO_3, the (*ortho*-aminoaryl)amide (**3** or **4**) would undergo a lactamization to deliver the cyclized oxindoles **5**. Therefore, the deuterium atom of [D]-**1a** would be incorporated on the α-methylene of amide, and the deuterium of [D]-**2a** did not show difference with H-atom in the deprotonation of [3,3] sigmatropic rearrangement.

In summary, an oxoarylation of ynamides with hydroxamic acids has been successfully developed. Both the terminal and internal ynamides could undergo addition/[3,3] sigmatropic rearrangement with hydroxamic acids to constitute an oxoarylation process. This method would produce (*ortho*-aminoaryl)-amides and oxindoles with mild reaction condition, broad substrate scope and high efficiency.



Scheme 4. Isotope labelling experiments.



Scheme 5. Proposed reaction mechanism.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.cclet.2021.02.054.

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