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# Iridium-Catalyzed Highly Regioselective Azide−Ynamide Cycloaddition to Access 5-Amido Fully Substituted 1,2,3-Triazoles under Mild, Air, Aqueous, and Bioorthogonal Conditions

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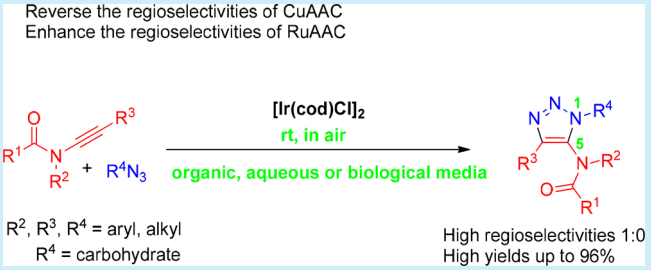
Supporting Information

**ABSTRACT:** A highly regioselective method to access 5-amido fully substituted 1,2,3-triazoles by iridium-catalyzed azide−ynamide cycloaddition under mild, air, aqueous, and bioorthogonal conditions is reported. The excellent regioselectivities may derive from the strong coordination between the carbonyl oxygen of ynamide and the π-acidic iridium. Since the iridium ion is insensitive to oxygen/water and exhibits low cytotoxicity, it could catalyze this reaction in both organic and biological environments efficiently. Preparation in gram-scale and application in carbohydrates highlight this method.




5-Amido fully substituted 1,2,3-triazole, as the unique fully substituted-1,2,3-triazole, is an important drug scaffold and has diverse biological activities.[1] It is the core structure of the heat shock protein 90 (HSP90) inhibitor[2a] and the selective lysophosphatidic acid receptor-1 (LPA1) anatagonist.[2b] How to efficiently access it with high regioselectivity is a long-standing problem. It seems that Huisgen 1,3-dipolar cycloaddition between azides and internal alkynes is one of the most ideal atom-efficient ways. However, low regioselectivities are acquired by azide−alkyne cycloaddition (AAC) at high temperature without any catalysts.[3] The concept of "Click Chemistry" is proposed due to the excellent performance of copper-catalyzed AAC (CuAAC) reaction, which was independently developed by the Meldal and Sharpless groups in 2001.[4] However, the extended application of CuAAC is often limited by several serious drawbacks. First, the high cytotoxicity of copper ions and the reductants (such as sodium ascorbate) are not biocompatible.[5] Cu-free strain-promoted AAC (SPAAC) is an alternative to solve the cytotoxicity issue, but the substrates for SPAAC are limited and complicated.[6] Second, it is still a challenge for the electron-rich internal alkynes to accomplish CuAAC under mild and bioorthogonal conditions. Ynamides,[7] as the versatile electron-rich internal alkynes, could react with azides by copper-catalyzed cycloaddition. However, 4-amido-fully substituted triazoles are afforded exclusively at high temperature (Scheme 1a).[8] Haloalkynes are used to prepare 5-halo-1,2,3-triazoles, which could be further derivatized to 5-amido fully substituted triazoles after halogen exchange and treatment with base.[9] It is an advanced modification for CuAAC, but not an atom- or step-economic strategy (Scheme 1a). Ruthenium, as a novel catalyst for the AAC reaction to selectively prepare 1,5-disubstituted and 1,4,5-trisubstituted 1,2,3-triazoles, was first reported by Fokin and Jia.[10] However, for the synthesis of 5-amido fully substituted 1,2,3-triazoles, regiomers are occasionally obtained when alkyl substituted internal ynamides are used as substrates (Scheme 1b).[2a] Recently, the López and Mascareñas group reported Ru-catalyzed azide-thioalkyne cycloadditions in aqueous media.[10d] The Hong group developed nickel-catalyzed AAC (NiAAC) to regioselectively synthesize disubstituted 1,2,3-triazoles under air and water.[11a] The Huang group disclosed a rhodium-catalyzed AAC (RhAAC) to give 5-amino-substituted 1,2,3-trazoles efficiently.[11b] Taran, Jia, Sun, and others reported iridium-promoted azide−alkyne cycloaddition in organic solvents or water.[12] The development and application of various transition metal catalysts in AAC reactions indicated that the metal-catalyzed azide−alkyne cycloaddition (MAAC) has become popular and is the focus of many chemists.[13] Herein, we report a highly regioselective method to access 5-amido fully substituted 1,2,3-triazoles by Ir-catalyzed azide−ynamide cycloaddition under mild, air, aqueous, and bioorthogonal conditions (Scheme 1c). A much stronger coordination between ynamides and iridium would lead to high regioselectivities for the AAC reaction. Besides, the cytotoxicity of iridium ion is much lower compared to copper and ruthenium ions.[14] Moreover, the catalytic activity of iridium could be maintained and robust in various biological media and air.

Substrate **1a** was prepared according to Hsung's method.[15] We first optimized the cycloaddition between **1a** and **2a** using dichloromethane (DCM) as solvent at rt without inert gas

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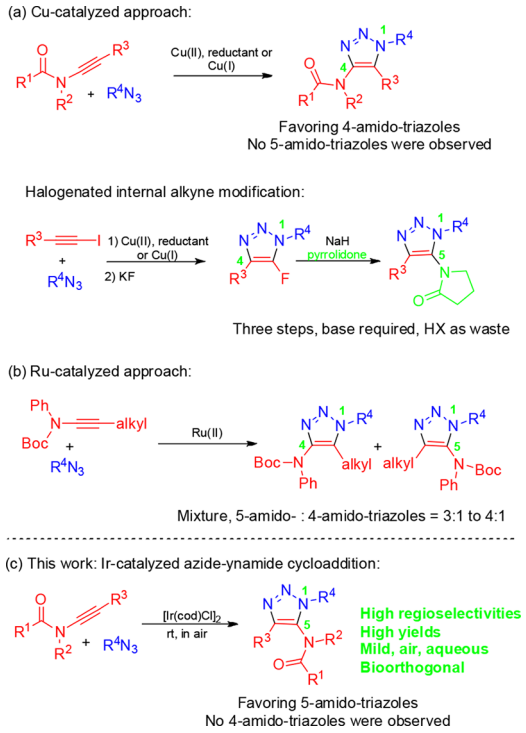
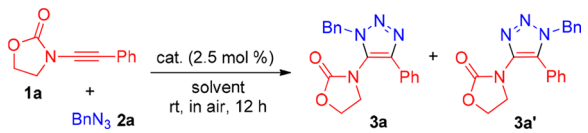
**Scheme 1. Synthesis of 5-Amido Fully Substituted 1,2,3-Triazoles**




protection (Table 1). The CuAAC failed to occur for the internal alkyne **1a** in the presence of CuI or $CuSO_4$ (Table 1, entries 1 and 2). Neither Rh(III) nor Rh(I) could generate any desired cycloaddition product in this transformation (Table 1, entries 3 and 4). [Cp*Ru(cod)Cl] and [Cp*Ru($PPh_3$)$_2$Cl] were reported to catalyze the [3 + 2] reaction with excellent yields and regioselectivities in RuAAC.[10] However, only mediocre regioselectivities were acquired for azide−ynamide cycloaddition (Table 1, entries 5 and 6). It was not a regioselective reaction for Ru as the catalyst. $[Ir(cod)Cl]_2$ was demonstrated to be the best catalyst for this process due to the nearly quantitative yield and absolute regioselectivity (Table 1, entry 7). This Ir-catalyzed [3 + 2] cycloaddition proceeded well in various polar and nonpolar solvents, such as THF, toluene, EtOH, and MeCN, and especially smoothly in water with high yields and regioselectivities (Table 1, entries 8 and 9). The other conditions could be found in the Supporting Information. Remarkably, this reaction could be carried out under mild, air, and aqueous conditions, which paved the way to investigate the application in bioorthogonal fields.

**Table 1. Optimization of Reaction Conditions**[a]

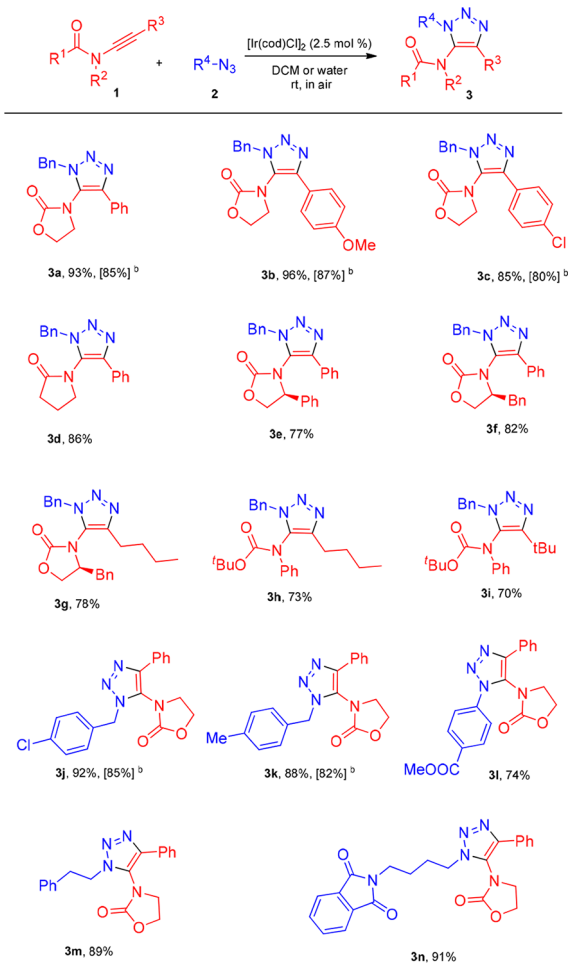



| entry | cat. | solv | yield (3a + 3a′) [%][b] | 3a/3a′[b] |
|---|---|---|---|---|
| 1 | CuI | DCM | 0 | – |
| 2 | $CuSO_4$ | DCM | 0 | – |
| 3 | $[Cp^*RhCl_2]_2$ | DCM | 0 | – |
| 4 | $[Rh(cod)Cl]_2$ | DCM | complex | – |
| 5 | [Cp*Ru(cod)Cl] | DCM | 85 | 4:1 |
| 6 | [Cp*Ru($PPh_3$)$_2$Cl] | DCM | 79 | 4:1 |
| 7 | $[Ir(cod)Cl]_2$ | DCM | **96** | **1:0** |
| 8 | $[Ir(cod)Cl]_2$ | water | **87** | **1:0** |
| 9 | $[Ir(cod)Cl]_2$ | other solvent[c] | **>90** | **1:0** |

[a]Conditions: **1a** (1.0 equiv), **2a** (1.5 equiv), solvent (0.1 M), catalyst (2.5 mol %), at rt under air for 12 h. [b]Determined by $^1$H NMR of the crude mixture with an internal standard. [c]Other solvents were evaluated (including THF, toluene, EtOH, MeCN), all giving a high yield. Cp* = pentamethylcyclopentadiene, cod = 1,5-cyclooctadiene.

With the optimized conditions in hand, we explored the scope of Ir-catalyzed azide−ynamide cycloaddition. Various cyclic and acyclic ynamides were used as substrates at rt in organic solvent or water without inert gas protection to afford 5-amido-fully substituted 1,2,3-triazoles in good yields (up to 96%) and excellent regioselectivities (more than 20:1) (Scheme 2). For cyclic ynamides, the yield (**3b**) for an electron-donating aryl substrate was slightly higher (96%) than the phenyl one (**3a**). But the yield of **3c** with an electron-withdrawing aryl group reduced to 85%. If pyrrolidinone was used instead of oxazolidione, the yield of **3d** dropped to 86%. The introduction of bulky groups to the

**Scheme 2. Substrate Scope of the Ir-Catalyzed Azide−Ynamide Cycloaddition**[a]




[a]Conditions: **1** (1.0 equiv), **2** (1.5 equiv), and DCM or water (0.1 M) were sequentially added to a vial containing the $[Ir(cod)Cl]_2$ (2.5 mol %) under air. The vial was closed, and the mixture was stirred at rt for 12 h. Regioselectivities (**3**/**3′**) were >20:1 unless otherwise noted (determined by $^1$H NMR of the crude reaction mixture). Yield of isolated product. [b]The isolated yields of the reactions carried out in water are shown in brackets.



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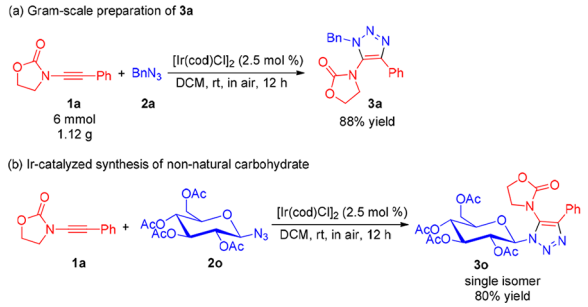
adjacent position of ynamides notably led to the decrease of the yield to 77% (**3e**, phenyl substituted) and 82% (**3f**, benzyl substituted) respectively. The alkyl substituted internal alkyne could be tolerated in this process in spite of the low yield (78%) for **3g**. For acylic ynamides, the reactions could also occur. The yield for the *n*-butyl substituted internal alkyne was 73% (**3h**), and for the *tert*-butyl one it was 70% (**3i**). The absolute regioselectivities were confirmed by **3d**, **3e**, and **3h** (see Supporting Information). We also evaluated different azides for this cycloaddition. We were pleased to find that alkyl and aryl azides as substrates could give desired products in good yields and excellent regioselectivities. The electronic effect was not obvious for **3j** and **3k**. The yield decreased to 74% for **3l** when aryl azide was used as the substrate. Good yields (**3m** and **3n**) were obtained for ethyl or butyl azides as substrates. When water was used instead of organic solvent, a similar trend was observed (Scheme 2, brackets). The yields in water were not as high as in the case of organic solvent due to the relatively poor solubility of some azides and ynamides.

Subsequently, the applicability of this reaction was examined. We scaled up the reaction to the gram scale. Treatment with **1a** (6.0 mmol, 1.12 g) under the standard conditions afforded **3a** in 88% yield (5.28 mmol, 1.69 g) after column chromatography (Scheme 3a). This highly efficient cycloaddition could be further

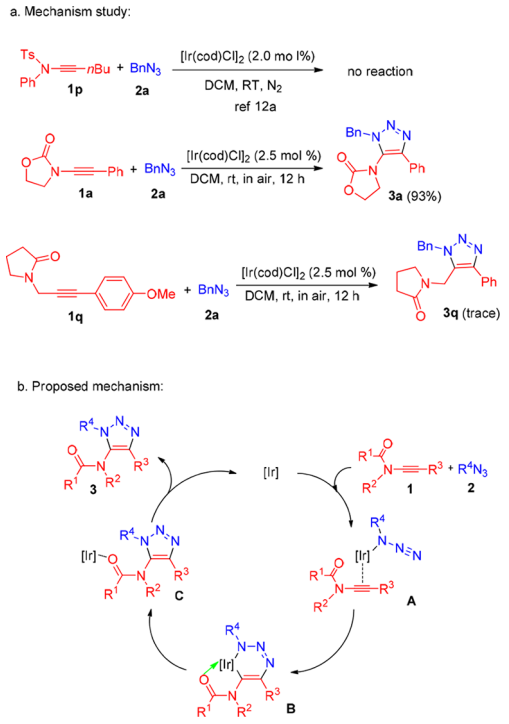
**Scheme 3. Application of Ir-Catalyzed Azide−Ynamide Cycloaddition**




extended to the synthesis of non-natural carbohydrates using glycosyl azide and ynamide as substrates. The functionalization of carbohydrates is crucial in glycomics study. This method could potentially be applied in bioconjugation to reveal delicate biological processes (Scheme 3b).

The Ir-catalyzed azide−ynamide cycloaddition could result in excellent regioselectivities under mild, air, and aqueous conditions. To further understand the Ir-catalyzed process, we performed a mechanistic study. According to a previous report, tosyl ynamide **1p** could not achieve the cycloaddition.[12a] But in our study, when the tosyl ynamide was replaced by carbonyl ynamide, highly regioselective products were obtained. When an extra carbon was introduced between the alkyne and amide, the reaction failed to occur for **1q**, which disclosed the position of the amide connected with the alkyne was crucial for this cycloaddition. The electronic difference between **1a** and **1q** may be another factor for this Ir-catalyzed cycloaddition (Scheme 4a). Based on the above-mentioned experiments, the mechanism of Ir-catalyzed azide−ynamide cycloaddition is proposed in Scheme 4b. The cycloaddition is initiated by the combination of $\pi$-acidic Ir with ynamide and azide to give intermediate **A**. The azide coordinates with Ir by the internal N atom in intermediate **A**.[16] We hypothesize the coordination of carbonyl oxygen with Ir in intermediate **B** leads to the high regioselectivities.[17] There is no

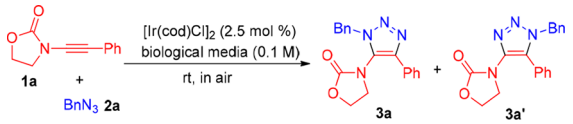
**Scheme 4. Proposed Mechanism for Ir-Catalyzed Azide−Ynamide Cycloaddition**




coordinated site at the other moiety of ynamide. 4-Amido fully substituted 1,2,3-triazoles are therefore not observed. Then reductive elimination of intermediate **B** generates intermediate **C**. The final products, 5-amido fully substituted 1,2,3-triazoles, are formed from intermediate **C**.

The low cytotoxicity of the iridium ion encouraged us to investigate the bioorthogonality of this cycloaddition under various biological conditions, which mimicked *in vitro* and *in vivo* environments (Table 2). Phosphate-buffered saline (PBS) with varying pH were tested first. The cycloaddition could occur efficiently with high regioselectivities in PBS with the pH ranging from an acidic value (5.7) to a basic one (8.0), which represented the typical *in vitro* and *in vivo* environments (Table 2, entries 2−4). DMEM and cell lysates were frequently used as *in vitro*

**Table 2. Exploration of the Bioorthogonality of the Reaction**[a]




| entry | conditions | yield (**3a**) [%] | **3a**/**3a'**[b] |
|---|---|---|---|
| 1 | water | 87 | 1:0 |
| 2 | PBS (pH = 5.7) | 89 | 1:0 |
| 3 | PBS (pH = 7.4) | 84 | 1:0 |
| 4 | PBS (pH = 8.0) | 83 | 1:0 |
| 5 | cell cultured media (DMEM) | 85 | 1:0 |
| 6 | cell lysates (UM-1) | 90 | 1:0 |
| 7 | 50% normal mouse serum | 85 | 1:0 |
| 8 | 100% lung cancer patient serum | 86 | 1:0 |

[a]Conditions: **1a** (1.0 equiv), **2a** (1.5 equiv), $[Ir(cod)Cl]_2$ (2.5 mol %), biological media (0.1 M); the mixture was stirred at rt for 12 h in air. [b]Determined by $^1H$ NMR of the crude reaction mixture with an internal standard.



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environments, which were also excellent solvents for this conversion. The desired triazoles were afforded in good yields and excellent regioselectivities, indicating that the reaction could be carried out under both extra- and intracellular environments (Table 2, entries 5, 6). Serum was most commonly used to mimic the blood to provide an *in vivo* biological condition. Expectedly, the reaction could also work perfectly in 50% normal mouse serum and 100% lung cancer patient serum (Table 2, entries 7, 8). The excellent yields and regioselectivities of the Ir-catalyzed cycloaddition under various bioorthogonal conditions exhibited significant potential for further applications.

In summary, we have developed iridium-catalyzed azide−ynamide cycloaddition for the synthesis of 5-amido-fully substituted 1,2,3-triazoles under mild, air, aqueous, and bioorthogonal conditions. This strategy shows broad substrate scope, high yields, and excellent regioselectivities. It switches the intrinsic regioselectivities for CuAAC and improves the initial regioselectivities for RuAAC to afford 5-amido fully substituted 1,2,3-triazoles exclusively. The iridium ion is low in cytotoxicity and insensitive to oxygen/water, determining its biocompatibility and potential clinical applications. The comprehensive mechanistic studies and advanced theoretical calculations for the catalysts and intermediates are underway in our laboratory.

## ■ ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b03123.

Detailed experimental procedures and characterization of new compounds ($^1$H NMR, $^{13}$C NMR, HRMS) (PDF)

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### Notes

The authors declare no competing financial interest.

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