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[3 + 2] Cycloaddition of Isocyanides with Aryl Diazonium Salts: Catalyst-Dependent Regioselective Synthesis of 1,3- and 1,5-Disubstituted 1,2,4-Triazoles

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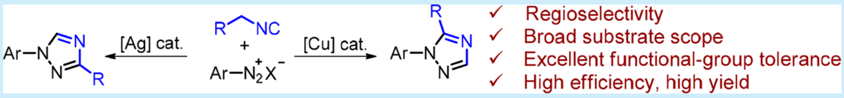
Supporting Information



ABSTRACT: An unprecedented catalyst-dependent regioselective [3 + 2] cycloaddition of isocyanides with aryl diazonium salts is reported. 1,3-Disubstituted 1,2,4-triazoles were selectively obtained in high yield under Ag(I) catalysis, whereas 1,5-disubstituted 1,2,4-triazoles were formed by Cu(II) catalysis. These catalytic methodologies provide a controlled, modular, and facile access to 1,2,4-triazole scaffolds with high efficiency, broad substrate scope, and excellent functional group compatibility.

Isocyanides are extraordinarily versatile building blocks in organic synthesis, widely applied in the formation of *N*-heterocycles.[1] To date, the significant advances have been achieved.[2] Among these reported protocols, the [3 + 2] dipolar addition pathway is the most powerful and representative route to construct five-membered nitrogen heterocyclic compounds, which have been well developed.[3] However, all of them only afford the unitary products, owing to the carbene-like reactivity of isocyanide divalent carbon atoms or the activity of α-H. (Figure 1a). Thus, utilizing the competitive group properties and altering reaction conditions could control the selectivity of a reaction to diversified products from the same starting material of isocyanides, which is a challenging issue to be explored in isocyanide chemistry.

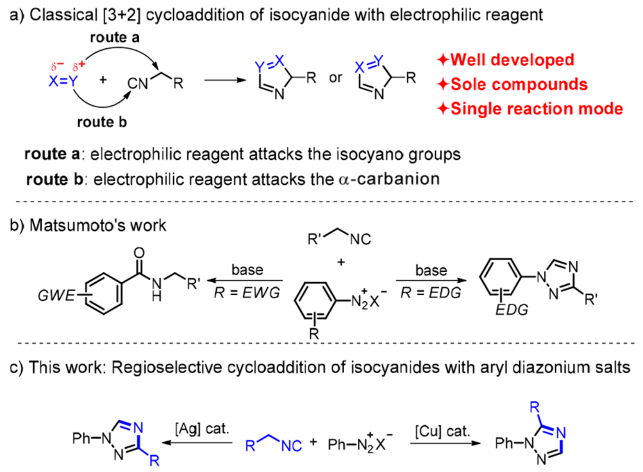


Figure 1. State of the art for the reaction of isocyanides with diazonium salts.

1,2,4-Triazole is a class of important heterocyclic frameworks with multiple impressive applications in biological and pharmacological arenas as well as in materials science.[4] In this context, we envisioned isocyano groups acting both as a polarized triple bond and as a carbine and a regioselective [3 + 2] cycloaddition of isocyanides with diazonium salts giving access to 1,2,4-triazoles in a one-step straightforward synthesis, which would benefit from the ready availability of the starting materials.[5] To the best of our knowledge, so far only two reaction modes of isocyanides with diazonium salts have been described (Figure 1b).[6] The pioneering work by the Matsumoto group disclosed the significant impact of the electronic effect of diazonium salts on the reaction outcome.[6a] Specifically, the diazonium salts with an electron-donating group readily underwent a [3 + 2] cycloaddition with isocyanides to give 1,3-disubstituted 1,2,4-triazoles, whereas diazonium salts with an electron-withdrawing group afforded arylcarboxyamides via the nucleophilic displacement of nitrogen, followed by hydration of the nitrilium ion intermediate species. The broadening of the reaction scope and an improvement of the regioselectivity for these cycloaddition reactions remain challenging. In recent years, transition-metal catalysts, such as copper and silver salts, have proven effective in the exploration of the chemistry of isocyanides,[7] particularly for its cycloaddition reactions.[8,9] In alignment with our continuing interest in copper- and silver-catalyzed organic transformations,[10] we herein report the first regioselective cycloaddition of isocyanides to diazonium

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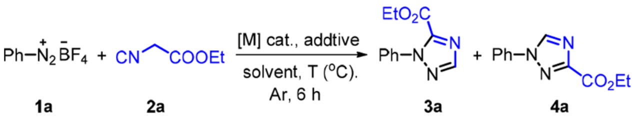
salts (Figure 1c), thereby providing in good yield and functional group compatibility either 1,3- or 1,5-disubstituted 1,2,4-triazoles, depending on the catalyst (i.e., silver(I) or copper(II) salts).

We began by using benzenediazonium tetrafluoroborate (**1a**) and ethyl 2-isocyanoacetate (**2a**) as model substrates for our investigation into this reaction. In the presence of Ag_2CO_3 (10 mol %), the reaction in *N*,*N*-dimethylformamide (DMF) exclusively afforded after 6 h at room temperature the 1,3-disubstituted 1,2,4-triazole (**4a**) in 65% isolated yield (Table 1, entry 1). Upon screening a range of silver salts, we observed that both AgOAc and AgF were efficient catalysts, while Ag_3PO_4 was unreactive under the same conditions (entries 2−4). In contrast, other known metal catalysts, such as CuI, $Pd(OAc)_2$, and $AuCl(PPh_3)_2$, were not reactive or gave **4a** in poor yield (entries 5−7). Solvent effects were also investigated (entries 8−12). Although 1,4-dioxane, THF, and toluene (entries 8, 10, and 11) also allowed for a satisfactory reaction outcome, 1,2-dichloroethane (DCE) proved the most suitable, giving the highest yield even when the reaction was run at 0 °C (entry 12). Conversely, methanol produced **4a** in poor yield.

Table 1. Optimization of the Reaction Conditions[a]



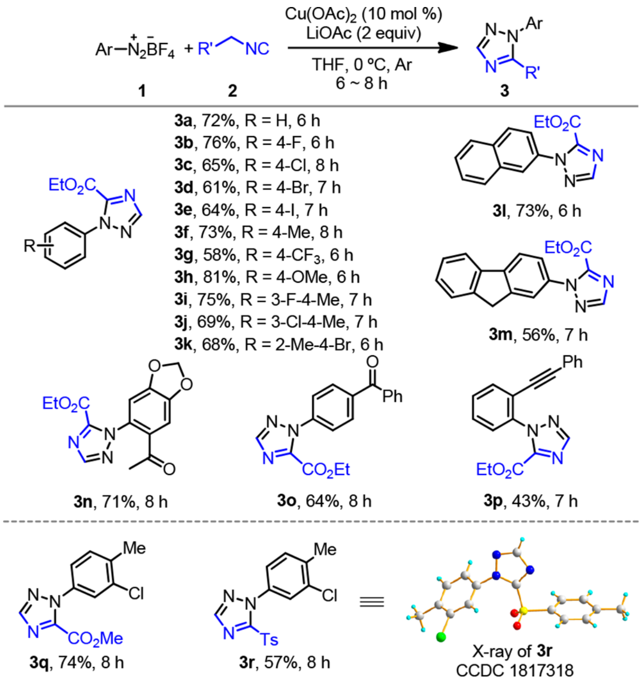
entry	[M]	additive	solvent	*T* (°C)	yield[b] (%) 3a	yield[b] (%) 4a
1	Ag_2CO_3		DMF	rt	0	65
2	AgOAc		DMF	rt	0	61
3	AgF		DMF	rt	0	58
4	Ag_3PO_4		DMF	rt	0	0
5	CuI		DMF	rt	0	0
6	$Pd(OAc)_2$		DMF	rt	0	23
7	$AuCl(PPh_3)_2$		DMF	rt	0	0
8	Ag_2CO_3		1,4-dioxane	rt	0	74
9	Ag_2CO_3		MeOH	rt	0	26
10	Ag_2CO_3		THF	rt	0	76
11	Ag_2CO_3		toluene	rt	0	79
12	**Ag_2CO_3**		**DCE**	**0**	**0**	**85**
13[c]	Ag_2CO_3	CuI	DCE	0	33	49
14[c]	Ag_2CO_3	$Cu(OAc)_2$	DCE	0	37	41
15[c]	AgOAc	$Cu(OAc)_2$	DCE	0	46	38
16[d]	$Cu(OAc)_2$	LiOAc	DCE	0	52	17
17[d]	**$Cu(OAc)_2$**	**LiOAc**	**THF**	**0**	**72**	**15**

[a] Standard reaction conditions: all reactions were carried out with **1a** (0.5 mmol), **2a** (0.6 mmol), and catalyst (10 mol %) in solvent (2.0 mL) under Ar atmosphere for 6 h. [b] Yield of isolated product. [c] The amount of additive is 10 mol %. [d] The amount of additive is 2.0 equiv.

We then turned our attention to the synthesis of 1,5-disubstituted 1,2,4-triazoles by varying the catalyst while maintaining a reaction temperature of 0 °C. Intriguingly, when CuI (10 mol %) was introduced as an additive in the Ag_2CO_3-catalyzed reaction, regioisomeric 1,5-disubstituted 1,2,4-triazole (**3a**) was formed instead in 33% yield, along with **4a** in 49% yield (entry 13). In an attempt to boost efficiency and selectivity, a range of binary metal catalysts incorporating silver were employed, such as Cu/Ag, Rh/Ag, and Pd/Ag (entry 14; see the Supporting Information for more details). We found that the combination of AgOAc with $Cu(OAc)_2$ provided increased yields of **3a** (entry 15), clearly suggesting that copper salts may control the product selectivity for **3a**, while AgOAc serves as a base. When LiOAc was used as a base, the yield of the target product **3a** increased (entry 16). Replacement of DCE with THF resulted in maximization of the product **3a** yield (entry 17). A comparative experiment between **1g** (4-(trifluoromethyl)phenyldiazonium tetrafluoroborate) and **2a** under Matsumoto's conditions[6a] failed to produce the expected products **3g** or **4d**.

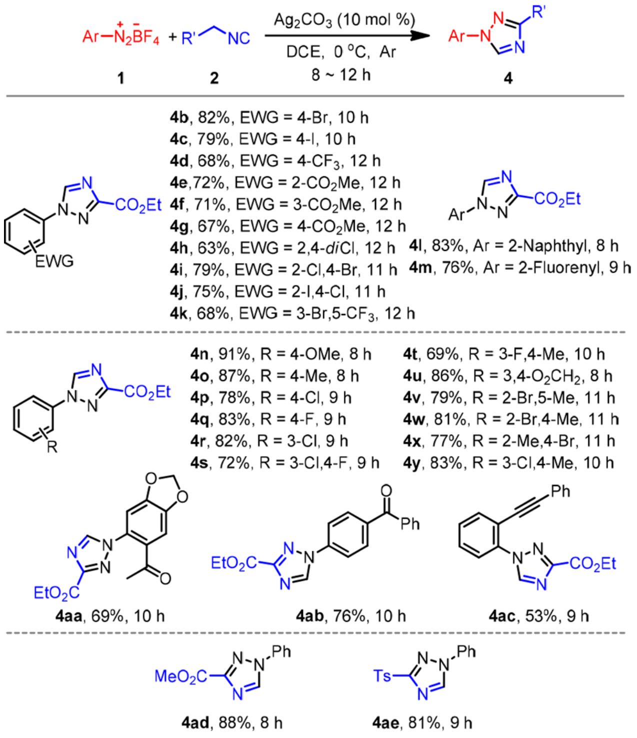
Under the optimized reaction conditions, we explored the versatility of the [3 + 2] cycloaddition to 1,5-disubstituted 1,2,4-triazoles in the presence of catalytic amounts of $Cu(OAc)_2$ (Scheme 1). A range of variously functionalized diazonium salts reacted with isocyanides to afford the corresponding products **3** in good yields. Both electron-donating and electron-withdrawing substituents on the benzenediazonium tetrafluoroborate reactants were tolerated in the reaction with isocyanide **2a**, leading to the desired products (**3a**−**h**) in moderate to good yields. Disubstituted benzenediazonium tetrafluoroborates were also compatible with the cycloaddition reaction conditions, affording the corresponding products (**3i**−**k**) in high yields. Treatment of fused aromatic (**1l** and **1m**) diazonium salts with **2a** also efficiently afforded the expected products **3l** and **3m**. Substrates with potentially reactive functional groups, such as keto and alkynyl groups, were productive under the optimized conditions, giving compounds **3n**−**p** in 43−71% yield.[1,11] Methyl isocyanoacetate (**2b**) and toluenesulfonylmethyl isocyanide (**2c**) also smoothly reacted with diazonium salt **1j**, producing 1,5-disubstituted cycloadducts **3q** and **3r** in 74% and 57% yield, respectively. The structure of product **3r** was conclusively assigned by single-crystal X-ray analysis.

Scheme 1. Scope of 1,5-Disubstituted 1,2,4-Triazoles



The scope and limitations of the silver-catalyzed cycloaddition of isocyanides to diazonium salts to give 1,3-disubstituted 1,2,4-triazoles were subsequently investigated. As shown in Scheme 2, benzenediazonium tetrafluoroborates bearing electron-withdrawing groups (Br, I, Cl, CF_3, and

Scheme 2. Scope of 1,3-Disubstituted 1,2,4-Triazoles

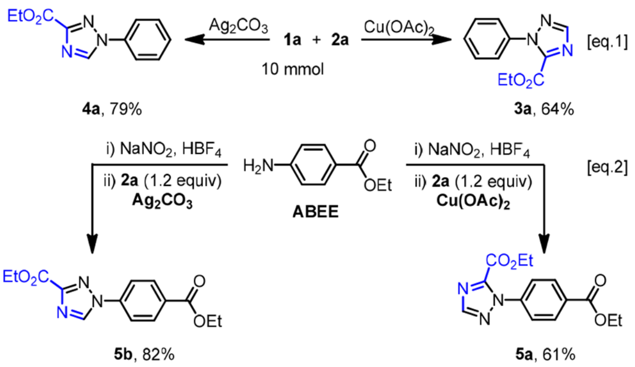


CO$_2$Me) were well tolerated in the reaction with **2a**, delivering the corresponding cycloadducts **4b**−**k** in up to 82% yield. Under the conditions described by Matsumoto, the same reactants failed to give the same products.[6] Diazonium tetrafluoroborates featuring fused aromatics, such as the 2-naphthyl and 2-fluorenyl groups, or electron-donating (Me, OMe) substituents provided the corresponding products (**4l**−**o**) in yields comparable to or higher than that recorded for substrates with electron-withdrawing substituents. The structure of **4o** (CCDC 1816490) was unequivocally confirmed by X-ray diffraction analysis. Similar to the copper-catalyzed cycloaddition, the silver-catalyzed protocol could also be applied to a variety of disubstituted diazonium salts (**4s**−**y**), including those with a keto or alkynyl functionality, from which the target products **4aa**−**ac** were obtained in good yields. Methyl 2-isocyanoacetate (**2b**) and toluenesulfonylmethyl isocyanide (**2c**) also proved reactive and gave the corresponding products **4ad** and **4ae** in high yields.

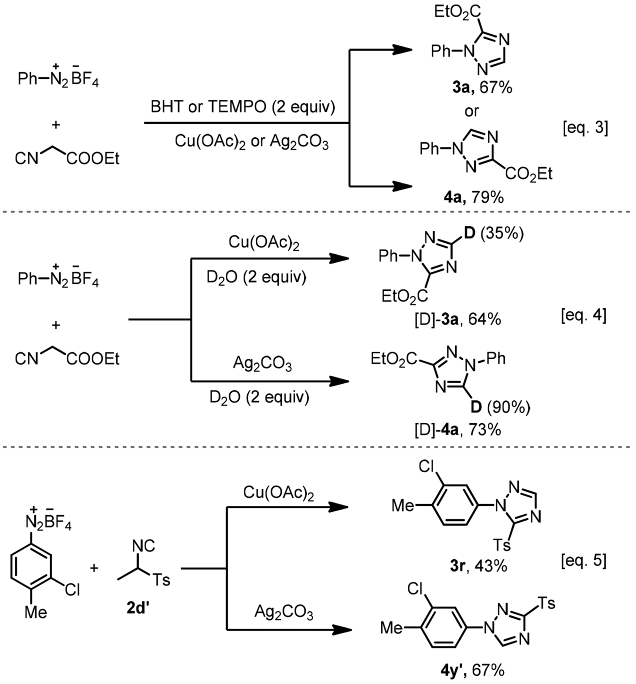
To determine the robustness of this method, two reactions between benzenediazonium tetrafluoroborate **1a** and ethyl 2-isocyanoacetate **2a** were conducted on a 10 mmol scale (1.92 g of **1a**) under both catalytic optimized conditions. The two desired products **3a** and **4a** were obtained in moderate to good yield (Scheme 3, eq 1). When the optimized cycloaddition reaction conditions were applied to commercially available benzocaine (ABEE) as starting material,[12] 1,2,4-triazole derivatives **5a** and **5b** were obtained in good yield (eq 2).

A series of control experiments was executed to investigate the reaction mechanism (Scheme 4). Under the optimized conditions, the addition of 2 equiv of radical scavengers such as TEMPO or BHT to the reaction mixture (Scheme 4, eq 3) did not affect the reaction rate, with the desired cycloadducts **3a** and **4a** being produced in 67% and 79% yield, respectively. This result indicates that the reaction did not likely proceed via a radical process.[13]

Scheme 3. Gram-Scale Synthesis and Application to the Synthesis of ABEE Derivatives



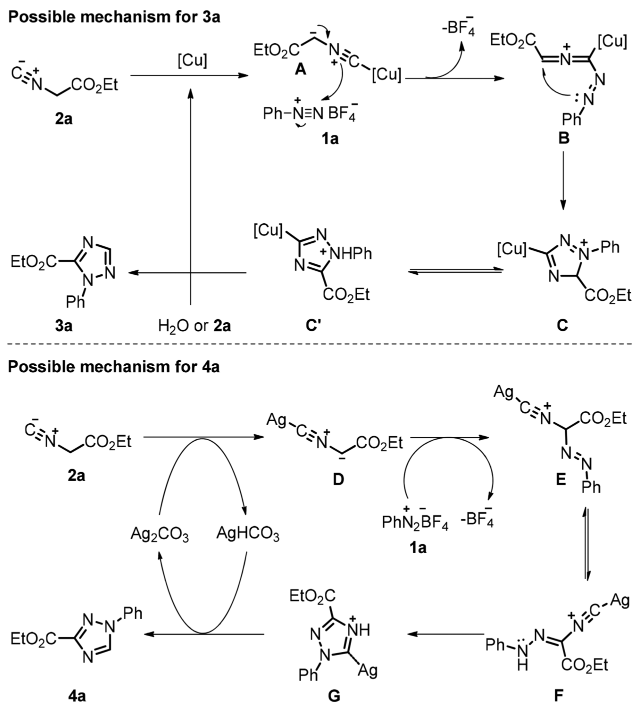
Scheme 4. Mechanistic Investigations



The addition of 2 equiv of D$_2$O to the reaction mixture resulted in the formation of deuterated 1,2,4-triazoles [D]-**3a** and [D]-**4a** in comparable yield. However, deuterium was incorporated in [D]-**3a** to a lesser extent (35%) than in [D]-**4a** (90%) (Scheme 4, eq 4). Based on these experimental observations, we surmised that the two regioisomeric 1,2,4-triazoles were formed via two different mechanistic routes, with water playing the role as a proton source in one of them. Moreover, when the reaction of **1j** and **2d′** was carried out under the optimized conditions, the desired methyl group fragmented products **3r** and **4y′** were obtained in 43% and 67% yields (Scheme 4, eq 5).

The described experiments and literature precedents[14] led us to propose the plausible mechanism shown in Scheme 5, whereby the nature of the interaction between the metal catalyst and the isocyanide determines the formation of either **3a** or **4a**. In the case of the copper-catalyzed reaction, isocyanide **2a** coordinates with Cu(OAc)$_2$ to generated the copper complex **A**.[1a,15] In the presence of base, cross-coupling between **A** and diazonium salt **1a** gives intermediate **B**, which undergoes an intramolecular nucleophilic addition to form cyclized cationic

Scheme 5. Proposed Reaction Mechanism



intermediate **C** or its tautomer **C′**.[16] The latter undergoes a proton shift to give the final product **3a** with regeneration of the catalyst.[17] In the case of silver-catalyzed cycloaddition, the interaction of **2a** with Ag_2CO_3 affords the silver-activated isocyanide **D**, whereby Ag_2CO_3 acts in the dual role of base and catalyst.[18] Isocyanide **D** reacts with diazonium **1a** to give **E**, which undergoes an intramolecular nucleophilic addition, followed by tautomerization, deprotonation, and reprotonation to deliver product **4a**[19] and regenerate the catalyst.

In summary, we have developed the first catalyst-controlled protocol for the regioselective [3 + 2] cycloaddition of isocyanides with diazonium salts that under mild conditions provides a convenient approach for the construction of 1,2,4-triazoles in good yield from an array of variously functionalized substrates. Synthetically useful 1,3-disubstituted and 1,5-disubstituted 1,2,4-triazoles could be easily prepared by utilizing Ag(I) and Cu(II) catalysts, respectively.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b03069.

Experimental procedures and spectra (PDF)

Accession Codes

CCDC 1816490 and 1817318 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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