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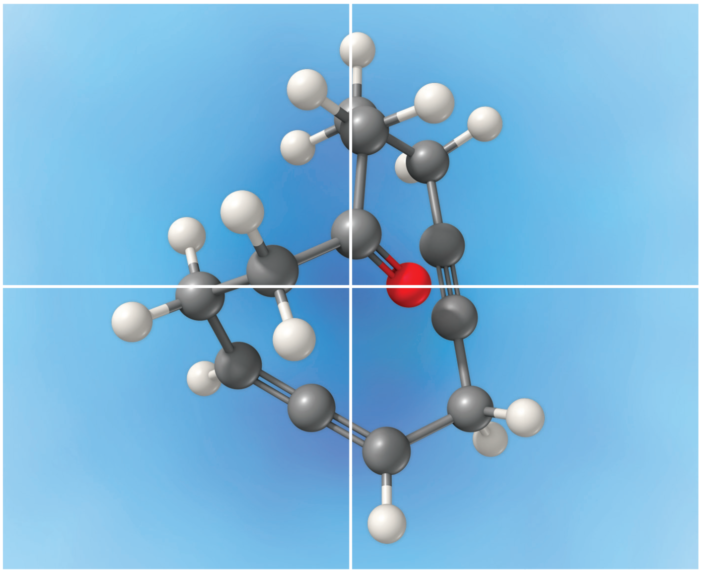

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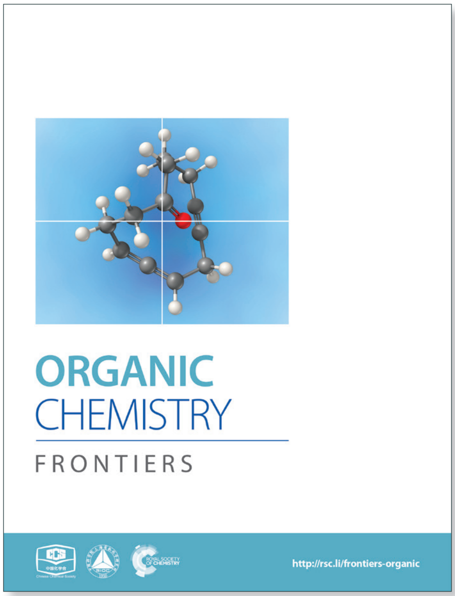

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Silver-Catalyzed [3 + 2] Cycloaddition of Isocyanides with Diazo Compounds: New Regioselective Access to 1,4-Disubstituted-1,2,3-triazoles

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An unprecedented silver-catalyzed 1,3-dipolar cycloaddition reaction of isocyanides with diazo compounds to afford 1,4-disubstituted 1,2,3-triazoles was reported. This reaction exhibits remarkable features, such as high regioselectivity, mild reaction conditions, easily available substrates with simple operation, and good yields with a broad spectrum of substrates. It constitutes an alternative to the well-known CuAAC click reaction.

Introduction

1,2,3-Triazoles, an important class of five-membered heterocycles, are widely used in chemistry, biology, and materials science.[1] Because of their characteristic properties, numerous processes have been developed for the preparation of various 1,2,3-triazole compounds.[2] In particular, the elegant work of Fokin, Sharpless, and Meldal on the copper-catalyzed azide–alkyne cycloaddition (CuAAC) has become a paradigm of the click reaction chemistry and plays a significant role in medicine and bioconjugation chemistry.[3] Despite these notable achievements, the development of new efficient methods for the facile construction of highly functional 1,2,3-triazole heterocycles is still in high demand.

From a retrosynthetic point of view, 1,4-disubstituted 1,2,3-triazoles could be assembled not only through the cycloaddition of alkynes and azides (Figure 1: top), but also through the cycloaddition of isocyanides with diazo compounds (Figure 1: bottom). In comparison with the tremendous progress that has been made toward the cycloaddition of alkynes and azides, the analogous reaction of isocyanides and diazo compounds remains largely unexplored. Only one report by Kiselyov has described a related process in one-pot three-component cycloaddition reaction of isocyanides and diazo compounds with *N*-fluoropyridinium fluoride species that produced a mixture of 2-pyridinyl-1*H*-1,2,3-triazoles with picolinamides and 2-fluoro-2-(pyridin-2-yl)acetates (Scheme 1: top).[4] Thus, this creates the interesting challenge and large room of developing direct metal-catalyzed cycloaddition processes of isonitriles and diazo compounds to construct 1,2,3-triazole heterocycles.[5, 6]

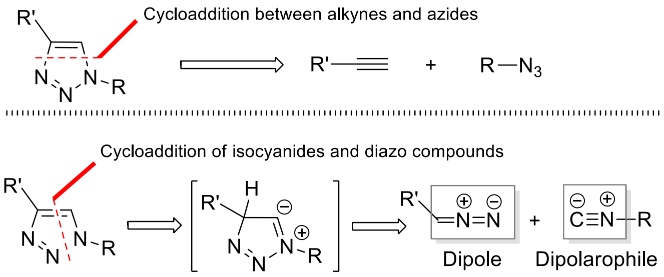

Figure 1 Retrosynthetic analysis of 1,4-disubstituted 1,2,3-triazoles.

Our idea was based on our recent finding that the silver salts could activate the terminal alkynes in the basic conditions, thus facilitating the cycloaddition reaction of terminal alkynes with 2,2,2-trifluorodiazoethane (CF_3CHN_2) in excellent regioselectivity.[7a, 8] Actually, isocyanides and terminal alkynes have a certain structural similarity. We envisioned that silver salts could also be utilized to coordinate and activate isocyanides,[9, 10] promoting the co-cyclization of isocyanides with diazo compounds (Scheme 1: bottom). In this article, we report the results of our exploration.

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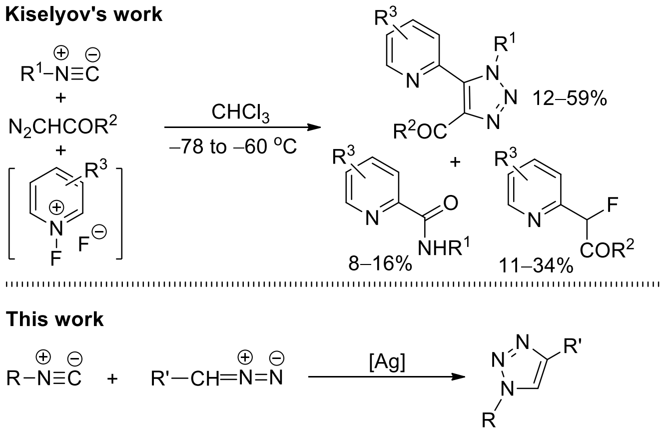


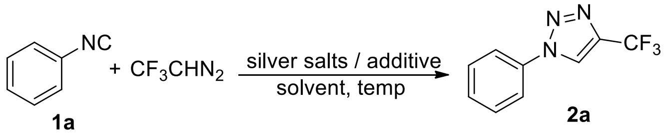
Scheme 1 Cycloaddition of isocyanides with diazo compounds.

Results and Discussion

Reaction Optimization. Isocyanobenzene **1a** and 2,2,2-trifluorodiazoethane were chosen as the model substrates for the optimization of cycloaddition conditions. The initial screening of a series of silver salts led us to identify AgOAc, Ag_2CO_3, or Ag_2O as the catalysts for the desired transformation, furnishing the cycloadduct **2a** as a single regioisomer in moderate yield (Table 1, entries 1–3). Other silver complexes gave inferior results (entries 4–6). The structure of compound **2a** was further confirmed to be 1-phenyl-4-(trifluoromethyl)-1*H*-1,2,3-triazole by means of X-ray crystallographic analysis (see the ESI).[11] These preliminary results encouraged us to further optimize the reaction conditions. The solvent was found to have an important effect on the reactivity (entries 7–10). Among the solvents tested, *N*,*N*-dimethylformamide (DMF) was found to be the solvent of choice for this reaction (entry 10).[12] After the change of the temperature (entries 11–13), the yield of **2a** could be further improved to 59%. Increasing the loading of CF_3CHN_2 resulted in much higher yield of **2a** (entries 14 and 15). A stoichiometric amount of water played a negative role in this reaction, as the addition of water afforded only 30% yield of the target product (entry 16). Subsequently, the introduction of the molecular sieve as the additive was found to significantly increase the reaction efficiency and yield (entry 17). A lesser loading of Ag_2CO_3 reduced the reaction yield (entry 18), but 0.2 equivalents of Ag_2CO_3 did not improve the yield when compared to that obtained with 0.1 equivalents of Ag_2CO_3 (entries 19 and 17). In sharp contrast, the reaction did not proceed without the silver catalyst (entries 20 and 21). Therefore, the combination of Ag_2CO_3 and 4Å MS in DMF at 40 °C was found to be the best reaction conditions for this silver-catalyzed cycloaddition reaction.

Scope of the Cycloaddition. By using the optimized protocol, we explored the scope of this silver-catalyzed 1,3-dipolar cycloaddition reaction of 2,2,2-trifluorodiazoethane with a variety of isocyanides, and the results are summarized in Scheme 2. The reaction was readily extended to various aryl-substituted isocyanides, and both electron-withdrawing and electron-donating substituents on the aryl ring were well tolerated under the current reaction conditions. Furthermore, the steric effects had little influence on this cycloaddition reaction. Regardless of the substitution pattern of the aryl ring (*ortho*, *meta*, or *para*) of the aryl isocyanides used in the reaction, the trifluoromethylated 1,2,3-triazoles (**2b**–**y**) were obtained in good to high yields. 2-Biphenyl and 1-naphthyl-substituted isocyanides were also found to be good substrates, thus delivering the cycloadducts **2z** and **2a’** in 66% and 88% yield, respectively. Subsequently, we investigated the cycloaddition reaction of 2,2,2-trifluorodiazoethane with alkyl-

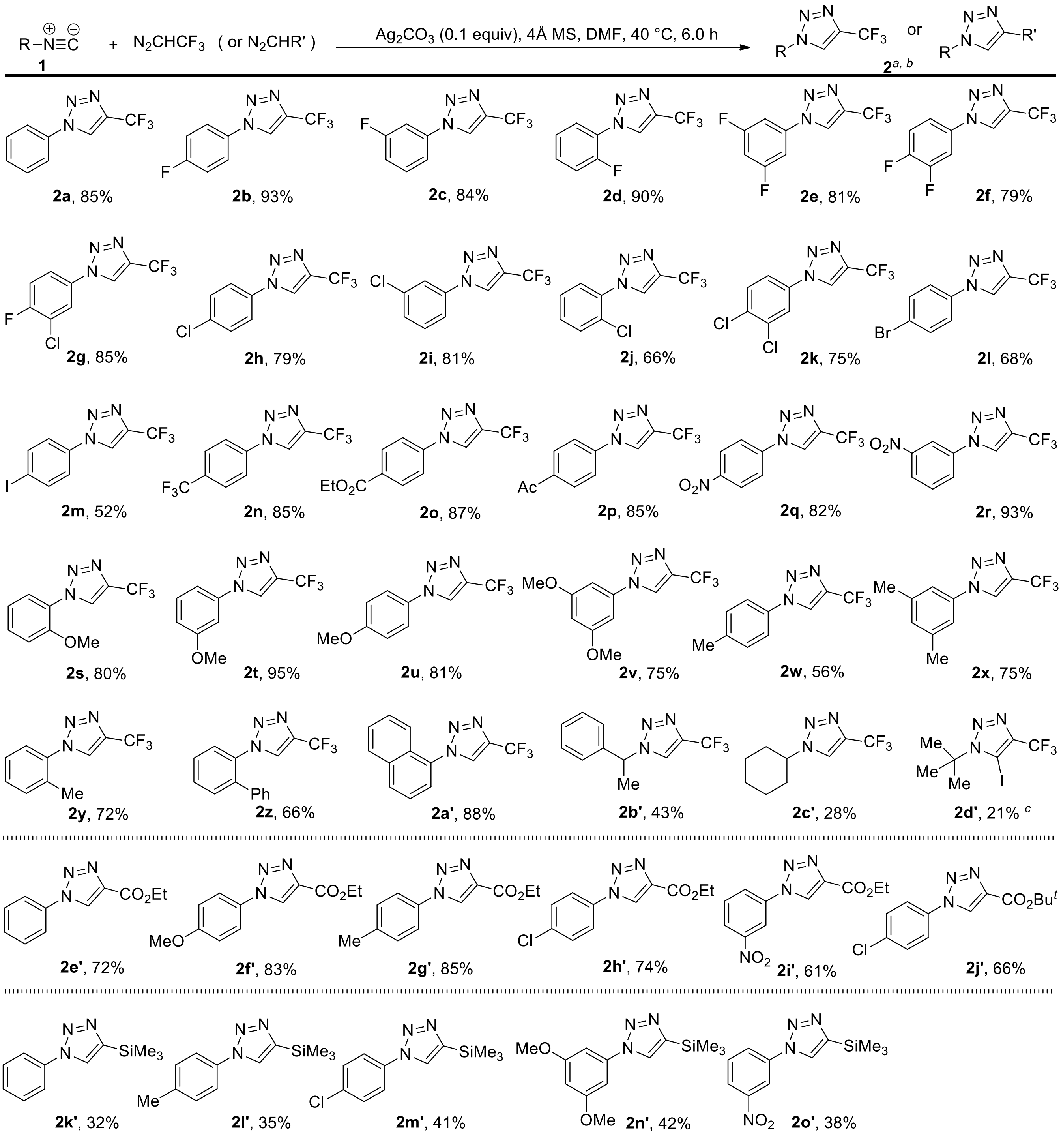
Table 1 Optimization for silver-catalyzed cycloaddition of isocyanide **1a** with CF_3CHN_2 [a]



Entry	[Ag] (equiv) / Additive (equiv)	Solvent	Temp (°C)	Yield (%)[b]
1	AgOAc (0.1)	THF	60	39
2	Ag_2CO_3 (0.1)	THF	60	43
3	Ag_2O (0.1)	THF	60	35
4	$AgNO_3$ (0.1)	THF	60	0
5	AgF (0.1)	THF	60	23
6	AgOTf (0.1)	THF	60	0
7	Ag_2CO_3 (0.1)	DCE	60	0
8	Ag_2CO_3 (0.1)	CH_3CN	60	20
9	Ag_2CO_3 (0.1)	toluene	60	39
10	Ag_2CO_3 (0.1)	DMF	60	51
11	Ag_2CO_3 (0.1)	DMF	80	21
12	Ag_2CO_3 (0.1)	DMF	40	59
13	Ag_2CO_3 (0.1)	DMF	25	40
14[c]	Ag_2CO_3 (0.1)	DMF	40	70
15[d]	Ag_2CO_3 (0.1)	DMF	40	69
16	Ag_2CO_3 (0.1) / H_2O (0.1)	DMF	40	30
17[e]	Ag_2CO_3 (0.1) / 4Å MS	DMF	40	85
18[e]	Ag_2CO_3 (0.05) / 4Å MS	DMF	40	74
19[e]	Ag_2CO_3 (0.2) / 4Å MS	DMF	40	86
20	4Å MS	DMF	40	0
21	Cs_2CO_3, or K_2CO_3, or KOH, or Na_2CO_3, or KF, or KOAc	DMF	40	0

[a] Reaction conditions: **1a** (0.20 mmol), CF_3CHN_2 (1.0 equiv) in the presence of silver catalyst in 1.0 mL solvent for 12 h. [b] Isolated yield was obtained from an average of two runs. [c] CF_3CHN_2 (1.2 equiv). [d] CF_3CHN_2 (1.5 equiv). [e] 25 mg 4 Å molecular sieves (MS) were used and stirred for 6 h.

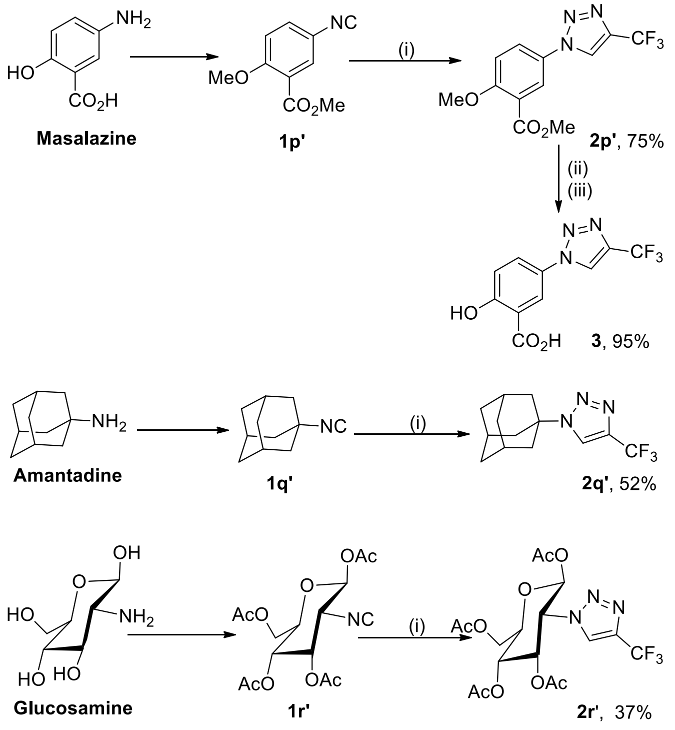
substituted isocyanides. As compared to aryl-substituted isocyanides, alkyl-substituted isocyanides are much less reactive. For example, the use of three alkyl-substituted isocyanides under the optimized conditions gave the corresponding 1,2,3-triazoles **2b'–d'** in relatively lower yields, together with a small amount of uncharacterized oligomers. However, we found that ethyl 2-isocyanoacetate cannot be converted using the present protocol, even when the reaction conditions were further optimized including the decrease of the temperature to 25 ^{o}C, the increase of the amounts of diazo compounds, and the utility of other silver salt catalysts.



Scheme 2 The silver-catalyzed cycloaddition of various isocyanides and diazo compounds. [a] Reaction conditions: **1** (0.20 mmol), diazo compound (0.24 mmol), Ag_2CO_3 (0.02 mmol), and 4Å MS (25 mg) in 1.0 mL DMF at 40 ^{o}C for 6 h. [b] Isolated yield was obtained from an average of two runs. [c] Due to high volatility, the cycloadduct of *tert*-butyl isocyanide was converted into the corresponding iodide **2d'** and characterised in 21% yield of two steps.

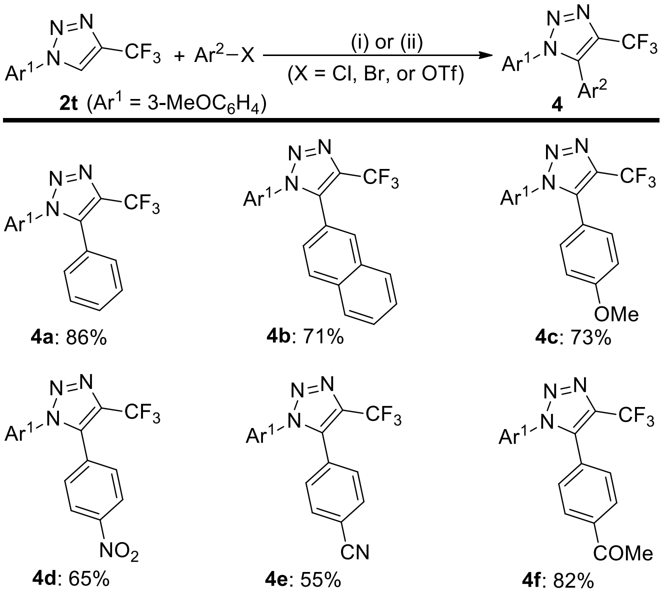
With the first method in hand for catalytic 1,3-dipolar cycloadditions of various isocyanides with 2,2,2-trifluorodiazoethane (CF_3CHN_2) to produce a series of 4-(trifluoromethyl)-1*H*-1,2,3-triazoles, we turned our attention to determining the scope of this process with respect to other diazo compounds, with the goal of providing a versatile approach. Under our standard conditions, two diazoacetates reacted with isocyanides to afford the cycloadducts **2e'**–**j'** in 61–83% yields. Use of trimethylsilyldiazomethane was also successful and the cycloaddition furnished the desired product **2k'**–**o'** in 32–42% yields. Therefore, trimethylsilyldiazomethane is compatible with this reaction, enabling additional modification at the trimethylsilylated position of the cycloadducts.

Synthetic Application and Transformation. To use this silver-catalyzed cycloaddition reaction for the modification of biologically interesting compounds, we tested the reaction of masalazine-, glucosamine-, and amantadine-derivatized isocyanides **1p'**–**1r'** with 2,2,2-trifluorodiazoethane (CF_3CHN_2) under our standard conditions (Scheme 3).[13] The reaction proceeded to afford the cycloadducts **2p'**–**2r'** in moderate to good yields. These and related compound **3** might be useful in the development of new therapeutics or biological tools.



Scheme 3 The synthesis of masalazine-, glucosamine-, and amantadine-derivatized isocyanides and relative siliver-catalyzed cycloaddition with CF_3CHN_2. Conditions: (i) Ag_2CO_3, 4Å MS (25 mg), DMF, 40 °C, 6 h. (ii) MeOH, NaOH (2M), reflux, 1.5 h. (iii) BBr_3, CH_2Cl_2, 0 °C to rt, 16 h.

Trifluoromethylated 1,2,3-triazoles can also be readily converted into fully functionalized triazoles that are otherwise difficult to access (Scheme 4).[2d, 14] For example, direct functionalization of C–H bond on the 1,2,3-triazole **2t** with bromobenzene in the presence of palladium catalyst proceeded smoothly to give 1,5-diaryl-substituted 4-trifluoromethyl-1,2,3-triazole **4a** in high yield. Furthermore, 2-naphthyl, electron-rich and electron-deficient phenyl groups can be also introduced into the 5-position of the triazole ring, delivering the fully substituted 1,2,3-triazoles **4b**–**f** in good yields.

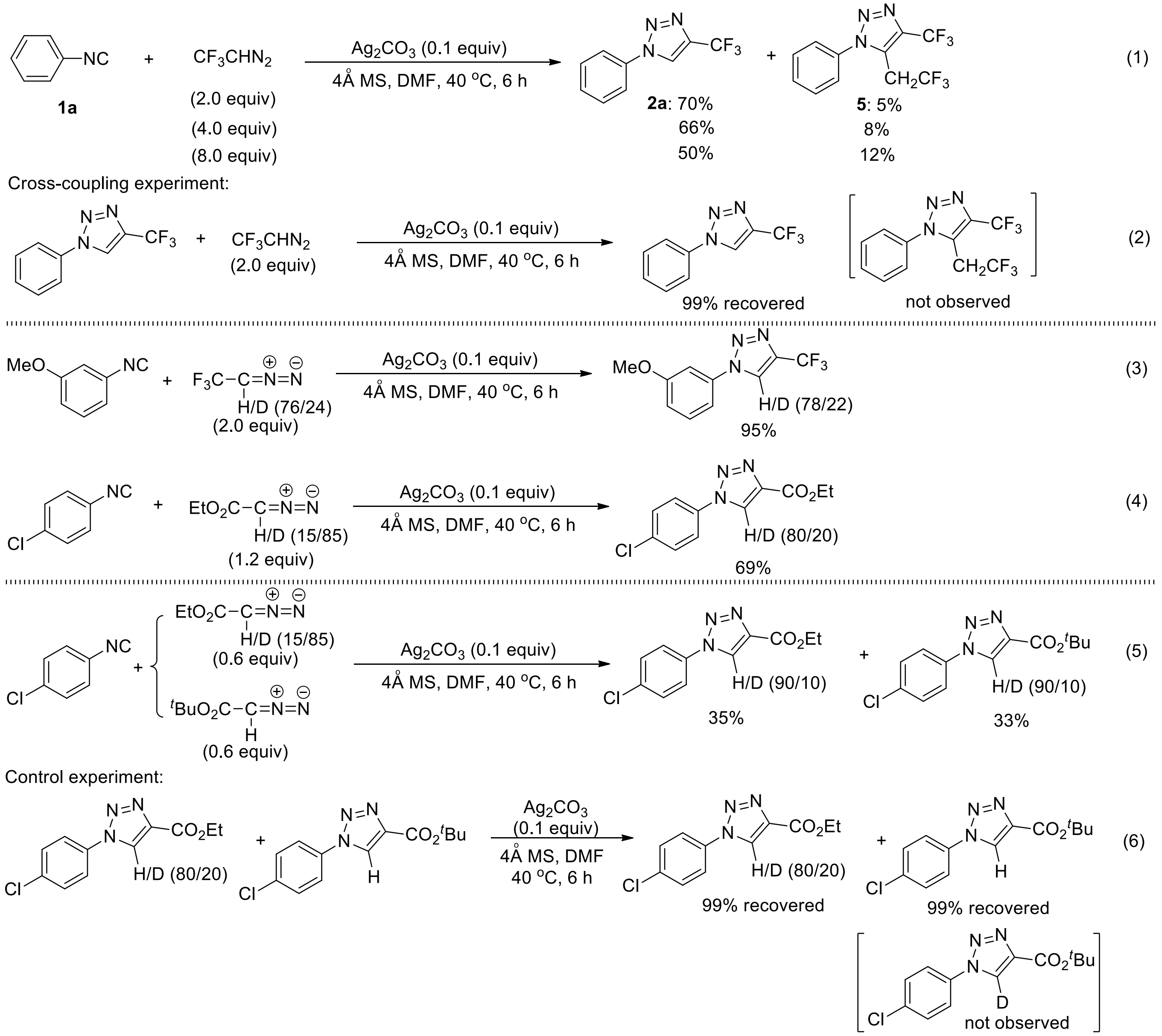


Scheme 4 Further synthetic transformation of the 1,4-disubstituted 1,2,3-triazoles into fully substituted 1,2,3-triazoles. Conditions: (i) $Pd(Ph_3P)_2Cl_2$ (5 mol%), Bu_4NOAc (0.3 mmol), aryl bromine (0.225 mmol), NMP (1.0 mL), 100 °C, 2 h. (ii) $Pd(OAc)_2$ (4.0 mol%), PCy_3 (8.0 mol%), K_2CO_3 (0.3 mmol), aryl chlorine or trifluoromethanesulfonate (0.225 mmol), PhMe (1.0 mL), 120 °C, 22 h. NMP = *N*-methyl-2-pyrrolidone.

Mechanistic Studies. Interestingly, the use of an excessive amount of 2,2,2-trifluorodiazoethane reduced the reaction yield, and led to the formation of the unexpected by-product **5** (eq 1 in Scheme 5). The structure of compound **5** was further confirmed to be 1-phenyl-5-(2,2,2-trifluoroethyl)-4-(trifluoromethyl)-1*H*-1,2,3-triazole by means of X-ray crystallographic analysis (see the ESI).[11] In the cross-coupling experiment of the cycloadduct **2a** with CF_3CHN_2, however, we did not observe this coupling product **5** (eq 2 in Scheme 5). Therefore, the compound **5** could be generated from another transformation of the cycloaddition intermediates with CF_3CHN_2.

To gain some insight into the reaction mechanism, we conducted ^{13}C NMR (in D_7-DMF) and IR spectroscopic experiments (see the ESI). When one equivalent of AgOAc was added to a solution of 1-isocyano-3,5-dimethoxybenzene, the signal peaks of -N≡C (at 164.55 ppm in the ^{13}C NMR spectra and at 2133 cm^{-1} in the IR spectra) disappeared, indicating that a coordination of isocyanide with silver salts had occurred.

In addition, we also carried out the silver-catalyzed cycloaddition of isocyanides with deuterium-labeled diazo compounds under the standard reaction conditions (eq 3 and 4 in Scheme 5). The corresponding deuterated 1,2,3-triazole products were detected by ^{1}H NMR spectroscopy as anticipated. These results indicate that the hydrogen atom at the 5-position of the 1,2,3-triazole products probably originates from diazo compounds. Notably, in a cross-over cycloaddition reaction two deuterated 1,2,3-triazole products were detected, whereas in a control experiment the intermolecular deuterium exchange was not observed (eq 5 and 6 in Scheme 5). These experimental results provide preliminary evidence that our cycloaddition could proceed by an intermolecular proton transfer process.



Scheme 5 Preliminary mechanistic studies.

A plausible reaction mechanism is proposed (Figure 2) on the basis of the above experiments. Initially, the silver isocyanide complex **A** is formed by the reaction of the isocyanide **1** with silver(I).[10a,b] The cycloaddition between complex **A** and diazo compound would give the intermediate **B** or Ag(I)-carbene complex, followed by deprotonation with Ag_2CO_3 to afford the corresponding intermediate **C**. Then, the protonation of **C** with $AgHCO_3$ produces the 1,4-disubstituted 1,2,3-triazole **2** and regenerates the silver complex **A**. In addition, the intermediate **C** or Ag(I)-carbene complex could also be trapped by the excess 2,2,2-trifluorodiazoethane (CF_3CHN_2) under the present conditions to form the intermediate **D** or **E**. Afterward, the intermediate **D** goes through the denitrogenation and protonation process, whereas the intermediate **E** proceeds via the 1,3-hydrogen shift, delivering the by-product **5**. Further analysis will be necessary to elucidate the nature of this cycloaddition more accurately.

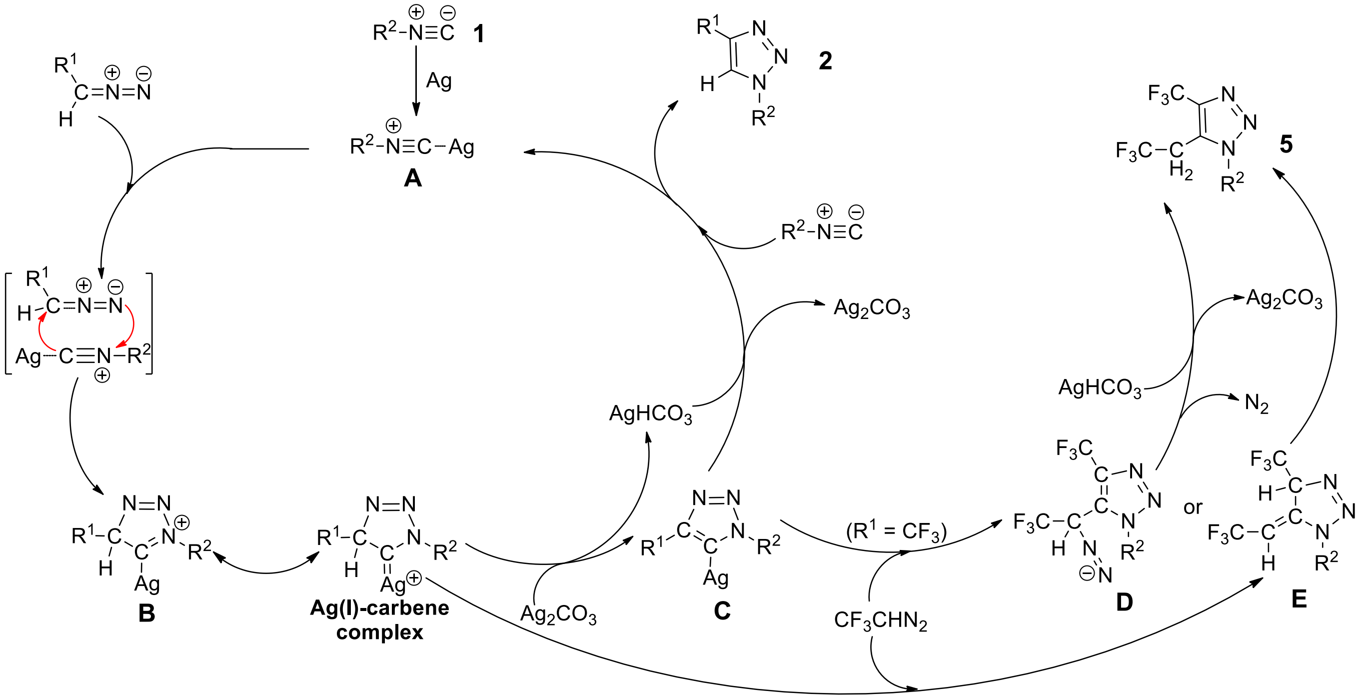


Figure 2 Proposed mechanism for the Ag-catalyzed cycloaddition of isocyanides with diazo compounds.

Conclusions

In summary, we have successfully developed a catalytic, simple, and efficient method for the cycloaddition of isocyanides with diazo compounds. This reaction exhibited good generality and regioselectivity with a variety of isocyanides and diazo compounds under mild conditions. Furthermore, the employment of this lynchpin approach allowed for the rapid and facile generation of highly functionalized 1,2,3-triazole heterocycles. In view of the convenient and divergent access of reaction substrates, this cycloaddition should find further application in organic synthesis and medicinal chemistry.

Experimental Section

Typical Procedure for the Silver-Catalyzed Cycloaddition of Isocyanide with Diazo Compounds. Isocyanobenzene (**1a**, 20.6 mg, 0.2 mmol), Ag_2CO_3 (5.5 mg, 0.02 mmol), 4Å MS (25.0 mg), and DMF (1 mL) were added into a 10.0 mL Schlenk tube. The tube was sealed well and 2,2,2-trifluorodiazoethane (26.4 mg, 0.24 mmol, 12 μL of 0.02 M in DMF) was added at room temperature. The reaction mixture was stirred at 40 °C for 6 h. After the reaction mixture was cooled down to room temperature, 10 mL water was added and extracted with EtOAc (8 mL × 3). The organic phases were collected, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. Purification by flash chromatography on silica gel with petroleum ether / ethyl acetate (25:1, v:v) afforded pure 1-phenyl-4-(trifluoromethyl)-1*H*-1,2,3-triazole (**2a**) as a white solid. Yield: 36.2 mg (85%).

Acknowledgements

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