Expedient Azide−Alkyne Huisgen Cycloaddition Catalyzed by a Combination of VOSO$_4$ with Cu(0) in Aqueous Media

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ABSTRACT: A series of vanadium(III), vanadyl(IV/V) species, inorganic metal oxides, and transition-metal oxides was examined as cocatalysts with Cu(0) powder for copper(I)-catalyzed azide-alkyne cycloaddition. Among them, vanadyl(IV) species bearing acetylacetonate, acetate, and sulfate, vanadyl(V) isopropoxide, and vanadate were suitable for the click reactions of per-acetyl and per-benzyl β-azido glycosides with three different terminal alkynes in CH$_3$CN. Water-

soluble vanadyl(IV) sulfate was further selected for efficient click reactions for unprotected β-glycosyl azides and even compatible with a thiol-containing substrate in aqueous media at ambient temperature.

KEYWORDS: vanadyl species, 1,3-dipolar cycloaddition, 1,4-disubstituted triazoles, thiol-compatible, green chemistry

Triazole heteroaromatics have widespread applications as synthetic templates,[1] drug candidates,[2] and natural product derivatives.[3] Gycosyl-containing analogues[4] bearing biological active cores and biomedicinal targeted designs have been booming interests both in both pharmaceutical industry and academic researches. In particular, N-linked glycosylation plays an important role in carbohydrate chemistry and the pharmaceutical functions of complex glycoproteins[5] and glycoconjugates.[6] In 1961, Huisgen et al. published the 1,3-dipolar cycloaddition between an azide and a terminal alkyne to give triazoles.[7] In 2001, Kolb, Finn, and Sharpless utilized this powerful tool[8] and coined the term "click chemistry" to demonstrate some unique advantages towards the synthesis of triazoles of diversified utilities with potential subsequent manipulations.[9]

To increase the efficacy of the click reactions, Fokin and Sharpless first reported the versatile usage of in situ-generated Cu(I) as a catalyst in 2002.[10] The judicious combination of copper(II) sulfate in the presence of a reductant (e.g., sodium ascorbate) triggered efficient regioselective cyclizations of terminal alkynes and organic azides leading to 1,4-disubstituted 1,2,3-triazoles.[11] The Cu(I)-catalyzed variant named as Copper(I)-catalyzed Azide−Alkyne Cycloaddition (CuAAC) offered an expedient strategy in organic, metal complex catalysis, biomedicinal, materials, and biological fields.[12] In the past 15 years, some alternative recipes for in situ Cu(I) generation by a redox process like (1) Cu(II)/Cu(0),[13] (2) Cu−Mn bimetallic catalyst,[14] (3) light-induced Cu(II)/Cu(I),[15] and (4) Cu(0)/FeCl$_3$ have been successfully developed.[16]

The CuAAC chemistry has been extended to biological systems and living organisms.[17] However, it remains somewhat limited in terms of selectivity, the bioincompability issue of residual Cu(II), solvent system, and operational temperature,[18]

because aqueous environment, physiological pH, and body temperature range are often required in biological processes. Therefore, biocompatibility and safety of the catalytic conditions are mandatory. Along the line, the potential uses of neutral, biocompatible, and water-soluble vanadyl catalysts as oxidants are evaluated in view of their low cost, commercial availability, and negligible environmental impact.[19] Vanadium salts have various III, IV, and V oxidation states; vanadyl catalysts of varying counteranions can be easily prepared and applied to aqueous media at ambient temperature.[20] As part of our ongoing research on the development of oxometallic species for catalytic transformations,[21] we sought to develop an efficient and environmentally friendly methodology for CuAAC chemistry without the use of Cu(II) species. We describe herein our in-depth and successful study toward this aim.

A series of vanadium salts (5−10 mol %) combined with Cu(0) powder (5−10 mol %) was screen for a test CuAAC reaction between phenylacetylene (1.2 equiv) and peracety-lated β-galactosyl azide **1** (Table S1) in CH$_3$CN (Table 1). The reaction performance was sensitive to the oxidation states and counteranions of the vanadium species. Among the vanadium salts examined, VCl$_3$ was completely inert (entries 1 and 2). Vanadyl(IV) species like VO(acac)$_2$ (acac = acetylacetonate), VO(OAc)$_2$, and VO(SO$_4$) were found to facilitate in situ Cu(I) formation for CuAAC, leading to the
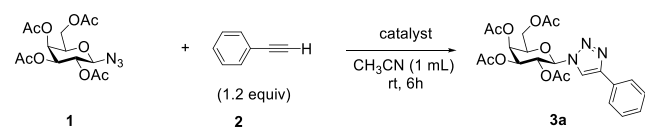
Table 1. Effects of Vanadyl Species and Relative Loadings on the In Situ Oxidation of Cu(0) for the CuAAC

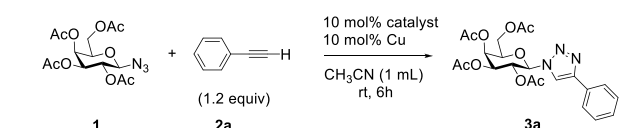| entry	Catalyst	mol %	Cu powder (mol %)	Yield[b] (%)
1	VCl$_3$	10	10	NR
2	VCl$_3$	10	none	NR
3	VO(acac)$_2$	10	10	90
4	VO(OAc)$_2$	10	10	98
5	VOSO$_4$	10	10	99
6	VOSO$_4$	10	5	17
7	VOSO$_4$	5	10	72
8	VO(OTf)$_2$	10	10	24
9	VOCl$_2$	10	10	7
10	NH$_4$VO$_3$	10	10	90
11	VO(OiPr)$_3$	10	10	95
12	VOCl$_3$	10	10	NR

[a]Carried out by using terminal alkyne (0.3 mmol, 1.2 equiv) and Cu-powder (0.025 mmol, 0.1 equiv) with 5−10 mol % catalyst in 1 mL of CH$_3$CN. [b]Isolated yield after chromatographic purification. NR indicates no reaction.

Table 2. Effects of Selected Alkaline Earth, Inorganic, and Oxometallic Catalysts on the In Situ Oxidation of Cu(0) for the Test CuAAC

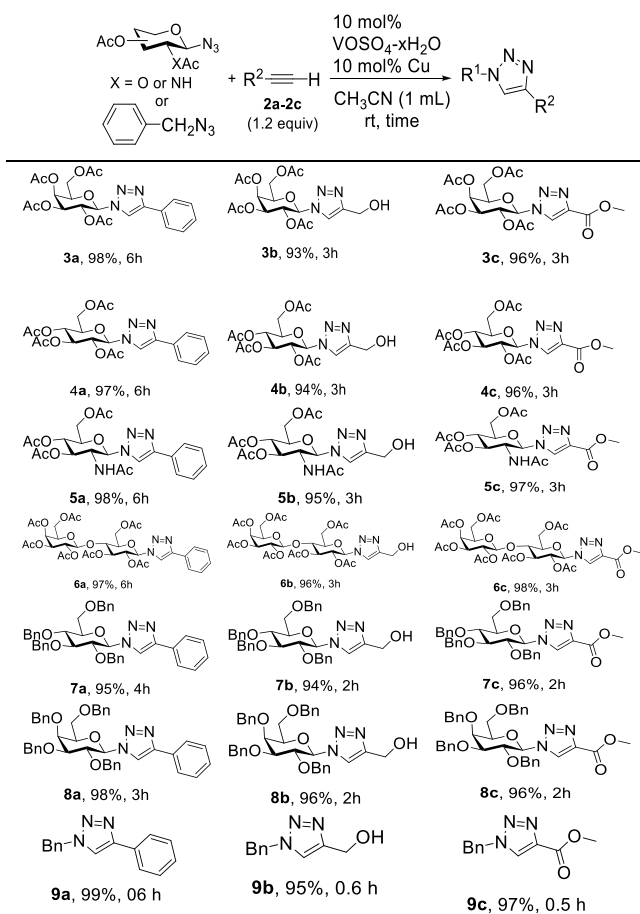| entry	metal oxide	conv.[a] (%)	yield[b] (%)
1	BaO	NR	
2	SeO$_2$	100	98
3	Ti(OEt)$_4$	NR	
4	CrO$_3$	NR	
5	MnO$_2$	100	89
6	Y$_2$O$_3$	23	21
7	MoO$_2$Cl$_2$	100	98
8	WO$_3$	100	97
9	Ag$_2$O	32	30
10	CdO	100	91
11	K$_2$[OsO$_2$(OH)$_4$]	80	77

[a]Carried out by using phenylethyne (0.3 mmol, 1.2 equiv), 10 mol % Cu-powder (0.025 mmol), and 10 mol % catalyst (0.025 mmol) in CH$_3$CN (1 mL). NR indicates no reaction. [b]Isolated yields after chromatographic purification.

corresponding β-galactosyl 1,2,3-triazole **3a** in 90−99% yields (entries 3−5 in Table 1). Notably, the chemical yields increase with decreasing basicity of the counteranions of the vanadyl species (acac$^-$ > OAc- > SO$_4^{2-}$). To further optimize the relative loading of Cu(0) powder vs VOSO$_4$, the amount of either Cu(0) or VOSO$_4$ was reduced to 5 mol %. Reducing the loading of Cu(0) to 5 mol % led to a dramatic drop in the product yield to only 17% (entry 7). It was speculated that the extra 5 mol % of VOSO$_4$ would further oxidize Cu(I) species to the corresponding Cu(II) species, thus suppressing catalytic reactivity in CuAAC. In contrast, the product yield was decreased from 99% to 72% (entry 6) upon reducing the loading of VOSO$_4$ to 5 mol %.

On the other hand, replacing VOSO$_4$ with VO(OTf)$_2$ or VOCl$_2$ led to the desired product in only 24% and 7% yields (entries 8 and 9), respectively. Gradual release of TfOH and HCl into the aqueous reaction media might be responsible for their poor performance. Next, oxidovanadium(V) species such as NH$_4$VO$_3$ and VO(OiPr)$_3$ were also satisfactory to combine with Cu(0) for in situ generation of Cu(I) species. The expected product was furnished in 90% and 95% yields (entries 10 and 11), respectively. In contrast, the use of VOCl$_3$ did not seem to facilitate any Cu(I) formation with Cu(0). Both coupling substrates were recovered (entry 12, in Table 1).

The neutral VOSO$_4$ was found to be the optimal catalyst for Huisgen 1,3-dipolar cycloadditions reaction in terms of its catalytic reactivity, cheapness, and availability (99%, entry 5).

With the unique and tunable oxidative capacity of oxidovanadium species in mind, we sought to gain insight into the redox compatibility of various oxometallic species and Cu(0) powder. Some representative alkaline earth (e.g., BaO), inorganic (e.g., SeO$_2$), and transition-metal (TM) oxides were tested with Cu(0) in CH$_3$CN for the same test CuAAC (Table 2). BaO and CrO$_3$ were found to be completely unproductive (entries 1 and 4). Further oxidation of Cu(I) to Cu(II) might be the major reason to shut down the cyclization in the case of CrO$_3$. Nonoxometallic Ti(OEt)$_4$ was also unreactive toward Cu(I) generation (entry 3). Interestingly, SeO$_2$ (6A) and

MnO$_2$ (7B) were the only inorganic and first-row TM oxides that can affect Cu(I) generation (98 and 89% yields, entries 2 and 5). Among several second- and third-row TM oxides examined, MoO$_2$Cl$_2$ (6B, entry 7), CdO (2B, entry 10), and WO$_3$ (6B, entry 8) led to satisfactory results. Complete conversion was achieved in 6 h in these three cases, leading to product **3a** in 98, 97, and 91% yields, respectively. On the other hand, Y$_2$O$_3$ (3B) and Ag$_2$O (1B) can also facilitate Cu(I) formation, albeit with a much slower rate. Only 23% and 32% conversions were observed in 6 h, and product **3a** was isolated in 21% and 30% yields (entries 6 and 9). Finally, potassium osmate was also tested. About 80% conversion was observed in 6 h, affording product **3a** in 77% isolated yield (entry 11). Metal oxides of high oxidation states can be reduced by oxidizing copper powder. However, the initially generated Cu(I) may readily be further oxidized to Cu(II), thus reducing the active concentration of Cu(I) species in the CuAAC.

Despite having several workable metal oxides in our hands, the optimal choice of biocompatible and water-soluble vanadyl sulfate was confirmed. The best catalyst recipe [10 mol %, 1/1 V(O)SO$_4$/Cu(0)] was then applied to the CuAAC between various O-protected β-glycosyl azides and terminal alkynes **2a-2c** bearing phenyl (R^2 = Ph), alcohol (R^2 = CH$_2$OH), and ester (R^2 = CO$_2$Me) groups (Table 3). In addition to **3a**, the other two peracetylated β-galactosyl 1,2,3-triazoles **3b** and **3c** were smoothly accessed in equal efficiency (93−98%) in 3−6 h. Encouraged by these results, we further examined peracetylated β-glucosyl, N-acetyl-glucosylamine, and lactosyl azides with **2a-2c** using the newly developed catalytic protocol. The corresponding β-glycosyl triazoles (**4a-c** to **6a-c**) were furnished in 3−6 h and in 94−98% yields. On the other hand, the analogous β-azido glycosides bearing benzyl protecting groups were equally amenable to the CuAAC with these three terminal alkynes **2a-2c**. The reactions were complete in 2−4 h, and the corresponding 1,2,3-triazole products **7a-c** and **8a-c** were obtained in 94−96% and 96−98% isolated yields, respectively. Benzyl azide was also tested with **2a-2c** under the optimal catalytic reaction conditions in view of the

Table 3. Representative Azide and Alkyne Substrates on the CuAAC with the Best V(O)SO₄/Cu(0) Recipe in CH₃CN at Ambient Temperature[a,b]

Reaction scheme:

AcO-(sugar)-N₃ with XAc (X = O or NH) or CH₂N₃ benzyl azide + R²≡H (2a–2c, 1.2 equiv) → with 10 mol% VOSO₄-xH₂O, 10 mol% Cu, CH₃CN (1 mL), rt, time → R¹-triazole-R²

Products (label, yield, time):

- **3a**, 98%, 6h
- **3b**, 93%, 3h
- **3c**, 96%, 3h
- **4a**, 97%, 6h
- **4b**, 94%, 3h
- **4c**, 96%, 3h
- **5a**, 98%, 6h
- **5b**, 95%, 3h
- **5c**, 97%, 3h
- **6a**, 97%, 6h
- **6b**, 96%, 3h
- **6c**, 98%, 3h
- **7a**, 95%, 4h
- **7b**, 94%, 2h
- **7c**, 96%, 2h
- **8a**, 98%, 3h
- **8b**, 96%, 2h
- **8c**, 96%, 2h
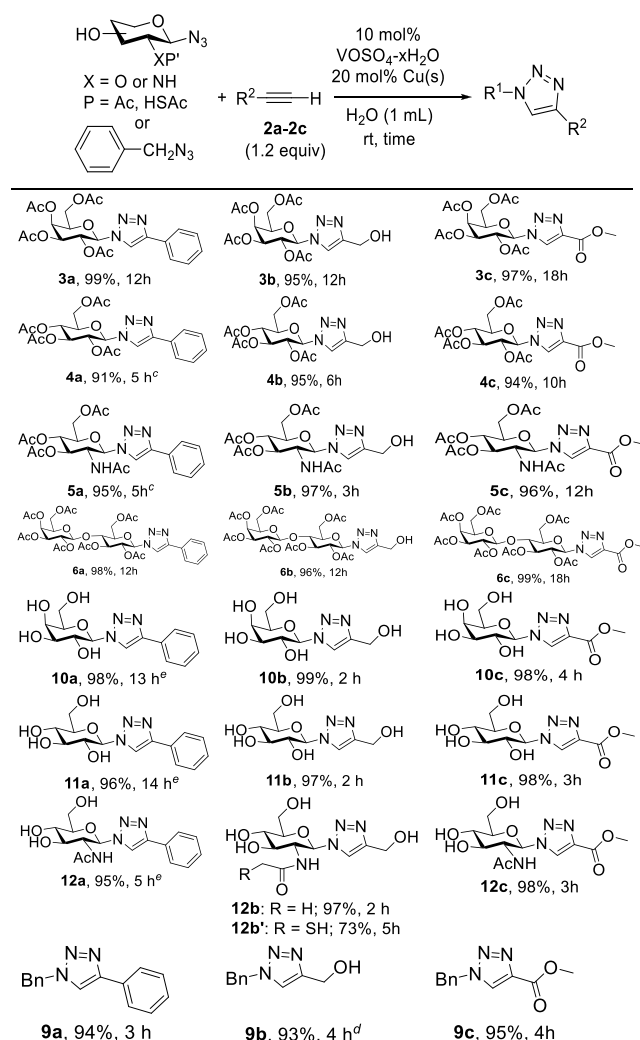- **9a**, 99%, 06h
- **9b**, 95%, 0.6h
- **9c**, 97%, 0.5h

[a]Carried out by using terminal alkyne (0.3 mmol, 1.2 equiv) and Cu powder (0.025 mmol, 0.1 equiv) with 10 mol % catalyst in 1 mL of CH₃CN. [b]Isolated yield after chromatographic purification.

Table 4. Synthesis of 1,2,3-Triazoles Via VOSO₄/Cu-Catalyzed 1,3-Dipolar Cycloaddition of Azides and Terminal Alkynes in Aqueous Media[a,b]

Reaction scheme:

HO-(sugar)-N₃ with XP' (X = O or NH, P = Ac, HSAc) or CH₂N₃ benzyl azide + R²≡H (2a–2c, 1.2 equiv) → with 10 mol% VOSO₄-xH₂O, 20 mol% Cu(s), H₂O (1 mL), rt, time → R¹-triazole-R²

Products (label, yield, time):

- **3a**, 99%, 12h
- **3b**, 95%, 12h
- **3c**, 97%, 18h
- **4a**, 91%, 5 h[c]
- **4b**, 95%, 6h
- **4c**, 94%, 10h
- **5a**, 95%, 5h[c]
- **5b**, 97%, 3h
- **5c**, 96%, 12h
- **6a**, 98%, 12h
- **6b**, 96%, 12h
- **6c**, 99%, 18h
- **10a**, 98%, 13 h[e]
- **10b**, 99%, 2 h
- **10c**, 98%, 4 h
- **11a**, 96%, 14 h[e]
- **11b**, 97%, 2 h
- **11c**, 98%, 3h
- **12a**, 95%, 5 h[e]
- **12b**: R = H; 97%, 2 h; **12b'**: R = SH; 73%, 5h
- **12c**, 98%, 3h
- **9a**, 94%, 3 h
- **9b**, 93%, 4 h[d]
- **9c**, 95%, 4 h

[a]Carried out by using 10 mol % VOSO₄ (0.025 mmol, 0.1 equiv) with 20 mol % Cu powder (0.05 mmol, 0.2 equiv) in H₂O for 80∼90 min then mixed glycosyl azides (0.25 mmol, 1.0 equiv) and terminal alkynes (0.3 mmol, 1.2 equiv). [b]Isolated yield after chromatographic purification. [c]10 mol % VOSO₄ with 10 mol % Cu powder in H₂O for 80∼90 min then mixed glycosyl azides and terminal alkynes. [d]50 °C. [e]10 mol % VOSO₄ with 15 mol % Cu powder in MeOH for 80∼90 min then mixed glycosyl azides and terminal alkynes.

potential materials applications of the products. These CuAAC reactions proceeded to completion in 0.5−0.6 h, leading to the corresponding triazoles **9a-9c** in 95−99% yields. Notably, the current catalytic protocol facilitates 1,3-dipolar cyclization under essentially neutral conditions. Conversely, the direct use of CuI in the CuAAC often requires the use of Hünig's base in CH₃CN to achieve good yields of the same glycosyl triazole conjugates.[4a,22]

After achieving these successful CuAAC reactions in CH₃CN, the syntheses of these 1,2,3-triazoles in nontoxic and environmentally friendly solvents were further explored (See Supporting Information, Table S2).[23] And the catalytic protocol was adjusted to 10 mol % V(O)SO₄ and 20 mol % Cu(0) powder in some cases. With the optimal conditions in aqueous media in hands, the same combinations of β-azido glycosides derived from peracetylated galactose, glucose, N-Ac 2-deoxy-glucosamine, and lactose with the three terminal alkynes **2a-2c** were investigated (**3−6**, in Table 4). In the reactions with phenylacetylene, a catalytic loading of 10 mol % V(O)SO₄ and 15 mol % Cu(0) powder was employed. In addition, methanol or ethanol was needed to help improve its solubility. Other than that, all the other regiospecific CuAAC reactions proceeded smoothly within 3−18 h (Figure 1) to

form the corresponding 1,4-disubstituted glycosyl 1,2,3-triazoles in excellent yields of 90−99% (from **3a-c** to **6a-c**).
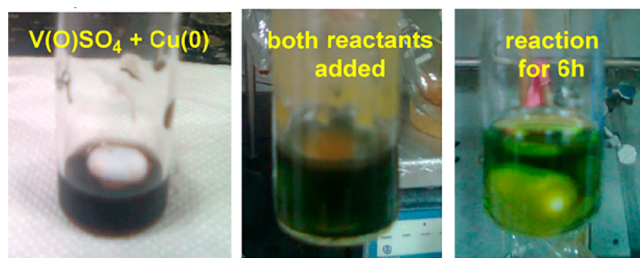
**Figure 1.** Monitored reaction progress.

With this preliminary success, the generality of the newly developed catalytic protocol in aqueous media was further investigated with unprotected water-soluble β-azido glycosides. Under the optimal reaction conditions, the resulting cyclization products were afforded in 2−4 h in 95%−98% yields with terminal acetylenes **2b** and **2c** (**10b,c-12b,c**, in Table 4). Conversely, the CuAAC of unprotected β-azido glycosides with phenylacetylene still required MeOH or EtOH as a cosolvent. Products **10a-12a** were obtained in 95−98% isolated yields within 5−14 h.[24] The successful 1,3-dipolar cyclizations between benzyl azide and the three alkynes **2a-2c** in warm water (50 °C) were also realized. 1,2,3-Triazoles **9a-c** were isolated in 93−95% yields within 3−4 h. In comparison, reactions in refluxing solvents were essential for Fokin and Sharpless's CuAAC reaction (CuSO$_4$, sodium ascorbate, t-BuOH, H$_2$O)[25] by using the same glycosyl triazole conjugates. Our protocol also offered a much promising improvement over our previous FeCl$_3$/Cu recipe (20 mol %/100 mol %)[16] in aqueous t-BuOH. As a demonstration to show the mildness of the catalytic protocol, N-2-mercaptoacetyl-glucosyl azide was also tested with alkyne **2b**. Copper species have been known to interact with cysteine thiols leading to oxidative stress.[26] Nevertheless, the current CuAAC protocol proceeded to completion at ambient temperature in 5 h, leading to the corresponding 1,2,3-traizole **12b'** in 73% isolated yield with the thiol unit remaining intact.

The overall redox process between vanadyl(IV/V) species and Cu(0) requires a delicate balance of the individual half-reactions for both oxidation and reduction with single electron transfer (SET). In particular, for redox reactions in water-containing media, the inclusion of H$^+$, OH$^-$, and/or H$_2$O into the half and balanced equation is often necessary to compensate for the oxidation and reduction state changes.

Smooth in situ oxidation of Cu(0) to both Cu(I) [Cu$_{(s)}$ → Cu$^+$ + e$^-$; E_{ox} = −0.52 eV] and Cu(II) [Cu$_{(s)}$ → Cu^{2+} + 2e$^-$; E_{ox} = −0.34 eV] species by the two vanadyl(V) species [NH$_4$VO$_3$ and V(O)(O-iPr)$_3$)] would be expected and may be rationalized in view of their favorable single-electron reduction process (VO$_2^+$ + 2H$^+$ + e$^-$ → VO^{2+} + H$_2$O; ΔE_{red} = +1.00 eV).[27,28] Notably, both of these two redox-coupled processes require an acidic source (Scheme 1a). Therefore, the use of NH$_4$VO$_3$ may be beneficial in practical applications.

On the other hand, the single-electron reduction process for vananyl(IV) species [VO^{2+} + 2H$^+$ + e$^-$ → V^{3+} + H$_2$O; ΔE_{red} = +0.34 eV] seems somewhat matched with direct or sequential oxidation of Cu(0) to Cu(II) [Cu$_{(s)}$ → Cu^{2+} + 2e$^-$; E_{ox} = −0.34 eV], Scheme 1b. However, the combination of Lewis
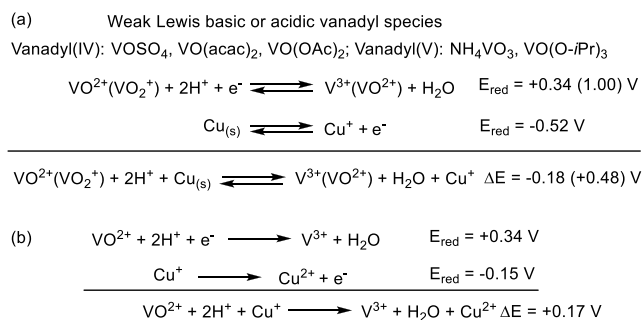
acidic V(O)(OTf)$_2$, V(O)Cl$_2$, or V(O)Cl$_3$ with Cu(0) led to very poor performance in the CuAAC (entries 8, 9, and 12 in Table 1). Therefore, the in situ formation of Cu(II) did not facilitate a subsequent generation of Cu(I) in the presence of Cu(0) or the formation of Cu acetylide en route to cyclization was suppressed in acidic media. The successful uses of V(O)(acac)$_2$, V(O)(OAc)$_2$, and V(O)(O-iPr)$_3$ that bear basic acac, acetate, and isopropoxide ligands for the CuAAC may support the presumption about an important step of Cu acetylide formation.

In conclusion, we have identified several vanadyl(IV/V) species, SeO$_2$, and transition-metal oxides as catalytic partners for efficient CuAAC with Cu(0) powder. Among them, water-soluble vanadyl(IV) sulfate was ultimately selected for in situ generation of Cu(I) species for the click reactions with β-azido glycosides in either homogeneous (CH$_3$CN) or heterogeneous (H$_2$O) solvent condition.[29] For the redox process in the click reaction, H$^+$ concentration plays an important role to stabilize Cu(I) species, and a pronounced ligand effect was observed. This methodology is attractive because it is applicable to aqueous solution at ambient temperature even for substrates bearing a thiol group. Further research and development on click reaction manipulations of biological active templates of carbohydrates are underway and will be reported in due course.

■ ASSOCIATED CONTENT

Data Availability Statement

The data underlying this study are available in the published article and its Supporting Information.

ⓈⒾ Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acsorginorgau.3c00059.

Representative experimental procedures for the preparation of vanadyl triflate and chloride, glycosyl azides, the click chemistry as well as analytical data and scanned ^{1}H and ^{13}C NMR spectra for 1,2,3-triazoles **3a-c**, **4a-c**, **5a-c**, **6a-c**, **7a-c**, **8a-c**, **9a-c**, **10a-c**, **11a-c**, **12a-c**, and **12b'** (PDF)

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Author Contributions

CRediT: **Wen-Chieh Yang** data curation, methodology, writing-original draft.

Notes

The authors declare no competing financial interest.

Scheme 1. Proposed Half-Reactions for Oxidation and Reduction in the Presence of Different Vanadyl(IV/V) Species and Copper Powder

(a)   Weak Lewis basic or acidic vanadyl species

Vanadyl(IV): VOSO$_4$, VO(acac)$_2$, VO(OAc)$_2$; Vanadyl(V): NH$_4$VO$_3$, VO(O-iPr)$_3$

VO^{2+}(VO$_2^+$) + 2H$^+$ + e$^-$ ⇌ V^{3+}(VO^{2+}) + H$_2$O E_{red} = +0.34 (1.00) V

Cu$_{(s)}$ ⇌ Cu$^+$ + e$^-$ E_{red} = -0.52 V

VO^{2+}(VO$_2^+$) + 2H$^+$ + Cu$_{(s)}$ ⇌ V^{3+}(VO^{2+}) + H$_2$O + Cu$^+$ ΔE = -0.18 (+0.48) V

(b)   VO^{2+} + 2H$^+$ + e$^-$ → V^{3+} + H$_2$O E_{red} = +0.34 V

Cu$^+$ → Cu^{2+} + e$^-$ E_{red} = -0.15 V

VO^{2+} + 2H$^+$ + Cu$^+$ → V^{3+} + H$_2$O + Cu^{2+} ΔE = +0.17 V

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