Received: 13 October 2020 | Revised: 18 January 2021 | Accepted: 20 January 2021

DOI: 10.1002/jccs.202000452

ARTICLE

JOURNAL OF THE CHINESE CHEMICAL SOCIETY

Synthesis of biologically important 4-Phenyl-*C*-glycosyl-1,2,3-triazole derivatives by Cu(I)-catalyzed azide–alkyne cycloaddition

Kalyana K. Ponnapalli[1] | **Sachin K. Kawade**[1] | **Avijit K. Adak**[1] | **Hsin-Ru Wu**[2] | **Chun-Cheng Lin**[1,3]

[1]Department of Chemistry, National Tsing Hua University, Hsinchu, Taiwan

[2]Instrumentation Center, National Tsing Hua University, Hsinchu, Taiwan

[3]Department of Medicinal and Applied Chemistry, Kaohsiung Medical University, Kaohsiung, Taiwan

Correspondence
Chun-Cheng Lin, Department of Medicinal and Applied Chemistry, Kaohsiung Medical University, Kaohsiung 80708, Taiwan.
Email: cclin66@mx.nthu.edu.tw

Funding information
Ministry of Education; Academia Sinica; Ministry of Science and Technology; National Tsing Hua University

Abstract

A new series of 4-phenyl-*C*-glycosyl-1,2,3-triazoles were synthesized using Cu(I)- catalyzed azide–alkyne cycloaddition. The key step in the synthesis involved the coupling of unprotected glycosyl azides with substituted *C*-glycosylated phenyl acetylenes. Using *o*-phenylenediamine as a ligand, we could significantly reduce the reaction time, improve the product yield, and simplify the purification process. Broad substrate scope in terms of sugars was achieved.

KEYWORDS

1,2,3-triazoles, *C*-glycosides, click chemistry, CuAAC, disaccharide

1 | INTRODUCTION

Cu(I)-catalyzed Huisgen 1,3-dipolar cycloaddition reactions between an azide and terminal alkyne are click chemistry reactions that produce triazoles.[1] Click chemistry has emerged as one of the most powerful tools for drug discovery, chemical biology, and proteomic applications, and it is an important reaction for the development of carbon–heteroatom–carbon bonds.[2] Among these molecular structures, sugar-based triazoles play a vital role in enzyme inhibition.[3] The heterocyclic triazoles act as a bridge between the carbohydrate and other biomolecules, generating glycoconjugates such as glycoproteins, neoglycoconjugates, oligomers, glycol lipids, glycopeptides, and oligonucleotides.[4]

Various glycosidic bonds that are formed or broken during physiological or pathological processes can be synchronized by developing new glycosidase or glycosyl transferase inhibitors; both types of enzymes act as catalysts in these processes.[5] Because of the poor basicity of triazole, it can remain unprotonated at physiological pH. Moreover, the sp^2-hybridized nitrogen atom of triazole acts as positively charged center to mimic the transition state in glycosidase-catalyzed reactions. Recent studies have developed several 1,2,3-triazole analogs as potential glycosidase inhibitors; they have shown promise as treatments for viral infections, cancer, and diabetes.[6] Notably, 1-β-glucoyl-4-phenyl-1,2,3-triazole (**1**) and 1-β-galactosylosyl-4-phenyl-1,2,3-triazole (**2**) (Figure 1) were synthesized by utilizing the copper(I)-catalyzed azide–alkyne click chemistry between glycosyl azide and phenylacetylene.[6] The glucosyl triazole analog **1** had a half maximal inhibitory concentration (IC_{50}) of 0.24 mM against bovine liver galactosidase, and galactosyl triazole analog **2** afforded modest inhibition of *Escherichia coli* galactosidase.[7]

Furthermore, Ramtohul et al.[8] developed the mannose-based triazole analog **3**, as shown in Figure 2. The competitive binding assay of **3** with FimH protein

showed that this type of compound may be effective for the treatment of bacterial infections caused by adherent invasive *E. coli*,[8] which is known to be prevalent in patients with ulcerative colitis and Crohn's disease.[9] However, major drawbacks are the low total synthetic yield of triazole **3** and the lengthy synthetic steps involving the palladium-catalyzed coupling of glucal **4** with aryl boronic acid **5**, followed by the *syn*-hydroxylation of **6** using osmium tetroxide to generate the mannose derivative **7**. The phenolic group of **7** was further functionalized to give alkyne **8,** and the subsequent Cu(1)-catalyzed alkyne–azide cycloaddition (CuAAC) with azido mannose generated bis-mannose triazole **3**. Moreover, the synthetic methodology was restricted to the synthesis of mannose derivatives only. Considering the potential for biological applications associated with triazole-linked disaccharide analogs, developing novel phenyl-*C*-glycosyl triazoles with a high degree of structural diversity is advantageous. In this study, we report an efficient synthetic strategy for generating triazole-linked disaccharides **9a**–**p** with a broad substrate scope (Figure 2). In our synthetic strategy, we used a sequence of reactions involving Lewis acid catalyzed *C*-glycosylation of various trichloroimidates (**10**)

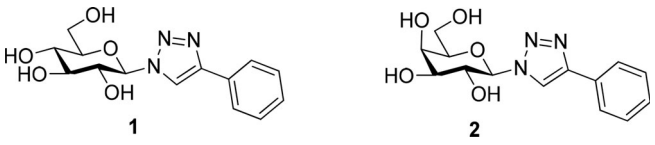


FIGURE 1 Structures of glycosidase inhibitors **1** and **2**

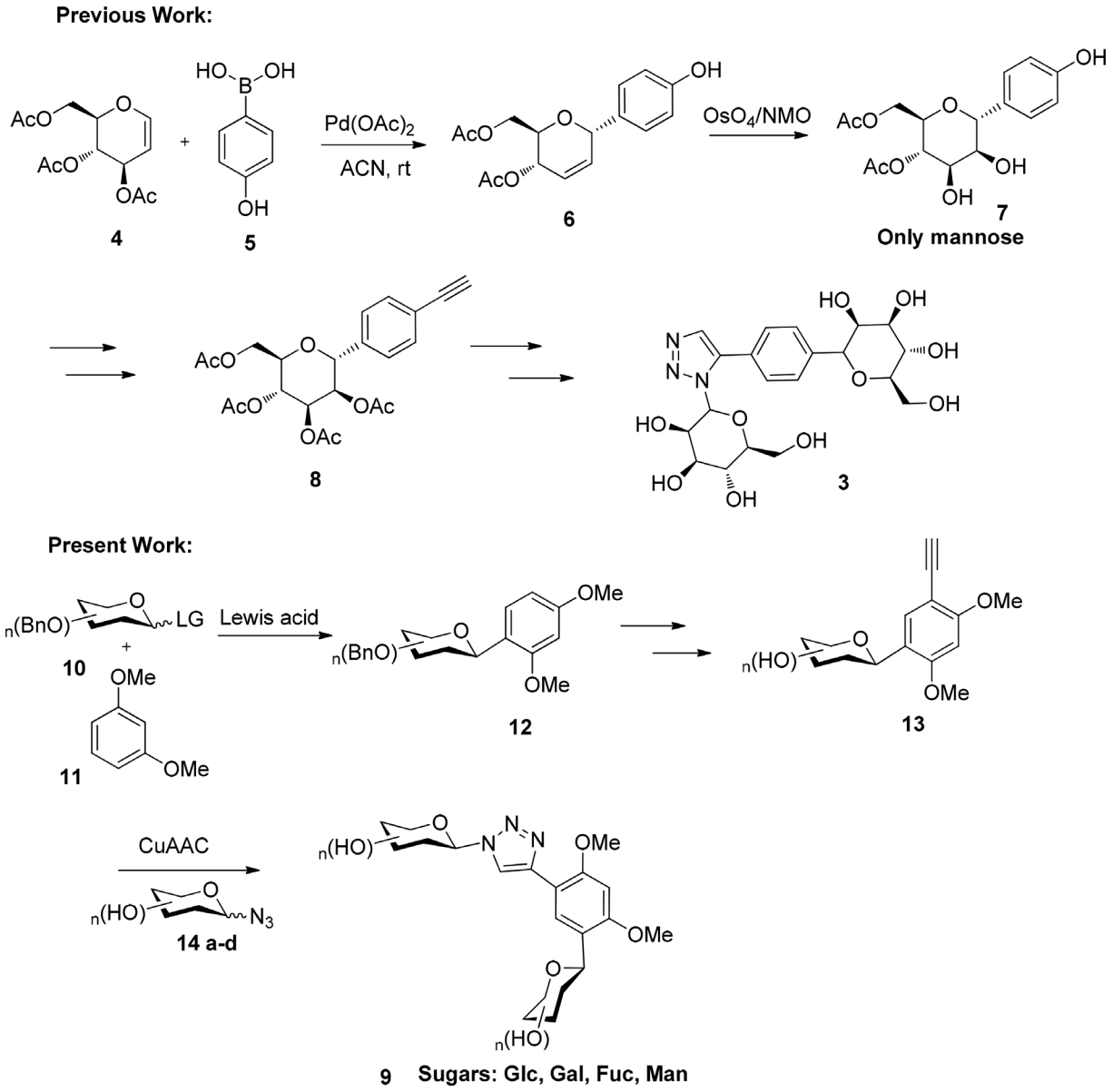
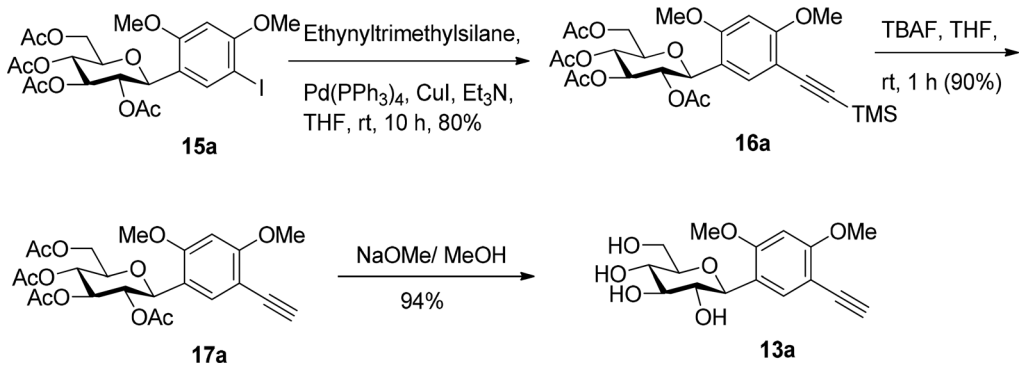


FIGURE 2 Comparison of synthetic approaches for triazole-based glycosides



SCHEME 1 Synthesis of alkyne derivatives

with 1,3-dimethoxy benzene, functional group manipulation, iodination, Sonogashira coupling with trimethysilyl acetylene (TMS–acetylene), and silyl cleavage. From these reactions, we obtained alkyne analogs (**13**) with excellent yields. Cu(I)-catalyzed azide–alkyne cycloaddition between azido sugar (**14a–d**) and *C*-glycosylated phenyl acetylene analogs (**13**) resulted in triazoles (**9**) with a high degree of structural diversity.

2 | RESULTS AND DISCUSSION

The general synthetic route for the alkynylated *C*-aryl glycoside **13a** is shown in Scheme 1. The compound **13a** was formed from the C-glucosylated aryl iodide **15a** using our previously developed method.[10] Pd(0) catalyzed the Sonogashira coupling of **15a** with trimethylsilyl acetylene, resulting in the TMS-protected alkyne derivative **16a** in 80% yield. Tetrabutylammonium fluoride (TBAF)-mediated silyl cleavage yielded the alkyne **17a** (90% yield), which was then deacetylated under Zemplen conditions to produce a quantitative yield of **13a**.

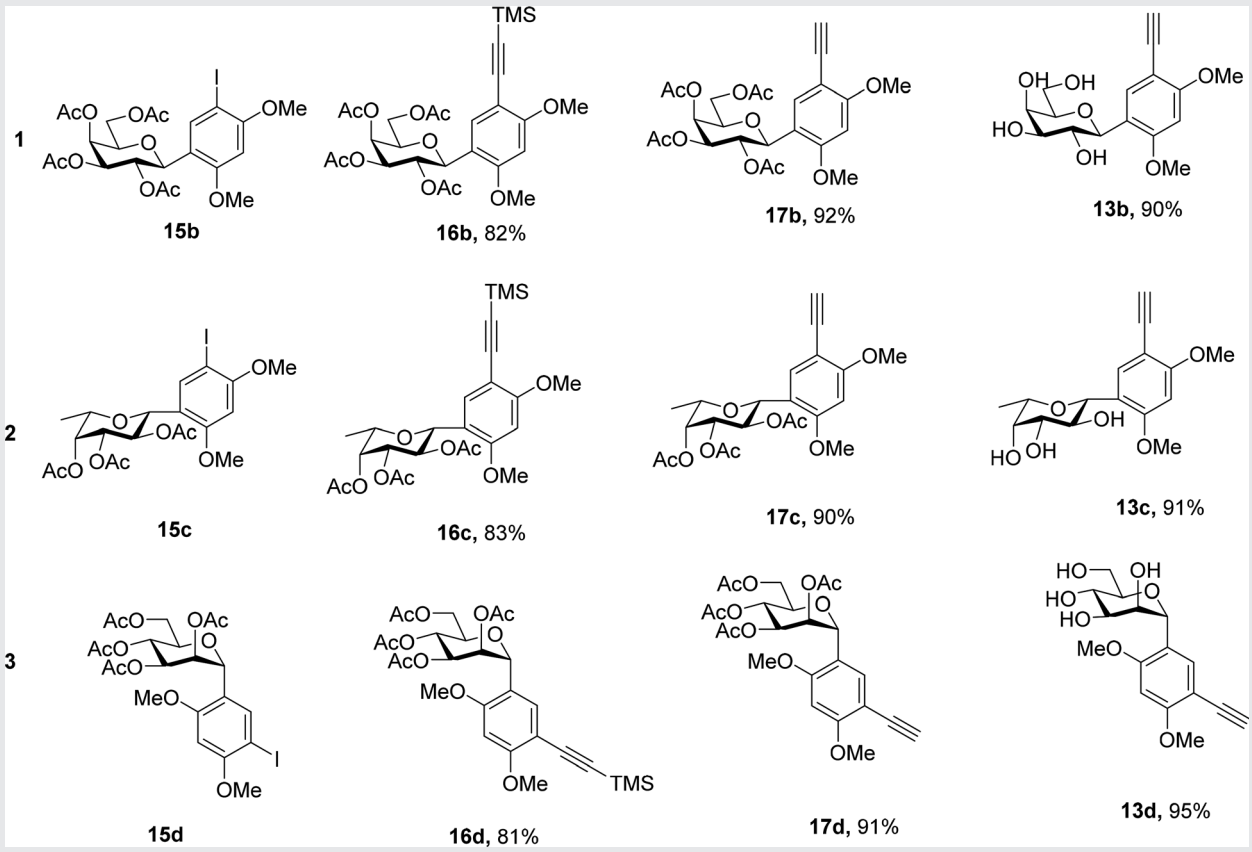
Using the same synthetic strategy, we synthesized the alkyne derivatives **13b–d** (Table 1) with the sugars galactose, fucose, and mannose. The yields for the Sonogashira coupling (used to produce **16b–d**) ranged from 80 to 83%. The silyl group cleavage using TBAF resulted in the alkyne derivatives **17b–d** (yields of 90–92%), which were further deacetylated to form **13b–d** in 90–95% yields. Thus, using this straightforward method, we synthesized alkyne derivatives **13a–d** with excellent total yields. The summary of the synthetic yield for each step is listed in Table 1.

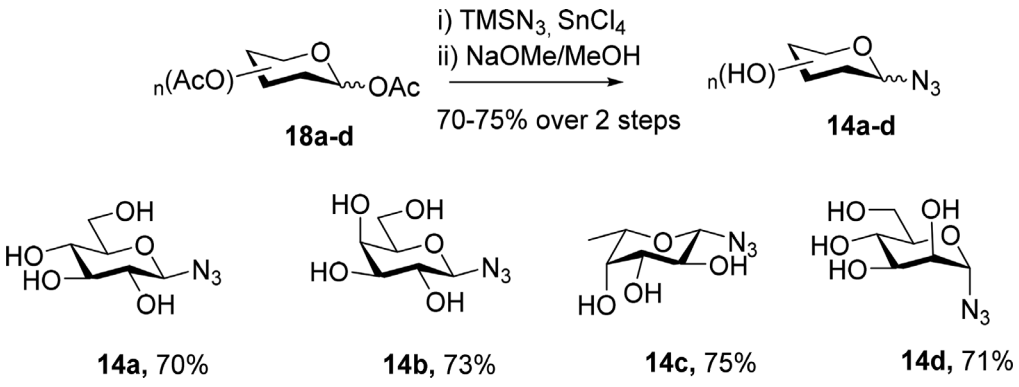
We synthesized deprotected glycosyl azides (**14a–d**) for coupling with alkynylated saccharides by CuAAC using a previously reported procedure,[11] as shown in Scheme 2. First, peracetylated sugar derivatives such as glucose, galactose, fucose, and mannose (**18a–d**) were each reacted with TMS–N_3 in the presence of $SnCl_4$ to produce corresponding 1,2-*trans* anomeric azido derivatives via neighboring-group participation. The resulting products were then deacetylated under Zemplen conditions to produce fully deprotected anomeric azides (**14a–d**) with good yields (70–75% over two steps).

Using both the azide and alkyne coupling partners, we performed CuAAC between **13a** and **14a** using $CuSO_4$ (10 mol%) and ascorbic acid (20 mol%) in a mixture of *t*-BuOH:H_2O (1:1), which resulted in the triazole analog **9a** at 80% yield, (Table 2). However, the reaction was relatively slow and required 8–10 hr to reach completion. Therefore, we further optimized the reaction conditions to reduce the reaction time and to improve the yield. Cu(I)-chelating ligands were used to improve the efficiency of the click reaction. Among the many Cu(I) chelating ligands, tris[(1-benzyl-1*H*-1,2,3-triazol-4-yl)methyl]amine (TBTA) has been widely used in click chemistry.[12] However, TBTA is limited to the click reactions in organic solvents. To efficiently perform CuAAC in water-soluble conditions, tris(3-hydroxypropyltriazolylmethyl)amine was developed as a biologically compatible ligand.[13] Similarly, tertiary amines such as triethylamine are known to assist in click reactions by serving as bases or ligands. Diamine-based ligands such as *N*,*N*,*N*′,*N*′-tetramethyl ethylenediamine and its analogs can also improve the reaction efficiency of click reactions.[14]

Moreover, Baron et al. showed that *o*-phenylenediamine acts as a promising Cu(I)-stabilizing ligand in click reactions carried out in water. *o*-Phenylenediamine accelerates the reaction possibly by forming a Cu(I) complex.[15] A kinetic study using nuclear magnetic resonance (NMR) spectrometry confirmed this rate acceleration.[15] In a system that uses ascorbic acid and $CuSO_4$ to generate Cu(I), the initial byproduct is dehydroascorbate. The oxidation of dehydroascorbic acid irreversibly leads to more than 50 species containing five carbon atoms or fewer.[16] By contrast, when *o*-phenylenediamine was used as a ligand, it trapped the dehydroascorbate formed by the first step by forming fluorescent quinoxaline derivatives.[17] Interestingly, these byproducts can be easily adsorbed onto activated charcoal and can be removed completely using simple filtration

TABLE 1 Synthesis of alkyne derivatives **13b–d**

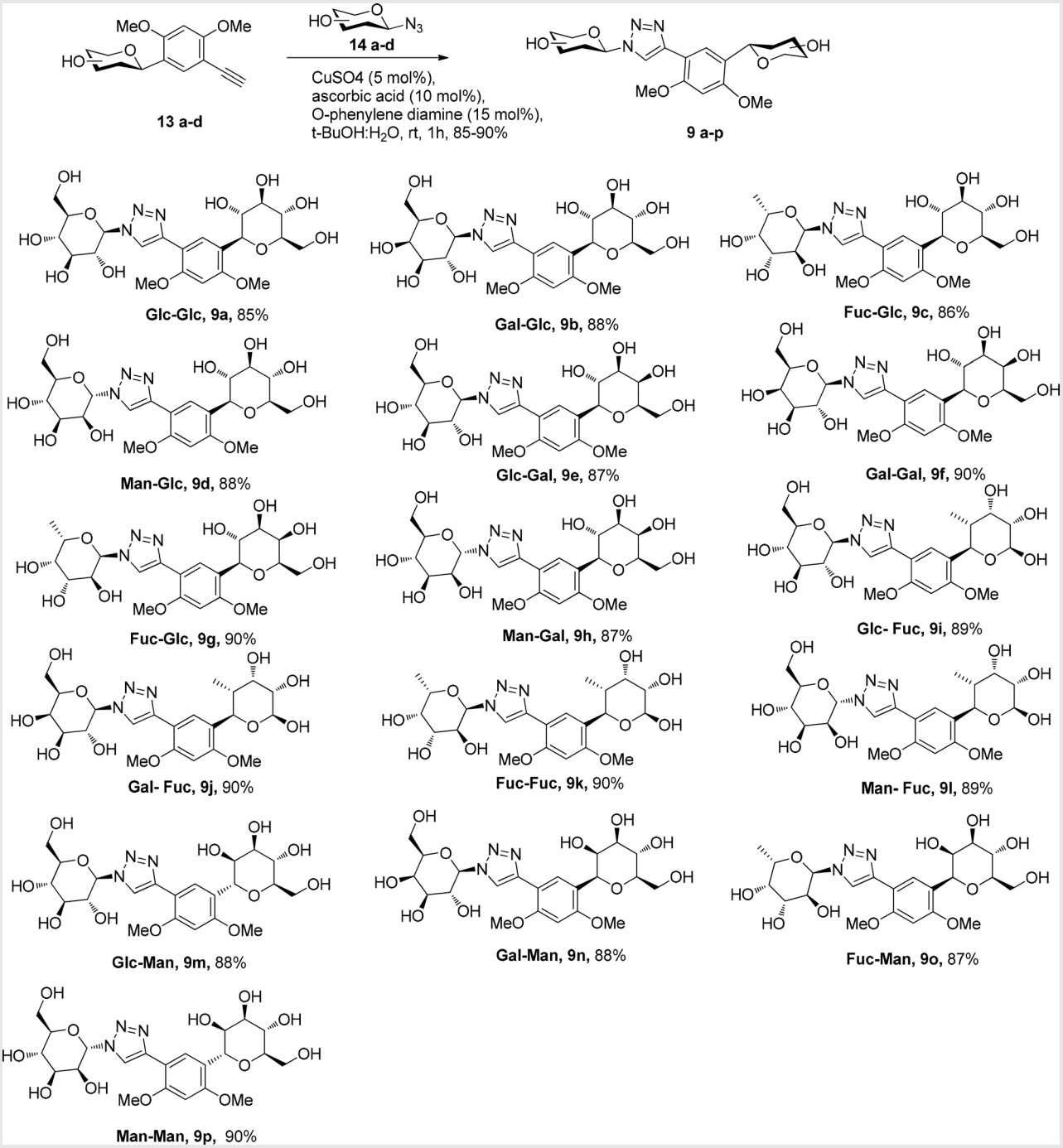




SCHEME 2 Synthesis of azide derivatives **14a–d**

with celite; thus, clean triazole analogs can be formed without the need for chromatographic purification. It was also reported that the residual copper percentage after this workup procedure was less than 0.03%.[15] Thus, *o*-phenylenediamine was used as a ligand to improve the reaction efficiency using alkyne **13a** and azide **14a** in the model reaction to afford **9a**. As expected, CuAAC in the presence of a ligand was completed in less than one hour, with a triazole **9a** yield of 85%. The desired triazole product could be generated using 5 mol% $CuSO_4$, 10 mol% ascorbic acid, and 15 mol% *o*-phenylenediamine. Using our optimized conditions, the CuAAC of **13a–d** with anomeric azide **14a–d** could synthesize a library of 16 triazoles (**9a–p**) with excellent yields (85–90%). The structures of **9a–p** are shown in Table 2. Each analog possesses two glycosidic-bond surrogates, namely *N*- and *C*-glycosides. Furthermore, each triazole analog contained two free common sugar units such as glucose, galactose, fucose, and mannose. Hence, analogs from this study provide great structural diversity and can be further used for studies of biological activity.

TABLE 2 Synthesis of triazole derivatives using alkynes **13** and **14**



3 | CONCLUSION

We synthesized a library of 4-phenyl-*C*-glycosyl-1,-2,3-triazoles using Cu(I)-catalyzed click chemistry. Using *o*-phenylenediamine as a ligand, we could remarkably shorten the reaction time, improve the yield, and simplify the purification process. The resulting triazole-based disaccharides were structurally diverse, with each derivative possessing two free sugar units (glucose, galactose, fucose, or mannose). The resulting compounds are promising for future studies of biological activity.

4 | EXPERIMENTAL SECTION

General experimental procedure for click chemistry. Sodium ascorbate (5 mol%, 250 mM solution in H_2O), $CuSO_4$ (10 mol%, 125 mM solution in H_2O), and *o*-phenylenediamine (15 mol%, 375 mM solution in H_2O)

were added to a solution of azide (**14a–d**) (1.0 eq) and alkyne (**13a–d**) (1.05 eq) in a 1:1 mixture of H_2O:*t*-BuOH (2 ml). The solution was stirred at room temperature for 1 hr. The progress of the reaction was monitored by thin-layer chromatography (TLC) analysis. After the reaction was completed, activated charcoal (20 mg) was added to the reaction mixture, which was then stirred at room temperature for 10 hr. The resulting solution was passed through a pad of celite and then washed with excess methanol. The organic layer was concentrated under reduced pressure. The crude compounds were purified in a reverse-phase silica gel (RP-C18) column eluted with 0–20% acetonitrile in H_2O to obtain triazoles (**9a–p**) with yields of 85–95%.

ACKNOWLEDGMENTS

This work was financially supported by the National Tsing Hua University, the Ministry of Science and Technology (107-2113-M-007-024-MY3), Academia Sinica (AS-TP-108-M06), the Ministry of Education of Taiwan, and the Frontier Research Center on Fundamental and Applied Sciences of Matters.

ORCID

Sachin K. Kawade https://orcid.org/0000-0002-3996-7118
Avijit K. Adak https://orcid.org/0000-0002-5907-3744
Chun-Cheng Lin https://orcid.org/0000-0002-2323-0920

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How to cite this article: Ponnapalli KK, Kawade SK, Adak AK, Wu H-R, Lin C-C. Synthesis of biologically important 4-Phenyl-*C*-glycosyl-1,2,3-triazole derivatives by Cu(I)-catalyzed azide–alkyne cycloaddition. *J Chin Chem Soc*. 2021;1–6. https://doi.org/10.1002/jccs.202000452