Glycosidation

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Stable Alkynyl Glycosyl Carbonates: Catalytic Anomeric Activation and Synthesis of a Tridecasaccharide Reminiscent of *Mycobacterium tuberculosis* Cell Wall Lipoarabinomannan

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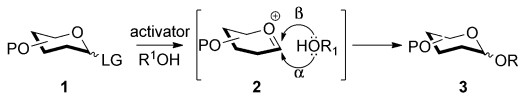
Abstract: *Oligosaccharide synthesis is still a challenging task despite the advent of modern glycosidation techniques. Herein, alkynyl glycosyl carbonates are shown to be stable glycosyl donors that can be activated catalytically by gold and silver salts at 25 °C in just 15 min to produce glycosides in excellent yields. Benzoyl glycosyl carbonate donors are solid compounds with a long shelf life. This operationally simple protocol was found to be highly efficient for the synthesis of nucleosides, amino acids, and phenolic and azido glycoconjugates. Repeated use of the carbonate glycosidation method enabled the highly convergent synthesis of tridecaarabinomannan in a rapid manner.*

The chemical synthesis of oligosaccharides has emerged as a viable approach offering advantages including homogeneity, scalability, and the ability to synthesize unnatural glycoconjugates, which can have great ramifications in modern medicine and materials science.[1] Two saccharides are chemically coupled by a glycosidation reaction that involves a glycosyl donor **1**, a fully protected saccharide with a leaving group at the anomeric position, and a glycosyl acceptor (R^1OH), usually containing a single hydroxy group.[2] Promoters activate the leaving group to give a highly reactive oxocarbenium ion intermediate **2** that will be susceptible to the attack of the acceptor, thus resulting in a glycoside **3** (Scheme 1).[2]

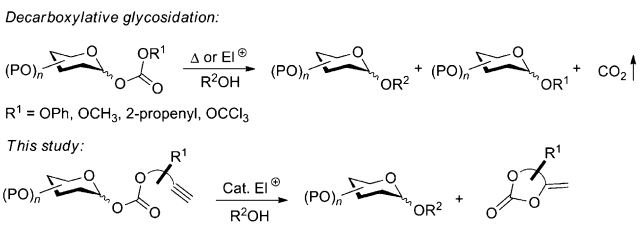


Scheme 1. General glycosidation reaction. LG = leaving group, P = protecting group.

Glycosidation methods that are reliable and scalable and involve stable glycosyl donors are still scarce even after several decades since the first glycoside synthesis. Well-studied glycosyl donors[3] include glycosyl halides,[3a–d] glycosyl esters,[3e] glycosyl trichloroacetamidates,[3f] glycals,[3g] selenoglycosides,[3h] thioglycosides,[3i–k] *n*-pentenyl glycosides,[3l] alkynyl glycosides,[3m] alkyl 1,2-*O*-orthoesters,[3n–p] glycosyl phosphates,[3q] and hemiacetals.[3r] The identification of alkyl glycosyl and thioglycosyl donors has been a transformative advance in the glycosciences, as the alkyl and thio groups serve as stable appendages at the anomeric position, and the compounds can be triggered to become glycosyl donors with an appropriate promoter.

Our own research efforts identified propargyl glycosides as glycosyl donors in the presence of a catalytic amount of $AuCl_3$.[3m] Subsequently, Yu and co-workers reported *o*-alkynyl esters[3s] and Zhu and co-workers reported *S*-but-3-ynyl glycosides[3t] as glycosyl donors with gold catalysts. Gold-catalyzed transglycosidation[3m] has proven to be a robust reaction for the synthesis of glycosides, but has limitations including I) the suitability of only an ether functional group at the C2 position,[3m] II) the lack of stereocontrol through anchimeric assistance,[4a] and III) the hydrolysis of the interglycosidic bond in some instances.[4b,c] Propargyl 1,2-orthoesters were utilized to enable 1,2-*trans* diastereoselectivity.[3p] In the search for a versatile and stable glycosyl donor that can be activated in a catalytic fashion, our attention was drawn to the most popular trichloroacetamidates. However, some glycosyl trichloroacetamidates have a short life time. The hemiacetal precursor to imidates is readily accessible and highly stable; hence, we hypothesized that the conversion of the hemiacetal into a stable, versatile, and reactive glycosyl donor could be highly rewarding.

Methods for the decarboxylative glycosidation of carbonate donors is known; however, they have not been widely utilized owing to forcing reaction conditions and poor yields.[5] Yu and co-workers reported gold-catalysis conditions that can activate *o*-alkynyl esters but not 2-butynyl carbonates even at an elevated temperature (Scheme 2).[6a] The failure to activate 2-butynyl carbonates can be attributed to the possible higher degree of freedom of the leaving group, thereby diminishing the chances of gold–alkyne coordination. In our



Scheme 2. Hypothesis for the use of alkynyl carbonate glycosyl donors.

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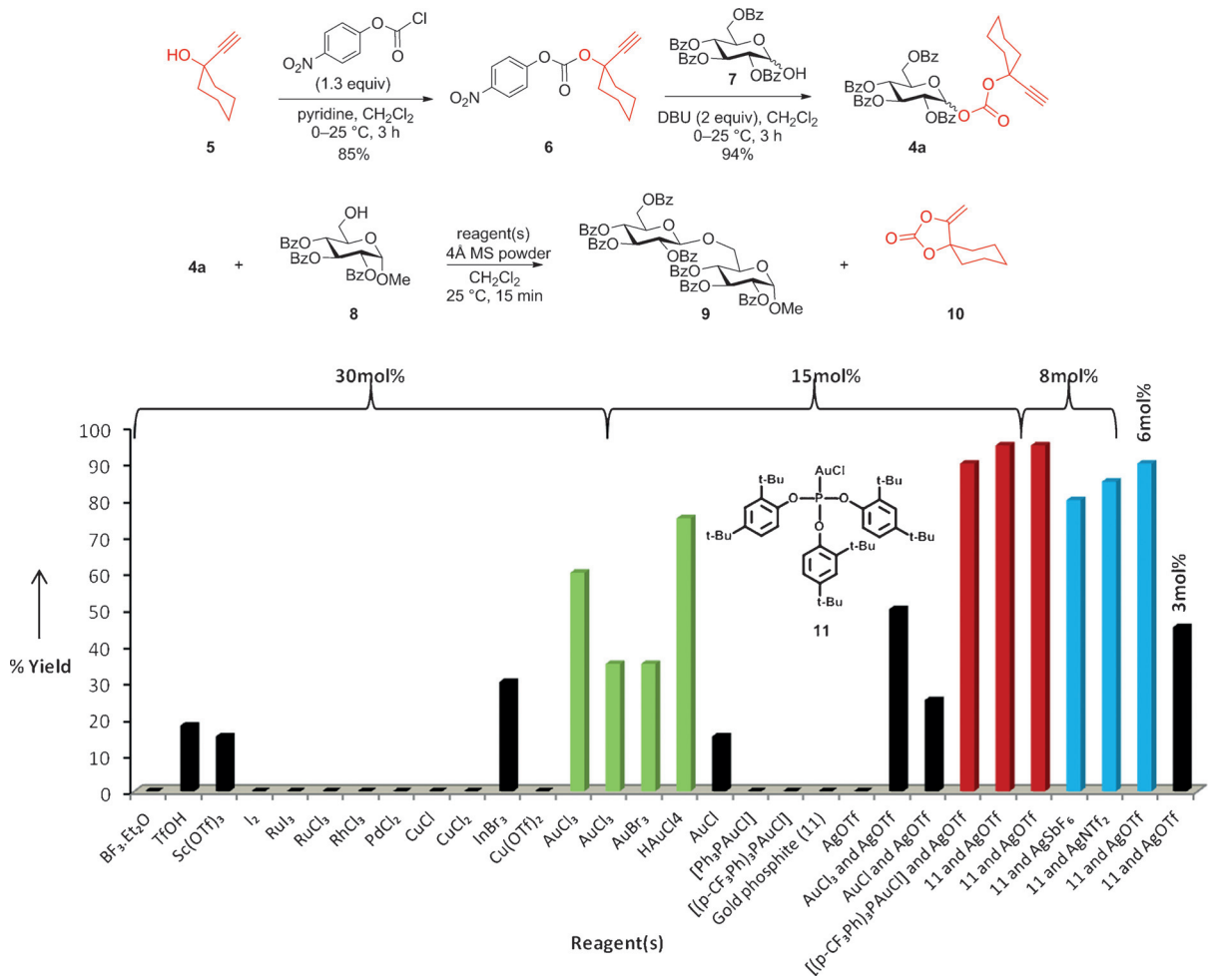
laboratory, acceleration of glycosidation was noticed upon shifting from propargyl to ethynylcyclohexyl glycosides owing to the well-understood Thorpe–Ingold effect.[4a] Furthermore, cyclohexyl alkynyl carbonates were demonstrated to cyclize into spirocyclic alkylidenes under gold-catalysis by Buzas and Gagosz.[6b]

Therefore, the conformationally rigid glucosyl ethynylcyclohexyl carbonate **4a** containing a strategically positioned alkyne was designed to bring the Thorpe–Ingold effect into the alkynyl carbonate donor. This key alkynyl glucosyl carbonate **4a** was synthesized in two simple steps. Commercially available 1-ethynylcyclohexanol (**5**) was first converted into the carbonate **6**, which was further treated with readily accessible per-*O*-benzoyl glucopyranose (**7**)[7] to give **4a**. We began our glycosidation studies by treating carbonate **4a** and glucosyl acceptor **8** with several Lewis and Brønsted acids known to be either carbonate activators or alkynophilic (Scheme 3).

Glycosyl donor **4a** did not react at all with 30 mol% of the known alkyne activators, such as $RuCl_3$, I_2, $RhCl_3$, $PdCl_2$, CuCl, $CuCl_2$, $Cu(OTf)_2$, or $BF_3{\cdot}Et_2O$, and reacted poorly with $Sc(OTf)_3$, $InBr_3$, and TfOH at 25–60 °C. However, alkynophilic $AuCl_3$ (30 mol%) produced the disaccharide **9** in 60% yield along with formation of the by-product **10**.[8]

The yield dropped when the amount of AuX_3 (X = Cl, Br) was reduced to 15 mol%; however, the introduction of $HAuCl_4$ (15 mol%) raised the yield to 72%. Discouraging results were observed with a range of Au complexes, such as 15 mol% of AuCl, $[Ph_3PAuCl]$, and $[(p\text{-}CF_3C_6H_4)_3AuCl]$. A highly alkynophilic gold phosphite complex[9] and AgOTf also failed to yield the desired disaccharide. However, the addition of 15 mol% each of the gold phosphite **11** and AgOTf dramatically improved the performance of the reaction to near-quantitative yields within 15 min. Individually, AgOTf and the gold phosphite complex were not reactive at all; however, a combination of the two was observed to be an effective catalytic system. Thus, the glycosidation by complex **11** and AgOTf falls under the recently propounded category of a type II Au–Ag bimetallic reaction.[9a]

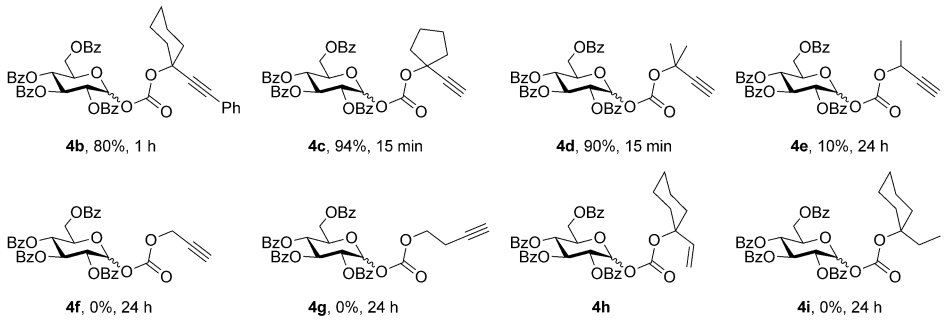
Complex **11** in combination with a silver salt, such as $AgSbF_6$ and $AgNTf_2$, gave the disaccharide **9** in 80–90% yield. A reduction in the amount of the gold phosphite complex **11** and AgOTf to 8 mol% each did not compromise the yield, but further reduction was not encouraging. There-



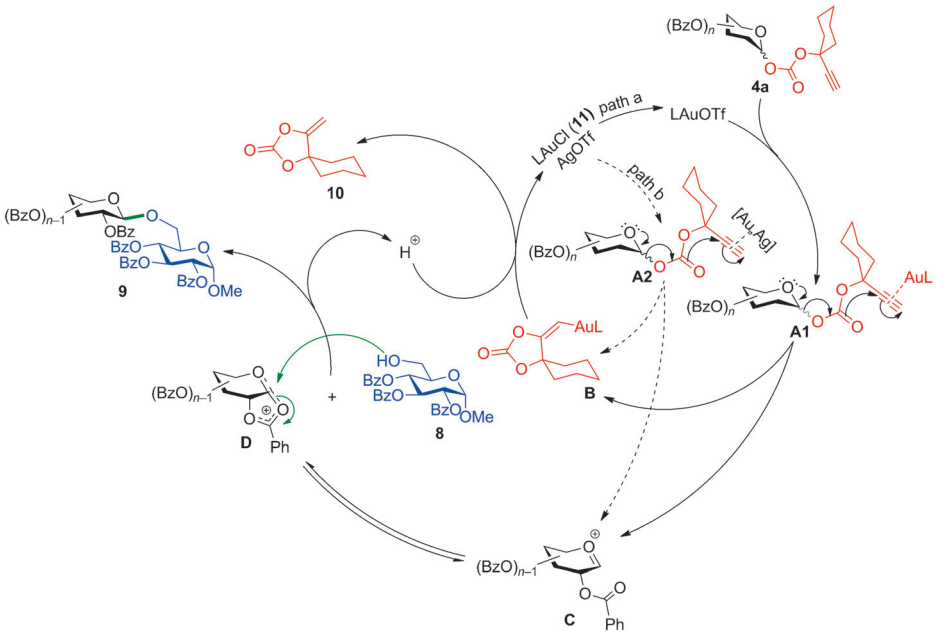
Scheme 3. Screening of reagents for the coupling of alkynyl carbonate glycoside **4a** with glucosyl acceptor **8**. Bz = benzoyl, DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene, MS = molecular sieves, Tf = trifluoromethanesulfonyl.

fore, future reactions were carried out with 8 mol% each of catalyst **11** and AgOTf in CH_2Cl_2 at 25 °C for 15 min as the optimal conditions. The 1,2-*trans* selectivity, the reaction time, and the yield of the glycosidation was found to be independent of the anomeric configuration of the initial glycosyl donor **4a**, thus signifying the intermediacy of an oxocarbenium ion.[8]

In contrast to the propargyl glycosides, substituted alkynes were tolerated in the carbonate glycosyl donors, as in **4b** (Scheme 4). The significance of the Thorpe–Ingold effect is apparent, since the performance of the reaction did not drastically change with other dialkyl substituents (glycosyl donors **4c**,**d**). However, the reaction yield dropped to 10% when there was only one CH_3 group (in **4e**), and no reaction was observed with the propargyl carbonate donor **4f** or homopropargyl carbonate donor **4g**. The vinyl carbonate **4h** could not be prepared owing to its unstable nature.[10] An alkyne is required for this glycosidation, as further evident from the total lack of reactivity of carbonate **4i** under the Au–Ag catalytic conditions.



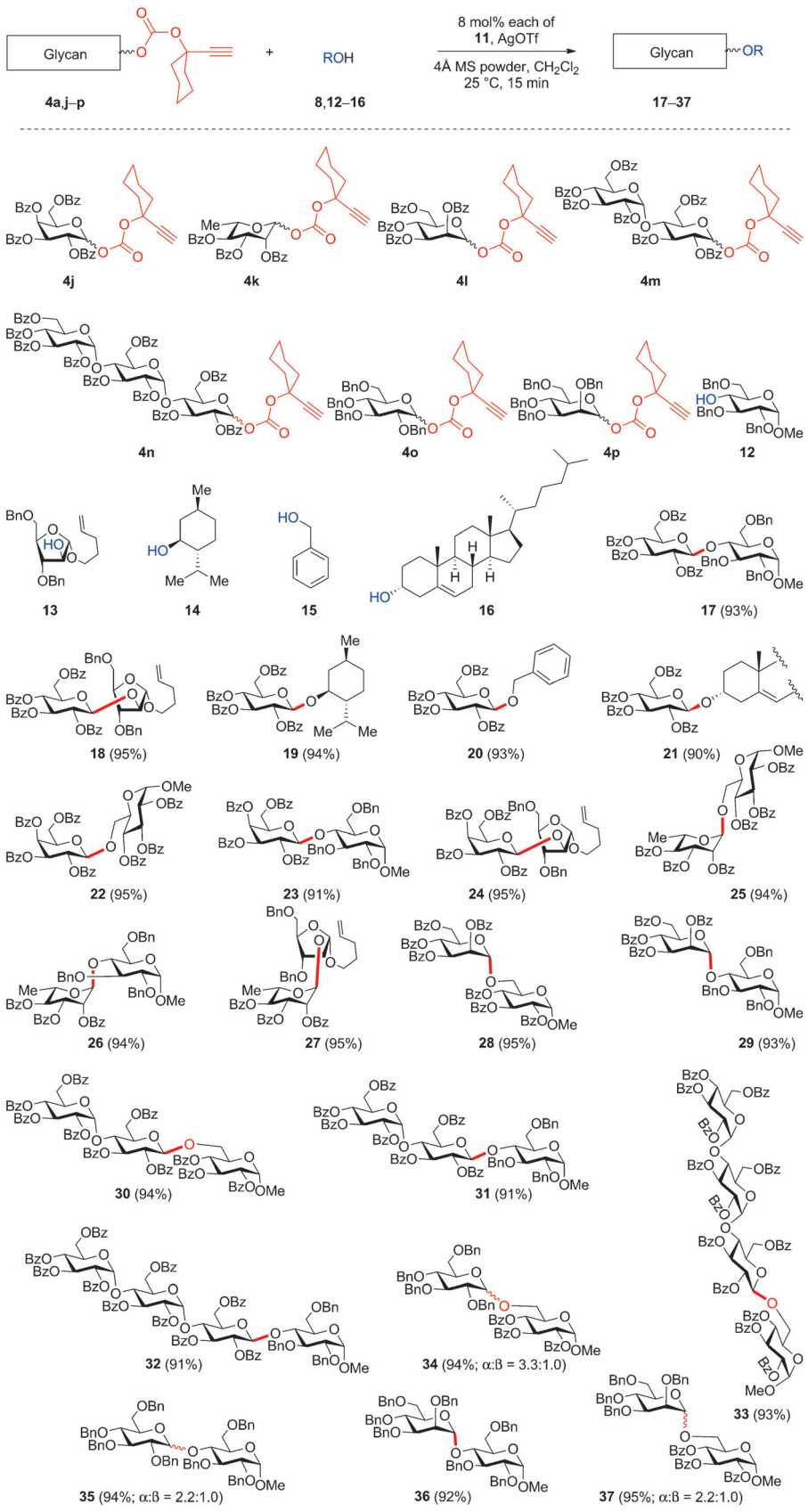
Scheme 4. Performance of carbonate glycosyl donors **4b–i** in the glycosidation of **8** in the presence of **11** (8 mol%) and AgOTf (8 mol%) in CH_2Cl_2 at 25 °C.



Scheme 5. Plausible mechanism for the alkynyl carbonate glycosidation.

The "silver effect" can be attributed to I) the chloride-ion-scavenging ability of silver to form [LAuOTf] (path a) and/or II) the prevention of the formation of unreactive chloride-bridged dinuclear species $[LAuClAuL]^+$ (path b; Scheme 5).[9] Although the detailed mechanism requires further investigation, a simple plausible mechanism can be put forward. The reaction of catalyst **11** with AgOTf can lead to the formation of the complex [LAuOTf] (path a), which can coordinate with the alkyne group of the donor **4a** to afford a gold–alkyne complex **A1** if Ag scavenges the chloride ion. Alternatively, both [Au] and [Ag] can arrest the formation of undesired dinuclear species $[LAuClAuL]^+$ by forming an Au/Ag–alkyne complex **A2** (path b). In either case, a lone pair of electrons from the endocyclic oxygen atom can trigger an electron-flow cascade to release the vinylgold cyclic carbonate **B** and the oxocarbenium ion **C**. The cationic charge on the intermediate **C** can get delocalized as shown in trioxolenium ion **D** through neighboring-group participation. Subsequently, intermediate **D** can react with glucosyl acceptor **8** to give the disaccharide **9** with the release of a proton, which causes intermediate **B** to undergo protodeauration to extrude alkene **10** and the catalytic species.

We explored the generality of the reaction with various glycosyl carbonates (compounds **4a**,**j–p**) and acceptors (compounds **8** and **12–16**) under these optimized glycosidation conditions. Glucosyl carbonate **4a** reacted with glycosyl acceptors containing secondary OH groups (compounds **12** and **13**) to smoothly provide disaccharides **17** and **18** in high yields (Scheme 6). Carbonate **4a** proved to be an excellent glycosyl donor: Alicyclic, benzylic, and steroidal acceptors **14–16** were all transformed into the expected glycosides **19–21**.[8] The generality of this new glycosidation protocol with respect to other glycosyl carbonates was also investigated. A number of glycosyl carbonates, **4j–p**, were observed to be

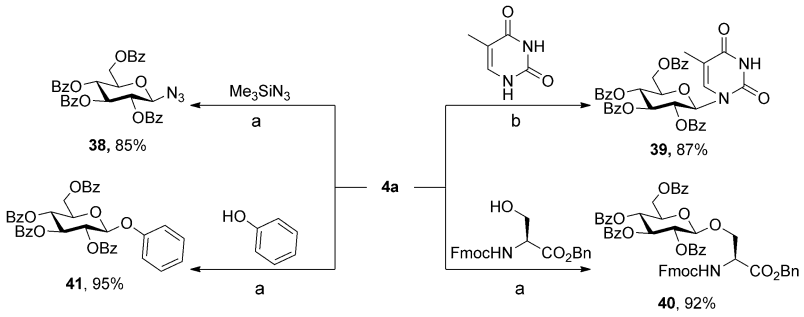


Scheme 6. Substrate-compatibility studies. Bn = benzyl.

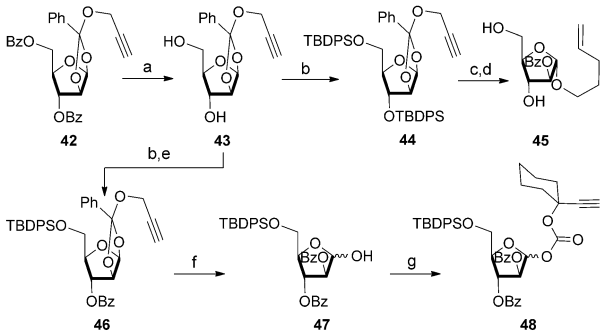
exemplary donors and afforded various glycosides, disaccharides, and oligosaccharides (products **22**–**37**). Noticeably, the use of per-*O*-benzyl-protected carbonate donors **4o**,**p** resulted in *trans*/*cis* glycosides **34**–**37**.[8] Furthermore, carbonate glucoside **4a** was observed to be a very good donor for the synthesis of azido glucoside **38** in the presence of azidotrimethylsilane (Scheme 7). Nucleoside **39** could be conveniently synthesized from carbonate **4a** in 15 min at 25 °C by using BSA and 8 mol % each of catalyst **11** and AgOTf, and the serinyl glucoside **40** and phenolic glucoside **41** were also synthesized in excellent yield under the standard reaction conditions.[8]

An enticing perspective for probing the nuances of this glycosyl carbonate chemistry was the synthesis of a mannose-capped arabinan reminiscent of the lipoarabinomannan complex of the *Mycobacterium tuberculosis* cell wall.[11] Assembly of the tridecasaccharide required two monosaccharide building blocks **45** and **47**, which could be readily accessed from the known 3,5-di-*O*-benzoyl-1,2-*O*-orthoester **42** of arabinofuranose (Scheme 8).[12] Saponification of orthoester **42** under Zemplén conditions afforded the diol **43**, which was converted into disilyl ether **44**. Gold-catalyzed glycosidation with 4-penten-1-ol, followed by fluoride-mediated desilylation, afforded the *n*-pentenyl furanoside **45**. Treatment with one equivalent of *tert*-butyldiphenylsilyl chloride (TBDPSCl) and subsequent benzoylation gave the orthoester **46**, which upon hydrolysis under gold-catalysis conditions afforded the required hemiacetal **47**. Finally, the treatment of **47** with carbonate **6** in DBU afforded the desired furanosyl donor **48**.

Synthesis of the tridecafuranoside commenced with an Au/Ag-catalyzed reaction between arabinofuranosyl donor **48** and acceptor **45**. Gratifyingly, the reaction between acceptor **45** and donor **48** (2.5 equiv) gave the trisaccharide **49** in 95 % within 15 min in the presence of 8 mol % each of the gold phosphite



Scheme 7. Further glycosylation reactions of **4a**: a) **11** (8 mol%), AgOTf (8 mol%), 4 Å MS powder, CH_2Cl_2, 25 °C, 15 min; b) bis(trimethylsilyl)acetamide (BSA), **11** (8 mol%), AgOTf (8 mol%), 4 Å MS powder, CH_2Cl_2, 25 °C, 15 min. Fmoc = 9-fluorenylmethoxycarbonyl.

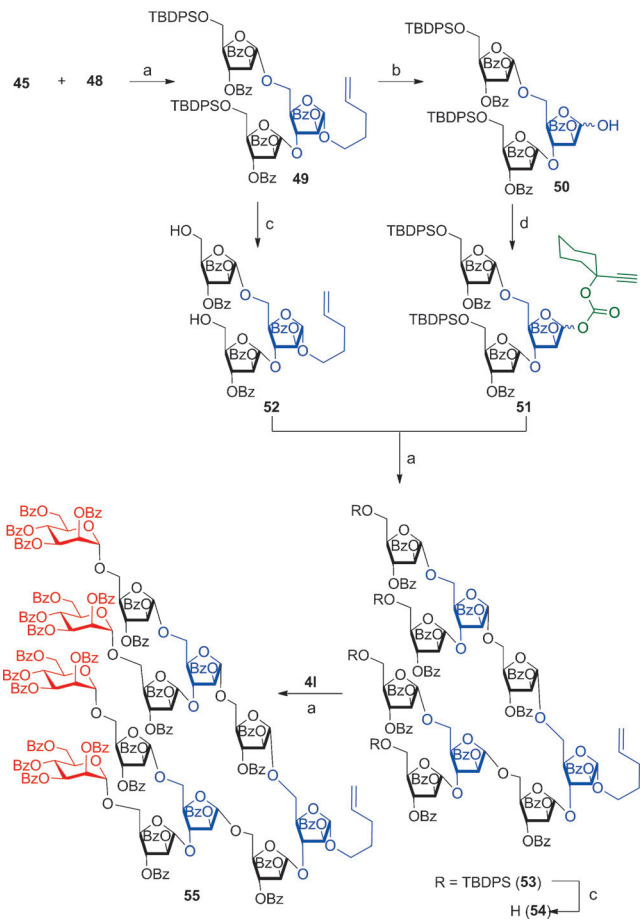


Scheme 8. Synthesis of glycosyl acceptor **45** and glycosyl donor **48**: a) $NaOCH_3$, CH_3OH, 25 °C, 30 min, 94%; b) TBDPSCl (2 equiv for **44** and 1 equiv for **46**), imidazole, DMF, 25 °C, 2 h, 90% for **44**, 76% for **46**; c) 4-penten-1-ol, $AuBr_3$ (6 mol%), CH_2Cl_2, 4 Å MS powder, 25 °C, 2 h, 87%; d) HF·py, 0–25 °C, 3 h, 95%; e) BzCl, pyridine, 25 °C, 2 h, 91%; f) $AuBr_3$ (6 mol%), CH_3CN–H_2O, 25 °C, 2 h, 92%; g) **6**, DBU, CH_2Cl_2, 0–25 °C, 3 h, 93%. DMF = *N*,*N*-dimethylformamide, py = pyridine.

catalyst **11** and AgOTf (Scheme 9).[8] Hydrolysis of *n*-pentenyl glycoside **49** to give hemiacetal **50**, followed by its conversion into the trisaccharide carbonate **51** occurred readily. Simultaneous cleavage of the silyl ethers of **49** resulted in the trisaccharide diol **52**.

The key glycosidation between acceptor **52** (1 equiv) and donor **51** (2.5 equiv) under the conditions of Au/Ag catalysis resulted in the formation of nonaarabinofuranoside **53** in 93% yield. Hydrolytic cleavage of the silyl ethers then afforded tetraol **54**. Glycosidation with the mannose carbonate donor **41** (5 equiv) under the Au/Ag conditions resulted in the targeted tridecasaccharide **55** in 95% yield (Scheme 9).[8]

In summary, we have identified alkynyl glycosyl carbonates as glycosyl donors that are stable solid compounds ideally suited for the fast and efficient synthesis of glycosides, nucleosides, oligosaccharides, and azido and amino acid glycoconjugates under mild catalytic conditions. Importantly, glycosyl carbonates containing benzoates were observed to be solids. With a simple operational protocol and low catalyst loading, this transformation was shown to be applicable to the synthesis of a biologically significant tridecasaccharide segment reminiscent of the mycobacterial cell surface.



Scheme 9. Synthesis of a tridecasaccharide: a) **11** (8 mol%), AgOTf (8 mol%), 4 Å MS powder, CH_2Cl_2, 25 °C, 15 min; b) *N*-iodosuccinimide, TfOH, H_2O, CH_3CN, 25 °C, 2 h, 76%; c) HF·py, 0–25 °C, 3 h, 86%; d) **6**, DBU, CH_2Cl_2, 0–25 °C, 3 h, 92%.

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[1] A. V. Demchenko in *Handbook of Chemical Glycoslation* (Ed.: A. V. Demchenko), Wiley-VCH, Weinheim, **2008**, pp. 1–28.
[2] a) H. Paulsen, *Angew. Chem. Int. Ed. Engl.* **1982**, *21*, 155–173; *Angew. Chem.* **1982**, *94*, 184–201; b) R. R. Schmidt, *Angew. Chem. Int. Ed. Engl.* **1986**, *25*, 212–235; *Angew. Chem.* **1986**, *98*,

213 – 236; c) K. Toshima, K. Tatsuta, *Chem. Rev.* **1993**, *93*, 1503 – 1531; d) P. H. Seeberger, D. B. Werz, *Nature* **2007**, *446*, 1046 – 1051; e) X. Zhu, R. R. Schmidt, *Angew. Chem. Int. Ed.* **2009**, *48*, 1900 – 1934; *Angew. Chem.* **2009**, *121*, 1932 – 1967; f) M. J. McKay, H. M. Nguyen, *ACS Catal.* **2012**, *2*, 1563 – 1595; g) S. Adhikari, X. Li, J. Zhu, *J. Carbohydr. Chem.* **2013**, *32*, 336 – 359.

[3] a) T. Mukaiyama, Y. Murai, S. Shoda, *Chem. Lett.* **1981**, 935 – 938; b) G. Wulff, G. Röhle, *Angew. Chem. Int. Ed. Engl.* **1974**, *13*, 157 – 216; *Angew. Chem.* **1974**, *86*, 173 – 187; c) W. Koenigs, E. Knorr, *Ber. Dtsch. Chem. Ges.* **1901**, *34*, 957 – 981; d) M. J. Hadd, J. Gervay, *Carbohydr. Res.* **1999**, *320*, 61 – 69; e) D. A. Ryan, D. Y. Gin in *Handbook of Chemical Glycoslation*, (Ed.: A. V. Demchenko), Wiley-VCH, Weinheim, **2008**, pp. 91 – 142; f) R. R. Schmidt, J. Michel, *Angew. Chem. Int. Ed. Engl.* **1980**, *19*, 731 – 732; *Angew. Chem.* **1980**, *92*, 763 – 764; g) S. J. Danishefsky, M. T. Bilodeau, *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 1380 – 1419; *Angew. Chem.* **1996**, *108*, 1482 – 1522; h) S. Mehta, B. M. Pinto, *J. Org. Chem.* **1993**, *58*, 3269 – 3276; i) D. Horton, D. H. Hudson, *Adv. Carbohydr. Chem.* **1963**, *18*, 123 – 199; j) H. B. Mereyala, G. V. Reddy, *Tetrahedron* **1991**, *47*, 6435 – 6448; k) A. V. Demchenko, N. N. Malysheva, C. D. Meo, *Org. Lett.* **2003**, *5*, 455 – 458; l) D. R. Mootoo, V. Date, B. Fraser-Reid, *J. Am. Chem. Soc.* **1988**, *110*, 2662 – 2663; m) S. Hotha, S. Kashyap, *J. Am. Chem. Soc.* **2006**, *128*, 9620 – 9621; n) A. F. Bochkov, G. E. Zaikov in *Chemistry of the O-Glycosidic Bond: Formation and Cleavage*, Pergamon Press, New York, **1979**; o) A. S. Campbell, B. Fraser-Reid, *J. Am. Chem. Soc.* **1995**, *117*, 10387 – 10388; p) G. Sureshkumar, S. Hotha, *Tetrahedron Lett.* **2007**, *48*, 6564 – 6568; q) O. J. Plante, R. B. Andrade, P. H. Seeberger, *Org. Lett.* **1999**, *1*, 211 – 214; r) J. D. C. Codée, L. H. Hossain, P. H. Seeberger, *Org. Lett.* **2005**, *7*, 3251 – 3254; s) Y. Li, Y. You, B. Yu, *Tetrahedron Lett.* **2008**, *49*, 3604 – 3608; t) S. Adhikari, K. N. Baryal, D. Zhu, X. Li, J. Zhu, *ACS Catal.* **2013**, *3*, 57 – 60.

[4] a) A. K. Kayastha, S. Hotha, *Chem. Commun.* **2012**, *48*, 7161 – 7163; b) A. K. Kayastha, S. Hotha, *Beilstein J. Org. Chem.* **2013**, *9*, 2147 – 2155; c) A. K. Kayastha, S. Hotha, *Tetrahedron Lett.* **2010**, *51*, 5269 – 5372.

[5] a) S. Inaba, M. Yamada, T. Yoshino, Y. Ishido, *J. Am. Chem. Soc.* **1973**, *95*, 2062 – 2063; b) T. Iimori, T. Shibazaki, S. Ikegami, *Tetrahedron Lett.* **1996**, *37*, 2267 – 2270; c) A. Marra, J. Esnault, A. Veyrieres, P. Sinay, *J. Am. Chem. Soc.* **1992**, *114*, 6354 – 6360; d) T. Mukaiyama, K. Miyazaki, H. Uchiro, *Chem. Lett.* **1998**, *27*, 635 – 636; e) W. Liu, Q. Chen, J. Liang, Z. Du, K. Zhang, X. Zheng, G. A. O'Doherty, *Synlett* **2015**, *26*, 1683 – 1686; f) A. Z. Aljahdali, P. Shi, Y. Zhong, G. A. O'Doherty, *Adv. Carbohydr. Chem. Biochem.* **2013**, *69*, 55 – 123.

[6] a) Y. Li, X. Yang, Y. Liu, C. Zhu, Y. Yang, B. Yu, *Chem. Eur. J.* **2010**, *16*, 1871 – 1882; b) A. Buzas, F. Gagosz, *Org. Lett.* **2006**, *8*, 515 – 518; c) Y.-X. Zhang, L. Guo, Y.-H. Wang, L.-L. Zhu, Z. Chen, *Tetrahedron* **2010**, *66*, 321 – 328.

[7] a) T. Yu, J. Li, Y. Zhu, Y. Li, B. Yu, *J. Am. Chem. Soc.* **2013**, *135*, 18396 – 18405; b) A. Páhi, K. Czifrák, K. E. Kövér, L. Somsák, *Carbohydr. Res.* **2015**, *403*, 192 – 201.

[8] See the Supporting Information.

[9] a) D. Wang, R. Cai, S. Sharma, J. Jirak, S. K. Thummanapelli, N. G. Akhmedov, H. Zhang, X. Liu, J. L. Petersen, X. Shi, *J. Am. Chem. Soc.* **2012**, *134*, 9012 – 9019; b) X.-R. Song, X.-F. Xia, Q.-B. Song, F. Yang, Y.-X. Li, X.-Y. Liu, Y.-M. Liang, *Org. Lett.* **2012**, *14*, 3344 – 3347; c) A. Homs, I. Escofet, A. M. Echavarren, *Org. Lett.* **2013**, *15*, 5782 – 5785; d) Y. Su, M. Lu, B. Dong, H. Chen, X. Shi, *Adv. Synth. Catal.* **2014**, *356*, 692 – 696; e) B. Ranieri, I. Escofet, A. M. Echavarren, *Org. Biomol. Chem.* **2015**, *13*, 7103 – 7118.

[10] a) U. Albrecht, P. Langer, *Tetrahedron* **2007**, *63*, 4648 – 4654; b) M. Jegelka, B. Plietker, *Org. Lett.* **2009**, *11*, 3462 – 3465.

[11] a) B. Fraser-Reid, J. Lu, K. N. Jayaprakash, J. C. López, *Tetrahedron: Asymmetry* **2006**, *17*, 2449 – 2463; b) S. Borman, *Chem. Eng. News* **2006**, *84*, 13 – 22; c) A. M. Ginsberg, M. Spigelman, *Nat. Med.* **2007**, *13*, 290 – 294; d) T. L. Lowary, *Curr. Opin. Chem. Biol.* **2003**, *7*, 749 – 756.

[12] S. A. Thadke, B. Mishra, S. Hotha, *Org. Lett.* **2013**, *15*, 2466 – 2469.

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