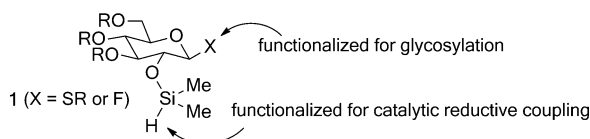


A Streamlined Strategy for Aglycone Assembly and Glycosylation**

Katherine M. Partridge, Scott J. Bader, Zachary A. Buchan, Christopher E. Taylor, and John Montgomery*

The assembly of glycosylated structures, even with relatively simple aglycones, often presents a significant challenge in chemical synthesis.^[1] Much of this complexity derives from the linear approach required by existing synthetic strategies. A typical strategy involves initial assembly of the aglycone by a collection of stereoselective C–C bond-forming processes. During the sequence, orthogonal protecting groups are installed, and at a late stage, a single hydroxy group is then unmasked for a glycosylation event at the end of the synthesis. We envision that an alternate, more efficient approach might allow a C–C bond-forming step to be merged with a glycosylation event. Since carbonyl addition reactions, which are routine in many aglycone synthesis strategies, inherently generate an alcohol functionality, the direct capture of the forming hydroxy group in a glycosylation event could provide an alternate strategy with advantages in efficiency. Towards this end, our laboratory has devised a new class of reagents (**1**) which possesses a carbohydrate core with the anomeric position functionalized for glycosylation and with the C2 hydroxy protected as a reactive silicon hydride (Scheme 1).^[2]

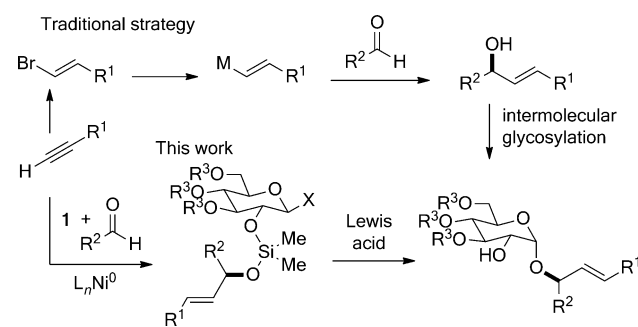


Scheme 1. Sugar silane reagents.

These multifunctional sugar silane reagents thus possess a silyl hydride which could enable a variety of catalytic reductive processes including C–C bond formations, while the anomeric position is derivatized to directly enable glycosylation.

The appeal of such reagents derives from the broad array of transition-metal-catalyzed processes which are enabled by the reactivity of silicon hydrides,^[3] coupled with the considerable utility of silicon-tethered intramolecular glycosylations demonstrated by Stork et al. and Bols et al.^[4] Sugar silane

reagents were previously utilized in a ketone hydrosilylation/intramolecular glycosylation sequence to provide site-selective reductive glycosylations of simple ketones.^[2] However, their use in a process wherein the silane mediates formation of a new C–C bond or where a multicomponent coupling process occurs is without precedent. Herein, we illustrate that sugar silanes can mediate catalytic carbon–carbon bond-forming reactions followed directly by intramolecular glycosylation. This multicomponent approach thus allows both the aglycone skeletal assembly and the glycoside bond formation to be addressed in a single strategy from simple precursors including the sugar silane **1** rather than through stepwise operations that conventional procedures require (Scheme 2).



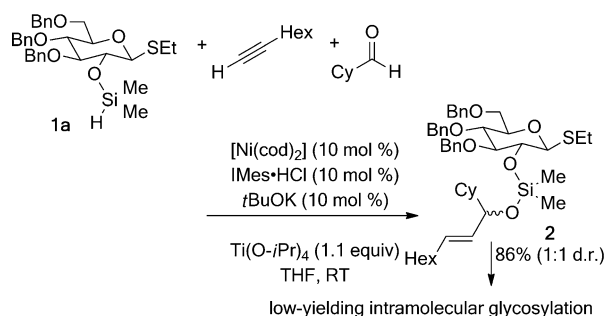
Scheme 2. Strategy for glycoside synthesis.

The synthesis of sugar silane reagents is straightforward, thus requiring initial preparation of glycosyl sulfide or fluoride precursors with all the hydroxy groups protected, aside from the C2 hydroxy. Protection of the C2 hydroxy with commercially available chlorodimethylsilane then affords sugar silane reagents in high yield. Although unstable to chromatography, these reagents may be stored for months and are easily manipulated in air. The reagents are generally robust in catalytic operations, with the silicon hydride functionality undergoing a range of metal-mediated additions without affecting the anomeric leaving group. Our preliminary explorations involved catalytic additions of thioglycosides.^[5] Although aldehyde–alkyne reductive couplings with thioethyl and thiophenyl sugar silanes were generally effective, efforts to develop the ensuing intramolecular glycosylations were unsatisfactory. A representative coupling with cyclohexane carboxaldehyde and octyne utilizing the glucose-derived thioethyl sugar silane **1a** is depicted (Scheme 3), but a variety of glycosylation methods with the intermediate **2**, utilizing standard protocols such as TMSOTf/*N*-iodosuccinimide methods^[6] or radical-cation-based methodology,^[7] were low yielding. The origin of the complexity in glycosylation is clearly the sensitivity of the allylic alcohol, as mixtures of

[*] Dr. K. M. Partridge, Dr. S. J. Bader, Dr. Z. A. Buchan, Dr. C. E. Taylor, Prof. J. Montgomery
Department of Chemistry, University of Michigan
Ann Arbor, MI 48109-1055 (USA)
E-mail: jmontg@umich.edu
Homepage: <http://www.umich.edu/~jmggroup>

[**] We thank the National Institutes of Health (GM-57014) and Thermo Fisher (pilot project grant administered by the University of Michigan Life Sciences Institute) for support of this research.

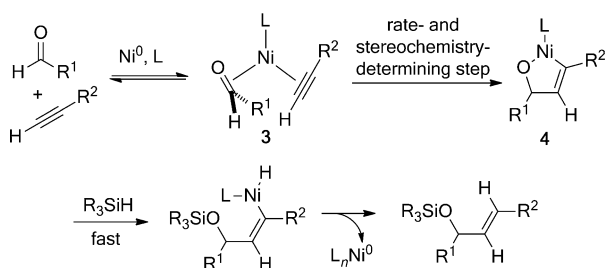
Supporting information for this article is available on the WWW under <http://dx.doi.org/10.1002/anie.201307680>.



Scheme 3. Couplings of thioglycosides. cod = 1,5-cyclooctadiene, IMes = 1,3-bis(2,4,6-trimethylphenyl)imidazol-2-ylidene.

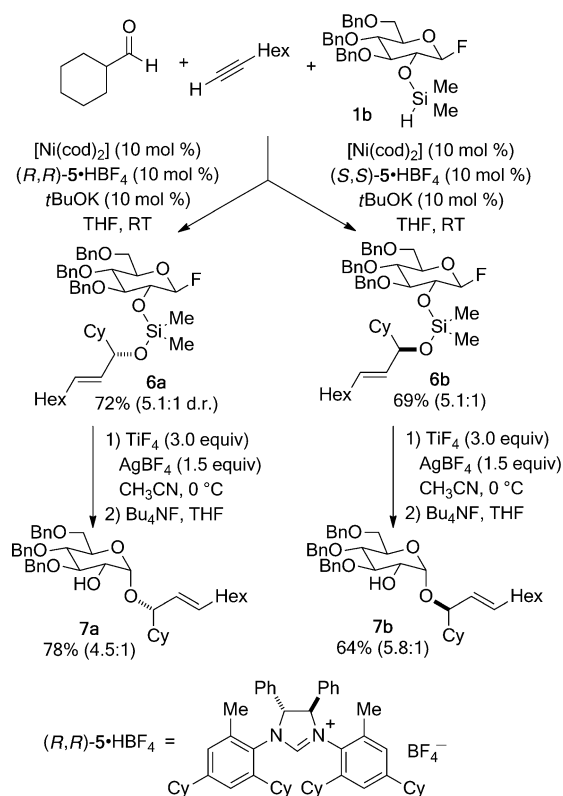
elimination products were observed, whereas intramolecular glycosylations of structurally related saturated alcohols were straightforward and high yielding.^[2]

The above example illustrates that the sugar chirality plays no role in the creation of the stereogenic center, as 1:1 mixtures of diastereomers were routinely observed. This outcome was in fact expected since the silane involvement was previously illustrated to occur after the rate-determining oxidative cyclization of the nickel/aldehyde/alkyne π -complex **3** (Scheme 4).^[8] A σ -bond metathesis of the sugar silane with the metallacycle intermediate **4** follows the stereochemistry-determining oxidative cyclization which leads to metallacycle formation. This outcome illustrates that ligand control during the oxidative cyclization is a likely requirement for controlling stereochemistry in this multicomponent addition process.



Scheme 4. Reaction mechanism.

Based on the above limitations in diastereoselectivity of the C–C bond-forming step and yield of the glycosylation, we turned our attention to chiral-ligand-based processes using alternative glycosyl donors. The corresponding glycosyl fluorides^[9] behaved analogously to the thioethyl glycoside depicted above using IMes as a ligand, therefore we explored the use of chiral N-heterocyclic carbene ligands in the aldehyde–alkyne addition process. Couplings of cyclohexane carboxyaldehyde and 1-octyne with the sugar silane **1b**, derived from tribenzylglucosyl fluoride, were examined utilizing the chiral N-heterocyclic carbene ligand **5** previously developed in our labs (Scheme 5).^[10] As anticipated, sugar chirality played no role in stereoinduction, and the diastereomeric ratios for generation of the reductive coupling products **6a** (from the *R,R*-**5**) and **6b** (from *S,S*-**5**) were opposite and of very similar magnitude, with diastereoselec-



Scheme 5. Glycosyl fluoride reductive coupling/glycosylation.

tivities being governed by ligand chirality. Following procedures previously developed for intermolecular glycosylations of glycosyl fluorides,^[11] intramolecular glycosylation of the silyl-linked intermediates **6a** and **6b** afforded exclusively the α -gluco stereochemistry of the diastereomeric glycosidic linkages of the glycosides **7a** and **7b**, respectively. The stereochemistry of the aldehyde–alkyne addition step was confirmed by desilylation of **6a** and subsequent Mosher ester analysis of the resulting allylic alcohol. The newly formed α -glucoside linkages of **7a** and **7b** were confirmed by characteristic *J* values of the anomeric protons.

A series of aldehyde–alkyne combinations were explored for this catalytic C–C bond formation/intramolecular glycosylation sequence (Table 1). Products **7a–j** were obtained as single diastereomers by standard column chromatographic separation. In analogy to the above examples (Scheme 5), two additional combinations of simple aliphatic aldehydes and terminal alkynes underwent efficient couplings with comparable degrees of diastereocontrol in the reductive coupling step (Table 1, entries 1 and 2). An internal alkyne underwent the reductive coupling in relatively good yield, although intramolecular glycosylations of allylic alcohols derived from internal alkynes generally proceeded in modest yield as illustrated by this example (entry 3). Several examples were then conducted to examine the chemoselectivity of the process. The reaction proved to be very selective for the combination of aldehyde–alkyne couplings in the presence of isolated ketones (entry 4), unprotected hydroxy groups (entry 5), silyl ethers (entry 6), and esters (entry 7). The ability to tolerate simple ketones in the process (entry 4) is

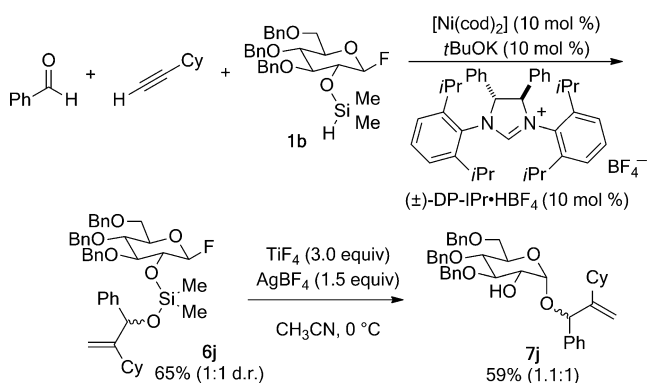
Table 1: Scope of reductive coupling/glycosylation.

$\text{R}^1\text{CHO} + \text{R}^2\text{C}\equiv\text{CR}^3 + \text{Sugar-Silane} \xrightarrow[\text{THF, RT}]{[\text{Ni}(\text{cod})_2] (10 \text{ mol } \%), (\text{R},\text{R})\text{-5-HBF}_4 (10 \text{ mol } \%), t\text{BuOK} (10 \text{ mol } \%)}$ (1.0 equiv) (2.0 equiv) (1.3 equiv)		
$\text{Intermediate} \xrightarrow[\text{2) Bu}_4\text{NF, THF}]{\text{1) TiF}_4 (3.0 \text{ equiv}), \text{AgBF}_4 (1.5 \text{ equiv}), \text{CH}_3\text{CN}, 0^\circ\text{C}}$		
Entry	6 (yield, d.r.) ^[a]	7 (yield, d.r.) ^[b]
1	 6c (78 %, 5.7:1)	 7c (63 %, 6.8:1)
2	 6d (58 %, 5.5:1) ^[c]	 7d (57 %, 3.2:1) ^[c]
3	 6e (64 %, 3.7:1)	 7e (41 %, 2.8:1)
4	 6f (54 %, 3.5:1)	 7f (60 %, 3.0:1)
5	 6g (62 %, 5.1:1)	 7g (43 %, 5.6:1)
6	 6h (81 %, 5.3:1)	 7h (57 %, 4.3:1)
7	 6i (73 %, 5.0:1)	 7i (52 %, 4.2:1)

[a] Diastereomeric ratio determined by ^{19}F NMR spectroscopy. [b] Diastereomeric ratio determined by ^1H NMR spectroscopy. [c] For **6d**, 10% of a regioisomer was observed. For **7d**, 7% of a regioisomer was observed. TBS = *tert*-butyldimethylsilyl.

notable in that hydrosilylations of ketones with sugar silanes were efficient using closely related catalyst systems in cases where the aldehyde–alkyne combination was not present.^[2] Additionally, the tolerance of an unprotected hydroxy (entry 5) is notable for both the reductive coupling reaction as well as the glycosylation. The advantages of the kinetic bias of intramolecular aglycone delivery contribute to chemo-selectivity of glycosylation in the presence of an unprotected hydroxy group. While silyl removal occurred during Bu_4NF treatment of the crude reaction mixture (entry 6), the directing influence of the silyl tether nonetheless allowed selective glycosylation of the secondary allylic alcohol. While the three-component couplings involving mannose silanes efficiently produced silyl intermediates analogous to **6**, the intramolecular glycosylations to produce β -mannosides were low yielding using the current procedure.

The above examples illustrate that ligand chirality allows either diastereomer to be accessed by controlling the stereochemistry of the aldehyde–alkyne addition step. Similarly, we anticipated that ligand control might also allow access to different constitutional isomers of the aglycone by altering regioselectivity of the addition reaction. Since the terminal alkyne addition processes studied above exclusively favor addition of the unsubstituted alkyne terminus to the aldehyde, we examined an alternate ligand class [($\pm$)-DP-IPr; Scheme 6]. While only available in racemic form, this ligand



Scheme 6. Ligand-controlled regiochemistry reversal.

has previously been illustrated to be highly selective for reversing regioselectivities of terminal alkyne reductive couplings.^[12] As an example of this capability in the glycoside bond-forming sequence, reductive coupling of benzaldehyde with cyclohexylacetylene and **1b** utilizing ($\pm$)-DP-IPr as the ligand afforded exclusively the regioisomer of the silicon-linked intermediate **6j**, where the substituted alkyne terminus had undergone addition to the aldehyde (Scheme 6). By using racemic ligand, a 1:1 mixture of diastereomers was obtained, and was converted to a 1:1 ratio of diastereomers of the expected product **7j** upon treatment to the glycosylation conditions described above.

In summary, sugar silanes have been utilized as versatile reagents for the synthesis of glycosylated allylic alcohols. The sugar silanes serve as the reducing agent in stereocontrolled catalytic C–C bond formations, and then serve to stereose-

lectively deliver a glycosidic bond through an intramolecular glycosylation process. The full sequence is stereo- and regioselective and is compatible with numerous functional groups. Use of the multifunctional sugar silanes serves to unify the strategy by which aglycone preparation and ensuing glycosylation may be accomplished. On this basis, we anticipate that complex synthesis strategies and challenging site-selective glycosylations may benefit from approaches of this type.

Experimental Section

General procedure for three-component coupling of an aldehyde, an alkyne, and the sugar silane **1b**: A solid mixture of $[\text{Ni}(\text{cod})_2]$ (4.2 mg, 0.015 mmol), $R,R\text{-5-HBF}_4$ (12.3 mg, 0.015 mmol), and KOtBu (1.7 mg, 0.015 mmol) was dissolved in dry THF (0.75 mL) at RT under an inert atmosphere of N_2 . The solution quickly turned a deep, brick red and was stirred for 30–45 min. The aldehyde (0.15 mmol, 1.0 equiv) was added directly to the catalyst solution by microsyringe. A solution of sugar silane (102 mg, 0.2 mmol, 1.3 equiv) and alkyne (0.15 mmol, 1.0 equiv) in THF (0.75 mL) was added to the catalyst solution over 50 min by a syringe drive, after which a second aliquot of alkyne (0.15 mmol, 1.0 equiv) in 0.5 mL dry THF was added over 80 min. The reaction was stirred either until disappearance of aldehyde was clearly observed by TLC or overnight, in the instance of incomplete conversion. The reaction mixture was diluted with an equal volume of hexanes and filtered through a short plug of silica gel, and then washed with a mixture of EOtAc /hexanes. The solution was concentrated by rotary evaporation and the residue was purified by flash chromatography (SiO_2) to afford the desired product.

Received: September 1, 2013

Published online: October 21, 2013

Keywords: glycosylation · multicomponent reactions · nickel · silicon · synthetic methods

- [1] a) K. Toshima, K. Tatsuta, *Chem. Rev.* **1993**, *93*, 1503–1531; b) X. M. Zhu, R. R. Schmidt, *Angew. Chem.* **2009**, *121*, 1932–1967; *Angew. Chem. Int. Ed.* **2009**, *48*, 1900–1934.

- [2] Z. A. Buchan, S. J. Bader, J. Montgomery, *Angew. Chem.* **2009**, *121*, 4934–4938; *Angew. Chem. Int. Ed.* **2009**, *48*, 4840–4844.
- [3] a) J. Montgomery, *Angew. Chem.* **2004**, *116*, 3980–3998; *Angew. Chem. Int. Ed.* **2004**, *43*, 3890–3908; b) O. Riant, N. Mostefai, J. Courmarcel, *Synthesis* **2004**, 2943–2958; c) I. Ojima, N. Clos, R. J. Donovan, P. Ingallina, *Organometallics* **1990**, *9*, 3127–3133; d) I. Ojima, T. Kogure, *Organometallics* **1982**, *1*, 1390–1399.
- [4] a) G. Stork, G. Kim, *J. Am. Chem. Soc.* **1992**, *114*, 1087–1088; b) G. Stork, J. J. LaClair, *J. Am. Chem. Soc.* **1996**, *118*, 247–248; c) M. Bols, *J. Chem. Soc. Chem. Commun.* **1992**, 913–914; d) M. Bols, *J. Chem. Soc. Chem. Commun.* **1993**, 791–792; e) K. H. Jung, M. Muller, R. R. Schmidt, *Chem. Rev.* **2000**, *100*, 4423–4442; f) I. Cumpstey, *Carbohydr. Res.* **2008**, *343*, 1553–1573. For pioneering studies using other strategies for intramolecular aglycone delivery: g) F. Barresi, O. Hindsgaul, *J. Am. Chem. Soc.* **1991**, *113*, 9376–9377; h) Y. Ito, T. Ogawa, *Angew. Chem.* **1994**, *106*, 1843–1845; *Angew. Chem. Int. Ed. Engl.* **1994**, *33*, 1765–1767.
- [5] J. D. C. Codée, R. Litjens, L. J. van den Bos, H. S. Overkleef, G. A. van der Marel, *Chem. Soc. Rev.* **2005**, *34*, 769–782.
- [6] a) P. Konradsson, U. E. Udodong, B. Fraserreid, *Tetrahedron Lett.* **1990**, *31*, 4313–4316; b) G. H. Veeneman, S. H. Vanleeuwen, J. H. Vanboom, *Tetrahedron Lett.* **1990**, *31*, 1331–1334; c) S. C. Ennis, A. J. Fairbanks, R. J. Tennant-Eyles, H. S. Yeates, *Synlett* **1999**, 1387–1390.
- [7] A. Marra, J. M. Mallet, C. Amatore, P. Sinay, *Synlett* **1990**, 572–574.
- [8] a) R. D. Baxter, J. Montgomery, *J. Am. Chem. Soc.* **2008**, *130*, 9662–9663; b) P. Liu, J. Montgomery, K. N. Houk, *J. Am. Chem. Soc.* **2011**, *133*, 6956–6959; c) for related studies with other reductants: P. R. McCarren, P. Liu, P. H. Y. Cheong, T. F. Jamison, K. N. Houk, *J. Am. Chem. Soc.* **2009**, *131*, 6654–6655.
- [9] a) M. Shimizu, H. Togo, M. Yokoyama, *Synthesis* **1998**, 799–822; b) K. Toshima, *Carbohydr. Res.* **2000**, *327*, 15–26.
- [10] M. R. Chaulagain, G. J. Sormunen, J. Montgomery, *J. Am. Chem. Soc.* **2007**, *129*, 9568–9569.
- [11] a) M. Kreuzer, J. Thiem, *Carbohydr. Res.* **1986**, *149*, 347–361; b) H. P. Wessel, *Tetrahedron Lett.* **1990**, *31*, 6863–6866.
- [12] a) H. A. Malik, G. J. Sormunen, J. Montgomery, *J. Am. Chem. Soc.* **2010**, *132*, 6304–6305; b) A. R. Shareef, D. H. Sherman, J. Montgomery, *Chem. Sci.* **2012**, *3*, 892–895.