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Ketone Hydrosilylation with Sugar Silanes Followed by Intramolecular Aglycone Delivery: An Orthogonal Glycosylation Strategy

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Keywords

Ni; Cu; hydrosilylation; glycosylation; chemoselectivity

Many classes of biomolecules derive their biological activity from the synergistic effects of carbohydrate and non-carbohydrate (aglycone) functionality.[1] From the standpoint of chemical synthesis, the assembly of the aglycone and attachment of a carbohydrate (glycosylation) are viewed as distinct operations. As a result, the independent synthesis of a suitably-protected aglycone and a suitably-protected carbohydrate is typically followed by a separate sequence involving Lewis acid activation of the sugar anomeric substituent and assembly of the *O*-glycoside bond via addition of a hydroxyl-bearing aglycone.[2] The powerful glycal oxidation method similarly involves addition of a hydroxyl nucleophile to the electrophilic anomeric position.[3] An important complement to these strategies involves intramolecular aglycone delivery.[4] Seminal work from Hindsgaul[5] and Ogawa[6] using acetal linkages and from Stork[7] and Bols[8] using silane linkages demonstrated that intramolecular aglycone delivery strategies provide a powerful entry to *cis*-1,2 glycoside linkages, namely the synthetically challenging β-mannose and α-glucose configurations. Whereas the intramolecular strategies involve glycoside bond assembly directly from an acetal- or silyl-protected hydroxyl, preparation of the tethered aglycone-carbohydrate assembly is ultimately derived from a free hydroxyl on the aglycone earlier in the synthesis. An alternate strategy involving *O*-alkylation of a C-1-*O*-hemiacetal nucleophile with an electrophilic aglycone provides a powerful entry to glycoconjugates and oligosaccharides, although this method also requires that potentially nucleophilic sites in the aglycone are protected.[9] As a complement to all of the above strategies, a glycosylation method that does not require a nucleophilic free hydroxyl on the aglycone at any point in the synthesis, and that tolerates spectator free hydroxyls on the aglycone, could have important implications as a strategy for native glycoside bond construction that is orthogonal to conventional glycosylation methods.[10]

With this challenge in mind, we were attracted to the notion of developing transition metal-catalyzed hydrosilylations of ketones by silyl hydride reagents that possess glycosyl donors as a silyl substituent. Such a strategy could allow site-selective installation of installing stereochemical features of the aglycone via reduction of the carbonyl. Herein we describe the

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efficient synthesis of “sugar silanes” to enable such a strategy, along with the first examples of the direct glycosylation of ketones as a fundamentally new and orthogonal strategy for preparing glycoside bonds.

Glycosyl donor reagents that possess a C-2 free hydroxyl, protecting groups at the 3, 4, and 6-positions, and a thioalkyl anomeric substituent are readily prepared in the glucose or mannose configurations by known procedures.[11] The C-2 hydroxyl may be silylated in near quantitative yield using commercially available Me_2SiHCl and Et_3N in dichloromethane to afford reagents **1** or **2** (Scheme 1). The synthesis of **1** or **2** may be performed on multigram scale, requiring only a single chromatographic purification. While **1** and **2** are not stable to chromatography, they are obtained in pure form and may be stored for months with comparable results in subsequent reactions compared with reagents that are freshly prepared.

In this intial study, we first examined ketone hydrosilylations with reagents **1a** and **1b** using either nickel[12] or copper[13] catalysts with IMes as the ligand, generated from 1,3-dimesitylimidazolium chloride, and KO-*t*Bu or NaO-*t*Bu. A variety of unhindered ketones underwent efficient couplings with the catalyst derived from $Ni(COD)_2$ and IMes in THF, using $Ti(O\text{-}iPr)_4$ as a Lewis acidic additive (Table 1) to afford hydrosilylation products **4** (starting from glucose) or **5** (starting from mannose). Control experiments demonstrated that no conversion was observed in the absence of the nickel catalyst. The procedure (Scheme 2) was generally effective with unhindered ketones, whereas the corresponding copper-IMes catalyst, generated in toluene following the procedure from Nolan,[13] was more effective with hindered ketones. Once substrates **4** or **5** were prepared via hydrosilylation, intramolecular glycosylation was carried out using *N*-iodosuccinimide and trimethylsilyltriflate with 2,6-di-*t*-butyl-4-methylpyridine (2,6-DTBMP) in dichloromethane at −40 to 0 °C to produce α-glucosides **6** (from **4**) or β-mannosides **7** (from **5**).[14] As described below, both ethylthio and phenylthio sugar silanes **1a**/**b** and **2a**/**b** were similarly effective in hydrosilylations, although the phenylthio donors were more effective in subsequent intramolecular glycosylations when hindered ketones were employed.

As a first example, coupling with benzyl acetone proceeded in high yield with the Ni(0)-IMes catalyst to afford a 54:46 mixture of diastereomers of **4a** epimeric at the newly formed stereogenic center, thus illustrating that sugar chirality has little impact on the diastereoselectivity of the hydrosilylation (Table 1, entry 1). Glycosylation of **4a** provided α-glucoside **6a** in 97 % isolated yield with excellent diastereoselectivity at the anomeric position. Cyclic acetals and basic tertiary amines were tolerated in high yielding transformations with the Ni(0)-IMes catalyst to produce **4b** and **4c** (entries 2–3), and glycosylation of these substrates afforded the α-glucosides **6b** and **6c** in high yield and excellent diastereoselectivity. Hydrosilylations of (−)-menthone (**3d**) were low yielding with the nickel catalyst system (ca. 20–25 % yield); however, the more reactive Cu-IMes catalyst led to faster and higher yielding reactions (entry 4). Using either ethylthio or phenylthio sugar silanes **1a** or **1b**, hydrosilylations using **3d** were effective to produce **4d** or **4e** in good yield with 2:1 diastereoselectivity. Subsequent glycosylations, however, were much higher yielding with phenylthioglycosyl donor **4e**, which generated product **6d** in 72 % isolated yield, compared with 20 % isolated yield from **4d**. The enhancement of diastereoselectivity observed in the glycosylation is derived from significantly different rates of glycosylation of the two diastereomers of **4d** or **4e**. Efficiency of the process in β-mannosylations was next examined. Hydrosilylation of ketone **3b** with mannose silane **2a** was efficient with the Ni-IMes catalyst, affording product **5a** in 86% isolated yield (entry 5). Glycosylation of **5a** was moderately effective to generate exclusively the β-mannoside **7a** in 58 % isolated yield with excellent control of the anomeric stereochemistry. Hydrosilylation of (−)-menthone (**3d**) with mannose silane **2b** using the Cu-IMes catalyst afforded **5b** in 75 % isolated yield with 2:1 diastereoselectivity (entry 6), and subsequent glycosylation afforded β-mannoside **7b** in 74 % isolated yield and excellent control

of the anomeric configuration. Enhancement of the diastereomeric ratio derived from carbonyl reduction was again noted as described above (entry 4). These examples suggest that a broad range of ketones may be efficiently converted to either α-glucosides or β-mannosides.[15,16]

As noted above, an important implication of a glycosylation procedure that does not require addition of a free hydroxyl on the aglycone to a glycosyl donor is its potential to allow site selective glycosylation of aglycones that possess unprotected hydroxyls.[17,18] Silanes are well known to undergo ketone hydrosilylations[13] and alcohol dehydrogenative silylations [19] with a broad range of transition metal catalysts, although remarkably little quantitative data is available regarding the relative rates of the two processes. Our initial examinations of the Cu-IMes catalyst employed herein illustrated that addition of sugar silanes **1** and **2** are efficient with both ketones (hydrosilylation) and alcohols (dehydrogenative silylation), but generally fastest with unhindered hydroxyls. Alternatively, with the Ni-IMes catalyst, hydrosilylations of unhindered ketones proceed much more rapidly than dehydrogenative silylations of alcohols.[20]

In order to illustrate the opportunity for site-selective glycosylation of a hydroxy ketone, dihydrotestosterone (**7**) was subjected to the nickel-catalyzed hydrosilylation procedure, and only the ketone functionality was affected (Scheme 3). Starting with glucosilane **1a**, silyl ether **8a** was prepared in 89% isolated yield with 5:1 diastereoselectivity. Treatment of **8a** to the conditions for intramolecular glycosylation afforded α-glucoside **9a** in 95% isolated yield with complete control of anomeric configuration. Purification of the products of intramolecular glycosylation involves treatment with nBu$_4$NF, so any competitive silylation of the free hydroxyl by TMSOTf during the glycosylation event is inconsequential since the site selectivity is derived from the previous hydrosilylation event. Using the same hydroxyketone **7** combined with mannosilane **2a**, efficient nickel-catalyzed site-selective hydrosilylation proceeds to generate product **8b** in 80 % isolated yield with 6:1 diastereoselectivity. As anticipated based on the lack of impact of sugar structure in controlling the hydrosilylation diastereoselectivity (Table 1, entry 1), diastereoselectivities involving hydrosilylation of chiral substrate **7** were comparable with both gluco- and mannosilanes **1a** and **2a**. Treatment of compound **8b** to the glycosylation conditions afforded β-mannoside **9b** in 92 % isolated yield with complete control of anomeric stereochemistry.

Since the above example (Scheme 3) involves functionalization of an inherently biased substrate with a highly hindered free hydroxyl, we examined the site selectivity of a simpler substrate **10**, which possess both an unhindered ketone and a primary hydroxyl. In this instance, we found highly complementary behavior of the nickel and copper catalytic systems. Treatment of **10** with glucosilane **1a** using the Ni-IMes catalyst led to clean ketone hydrosilylation, affording product **11** in 86 % isolated yield, whereas the corresponding reaction of **10** and **1a** with the Cu-IMes catalyst afforded product **12** from dehydrogenative silylation of the alcohol in 57 % isolated yield, along with 7 % yield of the bis-silylated product derived from reaction of both the ketone and alcohol. Products **11** and **12** were then converted to glycosides **13** and **14** by the standard procedure described above. This catalyst-controlled reversal of chemoselectivity in hydroxyketone functionalization with silanes is unprecedented to our knowledge.[21]

In summary, a new method has been developed that allows the conversion of ketones to native glycoside bonds without the intermediacy of free alcohols. Starting from a hydroxy ketone, the site-selective installation of a glycoside bond at only the ketone or at only the alcohol is possible based on catalyst structure without separate steps involving the protection and deprotection of the alcohol functionality. Additionally, generation of a new stereogenic center, subject to substrate-controlled diastereoselection, is possible during the hydrosilylation-glycosylation sequence, thus allowing aglycone tailoring and glycoside bond installation to be

accomplished in a single strategy. We anticipate that these advances will facilitate the rapid synthesis of various classes of synthetic and natural product-derived glycoconjugates. Application of this concept to other catalytic processes involving sugar silanes, including C-C bond-forming processes, is in progress.

Experimental Section

General Procedure for the $Ni(COD)_2$/IMes Promoted Hydrosilylation of Ketones: A solid mixture of $Ni(COD)_2$ (10%), IMes·HCl (10%), and KO-*t*Bu (10%) was dissolved in dry THF (0.02M) at rt under an inert atmoshphere (N_2), and stirred for 10–15 minutes until the catalyst mixture was a dark blue color. $Ti(O\text{-}iPr)_4$ (1.1–2.2 equiv) was then added to the catalyst mixture followed by the addition of the sugar silane (1.1 equiv), and ketone (1.0 equiv) as a solution in dry THF (0.2M). Upon completion of the reaction, as monitored by TLC, the reaction mixture was filtered through a short plug of silica gel with a mixture of EtOAc/hexanes and concentrated by rotary evaporation. The resulting residue was purified via flash chromatography (SiO_2) to afford the desired product. Note – When doing the site-selective hydrosilylation of a ketone in the presense of a free hydroxyl group, the use of 2.2 equiv of $Ti(O\text{-}iPr)_4$, and a 0.05 M solution in THF results in higher yields of the desired product.

General Procedure for the CuCl/IMes Promoted Hydrosilylation of Ketones: A solid mixture of CuCl (5%), IMes·HCl (5%) and KO-*t*Bu (10%) was dissolved in dry toluene (0.015M) at rt under an inert atmosphere (N_2), and stirred for 20 minutes. A mixture of ketone (1.0 equiv) and silane (1.1 equiv) was dissolved in dry toluene (0.2M), the catalyst was then added to this mixture as a solution in a minimum of dry toluene. Upon completion of the reaction, as monitored by TLC, the reaction mixture was filtered through a short plug of silical gel with a mixture of EtOAc/hexanes and concentrated by rotary evaporation. The resulting residue was purified via flash chromatography (SiO_2) to afford the desired product.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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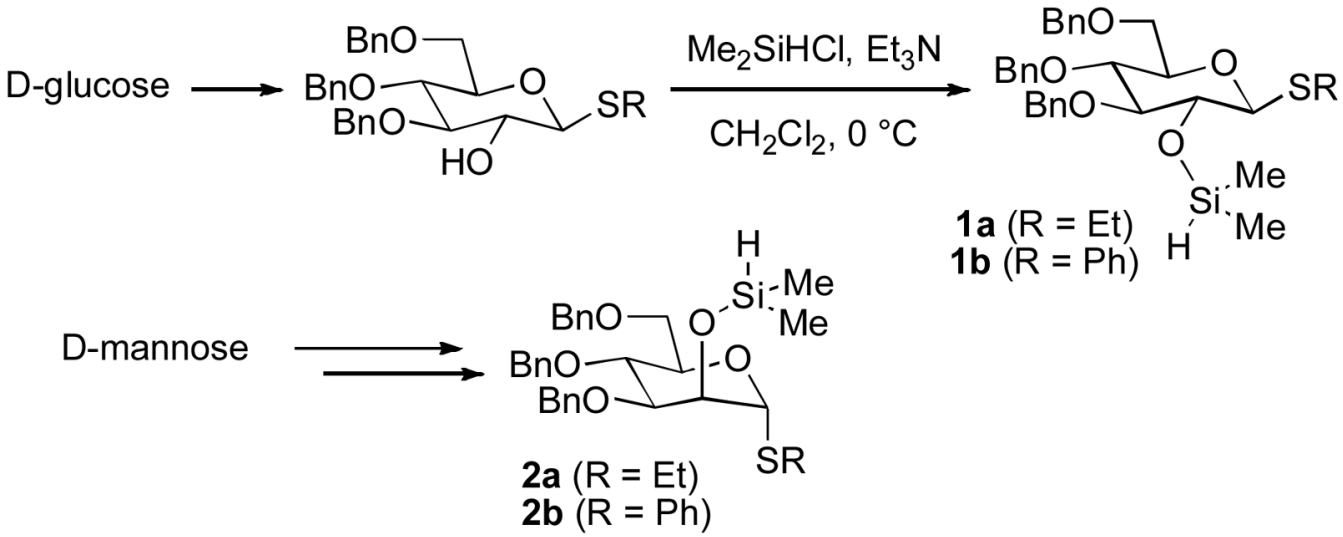
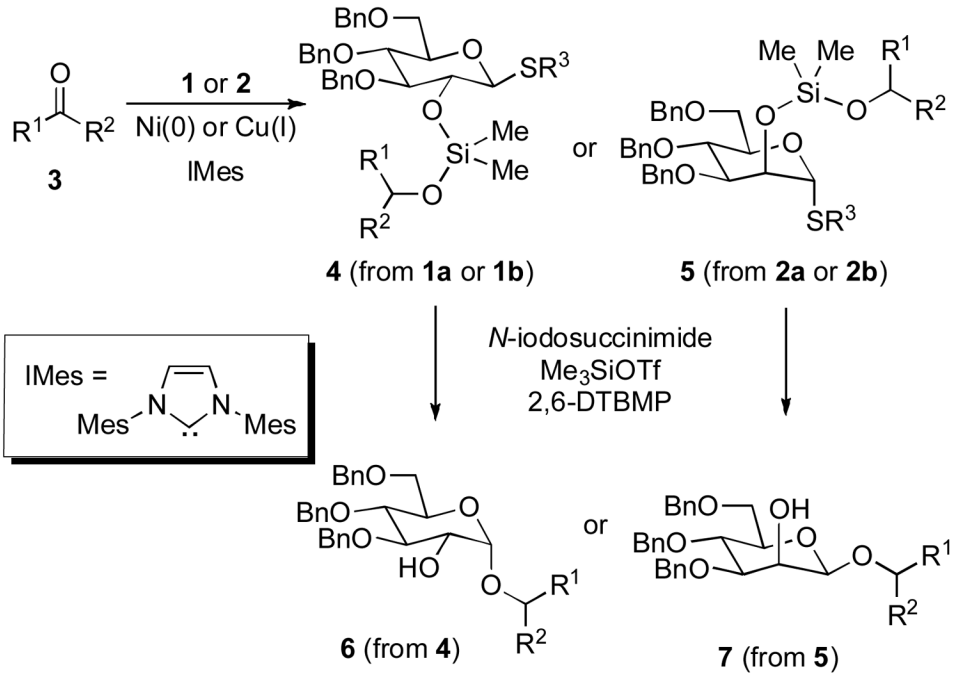
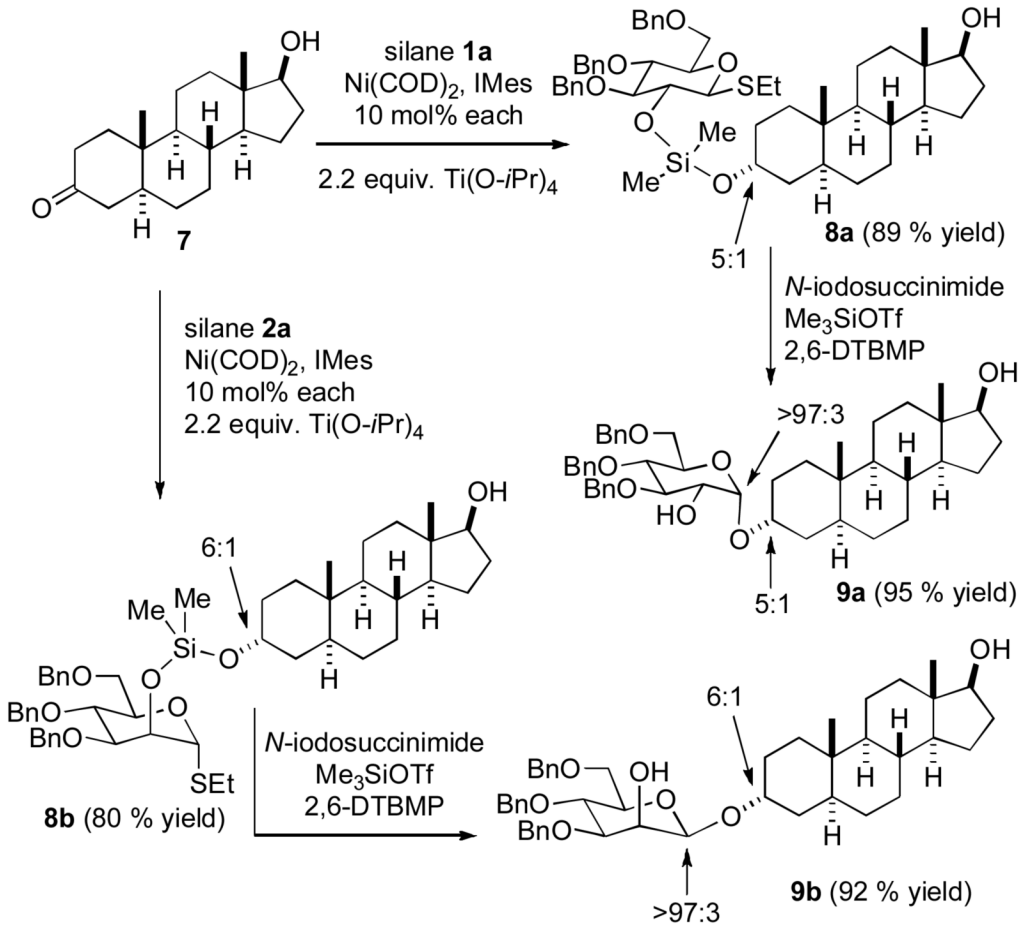
21. The reversal of selectivity is not due solely to the presence of $Ti(O\text{-}iPr)_4$ in the nickel-catalyzed procedure. Adding this reagent to the copper protocol led only to the corresponding isopropoxy sugar silane.



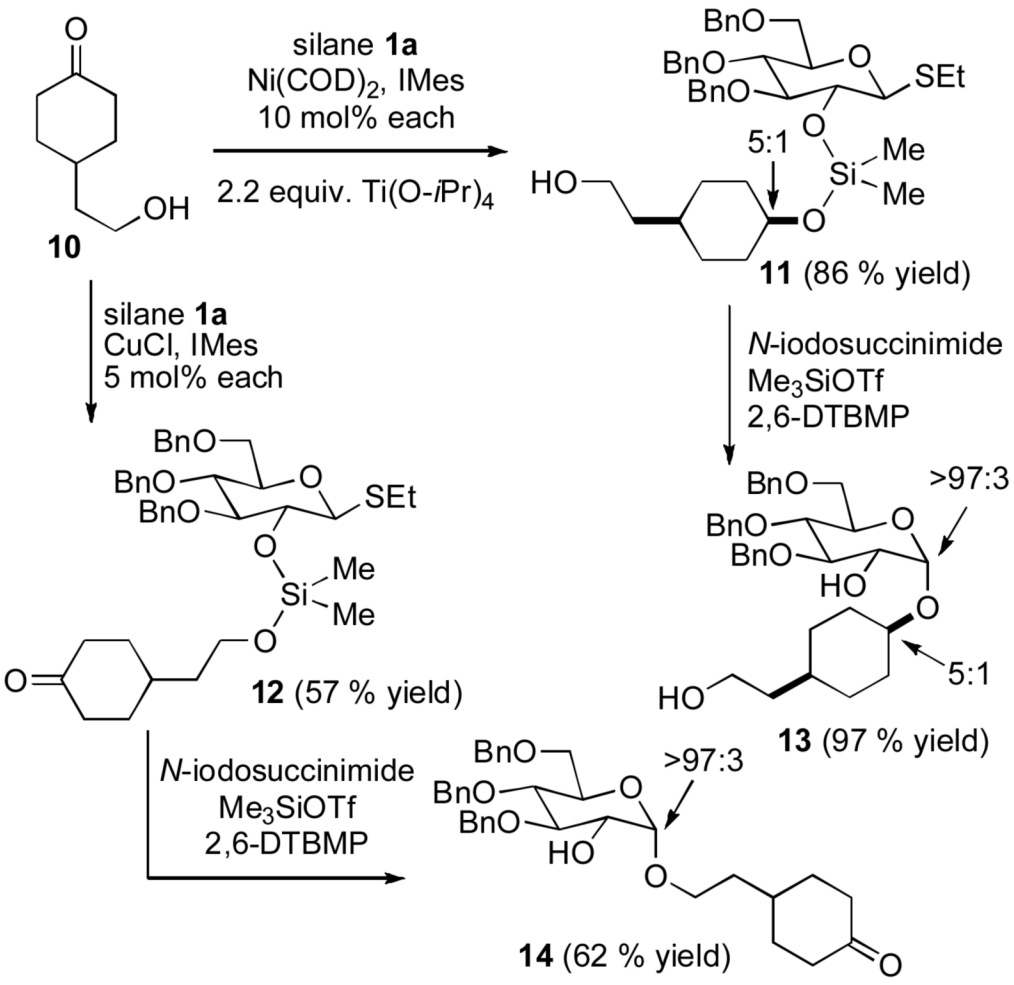
Scheme 1.
Preparation of Sugar Silane Reagents



Scheme 2.
Strategy for Conversion of Ketones to Glycosides.



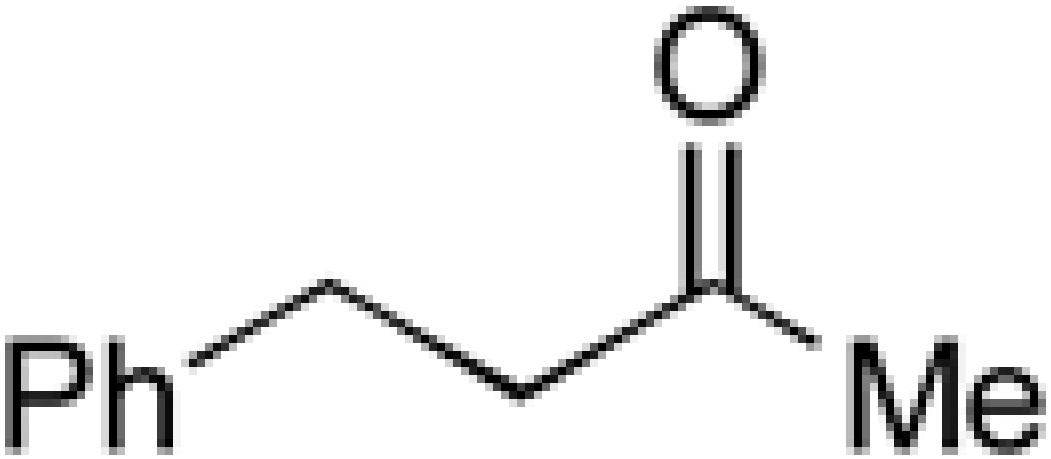
Scheme 3.
Hydroxyketone Site-selective Glycosylation.



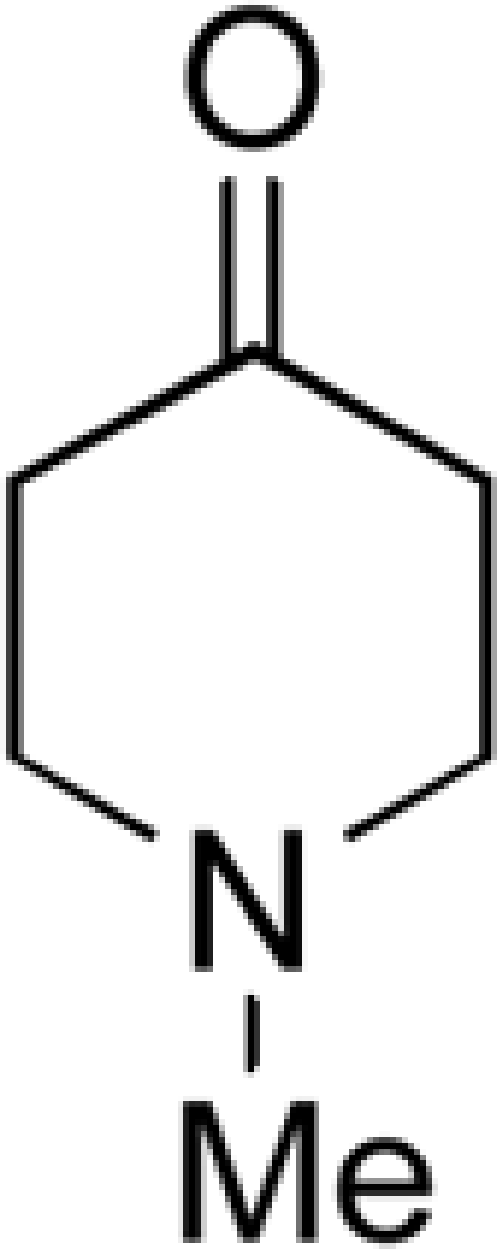
Scheme 4.
Catalyst-Controlled Site Reversal.

Table 1

Ketone Glycosylations.

entry	Ketone 3
1	 **3a**

entry	Ketone 3
2	**3b**

entry	Ketone 3	
3		**3c**

entry	Ketone 3
4	**3d**
5	**3d**
6	**3b**

entry	Ketone 3
7	**3d**

[a] Method A was employed: $Ni(COD)_2$ (10 mol %), IMes·HCl (10 mol %), KO-*t*Bu (10 mol %), $Ti(O\text{-}iPr)_4$ (1.1 equiv), silane **1** or **2** (1.1 equiv), ketone (1.0 equiv), THF (0.1 M), rt, 3–13 h.

[b] Method B was employed: CuCl (5 mol %), IMes·HCl (5 mol %), NaO-*t*Bu (10 mol %), silane **1** or **2** (1.1 equiv), ketone (1.0 equiv), toluene (0.12 M), rt, 4–8 h.

[c] In cases where diastereomeric mixtures are present, the major isomer is depicted.

[d] Glycosylation procedure: Compound **4** or **5** (1.0 equiv), *N*-iodosuccinimide (1.3 equiv), 2,6-di-*t*-butyl-4-methylpyridine (2,6-DTBMP, 2.0 equiv), trimethylsilyl triflate (1.2 equiv), CH_2Cl_2, −40 to 0 °C, then nBu_4NF.