

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

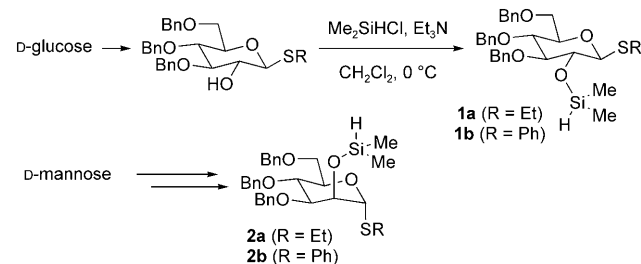
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Many classes of biomolecules derive their biological activity from the synergistic effects of carbohydrate and noncarbohydrate (aglycone) functionalities.^[1] From the standpoint of chemical synthesis, the assembly of the aglycone and attachment of 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 anomeric substituent on the sugar and assembly of the O-glycoside bond through the addition of an aglycone bearing a hydroxy group.^[2] The powerful glycal-oxidation method similarly involves the addition of a hydroxy nucleophile to the electrophilic anomeric position.^[3]

Intramolecular aglycone delivery is an important alternative to these strategies.^[4] Seminal studies by Barresi and Hindsgaul,^[5] Ito and Ogawa^[6] with acetal linkages, and by the research groups of Stork^[7] and Bols^[8] with silane linkages, demonstrated that strategies for intramolecular aglycone delivery provide a powerful entry to *cis*-1,2-glycosides, namely, the synthetically challenging β -mannose and α -glucose configurations. These intramolecular strategies involve glycoside-bond assembly directly from an acetal- or silyl-protected hydroxy group; however, a free hydroxy group is required on the aglycone earlier in the synthesis for the preparation of the tethered aglycone-carbohydrate assembly. An alternate strategy involving O-alkylation of a C1-O-hemiacetal nucleophile with an electrophilic aglycone provides a powerful entry to glycoconjugates and oligosaccharides, although this method also requires that potentially nucleophilic sites on the aglycone are protected.^[9] A glycosylation method that does not require a nucleophilic free hydroxy group on the aglycone at any point in the synthesis, and that tolerates spectator free hydroxy groups on the aglycone, would complement all of the above strategies and could have important implications for native-glycoside-bond construction that is orthogonal to conventional glycosylation methods.^[10]

With this challenge in mind, we sought to develop a transition-metal-catalyzed hydrosilylation of ketones with silyl hydride reagents that contain a glycosyl donor as a silyl substituent. Such a strategy could enable the site-selective construction of glycoside bonds at a carbonyl functionality in the presence of unprotected hydroxy groups on the aglycone, with the simultaneous installation of stereochemical features of the aglycone through reduction of the carbonyl group. Herein we describe the efficient synthesis of “sugar silanes” and present the first examples of the direct glycosylation of ketones as a fundamentally new and orthogonal strategy for the construction of glycoside bonds.

Glycosyl donor reagents with a C2 free hydroxy group, protecting groups at the 3-, 4-, and 6-positions, and a thioalkyl anomeric substituent were prepared readily with the glucose or mannose configuration by known procedures.^[11] The C2 hydroxy group was silylated in near quantitative yield by using commercially available Me₂SiHCl and Et₃N in dichloromethane to afford reagents **1** or **2** (Scheme 1). The synthesis



Scheme 1. Preparation of sugar silane reagents. Bn = benzyl.

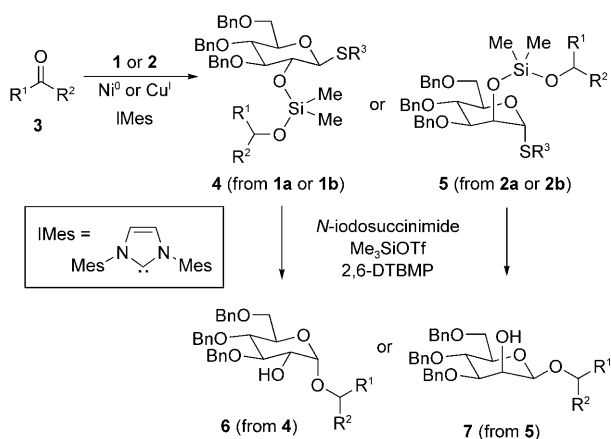
of **1** or **2** may be performed on a multigram scale, and requires only a single chromatographic purification. Although **1** and **2** are not stable to chromatography, they were obtained in pure form and may be stored for months. They can be used after storage in subsequent reactions with comparable results to those obtained with freshly prepared reagents.

In this initial study, we first examined ketone hydrosilylation reactions with reagents **1a,b** or **2a,b**, either a nickel^[12] or a copper^[13] catalyst, and the ligand IMes generated from 1,3-dimesitylimidazolium chloride and KO^{*t*}Bu or NaO^{*t*}Bu (Scheme 2). A variety of unhindered ketones underwent efficient coupling reactions with the catalyst derived from [Ni(cod)₂] and IMes in THF in the presence of Ti(O^{*i*}Pr)₄ as a Lewis acidic additive to afford hydrosilylation products **4** (starting from glucose) or **5** (starting from mannose; Table 1). Control experiments demonstrated that no conversion occurred in the absence of the

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Scheme 2. Strategy for the conversion of ketones into glycosides. Mes = mesityl, Tf = trifluoromethanesulfonyl.

nickel catalyst. The procedure was generally effective with unhindered ketones, whereas the corresponding Cu^I-IMes catalyst, generated in toluene according to the procedure of Nolan and co-workers,^[13] was more effective with hindered ketones. After the preparation of substrates **4** and **5** by hydrosilylation, intramolecular glycosylation by treatment with *N*-iodosuccinimide, trimethylsilyl triflate, and 2,6-di-*tert*-butyl-4-methylpyridine (2,6-DTBMP) in dichloromethane at -40°C and warming of the mixture to 0°C produced α -glucosides **6** (from **4**) and β -mannosides **7** (from **5**).^[14] Both ethylthio and phenylthio sugar silanes, **1a,b** and **2a,b**, were similarly effective in the hydrosilylation reactions, although the phenylthio donors were more effective in subsequent intramolecular glycosylation reactions when hindered ketones were employed.

As a first example, the coupling with benzyl acetone with **1a** proceeded in high yield with the Ni⁰-IMes catalyst to afford **4a** as a 54:46 mixture of diastereomers epimeric at the newly formed stereogenic center (Table 1, entry 1). This result indicates that the chirality of the sugar reagent has little impact on the diastereoselectivity of the hydrosilylation. Glycosylation of **4a** provided the α -glucoside **6a** in 97% yield with excellent diastereoselectivity at the anomeric position. A cyclic acetal and a basic tertiary amine were tolerated in high-yielding transformations with the Ni⁰-IMes catalyst to produce **4b** and **4c** (Table 1, entries 2 and 3), and glycosylation of these substrates afforded the α -glucosides **6b** and **6c** in high yield with excellent diastereoselectivity.

Hydrosilylation reactions 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 (Table 1, entry 4). The hydrosilylation of **3d** with the ethylthio or phenylthio sugar silane **1a** or **1b** produced **4d** or **4e** in good yield with 2:1 diastereoselectivity. The subsequent glycosylation, however, was much more efficient with the phenylthioglycosyl donor **4e**, which gave the product **6d** in 72% yield. Compound **6d** was formed in just 20% yield from **4d**. The enhancement of diastereoselectivity observed in the glycosylation is derived from the significantly different rates of glycosylation of the two diastereomers of **4d** or **4e**.

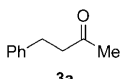
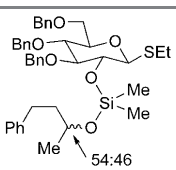
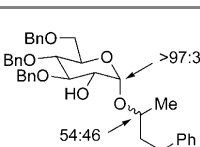
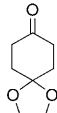
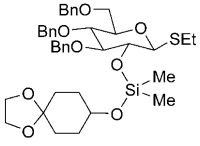
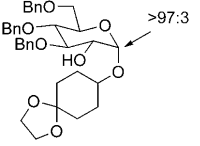
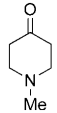
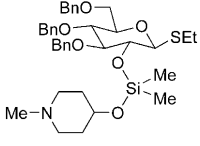
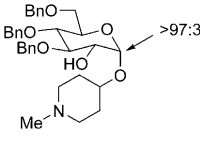
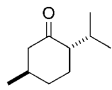
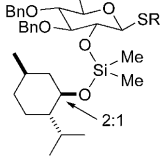
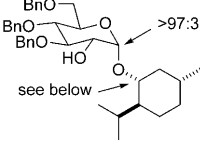

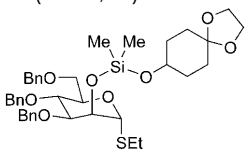
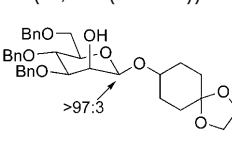

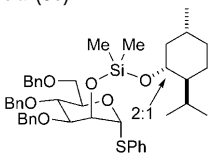
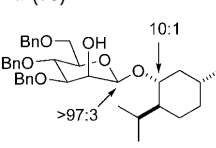
The efficiency of the process in β mannosylations was next examined. The hydrosilylation of ketone **3b** with the mannose silane **2a** proceeded efficiently with the Ni-IMes catalyst to afford **5a** in 86% yield (Table 1, entry 5). The glycosylation of **5a** was moderately effective: The β -mannoside **7a** was generated exclusively in 58% yield with excellent control of the anomeric configuration. The hydrosilylation of (–)-menthone (**3d**) with the mannose silane **2b** in the presence of the Cu-IMes catalyst afforded **5b** in 75% yield with 2:1 diastereoselectivity (Table 1, entry 6), and subsequent glycosylation afforded β -mannoside **7b** in 74% yield with excellent control of the anomeric configuration. Enhancement of the diastereomeric ratio derived from carbonyl reduction was again observed (compare Table 1, entry 4). These examples suggest that a broad range of ketones may be converted efficiently into either α -glucosides or β -mannosides.^[15,16]

An important implication of a glycosylation procedure that does not require the addition of a free hydroxy group on the aglycone to a glycosyl donor is its potential to enable the site-selective glycosylation of aglycones that contain unprotected hydroxy groups.^[17,18] Silanes are well known to undergo ketone hydrosilylation^[13] and alcohol dehydrogenative silylation^[19] reactions 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 investigations of the Cu-IMes catalyst employed herein indicated that the addition of sugar silanes **1** and **2** is efficient with both ketones (hydrosilylation) and alcohols (dehydrogenative silylation), but generally fastest with unhindered hydroxy groups. In contrast, with the Ni-IMes catalyst, hydrosilylation reactions of unhindered ketones proceeded much more rapidly than dehydrogenative silylation reactions of alcohols.^[20]

To illustrate the opportunity for the site-selective glycosylation of a hydroxyketone, dihydrotestosterone was subjected to the nickel-catalyzed hydrosilylation procedure: Only the ketone functionality was affected (Scheme 3). With glucosilane **1a**, silyl ether **8a** was prepared in 89% yield with 5:1 diastereoselectivity. Treatment of **8a** under the conditions for intramolecular glycosylation afforded α -glucoside **9a** in 95% yield with complete control of the anomeric configuration. Purification of the products of intramolecular glycosylation involves treatment with *n*Bu₄NF, so any competitive silylation of the free hydroxy group by TMSOTf during the glycosylation event is inconsequential. When the same dihydrotestosterone was used in combination with mannosilane **2a**, an efficient nickel-catalyzed site-selective hydrosilylation generated product **8b** in 80% yield with 6:1 diastereoselectivity. As anticipated on the basis of the lack of impact of the sugar structure on the diastereoselectivity of the hydrosilylation (Table 1, entry 1), the diastereoselectivities observed in the hydrosilylation of dihydrotestosterone with the gluco- and mannosilanes **1a** and **2a** were comparable. The treatment of compound **8b** under the glycosylation conditions afforded β -mannoside **9b** in 92% yield with complete control of the anomeric configuration.

Since the example in Scheme 3 involves functionalization of an inherently biased substrate with a highly hindered free hydroxy group, we examined the site selectivity of a simpler

Table 1: Ketone glycosylation.

Entry	Ketone 3	Silyl ether 4 or 5 ^[a] (Yield [%])	Glycoside 6 or 7 ^[a,b] (Yield [%])
1	 3a	 4a (97) ^[c] 54:46	 6a (97) >97:3 54:46
2	 3b	 4b (96) ^[c]	 6b (82) >97:3
3	 3c	 4c (99) ^[c]	 6c (70) >97:3
4	 3d	 4d (R = Et, 68) ^[d] 4e (R = Ph, 64) ^[d] 2:1	 6d (20, 4:1 (from 4d)) 6d (72, 5:1 (from 4e)) see below
6	 3b	 5a (86) ^[c]	 7a (58) >97:3
7	 3d	 5b (75) ^[d] 2:1	 7b (74) >97:3 10:1

[a] In cases of diastereomeric mixtures, the major isomer is depicted. [b] Glycosylation procedure: **4** or **5** (1.0 equiv), *N*-iodosuccinimide (1.3 equiv), 2,6-DTBMF (2.0 equiv), trimethylsilyl triflate (1.2 equiv), CH₂Cl₂, -40→0°C, then *n*Bu₄NF. [c] Method A was employed: [Ni(cod)₂] (10 mol%), IMes-HCl (10 mol%), KO^tBu (10 mol%), Ti(OiPr)₄ (1.1 equiv), silane **1** or **2** (1.1 equiv), ketone (1.0 equiv), THF (0.1 M), room temperature, 3–13 h. [d] Method B was employed: CuCl (5 mol%), IMes-HCl (5 mol%), NaO^tBu (10 mol%), silane **1** or **2** (1.1 equiv), ketone (1.0 equiv), toluene (0.12 M), room temperature, 4–8 h. cod = 1,5-cyclooctadiene.

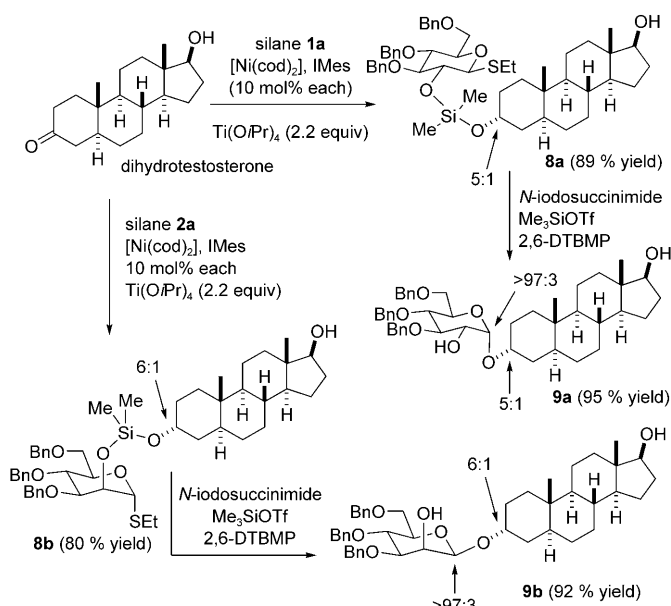
substrate **10**, which contains both an unhindered ketone and a primary hydroxy group. In this instance, we found highly complementary behavior of the nickel and copper catalytic systems. The treatment of **10** with glucosilane **1a** in the presence of the Ni-IMes catalyst led to clean ketone hydrosilylation to afford product **11** in 86% 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% yield, along with the bissilylated

product derived from the reaction of both the ketone and alcohol functionalities in 7% yield (Scheme 4). Products **11** and **12** were then converted into 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]

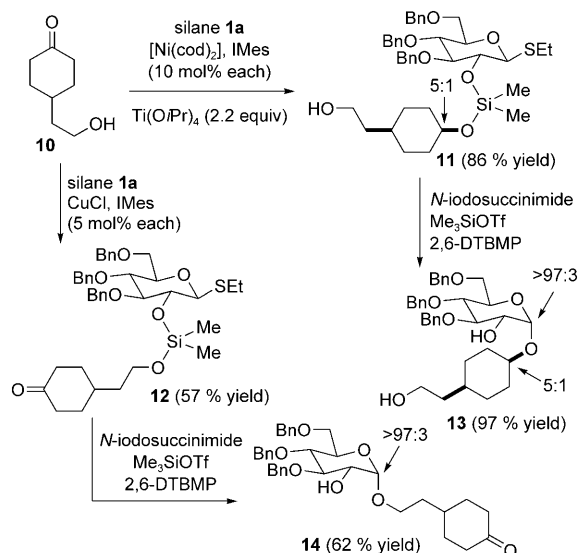
In summary, we have developed a method for the conversion of keto groups into native glycoside bonds without the intermediacy of free alcohols. The site-selective installation of a glycoside bond at only the ketone or only the alcohol functionality of a hydroxyketone is possible through selection of the appropriate catalyst without separate steps involving the protection and deprotection of the alcohol functionality. Furthermore, the generation of a new stereogenic center with substrate-controlled diastereoselectivity is possible during the hydrosilylation–glycosylation sequence. Thus, a single strategy enables aglycone tailoring and glycoside-bond installation. We anticipate that these advances will facilitate the rapid synthesis of various classes of synthetic and natural product derived glycoconjugates. The application of this concept to other catalytic processes involving sugar silanes, including C–C bond-forming processes, is in progress.

Experimental Section

Method A: A solid mixture of [Ni(cod)₂] (10 mol%), IMes-HCl (10 mol%), and KO^tBu (10 mol%) was dissolved in dry THF (0.02 M) at room temperature under an inert atmosphere (N₂), and the resulting mixture was stirred for 10–15 min until it was dark blue. Ti(OiPr)₄ (1.1–2.2 equiv) was then added to the catalyst mixture, followed by the sugar silane (1.1 equiv) and the ketone (1.0 equiv) as a solution in dry THF (0.2 M). Upon completion of the reaction, as indicated by TLC, the reaction mixture was filtered through a short plug of silica gel with a mixture of EtOAc and hexanes and concentrated by rotary evaporation. The resulting residue was purified by flash chromatography (SiO₂) to afford the desired product. Note: For the site-selective hydrosilylation of a ketone in the presence of a free hydroxy group, the use of 2.2 equivalents of Ti(OiPr)₄ and a 0.05 M solution in THF results in a higher yield of the desired product.



Scheme 3. Site-selective glycosylation of dihydrotestosterone.



Scheme 4. Catalyst-controlled silylation-site reversal.

Method B: A solid mixture of CuCl (5 mol%), IMes·HCl (5 mol%), and KO^tBu (10 mol%) was dissolved in dry toluene (0.015 M) at room temperature under an inert atmosphere (N₂). The resulting mixture was stirred for 20 min and then added to a solution of the ketone (1.0 equiv) and the silane (1.1 equiv) in dry toluene (0.2 M). Upon completion of the reaction, as indicated by TLC, the reaction mixture was filtered through a short plug of silica gel with a mixture of EtOAc and hexanes and concentrated by rotary evaporation. The resulting residue was purified by flash chromatography (SiO₂) to afford the desired product.

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