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Perspective

Aromatic O-glycosylation

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Abstract—Carbohydrates carrying an aromatic aglycon are important natural products and thus key synthetic targets. However, due to the electron-withdrawing properties of aromatic rings, phenols are difficult to glycosylate. This review covers the most common carbohydrate donors used for aromatic O-glycosylation (anomeric acetates, halides, trichloroacetimidates and thioglycosides) as well as some less common donors. The scope of the review is to give practical examples of aromatic O-glycosylations and to offer guidelines for glycosylation of typical aromatic residues. Anomeric acetates or trichloroacetimidates, activated under acidic conditions, are preferred for electron rich aromatic aglycons, while glycosyl halides, activated using basic conditions, are preferred for electron deficient aromatic residues.

Keywords: Glycosylation; Aromatic; Anomeric acetate; Trichloroacetimidate; Halide

1. Introduction

Naturally occurring carbohydrates carrying aromatic aglycons are important compounds with examples such as antibiotics (e.g., vancomycin and chromomycin) and a range of more or less complex glycosylated phenols of plant origin (e.g., arbutin, sennoside A and glucofrangulin A, Fig. 1).

The first synthesis of a glycosidic linkage was the coupling of peracetylated glucosyl chloride to potassium phenolate, which was reported by Michael in 1879.[1] Since then, carbohydrate synthesis has evolved into a thriving

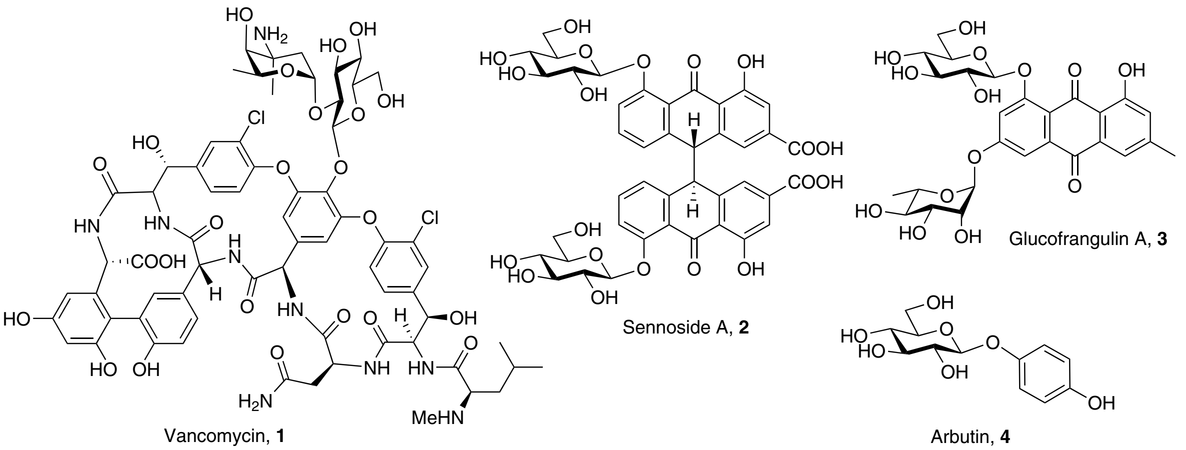

Figure 1. Examples of naturally occurring glycosylated aromatic compounds.

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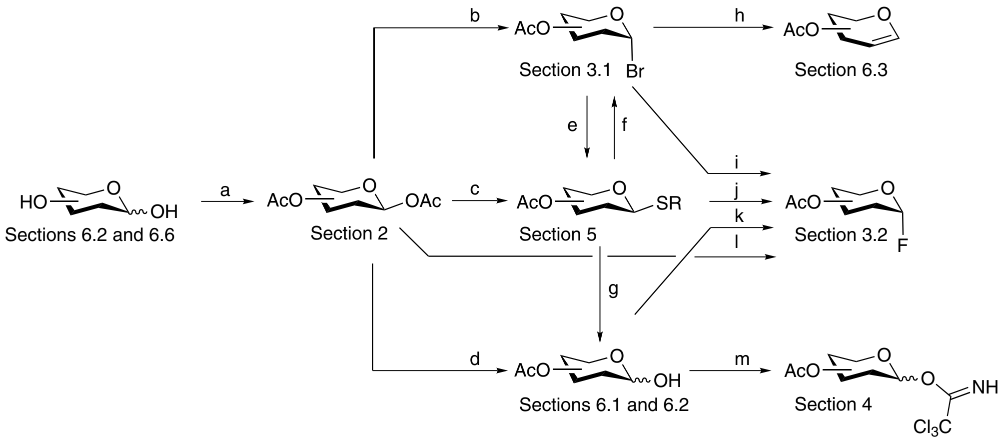


Scheme 1. Examples of donor interconversions. Reagents and conditions: (a) Ac_2O, NaOAc, 140 °C, 1 h;[3] (b) HBr/HOAc, Ac_2O, rt, 1 h;[4] (c) RSH, $BF_3{\cdot}OEt_2$, CH_2Cl_2, 0 °C, 45 min;[5] (d) amine, THF, 75 °C, 18 h;[6] (e) NaSPh, Et_2O, rt, 2 d;[7] (f) IBr, CH_2Cl_2, 0 °C, 10 min;[8] (g) NBS, acetone, H_2O, rt, 1 h;[9] (h) Zn/Ag–C, THF, −20 °C, 10 min;[10] (i) AgF, CH_3CN, rt, 2 h;[11] (j) DAST, NBS, CH_2Cl_2, 0 °C to rt, 25 min;[12,13] (k) DAST, CH_2Cl_2, −78 °C, 15 min;[13] (l) HF/pyridine, 0 °C, 6 h;[14] (m) Cl_3CCN, DBU, CH_2Cl_2, −10 °C to rt, 3 h.[15]

field with an abundance of methods for the formation of the glycosidic linkage. The most common donors and their interconversions are summarized in Scheme 1. Conditions for activation of different donors can be found in the recent review by Nicolaou and Mitchell.[2]

Glycosidic bonds can be formed either through an S_N2 type mechanism, usually under basic conditions with glycosyl halides, or through an S_N1 type mechanism under acidic conditions. The stereochemical outcome of Lewis acid-promoted glycosylations is influenced by several factors. The anomeric effect generally directs the aglycon to the thermodynamically preferred axial orientation. However, participating groups (e.g., esters) at C2 can interact with the intermediate oxacarbenium ion to form a cyclic dioxolenium ion. The dioxolenium ion is subsequently opened by the acceptor in an S_N2 manner, which results in a 1,2-*trans*-glycosidic bond (i.e., β-glucosides and α-mannosides). β-D-Glucosides and galactosides, as well as α-D-mannosides, are therefore fairly easily synthesized by standard methods, whereas α-D-glucosides and galactosides can be formed by anomerization of the kinetic β-products. However, β-D-mannosides are difficult to synthesize and usually special methods need to be used.

A search of the literature concerning aromatic O-glycosylations revealed increasing interest in the recent years. The search was separated into the four most common donors, that is, anomeric acetates, glycosyl halides, trichloroacetimidates and thioglycosides (Fig. 2). Halides are most common, followed by anomeric acetates and trichloroacetimidates, while thioglycosides are less commonly used for aromatic O-glycosylation. There are also examples of aromatic O-glycosylation using sugars unprotected at the anomeric centres (e.g., by Mitsunobu conditions or S_NAr), glycals, anomeric phosphates and also enzymatic methods.

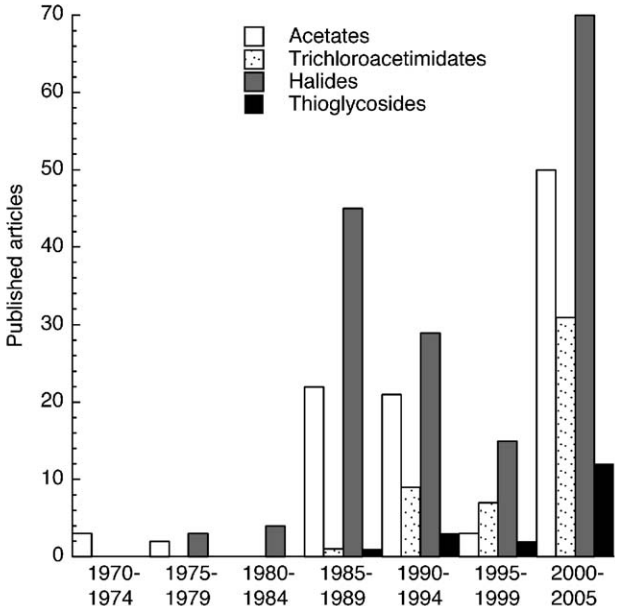
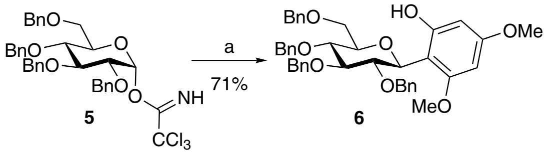


Figure 2. Published articles concerning aromatic O-glycosylation, 1970–2005.

There are several specific problems associated with glycosylation of phenols. First, compared to the aliphatic chain in alcohols, the aromatic ring in a phenol is electron withdrawing. Under acidic conditions, this results in phenols being weaker nucleophiles compared to alcohols. Nevertheless, acceptable yields can usually be obtained using phenols carrying electron-donating groups (e.g., *p*-methoxyphenol). Phenols are also considerably more acidic than alcohols, usually by 6–8 pK_a units, which means that they are easily deprotonated and usually give good yields under basic conditions, especially with phenols carrying electron-withdrawing substituents.



Scheme 2. Reagents and conditions: (a) appropriate phenol, TMSOTf, CH_2Cl_2, −30 °C to rt, 3 h.

Second, due to the electron donating properties of the hydroxyl group, phenols are ambident nucleophiles. Glycosylation of phenols under acidic conditions can therefore, especially at elevated temperatures, give considerable amounts of C-glycosides. This observation has been used for synthetic purposes as exemplified by the synthesis of compound **6** (Scheme 2).[16]

A third problem is steric hindrance from substituents on the phenolic compound. The nucleophilicity of phenols and alcohols in glycosylation reactions can be enhanced by tributylstannylation or trimethylsilylation,[17–19] which gives better yields in some reactions, but fails in others.[20]

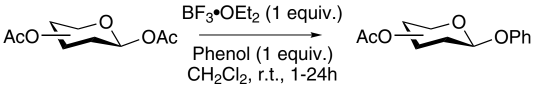
Apart from the excellent review, covering O-glycosylations under neutral or basic conditions, by Jensen in 2002, there have been few reviews on aromatic O-glycosylations.[21,22] The scope of this review is to give practical examples of aromatic O-glycosylations and to offer guidelines for glycosylation of typical phenols. In the following text, the terms α- or β-selectivity refer to a normal D-pyranoside system (e.g., glucose or galactose). For rules on the anomeric nomenclature for other compounds, we use the IUPAC carbohydrate nomenclature recommendations.[23]

2. Use of glycosyl acetates

Glycosyl acetates can be activated by Lewis as well as Brønsted acids (Helferich conditions) and used as donors in aromatic O-glycosylations (Scheme 3).

2.1. General considerations

The strength of glycosyl acetates as donors in glycoside synthesis lies in their simplicity, i.e., the peracetylated compounds are inexpensive and either commercially available or easily synthesized in one step from the corresponding free sugars. As a result, virtually all glycosylation reactions using anomeric acetates are performed with the peracetylated compounds. If several protecting groups are essential, usually some other donor is used.



Scheme 3. General $BF_3{\cdot}OEt_2$ catalyzed aromatic O-glycosylation.

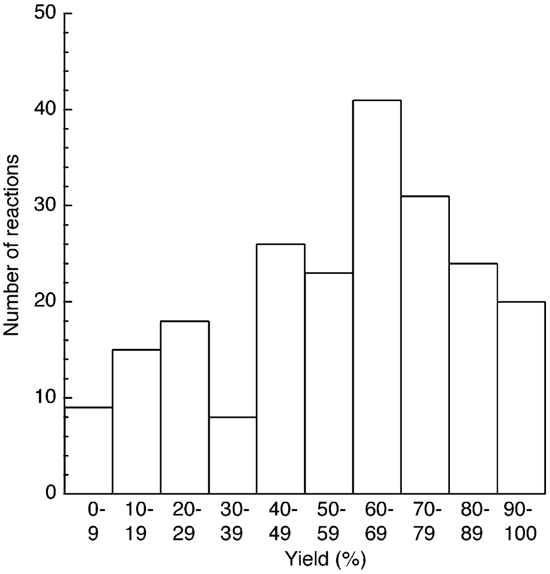
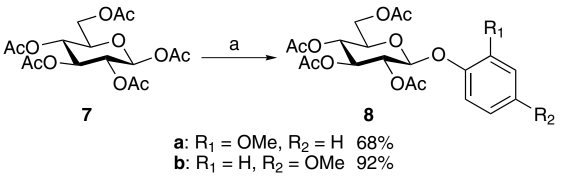


Figure 3. Distribution of yields in 213 aromatic O-glycosylations using anomeric acetates.

A literature search of one-step aromatic O-glycosylations using glycosyl acetates generated 213 hits, which were analyzed with reference to yield (Fig. 3). The yields of aromatic O-glycosylation using anomeric acetates are usually lower compared to trichloroacetimidates.[20,24] One reason is the anomerization of both the starting material and the product. For example, in a few hours using 3 equiv of $BF_3{\cdot}OEt_2$ peracetylated β-glucose pentaacetate anomerized to α-glucose pentaacetate, which was shown to be inert.[25] Long reaction times, high temperature and polar solvents usually tend to give more of the α-glucoside.[26] However, contrary to glycosylation of alcohols and other sugars, it is not easy to obtain good yields of the α-glucosides of aromatic aglycons due to the formation of C-glycosides, especially in the case of activated aromatic compounds. The yield of the α-product can be optimized in benzene at reflux.[26]

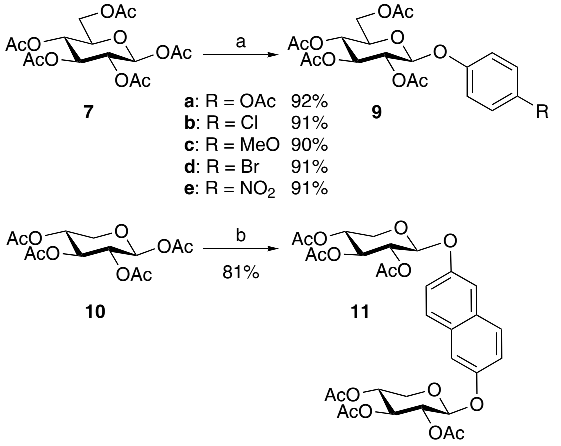
Typical aromatic β-glycosylations are performed in dichloromethane as solvent with equimolar amounts of $BF_3{\cdot}OEt_2$ and reactants for 1–24 h at room temperature (Scheme 3). $SnCl_4$, *p*-toluenesulfonic acid (*p*TSA) and other Lewis acids have also been used, but most often with substantially lower yields.[27,28] The yields and reaction rates are clearly dependent on the nucleophilicity of the phenol; electron donating groups (e.g., alkoxy) usually give better yields. Generally, substituents in the *ortho*-position tend to give lower yields irrespective of the electronic properties (Scheme 4).[26,29]



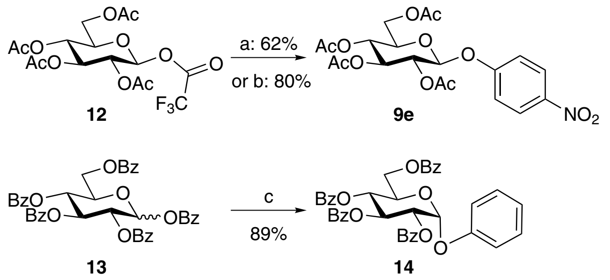
Scheme 4. Reagents and conditions: (a) appropriate phenol, $BF_3 \cdot OEt_2$ (0.1 equiv), CH_2Cl_2, rt, 48 h.

2.2. Prevention of product anomerization

It is known that phenyl glucosides do not anomerize to any appreciable amount using Lewis acid catalysis.[30] However, in the presence of a catalytic amount of phenol, the anomerization is fast and the rate of anomerization is dependent on the aromatic moiety; that is, aglycons carrying electron donating substituents anomerize faster.[26,30] It is also possible to convert β-glycosides of very acidic phenols to α-glycosides using alkali as catalyst.[31] To prevent anomerization, Lee et al. presented the use of a sub-equimolar amount of base.[29] The use of 2.5 equiv of $BF_3 \cdot OEt_2$ and 0.5 equiv of triethylamine (TEA) resulted in excellent glucosylation yields of different phenols (Scheme 5). However, higher ratios of base compared to Lewis acid prevent any reaction as exemplified by a quantitative recovery of the starting material in the reaction with 3-diethylaminophenol.[26] We have also observed a much lower rate of anomerization in glycosylations performed on solid support and the aminomethylated resin may possibly act in the same way as the added base.[32] We evaluated Lee's method by dixylosylation of a dihydroxynaphthalene in an excellent 81% yield (unpublished result, Scheme 5).



Scheme 5. Reagents and conditions: (a) appropriate phenol, $BF_3 \cdot OEt_2$ (2.5 equiv), TEA (0.5 equiv), CH_2Cl_2, rt, 6–41 h; (b) 2,6-dihydroxynaphthalene, $BF_3 \cdot OEt_2$ (2.5 equiv), TEA (0.5 equiv), CH_2Cl_2, rt, overnight.



Scheme 6. Reagents and conditions: (a) *p*-nitrophenol, $BF_3 \cdot OEt_2$, CH_2Cl_2, −20 °C, 50 min, 62%; (b) *p*-nitrophenol, TMSOTf, CH_2Cl_2, −20 °C, 50 min, 80%; (c) phenol, $BF_3 \cdot OEt_2$, CH_2Cl_2, 50 °C, 48 h.

2.3. Use of other glycosyl esters

Anomeric trifluoroacetates have been used for the synthesis of a number of aromatic glycosides.[33] The trifluoroacetate was activated either by $BF_3 \cdot OEt_2$ or TMSOTf and gave good yields (85–90%) using activated aromatic aglycons. Deactivated aromatic acceptors gave lower yields using $BF_3 \cdot OEt_2$, but the yields could be improved using TMSOTf (Scheme 6). The drawback of this method is the multi-step synthesis of donor **12**. Perbenzoylated glucose (**13**) has also been used as donor and gave an excellent yield of α-glucoside **14** upon prolonged reaction times (Scheme 6).[34] There are also examples of the use of other anomeric benzoates.[35]

3. Use of glycosyl halides

Glycosyl halides are by far the most used carbohydrate donors for aromatic O-glycosylation. Of these, the vast majority are glycosyl bromides as indicated by Figure 4. Glycosyl bromides are generally more reactive compared to glycosyl chlorides, yet not as unstable as the corresponding iodides. There are very few examples of aromatic O-glycosylations using glycosyl iodides.[36]

3.1. Glycosyl bromides and chlorides

A literature search of one-step aromatic O-glycosylations using glycosyl bromides and chlorides generated

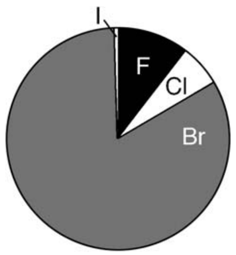


Figure 4. Distribution of publications concerning aromatic O-glycosylation using glycosyl halides (1970–2005).

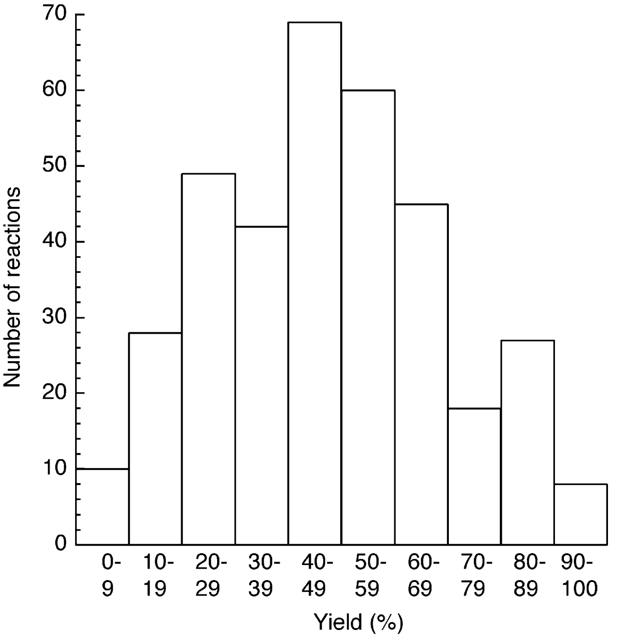


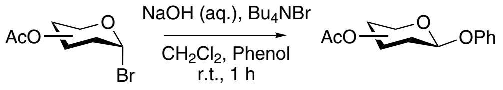
Figure 5. Distribution of yields in 356 aromatic O-glycosylations using glycosyl bromides and chlorides.

356 hits, which were analyzed with reference to yield (Fig. 5.)

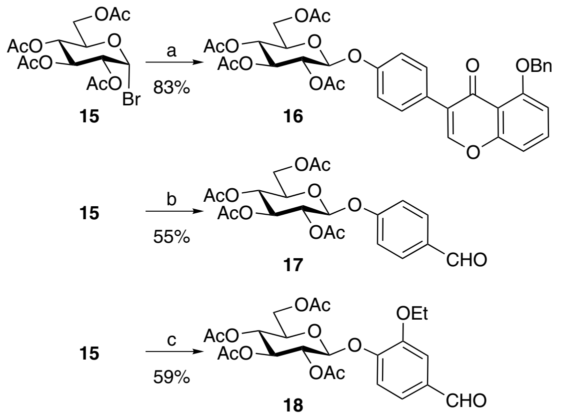
Generally, the glycosyl halides give less than 60% yield of the product but their strength lies in their simplicity and well-known procedures; they are especially useful for glycosylation under basic conditions. Glycosyl bromides are usually isolated as the thermodynamically favored α-anomer and glycosylation generally results in the inversion of stereochemistry.

The original Michael procedure (i.e., the use of a halide in combination with a phenolate) has evolved into three variations: phase transfer catalysis (PTC), use of mixed solvents (e.g., aqueous methanol) and use of aprotic solvents (Scheme 7).

The most common procedure is phase transfer catalysis. In these reactions, the glycosyl bromide is dissolved in dichloromethane or chloroform and a water/methanol solution of the base (NaOH, K_2CO_3 or LiOH) is added together with a suitable phase transfer catalyst such as tetrabutylammonium salts (TBA or Q salts) or crown ethers. A few typical examples are shown in Scheme 8. The synthetically challenging compound **18** was prepared using the corresponding protected glucosyl bromide under PTC conditions, which gave better results compared to both acetate and trichloroacetimidate donors.[20]



Scheme 7. General aromatic O-glycosylation using a glycosyl bromide and PTC conditions.

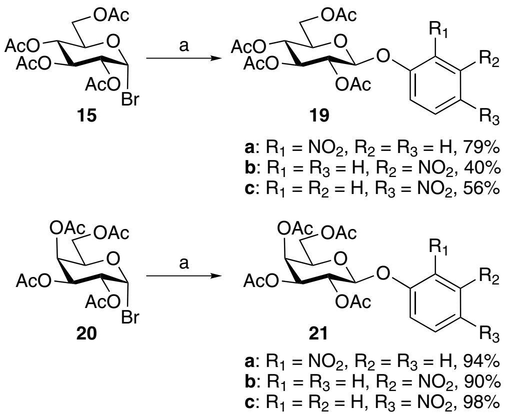


Scheme 8. Reagents and conditions: (a) appropriate phenol, K_2CO_3 (aq), $CHCl_3$, $BnEt_3NCl$, rt, 2 d;[37] (b) appropriate phenol, n-Bu_4NBr, $CHCl_3$, NaOH (aq), 60 °C, 6 h;[38] (c) appropriate phenol, n-Bu_4NBr, CH_2Cl_2, NaOH (aq), rt, 45 min.[20]

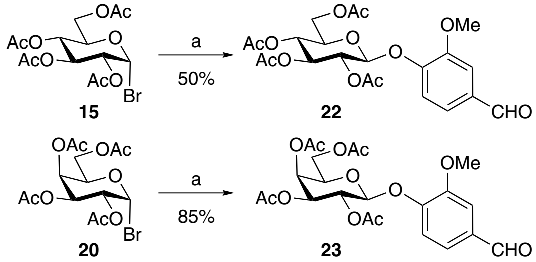
An anionic exchange resin was used for the formation of nitrophenoxides and subsequent glycosylation, which provided the products in yields from 40% up to 98% as shown in Scheme 9.[39] The use of DMF as a solvent resulted in increased formation of 2-substituted glycols, which are produced by elimination.

Apparently, due to less β-elimination, galactose generally seems to give better yields compared to glucose as illustrated in Schemes 9 and 10.[40,41] Another general observation is that aromatic residues with electron-withdrawing groups tend to give better yields, possibly due to easier deprotonation and subsequent phase transfer. A few examples are given in Scheme 11.[41,42] PTC conditions have also been used in a solid phase approach to phlorizin analogs as shown by the xylosylation and subsequent cleavage to give compound **28** in 92% yield and 88% purity (Scheme 12).[43]

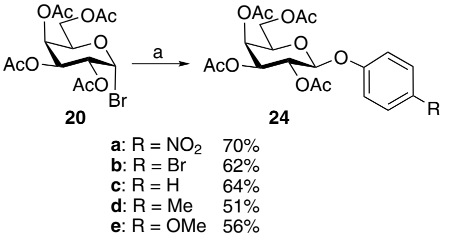
Investigations using tetra-*O*-benzyl-α-D-glucopyranosyl bromide and several phenols, as well as different phase transfer catalysts, showed no differences in yields



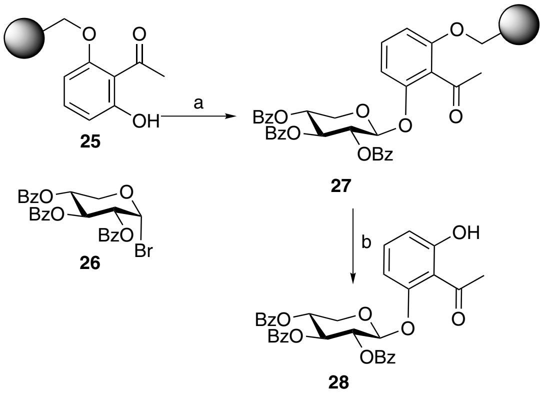
Scheme 9. Reagents and conditions: (a) appropriate phenol bound to Amberlyst A-26, 2-propanol, rt, 8 h.



Scheme 10. Reagents and conditions: (a) appropriate phenol, Bu_4NBr, $CHCl_3$, NaOH (aq), rt, 1 h.



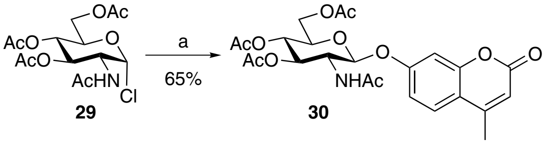
Scheme 11. Reagents and conditions: (a) appropriate phenol, NaOH (aq), $CHCl_3$, $BnEt_3NBr$, 60 °C, 3 h.



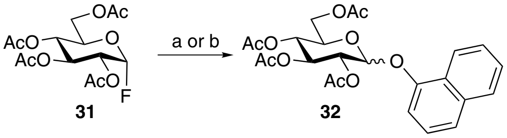
Scheme 12. Reagents and conditions: (a) NaOH (5% aq), dichloroethane, *n*-Bu_3BnNCl, rt, 15 h; (b) TFA (10% in CH_2Cl_2), rt, 30 min.

between the catalysts and no obvious trend in the reactivity of phenols carrying electron-donating or withdrawing groups, possibly due to the high reactivity of the per-*O*-benzylated compound.[44] One problem associated with phase transfer reactions is low solubility of some aromatic aglycons.[42,45,46] Another variation of the original Michael protocol is the use of aprotic solvents such as DMF, HMPA or DMSO.[47] A very interesting example is the glycosylation of 4-methyl umbelliferone with chloride **29**, one of the few good yielding glycosylations reported for 2-acetamido-2-deoxy sugar derivatives (Scheme 13).[48]

Apart from Michael type reactions, glycosyl halides can be activated using the Koenigs–Knorr procedure, i.e., the use of silver salts (e.g., Ag_2CO_3,[49] AgOTf[20] or Ag_2O[50]) or mercury salts.[20] Typical solvents are CH_2Cl_2,[20] quinoline[50] and pyridine.[49]



Scheme 13. Reagents and conditions: (a) 4-methyl umbelliferone, DMF, rt, 16 h.



Scheme 14. Reagents and conditions: (a) 1-naphthol, $BF_3{\cdot}OEt_2$, CH_3CN, rt, 3 h, 90%, α:β = 40:60; (b) 1-naphthol, $BF_3{\cdot}OEt_2$, 1,1,3,3-tetramethylguanidine, CH_3CN, rt, 3 h, 93%, α:β = 3:97.

3.2. Fluorides

Glycosyl fluorides are relatively stable (both α and β), which facilitates synthesis and purification but hampers their use as donors in glycosylation reactions. Mukaiyama introduced the use of glycosyl fluorides, and a number of different promoter systems have been developed.[51,52] For aromatic O-glycosylations, the use of $BF_3{\cdot}OEt_2$ is most common and typical reaction conditions are given in Scheme 14. The addition of a hindered base (1,1,3,3-tetramethylguanidine) resulted in excellent β-selectivity,[53,54] and also lowered the amount of C-glycosides formed.[55] Another promoter system that gives good yield is $Cp_2HfCl_2/AgClO_4$.[55,56] Finally, glycosyl fluorides have been used in Michael type reactions using sodium phenolate in ethanol–CH_2Cl_2.[57]

3.3. Glycosylation of aromatic heterocycles

There are very few reported examples of glycosylation of aromatic heterocycles. Most syntheses are reported by Hanessian et al. in the search for new donors for glycosylation (especially 3-methoxypyridyl, MOP).[58] A few examples, synthesized from glycosyl bromides (Glc, Fuc, $GlcN_3$, $GalN_3$, GlcNAc, GalNAc, Xyl, Ara) and silver salts of the heterocycles in 30–77% yield, are

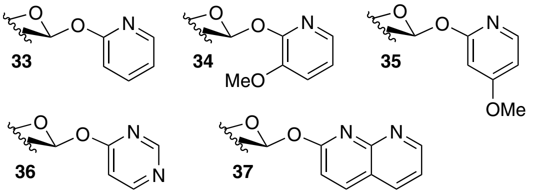


Figure 6. Examples of glycosylated aromatic heterocycles.

shown in Figure 6. There are also examples of glycosylation of heterocycles carrying nitro groups.[59,60]

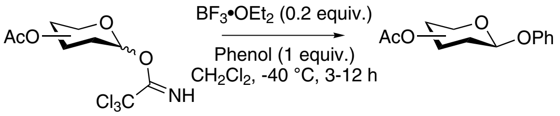
4. Use of glycosyl trichloroacetimidates

Trichloroacetimidate donors can be activated even at low temperatures by a catalytic amount of Lewis acid and thus this is the method of choice for sensitive or complicated targets (Scheme 15). The trichloroacetimidate method usually works well for the synthesis of 1,2-*trans*-glycosides.[15]

A literature search of one-step aromatic O-glycosylations using trichloroacetimidate donors generated 115 hits, which were analyzed with reference to yield (Fig. 7). As can be seen, the trichloroacetimidate method generally gives excellent yields.

4.1. General considerations

Anomerically pure trichloroacetimidates can be synthesized from the corresponding hemiacetal by treatment with trichloroacetonitrile in CH_2Cl_2 and a suitable base (K_2CO_3 for β-imidate, NaH for α-imidate or DBU for an anomeric mixture). One difference from the acetates is the very fast and complete activation of the trichloroacetimidate donor which usually results in better yields compared to anomeric acetates (Scheme 16).[20,24] Seeberger and co-workers have shown that some reactions are optimally run for just a few minutes at −60 °C.[61]



Scheme 15. General trichloroacetimidate reaction.

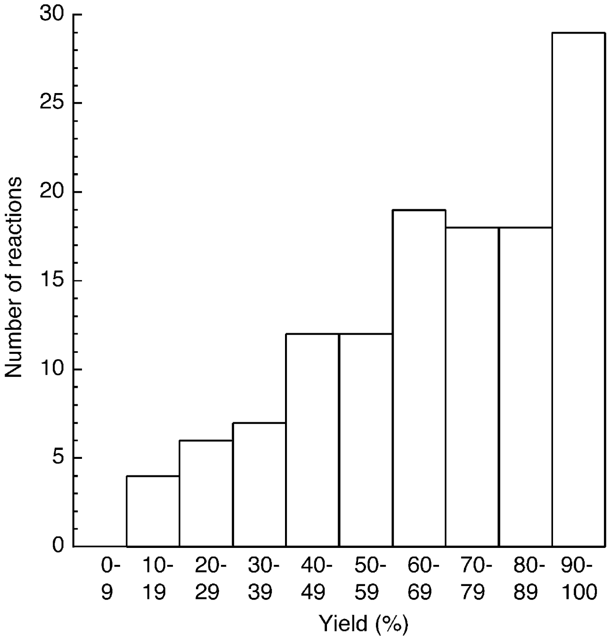
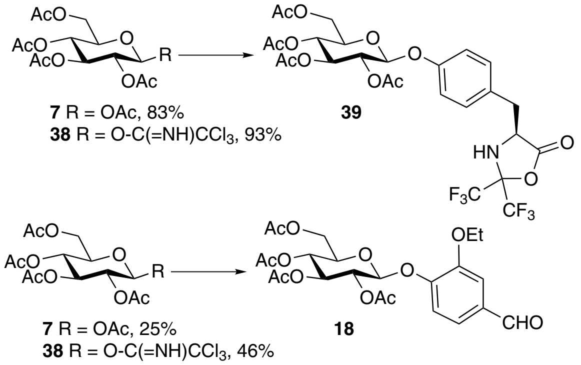


Figure 7. Distribution of yields in the 115 one-step aromatic O-glycosylations using trichloroacetimidates found in the literature.

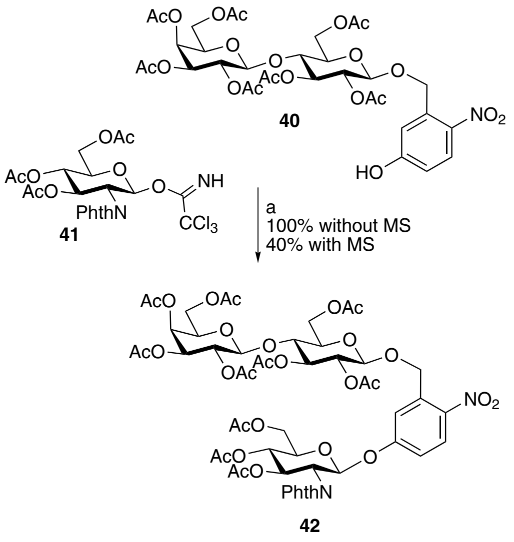


Scheme 16. Comparison of yields of β-glucosides produced using glycosyl acetate **7** or corresponding trichloroacetimidate **38**.

Typical aromatic β-glycosylations using trichloroacetimidates are performed in CH_2Cl_2 as solvent, using a sub-stoichiometric amount of the promoter, usually $BF_3{\cdot}OEt_2$. There are also examples of reactions run in dichloroethane,[62] acetonitrile[16] or diethylether.[63] $BF_3{\cdot}OEt_2$ is the far most common promoter (>90%) but there are examples of other promoters such as TMSOTf,[16,64] AgOTf[45] and even $LiClO_4$ (which was used as a nearly neutral system).[63] The promoter has been used in as little as 0.16 equiv[65] up to several equivalents.[66] Normal temperatures are between −40 °C up to room temperature but there are examples of reactions run at −78 °C[67] and in CH_2Cl_2 at reflux.[65] However, high temperatures might result in C-glycosylation.[16] Even if the reaction is likely complete in a few minutes, typical reaction times are 3–12 h. There are no reports of significant anomerization using the trichloroacetimidate method, which is probably due to the small amounts of acid used. Usually, activated molecular sieves (MS AW-300 is the preferred choice) are used to ensure anhydrous conditions. However, in the synthesis of compound **42** (Scheme 17) the yield dropped from quantitative to less than 40% with the addition of MS AW-300.[68] There are also reports that the molecular sieves in themselves can activate the donor.[36]

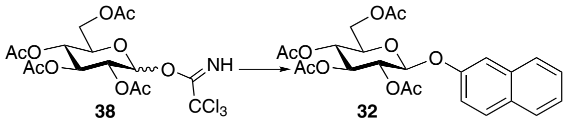
In a search for optimized conditions for glycosylation of naphthols we investigated the use of trichloroacetimidates in acetonitrile, which we found superior over CH_2Cl_2 (unpublished results). The results are shown in Table 1. A slight excess of donor compared to acceptor and catalytic amounts of $BF_3{\cdot}OEt_2$ and activated molecular sieves (3 Å) gave the best results.

Some examples of compounds synthesized using the trichloroacetimidate methodology are shown in Figure 8. The aromatic O-glycosylation in the synthesis of vancomycin (**1**), was performed in 70% yield in solution and



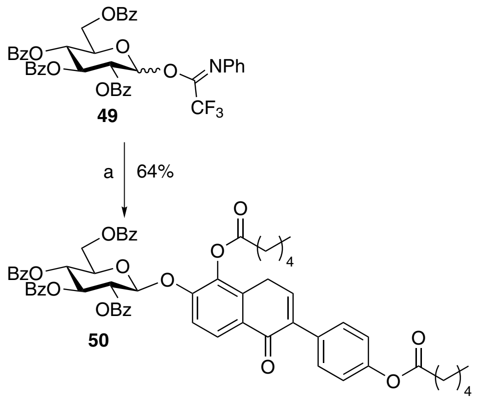
Scheme 17. Reagents and conditions: (a) $BF_3{\cdot}OEt_2$ (0.5 equiv), CH_2Cl_2, rt, 1 h.

Table 1. Optimization of glucosylation of 2-naphthol using 2,3,4,6-tetra-*O*-acetyl-D-glucopyranosyl trichloroacetimidate in acetonitrile



Acceptor (equiv)	Donor (equiv)	$BF_3{\cdot}OEt_2$ (equiv)	3 Å MS	Yield (%)
1	0.5	0.5	No	23
1	1.5	1	No	—[a]
1	1.5	0.5	No	69
1	1.5	0.1	No	74
1	1.5	0.1	Yes	98
1	2.3	0.5	No	100

[a] Decomposition.



Scheme 18. Reagents and conditions: (a) appropriate phenol, $BF_3{\cdot}OEt_2$ (0.3 equiv), CH_2Cl_2, 4 Å MS, rt, overnight.

>90% on solid support using the trichloroacetimidate method.[67,69]

4.2. Use of other glycosyl imidates

The first imidate used for glycoside synthesis was an *N*-methyl-acetimidate[74] and a few other imidates have been used for aromatic O-glycosylation. An example is the use of an *N*-phenyltrifluoroacetimidate for the synthesis of flavonoid 7-*O*-glucosides (Scheme 18).[75]

5. Use of thioglycosides and related compounds

Thioglycosides are relatively stable carbohydrate derivatives that can be activated by thiophilic reagents, usually iodonium species generated from, for example, *N*-iodosuccinimide and triflic acid (NIS/TfOH, Scheme 19). There are also anomeric sulfoxides as well as a few examples of glycosylselenides and -tellurides used for

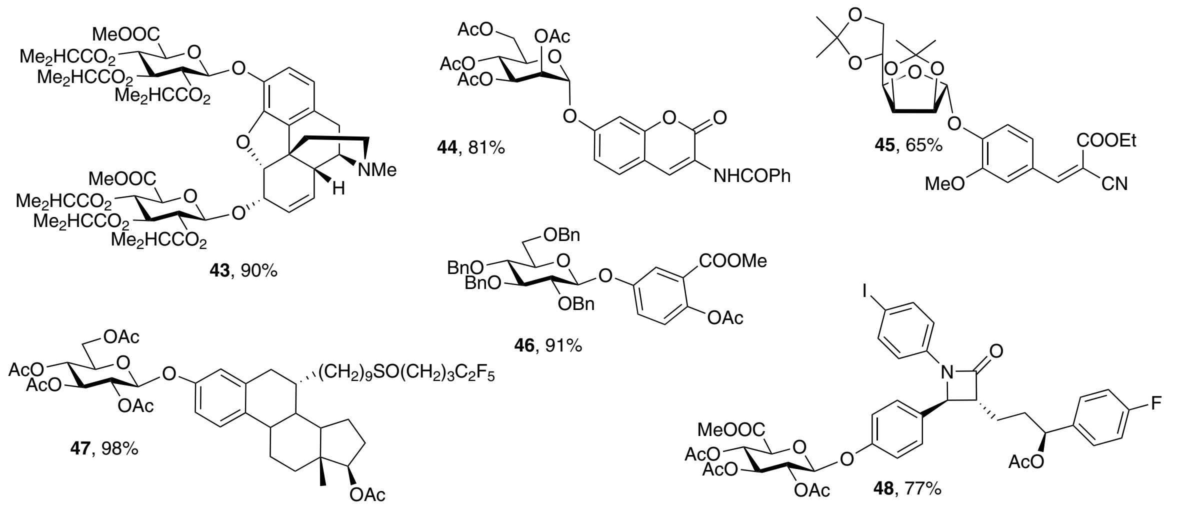
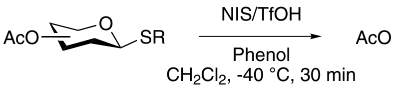


Figure 8. Examples of compounds synthesized using the trichloroacetimidate methodology. Compounds **43**,[70] **44**,[65] **45**,[71] **46**,[72] **47**[62] and **48**.[73]



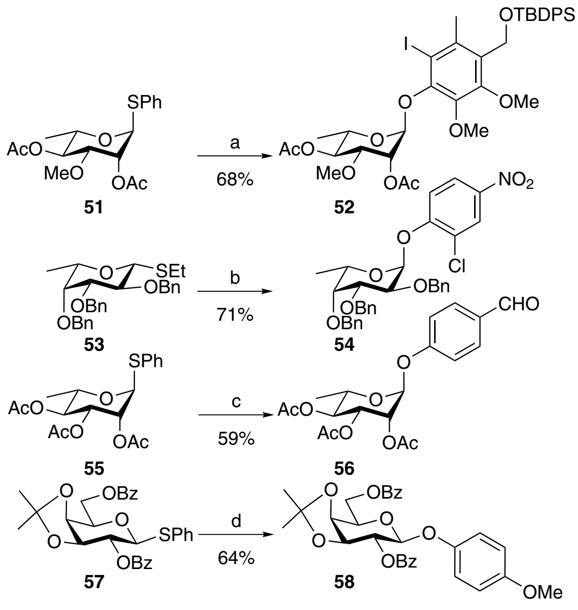
Scheme 19. General thioglycoside reaction.

aromatic O-glycosylation. Generally, the thioglycosides give lower yields compared to other donors.

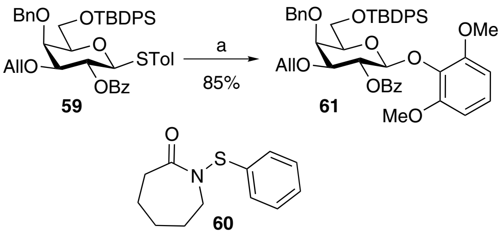
5.1. Alkyl- and arylthioglycosides

Despite the fact that thioglycosides are the most popular donors in carbohydrate synthesis (approx 50% of all donors used in carbohydrate synthesis the year 2000 were thioglycosides),[76] they are not frequently used for aromatic O-glycosylation. The major reason is probably incompatibilities between the promoter systems used for thioglycoside activation and the aromatic residues. In particular, activated aromatic compounds are prone to react with iodonium ions, an observation that has been used for the synthesis of iodoarenes.[77] The aromatic residues that have been glycosylated using thioglycosides are usually relatively simple phenols and the yields are moderate to good. A few examples are given in Scheme 20.

The complex aromatic acceptor of vancomycin could not be glycosylated using thioglycosides under a variety of conditions (NIS, DMTST) and instead the synthesis was performed using a trichloroacetimidate donor.[82] The difficulties using thioglycosides for aromatic O-glycosylation stimulated the development of a new promoter system, that is, *N*-(phenylthio)-ε-caprolactam (**60**), which was used to synthesize compound **61** in 85% yield (Scheme 21).[83]



Scheme 20. Reagents and conditions: (a) appropriate phenol, NIS, TMSOTf, CH_2Cl_2, 4 Å MS, 0 °C, 2 h;[78] (b) appropriate phenol, NIS, TMSOTf, CH_2Cl_2, −42 °C, 30 min;[79] (c) appropriate phenol, NIS, TfOH, CH_2Cl_2;[80] (d) appropriate phenol, NIS, TMSOTf, CH_2Cl_2, −15 °C, 1 h.[81]



Scheme 21. Appropriate phenol, **60**, MS AW-300, Tf_2O, CH_2Cl_2, −45 °C to rt, 1 h.

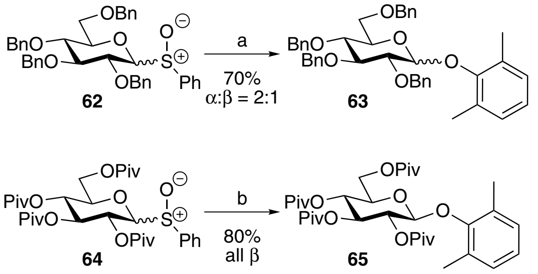
5.2. Glycosyl sulfoxides and sulfimides

Glycosyl sulfoxides were introduced for glycosylation of unreactive substrates, such as phenols, in 1989.[84] Thioglycosides can easily be oxidized to sulfoxides, which can be used as donors by activation with triflic anhydride (Tf_2O). Interestingly, the α/β-ratios can be controlled by careful choice of protecting groups and solvent as shown in Scheme 22.

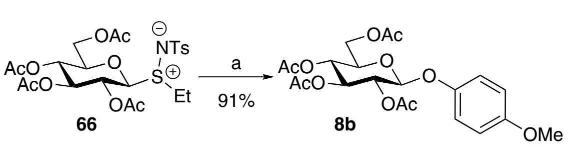
Subsequently, the methodology was used for glycosylation of 2,6-dimethoxyphenol, activated as the tributyltin derivative, in an excellent 92% yield.[85] One problem associated with the use of Tf_2O for activation was interference with amides, but this could be suppressed by pretreatment with $BF_3{\cdot}OEt_2$ and vancomycin was glycosylated in 13% yield over two steps.[85,86] The analogous sulfimides, formed from the thioglycoside by reaction with chloramine T, can also be used for glycosylation, upon activation with $Cu(OTf)_2/CuO$.[87] Sulfimides have been used for glycosylation of *p*-methoxyphenol in excellent yields (Scheme 23).

5.3. Glycosyl selenides and tellurides

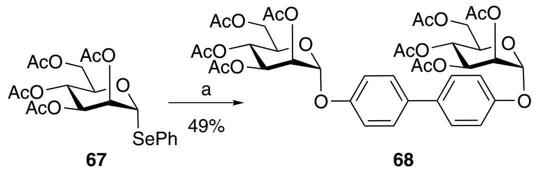
To our knowledge, there is only one example of an aromatic O-glycosylation using a selenide, that is, the digly-



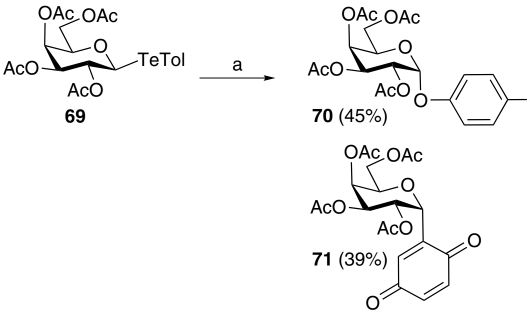
Scheme 22. Reagents and conditions: (a) appropriate phenol, Tf_2O, 2,6-di-*t*-butyl-4-methylpyridine, toluene, −78 °C; (b) appropriate phenol, Tf_2O, 2,6-di-*t*-butyl-4-methylpyridine, CH_2Cl_2, −78 °C.



Scheme 23. Reagents and conditions: (a) *p*-methoxyphenol, $Cu(OTf)_2$, CuO, 4 Å MS, CH_2Cl_2, rt, 2.5 h.



Scheme 24. Reagents and conditions: (a) 4,4′-biphenol, NIS, TfOH, 4 Å MS, CH_2Cl_2, 0 °C to rt, 50 min.



Scheme 25. Reagents and conditions: (a) 1,4-benzoquinone, benzene, hν, 100 °C, 1 h.

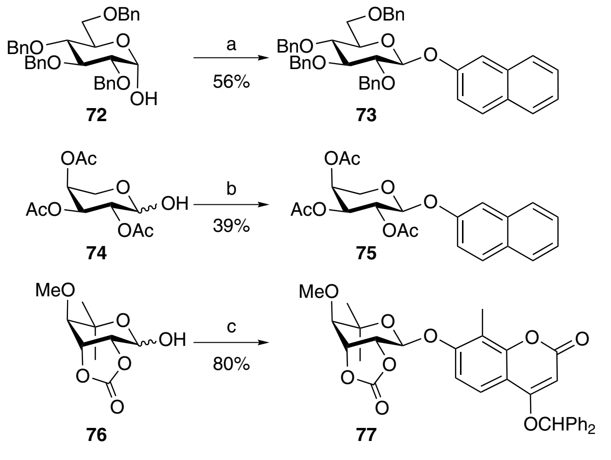
cosylation of 4,4′-dihydroxybiphenyl in 49% yield, using peracetylated α-selenomannoside **67** and the NIS/TfOH promoter system (Scheme 24).[88] Galactosyl telluride **69** was used in the attempted synthesis of a C-glycoside but gave α-glycoside **70** in 45% yield in addition to 39% of the expected C-glycoside **71** (Scheme 25).[89]

6. Other methods for aromatic O-glycosylation

Carbohydrate derivatives unsubstituted at the anomeric centre can be used directly, either by in situ activation or by using the carbohydrate as the nucleophile. Other possibilities are glycals and anomeric phosphates; Fischer glycosylation is usually not viable.

6.1. Mitsunobu reaction

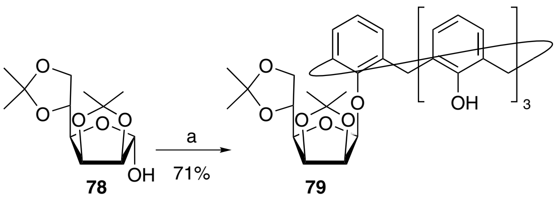
Carbohydrate hemiacetals can be activated in situ by using Mitsunobu conditions. The sugar hemiacetal and a suitable phenol are stirred with triphenylphosphine and diethyl azadicarboxylate (DEAD) to give aromatic glycosides. Perbenzylated 2-naphthyl glucoside **73** was thus synthesized in 56% yield in THF at 0 °C (Scheme 26).[90] α-L-arabinopyranoside **75** and noviose derivative **77** were synthesized using similar conditions.[91,92]



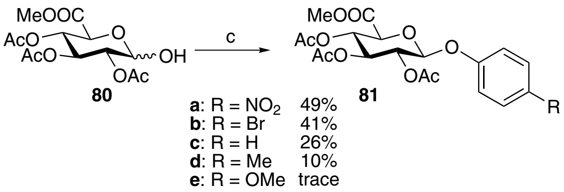
Scheme 26. Reagents and conditions: (a) 2-naphthol, PPh_3, DEAD, THF, 0 °C to rt, 12 h; (b) 2-naphthol, PPh_3, DEAD, toluene, 0 °C, 2.75 h; (c) appropriate phenol, PPh_3, DEAD, DMF, rt, 30 min.

Mitsunobu conditions were also used for glycosylation of calixarenes in toluene.[93] The reaction of calix[4]arene with 1.1 equiv of 2,3:5,6-di-*O*-isopropylidene-α-D-mannofuranose using 1.5 equiv of DEAD and PPh_3 in toluene gave monoglycosylated compound **79** in 71% yield (Scheme 27). Bisglycosylation using tetraacetyl-α,β-D-glucopyranose (2.2 equiv) gave 50% yield of a mixture of the α,α- and α,β-diglucopyranosides.

Finally, Mitsunobu glycosylation was evaluated using several different phenols, where the acidity of the phenols was varied using electron donating or withdrawing substituents in the *para*-position (Scheme 28).[94] The yields were clearly dependent on the acidity of the phenols, that is, the least acidic compounds gave low yields.



Scheme 27. Reagents and conditions: (a) calix[4]arene, PPh_3, DEAD, toluene, 70 °C, 30 min.



Scheme 28. Reagents and conditions: (a) appropriate phenol, PPh_3, DEAD, THF, rt, 24 h.

The yields of **81d** and **81e** could be improved (35% for **81d** and 21% for **81e**) by prior complexation of the phenols with chromium tricarbonyl, which increased the acidities.

6.2. Nucleophilic aromatic substitution

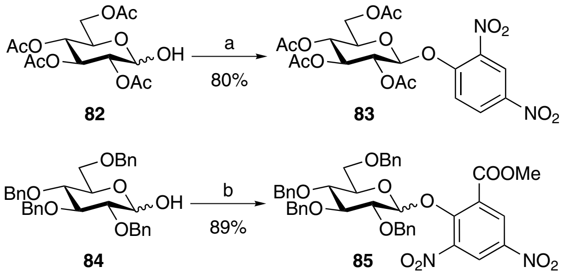
Carbohydrate hemiacetals can also be used as the nucleophile in aromatic substitutions using activated fluoroarenes. Unprotected glucose and nine other unprotected mono and disaccharides were reacted with 1-fluoro-2,4-dinitrobenzene in saturated aqueous $NaHCO_3$ solution to give the corresponding β-glycosides in 15–30% yield.[95] The low yields can be explained by the formation of both α- and β-pyranosides as well as furanosides, but the simplicity makes the method valuable. Reaction with acetylated compound **82**, using 1,4-diazabicyclo-[2,2,2]octane (DABCO) as base, gave 80% yield of **83** which could be converted to the α-anomer with K_2CO_3 in DMF.[96]

Glycosides of methyl 2-hydroxy-3,5-dinitrobenzoate (DISAL, e.g., compound **85**) are used for glycosylation under neutral or mildly basic conditions. These glycosides are synthesized from methyl 2-fluoro-3,5-dinitrobenzoate under basic conditions as exemplified by compound **85** (Scheme 29).[97] The anomeric ratio of the product was directed by the anomeric ratio of the starting material, that is, the pure α-hemiacetal gave an 8.4:1 α:β ratio.

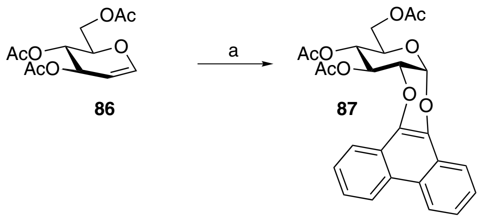
6.3. Use of glycals

An unusual aromatic O-glycosylation was performed by Helferich et al. where glucal **86** was reacted with 9,10-phenanthrenequinone in a UV-promoted [4+2] cycloaddition to give compound **87** in 50% yield (Scheme 30).[98,99] Compound **87** was then subsequently opened by ozonolysis to remove the aromatic moiety.

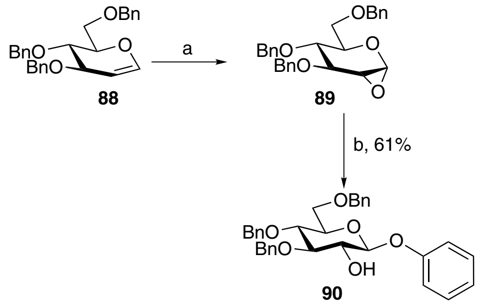
Glucals can also be oxidized to the corresponding α-1,2-anhydroglucoside by treatment with 3,3-dimethyldioxirane. The anhydrosugar can then react with nucleophiles such as phenols (Scheme 31).[100,101] Danishefsky et al. noted that anhydroglucoside **89** reacted slowly with phenol under Lewis acidic conditions ($ZnCl_2$) to give a 1.8:1 ratio of α- and β-phenylglucoside **90**. However, reaction with potassium phenolate gave a clean conversion to the β-glucoside without any trace of the α-anomer.[100] Glycal derivatives with good leaving groups at the allylic position are readily converted into aryl 2,3-unsaturated aldosides by heating with phenols.[102]



Scheme 29. Reagents and conditions: (a) 1-fluoro-2,4-dinitrobenzene, DABCO, DMF, rt, 90 min; (b) methyl 2-fluoro-3,5-dinitrobenzoate, Li_2CO_3, DMAP, CH_2Cl_2, rt, 0.5 h.



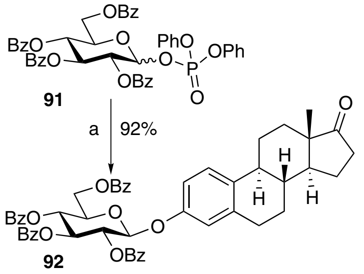
Scheme 30. Reagents and conditions: (a) 9,10-phenanthrenequinone, hν, benzene.



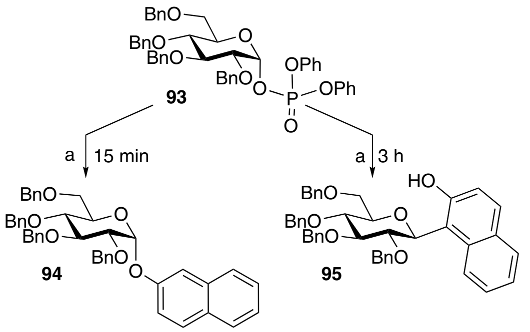
Scheme 31. Reagents and conditions: (a) 3,3-dimethyldioxirane, acetone, CH_2Cl_2, 0 °C, 10 min; (b) phenol, K_2CO_3, 18-crown-6, acetone, reflux, 4 h.

6.4. Use of glycosyl phosphates

Anomeric phosphates were introduced as synthetic carbohydrate donors by Ikegami and co-workers,[103] and compound **92** was synthesized in an excellent 92% yield (Scheme 32). It was later shown that O-glycosides were formed in good yields (79%) in 15 min but then rearranged to C-glycosides on prolonged reaction times



Scheme 32. Reagents and conditions: (a) appropriate phenol, TMSOTf, 1,1,3,3-tetramethylurea, CH_2Cl_2, rt, 1 h.



Scheme 33. Reagents and conditions: (a) 2-naphthol, TMSOTf, CH_2Cl_2, 0 °C.

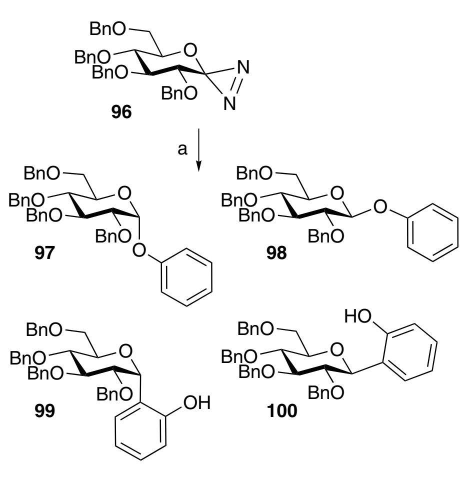
(3 h, Scheme 33).[104,105] Anomeric dimethylphosphinothioates gave aromatic glycosides in moderate yields (79%, α:β 65:35 for *p*-methoxyphenol) upon activation by silver perchlorate.[106]

6.5. Use of glycosylidene carbenes

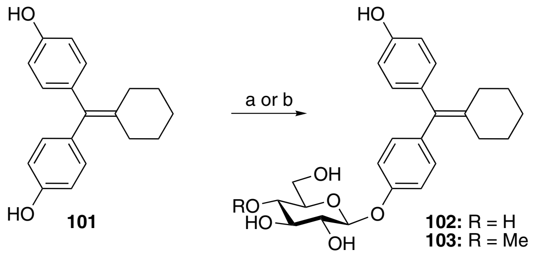
A very interesting, however not yet generally applicable, method for glycosylation is the use of glycosylidene carbenes (Scheme 34).[107] The carbenes are formed by decomposition of, for example, diazirine **96**, without any use of promoter, and O-glycosides are formed in 75% yield (α:β, 20:80) together with C-glycosides. *p*-Nitrophenol yielded only O-glycosides (α:β, 40:60).

6.6. Glycosylation by biotransformation

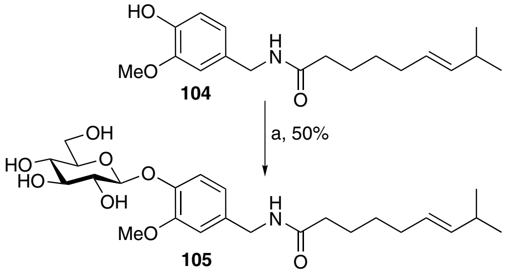
Despite the natural abundance of aromatic glycosides, there are few examples of biotransformations for glycosylation of phenolic compounds. Kieslich et al. published glucosylations of a number of aromatic compounds, exemplified by the reaction with *Sporotrichum sulfurescens*, which gave 4-O-methylated glucoside **102**, and *Rhizopus colinii*, which gave **103** (Scheme 35).[108] Recently, capsaicin was glucosylated to give compound **105** in 50% yield by *Phytolacca americana* (Scheme 36).[109]



Scheme 34. Reagents and conditions: (a) phenol, rt.



Scheme 35. Reagents and conditions: (a) *Sporotrichum sulfurescens*, 60 h; (b) *Rhizopus colinii*, 90 h. The medium contained 3% glucose.



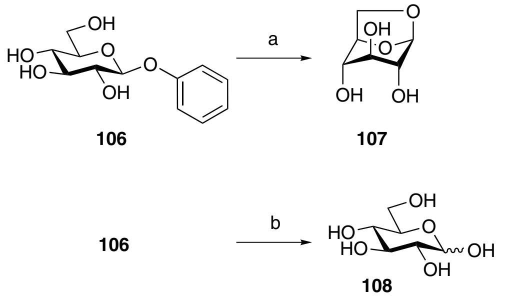
Scheme 36. Reagents and conditions: (a) *Phytolacca americana*, 25 °C, 3 days. The medium contained 3% sucrose.

There are several examples of glycosylations using UDP activated glucose[110–112] or glucuronic acid.[113–116] A wide range of phenols were tested for UDP-glucose dependent glycosylation by *Rauvolfia* arbutin synthase and gave yields from 0.8% up to 100%.[110] Other sugars (e.g., L-noviose) can also be used by specific enzymes (e.g., L-noviosyl transferase).[117] Recently, use of nucleotide diphosphosugars (NDP-sugars) was presented for glycorandomization using a large set of carbohydrates and four aromatic aglycons,[118] and a similar approach was used for randomization of vancomycin.[119]

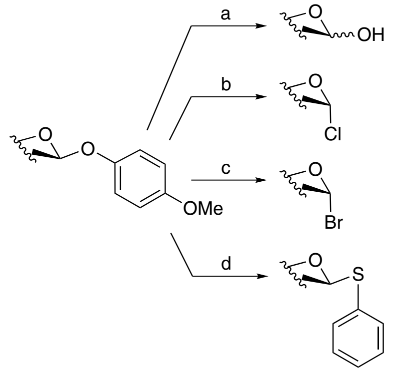
7. Aromatic anomeric protecting groups

Aromatic residues have been used as anomeric protecting groups and methods for their cleavage are shown below. β-Phenyl glucosides can be hydrolyzed by sodium hydroxide to yield 1,6-anhydroglucose in excellent yields (Scheme 37). Because the α-glucosides are inert, 1,2-anhydro-α-glucopyranose is probably an intermediate. Several phenyl glucosides, carrying electron donating or withdrawing groups, have been examined.[120] Phenyl glucosides can also be cleaved by photoinduced electron-transfer with sensitization with 1,4-dicyanonaphthalene to give free glucose (Scheme 37).[121]

The *p*-methoxyphenyl group (*p*MP) have turned out to be a stable, yet easily removed anomeric protecting group. The *p*-methoxyphenyl glycosides can be cleaved

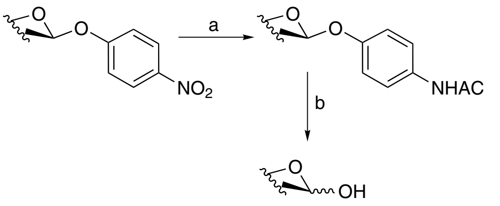


Scheme 37. Reagents and conditions: (a) NaOH (aq, 1.7 M); (b) 1,4-dicyanonaphthalene, CH_3CN, H_2O, hν.



Scheme 38. Reagents and conditions: (a) CAN, CH_3CN, H_2O, 0 °C, 10 min; (b) BzCl, $ZnCl_2$, CH_2Cl_2, 30 °C, 8 h; (c) AcBr, $ZnBr_2$, CH_2Cl_2, rt, 24 h; (d) thiophenol, $BF_3{\cdot}OEt_2$, toluene, 60 °C, 16 h.

to yield the hemiacetal, but also converted directly into glycosyl chlorides, bromides and thiophenyl glycosides according to Scheme 38.[122,123] Similarly, the *p*-nitrophenyl group is a very stable anomeric protecting group that can be reduced to a corresponding *p*-acetamidophenyl group and then cleaved by ammonium cerium(IV) nitrate (CAN) oxidation. The concept is shown in Scheme 39.[124]

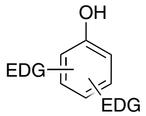
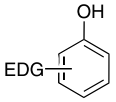
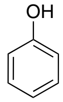
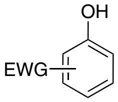
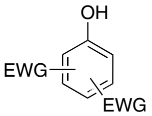
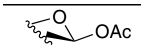
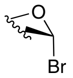
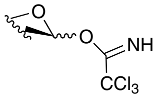
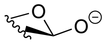


Scheme 39. Reagents and conditions: (a) H_2, Pd, Ac_2O; (b) CAN, CH_3CN, H_2O, 0 °C, 20 min.

8. Conclusions

The advantages and limitations of different O-glycosylation methods for aromatic compounds are summarized below and are listed in Table 2. Peracetylated carbohydrates are very simple to synthesize in a one-step procedure and give moderate to good yields in glycosylation of activated phenols. The problem of anomerization can be minimized by addition of 0.5 equiv of triethylamine to the reaction mixtures. For more difficult phenols or more complex carbohydrates, other methods are preferable. Anomeric halides are simple to synthesize from the peracetylated compounds and other anomeric protecting groups, and are especially valuable for glycosylation under basic conditions and for electron deficient phenols. Trichloroacetimidates are more difficult to synthesize, compared to acetates or halides, but usually give better yields, especially with more complex phenols. The trichloroacetimidate method is preferred for expensive donors; however, they are less preferred for strongly activated phenols or for α-glycosylation. Despite their

Table 2. Preferred donors for glycosylation of various phenols[a,b]

					
	+++	++	+	–	–
	–	–	+	++	++
	+[c]	++	+++	+	–
 S_NAr	–	–	–	–	+++[d]

[a] EDG = electron donating group, EWG = electron-withdrawing group.

[b] The reactivities of different donor–acceptor combinations are indicated as: preferred (+++), suitable (++), less suitable (+), not suitable (–).

[c] Short reaction time (min) necessary for good yields.

[d] The aromatic residue is a fluoroarene.

popularity for the synthesis of glycosides from aliphatic alcohols, thioglycosides have not been extensively used for aromatic O-glycosylation. Nucleophilic aromatic substitution is the method of choice for aromatic residues carrying several electron-withdrawing groups. Finally, Mitsunobu conditions can also work well for electron deficient phenols.

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