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Transition metal catalyzed glycosylation reactions – an overview

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Carbohydrates are a large class of natural products that play key roles in a number of biological processes such as in cellular communication or disease progression. Carbohydrates are also used as vaccines and pharmaceuticals. Their synthesis through glycosylation reactions is challenging, and often stoichiometric amounts of promoters are required. Transition metal catalyzed glycosylation reactions are far less common, but can have advantages with respect to reaction conditions and selectivity. The review intends to approach the topic from the catalysis and carbohydrate perspective to encourage researchers from both the fields to perform research in the area. The article covers the basics in glycosylation and catalysis chemistry. The catalysts for the reaction can be roughly divided into two groups. In one group, the catalysts serve as Lewis acids. In the other group, the catalysts play a higher sophisticated role, are involved in all elementary steps of the mechanism and remain coordinated to the substrate throughout the whole catalytic cycle. Based on selected examples, the main trends in transition metal catalyzed glycosylation reactions are explained. Lewis acid catalysts tend to require a somewhat higher catalyst load compared to other organometallic catalysts. The reaction conditions such as the temperature and time depend in many cases on the leaving group employed. An outlook is also presented. The article is not meant to be comprehensive; it outlines the most common transition metal catalyzed processes with the intention to bring the catalysis and carbohydrate communities together and to inspire research activities in both areas.

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1. Introduction

Carbohydrates are a large, structurally diverse class of natural products that play key roles in a number of biological processes.[1,2] Originally viewed as energy storage for living systems,[3] research in the past decades have identified carbohydrates as a versatile compound class with a whole variety of biological functions. For example, they are involved in cellular communication.[4] Furthermore, carbohydrates can be part of disease progression. For instance, they can regulate tumor proliferation and metastasis[5] or can affect the susceptibility to infection.[6] Carbohydrates decorate cell surfaces[4] and can stimulate the immune system,[7] and consequently, it is not surprising that carbohydrates are also used as vaccines and pharmaceuticals.[8,9] The antiviral drug oseltamivir (sold under the tradename Tamiflu™) is a carbohydrate-inspired, glycomimetic inhibitor used to treat influenza infections.[10] The naturally occurring glycosaminoglycan heparin is used as an anticoagulant (*i.e.* blood thinner)[11] and may even be effective in the treatment of COVID-19.[12] These examples demonstrate the importance of carbohydrates and their physiological roles as well as synthetic pathways to their production are widely researched.

Given the outstanding role of carbohydrates in biological processes and drug development, their synthesis is of great

importance. The principal, most common chemical reaction to assemble carbohydrate monomer building blocks to oligo- and polysaccharides is glycosylation. The production of carbohydrates is more challenging than the synthesis of peptides, because the carbohydrate synthesis *in vivo* is non-templated and, as such, more difficult to control.[11] The *in vitro* synthesis of carbohydrates is challenging due to the multifunctionality of the monosaccharide building blocks.[11] For example, the aforementioned drug heparin is currently obtained from animal sources and a synthetic pathway would be safer with respect to potential contamination.[11] As such, glycosylation, as the most common reaction in the synthesis of carbohydrates, is a widely researched topic. Access to large quantities of carbohydrates in an efficient way is crucial for pharmaceutical development and production, triggering vigorous research activities in the area.

Glycosylation reactions are also challenging due to the multifunctionality of carbohydrates. The hydroxyl groups not to be involved in glycosylation often need to be protected,[13] and activators, in most cases in stoichiometric amounts, need to be employed to connect two monosaccharide molecules. Efforts to make glycosylation reactions more efficient have led to, *e.g.*, solid phase[14] and automated synthesis protocols,[15] to "one-pot" strategies[16] or to glycosylation in continuous flow reactors.[17]

Many glycosylation reactions employ stoichiometric activators.[18,19] However, catalyzed glycosylation reactions are increasingly investigated as well. The obvious advantages of catalysts are that they save resources compared to stoichiometric agents. Also, they can increase the selectivity of a glycosylation reaction, which is especially important when considering the multifunctionality of carbohydrates. Finally, catalysts can reduce reaction times and reaction temperatures, further saving resources.

Catalyzed glycosylation reactions face similar challenges to non-catalyzed glycosylation reaction, *i.e.* achieving high regio- and stereoselectivities. A number of catalytic systems are known for the reaction. They can be organocatalytic[20] or based on Brønsted acids.[21] Transition metals play a ubiquitous role in catalysis. They form the base of a whole variety of catalytic systems, allowing for chemo-, regio- and enantioselective reactions that would otherwise be difficult or impossible to achieve. Consequently, transition metal-based glycosylation catalysts are being increasingly investigated, and they can make glycosylation reactions more efficient.

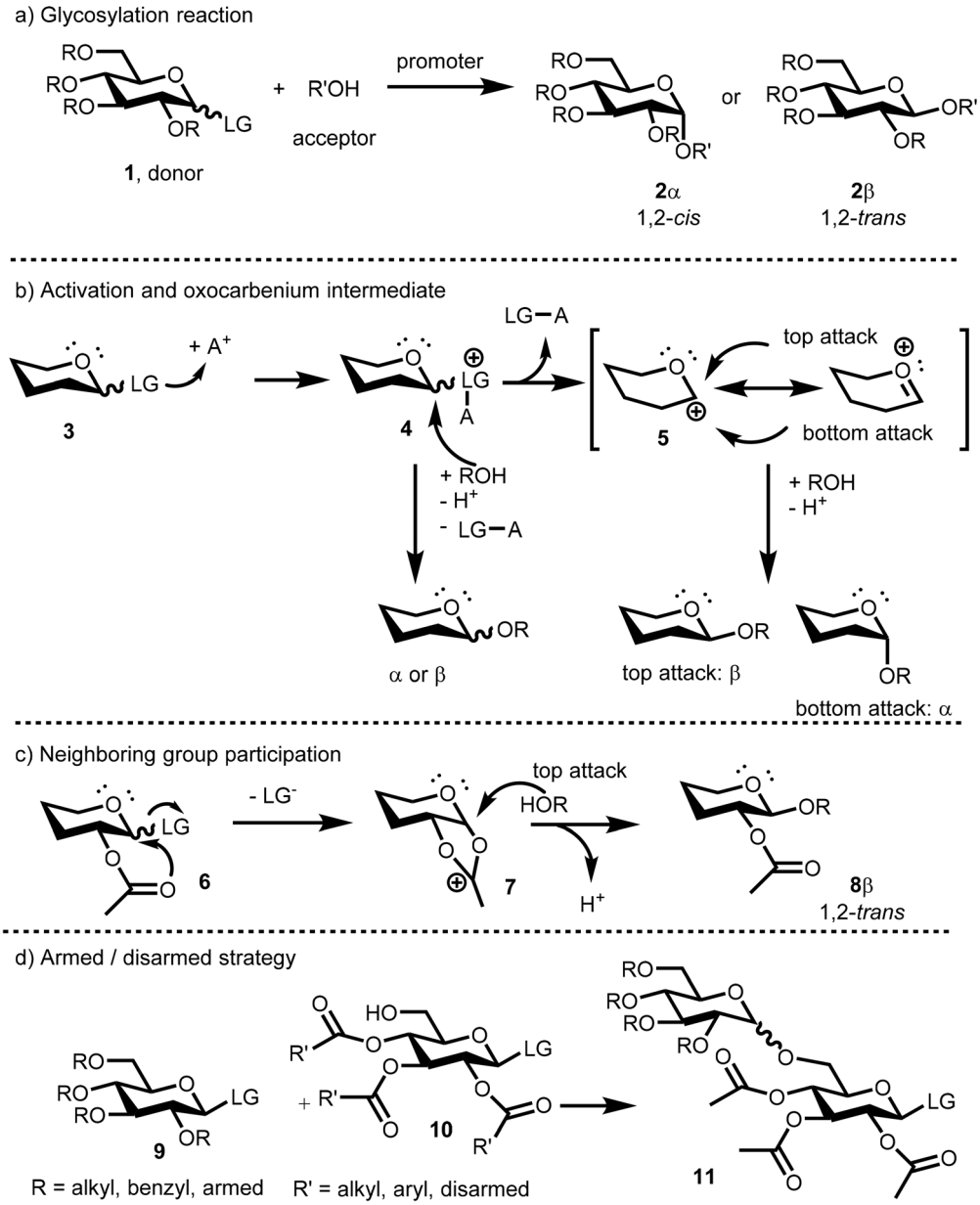
The field of transition metal catalyzed glycosylation reactions has recently been reviewed several times.[22–25] The intent of this review article is to introduce catalysis researchers not so familiar with glycosylation reactions to the topic. It appears that catalysis research activities in the carbohydrate field are far less common than in other areas of organic synthesis. This article aims at convincing catalysis researchers to consider their catalytic systems in glycosylation reactions as well. A short introduction of the main concepts of glycosylation reactions is given for researchers not so familiar with the field. This article categorizes transition-metal catalyzed reactions not by metal, but by activation type. Also, trends and patterns in catalyzed carbohydrate synthesis are outlined, mainly drawn from most recent examples. The article is not intended to be comprehensive; it outlines the most common transition metal catalyzed processes with a focus on *O*-glycosylation reactions, albeit *C*-glycosylation reactions are mentioned as well. The article aims to bring the catalysis and carbohydrate communities together to inspire research activities in both the areas. Synthetic carbohydrate chemists may consider catalysis in their research as much as catalysis researchers may intensify investigating catalytic systems for glycosylation reactions. That way, both communities will benefit.

2. Basics of glycosylation chemistry

The formation of a glycosidic bond, glycosylation, is a central reaction in carbohydrate research.[18,26] As depicted in Scheme 1a, glycosylation is the conversion of a hemiacetal (for LG = OH in **1**) or its derivative to an acetal **2**. The carbon atom next to the oxygen atom on the ring system, where the chemistry is taking place is called anomeric carbon. While glycosylation reactions with LG = OH in **1** are possible, in the majority of the cases the OH group is first converted to a better leaving group LG. That way, the system becomes more reactive, lowering reaction times and temperatures and making the reaction more selective. The compound that provides the anomeric carbon in the glycosidic linkage is called a glycosyl donor (**1** in Scheme 1a). The other reaction partner that provides an oxygen in the glycosidic linkage is called a glycosyl acceptor, and it can be either a simple alcohol or another carbohydrate with a free hydroxyl group.

At the anomeric carbon, two stereoisomers can form, which are anomers, are denoted α or β and have a diastereomeric relationship (1,2-*cis* or 1,2-*trans*). Based on the "anomeric effect", an electronegative substituent attached to the anomeric carbon has a tendency to reside in the axial position.[1] As such, the α-isomer is the thermodynamically controlled product, whereas the β isomer is the kinetic product for D-sugars residing in the $^4C_1$ conformation. It is desirable that one isomer forms in large excess over the other isomer. Vigorous research activities are centered around investigating synthetic protocols, where high selectivity of one isomer over the other one is achieved.[26] This is of high importance in the pharmaceutical industry, because only a single stereoisomer can be administered as a drug. As can be seen in **1** in Scheme 1a, the other OH groups in the carbohydrate molecule are typically protected to achieve high regioselectivity. If the substituent next to the anomeric carbon is located in an equatorial position, for the α isomer, a 1,2-*cis* relationship to the neighboring OR group results, and for the β isomer it is a 1,2-*trans* relationship.[26]

The reaction typically requires an activator or a promoter.[18] As outlined in Scheme 1b, the activator – in many cases a positively charged species – is attacked by the leaving group. From there, the leaving group departs to form an oxocarbenium ion **5** (Scheme 1b). The oxocarbenium ion is flattened and reso-



Scheme 1 Basics of glycosylation chemistry.

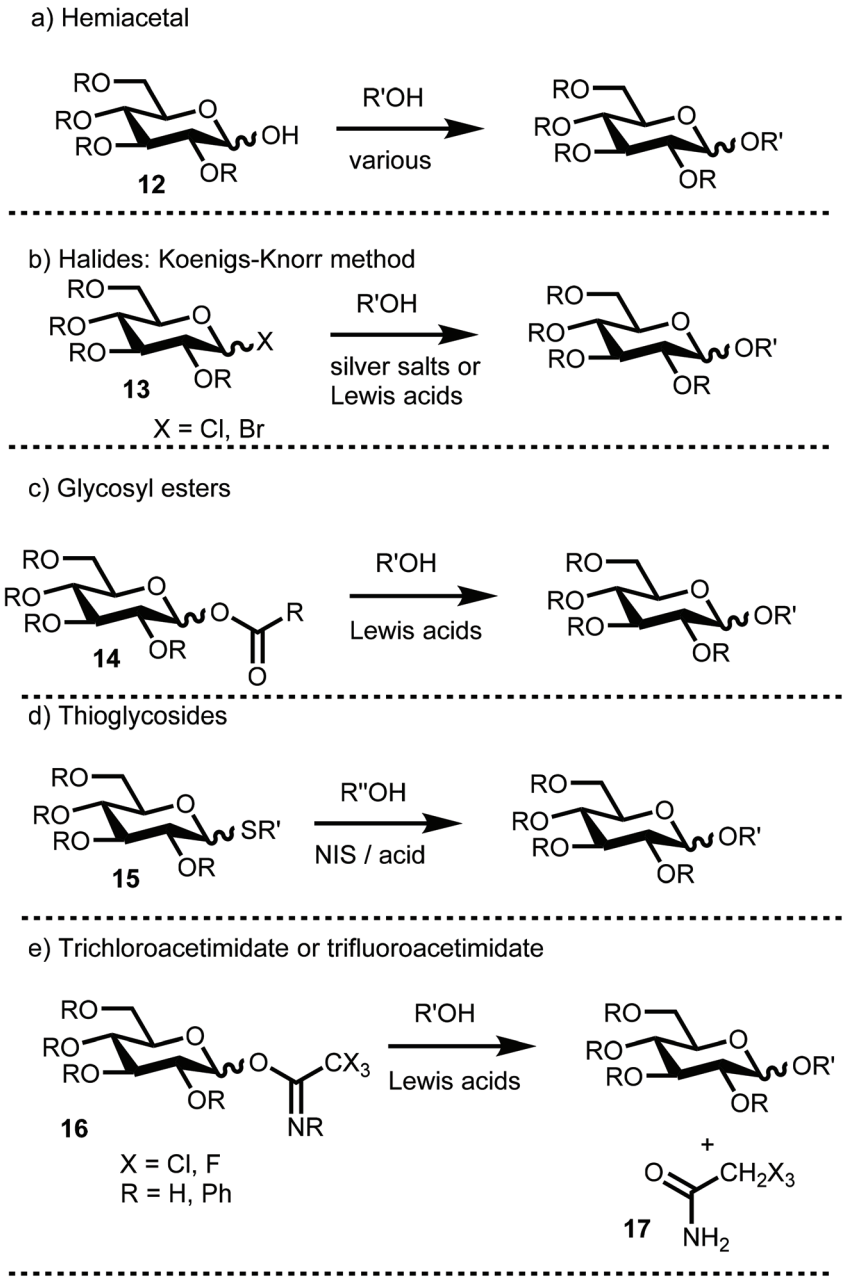
nance-stabilized. It can be either attacked by the acceptor from the bottom or from the top face, giving rise to the formation of either the α or β isomer. This pathway is comparable to an S_N1 reaction. However, the acceptor can also attack the donor while the (activated) leaving group is still connected to the anomeric carbon (**4** in Scheme 1b), which would be comparable to an S_N2 reaction, and an inversion of the configuration at the anomeric carbon would occur.[26] However, the reaction can occur on a "continuum" between S_N1 and S_N2 reactions and mechanistically proceed through more or less tightly associated ion-pairs.[27]

The stereoselective formation of 1,2-*cis* glycosidic bonds remains challenging.[27,28] As depicted in Scheme 1c, neighboring group participation can occur.[29] For example, in the acetate-protected sugar **6**, the carbonyl carbon of the acetate group can temporarily coordinate to the anomeric carbon of the oxocarbenium ion and stabilize it as an acyloxonium ion (**7**). The assembly in **7** blocks the bottom face of the acyloxonium ion, and the acceptor can only attack from the top face, resulting in the formation of a 1,2-*trans* glycosidic bond.[26] Such neighboring group participation usually cannot afford the *cis* isomer, which is one of the reasons why the *cis* isomer is more challenging to construct. Other factors also contribute to the fact that the formation of the *trans* isomer is easier. For example, the glycosyl acceptor can attack the neighboring acetyl group in **6** to form an orthoester, which can rearrange to

the *trans* product.[30] However, the use of chiral auxiliaries can lead to the formation of 1,2-*cis* glycosides *via* trans-decalin-like intermediates.[30] Selectivity can also be achieved by directed acceptor delivery[31] or by S_N2-type reactions involving stable intermediates.[32]

The reactivity of carbohydrates can be tuned.[33] According to the "armed – disarmed" concept first formulated by Fraser-Reid,[34] glycosyl donors protected with ether groups are armed and more reactive (**9** in Scheme 1d), and glycosyl donors protected with ester groups are disarmed and less reactive (**10** in Scheme 1d).[35] If the armed donor **9** is reacted with the disarmed acceptor **10**, a reaction between the two will occur to form the disaccharide **11**. However, two disarmed carbohydrate molecules **10** will usually not couple to each other, if the promoter is mild enough to only activate **9**. A strong promoter would also lead to the coupling of **10** to each other. The electron-withdrawing groups in disarmed glycosyl donors deactivate the leaving group, thereby hampering its propensity to interact with the activator. A disarmed carbohydrate can still function as an acceptor, as shown in Scheme 1d.

Glycosylation reactions involving donor **12** bearing an unprotected OH group are possible (Scheme 2a).[18] The use of 1-hydroxyl sugars **12** in glycosylations is mainly suitable for the synthesis of simple glycosides and thioglycosides[18] and



Scheme 2 Common leaving groups.

converting the OH group temporarily to a better leaving group in solution is a viable strategy.[36] However, the glycosyl donor is in most cases equipped with a leaving group. Common leaving groups in the present context are compiled in Scheme 2.[18,22]

One of the earliest leaving groups to be employed were halides (**13**, Scheme 2b). The Koenigs–Knorr reaction has been published 120 years ago and it employs donors with chloride or bromide leaving groups activated by Ag^{I} salts.[37] Numerous other salts have been employed as activators for the reaction as well, mainly based on Ag^{I} and Hg^{II}. However, stoichiometric amounts of the activator are often required, sometimes even multiple equivalents.[38] The side products for glycosylations with halide donors are HCl and HBr, which are strong acids, and generally, one equivalent of an acid scavenger needs to be added to the reaction mixture.[22] Fluoride and iodide as leaving groups have been explored as well.[1,18,22,39] Higher sophisticated protocols utilize ruthenium complexes that perform *C*-glycosylation reactions mediated by visible light.[40]

The glycosyl ester group (**14**, Scheme 2c) is also a frequently employed leaving group in carbohydrate chemistry. Its advantage is the easiness of its preparation, and the acetyl group is most commonly employed.[18] Numerous Lewis acids can function as activators for the ester group, *e.g.* salts based on Fe, Sn, or Cu or on organic activators such as TMSOTf or $BF_3{\cdot}Et_2O$ (TMS = trimethylsilyl and OTf = trifluoromethanesulfonate or triflate, $CF_3SO_3^-$).[18] Originally, stoichiometric amounts of the acid promoter were investigated, but more recent work investigated catalytic protocols.[22] Efficient catalytic promoters, such as $Sc(OTf)_3$, make the acetate leaving group more attractive, as its activation typically requires harsh reaction conditions employing strong acids.[22]

Thioglycoside donors also have been extensively studied (**15**, Scheme 2d); they exhibit high chemical stability (*e.g.* during protecting group manipulations), are easy to establish and can be activated by a number of promoters.[1,18] Originally introduced by Ferrier,[41] early activators included Hg^{II} salts, presumably due to the high thiophilicity of mercury. Other salts as activators, based on Pd, Cu, or Ag, have been reported as well.[18] Also, non-metallic activators such as *N*-bromosuccinimide or *N*-iodosuccinimide in combination with Lewis acid catalysts or $NOBF_4$ have been employed.[1,22] When utilizing halonium ions as activators, at least a stoichiometric amount is required and the negatively charged counterion needs to be sufficiently non-nucleophilic to not interfere with the reaction.[38] Visible light mediated *O*-glycosylation reactions catalyzed by Ir or Ru complexes have been reported as well.[42] Catalytic activators for thioglycosides are still rare, though.[22]

A very efficient leaving group is trichloro- or trifluoroacetimidate (**16**, Scheme 2d).[18,38] Originally employed by Schmidt,[43] the group is easily introduced into a sugar molecule and activated by Lewis acids such as $BF_3{\cdot}Et_2O$ or AgOTf.[1,22] Trichloro- or trifluoroacetimidate sugars with R = H in **16** are very reactive, and glycosylation reactions can be performed at temperatures as low as −78 °C.[18] Often, a catalytic amount of the activator is sufficient for the glycosylation reaction to proceed, and consequently, imidates have been employed in transition metal catalyzed glycosylation reactions,[22,44] as will be outlined below. Yu introduced the somewhat more stable *N*-phenyltrifluoroacetimidate leaving group (R = Ph in **16**).[45] It can be employed at or near room temperature. In general, glycosylation reactions close to room temperature are favorable, because no special equipment is needed to perform the reaction. One advantage of imidates as leaving groups is the fact that their protonated form **17** (Scheme 2d) is largely inert and will not easily interfere with the donor, the acceptor or the catalyst. Weak Lewis acids favor an S_N2 type reaction mechanism with imidates.[22]

Scheme 2 gives only a short overview of leaving groups commonly employed in glycosylation reactions, and the examples were selected in the context of transition-metal catalyzed glycosylation reactions. Alkene and alkyne leaving groups will be discussed in the context of their catalytic activation by transition metals below. Leaving groups based on other functionalities such as *O*-glycosides, phosphates, phosphites, sulfoxides, carbonates, thioimidates or orthoesters, among many others, have been investigated as well, and readers are referred to review articles and monographs covering their potential.[1,22,26]

3. Transition metal catalyzed glycosylation reactions

Transition metal catalyzed glycosylation reactions are less common compared to those where a stoichiometric amount of the activator is employed, albeit research activities in the area are increasing.[22] Transition metal catalysts face similar problems in glycosylation reactions compared to stoichiometric reagents; the multifunctionality of sugars offers for a catalyst many "docking points" in the molecule, which may lead to catalyst deactivation and side reactions. Still, the search for catalysts is ongoing and has led to a number of efficient catalytic systems.

When reviewing the literature, it appears that two major groups of transition metal catalyzed glycosylation reactions dominate. In one group, the catalyst plays mainly the role of a Lewis acid. This approach is not surprising given the fact that many leaving groups are activated by Lewis acids (Scheme 2). In Lewis acid catalyzed reactions, the catalyst must not have a strong affinity to the leaving group, but must be reactive enough to activate it. For example, mercury salts are often employed as stoichiometric promoters for glycosylation reactions with thioether leaving groups.[1] Due to the thiophilicity of mercury, a stoichiometric amount of the mercury promoter is required because once bonded to the mercury, the sulfur will not dissociate easily, blocking mercury from further activation of a thioether in another carbohydrate molecule. As such, a balance needs to be found when employing Lewis acids as catalysts. In many Lewis acid catalyzed glycosylation reactions, the formation of an oxocarbenium ion is suggested, where the metal is not bound to the sugar substrate anymore. As such, the metal does not participate in the nucleophilic

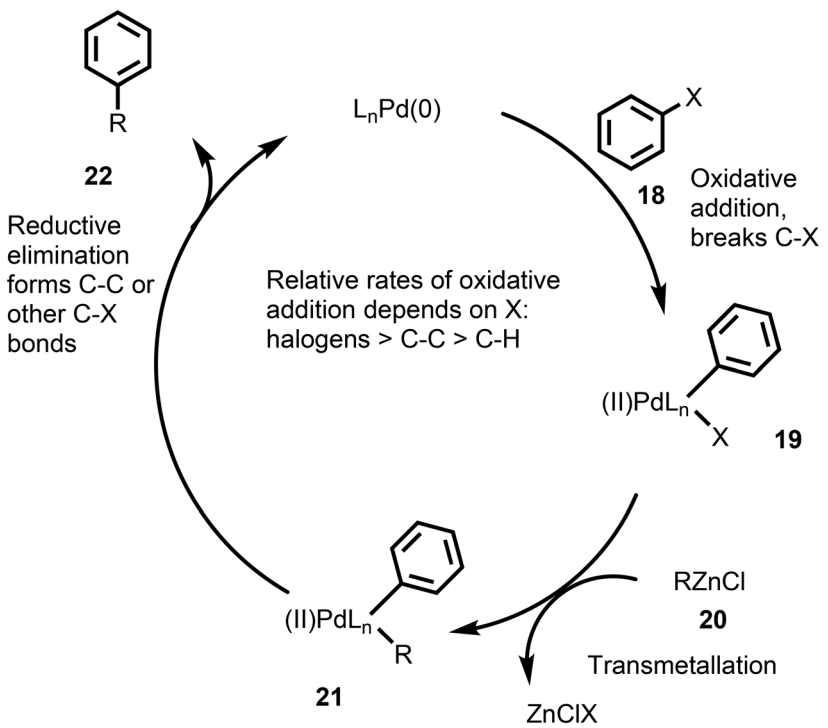
attack of the acceptor, which is the stereodifferentiating step. In that case, catalyst tuning to improve stereodifferentiation would be futile.

In the other group of transition metal catalyzed glycosylation reactions, the catalyst does not merely play the role of a Lewis acid. Transition metal catalyzed reactions typically proceed through a number of elementary steps, such as oxidative addition, migratory insertion or reductive elimination. A variety of organic reactions is catalyzed by transition metals, and the mechanisms of these reactions are much more sophisticated and complex compared to Lewis acid catalysis. In these reactions, the metal participates in all steps of the catalytic cycle, which is the main difference compared to Lewis acid catalysts which often (but not always) assist in the formation of the oxocarbenium ion.

A generic catalytic cycle for cross coupling reactions is depicted in Scheme 3. First, a compound is oxidatively added to a metal center (here palladium) by breaking a polar bond. In the generic example shown in Scheme 3, an aryl halide **18** is depicted but a wide variety of substrates can undergo oxidative additions to a metal center. During the oxidative addition, the aryl–halogen bond is broken and the oxidation state of the metal increases by two. Then, the second coupling partner is transferred to the metal center by a process called transmetallation to afford species **21**. Typically, a nucleophile bonded to a metal center is utilized for that step, *e.g.* the zinc reagent **20**; many other transmetallation agents are known, such as Grignard reagents. Finally, the two partners in **21** couple to each other at the metal center through a step called reductive elimination, which is the reverse of oxidative addition, and where the oxidation state of the metal decreases by two. The catalyst can then enter another catalytic cycle.

As can be seen from Scheme 3, transition metal catalysts follow mechanistic pathways that are not as simple as those for metal salts functioning as Lewis acids. The oxidation state of the metal does not change when it is utilized as a Lewis acid. In a catalytic cycle as that in Scheme 3, the metal undergoes a change in the oxidation state, albeit there are cycles known where the oxidation state does not change. Organometallic catalysts are coordination compounds with "ligands" attached to them. Through the ligands L on the metal complex, the reactivity of the catalyst can be tuned, allowing for rational catalyst design. Also, the ligands may increase the solubility of the metal complex in organic solvents such as CH_2Cl_2, which is frequently utilized in glycosylation reactions.

However, most importantly, in a transition metal catalyzed cross coupling reaction, the metal center is part of each elementary step and coordinated to the substrate(s) throughout the whole cycle. As such, tuning of the metal complex can increase regio- and stereoselectivities. Furthermore, the oxidative addition step can be remarkably chemoselective. There are several mechanisms for oxidative additions and selectivities depend on the metal and the substrates.[46] However, generally, oxidative additions are easier for C–X bonds where X = halogen, compared to X = C or H. Also, oxidative addition is slower for C–O bonds where the oxygen is part of an ester, ether or OH group. As such, the chemoselectivity often



Scheme 3 Generic catalytic cycle of a cross coupling reaction as can be utilized in glycosylation reactions.

observed in glycosylation reactions originates from the relative ease of oxidative additions. In a sugar molecule with ester, ether or OH groups, the oxidative addition will mainly take place across the C–X bond, if a halogen is present.

These two major groups of catalysis modes will be discussed separately in the subsequent sections.

4. Lewis acid catalyzed glycosylations based on transition metals

The most common application of transition-metal based catalysts is their use as Lewis acids.[22] Lewis acids can act as activators in the formation of an oxocarbenium ion **5** (Scheme 1) or can polarize the bond between the leaving group and the sugar molecule to facilitate S_N2 reactions. Typically, fairly simple metal salts are employed, such as metal triflates $M(OTf)_x$, halides MX_x or acetates $M(OAc)_x$. Pretty much all common transition metals have been employed as Lewis acid catalysts in glycosylation reactions.[22]

In order to demonstrate the trends in Lewis acid catalyzed reactions, in the first part of this section, applications of a commonly used Lewis acid, $FeCl_3$, will be discussed. In the second part of this section, trends among different metal salts will be outlined.

The simple salt $FeCl_3$ has been utilized as a catalyst in a number of glycosylation reactions, and representative examples are compiled in Table 1. Gosh utilized $FeCl_3$ in synthetic routes toward an acidic pentasaccharide related to the *O*-antigen of *E. coli* 120 (Table 1, entry 1).[47] One-pot strategies were employed, and entry one depicts a $FeCl_3$ catalyzed step, where a trichloroacetimidate carbohydrate was glycosylated with an armed thio-disaccharide. The reaction temperature was only −60 °C, and the trisaccharide was formed in virtually quantitative yield. The same authors performed an $FeCl_3$-catalyzed modulated selective 1,2-*trans* glycosylation also based on glycosyl trichloroacetimidate donors (entry 2).[48] Here, the coupling partner was disarmed; however, the reaction temperature was also −60 °C, and the products were obtained mainly as the β isomer in yields between 85 and 96%.

Demchenko demonstrated that $FeCl_3$ also catalyzes glycosylation reactions with glycosyl chlorides (entry 3).[49] At room temperature after 0.5 to 16 hours, the disaccharides could be isolated in 52 to 90% yields and varying α : β ratios ranging from pure α to pure β. One example with an armed glycosyl chloride is shown, but disarmed glycosyl chlorides worked as well.

Zhang showed that substoichiometric amounts of $FeCl_3$ can be used in the activation of propargyl glycosides for the synthesis of disaccharides and glycoconjugates (entry 4).[50] The propargyl glycosides were glycosylated with steroids and sugar-derived armed and disarmed glycosyl acceptors to obtain disaccharides and glycoconjugates in 66 to 91% yields. The α : β ratios ranged from 1.5 : 1 to 1 : 3, the reaction times were between 12 and 36 h and the reaction temperature was 60 °C. The same research group showed that $FeCl_3$ can be employed in the synthesis of deoxy-sugars at temperatures as low as 0 °C employing acetate leaving groups.[51]

Paixão utilized $FeCl_3$ as a catalyst for the glycosylation of peracylated sugars with allyl- and alkynyl-alcohols.[52] After 8 h at room temperature, the products were isolated in 48 to 64% yields (β only), and one example is given in entry 5. Lower catalyst loads afforded lower yields, and the authors assume that $FeCl_3$ plays the role of a Lewis acid assisting with the departure of the acetate leaving group. The authors also reported uncharacterized polymerization side products in their system.

Augé described the glycosylation of alcohols and amino acids mediated by the ionic liquid 1-butyl-3-methylimidazolium trifluoromethanesulfonate [BMIM][OTf] as recyclable solvent.[53] Here, $Sc(OTf)_3$ was employed as a catalyst, but $FeCl_3$ worked as well for one example (entry 6). After 5 h at 80 °C, the glycosylation of a serine derivative gave the product in 60% yield at an α : β ratio of 1 : 1. Under these conditions, unprotected glucose could be utilized as a donor. Interestingly, when *N*-acetylglucosamine was employed, a stoichiometric amount of $FeCl_3$ at 110 °C for 2 h 30 min was required to obtain only 34% of the product.

Chen reported $FeCl_3$ as an efficient catalyst for the stereoselective synthesis of glycosyl azides (entry 7).[54] Here, an azido glycosylation of glycosyl β-peracetates to 1,2-*trans* glycosyl azides was performed. At a catalyst load of 5 mol% and a reaction time of 6 h, the β products were isolated in 87 to 96% yields. The azides were subsequently converted to glycosyl 1,2,3-triazoles *via* $FeCl_3$/Cu catalyzed 1,3-dipolar cycloaddition of terminal alkynes.

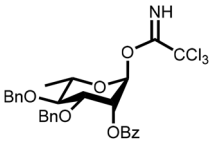
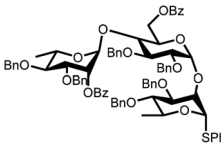
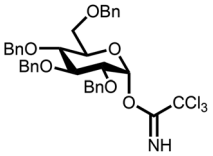
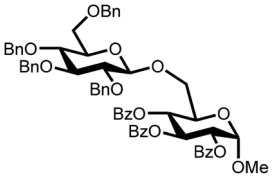
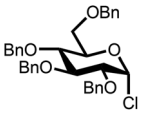
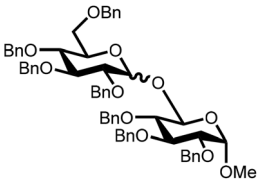
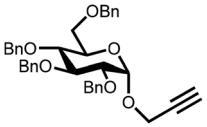
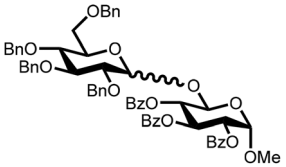
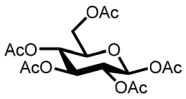
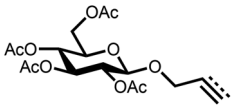
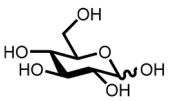
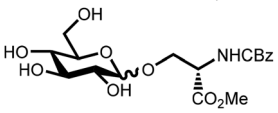
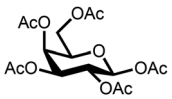
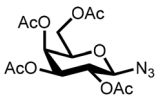
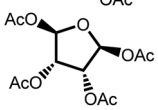
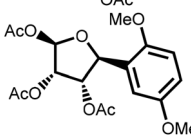
Finally, Bougrin and Benhida showed *C*-glycosylations through $FeCl_3$-catalyzed Friedel–Crafts alkylations (entry 8).[55] Here, a carbon–carbon bond between the anomeric carbon and an aromatic ring system is formed after 10 minutes of reflux to afford the β products in 32–72% yields. Polyaromatics such as naphthalene could be utilized as well, and the method can potentially be employed in nucleic acid labelling.

As can be seen from Table 1, $FeCl_3$ can be employed as a catalyst in a wide variety of glycosylation reactions. The reaction conditions (such as temperature and time) differ between applications, and so do the α/β ratios. However, a few trends are obvious.

As expected, the reaction temperature is very low for the very efficient trichloroacetimidate leaving group (−60 °C, entries 1 and 2). The acetate and chloride leaving groups (entries 3, 5 and 7) could be activated at room temperature, whereas the OH and *O*-propargyl leaving groups required elevated temperatures of 60 or 80 °C (entries 4 and 6). It appears that the leaving group has an impact on the reaction temperature, which is not surprising. As the catalyst to be employed is always $FeCl_3$, the reactivity is determined by the leaving group and a reactivity trend trichloroacetimidate > chloride, acetate > OH, OR is observable. The better the leaving group, the milder the reaction conditions.

In some cases, the α/β ratios are high, especially if neighboring group participation is possible (entries 1, 5 and 7). The catalyst loads are at times quite high (up to 30%), which may

Table 1 $FeCl_3$-catalyzed glycosylation reactions

Entry	Starting material	Product	Conditions	Yield/α : β ratio	Ref.
1			$FeCl_3$ (10 mol%) CH_2Cl_2 −60 °C, 45 min	Quantitative β only	47
2			$FeCl_3$ (10 mol%) CH_2Cl_2 −60 °C, 45 min	96% 1 : 9	48
3			$FeCl_3$ (20 mol%) CH_2Cl_2 rt, 2 h	67% 1.1 : 1	49
4			$FeCl_3$ (30 mol%) CH_3CN 60 °C 15 h	83% 1 : 3	50
5			$FeCl_3$ (10 mol%) CH_2Cl_2 rt, 8 h	53 to 64% β only	52
6			$FeCl_3$ (5 mol%) [BMIM][OTf] 80 °C, 5 h	62% 1 : 1	53
7			$FeCl_3$ (5 mol%) CH_2Cl_2 rt, 6 h	96% β only	54
8			$FeCl_3$ (10 mol%) CH_2Cl_2 Reflux, 10 min	62% 4 : 6	55

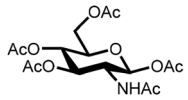
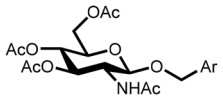
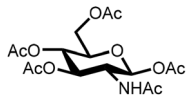
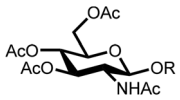
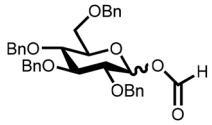
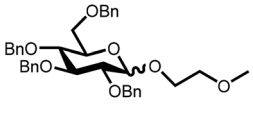
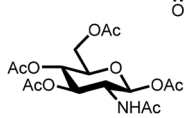
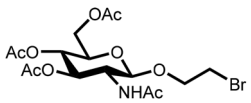
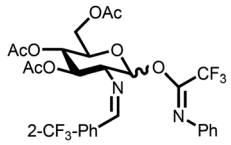
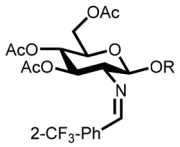
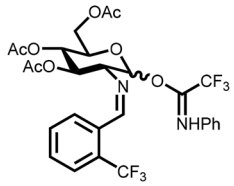
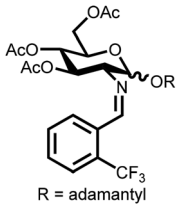
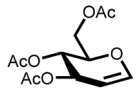
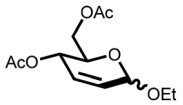
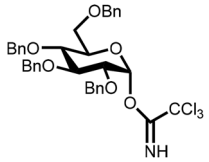
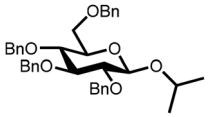
be due to the fact that $FeCl_3$ can also coordinate to ester carbonyl units, deactivating the catalyst. Finally, CH_2Cl_2 appears to be the solvent of choice, which was employed in all reactions except for those in entries 4 and 6. The relatively low polarity and basicity of CH_2Cl_2 may prevent the deactivation of the promoter or catalyst and it may dissolve the carbohydrates well. Polar solvents such as those in entries 4 and 6 may facilitate the formation of the oxocarbenium ion and are obviously used with less reactive donors.

In order to analyze the influence of different Lewis acids on the catalytic efficiency, representative examples of different Lewis acid catalysts and their efficiency in glycosylation reactions are compiled in Table 2.

Metal triflates are frequently employed as stoichiometric and catalytic activators.[22] The weakly coordinating triflate anion improves the solubility of the salt and typically does not interfere with the acceptor. Beau reported glycosylations with *N*-acetyl-glycosamine donors using catalytic iron(III) triflate (Table 2, entry 1).[56] After microwave irradiation at 80 to 120 °C for 30 to 180 min, various glycosylation products were isolated in 21 to 95% yields, mainly as β isomers. Two equivalents of 2,4,6-tri-*tert*-butylpyrimidine (TTBP) were added to the reaction mixture, and the reaction was also performed under flow chemistry conditions, in which case TTBP was not required. Microwave irradiation obviously promotes the reaction, and a related glycosylation reaction by conventional CH_2Cl_2 reflux (entry 2) reported by the same authors required higher reaction times and provided lower yields.[57]

Pedersen reported glycosylation reactions employing glycosyl formates and triflate salts based on iron and bismuth (entry 3).[58] Both $Fe(OTf)_3$ and $Bi(OTf)_3$ catalyzed the glycosylation. However, it turned out that $Bi(OTf)_3$ in combination with

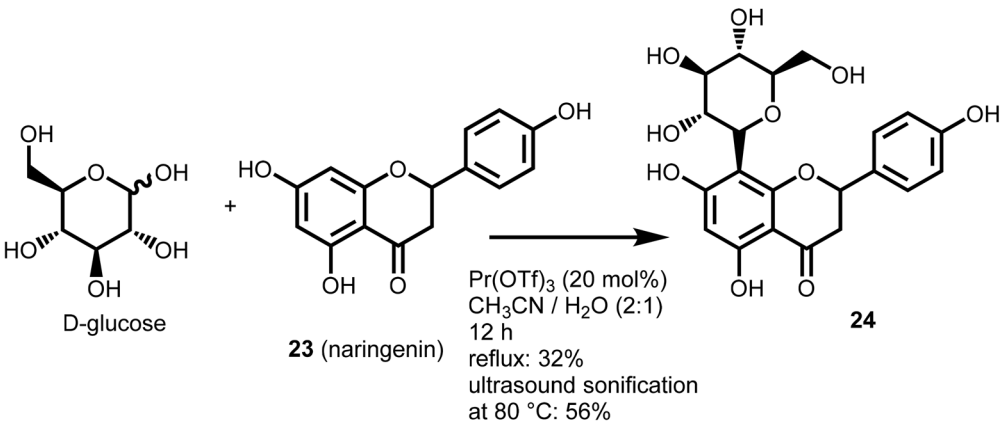
Table 2 Transition metal Lewis acid catalysts in glycosylation reactions

Entry	Starting material	Product	Conditions	Yield /α : β ratio	Ref.
1		 Ar = 4-(chloromethyl)phenyl	$Fe(OTf)_3$·6.2DMSO (15 mol%) CH_2Cl_2, 30 min, 110 °C, microwave	95% β only	56
2			$Fe(OTf)_3$·6.2DMSO (15 mol%), CH_2Cl_2, reflux, 24 h	61% β only	57
3		 R = 1-isopropyl-4-methylcyclohexyl	$Bi(OTf)_3$ (25 mol%), KPF_6, THF, rt, 20 h	79% 1 : 1	58
4			$Sc(OTf)_3$ (15 mol%), CH_2Cl_2, 45 °C, 27 h	67% β only	59
5			$[Ni(4\text{-F-PhCN})_4](OTf)_2$ (10 mol%), CH_2Cl_2, 35 °C, 14 h	81% α only	60
6		 R = rhamnose R = adamantyl	$NiCl_2$ (15 mol%), AgOTf (30 mol%), CH_2Cl_2, 35 °C, 12 h	90% 10 : 1	61
7			$Bi(NO_3)_3$·5H_2O (10 mol%), CH_3CN, rt, 5 h, similar results with $Fe(NO_3)_3$·9H_2O	89% 9 : 1	62
8			$AuCl_3$ (15 mol%), CH_2Cl_2, −70 °C, 30 min	90% β only	63

1.2 equivalents of KPF_6 showed superior results, affording glycosylated products in 32 to 79% isolated yields with varying ratios after 20 h at room temperature. The role of KPF_6 is not entirely clear, but it did not activate the donor by itself, but only in the presence of the metal triflates. With KPF_6 added, the selectivity diminished with $Fe(OTf)_3$, but increased with $Bi(OTf)_3$. Addition of TTBP to the reaction mixture resulted in the deactivation of the catalytic system, either by deactivating the metal triflates or by capturing HOTf that may have formed during the reaction (*vide infra*).

Pedersen also showed that a number of rare earth metal triflates catalyze the glycosylation of *N*-acetyl-glycosamines.[59] It turned out that $Sc(OTf)_3$ was somewhat more efficient than other triflates based on, *e.g.*, samarium or ytterbium. Again, the acetate leaving group worked well (entry 4) and microwave irradiation accelerated the reaction.

Nguyen reported a nickel-catalyzed 1,2-*cis*-2-amino glycosylation using a glycosyl donor bearing a *N*-phenyl trifluoroacetimidate leaving group and various armed and disarmed carbohydrate acceptors (entry 5 shows an example).[60] After 14 h at 35 °C, the corresponding disaccharides were isolated in 55 to 98% yields, and in most cases, only the α isomer was obtained. A nickel nitrile complex $[Ni(4\text{-FPhCN})_4](OTf)_2$ served as a catalyst. The presence of thioether groups on the acceptor was tolerated under the reaction conditions, as no sulfide transfer from the acceptor to the donor occurred (which is a common side reaction). The method allows access to 1,2-*cis*-2-amino glycosidic linkages, but is still a challenging task. A related



Scheme 4 *C*-Glycosylation of naringenin with D-glucose.

system was reported by Schlegel and Nguyen, where *in situ* generated [Ni(OTf)$_2$] served as the catalyst (entry 6).[61] Here, the authors assume that HOTf, generated from the metal triflate salt and either water in the system or the acceptor, is the actual catalyst, which is a common problem when metal triflates are employed as catalysts. This point will be discussed further below.

Simple metal salts besides triflates can be employed in glycosylation reactions as well. For example, metal nitrates catalyzed *O*-glycosylation using acetylated glycal derivatives in organic solvents and ionic liquids (entry 7).[62] Glycals are 1,2-unsaturated carbohydrates, and versatile chiral building blocks in glycosylation reactions; they will be further discussed below. Here, an allylic substitution of the OAc group took place, where the 1,2-double bond was shifted at the 2,3 position (Ferrier rearrangement, *vide infra*). Glycosidation of the glycal with primary and secondary alcohols was performed using Bi(NO$_3$)$_3$·5H$_2$O (10 mol%) as the catalyst, and after 5 h at room temperature, the products were isolated in 87 to 95% isolated yields with α/β ratios of 7 : 3 to 9 : 1. The reactions worked also with Fe(NO$_3$)$_3$·9H$_2$O, which exhibited lower reactivity, though, and 50 mol% of the salt needed to be employed.

Finally, Schmidt demonstrated that *O*-glycosidations with *O*-glycosyl trichloroacetimidates as glycosyl donors and AuCl$_3$ as a catalyst are also feasible.[63] Glycosylations with a number of primary and secondary alcohols as well as with other monosaccharides were possible at −70 °C with an AuCl$_3$ load of 15 mol% to afford the products after 30 min reaction times in 80 to 93% isolated yields, either as the β isomer or with high β selectivity (entry 8 shows an example). Here, the authors assume that a catalyst-acceptor adduct forms. In the transition state, the catalyst activates both the donor and acceptor, and the transfer of the acceptor to the donor occurs in an S$_N$2 type fashion. This explains the β selectivity from the α donor. Related gold-catalyzed glycosylation reactions have been reported by others.[64]

Table 2 gives an overview of common transition metals employed in glycosylation reactions. However, other metals such as Co,[65] Yb[66] or Pd[67] have been applied as well.

C-Glycosylations (*i.e.* the formation of a carbon–carbon bond on the anomeric carbon) catalyzed by Lewis acids are possible as well (Scheme 4). Rauter described a regio- and stereoselective, direct *C*-glycosylation of the flavanone naringenin catalyzed by 20 mol% Pr(OTf)$_3$ under conventional heating or ultrasound irradiation.[68] D-Glucose and other unprotected, reducing saccharides were *C*-glycosylated with naringenin (**23**, Scheme 4), and after 12 h under reflux in acetonitrile/water, the products were isolated in 28 to 38% yields with the glycosidic bond in an equatorial position. Under ultrasound irradiation, the yields increased to 43 to 56%. Other rare earth metal triflates catalyzed the reaction as well, albeit at much lower yields.

As can be seen from the data in Tables 1 and 2 and Scheme 4, a variety of metal salts catalyze glycosylation reactions. The trends are similar to those of the FeCl$_3$-catalyzed glycosylation reactions described above (Table 1). Relatively low reaction temperatures were sufficient with good leaving groups or with an activated substrate (Table 2, entries 3, 6 and 8), albeit the reaction times are long for some examples. Again, the leaving group has a major impact on the reaction temperature. A variety of metal salts can be employed; however, metal chlorides do not seem to be the first choice. Triflates, in turn, appear to be very common.

4.1 HOTf as the actual catalyst?

As mentioned earlier, metal triflates are frequently employed in glycosylation reactions, catalytically as well as stoichiometrically. However, as pointed out by Nguyen, when employing metal triflates as catalysts, the actual catalyst may be triflic acid (HOTf).[61]

It is known that metal triflates can, in the presence of water, forms small amounts of HOTf. Metal triflates catalyze a whole variety of organic reactions.[69,70] It has been speculated that in some of these cases, not the metal, but HOTf formed during the reaction is the actual catalyst,[69] termed "hidden Brønsted acid catalysis".[70] It is also known that HOTf catalyzes glycosylation reactions.[22] As such, metal triflate catalyzed reac-

tions may actually be proton-catalyzed reactions, and the metal is not part of the catalytic cycle.

With a number of experiments, Nguyen investigated the potential involvement of triflic acid in the $Ni(OTf)_2$ catalyzed glycosylation utilizing *N*-phenyl trifluoroacetimidate donors (Table 2, entry 5). He concludes that triflic acid indeed may be the catalytically active species in his system. He first observed that different batches of the $Ni(OTf)_2$ catalyst gave different results, whereas freshly prepared $Ni(OTf)_2$ (by an *in situ* reaction of $NiCl_2$ with AgOTf) gave consistent results. This may be due to the fact that aged $Ni(OTf)_2$ samples contain various amounts of HOTf, resulting from hydrolysis. When 2,6-di-*tert*-butyl-4-methylpyridine (DTBMP) as an acid scavenger was added to the reaction mixture, the reaction was almost completely suppressed. This is strong evidence that HOTf may be the catalyst, because DTBMP is a non-nucleophilic base, and should not attack the metal center. Furthermore, triflic acid also catalyzed a reaction similar to the one in Table 2, entry 4. Also, ^{19}F NMR showed that moisture from carbohydrates formed HOTf in solution. Nguyen points out that a small amount of triflic acid may perform better as a catalyst due to suppressed product decomposition and side reactions. Finally, he identified by NMR a glycosyl triflate as a potential intermediate.

These experiments demonstrate that caution is advised when metal triflates are utilized as catalysts in glycosylation reactions.[61] An underutilized test for proton catalysis is the addition of non-nucleophilic bases to the reaction mixture.[61] This method has, for example, also been applied by Pedersen in the reaction in Table 2, entry 3.[58] The reaction was shut down when a base was added, and the authors concluded that HOTf could indeed be the actual catalyst.

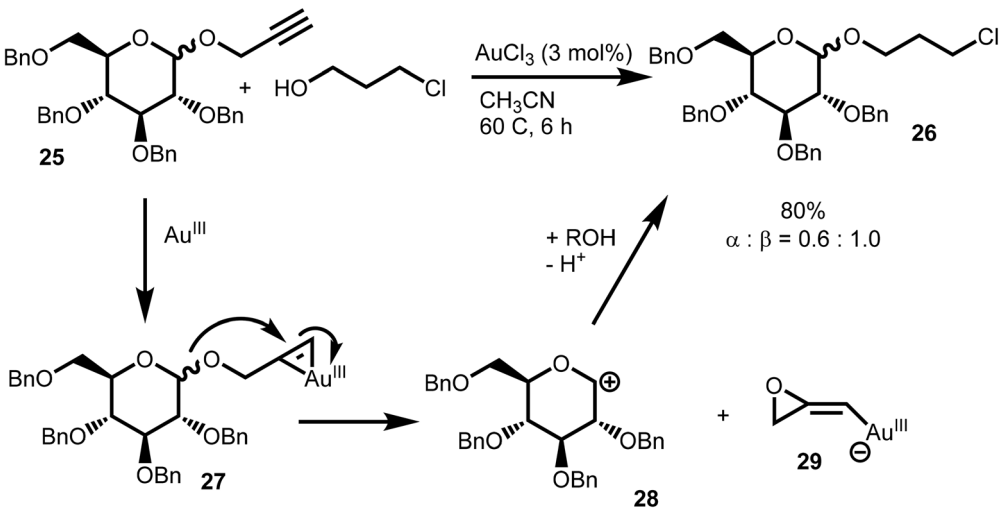
Overall, Lewis acids are a versatile catalyst class in glycosylation reactions. They are structurally simple, and easy to access. However, some of their disadvantages (like high catalyst load and at times a lack of chemoselectivity) can be overcome by transition-metal catalyzed reactions as defined and discussed in the next section.

5. Transition metal catalyzed glycosylation reactions not based on Lewis acids

As outlined in the Introduction, "transition-metal catalyzed glycosylation reactions" are defined in the present context as reactions where the metal does not only play the role of a Lewis acid. As outlined in Scheme 3, classic transition-metal catalyzed reactions follow somewhat more complex pathways, where the formal oxidation state of the metal changes and where the metal is coordinated to the substrate throughout the whole catalytic cycle. Some transition-metal catalysts can be remarkably chemoselective, and this fact is increasingly taken advantage of in glycosylation reactions. Representative examples are presented in this section based on the activation mode of the donor.

Gold is known to have a high affinity to alkynes.[71] Alkyne-based leaving groups in combination with gold catalysts offer the possibility of selective activation of the leaving group in the presence of other functional groups in the carbohydrate. This principle has been exploited for several catalytic systems, most of which are gold-based.

Hotha reported propargyl glycosides as donors, which can be activated for glycosidic bond formation (Scheme 5 gives an example).[72] The propargyl donors **25** were glycosylated with a variety of primary and secondary alcohols as well as with another monosaccharide to give the glycosylation products such as **26** in 39 to 95% isolated yields with α/β ratios ranging from 1.2 : 1 to 0.2 : 1. The reactions were performed at 60 °C for 6 h in acetonitrile in the presence of $AuCl_3$ (3 mol%). A related 1-ethynylcyclohexyl leaving group was employed by the



Scheme 5 Gold-catalyzed glycosylation of propargyl glycosides.

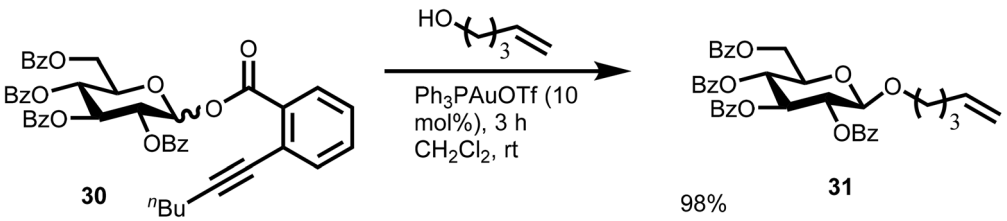
same authors, where a mixture of $AuCl_3$ and $AgSbF_6$ (5 mol% each) was employed as the catalytic system.[73] Here, a reaction time of 8 h was sufficient to give the glycosylation products in improved 71 to 95% yields with higher α/β ratios ranging from 1 : 1.3 to 1 : 8.9. Propargyl 1,2-orthoesters have been employed by the same researchers in a similar fashion in the synthesis of thioglycosides.[74]

A potential mechanism for activation is presented in Scheme 5. The Au^{III} species coordinated to the triple bond to give intermediate **27**. The triple bond is, due to the coordination of the gold species, now more electron-deficient and thereby activated. Heterolytic bond cleavage of the C–O bond of the anomeric carbon affords the oxocarbenium ion **28**, which is then attacked by the acceptor. The proton released through this attack can protonate the intermediate gold species **29** to release Au^{III}, which then enters a second cycle. As can be seen, gold does not play just a role as a Lewis acid, but it forms intermediate species **27** and **28** as a result of the leaving group departure. Also, the high affinity of gold may prevent it from interfering with other parts of the sugar molecule, lowering the catalyst load.

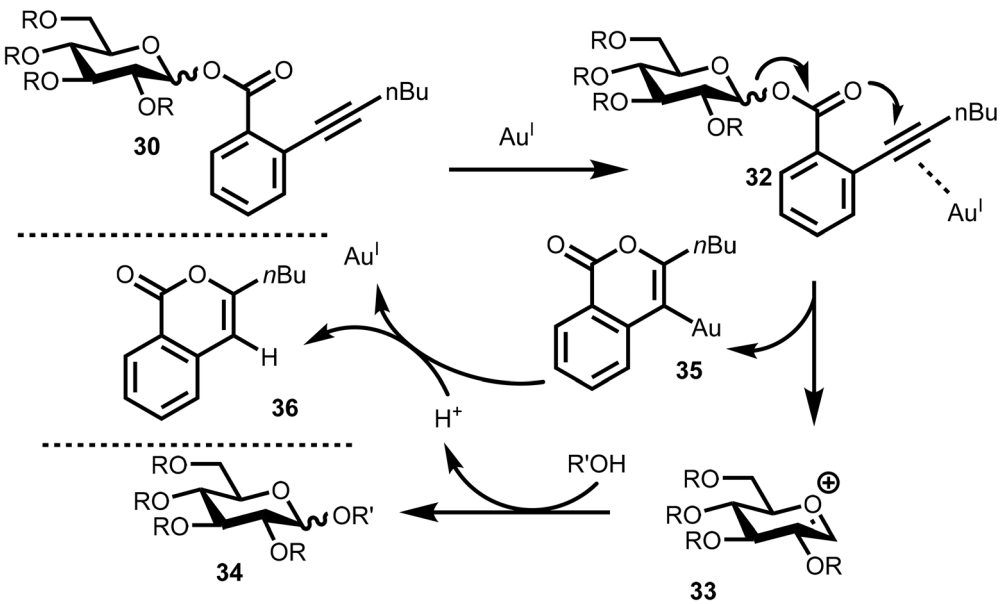
In a related fashion, Yu employed glycosyl *ortho*-alkynylbenzoates as donors (**30** in Scheme 6).[75] These donors were also activated by gold complexes. In an earlier case, a Au^{I} complex of the formula $Ph_3PAuOTf$ (10 mol%) was employed to give the β-glycosylation products in 63 to 99% yields after 3 h at room temperature, and an example is presented in Scheme 6.[75a] Similar protocols have been employed by others,[76] also in *N*-glycosylation reactions.[77]

The mechanism of the glycosylation reaction of this donor is depicted in Scheme 7. Again, the gold coordinates to the triple bond, making it more electrophilic. The carbonyl group in **32** attacks the triple bond intramolecularly to afford the oxocarbenium ion **33** and the gold intermediate **35**. The attack of **33** by the alcohol R'OH generates the glycosylation product **34**. The proton released through this process protonolyses the Au–C bond in **35**, thereby releasing the isochromen-1-one side product **36** and liberating the gold(I) species, which can then enter another catalytic cycle.

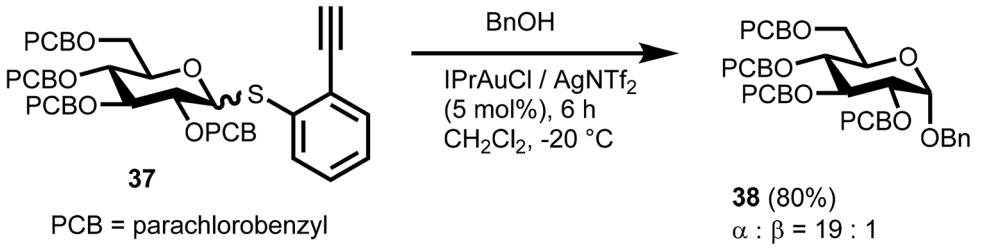
Somewhat related *o*-ethynylphenyl thioglycoside donors **37** (Scheme 8) were employed in gold-catalyzed glycosylation reactions as well.[78] As investigated by Zhang, **37** reacted with an alcohol acceptor when activated by 5 mol% of a mixture of IPrAuCl and the halide abstractor $AgNTf_2$ (IPr = bis(2,4,6-triisopropylphenyl)imidazol-2-ylidene; NTf_2 = bis(trifluoromethane) sulfonamide). After 6 h at −20 °C, the glycosylation products



Scheme 6 Gold-catalyzed glycosylation with glycosyl *ortho*-alkynylbenzoates as donors.



Scheme 7 Mechanism of the Au1 catalyzed glycosylation reaction with glycosyl orthoalkylbenzoate donors.



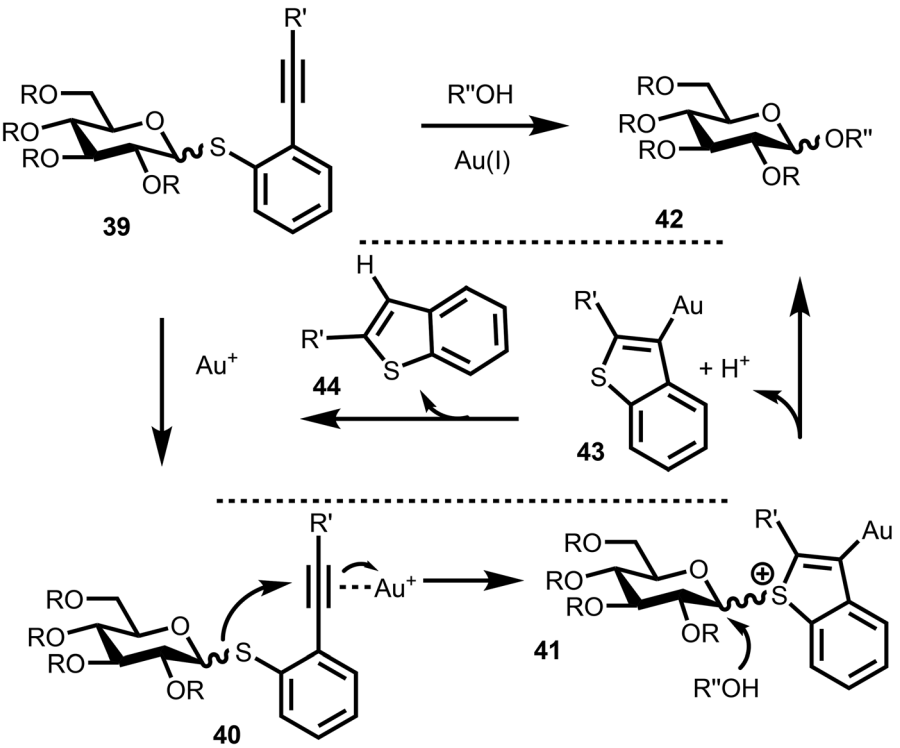
Scheme 8 Gold-catalyzed synthesis of glucosides using an *o*-ethynylphenyl thioglycoside donor.

such as **38** were obtained in 63 to 80% isolated yields with α/β ratios ranging from 5 : 1 to 19 : 1.

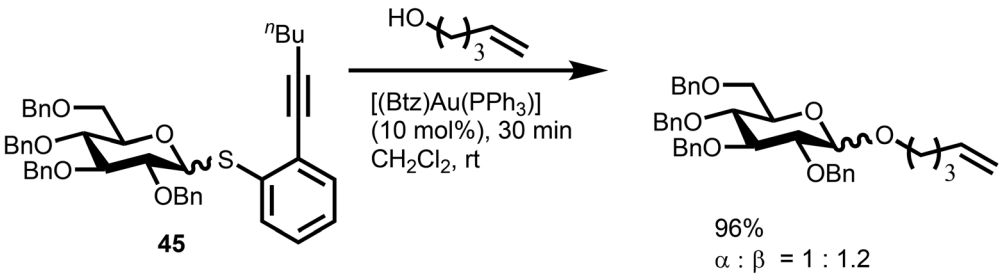
A suggested mechanism is shown in Scheme 9. Again, the gold(I) species coordinates to the triple bond to give **40**, facilitating an intramolecular attack of the sulfur atom on the triple bond. The resulting species **41** still features a C–S bond and is attacked by the alcohol in an S_N2 type fashion to afford the glycosylation product **42** and a proton. The intermediate gold species **43** is protodemetallated by that proton, resulting in the side product **44** and regenerating the gold(I) species, which can then enter another catalytic cycle.

Related *ortho*-alkynylphenyl thioglycosides **45** (Scheme 10) were employed by Yu, where [(Btz)Au(PPh_3)] (10 mol%, Btz = benzotriazole) was employed as the catalyst.[79] After 30 min at room temperature, the glycosylation products were isolated in virtually quantitative yields with α/β ratios ranging from 1 : 1.2 to 2.9 : 1; three products were obtained as pure β isomers. Other sulfide-based donors such as *S*-but-3-ynyl thioglycoside have been employed as well.[80]

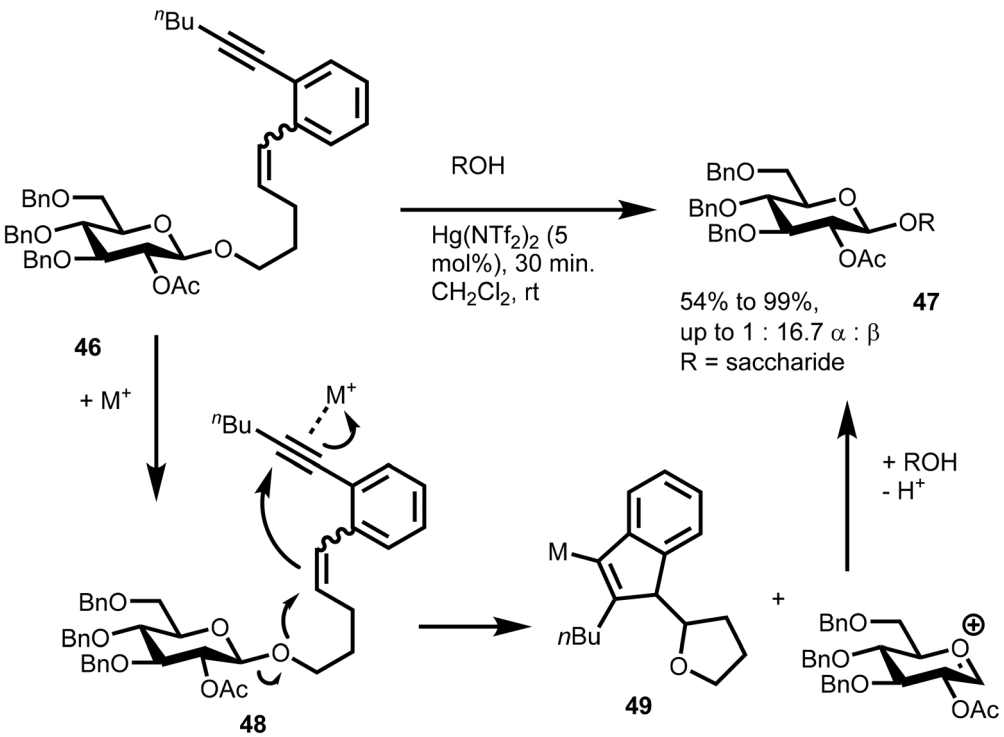
n-Pentenyl groups were employed as leaving groups as well.[1] In a somewhat higher sophisticated example, Zhang and Chai employed a 4-*n*-pentenyl-1,5-enynyl leaving group (**46** in Scheme 11).[81] It can be activated by catalytic amounts of $Hg(NTf_2)_2$ or $PPh_3AuCl/AgNTf_2$ (5 to 10 mol%) at room temperature. At a reaction time of 30 minutes, various disaccharides were isolated in 54 to 99% yields, either as β isomers or with a high β/α ratio. Here, the authors also suggest that the activation takes place through the triple bond, which is first attacked by the metal to afford species **48**. An intramolecular cascade reaction generates the oxocarbenium ion, which is subsequently attacked by the acceptor to afford the glycosylation product. Protodemetallation of intermediate **49** liberates the metal, which can undergo another catalytic cycle.



Scheme 9 Mechanism of the activation of the *o*-ethynylphenyl thioglycoside donor.



Scheme 10 Gold(I) catalyzed glycosylation of *ortho*-alkynylphenyl thioglycosides.



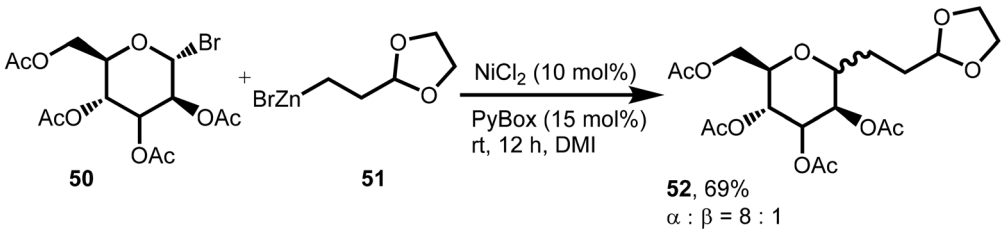
Scheme 11 *n*-Pentenyl-type glycosides for catalytic glycosylation.

The examples outlined above involve alkyne units, through which the glycosyl donor is chemoselectively activated by a metal, mainly gold. As can be seen, the yields and α/β ratios of these reactions can be high, and the reaction temperatures and catalyst loads low.

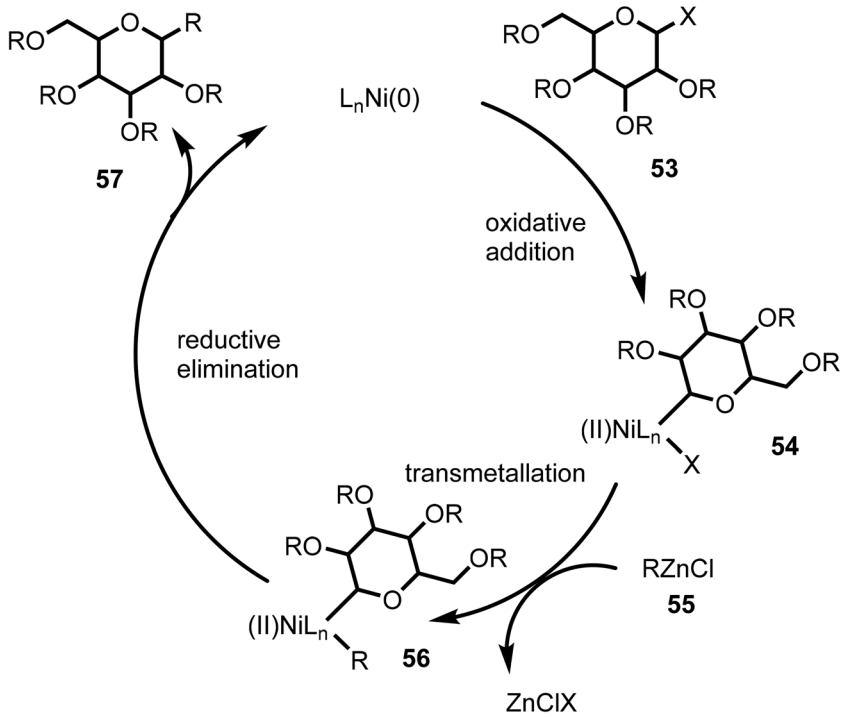
So far, *O*-glycosylations have been covered, where a carbon–oxygen bond is formed at the anomeric carbon. However, *O*-glycosides are susceptible to enzymatic or acidic degradation.[82] The corresponding *C*-glycosides have recently attracted attention due to their higher stability to glycosidases and hydrolases.[82] *C*-Glycosides can be found in nature, but their synthetic access is by far less investigated than the synthesis of the corresponding *O*-glycosides.

There is a vast number of transition-metal catalyzed carbon–carbon bond forming reactions known. Some of them also have been employed in the synthesis of *C*-glycosides. For example, Gagné presented a Negishi cross-coupling approach to *C*-alkyl glycosides.[83] As shown in Scheme 12, 10 mol% of $NiCl_2$ in combination with 15 mol% of the ligand PyBox (1,6-pyridyl bisoxazoline) catalyzed the coupling of glycosyl bromides (**50**) and chloride with alkyl zinc reagents **51** to afford the corresponding *C*-glycosides such as **52** in 40 to 76% yields. The reaction was performed at room temperature for 12 h and α/β ratios ranging from 1 : 1.1 to pure α were obtained.

This is a Negishi-type reaction, which is a coupling reaction between a zinc organyl compound (comparable to a Grignard reagent) and an aryl halide. The catalytic cycle is presented in Scheme 13 with the glycosyl donor as a coupling partner. The C–X bond of the sugar **53** first oxidatively adds to the nickel center; the C–X bond is cleaved in that step, and the oxidation state of nickel increases by two. Next, the R group of the RZnCl reagent **55** is transmetallated to the nickel center in **54**, forming species **56**. Reductive elimination affords product **57**, and nickel is recovered. During this last step, the oxidation



Scheme 12 Negishi-type *C*-glycosylation.

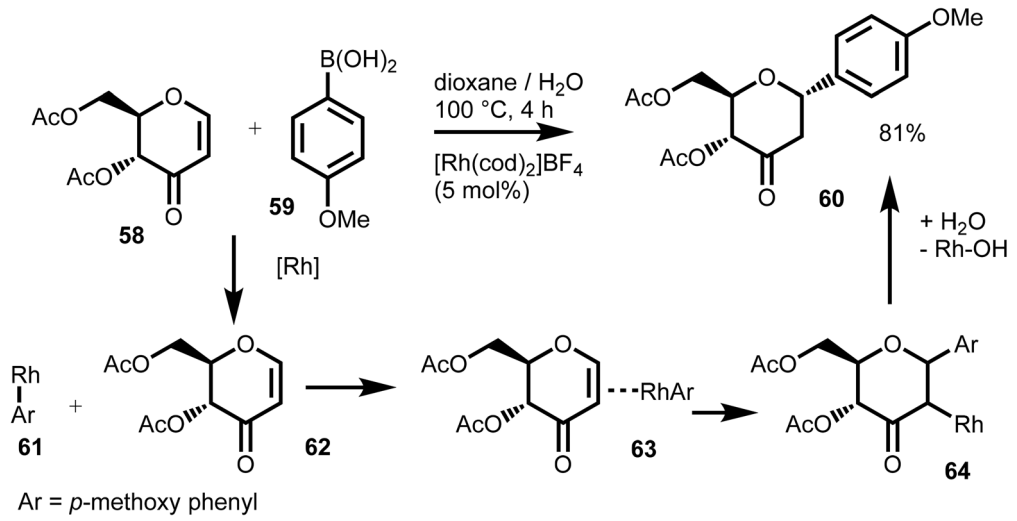


Scheme 13 Mechanism of Negishi-type *C*-glycosylation reactions.

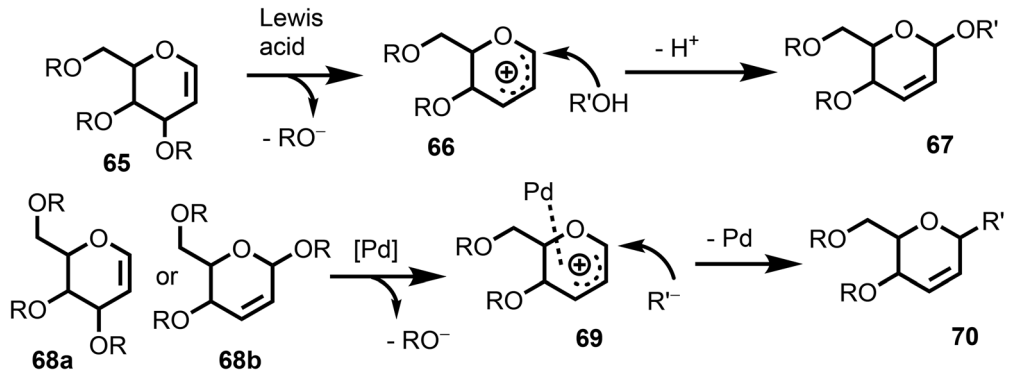
state of nickel decreases by two. The remarkable selectivity is achieved because oxidative additions occur into C–X bonds (X = halogen) much easier than those into C–O bonds. Consequently, the other C–O bonds in the sugar molecule do not interfere with the reaction, resulting in a high chemoselectivity.

Phenyl boronic acids are widely used coupling reagents in organometallic catalysis. It has also been employed in *C*-glycosylation reactions. Maddaford described a stereoselective *C*-glycoside formation by rhodium(I)-catalyzed 1,4-addition of arylboronic acids (**59**) to acetylated enones (**58**) derived from glycals (Scheme 14).[84] As the catalyst, $[Rh(cod)_2]BF_4$ (5 mol%, cod = 1,5-cyclooctadiene) was employed; the 1,4-addition of arylboronic acids such as **59** and the acetylated enone **58** afforded the *C*-glycosylated products in 50 to 81% isolated yields, and only the α anomers were obtained. Again, the selectivity can be explained by the mechanism presented in Scheme 14. The aryl portion of the arylboronic acid first transmetallates to rhodium, which is a common elementary step for this type of reaction. The rhodium species **61** coordinates to the double bond of the enone to afford **63**, because rhodium has a high affinity to alkenes. The Rh–Ar unit then adds across the double bond (while the Rh–Ar bond is broken) to afford species **64**. Hydrolysis of the Rh–C bond in **64** generates the product **60**. The tendency of rhodium to not interfere with oxygen may be the reason why the reaction is again very chemoselective, as the other functional groups in the glycosyl donor **58** remain intact.

As mentioned above, glycals (**65** in Scheme 15) are 1,2-unsaturated carbohydrates and versatile building blocks in glycosylation chemistry. When bearing a leaving group, they can be activated by forming an allylic cation **66** (Scheme 15, top) which can be attacked by an acceptor to give the glycoside **67**. Here, a double bond shift takes place, and the process is referred to as Ferrier rearrangement. The ring oxygen presumably stabilizes the positive charge on the carbon atom adjacent to it, making it more electrophilic and causing the double bond shift. Species **66** is often described as an intermediate



Scheme 14 Rhodium(I)-catalyzed 1,4-addition of arylboronic acids to acetylated enones derived from glycals.



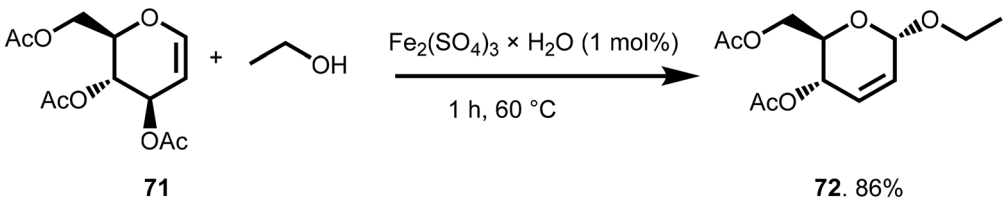
Scheme 15 Ferrier rearrangement (top) and transition metal catalyzed allylic substitution involving glycals (bottom).

for the reaction, and as can be seen, the metal is not coordinated to the oxocarbenium intermediate. As such, the metal is not part of the stereodifferentiation that takes place during the nucleophilic attack of the oxocarbenium ion. The catalyst just assists in the formation of the intermediate and catalyst tuning to improve stereoselectivity would be futile.

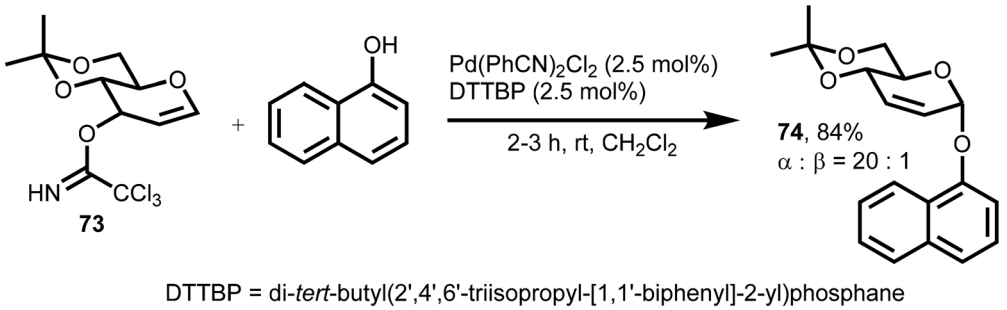
A similar process is transition-metal catalyzed allylic alkylation. As shown in Scheme 15, bottom, no free oxocarbenium ion is formed, but an allylic cation that is coordinated to a transition metal, mainly palladium, forms species **69**. It can be attacked by a nucleophile to give the allylic substitution product **70**. Here, a shift can also take place, depending on which substrate (**68a** or **68b**) is used in the reaction. The nucleophile to be utilized can be oxygen- or carbon-centered. Here, the metal stays coordinated to the substrate throughout the whole catalytic cycle, and stereodifferentiation based on the nature and steric bulk of the metal complex is possible.

An example of an iron catalyzed Ferrier-type rearrangement was provided by Zhang.[85] When glycal **71** was treated with alcohol in the presence of $Fe_2(SO_4)_3 \times H_2O$ (1 mol%), the corresponding α *O*-glycosylation products were obtained in 70 to 91% yields (60 °C, 1 to 2.5 h reaction time). One example is shown in Scheme 16. The reaction time was lowered to minutes when microwave irradiation was employed (80 °C). Here, the authors assume a carbocation intermediate similar to intermediate **66** in Scheme 15. Stereodifferentiation presumably takes place through neighboring group assistance. Krishna and Kashyap utilized $RuCl_3$ in related Ferrier glycosylation reactions.[86] Albeit a mechanism was not presented, the Lewis acidic $RuCl_3$ presumably also assisted in the formation of an oxocarbenium intermediate.

In turn, Nguyen provided an example of a palladium-catalyzed stereoselective synthesis of α-*O*-glycosides.[87] When glycal imidates like **73** (Scheme 17) were treated with 1-naphthol or other phenolic acceptors in the presence of 2.5 mol% [Pd $(PhCN)_2Cl_2$] and 2.5 mol% DTTBP ligand, the corresponding α products were isolated in 70 to 97% isolated yields after 2 to 6 h at room temperature; Scheme 17 shows an example. The authors suggest that during the whole catalytic cycle, the Pd center stays coordinated to the substrate, similar to intermediate **69** in Scheme 15. As such, the stereoselection is controlled by the metal, and not by the neighboring groups. Similar palla-



Scheme 16 Iron-catalyzed Ferrier-type rearrangement.



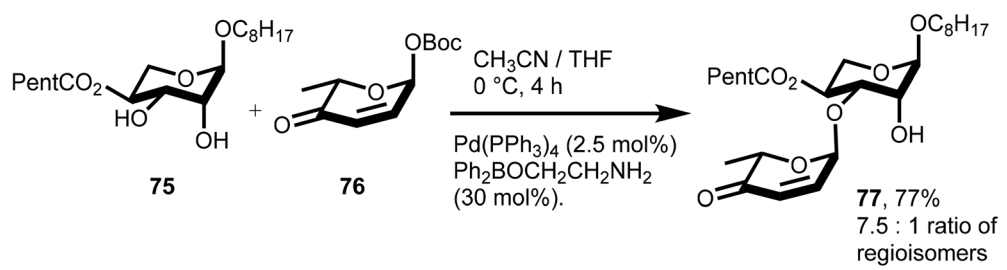
Scheme 17 Palladium-catalyzed allylic substitution-type rearrangement.

dium catalyzed reactions where a Ferrier rearrangement took place were published by Lee.[88] Here, the metal also stays coordinated to the substrate and the stereochemistry is controlled by the catalyst.

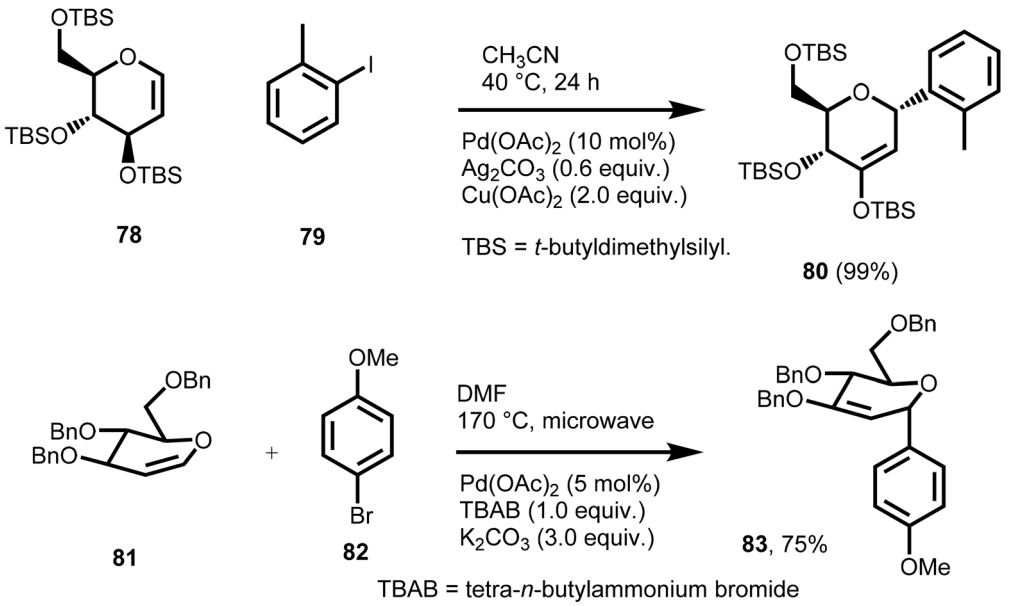
The examples in Schemes 16 and 17 demonstrate the difference between Lewis-acid catalyzed glycosylations and those catalyzed by transition metals that can proceed through metal–substrate intermediates. In many cases, Lewis-acid catalyzed processes may generate an oxocarbenium ion and the follow-up reactions take place without the participation of the metal. In the case of palladium-catalyzed allylic substitution reactions, the metal is involved in all steps of the catalytic cycle and metal-centered stereocontrol is possible. This principle has also been demonstrated by Liu in a number of palladium-catalyzed decarboxylative allylic substitution reactions[89] or allylic substitution reactions involving aryl sulfinates.[90] Feringa published similar palladium-catalyzed chemistry.[91]

The remarkable selectivity that transition metal catalyzed glycosylation reactions can exhibit is demonstrated with a boron/palladium catalyst used by O'Doherty (Scheme 18).[92] When the diol **75** and glycal **76** were treated with a Pd/B catalytic system (2.5 mol% in palladium, 30 mol% in boron) at 0 °C for 4 h, the glycosylation product **77** was isolated in 77% yield. The two coupling partners exhibit OH, ester, acetal, and carbonate groups. However, the palladium activates chemoselectively the carbonate unit for glycosylation. One might argue that the carbonate group on the anomeric carbon is preactivated to begin with; however, the low catalyst load of only 2.5 mol% in palladium demonstrates that there appears to be little interaction with the other functional groups in the starting materials, which is an advantage of systems like this compared to Lewis acid catalysts. O'Doherty published other highly selective palladium-catalyzed glycosylation reactions.[93]

The Heck reaction is a transition metal catalyzed coupling of an unsaturated halide and an alkene. It has been employed in a number of *C*-glycosylation reactions. Ye reported the regio- and stereo-selective synthesis of aryl 2-deoxy-*C*-glycopyranosides by palladium-catalyzed Heck coupling reactions of glycals and aryl iodides (Scheme 19, top). When the pyranoid glycal **78** was heated with the aryl iodide **79** in the presence of Ag_2CO_3, $Cu(OAc)_2$ and catalytic amounts of $Pd(OAc)_2$, the corresponding coupling products such as **80** were obtained in



Scheme 18 Palladium/boron catalyzed selective glycosylation.



Scheme 19 Heck-type glycosylation reactions.

59 to 99%.[94a] The same research group reported a related coupling reaction utilizing boronic acids as coupling partners.[94b] Yang reported microwave-assisted palladium-catalyzed cross-coupling reactions between pyranoid glycals such as **81** and aryl bromides like **82**.[95] Here, $Pd(OAc)_2$ was employed as the catalyst as well, and the reaction was performed at 170 °C for 30 minutes to afford the coupling products such as **83** in 74 to 81% isolated yields; Scheme 19 (bottom) shows an example. As can be seen, the Heck-type reactions need only low catalyst loadings. A disadvantage may be the stoichiometric amounts of a base required for the reaction and that the reaction is restricted to glycal starting materials.

Finally, Liu provided a very good example of how powerful transition metal catalyzed glycosylations can be.[96] Liu applied the principle of palladium-catalyzed allylic alkylation to the formation of an *O*-glycosylic bond. The starting point is the glycal **84** featuring a picoloyl leaving group (Scheme 20). When it was treated with a soft, aromatic alcohol such as phenol in the presence of $[Pd(PPh_3)_4]$ and dppb (1,4-bis(diphenylphosphino)butane, both 10 mol%) for 48 h at 60 °C, the corresponding α glycals such as **85** were isolated in 56 to 88% yields. When **84** was treated with a hard, aliphatic alcohol such as allyl alcohol under the same conditions (but with the addition of NEt_3), the corresponding glycals such as **86** were isolated in 69 to 94% yields either as pure β isomers or with a high excess of the β isomer. As such, the stereochemical outcome of the reaction depended on the alcohol to be utilized in the reaction.

Again, this remarkable selectivity can be explained by the mechanism presented in Scheme 20. In the case of a soft alcohol, such as phenol, the authors assume that the intermediate **87** forms, where the leaving group is still bonded to the carbohydrate, and an intermolecular (or outer sphere) attack of phenol occurs to provide the α glycal **85**. In the case of hard aliphatic alcohols in the presence of NEt_3 as a base, the authors suggest the formation of intermediate **88**. Here, the picoloyl group leaves and the OR unit is coordinated to the palladium center, giving rise to an intramolecular (or inner-sphere) delivery of the alcohol acceptor from the top face to afford the β glycans (**86**).

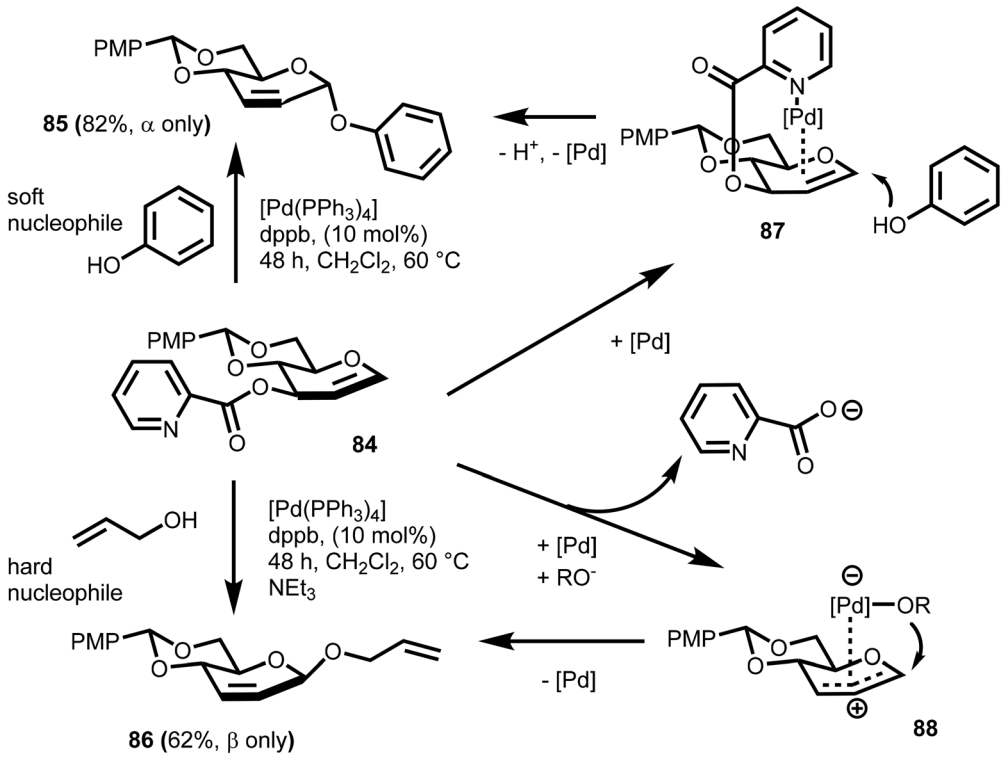
This glycosylation reaction demonstrates the power of transition-metal catalyzed glycosylation reactions. The unique properties of transition-metal based catalysts can lead to high chemo- and stereoselectivities, and consequently, the application of these systems in glycosylation reactions is increasing.

6. Lewis acids *vs.* transition metal catalysis and outlook

The examples presented above not only clearly demonstrate the power of catalyzed glycosylation reactions, but also outline similarities and differences in processes where the transition metal plays the role of a Lewis acid or has a somewhat more sophisticated task in the whole process.

When looking at the data, it is clear that the leaving group still plays a major role in the glycosylation reactions. The better the leaving group character, the milder would be the reaction conditions. Also, protecting groups are generally required. However, there are also notable differences.

In general, it appears that transition metal, non-Lewis acid catalyzed processes require lower catalyst loads. As shown in Tables 1 and 2, Lewis acid catalysts need to be used at catalyst loads as high as 30%. For transition-metal catalyzed reactions, a catalyst load of 5 to 10 mol% is typically sufficient, and it can be as low as 2.5 mol% (Scheme 18). This is still higher than



Scheme 20 Palladium-catalyzed *O*-glycosylation through an inner-sphere or outer-sphere.

those for many other transition-metal catalyzed organic reactions, and may be due to the multifunctionality of carbohydrates. Still, transition metals can exhibit high selectivity towards special functional groups compared to others present in the molecule. Also, it appears that the reaction temperatures tend to be higher in the cases where the transition metal acts as a Lewis acid.

In many glycosylation reactions, CH_2Cl_2 is employed as the solvent. However, many metal salts, such as $FeCl_3$, are not very well soluble in CH_2Cl_2. Often, researchers report that their glycosylation reaction mixture is an emulsion,[52,53] and under these conditions, the actual catalysis may proceed heterogeneously. From a catalysis point of view, this may not necessarily be problematic, as there are many heterogeneous catalytic systems. However, in the present context, the heterogeneous conditions may not be on purpose, and heterogeneous catalytic processes are much more complex and much less understood compared to homogeneous processes. Some of the low yields and stereoselectivities reported in the literature may be due to the fact that catalysis takes place, in fact, heterogeneously in some cases.

If catalysis still takes place under homogeneous conditions in emulsions (which is a possibility), then the poor solubility of the catalyst greatly reduces the amount of catalytically active species in solution. As such, the search for highly Lewis-acidic, yet well soluble catalysts may be intensified. For example, the Lewis acid $[Ni(4\text{-F-PhCN})_4]OTf_2$ employed by Nguyen (Table 2, entry 5) appears to be soluble in CH_2Cl_2, presumably due to the nitrile ligand on nickel.[60] As mentioned above, many transition metal catalysts bear ligands, which can increase the solubility in moderately polar solvents. Dong demonstrated that $FeCl_3$ can be modified with acetylacetonate or related ligands to serve as a regioselective benzoylation,[97a] sulfonylation or acylation catalyst.[97b] As such, ligands can improve solubilities and selectivities. Research activities in this area should be intensified.

As mentioned earlier, it appears that catalytic systems, where the catalyst does not just play the role of a Lewis acid, are obviously not as well investigated compared to Lewis acid catalysts. There are a number of transition metal catalysts known that catalyze acetal formation.[98] These existing examples may be worthwhile to be investigated in glycosylation reactions, which is, overall, an acetal forming reaction.

7. Conclusions

The recent years have seen a growing number of transition metal catalyzed glycosylation reactions. The systems that appear in the literature show increasing yields and stereoselectivities. The advantages of catalyzed glycosylation reactions are obvious; catalysis saves time, energy, and resources and potentially increases stereoselectivities. However, there is still room for improvement. Many systems require high catalyst loadings or high temperatures. In many cases, the reactions are substrate-controlled – a "universal" catalytic system has not been identified (it may be possible or not). As such, this review article aimed at bringing the catalysis and carbohydrate com-

munities together to intensify their efforts in finding more catalytic systems with improved efficiency and selectivity.

Conflicts of interest

There are no conflicts to declare.

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