Site-switchable mono-O-allylation of polyols

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Site-selective modification of complex molecules allows for rapid accesses to their analogues and derivatives, and, therefore, offers highly valuable opportunities to probe their functions. However, to selectively manipulate one out of many repeatedly occurring functional groups within a substrate represents a grand challenge in chemistry. Yet more demanding is to develop methods in which alterations to the reaction conditions lead to switching of the specific site of reaction. We report herein the development of a Pd/Lewis acid co-catalytic system that achieves not only site-selective, but site-switchable mono-O-allylation of polyols with readily available reagents and catalysts. Through exchanging the Lewis acid additives that recognize specific hydroxyls in a polyol substrate, our system managed to install a versatile allyl group to the target in a site-switchable manner. Our design demonstrates remarkable scope, and is amenable to the direct derivatization of various complex, bioactive natural products.
Molecules containing multiple copies of the same functional group are ubiquitous in Nature and in drug candidates. Site-selective transformations—reactions that can manipulate one of these repeating functional groups while keeping others unaffected—provide efficient access to analogues and derivatives of these compounds, thereby facilitating the interrogation and exploitation of their properties. The same kind of functional groups tend to undergo similar transformations, however, and differentiation typically only occurs due to subtle steric and electronic environments. Accordingly, to achieve high site-selectivity following a generalizable strategy remains a significant task in chemistry. Even more demanding is the development of methods in which alterations to the reaction conditions result in switching of the specific site of reaction, since it necessitates the selective modification at positions that are inherently less reactive.

Polyhydroxylated natural products, carbohydrates in particular, play critical roles in virtually all biological processes and they are essential components of many pharmaceuticals. Rapid access to the derivatives of these compounds holds tremendous promise and potential for the direct, site-selective modification of complex polyols. In this realm, various methods have been established to selectively modify the intrinsically most reactive hydroxyl groups within a substrate (substrate control). Recently, systems that can override the intrinsic reactivity preferences and accomplish catalyst-controlled, site-switchable modification of complex polyols have emerged. As eminent examples, in a series of landmark studies, the Miller group has identified several oligopeptide-based catalysts that enable site-switchable modification of complex antibiotics, such as vancomycin, teicoplanin, and erythromycin. In these studies, the oligopeptide catalysts were designed as mimetics of the catalytic domains of enzymes. Kawabata et al. devised chiral pyridine derivatives that were used in the site-selective modification of C4-OH of glucopyranosides as well as natural products such as lanatoside C and avermectin B2a. The Tan group invented a pair of pseudoenantiomeric imidazole-based catalysts that allow site-divergent modification of polyols containing cis-1,2-diol moieties, including anticancer agent digitoxin. Nargony and coworkers employed chiral phosphonic acid catalysts to accomplish site-switchable glycosylation of 6-deoxy erythronolide. Our group reported the site-divergent O-propargylation of various monosaccharides as well as digitoxin employing a pair of chiral Cu-catalysts. These achievements notwithstanding, to develop general systems that can achieve catalyst-controlled, switchable site-selectivity still represents a challenge. In particular, methods capable of introducing a metabolically stable ether bond remain rather limited.

**Fig. 1 Site-switchable modification of molecules containing multiple identical functional groups.** a Reagent/catalyst-controlled, site-selective modification of complex molecules: a challenge in synthetic chemistry. b Some representative, naturally occurring polyols. c Pd/Lewis acid co-catalyzed, site-switchable modification of polyols (this work).
Here we report a strategy that enables site-switchable mono-O-allylation of polyols by Pd/Lewis acid co-catalysis. As a distinct feature of our system, the task of activating electrophiles but changing the identity of the Lewis acid additive, we accomplish highly selective allylation of various polyols (Fig. 1c). Interestingly, such a strategy is akin to the switchable screwdrivers we use in our daily lives. The potential of this principle, however, has not been systematically exploited and exploited in chemistry to develop site-selective methodologies. The derivatization of cardiac glycoside ouabain provides an excellent example to illustrate our strategy. As will be discussed in more detail below, using the same Pd-catalyst and the Lewis acid additive. Resembling the role of a Lewis acid additive, we accomplish highly selective allylation of various polyols (Fig. 1c). Interestingly, such a strategy is akin to the switchable screwdrivers we use in our daily lives. The potential of this principle, however, has not been systematically exploited and exploited in chemistry to develop site-selective methodologies. The derivatization of cardiac glycoside ouabain provides an excellent example to illustrate our strategy. As will be discussed in more detail below, using the same Pd-catalyst and the Lewis acid additive. Resembling the role of a Lewis acid additive, we accomplish highly selective allylation of various polyols (Fig. 1c).

**Results**

**Reaction design.** We were interested in the selective O-allylation of polyols because the allyl group is among the smallest, yet most versatile, units in chemistry. Among all of the allylic alkylation methods established to date, a well-studied and often utilized one is the Pd-catalyzed Tsuji–Trost reaction. Intriguingly, the allylation of aliphatic alcohols by the Tsuji–Trost reaction is often a slow process, but it can be accelerated by using Lewis acid additives (Fig. 2a, orange arrow), but it can be accelerated by using Lewis acid additives (Fig. 2a, orange arrow), but it can be accelerated by using Lewis acid additives (Fig. 2a, orange arrow), but it can be accelerated by using Lewis acid additives (Fig. 2a, orange arrow). Our initial supposition was that the unique reactivity of aliphatic alcohols in the Tsuji–Trost reaction could be leveraged to achieve reagent-controlled site-selectivity during the modification of polyols. Specifically, we reasoned that if a Lewis acid additive (e.g., the allylation of aliphatic alcohols by the Tsuji–Trost reaction is often a slow process).
Fig. 3 Site-switchable mono-O-allylation of monosaccharides. Product ratios were determined by $^1$H NMR analysis of crude reaction mixtures. Reported yields are isolated yields of products that are underlined. * A small amount of diallylated product was formed. See Supplementary Information for experimental details. L ligand.
The validity of our design was first established in the site-divergent mono-O-allylation of glucopyranoside 9 (Fig. 2c). Compound 9 contains two vicinal, equatorial hydroxyl groups that are similarly reactive toward an electrophilic π-allylpalladium intermediate. Under the standard Pd-catalyzed O-allylation conditions and in the absence of any additives, the C2-OH modified product 9a and the C3-OH modified 9b were formed in almost equal amounts (entry 1, Fig. 2c). We then attempted adding each of the Lewis acid complexes listed in Fig. 2c individually to the reaction mixture so as to explore their effects on the site-selectivity profile of this transformation (entry 2–7). We found that the use of Ph2BOH as an additive resulted in the predominant formation of 9b in an efficient fashion (entry 6). Notably, the O’Doherty group40,41 reported the use of Ph2BOH to achieve Pd-catalyzed site-selective glycosylation. More intriguingly, the use of MgBu2 as an additive led to the preferential formation of the other isomer 9a, albeit with moderate selectivity (entry 7). Further optimization of reaction conditions revealed that simultaneous addition of MgBu2 with BINOL afforded 9a in dramatically improved site-selectivity and efficiency (entry 8). Thus, we identified two sets of conditions that install an allyl group onto the two different hydroxyl groups in 9 (see below for a mechanistic rationalization). These conditions employ an identical transition metal complex [i.e., Pd0-(PPh3)2] and differ only in the oxophilic additives utilized [Mg(II) vs. B(III)]. Collectively, these results validated the proof of principle of a strategically distinct approach to achieve reagent-controlled, site-switchable modification of polyols.

**Reaction scope.** Following the above protocol, we proceeded to explore the generality of our strategy. We first examined this method in the site-selective modification of various...
Fig. 5 Site-switchable mono-O-allylation of polyhydroxylated natural products. Product ratios were determined by $^1$H NMR analysis of crude reaction mixtures. Reported yields are isolated yields of products that are underlined. A small amount of diallylated product was also formed. Small amounts of C3-OH and C4-OH modified products were also formed. DMA, $N,N$-dimethyl acetamide. See Supplementary Information for experimental details.
monosaccharides (Fig. 3), including those derived from glucose (10), galactose (11–12), and fucose (13). All of these monosaccharides contain three contiguous secondary hydroxyls. In these cases, the alkylation occurs at the C3-OH of the pyranose ring if an organoboron compound was used as additive (green arrows), but at the C2-OH when ZnEt2-prophenol complex was employed (orange arrows). To rationalize the switchable site-selectivity observed in these cases (10–13, Fig. 3) and in the case of 9 (Fig. 2c), we propose that the C3-OH is the most nucleophilic hydroxyl in each of these substrates, and it therefore most readily complexes with the organoboron compound (cf. structure A). The C2-OH, on the other hand, is most readily deprotonated by a base since it is closest to the electron-withdrawing anumeric center (cf. structure B).

Each of the three hydroxyls in mannopyranoside 14 could be selectively alkylated in a controllable manner. As can be explained by the structures A and B shown above, the use of LiHMDS (orange arrow) and quinolin-8-ylboronic acid (green arrow) furnished the C2-OH alkylated product 14a and the C3-OH alkylated product 14b, respectively. The C4-OH alkylated product 14c could be obtained by using 4-dimethylaminophenylboronic acid, which, through formation of a stable boronic ester (cf. structure C), deactivates the C2-OH and C3-OH and simultaneously enhances the reactivity of the C4-OH position.

We then showed this strategy could be adopted toward the site-switchable alkylation of structurally more complex disaccharides (Fig. 4). For example, the lactose derivative 15 contains five free hydroxyl groups. The use of ZnEt2-prophenol complex directed the allyl group to the C2-OH of 15 with high selectivity (orange arrow). Switching the additive to phenylboronic acid altered the preferential reaction site to the C3-OH (green arrow). Moving to maltoside 16, we found the use of Taylor’s catalyst (10H-dibenzo[b,e][1,4]oxaborinin-10-ol) guided the installation of the allyl group to the C3-OH, while employment of Cu(OAc)2 steered the allyl group to the C2-OH instead. It is worth noting that synthetically versatile but chelating thioether groups present in 15 and 16 were well tolerated by our conditions. We further applied this method to the site-divergent modification of fructose 17, which contains a pyranoside ring linked to a furanoside ring. We precisely delivered the allyl group to the C3-OH of the pyranoside ring using Taylor’s catalyst as an additive, or to the C3’-OH of the furanoside ring if applying Cu(OAc)2, instead. Here, we rationalize that Taylor’s catalyst complexes with the C3-OH of the pyranose ring (see structure E), but Cu(OAc)2 chelates with the C2-OH and the C3’-OH of 17 and activates the C3’-OH (cf. structure D). It is worth highlighting that, in this case, the selectivity switches between two hydroxyls that are six atoms apart. Therefore, it would be challenging to achieve a selectivity switch between these two hydroxyls through designing Pd-ligand complexes.

Modification of natural products. We continued to apply our strategy to the site-switchable modification of polyhydroxylated natural products (Fig. 5). 20-Hydroxyecdysone (18) is an ecystero-steroid hormone that controls the metamorphosis and ecdysis of arthropods. This compound contains six free hydroxyls, three of which are secondary. Site-divergent modification of 18 could be achieved. If Taylor’s catalyst was employed as additive, the alkylation occurred preferentially at the C2-OH (green arrow), whereas if Zn(II)-Prophenol complex was used, the alkylation occurred at the C3-OH (orange arrow). Geniposide (19) is an iridoid glycoside that exhibits diverse biological activities. In addition to five free hydroxyls, this compound also contains a sensitive enol ether moiety and an enoate ester group. Employing our strategy, we could selectively install an allyl group to the C6-OH of the glucose

Fig. 6 Product derivatization. a Derivatization of 20b. b Derivatization of 21c. Product ratios were determined by 1H NMR analysis of crude reaction mixtures. See Supplementary Information for experimental details. L’ = (R,R)-(−)-N,N’-Bis(3,5-di-tert-butylsalicylidene)-1,2-cyclohexanediamine. ox oxoate.
Using Taylor’s catalyst, or to the C1'-OH with phenylboronic acid as an additive. Here, the site of reaction switches cleanly between two primary hydroxyls.

Following the above principle, we were able to selectively modify up to three different hydroxyl groups within some complex polyols. For example, salicin (19) is a natural product that acts as an anti-inflammatory agent in the human body. The C2-OH of the glucopyranoside ring in 19 is intrinsically the most reactive hydroxyl and gets allylated preferentially in the absence of any additives (blue arrow). Intriguingly, applying Taylor’s catalyst as an additive in the standard reaction conditions delivered the allyl group to the C6-OH of 19 (green arrow), presumably via the intermediacy of the ate complex F. If the bulky, monovalent BPh3 was employed instead (orange arrow), the allylation occurs at the benzylidene hydroxyl (C1'-OH) with high site-selectivity (cf. G). Thus, three individual hydroxyls within salicin could be selectively modified in a controllable fashion.

Ouabain (21) exhibits potent antiproliferative activities against several cancer cell lines at nanomolar concentrations. This molecule contains eight free hydroxyls, including one primary, five secondary, and two tertiary ones. When no Lewis acid additive is used, the Pd-catalyzed allylation occurs at the secondary C1'-OH to afford 21a with decent selectivity and efficiency (orange arrow). When we used methylboronic acid as an additive, the primary C19-OH was selectively modified to give product 21b in high yield (blue arrow). We hypothesize that methylboronic acid simultaneously complexed with the C1-OH, C5-OH and C19-OH of 21 (see structure H), and activated the least hindered primary hydroxyl in the Pd-catalyzed allylation reactions. If the oxaborole derivative 22 was employed instead, the site-selectivity changed again. This time the C3'-OH of the sugar ring was modified with high efficiency (green arrow). We assume that the bulky oxaborole 22 will preferentially form an ate complex with the vicinal diol moiety in the sugar ring (see structure I), which renders the equatorial C3'-OH most reactive. Lastly, the group that can be transferred by our method is not restricted to the parent allyl unit. For instance, cinnamyl groups bearing various substituents could be installed onto ouabain with good site-selectivities as well, if the corresponding electrophiles are employed (see Supplementary Fig. 3).

### Product derivatization.

To further demonstrate the utility of this method as a tool for the late stage functionalization of naturally occurring polyols, we have performed the reactions shown in Fig. 6. We show that the alkene group installed on salicin could be conveniently converted to a variety of other functional groups in one step (Fig. 6a). For instance, we showed that a cobalt-catalyzed hydroarylation reaction smoothly incorporated an azide group onto 20b. The resulting product 22a is thus primed for the vernalize azide alkyne coupling reactions that are extensively utilized in the fields of chemical biology and material science. By using similar hydrofunctionalization reactions of alkynes, we also successfully attached a nitrile group (22b), a fluoro atom (22c), or a pyridine ring (22d) onto the target molecule. Furthermore, a cross-metathesis reaction readily converted 20b to a dimeric structure 22e. Lastly, we prepared a conjugate of ouabain and glucose (24) from 21c and 23, taking advantage of the potent thiol–ene click reaction. Therefore, when coupled with the synthetic versatility of alkynes, our site-switchable O-allylation reaction provides rapid and efficient access to derivatives and analogues of complex polyols.

### Discussion

This study showcased the power of a dual catalytic strategy for site-switchable modification of target molecules, a key challenge in chemistry. This design allocates the task of activating electrophiles and that of controlling site-selectivity to, respectively, the Pd-catalyst and the Lewis acid additive. Thus, switch of reaction site was achieved simply through changing the identity of Lewis acid additives, a tactic that has not been systematically explored before. The allyl unit installed by this method could serve as an entry point to various other functional groups. We anticipate that the generality, immediate utility, and the operational ease of this method will inspire further exploration that ultimately leads to precise control of site-selectivity during modification of complex compounds.

### Methods

**Synthesis of 9a.** In a N2-filled glovebox, nBu4Mg (1 M in heptane, Energy Chemicals, Lot DL140184, 45 mL, 0.045 mmol, 0.3 equiv), (-)-BINOL (8.6 mg, Energy Chemicals Lot DI241032, 0.03 mmol, 0.2 equiv) and THF (200 μL) were weighed into a screw capped vial (labeled as Vial A) containing a stir bar. The mixture was stirred for 5 min, at which time compound 9 (42.6 mg, 0.15 mmol, 1.0 equiv) was added. The resulting solution was stirred for an additional 30 min.

To another vial, compound 2 (36.4 mg, 0.23 mmol, 1.5 equiv), Pd(dba)2·CHCl3 (7.8 mg, 7.5 mg, 0.05 equiv), PPh3 (7.8 mg, 0.03 mmol, 0.2 equiv), and THF (200 μL) were added in sequence. The mixture was stirred for 10 min, and then transferred to Vial A. An additional portion of THF (2.6 mL) was added to Vial A so that [9] was adjusted to 0.05 M. Vial A was tightly capped, taken out of the glovebox, and stirred at −10 ºC for 12 h (400 rpm). The reaction mixture was then concentrated in vacuo. An aliquot of the residue was taken for 1H NMR analysis, which indicated that products 9a and 9b were formed in a ratio of ca. 101:11. Flash chromatography (SiO2) using petroleum ether/EtOAc (6:1–3:1) as eluent afforded 9a as a yellow solid (41 mg, 0.127 mmol, 83%).

**Synthesis of 9b.** In a N2-filled glovebox, compound 9 (56.5 mg, 0.20 mmol, 1.0 equiv) and 2-(diphenylboroxyl)-ethanamine (2.4 mg, Aladdin Lot J1824016, 0.01 mmol, 0.05 mol%), and THF (500 μL) were weighed into a screw capped vial (labeled as Vial A) containing a stir bar. The resulting solution was stirred for an additional 30 min.

To another vial, compound 2 (38.0 mg, 0.24 mmol, 1.2 equiv), Pd(dba)2·CHCl3 (5.2 mg, 5.5 mg, 0.025 equiv), PPh3 (5.2 mg, 0.02 mmol, 0.1 equiv), and THF (200 μL) were added in sequence. The mixture was stirred for 10 min, and then transferred to Vial A. An additional portion of THF (0.3 mL) was added to Vial A so that [9] was adjusted to 0.2 M. Vial A was tightly capped, taken out of the glovebox, and stirred at 25 ºC (outside temperature) for 12 h (400 rpm). The reaction mixture was then concentrated in vacuo. An aliquot of the residue was taken for 1H NMR analysis, which indicated that products 9a and 9b were formed in a ratio of 1:13. Flash chromatography (SiO2) using petroleum ether/EtOAc (3:1–1:1) as eluent afforded 9b as a pale yellow oil (55.4 mg, 0.172 mmol, 86%).

### Data availability

Additional data supporting the findings described in this paper are available in the Supplementary Information, and also are available from the corresponding author upon reasonable request.

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