Site-Selective Molecular Transformation: Acylation of Hydroxy Groups and C–H Amination

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Control of site selectivity is an exciting direction for synthetic organic chemistry owing to the possibility of selective modification of multifunctionalized molecules, ultimately including biomacromolecules. In this review, our recent research related to site selectivity in two types of transformation, namely, the acylation of hydroxy groups and C–H amination, is summarized. Regarding the acylation of hydroxy groups, catalyst-controlled site selectivity enables unconventional retrosynthetic analysis, leading to efficient syntheses of sugar-related natural and unnatural products. Regarding C–H amination, the discovery of unprecedented reaction sites in intermolecular amination mediated by dirhodium nitrenes is described. The findings of this research demonstrate the power of site-selective transformation in the synthesis of a particular class of compounds.

Key words site selectivity; catalyst; acylation; C–H amination; glucose; total synthesis

1. Introduction

Site-selective transformation,1–5) involving the development of methods for selective modification of one among several identical functional groups, remains a major challenge in modern synthetic organic chemistry. However, the development of site-selective transformation can reap enormous rewards. The selective modification of biologically active multifunctional molecules can be a powerful tool for drug candidate discovery.6–8) Chemo- and site-selective functional group interconversion can eliminate multistep protection/deprotection procedures, which are frequently required in the synthesis of complex natural products and fine chemicals.9–12) In this review, our investigations into the development of site-selective molecular transformations are described (Fig. 1).

The first topic is the site-selective acylation of sugar derivatives, which are representative polyol compounds13) (Fig. 1a). Sugars, along with amino acids, are major components of biomacromolecules and are involved in a wide range of reactions in biological systems, including infection, metastasis, differentiation, regulation of signaling, and so on.14) To clarify the mechanisms of these events and develop therapeutics, the chemical synthesis of sugar derivatives in a pure form is indispensable. Owing to their structural features, multistep protection/deprotection procedures have been required to discriminate multiple hydroxy groups.15,16) Therefore, the rational precursors to the target sugar derivatives are protected glycosyl donors (route A). In contrast, our synthetic strategy depends on site-selective transformations of unprotected sugar derivatives (route B). We have reported several examples of late-stage diversification of biologically active natural products and concise total syntheses of natural glycosides, demonstrating that site-selective transformations dramatically improve synthetic efficiency.

The second topic is site-selective C–H amination using dirhodium catalysts (Fig. 1b). In recent years, transition-metal-catalyzed C–H amination has provided straightforward access to diverse nitrogen-containing molecules.17–22) Although C–H bond cleavage is position-limited in intramolecular reactions,23) the control of site selectivity is an issue in intermolecular reactions.21,24–28) Dirhodium nitrenes have emerged as powerful intermediates for C(sp3)–H amination reactions.18,21,24–28) To date, electron-rich C(sp3)–H bonds, such as C(sp3)–H bonds in the α-position to C–C multiple bonds and oxygen atoms, and tertiary C(sp3)–H bonds, have been selectively converted to C–N bonds, even in intermolecular reactions.29,30) (Fig. 1b(i)). We recently discovered two unexplored reaction sites in dirhodium-catalyzed C–H amination reactions (Fig. 1b(ii)). Although our investigation of site-selective C–H functionalization reactions remains at a preliminary stage, these advances might lead to further selective transformations of multifunctionalized molecules.

2. Site-Selective Acylation of Glucose and Its Derivatives

2.1. Direct Derivatization of Natural Glycosides by Catalyst-Controlled Site-Selective Acylation

Enzymatic methods are powerful tools for introducing an acyl group selectively to one of multiple hydroxy groups in polyol compounds, including carbohydrates.31) Although selective introduction of an acyl group onto primary hydroxy groups in carbohydrates can be effectively achieved using enzymatic
protocols, selective introduction of an acyl group onto a secondary hydroxy group in the presence of intrinsically more reactive primary hydroxy groups remains a fundamental challenge in synthetic organic chemistry. Following some pioneering studies, in 2007, Kawabata et al. reported catalyst-controlled site-selective acylation of octyl-β-D-glucopyranoside (1) using organocatalyst C1, possessing a 4-pyrrolidinopyridine (PPY) moiety as the active catalytic site (Fig. 2). The prominent feature of this reaction is that the C2-symmetric catalyst enables selective acylation of intrinsically less reactive secondary C(4)–OH group in the glucopyranoside, even in the presence of the primary C(6)–OH group (Fig. 2a). A molecular recognition process via multiple H-bonding interactions between the substrate and catalytic intermediate was proposed to explain the catalyst-controlled selectivity (Fig. 2b). The site-selective acylation catalyzed by C1 also showed high functional groups tolerance, with various functionalized acid anhydrides and some disaccharides used. Based on this background, the application of this method to the late-stage diversification of biologically active natural glycosides was investigated.

Lanatoside C (3) is a clinically used cardiac glycoside com-

**Fig. 1. Contents of This Review of Site-Selective Transformation**

**Fig. 2. Catalyst-Controlled Site-Selective Acylation:** (a) C(4)–OH Selective Acylation of Glucopyranoside 1; (b) Proposed Molecular Assembly

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**Biography**

Yoshihiro Ueda was born in Aichi, Japan in 1984. He received his B.Sc. (2008), M.Sc. (2010), and Ph.D. (2013) from Kyoto University under the supervision of Professor Takeo Kawabata. During the period, he spent 3 months as a visiting student with Professor Alois Fürstner in Max-Planck-Institut für Kohlenforschung, Germany (2011). After receiving the Ph.D., he moved to the University of Tokyo as a postdoctoral researcher and studied supramolecular chemistry in the group of Professor Makoto Fujita. In 2014, he joined again Professor Kawabata’s group at Kyoto University as a Program-Specific Assistant Professor and became an Assistant Professor one year later. Dr. Ueda has received several awards, including the Pharmaceutical Society of Japan Kansai Branch Award for Young Scientists (2016), the Chemical Society of Japan Presentation Award [Academic] (2019), Poster Award for Excellence in the 47th Naito Conference (2019), and The Pharmaceutical Society of Japan Award for Young Scientists (2020). His research interests include synthetic organic chemistry and supramolecular chemistry, especially for site-selective catalysis and asymmetric catalysis.
posed of a tetrasaccharide and an aglycon named digoxigenin (Chart 1). As natural product 3 possesses a terminal glucopyranoside moiety, we envisaged that catalyst C1 would enable 4‴‴-OH selective acylation, even in the presence of a total of eight free hydroxy groups. Treatment of 3 with isobutyric anhydride in the presence of 10 mol% of 4-dimethylaminopyridine (DMAP) in CHCl₃/tetrahydrofuran (THF) (9:1, v/v) at −60°C gave 3‴‴-O-acylate 4 as a major product with 97% site selectivity in 85% yield. This result indicated that C(3‴‴)-OH had the highest intrinsic reactivity among the eight free hydroxy groups of 3 in CHCl₃/THF (9:1, v/v) solution. In contrast, site-selective acylation at C(4‴‴)-OH was achieved using catalyst C1, as expected. Improved selectivity was observed in the acylation using catalyst C2, giving 4‴‴-O-acylate 5 with 90% site selectivity in 87% yield for monoacylation. Acylation of 3 in dimethylformamide (DMF) occurred selectively at the primary hydroxy group, giving 6‴‴-O-acylate 6 as a major product independent from the nature of catalysts. Based on the solvent dependency of site selectivity and conformational analysis using molecular mechanics calculations, the intramolecular H-bonding interaction of 3 in CHCl₃/THF (9:1, v/v) solution was responsible for the high reactivity of C(3‴‴)-OH. Notably, catalysts C1 and C2 allowed catalyst-controlled site-selective acylation at C(4‴‴)-OH by overcoming the extraordinarily high intrinsic reactivity of C(3‴‴)-OH. Therefore, a method for three directional site-selective derivatizations of multifunctional natural glycoside 3 was developed. Catalyst C1 was also useful for the site-selective derivatization of non-
glycoside polyol natural products.\textsuperscript{43,44)\textsuperscript{1}}

Catalyst-controlled site-selective acylation is also a powerful tool for the total synthesis of natural glycosides.\textsuperscript{45)\textsuperscript{1}} Target natural glycoside, multifidoside B (7), was isolated in 2008 by Zhao and colleagues from whole plants of \textit{Pteris multifida}, which are used in traditional Chinese medicine.\textsuperscript{46)\textsuperscript{1}} Compound 7 has been reported to show significant cytotoxicity against HepG2 tumor cells. As this glycoside possesses a \textit{p}-coumaroyl group at C(4)–OH of the glucopyranoside moiety, the rational precursor to target compound 7, based on a conventional protection/deprotection strategy, should be appropriately protected precursor 8 containing a free C(4)–OH moiety (route B). In contrast, we expected catalyst C1 to enable direct introduction of a \textit{p}-coumaroyl group at the C(4)–OH moiety of unprotected precursor 9 at the final stage of the total synthesis (route A). In most cases, the unprotected precursor of an acylglycoside is also naturally occurring, making this synthetic route a direct conversion of one natural product into another.

Owing to its low availability, the precursor natural product, (2R,3S)-wallichoside (9),\textsuperscript{47,48)} was synthesized in 13 steps from commercially available tetrasubstituted benzene 10, including a novel intramolecular asymmetric aldol reaction of ketoaldehyde 11 using organocatalyst C3 and stereoselective glycosylation of the resulting alcohol 12 (Chart 3). In the final-stage site-selective acylation, adding small amounts of dimethylsulfoxide (DMSO) as cosolvent was key,\textsuperscript{49)\textsuperscript{1}} as substrate 9 was totally insoluble in less coordinating solvents, such as CHCl\textsubscript{3}, allowing effective molecular recognition via H-bonding interactions (Fig. 2b). Irrespective of the presence of the strongly H-bond-accepting nature of DMSO, catalyst C1 enabled introduction of the \textit{p}-coumaroyl group with the phenol protected by triethylsilyl (TES) group at the desired C(4)–OH position, giving multifidoside B (7) in 54% yield after one-pot deprotection of the TES group (91% site selectivity among monoacylates obtained in a combined yield of 59%). This strategy also had the advantage of avoiding the risk of undesired side reactions in the final deprotection steps of the total synthesis, which were also encountered in the synthesis of 7 using a partially protected precursor.

Two related natural products, multifidosides A (16) and C (17), were also successfully synthesized using the same strat-
egy (Chart 4). Precursor natural products (2S,3S)-wallichoside (18)\(^{47,48}\) and pteroside B (19)\(^{50}\) were readily prepared from intermediate 14 in three steps and intermediate 12 in five steps, respectively. Fortunately, the final-stage site-selective acylation occurred at the desired position. Therefore, the first total syntheses of multifidosides A–C were achieved. The synthetic utility of the present strategy was also demonstrated by Judeh’s total synthesis of phenylpropanoid glycosides calceolarioside A and syringalide B.\(^{51}\)

2.2. Total Synthesis of Ellagitannins Based on Sequential Site-Selective Functionalization of Glucose

Ellagitannins constitute a major class of hydrolysable tannins. More than 500 natural products in the ellagitannin family have been structurally characterized, exhibiting various biological activities, including antioxidative, anticancer, and antiviral activities.\(^{52–55}\) Their structures are basically composed of a central sugar core, typically D-glucose, esterified with gallic acid (3,4,5-trihydroxybenzoic acid) and hexahydroxydiphenic (HHDP) acid (Fig. 3). Owing to their structural features, differentiating particular hydroxy groups in D-glucose is required to synthesize ellagitannins. Reported total syntheses of ellagitannins strictinin (20)\(^{56,57}\), tellimagrandin II (21)\(^{58}\), and pterocarinin C (22)\(^{59}\) have been achieved using a protection/deprotection sequence (Fig. 3, route A). Based on this reliable protection/deprotection strategy, the authors focused on developing methods for the challenging introduction or construction of HHDP groups at suitable positions. We expected the direct site-selective introduction of sufficient galloyl groups onto hydroxy groups of D-glucose to allow the protection/de-protection steps to be eliminated and streamline the synthetic routes to ellagitannins (Fig. 3, route B). Compared with the previous total syntheses based on the protection/deprotection strategy, the number of steps from D-glucose was reduced by almost half in our synthesis based on a sequential site-selective strategy.\(^{60,61}\)

The retrosynthetic analysis of strictinin (20)\(^{62–64}\) is described in Chart 5. As 20 possesses a galloyl group on the C(1)–OH moiety and HHDP groups on the C(4)–OH and C(6)–OH moieties, the C(1)–OH, C(4,6)–OH, and C(2,3)–OH groups can inevitably be distinguished. As the first step, we planned to employ glycosylation of the gallic acid derivative with unprotected D-glucose to discriminate the hemiacetal hydroxy group, C(1)–OH. We then envisaged that catalyst-controlled C(4)–OH acylation of glucoside 23 and subsequent acylation of the inherently most reactive primary C(6)–OH in 1,4-digallate 24 would provide 1,4,6-trigallate 25, possessing...
all carbon atoms of 20, in just three steps from β-glucose. Oxidative phenol coupling between the 4-O-gallate and 6-O-gallate of 25 was expected to afford the HHDP moiety of 20 according to the established protocol.\(^{57,65}\)

In the first step, glycosylation methods using an acidic nucleophile and unprotected glucose were employed under Mitsunobu conditions.\(^{66}\) Although the substitution reaction occurs selectively at the anomeric carbon, the glycoside is afforded as a mixture of α- and β-anomers in the reported literature.\(^{67-71}\)

We investigated the highly stereoselective glycosylation of gallic acid derivative 26 with unprotected glucose (Table 1). Using polar solvent DMF, the glycoside was obtained as an anomeric mixture (entry 1, \(\alpha/\beta = 1 : 1\)), as previously reported. In contrast, in less polar solvents, such as THF and dioxane, the reaction gave desired β-glycoside 23 with high stereoselectivity (entries 2 and 3, \(\alpha/\beta = 1 : 99\)). Finally, using an excess amount of glucose (3.0 equivalent (equiv.)) improved the yield of glycoside 23 to 78% (entry 5). Mechanistic analysis of the reaction showed that commercially available D-glucose was almost pure α-form, and that SN2 displacement at the anomeric carbon without anomerization in less-polar solvent was responsible for the high β-selectivity.\(^{72}\)

With β-glycoside 23 in hand, the introduction of sufficient galloyl groups to C(4)–OH and C(6)–OH groups for construction of an HHDP group was investigated (second and third steps). After thorough screening of conditions, the second and third steps were conducted in a one-pot procedure (Chart 6).

The catalyst-controlled C(4)–OH selective galloylation of glycoside 23 using catalyst C1 and acid anhydride 27 occurred as expected under modified conditions. The subsequent addition of 2-chloro-1,3-dimethylimidazolium chloride (DMC) as a condensation agent activated carboxylic acid 28, generated in situ from acid anhydride 27, and generated 1,4-digallate 24 underwent primary C(6)–OH selective galloylation in the presence of a stoichiometric amount of DMAP and excess pyridine as cosolvent, affording 1,4,6-trigallate 25 in 51% yield. Finally, three steps, including benzyl group deprotections, an oxidative phenol coupling reaction according to the procedure of Yamada,\(^{57,65}\) and MOM group deprotections completed the total synthesis of strictinin (20) in five steps from naturally abundant glucose.

This sequential site-selective functionalization strategy was applied to step-economic total syntheses of tellimagrandin II (21)\(^{73,74}\) and pterocarinin C (22)\(^{75,76}\) (Chart 7). Compounds 21 and 22 have the same molecular formula, but differ in the position of the HHDP group, with 21 a 4,6-HHDP-type ellagitannin and 22 a 2,3-HHDP-type ellagitannin. Total syntheses of these regiosomeric natural products were achieved via the same synthetic route, but with the order of galloyl group introductions changed (G1 and G2).\(^{61}\) According to the protocol established in the synthesis of 20, the introduction of G2 on C(4)–OH and C(6)–OH groups, and G1 on the remaining C(2)–OH and C(3)–OH groups, under condensation conditions, followed by benzyl group deprotections afforded

Table 1. Representative Optimization Studies for Stereoselective Mitsunobu Glycosylation Using Glucose

| Entry | Solvent     | Time (min) | Yield (%) | \(\alpha/\beta\) |
|-------|-------------|------------|-----------|----------------|
| 1     | DMF         | 45         | 60        | 50/50          |
| 2     | THF         | 45         | 17        | 1/99           |
| 3     | 1,4-Dioxane | 45         | 64        | 1/99           |
| 4     | 1,4-Dioxane | 30         | 66        | 1/99           |
| 5\(^a\) | 1,4-Dioxane | 30         | 78        | 1/99           |

\(^a\) Glucose (3.0 equiv.), DIAD (2.0 equiv.), and PPh\(_3\) (2.0 equiv.) were employed. MOM = methoxymethyl, DIAD = diisopropyl azodicarboxylate.
phenol 30, the precursor to 21. The same procedure, but with the order of $G_1$ and $G_2$ introduction steps changed, afforded phenol 31, the precursor to 22, in a similar yield. The intramolecular oxidative coupling reaction of 30 and 31, and MOM group deprotection, successfully provided natural products 21 and 22, respectively. Therefore, total syntheses of three ellagitannins were accomplished without protecting groups for glucose OH groups. Recently, total syntheses of other regiosomeric ellagitannins have been achieved with further site-selective acylation reactions.\(^{77,78}\) These examples show that this strategy can be applied to streamlined and unified total syntheses of ellagitannin family compounds.

2.3. Improvement of Catalytic Performance and Application to Rapid Synthesis of 4-Deoxy Sugars

As described above, we achieved several efficient total syntheses of natural glycosides based on catalyst-controlled site-selective acylation.\(^{45,60,61}\) However, the relatively high catalyst loading (10–20 mol%) required was a fundamental problem. In particular, introducing a less electrophilic acyl group, such as a benzoyl group, required a longer reaction time (Charts 3, 4, and 6). As many natural glycosides contain substituted benzoyl groups and cinnamoyl groups,\(^{52,79}\) improving the catalytic performance (such as shorter reaction-time, lower catalyst loading) in site-selective acylation would contribute to the further efficient total synthesis and late-stage derivatization of natural glycosides. Therefore, we investigated improving the catalytic performance in site-selective acylation.\(^{80}\)

The use of a highly reactive acyl donor (acyl chloride) instead of an acid anhydride might solve the problem of relatively low efficiency in the catalytic system. However, using isobutyryl chloride in the acylation reaction of 2 gave the 6-O-acylate as a major product in low yield\(^{39,40}\) (Chart 8). The dependency of site selectivity on the acyl donor prompted us to reconsider the catalytic cycle of the DMAP-mediated acylation of alcohols.

The currently accepted catalytic cycle for DMAP-catalyzed acylation of alcohols using acid anhydride and acyl chloride as acyl donors is described in Charts 9a and 9b, respectively.\(^{81}\) In each case, the first step is an equilibrium process in which the active intermediate, acylpyridinium salt A or B, is formed from DMAP and the acyl donor. The second step is the nu-
cleophilic addition of alcohol to the acylpyridinium salt, which is considered to be the rate-determining step.

The equilibrium process (first step) has been well studied, with the acylpyridinium chloride already known to produce quantitatively, while the acylpyridinium carboxylate is produced in small amounts (Chart 10a). We determined the thermodynamic parameters of the equilibrium process in formation of the acylpyridinium carboxylate from PPY and acetic anhydride or benzoic anhydride using variable-temperature NMR experiments (Chart 10b). Based on these parameters, the salts had estimated yields of 0.12% (acetate) and 3.6 × 10⁻³% (benzoate) in a solution comprising a 1 : 1 mixture of PPY and the corresponding anhydride in CDCl₃ (0.07 M) at 20 °C (Chart 10a). Only a small amount of acylpyridinium salt was found to be formed when acid anhydrides were used, while the salts were quantitatively formed from PPY and acyl chlorides. However, the acetylation of alcohols catalyzed by PPY or DMAP is known to proceed faster using acetic anhydride compared with acetyl chloride (Chart 8). In contrast, when isobutyryl chloride was employed, the acylation catalyzed by C1 proceeds exclusively at C(4)–OH, even in the presence of a small amount of the active intermediate (Fig. 2). Therefore, we hypothesized that high catalytic performance would be achieved if acylpyridinium chloride could be generated in high concentration using an acyl chloride and converted into highly reactive acylpyridinium salt A by in situ counteranion exchange (Chart 11a). The expected reaction was complete within 5 min in the presence of 0.1 mol% of catalyst, by treating of 1 with isobutyryl chloride as the acyl donor, along with pivalic acid and tertiary amine as the carboxylate source, affording 4-O-acylate 2 in almost quantitatively, while the corresponding reaction using the acid anhydride method afforded 2 in only a trace amount (Chart 11b). Even when the catalyst loading was reduced to 0.02 mol%, the reaction was complete in 25 min, giving product 2 in 93% yield (turnover number (TON) = 4,600).

Inspired by pioneering examples of site-selective deoxygenation of sugar derivatives, the improved method was effectively applied to the rapid synthesis of 4-deoxy sugars. Using the acid anhydride method, introducing a p-toluoyl group onto the C(4)–OH of a glucose using base (collidine) as cosolvent took 48 h (Fig. 4a, method I). In contrast, using the counteranion-exchange method, the reaction was complete within 15 min, giving 4-O-acylate 33 with both yield and site selectivity slightly reduced (Fig. 4a, method II). Product 33 then underwent reductive deacetylation by treatment with SmI₂-hexamethylphosphoramide (HMPA) complex, according to the protocol of Marko, affording 4-deoxyglucosamine 34a in just two steps from 1. This two-step deoxygenation method could be applied to various types of pyranoside (Fig. 4b). 4-Deoxysugars are expected to exhibit various biological activities owing to their ability to act as chain terminators for the biosynthesis of oligosaccharides with 1,4-glycoside linkages. Compound 34d can be considered a precursor to 4-deoxy-N-acetylglucosamine, which shows significant angiogenesis inhibitory activity.
3. Dirhodium-Catalyzed Intermolecular Site-Selective C–H Amination

Arylamine motifs are privileged structural units for the development of functional materials and bioactive molecules.\(^\text{97,98}\) Tremendous effort has been devoted to the development of synthetic methods for arylamines.\(^\text{99,100}\) Recently, the C(sp\(^2\))–H amination of parent aromatics has become a candidate for the most straightforward method for arylamine synthesis.\(^\text{101–108}\)

Since the first example of an intramolecular C(sp\(^2\))–H amination reaction mediated by dirhodium nitrene complexes was reported by Breslow in 1983,\(^\text{109}\) dirhodium-catalyzed C(sp\(^2\))–H amination has been extensively developed and efficiently utilized in the total synthesis of complex natural products.\(^\text{110–113}\)

In contrast, before our investigation, dirhodium-catalyzed C(sp\(^2\))–H amination had been limited to a few reports concerning intramolecular reaction.\(^\text{114–116}\) This was probably due to competitive C(sp\(^2\))–H amination occurring preferentially over C(sp\(^2\))–H amination in intermolecular reactions.

A rare example of intermolecular C(sp\(^2\))–H amination mediated by dirhodium nitrene complexes was reported as a side reaction of the amination of ketene silyl acetals by the Hashimoto group in 2007\(^\text{117}\) (Chart 12a). The treatment of ketene silyl acetals with highly reactive diphenylmethanide resulted in negligible C(sp\(^2\))–H amination (Fig. 4).

A working hypothesis for selective C(sp\(^2\))–H amination using dirhodium carboxylate was critical for aromatic C(sp\(^2\))–H amination in intermolecular reactions. In 2016, Falck and colleagues reported a general method for dirhodium-catalyzed intermolecular C(sp\(^2\))–H amination, claiming that the generation of protonated dirhodium nitrenes, nitrenium ion species, in the acidic medium was key to the electrophilic aromatic amination\(^\text{118}\) (Chart 12b). In contrast, we expected substrates with electron-rich aromatic rings to undergo chemoselective C(sp\(^2\))–H amination using neutral dirhodium nitrene complexes, even in the presence of C(sp\(^2\))–H bonds (Fig. 5).

By screening various combinations of substrates, aminating reagents, and dirhodium catalysts, the aromatic C(sp\(^2\))–H amination of anisole (40) was found to occur para to the methoxy group when treated with a catalytic amount of Rh\(_2\)(tpa)\(_4\), O-tosyl-N-trichloroethoxy carbonylhydroxylamine (TrocNHOTs),\(^\text{120,121}\) and K\(_2\)CO\(_3\) in chlorobenzene (Table 2). The choice of dirhodium carboxylate was critical for aromatic C(sp\(^2\))–H amination (entries 1–5). Using Rh\(_2\)(ocic)\(_4\), Rh\(_2\)(piv)\(_4\), or Rh\(_2\)(n-C\(_3\)F\(_2\)CO\(_3\))\(_4\) resulted in negligible C(sp\(^2\))–H amination, while Rh\(_2\)(esp)\(_4\) gave the C(sp\(^2\))–H aminated product in low yield. Rh\(_2\)(tpa) promoted aromatic C(sp\(^2\))–H amination most effectively, giving para-aminated product 41a selectively at 0°C (entry 6, 60% yield, 41a/41b = 1:11). Furthermore, a significant solvent effect was observed (entries 6–12). Although reactions in benzene-derived solvents gave the products in moderate yields, the yields dramatically decreased in other solvents frequently used for C–H amination, such as dichloromethane and ethyl acetate.

The important feature of the present reaction is chemoselectivity that favors aromatic C(sp\(^2\))–H amination rather than electron-rich C(sp\(^2\))–H amination. Under the present conditions, anisole derivative 42 with highly reactive diphenylmethyl C(sp\(^2\))–H bonds also underwent aromatic C(sp\(^2\))–H
amination, affording product 43 (Chart 13a). The reaction of substrate 44 without C(s^2p)–H bonds at the para position of the alkoxy group gave C(s^3p)–H aminated product 45 selectively under similar conditions \(^\text{121}\) (Chart 13b). These results suggested that the assumed active species, a dirhodium nitrone complex, mediated C–H amination in both cases. The developed method was successfully applied to the selective modification of calix[4]arene derivatives with multiple benzylic C(s^3p)–H bonds and those in \(\alpha\)-positions to etherial oxygens. Chemoselective C(s^2p)–H amination of 46 occurred at the para-position of the hydroxy group, affording compound 47 as a single product (Chart 13c). The reaction position was unambiguously determined by X-ray crystallographic analysis, which supported that the reaction proceeded via electrophilic aromatic substitution. The proposed mechanism was also sup-

| Entry | Catalyst          | Solvent     | Temperature | Yield of 41 (%) | 41a/41b |
|-------|-------------------|-------------|-------------|-----------------|---------|
| 1     | Rh\(_2\)(oct)\(_4\) | PhCl        | 20 °C       | Trace —         | —       |
| 2     | Rh\(_2\)(piv)\(_4\) | PhCl        | 20 °C       | Trace —         | —       |
| 3     | Rh\(_2\)(n-C\(_3\)F\(_7\))\(_2\) | PhCl        | 20 °C       | 0 —             | —       |
| 4     | Rh\(_2\)(esp)\(_2\) | PhCl        | 20 °C       | 12 7.8/1        | —       |
| 5     | Rh\(_2\)(tpa)\(_4\) | PhCl        | 20 °C       | 50 6.6/1        | —       |
| 6     | Rh\(_2\)(tpa)\(_4\) | CH\(_3\)Cl\(_2\) | 0 °C       | 60 11/1         | —       |
| 7     | Rh\(_2\)(tpa)\(_4\) | AcOEt       | 0 °C       | 9 8.0/1         | —       |
| 8     | Rh\(_2\)(tpa)\(_4\) | CH\(_3\)CN   | 0 °C       | Trace —         | —       |
| 9     | Rh\(_2\)(tpa)\(_4\) | PhCF\(_3\)  | 0 °C       | 30 10/1         | —       |
| 10    | Rh\(_2\)(tpa)\(_4\) | PhF         | 0 °C       | 39 10/1         | —       |
| 11    | Rh\(_2\)(tpa)\(_4\) | \(\alpha\)-ClC\(_6\)H\(_4\) | 0 °C       | 44 14/1         | —       |
ported by experimental results for kinetic isotope effects and theoretically estimated low activation free energy for nucleophilic attack of a dirhodium nitrene complex by an aromatic ring.

While investigating the substrate scope of the above reaction, we encountered an interesting side reaction (Fig. 6). Treatment of tert-butyldimethylsiloxybenzene (48) under C(sp³)–H amination conditions gave desired C(sp³)–H aminated product 49 as a major product, along with alternative isomer 50 in a trace amount (Fig. 6a). Structural analysis of product 50 indicated that C–H amination occurred at the neopentyl position, which possessed sterically demanding and electronically less reactive primary C(sp³)–H bonds. This result prompted us to consider the stereoelectronic effects of the silyl group (β-silicon effect).

The strong σ-donor ability of the C–Si bond was expected to stabilize the transition state for C–H insertion of dirhodium nitrene at the β-position (Fig. 6b). Although the β-silicon effect is an established concept in synthetic organic chemistry, prior investigation into the β-silicon effect in intermolecular C–H functionalization reactions has mainly focused on carbene insertion reactions. Based on this background, we investigated β-silicon-effect-promoted intermolecular site-selective C(sp³)–H amination reactions.

The reaction of triethylysilylbenzene 51a gave desired primary C(sp³)–H aminated product 52a in an intermolecular manner, despite using an excess amount of the substrate (Chart 14). To investigate the β-activating effect of the silicon atom, the conditions were applied to 1,1,1-trimethylsilacyclohexane (53) and triethylphenylsilane (55), as the carbon and germane congeners of 51a, respectively. Although the reaction of 53 did not provide any C–H aminated products, 55 underwent C(sp³)–H amination selectively at the β-position of the germane atom. These results clearly showed that the β-effect from the heavier group 14 element controlled the reactive position and its reactivity.

The β-selective primary C(sp³)–H amination of various organosilicon compounds was observed (Table 3). The C–H amination of substrates 51e–h, 51j, and 51k with benzylic C(sp³)–H bonds, tertiary C(sp³)–H bonds, and C(sp³)–H bonds in the α-position to etherial oxygen occurred exclusively at the primary C(sp³)–H bond. The reaction of 2-triethylsilylindane (51l) proceeded at two β-positions, affording primary C(sp³)–H aminated product 52la and benzylic C(sp³)–H aminated product 52lb in 31 and 34% yields, respectively. Although the C–H aminations of tripropylphenylsilane (51m) and triisobutylphenylsilane (51n) proceeded exclusively at the β-position, the efficiency was significantly decreased. In contrast, the endocyclic secondary C(sp³)–H bonds of silacycloalkanes are highly reactive. In particular, for silacycloptane 51p and silacyclohexane 51q, 2 equiv. of the substrate was sufficient to obtain the β-aminated products in excellent yield. A similar tendency was observed in the C–H amination of organogermaine compound 51r. The reactivity difference among substrates was attributed to the efficiency of hyperconjugation between σ_C-Si and σ_C-H*.

To confirm the β-silicon effect in the transition state of the C–H insertion step, the model structure of the transition state was explored by DFT calculations with 1,1-dimethylsilacycloptane as the substrate and Rh₂(OAc)₆ as the catalyst model (Fig. 7). The results showed that the singlet pathway was a favored process, while a trigonal N–H–C angle of 152.6° in the TS indicated that both hydride transfer and C–N bond formation occurred in an asynchronous concerted manner. From natural bond orbital (NBO) calculations, the second order perturbation of the TS structure based on donation of the endocyclic C–Si σ-bond to the reactive C–H σ* orbital was 4.07 kcal/mol.

| Table 3. β-Selective C(sp³)-H Amination of Organosilanes |
|----------------------------------------------------------|
| ![TS Structures](image) |

Fig. 7. Calculated TS Structures of C–H Amination Step and NBO Analyses
kcal/mol. From NBO analysis of the corresponding TS structure derived from 1,1-dimethylcyclopentane, the donation of the endocyclic C–C σ-bond to the reacting C–H σ* orbital was calculated to be 2.12 kcal/mol. These results indicated that the strong σ-donor ability of the C–Si bonds was responsible for site selectivity in the present protocol. As organosilicon compounds are an important area of chemistry in diverse fields, such as materials science\(^{136–138}\) and pharmaceutical chemistry,\(^{139–145}\) the present protocol could provide useful tools for exploring new functional molecules.

4. Conclusion

Our recent achievements regarding two types of site-selective transformation, namely, the acylation of hydroxy groups and C–H amination, have been described in this review. The site-selective acylation of multiple hydroxy groups in sugar derivatives has enabled unprecedented late-stage diversification of bioactive natural products and streamlined syntheses of natural and unnatural sugar derivatives. Investigations aiming to improve catalyst-controlled site-selective acylation have provided fundamental insight into the acylation of alcohols by nucleophilic catalysis. The intermolecular dirhodium-catalyzed site-selective C–H amination of alkoxyarenes and organosilicon compounds was also discussed. Further investigations will contribute to the development of other site-selective C–H amination reactions.\(^{149}\) Owing to the great potential of C–H functionalization chemistry in the efficient synthesis and diversification of drug-like molecules, further investigation of site-selective C–H functionalization reactions, especially catalyst-controlled selectivity via molecular recognition processes,\(^{147–152}\) will realize ideal molecular transformations that cannot even be conducted using enzymes.

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