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Friedel-Crafts Reactions for Biomolecular Chemistry

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Chemical tools and principles have become central to biological and medical research/applications by leveraging a range of classical organic chemistry reactions. Friedel-Crafts alkylation and acylation are arguably one of the most well-known and used synthetic methods for preparation of small molecules but its use in biological and medical fields are relatively less frequent than the other reactions, possibly owing to the notion about its plausible incompatibility with biological systems. This Review demonstrates advances of Friedel-Crafts alkylation and acylation reactions in a variety of biomolecular chemistry fields. With the discoveries and applications of numerous biomolecule-catalyzed or –assisted processes, the reactions have garnered considerable interests in biochemistry, enzymology, and biocatalysis. Despite the challenges of reactivity and selectivity of biomolecular reactions, the alkylation and acylation reactions demonstrated its utility for construction and functionalization of all the four major biomolecules (i.e., nucleosides, carbohydrates/saccharides, lipids/fatty acids, and amino acids/peptides/proteins), and their diverse applications in biological, medical, and material fields are discussed. As the alkylation and acylation reactions are often fundamental educational components of organic chemistry courses, the Review is intended for both experts and nonexperts by discussing their basic reaction patterns (with the depiction of each reaction mechanism in the Electronic Supplementary Information) and relevant real-world impacts in order to enrich chemical research and education. The significant growth of biomolecular Friedel-Crafts reactions described here is a testament to its broad importance and utility, and the further development and investigation of the reactions will surely be the focus in the organic biomolecular chemistry fields.

1. Introduction

Organic chemistry reactions are the core element for advancement of fields at the interface of chemistry and biology, offering control over bond formation and scission processes of polyfunctional biomolecules. Even if biomolecules and cellular systems differ substantially from small molecule substrates in many ways such as unique three dimensional structure and presence of multiple copies of certain functional groups, the principles of reaction development in synthetic organic chemistry are still applicable to that of reactions for biomolecular study that addresses reactivity and selectivity challenges. Indeed, many of the state-of-the-art strategies for studying and utilizing biomolecules are predicated heavily on classical organic chemistry reactions (Scheme 1A).[1–12] Many of those reactions follow basic mechanistic patterns often taught in undergraduate-level courses yet enabled a wide range of powerful chemical strategies including activity-based profiling/sensing/imaging,[13,14] enhancement of drug potency,[15] drug delivery,[16] and bioorthogonal chemistry/click chemistry.[17] In other words, translation of classical chemical reactions has been one of the major approaches to create chemical tools for biological and medical applications.[18] This Review discusses classical organic chemistry reactions, Friedel-Crafts alkylation and acylation in the multifaceted areas of biomolecular chemistry (Scheme 1B).

Friedel-Crafts reactions are alkylation and acylation processes inducing C-C bond formation. The original reaction was discovered by Friedel and Crafts in the late 19th century, as the historical account has been documented in previous literature.[19,20] The reactions are often considered one of the basic organic chemistry reactions, as the reactions represent quintessential examples of electrophilic-aromatic substitution covered in most of undergraduate-level textbooks,[21] and, therefore, have been an important subject in the chemical education community.[22–24] Beyond the educational significance, chemical industry relies on the reactions for production of numerous carbon-based molecules over a century too.[25,26]

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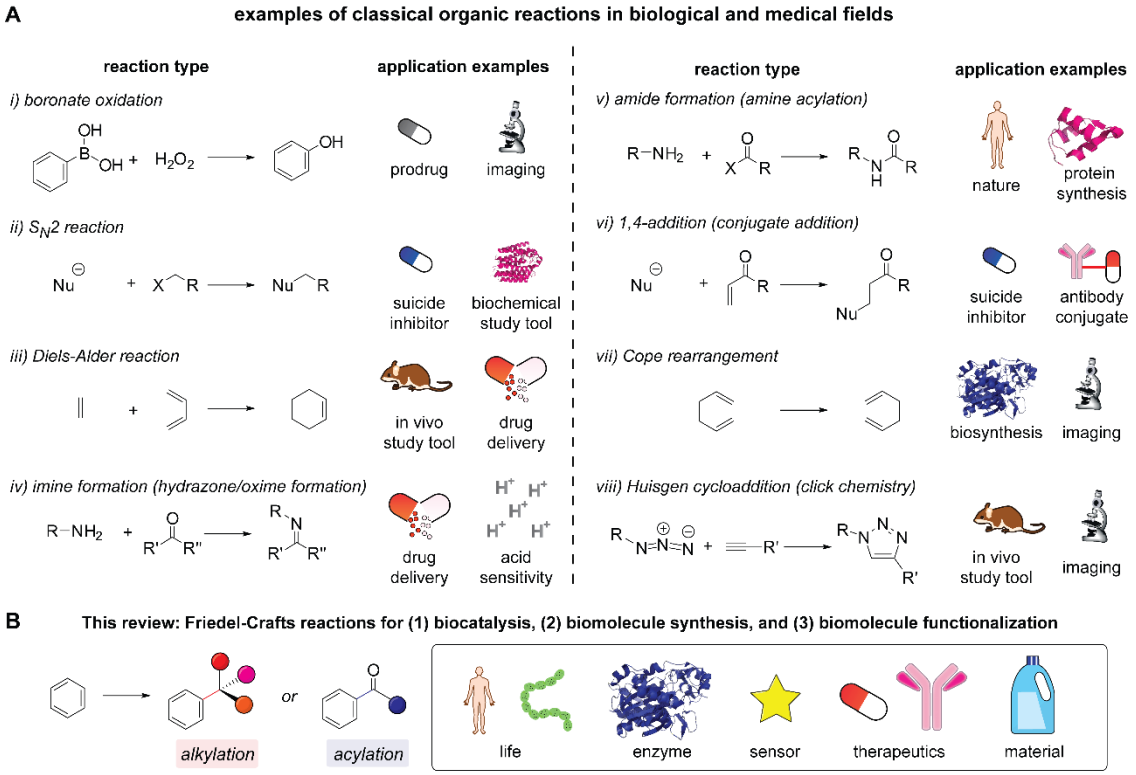
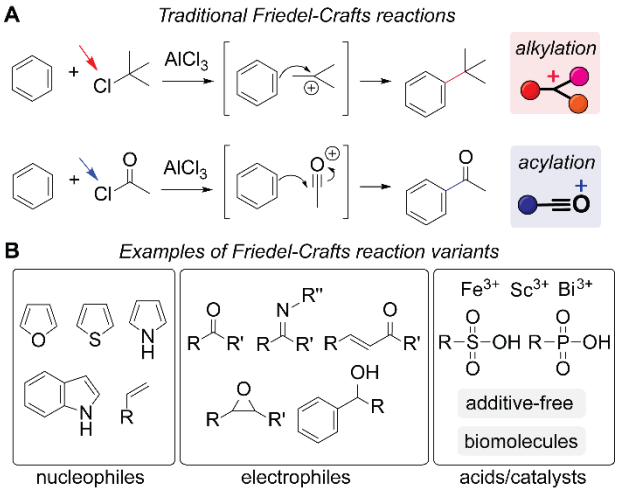


Scheme 1. Classical organic reactions in biological and medical fields. (A) Examples of the classical organic reactions including: (i) boronate oxidation,[1,2] (ii), S_N2 reactions with fluoro- and iodoacetamide,[3,4] (iii) Diels-Alder reactions for bioorthogonal chemistry,[5,6] (iv) imine and relevant C=N bond formation such as hydrazone and oxime,[7,8] (v) amide formation such as protein expression and native chemical ligation,[9,10] (vi) 1,4-addition to a carbonyl group such as acrylamide and maleimide,[11,12] (vii) Cope rearrangement,[27–29] and (viii) Huisgen cycloaddition or azide-alkyne cycloaddition.[18,30] The organization of the reactions is based on the appearance in an organic chemistry textbook (Marc Loudon and Jim Parise. Sixth edition). (B) Friedel-Crafts alkylation and acylation for biomolecular chemistry as a theme of this Review.

Diverse reaction types have become possible for Friedel-Crafts reactions through mechanisms different from traditional carbocation and acylium generations (Scheme 2 and Fig. S1). Their simple and traditional examples involve alkyl or acyl chloride starting materials that undergo generation of carbocation or acylium ions by aluminum chloride, which eventually react with an aromatic molecule to form carbon-carbon bond (Scheme 2A). Broader definition of the alkylation and acylation reactions is also based on the process of carbon-carbon bond formation often catalyzed/mediated by acids but with a wide collection of nucleophiles, electrophiles, and catalysts/additives (Scheme 2B).[31] In addition to hetero-aromatic compounds (i.e., aromatic molecule with heteroatoms such as nitrogen, oxygen, and sulfur in the ring system), even nonaromatic alkenes can be considered possible nucleophiles.[32] While separation of a distinct leaving group from an electrophile is a hallmark of the traditional reaction pattern, electrophiles such as carbonyl and epoxide derivatives are also considered Friedel-Crafts reaction reagents. Aluminum chloride remains a common catalyst/reagent but many other additives now are known to be able to induce the alkylation and acylation reactions including Brønsted acids and enzymes.[33] Notably, even additive- or catalyst-free reactions have been realized by use of fluorinated alcohol as a reaction solvent.[34] Unsurprisingly, a number of review articles have been published regarding growth of the reactions from a synthetic organic chemistry viewpoint.[33,35–37]

Friedel-Crafts alkylation and acylation are increasingly used and studied for biomolecular chemistry more recently. It is interesting that the alkylation and acylation reactions have not been as much studied as the other classical chemistries, perhaps due to the idea of potential incompatibility of reactive intermediates and strong Lewis acids with biological samples.[38] In fact, even though toxicity of aluminum at high concentration is known,[39] aluminum salts have been used as vaccine adjuvant widely from the early 20th century.[40] In addition, the alkylation and acylation does not always involve the generation of carbocation or acylium intermediates. Those attributes probably enabled the study and development of biomolecular Friedel-Crafts reactions. This Review is not intended just for experts of the chemistry fields but also instructors and students, by focusing on basic reaction patterns and representative applications of each method. Thus, rather than a comprehensive collection of all the previous research publications, only selected examples of notable reactions and applications are discussed. Two major sections of the article are reactions catalyzed/mediated by biomolecules and synthesis/functionalization of biomolecules. Each reaction described below is labeled with alkylation (red rectangle with depiction of carbocation species) or acylation (blue rectangle

with depiction of acylium species) as visual aids for readers, even though those species are not always the active intermediate of a given reaction. In order to clarify the mechanistic details, arrow-pushing mechanisms of each reaction are shown in the Electronic Supplementary Information (available as both pdf and ChemDraw files).



Scheme 2. Friedel-Crafts reactions. (A) Traditional alkylation (top) and acylation (bottom) processes with aluminum chloride through carbocation and acylium ion generation, respectively. Even though reactions may not always proceed via such carbocation and acylium intermediates, all the reactions described below in the following sections are labeled as alkylation (red rectangle) and acylation (blue rectangle) as visual aids for readers. Leaving groups are highlighted with arrows. The mechanisms are shown in Fig. S1 (ESI). (B) Examples of more broadly defined reaction substrates and catalysts/additives than the traditional versions with alkyl and acyl chlorides with aluminum chloride.

2. Friedel-Crafts reactions mediated by biomolecules (biocatalysis)

Similar to many classical organic chemistry reactions, a class of Friedel-Crafts reactions can be also mediated by enzymes (i.e., proteins) and other biomolecules. An enzyme act as a catalyst to facilitate a reaction through various mechanisms such as stabilization of reactive intermediates in a unique environment of the biomolecule binding pockets.[41,42] Examples of such biomolecule-catalyzed reactions include Diels-Alder reactions[43] and cyclopropanation.[44] Alkylation reactions of nucleotide base (i.e., cytosine methylation) are also enzyme-mediated processes, and though their formal reaction patterns would appear to be Friedel-Crafts alkylation of a heteroaromatic group, the reactivity enhancement mechanism occurs through formation of non-aromatic species which would not be considered an electrophilic aromatic substitution reaction (Fig. S2, ESI).[45] A class of enzymes can catalyze Friedel-Crafts reactions through various mechanisms such as activation of eletrophiles without generation of carbocation and acylium intermediates, as proposed reaction mechanisms of the enzymatic Friedel-Crafts reactions are shown in Figs. S2–S6 (ESI). Other types of biomolecules such as DNA,[46] RNA,[47] and carbohydrates (saccharides)[48] are also known to catalyze a series of organic reactions. While such biomolecule-catalyzed or –assisted chemical reactions are known in living systems, utilization of such biomolecule catalysts are also possible for reactions with unnatural reactants, allowing for synthetic applications of the catalytic transformation. There have been comprehensive review articles about such biocatalytic Friedel-Crafts reactions,[49,50] and the following sections are representative examples of (1) natural and (2) artificial/unnatural Friedel-Crafts reactions mediated by biomolecules.

2.1. Natural Friedel-Crafts reactions in living systems

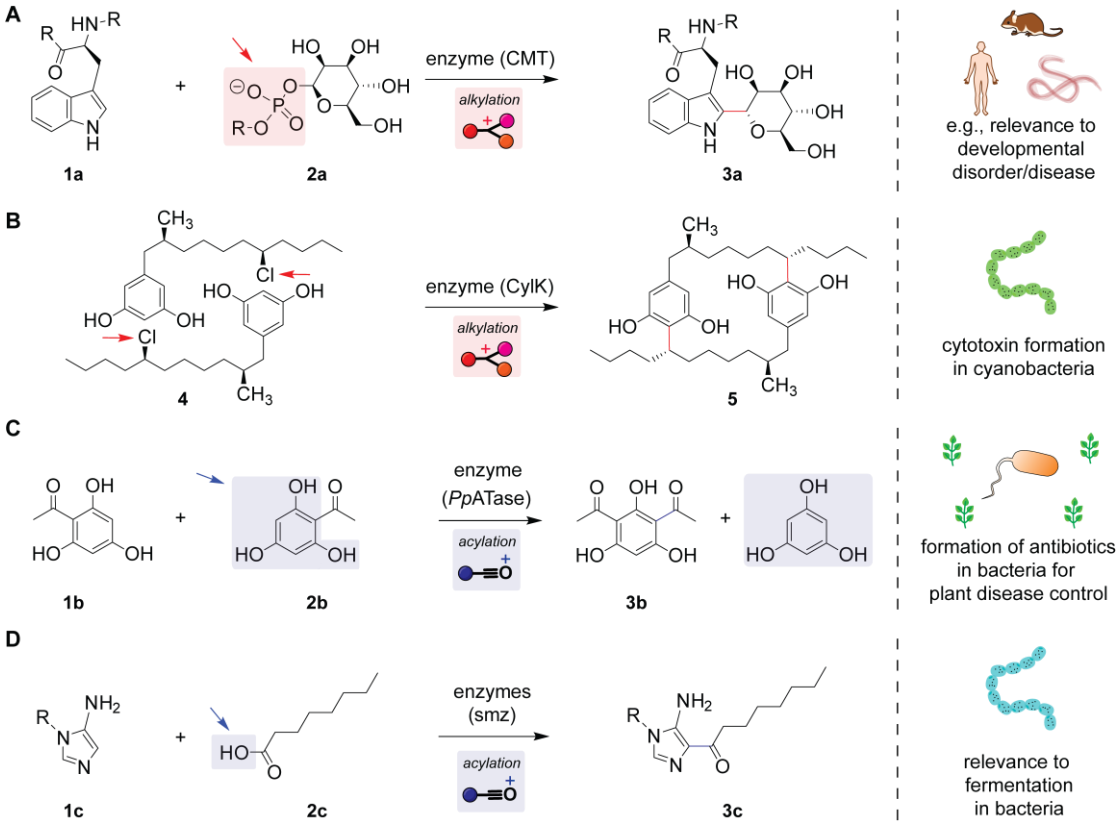
Enzymatic modification of proteins with carbohydrate groups occurs in mammals and viruses through Friedel-Crafts alkylation of a tryptophan residue (Scheme 3A). Proteins produced according to genomic sequence often undergo additional modification processes called post-translational modification,[51] and this Friedel-Crafts reaction of tryptophan amino acid is such modification through attachment of carbohydrate to a protein (known as C-mannosylation or more broadly glycosylation).[52] This alkylation process is found in diverse species including mammals and Ebola virus and has relevance to types of disease and disorder such as developmental disease.[53] Indole groups of tryptophan residues (**1a**) act as nucleophiles with the aid of electron donation from the nitrogen atom in the ring system, and elimination of the phosphate as a leaving group would occur when the carbohydrate electrophile (**2a**) is nucleophilically attacked, as recent structural biology study suggested (Fig. S3, ESI).[54]

A metabolite with electron-rich benzene rings and chloroalkanes is known to cause an enzymatic homo-dimerization process, generating a cytotoxin in cyanobacteria (Scheme 3B). Cylindrocyclophane derivatives are cytotoxins, and their biological importance is increasingly studied.[55] With two hydroxyl groups and one alkyl group, the aromatic ring would be a great nucleophile that reacts with the secondary alkyl chloride in another molecule. Balskus and co-workers revealed the mechanism of action for the enzymatic biosynthesis pathways, which showed activation of the nucleophiles through deprotonation of the phenolic proton by the aspartate residue of the enzyme during the alkylation reaction (Fig. S4, ESI).[56,57]

Plants utilize formation of antibiotics 2,4-diacetylphloroglucinol through enzymatic acylation reactions for their disease control against certain bacteria (Scheme 3C). The product of the acylation reaction 2,4-diacetylphloroglucinol (**3b**) displays antibiotic activity and is of agricultural importance. In this acylation reaction, two identical acetylated aromatic compounds react with each other, where formally one of the molecules acts as nucleophile and the other electrophile/acetyl donor.[58,59] Normally, ketone groups would not typically participate in Friedel-Crafts acylation as an electrophile since C-C bond would not be easily broken to liberate a leaving group, this reaction occurs in the enzymatic pocket activating the acetyl group to generate a thioester group linked onto an enzyme (Fig. S5, ESI). Afterward, nucleophilic attack by the other molecule to the thioester group causes the acylation reaction to produce the bis-acetylated product. Plants utilizes

certain bacteria (*Pseudomonas fluorescens*) that can induce the acylation reaction to produce the antibiotics controlling pathogens in soil, which highlights the interplay between plants and a type of bacteria mediated by the acylation reaction.[60]

Recently, a nucleotide derivative with an aminoimidazole group was found to undergo enzymatic acylation reactions with fatty acid in bacteria during fermentation (Scheme 3D).[61] Imidazole derivatives can cause a nucleophilic attack often at the nitrogen atom in the ring.[62,63] Likely, for this particular case of the nucleotide derivative, nucleophilicity of the ring system is increasing the nucleophilicity of the carbon center through the electron donation by the amine substitution, leading to the C-C bond forming reaction (Fig. S6). Carboxylic acids are not a typical electrophile of Friedel-Crafts acylation reactions due to the modest leaving capability of the OH group as well as poor electrophilicity of a deprotonated form of the COOH group, and this reaction proceed through activation of the carboxylic acid to its derivative by the action of the enzyme. The acylated imidazole product is further modified by enzymatic reactions to be connected with adenosine triphosphate (ATP), enabling the fermentation process in bacteria.

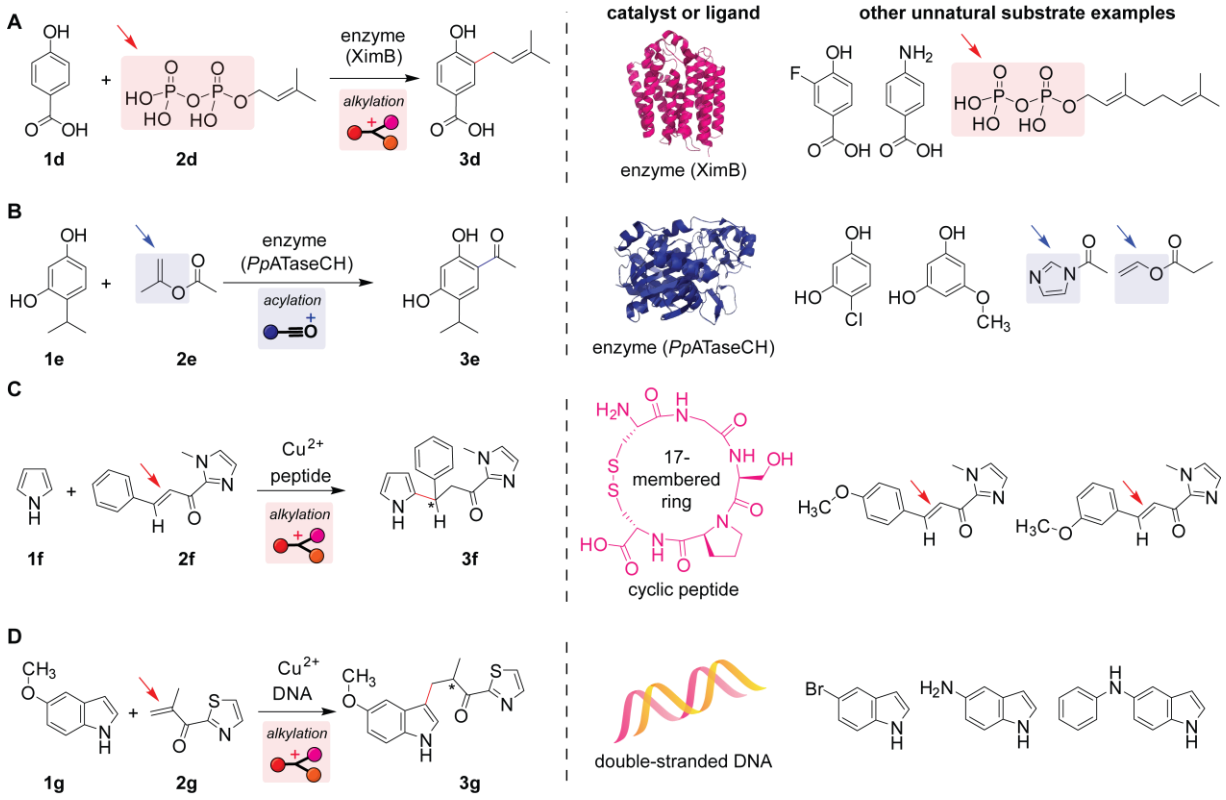


Scheme 3. Friedel-Crafts reactions that occur in living systems catalyzed by a series of enzymes. Leaving groups are highlighted with arrows. Simplified mechanisms with selected amino acid functions of enzymes are shown in Figs. S3–S6 (ESI). (A) Mannosylation (glycosylation) of proteins through an alkylation of a tryptophan residue with phosphorylated mannose in living organisms such as mammals and Ebola virus.[54] (B) Formation of a cytotoxin cylindrocyclophane (**5**) in cyanobacteria through intermolecular dimerization by alkylation reactions.[56] (C) Formation of antibiotics 2,4-diacetylphloroglucinol in bacteria *Pseudomonas fluorescens*.[59] (D) Attachment of fatty acid to an imidazole derivative in bacteria *Streptomyces* sp. OUCMDZ-944.[61]

2.2. Biomolecule-catalyzed or -assisted Friedel-Crafts reactions of unnatural substrates

Inspired by natural reactions occurring in living systems, Friedel-Crafts alkylation and acylation reactions of unnatural reactants have been developed. Although some enzymes tend to show high substrate specificity and may not be able to host unnatural substrates, other classes of enzymes indeed would not recognize a slight structural modification of substrates, and such reactions of unnatural substrates can be facilitated by modulation of enzyme pockets/structure through mutation processes (i.e., change of an amino acid residue). For instance, alkylation reactions of phenol derivatives with unnatural allyl phosphate electrophiles (known as prenyl phosphates with trisubstituted alkene groups) have been realized using the natural enzyme with a slight modification on their amino acid composition (Scheme 4A and Fig. S7, ESI).[64] Similarly, indole derivatives can be also alkylated in an unnatural fashion.[65] By employing the natural enzyme mentioned above (Scheme 3C), acylation reactions of aromatic compounds bearing a hydroxyl group(s) with several electrophiles such as esters and acyl-imidazoles has been demonstrated (Scheme 4B and Fig. S5, ESI).[66] While those enzymatic reactions are performed in a test tube with a pure enzyme and substrates, Roelfes and co-workers showed that enzymatic Friedel-Crafts reactions of unnatural substrates in vivo are also feasible.[67]

Peptides and DNAs can act as auxiliary ligands for copper-catalyzed alkylation reactions with α,β-unsaturated carbonyl compounds electrophiles. Aforementioned enzymatic reactions (i.e., protein-catalyzed reactions) offer high reaction efficiency and chemo-/regio-/enantio-selectivity. Without the large, intricate three-dimensional structures of enzymes, types of smaller biomolecules such as peptides could also exert enantiocontrol (Scheme 4C) even in the presence of competing aromatic rings (e.g., a substrate with a methoxy-substituted benzene ring shown on the right of Scheme 4C).[68,69] Unlike typical Friedel-Crafts reactions that involve activations of electrophiles through elimination of a leaving group such as halides, α,β-unsaturated carbonyl compounds could be an electrophile of the alkylation reaction through 1,4-addition, forming a new chiral center at the β position (Fig. S8, ESI). Such a class of reactions generating a specific enantiomer over the other (i.e., asymmetric reactions) has been an important diversification of Friedel-Crafts alkylations.[31,36,70–72] A similar asymmetric transformation is also possible with double-stranded DNA as a ligand that binds to the copper catalyst (Scheme 4D).[73]



Scheme 4. Biomolecule-catalyzed or –assisted Friedel-Crafts reactions of unnatural substrates in test tubes. Leaving groups or bonds that undergo cleavage are highlighted with arrows. Mechanisms of the reactions are shown in Figs. S7, S5, and S8 (ESI). (A) Enzyme-catalyzed alkylation of benzoic acid derivatives with allylic phosphates.[64] Predicted structure of enzyme XimB is from AlphaFold Protein Structure Database (uniprot code: Q96H96). (B) Enzyme-catalyzed acylation of phenol derivatives with esters.[66] Partial structure of enzyme *Pp*ATaseCH is from Protein Data Bank (PDB ID: 5MG5). (C) Copper(II)-catalyzed alkylation reaction of pyrrole with α,β-unsaturated carbonyl compounds assisted by a peptide as a ligand to the metal catalyst.[68] (D) Copper(II)-catalyzed alkylation reaction of indole derivatives with α,β-unsaturated carbonyl compound assisted by a double-stranded DNA as a ligand to the metal catalyst.[73]

3. Friedel-Crafts reactions for synthesis and functionalization of biomolecules

Friedel-Crafts alkylation and acylation are commonly used for synthesis of biomolecules/their analogues as well as addition of unique functionalities to biomolecules through formation of a stable carbon-carbon bond. The four basic biomolecules contain components for the Friedel-Crafts alkylation and acylation reactions including aromatic rings in nucleosides and amino acids/peptides/proteins, alkyl group with a leaving group on carbohydrates, and acyl groups in fatty acids and amino acids/peptides/proteins. As nature takes advantage of those functional groups (e.g., tryptophan, mannose, and fatty acid in Scheme 3), numerous strategies were developed for various purposes of synthesis and functionalization of biomolecules. The following sections discuss the synthesis and functionalization of biomolecules and are organized based on biomolecule types: nucleosides, carbohydrates, fatty acids, and amino acids/peptides/proteins.

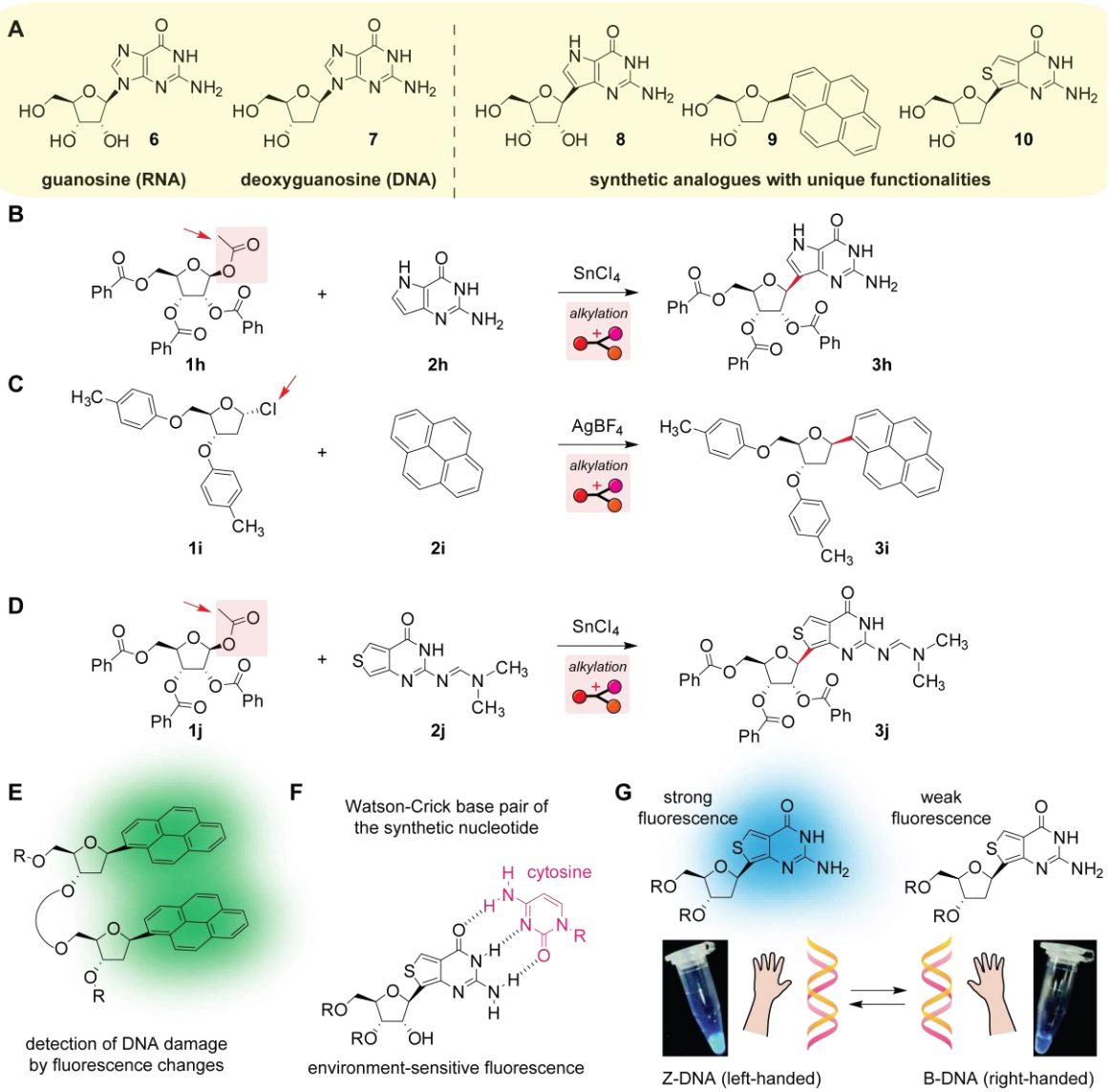
3.1. Synthesis of nucleoside analogues through Friedel-Crafts alkylation

Friedel-Crafts reactions on the canonical aromatic nucleobases in ribonucleic acid (RNA) and deoxyribonucleic acid (DNA) are not facile processes without protection strategies or

enzymatic aids (Scheme 5A). Probably due to the presence of the amine groups and electron-deficient nature of nucleobases, Friedel-Crafts reactions of natural nucleotides are virtually unknown both in nature and for synthetic purposes. As discussed above, frequently occurring methylation of cytosine in nature are not considered electrophilic aromatic substitution reaction (Fig. S2, ESI),[45] and other nucleotide methylation occurs on nitrogen atoms rather than a carbon-carbon bond forms.[74] Indeed, the enzymatic acylation reaction of DNA analogues in living systems has not been reported until recently (Scheme 3D).[61] Nucleobase acetylation is a well-known natural process among many species but the amine acylation (i.e., amide bond formation) is a predominant pathway.[75] Friedel-Crafts reactions for synthesis or functionalization of natural nucleobases/nucleosides/nucleotides have not been reported,[76] though synthesis of RNA analogues through the acylation is known (Scheme 5B and Fig. S9, ESI).[77] The challenges of nucleotide synthesis and functionalization may not only be because of the reactivity of amines and nucleobases, but compatibility of acid catalysts/additives may also be relevant, as binding of nucleobases to metals have been commonly observed including an example of cisplatin a platinum-based anti-tumor agent.[78] Thus, synthesis of nucleoside analogues often rely on functional group protections as shown below.

Synthetic analogues of nucleosides with unique photophysical capabilities can be prepared through Friedel-Crafts alkylation reaction with ribose derivatives (Scheme 5C,D and Figs. S9,S10, ESI).[79,80] As nucleosides are constructed with carbohydrate (i.e., ribose or deoxyribose) and nucleobase units, one of the general strategies for synthesis of nucleoside analogues is to use nucleobase analogues as nucleophiles with carbohydrate electrophiles bearing a leaving group on the anomeric position—that is an acetal carbon in a cyclic ether. The OH and NH_2 groups are normally protected as an ether, ester, and imine/amidine, likely to suppress side reactions on those elements as well as to increase solubility of the starting materials and products in organic solvents for synthetic ease. Protecting groups could enhance stereoselectivity of the alkylation process as well (e.g., Silyl-Hilbert-Johnson type mechanism), as the actions of the groups during the reactions are depicted in Figs. S9–S11 (ESI). It is noteworthy that the desired alkylation reactions by fluorescent aromatic groups in those examples occurs in the presence of other arene groups, even though some substrates (e.g., pyrene **1i**) may not be significantly more electron-rich compared to the alkoxy-substituted benzenes.

The synthetic analogues with the fluorescent aromatic rings are useful for visualization of molecular events and behaviours of oligonucleotides such as DNA damage and conformational changes. Conjugated aromatic rings can offer fluorescence capabilities with sensitivity toward changes of local environments. One of the applications of pyrene nucleotide is detection of DNA damage (Scheme 5E).[81] The pyrene groups are known to display fluorescence color change and increase upon a noncovalent dimerization process known as excimer formation,[82] and the design by Kool and co-workers took advantage of the excimer formation when DNA undergoes deletion of a specific nucleotide.[81] In addition to pyrene as a fluorescence reporter, thienoguanosine with a sulfur atom in the ring structure is also a fluorescent analogue with ability of Watson-Crick base pairing (Scheme 5F).[83] Thienoguanosine-based nucleotides possesses unique photophysical features[84] making it useful for numerous applications including detection of DNA conformational changes (Scheme 5F)[85] and compatibility with gene-editing processes.[86] Many other examples of applications of fluorescent nucleotides were described in a review by Kool and co-workers.[87]

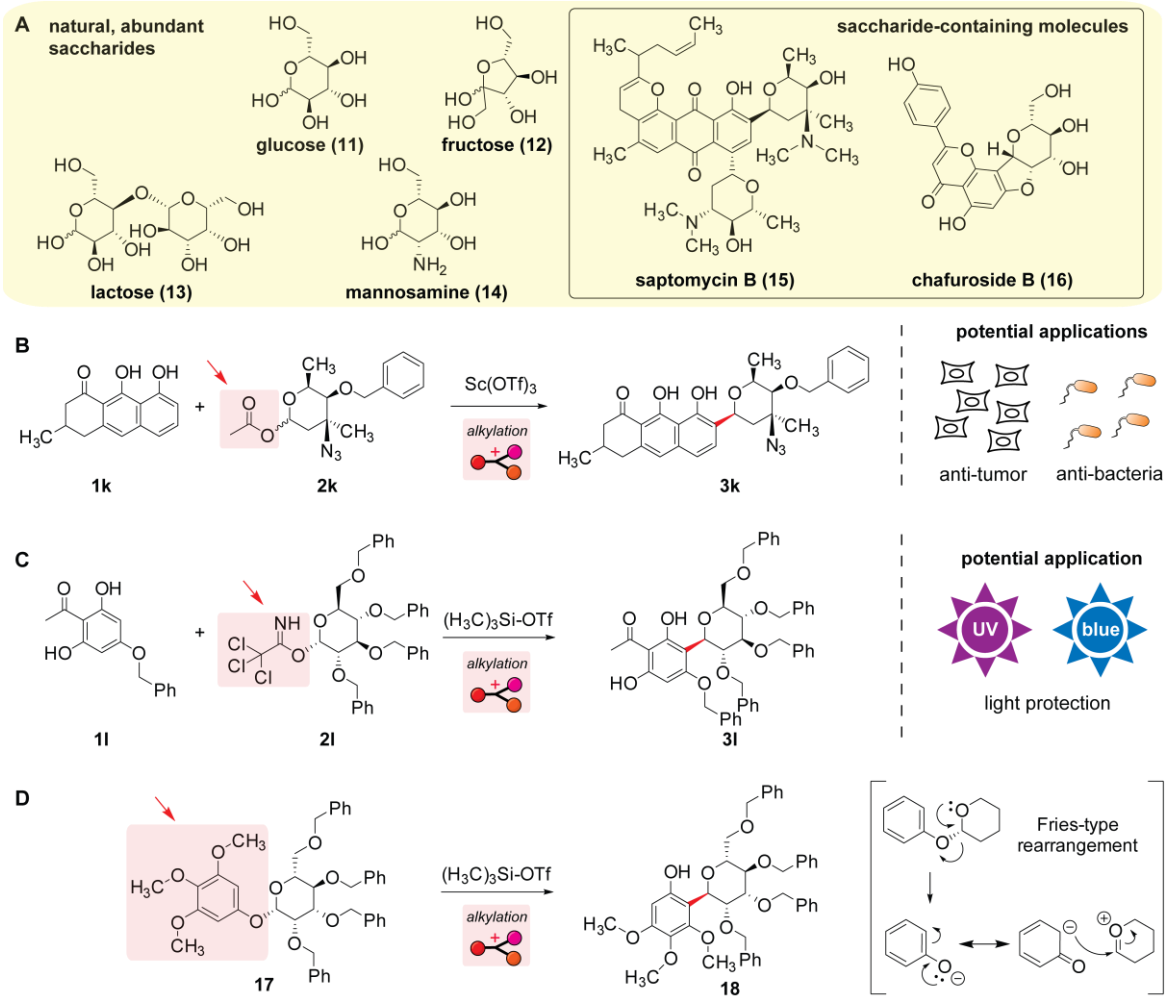


Scheme 5. Friedel-Crafts alkylation reactions for construction and applications of synthetic nucleoside analogues. Leaving groups are highlighted with arrows. Mechanisms of the reactions are shown in Figs. S9–S11 (ESI). (A) Chemical structures of natural (left) and synthetic (right) nucleosides. (B) Synthesis of a guanine analogue.[77] (C) Synthesis of pyrene-substituted DNA.[79] (D) Synthesis of sulfur-containing RNA (thienoguanosine).[80] (E) An application of pyrene-substituted nucleotide for detection of DNA damage.[81] (F) Complementarity of the sulfur-containing synthetic RNA analogue (thienoguanosine) with cytosine through Watson-Crick base pairing.[83] (G) An application of the sulfur-containing RNA (thienoguanosine) for detection of left-handed helical structure.[85] The images of the cyan fluorophore solutions were reproduced with permission.[85] Copyright 2014, Royal Society of Chemistry.

3.2. Functionalization of carbohydrate derivatives through Friedel-Crafts alkylation

With the carbon- and oxygen-based scaffolds, carbohydrate (or saccharide) units are often used as electrophiles of Friedel-Crafts alkylation reactions to construct intricate, functional molecules (Scheme 6A). Monomeric carbohydrates typically have no aromatic rings,[88] and the presence of the acetal group known as anomeric position enables generation of cationic intermediate from carbohydrate derivatives. The reaction patterns for the carbohydrate alkylation processes follow those in the DNA section of ribose where carbohydrates act as electrophiles (Scheme 5), and the alcohol groups are often protected in a similar fashion to the ribose system. Many biologically active small-molecule products are composed of carbohydrate groups with useful capabilities,[89] and the alkylation reactions of carbohydrates with a leaving group on the acetal position can be a convenient approach. For instance, an intermediate molecule during total synthesis of saptomycin B (**15**) with antitumor and antibacterial activities[90] was facilitated by the scandium-mediated alkylation process with a carbohydrate group bearing an acetate moiety. (Scheme 6B and Fig. S12, ESI).[91] Another example includes a formation of an intermediate species for total synthesis of chafuroside B (**16**) by the silyl triflate (Me_3Si-OTf)-mediated alkylation reaction;[92] the synthesis may have been motivated by the light protection abilities of the natural product (Scheme 6C and Fig. S13, ESI).[93] Noteworthy, those reactions allowed for isolation of specific diastereomer products.

Fries-type rearrangement that are mechanistically related to Friedel-Crafts reactions provides opportunities for stereoselective functionalization of carbohydrate derivatives (Scheme 6D and Fig. S14, ESI).[94] Fries-type rearrangements are reactions of phenol derivatives transferring substitution on the phenolic oxygen to its ortho position.[95] The elimination of a phenolic anion as a leaving group generates cation intermediates on the carbohydrate group, assisted by electron donation from the oxygen in the ring system. An electrophilic aromatic substitution-type process occurs afterward to form the ortho-substituted product. Although the rearrangement can be considered an intermolecular reaction between the phenolic anion and oxonium cation intermediates, the characteristic inversion of the stereochemistry at the anomeric position is often observed. One of the rationalizations of such stereospecificity is that the generated cation and anion would have intimate charge-charge interaction (as an ion pair),[96,97] which may spatially control the orientation of two intermediates in a specific position to give the specificity. Many similar intramolecular chemistry examples have been reported too.[98–100]



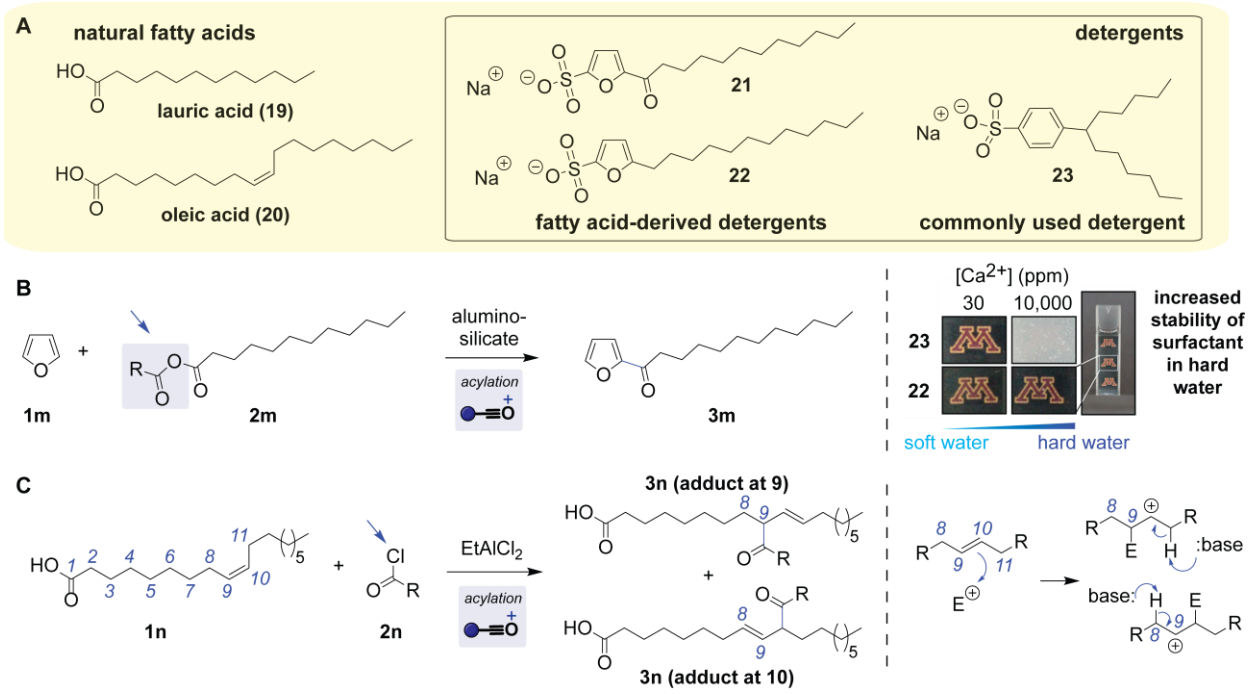
Scheme 6. Friedel-Crafts alkylation reactions for construction and applications of carbohydrate derivatives. Leaving groups are highlighted with arrows. Mechanisms of the reactions are shown in Figs. S12–S14 (ESI). (A) Chemical structures of common, abundant (left) and complex (right) carbohydrates. (B) Formation of an intermediate for total synthesis of saptomycin B (**15**) that may have potentials of anti-tumor and anti-bacteria applications.[90,91] (C) Formation of an intermediate for total synthesis of chafuroside B (**16**) that may have a potential of a light-protection application.[92,93] (D) Fries-type rearrangement of a carbohydrate derivative causing the C–C bond formation on the oxygen-rich aromatic ring.[94]

3.3. Functionalization of fatty acids through Friedel-Crafts reactions

Long alkyl chains of fatty acids are useful for chemical and biological materials including detergents, and carboxylic acid moieties of the fatty acids can be employed for synthesis of such materials through Friedel-Crafts acylation (Scheme 7A). Fatty acids are essential components in life forms and also abundant, useful building blocks for organic synthesis. Furan-based detergent with enhanced stability for hard water can be synthesized through Friedel-Crafts acylation using anhydride form of lauric acid (Scheme 7B).[101] With use of a solid acid catalyst mesoporous aluminosilicate, the reaction of furan nucleophile and lauric anhydride electrophile produced the product through the acylation reaction. Mechanistic study of the reaction with the alumino-silicate catalyst suggested that activation of the acylating reagent would occur through

activation of the acyl group by an oxygen atom on the catalyst (Fig. S15, ESI).[102] The acylated furan was further reduced to the alkyl product **22** that was tested in hard water where micelle aggregation tends to be disrupted.[101] Indeed, compared to frequently used detergent **23** that became turbid at higher concentration of calcium ions, solution of alkyl-furan detergent (**22**) remained clear, demonstrating the practical utility of the furan detergent made from the fatty acid through the acylation and reduction reactions.

As the breadth of nucleophilic reactivity of alkene groups is well-known, unsaturated fatty acids with an alkyl-substituted, nonaromatic alkene are also known to act as nucleophiles for Friedel-Crafts reactions (Scheme 7C).[103] Friedel-Crafts reactions with nonaromatic alkene nucleophiles have been known for decades and actively studied to date.[32] Even if the nonaromatic systems are a relatively rarer type of Friedel-Crafts reactions than the aromatic counterparts, a number of alkylation reactions with nonaromatic alkene nucleophiles are reported in synthetic organic chemistry fields.[104–107] Such nonaromatic reactions often produce regioisomers, depending on which alkene carbons forms a new σ bond with an electrophile (Fig. S16, ESI).



Scheme 7. Friedel-Crafts acylation reactions of fatty acids. Leaving groups are highlighted with arrows. Mechanisms of the reactions are shown in Figs. S15–S16 (ESI). (A) Chemical structures of natural fatty acids (left) and detergent molecules that contain fatty alkyl chains. Linear alkylbenzene sulfonates are often a mixture of isomers but a single isomer structure (**23**) is shown for brevity. (B) Formation of an intermediate for synthesis of furan-based detergents that display higher tolerance to hard water (right). The image of hard water was reproduced with permission.[101] Copyright 2016, American Chemical Society (https://pubs.acs.org/doi/10.1021/acscentsci.6b00208). (C) An acylation reaction of oleic acid as a nucleophile using its alkene group, rather than aromatic rings for typical Friedel-Crafts reactions.[103]

3.4. Synthesis and functionalization of amino acids, peptides, and proteins through Friedel-Crafts alkylation

Although Friedel-Crafts reactions can be useful strategies for constructing carbon-carbon bonds in amino acid-based biomolecules (Scheme 8A), selectivity of the reactions in the presence of other nucleophilic functional groups often is a substantial challenge. Among the 20 canonical amino acids, four aromatic amino acid residues could be potential nucleophile substrates: phenylalanine with an alkylbenzene, tyrosine with a phenol, tryptophan with an indole, and histidine with an imidazole. In particular, phenol (tyrosine) and indole (tryptophan) are relatively electron-rich aromatic systems and often good nucleophiles for Friedel-Crafts reactions as similar/relevant substrates are covered in the previous sections (e.g., Scheme 4) whereas an alkylbenzene (phenylalanine) with a mildly electron-donating alkyl group and imidazole (histidine) with the C=N bond acting as an electron-withdrawing group are often challenging substrates. In the presence of the four potentially reactive aromatic amino acids, nature addresses reactivity and selectivity challenges through enzymatic processes as discussed above (e.g., acylation of imidazole derivatives shown in Scheme 3D). Theoretically, carboxylic acid and its derivatives could serve as electrophiles of acylation reactions, though such reactions can be challenging or require harsh conditions in practice.[108] The following sections describe putative synthesis of a type of amino acid in the early Earth (chemical evolution), functionalization of amino acids/peptides/proteins, and their potential implications and applications will be discussed.

3.4.1. Potential formation of tryptophan in a prebiotic era through Friedel-Crafts alkylation

Tryptophan amino acid was found in a deep ocean crust, and its formation in a prebiotic time was proposed to happen through Friedel-Crafts alkylation of an indole molecule with

pyruvate (Scheme 8B, top). Origin-of-life or chemical-evolution research is dependent highly on organic chemistry as one of its main focuses is to better understand how biomolecules originated without life forms or molecular machinery like in the current organisms and cells.[109,110] In other words, the research field is pursuing a plausible explanation for generation of biomolecules such as amino acids from simpler building blocks through chemical reactions in the early Earth. Geochemical and astrochemical evidence is one of the powerful materials to this end,[111,112] as preserved prebiotic chemical information could be buried within such systems. The discovery of tryptophan amino acid in a deep ocean crust (serpentinized harzburgite from Atlantic Massif)[113] led to the hypothesis that indole and pyruvate derivatives were connected to one another through Friedel-Crafts alkylation.[114] Iron is considered present in the prebiotic time,[115] and iron mineral was proposed as a potential Lewis acid for the process. Their proposal is that replacement of the oxygen unit of pyruvate to amine group of the amino acid backbone would proceed through some kind of amination reaction—perhaps the proposed process would be similar or related to transamination process of the present time.[116] It is true, however, that mechanistic details of the tryptophan formation have not been thoroughly discussed in the report and that tryptophan may not have been stable enough in the prebiotic time due to an intensified ultraviolet at the time.[117]

The proposed formation of tryptophan amino acid (Scheme 8B, top)[114] may be relevant to an enol form of pyruvate derivatives (Scheme 8B, bottom). No literature precedents in synthetic chemistry fields exist about the reactions of non-substituted indole and pyruvate eventually producing tryptophan or even derivatives. Nonetheless, there was a report of a reaction of indole with a ketone analogue bearing an O-acylated enol group (Scheme 8B, i and Fig. S17, ESI).[118] Although the keto-acylated enol compound is not an exact pyruvate derivative, the chemical structure is akin to the enol form of pyruvate to a certain extent (Scheme 8B, ii), perhaps suggesting that an enol form of pyruvate derivatives may be a reactant of the proposed tryptophan formation in the prebiotic time. Indeed, phosphoenolpyruvate (Scheme 8B, iii) is ubiquitous pyruvate derivatives with an enol unit as an intermediate species of glycolysis pathways in the living systems.[119] A recent report also suggested that the phosphoenolpyruvate intermediates might have been present in the prebiotic time too,[120] and even though further experimental investigations would be necessary to support those speculations, the set of the evidence may be crucial to account for the prebiotic origin of tryptophan.

3.4.2. Functionalization of amino acids through Friedel-Crafts reactions

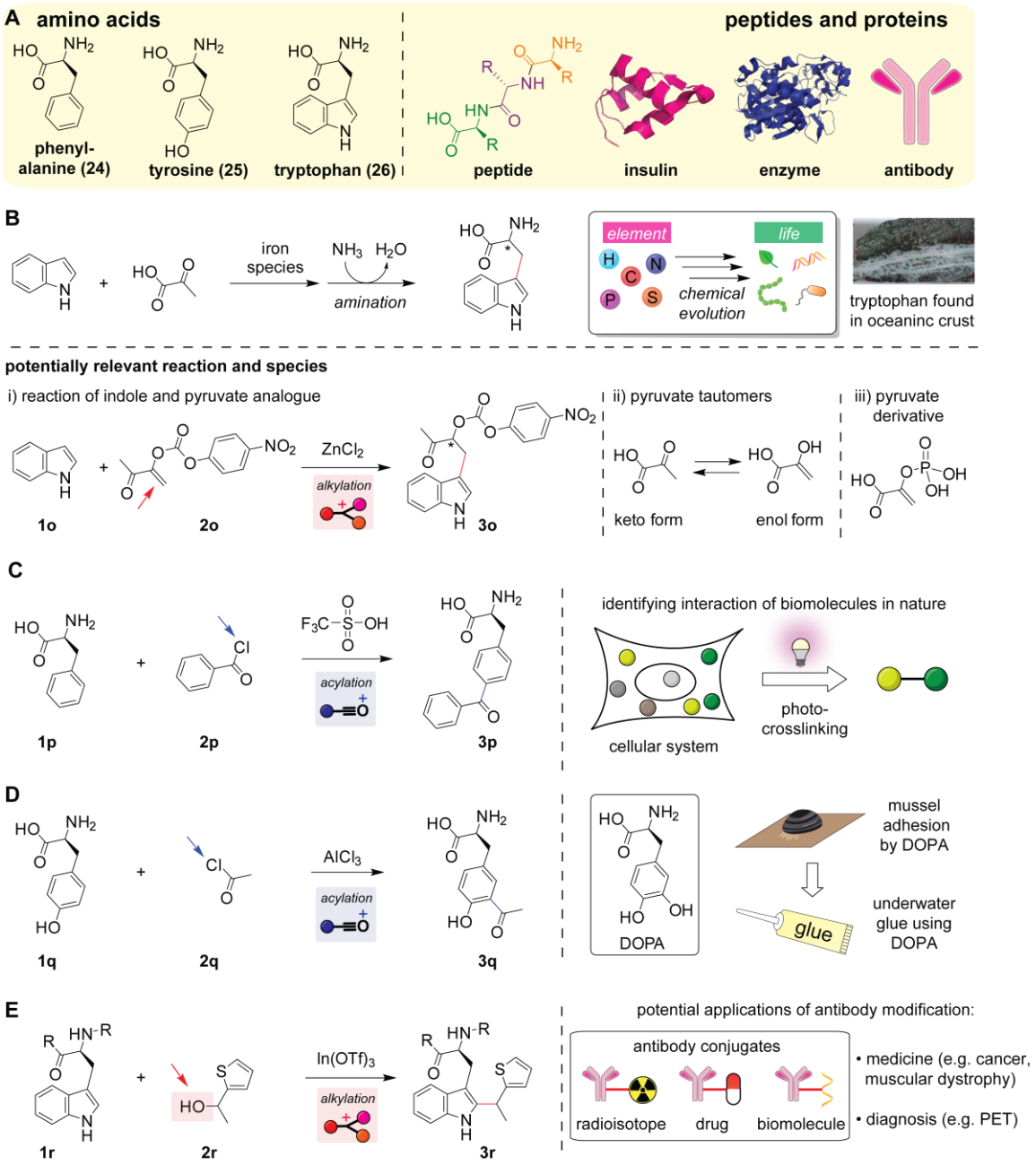
Utilization of unnatural amino acids has become essential chemical strategies in diverse chemistry fields, and the monomeric biomolecules can be synthesized through Friedel-Crafts acylation of unprotected canonical amino acids (Scheme 8C). Akin to the synthetic analogues of the nucleosides (Scheme 5), unnatural amino acids could offer a useful capability that enables their biological, medical, or material applications. Advancement in genetic engineering technologies allows for incorporation of such amino acids onto proteins (e.g., via amber stop codon suppression and a unique protein synthesis machinery), and there have been a series of unnatural amino acids that can be genetically encoded.[121] For instance, upon photo-irradiation, benzophenone-based amino acid or benzoyl-phenylalanine (**3p**) would generate radical species that can react with functional groups in proximity to induce crosslinking between biomolecules.[122] This crosslinking process has become a common approach to understand what kind of biomolecules communicate with each other in cellular systems.[123] One of the synthetic methods for preparation of benzophenone-based unnatural amino acids is the direct functionalization of phenylalanine natural amino acid with acetyl chloride (Scheme 8C and Fig. S18, ESI).[124] Use of the extremely strong acid (trifluoromethanesulfonic acid or triflic acid. pKa < –14) is plausibly necessary in order to fully suppress reactivity of the amine group through protonation.

Friedel-Crafts acylation can be of use for chemical synthesis of natural, noncanonical amino acid 3,4-dihydroxyphenylalanine (DOPA) that can exert adhesive effects (Scheme 8D). DOPA is a naturally occurring amino acid with adherent properties (as mussel adhesion is enabled by the property) though the natural amino acid is not one of the 20 canonical/proteinogenic amino acids. Since the adhesive property is effective even underwater conditions, synthetic glues often relies on DOPA compositions as a bioinspired material.[125,126] Simply speaking, though direct hydroxylation/oxidation of tyrosine amino acid would provide DOPA by formally inserting an oxygen atom to the C-H bond, phenol derivatives tend to undergo formation of various oxidation products include ortho-benzoquinone unless there is an enzymatic control of reactions,[127] representing a synthetic challenge of DOPA. An approach originally reported by Boger and co-workers was a selective acetylation reaction toward the aromatic ring of the tyrosine starting material using excess $AlCl_3$ at 100 °C (Scheme 8D and Fig. S19, ESI), followed by a unique oxidative C-C bond cleavage of the acetyl group to form protected DOPA.[128,129] The use of harsh reaction conditions with excess Lewis acid and high temperature is presumably key to achieve the selective acylation of aromatic rings over amines. However, such harsh conditions could induce loss of the enantiopurity (i.e., racemization) through keto-enol tautomerization of the backbone carbonyl of the amino acid.[130] In this context, asymmetric alkylation of amino acid derivatives/precursors could be a complimentary strategy,[131] or development of milder reactions would be necessary as described in the next section.

3.4.3. Functionalization of peptides and proteins through Friedel-Crafts alkylation

Friedel-Crafts reactions of unprotected peptides and proteins have not been achieved until recently, probably because of challenges related to the presence of various nucleophilic functional groups (e.g., amines in lysines and guanidines in arginines) and their incompatibility in many organic solvents. The amino acid labeling conditions including

use of nitromethane, $AlCl_3$, triflic acid, 100 °C (Scheme 8C,D) would not be compatible with proteins, as denaturation or aggregation of proteins would be inevitable.[132] Aqueous solutions would be often ideal for study of proteins to conserve their structure/activity/function, but aqueous Friedel-Crafts reactions are quite limited for specific reactants such as small molecule enzyme substrates and α,β-unsaturated carbonyl compounds as discussed above (Scheme 3,4). To this end, an alternative approach using nonaqueous media that are potentially compatible with both Friedel-Crafts alkylation and protein substrate has been devised (Scheme 8E).[133] Tryptophan-selective labeling of peptides and proteins were achieved by use of hexafluoroisopropanol (HFIP) as a solvent that is known to stabilize carbocation and enhance peptide secondary structure (i.e., α-helices).[134] The alkylation process is effective with thiophene-ethanol reagents which eliminate a hydroxyl group assisted by Lewis acid prior to the nucleophilic attack (Fig. S20, ESI). The nonaqueous labeling method was applicable to modification of a large, intricate protein such as an antibody. Antibodies are essential for treatment and diagnosis of a multitude of diseases, and chemical modification of antibodies grants additional capabilities for diverse applications such as visualization of cancer through positron emission tomography (PET)[135] and creation of antibody–drug conjugate a potent medicine with less side effects.[136]



Scheme 8. Friedel-Crafts reactions of amino acids, peptides, and proteins. Leaving groups are highlighted with arrows. Mechanisms of the reactions are shown in Figs. S17–S20 (ESI). (A) Chemical structures of amino acids (left) and peptides/proteins (right). Structures of insulin (shown in magenta) and enzyme *Pp*ATaseCH (shown in blue) are from Protein Data Bank (PDB ID: 5CNY and 5MG5, respectively). (B) Formation of tryptophan from indole and pyruvate, proposed as one of the chemical evolution pathways in prebiotic eras.[114] An image of a part of the oceanic crust (serpentinized harzburgite from Atlantic Massif) is shown on the right. The crust image was reproduced with permission.[113] Copyright 2011, the American Geophysical Union. Potentially relevant reactions to the proposed chemical evolution reaction are shown at the bottom: (i) Reaction of indole and pyruvate analoge (oxygen-substituted α,β-unsaturated carbonyl compound),[118] (ii) Tautomerization of pyruvate forming hydroxy-substituted α,β-unsaturated carboxylic acid as an enol form, and (iii) Chemical structure of phosphoenolpyruvate (α,β-unsaturated carbonyl compound with a substitution on the oxygen of the enol unit) that is a known intermediate for the modern glycolysis[119] as well as a possible species in the prebiotic time.[120] (C) Reaction of phenylalanine and benzoyl chloride forming benzophenone-substituted unnatural amino acid[124] that is useful for identification of interactions between biomolecules in cellular systems through irradiation of ultraviolet light (photo-crosslinking).[122] (D) Acetylation of tyrosine with acetyl chloride forming acetyltyrosine as an intermediate for chemical synthesis of 3,4-dihydroxyphenylalanine (DOPA).[128,129] Schematic description of utility of DOPA as a natural adherent is shown on the right. (E) Reaction of tryptophan residues in peptides or proteins with thiophene-ethanol, which can be used for labeling of antibodies.[133] Examples of antibody conjugates are shown on the right.

Conclusions

Since its inception approximately 150 years ago, Friedel-Crafts reactions have proven its significance not only for synthetic methods of small molecule compounds but also for biomolecular chemistry. Even during the past decade, a series of natural Friedel-Crafts reactions in living systems have been unraveled, and it would be reasonable to assume that there may be many other examples of undiscovered natural Friedel-Crafts reactions. Discovery of the natural reactions would expand the field of enzymology in conjunction with bioengineering strategies such as directed evolution.[137] Many synthesis and functionalization methods of biomolecules described above are dependent on protecting group strategies which require additional synthetic efforts and cost, and unique reaction control approaches for unprotected biomolecules would be an important focus for future development. In addition to the aforementioned relevance to chemical evolution (Scheme 8A), Friedel-Crafts alkylation has been employed for study of autocatalysis in part relevant to self-replication processes in the early Earth.[138] As such, the alkylation and acylation reactions remain to be essential for diverse aspects of chemistry and biology research fields.

It is interesting that, despite the significant advance in biomolecular Friedel-Crafts reactions, there have not been any examples of bioorthogonal Friedel-Crafts reactions reported to date. Many classical reactions can be used to achieve bioorthogonal chemistry such as Diels-Alder reactions[5] and even imine/hydrazone/oxime formation in certain circumstances[7] (Scheme 1A. iii, iv, and viii). Challenges of such a bioorthogonal Friedel-Crafts reaction may be related to general incompatibility of traditional Friedel-Crafts reagents (i.e., acyl chloride and aluminum chloride), although generation of acyl chloride in cellular environments could be possible at a low concentration.[139] However, reagents that are frequently considered too reactive/unstable in aqueous solutions (e.g., Wittig[140] and diazo[141] reagents) have been successfully used in cellular applications too, which indicates potential feasibility of Friedel-Crafts reactions in cellular systems. Development of methods with unique media could potentially be an alternative approach, as discussed above (Scheme 8E).[133] Even if intact small molecule reagents would not be usable for cellular contexts, there are other unique chemical strategies such as genetically encodable amino acids and peptides as bioorthogonal tags[142] as well as encapsulation methods of reactive molecules in aqueous solutions.[143] Biomolecular Friedel-Crafts reactions have rapidly grown in multiple ways, and alongside technological and strategic advances of chemical methods in various fields, the full potentials of the alkylation and acylation chemistry in biological systems may not have been seen yet.

Conflicts of interest

The author declare no conflict of interest.

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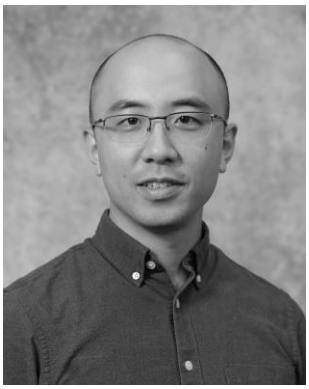

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References

(1) Lippert, A. R.; Van de Bittner, G. C.; Chang, C. J. Boronate Oxidation as a Bioorthogonal Reaction Approach for Studying the Chemistry of Hydrogen Peroxide in Living Systems. *Acc. Chem. Res.* **2011**, *44*, 793–804.
(2) Cadahía, J. P.; Previtali, V.; Troelsen, N. S.; Clausen, M. H. Prodrug Strategies for Targeted Therapy Triggered by Reactive Oxygen Species. *Med. Chem. Commun.* **2019**, *10*, 1531–1549.
(3) Lagoutte, R.; Patouret, R.; Winssinger, N. Covalent Inhibitors: An Opportunity for Rational Target Selectivity. *Curr. Opin. Chem. Biol.* **2017**, *39*, 54–63.
(4) Nakayasu, E. S.; Gritsenko, M.; Piehowski, P. D.; Gao, Y.; Orton, D. J.; Schepmoes, A. A.; Fillmore, T. L.; Frohnert, B. I.; Rewers, M.; Krischer, J. P.; Ansong, C.; Suchy-Dicey, A. M.; Evans-Molina, C.; Qian, W.-J.; Webb-Robertson, B.-J. M.; Metz, T. O. Tutorial: Best Practices and Considerations for Mass-Spectrometry-Based Protein Biomarker Discovery and Validation. *Nat Protoc* **2021**, *16*, 3737–3760.
(5) Oliveira, B. L.; Guo, Z.; Bernardes, G. J. L. Inverse Electron Demand Diels–Alder Reactions in Chemical Biology. *Chem. Soc. Rev.* **2017**, *46*, 4895–4950.
(6) Peplow, M. 'Clicked' Drugs: Researchers Prove the Remarkable Chemistry in Humans. *Nat. Biotechnol.* **2023**, *41*, 883–885.
(7) Kölmel, D. K.; Kool, E. T. Oximes and Hydrazones in Bioconjugation: Mechanism and Catalysis. *Chem. Rev.* **2017**, *117*, 10358–10376.
(8) Wahbeh, J.; Milkowski, S. The Use of Hydrazones for Biomedical Applications. *SLAS Technology* **2019**, *24*, 161–168.

(9) Pattabiraman, V. R.; Bode, J. W. Rethinking Amide Bond Synthesis. *Nature* **2011**, *480*, 471–479.
(10) Agouridas, V.; El Mahdi, O.; Diemer, V.; Cargoët, M.; Monbaliu, J.-C. M.; Melnyk, O. Native Chemical Ligation and Extended Methods: Mechanisms, Catalysis, Scope, and Limitations. *Chem. Rev.* **2019**, *119*, 7328–7443.
(11) Boike, L.; Henning, N. J.; Nomura, D. K. Advances in Covalent Drug Discovery. *Nat. Rev. Drug Discov.* **2022**, *21*, 881–898.
(12) Beck, A.; Goetsch, L.; Dumontet, C.; Corvaïa, N. Strategies and Challenges for the next Generation of Antibody–Drug Conjugates. *Nat Rev Drug Discov* **2017**, *16*, 315–337.
(13) Niphakis, M. J.; Cravatt, B. F. Enzyme Inhibitor Discovery by Activity-Based Protein Profiling. *Annu. Rev. Biochem.* **2014**, *83*, 341–377.
(14) Bruemmer, K. J.; Crossley, S. W. M.; Chang, C. J. Activity-Based Sensing: A Synthetic Methods Approach for Selective Molecular Imaging and Beyond. *Angew. Chem. Int. Ed.* **2020**, *59*, 13734–13762.
(15) Sutanto, F.; Konstantinidou, M.; Dömling, A. Covalent Inhibitors: A Rational Approach to Drug Discovery. *RSC Med. Chem.* **2020**, *11*, 876–884.
(16) Diamantis, N.; Banerji, U. Antibody-Drug Conjugates—an Emerging Class of Cancer Treatment. *Br. J. Cancer* **2016**, *114*, 362–367.
(17) Sletten, E. M.; Bertozzi, C. R. Bioorthogonal Chemistry: Fishing for Selectivity in a Sea of Functionality. *Angew. Chem. Int. Ed.* **2009**, *48*, 6974–6998.
(18) Sletten, E. M.; Bertozzi, C. R. From Mechanism to Mouse: A Tale of Two Bioorthogonal Reactions. *Acc. Chem. Res.* **2011**, *44*, 666–676.
(19) Ashdown, A. A. Earliest History of the Friedel-Crafts Reaction. *Ind. Eng. Chem.* **1927**, *19*, 1063–1065.
(20) Stadler, A.-M.; Harrowfield, J. Places and Chemistry: Strasbourg—a Chemical Crucible Seen through Historical Personalities. *Chem. Soc. Rev.* **2011**, *40*, 2061–2108.
(21) Marsi, K. L.; Wilen, S. H. Friedel-Crafts Alkylation. *J. Chem. Educ.* **1963**, *40*, 214.
(22) Reeve, A. M. A Discovery-Based Friedel-Crafts Acylation Experiment: Student-Designed Experimental Procedure. *J. Chem. Educ.* **2004**, *81*, 1497.
(23) Dintzner, M. R.; Maresh, J. J.; Kinzie, C. R.; Arena, A. F.; Speltz, T. A Research-Based Undergraduate Organic Laboratory Project: Investigation of a One-Pot, Multicomponent, Environmentally Friendly Prins–Friedel–Crafts-Type Reaction. *J. Chem. Educ.* **2012**, *89*, 265–267.
(24) Elford, D.; Lancaster, S. J.; Jones, G. A. Augmented Reality and Worked Examples: Targeting Organic Chemistry Competence. *Computers & Education: X Reality* **2023**, *2*, 100021.
(25) Macquarrie, D. J. Industrial Friedel–Crafts Chemistry. In *Catalytic Asymmetric Friedel–Crafts Alkylations*; John Wiley & Sons, Ltd, 2009; pp 271–288.
(26) Groggins, P. H.; Detwiler, S. B. Friedel-Crafts Reactions. *Ind. Eng. Chem.* **1952**, *44*, 2012–2015.
(27) Luk, L. Y. P.; Qian, Q.; Tanner, M. E. A Cope Rearrangement in the Reaction Catalyzed by Dimethylallyltryptophan Synthase? *J. Am. Chem. Soc.* **2011**, *133*, 12342–12345.
(28) Li, Z.; Xu, B.; Alsup, T. A.; Wei, X.; Ning, W.; Icenhour, D. G.; Ehrenberger, M. A.; Ghiviriga, I.; Giang, B.-D.; Rudolf, J. D. Cryptic Isomerization in Diterpene Biosynthesis and the Restoration of an Evolutionarily Defunct P450. *J. Am. Chem. Soc.* **2023**, *145*, 22361–22365.
(29) Ohata, J.; Bruemmer, K. J.; Chang, C. J. Activity-Based Sensing Methods for Monitoring the Reactive Carbon Species Carbon Monoxide and Formaldehyde in Living Systems. *Acc. Chem. Res.* **2019**, *52*, 2841–2848.
(30) Devaraj, N. K. The Future of Bioorthogonal Chemistry. *ACS Cent. Sci.* **2018**, *4*, 952–959.
(31) Poulsen, T. B.; Jørgensen, K. A. Catalytic Asymmetric Friedel-Crafts Alkylation Reactions--Copper Showed the Way. *Chem Rev* **2008**, *108*, 2903–2915.
(32) Groves, J. K. The Friedel–Crafts Acylation of Alkenes. *Chem. Soc. Rev.* **1972**, *1*, 73–97.
(33) Rueping, M.; Nachtsheim, B. J. A Review of New Developments in the Friedel–Crafts Alkylation – From Green Chemistry to Asymmetric Catalysis. *Beilstein J. Org. Chem.* **2010**, *6*, 6.
(34) Motiwala, H. F.; Vekariya, R. H.; Aubé, J. Intramolecular Friedel–Crafts Acylation Reaction Promoted by 1,1,1,3,3,3-Hexafluoro-2-Propanol. *Org. Lett.* **2015**, *17*, 5484–5487.
(35) You, S.-L.; Cai, Q.; Zeng, M. Chiral Brønsted Acid Catalyzed Friedel–Crafts Alkylation Reactions. *Chem. Soc. Rev.* **2009**, *38*, 2190–2201.
(36) Heravi, M. M.; Zadsirjan, V.; Heydari, M.; Masoumi, B. Organocatalyzed Asymmetric Friedel-Crafts Reactions: An Update. *Chem. Rec.* **2019**, *19*, 2236–2340.
(37) Heravi, M. M.; Zadsirjan, V.; Saedi, P.; Momeni, T. Applications of Friedel–Crafts Reactions in Total Synthesis of Natural Products. *RSC Adv.* **2018**, *8*, 40061–40163.
(38) Evano, G.; Theunissen, C. Beyond Friedel and Crafts: Directed Alkylation of C−H Bonds in Arenes. *Angew. Chem. Int. Ed.* **2019**, *58*, 7202–7236.
(39) Igbokwe, I. O.; Igwenagu, E.; Igbokwe, N. A. Aluminium Toxicosis: A Review of Toxic Actions and Effects. *Interdiscip. Toxicol.* **2019**, *12*, 45–70.
(40) Danielsson, R.; Eriksson, H. Aluminium Adjuvants in Vaccines – A Way to Modulate the Immune Response. *Semin. Cell Dev. Biol.* **2021**, *115*, 3–9.
(41) Winkler, C. K.; Schrittwieser, J. H.; Kroutil, W. Power of Biocatalysis for Organic Synthesis. *ACS Cent. Sci.* **2021**, *7*, 55–71.
(42) Sheldon, R. A.; Brady, D.; Bode, M. L. The Hitchhiker's Guide to Biocatalysis: Recent Advances in the Use of Enzymes in Organic Synthesis. *Chem. Sci.* **2020**, *11*, 2587–2605.
(43) Byrne, M. J.; Lees, N. R.; Han, L.-C.; van der Kamp, M. W.; Mulholland, A. J.; Stach, J. E. M.; Willis, C. L.; Race, P. R. The Catalytic Mechanism of a Natural Diels–Alderase Revealed in Molecular Detail. *J. Am. Chem. Soc.* **2016**, *138*, 6095–6098.
(44) Coelho, P. S.; Brustad, E. M.; Kannan, A.; Arnold, F. H. Olefin Cyclopropanation via Carbene Transfer Catalyzed by Engineered Cytochrome P450 Enzymes. *Science* **2013**, *339*, 307–310.
(45) Du, Q.; Wang, Z.; Schramm, V. L. Human DNMT1 Transition State Structure. *Proc. Natl. Acad. Sci. U.S.A.* **2016**, *113*, 2916–2921.
(46) Boersma, A. J.; Megens, R. P.; Feringa, B. L.; Roelfes, G. DNA-Based Asymmetric Catalysis. *Chem. Soc. Rev.* **2010**, *39*, 2083–2092.
(47) DeRose, V. J. Two Decades of RNA Catalysis. *Chem Biol* **2002**, *9*, 961–969.
(48) Liu, X.; Xiao, Y.; Zhang, Z.; You, Z.; Li, J.; Ma, D.; Li, B. Recent Progress in Metal-Organic Frameworks@Cellulose Hybrids and Their Applications. *Chin. J. Chem.* **2021**, *39*, 3462–3480.
(49) Leveson-Gower, R. B.; Roelfes, G. Biocatalytic Friedel-Crafts Reactions. *ChemCatChem* **2022**, *14*, e202200636.
(50) Kumar, V.; Turnbull, W. B.; Kumar, A. Review on Recent Developments in Biocatalysts for Friedel–Crafts Reactions. *ACS Catal.* **2022**, *12*, 10742–10763.
(51) Keenan, E. K.; Zachman, D. K.; Hirschey, M. D. Discovering the Landscape of Protein Modifications. *Mol. Cell* **2021**, *81*, 1868–1878.
(52) Crine, S. L.; Acharya, K. R. Molecular Basis of C-Mannosylation - a Structural Perspective. *FEBS J.* **2022**, *289*, 7670–7687.
(53) Minakata, S.; Manabe, S.; Inai, Y.; Ikezaki, M.; Nishitsuji, K.; Ito, Y.; Ihara, Y. Protein C-Mannosylation and C-Mannosyl

Tryptophan in Chemical Biology and Medicine. *Molecules* **2021**, *26*, 5258.
(54) Bloch, J. S.; John, A.; Mao, R.; Mukherjee, S.; Boilevin, J.; Irobalieva, R. N.; Darbre, T.; Scott, N. E.; Reymond, J.-L.; Kossiakoff, A. A.; Goddard-Borger, E. D.; Locher, K. P. Structure, Sequon Recognition and Mechanism of Tryptophan C-Mannosyltransferase. *Nat. Chem. Biol.* **2023**, *19*, 575–584.
(55) Chlipala, G. E.; Sturdy, M.; Krunic, A.; Lantvit, D. D.; Shen, Q.; Porter, K.; Swanson, S. M.; Orjala, J. Cylindrocyclophanes with Proteasome Inhibitory Activity from the Cyanobacterium Nostoc Sp. *J. Nat. Prod.* **2010**, *73*, 1529–1537.
(56) Nakamura, H.; Schultz, E. E.; Balskus, E. P. A New Strategy for Aromatic Ring Alkylation in Cylindrocyclophane Biosynthesis. *Nat. Chem. Biol.* **2017**, *13*, 916–921.
(57) Braffman, N. R.; Ruskoski, T. B.; Davis, K. M.; Glasser, N. R.; Johnson, C.; Okafor, C. D.; Boal, A. K.; Balskus, E. P. Structural Basis for an Unprecedented Enzymatic Alkylation in Cylindrocyclophane Biosynthesis. *eLife* **2022**, *11*, e75761.
(58) Hayashi, A.; Saitou, H.; Mori, T.; Matano, I.; Sugisaki, Hi.; Maruyama, K. Molecular and Catalytic Properties of Monoacetylphloroglucinol Acetyltransferase from Pseudomonas Sp. YGJ3. *Biosci. Biotechnol. Biochem.* **2012**, *76*, 559.
(59) Sheng, X.; Kazemi, M.; Żądło-Dobrowolska, A.; Kroutil, W.; Himo, F. Mechanism of Biocatalytic Friedel–Crafts Acylation by Acyltransferase from Pseudomonas Protegens. *ACS Catal.* **2020**, *10*, 570–577.
(60) Yang, F.; Cao, Y. Biosynthesis of Phloroglucinol Compounds in Microorganisms--Review. *Appl. Microbiol. Biotechnol.* **2012**, *93*, 487–495.
(61) Xia, Y.; Zhu, G.; Zhang, X.; Li, S.; Du, L.; Zhu, W. Biosynthesis of 4-Acyl-5-Aminoimidazole Alkaloids Featuring a New Friedel–Crafts Acyltransferase. *J. Am. Chem. Soc.* **2023**, *145*, 26308–26317.
(62) Jia, S.; He, D.; Chang, C. J. Bioinspired Thiophosphorodichloridate Reagents for Chemoselective Histidine Bioconjugation. *J. Am. Chem. Soc.* **2019**, *141*, 7294–7301.
(63) Peciak, K.; Laurine, E.; Tommasi, R.; Choi, J.; Brocchini, S. Site-Selective Protein Conjugation at Histidine. *Chem. Sci.* **2019**, *10*, 427–439.
(64) He, B.-B.; Bu, X.-L.; Zhou, T.; Li, S.-M.; Xu, M.-J.; Xu, J. Combinatory Biosynthesis of Prenylated 4-Hydroxybenzoate Derivatives by Overexpression of the Substrate-Promiscuous Prenyltransferase XimB in Engineered E. Coli. *ACS Synth. Biol.* **2018**, *7*, 2094–2104.
(65) Lund, S.; Hall, R.; Williams, G. J. An Artificial Pathway for Isoprenoid Biosynthesis Decoupled from Native Hemiterpene Metabolism. *ACS Synth. Biol.* **2019**, *8*, 232–238.
(66) Schmidt, N. G.; Pavkov-Keller, T.; Richter, N.; Wiltschi, B.; Gruber, K.; Kroutil, W. Biocatalytic Friedel–Crafts Acylation and Fries Reaction. *Angew. Chem. Int. Ed*. **2017**, *56*, 7615–7619.
(67) Chordia, S.; Narasimhan, S.; Lucini Paioni, A.; Baldus, M.; Roelfes, G. In Vivo Assembly of Artificial Metalloenzymes and Application in Whole-Cell Biocatalysis**. *Angew. Chem. Int. Ed.* **2021**, *60*, 5913–5920.
(68) Zheng, L.; Marcozzi, A.; Gerasimov, J. Y.; Herrmann, A. Conformationally Constrained Cyclic Peptides: Powerful Scaffolds for Asymmetric Catalysis. *Angew. Chem. Int. Ed.* **2014**, *53*, 7599–7603.
(69) Metrano, A. J.; Chinn, A. J.; Shugrue, C. R.; Stone, E. A.; Kim, B.; Miller, S. J. Asymmetric Catalysis Mediated by Synthetic Peptides, Version 2.0: Expansion of Scope and Mechanisms. *Chem. Rev.* **2020**, *120*, 11479–11615.
(70) Paras, N. A.; MacMillan, D. W. C. New Strategies in Organic Catalysis: The First Enantioselective Organocatalytic Friedel–Crafts Alkylation. *J. Am. Chem. Soc.* **2001**, *123*, 4370–4371.
(71) Evans, D. A.; Fandrick, K. R.; Song, H.-J.; Scheidt, K. A.; Xu, R. Enantioselective Friedel-Crafts Alkylations Catalyzed by Bis(Oxazolinyl)Pyridine-Scandium(III) Triflate Complexes. *J. Am. Chem. Soc.* **2007**, *129*, 10029–10041.
(72) Trost, B. M.; Müller, C. Asymmetric Friedel–Crafts Alkylation of Pyrroles with Nitroalkenes Using a Dinuclear Zinc Catalyst. *J. Am. Chem. Soc.* **2008**, *130*, 2438–2439.
(73) García-Fernández, A.; Megens, R. P.; Villarino, L.; Roelfes, G. DNA-Accelerated Copper Catalysis of Friedel-Crafts Conjugate Addition/Enantioselective Protonation Reactions in Water. *J. Am. Chem. Soc.* **2016**, *138*, 16308–16314.
(74) Boulias, K.; Greer, E. L. Means, Mechanisms and Consequences of Adenine Methylation in DNA. *Nat. Rev. Genet.* **2022**, *23*, 411–428.
(75) Sinclair, W. R.; Arango, D.; Shrimp, J. H.; Zengeya, T. T.; Thomas, J. M.; Montgomery, D. C.; Fox, S. D.; Andresson, T.; Oberdoerffer, S.; Meier, J. L. Profiling Cytidine Acetylation with Specific Affinity and Reactivity. *ACS Chem. Biol.* **2017**, *12*, 2922–2926.
(76) Preparation of guanine nucleoside by a Friedel-Crafts catalyst is reported (W. W. Lee, A. P. Martinez, and L. Goodman, J. Org. Chem. 1971, 36, 842) but this C-N bond forming reaction would not be considered a Friedel-Crafts alkylation reaction. .
(77) Girgis, N. S.; Michael, M. A.; Smee, D. F.; Alaghamandan, H. A.; Robins, R. K.; Cottam, H. B. Direct C-Glycosylation of Guanine Analogues: The Synthesis and Antiviral Activity of Certain 7- and 9-Deazaguanine C-Nucleosides. *J. Med. Chem.* **1990**, *33*, 2750–2755.
(78) Ghosh, S. Cisplatin: The First Metal Based Anticancer Drug. *Bioorg. Chem.* **2019**, *88*, 102925.
(79) Hainke, S.; Arndt, S.; Seitz, O. Concise Synthesis of Aryl-C-Nucleosides by Friedel–Crafts Alkylation. *Org. Biomol. Chem.* **2005**, *3*, 4233–4238.
(80) Shin, D.; Sinkeldam, R. W.; Tor, Y. Emissive RNA Alphabet. *J. Am. Chem. Soc.* **2011**, *133*, 14912–14915.
(81) Jun, Y. W.; Wilson, D. L.; Kietrys, A. M.; Lotsof, E. R.; Conlon, S. G.; David, S. S.; Kool, E. T. An Excimer Clamp for Measuring Damaged-Base Excision by the DNA Repair Enzyme NTH1. *Angew. Chem. Int. Ed.* **2020**, *59*, 7450–7455.
(82) Wu, C.; Wang, C.; Yan, L.; Yang, C. J. Pyrene Excimer Nucleic Acid Probes for Biomolecule Signaling. *J Biomed. Nanotechnol.* **2009**, *5*, 495–504.
(83) Li, Y.; Fin, A.; McCoy, L.; Tor, Y. Polymerase-Mediated Site-Specific Incorporation of a Synthetic Fluorescent Isomorphic G Surrogate into RNA. *Angew. Chem. Int. Ed.* **2017**, *56*, 1303–1307.
(84) Kuchlyan, J.; Martinez-Fernandez, L.; Mori, M.; Gavvala, K.; Ciaco, S.; Boudier, C.; Richert, L.; Didier, P.; Tor, Y.; Improta, R.; Mély, Y. What Makes Thienoguanosine an Outstanding Fluorescent DNA Probe? *J. Am. Chem. Soc.* **2020**, *142*, 16999–17014.
(85) Park, S.; Otomo, H.; Zheng, L.; Sugiyama, H. Highly Emissive Deoxyguanosine Analogue Capable of Direct Visualization of B–Z Transition. *Chem. Commun.* **2014**, *50*, 1573–1575.
(86) Yang, H.; Eremeeva, E.; Abramov, M.; Jacquemyn, M.; Groaz, E.; Daelemans, D.; Herdewijn, P. CRISPR-Cas9 Recognition of Enzymatically Synthesized Base-Modified Nucleic Acids. *Nucleic Acids Res.* **2023**, *51*, 1501–1511.
(87) Xu, W.; Chan, K. M.; Kool, E. T. Fluorescent Nucleobases as Tools for Studying DNA and RNA. *Nat. Chem.* **2017**, *9*, 1043–1055.
(88) Dashti, H.; Westler, W. M.; Wedell, J. R.; Demler, O. V.; Eghbalnia, H. R.; Markley, J. L.; Mora, S. Probabilistic Identification of Saccharide Moieties in Biomolecules and Their Protein Complexes. *Sci. Data* **2020**, *7*, 210.
(89) Mettu, R.; Chen, C.-Y.; Wu, C.-Y. Synthetic Carbohydrate-Based Vaccines: Challenges and Opportunities. *J. Biomed. Sci.* **2020**, *27*, 9.

(90) Abe, N.; Nakakita, Y.; Nakamura, T.; Enoki, N.; Uchida, H.; Munekata, M. Novel Antitumor Antibiotics, Saptomycins. I. Taxonomy of the Producing Organism, Fermentation, HPLC Analysis and Biological Activities. *J. Antibiot. (Tokyo)* **1993**, *46*, 1530–1535.
(91) Kitamura, K.; Maezawa, Y.; Ando, Y.; Kusumi, T.; Matsumoto, T.; Suzuki, K. Synthesis of the Pluramycins 2: Total Synthesis and Structure Assignment of Saptomycin B. *Angew. Chem. Int. Ed.* **2014**, *53*, 1262–1265.
(92) Furuta, T.; Nakayama, M.; Suzuki, H.; Tajimi, H.; Inai, M.; Nukaya, H.; Wakimoto, T.; Kan, T. Concise Synthesis of Chafurosides A and B. *Org. Lett.* **2009**, *11*, 2233–2236.
(93) Hasegawa, T.; Shimada, S.; Ishida, H.; Nakashima, M. Chafuroside B, an Oolong Tea Polyphenol, Ameliorates UVB-Induced DNA Damage and Generation of Photo-Immunosuppression Related Mediators in Human Keratinocytes. *PLOS ONE* **2013**, *8*, e77308.
(94) Plante, O. J.; Palmacci, E. R.; Andrade, R. B.; Seeberger, P. H. Oligosaccharide Synthesis with Glycosyl Phosphate and Dithiophosphate Triesters as Glycosylating Agents. *J. Am. Chem. Soc.* **2001**, *123*, 9545–9554.
(95) Korb, M.; Lang, H. The Anionic Fries Rearrangement: A Convenient Route to Ortho-Functionalized Aromatics. *Chem. Soc. Rev.* **2019**, *48*, 2829–2882.
(96) Dewar, M. J. S.; Hart, L. S. Aromatic Rearrangements in the Benzene Series—I: The Fries Rearrangement of Phenyl Benzoate: The Benzoylation of Phenol. *Tetrahedron* **1970**, *26*, 973–1000.
(97) Gibson, J. L.; Hart, L. S. Aromatic Rearrangements in the Benzene Series. Part 6. The Fries Rearrangement of Phenyl Benzoate: The Role of Tetrabromoaluminate Ion as an Aluminium Bromide Transfer Agent. *J. Chem. Soc., Perkin Trans. 2* **1991**, No. 9, 1343–1348.
(98) Liu, H.; Lang, M.; Hazelard, D.; Compain, P. A Fries-Type Rearrangement Strategy for the Construction of Stereodefined Quaternary Pseudoanomeric Centers: An Entry into C-Naphthyl Ketosides. *J. Org. Chem.* **2023**, *88*, 13847–13856.
(99) Liu, M.; Li, B.-H.; Li, T.; Wu, X.; Liu, M.; Xiong, D.-C.; Ye, X.-S. C-Glycosylation Enabled by N-(Glycosyloxy)Acetamides. *Org. Biomol. Chem.* **2020**, *18*, 3043–3046.
(100) Palmacci, E. R.; Seeberger, P. H. Synthesis of C-Aryl and C-Alkyl Glycosides Using Glycosyl Phosphates. *Org. Lett.* **2001**, *3*, 1547–1550.
(101) Park, D. S.; Joseph, K. E.; Koehle, M.; Krumm, C.; Ren, L.; Damen, J. N.; Shete, M. H.; Lee, H. S.; Zuo, X.; Lee, B.; Fan, W.; Vlachos, D. G.; Lobo, R. F.; Tsapatsis, M.; Dauenhauer, P. J. Tunable Oleo-Furan Surfactants by Acylation of Renewable Furans. *ACS Cent. Sci.* **2016**, *2*, 820–824.
(102) Naik, A. V.; Joseph, K. E.; Shetty, M.; Ardagh, M. A.; Dauenhauer, P. J. Kinetics of 2-Methylfuran Acylation with Fatty Acid Anhydrides for Biorenewable Surfactants. *ACS Sustainable Chem. Eng.* **2020**, *8*, 18616–18625.
(103) Metzger, J. O.; Biermann, U. Lewis Acid Induced Additions to Unsaturated Fatty Compounds IV: Synthesis of Cyclopentenones from Friedel- Crafts Acylation Products of Unsaturated Fatty Compounds with α,β-Unsaturated Acyl Chlorides. *Lipid / Fett* **1998**, *100*, 2–6.
(104) Xiang, B.; Xu, T.-F.; Wu, L.; Liu, R.-R.; Gao, J.-R.; Jia, Y.-X. Lewis Acid Catalyzed Friedel-Crafts Alkylation of Alkenes with Trifluoropyruvates. *J. Org. Chem.* **2016**, *81*, 3929–3935.
(105) Tanaka, S.; Kunisawa, T.; Yoshii, Y.; Hattori, T. Acylation of Alkenes with the Aid of AlCl3 and 2,6-Dibromopyridine. *Org. Lett.* **2019**, *21*, 8509–8513.
(106) Ishii, A.; Kojima, J.; Mikami, K. Asymmetric Catalytic Friedel–Crafts Reaction of Silyl Enol Ethers with Fluoral: A Possible Mechanism of the Mukaiyama-Aldol Reactions. *Org. Lett.* **1999**, *1*, 2013–2016.
(107) Snider, B. B.; Jackson, A. C. Use of Ethylaluminum Dichloride as a Catalyst for the Friedel-Crafts Acylation of Alkenes. *J. Org. Chem.* **1982**, *47*, 5393–5395.
(108) Sumita, A.; Ohwada, T. Friedel-Crafts-Type Acylation and Amidation Reactions in Strong Brønsted Acid: Taming Superelectrophiles. *Molecules* **2022**, *27*, 5984.
(109) Lehn, J.-M. Perspectives in Chemistry—Steps towards Complex Matter. *Angew. Chem. Int. Ed.* **2013**, *52*, 2836–2850.
(110) Eschenmoser, A. The Search for the Chemistry of Life's Origin. *Tetrahedron* **2007**, *63*, 12821–12844.
(111) Barge, L. M.; Price, R. E. Diverse Geochemical Conditions for Prebiotic Chemistry in Shallow-Sea Alkaline Hydrothermal Vents. *Nat. Geosci.* **2022**, *15*, 976–981.
(112) Sandford, S. A.; Nuevo, M.; Bera, P. P.; Lee, T. J. Prebiotic Astrochemistry and the Formation of Molecules of Astrobiological Interest in Interstellar Clouds and Protostellar Disks. *Chem. Rev.* **2020**, *120*, 4616–4659.
(113) Blackman, D. K.; Ildefonse, B.; John, B. E.; Ohara, Y.; Miller, D. J.; Abe, N.; Abratis, M.; Andal, E. S.; Andreani, M.; Awaji, S.; Beard, J. S.; Brunelli, D.; Charney, A. B.; Christie, D. M.; Collins, J.; Delacour, A. G.; Delius, H.; Drouin, M.; Einaudi, F.; Escartín, J.; Frost, B. R.; Früh-Green, G.; Fryer, P. B.; Gee, J. S.; Godard, M.; Grimes, C. B.; Halfpenny, A.; Hansen, H.-E.; Harris, A. C.; Tamura, A.; Hayman, N. W.; Hellebrand, E.; Hirose, T.; Hirth, J. G.; Ishimaru, S.; Johnson, K. T. M.; Karner, G. D.; Linek, M.; MacLeod, C. J.; Maeda, J.; Mason, O. U.; McCaig, A. M.; Michibayashi, K.; Morris, A.; Nakagawa, T.; Nozaka, T.; Rosner, M.; Searle, R. C.; Suhr, G.; Tominaga, M.; von der Handt, A.; Yamasaki, T.; Zhao, X. Drilling Constraints on Lithospheric Accretion and Evolution at Atlantis Massif, Mid-Atlantic Ridge 30°N. *J. Geophys. Res. Solid Earth* **2011**, *116*, B07103.
(114) Ménez, B.; Pisapia, C.; Andreani, M.; Jamme, F.; Vanbellingen, Q. P.; Brunelle, A.; Richard, L.; Dumas, P.; Réfrégiers, M. Abiotic Synthesis of Amino Acids in the Recesses of the Oceanic Lithosphere. *Nature* **2018**, *564*, 59–63.
(115) Camprubi, E.; Jordan, S. F.; Vasiliadou, R.; Lane, N. Iron Catalysis at the Origin of Life. *IUBMB Life* **2017**, *69*, 373–381.
(116) Sato, A.; Soeno, K.; Kikuchi, R.; Narukawa-Nara, M.; Yamazaki, C.; Kakei, Y.; Nakamura, A.; Shimada, Y. Indole-3-Pyruvic Acid Regulates TAA1 Activity, Which Plays a Key Role in Coordinating the Two Steps of Auxin Biosynthesis. *Proc. Natl. Acad. Sci. U.S.A.* **2022**, *119*, e2203633119.
(117) Kirschning, A. On the Evolutionary History of the Twenty Encoded Amino Acids. *Chem. Eur. J.* **2022**, *28*, e202201419.
(118) Zárate-Zárate, D.; Aguilar, R.; Hernández-Benitez, R. I.; Labarrios, E. M.; Delgado, F.; Tamariz, J. Synthesis of α-Ketols by Functionalization of Captodative Alkenes and Divergent Preparation of Heterocycles and Natural Products. *Tetrahedron* **2015**, *71*, 6961–6978.
(119) Kondo, Y.; Ishitsuka, Y.; Kadowaki, D.; Kuroda, M.; Tanaka, Y.; Nagatome, M.; Irikura, M.; Hirata, S.; Sato, K.; Maruyama, T.; Hamasaki, N.; Irie, T. Phosphoenolpyruvic Acid, an Intermediary Metabolite of Glycolysis, as a Potential Cytoprotectant and Anti-Oxidant in HeLa Cells. *Biol Pharm Bull* **2012**, *35*, 606–611.
(120) Zimmermann, J.; Mayer, R. J.; Moran, J. A Single Phosphorylation Mechanism in Early Metabolism – the Case of Phosphoenolpyruvate. *Chem. Sci.* **2023**, *14*, 14100–14108.
(121) Lang, K.; Chin, J. W. Cellular Incorporation of Unnatural Amino Acids and Bioorthogonal Labeling of Proteins. *Chem. Rev.* **2014**, *114*, 4764–4806.
(122) Dormán, G.; Nakamura, H.; Pulsipher, A.; Prestwich, G. D. The Life of Pi Star: Exploring the Exciting and Forbidden Worlds of the Benzophenone Photophore. *Chem. Rev.* **2016**, *116*, 15284–15398.
(123) Nguyen, T.-A.; Cigler, M.; Lang, K. Expanding the Genetic Code to Study Protein–Protein Interactions. *Angew. Chem. Int. Ed.* **2018**, *57*, 14350–14361.

(124) Murai, Y.; Wang, L.; Muto, Y.; Sakihama, Y.; Hashidoko, Y.; Hatanaka, Y.; Hashimoto, M. Simple and Stereocontrolled Preparation of Benzoylated Phenylalanine Using Friedel–Crafts Reaction in Trifluoromethanesulfonic Acid for Photoaffinity Labeling. *Heterocycles* **2013**, *87*, 2119–2126.
(125) Giuri, D.; Ravarino, P.; Tomasini, C. L-Dopa in Small Peptides: An Amazing Functionality to Form Supramolecular Materials. *Org. Biomol. Chem.* **2021**, *19*, 4622–4636.
(126) Li, Y.; Cheng, J.; Delparastan, P.; Wang, H.; Sigg, S. J.; DeFrates, K. G.; Cao, Y.; Messersmith, P. B. Molecular Design Principles of Lysine-DOPA Wet Adhesion. *Nat. Commun.* **2020**, *11*, 3895.
(127) Honisch, C.; Gazziero, M.; Dallocchio, R.; Dessì, A.; Fabbri, D.; Dettori, M. A.; Delogu, G.; Ruzza, P. Antamanide Analogs as Potential Inhibitors of Tyrosinase. *Int. J. Mol. Sci.* **2022**, *23*, 6240.
(128) Boger, D. L.; Yohannes, D. Selectively Protected L-Dopa Derivatives: Application of the Benzylic Hydroperoxide Rearrangement. *J. Org. Chem.* **1987**, *52*, 5283–5286.
(129) Chen; Zhu, Y.-F.; Wilcoxen, K. An Improved Synthesis of Selectively Protected L-Dopa Derivatives from l-Tyrosine. *J. Org. Chem.* **2000**, *65*, 2574–2576.
(130) Urruzuno, I.; Andrade-Sampedro, P.; Correa, A. Late-Stage C–H Acylation of Tyrosine-Containing Oligopeptides with Alcohols. *Org. Lett.* **2021**, *23*, 7279–7284.
(131) Brunen, S.; Mitschke, B.; Leutzsch, M.; List, B. Asymmetric Catalytic Friedel–Crafts Reactions of Unactivated Arenes. *J. Am. Chem. Soc.* **2023**, *145*, 15708–15713.
(132) Rajan, R.; Ahmed, S.; Sharma, N.; Kumar, N.; Debas, A.; Matsumura, K. Review of the Current State of Protein Aggregation Inhibition from a Materials Chemistry Perspective: Special Focus on Polymeric Materials. *Mater. Adv.* **2021**, *2*, 1139–1176.
(133) Nuruzzaman, M.; Colella, B. M.; Uzoewulu, C. P.; Meo, A. E.; Gross, E. J.; Ishizawa, S.; Sana, S.; Zhang, H.; Hoff, M. E.; Medlock, B. T. W.; Joyner, E. C.; Sato, S.; Ison, E. A.; Li, Z.; Ohata, J. Hexafluoroisopropanol as a Bioconjugation Medium of Ultrafast, Tryptophan-Selective Catalysis. *J. Am. Chem. Soc.* **2024**.
(134) Colomer, I.; Chamberlain, A. E. R.; Haughey, M. B.; Donohoe, T. J. Hexafluoroisopropanol as a Highly Versatile Solvent. *Nat. Rev. Chem.* **2017**, *1*, 1–12.
(135) Santangelo, P. J.; Rogers, K. A.; Zurla, C.; Blanchard, E. L.; Gumber, S.; Strait, K.; Connor-Stroud, F.; Schuster, D. M.; Amancha, P. K.; Hong, J. J.; Byrareddy, S. N.; Hoxie, J. A.; Vidakovic, B.; Ansari, A. A.; Hunter, E.; Villinger, F. Whole-Body immunoPET Reveals Active SIV Dynamics in Viremic and Antiretroviral Therapy–Treated Macaques. *Nat. Methods* **2015**, *12*, 427–432.
(136) Shen, B.-Q.; Xu, K.; Liu, L.; Raab, H.; Bhakta, S.; Kenrick, M.; Parsons-Reponte, K. L.; Tien, J.; Yu, S.-F.; Mai, E.; Li, D.; Tibbitts, J.; Baudys, J.; Saad, O. M.; Scales, S. J.; McDonald, P. J.; Hass, P. E.; Eigenbrot, C.; Nguyen, T.; Solis, W. A.; Fuji, R. N.; Flagella, K. M.; Patel, D.; Spencer, S. D.; Khawli, L. A.; Ebens, A.; Wong, W. L.; Vandlen, R.; Kaur, S.; Sliwkowski, M. X.; Scheller, R. H.; Polakis, P.; Junutula, J. R. Conjugation Site Modulates the *in Vivo* Stability and Therapeutic Activity of Antibody-Drug Conjugates. *Nat. Biotechnol.* **2012**, *30*, 184.
(137) Leveson-Gower, R. B.; Zhou, Z.; Drienovská, I.; Roelfes, G. Unlocking Iminium Catalysis in Artificial Enzymes to Create a Friedel–Crafts Alkylase. *ACS Catal.* **2021**, *11*, 6763–6770.
(138) Kamioka, S.; Ajami, D.; Rebek, J. Autocatalysis and Organocatalysis with Synthetic Structures. *Proc. Natl. Acad. Sci. U.S.A.* **2010**, *107*, 541–544.
(139) Pani, S.; Qiu, T.; Kentala, K.; Azizi, S.-A.; Dickinson, B. Biorthogonal Masked Acylating Agents for Proximity-Dependent RNA Labeling. *ChemRxiv* **2023**.
(140) Shi, Y.; Fu, L.; Yang, J.; Carroll, K. S. Wittig Reagents for Chemoselective Sulfenic Acid Ligation Enables Global Site Stoichiometry Analysis and Redox-Controlled Mitochondrial Targeting. *Nat. Chem.* **2021**, *13*, 1140–1150.
(141) Andersen, K. A.; Aronoff, M. R.; McGrath, N. A.; Raines, R. T. Diazo Groups Endure Metabolism and Enable Chemoselectivity in Cellulo. *J. Am. Chem. Soc.* **2015**, *137*, 2412–2415.
(142) Ohata, J.; Zeng, Y.; Segatori, L.; Ball, Z. T. A Naturally Encoded Dipeptide Handle for Bioorthogonal Chan–Lam Coupling. *Angew. Chem. Int. Ed.* **2018**, *57*, 4015–4019.
(143) La Manna, P.; Talotta, C.; Floresta, G.; De Rosa, M.; Soriente, A.; Rescifina, A.; Gaeta, C.; Neri, P. Mild Friedel–Crafts Reactions inside a Hexameric Resorcinarene Capsule: C–Cl Bond Activation through Hydrogen Bonding to Bridging Water Molecules. *Angew. Chem. Int. Ed.* **2018**, *57*, 5423–5428.