Electronic Supplementary Information

Friedel-Crafts Reactions for Biomolecular Chemistry

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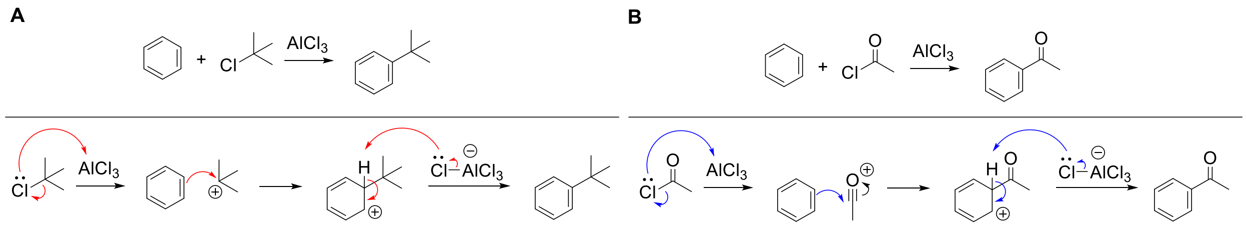
Contents

Traditional Friedel-Crafts reaction mechanisms

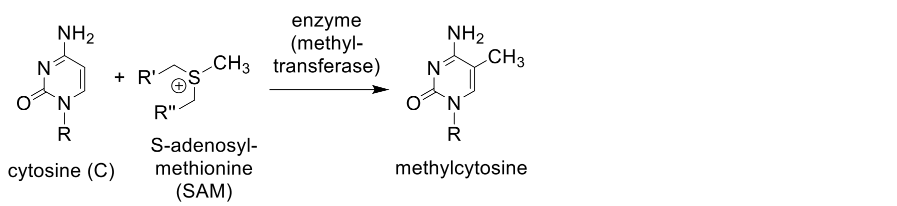


the mechanisms shown above are based on general Friedel-Crafts reactions
(e.g., Organic Chemistry, Marc Loudon and Jim Parise. Sixth edition).

Fig. S1. Reaction mechanisms of traditional Friedel-Crafts alkylation (A) and acylation (B) with aluminum chloride.

DNA methylation mechanism

Methylation of cytosine is considered to proceed through an enamine-like intermediate rather than typical electrophilic aromatic substitution. However, since Friedel-Crafts reactions of nonaromatic nucleophiles (e.g., alkene) are possible, perhaps this process can be considered Friedel-Crafts alkylation in a broader sense.



the mechanism shown below is based on a report: Schramm et al. *Proc. Nat. Acad. Sci.* 2016, **113**, 2916.

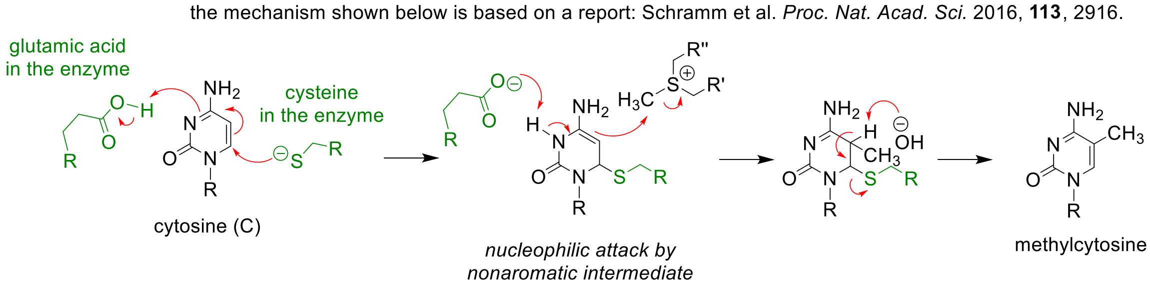
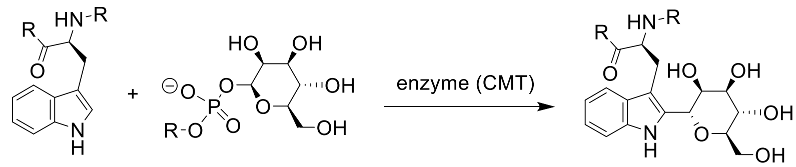


Fig. S2. A reaction mechanism of cytosine methylation shown in a previous report.[1]

Natural Friedel-Crafts reaction mechanisms



the mechanism shown below is based on a report: K. P. Locher et al. *Nat. Chem. Biol.* 2023, **19**, 575.

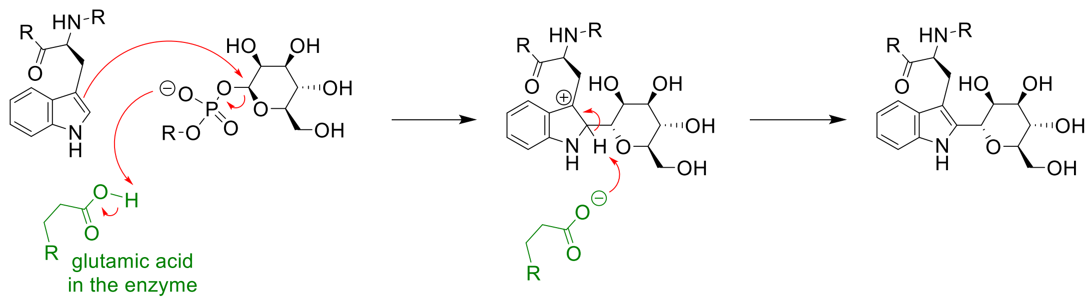
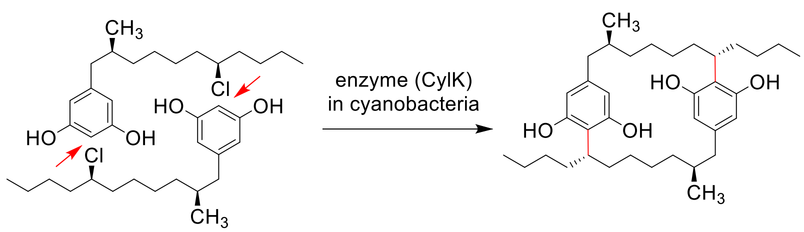


Fig. S3. A simplified reaction mechanism of enzymatic tryptophan mannosylation proposed in a previous report.[2] Full depiction of the enzyme actions during the reaction is shown in the previous report.



the mechanism shown below is based on a report: E. P. Balskus et al. *eLife.* 2022, **11**, e75761.

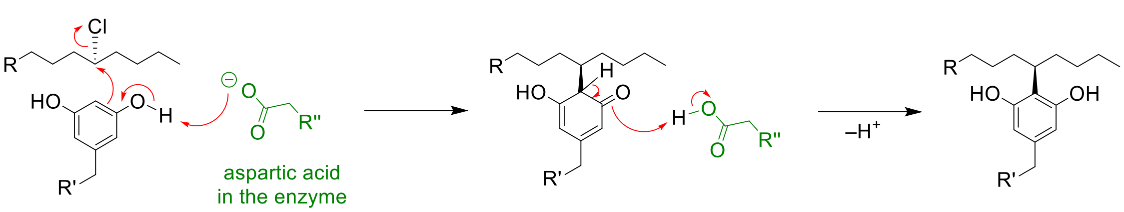


Fig. S4. A simplified reaction mechanism of enzymatic formation of cylindrocyclophane proposed in a previous report.[3] Full depiction of the enzyme actions during the reaction is shown in the previous report.

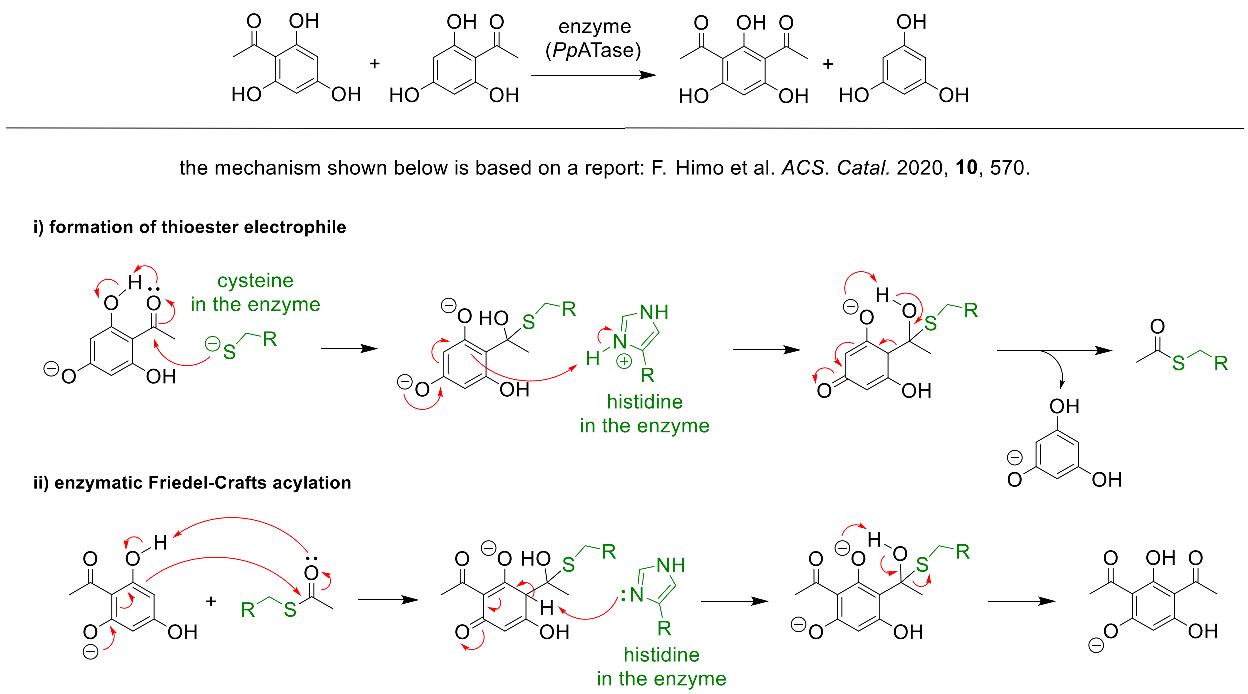


Fig. S5. A simplified reaction mechanism of enzymatic formation of 2.4-diacetylphloroglucinol proposed in a previous report.[4] Full depiction of the enzyme actions during the reaction is shown in the previous report.

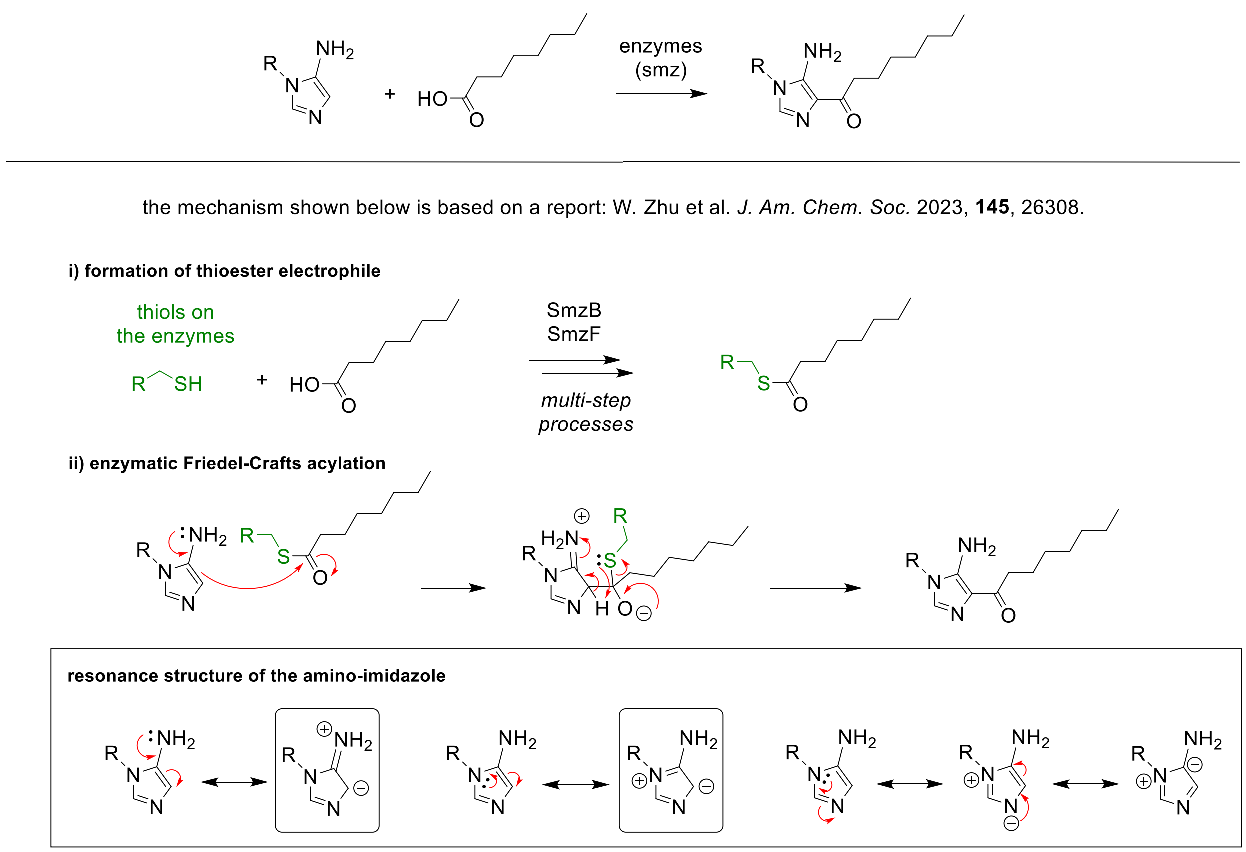
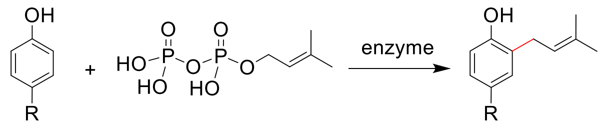


Fig. S6. A simplified reaction mechanism of enzymatic acylation of an imidazole derivative proposed in a previous report.[5] Full depiction of the enzyme actions during the reaction is shown in the previous report.

Biomolecule-mediated Friedel-Crafts reaction mechanisms for unnatural substrates



the mechanism shown below is based on general reaction mechanisms of aromatic prenyltransferases (e.g., Zhou et al. *PLOS Biol.* 2014, **12**, e1001911. and Vincken et al. *PLOS One.* 2017, **12**, e0174665.).

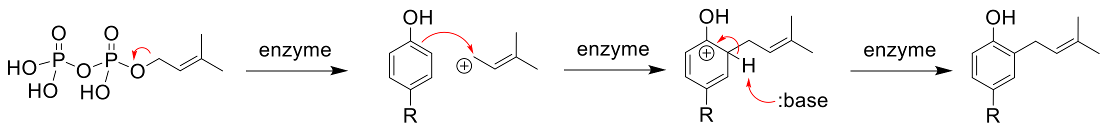
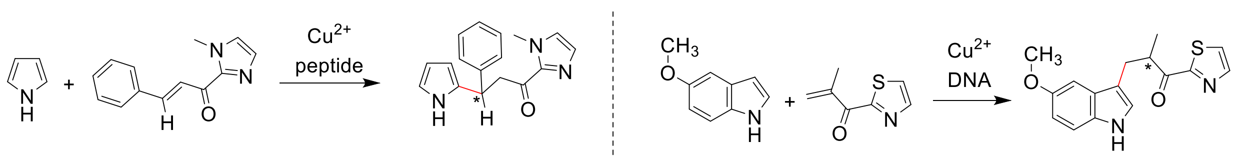


Fig. S7. A simplified reaction mechanism of prenyltransferase-mediated alkylation, based on relevant reports.[6,7] Full depiction of the enzyme actions during relevant reactions are shown in the previous reports.



the mechanism shown below is based on general reaction mechanisms of alkylation reaction through 1,4-addition (e.g., Trost et al. *J. Am. Chem. Soc.* 2008, **130**, 2438. and Pitchumani et al. *Tetrahedron Lett.* 2014, **55**, 2061.

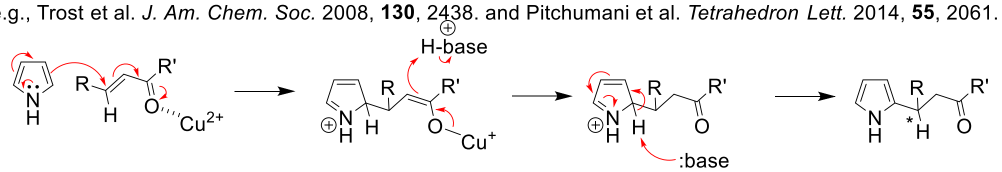
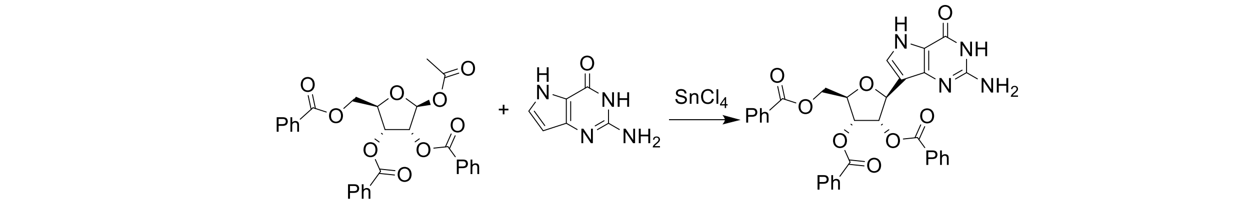


Fig. S8. A reaction mechanism of copper-mediated alkylation of α,β-unsaturated carbonyl groups, based on relevant reports.[8,9] Effects of biomolecule ligands are not considered for the shown mechanism.

Nucleoside synthesis mechanisms



the mechanism is based on reports of relevant reactions (e.g., Silyl-Hilbert-Johnson reaction): Vorbruggen et al. *Acc. Chem. Res.* 1995, **28**, 509. and Mao et al. *Molecules* 2017, **22**, 84.

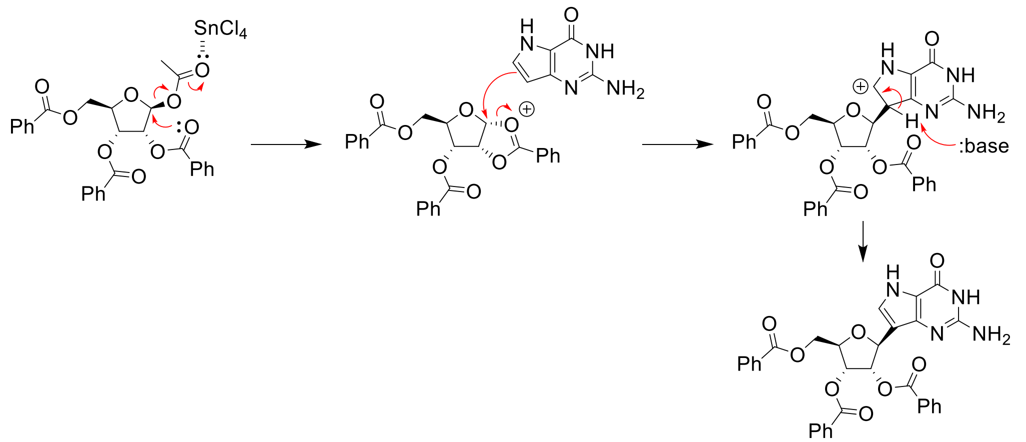
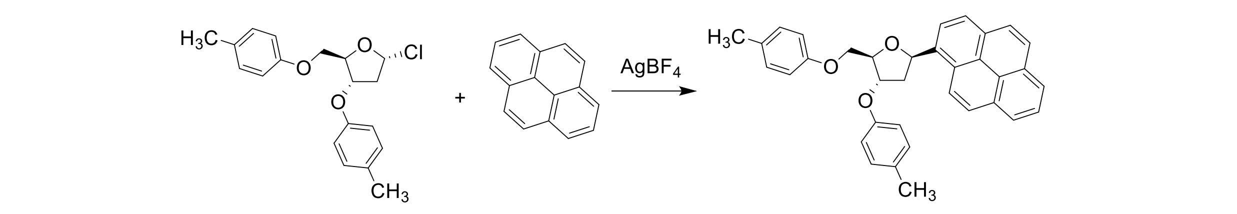


Fig. S9. A reaction mechanism of alkylation of a guanosine analogue, based on relevant reports.[10,11]



the mechanism is based on general reactions of glcosyl chloride such as Wang et al. *Chem. Eur. J.* 2013, **19**, 846.

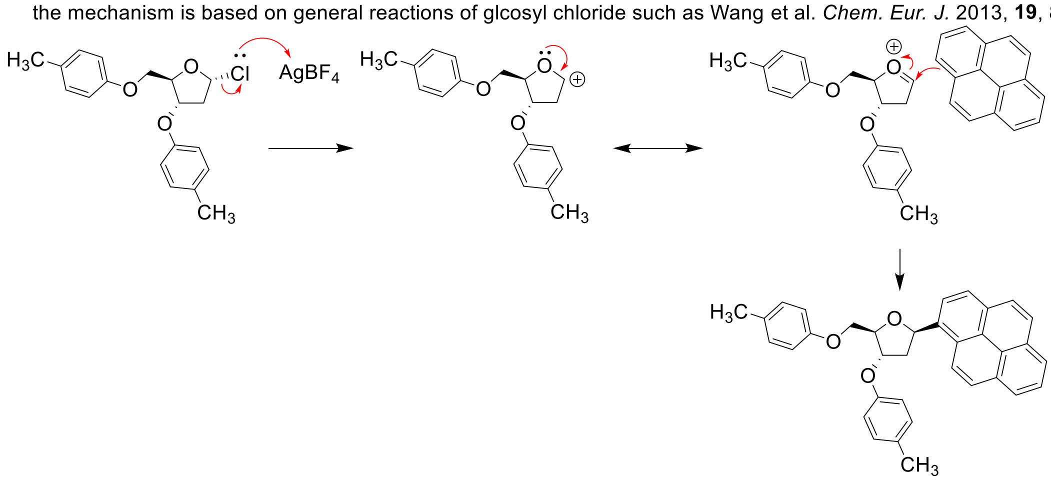
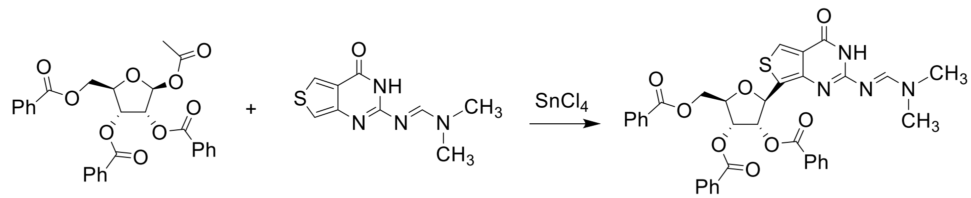


Fig. S10. A reaction mechanism of alkylation of pyrene with a deoxyribose derivative, based on a relevant report.[12]



the mechanism is based on reports of relevant reactions (e.g., Silyl-Hilbert-Johnson reaction): Vorbruggen et al. *Acc. Chem. Res.* 1995, **28**, 509. and Mao et al. *Molecules* 2017, **22**, 84.

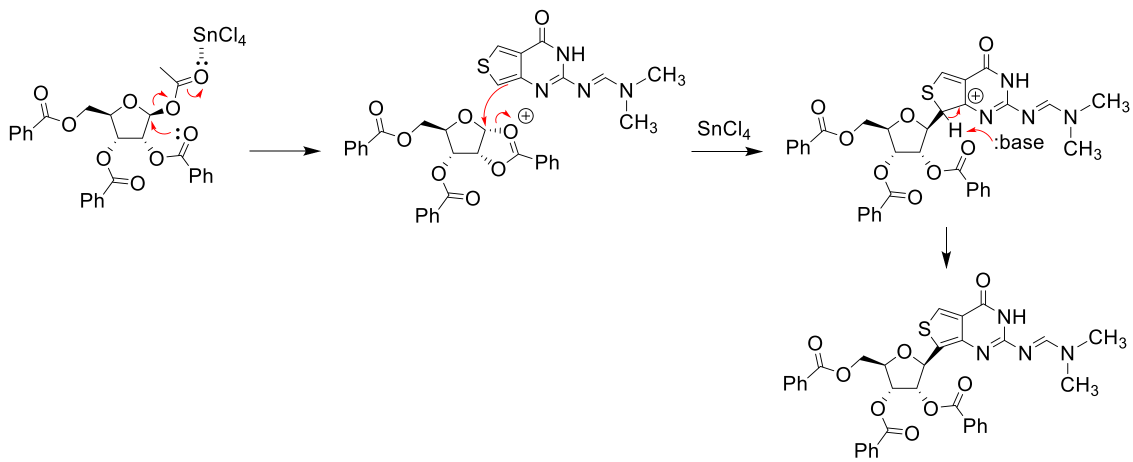
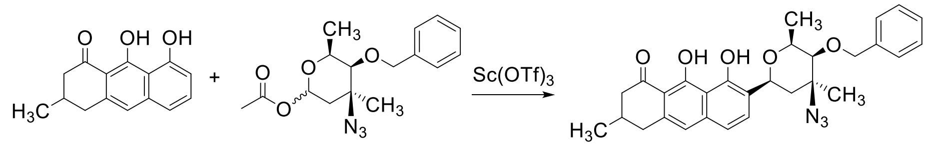


Fig. S11. A reaction mechanism of alkylation of thienoguanosine, based on relevant reports.[10,11]

Carbohydrate functionalization mechanisms



the mechanism is based on a general alkylation reaction with O-acyl leaving group (e.g., Vankar et al. *Carbohydr. Res.* 2005, **340**, 2688.)

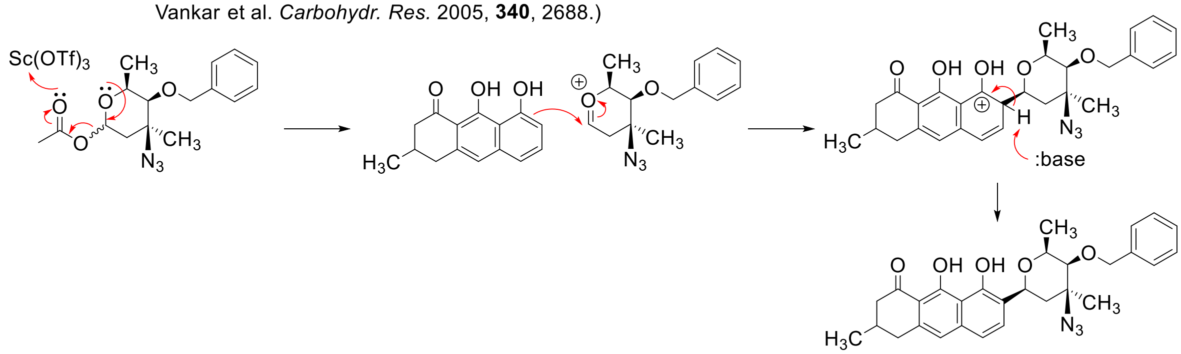
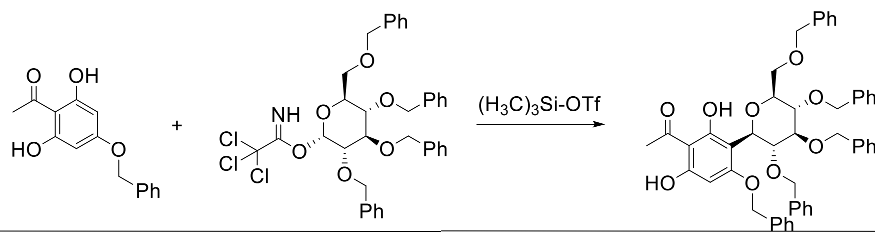


Fig. S12. A reaction mechanism of formation of an intermediate for saptomycin B total synthesis, based on a relevant report.[13]



the first part of the mechanism with silyl triflate is based on relevant reports (OTf addition could be a possible pathway as well): Kim et al. *J. Am. Chem. Soc.* 2009, **131**, 17705. and Pedersen et al. *Chem. Commun.* 2016, **52**, 11418.
The second part (Fries rearragnement) is proposed in a report: Kan et al. *Org. Lett.* 2009, **11**, 2233.

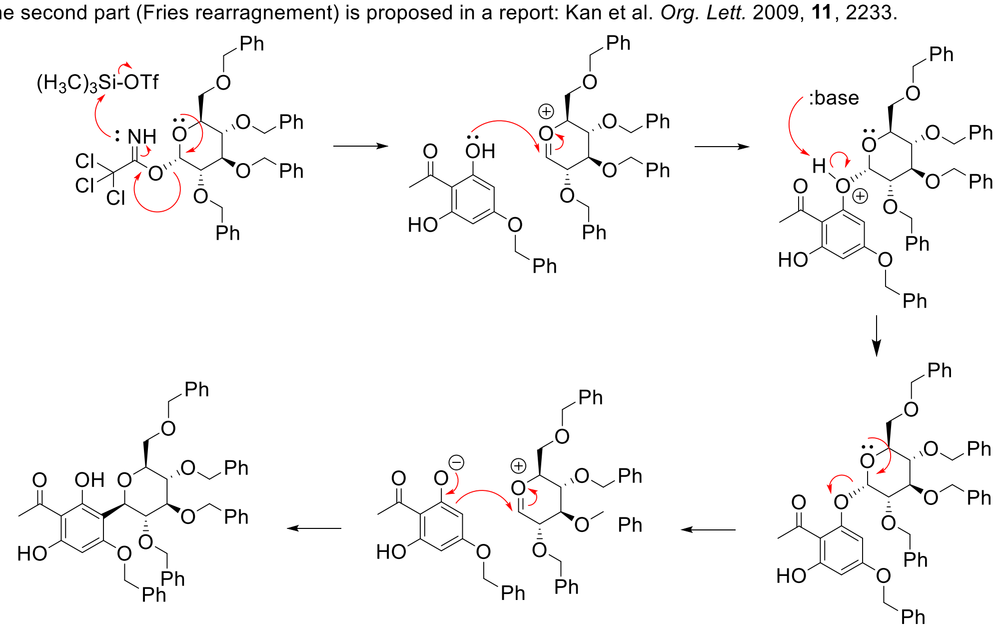
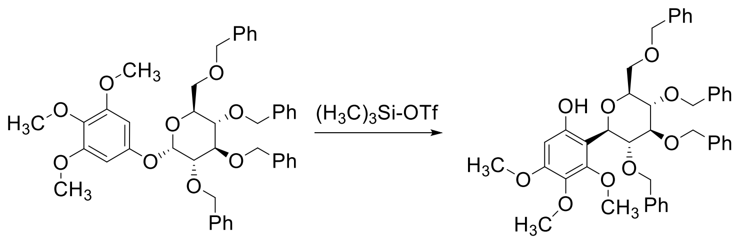


Fig. S13. A reaction mechanism of formation of an intermediate for chafuroside B total synthesis, based on relevant reports.[14–16]



the mechanism is based on a general Fries-type rearrangement (e.g.,
Compain and Hazelard et al. *J. Org. Chem.* 2023, **88**, 13847. and Lang et al. *Chem. Soc. Rev.* 2019, **48**, 2829.)

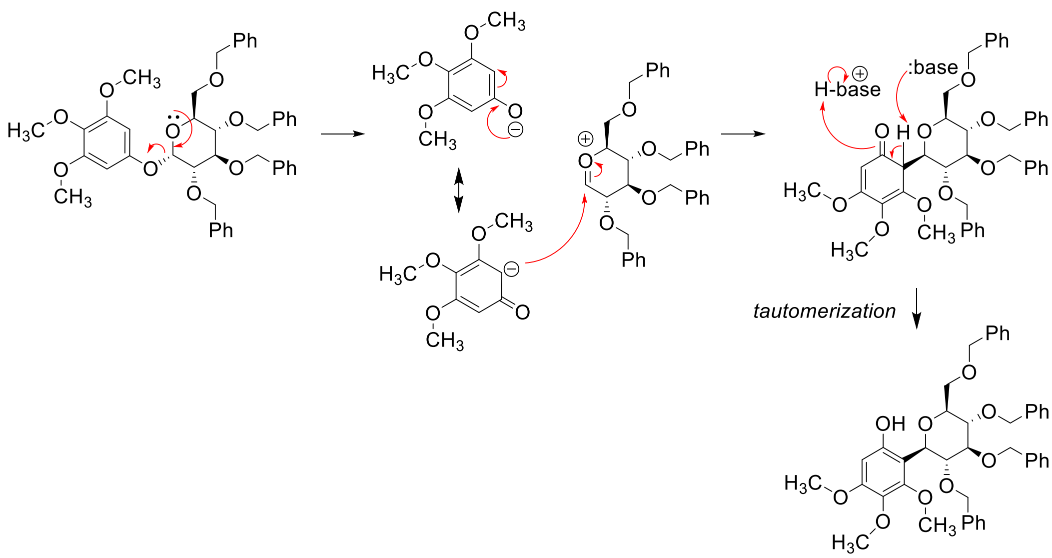


Fig. S14. A reaction mechanism of Fries-type rearrangement, based on relevant reports.[17,18]

Fatty acid functionalization mechanisms

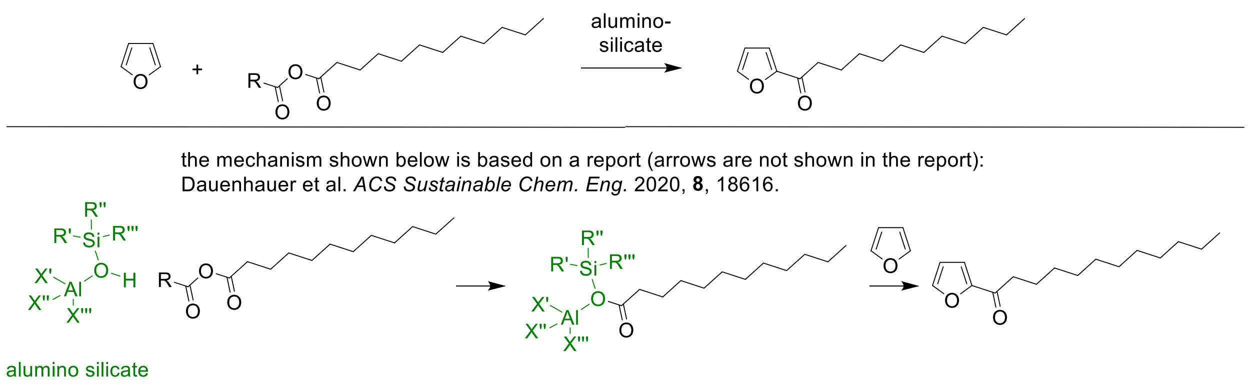


Fig. S15. A reaction mechanism of acylation of furan reported in previous literature.[19]

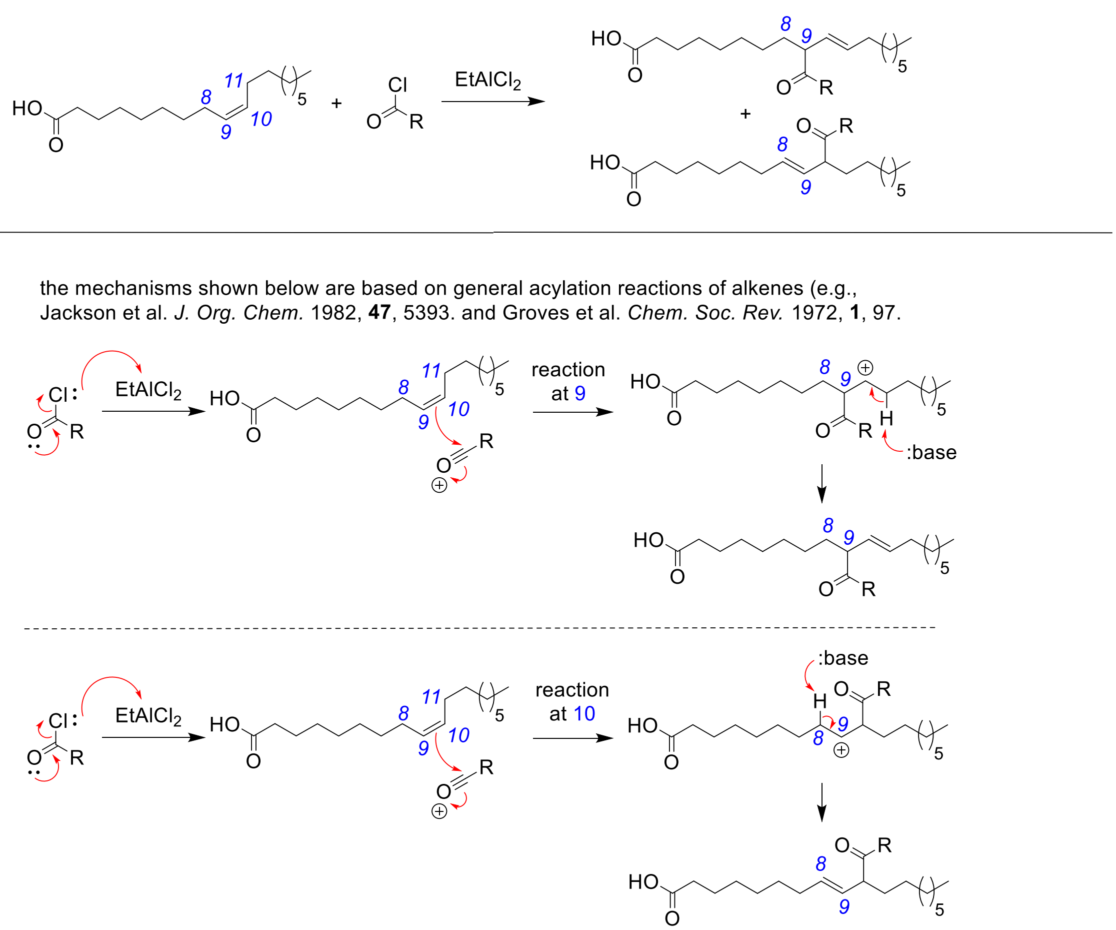
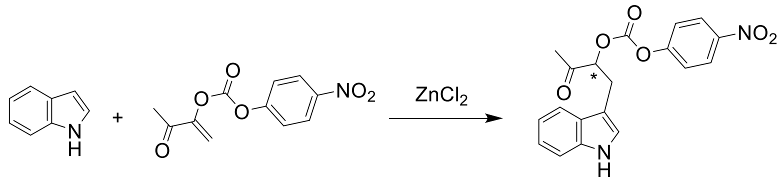


Fig. S16. A reaction mechanism of acylation of an unsaturated fatty acid as a nucleophile, based on relevant reports.[20,21]

Amino acid/polypeptide synthesis and functionalization mechanisms



the mechanism shown below is based on general reaction mechanisms of alkylation reaction through 1,4-addition
(e.g., Trost et al. *J. Am. Chem. Soc.* 2008, **130**, 2438. and Pitchumani et al. *Tetrahedron Lett.* 2014, **55**, 2061.)

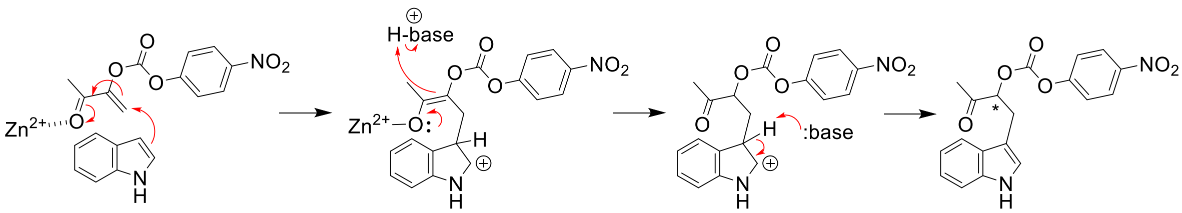
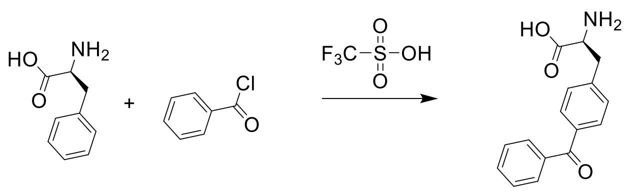


Fig. S17. A reaction mechanism of zinc-mediated alkylation of α,β-unsaturated carbonyl groups, based on relevant reports.[8,9]



the mechanism shown below is based on general acylation mechanisms
(e.g., Organic Chemistry, Marc Loudon and Jim Parise. Sixth edition).
Protonated amines are shown since the reported reaction is under triflic acid (Hashimoto et al. *Heterocycles* 2013, **87**, 2119.)

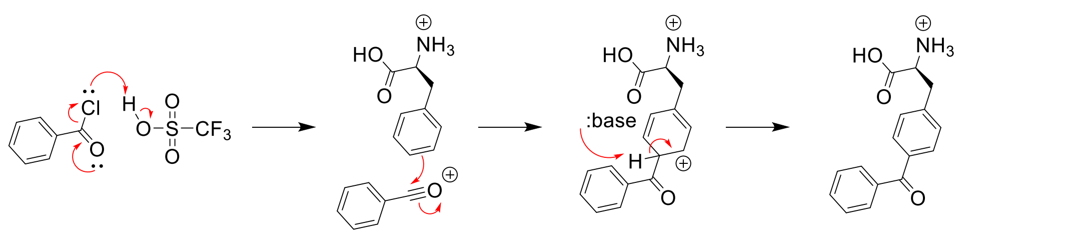
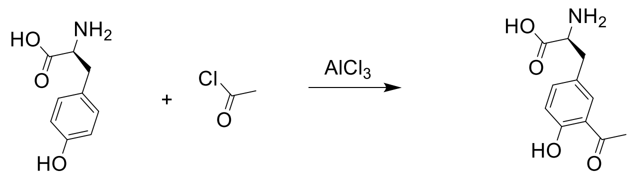


Fig. S18. A reaction mechanism of acylation of phenylalanine acid, based on general Friedel-Crafts acylation reactions.[22]



the mechanism shown below is based on general acylation mechanisms
(e.g., Organic Chemistry, Marc Loudon and Jim Parise. Sixth edition).

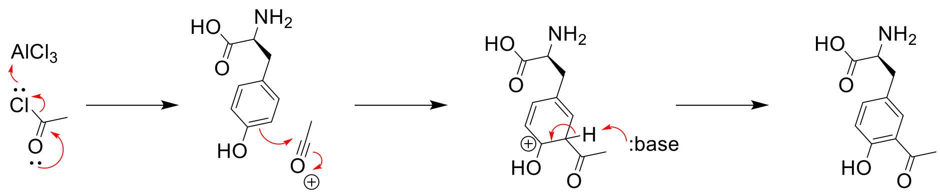


Fig. S19. A reaction mechanism of acylation of tyrosine amino acid, based on general Friedel-Crafts acylation reactions.

the mechanism shown below is based on a report
(Ohata et al. *J. Am. Chem. Soc.* 2024, DOI: 10.1021/jacs.3c13447.)

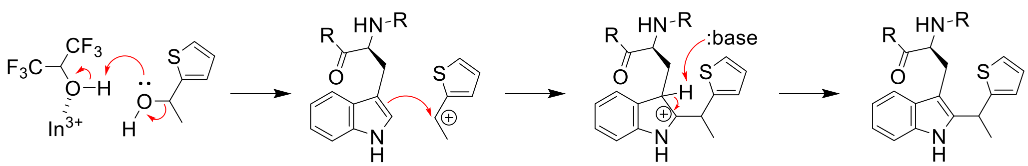


Fig. S20. A reaction mechanism of tryptophan alkylation on proteins reported in previous literature.[23]

References for Electronic Supplementary Information

(1) Du, Q.; Wang, Z.; Schramm, V. L. Human DNMT1 Transition State Structure. *Proc. Natl. Acad. Sci. U.S.A.* **2016**, *113* (11), 2916–2921. https://doi.org/10.1073/pnas.1522491113.

(2) 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* (5), 575–584. https://doi.org/10.1038/s41589-022-01219-9.

(3) 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. https://doi.org/10.7554/eLife.75761.

(4) 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* (1), 570–577. https://doi.org/10.1021/acscatal.9b04208.

(5) 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* (48), 26308–26317. https://doi.org/10.1021/jacs.3c09522.

(6) Huang, H.; Levin, E. J.; Liu, S.; Bai, Y.; Lockless, S. W.; Zhou, M. Structure of a Membrane-Embedded Prenyltransferase Homologous to UBIAD1. *PLOS Biology* **2014**, *12* (7), e1001911. https://doi.org/10.1371/journal.pbio.1001911.

(7) Araya-Cloutier, C.; Martens, B.; Schaftenaar, G.; Leipoldt, F.; Gruppen, H.; Vincken, J.-P. Structural Basis for Non-Genuine Phenolic Acceptor Substrate Specificity of Streptomyces Roseochromogenes Prenyltransferase CloQ from the ABBA/PT-Barrel Superfamily. *PLOS ONE* **2017**, *12* (3), e0174665. https://doi.org/10.1371/journal.pone.0174665.

(8) Trost, B. M.; Müller, C. Asymmetric Friedel−Crafts Alkylation of Pyrroles with Nitroalkenes Using a Dinuclear Zinc Catalyst. *J. Am. Chem. Soc.* **2008**, *130* (8), 2438–2439. https://doi.org/10.1021/ja711080y.

(9) Jeganathan, M.; Kanagaraj, K.; Dhakshinamoorthy, A.; Pitchumani, K. Michael Addition of Indoles to β-Nitrostyrenes Catalyzed by HY Zeolite under Solvent-Free Conditions. *Tetrahedron Letters* **2014**, *55* (13), 2061–2064. https://doi.org/10.1016/j.tetlet.2014.01.112.

(10) Vorbrueggen, H. Adventures in Silicon-Organic Chemistry. *Acc. Chem. Res.* **1995**, *28* (12), 509–520. https://doi.org/10.1021/ar00060a007.

(11) Liang, C.; Ju, W.; Ding, S.; Sun, H.; Mao, G. Effective Synthesis of Nucleosides Utilizing O-Acetyl-Glycosyl Chlorides as Glycosyl Donors in the Absence of Catalyst: Mechanism Revision and Application to Silyl-Hilbert-Johnson Reaction. *Molecules* **2017**, *22* (1), 84. https://doi.org/10.3390/molecules22010084.

(12) Verma, V. P.; Wang, C.-C. Highly Stereoselective Glycosyl-Chloride-Mediated Synthesis of 2-Deoxyglucosides. *Chemistry – A European Journal* **2013**, *19* (3), 846–851. https://doi.org/10.1002/chem.201203418.

(13) Jayakanthan, K.; Vankar, Y. D. Glycosyl Trichloroacetylcarbamate: A New Glycosyl Donor for O-Glycosylation. *Carbohydrate Research* **2005**, *340* (17), 2688–2692. https://doi.org/10.1016/j.carres.2005.07.024.

(14) Baek, J. Y.; Lee, B.-Y.; Jo, M. G.; Kim, K. S. β-Directing Effect of Electron-Withdrawing Groups at O-3, O-4, and O-6 Positions and α-Directing Effect by Remote Participation of 3-O-Acyl and 6-O-Acetyl Groups of Donors in Mannopyranosylations. *J. Am. Chem. Soc.* **2010**, *132* (20), 7229–7229. https://doi.org/10.1021/ja103131s.

(15) Qiao, Y.; Ge, W.; Jia, L.; Hou, X.; Wang, Y.; Pedersen, C. M. Glycosylation Intermediates Studied Using Low Temperature 1H- and 19F-DOSY NMR: New Insight into the Activation of

Trichloroacetimidates. *Chem. Commun.* **2016**, *52* (76), 11418–11421. https://doi.org/10.1039/C6CC05272J.
(16) 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* (11), 2233–2236. https://doi.org/10.1021/ol900689m.
(17) 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* (19), 13847–13856. https://doi.org/10.1021/acs.joc.3c01474.
(18) Korb, M.; Lang, H. The Anionic Fries Rearrangement: A Convenient Route to Ortho-Functionalized Aromatics. *Chem. Soc. Rev.* **2019**, *48* (10), 2829–2882. https://doi.org/10.1039/C8CS00830B.
(19) 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* (50), 18616–18625. https://doi.org/10.1021/acssuschemeng.0c06847.
(20) 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* (27), 5393–5395. https://doi.org/10.1021/jo00148a032.
(21) Groves, J. K. The Friedel–Crafts Acylation of Alkenes. *Chem. Soc. Rev.* **1972**, *1* (1), 73–97. https://doi.org/10.1039/CS9720100073.
(22) 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. https://doi.org/10.3987/COM-13-12815.
(23) 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**. https://doi.org/10.1021/jacs.3c13447.