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Dialkyl ether synthesis through heteroatom homolytic substitution

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The modular and selective synthesis of dialkyl ethers, particularly sterically congested variants, remains a longstanding challenge in drug discovery and medicinal chemistry.^{1,2} Hindered alkyl ethers are especially desirable given their prevalence in bioactive natural products and favorable physicochemical properties.³ Classically, dialkyl ether synthesis relies on nucleophilic substitution strategies; however, S_N2 reactions are fundamentally limited by steric congestion at the transition state, while S_N1 pathways proceed through promiscuous carbocation intermediates prone to elimination, rearrangement, and loss of stereogenic information.⁴⁻⁶ Herein, we report a radical-based paradigm for general dialkyl ether synthesis enabled by an underutilized heteroatom homolytic substitution (het-S_H2) mechanism. This mechanistic paradigm overcomes the intrinsic limitations of classical polar substitution chemistry by leveraging carbon-centered radicals generated under mild conditions that are insensitive to steric congestion in the bond-forming transition state. Utilizing a titanium-based catalytic platform in combination with visible-light photoredox catalysis, we demonstrate the efficient coupling of carboxylic acid-derived redox-active esters with alcohols across a broad range of substitution patterns, including 3°–2°, 3°–1°, 2°–2°, and 2°–1° architectures. This strategy grants access to dialkyl ether chemical space largely inaccessible through conventional approaches, including sterically demanding BCP ether bioisosteres, and enables late-stage diversification of complex pharmaceutical scaffolds. This platform is expected to serve as a broadly applicable blueprint for radical-mediated heteroatom bond formation.

Dialkyl ethers are ubiquitous structural motifs in natural products and serve as key building blocks in medicinal chemistry owing to their favorable physicochemical properties.³ Despite their apparent simplicity, the general and modular synthesis of dialkyl ethers remains a longstanding challenge, particularly for sterically congested architectures.^{1,2} Classical substitution-based strategies suffer from fundamental limitations: bimolecular nucleophilic substitution (S_N2) reactions are highly sensitive to steric congestion during the transition state,⁴⁻⁶ while unimolecular pathways (S_N1) proceed through high-energy carbocation intermediates that are prone to rearrangement and elimination (Figure 1A). While recent advances have expanded access to hindered dialkyl ethers through carbocation-based strategies⁷ and methods proceeding via intermediates with carbocation-like character,^{8,9} substrates incompatible with such electrophilic intermediates, including strained, rearrangement-prone, and oxidatively sensitive intermediates, remain challenging to address generally.

Inner-sphere cross-coupling approaches have likewise struggled to provide general solutions to C(sp³)–O bond formation en route to dialkyl ethers. The weak nucleophilicity of alcohols, the strong basicity of intermediate metal alkoxides, and sluggish C(sp³)–O reductive elimination¹⁰⁻¹² collectively limit the efficiency of these processes (Figure 1B). Accordingly, a broadly applicable solution to dialkyl ether synthesis requires a fundamentally different

mechanistic paradigm, one that forges C(sp³)-O bonds with-out invoking high-energy carbocations or slow inner-sphere reductive elimination, and that exhibits minimal sensitivity to steric congestion.

In considering this challenge, we were inspired by nature's approach to C-O bond formation. Cytochrome P450 (CYP450) enzymes catalyze C-H oxidation through a radical pathway involving hydrogen-atom abstraction followed by outer-sphere radical rebound to generate hydroxylated products.^{13,14} Notably, this radical recombination step is mechanistically analogous to a heteroatom homolytic bimolecular substitution (het-S_{H2}) event (Figure 1C). This analogy suggested that a synthetically underexplored radical substitution paradigm could provide a general solution to the formation of substituted dialkyl ethers, circumventing the intrinsic limitations of classical ionic substitution chemistry.

A biomimetic heteroatom S_{H2} reaction between an alkyl radical and a metal alkoxide would satisfy our design criteria for di-alkyl ether formation. Such a mechanism bypasses high-energy carbocation intermediates and instead leverages carbon-centered radicals, which can be generated under mild conditions from a broad range of readily available feedstocks¹⁵ and are less susceptible to deleterious two-electron decomposition pathways¹⁶.

Moreover, the outer-sphere heteroatom S_{H2} manifold circumvents the sluggish inner-sphere reductive elimination that affects conventional cross-coupling and instead proceeds through a bond-forming transition state in which steric bulk is spatially distal from the site of C-O bond formation.

Central to the realization of this strategy is the identification of a metal that is both highly oxophilic—enabling efficient alcohol binding and metal alkoxide formation—and capable of serving as an effective radical leaving group in the key heteroatom S_{H2} step (Figure 1D). Herein, we introduce a titanium-based catalytic platform as a privileged system that enables the general synthesis of dialkyl ethers from alcohols and carboxylic acid-derived redox-active esters (RAE) via a heteroatom S_{H2} pathway. The generality and functional-group tolerance of this titanium-catalyzed process are demonstrated through the synthesis of dialkyl ethers spanning a wide range of substitution patterns, including 3°-2°, 3°-1°, 2°-2°, and 2°-1° couplings, across more than 80 examples (Figure 1E).

Reaction design

The construction of C(sp³)-O bonds beyond alcohols via radical intermediates represents a longstanding challenge in synthesis, as most radical C-O bond-forming platforms require a HAT-active metal complex in a high oxidation state to generate both the radical intermediate and the transferable oxygen fragment simultaneously — a mechanistic constraint that couples radical generation and oxygen-fragment delivery to the same oxidative event, precluding the modular use of simple alcohols and rendering ether synthesis via this manifold inaccessible.¹³ A more enabling approach would decouple these two functions: if an unactivated alcohol could ligate directly to a redox-active metal center, the resulting alkoxide complex could serve as the transferable leaving group upon interception by an exogenously generated radical via an S_{H2} mechanism. Mechanistically, this elementary step constitutes a heteroatom homolytic substitution (het-S_{H2}) at the alkoxide oxygen and falls within the broader framework of radical ligand transfer (RLT), in which a ligand is transferred from a metal center to a carbon-centered radical;¹⁷ we use the het-S_{H2} designation to specify the atom-level substitution mechanism that delivers the C-O bond. This concept is supported by work conducted in our¹⁸⁻²⁰ as well as other groups^{21,22} demonstrating that iron complexes operating through S_{H2} pathways can simultaneously be intercepted by carbon-centered radicals and act as radical leaving groups with high efficiency. Despite these efforts, extending this reactivity to the formation of C-heteroatom bonds in catalytic fashion has remained unrealized. Only a single stoichiometric iron complex has been shown to coordinate methanol and permit radical interception,²³ and no general catalytic platform for direct alcohol engagement in this fashion has been reported.²⁴

In seeking metals capable of both facile alkoxide formation and participation in single-electron processes, we identified titanium-based catalysts as promising candidates. Prior studies have shown that Cp₂Ti(III)Cl reductively opens epoxides to generate alkyl radicals alongside Ti(IV) alkoxide intermediates, demonstrating the ability of titanium species to efficiently form alkoxides while supporting radical chemistry.²⁵⁻²⁷ Although titanium catalysts have seen limited application in bimolecular cross-coupling as the organic radical generator,^{28,29} to the best of our knowledge no general cross-coupling platform has been reported engaging a titanium catalyst in the bond forming step. Isolated reports of titanium-mediated radical cyclizations leading to cyclic ethers suggested their potential relevance to heteroatom S_{H2} processes.³⁰ These precedents prompted us to evaluate whether benchstable titanocene dichloride could be employed in a photocatalytic, intermolecular heteroatom S_{H2} reaction.

Implementing this transformation posed several fundamental challenges. The key S_H2 step requires a persistent population of Ti(IV) alkoxide intermediates, which are known to undergo photodecomposition via ligand-to-metal charge transfer (LMCT) pathways. In addition, Ti(III) and Ti(IV) oxidation states are redox non-innocent, complicating control over catalytic speciation, while Ti(III) species exhibit strong coordination to Lewis-basic functionalities, often leading to unproductive substrate reduction and decomposition.³¹

Reaction Development and Mechanism

The titanium-catalyzed heteroatom S_H2 reaction is proposed to proceed through the mechanism outlined in Figure 2A. Upon visible light irradiation, the organic photocatalyst 2,4,5,6-tetrakis(diphenylamino)isophthalonitrile (4DPAIPN) (**1**) is excited to a long-lived excited state (**2**).³² Stern-Volmer studies (see Supplementary Information Fig S6.1 for additional details) reveal that this excited state is sufficiently oxidizing [$E_{1/2}^{\text{red}}(4\text{DPAIPN}^*/4\text{DPAIPN}^-) = +1.10$ V vs SCE in MeCN]³² to oxidize Ti(III) (**3**) [$E_{1/2}^{\text{red}}(\text{Ti}^{\text{IV}}/\text{Ti}^{\text{III}}) = -0.76$ V vs SCE in DCE] to Ti(IV) (**4**). This resulting Ti(IV) species subsequently binds to the alcohol (**5**) to form the corresponding Ti(IV) alkoxide (**6**). To close the photocatalytic cycle, the reduced-state 4DPAIPN radical anion (**7**) [$E_{1/2}^{\text{red}}(4\text{DPAIPN}^*/4\text{DPAIPN}^-) = -1.52$ V vs SCE in MeCN] reduces the redox-active ester (**8**) [$E_{1/2}^{\text{red}}(\text{RAE}/\text{RAE}^-) = -1.24$ V (for RAE-H) or -1.31 V (for RAE-OMe) vs SCE in DCE] to generate an alkyl radical (**9**) upon rapid decarboxylation.³³ This alkyl radical (**9**) then engages the Ti(IV) alkoxide (**6**) in a heteroatom S_H2 step, forging the C–O bond to deliver the dialkyl ether product (**10**) and regenerating Ti(III), thereby closing the titanium catalytic cycle.

Central to the proposed mechanism is the formation and persistence of a Ti(IV) alkoxide intermediate. Initial optimization studies under blue-light irradiation only generated the desired product in modest yields. Simultaneously, we observed that combining the Ti(IV) precatalyst with an alcohol in the presence of base resulted in the rapid development of a pale yellow–orange solution (see Supplementary Information), consistent with the formation of a titanium alkoxide species. We attribute this color change to a ligand-to-metal charge transfer (LMCT) band associated with a Ti(IV) alkoxide complex that absorbs in the blue region of the visible spectrum. While this study was in progress, independent work from the Lipshultz laboratory demonstrated that titanium alkoxide complexes are highly susceptible to light-induced LMCT followed by β -scission, a pathway that is deleterious under photoredox conditions.³⁴

UV–visible absorption spectra of the Ti(IV) alkoxide, compared with those of Cp₂TiCl₂ and the photocatalyst 4DPAIPN, revealed that although the alkoxide complex exhibits weak absorption in the blue region, it displays negligible absorption at 505 nm (Figure 2B). These data suggested that shifting the irradiation wavelength from blue (450 nm) to cyan (505 nm) would suppress undesired titanium-centered LMCT processes, thereby increasing the lifetime and steady-state concentration of the Ti(IV) alkoxide intermediate and favoring productive heteroatom S_H2 reactivity. Consistent with this hypothesis, cyan light irradiation (505 nm) increased the yield of the desired dialkyl ether (**10**) from 54% to 81%. Moreover, LMCT-driven decomposition was suppressed at this wavelength, as evidenced by the near-complete absence of β -scission byproducts (see Supplementary Information , Fig S5.2).

To probe the involvement of titanium in the bond-forming step, we examined its influence on product diastereoselectivity, as coordination to titanium is expected to introduce steric bias in the transition state and thereby impact the diastereomeric ratio (d.r.). Redox active ester (**11**) and secondary alcohol (**12**) were coupled under standard conditions (see Supplementary Information) (a) in the presence of titanium and zinc base, (b) in the absence of titanium with zinc base, (c) in the absence of titanium with sodium base, and (d) under reported electrochemical conditions⁷. Under standard conditions (a), **13** was obtained in 59% yield and 2.2:1 d.r. In the absence of titanium (b and c), the yield was significantly reduced (8–9%) and negligible diastereoselectivity was observed (1.1:1 d.r.), consistent with direct involvement of titanium in the bond-forming event. Moreover, the electrochemical reaction (d), which proceeds through a carbocationic intermediate, furnished **13** in 44% yield with essentially no diastereoselectivity (1.1:1 d.r.). (Figure 2C). Furthermore, the key Ti(IV) alkoxide intermediate was observed by photo-NMR (NMR spectroscopy performed while the sample is irradiated in situ within the spectrometer) under standard irradiation conditions. (Figure 2D, see Supplementary Information for details).

A stoichiometric experiment was performed to evaluate the involvement of a radical species in the key C–O bond-forming step. We conducted parallel experiments using either a preformed, isolated titanium alkoxide (**6**) or a titanium alkoxide formed in situ from alcohol (**5**). Upon addition of redox-active ester (**8**), TMSCl-activated zinc was introduced to establish strongly reducing conditions. Under these conditions, single-electron reduction of the redox-active ester is expected to generate an alkyl radical via rapid decarboxylation.³³ Importantly, the reducing environment precludes oxidation of the alkyl radical to a carbocation and disfavors formation of a carbanion,

thereby biasing the reaction toward radical reactivity. Consistent with our hypothesis, the desired dialkyl ether (**10**) was formed in 6% and 13% yield, respectively, under stoichiometric conditions (Figure 2E). Although modest, these yields provide evidence for direct engagement of an alkyl radical with a Ti(IV) alkoxide intermediate, consistent with C–O bond formation via a heteroatom S_H2 pathway and formation of titanium alkoxide under our reaction conditions. Additional discussion of this experiment and its mechanistic implications is provided in the Supplementary Information (Section S8).

To interrogate the feasibility of the proposed het-S_H2 step, we performed DFT calculations on a model system comprising a *tert*-butyl radical and titanocene(IV) ethoxide Cp₂Ti(Cl)(OEt) (Figure 2F). A single transition state was located ($\Delta G^\ddagger = 16.2$ kcal mol⁻¹) featuring a three-center C···O···Ti arrangement with no direct metal–carbon contact, suggesting that the reaction proceeds in a single concerted step, consistent with a homolytic substitution at oxygen. The substitution is exergonic ($\Delta G = -10.6$ kcal mol⁻¹), reflecting the exchange of the weaker Ti–O bond for the stronger C–O bond of the ether (see Supplementary Information for details).

Scope Evaluation

We first examined the scope of the titanium-catalyzed heteroatom S_H2 reaction using tertiary carboxylic acids and primary alcohols to access 3°–1° substituted dialkyl ethers (Figure 3). A broad range of primary alcohols (**10**, **15–27**) and tertiary acids (**28–42**) proved compatible, affording the desired ethers in good to high yields. Protic functionality was well tolerated on both coupling partners, including unprotected protic groups on both the alcohol substrate (**20**, **27**) and the carboxylic acid precursor (**32**). Despite the well-documented Lewis acidity of titanium complexes^{35,36}, a variety of Lewis-basic functionalities were accommodated, including carbamates (**10**, **15–22**) and medicinally relevant heterocycles such as pyridines (**23**, **36**), pyrimidines (**35**, **37**), and pyrazoles (**39**).³⁷ This functional-group tolerance is consistent with the low steady-state concentration of Ti(III) under the reaction conditions and the attenuated Lewis acidity of Ti(IV) following titanium alkoxide formation.

The reaction efficiently converted biomass-derived alcohols, including citronellol (**25**), D-galactopyranose (**26**), and serine (**27**), to the corresponding dialkyl ether scaffolds. Aryl bromides (**41**), which provide a reactive handle for subsequent derivatization, were likewise tolerated. Notably, strained cyclic radicals (**42**), for which carbocation-based pathways are inaccessible (see Supplementary Material for a comparison to established carbocation-based strategies), readily participated in the heteroatom S_H2 reaction, furnishing the corresponding ethers in good yields.

We next evaluated secondary alkyl radicals to access 2°–1° and 2°–2° ether motifs (Figure 4). Secondary radicals derived from both cyclic (**44–46**) and acyclic (**43**, **47**) substrates reacted efficiently to afford a range of 2°–1° ethers, including stable hemiaminals (**43**) and β -lactam-containing products bearing silyl-protected alcohols (**47**). Importantly, the method provides access to highly sought-after 2°–2° dialkyl ethers, which typically undergo sluggish S_N2 reactions. A wide range of diverse ring-size combinations were efficiently formed under the reaction conditions (**48–57**). In addition, stable acetal motifs (**56**, **57**), including an ether (**57**) derived from (+)-galacturonic acid, were obtained in good yield.

The coupling of tertiary carboxylic acids and secondary alcohols to form 3°–2° dialkyl ethers represents a significant challenge due to severe steric congestion around the oxygen center. Using our titanium-based catalytic platform, these motifs were accessed efficiently via heteroatom S_H2 reactivity. A broad range of secondary alcohols—including linear (**58**, **59**, **68**, **72**) and cyclic (**60–67**, **69–71**) substrates—proved compatible, enabling entry into chemical space largely inaccessible through classical substitution strategies. Notably, alcohols bearing α -stereogenic centers underwent coupling without racemization (**58–60**, **72**) to afford dialkyl ethers with preserved stereochemical integrity.

Cyclic secondary alcohols—including four- (**61–64**), five- (**65**, **66**), and six-membered (**67**, **69–71**) as well as spirocyclic systems—coupled efficiently with a variety of cyclic tertiary carboxylic acids to deliver the corresponding ethers in high yields. Both linear (**70**, **71**) and strained (**72**) tertiary radicals also participated efficiently. Notably, the functional-group tolerance of this approach is further underscored by compound (**70**), which bears a primary alkyl chloride typically susceptible to substitution under basic S_N2 conditions.

In substrates containing multiple alcohol functionalities, classical S_N1-based etherification would be expected to proceed with minimal site selectivity. In contrast, the titanium-catalyzed heteroatom S_H2 manifold exhibits pronounced diol site selectivity favoring etherification at the less substituted alcohol. This selectivity arises from preferential binding of the less substituted alcohol to titanium, combined with the sensitivity of the heteroatom S_H2 step to steric bulk. Together, these factors bias product formation toward the less substituted ether. Consistent with this rationale, diols bearing primary and tertiary alcohols afforded exclusively the ether derived from reaction at

the primary alcohol (**73**, **74**). When primary and secondary alcohols were present, modest but reproducible selectivity was observed in favor of the primary alcohol-derived ether (**75**) (1.8:1). Finally, diols comprising secondary and tertiary alcohols yielded exclusively the ether arising from functionalization at the secondary alcohol (**76**).

In line with our group's interest in developing bioisosteric replacements for prevalent motifs in drug discovery,^{38,39} we sought to apply the heteroatom S_H2 platform to the synthesis of bicyclo[1.1.1]propane (BCP)–substituted ethers. These sp³-rich phenol ether bioisosteres have garnered increasing attention in medicinal chemistry owing to their favorable physicochemical properties.⁴⁰ Although recent advances have expanded the synthetic accessibility of BCP derivatives,^{41,42} the installation of sterically demanding substituents remains challenging due to the lack of general, functional-group-tolerant strategies. In particular, direct etherification of BCP alcohols via S_N2 or cationic S_N1 pathways remains problematic, as these substrates are unstable under basic conditions, undergo rapid decomposition via the corresponding alkoxide and exhibit low nucleophilicity.⁴³ Under the mild conditions of our titanium-catalyzed heteroatom S_H2 protocol, we observed efficient formation of the desired BCP ethers when engaging tertiary alkyl radicals. This strategy enabled the synthesis of a diverse array of sterically hindered BCP ethers in good yields (**77–81**), highlighting the capacity of this platform to access sp³-rich bioisosteric ether architectures that are difficult to obtain using conventional approaches.

Given the mild reaction conditions and high functional-group tolerance of this protocol, we anticipated its utility for incorporating ether linkages into functionality-dense, drug-like scaffolds (Figure 5A). To evaluate its applicability in complex, late-stage settings, we examined the reaction across a range of heterocycle-rich building blocks and structurally complex pharmaceutical substrates. Owing to the intrinsic value and limited availability of these advanced intermediates, the more elaborate coupling partner—either the alcohol or the carboxylic acid—was employed as the limiting reagent. Pleasingly, efficient C(sp³)–O bond formation was observed across diverse molecular architectures, including cases in which the alcohol served as the limiting substrate. This enabled the synthesis of a broad array of complex ethers, encompassing sugars and sugar-like motifs (**82**, **83**) as well as scaffolds bearing Lewis-basic heterocycles such as pyrimidines (**84**, **87**, **89**), pyridines (**85**), pyrazoles (**86**), and triazoles (**88**). Notably, even highly elaborated drug derivatives proved compatible with the reaction conditions, allowing late-stage etherification of compounds such as alogliptin (**90**), losartan (**91**), empagliflozin (**92**), RU-58841 (**93**), febuxostat (**94**), and lumacaftor (**95**) (Figure 5B). Collectively, these results demonstrate the broad functional group tolerance of this protocol and its utility for late-stage diversification.

To further assess the breadth of this reaction platform, we benchmarked the evaluated substrates against the chemical space of commercially available alcohols (Figure 5C). We analyzed the Enamine alcohol library, comprising over 55,000 compounds,⁴⁴ using Morgan fingerprints (2048-bit) followed by dimensionality reduction to generate a representative chemical space map (see Supplementary Information for details).^{45,46} Projection of the experimentally tested alcohols onto this map revealed broad coverage across diverse regions of alcohol chemical space. Nevertheless, several underrepresented areas were identified, from which representative substrates were selected for further evaluation. To efficiently interrogate these regions, we implemented high-throughput experimentation (HTE) to accelerate data acquisition and enable matrix-style screening relevant to medicinal chemistry.⁴⁷ Of the eight previously unexplored alcohols selected from underrepresented regions, seven delivered the desired ether products in synthetically useful yields, with an imidazole-containing alcohol representing the sole exception. Evaluation of a 48-well matrix library further demonstrated broad compatibility, with 40 of 48 substrate combinations affording yields exceeding 30%, highlighting the suitability of this platform for rapid library synthesis and medicinal chemistry screening.

Outlook

The development of a general and modular strategy for dialkyl ether synthesis has remained a longstanding challenge in synthetic organic chemistry. Here, we introduce a titanium-catalyzed heteroatom S_H2 reaction that provides a general solution to this problem under mild and functional group-tolerant conditions. This transformation enables access to sterically demanding dialkyl ether architectures that are inaccessible or inefficient using classical substitution pathways. More broadly, this work establishes heteroatom S_H2 reactivity as a general mechanistic framework for controlled radical–heteroatom bond formation. We anticipate that this mechanistic paradigm will inform the development of new catalytic platforms for constructing other challenging heteroatom linkages and will further broaden the scope of radical substitution chemistry.

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371

372 Main Figure Legends

373 **Fig 1 | Reaction Design.** (A) Challenges with using traditional substitution reactions for dialkyl ether synthesis. (B) Metal catalyzed
374 approaches have been underdeveloped for generally forming dialkyl ethers. (C) Biomimetic heteroatom S_H2 inspired by CYP450 radical
375 rebound could forge hindered C–O bonds from radicals. (D) Titanium-based catalysts possess the required properties for het-S_H2 (E) General
376 access to dialkyl ethers enabled by titanium catalyzed het-S_H2.

377 **Fig 2 | Mechanistic Studies.** (a) Proposed mechanism. (b) Cyan light irradiation avoids deleterious ligand-to-metal charge transfer (LMCT)
378 processes of the crucial titanium alkoxide species. (c) Involvement of titanium in the bond formation effects the diastereomeric ratio of the
379 product and comparison to the carbocationic pathway. (d) PhotoNMR shows the formation and consumption of titanium alkoxide as the
380 reaction progresses. (e) Stoichiometric studies demonstrate the capability of radicals to undergo het-S_H2 with the titanium alkoxide to form
381 the corresponding dialkyl ethers. (f) DFT studies (B3LYP-D3/def2-TZVPP basis set) demonstrate the thermodynamic feasibility of the
382 radical ether formation as well as the transition state of the het-S_H2 step; NPhth: phthalimidyl, PC: photocatalyst, RAE: redox-active ester.

383 **Fig 3 | Tertiary-Primary Ether Scope.** All yields are isolated. See Supplementary Information for detailed experimental conditions. DCE:
384 dichloroethane; 4DPAIPN: 1,3-Dicyano-2,4,5,6-tetrakis(diphenylamino)-benzene, NPhth(OMe): 4-methoxyphthalimidyl, PC:
385 photocatalyst.

386 **Fig 4 | Modular construction of dialkyl ethers with varying substitution.** All yields are isolated. Reactions were performed using
387 4DPAIPN (5 or 10 mol%), Cp₂TiCl₂ (10 or 20 mol%), Zn₃(PO₄)₂ (0.75 equiv.) or [ZnCO₃]₂·[Zn(OH)₂]₃ (0.5 equiv.), redox-active ester
388 (RAE-H or RAE-OMe; 1.0 or 3.0 equiv.), alcohol (1–3 equiv.) in dichloroethane (DCE, 0.2 or 0.1 M) under cyan light irradiation. See
389 Supplementary Information for detailed experimental conditions; TBDMS: *tert*-butyldimethylsilyl.

390 **Fig 5 | Complex scope and HTE.** All yields are isolated. See Supplementary Information for detailed experimental conditions; HTE: high-
391 throughput experimentation, RAE: redox-active ester, Trt: trityl.

392 Data availability

393 All data supporting the findings of this study are available in the main text or in the Supplementary Information.

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Author contributions: J.J.G. and D.W.C.M. conceived the work. J.J.G. and J.Z.W. optimized the reaction. J.J.G., J.Z.W. and J.W.G. designed and performed the experiments. J.J.G. and Y.-h. L. performed the computational studies. J.J.G., J.Z.W. and D.W.C.M. prepared the manuscript with input from J.W.G., C.B., S.N.D., X.M., and Y.-h. L.

Competing interests: D.W.C.M. declares an ownership interest in the Penn PhD photoreactor, which is used to irradiate reactions in this work. C.B., S.N.D., X.M., and Y.-h. L. are employed by Merck & Co., Inc. The other authors declare no competing interests.

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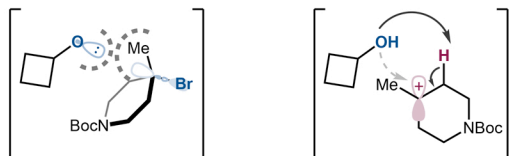
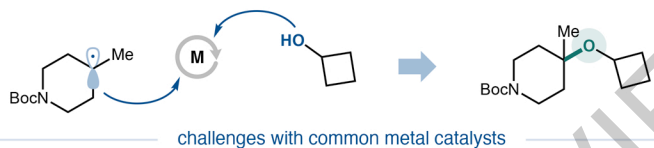
David W. C. MacMillan – *Merck Center for Catalysis at Princeton University, Princeton, New Jersey 08544, United States*; orcid.org/0000-0001-6447-0587;
Email: dmacmill@princeton.edu

A Limitations of classical ether synthesis**S_N2** (Williamson ether)

inaccessible transition state

S_N1

competing/non-selective reactivity

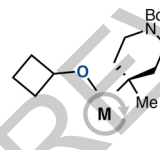
**B Desirable: Metal-mediated etherifications using open-shell intermediates**

challenges with common metal catalysts



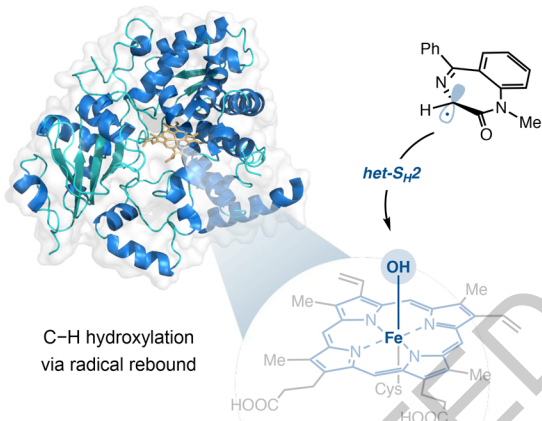
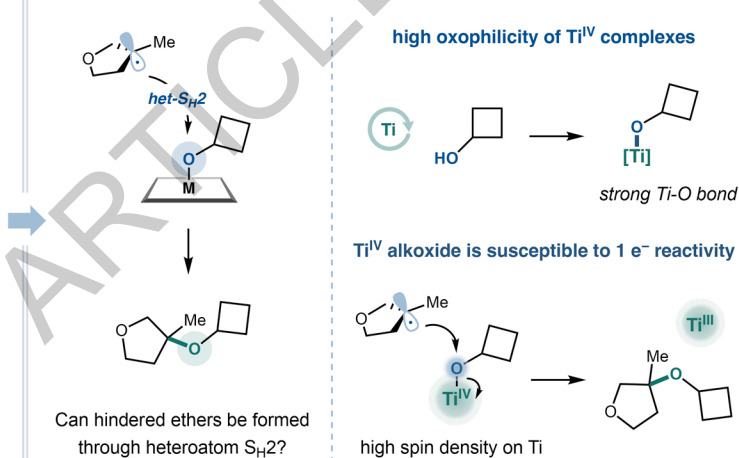
poorly bind to alcohol

highly basic metal alkoxide

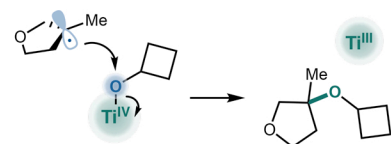


sluggish reductive elimination

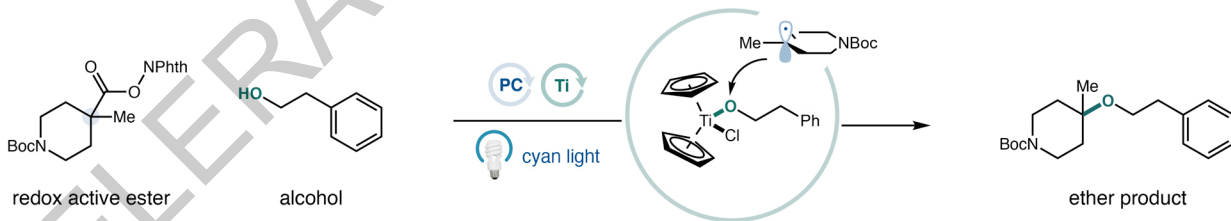
sterically demanding coordination

C Inspiration: Enzymatic C(sp³)-H hydroxylation*Cytochrome P450*C-H hydroxylation
via radical rebound**D Titanium catalysis enables heteroatom S_H2 reactivity**high oxophilicity of Ti^{IV} complexes

strong Ti-O bond

Ti^{IV} alkoxide is susceptible to 1 e⁻ reactivity

high spin density on Ti

E This Work: Access to hindered ethers through a titanium-catalyzed heteroatom S_H2 reaction

redox active ester

alcohol

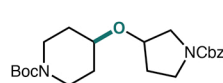
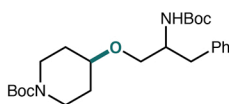
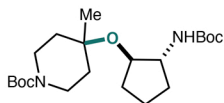
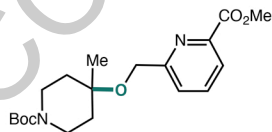
ether product

3°-1°

3°-2°

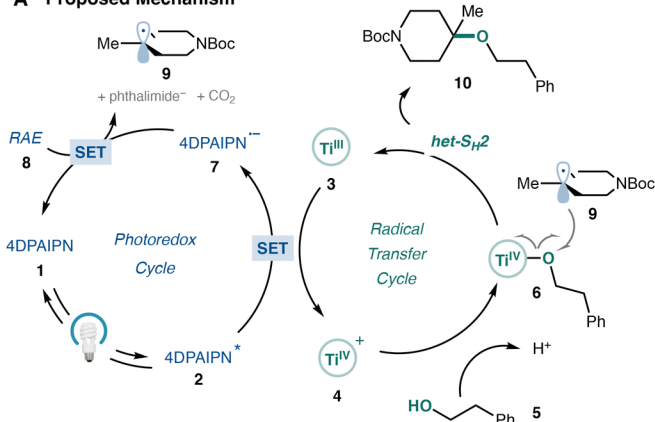
2°-1°

2°-2°

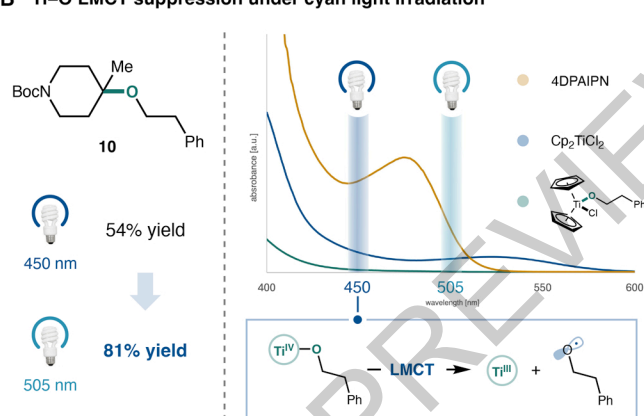


> 80 examples

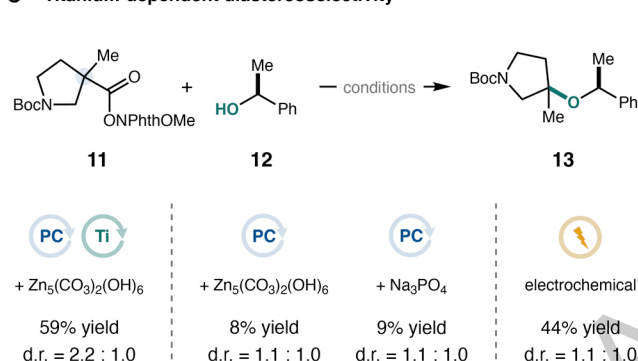
A Proposed Mechanism



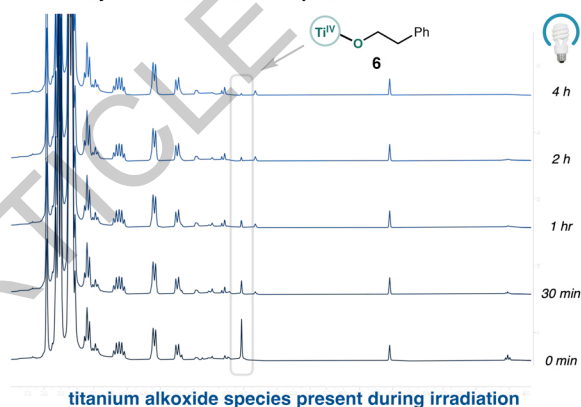
B Ti-O LMCT suppression under cyan light irradiation



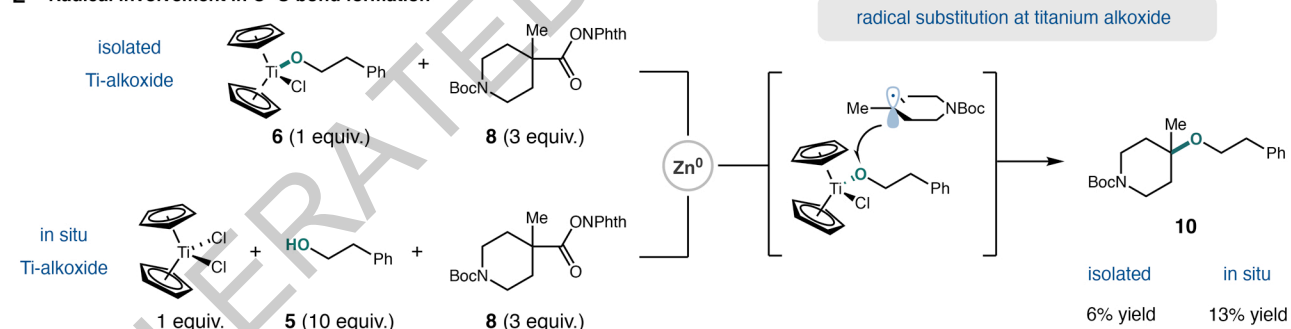
C Titanium-dependent diastereoselectivity



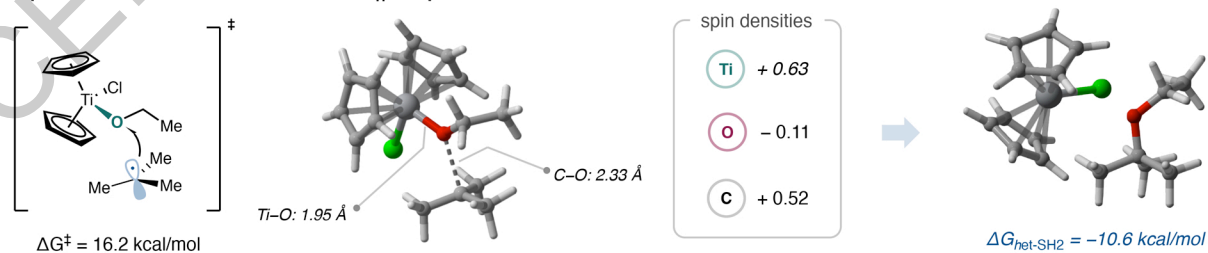
D Intermediacy of titanium alkoxide species

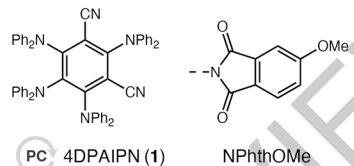
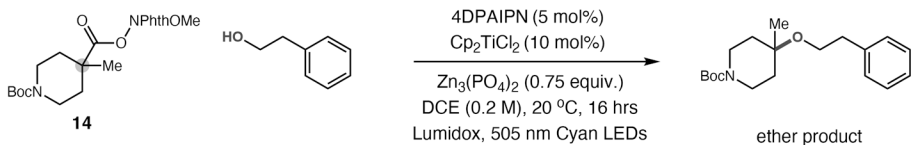


E Radical involvement in C-O bond formation

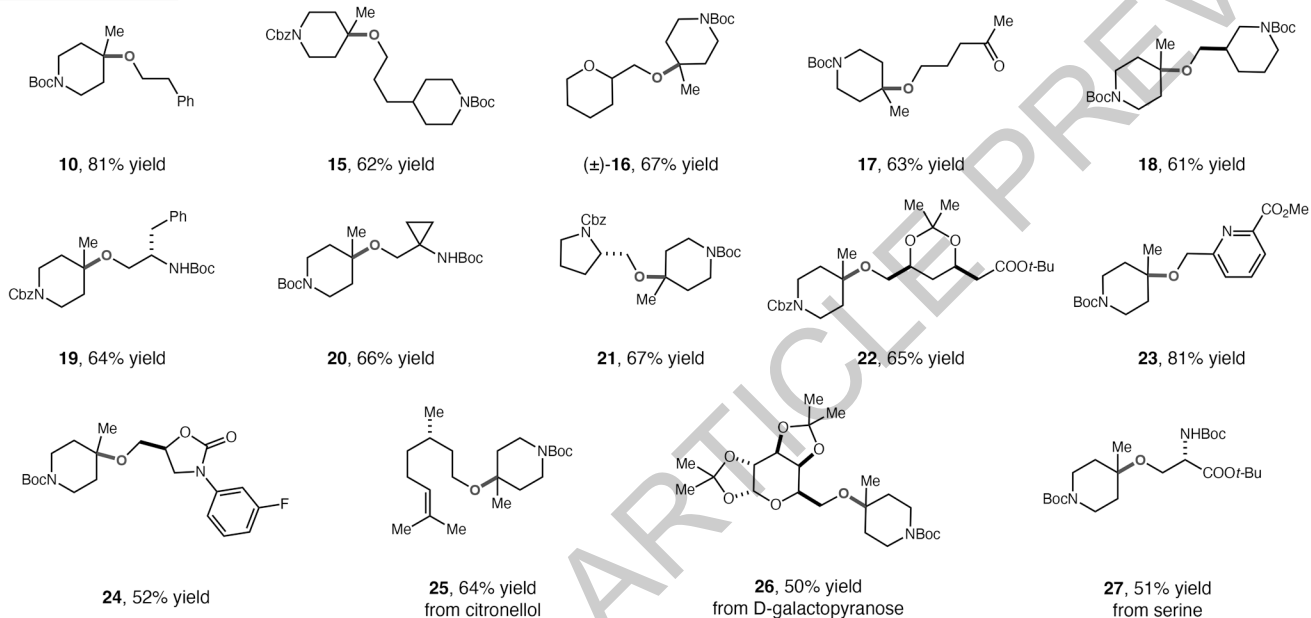


F Computational evidence for concerted het-S_H2 step

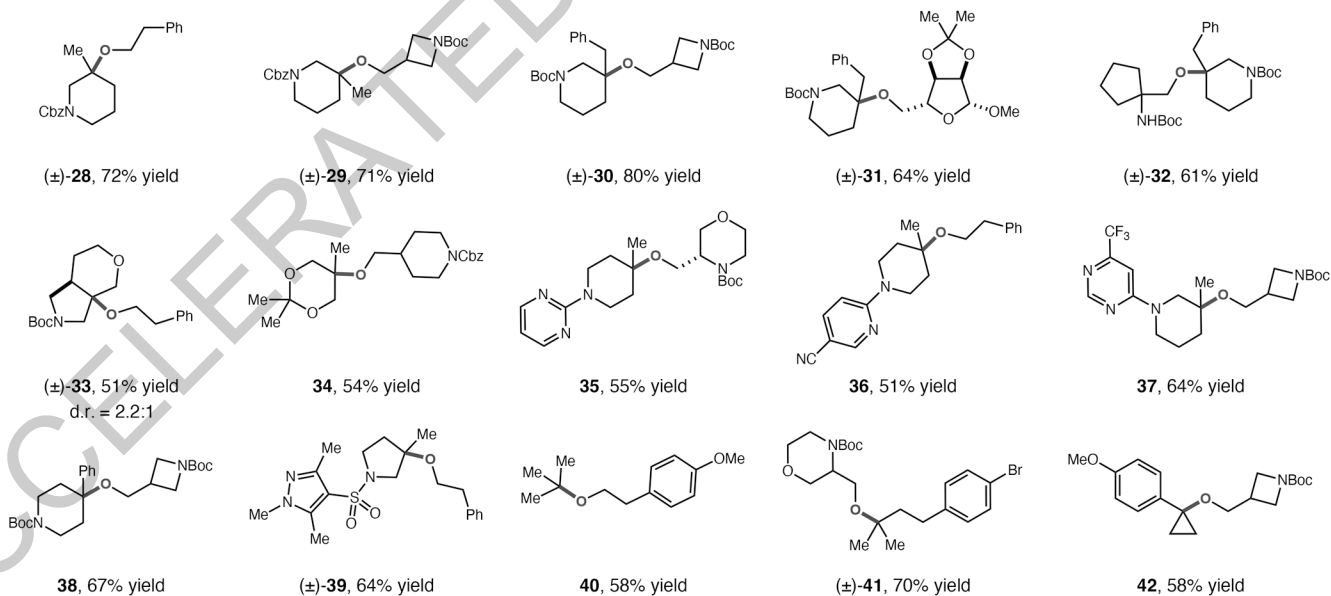




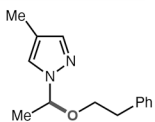
3°–1° (alcohol scope)



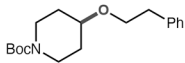
3°–1° (acid scope)



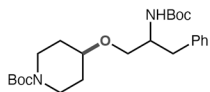
2°-1° scope



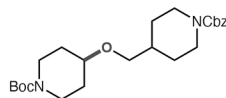
(±)-**43**, 71% yield



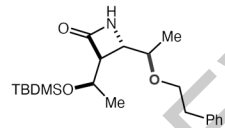
44, 62% yield



(±)-**45**, 70% yield

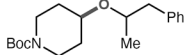


46, 76% yield

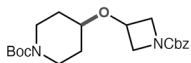


47, 48% yield

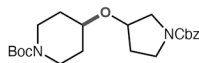
2°-2° scope



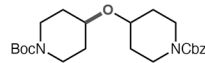
(±)-**48**, 79% yield



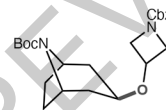
49, 64% yield



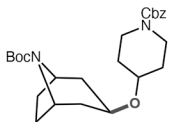
(±)-**50**, 70% yield



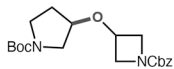
51, 81% yield



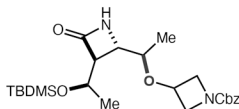
52, 90% yield



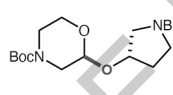
53, 92% yield



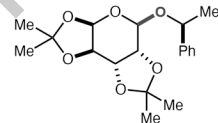
(±)-**54**, 33% yield



55, 35% yield

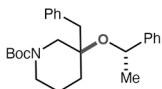


56, 68% yield

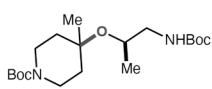


57, 47% yield

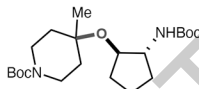
3°-2° scope



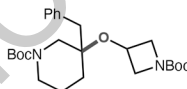
58, 52% yield



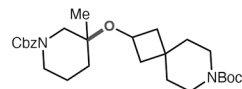
59, 61% yield



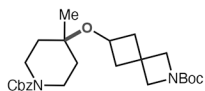
60, 50% yield



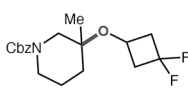
(±)-**61**, 68% yield



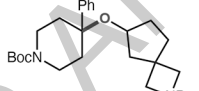
(±)-**62**, 60% yield



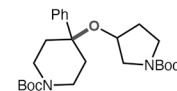
63, 57% yield



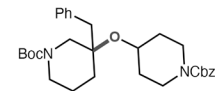
(±)-**64**, 77% yield



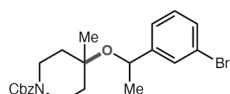
(±)-**65**, 57% yield



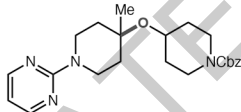
(±)-**66**, 61% yield



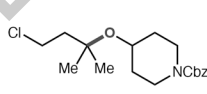
(±)-**67**, 66% yield



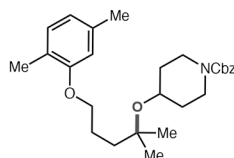
(±)-**68**, 54% yield



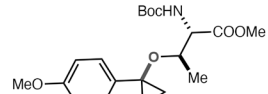
69, 53% yield



70, 60% yield

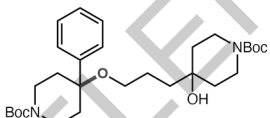


71, 52% yield

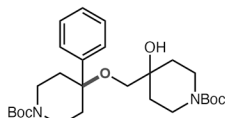


72, 49% yield

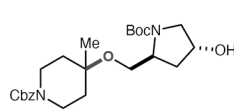
diol scope



73, 79% yield

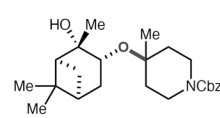


74, 56% yield



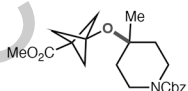
75, 57% yield

r.r. (1°/2°) = 1.8:1

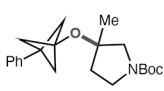


76, 41% yield

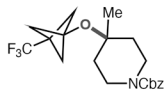
3°-BCP scope



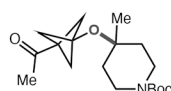
77, 44% yield



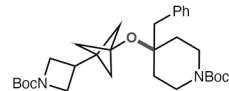
(±)-**78**, 58% yield



79, 45% yield

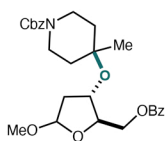


80, 51% yield

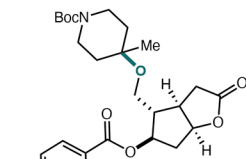


81, 54% yield

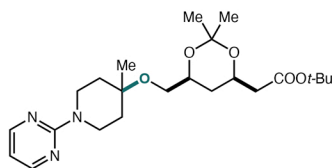
A - Complex and drug-like examples



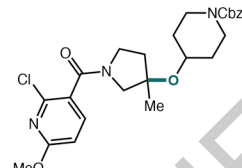
82, 60% yield



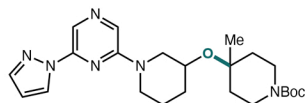
83, 51% yield



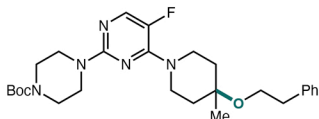
84, 63% yield



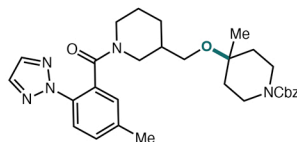
(±)-**85**, 56% yield



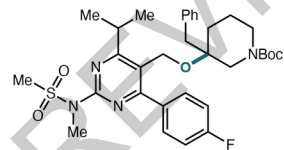
(±)-**86**, 59% yield



87, 51% yield

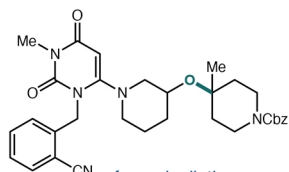


(±)-**88**, 49% yield



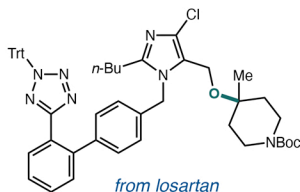
(±)-**89**, 72% yield

B - Pharmacologically active compounds



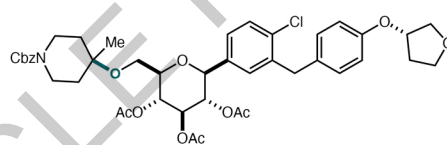
from alogliptin

(±)-**90**, 54% yield



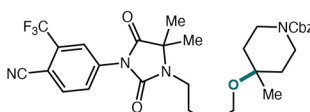
from losartan

91, 45% yield



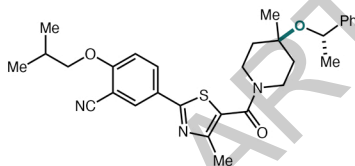
from empagliflozin

92, 40% yield



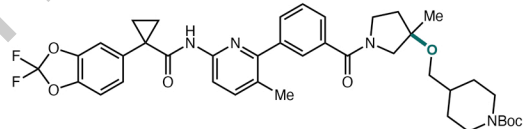
from RU-58841

93, 59% yield



from febuxostat

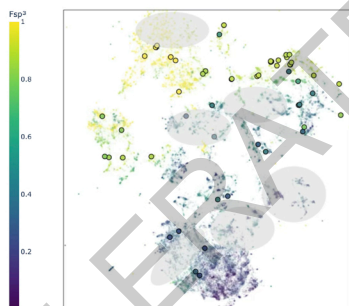
94, 41% yield



from lumacaftor

(±)-**95**, 49% yield

C - Chemical space expansion via HTE



identification of orphaned regions

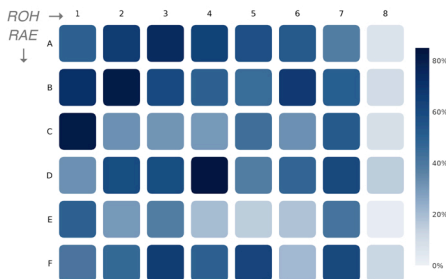
matrix screen using 6 RAE and 8 alcohols



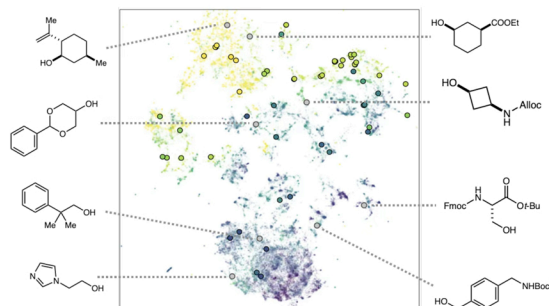
PC

Ti

40 out of 48 examples >30% assay yield



UPLC conversion / ¹H-NMR yield



high coverage of chemical space

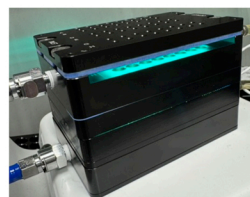


photo-HTE setup