

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 their favourable physicochemical properties³. Classically, dialkyl ether synthesis relies on nucleophilic substitution strategies; however, S_N2 reactions are fundamentally limited by steric congestion at the transition state, whereas S_N1 pathways proceed through promiscuous carbocation intermediates that are prone to elimination, rearrangement and loss of stereogenic information^{4–6}. Here 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-centred radicals generated under mild conditions that are insensitive to steric congestion in the bond-forming transition state. Using a titanium-based catalytic platform in combination with visible-light photoredox catalysis, we demonstrate 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 a dialkyl ether chemical space that is largely inaccessible through conventional approaches, including sterically demanding bicyclo[1.1.1]propane 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 favourable physicochemical properties³. Despite the apparent simplicity of dialkyl ethers, their general and modular synthesis has remained a longstanding challenge, particularly for sterically congested architectures^{1,2}. Classical substitution-based strategies have fundamental limitations: bimolecular nucleophilic substitution (S_N2) reactions are highly sensitive to steric congestion during the transition state^{4–6}, whereas unimolecular pathways (S_N1) proceed through high-energy carbocation intermediates that are prone to rearrangement and elimination (Fig. 1a). Recent advances have expanded access to hindered dialkyl ethers through carbocation-based strategies⁷ and methods proceeding through intermediates with carbocation-like character^{8,9}; however, substrates incompatible with such electrophilic intermediates, which include 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 elimination^{10–12} collectively limit the efficiency of these processes (Fig. 1b). Accordingly, a broadly applicable solution to dialkyl ether synthesis requires a fundamentally different mechanistic paradigm: one that forges C(sp³)–O bonds without invoking high-energy carbocations or slow inner-sphere reductive elimination and exhibits minimal sensitivity to steric congestion.

When considering this challenge, we were inspired by nature's approach to C–O bond formation. Cytochrome P450 enzymes catalyse 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 (Fig. 1c). This analogy suggests that a synthetically underexplored radical substitution paradigm could provide a general solution to the formation of substituted dialkyl ethers that would circumvent the intrinsic limitations of classical ionic substitution chemistry.

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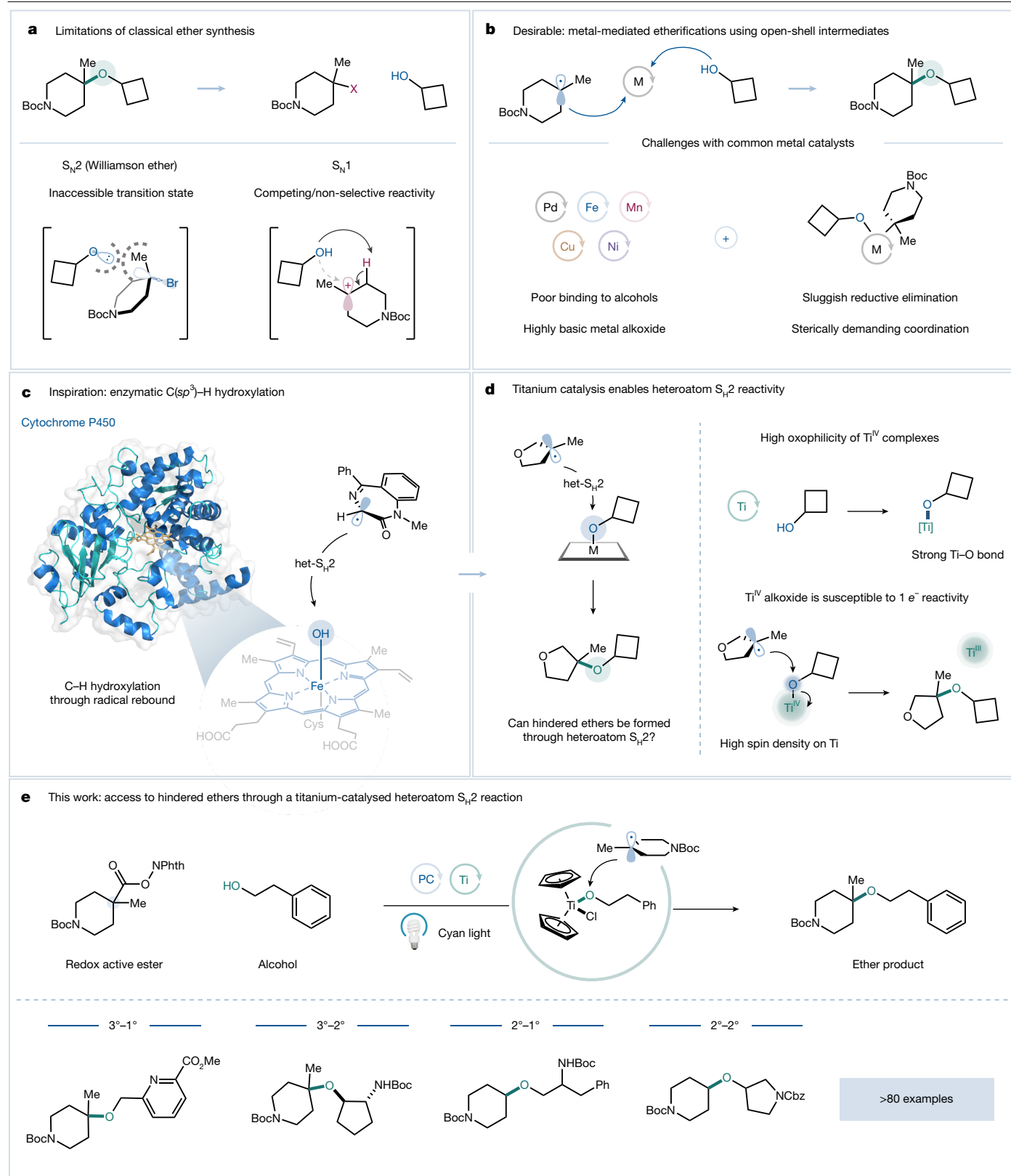


Fig. 1 | Reaction design. **a**, Challenges with using traditional substitution reactions for dialkyl ether synthesis. **b**, Metal-catalysed approaches have been underdeveloped for formation of dialkyl ethers. **c**, Biomimetic heteroatom S_H2

A biomimetic heteroatom S_H2 reaction between an alkyl radical and a metal alkoxide would satisfy our design criteria for dialkyl ether formation. Such a mechanism would bypass high-energy carbocation intermediates and instead leverage carbon-centred radicals, which can

inspired by cytochrome P450 radical rebound could forge hindered C-O bonds from radicals. **d**, Titanium-based catalysts possess the required properties for het- S_H2 . **e**, General access to dialkyl ethers enabled by titanium-catalysed het- S_H2 .

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 would circumvent the sluggish inner-sphere reductive

elimination that affects conventional cross-coupling, instead proceeding 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 was identification of a metal that was 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 (Fig. 1d). Here 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) through a heteroatom S_{H2} pathway. The generality and functional group tolerance of this titanium-catalysed process are demonstrated through 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 (Fig. 1e).

Reaction design

The construction of C(sp^3)–O bonds beyond alcohols through radical intermediates represents a longstanding challenge in synthesis, as most radical C–O bond-forming platforms require a hydrogen atom transfer-active metal complex in a high oxidation state to generate the radical intermediate and the transferable oxygen fragment simultaneously; this mechanistic constraint couples radical generation and oxygen fragment delivery to the same oxidative event, thereby precluding the modular use of simple alcohols and rendering ether synthesis by means of this manifold inaccessible¹³. A more enabling approach would decouple these two functions: if an unactivated alcohol could be ligated directly to a redox-active metal centre, the resulting alkoxide complex could serve as a transferable leaving group upon interception by an exogenously generated radical through an S_{H2} mechanism. Mechanistically, this elementary step would constitute a heteroatom homolytic substitution (het- S_{H2}) at the alkoxide oxygen and would fall in the broader framework of radical ligand transfer, in which a ligand is transferred from a metal centre to a carbon-centred radical¹⁷; 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 by our group^{18–20} and others^{21,22} demonstrating that iron complexes operating through S_{H2} pathways can simultaneously be intercepted by carbon-centred radicals and function as radical leaving groups with high efficiency. Despite these efforts, this reactivity has not been extended to the formation of C–heteroatom bonds in a catalytic fashion. Only one stoichiometric iron complex has been shown to coordinate methanol and permit radical interception²³, and no general catalytic platform for direct alcohol engagement in this fashion has been reported²⁴.

We identified titanium-based catalysts as candidates that might be capable of both facile alkoxide formation and participation in single-electron processes. Previous studies have shown that $Cp_2Ti(III)Cl$ 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 as the organic radical generator in bimolecular cross-coupling^{28,29}, a general cross-coupling platform that uses a titanium catalyst in the bond-forming step has been lacking. Isolated reports of titanium-mediated radical cyclizations leading to cyclic ethers have suggested potential relevance to heteroatom S_{H2} processes³⁰. These precedents prompted us to evaluate whether bench-stable titanocene dichloride could be used in a photocatalytic, intermolecular heteroatom S_{H2} reaction.

Implementation of this transformation posed several fundamental challenges. The key S_{H2} step required a persistent population of Ti(IV) alkoxide intermediates, which are known to undergo photodecomposition through ligand-to-metal charge transfer (LMCT) pathways.

In addition, Ti(III) and Ti(IV) oxidation states are redox non-innocent, which complicates control over catalytic speciation, whereas Ti(III) species exhibit strong coordination to Lewis-basic functionalities, often leading to unproductive substrate reduction and decomposition³¹.

Reaction development and mechanism

The proposed mechanism for the titanium-catalysed heteroatom S_{H2} reaction is outlined in Fig. 2a. Upon visible-light irradiation, 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 Fig. 6.1 for further details) show that this excited state is sufficiently oxidizing ($E_{1/2}^{red}(4DPAIPN^*/4DPAIPN^-) = +1.10$ V versus saturated calomel electrode (SCE) in MeCN)³² to oxidize Ti(III) (**3**) ($E_{1/2}^{red}(Ti^{IV}/Ti^{III}) = -0.76$ V versus SCE in dichloroethane (DCE)) to Ti(IV) (**4**). The 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**) ($E_{1/2}^{red}(4DPAIPN/4DPAIPN^-) = -1.52$ V versus SCE in MeCN) reduces the RAE (**8**) ($E_{1/2}^{red}(RAE/RAE^-) = -1.24$ V (for RAE-H) or -1.31 V (for RAE-OMe) versus SCE in DCE) to generate an alkyl radical (**9**) upon rapid decarboxylation³³. 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.

Formation and persistence of a Ti(IV) alkoxide intermediate are central to the proposed mechanism. Initial optimization studies under blue-light irradiation generated the desired product in only modest yields. Simultaneously, combining the Ti(IV) precatalyst with an alcohol in the presence of base resulted in rapid development of a pale yellow–orange solution (Supplementary Information), consistent with formation of a titanium alkoxide species. We attributed this colour change to an LMCT band associated with a Ti(IV) alkoxide complex that absorbed 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 conditions³⁴.

Ultraviolet–visible-light absorption spectra of the Ti(IV) alkoxide, compared with those of Cp_2TiCl_2 and photocatalyst 4DPAIPN, showed that although the alkoxide complex exhibited weak absorption in the blue region, it had negligible absorption at 505 nm (Fig. 2b). These data suggested that shifting the irradiation wavelength from blue (450 nm) to cyan (505 nm) would suppress undesired titanium-centred LMCT processes, thereby increasing the lifetime and steady-state concentration of the Ti(IV) alkoxide intermediate and favouring 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 by-products (Supplementary Fig. 5.2).

We examined the influence of titanium on product diastereoselectivity to probe its involvement in the bond-forming step, as coordination to titanium was expected to introduce steric bias in the transition state and thereby affect the diastereomeric ratio (d.r.). Redox-active ester **11** and secondary alcohol **12** were coupled under standard conditions (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 substantially 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

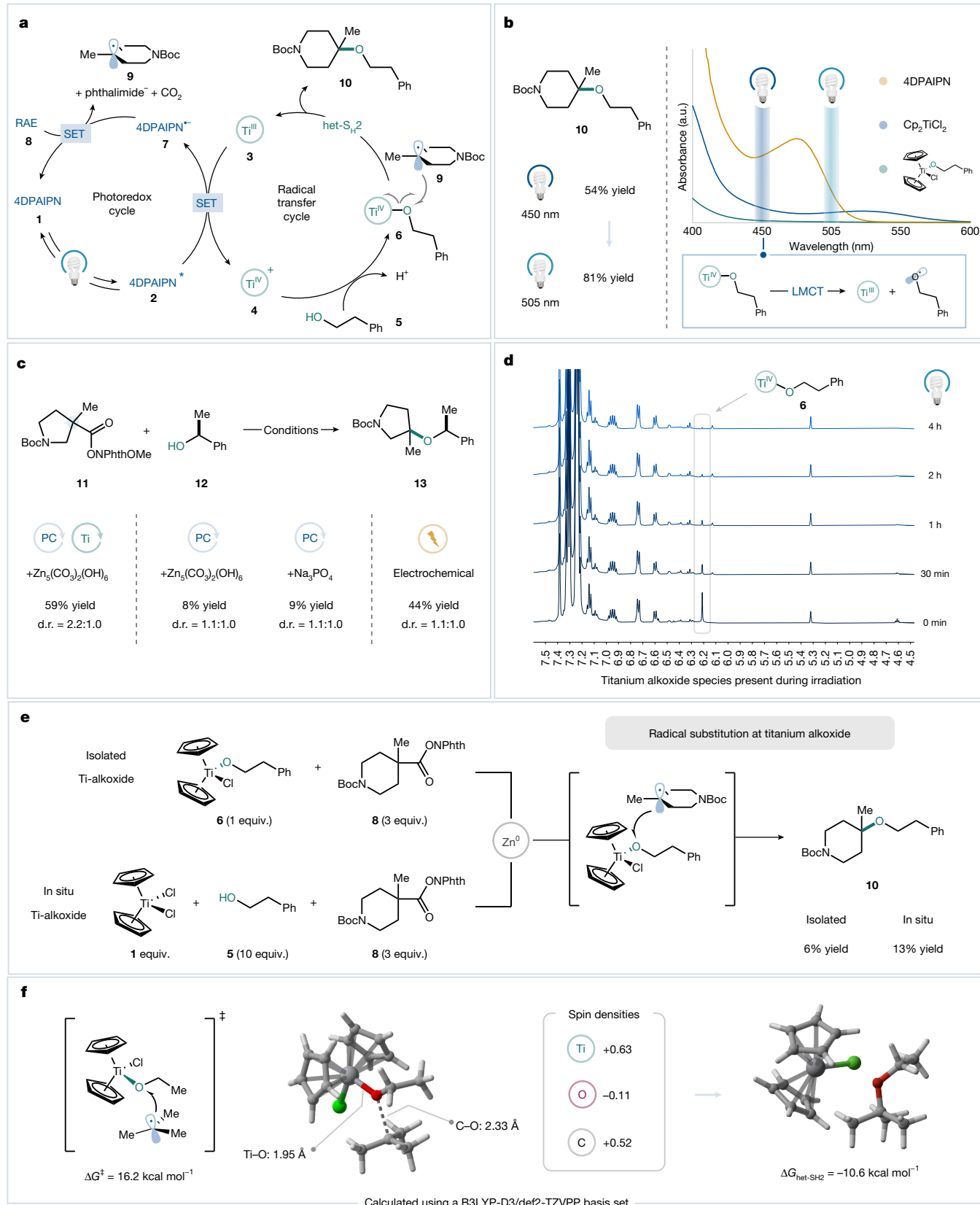


Fig. 2 | Mechanistic studies. **a**, Proposed mechanism. **b**, Ti-OLMCT suppression under cyan light irradiation. Cyan light irradiation avoids deleterious LMCT processes of the crucial titanium alkoxide species. **c**, Titanium-dependent diastereoselectivity. Effect of involvement of titanium in bond formation on the d.r. of the product and comparison with the carbocationic pathway. **d**, Intermediacy of titanium alkoxide species. Photo-NMR showed the formation and consumption of titanium alkoxide as the reaction progresses. **e**, Radical

involvement in C–O bond formation. Stoichiometric studies demonstrated the capability of radicals to undergo $\text{het-S}_{\text{H}}2$ with the titanium alkoxide to form the corresponding dialkyl ethers. **f**, Computational evidence for concerted $\text{het-S}_{\text{H}}2$ step. Density functional theory studies (B3LYP-D3/def2-TZVPP basis set) demonstrated the thermodynamic feasibility of the radical ether formation, as well as the transition state of the $\text{het-S}_{\text{H}}2$ step; NPhth, phthalimidyl; PC, photocatalyst.

essentially no diastereoselectivity (1.1:1 d.r.) (Fig. 2c). Furthermore, the key Ti(IV) alkoxide intermediate was observed by photo-NMR (nuclear magnetic resonance spectroscopy performed while the sample was irradiated in situ in the spectrometer) under standard irradiation conditions (Fig. 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 RAE (**8**), trimethylsilyl chloride-activated zinc was introduced to establish strongly reducing conditions. Under these conditions, single-electron reduction of the RAE is expected to generate an alkyl radical through rapid decarboxylation³³. Notably, the reducing environment precludes oxidation of the alkyl radical to a carbocation and disfavours formation of a carbanion, thereby biasing the reaction towards radical reactivity. Consistent with our hypothesis, the desired dialkyl ether (**10**) was formed in 6% and 13% yield, respectively, under stoichiometric conditions (Fig. 2e). Although these yields were modest, they provided evidence of direct engagement of an alkyl radical with a Ti(IV) alkoxide intermediate, consistent with C–O bond formation through a heteroatom S_H2 pathway and formation of titanium alkoxide under our reaction conditions. Further discussion of this experiment and its mechanistic implications is provided in section 8 of the Supplementary Information.

To interrogate the feasibility of the proposed het-S_H2 step, we performed density functional theory calculations on a model system comprising a *tert*-butyl radical and titanocene(IV) ethoxide Cp₂Ti(Cl)(OEt) (Fig. 2f). A single transition state was located ($\Delta G^\ddagger = 16.2 \text{ kcal mol}^{-1}$), featuring a three-centre C...O...Ti arrangement with no direct metal–carbon contact; this suggested that the reaction proceeded in a single concerted step, consistent with a homolytic substitution at oxygen. The substitution was exergonic ($\Delta G = -10.6 \text{ kcal mol}^{-1}$), reflecting the exchange of the weaker Ti–O bond for the stronger C–O bond of the ether (see the Supplementary Information for details).

Scope evaluation

We first examined the scope of the titanium-catalysed heteroatom S_H2 reaction using tertiary carboxylic acids and primary alcohols to access 3°–1° substituted dialkyl ethers (Fig. 3). A broad range of primary alcohols (**10** and **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** and **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** and **15–22**) and medicinally relevant heterocycles such as pyridines (**23, 36**), pyrimidines (**35, 37**) and pyrazoles (**39**)³⁷. This functional group tolerance was consistent with a low steady-state concentration of Ti(III) under the reaction conditions and attenuated Lewis acidity of Ti(IV) following formation of titanium alkoxide.

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 the Supplementary Information for a comparison with established carbocation-based strategies), readily participated in the heteroatom S_H2 reaction, furnishing the corresponding ethers in good yields.

We next evaluated the use of secondary alkyl radicals to access 2°–1° and 2°–2° ether motifs (Fig. 4). Secondary radicals derived from both cyclic (**44–46**) and acyclic (**43** and **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**). Notably, this method provided 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** and **57**), including an ether (**57**) derived from (+)-galacturonic acid, were obtained in good yield.

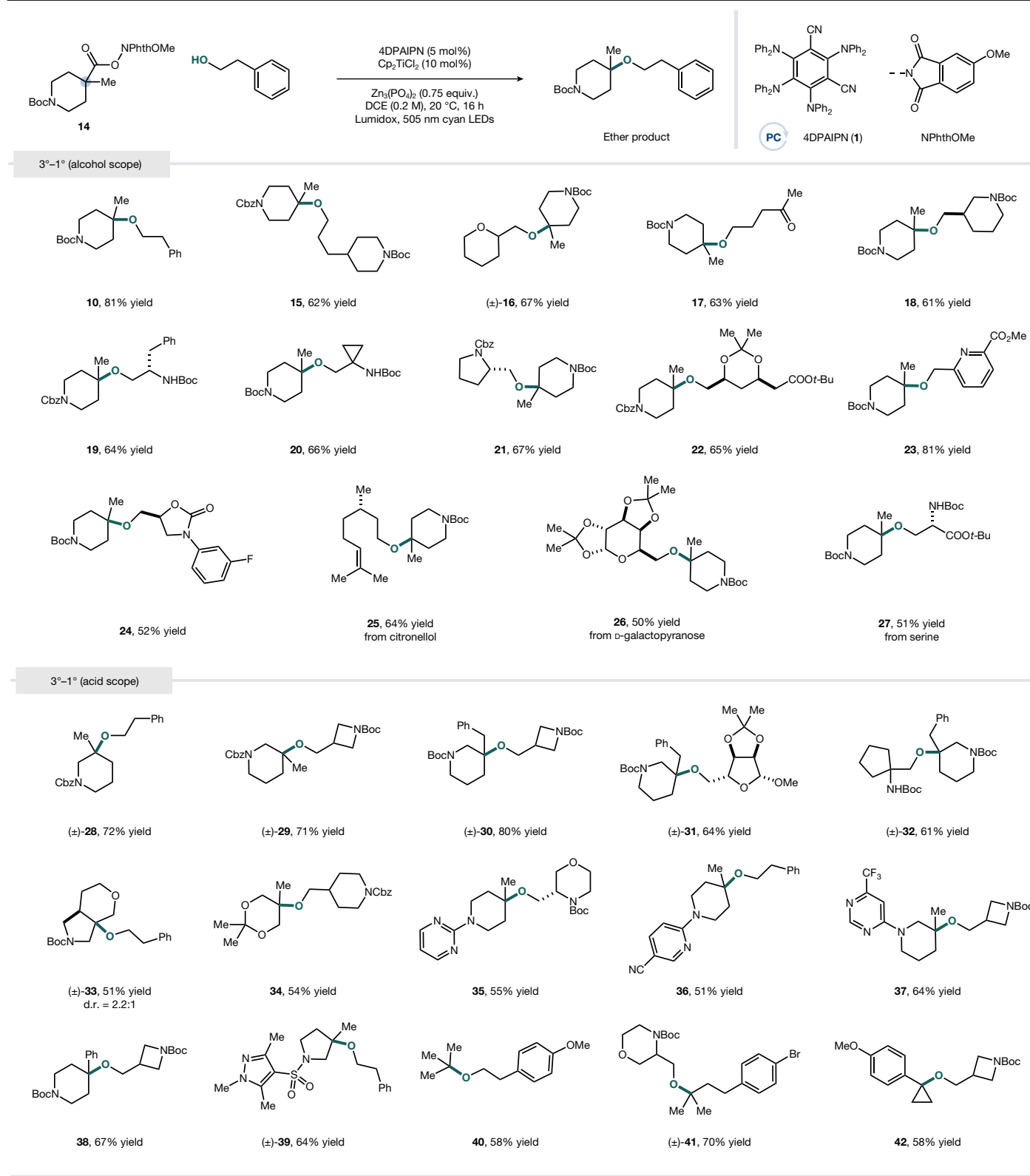
Coupling of tertiary carboxylic acids and secondary alcohols to form 3°–2° dialkyl ethers represents a significant challenge owing to severe steric congestion around the oxygen centre. Using our titanium-based catalytic platform, we could access these motifs efficiently through heteroatom S_H2 reactivity.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

Cyclic secondary alcohols, including four-membered (**61–64**), five-membered (**65** and **66**) and six-membered (**67** and **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** and **71**) and strained (**72**) tertiary radicals also participated efficiently. Notably, the functional group tolerance of this approach was further demonstrated by compound **70**, which bears a primary alkyl chloride that would typically be 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. By contrast, the titanium-catalysed heteroatom S_H2 manifold exhibited pronounced diol site selectivity, favouring etherification at the less substituted alcohol. This selectivity arose 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 biased product formation towards 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** and **74**). When primary and secondary alcohols were present, modest but reproducible selectivity in favour of the primary alcohol-derived ether (**75**) was observed (1.8:1). Finally, diols comprising secondary and tertiary alcohols yielded exclusively the ether arising from functionalization at the secondary alcohol (**76**).

Given the interest of our group 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 *sp*³-rich phenol ether bioisosteres have garnered increasing attention in medicinal chemistry owing to their favourable physicochemical properties⁴⁰. Although recent advances have expanded the synthetic accessibility of BCP derivatives^{41,42}, the installation of sterically demanding substituents remains challenging owing to a lack of general functional-group-tolerant strategies. In particular, direct etherification of BCP alcohols through S_N2 or cationic S_N1 pathways remains problematic, as these substrates are unstable under basic conditions, undergo rapid decomposition through the corresponding alkoxide and exhibit low nucleophilicity⁴³. Under the mild conditions of our titanium-catalysed heteroatom S_H2 protocol, we observed efficient formation of the desired BCP ethers when engaging tertiary alkyl radicals. This strategy enabled synthesis of a diverse array of sterically hindered BCP ethers in good yields (**77–81**), highlighting the capacity of this platform to access *sp*³-rich bioisosteric ether architectures that would be difficult to obtain using conventional approaches.

Given the mild reaction conditions and high functional group tolerance of this protocol, we anticipated that it could be used to incorporate ether linkages into functionality-dense drug-like scaffolds (Fig. 5a). To evaluate its applicability in complex late-stage settings,



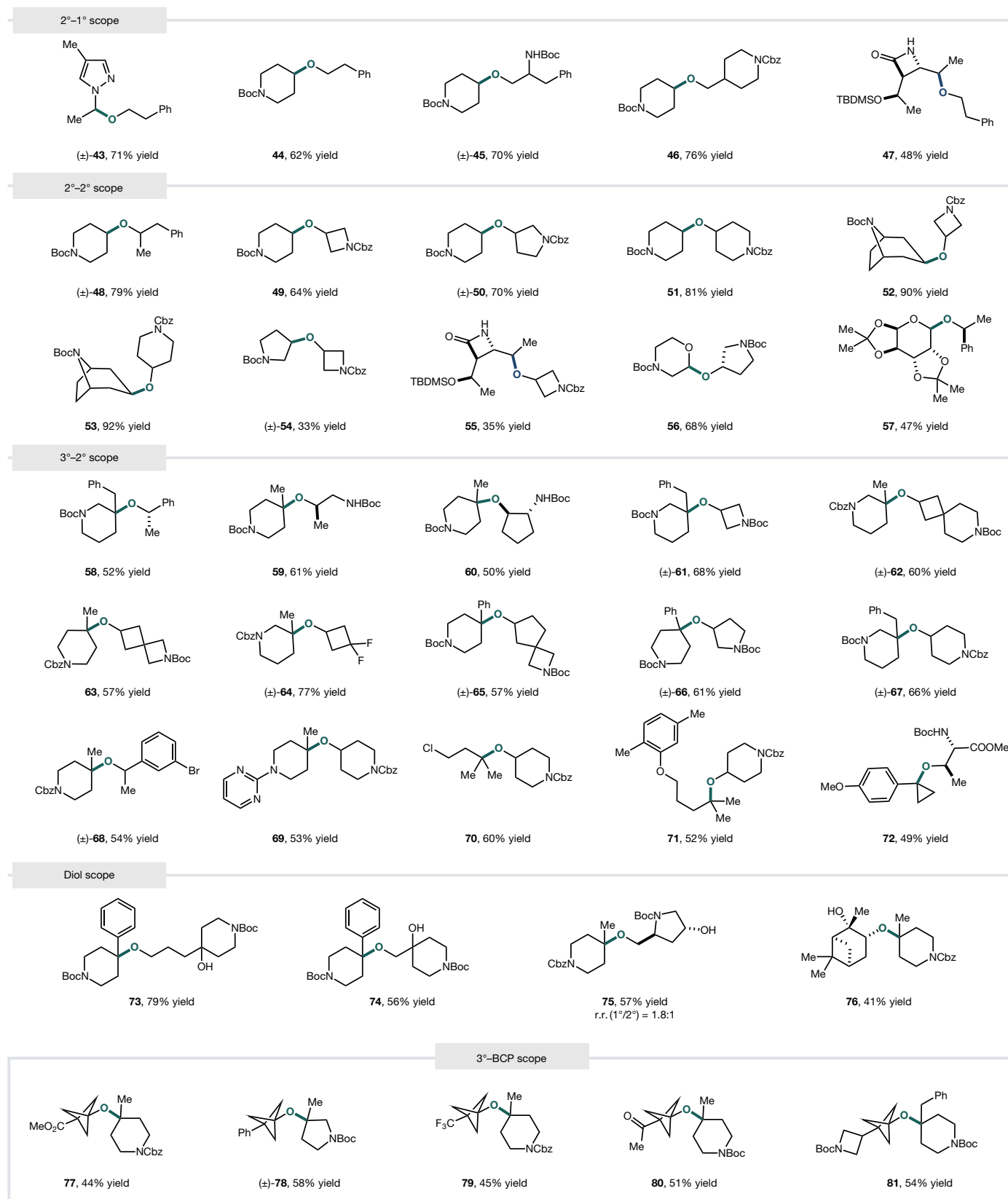


Fig. 4 | Modular construction of dialkyl ethers with varying substitution. All yields were isolated. Reactions were performed using 4DPAIPN (5 mol% or 10 mol%), Cp_2TiCl_2 (10 mol% or 20 mol%), $\text{Zn}_3(\text{PO}_4)_2$ (0.75 equiv.) or $[\text{ZnCO}_3]_2\cdot[\text{Zn}(\text{OH})_2]_3$ (0.5 equiv.), RAE (RAE-H or RAE-OMe; 1.0 or 3.0 equiv.),

alcohol (1–3 equiv.) in DCE (0.2 M or 0.1 M) under cyan light irradiation. See Supplementary Information for detailed experimental conditions. TBDMS: *tert*-butyldimethylsilyl.

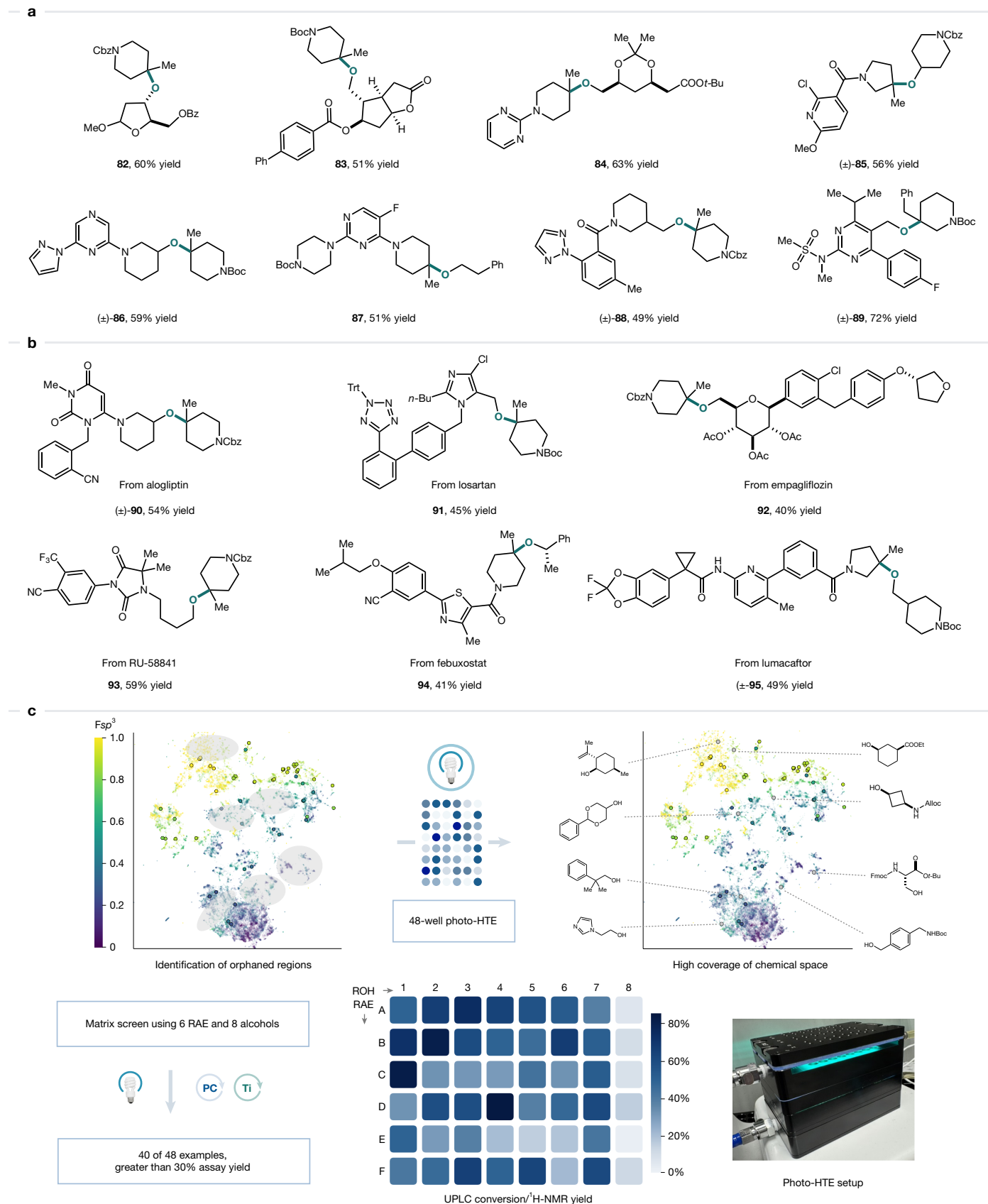


Fig. 5 | Complex scope and high-throughput experimentation. **a**, Complex and drug-like examples. **b**, Pharmacologically active compounds. **c**, Chemical space expansion by means of high-throughput experimentation (HTE).

All yields were isolated. See the Supplementary Information for detailed experimental conditions. Trt, trityl; UPLC, ultra-performance liquid chromatography.

conditions, allowing late-stage etherification of compounds including alogliptin (**90**), losartan (**91**), empagliflozin (**92**), RU-58841 (**93**), febuxostat (**94**) and lumacaftor (**95**) (Fig. 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 (Fig. 5c). We analysed the Enamine alcohol library, which comprises more than 55,000 compounds (SMILES strings for alcohols in the Enamine catalogue were retrieved from the Enamine website <https://enamine.net/building-blocks/functional-classes> (version dated 7 October 2025))⁴⁴, using Morgan fingerprints (2,048-bit) followed by dimensionality reduction to generate a representative chemical space map (see the 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, we identified several under-represented areas, from which we selected representative substrates for further evaluation. To efficiently interrogate these regions, we implemented high-throughput experimentation to accelerate data acquisition and enable matrix-style screening relevant to medicinal chemistry⁴⁷. Of the eight previously unexplored alcohols selected from underrepresented regions, seven delivered the desired ether products in synthetically useful yields; an imidazole-containing alcohol was the sole exception. Evaluation of a 48-well matrix library further demonstrated broad compatibility, with 40 of 48 substrate combinations affording yields exceeding 30%. These results indicate 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-catalysed heteroatom $S_{\text{H}}2$ 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 would be inaccessible or inefficient using classical substitution pathways. More broadly, this work establishes heteroatom $S_{\text{H}}2$ reactivity as a general mechanistic framework for controlled radical-heteroatom bond formation. We expect this mechanistic paradigm to inform the development of new catalytic platforms for construction of other challenging heteroatom linkages and to further broaden the scope of radical substitution chemistry.

Online content

Any methods, additional references, Nature Portfolio reporting summaries, source data, extended data, supplementary information, acknowledgements, peer review information; details of author contributions and competing interests; and statements of data and code availability are available at <https://doi.org/10.1038/s41586-026-11043-z>.

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Data availability

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

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Competing interests D.W.C.M. declares an ownership interest in the Penn PhD photoreactor, which was 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.

Additional information

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