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Branching out: redox strategies towards the synthesis of acyclic α-tertiary ethers

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Acyclic α-tertiary ethers represent a highly prevalent functionality, common to high-value bioactive molecules, such as pharmaceuticals and natural products, and feature as crucial synthetic handles in their construction. As such their synthesis has become an ever-more important goal in synthetic chemistry as the drawbacks of traditional strong base- and acid-mediated etherifications have become more limiting. In recent years, the generation of highly reactive intermediates *via* redox approaches has facilitated the synthesis of highly sterically-encumbered ethers and accordingly these strategies have been widely applied in α-tertiary ether synthesis. This review summarises and appraises the state-of-the-art in the application of redox strategies enabling acyclic α-tertiary ether synthesis.

1. Introduction

As the demand for ever greater three-dimensional complexity in target molecule synthesis increases,[1–3] hindered ethers, in particular α-tertiary ethers, have assumed a role of fundamental importance. Notoriously challenging to synthesise by classical methods, the past decades have witnessed a concerted effort to improve access to this unique functionality and rectify the dearth of widely-applicable and mild methodologies for their synthesis.

Driving this interest in hindered ether synthesis is the widespread occurrence of this motif within synthetic chemistry (Fig. 1).[4–7] While familiar components in fuels and commodity chemicals,[8–10] α-tertiary ethers have also become key motifs in pharmaceuticals, agrochemicals and functional materials and are frequently observed in natural products.[11–14] Within medicinal chemistry programs, the combination of Lewis basicity, enhanced polarity, resistance to α-oxidation and steric influence, offered by α-tertiary ethers, can confer profound effects on a lead compound's physical and biochemical properties.[15–17]

As a result of this, such structural modifications are apparent in a preponderance of active pharmaceutical ingredients (APIs) in a broad range of medical fields, including antidepressants, antibiotics, and antihistamines, among others.[18,19]

Etherification has also been the focus of intense study in natural product synthesis with numerous highly potent macrocyclic antibiotics containing hindered alkyl-aryl ether linkages.[20] Notably, both tetrahydrocannabinol (THC),[21] a prominent cannabinoid with promising and broad therapeutic applications, and tocopherols and tocotrienols (vitamin E), implicated as antioxidants in cell membrane protection,[22] feature α-tertiary alkyl-aryl cyclic ethers.

It is noteworthy that alongside the prevalence of such ethers in high-value compounds, the importance of ethers as versatile synthetic intermediates is beginning to be recognised, transitioning from unreactive moieties or protecting groups[10,23] to key synthetic handles.[24,25]

The harsh conditions traditionally required for the synthesis of α-tertiary ethers have limited their facile construction.[6] While historical ether syntheses exhibit broad applicability and tolerance, it is noteworthy that most of these methods demonstrate significantly lower efficiency as steric bulk increases and, in some cases, are totally inapplicable for the synthesis of α-tertiary ethers. The venerable Williamson ether synthesis, involving nucleophilic substitution of an alkyl halide by a deprotonated alcohol (Scheme 1), is largely limited to primary or secondary systems with only a few notable tertiary cases – typically enabled by activation from an adjacent group or forcing conditions.[26,27] An alternative traditional strategy involves the treatment of an alkene with strong acid to form the corresponding carbocation which can be trapped by a wide range of alcohol nucleophiles.[28] While this strategy has seen widespread adoption in hindered ether synthesis, a highly acid-tolerant substrate is required given the forcing conditions. Expanding upon these early methods, the Mitsunobu reaction has been widely applied in ether synthesis however classically is not applicable to the synthesis of α-tertiary ethers (see Section 5).[29,30]

As the drawbacks and challenges integral to these traditional techniques have become more apparent and more limiting, the

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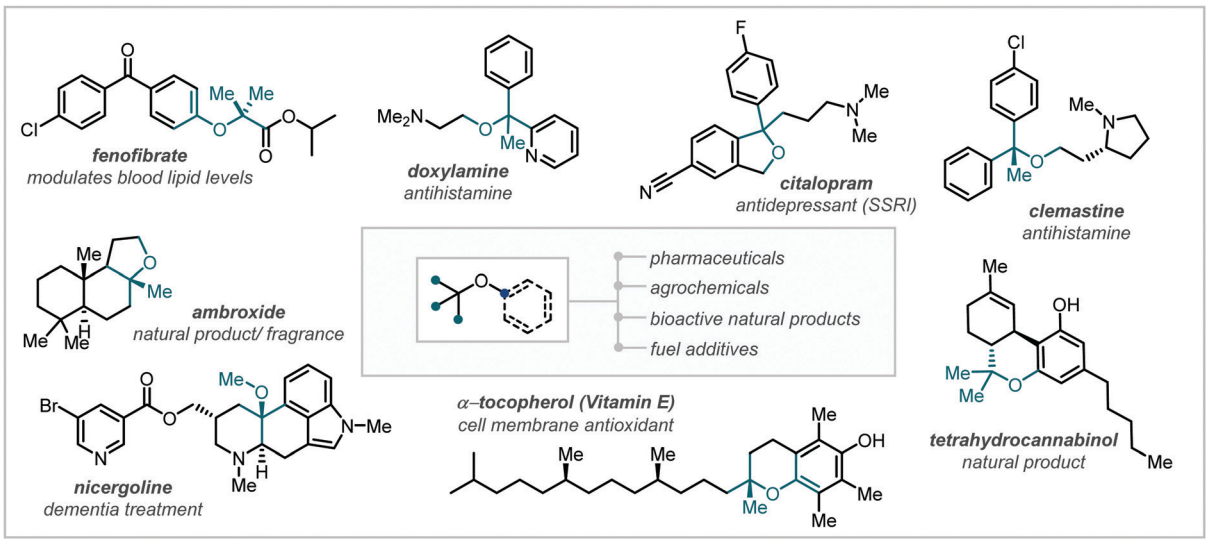
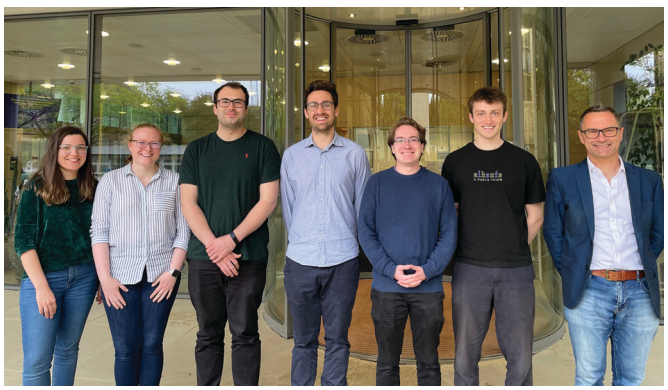


Fig. 1 The prevalence of (α-tertiary) ethers.

synthetic community has responded with a host of powerful, enabling etherification strategies for the synthesis of hindered ethers.

It is no surprise that shortly after the disclosure of the Buchwald–Hartwig amination,[31,32] now commonplace in the synthesis of C–N bonds, the transformation was adapted to C–O bond formation, rapidly enabling access to a plethora of ether-containing motifs.[33,34] Notably, in order to prevent competitive and deleterious β-H-elimination, the early reports of Pd-catalysed



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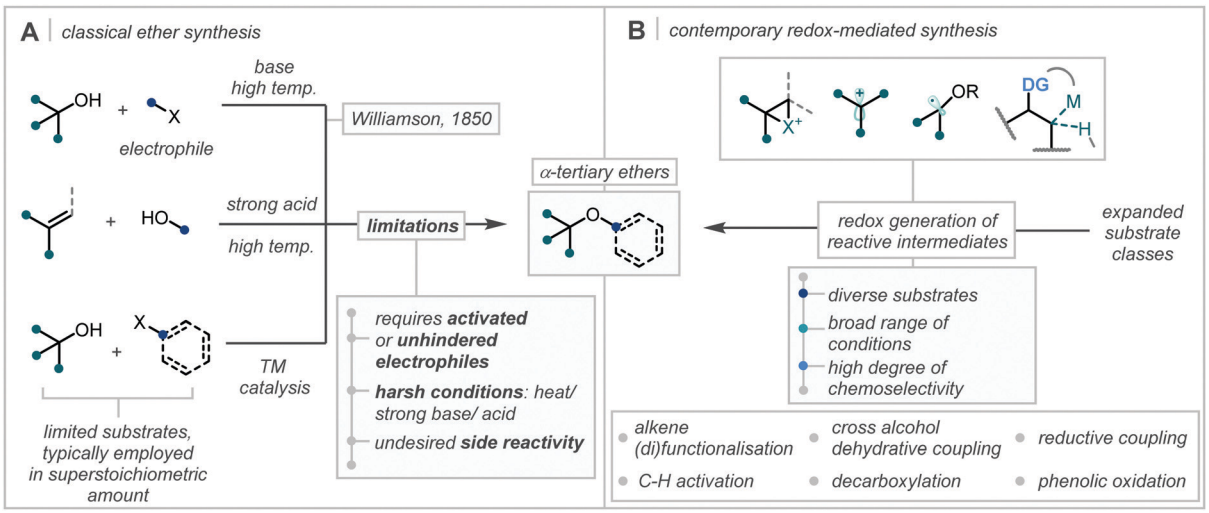


Scheme 1 (A) Classical synthesis of α-tertiary ethers; (B) contemporary redox-mediated synthesis of α-tertiary ethers.

C–O etherification opted for, and almost exclusively reported, the use of tertiary alcohols as coupling partners.[35] The application of the Buchwald–Hartwig coupling systems to etherification obviated the use of the Ullmann reaction and the associated harsh conditions.[36]

Additionally, the traditional base-mediated Williamson ether synthesis and the acid-mediated activation approaches have continued to be refined and a suite of catalytic – Brønsted and Lewis, acidic and basic – methodologies have been reported vastly expanding the scope of accessible α-tertiary ethers.

However, most striking is the vast expansion of etherification strategies that employ redox chemistry to generate reactive intermediates, or facilitate new mechanistic frameworks, capable of affording hindered ethers and, in most cases, resulting in formal oxidation or reduction of the substrate. It is these methods that will be the focus of this review, namely, etherification reactions that are driven by an associated reduction or oxidation process, typically accompanied by a change in the formal oxidation state of one of the ether linked carbons.

Given the traditional limitations associated with ether bond formation, the review will focus on the formation of *acyclic* α-tertiary ethers thereby collating proven methods that are applicable in cases of high steric hindrance and able to synthesise the most challenging ethers. It is notable that in the acyclic case, the C–O bond formation is typically intermolecular, asserting even greater kinetic and thermodynamic challenges on the associated etherification. With this in mind it is worth noting that the broad and exciting applications of and synthesis of cyclic ethers, among other oxygen-containing heterocycles, has been elegantly reviewed elsewhere.[37–39]

The vast expansion in new methodologies employing contemporary redox chemistry has dramatically increased the diversity of suitable substrates for α-tertiary ether synthesis. This has enabled alkene di- and mono-functionalisation, C–H activation, cross-alcohol coupling, decarboxylative strategies, phenolic oxidations and a plethora of more specialised approaches to dramatically diminish the once considerable challenge associated with intermolecular α-tertiary ether formation. Due to the extensive review literature covering the application of metal-catalysed cross-coupling to C–O bond formation, this important class of reaction is considered outside the scope of this review.[40–43]

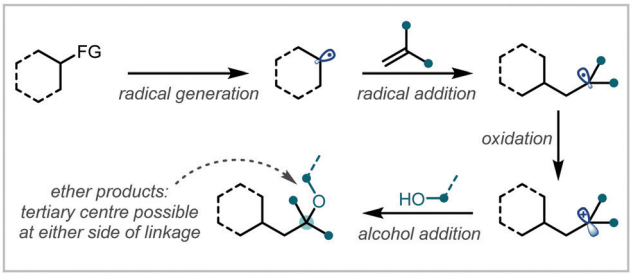
2. Alkene difunctionalisation

The synthesis of substituted alkenes and their subsequent oxy-functionalisation is well-established in synthetic chemistry. This mode of reactivity has proven particularly well-suited to the installation of α-tertiary ethers due to the highly reactive intermediates that are readily accessed from alkenes under oxidative or reductive activation. The following section will detail such approaches and broadly classify them by the mode of alkene activation and the nature of functionalisation coupled with alkoxylation.

2.1 Photochemical alkene difunctionalisation

In recent years, the application of photochemistry in synthetic organic chemistry has seen a significant resurgence, becoming an important and widely applicable reaction manifold.[44,45] Novel photochemical reaction manifolds have enabled the generation of reactive chemical species from accessible precursors under mild conditions, greatly expanding the toolbox of reactions available to the synthetic chemist and enabling diverse access to single-electron chemistry and mechanistic frameworks.

In the context of alkene difunctionalisation for α-tertiary ether synthesis, many of the transformations discussed in this review share a similar reaction design or mechanistic proposal (Scheme 2). An initiation event leads to the formation of a reactive radical species, capable of adding to the π-bond of an alkene. This generates a carbon-centred radical, usually at the most-stabilised position. Oxidation of the resultant radical then yields the corresponding carbocation and often enables

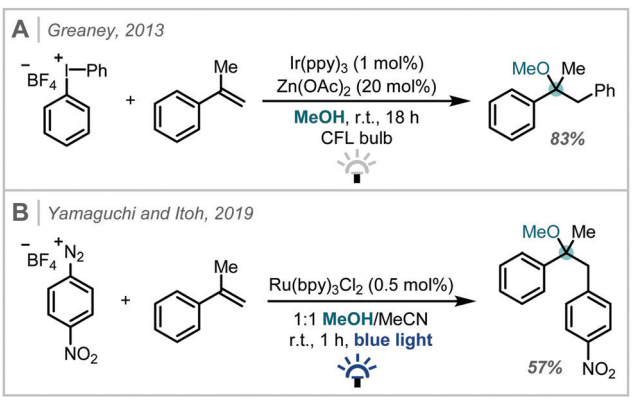


Scheme 2 General mechanism for alkene difunctionalisations involving RPC.

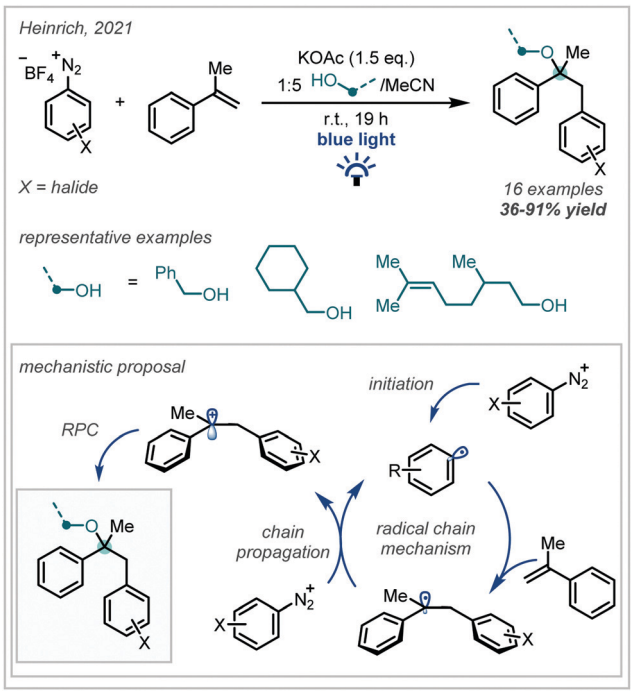
completion of the catalytic cycle of a photoredox catalyst, or additives such as metal salts can also mediate this process. This involvement of both radical and polar species in a mechanism is described as radical-polar crossover (RPC).[46–50] The carbocation can finally be trapped by an external nucleophile, such as an alcohol, to form the ether product.

2.1.1 Concurrent C–C bond formation. The addition of an aryl radical to an alkene represents an important class of alkene difunctionalisation reactions, forming a $C(sp^2)$–$C(sp^3)$ bond that can be difficult to forge *via* alternative methods. In 2013, Greaney reported the oxyarylation of styrenes using diaryliodonium salts as the aryl radical precursor (Scheme 3).[51] Irradiation of diphenyliodonium tetrafluoroborate with 30 W domestic light bulbs in the presence of α-methylstyrene, 1 mol% $Ir(ppy)_3$ [ppy = 2-phenylpyridine] and methanol led to the formation of the desired α-tertiary methyl ether. The proposed mechanism proceeded *via* photocatalytic reduction of the diaryliodonium salt to yield an aryl radical, which engaged in alkene addition and RPC (as shown in Scheme 2). Yamaguchi & Itoh extended this approach in 2019, employing diazonium salts as the aryl radical precursor with a $Ru(bpy)_3Cl_2$ [bpy = 2,2′-bipyridine] photocatalyst.[52] Using this protocol, an α-tertiary ether was formed in moderate yield.

Recently, Heinrich published a catalyst-free carboetherification of α-methylstyrene using aryl diazonium salts and alcohols under visible light irradiation (Scheme 4).[53] A broad scope of primary alcohols was used to form α-tertiary ethers in good



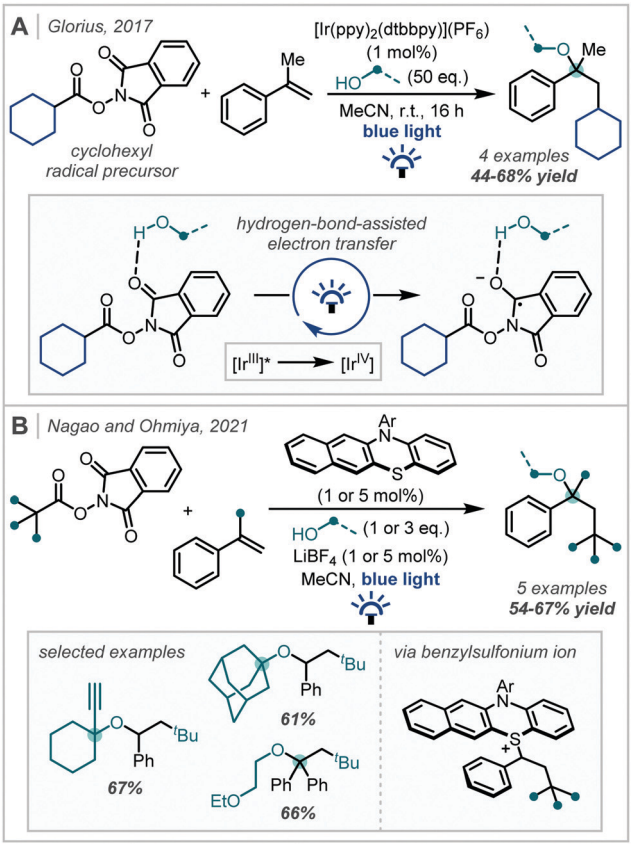
Scheme 3 Photoredox-catalysed oxyarylation of styrenes using: (A) diaryliodonium salts, and; (B) aryl diazonium salts.



Scheme 4 Styrene oxyarylation mediated by visible light irradiation of weak electron donor–acceptor complexes.

yields with useful pendant functionality, including olefins. The reaction was found to proceed without irradiation, albeit in lower yields, which is consistent with prior work on this transformation.[54] The beneficial effect of irradiation was attributed to the formation of very weak electron donor–acceptor complexes between the substrates, which increased the efficiency of the initiation step. Once initiated, a radical chain mechanism propagated, which yielded ethers upon oxidation of the benzylic radical and subsequent alcohol addition.

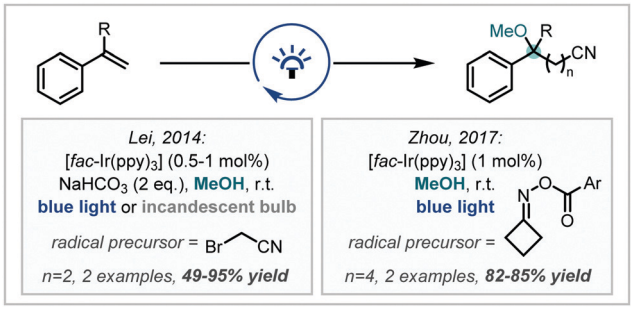
Under photoredox catalysis, the generation of $C(sp^3)$-centred radicals for addition into π-systems has become a widely explored concept. In 2017, Glorius reported a multicomponent reaction for the decarboxylative oxyalkylation of styrenes using *N*-(acyloxy)phthalimides (Scheme 5).[55] The reduction of *N*-(acyloxy)phthalimides has previously been used as a method to generate alkyl radical precursors under photoredox catalysis,[56,57] but this required strongly reducing conditions which limited the scope to net reductive transformations. Glorius showed that the reduction of the *N*-(acyloxy)phthalimide substrate could be made more favourable by exploiting hydrogen bonding interactions, which removed the requirement for strongly reducing conditions and thus enabled the reported redox–neutral process. This reaction between various primary alcohols, α-methylstyrene and the cyclohexyl radical proceeded in good yields to afford α-tertiary ether products. However, analogous reactions using more hindered alcohols such as isopropanol proceeded in lower yields, even though higher catalyst loadings were employed, emphasising the challenge associated with forming sterically-hindered α-tertiary ethers.



Scheme 5 (A) Photochemical alkoxyalkylation of styrenes using *N*-(acyloxy)phthalimides, enabled by hydrogen bond-assisted electron transfer. (B) Organophotoredox-catalysed alkoxyalkylation of styrenes. dtbbpy = 4,4′-di-*tert*-butyl-2,2′-dipyridyl, Ar = 4-trifluoromethylphenyl.

N-(acyloxy)phthalimides were later used by Nagao & Ohmiya to enact a similar transformation (Scheme 5) using a benzo[*b*]-phenothiazine organic photocatalyst (see Section 3.2, Scheme 65 for leading studies on benzo[*b*]phenothiazine-catalysed decarboxylative etherification).[58] A wide scope of alcohols and alkyl radicals could participate in the reaction, yielding a range of α-tertiary ether examples in typically good yields. Since the alcohol was used in stoichiometric quantities, more elaborate alcohols with pendant functionality could be incorporated. Moreover, tertiary alcohols were competent nucleophiles in contrast to previously reported methods. An RPC mechanism was invoked for the transformation, featuring a benzylsulfonium intermediate, displaced in a nucleophilic substitution by the alcohol to yield the ether products.

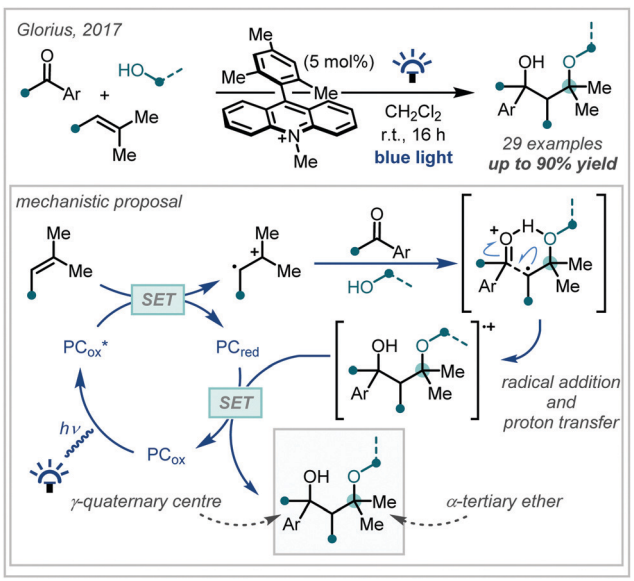
Seeking to introduce additional functional handles in tandem with etherification, in 2014, Lei published the synthesis of γ-alkoxynitriles containing tertiary methyl ethers, mediated by reduction of bromoacetonitrile by $Ir(ppy)_3$ and subsequent radical addition into styrenes (Scheme 6).[59] Zhou later reported a cyanopropylation strategy using *O*-acyl oximes as radical precursors. Upon photochemical activation, β-scission yielded a reactive alkyl radical which added to the alkene π-bond of substituted styrenes, affording α-tertiary ether products in good to excellent yields.[60]



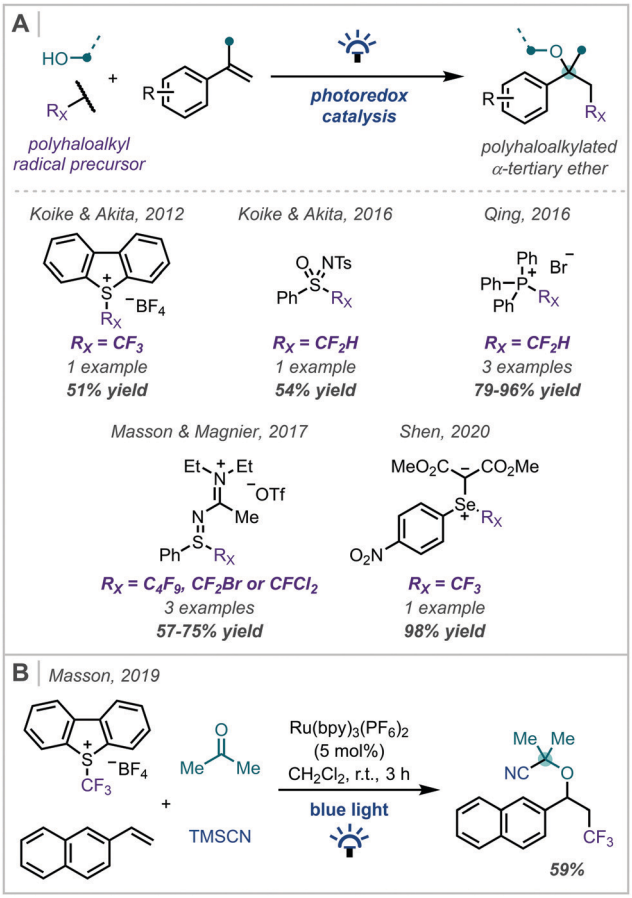
Scheme 6 Strategies for the photochemical synthesis of α-tertiary ethers containing nitrile functionality from styrenes. Ar = 4-trifluoromethylphenyl.

In 2017, Glorius reported the synthesis of γ-hydroxy-α-tertiary ethers *via* radical addition into aryl carbonyl compounds (Scheme 7).[61] Such a transformation is rare because the reaction is readily reversible – it was shown that this limitation could be overcome using hole catalysis.[62,63] Mechanistically, this involved oxidation of a styrene derivative by a strongly oxidising photoexcited acridinium species,[64] with subsequent interception of the radical cation by methanol. It was suggested that the protonated ether intermediate was able to form an intermolecular hydrogen bond with the incoming carbonyl, facilitating the subsequent radical addition by enhancing the rate of alkoxy radical quenching and thus preventing the reverse reaction. An impressive 30 α-tertiary ethers were reported, formed in excellent yields of up to 90%. Although yields were generally higher when aldehydes were used as the radical acceptor, ketones were nonetheless effective, allowing the efficient formation of α-tertiary ethers containing a hydroxylated γ-quaternary centre.

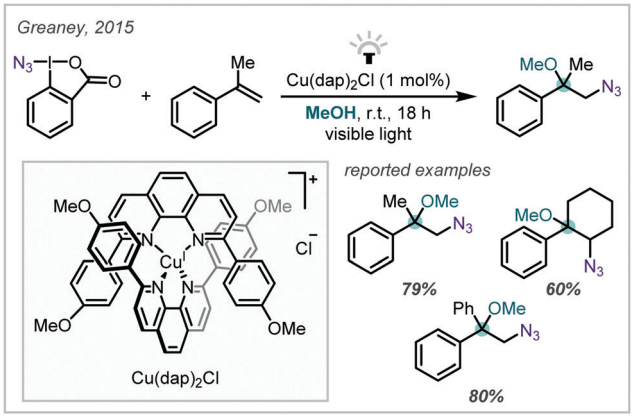
The introduction of halogen atoms, particularly fluorine, into pharmaceuticals and other bioactive molecules has



Scheme 7 Multicomponent synthesis of γ-hydroxy-α-tertiary ethers *via* hydrogen bond-assisted radical addition into carbonyl compounds. SET = single electron transfer.



Scheme 8 (A) Photochemical synthesis of polyhaloalkylated α-tertiary ethers from styrene precursors. (B) Multicomponent reaction enabling the synthesis of trifluoromethylated α-cyano-α-tertiary ethers.



Scheme 9 Alkoxyazidation of styrenes mediated by a Cu-based photocatalyst.

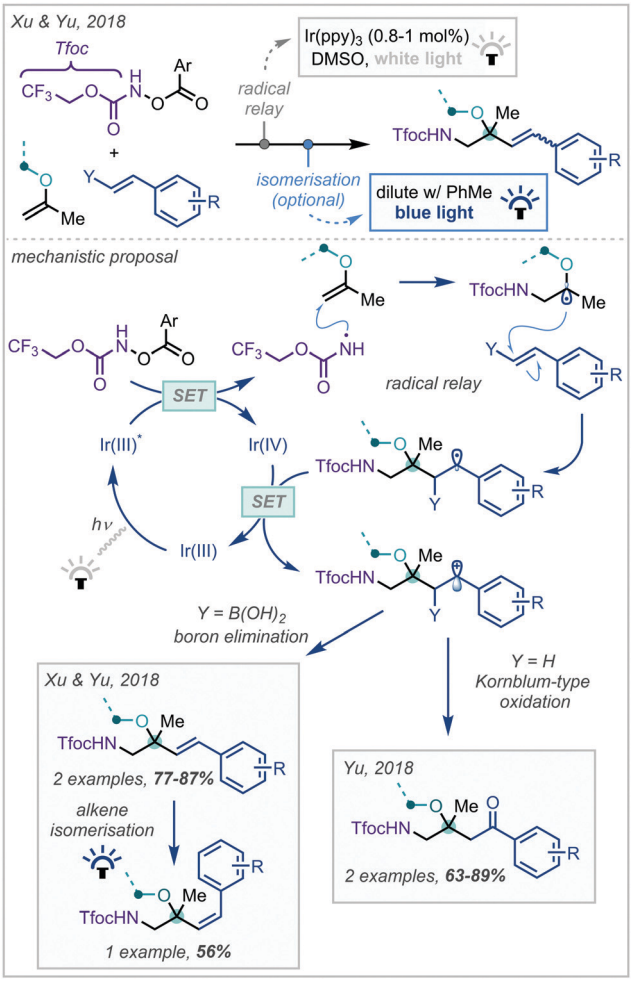
well-documented benefits on pharmacokinetics and efficacy.[65–70] Oxyhaloalkylation of alkenes mediated by photoredox catalysis therefore represents a step-economical method for the simultaneous introduction of valuable haloalkyl and α-tertiary ether functionalities into a molecule (Scheme 8). Since Koike & Akita's report of alkoxytrifluoromethylation using Umemoto's reagent in 2012,[71] several reaction manifolds have been published that achieve this transformation using alternative haloalkyl radical precursors.[72–75] In general, these reactions proceed *via* the RPC mechanism depicted in Scheme 2, yielding halogenated α-tertiary ethers in moderate to excellent yields. A noteworthy example was disclosed by Masson in 2019, involving a four-component coupling to forge a nitrile-substituted α-tertiary ether in 59% yield.[76]

2.1.2 Concurrent C–X bond formation. Alongside the aforementioned methodologies which facilitate the sequential formation of a C–O and C–C bond, etherification reactions can be coupled to C–X bond forming reactions to enable the synthesis of a wide variety of β-functionalised products. In 1985, Masanobu reported the dimethoxylation of styrenes mediated by the irradiation of copper(II) perchlorate with a 160 W mercury lamp, although the scope was narrow and yields generally low.[77] More recently, Greaney reported the use of a Cu-based photocatalyst, $Cu(dap)_2Cl$ [dap = 2,9-bis(*p*-anisyl-1,10-phenanthroline], to facilitate the alkoxyazidation of aromatic alkenes using visible light (Scheme 9).[78] Reaction of the photogenerated azido radical with 1,1-disubstituted alkenes, followed by oxidation and trapping with methanol yielded the desired α-tertiary ether products.

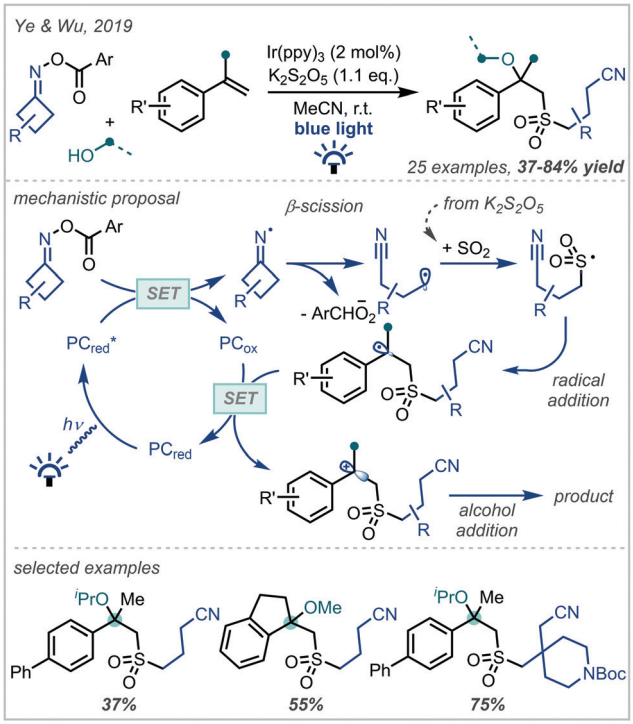
In 2018, Xu & Yu disclosed a radical relay strategy towards the synthesis of protected β-amino alcohols and ethers (Scheme 10).[79] This hinged upon the use of Tfoc [Tfoc = $-CO_2CH_2CF_3$] protected hydroxylamine derivatives as photolabile nitrogen radical precursors. Upon radical addition across an enol ether, the α-oxy radical could react further with a styryl boronic acid, forming cinnamyl α-tertiary ether products after oxidation of the resulting radical and elimination of boron. It was also shown that the geometry of the cinnamyl olefin could be subsequently isomerised under photocatalytic conditions. Soon afterwards, Yu reported a similar transformation, instead enacting a Kornblum-type oxidation of the intermediate carbocation to yield ketones at the benzylic position.[80]

In 2019, Ye & Wu reported a four-component reaction of cyclobutanone-derived *O*-acyl oximes with $K_2S_2O_5$-derived sulfur dioxide, styrene derivatives and primary alcohols to produce α-tertiary ethers with sulfones in the β-position (Scheme 11).[81] This proceeded *via* reductive decomposition of the *O*-acyl oxime precursor, forming an alkyl radical. The radical was subsequently intercepted by *in situ* generated SO_2, affording a sulfur-centred radical that added to the alkene π-bond of aromatic olefins. A variety of 1,1-disubstituted styrenes, both electron-poor and electron-rich, were tolerated in the reaction, and it was demonstrated that *O*-acyl oximes of substituted cyclobutanones were competent radical precursors, allowing the introduction of aromatic groups, an ester, and a protected piperidine moiety onto the alkyl chain.

In 2018, Knowles reported an efficient two-step procedure for the enantioselective synthesis of substituted pyrroloindolines (Scheme 12).[82] Inspired by the reactivity of tryptophan radical cations in enzymatic systems, hydrogen bonding between a tryptamine substrate and a chiral phosphoric acid catalyst enabled proton-coupled electron transfer (PCET) from



Scheme 10 Synthesis of Tfoc-protected β-amino-α-tertiary ethers from styrenes and enol ethers. Ar = 4-trifluoromethylphenyl.



Scheme 11 Multicomponent synthesis of sulfonylated α-tertiary ethers using *O*-acyl oximes as alkyl radical precursors and $K_2S_2O_5$ as a sulfur dioxide source. Ar = 4-trifluoromethylphenyl.

$Ir(ppy)_3$ under visible light irradiation, resulting in a chiral radical cation–phosphate anion pair. This could be enantioselectively intercepted by 2,2,6,6-tetramethyl piperidine 1-oxyl (TEMPO) to give an iminium ion intermediate, upon which the pendant Cbz-protected amine functionality could cyclise in a diastereoselective manner. The inclusion of the stoichiometric oxidant triisopropylsilyl-ethynyl benziodoxolone (TIPS-EBX) maintained optimal reaction efficiency, since the carboxylate base formed upon reduction negated the formation of deleterious TEMPO-H. In a subsequent photoinduced step, the TEMPO moiety could be efficiently substituted to yield the corresponding α-tertiary ethers while maintaining good enantiomeric excess. Impressively, *t*-BuOH was a proficient nucleophile in the reaction, giving access to synthetically challenging α,α′-tertiary ether products.

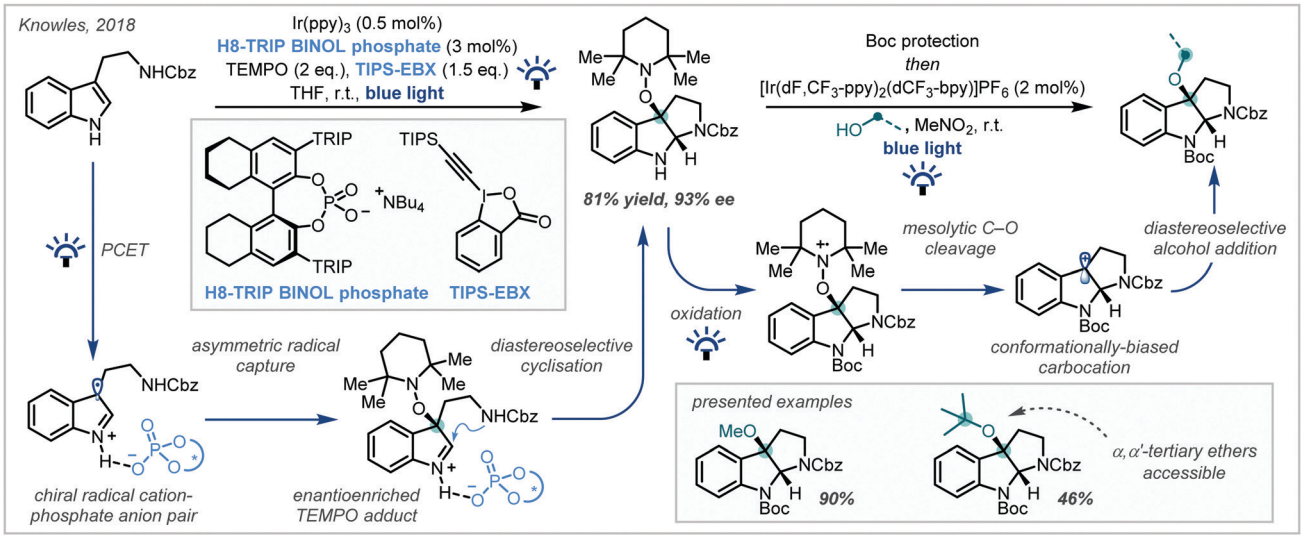
2.1.3 Dicarbofunctionalisation. The aforementioned methodologies couple the formation of the ether C–O bond with the formation of a second C–C or C–X bond. An alternative, contemporary strategy is to elaborate the α-position of a preformed α-secondary ether, presenting a complementary disconnection for the formation of α-tertiary ethers.

In 2021, Gutierrez and Molander reported a dicarbofunctionalisation methodology that exemplifies the synthetic utility of this disconnection (Scheme 13).[83] It was shown that benzophenone-derived hydrogen atom transfer (HAT) catalysts, under irradiation at 390 nm, enacted hydrogen atom abstraction from the α-position of cyclopentylmethyl ether (CPME) or diisopropyl ether to yield a nucleophilic α-oxy radical. Giese addition across activated alkenes ensued and subsequent Ni-mediated cross-coupling with an aryl bromide afforded a variety of arylated α-tertiary ethers. Although a significant excess of the ether precursor was necessary, excellent product yields could be obtained.

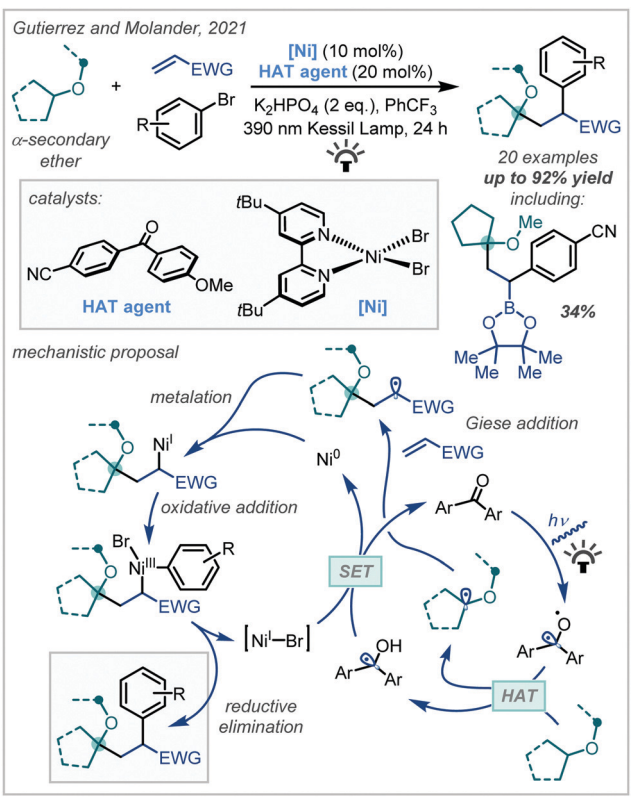
In a conceptually distinct approach, in 2017, Yoon reported that enol ethers could participate in such a transformation with thiophenol-substituted alkenes to yield ether products (Scheme 14).[84] The thiophenol moiety acted as a redox auxiliary, making the alkene more susceptible to oxidation by the $Ru(bpz)_3(BArF)_2$ photocatalyst [bpz = 2,2′-bipyrazine, BArF = tetrakis(3,5-bis(trifluoromethyl)phenyl)borate]. The resultant radical cation then underwent a [2+2] cycloaddition, followed by photoinduced reduction allowing catalyst turnover and release of the cyclobutane product. After the reaction, the sulfur moiety could be removed using standard reductive methods. Notably, the reaction was tolerant of steric bulk at the enol ether, and vinyl *tert*-butyl ether reacted to form the corresponding α-tertiary ether in high yield.

2.2 Electrochemical alkene difunctionalisation

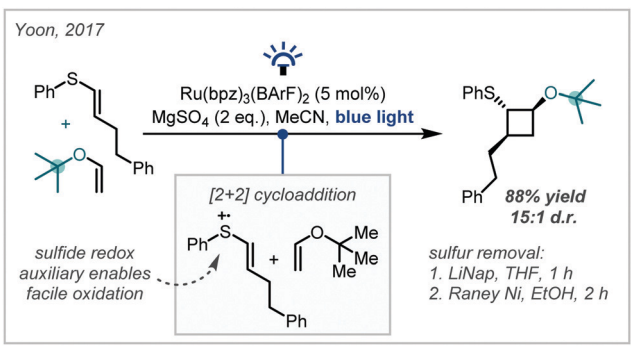
Electrochemistry offers a highly versatile framework in which to enact redox-mediated transformations and has been widely



Scheme 12 Biomimetic, enantioselective synthesis of substituted pyrroloindolines under cooperative photoredox/organocatalysis. TRIP = (2,4,6-triisopropyl)phenyl, TIPS = triisopropylsilyl, [dF,CF_3-ppy] = 3,5-difluoro-2-[5-(trifluoromethyl)-2-pyridinyl]phenyl, [dCF_3-bpy] = 5,5′-bis(trifluoromethyl)-2,2′-bipyridine.



Scheme 13 Synthesis of α-tertiary ethers *via* α-functionalisation of secondary ethers. EWG = electron-withdrawing group.

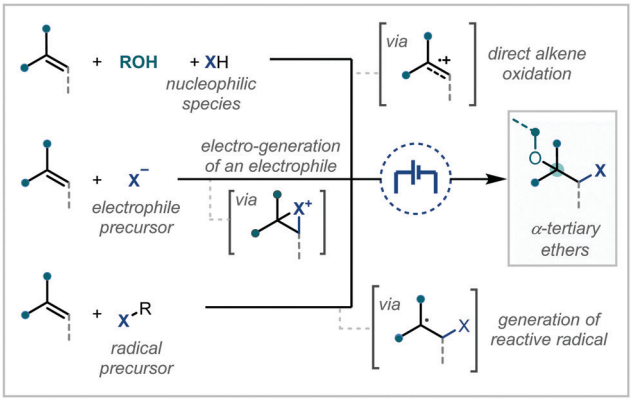


Scheme 14 Radical cation-mediated [2+2] cycloadditions promoted by the installation of a sulfur-based redox auxiliary.

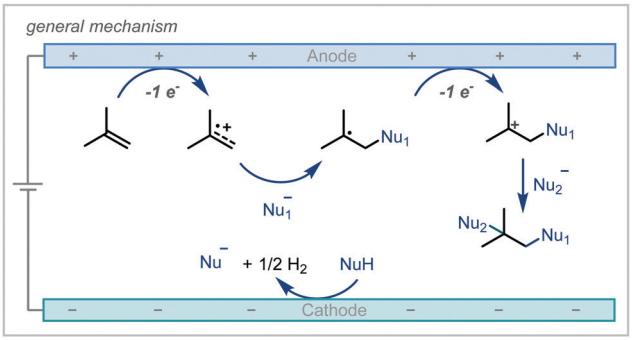
cited as offering more sustainable and atom-economical solutions to these reactions.[85] Accordingly, electrochemistry has been widely applied in the synthesis of ethers and notably shows broad applicability to acyclic α-tertiary ether synthesis. The difunctionalisation of alkenes to afford the corresponding β-functionalised ethers has predominated in the applications of electrochemistry for ether synthesis.

Among these approaches, the various reports can be broadly divided by the mechanistic framework in operation and the specific role the electrochemical cell is performing (Scheme 15). In this manner, we can view the role of the electrochemical cell as either generating a radical cation from anodic oxidation of the alkene; oxidative generation of an electrophilic species which engages in polar reactivity with the substrate; or oxidative generation of an electrophilic radical which is able to react further with the alkene.

2.2.1 Direct alkene oxidation. The most traditional and more commonly reported strategy features the direct anodic oxidation of an activated alkene, such as a styrene, to afford the radical cation (Scheme 16). This species is intercepted by an alcohol nucleophile, typically employed as the solvent or co-solvent, or the corresponding alkoxide to afford a radical which is able to undergo further oxidation to a carbocation capable of reaction with a range of nucleophiles. While early



Scheme 15 Mechanistic approaches to the electrochemically-mediated synthesis of α-tertiary ethers *via* alkene difunctionalisation.

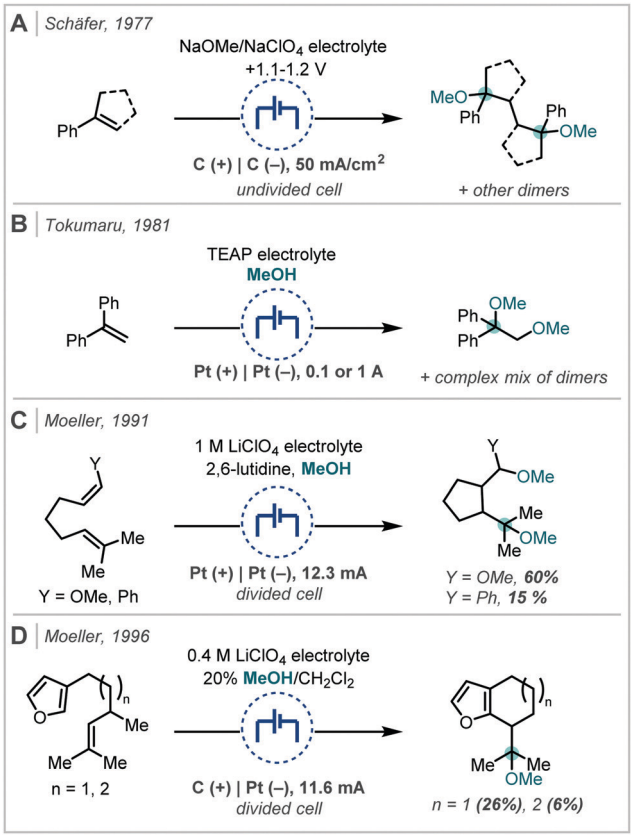


Scheme 16 General mechanism for alkene difunctionalisation *via* electrochemical oxidation.

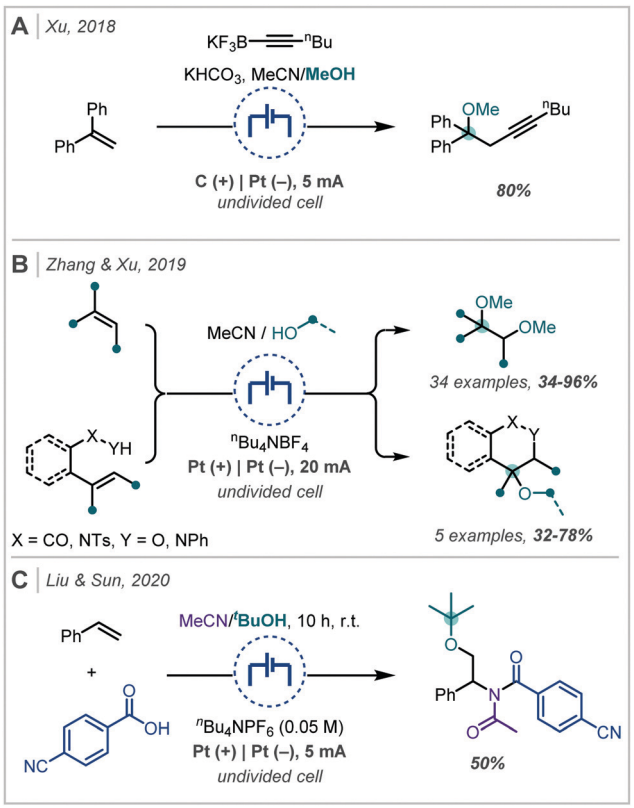
reports of such a strategy described the formation of complex mixtures of dimers,[86,87] entailing both head-head and head-tail combinations, Moeller demonstrated that, by incorporating an intramolecular trap, C–C bond formation could intercept the transiently formed radical cation with good regioselectivity (Scheme 17).[88,89] While the study focussed more on the overall behaviour of these systems, α-tertiary ethers were observed both when using enol ethers and electron-rich (hetero)arenes as the nucleophilic trap, in the presence of methanol.

Following the recent renewal of interest in electrochemical transformations, this approach towards the synthesis of hindered ethers has been revisited and significantly developed. In 2018, Xu reported a broad scope strategy towards the electrochemical carbohydroxylation of alkenes and successfully demonstrated an extension of this method in the synthesis of α-tertiary ethers (Scheme 18A).[90] Organotrifluoroborates were employed as the nucleophilic component which could intercept the electro-generated alkene radical cation. The resulting radical could be further oxidised and intercepted with MeOH. The etherification occurred in a high yield employing 1,1-diphenylethylene as the substrate and a hexynyl trifluoroborate as the nucleophile.

In an alternative difunctionalisation approach, Zhang and Xu described the dimethoxylation of alkenes, in which



Scheme 17 Early electrochemical ether syntheses *via* direct alkene oxidation; TEAP = tetraethylammonium perchlorate.



Scheme 18 Contemporary applications of electrochemical alkene oxidation.

methoxide reacts with both the alkene radical cation and the resulting carbocation after each anodic oxidation event (Scheme 18B).[91] The procedure demonstrated very broad applicability to α-tertiary ether synthesis and could be up-scaled to >5 g. Notably in a number of cases when secondary ether synthesis was attempted, the correspondingly less stable carbocation could undergo rearrangement, resulting in acetal synthesis. Liu & Sun extended this strategy to interception with acetonitrile, generating a nitrilium ion which could react with a carboxylic acid (Scheme 18C).[92] The resulting acyl imidate was capable of undergoing a Mumm rearrangement to afford the imide. When *t*-BuOH was employed as co-solvent, an α-tertiary ether was afforded in 50% yield.

2.2.2 Use of electro-generated electrophiles. In a mechanistically distinct application of electrochemistry, anodic oxidation has been employed to generate reactive electrophiles *in situ*. This has been successfully applied in the oxidation of halides to generate either the reactive halogen (0) species or halogen (+1) cations.

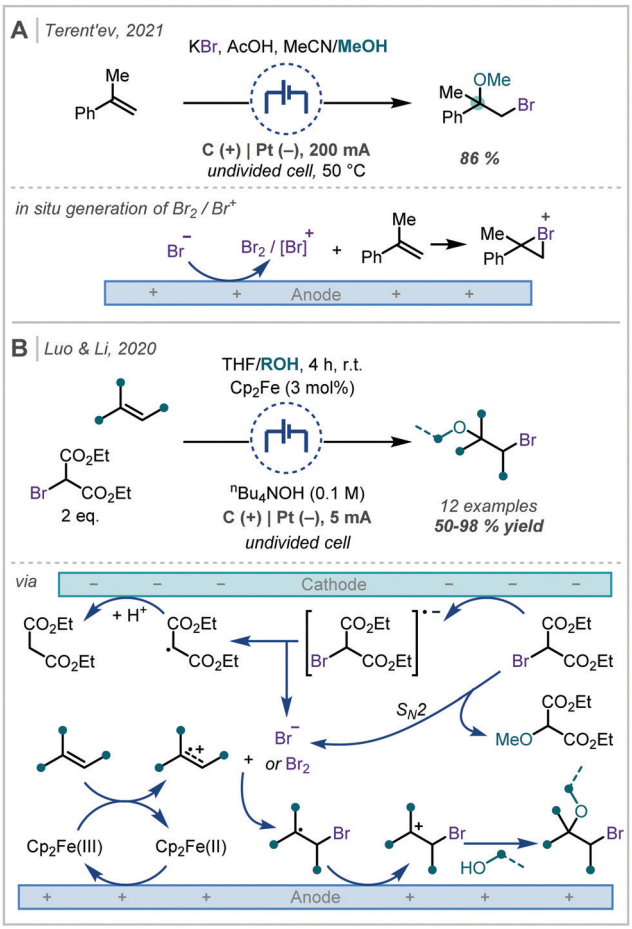
Terent'ev applied this strategy, using a bromide source, to the synthesis of both bromohydrins and β-bromoethers (Scheme 19A).[93] In the latter case, MeOH was employed as a co-solvent and was proposed to open the bromonium ion resulting from reaction with α-methyl styrene.

In a modified approach, Luo and Li reported a similar transformation (Scheme 19B); however, the authors employed Cp_2Fe as an electro-catalyst capable of effecting the direct oxidation of an alkene.[94] This could undergo further reaction either with *in situ* generated bromide or with bromine and the resulting radical followed the same course as previously described. Notably, bromomalonates were employed as both the bromide source and implicated in the reaction at the cathode. The authors demonstrated that α-tertiary ether synthesis was possible by use of either α-substituted styrenes or by changing the incoming nucleophile to a tertiary alcohol such as *t*-BuOH.

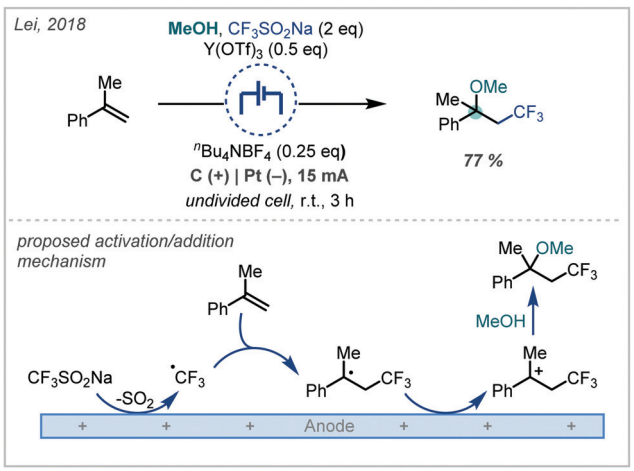
2.2.3 Use of electro-generated radical species. The reaction of radicals of appropriate philicity with ground-state styrenes is a well-understood transformation and has been extended to electrochemical oxidation.[95,96] In 2018, Lei reported the anodic oxidation of triflate salts, for example the Langlois reagent (CF_3SO_2Na), to generate trifluoromethyl radicals capable of reacting with ground state alkenes in a Markovnikov fashion (Scheme 20).[97] The resulting radical was oxidised and intercepted as previously described. A single tertiary example derived from α-methyl styrene was reported in good yield. Notably, sub-stoichiometric quantities of Lewis acidic yttrium triflate were demonstrated to improve the efficiency of the reaction.

In an analogous fashion, sulfonyl radicals have been widely applied to such difunctionalisation reactions (Scheme 21A). Lei has demonstrated the application of sulfonyl hydrazides in this transformation, which, upon oxidation, afford the desired sulfonyl radical;[98] and subsequently Sun and Han reported the use of sulfinic acids and sulfonate salts, respectively.[99,100] Han's report is notable given the extensive range of α-tertiary ethers afforded.

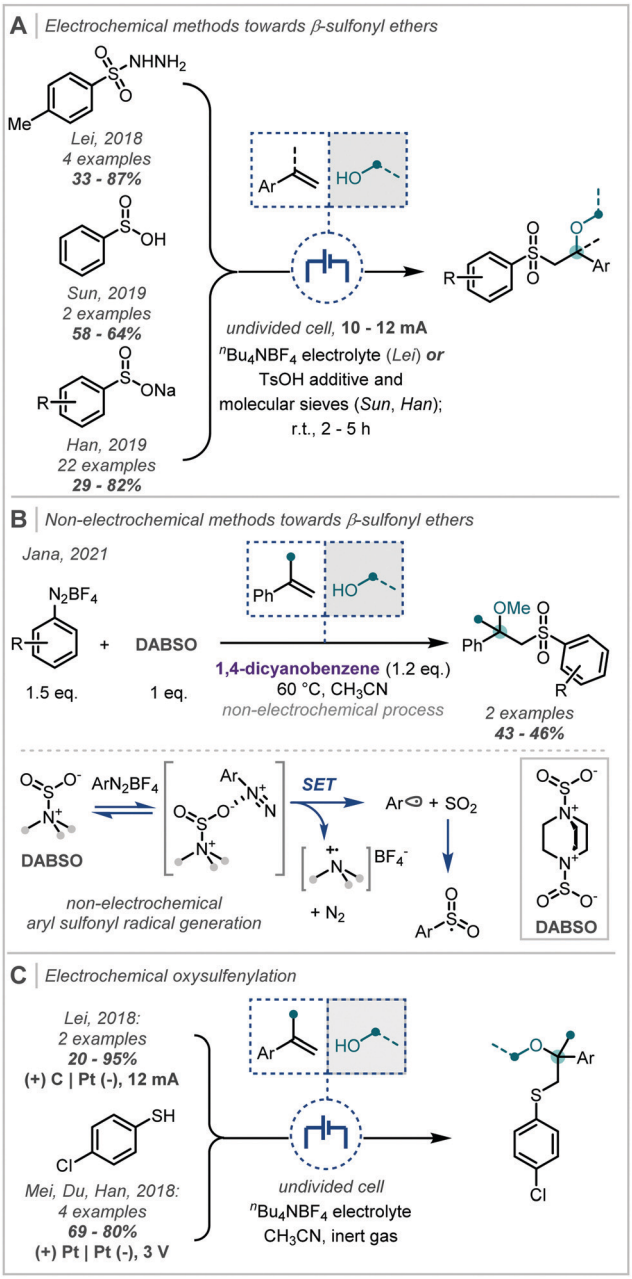
It should be noted that a related alkoxysulfonylation was reported by Jana without the use of electrochemical activation (Scheme 21B).[101] In this work, the authors employed



Scheme 19 Electrochemical generation of halogen electrophiles capable of reaction with alkenes. Note: proposed anodic oxidation of bromide ions to bromine has been omitted for clarity.



Scheme 20 Electrochemical generation of the trifluoromethyl radical and subsequent reactivity to afford α-tertiary ethers.



Scheme 21 Alkoxy-sulfonylation and -sulfenylation routes to α-tertiary ethers.

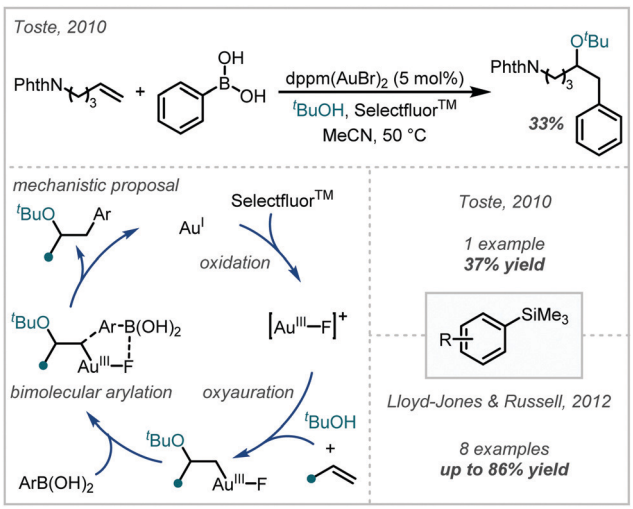
1,4-diazabicyclo[2.2.2]octane bis(sulfur dioxide) (DABSO), in the presence of aryl diazonium salts, to generate *in situ* the desired aryl sulfonyl radical. Mechanistically, it was proposed that SET from DABSO brought about fragmentation of the diazonium salt and produced an aryl radical capable of combination with SO_2. Subsequent reactivity was as described above, however, the oxidation of the alkyl radical, resulting from sulfonyl addition to the alkene, was effected by 1,4-dicyanobenzene (DCB).

Through minor modification to the electrochemical system described for oxidation of sulfonyl hydrazides, Lei additionally reported the oxysulfenylation of alkenes (Scheme 21C).[102] Employing thiols in this case, the authors observed Markovnikov regioselectivity following the addition of a thiyl radical. The study demonstrated that the subsequently formed carbocations could be trapped with a broad range of alcohols and even extended this to amine nucleophiles. α-Tertiary ethers could be afforded in variable yields, with variation on either side of the ether linkage. Shortly after, Mei, Du & Han reported the oxysulfenylation of alkenes and demonstrated that this system could be extended to etherification, with α-tertiary ether examples afforded in good yields.[103] Notably, Lei proposed a putative alternative mechanism in which an electrophilic sulfur species could be generated following oxidation of transiently formed disulfides.

2.3 Transition metal-mediated alkene difunctionalisation

The extensive redox chemistry of transition metals presents significant opportunity for catalysis under both one- and two-electron manifolds. Accordingly, this behaviour has been applied to the redox-mediated synthesis of α-tertiary ethers. The following section will highlight such methods, and discuss their pertinent mechanistic aspects. Due to their inclusion in the Section 2.1, however, reactions mediated by transition metal-based photocatalysts will not be included. In addition, cross coupling reactions mediated by Pd and other metals will not be covered, since they have been extensively reviewed elsewhere.[40–43,104]

2.3.1 Concurrent C–C bond formation. In 2010, Toste reported that readily available aryl boronic acids could participate in Au-catalysed oxyarylation reactions to form arylated α-tertiary ethers (Scheme 22).[105] The combination of catalytic dppm(AuBr)$_2$ [dppm = bis(diphenylphosphanyl)-methane] and excess Selectfluor™ afforded a *tert*-butyl ether from 5-phthalimidopentene in 33% yield, in the presence of *t*-BuOH. Mechanistically, a Au(I)/Au(III) redox cycle was proposed, in contrast to the π-Lewis acid catalysis traditionally associated with related transformations. Oxidation of the Au(I) bromide by



Scheme 22 Au-catalysed oxyarylation of alkenes with aryl boronic acids, and extension to aryltrimethylsilanes.

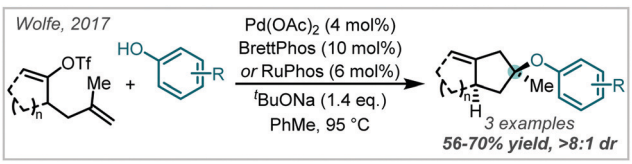
Selectfluor™ afforded a cationic Au(III) species, which underwent oxyauration to yield the β-metalated α-tertiary ether. C–C bond formation at the terminal carbon, without prior transmetalation to the Au centre, released the product and closed the catalytic cycle.

The realisation that no transmetalation occurred during this reaction inspired the use of aryltrimethylsilanes in analogous works.[106,107] Consequently, stable and readily accessible silane reagents could be used to good effect without the need for exogenous fluoride or hydroxide, which is typically required to facilitate their transmetalation to metal centres. Additionally, the use of silanes reduced the formation of biaryl side-products associated with Toste's boronic acid protocol. Reports by Toste and Lloyd-Jones & Russell established the efficacy of the silane protocol for forming α-tertiary ethers when 1,1-disubstituted olefins were employed, with slight modifications to the catalytic systems in each case.

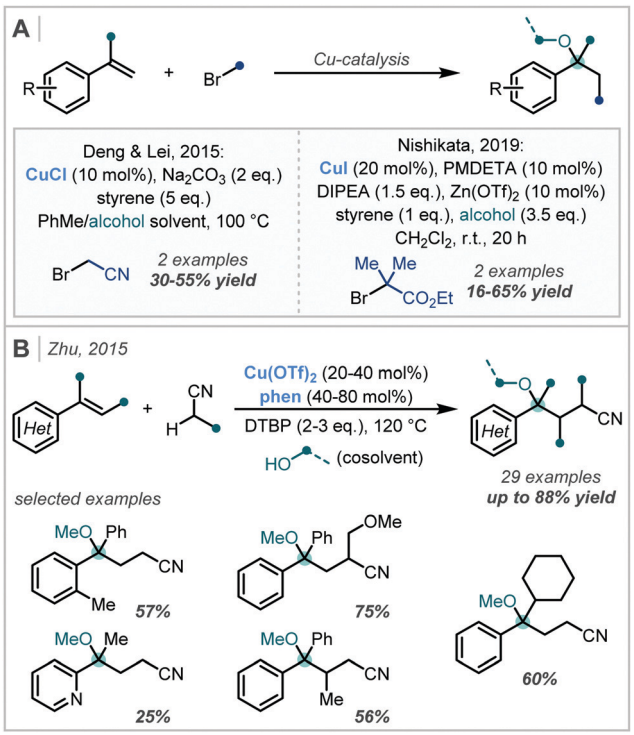
In 2017, Wolfe detailed an oxidative carboalkoxylation of alkenes for the synthesis of carbocyclic scaffolds (Scheme 23).[108] The authors proposed that upon oxidative addition of a Pd catalyst into a preinstalled alkenyl or aryl triflate, pendant alkenes underwent oxypalladation with phenol nucleophiles to install the ether moiety. Subsequent reductive elimination formed the C–C bond and released the bicyclic products. This protocol was shown to be effective for the formation of a collection of carbocyclic α-tertiary ethers, which were afforded in good yield with high levels of diastereoselectivity.

Additionally, the single-electron redox chemistry of transition metal salts has been effectively employed in alkene difunctionalisation reactions for the formation of α-tertiary ethers. In 2014, Deng and Lei reported that CuCl can facilitate the single electron reduction of α-bromonitriles to yield the corresponding alkyl radical.[109] This then participated in a radical addition/RPC mechanism with styrenes (Scheme 24A), which yielded an α-tertiary ether in 30% yield. A mechanistically similar transformation was later reported by Nishikata, in which α-bromoesters were used as the alkyl radical precursor.[110] However, the yields of α-tertiary ether products were low: a single example with *t*-BuOH as the nucleophile was reported in 16% yield.

In 2015, Zhu reported a method for the formation of a wide scope of styrene-derived α-tertiary ethers (Scheme 24C).[111] It was shown that a Cu(II) catalyst could selectively metalate the α-C–H bond of alkyl nitriles *via* a deprotonation–metalation pathway, facilitating addition of the nitrile moiety to the alkene π-bond of styrene derivatives. Following Cu-mediated oxidation of the resultant alkyl radical, reaction with an alcohol co-solvent yielded the final products – di-*tert*-butyl peroxide (DTBP) was used to enable turnover of the catalytic cycle. The



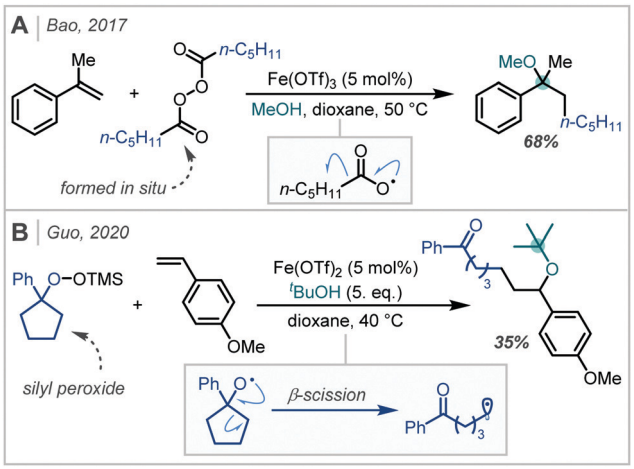
Scheme 23 Pd-catalysed carboalkoxylation of alkenes.



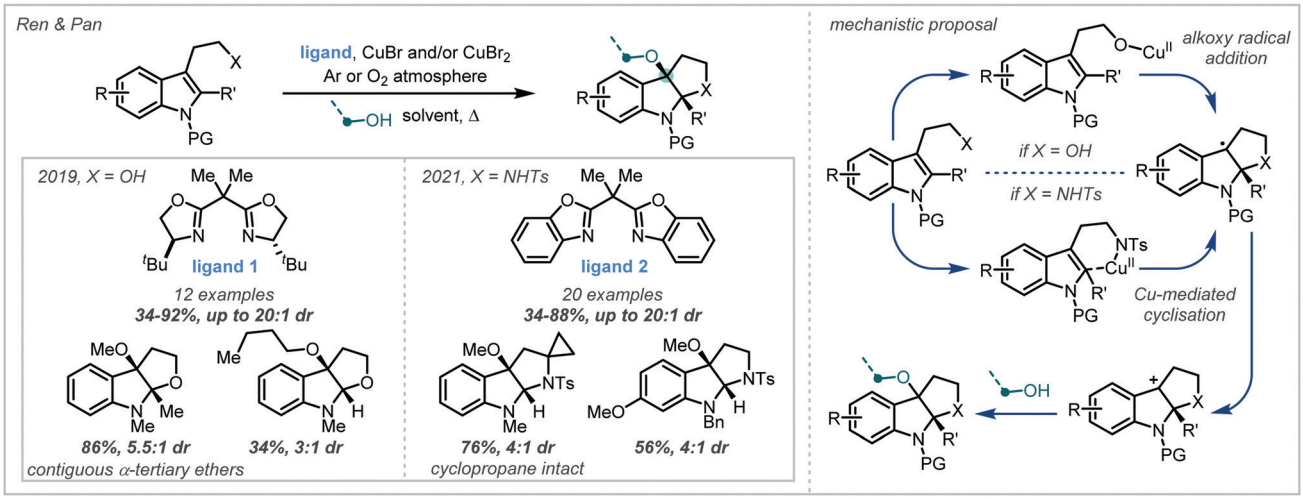
Scheme 24 Cu-catalysed carboetherification reactions *via*: (A) single-electron reduction of alkyl bromides; (B) C–H activation at the α-position of alkyl nitriles. PMDETA = *N,N,N′,N″,N″*-Pentamethyldiethylenetriamine; phen = 1,10-phenanthroline.

intermediate steps were proposed to proceed either *via* free radical species or Cu-bound intermediates. A variety of examples were reported with excellent yields, including those containing both electron-rich, poor and *ortho*-substituted aromatics, heterocycles and hindered trisubstituted alkenes.

In 2017, Bao demonstrated that Fe salts were capable of single electron reduction of diacyl peroxides, affording nucleophilic alkyl radicals (Scheme 25A).[112] Addition of the alkyl radical to the alkene π-bond of styrene derivatives, RPC, and



Scheme 25 Fe-catalysed formation of α-tertiary ethers using: (A) diacyl peroxides; (B) silyl peroxides.



Scheme 26 Cu-catalysed synthesis of furoindolines and pyrroloindolines from tryptophan derivatives.

methanol addition yielded an α-tertiary ether in good yield. Recently, Guo reported the Fe-catalysed carboetherification of styrenes using silyl peroxides as the alkyl radical source (Scheme 25B).[113] In this case, radical generation proceeded *via* peroxide reduction and subsequent β-scission of the alkoxy radical. The formation of a single α-tertiary ether was reported employing *t*-BuOH as the nucleophile.

2.3.2 Concurrent C–X bond formation. In 2019, Ren & Pan disclosed a method for the diastereoselective synthesis of furoindolines containing α-tertiary ether motifs (Scheme 26).[114] Using a copper oxazoline catalyst, the authors proposed the generation of typically unstable alkoxy radicals, which subsequently underwent intramolecular cyclisation onto an indole.

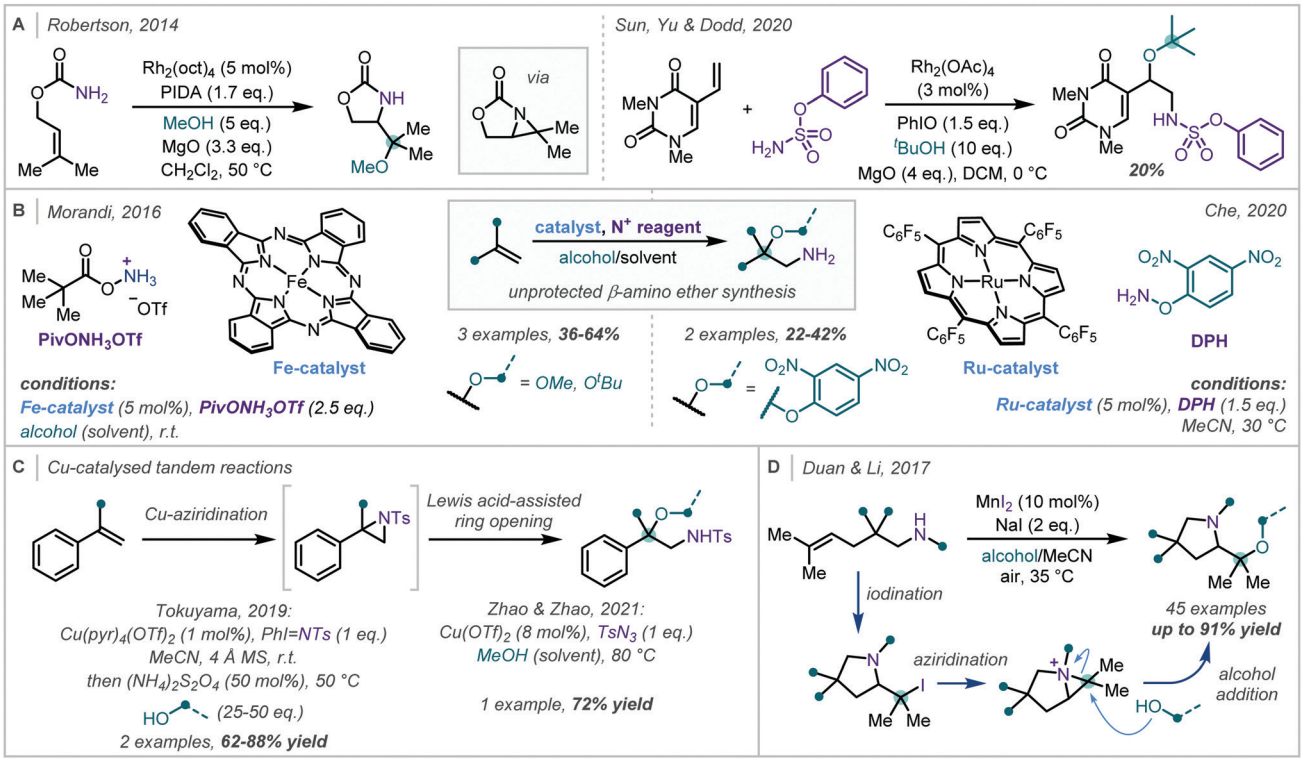
Oxidation of the resultant radical by a Cu(II) species generated a stabilised carbocation that could be intercepted by a primary alcohol in a diastereoselective manner. In 2021, the authors extended this methodology to the synthesis of the related pyrroloindolines.[115] The proposed mechanism was quite different, implicating Cu-mediated delivery of the pendant amine rather than the generation of free aminyl radicals. Conducting the reactions under an atmosphere of O_2 was shown to increase product yields and it was therefore proposed that O_2 acted as the terminal oxidant, responsible for turning over the copper catalyst and closing the catalytic cycle. A wide scope of α-tertiary ether-containing products were reported, many of which were formed with excellent diastereoselectivity.

Transition metal catalysis has also found use in the oxidative formation of β-amino-α-tertiary ethers from alkene starting materials. In 2014, following investigations into tethered aminohydroxylation reactions, Robertson developed a Rh-catalysed oxyamination of allylic carbamates (Scheme 27A).[116] It was proposed that in the presence of (diacetoxyiodo)benzene (PIDA) and $Rh_2(oct)_4$ [oct = octanoate], a Rh-nitrenoid was formed at the carbamate nitrogen, which was capable of cyclising onto a pendant alkene to yield a bicyclic aziridine intermediate. In a single example, the authors showed that when an excess of methanol was used in the reaction, regioselective ring opening of the aziridine was achieved, yielding the α-tertiary ether product. Following this report, the application of aziridines in oxidative alkoxyamination reactions has been expanded upon. In 2020, Sun, Yu & Dodd reported the intermolecular aminoalkoxylation of 1,3-dimethyl-5-vinyluracil with *t*-BuOH, utilising a similar Rh-based catalytic system, with phenyl sulfamate to generate an electrophilic nitrogen centre (Scheme 27A).[117] However, competitive elimination of the alkoxide moiety in the product severely limited the yield in this case.

Porphyrin-derived metal catalysts have also been employed to good effect in oxyamination reactions (Scheme 27B). In 2016, Morandi reported that unprotected β-amino-α-tertiary ethers could be forged from unactivated alkenes under Fe catalysis.[118] This challenging transformation was realised using a macrocyclic Fe(II)-phthalocyanine catalyst and $PivONH_3OTf$ (Piv = pivaloyl) as an electrophilic nitrogen source. Three examples of α-tertiary ethers were reported in moderate to good yield and, impressively, *t*-BuOH was found to be a competent nucleophile in this reaction. Later, Che reported a similar methodology that used *O*-(2,4-dinitrophenyl)hydroxylamine (DPH) as the aminating reagent alongside a Ru–porphyrin catalyst.[119] A few examples of α-tertiary ethers were synthesised in this manner, however, no exogenous alcohol could be incorporated into the product – only ethers derived from the 2,4-dinitrophenol moiety could be formed.

Cu catalysis has also been used in related transformations, particularly since the Lewis acidity of copper salts can be used to assist the subsequent ring-opening reaction of the aziridine (Scheme 27C). Tokuyama and Zhao & Zhao exploited this dual catalytic role of copper in recent reports and detailed the synthesis of a small number of α-tertiary ether examples in good to excellent yield.[120,121]

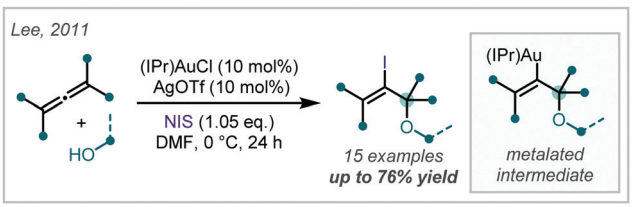
In 2017, Duan and Li employed aziridinium ions as reactive intermediates in a one-pot synthesis of valuable prolinol ethers from unfunctionalised olefins (Scheme 27D).[122] This was realised using a combination of NaI and catalytic MnI_2, under an air atmosphere, to iodinate the double bond with concomitant



Scheme 27 Metal-catalysed oxyamination of alkenes utilising: (A) rhodium and hypervalent iodine; (B) metal-porphyrin catalysts; (C) Cu-catalysed tandem reactions; (D) a one-pot iodination-aziridination approach.

formation of the pyrrolidine moiety. Subsequent aziridinium formation and ring opening by an exogenous alcohol afforded a diverse array of α-tertiary prolinol ethers in moderate to excellent yields.

Investigating the reactivity and selectivity of allenes, Lee disclosed the use of Au-catalysis in the formation of iodinated α-tertiary ethers from the parent allene (Scheme 28).[123,124] Based upon the authors' earlier work, it was shown that a combination of (IPr)AuCl [IPr = bis-2,6-diisopropylphenyl imidazolylidene], AgOTf and a ten-fold excess of alcohol enabled the regioselective oxyauration of substituted allenes to yield β-metalated-α-tertiary ethers. Terminal oxidation by *N*-iodosuccinimide (NIS) then formed the iodinated products; notably, NIS could not facilitate the reaction in the absence of the Au catalyst. The authors also demonstrated that the alkenyl iodide could be used as a functional handle for further elaboration *via* Pd-catalysed Sonogashira and Heck reactions.

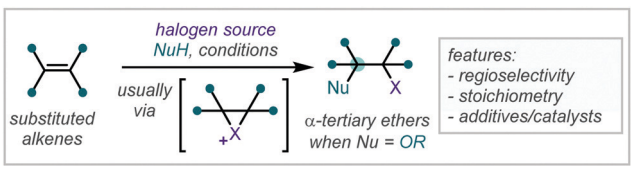


Scheme 28 Au-catalysed synthesis of β-iodo-α-tertiary ethers from allenes.

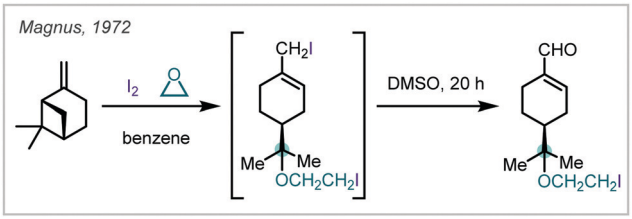
2.4 Halogen-mediated alkene difunctionalisation

The direct application of halogens in the oxidation of alkenes has become well-established as a versatile method for installing β-haloether moieties (Scheme 29). The appropriate combination of an alcohol nucleophile in the presence of oxidising halogen compounds can enable the synthesis of acyclic α-tertiary ethers, and is often dramatically improved by the application of additives and catalysts. This synthetically useful transformation gives a variety of halogenated products which are used in pharmaceuticals,[65–67] agrochemicals,[125,126] and as important synthons in the synthesis of complex scaffolds.[127–130] These methods often employ inexpensive, commercially available reagents, with short reaction times and operate under ambient conditions.

In order to ensure high yields, such reactions are more commonly observed for substrates that result in regioselective Markovnikov reactions, typically featuring 1,1-di- or 1,1,2-trisubstituted alkenes. Moreover, these strategies typically rely on superstoichiometric, if not solvent, quantities of alcohol, thus



Scheme 29 Co-halogenation of alkenes to afford β-haloethers.



Scheme 30 Ring opening of (−)-pin-2(10)-ene with I_2 to give an α-tertiary ether.

limiting widespread application of these methods to high-value alcohols, or to substrates that are insoluble in an alcohol or alcohol–cosolvent mixture. Nonetheless, the methods presented in this chapter offer efficient and robust routes to access important α-tertiary β-haloethers.

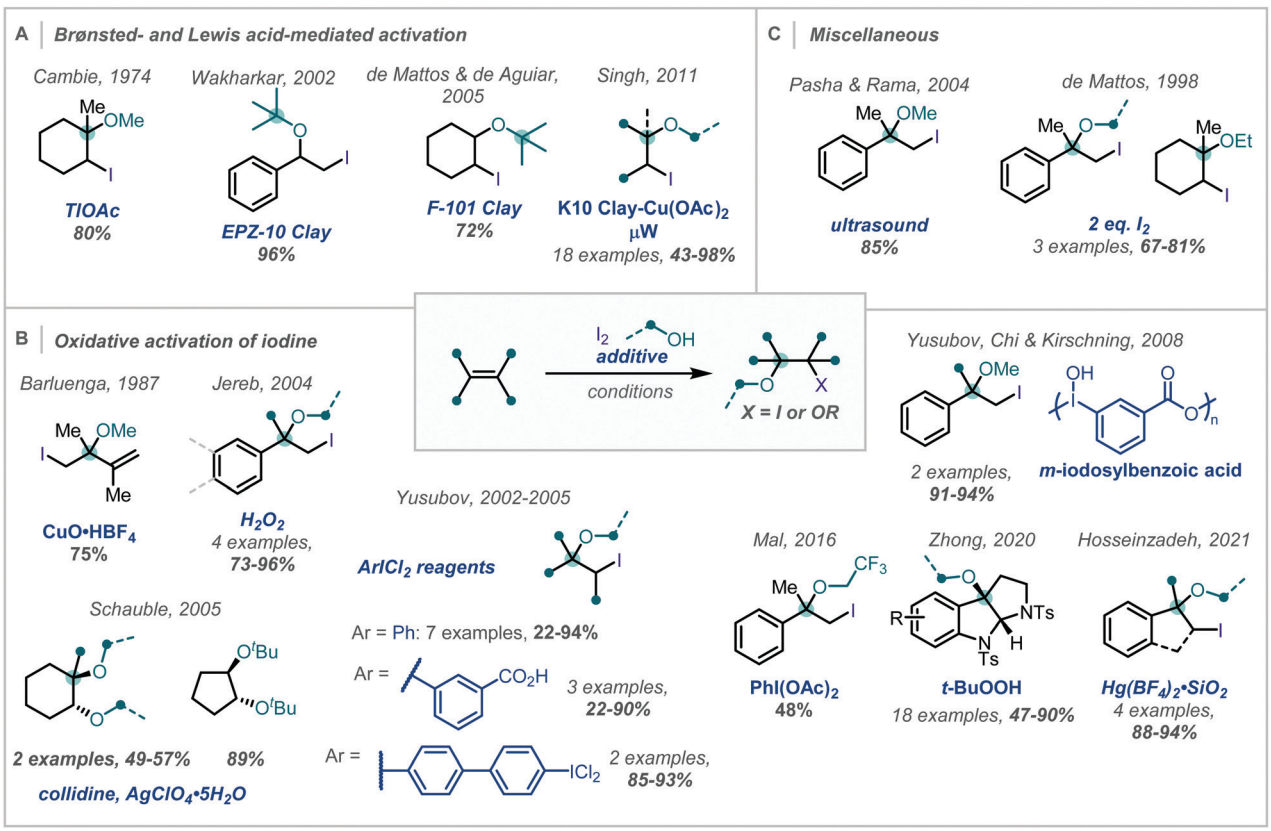
2.4.1 Iodine (0). One major class of transformations involves the reaction of I_2 with alkenes, often promoted by additives and catalysts, usually affording β-iodoethers as products (Scheme 31). However, as early as 1972, Magnus investigated the iodination of (−)-pin-2(10)-ene with iodine in ethylene oxide and benzene to give the ring-opened framework product, containing an α-tertiary β-iodoether (Scheme 30).[131] The role of additives in such iodoetherification reactions can broadly be distinguished by either (Brønsted or Lewis) acidic mediation or oxidative activation of iodine.

Despite early studies detailing the capability of weakly Lewis acidic cations, for example Tl(I), to promote the ring opening of transiently formed iodonium intermediates (Scheme 31A),[132] there has been a concerted effort to avoid the use of potentially toxic metal salts and move towards additives which are environmentally benign or that give by-products which are more easily removed on work-up.

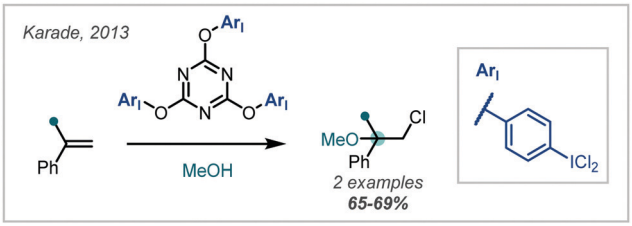
In the spirit of this, de Mattos showed, in 1998, that simply using two equivalents of iodine in an alcohol solvent afforded the corresponding β-iodoethers in good to excellent yields, several bearing an α-tertiary ether (Scheme 31C).[133] It is proposed that activation of one molecule of iodine by another occurs *via* halogen–halogen bonding in an alkene-I_2 complex.

This drive for more environmentally-benign reagents has led to considerable investigation into the beneficial effects of aluminosilicates present in clays (Scheme 31A). Wakharkar, de Mattos, de Aguiar and Singh have independently highlighted this effect in the synthesis of α-tertiary ethers in good yields.[134–136]

Methods which employ oxidants as additives, in combination with iodine, also afford β-iodoethers in good to excellent yields. In 1987, Barluenga disclosed a $CuO{\cdot}HBF_4$ promoted iodoetherification of 2,3-dimethylbuta-1,3-diene with quantitative recovery of CuI from the crude reaction mixture (Scheme 31B).[137] Recently, Hosseinzadeh reported the use of $Hg(BF_4)_2$ supported on SiO_2 to facilitate the reaction of molecular iodine with



Scheme 31 Iodine-mediated synthesis of α-tertiary ethers facilitated by: (A) acidic additives, (B) oxidative additives, and (C) miscellaneous activation strategies.



Scheme 32 A novel I(III)–Cl reagent for the chloroetherification of alkenes.

α-methylstyrene and various alcohols in over 88% yield, including an α,α′-tertiary ether.[138]

Yusubov demonstrated the use of hypervalent iodine reagents, such as $PhICl_2$, as oxidative additives to give more electrophilic "IX" species *in situ* (Scheme 31B).[139,140] These reacted smoothly with alkenes, giving two examples of α-tertiary ethers in good yield; this method was also applied to halomethoxylation of monoterpenes.[141] This concept was further extended to a number of modified $ArICl_2$ reagents[142] and polymeric *m*-iodosyl benzoic acid species,[143] capable of facile recovery and recycling of the reduced species. Notably, exclusion of iodine in these approaches leads to the β-chloroethers as demonstrated in the reports from Yusubov and in subsequent work from Karade (Scheme 32), employing a modified triazine "ICl_2" reagent.[144]

In 2016, Mal demonstrated that PIDA can react with I_2, giving IOAc (Scheme 31B).[145] This stronger electrophile reacted in a facile manner with α-methylstyrene in CF_3CH_2OH to give the corresponding β-iodoether, albeit in only 48% yield.

A related strategy had previously been employed by Jereb, using H_2O_2 as an oxidant to form β-iodoethers from α-methylstyrene and 1,1-diphenylethene in methanol or ethanol.[146]

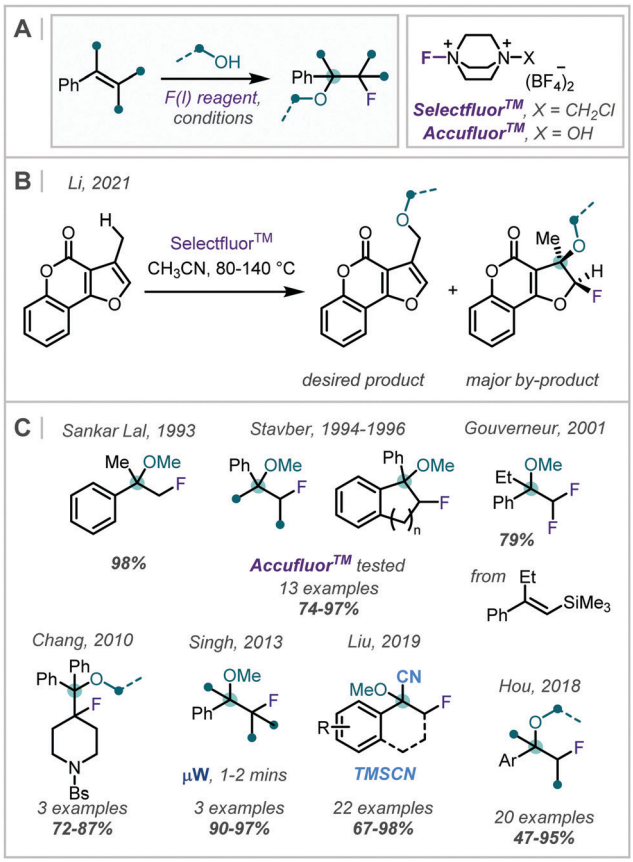
An isolated report from Schauble involved 1,2-dialkoxylation of cyclopentene and cyclohexene-type olefins using I_2, silver perchlorate, and collidine to give a β-iodoether intermediate (Scheme 31B).[148] Ag^+-assisted iodide abstraction facilitated substitution – notably even with hindered *t*-BuOH; however, undesired 1,2-hydroxyethers were frequently observed unless anhydrous silver perchlorate was used.

Zhong reported an oxidative cascade towards pyrroloindoline derivatives, employing alkyl peroxides as terminal oxidants in an etherification of the tryptamine moiety (Scheme 31B).[149] This constitutes a complementary strategy in which the addition of an oxidant enables catalytic turnover of the halogenating reagent, rather than its activation. Notably PIDA was reportedly unsuccessful, with the authors identifying *t*-butyl hydroperoxide as a superior oxidant to re-oxidise the iodide to molecular iodine. Once the iodonium ion was formed, the pendant amino group of the tryptamine moiety cyclised onto this to give the tertiary alkyl iodide. Nucleophilic substitution of the newly generated alkyl iodide gave the α-tertiary ether and the released iodide ion was re-oxidised to molecular iodine by the peroxide, facilitating the use of catalytic I_2 (10 mol%).

Interestingly, there has been one report, by Pasha & Rama, where ultrasound sonication was demonstrated to promote the reaction of iodine with α-methylstyrene in methanol (Scheme 31C).[147]

2.4.2 Fluorine(I) reagents. Fluorination of organic compounds is fundamentally important yet synthetically challenging, with a variety of unselective fluorinating reagents, such as XeF_2, being historically utilised.[65–67,150] Pre-generated electrophilic halogenation reagents in the formal +1 oxidation state are now used widely in the synthesis of α-tertiary ethers *via* difunctionalisation of alkenes. A prominent example of these reagents in fluorination chemistry is Selectfluor™, (Scheme 33A) owing to its mild reactivity and good stability.[151] Selectfluor™ has been applied to the haloetherification of alkenes with alcohol nucleophiles, thus resulting in β-fluoroethers, and this approach has successfully afforded α-tertiary ethers from the corresponding 1,1-disubstituted alkenes. Notably, F(I)-mediated alkene difunctionalisations are so robust that fluoroalkoxylation has been observed as the major by-product in the C–H alkoxylation of furanocoumarins reported by Li (Scheme 33B).[152]

Sankar Lal reported the use of Selectfluor™ to synthesise a β-fluoro-α-tertiary ether in very high yield, and Stavber subsequently investigated the diasteroselectivity for the same transformation with benzocyclenes (Scheme 33C).[153,154] It was shown that ring size and steric hindrance of the alcohol played a significant role in the stereochemical outcome. Later, Stavber reported an analogous reaction on acyclic alkenes but with the



Scheme 33 Methods for the formation of β-fluoro-α-tertiary ethers employing Selectfluor™ and Accufluor™. Bs = $SO_2C_6H_4Br$.

alternative fluorinating reagent Accufluor™ and demonstrated similar yields and rates.[155] The kinetics and stereochemical course of this transformation with Selectfluor™ were also thoroughly investigated and compared with analogous reactions utilising XeF_2 and $CsSO_4F$.[156]

In 2010, Chang applied this transformation to piperidinyl olefins, affording pharmaceutically relevant 4-functionalised piperidines (Scheme 33C).[157] Later, Singh showed that by applying microwave irradiation, the reaction time for such transformations was drastically reduced.[158] Investigating alternative substrates, Gouverneur disclosed that the application of two equivalents of Selectfluor™ with alkenyltrimethylsilanes gave the difluorodesilyation product.[159]

In 2018, Hou reported that the use of Selectfluor™ with 10 equivalents of MeOH in MeCN afforded β-fluoro-α-tertiary ethers (Scheme 33C).[160] An impressive 20 examples were demonstrated, including a range of olefins and alcohols, with yields in the range 47–95%.

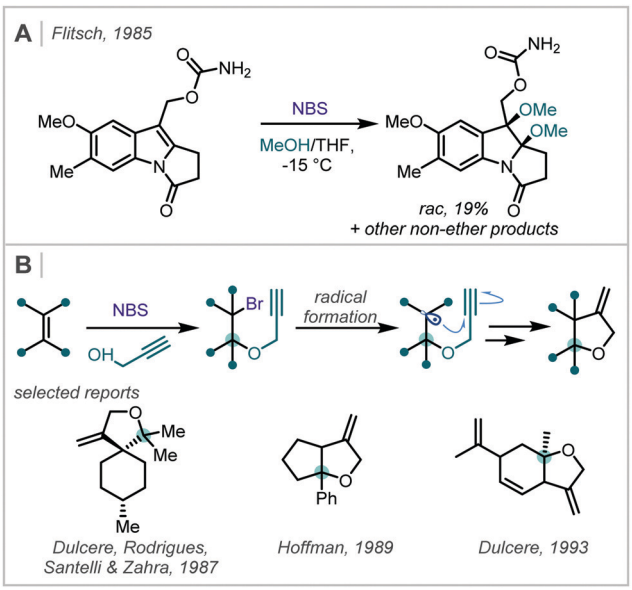
In an alternative approach, Liu reported cyanofluorination of a range of enol ethers using Selectfluor™.[161] However, instead of the usual direct interception by Selectfluor™ as an electrophile, a single-electron-transfer from the olefin to Selectfluor™ *via* an electron donor–acceptor (EDA) complex was suggested. F-Atom transfer from Selectfluor™ to this radical cation intermediate gave an oxocarbenium ion, which was intercepted by TMSCN, forming the α-oxynitrile product.

2.4.3 Halogen(I) and *N*-halosuccinimides. The *N*-halosuccinimide reagents (NXS) are inexpensive, commercially available, and routinely used as stable sources of halogens.[162] In 1985, Flitsch reported that the reaction of benzopyrrolizinones with NBS in MeOH gave an unexpected side product bearing an α-tertiary ether, however the yield was only 19% (Scheme 34A).[163]

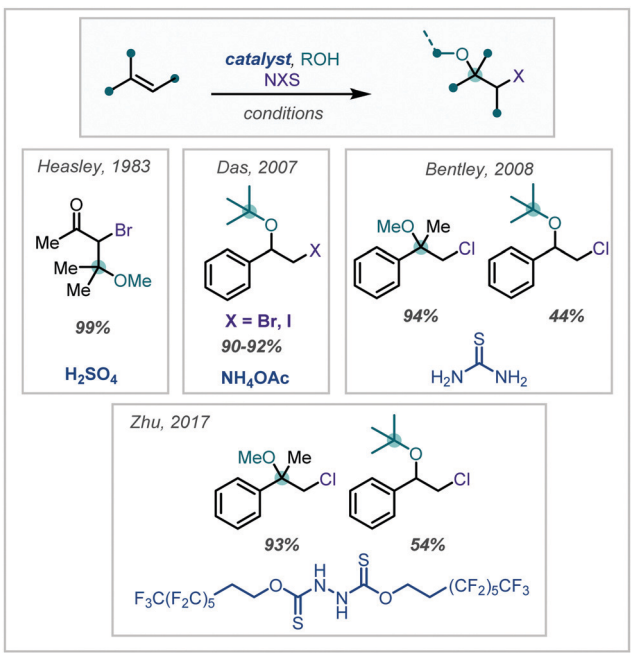
Several groups have since employed these stable halogen sources to form β-halo-α-tertiary ethers. They have been effectively utilised in the synthesis of β-bromoprop-2-ynyl ethers which were applied in radical cyclisations towards high-value oxygen-containing heterocycles, for example β-methylene tetrahydrofurans (Scheme 34B).[164–167] The olefin scope of such reactions includes enones, styrenes, 1,1-diarylethenes and cycloalkenes. In 1993, Dulcère extended this method through use of other alkene- and alkyne-containing alcohols to investigate further reactivity and intramolecular Diels–Alder reactions of the products.[168,169] Similar haloetherifications have also been utilised by others in the synthesis of 2-alkoxy-3-bromoindolines and substituted deltacyclenes.[170,171]

It has since been shown that, by introducing Brønsted acid catalysts in NXS-mediated haloalkoxylation reactions, times could be reduced and the scope of the reactions increased, all while retaining Markovnikov selectivity. Such halogenation reactions have been demonstrated to be promoted by H_2SO_4,[172] NH_4OAc,[173] thiourea[174] and a more elaborate recyclable polyfluorinated hydrazine 1,2-bis(carbothioate) organocatalyst[175] (Scheme 35). Typically, the Brønsted acidity of the additive is implicated in activation of the succinimide carbonyl oxygen, *via* a hydrogen bonding interaction, to promote electrophilic halogen formation.

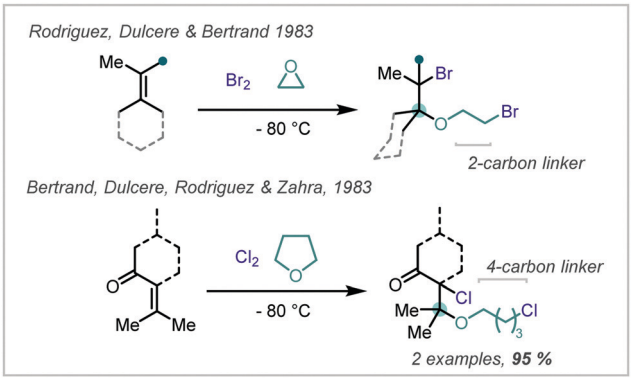
Multicomponent reactions (MCRs) comprise of three or more reagents incorporated into a single product molecule in a one-pot operation and represent an atom-economic approach to access complex scaffolds directly. Early work in 1983 by Dulcère, Rodriguez, Bertrand and Zahra investigated the MCR of alkenes with solvent participation, either ethylene oxide or THF, and either Br_2 or Cl_2 to give β-haloethers (Scheme 36).[176,177]



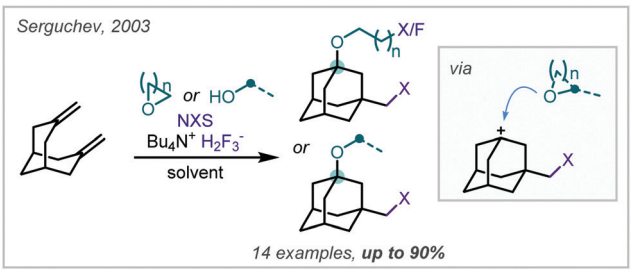
Scheme 34 (A) Dimethoxylation of an indole-type structure with NBS in MeOH. (B) NBS-mediated bromoalkynoxylation of alkenes to afford propargylated β-bromoethers.



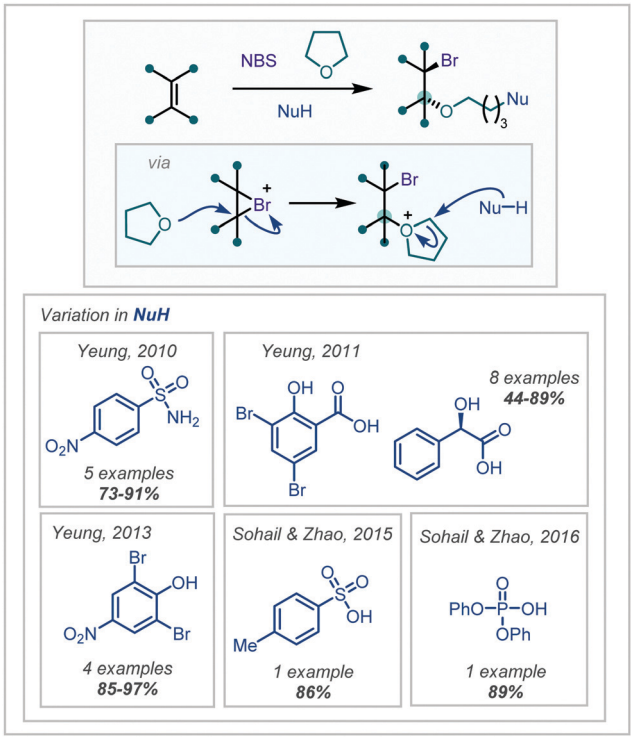
Scheme 35 NXS-mediated methods affording β-halo-α-tertiary ethers under Brønsted acid catalysis.



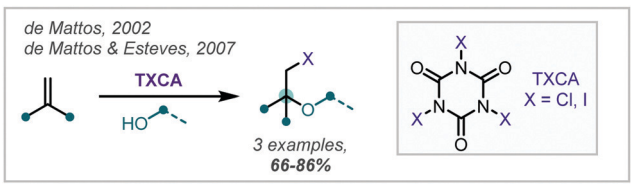
Scheme 36 Application of MCR reactions to haloetherification reactions.



Scheme 37 MCR reaction investigated by Serguchev, giving an α-tertiary ether.



Scheme 38 MCR employing THF to install α-tertiary ethers, with terminal incorporation of a variety of nucleophiles. The highest-yielding nucleophile used in each case is shown.



Scheme 39 TCCA and TICA-mediated haloetherification of styrene-type olefins.

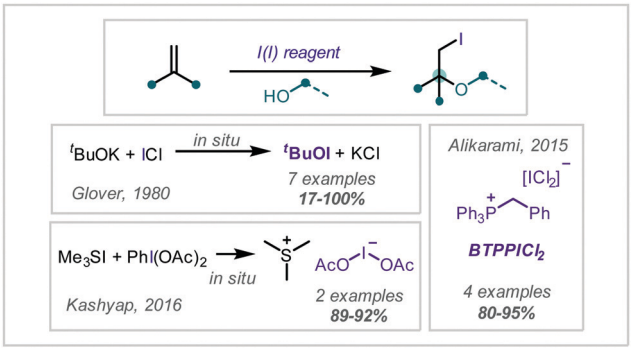
In 2003, Serguchev noted a side-product formed *via* a similar MCR with solvent participation when NBS and a bridged bicyclic diene were reacted in THF with the fluoride source $Bu_4NH_2F_3$ (Scheme 37).[178] The authors also employed an analogous method without solvent participation when the solvent was changed to CH_2Cl_2 and a perfluorinated alcohol nucleophile was added.

This class of MCRs involving NBS and solvent participation has continued to be expanded and in 2010, Yeung disclosed the use of electron-poor sulfonamide nucleophiles in such a reaction, forming α-tertiary ethers in moderate to excellent yields (Scheme 38).[179] Yeung also demonstrated in 2011 and 2013 that carboxylic acids and phenols could also act as the nucleophile in this transformation.[180,181] Following mechanistic investigations, the acidic proton was reported to play a key role, and was suggested to either activate NBS in a Brønsted acidic manner, or *via* full bromine atom transfer to form the more electrophilic RCOOBr species, which could rapidly brominate the alkene. With phenols, bromination at any unsubstituted *ortho* and *para* positions occurred first, leading the authors to simply use the brominated phenols, giving the desired products in excellent yields.

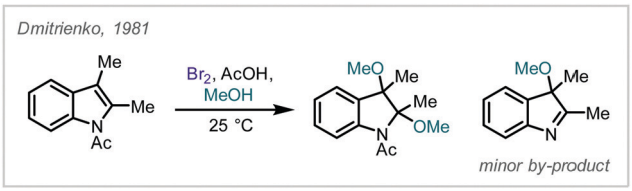
Sohail and Zhao extended this principle to sulfonic and phosphoric acids (Scheme 38).[182,183] Interestingly, under more concentrated conditions, there was an observed tendency for a second THF molecule to attack the initial oxonium ion intermediate, with the nucleophile opening the second oxonium ion formed.

2.4.4 Other halogen(I) reagents. The previous sections on F(I) and NXS-mediated transformations highlight the utility of having stable, pre-formed X(I) reagents. Numerous alternative X(I) reagents have been developed, and applied successfully in α-tertiary ether synthesis (Scheme 39), for example $CsSO_4F$,[184–186] trichloroisocyanuric acid (TCCA),[187,188] triiodoisocyanuric acid (TICA)[191] and $TsNBr_2$.[189]

Reagents containing iodine in the formal +1 oxidation state have been used in the reaction with alkenes to give β-iodoethers (Scheme 40). Glover disclosed that treatment of ICl with *t*-BuOK generated *t*-BuOI *in situ*, which enabled the β-iodo-*tert*-butoxylation of a range of alkenes in modest to excellent yields.[190] Later, Alikarami reacted α-methylstyrene with alcohol nucleophiles in the presence of benzyl(triphenyl)phosphonium dichloroiodate ($BTPPICl_2$), (Scheme 40) to give the corresponding products in very good yields.[191] In 2016, Kashyap reported similar transformations of α-methylstyrene and 1,1-diphenylethene with methanol in 70–90% yield when using the *in situ*-generated iodinating reagent $Me_3SI(OAc)_2$.[192]



Scheme 40 A range of I(I) reagents employed in α-tertiary ether synthesis.

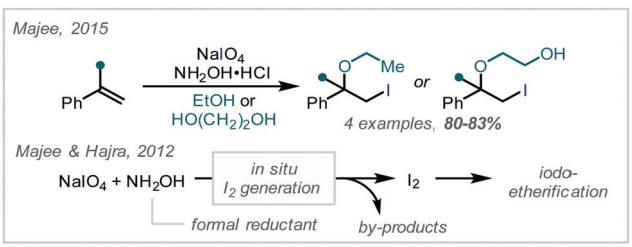


Scheme 41 Conversion of di-alkylindoles to β-bromo-α-tertiary ethers using Br_2.

2.4.5 Halogenating reagents in other oxidation states. In 1981, Dmitrienko reported alkoxybromination of 2,3-dialkylindoles with Br_2 directly (Scheme 41). This gave a 3-bromo-2-methoxydialkylindoline intermediate which, in an acidic solution of methanol, gave 3-methoxy-2,3-dialkylindolines, which contain an α-tertiary ether.[193]

A few reports involve the use of a halide source, where the halogen is in the −1 oxidation state, with an oxidant to generate an electrophilic halogenating reagent *in situ*. In 2009, Ghosh investigated the use of 2 : 1 ratios of X^- : XO_3, (X = Br or I) to generate X_2 *in situ*, in the synthesis of β-haloethers, including one α-tertiary example.[194]

In contrast, Majee reported that $NaIO_4$ in the presence of $NH_2OH{\cdot}HCl$ oxidises olefins to form β-iodoethers.[195] In this case, the electrophilic halogenating reagent is generated *via* introduction of a terminal reductant and the authors suggest I_2 is generated *in situ* while hydroxylamine is oxidised (Scheme 42).[196] Reaction with α-methylstyrene and 1,1-diphenylethene in ethanol or ethylene glycol gave the corresponding ethers in around 80% yield.



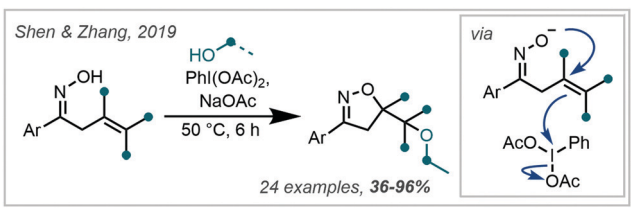
Scheme 42 *In situ* generation of I_2 to facilitate the iodoalkoxylation of styrenes.

In 2014, Narender disclosed that the use of environmentally benign, commercially available and inexpensive Oxone® ($2KHSO_5{:}KHSO_4{:}K_2SO_4$) with either NH_4Br or NH_4Cl transformed selected olefins to β-bromo-α-tertiary ethers and β-chloro-α-tertiary ethers respectively in good yields.[197,198] In a complementary fashion, Le Bras reported that omission of a halide source resulted in formation of β-alkoxy alcohols.[199]

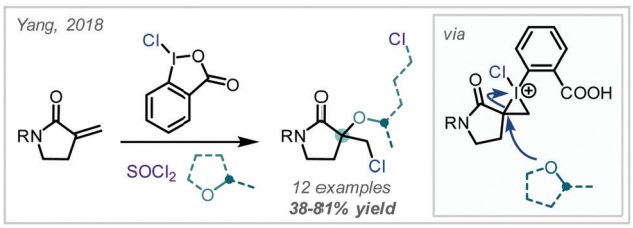
In 2019, Shen & Zhang reported a related transformation employing PIDA as the oxidant and the use of a proximal oxime as an intramolecular trap, concurrently forming an isoxazoline (Scheme 43).[200] A two-electron pathway is proposed, whereby PIDA oxidised the alkene directly, with subsequent cyclisation of the adjacent oxime moiety (see Section 6.4 for related transformations). Loss of PhI and an acetate anion generated a carbocation, which was intercepted by an alcohol. Many examples containing an α-tertiary ether were afforded in good to excellent yield.

Employing a related approach, Yang reported a MCR, in which an alternative hypervalent I–Cl reagent was proposed to oxidise directly an unsaturated lactam which could follow a related reaction course, albeit incorporating a butyl-oxy linker *via* THF trapping of the proposed iodonium intermediate (Scheme 44).[201]

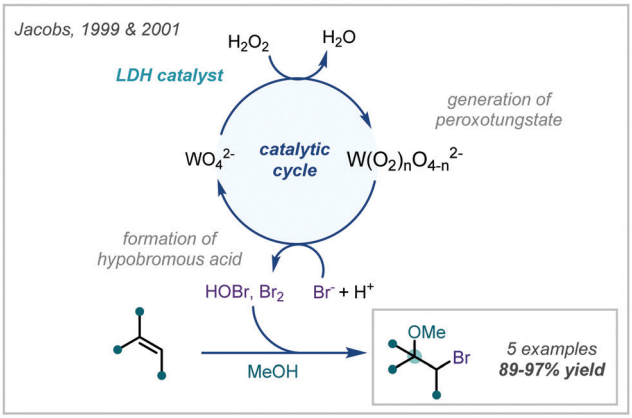
Taking a different approach, mimicking the enzyme vanadium bromoperoxidase, Jacobs reported that a tungstate-exchanged layered double hydroxide ((Ni,Al)-LDH-WO_4^{2-}) could serve as an effective oxidant of bromide (Scheme 45).[202] In the presence of hydrogen peroxide, the WO_4^{2-} is oxidised to the peroxotungstate species, $WO_{4-n}(O_2)_n^{2-}$, which oxidised bromide ions to electrophilic bromine species. These facilitated the β-bromo-α-tertiary etherification of olefins in the presence of MeOH. Hammett analysis confirmed a positively charged transition state and the observed product distributions ruled out a radical mechanism. A wider synthetic scope was



Scheme 43 Direct oxidation of an alkene with PIDA to facilitate formation of an α-tertiary ether.



Scheme 44 MCR reaction to give an α-tertiary ether from the unsubstituted lactam.



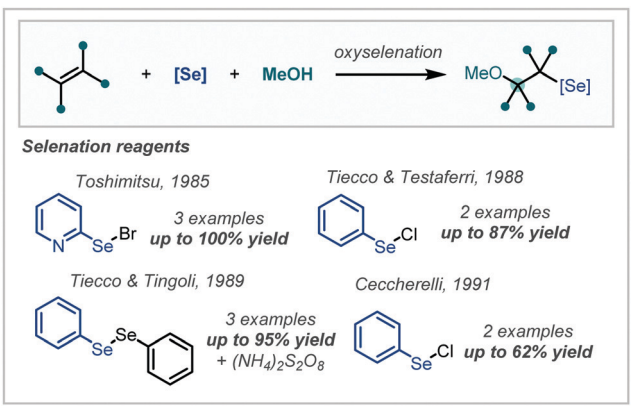
Scheme 45 Oxidative bromination of olefins utilising a tungstate-exchanged layered double hydroxide oxidant.

subsequently published with a range of relevant examples utilising both α-methylstyrene and linear and cyclic alkenes to give β-bromo-methyl-ethers in good yields.[203] Markovnikov selectivity was observed, and the anti-product was exclusively formed, however some alkenes gave 8–28% of the dibromo product as a by-product. Later in 2005, Jacobs applied this system to the oxidation of phenols to quinones, with interception by an alcohol, giving α-tertiary ethers (see Section 6.2).

2.5 Oxyselenation

In a similar approach to the halogenation reactions discussed previously, the electrophilic properties of organic selenyl halides have been applied to the functionalisation of alkenes followed by subsequent nucleophilic opening of the seleniranium ion. Notably this transformation extends to nucleophilic opening with co-solvent alcohols and as such the approach has been applied to α-tertiary ether synthesis (Scheme 46).

2.5.1 Traditional oxyselenation. In 1985, Toshimitsu highlighted the adventitious use of pyridylselenyl bromide in organoselenium chemistry, rather than the more well-established phenyl derivative. The installation of the pyridylseleno group was possible *via* an analogous electrophilic reaction with alkenes, followed by opening with methanol (Scheme 46).[204]

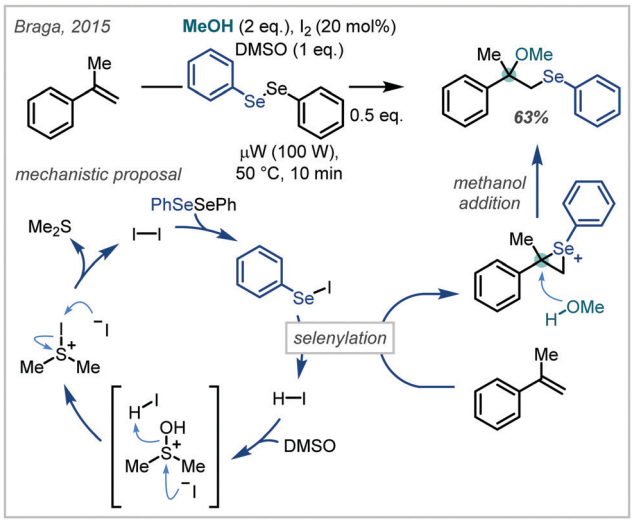


Scheme 46 Early studies on the synthesis of β-selenyl-α-tertiary ethers.

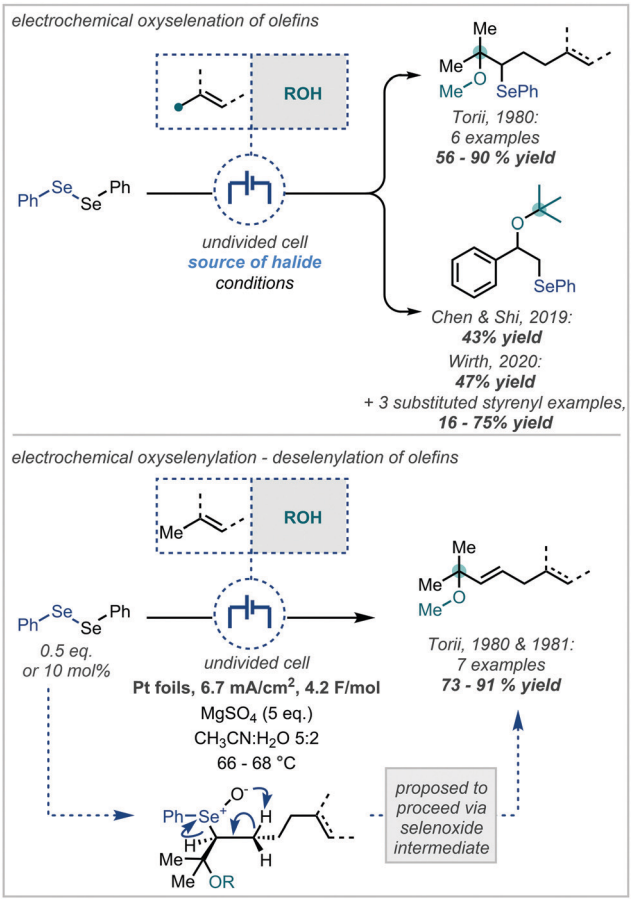
An early report from Tiecco & Testaferri demonstrated the use of phenylselenyl chloride in methanol to functionalise successfully both α-methyl- and α-phenyl-styrene.[205] The authors described how resubmission of the β-seleno-ethers to more forcing reaction conditions displaced the selenide with chloride, following electrophilic activation. Tiecco & Tingoli extended this strategy to a different oxidative system, employing peroxydisulfate to activate diphenyl diselenide.[206] Other oxidants were also applicable and the authors proposed formation of phenylselenium cations through either electron transfer or S_N2-type processes. A few α-tertiary ethers could be afforded in very good yields. Expanding this chemistry to more diverse substrates, Ceccherelli investigated a series of trisubstituted alkenes, derived from steroid and terpenoid frameworks.[207] Complex mixtures were observed, with deselenation facilitating numerous alternative nucleophilic substitutions at the β-carbon.

In a contemporary development to this system, Braga employed catalytic quantities of iodine as a redox catalyst for the *in situ* generation of arylselenyl iodides (Scheme 47).[208] Their subsequent reactivity followed that of the previous reports and the iodine catalyst was regenerated *via* acidic activation of DMSO and subsequent iodide oxidation. α-Tertiary ethers could be afforded by the use of α-methyl styrene but notably extension to *t*-BuOH as the nucleophile was unsuccessful.

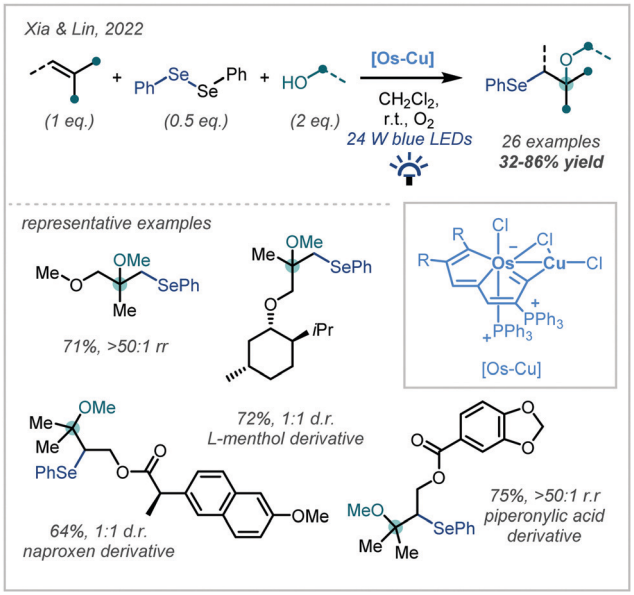
2.5.2 Electro- and photochemically-mediated oxyselenation. This facile activation of diselenides with a chemical oxidant highlights the potential of electrochemistry within the field of oxyselenation. Indeed, this potential was realised as early as 1980 in Torii's synthesis of racemic marmelolactone and rose oxide (Scheme 48).[209] An α-tertiary allylic ether, employed as an intermediate in the synthesis of rose oxide, was generated following an oxyselenation-deselenation sequence of citronellol. The authors proposed the role of an electrogenerated bromine cation as responsible for diselenide oxidation and that anodic oxidation of the oxyselenation product generated the selenoxide which could undergo facile elimination. Torii continued to greatly



Scheme 47 Modern application of halogen-mediated oxyselenation.



Scheme 48 Electrochemically-mediated oxyselenation.



Scheme 49 Application of metal-metallaaromatic systems to the photochemically-mediated oxyselenation of alkenes.

expand upon this work by applying the oxyselenation-deselenation chemistry to numerous isoprenoid and terpenoid alkenes, affording a corresponding plethora of α-tertiary ethers.[210] Given the regeneration of phenylselenic acid in this work, the authors demonstrated that the transformation was still feasible when diphenyl diselenide was reduced to substoichiometric levels (10–20 mol%).[211,212]

More recently, this approach has been expanded by Chen & Shi *via* the use of KI as a substoichiometric electrolyte, implicated in generating iodine cations to effect the oxidation of the diselenide (Scheme 48).[213] Despite mainly focussing on the hydroxyselenation of alkenes, a single example was reported employing *t*-BuOH as the co-solvent and therefore the nucleophilic component.

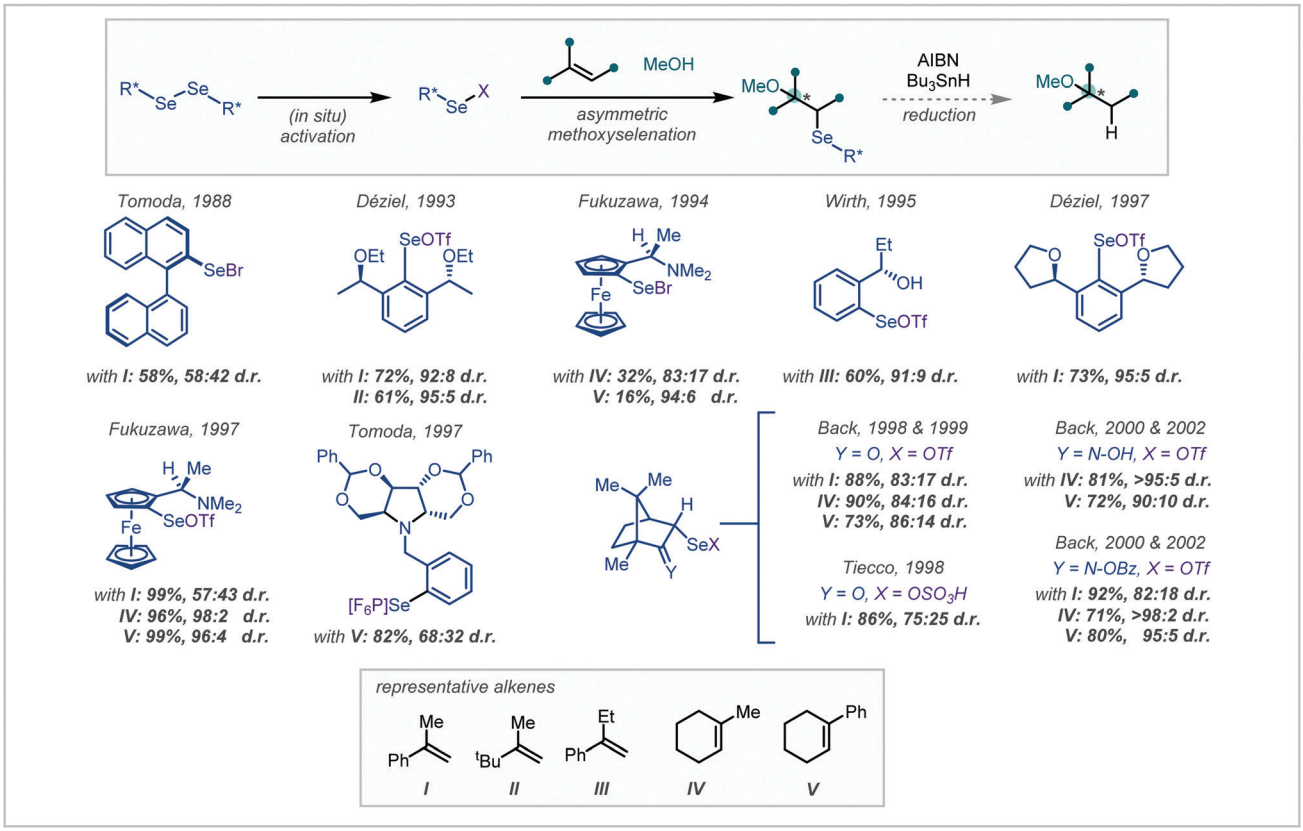
Further demonstrating the robustness of this chemistry, Wirth applied the electrochemical methoxylation to high-throughput automated flow synthesis.[214] Employing tetrabutylammonium iodide as the halide source, a library of β-selenyl ethers was afforded by systematic variation of the alkene. In this variation, three tertiary ethers were exhibited from the corresponding α-methyl, -isopropyl and -phenyl styrenes.

A prominent recent development, reported by Xia & Lin, demonstrated that metal-metallaaromatic catalytic systems are capable of efficiently mediating the oxyselenation of alkenes (Scheme 49).[215] The authors reported a novel Os–Cu bimetallic species in which the Os centre was incorporated into an aromatic system. The catalytic system was implicated in both nucleophile and alkene activation and in bringing the substrates into close proximity. The reaction was shown to be highly general for α-tertiary ether synthesis with 26 examples reported in good yields and exceptional regioselectivities, and the authors went on to demonstrate the late-stage derivatization of bioactive molecules. Light and oxygen were both shown to be critical for the transformation. Notably, the Os–Cu bimetallic catalytic system was compared to traditional oxyselenation procedures and demonstrated exceptional efficiency.

2.5.3 Asymmetric oxyselenation. Having been established as a robust approach to ether/selenide synthesis, the translation of this chemistry to asymmetric oxyselenations became a field of fervent study. Given the well understood chemistry of diselenides, the appendage of a broad range of chiral auxiliaries to the reactive selenium centres was possible (Scheme 50).

Leading the field in 1988, Tomoda reported the use of a binaphthyl skeleton.[216] It was proposed that this could retain the known regioselectivity in elimination of aryl selenoxides while introducing a backbone capable of asymmetric induction. Unfortunately, both the yield and the observed selectivity were low. Employing similar logic, Déziel synthesised a C_2 symmetric diaryl diselenide, featuring flanking stereogenic ether units.[217,218] The diselenides were activated *in situ* by treatment with Br_2 and AgOTf and the corresponding aryl selenyl triflate afforded diastereomeric adducts with alkenes in the presence of MeOH. The yields in the methoxyselenations were typically high and showed good diastereoselectivity in the synthesis of α-tertiary ethers.

Shortly afterwards, Fukuzawa reported the use of chiral ferrocenyl diselenides from the corresponding ferrocenylamines.[219,220] While the selectivities observed in α-tertiary ether examples were



Scheme 50 Asymmetric methoxyselenation for the synthesis of α-tertiary ethers (d.r.s rounded to integer values).

good, the yields were correspondingly lower for these more hindered substrates. Activation and reaction as the selenyl triflate resulted in a marked improvement in yield and selectivity.

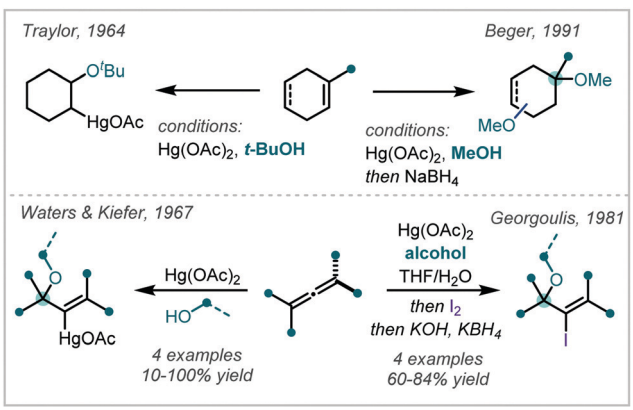
Developing upon the systems reported by Déziel, in 1995, Wirth applied aryl selenides bearing *ortho*-stereogenic centres, featuring a range of ether and alcohol functionality.[221] The methoxyselenation of α-ethylstyrene, to afford the corresponding α-tertiary ether, was reported in good yield and selectivity. Differing from Déziel's approach, Tomoda developed an alternative aryl diselenide bearing a chiral pyrrolidine sidechain.[222] This system imparted good selectivity in the methoxyselenation of simple styrenes however the selectivity was significantly lower when employing phenylcyclohexene.

Subsequently, Back and Tiecco independently reported the use of camphor-derived diselenides. Tiecco's report employed the corresponding selenyl sulfate, produced *in situ* from treatment of the diselenide with ammonium persulfate.[223] Despite high yields, Tiecco's report showed low selectivity for α-tertiary ether synthesis. On the other hand, Back explored a wide range of derivatized selenyl camphor reagents however the simple ketone-containing substrate performed best.[224,225] Further exploration of the selenyl reagent highlighted the camphor-derived oxime as a superior methoxyselenation reagent, with improved selectivity.[225,226]

The continued improvement of this asymmetric methoxylation regime combined with the electrochemical oxyselenation–deselenation described represents a powerful potential tool for the synthesis of enantio-enriched allylic ethers.

2.6 Oxymercuration

Complementing the traditional halogen and chalcogen-mediated oxidative difunctionalisation of alkenes, the oxymercuration of alkenes is a fundamental and well-studied transformation.[227] Typically associated with the nucleophilic opening of a transiently formed mercurinium ion by water or an alcohol, this transformation has been successfully applied to α-tertiary ether synthesis, as exemplified by Traylor's *tert*-butoxymercuration of cyclohexene.[228] Probing this elusive 3-membered mercurinium ion, Waters & Kiefer applied a range of alcohols in the reaction between $Hg(OAc)_2$ and 1,1-dimethylallene (Scheme 51).[229] α-Tertiary ether formation



Scheme 51 Application of oxymercuration to α-tertiary ether synthesis.

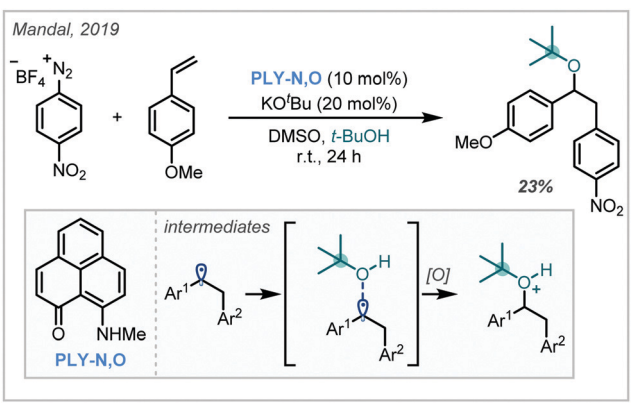
showed a strong dependence on the steric hindrance associated with the incoming nucleophile, with *t*-BuOH affording the corresponding allylic α,α′-tertiary ether in only 10% yield. Developing this application in the functionalisation of allenes, Georgoulis demonstrated that iodine could be employed as a terminal oxidant, capable of affording vinyl iodides with adjacent tertiary ether moieties.[230]

Employing an appropriate cyclohexadiene and $Hg(OAc)_2$, in 1991, Beger demonstrated the synthesis of a methyl α-tertiary ether, following a reductive cleavage of the C–Hg bond (Scheme 51).[231] The products of such oxymercuration reactions corresponded to Markovnikov opening of the mercurinium ion.

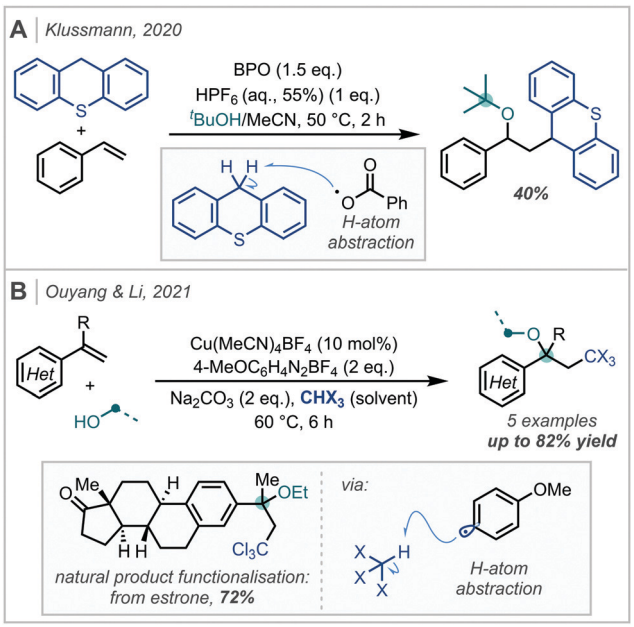
2.7 Alkene difunctionalisations enabled by alternative activation modes

In 2019, Mandal reported a transition metal-free carboalkoxylation of styrene derivatives by exploiting the chemistry of phenalenyl organocatalysts such as PLY-N,O (Scheme 52).[232] Without external stimuli such as light, it was shown that they could facilitate the reduction of aryl diazonium salts, yielding aryl radicals which added into styrenyl π-systems. DFT calculations suggested that alcohol addition into the resultant benzylic radical in fact preceded oxidation, representing a lower energy pathway than direct oxidation to the benzylic cation. Use of *t*-BuOH as the nucleophile led to the formation of the α-tertiary ether in 23% yield.

Reactive radical species can also be generated by the thermal decomposition of suitable precursors. In 2020, Klussmann disclosed that under acidic conditions, thermal decomposition of benzoyl peroxide (BPO), to the benzoyl radical could promote hydrogen-atom abstraction from the benzylic position of thioxanthene (Scheme 53).[233] The formed radical was subsequently able to participate in a C–C bond forming event with styrene, and following RPC, an α-tertiary ether was formed upon trapping with *t*-BuOH. Recently, Ouyang & Li achieved the alkoxypolyhaloalkylation of styrenes using a similar catalytic manifold.[234] Upon thermal decomposition, an aryl diazonium salt generated the corresponding aryl radical which enacted hydrogen atom abstraction from polyhaloalkanes such as chloroform. Following radical addition and oxidation, a variety of polyhalogenated α-tertiary ethers were formed. Depending on the substrate and alcohol used, adducts with tertiary centres at either side of the ether linkage could be formed. The method was also shown to be useful for the late-stage functionalisation of bioactive molecules, such as estrone which smoothly reacted in 72% yield.



Scheme 52 Transition metal-free synthesis of arylated α-tertiary ethers from aryl diazonium salts using a phenalenyl-derived catalyst.

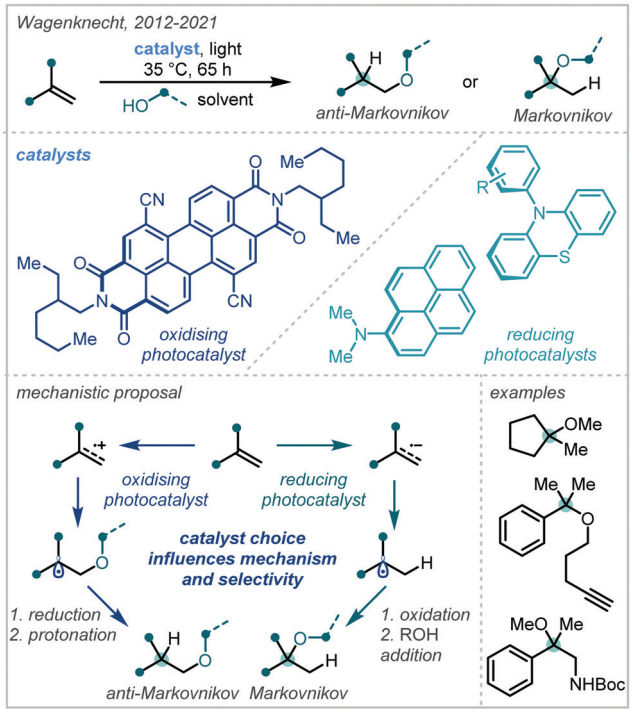


Scheme 53 (A) Radical carboalkoxylation of styrenes. (B) Alkoxypolyhaloalkylation of styrenes initiated by the thermal decomposition of aryl diazonium salts. BPO = benzoyl peroxide.

2.8 Alkene hydrofunctionalisations

Alkene hydrofunctionalisation reactions involve the addition of a hydrogen atom and another functional group across the π-bond of an olefin. A variety of reaction designs and manifolds have been developed to achieve this transformation in the context of α-tertiary ether synthesis, enabling retrosynthetic disconnections at various positions around the ether moiety; these will be the focus of the following discussion.

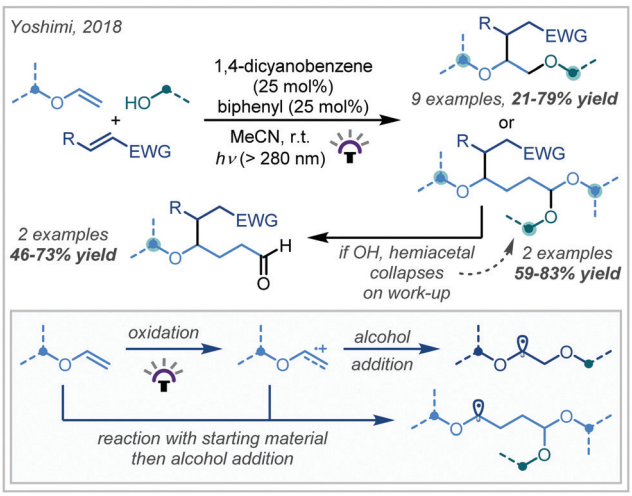
2.8.1 Photochemical alkene hydrofunctionalisation. The photochemical generation of radical cations and radical anions from alkenes, using organic photosensitisers, and their subsequent reactivity with alcohols, has been a field of extensive study following early work from Arnold in 1973 (for analogous oxidation of alkenes *via* electrochemical methods, see Section 2.2.1).[64,235–238] Inspired by these early works, in a series of reports spanning a decade, Wagenknecht described the photochemical nucleophilic alkoxylation of styrenes to form α-tertiary ethers (Scheme 54). Through the use of an electron-poor organophotocatalyst, upon photoexcitation, single electron oxidation of the styrene was achieved, which was then substituted in an anti-Markovnikov manner with methanol.[239] In contrast, use of an electron-rich photocatalyst promoted single electron reduction of the styrene, encouraging protonation followed by interception by a nucleophilic alcohol to yield



Scheme 54 Regiodivergent, photocatalytic hydroalkoxylation of alkenes.

ether products with Markovnikov selectivity.[240] Following these initial investigations, substituted *N*-arylphenothiazines were found to be strongly reducing catalysts, increasing the substrate scope of olefins that could be subjected to the Markovnikov alkoxylation conditions.[241,242]

In 2018, Yoshimi reported a protocol for the Giese addition of α-oxy radicals into electron-deficient alkenes, leading to a variety of α-tertiary ether products (Scheme 55).[243] In this case, radical generation was achieved by photocatalytic oxidation of enol ethers by a combination of 1,4-dicyanobenzene and biphenyl to afford a radical cation. Depending on the concentration of



Scheme 55 α-Tertiary ether synthesis *via* photochemical oxidation of enol ethers.

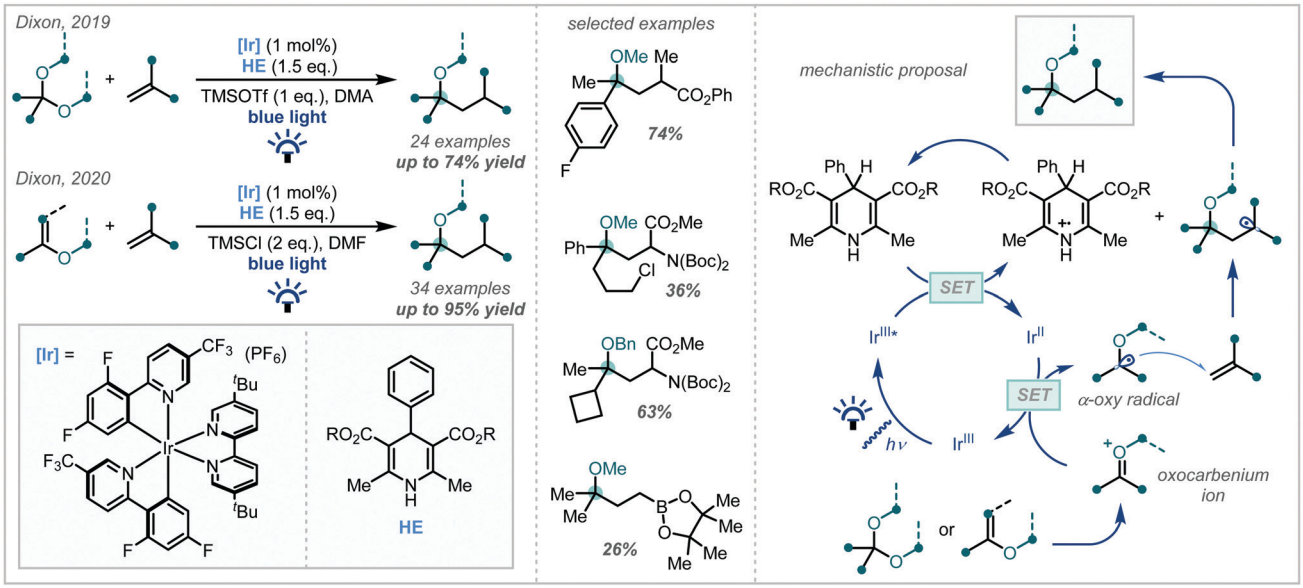
alcohol used, one of two pathways dominated: either the cation was directly trapped by a nucleophile to yield bis-ether or hydroxy-ether products, or the cation reacted with starting material, and the adduct was subsequently trapped to produce acetal-containing ether products. In either case, the α-oxy radical subsequently reacted with an electron-deficient alkene, giving rise to the hydrofunctionalised products after termination. *t*-Butyl enol ethers were very effective in the reaction, providing a range of *t*-butyl ether products in good yield; this was attributed to the increased nucleophilicity of the electron-rich α-oxy radicals. In contrast, using *t*-BuOH as a nucleophile led to lower yields due to the increased steric hindrance associated with this alcohol.

In 2019, Dixon disclosed the photocatalytic reductive formation of diverse α-tertiary ethers from ketals (Scheme 56).[244] Treatment of the ketal with Lewis acidic TMSOTf afforded the corresponding oxocarbenium ions. Umpolung reactivity was achieved through single electron reduction with an excited state iridium photocatalyst, affording nucleophilic α-oxy radicals that could engage in Giese addition chemistry with activated π-systems. Termination *via* HAT or a reduction/protonation sequence with a Hantzsch ester yielded the final products in good yields. Typically, yields were higher when ketals derived from electron-rich aryl ketones were employed, although electron-deficient and limited aliphatic substrates also reacted in acceptable yields. The alcohol component of the ketal could also be varied, allowing for variation at the other α-site of the ether. A key feature of this methodology was the stoichiometric quantities of ketal and radical acceptor used, allowing for potential application to more elaborate synthetic intermediates in multi-step syntheses.

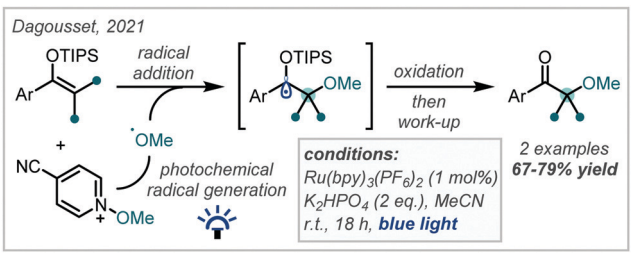
The authors later developed this further to utilise enol ethers as precursors to the α-oxy radical.[245] This significantly expanded the substrate scope of the reaction as all-alkyl substituted α-tertiary ethers, in addition to those with an aryl substituent, could now be more readily constructed: this was the most pertinent limitation of the authors' initial report. In addition, this second report presented a much broader scope of alkene radical acceptors, including alkenes with more sensitive functional groups such as vinyl sulfones and boronate esters.

The oxidation of silyl enol ethers with quinones such as 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) and *p*-chloranil has been reported to enable the synthesis of β-keto-α-tertiary ethers, with concomitant incorporation of the quinone-derived moiety.[246–248] In 2021, Dagousset reported a photocatalytic protocol to access similar structures from silyl enol ethers, predicated upon the oxidation of α-oxy radical intermediates (Scheme 57).[249] Alkoxy radicals were implicated as the key reactive species, formed from the reductive decomposition of alkoxypyridinium salts under photoredox catalysis. Radical addition into tetra-substituted enol ethers, followed by oxidation yielded the carbonyl-containing α-tertiary ether products in good yield.

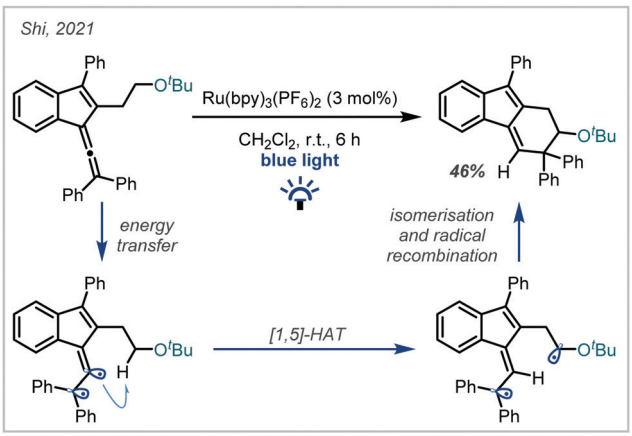
In 2021, Shi disclosed a mechanistically-distinct method for the hydrofunctionalisation of allenes (Scheme 58).[250] It was shown that energy transfer from an excited Ru-photocatalyst to the allene moiety allowed access to a reactive triplet state, which participated in selective [1,5]-HAT at the α-position of a



Scheme 56 Visible light-mediated synthesis of α-tertiary ethers from ketals and enol ethers.



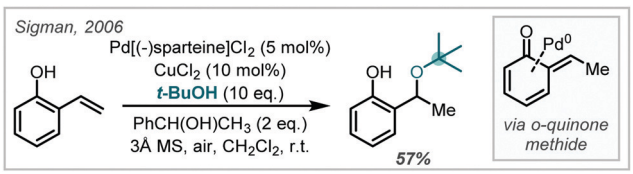
Scheme 57 Synthesis of β-keto-α-tertiary ethers from silyl enol ethers. TIPS = triisopropylsilyl.



Scheme 58 Photochemical hydrofunctionalisation of allenes enabled by energy transfer processes.

preformed ether moiety. Subsequent radical recombination yielded the elaborated α-tertiary ether product.

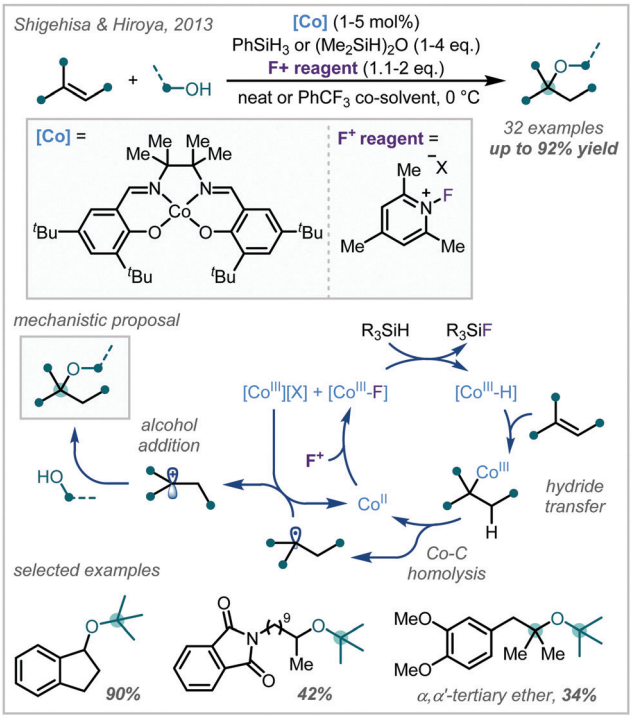
2.8.2 Transition metal-catalysed alkene hydrofunctionalisation. In 2006, Sigman reported a novel Pd-catalysed



Scheme 59 Pd-catalysed hydroalkoxylation of styrenes.

hydroalkoxylation of alkenes (Scheme 59).[251–253] *o*-Phenols with pendant alkene functionality underwent hydropalladation with a Pd(II)-hydride species, generated by the oxidation of the sacrificial benzylic alcohol, to form an *o*-quinone methide intermediate. Nucleophilic addition of an alcohol into this intermediate released the ether product, and the catalyst was turned over either by aerobic or Cu-mediated oxidation. Since then, it has been shown that other catalysts, such as Ir-pincer complexes, can also catalyse hydroalkoxylation reactions of simple alkenes to form α-tertiary ethers.[254]

In 2013, Shigehisa & Hiroya reported a Co-catalysed protocol for the hydroalkoxylation of unactivated olefins (Scheme 60).[255] Mechanistically, oxidation of a Co(II) complex using a pyridinium fluoride salt followed by reaction with a hydridic silane species generated a Co-hydride *in situ*, which underwent hydrometalation across double bonds with Markovnikov selectivity. Homolysis of the Co–C bond, followed by oxidation of the resultant radical by Co(III) yielded a carbocation, which could be trapped by alcohol nucleophiles. Remarkably, *t*-BuOH was an effective nucleophile in this reaction, yielding a variety of α-tertiary ethers in excellent yields. Particularly impressive was the reaction of *t*-BuOH at tertiary carbocations to yield very hindered α,α′-tertiary ethers. While excess alcohol was used in the majority of scope examples, more elaborate, high-value alcohols could be used in stoichiometric quantities.



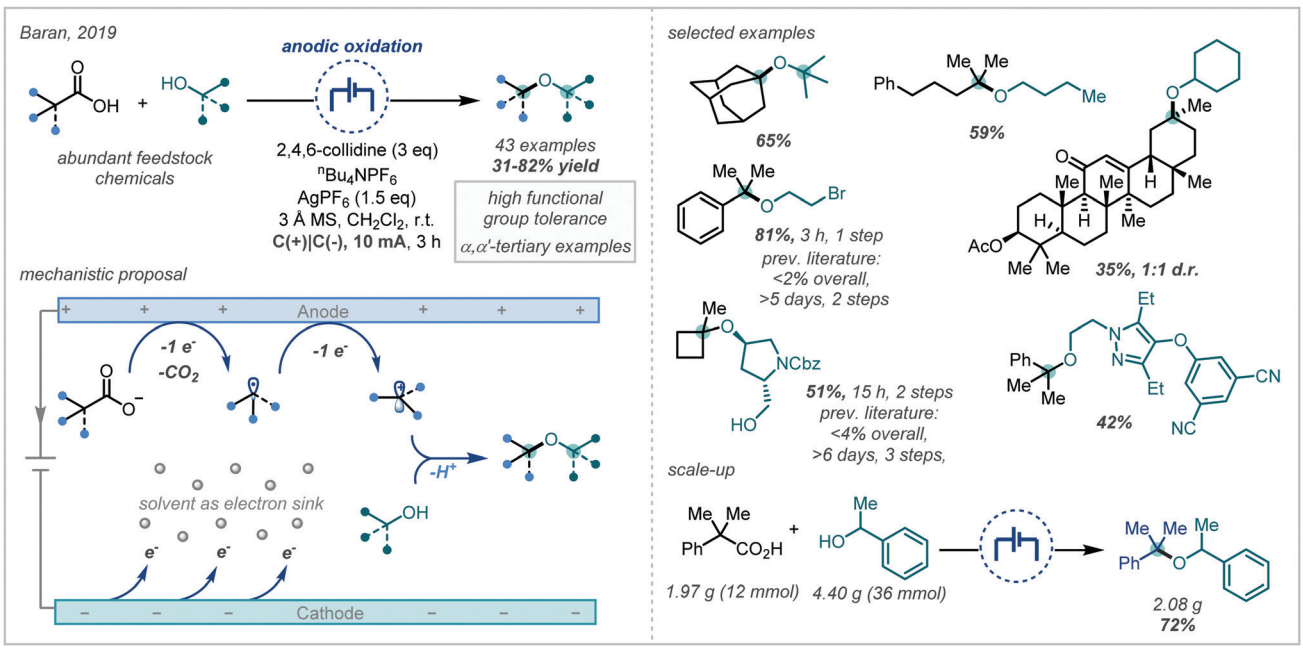
Scheme 60 Co-catalysed hydroalkoxylation of unactivated olefins.

3. Decarboxylation

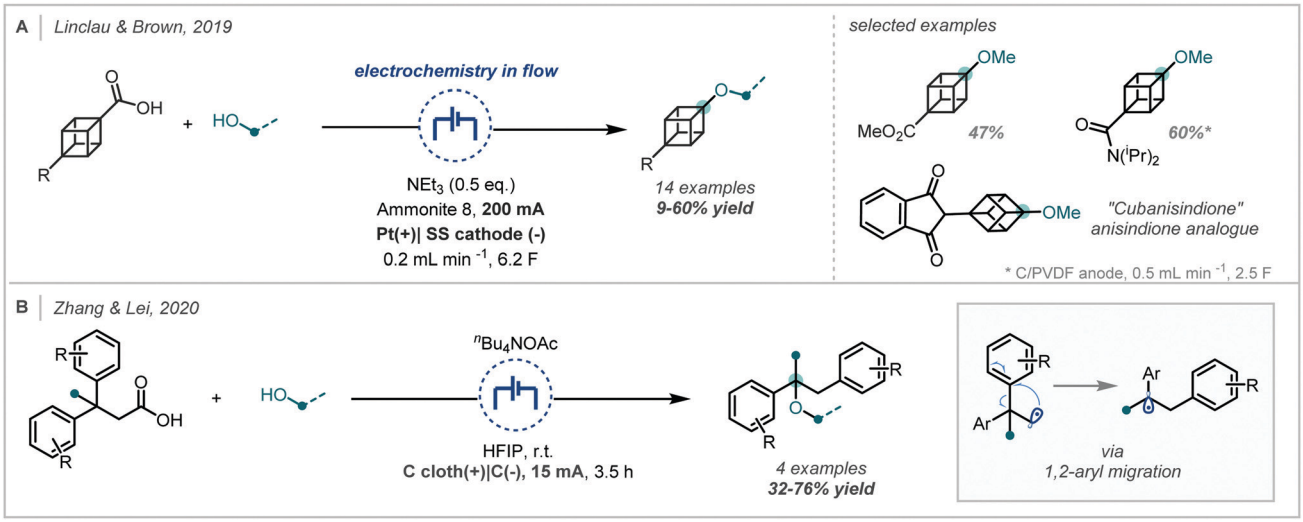
Given the ubiquity of carboxylic acids within feedstock chemicals and biological molecules, the direct application of such fragments in α-tertiary ether synthesis would greatly expand the accessible chemical space. In this way, the decarboxylation of such acids offers a new mode of reactivity, building upon well-established chemistry.[256–258] Fragmentation of a carboxyl radical, formed by oxidation of a carboxylate salt affords a C-centred radical capable of the same termination mechanisms previously described. An alternative mechanistic framework involves the reductive fragmentation of redox-active esters, typically derived from *N*-hydroxyphthalimides. Given the recent interest in such methods, it is unsurprising that both electrochemical and photochemical strategies have been employed to enable the decarboxylation of alkyl carboxylic acids to afford α-tertiary ethers. Since examples of decarboxylative alkene difunctionalisation have already been highlighted within the previous section, such methods will not be discussed further.

3.1 Electrochemically-mediated decarboxylation

Taking inspiration from the oldest known electrochemical transformation, the Kolbe electrolysis, and the related Hofer–Moest reaction,[86,259–261] Baran developed the synthesis of hindered dialkyl ethers, predominantly consisting of α-tertiary examples, using electrogenerated carbocations, arising from oxidative decarboxylation, (Scheme 61) and alcohol coupling partners.[262] This method allowed the direct synthesis of such ethers from ubiquitous and inexpensive carboxylic acids and tolerated a wide range of functional groups in both the acid and alcohol coupling partners. The potential of the methodology to expedite target molecule synthesis was demonstrated by its application in a number of small molecule syntheses and comparison against previously reported routes. It was shown that tertiary sites could be incorporated from both the carboxylic acid and alcohol coupling partners; furthermore, the synthesis of several α,α′-bis-tertiary ethers was demonstrated in good yields and an α-tertiary ether was also prepared on ~2 g scale in 72% yield. Extensive studies were undertaken to further



Scheme 61 Electrochemical decarboxylative etherification.



Scheme 62 Further electrochemical decarboxylative etherification reactions.

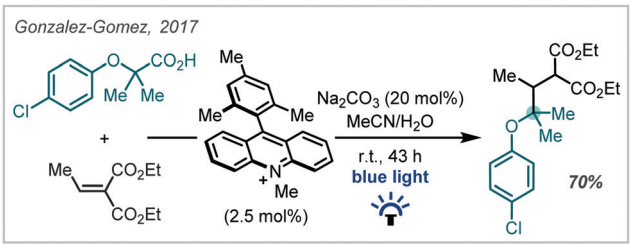
understand the process and it was proposed that the mechanism likely involved rate-limiting anodic oxidation of the carboxylate, followed by decarboxylative fragmentation and an additional anodic oxidation, to generate a carbocation, which was subsequently intercepted by a nucleophilic alcohol coupling partner.

The interception of such electrogenerated carbocations by alcohol nucleophiles has been employed and developed by others, further expanding access to α-tertiary ethers (Scheme 62). Linclau and Brown incorporated a similar strategy into flow chemistry to enable the synthesis of alkoxy cubanes;[263] the synthesis of an anisole bioisostere was possible by this method and the authors utilised this chemistry to make an analogue of the anticoagulant anisindione. Similarly, Zhang and Lei used electrochemical oxidative decarboxylation in their synthesis of 1,2-diaryl ethers.[264] Although this process involves 1,2-aryl migration, it was shown that α-tertiary centres could be incorporated either by employing β-tertiary acids or by using a tertiary alcohol coupling partner.

3.2 Photochemically-mediated decarboxylation

Given the recent resurgence of photoredox catalysis in organic synthesis, such methods have also been employed within the decarboxylative etherification manifold. In 2017, Gonzalez–Gomez reported the redox-neutral synthesis of an α-tertiary ether while investigating a decarboxylative Giese-type reaction promoted by visible light (Scheme 63), mediated by an acridinium photocatalyst.[265] In this case, decarboxylation afforded the stabilised α-oxy radical which could successfully take part in a Giese reaction.

In a mechanistically distinct approach to the oxidative decarboxylative couplings previously discussed, Hu developed a reductive catalytic system employing tandem photoredox and copper catalysis which allowed the synthesis of a broad range of ethers (Scheme 64).[266] Reduction of the redox-active phthalimide ester by Ir(II) enabled decarboxylation to the corresponding radical, which was then trapped by the Cu(II)-aryloxide complex.

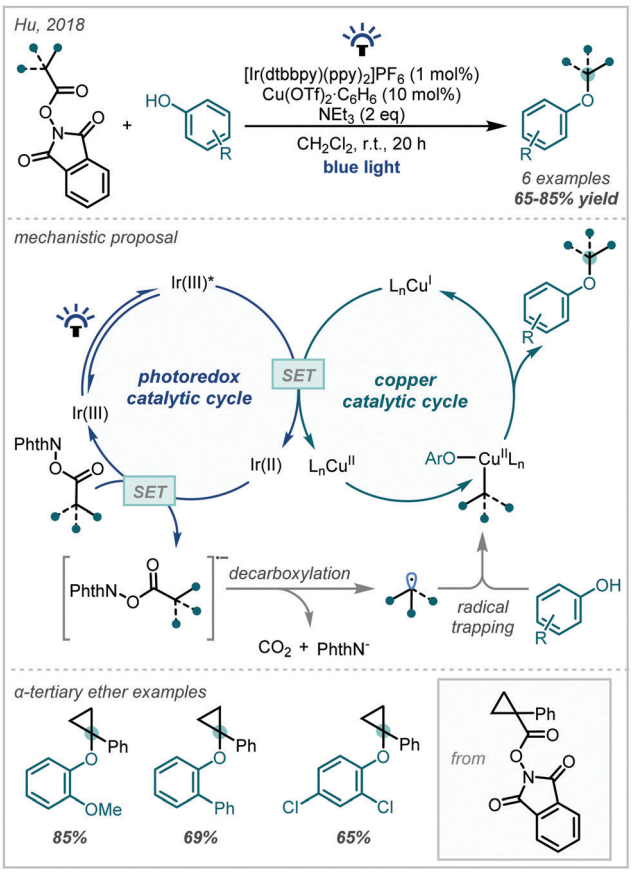


Scheme 63 Organophotoredox decarboxylative Giese-type addition.

Reductive elimination generated the alkyl-aryl ether and a Cu(I) complex, which was re-oxidised *via* SET from the photoexcited Ir(III), allowing catalytic turnover. While this method was limited to alkyl–aryl ethers, a variety of α-tertiary ethers were made using an α-cyclopropyl *N*-hydroxyphthalimide ester as a coupling partner.

In a seminal report, Nagao and Ohmiya described the application of a phenothiazine photocatalyst in a decarboxylative etherification of redox-active esters, operating *via* a radical-polar crossover manifold (Scheme 65, see Scheme 5B for subsequent alkene difunctionalisation study).[267] They demonstrated that tertiary sites could be incorporated from both the carboxylic acid-derived and alcohol coupling partners, allowing the synthesis of a variety of synthetically challenging α-tertiary ethers in fair to good yields over an extensive scope. They proposed that photo-excitation of the catalyst and subsequent SET to the phthalimide ester enabled a decarboxylation to give an intermediate (tertiary) radical **II**. The generated radical intermediate could then couple with the catalyst to give labile intermediate **III**, which underwent nucleophilic substitution to give the hindered ether product.

In 2020, Zbieg & Terrett reported a method for decarboxylative C–O couplings employing photoredox catalysis (Scheme 66).[268] They proposed that the iodine(III) oxidant (**Ox**) promoted *in situ* activation of the carboxylic acid to give **I**.[268] Subsequent decarboxylation



Scheme 64 Decarboxylative etherification *via* dual photoredox and Cu catalysis.

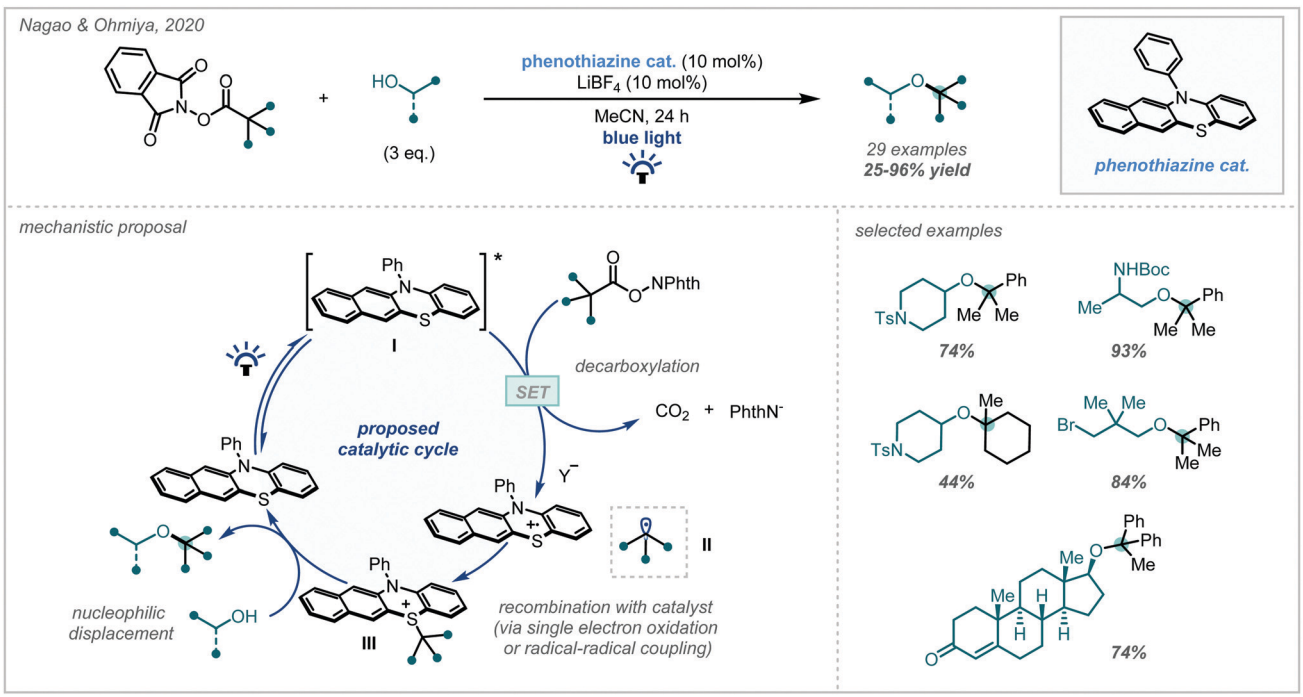
followed by SET could give a carbocation intermediate **III** which could then be trapped by an alcohol coupling partner. This new method displayed a large scope with many challenging α-tertiary ether motifs formed in moderate to good yields.

Recently, Yoon reported a Cu-mediated net-oxidative decarboxylative coupling of carboxylic acids directly with a range of nucleophiles under visible light irradiation.[269] It was proposed that a Cu(II) carboxylate species, formed *in situ*, (Scheme 67) was photoexcited, facilitating ligand-metal charge transfer (LMCT), giving the corresponding carboxyl radical which could undergo rapid decarboxylation. Subsequent oxidation to the corresponding cation and interception by a wide range of nucleophiles gave the coupled products, including a wide range of ethers, including an α-tertiary example. This method demonstrated good use of diverse carboxylic acid feedstocks without the need for pre-functionalisation and exhibited a wide functional group tolerance, making it a valuable tool for late-stage functionalisation of molecules.

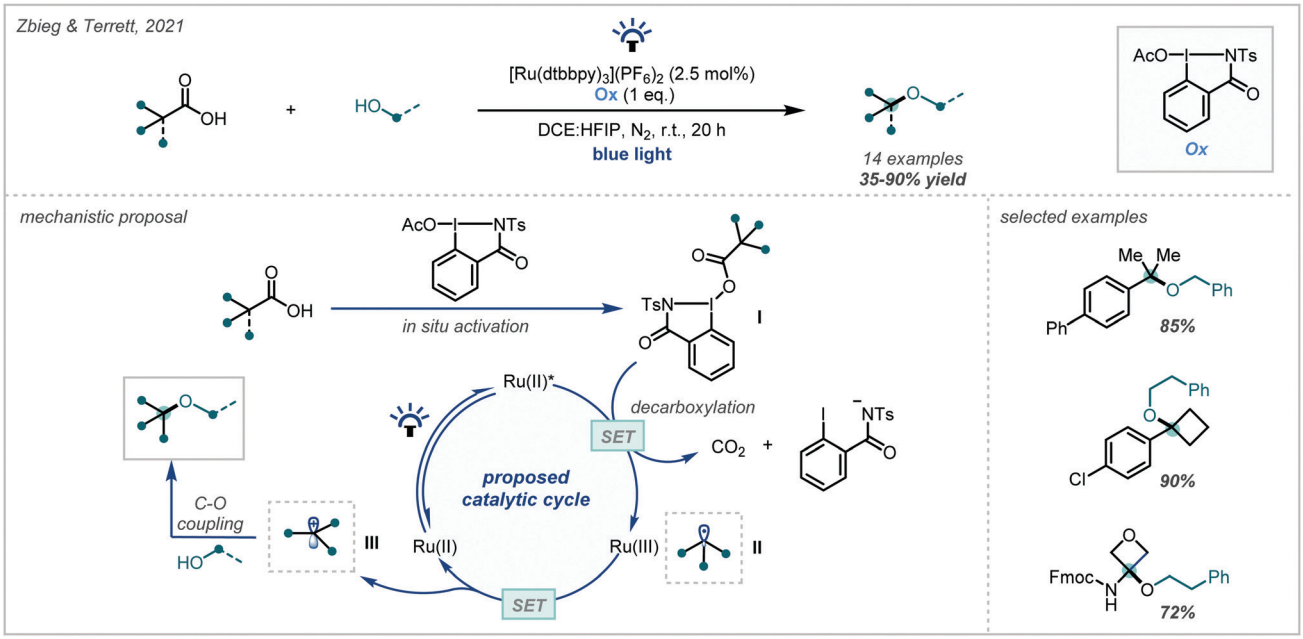
4. C–H activation

C–H activation has arisen as a powerful and attractive strategy in synthetic chemistry due to the typically high atom economy, the lack of a requirement for pre-functionalisation and the applicability to late-stage functionalisation in drug discovery programs.[270,271]

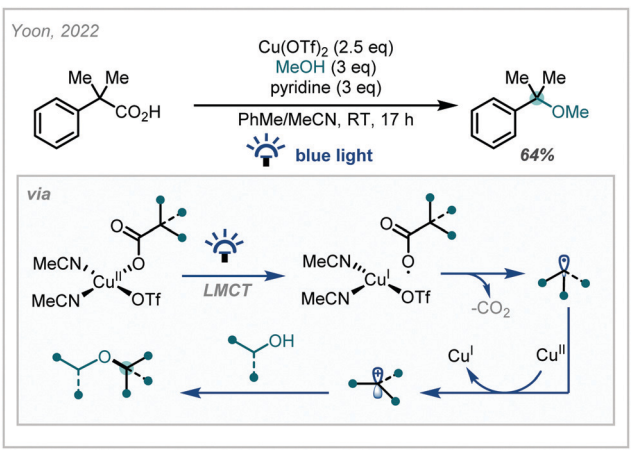
Although incredibly attractive from a synthetic point of view, C–H activation methods require delicate control of selectivity. Multiple ways to achieve this transformation have been explored, with many early methods harnessing the intrinsic difference in reactivity of C–H bonds within simple hydrocarbons.[272]



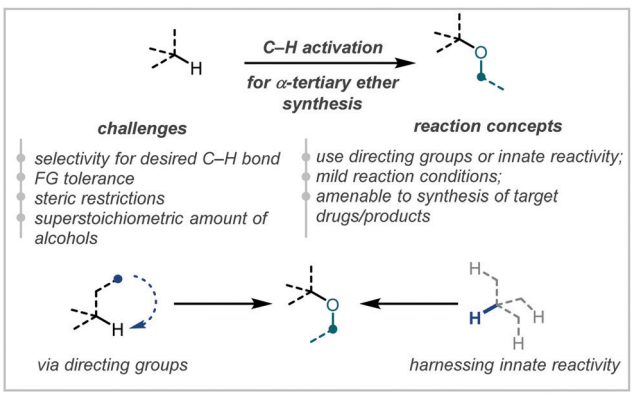
Scheme 65 Decarboxylative etherification of *N*-hydroxyphthalimide esters using organophotoredox catalysis.



Scheme 66 Decarboxylative C–O couplings using photoredox catalysis.



Scheme 67 Cu-catalysed net-oxidative decarboxylative coupling under visible light irradiation.



Scheme 68 Challenges in C–H activation for α-tertiary ether synthesis and conceptual approaches to overcome them.

More recently, however, use of directing groups has been favoured due to their compatibility with more complex systems which contain multiple competing sites.[273] This understanding and control of C–H reactivity has enabled the development of a broad suite of reactions, including C–C, C–O, C–N and C–S bond formations.

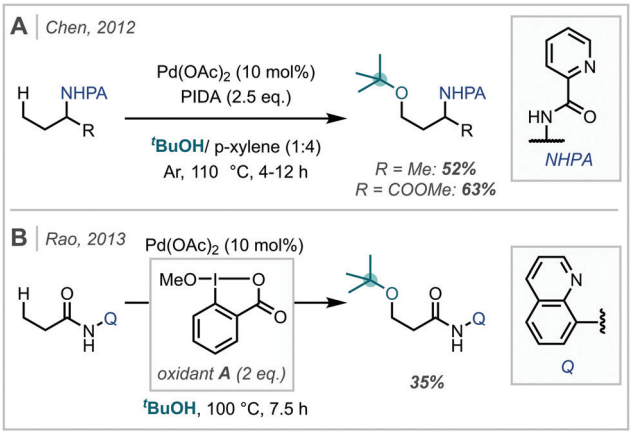
C–H bond alkoxylation to forge ether linkages is therefore an appealing strategy that would streamline synthetic approaches to high-value medicinal chemistry targets, natural products and other bioactive compounds (Scheme 68).[274,275] Such strategies have been reviewed elsewhere for the generation of cyclic tertiary ethers.[276]

4.1 Transition metal-directed C–H activation

Transition metal catalysis has enabled a myriad of chemical transformations in the past decades,[277] and has been used in the construction of C–O bonds from unactivated C–H bonds to afford α-tertiary ethers.[278]

A leading example of Pd-mediated alkoxylation of unactivated C(sp^3)–H bonds was reported in 2012 by Chen (Scheme 69A).[279] The authors demonstrated that the $Pd(OAc)_2$/PIDA couple is efficient in installing a variety of solvent alcohols at the γ-methyl site of amines bearing a picolinamide group.[279] Two examples of *t*-butyl ethers were reported in moderate yield. In a related approach, Rao explored the use of $Pd(OAc)_2$ and Dess-Martin periodinane (DMP) or 1-methoxy-1,2-benziodoxole-3(1*H*)-one (oxidant A) as oxidising agents of C–H bonds (Scheme 69B).[280] They found that carboxamides bearing an 8-aminoquinoline directing group ***Q*** would undergo C(sp^3)–H alkoxylation with a wide variety of alcohols, employed as solvents.[280]

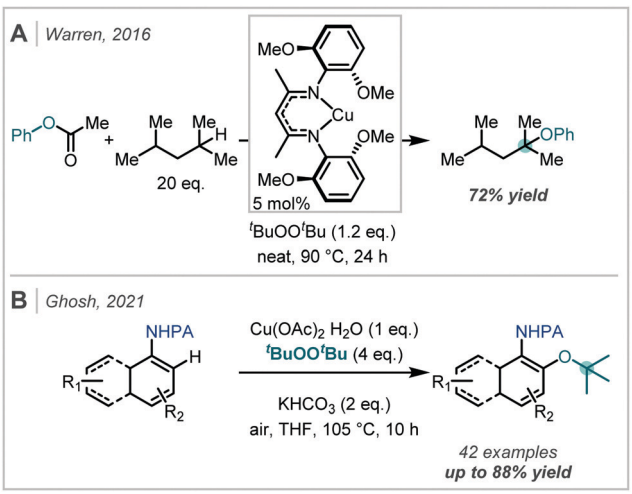
In a complementary approach, peroxides have been shown to act as effective terminal oxidants under both Pd- and Cu-catalysis.[281] In 2012, Warren & Cundari studied the catalytic



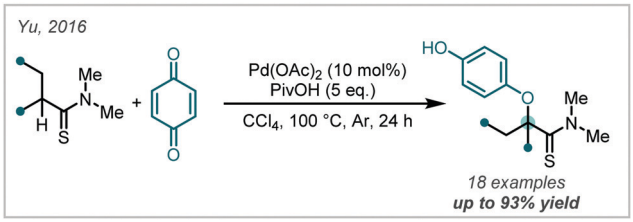
Scheme 69 Pd-mediated remote C(sp^3)–H activation utilising picolinamide (A) and quinoline (B) directing groups.

activity of Cu(II) alkoxides, generated with peroxides.[282] As part of their mechanistic studies, they demonstrated that *t*-butoxycyclohexane can be generated from cyclohexane in good yield, in the presence of Cu(II) and DTBP. This observation was expanded upon in 2016, when directing group-free C–H etherification method was developed by Warren (Scheme 70).[283] Where both secondary and tertiary sites were available for functionalisation, etherification occurred predominantly at the tertiary site but with minor quantities of α-secondary ether products also observed. Recently, Ghosh reported a Cu(II)-mediated oxidation of C–H bonds, utilising DTBP, focussing specifically on the synthesis of hindered ethers (Scheme 70).[284] This methodology made use of the *ortho*-directing picolinamide group and enabled the synthesis of a wide array of aryl–alkyl α-tertiary ethers.[284]

In 2016, Yu employed a thioamide α-directing group to achieve Pd-catalysed C(sp^3)–H etherification with *p*-benzoquinone serving as both the alkoxylating reagent and a stoichiometric oxidant (Scheme 71).[285] The process was exclusive to



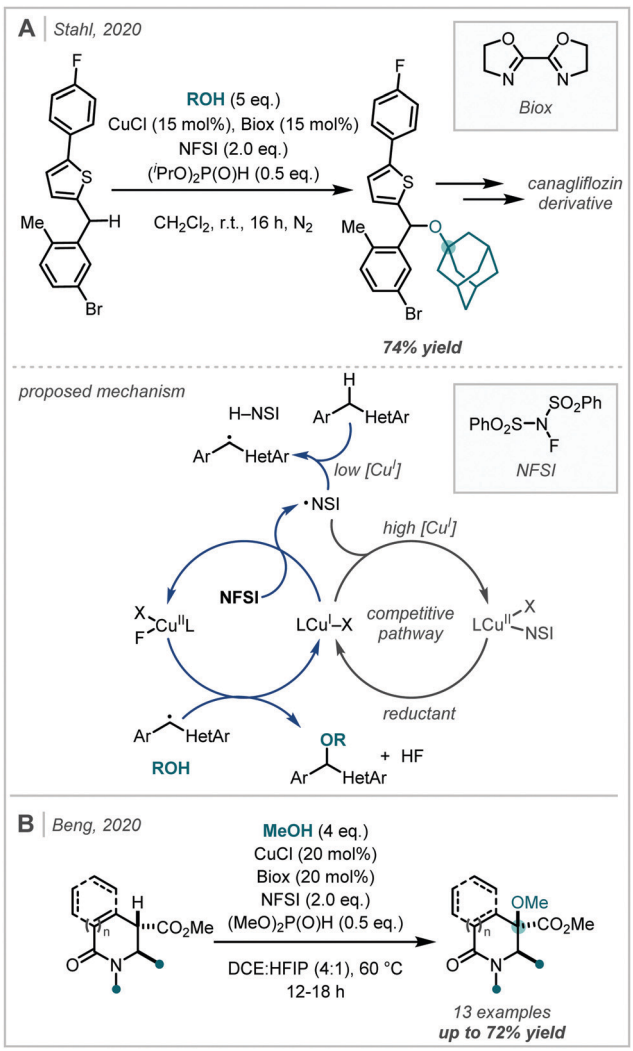
Scheme 70 Cu-catalysed C–H activations employing organic peroxides as the terminal oxidant (A) or as both the oxidant and the reagent (B).



Scheme 71 Pd-catalysed synthesis of α-tertiary aryl–alkyl ethers from thioamides.

the synthesis of α-tertiary ethers, with less substituted substrates shown to be unreactive to the conditions.[285]

Recently, Stahl has focused on the activation of benzylic C–H bonds towards etherification, aided by a Cu(I) catalyst and a *N*-fluorobenzenesulfonimide (NFSI) oxidant.[286] The Cu(I)/NFSI couple generated a *N*-centred radical capable of HAT of a benzylic hydrogen to generate a C-centred radical (Scheme 72A).[286] The procedure is highly selective for the benzylic C–H position,



Scheme 72 (A) Cu(I)/NFSI radical relay benzylic etherification; (B) related functionalisation of dihydroisoquinolones and δ-lactams.

but notably utilises the alcohol coupling partners in excess. The synthesis of an adamantyl ether was reported in good yield as part of a wide scope, which also showcased precursors to derivatives of type 2 diabetes drug canaglifozin. The same group utilised the Cu(I)/NFSI methodology to fluorinate benzylic C–H bonds.[287] The resulting benzylic fluorides were utilised *in situ* as electrophilic coupling partners to generate new C–O, C–N, or C–C bonds;[287] the authors demonstrated that *t*-BuOH is a competent coupling partner in this reaction, generating an α-tertiary ether. Shortly after this work, Beng reported a one-pot hydroxylation/etherification process from dihydroisoquinolones and δ-lactams employing the same Cu(I)/NFSI C–H activation strategy (Scheme 72B).[288]

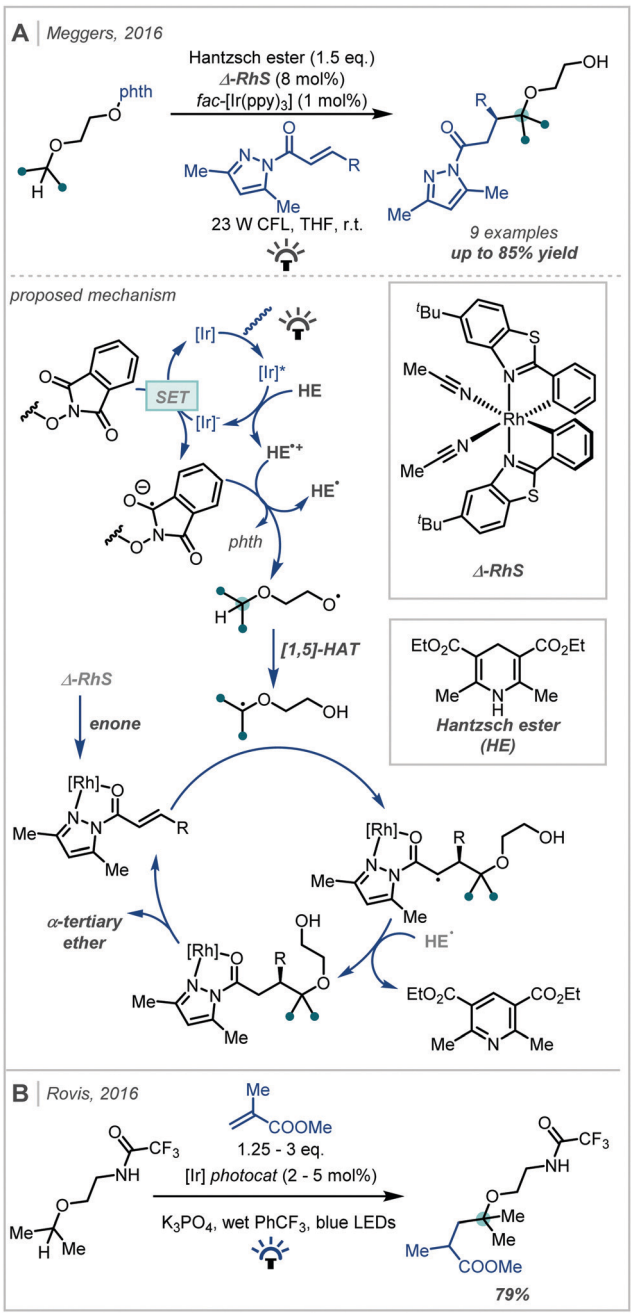
4.2 Photoredox-mediated C–H activation

Photoredox-mediated C–H activation has received increased attention recently, and has been applied in the synthesis of α-tertiary ethers. Numerous methods involve formation of high energy radical intermediates capable of [1,*n*]-HAT, which then trigger formation of carbon-centred radicals capable of trapping electron-deficient moieties. These approaches feature diverse radical precursors and photocatalysts and have proved amenable to a range of coupling partners.

In 2016, Meggers described an exciting merger of photoredox and enantioselective catalysis towards C–H alkoxylation, employing a chiral, Lewis acidic rhodium complex. The authors used *N*-alkoxyphthalimides as radical precursors capable of generating C-centred α-oxy radicals *via* 1,5-HAT, which then reacted with α,β-unsaturated *N*-acylpyrazoles to make hindered ethers (Scheme 73A).[289] The protocol achieved remarkable enantioselectivities (up to 97% ee) and was applied towards a wide variety of α-tertiary ethers. Similarly, Chen used a similar strategy, but trapped the resulting C-centred radical with allyl sulfones.[290] More recently, Wang and Xu used *N*-hydroxyphthalimide esters to achieve asymmetric C–H activation, with one report of α-tertiary ether formation.[291] The phthalimide redox handle was not retained in the products of these strategies.

In 2016, Rovis employed olefins as the electron-deficient coupling partners (Scheme 73B).[292] Through judicious choice of the amide handle, the N–H bond could be appropriately acidified to facilitate Ir(III)-mediated generation of an *N*-centred radical capable of reaction as above.[292] Using this method, they synthesised one example of an α-tertiary ether, arising due to HAT occurring from a secondary ether site.

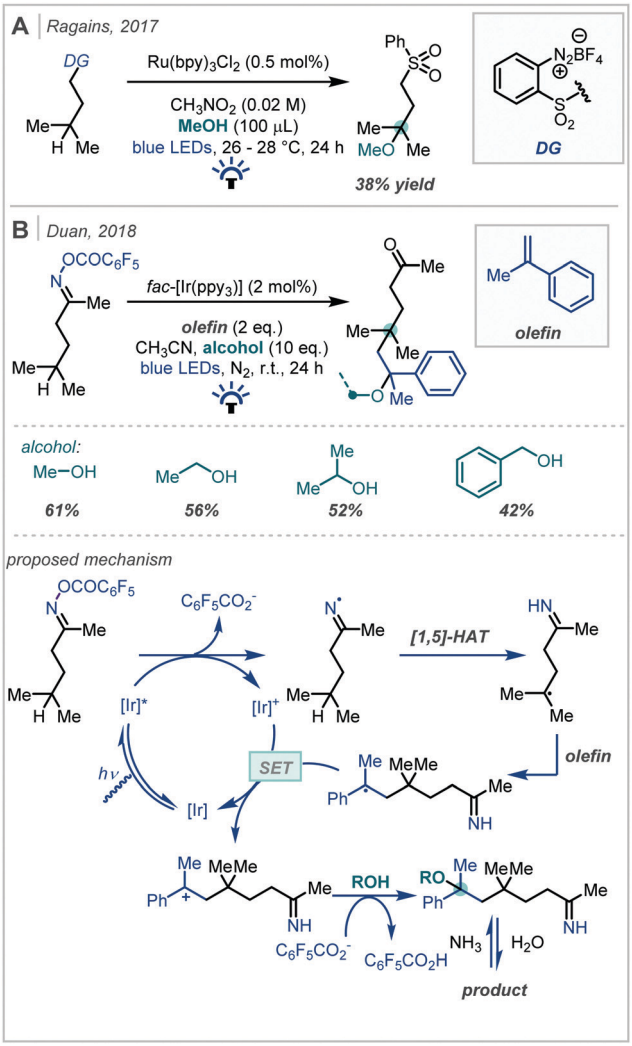
Alternative methods have explored the photoredox-mediated generation of C-centred radicals in a similar manner; once formed, the radicals would undergo SET to generate carbocations that would be trapped with alcohols, in a RPC approach. In 2015, Ragains focused on developing a photoredox-mediated C–H activation method using diazonium salts as redox-active moieties and reported the synthesis of two α-tertiary methyl ethers.[293] This was expanded upon in 2017, when a diazonium tetrafluoroborate sulfone directing group was shown to be suitable for triggering [1,6]-HAT of tertiary C(sp^3)–H bonds, followed by SET and alcohol trapping of the resultant carbocation (Scheme 74A).[294] In 2018, Duan designed a temporary



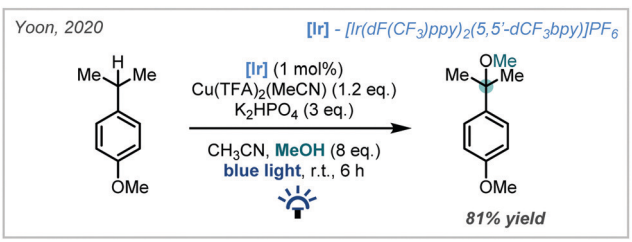
Scheme 73 Photoredox-mediated C–H activation methodologies towards α-tertiary ethers based on C-radical generation and trapping of electron-deficient olefins.

directing group strategy aimed towards C–H hydroxy- and alkoxylation. An iminyl radical was generated from the corresponding perfluorobenzoyl oxime upon irradiation with blue light.[295] This radical triggered [1,5]-HAT to activate a remote C–H bond, and subsequent SET followed by carbocation trapping with an alkene and methanol afforded α-tertiary ethers *via* a MCR (Scheme 74B).

A more recent example by Yoon focused on the benzylic C–H activation *via* tandem photoredox/Cu(II) catalysis.[275] This is an attractive approach for activating benzylic C–H bonds as it does



Scheme 74 Radical relay and SET sequences towards C–H etherification.

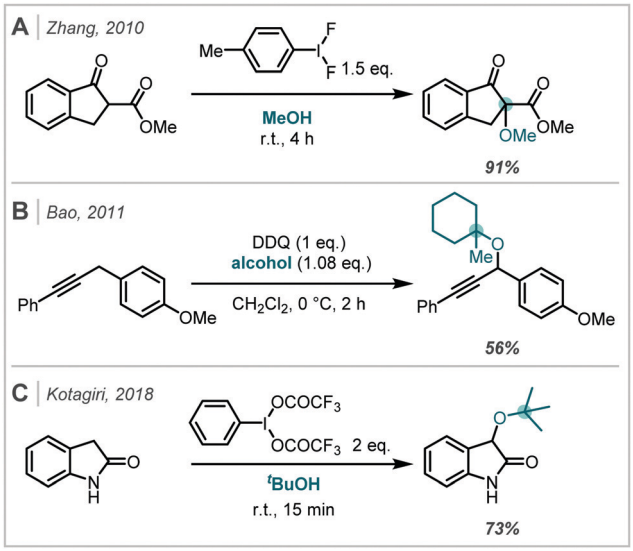


Scheme 75 Benzylic C–H activation to afford α-tertiary ethers.

not require pre-functionalisation of the substrate to install a radical precursor (Scheme 75).

4.3 Metal-free methods

Given the often-higher costs, handling difficulties and sustainability issues associated with metal-catalysed methods, the development of metal-free alternatives is attractive and such approaches have found application within the synthesis of α-tertiary ethers *via* C–H activation.



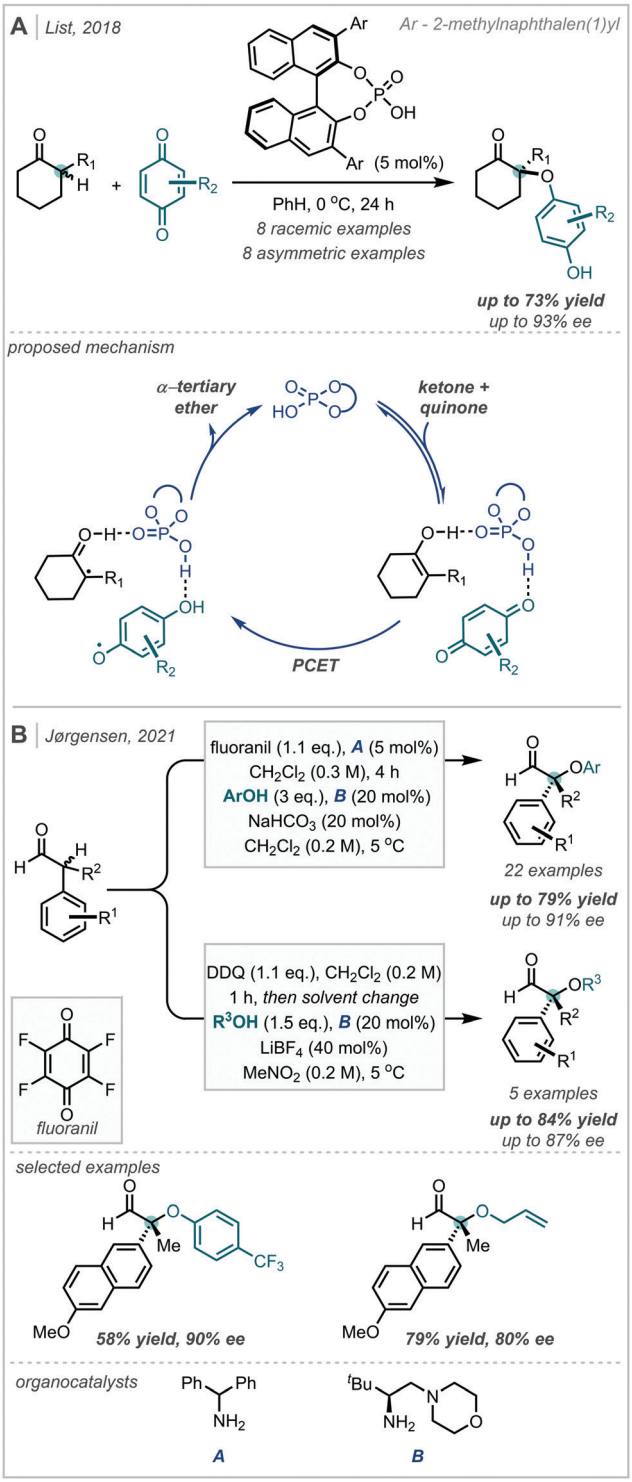
Scheme 76 Metal-free examples of C–H alkoxylation utilising hypervalent iodine (A and C) or quinone (B) terminal oxidants.

In 2010, Zhang employed *p*-iodotoluene difluoride and methanol as solvent to achieve C–H alkoxylation; two α-tertiary ethers were obtained (Scheme 76A).[296] A report by Bao highlighted the use of DDQ as a stoichiometric oxidant to achieve propargylic C–H functionalisation with alcohols (Scheme 76B).[297] Later, Kotagiri employed bis (trifluoroacetoxy)iodobenzene (PIFA) to activate the oxindole benzylic C–H bond towards *t*-BuOH addition (Scheme 76C).[298]

Alternatively, heterocyclic C–H bonds have been oxidised into phosphonium salt moieties, which were subsequently used in S_NAr etherification reactions by McNally[299] and Vilotijevic[300] respectively, who each reported one α-tertiary ether as part of the scope.

In 2018, List reported the application of phosphoric acids catalysts towards asymmetric α-aryloxylation of substituted ketones using *p*-benzoquinones (Scheme 77A).[301] The procedure afforded a wide range of α-tertiary ethers under mild conditions and, notably, the use of single enantiomer chiral phosphoric acids could afford the α-tertiary ether products in excellent enantioselectivity.[301] The mechanism proposed by the authors involved formation of the enol from the ketone, which was brought in close proximity to the quinone partner by the phosphoric acid catalyst. A PCET event led to a diradical complex, which underwent C–O bond formation to afford the product and regenerate the catalyst.

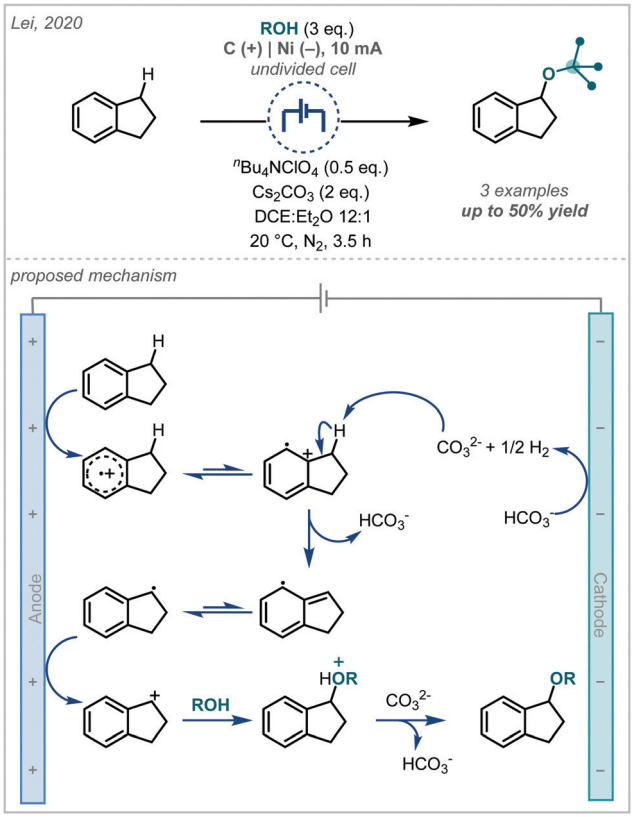
Subsequently, Jørgensen demonstrated that aldehydes can also react with benzoquinones under primary amine catalysis *via* enamine intermediates to afford α-tertiary thioethers.[302] Although the original method was not amenable to the synthesis of α-tertiary ethers, in 2021, the authors employed modified conditions to achieve α-aryloxylation and α-alkoxylation of α,α-disubstituted aldehydes (Scheme 77B).[303] Similar to List's report, the α-alkoxylation could be rendered enantioselective by employing readily available primary amine organocatalysts (such as diamine **B**).



Scheme 77 Organocatalytic approaches towards asymmetric α-tertiary ethers from racemic ketones (A) and aldehydes (B).

4.4 Electrochemical C–H functionalisation

Electrochemistry has also emerged as an alternative approach within the field of C–H oxidation to make hindered ethers. An early example was described by Kasch in 1979, where



Scheme 78 Electrochemical C–H alkoxylation of the benzylic site of indanes.

introduction of a methoxy group in the benzylic position of estradienes was achieved *via* anodic oxidation.[304]

In 2020, Lei synthesised α-tertiary ethers derived from indane *via* electrochemical benzylic C(sp^3)–H bond oxidation (Scheme 78). The procedure was carried out in an undivided cell and required an excess of the tertiary alcohol reaction partner. The proposed mechanism involved formation of a radical carbocation from indane *via* SET, which was then subjected to a hydrogen atom abstraction. A further anodic SET formed an indane carbocation, which was trapped by the alcohol nucleophile.[305] In a similar approach, Li employed W_2C nanocrystals as efficient electrodes for C–H activation and coupling of methanol with cumene, which proceeded in good yield to afford the corresponding α-tertiary ether.[306]

5. Cross-alcohol coupling

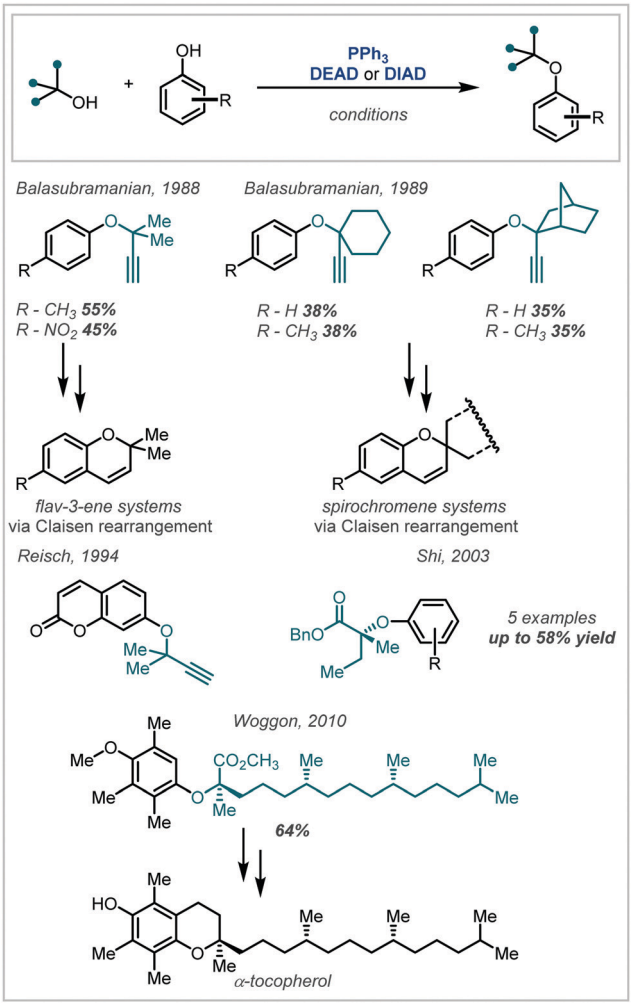
Alcohols are a naturally attractive starting material for the synthesis of ethers, and they are still employed extensively in the Williamson etherification. However, the aforementioned limitations of this approach have warranted the investigation of alternative methods. The eponymous Mitsunobu reaction, first disclosed in 1967,[307] complements the classical Williamson method and expands the scope of starting materials. This reaction traditionally employs the redox couple of triphenylphosphine and

diethylazodicarboxylate, which activates the alcohol towards substitution.

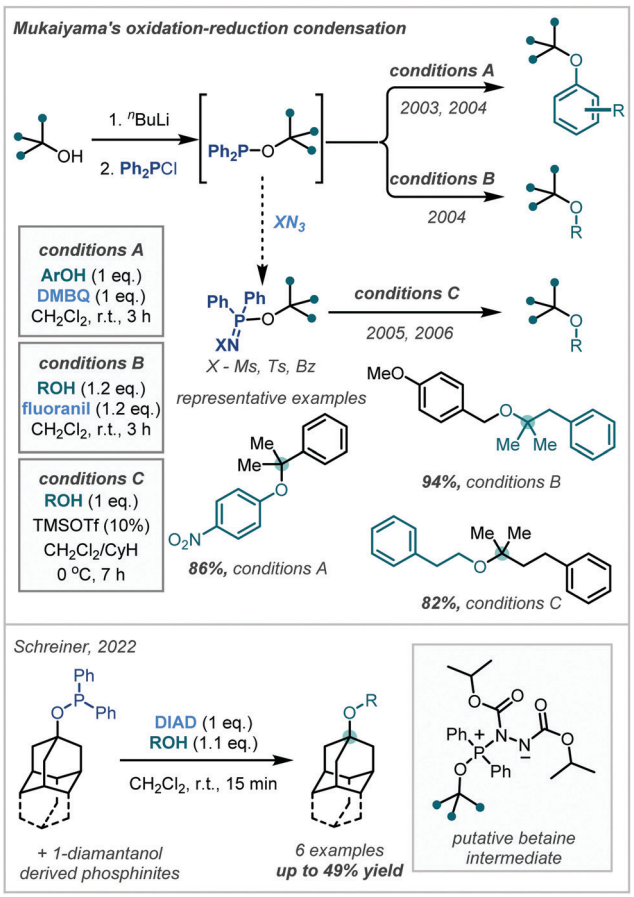
While traditionally not amenable to the synthesis of α-tertiary ethers, there are a few successful applications of the Mitsunobu reaction to such hindered C–O bond formation. Leading reports of such strategies were investigated in efforts towards important structural motifs, such as flav-3-enes,[308] spirochromenes,[309] or dihydropyrano-coumarin systems[310] (Scheme 79).

Further work by Shi enabled the synthesis of aryl–alkyl ethers from tertiary alcohols under Mitsunobu conditions.[311] The single enantiomer chiral ether products were employed as intermediates towards drug candidates. In 2010, Woggon generated α-tertiary ethers in a similar manner during efforts towards α-tocopherol.[312] Bracher also reported the unexpected formation of aryl–alkyl α-tertiary ethers when employing 4-hydroxy-*N*-Boc piperidines as substrates under Mitsunobu conditions.[313]

In a strategically distinct approach, Mukaiyama focused heavily on phosphorus-mediated oxidation–reduction condensations which can be exploited to condense alcohols to the



Scheme 79 Examples of the synthesis of α-tertiary ethers achieved *via* Mitsunobu reactions.



Scheme 80 Phosphorus-mediated oxidation–reduction condensations.

corresponding ethers (Scheme 80).[314,315] While early reports demonstrated that use of triphenylphosphine as the reducing agent was less compatible with tertiary ether formation, the use of alkoxydiphenylphosphines was found to be much more successful.[314,315] Utilising Ph_2POtBu as both reductant and alkylating agent, and 2,6-dimethoxybenzoquinone (DMBQ) as oxidant achieved *t*-butylation of *p*-nitrophenol in good yield (conditions A, Scheme 80);[314] *in situ* synthesis of Ph_2POR reagents bearing a tertiary alcohol of choice was shown to achieve aryl–alkyl α-tertiary ethers in good yields (conditions B, Scheme 80).[315,316] Likewise, this methodology was further extended to the synthesis of alkyl-alkyl α-tertiary ethers when using fluoranil as the quinone oxidant.[316] A key feature of Mukaiyama's work is that the reaction proceeds with exclusive inversion of stereochemical configuration as demonstrated using enantiopure substrates.

Later, Mukaiyama noticed that reacting these alkyl diphenylphosphinite reagents with azides provided diphenylphosphinimidates, which were efficient alkylating agents in the presence of Lewis acids, such as TMSOTf (conditions C, Scheme 80).[317] An extended study from 2006 showed that both pre-synthesised and *in situ*-generated diphenylphosphinimidates were able to provide α-tertiary ethers.[318]

A variation on this work was developed in 2022 by Schreiner, in which adamantyl phosphinites were activated towards

nucleophiles using diisopropyl azodicarboxylate (DIAD)—rather than the quinones employed by Mukaiyama. This methodology was shown to be an effective route towards the synthesis of congested α-tertiary ethers and preliminary mechanistic investigations suggested the formation of carbocation intermediates. A betaine intermediate was proposed to form, from reaction between the phosphinite and DIAD, which was capable of deprotonation of a pro-nucleophile.[319]

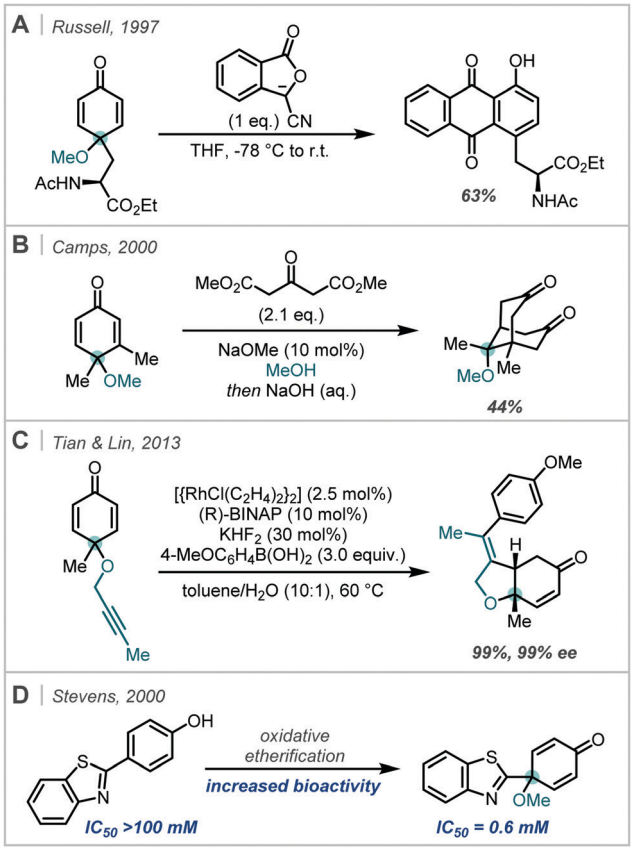
6. Phenolic oxidation

The reaction of phenolic cations with alcohols has enabled the synthesis of quinolic α-tertiary acyclic ethers, following Dimroth's seminal report on stable, isolable phenolic cations in 1967.[320] While originally seen as an academic curiosity, these compounds have now become valuable building blocks within modern synthesis and, additionally, can exhibit biological activity.

6.1 Importance and applications

The cyclohexa-2,5-dienone products generated from phenolic oxidation of *para*-substituted phenols have been widely derivatised. In 1997, Russell exemplified this in the synthesis of anthraquinones from *p*-quinol ethers by reacting them with a cyanophthalide anion (Scheme 81A).[321,322] Camps later reported a double Michael-decarboxylation sequence of dimethyl 1,3-acetonedicarboxylate to generate a three-dimensional bicyclo[3.3.1]-nonane-3,7-dione scaffold from widely available phenols, affording otherwise synthetically challenging α-tertiary ether motifs (Scheme 81B).[323] More recently, *p*-quinol ethers have been employed as substrates in asymmetric synthesis, elegantly demonstrated by Tian & Lin's Rh-catalysed desymmetrizing cyclisation, affording *cis*-hydrobenzofurans in excellent yield and enantioselectivity (Scheme 81C).[324]

Furthermore, α-tertiary acyclic quinol ethers have been shown to exhibit anti-tumour activity.[324] Stevens reported that benzothiazole quinol ethers show micromolar activity in human cancer cell lines HCT-116 and that quinol ethers show increased potency over the parent 2-(4-hydroxyphenyl)-benzothiazoles that they are derived from (Scheme 81D).[325]



Scheme 81 Applications of α-tertiary quinol ethers: (A) application to synthesis of anthraquinones; (B) synthesis of bicyclo[3.3.1]nonane-3,7-diones; (C) use in catalytic enantioselective synthesis; (D) biological properties.

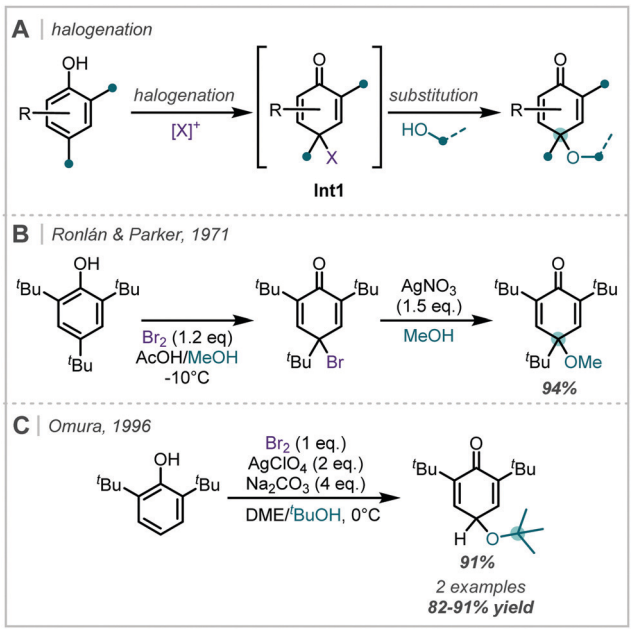
6.2 Halogenation

One strategy for the synthesis of α-tertiary quinol ethers is the halogenation of *para*-alkylated phenols to generate an intermediate *p*-halodienone species **Int1** which was able to be intercepted by an appropriate alcohol to deliver the desired tertiary ether (Scheme 82A). In 1971, Ronlán & Parker generated a bromo-quinol which was then subjected to a Ag-induced substitution with methanol to deliver the tertiary ether (Scheme 82B).[326] Ronlán later reported that *p*-alkylphenols could be monochlorinated using excess antimony pentachloride to give the *para*-chlorinated quinol which was then treated with methanol to give the desired tertiary ether.[327] In 1996, Omura utilised a different approach to introduce the α-tertiary motif, employing *p*-unsubstituted phenols, which could be intercepted by tertiary alcohols.[328] By bromination of 2,6-di-*tert*-butyl phenol, a secondary bromide intermediate was formed, which reacted smoothly with a hindered nucleophilic tertiary alcohol to give an α-tertiary ether (Scheme 82C).[328] However this tertiary ether was shown to be susceptible to irreversible re-aromatisation to the phenol on treatment with acid, base or silica gel.

In 2005, Jacobs developed a catalytic variant of this reaction using a WO_4^{2-} – exchanged layered double hydroxide (WO_4^{2-} – LDH) catalyst – an ionic solid comprised of layers of metal hydroxide with intercalated WO_4^{2-} anions. WO_4^{2-} – LDH catalyses the formation of hypobromite from ammonium bromide and hydrogen peroxide *in situ* (Scheme 83, also see Section 2.4.6). The resulting hypobromous acid was then able to brominate the phenol which was substituted with an alcohol to yield the desired α-tertiary ether and regenerate HBr to turn over the catalytic cycle.[329]

6.3 Anodic oxidation

Electrochemical methods have been shown to be particularly efficacious in the synthesis of quinol ethers (Scheme 84A), however they usually require a large excess of the nucleophile in order to generate the ether in appreciable yields. The mechanism for these reactions has been purported to go through stepwise electron-proton transfer sequences (Scheme 84B).[330]

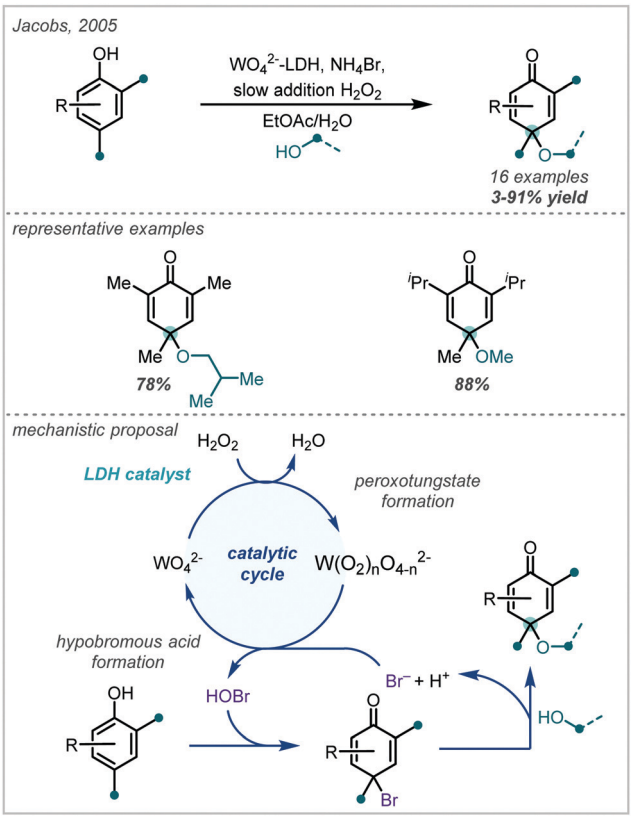


Scheme 82 Synthesis of quinol ethers *via* halogenation: (A) general scheme; (B) Ag(I) mediated substitution of a tertiary alkyl bromide; (C) Ag(I) mediated substitution of an *in situ*-generated secondary alkyl bromide.

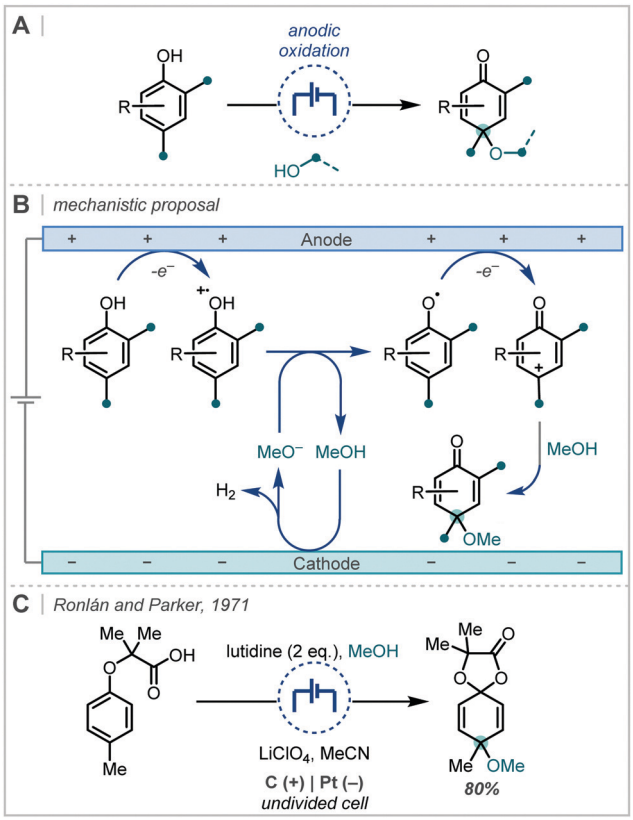
An early report by Ronlán & Parker demonstrated that it was possible to trap out an electrochemically-generated phenoxonium cation with methanol in an undivided cell under constant current.[326] α-*p*-Tolylisobutyric acids could also be anodically oxidised to give lactones bearing a tertiary ether in the *para* position (Scheme 84C). The authors later studied the mechanism and found that the reaction took place *via* direct oxidation of the phenol, not *via* the formation of methoxy radicals.[331]

In 1978, Rieker undertook a detailed investigation into the scope of the nucleophile (Scheme 85);[332] a wide range of nucleophiles including primary and secondary alcohols were able to trap the phenoxonium cation. More oxidatively resistant phenols such hexachlorophenol were also employed allowing selective cross-phenol coupling. Using this methodology, Rieker was able to synthesise a synthetically challenging α,α′-tertiary ether, albeit in low yield.

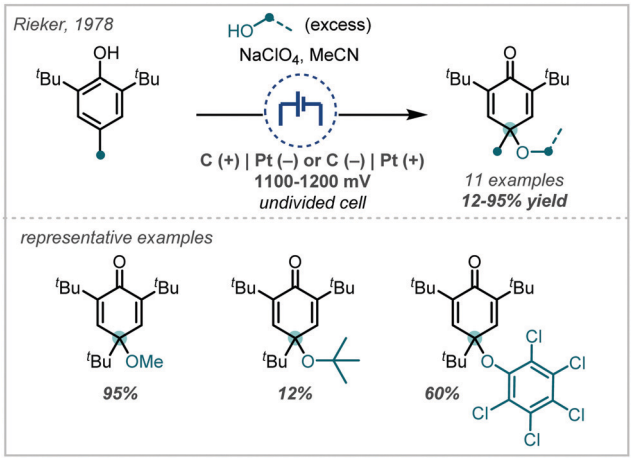
In 1991, Swenton applied the anodic oxidation of phenols to the synthesis of spirodienones (Scheme 86).[333,334] A mechanistic investigation of this transformation demonstrated that the reaction proceeds *via* the phenoxonium cation,[335] which is then intercepted by a pendant alkene in an intramolecular manner forging a C–C bond; the resultant carbocation was subsequently trapped by the solvent to form a tertiary ether. The scope of this transformation was later extended to include substrates with a methoxy group in the *para* and *meta* positions of the styrene.[336]



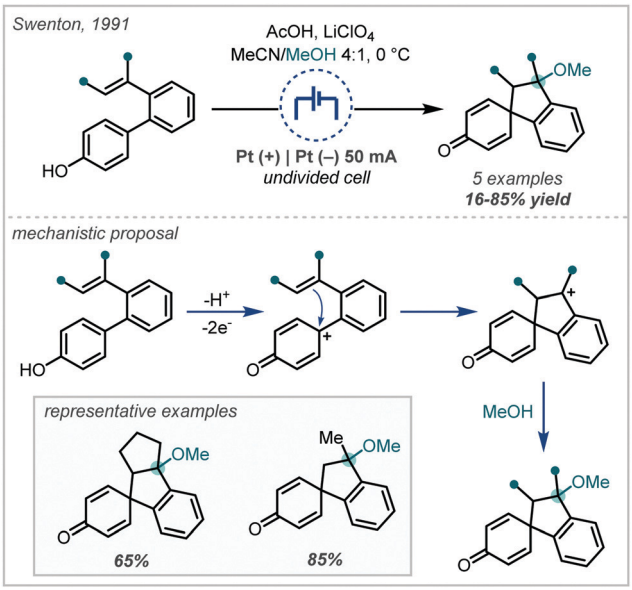
Scheme 83 Synthesis of quinol ethers *via* catalytic generation of hypobromous acid.



Scheme 84 (A) General equation. (B) General mechanism for anodic oxidation of phenols to form quinol ethers. (C) Anodic oxidation of α-*p*-tolylisobutyric acid.



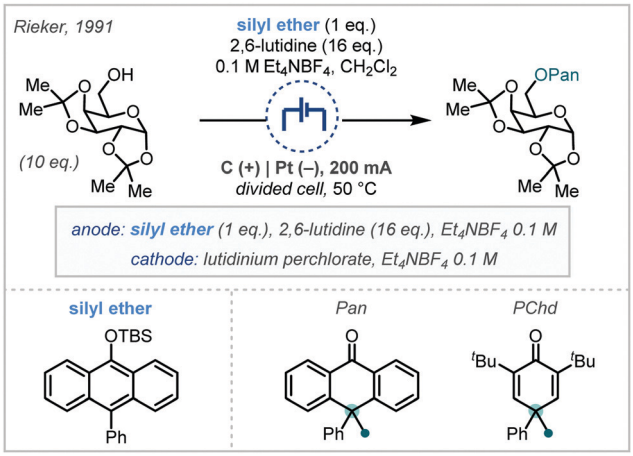
Scheme 85 Anodic oxidation of phenols and trapping with *O*-nucleophiles to give quinol ethers.



Scheme 86 Anodic oxidation of 2′-alkenyl substituted *p*-aryl phenols to give spirodienones bearing α-tertiary ethers.

Likewise, Rieker reported a procedure for the reaction of the exocyclic primary alcohols of sugars using the anodic oxidation of phenols to form quinol-protected alcohols.[330] The Pan and PChd groups could be introduced, in 78% and 50% yield respectively, in a divided cell using the pyranose in 10-fold excess (Scheme 87).[330] The Pan and PChd groups were shown to be orthogonal protecting groups to traditional sugar protecting groups as they are able to be selectivity cleaved in the presence of isopropylidene and benzoyl groups.

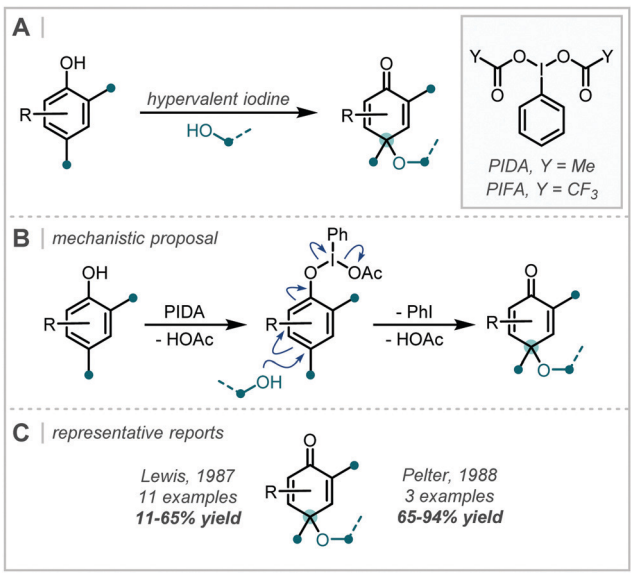
The anodic oxidation of less oxidisable biphenyls, phenolic biphenyls, anisoles and xylenes has also been reported by a number of different groups and, among other products, these reactions afforded tertiary ethers.[337–343] However, these reactions typically require very strongly oxidising conditions and proceed with lower selectivity.



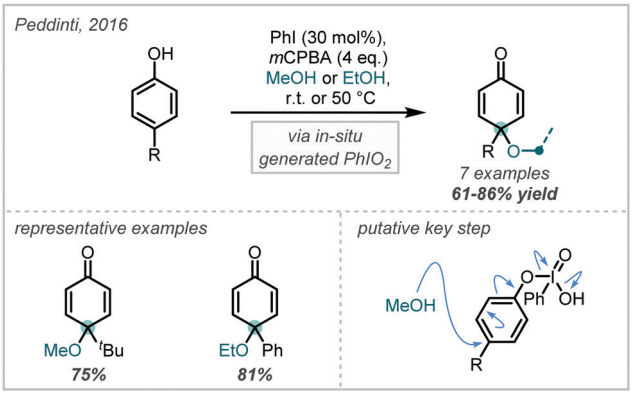
Scheme 87 Pan protection of sugars *via* anodically generated cations.

6.4 Hypervalent iodine

The dominant approach for generating phenoxonium cation equivalents for the synthesis of acyclic α-tertiary ethers involves oxidation of phenols by hypervalent iodine reagents (Scheme 88). Since a leading report by Becker,[344] PIDA has become the most commonly used hypervalent iodine reagent, further complemented by the use of PIFA in specialised circumstances when a non-oxygen centred nucleophile is involved.[345,346] In 1987, Lewis reported the synthesis of acyclic α-tertiary ethers using PIDA[347] and showed a valuable proof of concept and applicability to a range of nucleophiles and phenol coupling partners. This was further expanded by Pelter's report in 1988.[348,349] Swenton successfully translated their spirodienone synthesis from an electrochemical oxidation to oxidation mediated by PIDA.[350]



Scheme 88 (A) General mechanism for hypervalent iodine oxidation. (B) Proposed mechanism. (C) Reports of Lewis and Pelter.

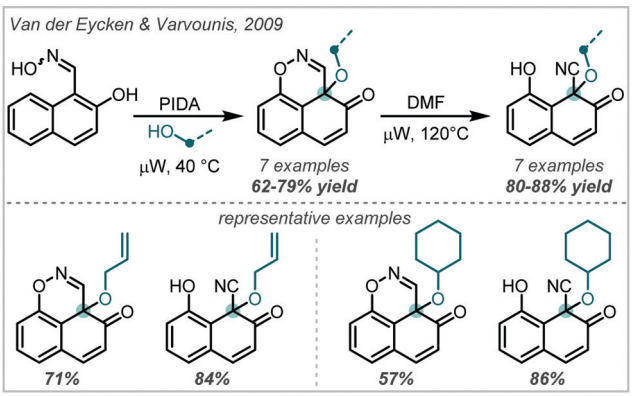


Scheme 89 Phenolic oxidation mediated by *in situ* generated $PhIO_2$.

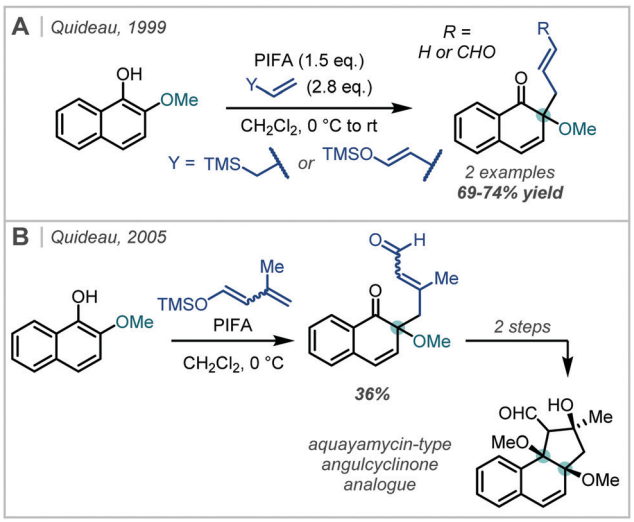
Peddinti later reported a catalytic oxidative alkoxylation of phenol whereby the hypervalent iodine oxidant $PhIO_2$ species was generated *in situ* from *meta*-peroxychlorobenzoic acid (*m*CPBA) and a substoichiometric amount of iodobenzene. In this case $PhIO_2$ functions as the electrophile which was able to give the tertiary ether *via* intermolecular trapping with a nucleophilic solvent (Scheme 89).[351]

Van der Eycken & Varvounis translated this chemistry to the synthesis of α-cyano naphthones from tricyclic naphthaldehyde oximes using PIDA to trigger the dearomative oxidative ring closure and alkoxylation (Scheme 90). The nascent ring could then be cleaved under thermal or microwave conditions to give the nitrile and a corresponding phenol, constituting a C–H oxidation, nitrile formation and concurrent etherification over 2 steps.[352]

In 1999, Quideau reported an alternative approach to synthesizing acyclic α-tertiary quinol ethers using a carbon-centred nucleophile, rather than an oxygen-centred nucleophile, to intercept the quinol intermediate with the ether oxygen already present. They reported the synthesis of naphthoid cyclohexa-2,4-dienones from naphthols *via* PIFA-mediated oxidative nucleophilic substitution.[353] In this example PIFA was chosen instead of PIDA due to the reduced nucleophilicity of trifluoroacetate anion (Scheme 91A). In a subsequent report they extended this



Scheme 90 Synthesis of tertiary ethers *via* oxidative cyclisation of naphthyl-oximes.



Scheme 91 (A) PIFA mediated oxidation of 2-alkyl-and 2-alkoxy-naphthols to give tertiary ether product by trapping with a C-centred nucleophile. (B) Applied to the synthesis of an aquayamycin analogue.

transformation to benzyl ethers[354] and later applied it to the synthesis of the ABC tricyclic unit of aquayamycin analogues (Scheme 91B).[355]

6.5 Metal-mediated oxidation

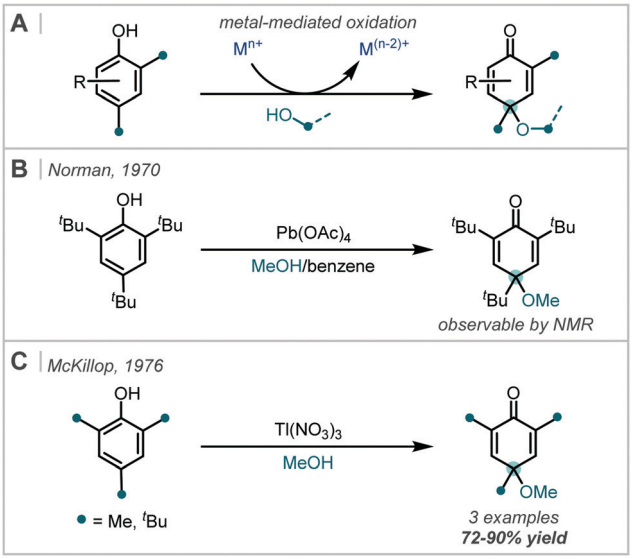
Metal-based oxidants have also been shown to be capable of oxidising phenols to their corresponding cations, enabling the synthesis of α-tertiary ethers. The metal can be implicated either as a stoichiometric oxidant or a catalyst and both copper and iron salts have been used as catalysts for the oxidative methoxylation of phenols.[356,357]

In 1970, Norman reported the two-electron oxidation of phenols using lead tetraacetate. This enabled the generation of the phenoxonium cation, which was subsequently trapped with methanol to afford the α-tertiary ether (Scheme 92B).[358] In a related approach, McKillop later reported a procedure whereby 2,4,6-substituted phenols reacted with thallium nitrate in methanol to give *p*-substituted ethers in good to excellent yields (Scheme 92C).[359] This approach has since been replaced by the more operationally straightforward conditions, described above, in order to avoid notoriously toxic reagents.

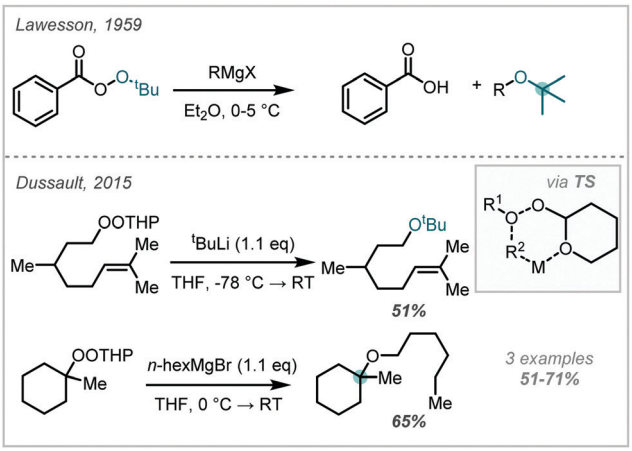
7. Miscellaneous

7.1 Peroxide-mediated methods

In 1959, Lawesson reported a convenient, scalable and reproducible synthesis of *t*-butyl ethers *via* the reaction of *t*-butyl perbenzoate with Grignard reagents (Scheme 93).[360,361] Recently, Dussault extended this synthetic strategy to peroxyacetals, employing both organolithiums and Grignard reagents in the reaction.[362] This method gave a range of ethers in good yields *via* the transfer of primary, secondary or tertiary alkoxides through the highly regioselective substitution on the non-acetal oxygen of the peroxide. Alkoxide transfer in previous dialkylperoxide-mediated etherification methods gave lower



Scheme 92 (A) General scheme of metal-mediated phenolic oxidation. (B) Quinol synthesis using Pb(IV) tetraacetate. (C) Quinol synthesis using thallium(III) nitrate.



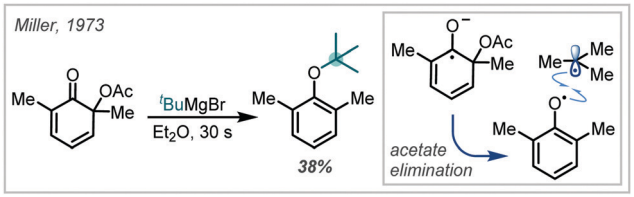
Scheme 93 Peroxide-mediated routes to α-tertiary ethers.

yields with sterically hindered alkoxides. Dussault, however, proposed that the adjacent acetal moiety relatively stabilised the transition state responsible for transfer of the alkoxide *via* the anomeric effect,[363] (see TS, Scheme 93) enabling efficient etherification.

7.2 Miscellaneous radical-based methods

In 1973, Miller reported the reaction of Grignard and organolithium reagents with *o*-quinol acetates.[364,365] The use of tertiary organometallic reagents enabled the synthesis of *t*-butyl ethers (Scheme 94). Miller proposed that this transformation was achieved by SET from the organometallic reagent to the quinone and that subsequent loss of acetate and combination of the resulting phenoxy radical with the alkyl radical resulted in ether formation.

The addition of alkyl radicals to quinones has been exploited for over 80 years as quinones are often used as free

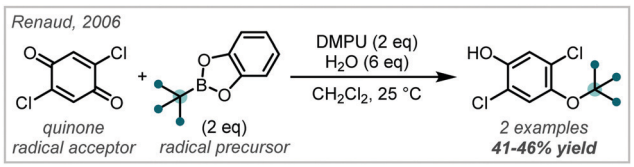


Scheme 94 Synthesis of α-tertiary ethers from *o*-quinol acetates.

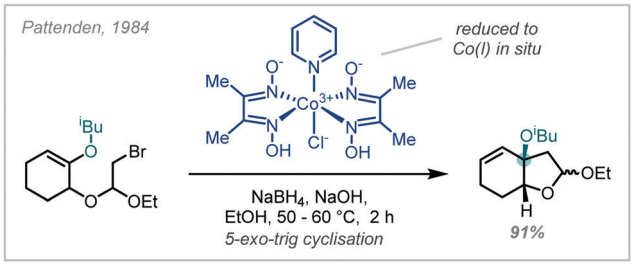
radical polymerisation inhibitors[366] and, more recently, quinones have been used as radical scavengers in heterogeneous photocatalysis.[367] A variety of benzoquinones have been used for this purpose and due to the prevalence of azobisisobutyronitrile (AIBN) as a radical initiator in such processes, a variety of α-tertiary aryl ethers have been synthesised as by-products.[368–370] Renaud exploited this reactivity and developed the reaction of 1,4-benzoquinones with alkyl radicals generated from *B*-alkylcatecholboranes. This method was shown to be selective for *O*-addition when using sterically hindered alkyl radicals and enabled the synthesis of α-tertiary ether examples (Scheme 95).[371]

As exemplified by these processes, the intermolecular addition of radicals to unsaturated systems has been utilised to synthesise α-tertiary ethers. In a conceptually distinct approach, Pattenden reported the intramolecular cyclisation of pendant primary alkyl radicals, generated from the primary alkyl bromides, with enol ethers, linked *via* an acetal tether, thus rendering the point of cyclisation an α-tertiary site (Scheme 96).[372]

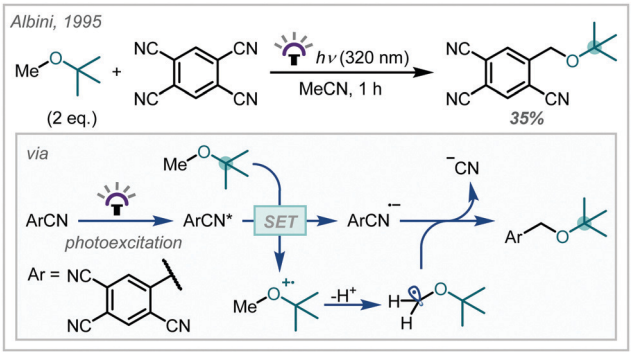
Alongside the alkene difunctionalisation, decarboxylative and C–H activation approaches previously discussed (see Sections 2.1, 3.2 and 4.2), numerous alternative applications of photochemistry have been developed for the synthesis of α-tertiary ethers. In 1995, Albini reported the formation of



Scheme 95 Addition of tertiary radicals to quinones to give α-tertiary aryl ethers.



Scheme 96 Cyclisation with pendant enol ethers to afford α-tertiary ethers.



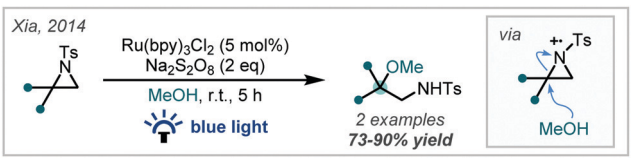
Scheme 97 Photoinduced ether exchange.

aliphatic radicals from ethers *via* photoinduced electron transfer (Scheme 97).[373] The resulting radicals were found to add to the 1,2,4,5-tetracyanobenzene radical anion, thus forming a new alkyl-aryl ether. Notably, this constitutes an example of α-tertiary ether elaboration at the α′ site.

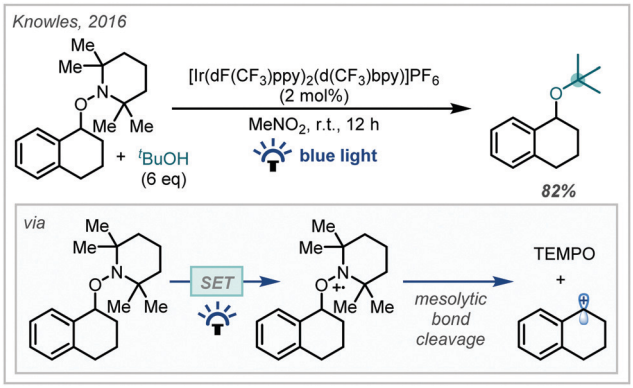
More recently, using substituted aziridines as substrates, Xia developed the regioselective ring opening of aziridines *via* nucleophilic addition (Scheme 98).[374] Notably, the nucleophilic ring opening was promoted by photo-oxidation of the aziridine nitrogen. It was proposed that this transformation occurred *via* SET from the aziridine to the photo-excited Ru(III), forming a reactive amino radical cation which could undergo concerted ring opening and nucleophilic substitution to give the product ether. This constitutes an example of photoredox catalysis promoting a traditionally polar reaction pathway.

In 2016, Knowles demonstrated that α-tertiary ethers could be formed using photoredox catalysis-enabled mesolytic cleavage.[375] In this process, electron transfer to an Ir photocatalyst from a TEMPO-derived alkoxyamine resulted in mesolytic cleavage to afford the nitroxyl radical and corresponding carbocation, which could be intercepted with a tertiary alcohol to give an α-tertiary ether in good yield and under mild conditions (Scheme 99).

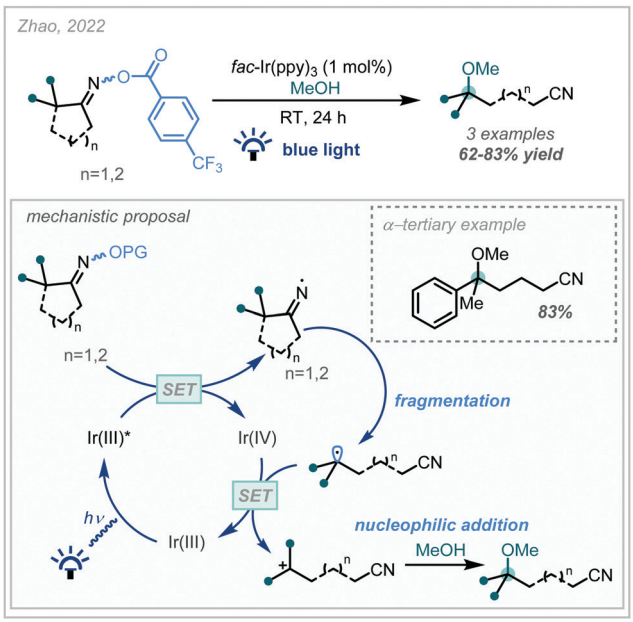
Recently, Zhao reported the photoinduced etherification of cycloketoxime esters.[376] It was proposed that the photoexcited Ir(III) photocatalyst was quenched *via* SET by the cycloketoxime substrate to give an imine radical, which subsequently rearranged *via* C–C bond cleavage to give a distal radical (Scheme 100). This radical could be further oxidised by the photocatalyst to give the corresponding cation, which was intercepted by an alcohol to yield the ether product. By employing these specialised substrates of varying ring sizes, the synthesis of a wide range of ethers using these mild conditions was demonstrated, including some α-tertiary examples.



Scheme 98 Regioselective aziridine opening *via* photoredox catalysis.



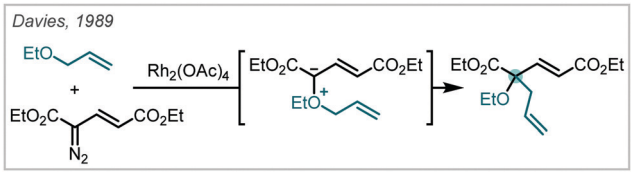
Scheme 99 Ether formation by photoinduced mesolytic bond cleavage.



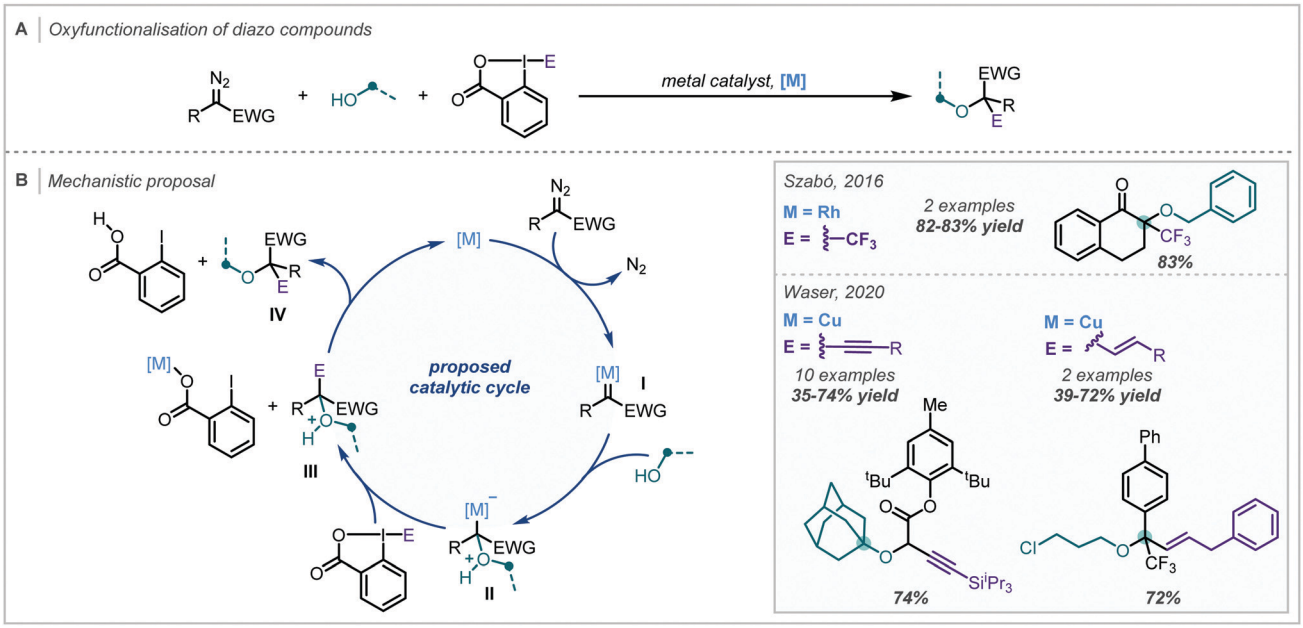
Scheme 100 Synthesis of cyano-α-tertiary ethers *via* photocatalytic C–C bond activation.

7.3 Carbene/carbenoid strategies

In 1989, Davies reported the formation of an undesired α-tertiary ether *via* 2,3-sigmatropic rearrangement while investigating the cyclopropanation of vinylcarbenoids (Scheme 101).[377] Such rearrangements have been employed with a wide range of nucleophiles to access useful functionalities *via* ylide formation.[378] In particular, the reactivity of oxygen nucleophiles with



Scheme 101 Ether synthesis *via* metal-carbenoid formation and subsequent 2,3-sigmatropic rearrangement.

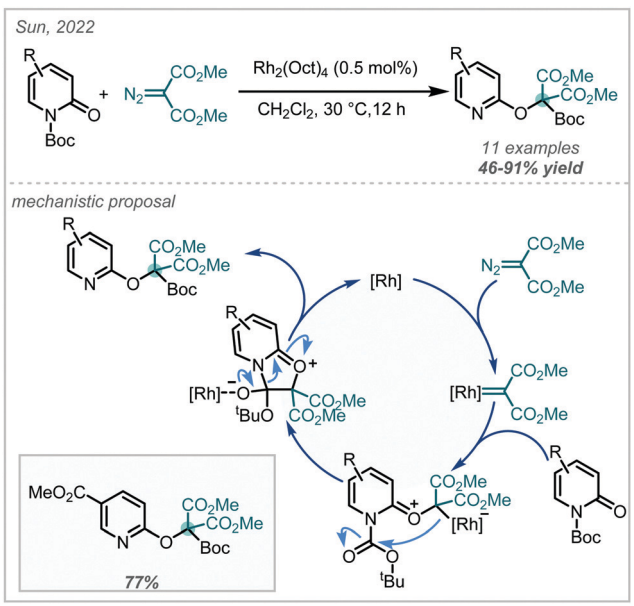


Scheme 102 Scope and proposed mechanism of oxyfunctionalisation reactions of diazo compounds.

metal (usually Rh) carbenoids has since been exploited in a large variety of multicomponent reactions to yield a vast array of chemical complexity, including α-tertiary ethers, in a single reaction and such methods have been reviewed elsewhere.[379]

Recently, substituted benziodoxoles have been employed to enable the oxyfunctionalisation of diazo compounds (Scheme 102). In 2016, Szabó employed Togni's reagent with $Rh_2(OAc)_4$ to allow oxytrifluoromethylation of α-diazocarbonyl compounds; the α-tertiary ether centre is generated by the addition of a nucleophilic alcohol component.[380] In 2016, Waser reported the oxyalkynylation of diazo compounds using a copper catalyst and EBX reagents.[381] While initially only used for the synthesis of esters derived from the EBX reagent, this methodology was subsequently extended to enable the synthesis of a broad range of ethers (including α-tertiary ethers) by variation of the nucleophilic alcohol component in the reaction.[382] Waser has also employed analogous vinylbenziodoxolone (VBX) reagents to enable oxyvinylation of diazo compounds and demonstrated the applicability to the synthesis of α-tertiary ethers.[383] The proposed mechanisms for the oxyfunctionalisation of diazo compounds are comparable:[384] the diazo compound is thought to form metal carbenoid **I** which is intercepted by the alcohol component to form an onium ylide **II**. The intermediate ylide **II** reacts with the electrophilic component of the appropriate benziodoxolone. Proton transfer from the resulting protonated ether **III** releases the product ether **IV**.

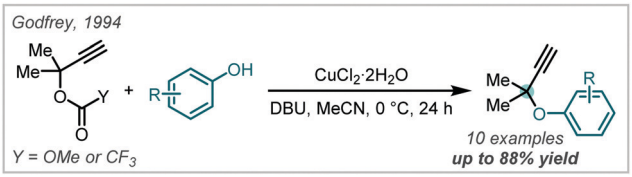
Recently, Sun reported the reaction of *N*-Boc pyridones with dimethyl 2-diazomalonate-derived carbenes (Scheme 103).[385] It was proposed that addition of the pyridone to the generated rhodium carbene could form an ylide intermediate, which could undergo a cyclisation onto the pendent carbamate. C–N cleavage in the resulting tetrahedral intermediate resulted in the formation of an α-tertiary pyridyl ether. Variation in the



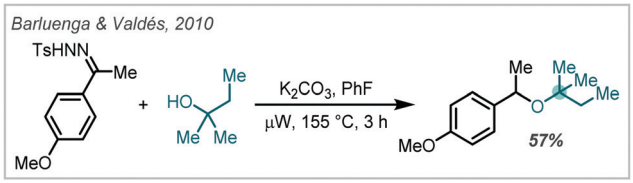
Scheme 103 Synthesis of α-tertiary pyridyl ethers featuring a 1,4-migration of a Boc group.

pyridone coupling partner demonstrated a wide functional group tolerance, in moderate to good yields.

While many propargylic substitutions are proposed to proceed *via* carbocation intermediates, derived from activation by Lewis acids or through formal metal-catalysed cross-coupling,[386] it has been shown that some reactions, under metal catalysis, proceed *via* unique metal-allenylidene or propargylic–metal intermediates. In 1994, Godfrey reported the Cu(I)-promoted reaction of propargylic carbonates with phenols to give α-tertiary ethers (Scheme 104);[387] in analogous work using amine nucleophiles,[388]



Scheme 104 Early propargylic substitution with proposed allenylidene intermediate.

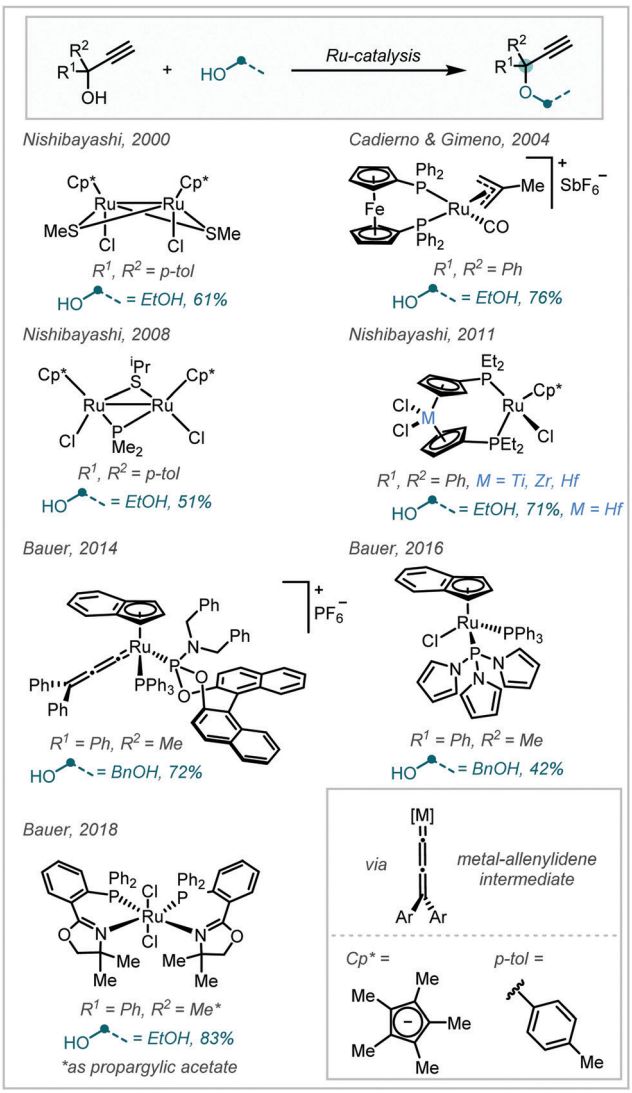


Scheme 106 Reductive coupling of alcohols with tosylhydrazones.

a Cu–allenylidene intermediate had been proposed but was not detected.

Nishibayashi confirmed the intermediacy of a metal–allenylidene or metal–propargylic intermediate when using a thiolate-bridged diruthenium complex (as shown in Scheme 105) and developed a wide range of propargylic substitutions, including the synthesis of a range of α-tertiary ethers utilising a broad range of ruthenium catalysts incorporating both mono- and di-nuclear systems and featuring a range of ligand classes[389–391] Bauer also developed mononuclear ruthenium catalysts for analogous processes[392–394] and others have reported the applicability of a wide variety of ruthenium complexes for the activation of propargylic alcohols.[395,396]

From appropriate precursors, analogous metal-free carbenoid strategies have also been successfully developed. In 2010, Barluenga & Valdés reported the metal-free reductive coupling of tosylhydrazones with alcohols or phenols, employing mechanistic principles related to the Bamford–Stevens reaction.[397] This strategy allowed the synthesis of an α-tertiary ether from readily prepared and stable starting materials (Scheme 106).



Scheme 105 Catalysts for propargylic substitution *via* allenylidene intermediate.

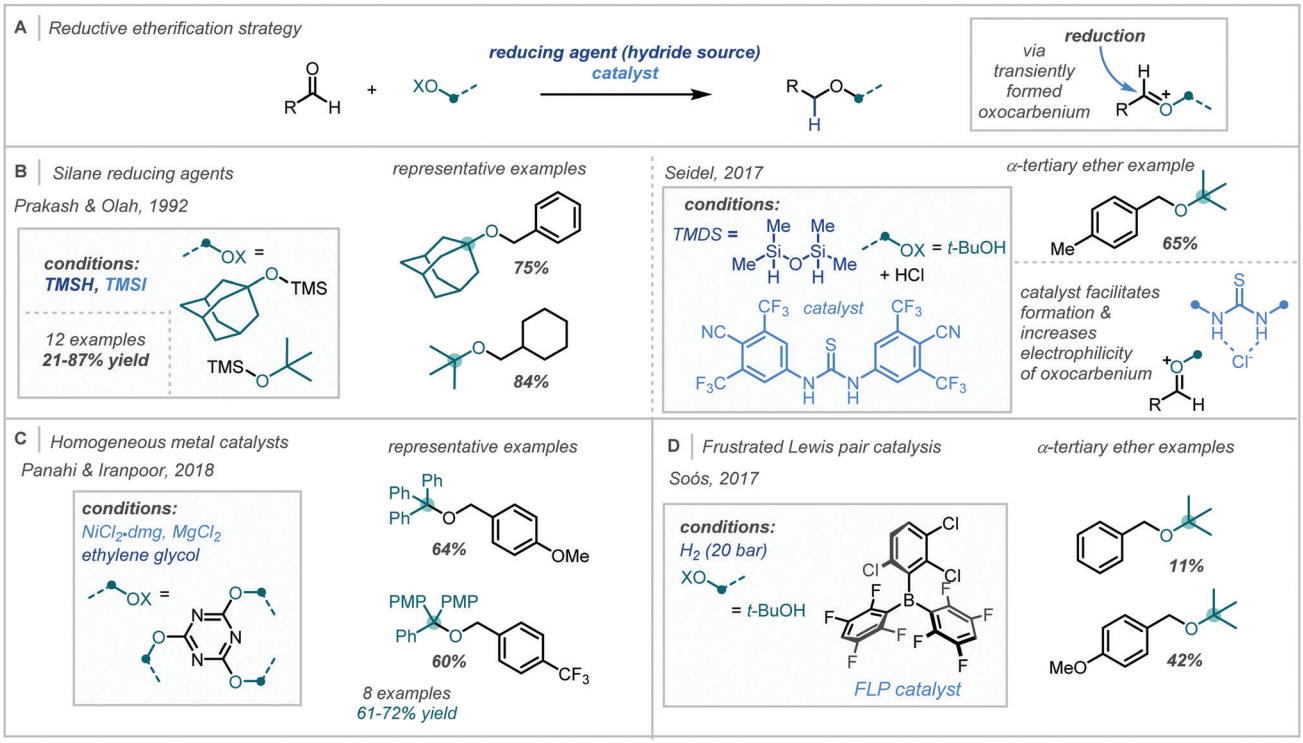
7.4 Reductive etherification

7.4.1 Aldehyde–alcohol reductive coupling. Conceptually distinct from all previously discussed strategies is the *in situ* formation and subsequent reduction of a hemi-acetal to afford an α-tertiary ether directly from a carbonyl compound and an alcohol (Scheme 107A). Many different reagents have been used to achieve ether formation *via* this strategy, including silane and borane reducing agents and both homogeneous and heterogeneous metal catalysts. Given the α-reduction implicit in this strategy, incorporation of an α-tertiary site is restricted to that of the incoming nucleophile.

In 1972, Doyle reported the silane-mediated reduction of carbonyl compounds to give ethers, however, this reaction required excess sulfuric or trifluoroacetic acid and therefore only gave low to moderate yields of acid-sensitive α-tertiary ethers.[398] Twenty years later, Prakash and Olah reported that hindered ethers could be prepared using such a reductive strategy with catalytic trimethylsilyl iodide to promote oxocarbenium ion formation (Scheme 107B).[399] The mild conditions of this method allowed the synthesis of a variety of α-tertiary ethers in high yield; a similar approach using TMSOTf was also detailed by Hatakeyama and Nishizawa.[400]

An Fe-catalysed alternative was reported by Oriyama in 2005 which demonstrated greater operational simplicity and shorter reaction times, although the yield of α-tertiary ethers obtained by this method was moderate.[401]

Recently, Seidel developed a reductive etherification reaction using anion-binding catalysis.[402,403] A derivative of Schreiner's thiourea catalyst was designed to facilitate the formation and increase the electrophilicity of the intermediate oxocarbenium ion and enabled the synthesis of an α-tertiary example in 65% yield.[404] Boron-based reducing agents have also been employed to generate α-tertiary ethers using this reductive etherification strategy; Scheunemann utilised decaborane as a mild and fairly stable



Scheme 107 Reductive etherification strategies. (A) General reductive etherification strategy. Reductive etherifications using: (B) silane reducing agents; (C) transition metal catalysis; and (D) FLP catalysis. dmg = dimethyl glyoxime; PMP = *para*-methoxyphenyl.

reducing agent to yield a *tert*-butyl ether while investigating a one-step reductive etherification of 4-[^{18}F] fluoro-benzaldehyde for use in positron emission tomography.[405]

Additionally, both homogeneous and heterogeneous metal catalytic systems have been exploited in such reductive etherification strategies to yield α-tertiary ethers. In 2018, Panahi and Iranpoor reported the Ni-catalysed reductive etherification of aldehydes with activated triazine tritylating agents using ethylene glycol as both the solvent and reducing agent to give α-tertiary ethers at room temperature and in good yields (Scheme 107C).[406] Heterogeneous systems such as Pd catalysts which have been modified with ethyl iodide have been used as bifunctional catalysts in the selective reductive etherification of bio-derived aldehydes with alcohols.[407]

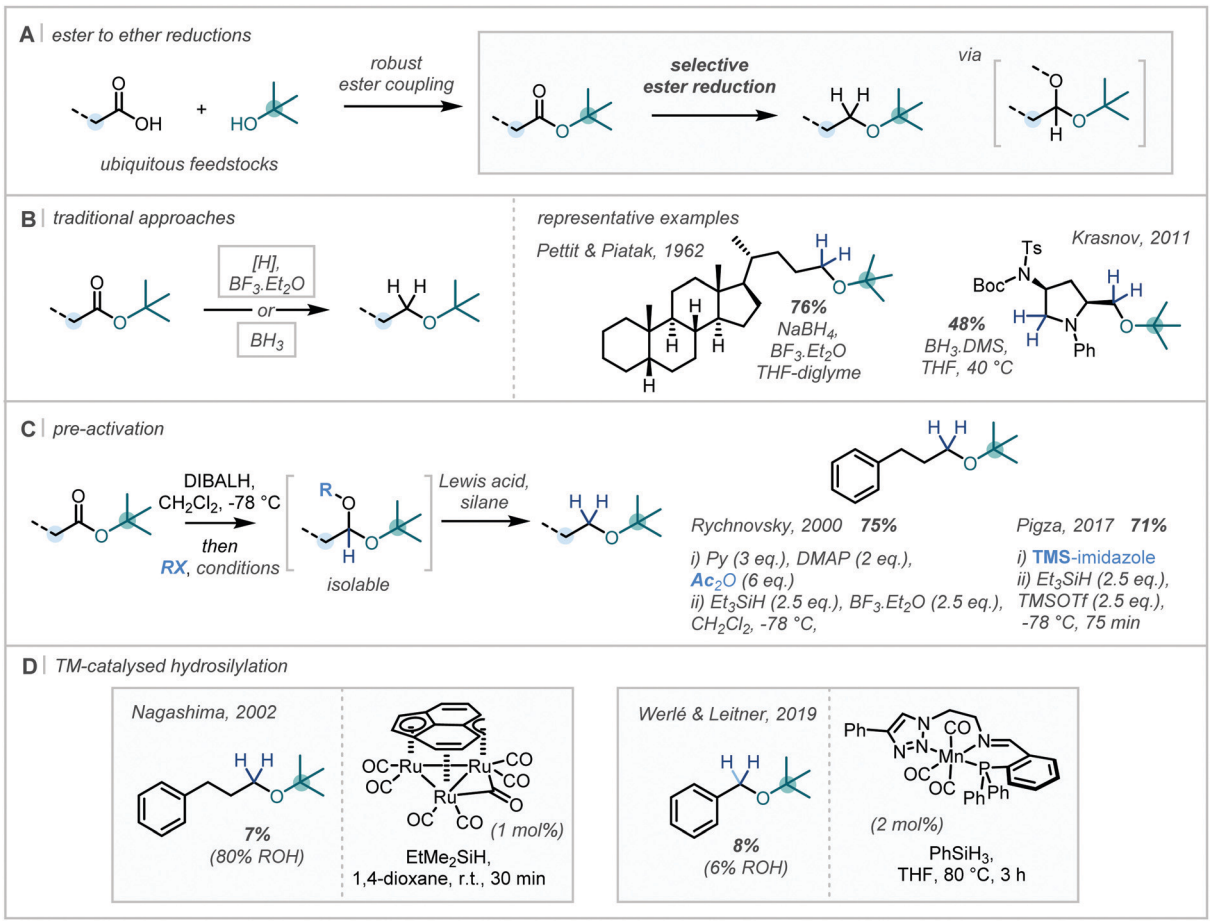
Although such metal-based catalytic systems have proven useful, Soós demonstrated a metal-free approach using a frustrated Lewis pair catalyst to promote reductive etherification by enabling hydrogen activation, thus forming both a reducing agent and a Brønsted acid (Scheme 107D).[408] Despite modest yields in the synthesis of α-tertiary ether examples, this represents a successful complimentary strategy to metal-based systems in achieving the synthesis of such a challenging motif.

7.4.2 Ester reduction. Given the robustness associated with ester coupling, the selective reduction from ester to ether represents an appealing and potentially versatile strategy towards ether synthesis (Scheme 108A).[409] A key challenge to overcome within this approach is the undesired formation of aldehyde rather than oxocarbenium intermediates, due to unfavourable collapse of the tetrahedral intermediate following initial reduction. There has been limited success in this field when applied to hindered acyclic ethers. Furthermore, given the requirement for a formal reduction at the carbonyl site, the α-tertiary site necessarily arises from the alcohol moiety.

Notably, this strategy has been more widely adopted in the synthesis of cyclic α-tertiary ethers, rather than acyclic ethers. While multi-step approaches, featuring complete reduction to the diol then subsequent nucleophilic substitution of an activated primary alcohol, have been widely adopted, single-step procedures have traditionally relied upon the combined action of a strong hydride source and a Lewis acidic activator (Scheme 108B). Most common is the combination of lithium aluminium hydride and boron trifluoride etherate, and this has been successfully applied in both cyclic and acyclic α-tertiary ether synthesis.[410,411] In a similar manner, borane reductions of amides are often associated with ether side products if esters are also present.[412]

Alternative strategies have sought to isolate the transiently formed mixed acetals as silyl-protected or acetyl-activated hemiacetals, which can be further reduced to the desired ethers (Scheme 108C).[413,414]

More recently, the application of transition–metal catalysed hydrosilylation has shown significant potential in selective ester reductions.[415] Early promising results were observed by Nagashima when using triruthenium carbonyl clusters in the presence of $EtMe_2SiH$.[416] While the reaction was broadly unselective for the ether product, both alcohol and ether products were observed, with the alcohol typically predominating. In a single example incorporating an α-tertiary site, the corresponding ether could be isolated in 7% yield.



Scheme 108 Reduction of esters to ethers: (A) general concept; (B) traditional approaches; (C) stepwise reduction-activation-reduction; (D) TM-catalysed hydrosilylation.

Following this study, Mn-catalysed hydrosilylation has also showed great promise in ester–ether reductions. A notable report from Werlé and Leitner described the application of Mn(I) catalysts bearing triazole ligands to carbonyl hydrosilylation (Scheme 108D).[417] Unfortunately, the reaction showed considerable sensitivity to sterics and, while *tert*-butyl benzoate could be reduced with moderate selectivity to the ether product (6 : 4 ether : alcohol), the conversion was very low (14%). The work was more widely applied to acid and ketone reduction.

8. Conclusion and outlook

The synthesis of acyclic α-tertiary ethers has traditionally represented an exacting challenge using classical etherification strategies. Given the unique physical and biochemical properties associated with such moieties and their potential as key motifs in high-value target molecule synthesis, it is no surprise that the synthetic community has dramatically altered this once-barren landscape. A key component enabling this resounding growth has been the multi-faceted application of redox strategies towards such challenging etherifications.

The difunctionalisation of alkenes has proven to be a particularly versatile strategy in accessing such hindered ethers. In particular, the renewed use of photo- and electrochemical manifolds has driven a vast expansion in the applicable functionalisation strategies that can be coupled to alkoxylation. In tandem with these strategies, more traditional redox mediators such as transition metal catalysts, halogen compounds in many different oxidation states, and main group oxidants, such as Hg and Se compounds, have also been widely applied in this field.

As an alternative ubiquitous substrate, the decarboxylation of carboxylic acids has enabled some of the most promising strategies, in particular, the development of photo- and electrochemical regimes has vastly expanded the scope, overcoming the steric limitations of hindered etherification.

Given the striking recent advances in C–H activation, it is encouraging to see that this has also had a considerable impact in this area and a wide range of structurally distinct C–H bonds are now readily converted to α-tertiary ether linkages. Additionally, the phosphorus-mediated activation of alcohols to enable etherification has been widely adopted in the synthetic community and the unique chemistry of phenols has led to diverse strategies enabling their oxidative alkoxylation, accessing complex α-cyclic

α-tertiary ethers. Numerous additional strategies have had considerable success including the application of peroxides and carbenoids to access reactive intermediates capable of facile etherification.

Notably, despite a select few promising early reports, the potential of reductive regimes to access ethers is broadly unrealised, given the preponderance of esters and analogous high oxidation state functionalities in molecular libraries.

A recurring feature of many of the methods described above that has prevented their widespread adoption by the community is the requirement for large excesses of one coupling partner, preventing the union of high-value or late-stage fragments *via* these approaches. This presents an opportunity to render these methods more applicable to contemporary, sustainability-driven research. Furthermore, in the coming years it will be exciting to witness how the rapidly expanding fields of photo- and electrochemistry take on the challenge of enantioselectivity in α-tertiary etherification. This challenge no longer rests on simply installing the α-tertiary ether but has extended to multicomponent reactions, cascades resulting in dramatic increases in structural complexity and pinpoint stereoselective introduction of asymmetry.

Without doubt, the α-tertiary ether is no longer the formidable and obscure exception it once was. As the strategic application of redox manipulations becomes ever more refined and broader in scope, the complexity and value of hindered ether synthesis will become truly established in synthetic chemistry.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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