α-Tertiary Dialkyl Ether Synthesis *via* Reductive Photocatalytic α-Functionalization of Alkyl Enol Ethers

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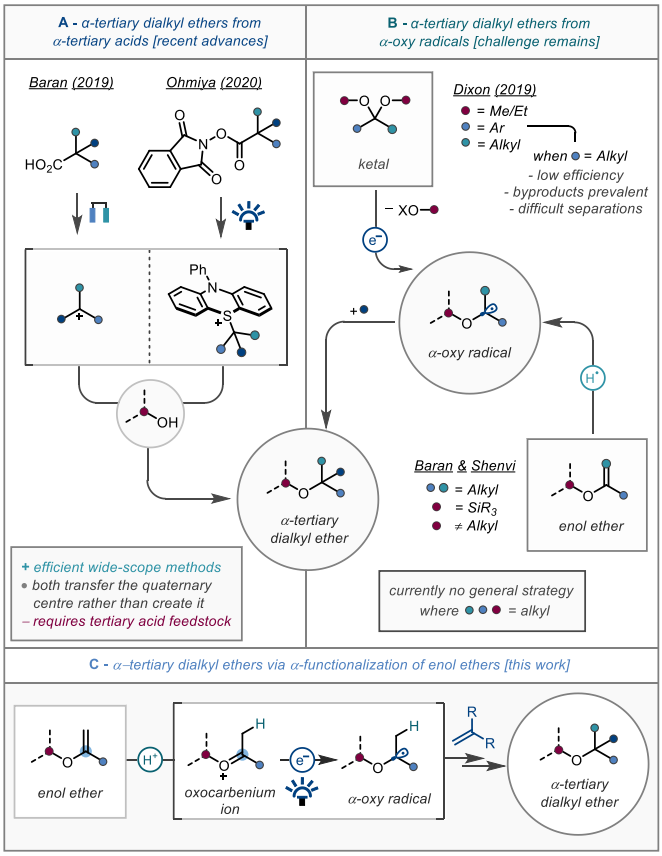
ABSTRACT: The photocatalytic construction of C(sp³)-rich α-tertiary dialkyl ethers through the reductive α-functionalization of alkyl enol ether substrates with conjugated alkenes in the presence of a Hantzsch ester terminal reductant under blue LED irradiation, is described. Pivoting on oxocarbenium ion generation *via* an initial TMSCl-facilitated protic activation of the enol ether substrate, subsequent single electron transfer delivers the putative nucleophilic α-oxy tertiary radical capable of productively combining with a variety of alkene substrates. The reductive functionalization strategy was simple to perform, efficient, broad in scope with respect to both alkene acceptor and enol ether donor fragments and delivered a wide range of complex α-tertiary dialkyl ether architectures.

Dialkyl ethers are commonplace structural motifs within biologically relevant molecules, including active pharmaceutical agents and natural products.[1] Accordingly, their synthesis – from the traditional Williamson ether synthesis[2] to recent developments in C–H functionalization[3] – has remained a common focus for classical and contemporary method development. Despite advances in recent years, synthetic access to sterically hindered dialkyl ethers remains a significant challenge, especially for the generation of α-tertiary dialkyl ethers, which are becoming increasingly desirable structures in drug design due to favorable metabolic profiles.[4] To this end, pioneering investigations from the Baran[5] and Ohmiya[6,7] groups have exploited decarboxylative single-electron pathways to access reactive carbocation intermediates from α-tertiary carboxylic acids and redox active ester derivatives (*via* electrochemical and photochemical means, respectively) which upon interception by alcohol nucleophiles yield the target dialkyl ether structures (Scheme 1A).

As a complementary entry to such ether architectures, we envisaged that the dialkyl α-oxy radical could be leveraged into creating such α-tertiary dialkyl structures (Scheme 1B). Previous contributions from the Doyle[8] and Wang[9] groups established reactivity employing nickel catalysis using a selection of aldehyde-derived acetals creating analogous α-secondary ethers. Our own photocatalytic studies[10] demonstrated efficiency with aryl substituted ketals (blue = Ar), however were largely unsuccessful when applied to dialkyl ketals. Furthermore, due to their synthetic origin, the above methods are entirely limited to small alkyl chains on the oxygen atom (purple).[11]

Notwithstanding the established polarity of enol ethers in two-electron reaction pathways (nucleophilic at the β-position,[12] and, following protonation, electrophilic at the α-position[13]), developments in redox catalysis[14] led by Baran and Shenvi have demonstrated that *via* the α-oxy radical, the polarity of the enol ether functionality can be reversed.[15] However, despite the breadth of chemical space accessible using the established metal-based hydrogen atom transfer (HAT) approach, α-tertiary dialkyl ethers remain out of reach.

Scheme 1. α-tertiary dialkyl ether synthesis in context of this work

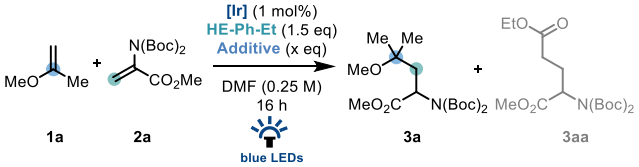


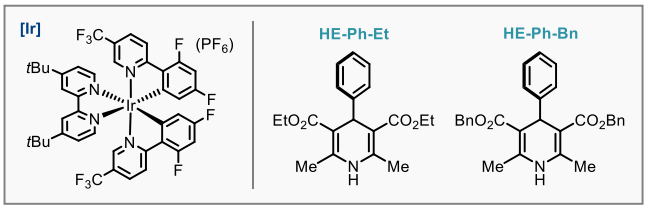
In such cases, the propensity for competitive oxocarbenium formation in the alcohol containing media hindered product formation when similar silyl enol ether derivatives were employed, a phenomenon even more pronounced in all C(sp^3)-substituted enol ethers.[14b]

Notwithstanding the above advances, to date there is no general strategy to construct all-alkyl substituted α-tertiary ethers *via* the α-oxy radical. As part of our ongoing work into the reductive synthesis of ethers,[16] we reasoned that controlled, photocatalytic single electron transfer to the oxocarbenium ion formed *via* β-protonation of the enol ether could provide an access point to the α-oxy radical.[17] These nucleophilic radical species would then be reactive towards electrophilic structures such as conjugated alkenes.[18] As enol ethers are abundant commodity chemicals, or readily accessed *via* alcohol isopropenylation[19] or ester methylenation,[20] this approach could offer a general method for α-tertiary dialkyl ether synthesis, and herein we wish to report our findings.

For a model system feedstock 2-methoxypropene (**1a**) as the alkyl enol ether substrate and a dehydroalanine derivative (**2a**) as the acceptor alkene was chosen. Initial reductive coupling experiments were performed using $[Ir(dFCF_3(ppy))_2(dtbbpy)]PF_6$ as photocatalyst, the phenyl-substituted Hantzsch ester derivative (HE-Ph-Et) as the terminal reductant, in DMF as solvent, under blue light irradiation (Table 1). In the absence of a Brønsted or Lewis acid additive, no reactivity was observed towards the desired C-C coupled product (**3a**). On addition of stoichiometric Brønsted acid additive *para*-toluenesulfonic acid (entry 2), conversion to an alternative ester addition product **3aa** was observed. This structure is proposed to form *via* a Hantzsch ester degradation pathway (see supporting information for more details). Use of stoichiometric triflic acid as a stronger Brønsted acid promoter indeed formed the desired product **3a** in 23% conversion, albeit again coupled with competitive formation of **3aa** (entry 5). Interestingly however, when TMSOTf was employed as additive without an additional exogenous proton source, moderate reactivity towards **3a** was again observed (20% yield, entry 6). The use of trimethylsilyl chloride gave a substantial uplift to reaction efficiency, creating the α-tertiary alkyl ether **3a** in decent yield (63%) when 1 equivalent was deployed (entry 7), notably in 48% yield with 30 mol% of the additive (entry 8), and in good yield (78%) with 2 equivalents (entry 9). Furthermore, TMSBr (20%) and TBSCl (52%) also enabled the reaction to proceed (entries 10-11).[21] Although a good yield of the desired product was attained in entry 9, both **3a** and **3aa** possessed identical polarity when attempting purification using standard chromatographic techniques. Accordingly, continued optimization of the reaction was required to suppress by-product formation. Exchange of the limiting reagent – from the feedstock 2-methoxypropene to the synthesized DHA derivative – readily achieved this and provided a yield of 95% of **3a**, and only trace of the glutamate adduct **3aa**, denoting a product selectivity of >20:1 (Conditions A, entry 14). Importantly, control experiments without photocatalyst, Hantzsch ester, or light irradiation gave no conversion to the α-tertiary ether product (entries 15-17).[22] To enhance the general utility of this method, an alternative protocol using the enol ether as the limiting reagent was also developed. To this end, when HE-Ph-Bn was employed as the terminal reductant, the C–C coupled product was indeed obtained in good yield (65%, entry 18). Although this proceeded with lower efficiency than with HE-Ph-Et (entry 9), lack of by-product formation enabled clean isolation of the ether product (Conditions B, entry 18).

Table 1. Optimization of the α-functionalization of alkyl enol ethers



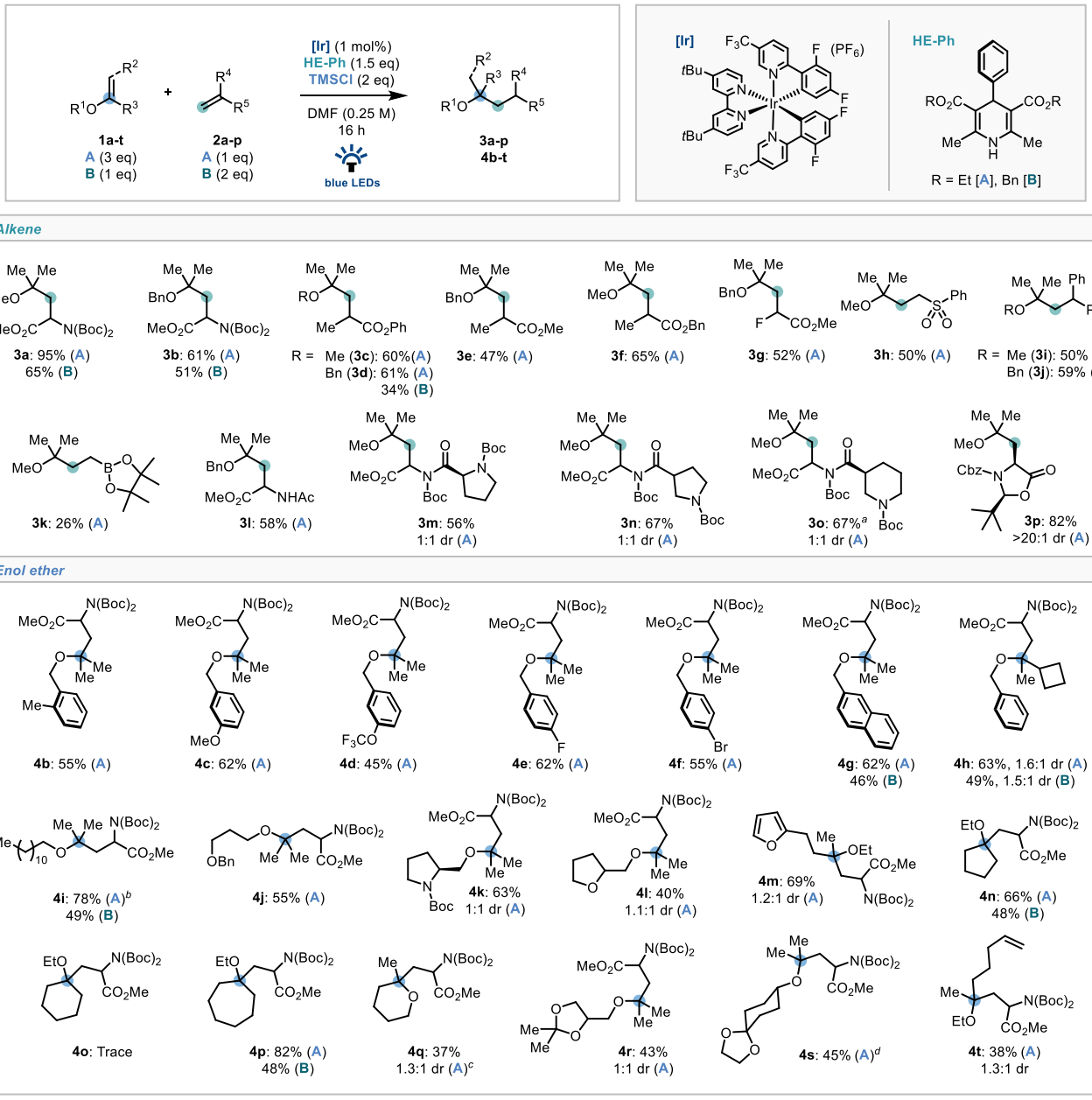


entry	Additive (x eq)	1a (eq)	2a (eq)	3a[a]	3aa[a]	3a:3aa[a]
1	-	1	2	-	-	n/a
2	*p*TSA (1)	1	2	-	56	n/a
3	PPTS (1)	1	2	-	-	n/a
4	PPTS (1)[b]	1	2	5	5	1 : 1
5	TfOH (1)	1	2	23	27	0.9 : 1
6	TMSOTf (1)	1	2	24	29	0.8 : 1
7	TMSCl (1)	1	2	63	20	2.5 : 1
8	TMSCl (0.3)	1	2	48	25	1.9 : 1
9	TMSCl (2)	1	2	78	20	3.9 : 1
10	TMSBr (2)	1	2	20	16	1.3 : 1
11	TBSCl (2)	1	2	52	22	2.4 : 1
12	TMSCl (2)	1.5	1	79	5	16 : 1
13	TMSCl (2)	2	1	78	5	16 : 1
A 14	**TMSCl (2)**	**3**	**1**	**95(95)[c]**	**1**	**>20 : 1**
	change from entry 14					
15	*no iridium photocatalyst*			-	-	n/a
16	*no Hantzsch Ester*			-	-	n/a
17	*no light*			-	-	n/a
	change from entry 9					
B 18	***HE-Ph-Bn** used as reductant*			(65)[c]	-	n/a

General Conditions: 2-methoxypropene **1a** (0.1 mmol), **2a** (0.2 mmol), $[Ir((dFCF_3)ppy)_2(dtbbpy)]PF_6$ (0.001 mmol, 1 mol%), HE-Ph-Et (0.15 mmol), DMF (0.25 M), 16 h, under a nitrogen atmopshere under blue light irradiation using 18 W LED lamp. [a] Formation of **3a** and **3aa** calculated by ^{1}H NMR analysis of the crude reaction mixture against 1,3,5-trimethoxybenzene as an internal standard. [b] DMA was used as solvent. [c] Isolated yield after silica gel column chromatography.

With optimal reaction conditions in hand, the scope of the method with respect to the α,β-unsaturated ester component, using both 2-methoxypropene (**1a**) and 2-benzyloxypropene (**1b**), was investigated (Scheme 2A). The reaction proceeded with good yields when α-substituted acrylate esters were used as the alkene substrate (**3c**-**3g**).

Scheme 2. Scope of the photocatalytic α-functionalization of alkyl enol ethers.



[a] TMSCl (3 eq) used. [b] Enol ether (2.5 eq) was used. [c] Enol ether (5 eq) was used. [d] TMSCl (4 eq) was used.

Furthermore, desirable reactivity was also achieved with a vinyl sulfone acceptor (**3h**), 1,1-diphenylethylene (**3i**-**3j**), and even a vinyl boronate derivative (**3k**), albeit with reduced yield. Commercially available methyl 2-acetamidoacrylate was amenable to the reaction conditions in comparable yields to the model DHA substrate (**3b**). Using dipeptide-derived DHA analogues, coupling of the 2-methoxypropyl fragment to proline-, 3-pyrrolidine carboxylic acid-, and nipecotic acid-derived alkene derivatives took place in good yields (**3m**-**3o**). A dehydroalanine-derived substrate (**2p**), which has found previous use as a chiral building block in addition reactions was also studied.[23] Using the standard protocol, it was shown to forge the C–C bond in excellent yield and diastereoselectivity (**3p**, 82% yield, >20:1 dr).

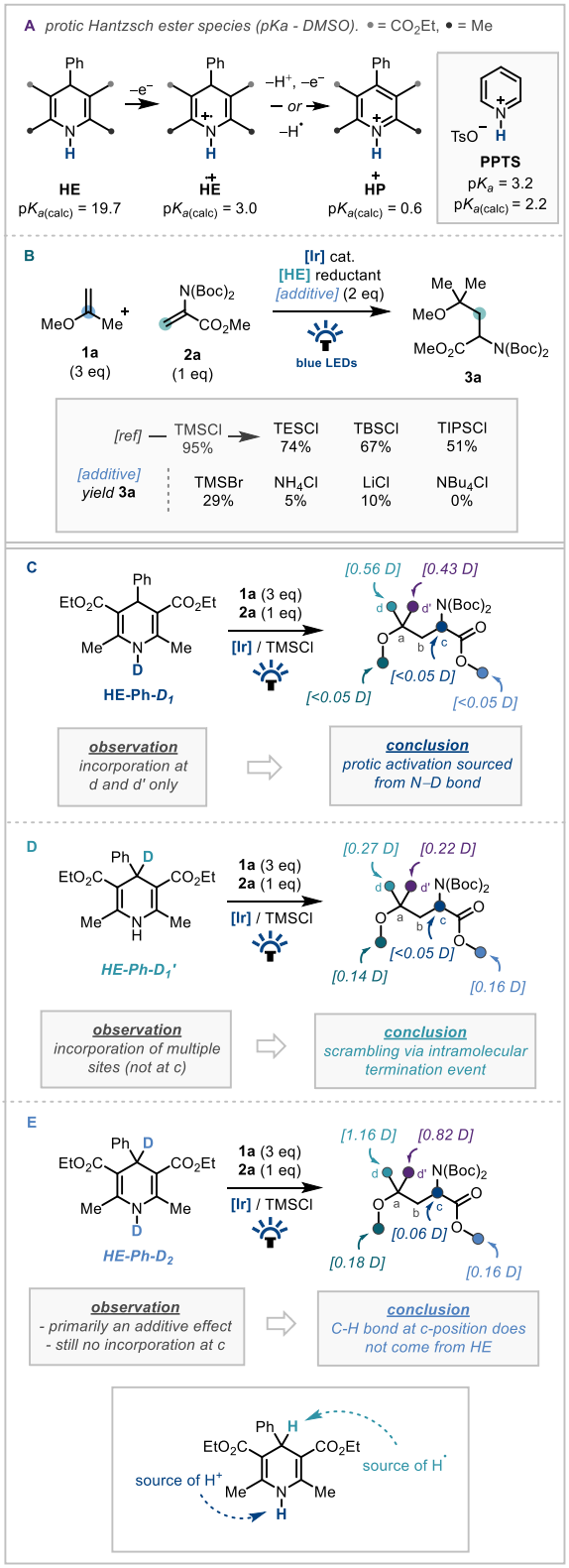
The scope with respect to the alkyl enol ether fragment was then studied (Scheme 2B). Substituted benzyloxypropene substrates were effective coupling partners leading to good yields of the α-tertiary ether architectures with electron-donating groups and electron-withdrawing groups functioning similarly (**4b**-**4g**). Pleasingly, a cyclobutane-substituted construct was also found to be applicable to the enol ether functionalization platform, creating a structurally complex α-tertiary alkyl ether in good yield (**4h**). A range of other alkoxypropene derivatives were also productive in this methodology forming further oxygenated leucine derivatives (**4i**-**4j**). Prolinol- and tetrahydrofurfuryl alcohol-derived enol ethers were also effective substrates (**4k**-**4l**). A furanyl-substituted enol ether motif was also amenable to this methodology, with no undesired reactivity observed on the heteroaromatic ring (**4m**). To demonstrate

applicability with tri-substituted enol ethers, 1-alkoxycyclopentene and cycloheptene derivatives were prepared and submitted to the reaction conditions. Pleasingly, they were well-tolerated giving the dialkyl ether materials in good to excellent yields (**4n**, **4p**).[24] Surprisingly, the cyclohexyl analogue was a comparatively poor substrate delivering the ether products **4o** in trace conversion. Despite this, using exocyclic enol ether 2-methylidenetetrahydropyran (**1q**) – where the oxygen atom is located inside the 6-membered ring – re-installed reactivity affording **4q** in moderate yield. This mild photocatalytic protocol was also shown to be compatible with acetal-protected ketones. Competitive acetal functionalization was not observed and the desired complex α-tertiary dialkyl ether architectures (**4r**-**4s**) were obtained in good yields.[10] Finally, a substrate bearing a pendant alkene was also shown to partake in the methodology (**4t**). Interestingly, no evidence of a competing 5-exo-trig cyclization pathway was observed.[25]

Furthermore, the alternative protocol using the enol ether as the limiting reagent (Conditions B) was exemplified with variety of enol ether donors (**3b**, **4g**, **4h**, **4i**, **4n**, & **4p**), affording the C–C coupled products in moderate yields. Accordingly, a combination of the two methods provides an effective α-tertiary dialkyl synthesis platform.

From a mechanistic viewpoint, how the enol ether substrate engages in the reaction pathway to generate the key radical was of interest. Our working hypothesis was that Brønsted acid activation to form the oxocarbenium ion was required prior to electron transfer. pK_a values of prospective Brønsted acid activators were computationally analyzed. pK_a calculations predict that the HE radical cation (Scheme 3A, p$K_{a(DMSO)}$ = 3.0) and Hantzsch pyridinium (p$K_{a(DMSO)}$ = 0.6) are substantially more acidic than the parent dihydropyridine (pK_a = 19.7). ^{1}H NMR experiments also revealed no visible interaction between the HE and TMSCl in the ground state. When compared to *para*-toluenepyridinium sulfonate (PPTS),[26] a Brønsted acid used in alcohol protections using 2-methoxypropene, these protic intermediates are comparably acidic. Despite this, the reaction does not proceed in the absence of any additive. Further additive studies were conducted to explore the key role of the TMSCl in producing the C–C coupled product **3a** (Scheme 3B). These studies demonstrated that halosilane additives were all effective in forming the α-tertiary dialkyl ether motif, with a decreasing trend in reactivity with increasing steric bulk of the silane. Conversely other chloride salts (NH_4Cl, LiCl, NBu_4Cl) were substantially inferior or ineffective. These results along with the noticeable difference in reactivity between TMSCl and TMSBr led us to conclude that both the silane and the halide counter ion are of importance to the reaction mechanism. Combining these mechanistic investigations, two potential roles of the chlorosilane additive are proposed. Firstly, as a promoter in the protic acid activation of the enol ether,[27] where one of oxidized forms of the Hantzsch ester is the Brønsted acid and TMSCl is the Lewis acid. Secondly, as a source of the nucleophilic counter ion which could stabilize such a resulting oxocarbenium intermediate.[28]

Scheme 3. pK_a studies, additive effects, and Deuterium Incorporation Studies



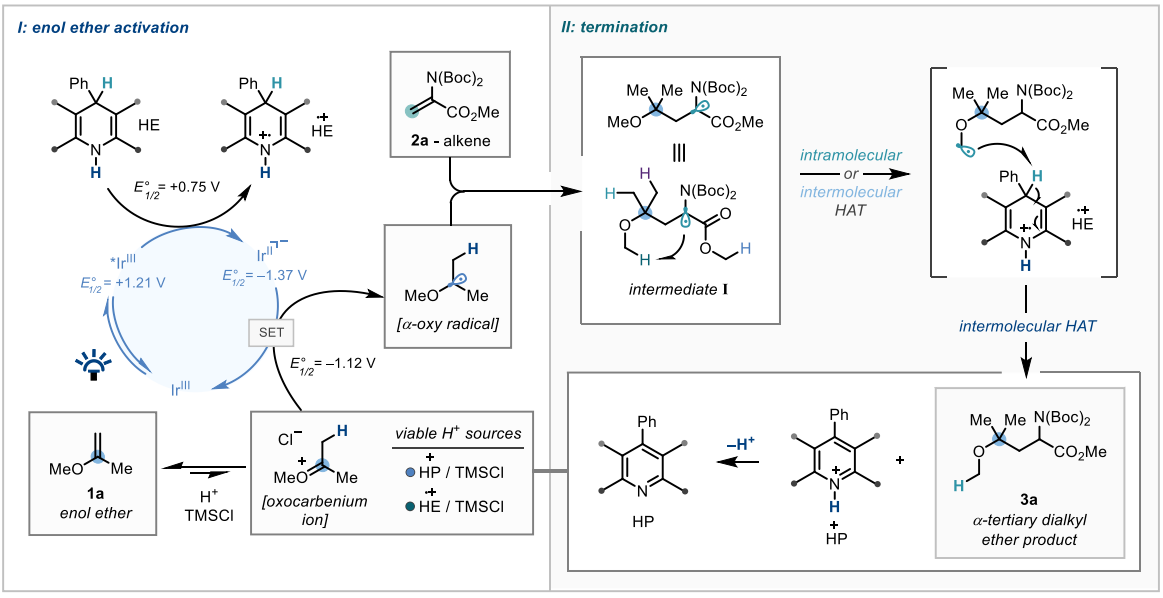
Next, a series of deuterium labelling experiments with isotopically-labelled Hantzsch ester reductants were conducted (Scheme 3, for further details see supporting information). In the first of these studies using **HE-Ph-*D*$_1$**, substantial deuterium incorporation in the diastereotopic **d** and **d'**-position of the product was observed, suggesting Brønsted acidity arises from the N–D bond (Scheme 3C). Interestingly when the reaction was conducted with **HE-Ph-*D*$_1$'** insignificant deuterium incorporation at the **c**-position occurred, instead, deuterium labelling was observed around multiple other positions in the product (Scheme 3D).[29] Furthermore, when using **HE-Ph-*D*$_2$** an additive relationship was observed, again with negligible deuterium incorporation at the **c**-position was observed, reinforcing this alternative termination pathway hypothesis (Scheme 3E). Similar findings were are also observed when an analogous experiments were conducted using benzyl methacrylate as the alkene substrate (see supporting information for more details). Taken together, these results point to an alternative termination process, whereby an intramolecular HAT event,[30,31] prior to intermolecular termination with a Hantzsch ester species, leads to the α-tertiary dialkyl ether product.[32]

Calculated electrophilicity indices[33] reveal that the positions where deuterium has been incorporated all provide a more nucleophilic radical species, which in turn would lead to a more favorable HAT with the Hantzsch radical cation.[34,35] Furthermore, kinetic effects in the termination of primary vs. tertiary radicals cannot be ruled out.[36]

Building on these data and previous work,[15a,31,34,37] a plausible mechanism is shown in Scheme 4. Initially, the Hantzsch ester derivative ($E°_{1/2\ (calc)}$ = +0.75 V) readily quenches the photoexcited iridium(III) species ($E°_{1/2}$ = +1.21 V)[38,39] to deliver the reducing iridium(II) species and the Hantzsch ester radical cation. Concurrent protic activation of the enol ether takes place to afford the key oxocarbenium ion. Single electron transfer from the iridium(II) species ($E°_{1/2}$ = −1.37 V) to the oxocarbenium ion ($E°_{1/2\ (calc)}$ = −1.12 V) gives rise to the putative nucleophilic α-oxy radical[32,40] which then undergoes Giese-type addition with the conjugated alkene to produce the addition intermediate **I**. Subsequent HAT[41] and then termination with an oxidized Hantzsch ester species would deliver the α-tertiary dialkyl ether **3a**.[41] The final termination HAT can take place from either HE radical cation (shown, Scheme 4, right), or HEH•, rendering either HP+ or HE radical cation as the potential respective proton sources for the corresponding mechanisms (see ESI for more details). Aligned to previous investigations, the pathway shown is most likely in operation.[32]

In conclusion, a mild photocatalytic reductive α-functionalization of alkyl enol ethers has been developed. Through Lewis acid-assisted protic activation of the enol ether to generate the corresponding oxocarbenium ion and subsequent proposed single electron reduction, a new approach to access the α-oxy dialkyl radical has been identified. The putative reactive intermediate was shown to engage in Giese-type coupling reactions with a wide range of alkene substrates to deliver 34 examples of α-tertiary dialkyl ether architectures. Work to understand the source of the acidity and applying this concept to further reaction systems is currently underway.

Scheme 4. Proposed mechanism for the photocatalytic α-functionalization of enol ethers



ASSOCIATED CONTENT

The Supporting Information is available free of charge at:

- Experimental procedures, characterization and computational data

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(40) For further experiments to probe the intermediacy of the putative α-oxy radical, see supporting information.

(41) As no polymeric adducts deriving from the resulting radicals after intramolecular HAT are observed, the full termination process is proposed to be outcompete any C–C bond forming event.