Photocatalytic Reductive Formation of α-Tertiary Ethers from Ketals

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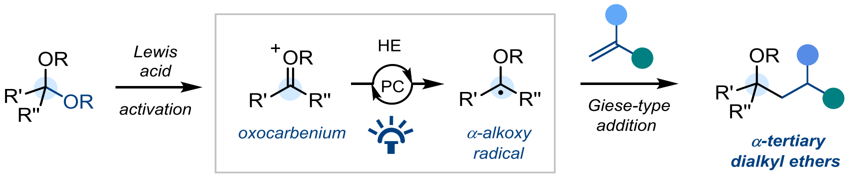


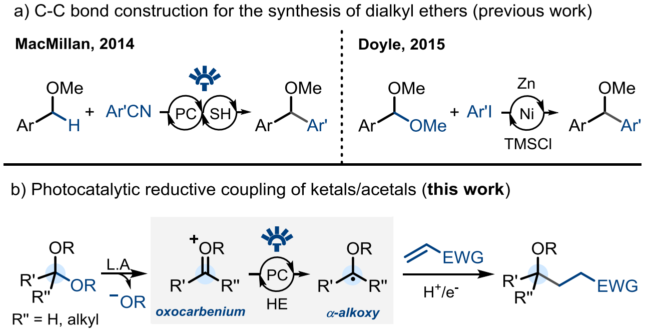
- photocatalytic oxocarbenium reduction
- aromatic and aliphatic ketals
- α-tertiary dialkyl ethers
- compatible with acetal substrates (R'' = H)

ABSTRACT: A general photocatalytic reductive strategy for the construction of unsymmetrical α-tertiary dialkyl ethers is reported. By merging Lewis acid-mediated ketal activation and visible-light photocatalytic reduction, in situ generated α-alkoxy radicals can engage in addition reactions with a variety of olefinic partners. Good reaction efficiency is demonstrated with a range of ketals of aromatic and aliphatic ketones. Extension to acetal substrates is also described, demonstrating the overall synthetic utility of this methodology for complex ether synthesis.

Despite the widespread relevance of dialkyl ethers in pharmaceuticals and bioactive compounds,[1] several challenges remain to access this structural unit. Approaches based upon the formation of the corresponding C(sp^3)-O bond – such as classical Williamson ether synthesis – are widely employed to access simple ethers, but are far from general for more complex systems.[2] To this end, a number of key advances exploiting bespoke reagents[3] and the intrinsic reactivity of various coupling partners[4] have been made in recent times, leading to new valuable C-C bond disconnections for ether construction.

Significant efforts in photoredox catalysis have offered mild and unique approaches for new reaction discovery via *in situ* generation of free-radical species which can partake in radical coupling or transition metal-catalyzed cross-coupling processes.[5] In the context of ether synthesis, MacMillan and coworkers have reported an elegant synthetic procedure for the generation of benzhydryl ethers exploiting a dual photoredox/organocatalytic strategy via C-H atom abstraction, utilizing cyanoarenes as coupling partners (Scheme 1a).[6]

Scheme 1. a) Reported methods for the synthesis of dialkyl ethers. b) Visible-light mediated direct strategy towards the formation of α-tertiary dialkyl ethers from ketals.



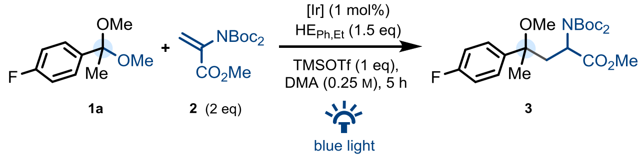
PC = photocatalyst, HE = Hantzsch ester.

More recently, the Doyle group has reported a powerful method to form similar products via a nickel-catalyzed reductive cross-coupling from acetals of aromatic aldehydes (Scheme 1a).[7] Although the above chemistries have advanced carbon-carbon bond-forming ether syntheses,[8] new and general synthetic approaches for accessing α-tertiary alkyl ethers remain desirable. To this end, and in an effort to expand the synthetic range of photocatalytic umpolung chemistry,[9] we sought to explore alternative and common functional groups to engage in radical coupling reactions.[10] We envisaged that ketal activation with a Lewis acid[7,11] followed by visible-light mediated single-electron transfer (SET) to the resulting oxocarbenium ion could deliver a putative nucleophilic α-alkoxy radical intermediate, which could participate in radical addition chemistry (Scheme 1b). If successful, this mild generation and controlled coupling of the α-alkoxy radical could provide direct access to α-tertiary ethers in one step from readily available starting materials.

Preliminary evaluation of the proposed photocatalytic reductive coupling process was carried out with 4'-fluoroacetophenone dimethyl ketal (**1a**), [Ir(dF(CF$_3$)ppy)$_2$(dtbbpy)]PF$_6$, and dehydroalanine (DHA) derivative **2** as a coupling partner[10d,12] (Scheme 2). Initial feasibility studies followed by reaction optimization elucidated that irradiation under blue LED light in DMA, with trimethylsilyl trifluoromethanesulfonate (TMSOTf) as Lewis acid and 4-phenyl Hantzsch ester (HE$_{\mathrm{Ph,Et}}$) as stoichiometric reductant, provided the desired tertiary methyl ether **3** in an optimal 78% NMR yield (entry 1).

Observations made during reaction optimization revealed the importance of concentration and solvent selection on reaction outcome (see SI for more details). Significant enhancement was achieved employing higher substrate concentration, with DMA proving to be the most suitable medium (entry 1-3). Notably, and in contrast to previous reports,[7,11] we recognized that trimethylsilyl chloride (TMSCl) was not an appropriate Lewis acid to promote ketal functionalization, as product **3** was afforded in negligible yield (entry 6). Additionally, Lewis acidic boron complexes, such as $BF_3{}^{\bullet}OEt_2$, were also found to be ineffective (entry 7).[13]

Scheme 2. Reaction Optimization.



Entry	Deviations from above	3 (%)[a]
1	none	78 (66)[b]
2	0.2 M in DMA	65
3	0.2 M in DMSO	56
4	4-CzIPN instead of [Ir]	71
5	$[Ir(dFppy)_2(dtbbpy)]PF_6$ instead of [Ir]	75
6[c]	TMSCl instead of TMSOTf	trace
7[c]	$BF_3\bullet OEt_2$ instead of TMSOTf	trace

a: ^1H NMR yield based on 1,3,5-trimethoxybenzene as internal standard. b: Isolated yield. c: 0.2 M in DMSO. [Ir] = $[Ir(dF(CF_3)ppy)_2(dtbbpy)]PF_6$, $HE_{Ph,Et}$ = diethyl 2,6-dimethyl-4-phenyl-1,4-dihydropyridine-3,5-dicarboxylate, DMA = *N*,*N*-dimethylacetamide.

With optimized conditions established, we sought to explore the scope of this photocatalytic carbon-carbon bond forming reductive coupling reaction with respect to the ketal moiety (Scheme 3A).[14] Initially, substitution around the aromatic ring was investigated (**3-8**). Efficient reaction outcomes were observed with electron-releasing functional groups (**5-6**), supporting a nucleophilic character of the putative α-alkoxy radical intermediate.[12] Conversely, suppressed reactivity was observed with electron-withdrawing groups; where, for example a bromine atom in the para position afforded product **8** in 33%.

Ketals bearing larger alkyl substituents underwent the reaction with good yields (**9-10**). The small drop in reactivity was consistent with the increasing steric hindrance compared to methyl-substituted **4**.[15] A chlorine-containing side chain was also tolerated and coupled product **11** was delivered in 36% yield. Importantly, the substrate scope of this transformation was successfully expanded to diethyl and diisopropyl ketals in moderate to good yields (**12-13**), and this reactivity represents a significant improvement considering previously reported limitations on acyclic acetals.[7] Moreover, ketals of aliphatic ketones were found to be competent substrates for radical generation, delivering the corresponding products in synthetically useful yields after conjugate addition (**14-16**), with dimethoxy cyclopentane affording compound **17** in 53% yield. In order to demonstrate the generality of this transformation, we looked to expand the scope to include acetal substrates. Pleasingly, good reaction efficiency was achieved with both acyclic and cyclic acetals (**18-19**), illustrating complementarity with previous works.[7,11b] Finally, the role of the alkoxide functionality was examined with mixed ketal **1s** (Scheme 3B). Interestingly, phenyl ether **14’** was not formed under the reaction conditions, however methyl ether **14** was isolated in 38% yield (comparable to dimethoxy propane ketal as starting material, Scheme 3A, **14**). This observation could be attributed to the better leaving group ability of the phenoxy group compared to the methoxy group.

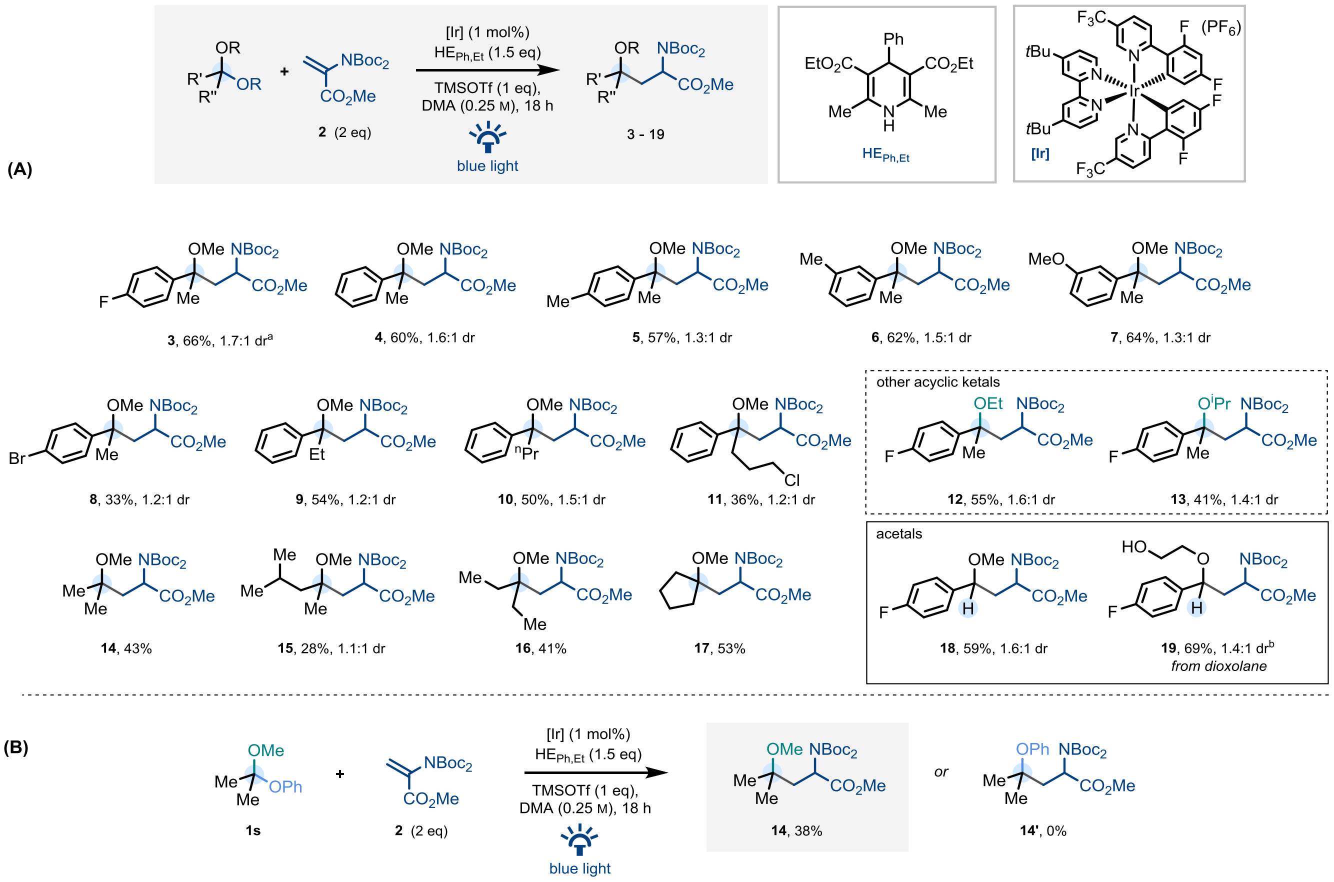
We next examined the scope of this reaction with respect to the acceptor component, using ketal **1a** as model substrate (Scheme 4A). It should be noted that in order to further improve reactivity with acrylate-type acceptors, we investigated alternative reagents to favor radical termination after Giese-type addition. In contrast to a radical reduction/protonation mechanism for DHA, a different termination via hydrogen atom transfer (HAT) has been proposed previously for acrylate substrates.[16] Catalytic methods involving thiols were not found to be viable for this purpose.[16,17] However, H-atom abstraction from stoichiometric 1,4-cyclohexadiene (CHD) proved to be beneficial in improving reaction yields (see SI for details).[18] Using these modified conditions, photocatalytic reductive coupling was achieved between **1a**, phenyl methacrylate, and methyl methacrylate to give the corresponding tertiary methyl ethers in 74% and 62% yield, respectively (**20-21**). Variations to the α-position of the acrylate component were found to play a pivotal role in reactivity. Pleasingly, fluorine incorporation was tolerated; mono-fluorinated **22** and trifluoromethylated **23** were both afforded in synthetically useful yields. No *gem*-difluoroalkene adducts were formed under these reaction conditions.[11b,19] Unsubstituted phenyl acrylate resulted in suppressed efficiency even when a large excess of coupling partner was used (**24**). Furthermore, coupling with methacryloyloxazolidinone furnished **25** with moderate yield. These results indicate a key stabilizing captodative effect arising from the α-substituent, a conclusion further supported by successful coupling with electron neutral alkenes. In fact, significant efficiency was observed with diphenylethylene as the acceptor olefin (**26**).

Under these reaction conditions reductive allylation of ketal **1a** with a sulfone derivative afforded compound **27** in 30%, despite the different reaction mechanism involved with these coupling partners.[9d,9e]

Finally, **1a** was subjected to reaction conditions without an acceptor partner, which afforded dimerized aryl methyl ether **28** in 52% yield as a 1:1 mixture of diastereomers. Rueping and coworkers have reported the reductive dimerization of aldehydes and ketones via ketyl radical generation under visible light irradiation.[20] Accordingly, this result supports a radical pinacol-type dimerization and provides direct access to ether pinacol adducts from easily accessible starting materials.

Control experiments established the essential role of the Lewis acid; no conversion of starting material was observed without TMSOTf (see SI for details). Moreover, none of the desired reactivity was achieved in the absence of light, photocatalyst, or Hantzsch ester. On the basis of these results, we propose the following reaction mechanism (Scheme 4B).[13] Initially, ketal **1** is activated by TMSOTf to form the oxocarbenium ion intermediate **I** as disclosed in previous reports.[7,11] A highly reducing Ir^{II} species ($E_{1/2red}$ = -1.37 V vs. SCE in MeCN),[5b] generated by electron transfer from the Hantzsch ester following photoexcitation of Ir^{III}, is capable of reducing **I** to generate the α-alkoxy radical **II**.[21] The key nucleophilic intermediate (**I**) can engage in radical addition with an appropriate acceptor olefin moiety. After this Giese-type addition, the resulting free radical intermediate (**III**) undergoes a reduction/protonation sequence mediated by the Hantzsch ester ($HE^{\bullet}$), or HAT termination favored by the presence of CHD, depending on the nature of the coupling partner.[16]

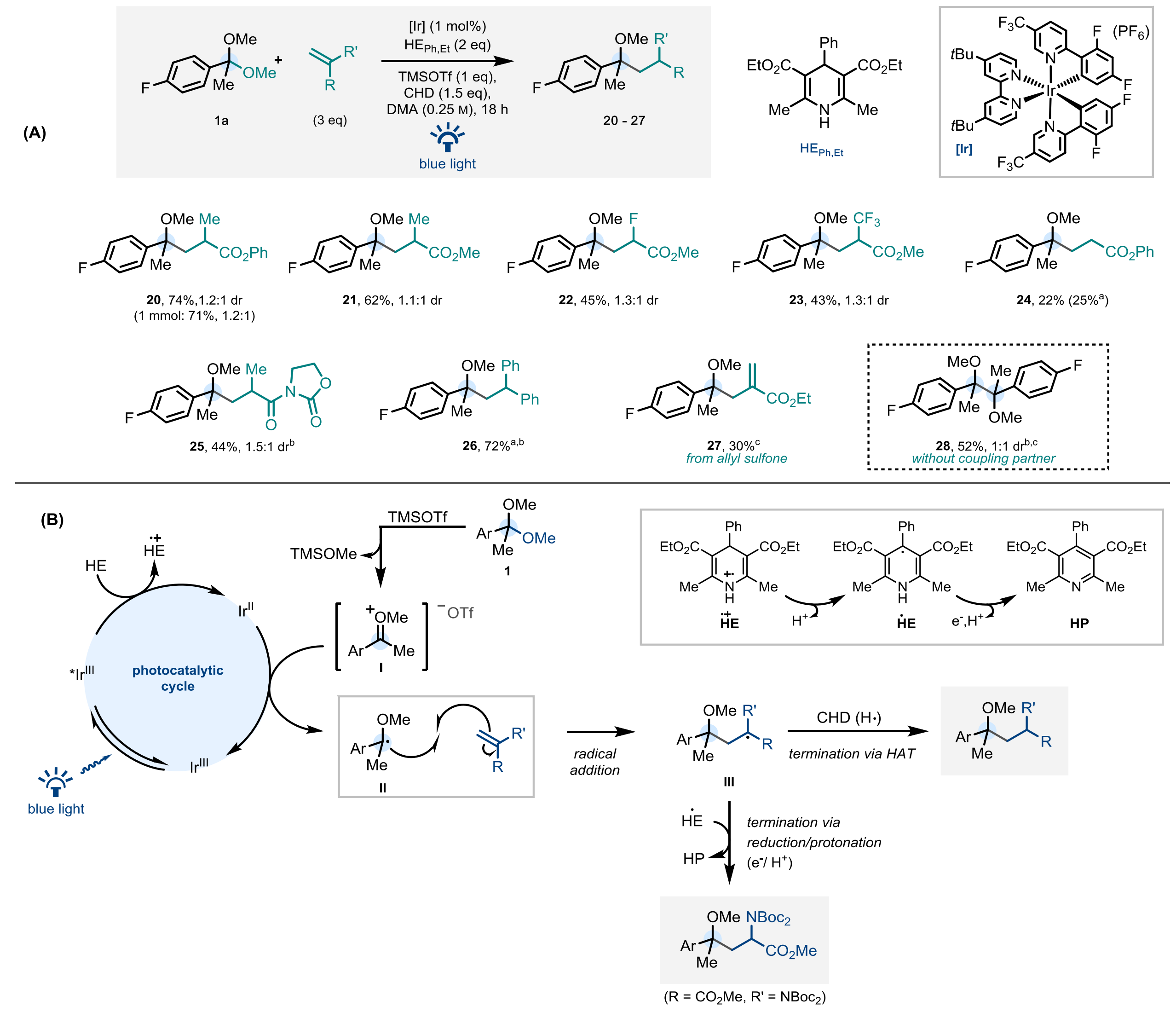
Scheme 3. (A) Scope with respect to the ketal substrate. (B) Performance evaluation of mixed ketal substrate 1s.



Combined isolated yields on 0.2 mmol scale. [a] Reaction time 5 h. [b] Reaction time 48 h.

In summary, the photocatalytic reductive coupling of easily accessible ketals and acceptor olefins has been developed. This methodology provides a new approach towards generating challenging α-tertiary dialkyl ethers in a single step, and is also amenable to acetal components. Extension to pinacol coupling adducts via an α-alkoxy radical dimerization process has been demonstrated thus providing insight into the mechanism. We believe that this methodology provides a complementary new approach to access complex α-tertiary ether architectures, and that the photocatalytic SET reduction of oxocarbenium ions will provide new opportunities for future reaction development.

Scheme 4. (A) Scope with respect to the alkene coupling partner. (B) Plausible reaction mechanism.



Combined isolated yields on 0.2 mmol scale. CHD = 1,4-cyclohexadiene. [a] 10 eq of coupling partner. [b] Reaction performed on 0.1 mmol scale. [c] Reaction performed without CHD.

ASSOCIATED CONTENT

The Supporting Information is available free of charge on the ACS Publications website. Synthetic procedures and full characterization data of compounds (PDF).

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(13) See Supporting Information (SI) for further details.

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(21) The TfOH would be neutralized by the Hantzsch pyridine (HP) generated in the reaction.