Alkyl Sulfoxides as Radical Precursors and Their Use in the Synthesis of Pyridine Derivatives

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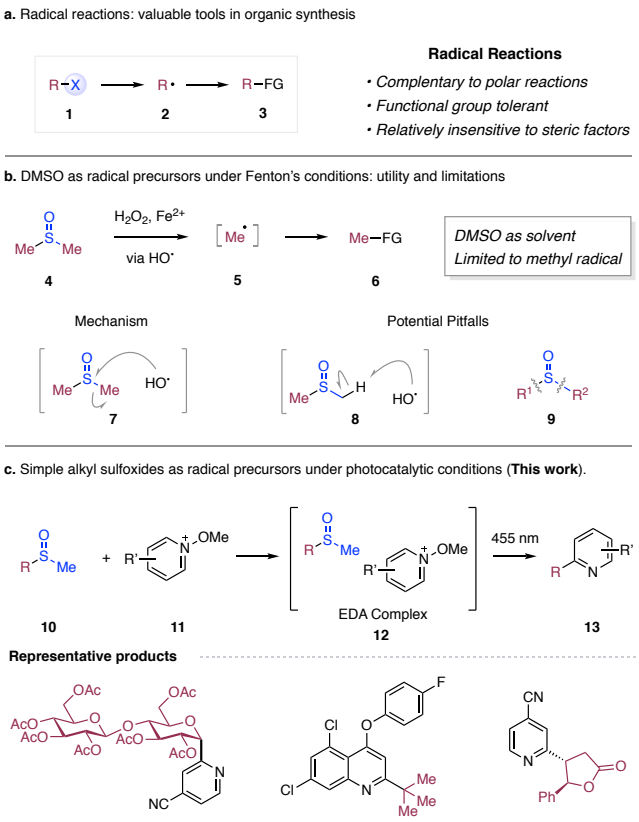
Supporting Information Placeholder

ABSTRACT: We report here the use of simple and readily available alkyl sulfoxides as precursors to radicals and their application in the preparation of pyridine derivatives. We show that alkyl sulfoxides form EDA complexes with *N*-methoxy pyridinium salts, which upon visible light irradiation, undergo a cascade of radical processes to afford pyridine derivatives smoothly. This method displays broad scope with respect to both reactants. The synthetic versatility of sulfoxides as a handle in chemistry adds to the power of this transformation. The method is further applied in the synthesis of various pyridyl *C*–glycosides that are previously difficult to access.

Radical reactions (**1** to **2** to **3**, Scheme 1a) represent important, complementary tools to polar reactions in organic synthesis.[1] Thanks to the intrinsic inertness of radical reactions to various functional groups, their power in making structurally complex products has been extensively exploited by chemists. Moreover, since reactions involving radical attack usually proceed through early transition state and are therefore relatively insensitive to steric interaction between reactants[2], they are highly useful in making congested C–C bonds. In part due to the above advantages, radical transformations have (re)gained significant attention from both academia and industry in recent years. An important theme in the field is the development of new types of radical precursors (e.g., **1**), since the stability and reactivity of these precursors often define the scope and versatility of the corresponding radical reactions. From a historical perspective, the oldest and most often used precursors to alkyl radicals include alkyl halides[3] and alkyl xanthate esters[4]. Lately, many alternative classes of radical precursors have emerged, such as alkyl borates and silicates[5], carboxylic acids[6], alcohols[7], pro-aromatic compounds[8], redox-active esters[9], and Katrizki's salts[10]. The use of these precursors has enabled development of myriad new bond-forming reactions, which opened door to some previously inaccessible chemical spaces.

Scheme 1. (a) Radical reactions are valuable tools in synthesis. (b) Dimethyl sulfoxide (DMSO) as radical precursors: utility and limitations. (c) This work: Use of sulfoxides as precursors to alkyl radicals.



Sulfoxides (cf. **4** and **10** in Scheme 1) represent a fundamental class of functional groups often involved in the synthetic schemes of complex products.[11] They are synthetically versatile and at the same time demonstrate significant stability toward air and moisture. Currently, most reactions employing sulfoxides exploit the polar reactivity of these species, as exemplified in name reactions such as the Pummerer reaction and the Swern reaction.[12] In general, sulfoxides are inert to classical radical processes: they have been used as (unreactive)

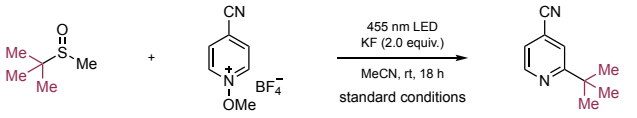
stereoinducing auxiliaries in radical transformations.[13] Regardless, the Renaud group reported the use of allyl sulfoxides as precursors to oxyl radicals by way of a [2,3]-sigmatropic rearrangement and S–O bond homolysis.[14] We recently reported the design and use of sulfoxides appended with an aryl iodide moiety as precursors to glycosyl radicals through an intramolecular radical substitution process.[15]

Should the conversion of simple alkyl sulfoxides to radicals be a general and routine process, the synthetic versatility of sulfoxides would impart tremendous flexibility in generating structurally elaborate alkyl radicals. In spite of the potential utility, to homolytically cleave the C–S in simple sulfoxides remains nontrivial. Under the Fenton's conditions [e.g., Fe^{2+}, H_2O_2], dimethyl sulfoxide (DMSO) is converted to methyl radical by attack of hydroxyl radicals (**4** to **5** to **6** via **7**, Scheme 1b).[16] However, the radical precursor DMSO (**4**) in these cases always has to be employed as a solvent reagent (or in large excess), rendering the use of more complex precursors impractical. In addition, the highly reactive hydroxyl radicals could undergo undesired processes such as hydrogen atom abstraction from sulfoxides (cf., **8**).[17] Moreover, in a typical sulfoxide as **9** in Scheme 1b, the R^1 and R^2 are not the same, and to cleave one of the two C–S bonds with high site-selectivity poses additional challenges.

These challenges notwithstanding, we report here a method that employs structurally elaborate sulfoxides as general precursors to alkyl radicals (Scheme 1c). We demonstrate alkyl sulfoxides as stoichiometric reactants can be converted to alkyl radicals efficiently under mild and simple conditions, which then react with *N*-methoxy pyridinium salts[18] to form pharmaceutically important pyridine derivatives (**10**+**11** to **13** via **12**). Key to the success of this reaction is the formation of EDA complexes[19] **12** between sulfoxides **10** and **11**. This method displays significant scope with respect to both reaction partners. Thanks to the synthetic versatility of sulfoxides, various alkyl radicals and pyridine derivatives that are previously hard to access have been generated smoothly. The utility of this method is further demonstrated in the synthesis of various pyridyl *C*-glycosides. Experimental and computational studies provide additional insights into the reaction mechanism.

We commenced our study by using *tert*-butyl methyl sulfoxide **14** and *N*-methoxypyridinium salt **15** as the model substrate (Table 1). After extensive condition optimization, we found that sulfoxide **14** reacted with **15** efficiently under very simple conditions, with KF employed as base and MeCN as solvent, under the irradiation of a 12 W 455 nm LED bulb (entry 1). Importantly, the sulfoxide precursor **14** was employed as the limiting reagent, which bodes well for the employment of more complex sulfoxides in this

Table 1. Condition Optimization.[a]



14 (1.0 equiv.) **15** (2.0 equiv.) **13a**

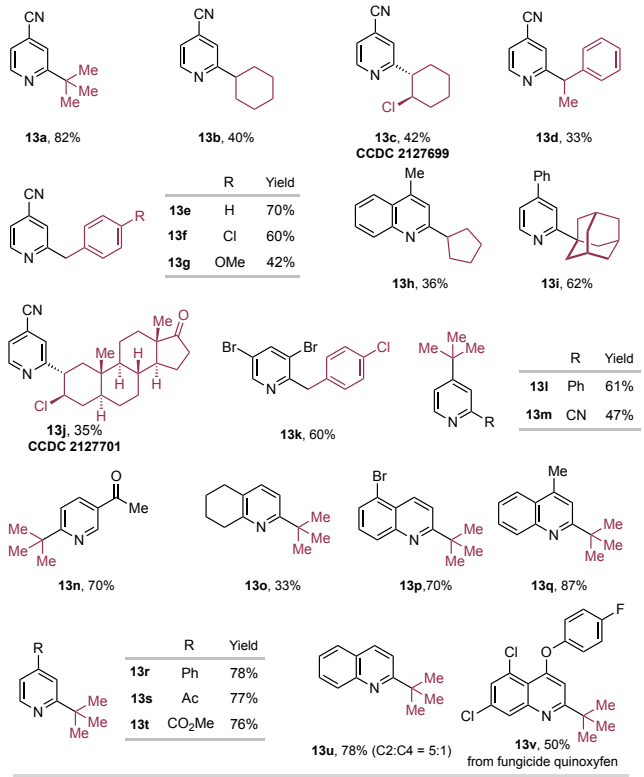
Entry	Variation from standard conditions	Yield[b]
1	none	85%
2	without visible light irradiation	< 5%
3	addition of Eosin Y (2.5 mol%)	63%
4	4-Cyanopyridine *N*-oxides instead of **15**	< 5%
5	KOAc instead of KF	15%
6	K_2CO_3 instead of KF	20%
7	NaOAc instead of KF	53%
8	TEA instead of KF	35%
9	pyridine instead of KF	30%
10	DCM instead of MeCN	50%
11	DMF instead of MeCN	13%
12	THF instead of MeCN	< 5%

[a] Unless otherwise noted, reactions were performed with mixtures of **14** (0.1 mmol), **15** (2.0 equiv.), MeCN (0.2 M), at rt under irradiation by blue LED for 18 h. [b] Yields were determined by ^{1}H NMR spectroscopy using 1,3,5-trimethoxybenzene as an internal standard.

transformation (see below). The formation of *tert*-butyl substituted product **13a** suggests the C–S cleavage proceeded with almost complete regioselectivity. Control experiments revealed factors that are crucial for the reaction performance. First, this transformation would not occur in the absence of light (entry 2), but it proceeds smoothly without using a typical photocatalyst (entry 1). Addition of an organic dye such as Eosin Y is tolerated by the process (entry 3). The use of *N*-methoxypyridinium salt **15** was essential, with no product formation observed if 4-cyanopyridine *N*-oxide (entry 4) was employed instead. Among various organic and inorganic bases that have been screened, KF was the most effective (entries 5-9). The property of solvent exerted remarkable effects on the reaction outcome: we found acetonitrile to be optimal of all solvents examined (entries 10-12). This is likely because acetonitrile contains no weak, electron-rich C–H bonds[20] and has good solubility of both reactants. Switching the reaction solvent to dichloromethane dramatically diminished the product yield. Employing DMF or THF almost completely inhibited the reaction.

Having established satisfactory reaction conditions, we next explored the scope of this method. A broad array of alkyl sulfoxides can be used as radical precursors in this reaction (Table 2). Both tertiary (**13a**, **13i**) and secondary alkyl sulfoxides (**13b-d**, **13h**) reacted smoothly to give the desired pyridine derivatives. Ketones (**13j**), aryl chlorides (**13f**) and alkyl chlorides (**13c**) were inert under the reaction conditions, which would serve as useful handles for further derivatizations. Primary benzyl radicals can be accessed readily (**13e-g**), but attempts to generate non-stabilized primary alkyl radicals were unsuccessful. During the formation of **13c** and **13j**, the existence of a vicinal chlorine atom provided sufficient

Table 2. Substrate Scope of the Alkyl Sulfoxides[a]



	R	Yield
13e	H	70%
13f	Cl	60%
13g	OMe	42%

	R	Yield
13l	Ph	61%
13m	CN	47%

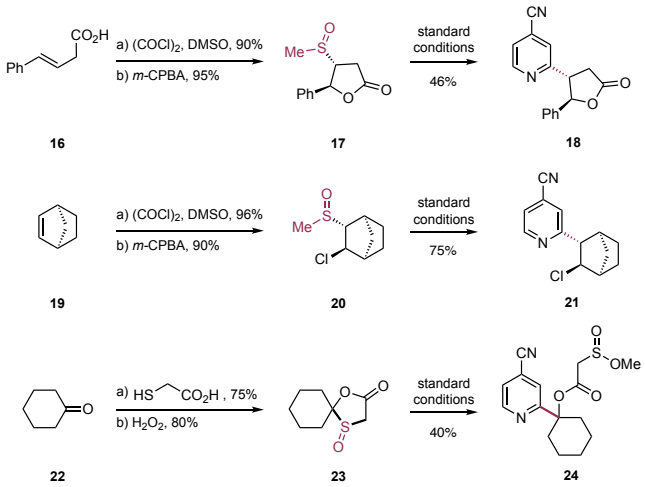
	R	Yield
13r	Ph	78%
13s	Ac	77%
13t	CO_2Me	76%

[a] Unless otherwise noted, reactions were performed with mixtures of **10** (0.20 mmol), **11** (2.0 eq.) at rt under irradiation by blue LED for 18 h. [b] Yields of isolated products.

steric bias to afford the 1,2-*trans* products with excellent diastereoselectivities. We converted natural product androst-2-en-17-one to the corresponding sulfoxide, which readily partook in our transformation to deliver a complex pyridine derivative **13j**. This method displays decent scope with respect to pyridine cores as well. As shown in Table 2, those bearing aryl halides (**13k**), esters (**13t**), nitriles (**13a**, **13m**), and ketones (**13n**, **13s**), were well accommodated by the method. Expanding the scope from pyridine to quinoline system was viable, as exemplified by the formation of products **13p-q** and **13u-13v**. To further demonstrate the generality of this reaction, we derived the fungicide quinoxyfen to the corresponding pyridinium methoxide, which successfully underwent the process to give the corresponding alkylated product **13v**.

Alkyl sulfoxides are readily available and synthetically versatile,[11,12] which adds significant utility to the current methodology. In order to demonstrate this point, we performed reactions in Scheme 2. Treating (*E*)-4-phenylbut-3-enoic acid **16** with oxalyl chloride in DMSO promoted a smooth cyclization process,[21] which followed by sulfide oxidation afforded sulfoxide **17** with high yield. Subjecting sulfoxide **17** into our standard conditions delivered the pyridine-containing γ-butyrolactone **18** readily. Likewise, norbornene **19** underwent efficient chlorosulfinylation when treated with oxalyl chloride in DMSO. A subsequent oxidation generates sulfoxide **20**, which under our standard

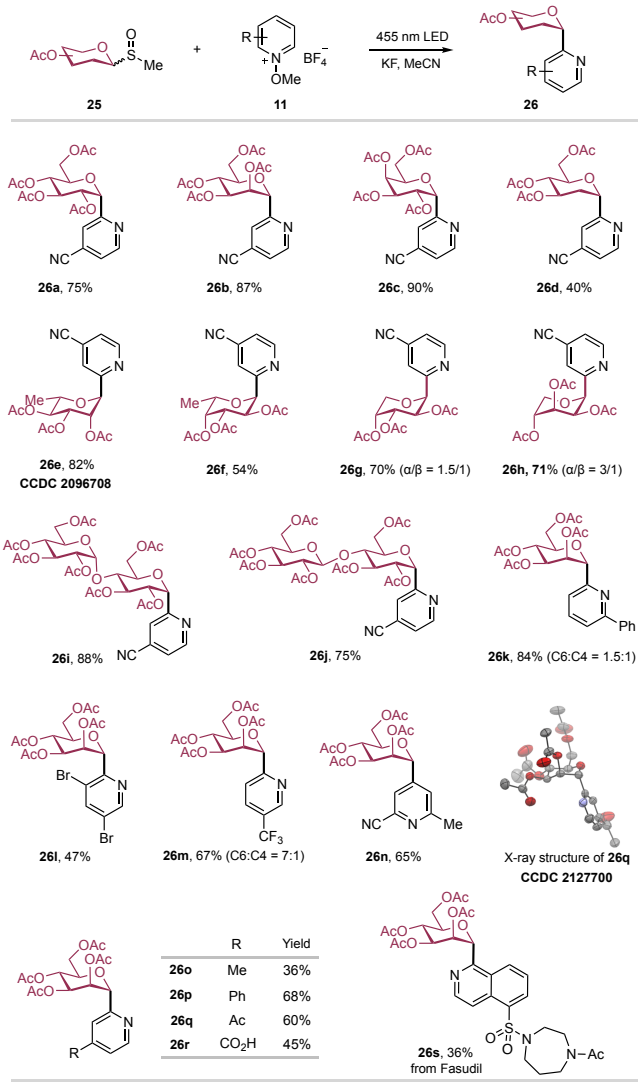
Scheme 2. Synthesis of complex alkyl sulfoxides and their use as radical precursors in this method.



conditions was transformed to the functionalized pyridine derivative **21** in excellent diastereomeric ratio. Lastly, the sulfoxide units could be rapidly prepared from ketones as well. Treating cyclohexanone **22** with thioglycolic acid followed by oxidation gave cyclic sulfoxide **23**. This sulfoxide partook in our transformation to give ester **24**, which upon hydrolysis afforded the corresponding tertiary alcohol (see SI). It is notable that the C–S bond cleavage in **23** was highly regioselective, presumably driven by the preferential formation of the oxygen-stabilized alkyl radical.

To further exploit the utility of our method, we applied it in the synthesis of pyridyl *C*-glycosides (Table 3). Glycosyl sulfoxides (e.g., **25**) are among the most readily available and most frequently used intermediates in carbohydrate synthesis. [22] Conventionally, glycosyl sulfoxides are activated by ionic methods to form oxocarbenium intermediates (or their equivalents), *en route* to *O*-glycosides, *N*-glycosides, or others. If these sulfoxides can be converted to the corresponding glycosyl radicals, subsequent trapping by radicalphiles may afford *C*-glycosides that are previously difficult to access. Interestingly, such reactivity of glycosyl sulfoxides remains underexplored. We found bench-stable glycosyl sulfoxides **25** are competent substrates in our reaction, affording smoothly the corresponding pyridyl *C*-glycosides **26**. Sulfoxides derived from various monosaccharides, including glucose (**26a**), mannose (**26b**), galactose (**26c**), 2-deoxyglucose (**26d**), rhamnose (**26e**), fucose (**26f**), arabinose (**26g**) and lyxose (**26h**) participated in this reaction. Those prepared from disaccharides such as maltose (**26i**) and cellobiose (**26j**) are also suitable substrates. In most of the above examples, the *C*-glycosides were obtained with excellent axial selectivities, consistent with the reactivity profiles of glycosyl radicals. [23] Formation of **26g** and **26h** proceeded with moderate diastereoselectivities, which might be a result of higher flexibility of the corresponding

Table 3. Synthesis of pyridyl C-glycosides[a]



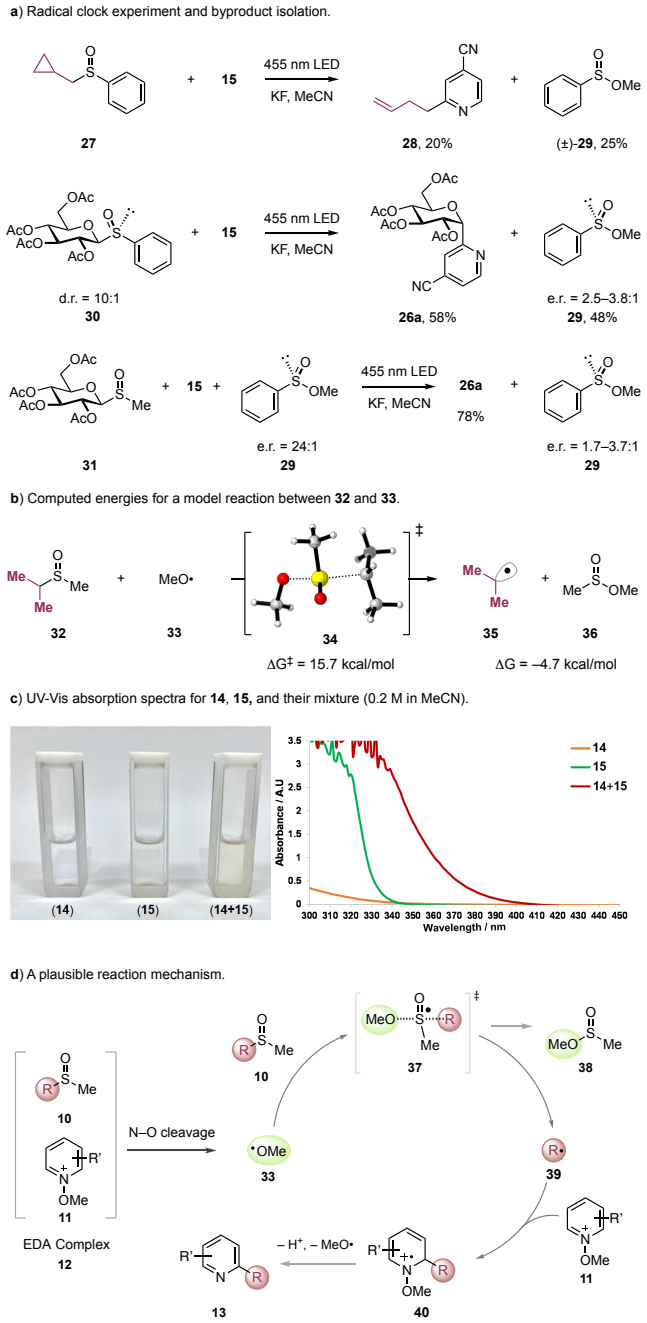
	R	Yield
26o	Me	36%
26p	Ph	68%
26q	Ac	60%
26r	CO_2H	45%

[a] Unless otherwise noted, reactions were performed with mixtures of **25** (0.20 mmol), **11** (2.0 eq.) at rt under irradiation by blue LEDs for 18 h. [b] Yields of isolated products.

ring systems. A variety of pyridine-containing units can be installed as well. Those bearing methyl (**26o**), phenyl (**26p**), ketone (**26q**), halogen (**26l**) and trifluoromethyl groups (**26m**) were accommodated uneventfully. Free carboxylic acid group was also tolerated (**26r**). To further demonstrate the generality of this method, we allowed mannosyl sulfoxide to react with the *N*-methoxy pyridinium derived from vasodilating drug fasudil, which afforded fasudil-mannose conjugate **26s** smoothly. The amide and sulfonamide groups in **26s** were tolerated by the process.

We performed preliminary studies in Scheme 3a to gain additional insights into the mechanism of this reaction. We first prepared phenyl sulfoxide **27** and allowed it to react with **15** under our standard conditions. The phenyl substituted sulfoxides participated in the reaction as well, albeit with moderate efficiency. We found the ring-opened product **28** was formed, consistent with the intermediacy of a cyclopropylmethyl radical. The high

Scheme 3. Mechanistic Studies and a proposed reaction mechanism.



boiling point of sulfinate **29** permitted us to isolate it as a byproduct, implying the homolysis of C-sulfoxide bond in **27** is induced by the attack of methoxy radicals.

Although stereomixtures of sulfoxides could be employed directly in our reaction, we reason a deeper understanding of the fate of these stereogenic sulfur(IV) centers bears relevance to the reaction mechanism. We therefore prepared glycosyl sulfoxide **30** with well-defined stereochemistry (d.r. = 10:1) and treated it with **15** under our standard conditions. Product **26a** was formed along with **29** as the byproduct. Comparing the configuration of **30** and that of **29**, we noted that the *S*-center in the starting material **30** was inverted and slightly

eroded (from 10:1 to 2.5–3.8:1) during the process. We were curious at which stage such stereoerosion occurred. We then prepared **29** in high enantiopurity[24] (e.r. = 24:1) and doped it to the reaction between **31** and **15**. When the reaction was complete, the e.r. of **29** diminished to 1.7–3.7:1. These results taken together, we surmised that in our reaction, the alkyl radicals were generated by an S_N2-like attack of methoxy radicals toward sulfoxides, itself a stereo-invertive process. However, the resulting sulfinate (cf. **29**) could be further attacked by methoxy radicals, an otherwise degenerate process but could cause erosion of the *S*-stereogenic center.

To substantiate the above hypothesis, we computed [ωB97X-D/def2tzvp/SDD/SMD (CH_3CN)//ωB97X-D/6-31G(d)/SMD (CH_3CN)] the radical substitution process between the model substrate **32** and methoxy radical **33** to form isopropyl radical **35** and sulfinate **36** (Scheme 3b). The reaction was calculated to be energetically favorable by 4.7 kcal/mol, with an activation energy of 15.7 kcal/mol. From the transition structure **34** located, we noted the approaching of oxygen atom to sulfur and breaking of C–S bond was simultaneous, akin to that in an S_N2 reaction.

Another feature of this method is that it does not require an external photocatalyst. We noted that mixing the colorless solutions of **14** and **15** gave a light-yellow mixture. UV-Vis spectra of these solutions revealed a significant red-shift effect upon mixing of the two reactants (Scheme 3c), indicating formation of an EDA complex[25] between the two reactants. Besides functioning as the light-absorbing species, the EDA complex formation might have brought another advantage: it increases the local concentration of sulfoxides, which helps to better trap the incipient reactive methoxy radicals and minimizes the undesired decomposition of these highly reactive species. Note our method does not require a large excess of sulfoxides.

With the above information, we proposed a plausible reaction mechanism as depicted in Scheme 3d. Upon irradiation with visible light, the N–O bond in the EDA complex **12** formed between sulfoxides **10** and pyridinium salts **11** undergoes a homolytic cleavage[26] to furnish a methoxy radical **33**. The resulting radical **33** attacks the sulfoxide group nearby to provide the corresponding alkyl radical **39** along with **38**, via transition structure **37**. The alkyl radical **39** is then trapped by pyridinium salts **11** to give radical cation **40**, which then undergoes deprotonation and aromatization to afford the final product **13**.

In conclusion, we have established in this work the use of readily accessible sulfoxides as precursors to alkyl radicals. In this method, alkyl sulfoxides employed as stoichiometric reactants are converted to pyridine derivatives via radical intermediates under visible light irradiation. The reaction proceeds under simple and mild conditions and tolerates a variety of functional groups. To further highlight the utility of this method, it converts various glycosyl sulfoxides to the corresponding pyridyl *C*-glycosides in high stereoselectivities. Mechanistic studies provide insights into the reaction pathway and suggest the formation of EDA complex between alkyl sulfoxides and pyridinium methoxides is critical for the reaction efficiency. Given the synthetic versatility and user-friendliness of sulfoxides in chemistry, we anticipate the current method will inspire the development of new reactions that exploit the potential of these valuable intermediates as radical precursors.

ASSOCIATED CONTENT

Supporting Information.

The Supporting Information is available free of charge on the ACS Publications website.

Experimental procedures and characterization data (PDF)

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