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Photoredox-Initiated 1,2-Difunctionalization of Alkenes with *N*-Chloro *S*-Fluoroalkyl Sulfoximines

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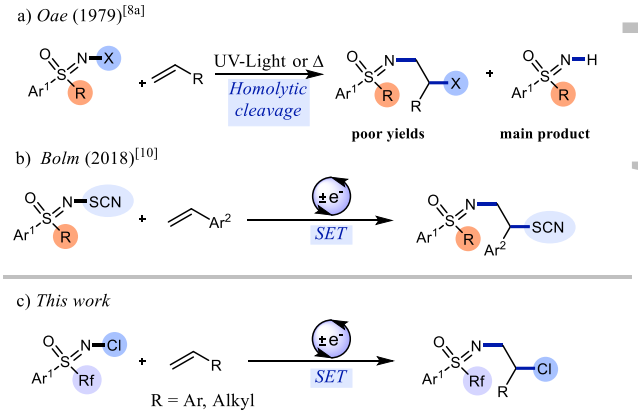
Abstract. We describe herein the photoredox-initiated 1,2-difunctionalization of alkene derivatives with *N*-chloro *S*-fluoroalkyl sulfoximines yielding novel fluoroalkyl sulfoximine scaffolds. The reaction is proposed to proceed through an atom-transfer radical addition (ATRA) mechanism involving the generation of fluorinated nitrogen-centered sulfoximidoyl radicals.

Keywords: Addition to alkenes; C-N bond formation; Photocatalysis; Radicals; Fluorine.

Over the years, nitrogen-containing compounds have displayed an incredible number of interesting features in various fields including medicine, agrochemistry and materials science.[1] Therefore, strategies aiming the construction of C-N bond in a selective manner have been widely investigated. Among them, the transition-metal catalyzed cross-coupling proved to be a powerful tool for their formation,[2] but novel methodologies using milder reaction conditions are still highly needed. Photochemical processes appear as a promising alternative for the promotion of challenging bond constructions. While the creation of C-C bond in a photocatalytic fashion is well established,[3] the construction of C-N bond based on nitrogen-centered radicals has been hitherto under-exploited.[4] Sulfoximines have gained tremendous interest in recent years owing to their unique properties,[5] and have shown promising results in various areas such as C-H activation, for which the sulfoximine moiety served as a directing group.[6] Some of us have been for a long time involved in the development of transformations related to those derivatives with a focus on *S*-perfluoroalkyl sulfoximine compounds and their *N*-functionalization.[7] Recently, *N*-halo sulfoximines have demonstrated their abilities to trigger upon light irradiation the generation of nitrogen-centered sulfoximidoyl radicals.[8,9] The first report pointing out this reactivity was described by Oae and co-workers.[8a] They demonstrated that UV-light or thermal activations could initiate atom transfer radical addition (ATRA) reactions to olefins by homolytic cleavage of the *N*-X (X = Cl, Br) bond of the sulfoximine (Scheme 1, a)). However, this process is poorly effective yielding to the dehalogenated sulfoximine as main product.



Scheme 1. Previous works and this work on regioselective 1,2-difunctionalisation of alkenes via generation of nitrogen-centered sulfoximidoyl radicals.

In 2018, the Bolm group has elegantly updated this reactivity using the photoredox catalysis concept and has described an efficient procedure for the difunctionalization of styrene derivatives using *N*-thiocyanato sulfoximines which are ex-situ obtained from the corresponding *N*-bromocyanato sulfoximines (Scheme 1, b)).[10,11] Despite its efficiency, this procedure is restricted to arylalkenes

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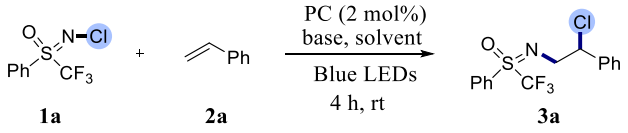
as the difunctionalization reaction is not operating with aliphatic alkene derivatives. With these previous works in mind, we considered to generate fluorinated sulfoximidoyl radicals *via* photoredox processes and explore their reactivities with radical acceptors. Herein, we disclose our preliminary investigations towards the regioselective photoredox-initiated 1,2-difunctionalization of alkene derivatives with *N*-chloro *S*-fluoroalkyl sulfoximines providing vicinal chloro *S*-fluoroalkyl sulfoximine compounds in moderate to excellent yields under mild reaction conditions (Scheme 1, c)).

On the basis of our hypothesis, we selected (chloroimino)(phenyl)(trifluoromethyl)-λ^6-sulfanone **1a** and styrene **2a** as model substrates, and initiated optimization studies. Gratifying, in our first experiment, room-temperature treatment of **1a** and **2a** in the presence of K_2CO_3 and $Ir(ppy)_3$ as photocatalyst (PC) under blue LEDs irradiation afforded the corresponding addition compound **3a** in 41% yield, and in a 1.2:1 diastereomeric ratio after full conversion and despite the observation of side-products (Table 1, entry 1). With this promising result in hand, we next changed the photocatalyst source and the base. While a change of photocatalyst source for $Ru(bpy)_3(PF_6)$ resulted in a significant increase of yield to 89% (Table 1, entry 2), lower yields were observed with the use of other inorganic bases or without any base (Table 1, entries 3-5).

Table 1. Optimization studies of the chloro-sulfoximidation reaction of **2a**.[a)]



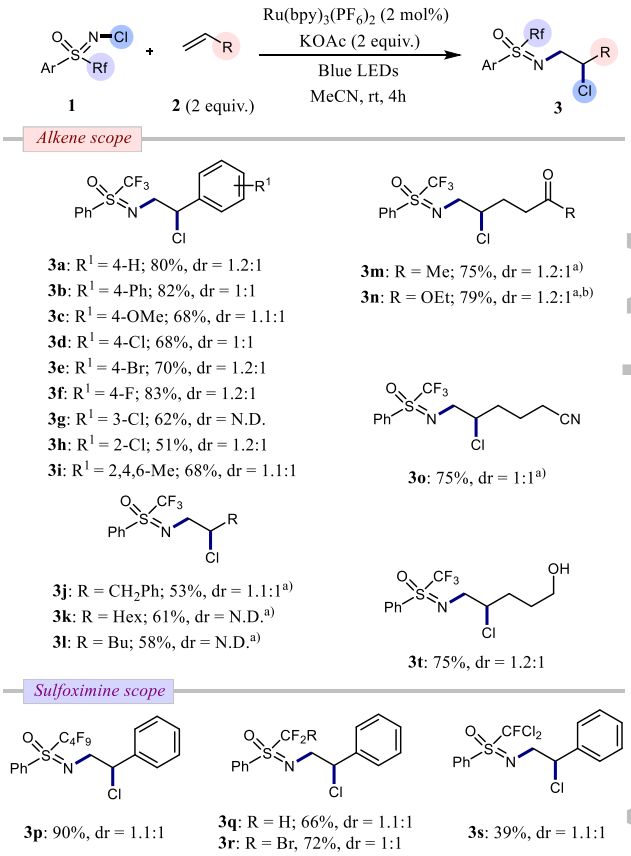
1a **2a** **3a**

Entry	PC	Solvent	Base	Yield (%)[b)]
1	$Ir(ppy)_3$	MeCN	KOAc	41
2	$Ru(bpy)_3(PF_6)_2$	MeCN	KOAc	89
3	$Ru(bpy)_3(PF_6)_2$	MeCN	K_2CO_3	72
4	$Ru(bpy)_3(PF_6)_2$	MeCN	K_2HPO_4	76
5	$Ru(bpy)_3(PF_6)_2$	MeCN	-	65
6	$Ru(bpy)_3(PF_6)_2$	DMF	KOAc	41
7	$Ru(bpy)_3(PF_6)_2$	DCE	KOAc	74
8[c)]	$Ru(bpy)_3(PF_6)_2$	MeCN	KOAc	89 (80[d)])
9[c)]	-	MeCN	KOAc	N.R.
10[c,e)]	$Ru(bpy)_3(PF_6)_2$	MeCN	KOAc	N.R.

[a)] Reaction conditions: **1a** (0.3 mmol), **2a** (1.5 mmol), photocatalyst (2 mol%), base (0.6 mmol), solvent (0.6 mL) for 4 h. [b)] Determined by ^{19}F NMR spectroscopy using α,α,α-trifluorotoluene as internal standard. [c)] 2 equiv. of **2a** were used. [d)] Isolated yield. [e)] No light irradiation, 72 h.

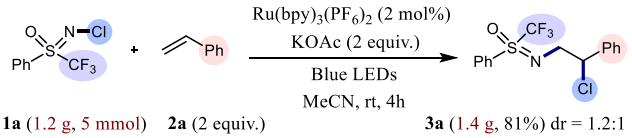
A short survey of polar solvents did not lead to any further improvement of yield of **3a** (Table 1, entries 6-7). Lowering the amount of **2a** to 2 equivalents did not affect the reaction outcome (Table 1, entry 8 vs 2). Finally, control experiments showed that the photocatalyst and the light irradiation are both required for the reaction efficiency (Table 1, entries 9-10).

With the optimized reaction conditions in hand, we next explored the scope of this photoredox-initiated chloro-sulfoximidation transformation (Scheme 2). Firstly, we evaluated the scope of the olefin coupling partners (**2**) with sulfoximine **1a**. Good to high yields were observed for styrene compounds, regardless the electron-donating or electron-withdrawing nature and the position of the substituents on the phenyl ring (**3a**-**3h**).[12] Our methodology was next tested with olefins bearing positions prone to H-atom transfer (HAT) processes and with less reactive aliphatic alkene derivatives. Pleasingly, the chloro-sulfoximidation transformation proceeded well with styrene compound **2i** bearing several benzylic positions affording selectively product **3i** in good yield. Even when allylbenzene (**2j**) was used as alkene acceptor, the transformation led to the formation of the expected compound **3j**, albeit in moderate yield.



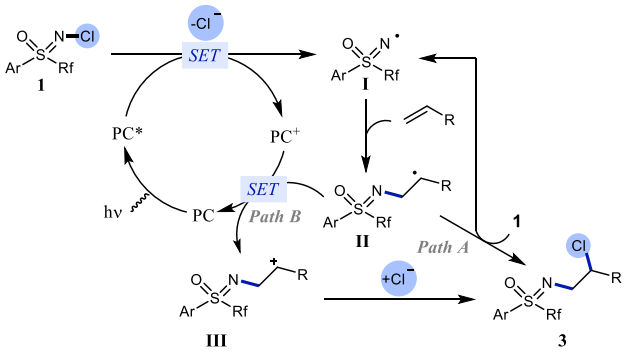
Scheme 2. Scope of the chloro-sulfoximidation of alkenes **2**. Reaction conditions: **1** (0.3 mmol), **2** (0.6 mmol), $Ru(bpy)_3(PF_6)_2$ (2 mol%), KOAc (0.6 mmol), MeCN (0.6 mL) for 4 h. Isolated yields are given. All compounds are isolated as a mixture of diastereomers (d.r = 1.2:1 to 1:1). [a)] Reaction time was extended to 18 h. [b)] ^{19}F NMR yield is given. The product was isolated with an impurity (<10%). N.D = not determined.

Subsequently, various functionalized and unfunctionalized aliphatic alkenes (**2k-2o**) were examined as coupling partners with **1a** under our optimized reaction conditions. To our delight, and in contrast to the photoredox-catalyzed difunctionalization of alkenes with *N*-SCN sulfoximines,[10] the transformation exhibited a good efficiency with such C-C double bond derivatives. Our methodology also displayed a good tolerance towards various functional groups including ester (**3n**), ketone (**3m**), cyano (**3o**), methoxyl (**3c**), halide (**3d-3f**) and free alcohol (**3t**) and consequently offers great opportunities for further structural diversifications. Finally, the transformation was explored with aryl sulfoximine derivatives bearing diverse fluorinated chain patterns. Pleasingly, whatever the fluorinated group, C_4F_9, CF_2H, CF_2Br or $CFCl_2$ engaged, the reaction afforded the corresponding compounds in moderate to excellent yields (**3q-3t**). It is worth noting that, for compound **2r**, no side-products stemming from the likely reduction of the CF_2Br moiety was detected. Finally, the synthesis of **3a** was performed on a semi-preparative 5 mmol scale without any decrease in yield demonstrating the robustness of our methodology (Scheme 3).



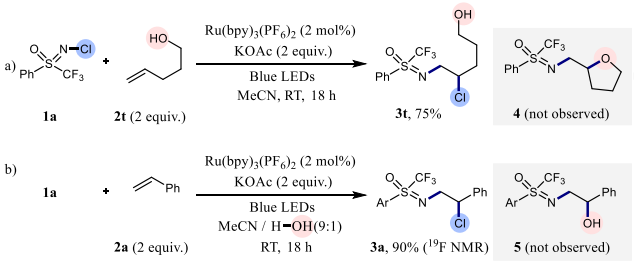
Scheme 3. Gram-scale experiment.

Based on previous reports,[13,14] two plausible mechanisms could be evoked for this transformation as displayed in Scheme 4. First, the photoexcitation of the photocatalyst would promote the photoreduction of the sulfoximine **1** by SET reduction, that would give rise to the formation of the sulfoximidoyl radical **I**. The latter would then react with the alkene compound **2** affording the formation of the radical intermediate **II**. At this stage, two distinct mechanistic pathways might be considered, namely the radical-chain pathway (Scheme 4, path A) and the catalytic pathway (Scheme 4, path B).



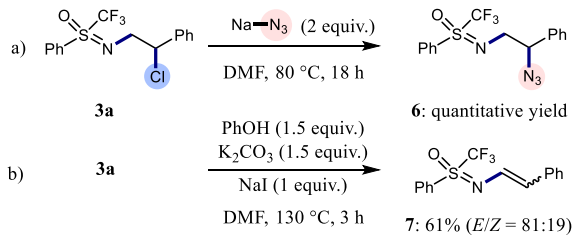
Scheme 4. Plausible mechanisms for the photoredox-catalyzed chloro-sulfoximidation reaction.

In the path A, intermediate **II** would abstract a chlorine atom from sulfoximine **1**, leading meanwhile to the formation of the compound **3** and the generation of the new sulfoximidoyl radical **I**. Regarding the path B, species II would undergo an oxidation from the oxidation form of PC into the cationic species **III**, which would restore the photocatalyst to its original oxidation state. Finally, species **III** would be trapped by a chloride atom affording compound **3**. To gain further insight into the operating pathway, several control experiments were performed (Scheme 5). We hypothesized that if the reaction was going through the formation of the cationic species **III** (via path B), the latter could be trapped by the addition of an external nucleophile to the reaction media. Thus, the transformation reactivity was investigated with an alkene partner bearing a free alcohol functionality on the tether (Scheme 5, a)).



Scheme 5. Control experiments.

Under these conditions, the ATRA-product **3t** was obtained in 75% yield as the sole product with no trace of the rival cyclized product resulting from direct intramolecular nucleophilic attack of the free alcohol moiety on the potentially generated carbocation intermediate **III**. Similarly, conducting the photocatalyzed reaction of **1a** and **2a** in water as a co-solvent only provides the chloro-sulfoximidation product **3a**. These control experiments are consistent with a transformation proceeding *via* a radical-chain mechanism (Scheme 4, path A).



Scheme 6. Post-functionalization.

Finally, the product **3a** exhibited a great potential for further synthetic manipulations, notably as valuable precursors for the synthesis of the azido *S*-perfluoroalkyl sulfoximine **6** and the *N*-alkenyl sulfoximine **7**, respectively in quantitative and moderate yields (Scheme 6). These last experiments demonstrate the synthetic usefulness of our methodology to access functionally diverse *N*-sulfoximine derivatives.

In summary, we have developed a practical and mild procedure for the synthesis of hitherto unknown vicinal chloro *S*-fluoroalkyl sulfoximine derivatives in good to excellent yields under ruthenium photocatalysis from easily available alkenes. This photoredox-initiated procedure displayed good efficiency regardless the aromatic or aliphatic nature of the alkene partners and the structure of the fluorinated chain. Control experiments ruled out the formation of cationic intermediate in the course of the reaction and supported that the transformation proceeded *via* an ATRA mechanism. Finally, applications of the methodology to functional-group transformations have been illustrated for the synthesis of 2-azido sulfoximines and *N*-alkenyl sulfoximines.

Experimental Section

General procedure

Preparation of N-functionalized sulfoximines **(3a-3t)**. In a glass tube, the selected alkene derivative (0.6 mmol, 2 equiv.), dry potassium acetate (58 mg, 0.6 mmol, 2 equiv.) and the $Ru(bpy)_3(PF_6)_2$ (5 mg, 2 mol%) were successively added to a solution of the selected *N*-chlorosulfoximine (0.3 mmol, 1 equiv.) in dry acetonitrile (0.6 mL). The reactor was flushed with argon and sealed. The reaction was stirred under visible light irradiation (Blue LED strip) at ambient temperature for the appropriate time. Then the reaction mixture was concentrated in vacuo and the residue was purified by flash chromatography (silica gel, appropriate mixture of hexane/ethyl acetate or pure toluene) to afford the corresponding *N*-functionalized sulfoximines as a mixture of diastereomers (d.r. between 1.2:1 and 1:1).

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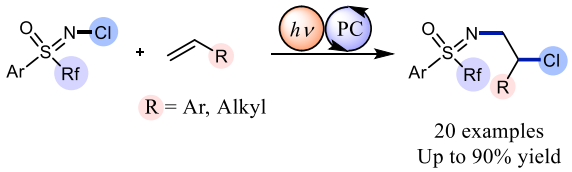

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