Photocatalytic Fluoro Sulfoximidations of Styrenes

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Abstract: Reactions of difluorotoluene with NH-sulfoximines provide new hypervalent iodine(III) reagents, which photocatalytically transfer a fluoro and a sulfoximidoyl group onto styrenes with high regioselectivity. The substrate scope is broad with respect to both sulfoximines and olefins. Following an operationally simple protocol, a large library of fluorine-containing N-functionalized sulfoximines can be accessed. Results from mechanistic investigations revealed the importance of radical intermediates.

Photocatalytic reactions of difluorotoluene with NH-sulfoximines provide new hypervalent iodine(III) reagents, which have elevated them from lab curiosities to indispensable in modern organic chemistry, and recent developments have expanded their potential in sulfoximidations of alkynes, [2] demonstrating their utility in a wide range of applications.

Figure 1. Reported sulfoximidoyl-containing iodine(III) reagents 1 and 2 and targeted analogous compounds 3.

Considering that both moieties are highly important in medicinal and crop protection chemistry,[8,9] the realization of this idea appeared attractive. The advance in this project is presented here.

As starting materials for the preparation of fluoro-containing iodine(III) reagents (3), difluoro iodoarenes (4) appeared most promising.[10] The fluorination chemistry of 4 is rich, and various ligand exchange reactions at the iodo core are known.[11] Furthermore, the accessibility of 4 has recently been significantly improved, leading to efficient fluorination reactions with even catalytic amounts of such interesting reagents.[12]

In the initial studies, difluoro iodoarene (4a) and sulfoximine 5a were applied as substrates (Scheme 1, top). Combining these two compounds in dichloromethane for 20 minutes led to a new fluorine-containing species as revealed by 1H and 19F NMR spectroscopy (see the Supporting Information). Evaporation of the solvent afforded an oil, which proved sensitive to standard conditions of chromatography. ESI-MS analysis showed a signal at m/z 357.97513 corresponding to a composition of [3a-F−]. Attempts to isolate analytically pure 3a failed.

Focusing on potential applications of 3a, an in situ approach was considered, thereby avoiding the need to isolate the apparently sensitive reagent. Functionalizing alkenes[13] was set into focus with the goal of adding both the sulfoximidoyl and the fluoro group to the double bond to give products such as 7 (Scheme 1, bottom). Such transformations would then be analogous to aminofluorinations developed by the groups of Liu,[14a] Zhang,[14b] Pérez,[14c] Xu,[14d] and Xu,[14e] but contrasting them by neither requiring a metal catalyst nor relying on an external fluoride source such as Selectfluor as demonstrated by the groups of Studer[15a] and Lectka[15b].

The first test reactions along these lines were performed with styrene (6a, R = Ph) as the olefinic component. The reagent 3a was prepared in situ by mixing difluorotoluene (4a, 1.5 equiv) and the sulfoximine 5a (1.8 equiv). An
extensive screening of the reaction conditions (for details see Table S2 in the Supporting Information) revealed that the highest yield of 7aa was achieved by following a stepwise process. First, 3a was prepared from 4a and 5a in a sealed tube with DCM as solvent under argon at ambient temperature, and then, after 20 minutes of stirring, 6a and Ru(bpy)$_3$-(PF$_6$)$_2$ (1 mol %) were sequentially added. Irradiation with a blue LED (24 W) for 12 hours followed by standard aqueous work-up and chromatography afforded 7aa in 83% yield (Scheme 2).$[14]$ Applying Ir(dtbpy)ppy)PF$_6$, Rose Bengal, Eosin yellowish, Rhodamine B, or Ru(bpy)$_3$ instead of Ru(bpy)$_3$-(PF$_6$)$_2$, the photocatalyst proved less efficient.$[17]$ Upon addition of CsF, AgF, or CuF$_2$ (2.0 equiv) the amount of 7aa was lowered. Without LED irradiation, the yield of 7aa was significantly reduced (up to 25%) in a range of solvents (DCM, DCE, MeCN, THF, and toluene).$[17]$ Neither changing the addition mode nor altering the substrate ratio was beneficial.

Consequently, the substrate scope was evaluated under the aforementioned optimal reaction conditions. First, various sulfoximines (5) were used with 6a as the olefinic acceptor [and difluoro iodosotoluene (4a) as iodine(III) source]. Scheme 2 shows the results. The substrate scope with respect to the sulfoximine component proved quite general, and a wide range of functional groups, including halo, alkyl, alkoxy, acetoxy, and nitro substituents were tolerated. In the next step, the olefinic component was varied. As precursors for the in situ formed iodine(III) reagent, a combination of 4a and 5f was used (Scheme 3). The applicability of 1-styrenes with monosubstituted aryl groups (6b–e) was studied first. Also in this series the substrate scope was broad. The yields varied, but generally, they were high. The best results were observed with para-substituted styrenes as exemplified by the products 7ff (91%) and 7fh (93%) bearing a para-tert-butyl and a para-phenyl group, respectively. Substrates with meta- and ortho-substituents gave products 7fk–fo in somewhat diminished yields with 56% being the lowest as observed in the formation of 7fk having a meta-fluoro substituent. Representing substrates with more than one substituent on the arenne, 1-naphthyl- and mesityl styrene (6s and 6i) gave the corresponding products 7si (85%) and 7ia (85%) in 86% and 85% yield, respectively. The latter result was particularly interesting because the dr was 4:1, thereby contrasting all other reactions with dr ratios of about 1:1. Using the 1,1-disubstituted styrenes 6u and 6v afforded 7ju (83%) and 7fv (85%), respectively. Finally, to our surprise and delight, also dihydronaphthalene 6w reacted well leading to the corresponding addition product 7fw in 73% yield. This result was remarkable because it showed that 1,2-disubstituted styrene derivatives could also react selectively.

To elucidate the reaction pathway, various process modifications were studied (Scheme 4, top). As noted before, 3a could be identified by mass spectrometry and NMR spectroscopy. The stepwise protocol involving an addition of 6a to a solution of in situ formed 3a followed by irradiation of the resulting mixture with a blue LED in the presence of the photocatalyst gave 7aa in 83% yield. If all reagents were mixed without the separate preformation of 3a, the yield of 7aa was reduced to 68%, suggesting that under these reaction conditions parts of the starting materials reacted differently.
stirring of the iodine reagent 4a in the presence of 6a for 20 minutes followed by the addition of 5a and the photocatalyst with subsequent blue LED irradiation did not lead to any detectable amounts of 7aa. Apparently, other (unidentified) reaction pathways dominated. Following the original protocol but generating 3a in the presence of base (3 equiv of K₂CO₃) reduced the yield of 7aa to 55%, indicating a decisive role of the intermediately formed HF. No product was observed when the reaction (after the in situ formation of 3a) was performed in the presence of TEMPO (2 equiv), suggesting an involvement of radicals as relevant intermediates.

Taking all observations into account, the following mechanistic scenario is suggested: After the initial formation of 3a (Scheme 4, step 1), the N—I bond of 3a is cleaved by single-electron transfer (SET) from the excited state of 
\[ \text{Ru(bpy)}_3^2+ (\text{PC}^*) \], which was generated from the ground state of the photocatalyst by visible light. As a consequence, the N-centered sulfoximidoyl radical A, a fluoride ion, p-tolyl iodide, and the oxidized photocatalyst \( \text{PC}^+ \) are formed. Subsequently, A adds to the double bond of 6a leading to the radical B. The benzylic stabilization is critical for the entire process and the basis for its high regioselectivity.\[19\] Oxidation of B by SET from \( \text{PC}^+ \) provides the benzylic cation C and closes the catalytic cycle by regenerating the ground-state photocatalyst PC. Finally, C reacts with fluoride to give 7aa.\[20\]

In summary, we developed a new in situ formed hypervalent iodine(III) reagent, which photocatalytically adds two of its iodine-bound substituents to styrenes, providing fluorne-containing N-functionalized sulfoximines in a single operational step. The fluoro sulfoximinations show a pronounced functional-group tolerance and occur with high regioselectivity. Mechanistic studies suggest the intermediacy of radicals.

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**Conflict of interest**

The authors declare no conflict of interest.

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[16] When the LED irradiation was stopped after 2 h, 7aa was obtained in 36% yield after 12 h.

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[19] Attempts to use olefinic substrates other than styrenes (vinylcyclohexan, 2-vinylisodoline-1,3-dione, 4-phenyl-1-butene, and vinyl hexanoate) under standard reaction conditions remain unsuccessful.

[20] In the presence of either TMSCF₃ or TMSCN as potential sources for other nucleophiles to react with C, no other products were observed.