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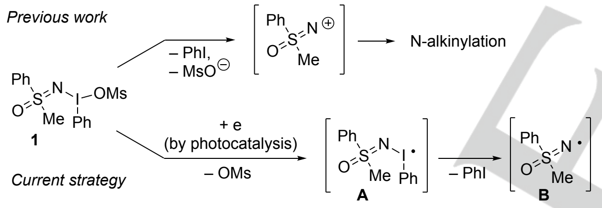
Sulfoximidations of Benzylic C–H bonds by Photocatalysis

Han Wang, Duo Zhang, and Carsten Bolm*

Abstract: An efficient photocatalytic functionalization of compounds with benzylic C–H bonds by sulfoximidation in visible light is described. The mild reaction conditions allow the use of a broad array of substrates, including diarylmethane, alkyl arenes, arylacetonitrile, 2-arylacetate, and alkynyl aryl methanes. The sulfoximidation process is highly chemoselective and leads to the corresponding sulfoximines in generally good yields. Mechanistic investigations suggested the intermediacy of sulfoximidoyl radicals.

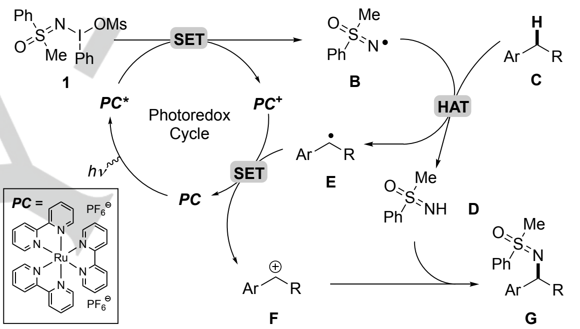
Owing to their unique bioactivities, sulfoximines[1] have found broad applications in medicinal and agrochemistry.[2] Our group has continuous interest in such compounds with a focus on the development of new approaches towards sulfoximidoyl moieties and their incorporation into 3-dimensional heterocycles.[3] N-Functionalizations of existing sulfoximines mostly involve formally *nucleophilic* nitrogens. Recently, we reported on novel sulfoximidoyl-containing hypervalent iodine(III) reagents such as **1** and their use in *electrophilic* sulfoximidoyl transfer reactions (Scheme 1, top).[4] We now wondered about the behavior of **1** in photoredox catalysis hypothesizing that **1** could eventually serve as convenient source for nitrogen-centered sulfoximidoyl radical **B** generated by electron-transfer (ET) processes via radical **A** (Scheme 1, bottom). Species of type **B** are unusual and in terms of synthetic applicability essentially unexplored.[5]



Scheme 1. Previous and current strategy for the use of hypervalent iodine reagent **1**.

Nitrogen-centered radicals (NCRs) are important intermediates in preparative organic chemistry.[6] Using NCRs in complex total synthesis, however, has proven difficult due to their limited accessibility and high reactivity.[7] In recent years, photoredox catalysis has emerged as powerful tool for the generation of radicals under mild conditions.[8] Along these lines, single-electron-transfer (SET) processes have been developed, which allow the conversion of NCR precursors into their corresponding N-centered radicals.[9]

For our concept design, a report by Toscano and co-workers proved inspiring.[5b] They had observed that the photochemical degradation of an N-benzoxysulfoximine predominately led to the corresponding *N*H-sulfoximine, which suggested that the proposed sulfoximidoyl radical intermediate had a good reactivity in an intermolecular hydrogen atom transfer (HAT) reaction and that, second, substrates with benzylic C–H bonds were suitable H donors in such processes. Consequently, we envisaged the following scenario (Scheme 2): Irradiation with blue (LED) light would promote a photocatalyst *PC* [here, Ru(II)] to its excited state (*PC**), and its oxidative quench by hypervalent iodine(III) reagent **1** leads to PC^+ [here, Ru(III)] and sulfoximidoyl radical **B** as key intermediate. Hydrogen atom transfer (HAT) reaction of **B** with benzylic substrates **C** then provides *N*H sulfoximine **D** and benzyl radical **E**. Oxidation of **E** by PC^+ transfers the photocatalyst to its original state (*PC*) and leads to benzylic cation **F**, which reacts with *N*H sulfoximine **D** giving product **G** upon deprotonation.[10]



Scheme 2. Proposed mechanism for the sulfoximdation of benzylic C–H bonds.

For the proof-of-concept study, we selected sulfoximidoyl-containing hypervalent iodine(III) reagent **1** and 4-benzylanisole (**2a**) as representative model substrates. To our delight, both reacted as hypothesized. Under irradiation with a blue LED strip, using 1 mol % of $Ir(dtbpy)(ppy)_2PF_6$ as the photocatalyst in MeCN, the reaction between **1** and **2a** gave the desired product *N*-[(4-methoxyphenyl)(phenyl)methyl]-*S*-phenyl-*S*-methylsulfoximine (**3a**) in 47% yield (Table 1, entry 1). Also other common photocatalysts provided **3a**, albeit mostly in only moderate yield (Table 1, entries 2-6). The screening revealed $Ru(bpy)_3(PF_6)_2$ to be superior over all other photocatalysts, leading to **3a** in 81% yield (Table 1, entry 6). Neither changing the solvent from MeCN to THF, DCE or $PhCF_3$ (Table 1, entries 7-9) nor the addition of bases (K_3PO_4, K_2CO_3, and $NaHCO_3$; Table 1, entries 10-12) had a positive effect on the yield of **3a**. Control experiments confirmed that both photocatalyst and light were essential for product formation (Table 1, entries 13 and 14).

Under the optimal reaction conditions, the scope of the sulfoximidation process was examined. First, diarylmethanes were applied (Scheme 3). In general, all substituted products **3a**-**l** were obtained in good yields. Neither electronic nor steric effects played a significant role. For example, the yield of **3f** bearing an electron-withdrawing *p*-CF_3 group at one of the arenes (80%) was essentially identical to the one of **3a** having an electron-

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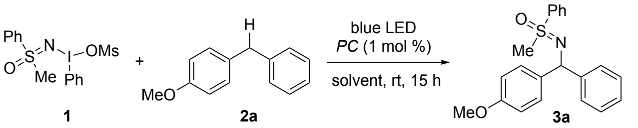
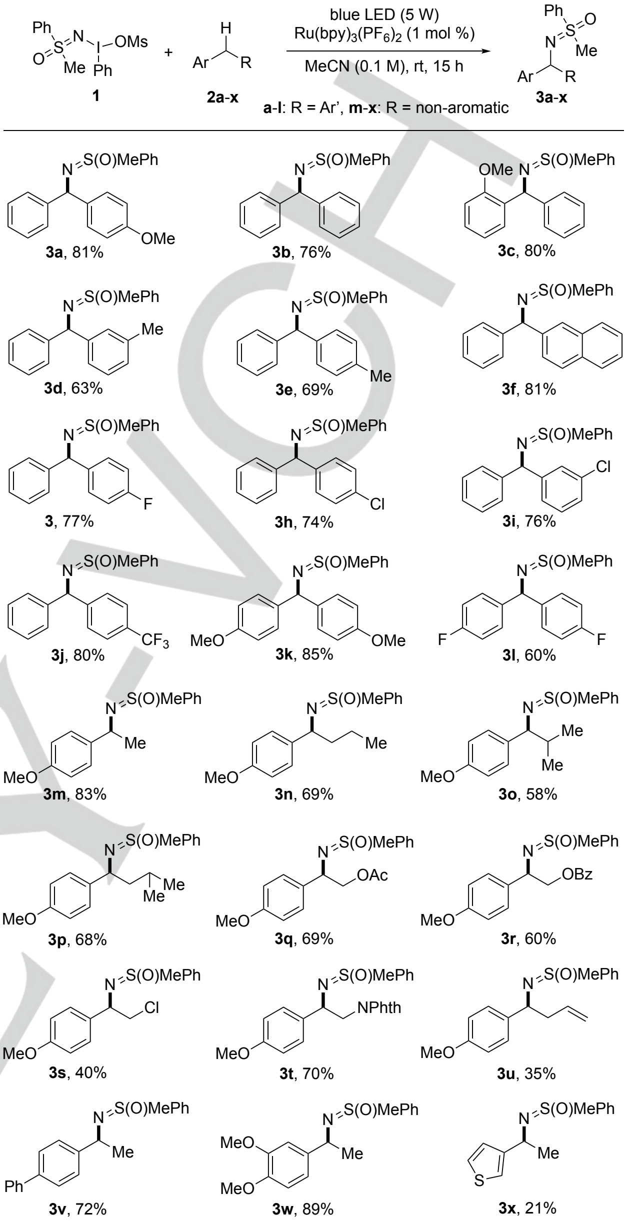
Table 1: Optimization of the sulfoximidation conditions.[a]



Entry	Photocatalyst	Solvent	Base	Yield [%]
1	$Ir(dtbpy)(ppy)_2PF_6$	MeCN	none	47
2	$Ir(ppy)_3$	MeCN	none	n.d.
3	Flurescein	MeCN	none	41
4	Rhodamine B	MeCN	none	31
5	Eosin Y	MeCN	none	32
6	$Ru(bpy)_3(PF_6)_2$	MeCN	none	81
7	$Ru(bpy)_3(PF_6)_2$	THF	none	n.d.
8	$Ru(bpy)_3(PF_6)_2$	DCE	none	54
9	$Ru(bpy)_3(PF_6)_2$	$PhCF_3$	none	n.d.
10	$Ru(bpy)_3(PF_6)_2$	MeCN	K_3PO_4	81
11	$Ru(bpy)_3(PF_6)_2$	MeCN	K_2CO_3	76
12	$Ru(bpy)_3(PF_6)_2$	MeCN	$NaHCO_3$	74
13	none	MeCN	none	n.d.
14[b]	$Ru(bpy)_3(PF_6)_2$	MeCN	none	n.d.

[a] Reaction conditions: **1** (0.2 mmol), **2a** (0.4 mmol), photocatalyst (1 mol %), base (0.2 mmol), solvent (2 mL), sealed tube. [b] No irradiation.



Scheme 3. Substrate scope: diarylmethanes (**2a**-**l**) and substituted alkyl arenes (**2m**-**x**).

donating *p*-MeO substituent (81%). If the MeO group was located in *ortho* position as in **3c**, the yield was 80%. Only for tolyl-containing products **3d** (63%) and **3f** (69%) and difluoro-substituted **3l** (60%) the yields were somewhat lower. With the exception of **3b** all products were formed as ca. 1:1 mixtures of diastereomers.

Next, substituted alkyl arenes were used as substrates (Scheme 3). In this series, the yields of the corresponding products **3m**-**x** varied significantly, ranging from 21% (for **3x**) to 89% (for **3w**). Anisols with linear or branched alkyl substituents proved to be good substrates, leading to **3m**-**p** in yields between 58% (for **3o**) and 89% (for **3m**). Similar results were obtained with anisols having heteroatoms in the alkyl substituent leading to products **3q**-**t**. Of particular interest was the conversion of 3-butenyl-containing anisol **2u**. Albeit the yield of **3u** was only 35%, the outcome was significant because it demonstrated that the HAT process was fast (compared to a competing olefin addition) allowing unsaturated molecules to be functionalized as well. Thus in that respect, the sulfoximidoyl radical proved superior over other nitrogen-centered radicals, which often show low addition/substitution selectivity in conversions of compounds with C–C double bonds.[6,7,11] Also the applying ethyl arenes with modified aryl groups was possible, as confirmed by the formations of **3v** and **3w**, which were obtained in 72% and 89% yield, respectively. 3-Ethylthiophene (**2x**) reacted sluggish leading to **3x** in only 21% yield. Also in this series (**3m**-**x**) the products were mixtures of diastereomers in ratios of ca. 1:1.

Chart 1 shows products **4a**-**h** obtained in photocatalytic reactions of **1** with substrates having electron-withdrawing groups (CN or CO_2R) directly bound to the benzylic carbon where the radical was generated. Although the yields were only moderate to good (39-52%), the transformations are noteworthy because they represent a rather unusual protocol for the preparation of a-amino acid derivatives. The same is true for propagylic amide-type compounds **5a**-**d**, which were photocatalytically prepared from **1** and the corresponding propagylic arenes.

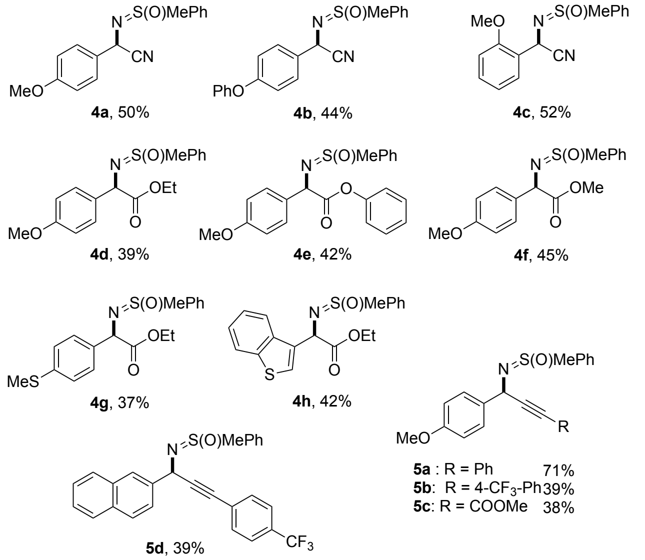
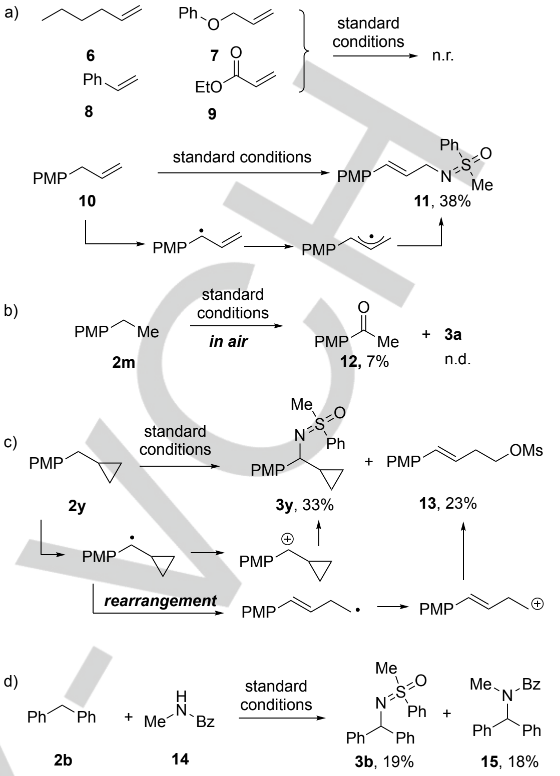


Chart 1. Products obtained from **1** by photocatalysis.



Scheme 4. Control experiments.

With the goal to validate the hypothesized reaction path presented in Scheme 2, various control experiments were performed. First, couplings of **1** with olefinic substrates were re-assessed. The formation of **3u** had already indicated that compounds with C–C double bonds could be applied and that the sulfoximidation occurred with high preference over radical addition. To further explore the inherent reactivity and selectivity of the proposed sulfoximidoyl radical, reactions with 1-hexene (**6**), propyl vinyl ether (**7**), styrene (**8**), ethyl acrylate (**9**), and 1-allyl-4-methoxybenzene (**10**) were attempted (Scheme 4, part a). While the first four substrates remained untouched (allowing to recover **1** almost quantitatively), doubly (allyl/benzyl) activated **10** was reactive enough to convert leading to substituted product **11** in 38% yield. Presumably, the latter transformation proceeded via the highly stabilized allyl radical and an attack of the sulfur component at its sterically less hindered terminal carbon. When 4-ethylanisole (**2m**) was applied under standard conditions in air (instead of argon), ketone **12** was isolated in 7% yield, which was consistent with the intermediacy of a radical species and its reaction with dioxygen. Sulfoximidation product **3m** was not observed (Scheme 4, part b). A "radical clock experiment" with cyclopropyl-containing **2y** as substrate led to **3y** and **13** in 33% and 23% yield, respectively (Scheme 4, part c). Both products indicated the presence of an α-cyclopropyl radical, which in part ring-opened and reacted further by substitution reactions via the resulting cations. Finally, *N*-methylbenzamide (**14**) was added to a standard photocatalysis with diphenylmethane (**2b**) (Scheme 4, part d). As a result, a mixture of substitution products **3b** (19%) and **15** (18%) was formed, which we interpreted as evidence for the existence of benzylic cations as intermediate.[12]

In summary, we developed a photoredox catalysis for sulfoximidation reactions using hypervalent iodine(III) reagent **1**. Under mild reaction conditions, various substrates with benzylic C–H bonds react chemoselectively at room temperature. Results of mechanistic studies suggest a sulfoximidoyl radical and benzylic radicals/cations as intermediates.

Acknowledgements

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Keywords: hypervalent iodine(III) reagent • photocatalysis • radicals • sulfoximidation • sulfoximine

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[10] Although the reaction path depicted here is in line with previously suggested mechanisms (comp. refs. 8e and 8g as well as the references therein), we cannot exclude the involvement of free radical chain reactions at this stage. Furthermore, a very different route was suggested by a reviewer, whom we gratefully acknowledge: Excited Ru(bpy)$_3$ could oxidize substrate **C** leading to an aromatic radical cation. The reduced photocatalyst then transfered an electron onto **1** to give nitrogen radical **B**, which could abstract a hydrogen atom from the radical cation providing **F** and **D**. Finally, the latter two intermediates combined to provide product **G**.

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[12] Treatment of N-methylbenzamide **14** with **1** in CD$_3$CN for 24 h did not lead to any detectable change of the ^{1}H NMR spectrum, suggesting that **15** did not interfere in the radical pathways (for details, see Supporting Information).

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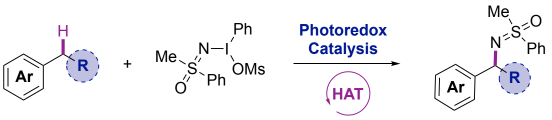

R = aryl, alkyl, CN, COOR, alkynyl

COMMUNICATION

*Han Wang, Duo Zhang, and Carsten Bolm**

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Sulfoximidations of Benzylic C–H bonds by Photocatalysis

Benzylic C–H bonds have selectively been functionalized by photoredox catalysis starting from a sulfoximidoyl-containing hypervalent iodine(III) reagent. The process is highly chemoselective and allows converting a broad range of substrates. Mechanistic studies suggest the intermediacy of a sulfoximidoyl radical. Conceptionally, a new approach towards sulfoximines has been developed.