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In this communication, a new photocatalytic strategy for the addition of alkyl-radical derivatives to *N*-sulfinimines with complete diastereoselectivity and moderate to good yields is presented. This is the first asymmetric photocatalytic addition to *N*-sulfinimines under visible light irradiation with smooth conditions and functional group tolerance.

Enantiopure sulfinimines, or *N*-sulfinyl imines, have been used in the asymmetric synthesis of diverse chiral amino derivatives, e.g. α -branched amines, α - and β -amino acids, and α - and β -amino phosphonic acids.¹ The *N*-sulfinyl group is one of the best chiral auxiliaries for imines because the C=N bond is activated for nucleophilic addition, diastereofacial selectivity is provided, and it is easily removable under mild acidic conditions. However, most reactions with *N*-sulfinimines employ organometallic compounds such as organolithium or Grignard reagents under very restrictive conditions (low temperature and minimal functional group tolerance).

In this regard, radical reactions offer a better functional group tolerance under more suitable reaction conditions. However, only a few examples involving radical-mediated intermolecular additions to *N*-sulfinimines have been reported,^{2–4} which are impractical because of the large amount of radical precursors and the use of toxic reagents (Bu₃SnH). These issues are impeding a simple gateway to valuable chiral amines, and therefore a new straightforward methodology capable of overcoming these limitations is required.

On the other hand, visible light photoredox catalysis has received significant attention over the past decade due to its

Asymmetric radical alkylation of *N*-sulfinimines under visible light photocatalytic conditions†‡

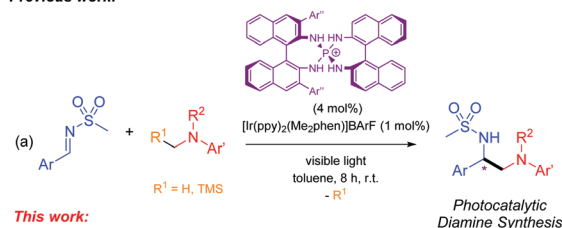
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ability to achieve bond constructions that are not possible using established procedures.⁵ At the same time, photoredox catalysts can also be employed to generate radicals to be used in a diverse range of proven radical strategies. This approach is based on the adeptness transition metal complexes⁶ and organic dyes⁷ display by engaging in SET processes following photoexcitation with visible light. Numerous photocatalytic examples of racemic radical transformations performed with imines have been published.⁸ However, only one asymmetric approach has been disclosed by Ooi and co-workers (Scheme 1a).⁹ In Ooi's work, the addition of α -alkylamine derivatives to *N*-sulfonylimines to afford diamine derivatives was described. Nonetheless, no examples of visible light photocatalytic reactions with *N*-sulfinimines exist to the best of our knowledge.

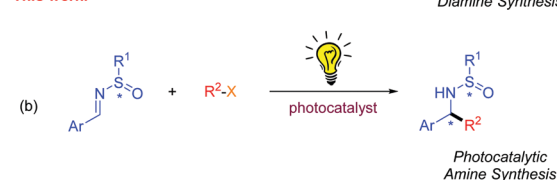
Therefore, our goal is to deliver a novel radical addition to *N*-sulfinimines, using photocatalysis and visible light irradiation as a viable radical-generating process, and the *N*-sulfinyl group as a chiral auxiliary to achieve complete stereoselectivity in the synthesis of amine derivatives (Scheme 1b).

In order to achieve this goal, we performed an initial study in which the reactivity of the enantiopure *N*-sulfinimine **1a** (R¹ = *p*-Tol) was tested with different radical donors (see ESI†

Previous work:



This work:



Scheme 1 Previous reaction and present work of this manuscript.

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† Authors dedicate this work to Prof. Jose Luis García Ruano on the occasion of his 70th birthday.

‡ Electronic supplementary information (ESI) available. See DOI: 10.1039/c7cc03724d

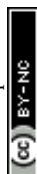
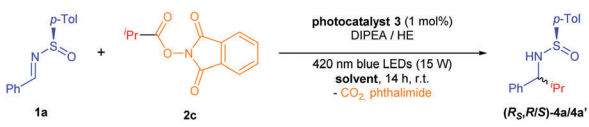


Table 1 Catalyst and solvent screening of the visible light-mediated alkylation of *N*-sulfinimines^a


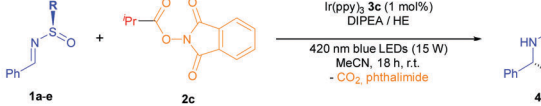
Entry	Photocatalyst	Solvent	Conv. ^b (%)	dr ^b
1	[Ru(bpy) ₃]Cl ₂ ·6H ₂ O (3a)	DCM	39	73 : 27
2	[Ir(ppy) ₂ (bpy)]PF ₆ (3b)	DCM	— ^c	—
3	Ir(ppy) ₃ (3c)	DCM	67	72 : 28
4	Ir(dFpp) ₃ (3d)	DCM	— ^c	—
5	[Ir{dF(CF ₃)ppy} ₂ (dtbpy)]PF ₆ (3e)	DCM	— ^c	—
6	Eosin Y (3f)	DCM	58	68 : 32
7	Rose bengal (3g)	DCM	46	75 : 25
8	Rhodamine 6G (3h)	DCM	29	67 : 33
9	Ir(ppy) ₃ (3c)	Tol	30	71 : 29
10	Ir(ppy) ₃ (3c)	DMF	100	69 : 31
11	Ir(ppy) ₃ (3c)	MeCN	100	66 : 34
12	Ir(ppy) ₃ (3c)	DMSO	100	68 : 32

^a Reaction conditions: 0.1 mmol scale using 1.5 equiv. of *N*-sulfinimine **1a**, 1.0 equiv. of phthalimide **2c**, 2.0 equiv. of DIPEA, 1.5 equiv. of Hantzsch ester (HE) and 1 mL of solvent. ^b Conversion and diastereomeric ratio were determined by ¹H NMR analysis of the crude mixture. ^c Reliable data could not be obtained due to partial *N*-sulfinimine hydrolysis.

for more details). Reactions performed with isobutyric acid (**2a**)¹⁰ and isopropyl oxalate (**2b**)¹¹ were unsuccessful; probably caused by the effect the required additives (K₂HPO₄ and water) inflicted upon the *N*-sulfinimine, observing its hydrolysis in the crude mixture. However, under fairly anhydrous conditions, the reaction of *N*-(isobutyryloxy)phthalimide **2c**¹² with *N*-sulfinimine **1a** catalyzed by [Ru(bpy)₃]²⁺ (**3a**) gave rise to our desired product in moderate conversion after 14 hours (entry 1, Table 1).

Following this positive result, we tried to identify the optimal photocatalyst that would allow us to increase the final conversion. As revealed in Table 1, the use of some metal photocatalysts (entries 2, 4 and 5) occasionally led to *N*-sulfinimine hydrolysis, whereas reactions performed with organic dyes (entries 6–8) yielded **4a** without hydrolysis of **1a**. Nicely, Ir(ppy)₃ **3c** displayed the highest conversion in DCM (entry 3), and it was consequently used as photocatalyst during the solvent screening (entries 9–12). Gratifyingly, reactions performed with Ir(ppy)₃ in highly polar solvents (entries 10–12) led to complete conversion to sulfinamide **4a/4a'**.

Despite reaching optimal conversion, dr values obtained during screening studies confirmed that the reaction displayed low diastereoselectivity under the optimized conditions. Variation of different reaction parameters such as temperature (0, –30 °C instead of r.t.) and concentration (0.03 M instead of 0.10 M) seemed to have no effect upon diastereoselectivity. We performed several tests with *N*-tert-butan sulfinimine **1b**, aiming to improve this feature by taking advantage of the bulkier ^tBu group. However, none of these trials provided the desired product, obtaining a complex mixture under the present conditions (Table 2). These results prompted us to conduct an evaluation of three different *N*-sulfinimines bearing bulkier aryl groups (**1c–e**), anticipating that the stereoinduction would improve upon increase of the steric size of the *N*-sulfinyl moiety (Table 2). To our delight, all

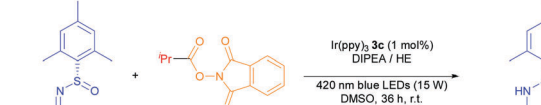
Table 2 *N*-Sulfinimine screening with different chiral auxiliaries^a


Entry	Product	Conv.	dr
4a/4a'	(R,S)-4a/4a'	conv. ^b = 100%	dr ^b = 66:34
4b	complex mixture	—	—
4c/4c'	(R,S)-4c/4c'	conv. = 100%	dr = 90:10
4d	(R,S)-4d	conv. = 43%	dr > 98:2
4e	(R,S)-4e	conv. = 100%	dr > 98:2

^a Reaction conditions: 0.1 mmol scale using 1.0 equiv. of *N*-sulfinimine **1**, 1.5 equiv. of phthalimide **2c**, 2.0 equiv. of DIPEA, 1.5 equiv. of Hantzsch ester (HE) and 1 mL of MeCN. ^b Determined by ¹H NMR.

three of them delivered excellent diastereoselectivity, especially the 2-methoxy-1-naphthyl- and mesityl-substituted *N*-sulfinimines (**1d** and **1e**, respectively). Since **1d** was less reactive than **1e** after 18 hours, we selected the latter as the optimal substrate to complete the scope with different imines (Table 3), and different radical donors (Table 4), using DMSO as solvent because higher yields were achieved after isolation by flash chromatography (see ESI†).

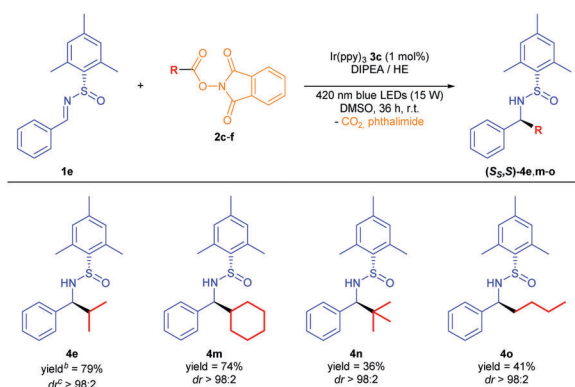
The reaction was found to be compatible with a large variety of aromatic rings (Table 3).¹³ Therefore, electron donating and electron withdrawing groups underwent the alkylation with excellent diastereoselectivity (**4f–4h**), and good chemoselectivity in the case of **1h**, where no addition to the nitrile group was detected. Pleasantly, this photocatalytic protocol tolerated the

Table 3 *N*-Sulfinimine scope with (isobutyryloxy)phthalimide **2c**^a


Entry	Product	Yield ^b	dr ^c
4e	(S,S)-4e	79%	dr > 98:2
4f	(S,S)-4f	59%	dr > 98:2
4g	(S,S)-4g	61%	dr > 98:2
4h	(S,S)-4h	63%	dr > 98:2
4i	(S,S)-4i	70%	dr > 98:2
4j	(S,S)-4j	60%	dr > 98:2
4k	(S,S)-4k	56%	dr > 98:2
4l	(S,S)-4l	64%	dr > 98:2

^a Reaction conditions: 0.1 mmol scale using 1.0 equiv. of *N*-sulfinimine **1**, 1.5 equiv. of phthalimide **2c**, 3.0 equiv. of DIPEA, 0.5 equiv. of Hantzsch ester (HE) and 1 mL of DMSO. ^b Isolated yields after flash chromatography. ^c Determined by ¹H NMR.



Table 4 Phthalimide screening with *N*-sulfinimine **1e**^a

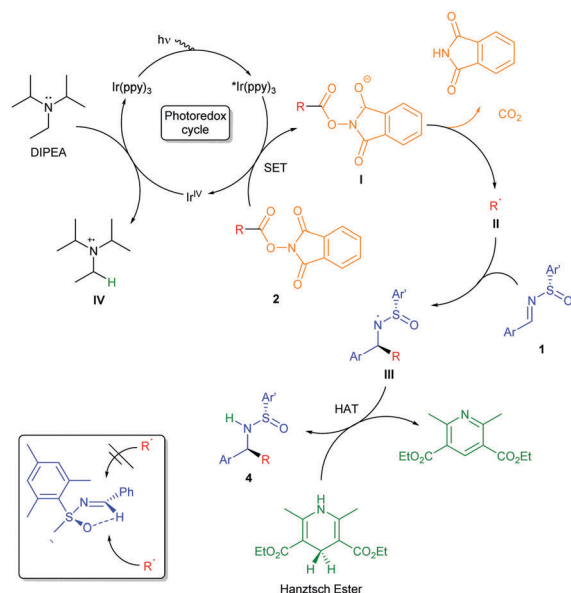
^a Reaction conditions: 0.1 mmol scale using 1.0 equiv. of *N*-sulfinimine **1**, 1.5 equiv. of phthalimide **2c**, 3.0 equiv. of DIPEA, 0.5 equiv. of Hantzsch ester (HE) and 1 mL of DMSO. ^b Isolated yields after flash chromatography. ^c Determined by ¹H NMR.

use of halogen substituents at *para* and *ortho* positions without reduction or loss of the bromide and iodide atoms (**4i** and **4j**). Different electron rich and poor heterocycles were used, yielding **4k** and **4l** with an excellent diastereoselectivity.

The simple one-step preparation of the phthalimide reagent (see ESI†) led us to conduct a study of the addition of different alkyl radicals derived from **2** to the imine **1e** (Table 4). As a result, secondary alkyl groups were easily added with excellent yields (74–79%) and diastereoselectivity, as well as the *tert*-butyl group (**4n**). Primary alkyl radicals have been traditionally problematic in terms of their generation, and other methods have failed to successfully complete the addition to the *N*-sulfinimine.^{4a} Remarkably, primary alkyl radical addition was achieved with an excellent dr, albeit in moderate yield due to its difficult isolation (**4o**).

The absolute configuration of compound **4e** was determined by comparison of the spectroscopic data of a known compound in the literature (see ESI†),¹⁴ assuming the same stereochemical behaviour for all compounds **4**. We carried out the desulfinylation under acidic conditions of **4e**, giving rise to amine **5** which has been correlated with a known (*S*)-amine in the literature (see ESI†). The stereoselectivity of these reactions can be rationalized from the more stable *s-cis* arrangement conformation of the sulfinylimine (enforced by the intramolecular hydrogen bond interaction).^{4a} The approach of the radical to the less hindered *si*-face of imines explains the *S* configuration assigned to the obtained compounds **4e–o** (bottom-left, Scheme 2).

A plausible mechanism of the radical addition to *N*-sulfinimines is depicted in Scheme 2. The radical formation of the reaction pathway is based on mechanistic studies performed on our system along with fundamental concepts related to photoredox catalytic mechanisms.^{5,6} Photoredox catalysts can reach an excited state upon irradiation with visible light. Therefore, Ir(ppy)₃ absorbs irradiation with blue light, populating the highly reducing excited *Ir(ppy)₃ species ($E_{1/2} \text{ Ir}^{\text{IV}}/\text{Ir}^{\text{III}} = -1.73 \text{ V vs. SCE}$).⁶ The photo-excited catalyst engages in a SET process with phthalimide **2c** ($E_{1/2}^{\text{red}} = -1.14 \text{ V vs. SCE}$, see cyclic voltammetry in ESI†), generating anion radical **I** through an oxidative quenching



Scheme 2 Proposed mechanism for the decarboxylative alkylation.

pathway (see Scheme 2). The photocatalytic cycle is completed with the reduction of the Ir^{IV} species ($E_{1/2} \text{ Ir}^{\text{IV}}/\text{Ir}^{\text{III}} = +0.77 \text{ V vs. SCE}$)⁶ by an electron donor such as DIPEA ($E_{1/2}^{\text{ox}} = +0.94 \text{ V vs. SCE}$, see cyclic voltammetry in ESI†), regenerating the photocatalyst. The resultant reductive elimination of the phthalimide group leads to decarboxylation and subsequent formation of radical **II**. Next, *N*-sulfinimine **1** undergoes radical addition to afford *N*-centered radical **III**. Finally, Hantzsch ester donates a hydrogen atom to **III**, giving rise to sulfinamide **4** via hydrogen atom transfer (HAT). The reaction also proceeds adequately in absence of Hantzsch ester, although requiring longer reaction times, because the oxidized species of DIPEA **IV** can transfer a hydrogen atom. This step is part of the widely-known DIPEA decomposition pathway in photocatalytic procedures following electron donation.^{5,6}

In order to validate this proposal, different mechanistic studies were performed. Stern–Volmer quenching evaluation allowed us to establish the first step of the mechanism (see ESI†). The excited state of our photocatalyst **3c** can decay via phosphorescence ($\lambda_{\text{em}} = 518 \text{ nm}$).¹⁵ However, we observed that phthalimide **2c** interfered with this process, quenching the excited state of the photocatalyst.

On the other hand, DIPEA and *N*-sulfinimine **1** did not display this quenching ability. Therefore, the mechanism should follow an oxidative quenching pathway, starting with reduction of phthalimide **2**.

Finally, to ensure whether this reaction is governed by a radical chain propagation process or a visible light-photocatalytic one, we carried out light/dark experiments, (Fig. 1).¹⁶ In addition, the radical chain mechanism seems to be incoherent since the *N*-centered radical **III** and phthalimide **2c** should both be reduced.¹⁷ Predictably, we observed that product formation (**4e**) only occurs during visible light irradiation periods, indicating that radical formation is taking place. Moreover, the quantum yield (ϕ) of this reaction was measured (see ESI†) to provide further information



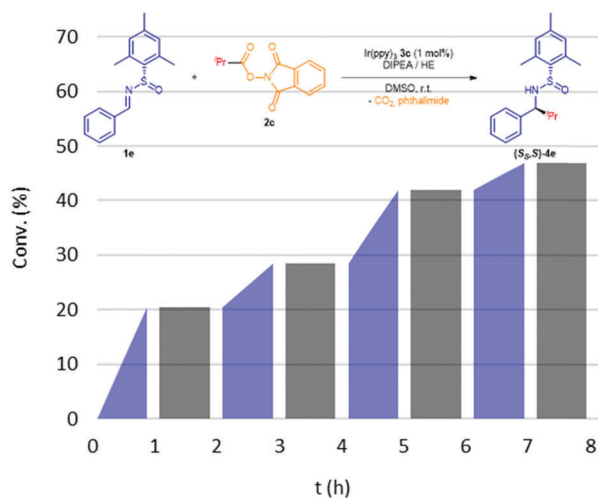


Fig. 1 Light/dark experiment for the decarboxylative alkylation of *N*-sulfinimines. Conversion determined by ¹H NMR. Areas shaded in blue indicate irradiation and those shaded in black indicate darkness.

in this regard. Since ϕ (420 nm) = 0.077, the photocatalyst must absorb 13 photons to afford one equivalent of product, indicating that a chain propagation-type mechanism should not be taking place.

In conclusion, the first highly diastereoselective photocatalytic addition to *N*-sulfinimines is presented. This is an efficient transformation with full conversion under mild conditions in absence of toxic reagents. The reaction presents a wide scope, affording different sulfinamides with high diastereomeric control. We propose a mechanism based on the reductive decarboxylation of the phthalimide to generate the alkyl radical which is added to the *N*-sulfinimine *via* oxidative quenching of the photocatalyst, as it is confirmed by Stern-Volmer studies. Furthermore, the quantum yield indicates that the reaction should not involve a radical chain mechanism.

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- Intermediate **III** (see Scheme 2) would be reduced to the corresponding anion followed by protonation to yield **4**.

