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To be cited as: *Adv. Synth. Catal.* 10.1002/adsc.201900298

Link to VoR: http://dx.doi.org/10.1002/adsc.201900298

DOI: 10.1002/adsc.201((will be filled in by the editorial staff))

Photocatalytic Oxidative Iodination of Electron-Rich Arenes

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Received: ((will be filled in by the editorial staff))

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/adsc.201######.((Please delete if not appropriate))

Abstract. A visible-light-mediated oxidative iodination of electron-rich arenes has been developed. 2.5 mol% of unsubstituted anthraquinone as photocatalyst were used in combination with elementary iodine, trifluoroacetic acid and oxygen as the terminal oxidant. The iodination proceeds upon irradiation in non- or weakly-electron donating solvents (DCM, DCE and benzene) wherein a spectral window in strongly coloured iodine solutions can be observed at around 400 nm. The method provides good to excellent yields (up to 98 %) and shows excellent regioselectivity and good functional group tolerance (triple bonds, ketone, ester, amide). Moreover, the photo-iodination was also upscaled to a 5 mmol scale (1.1 g). Mechanistic investigations by intermediate-trapping and competition experiments indicate a photocatalytic arene-oxidation and the subsequent reaction with iodine as a likely mechanistic pathway.

Keywords: Anthraquinone, Arenes; Iodination; Oxidative Iodination; Photocatalysis

Introduction

Aryl iodides are valuable building blocks in organic chemistry, as they are widely used as synthetic intermediates in various C–C couplings,[1] and for the preparation of hypervalent iodine reagents.[2] Furthermore, they are also used as radiopharmaceuticals.[3] Consequently, the preparation of iodoarenes attracts attention within the synthetic community and the development of new methods for their synthesis is highly desired. Usually, direct C–H bond iodofunctionalization is achieved by employing either iodonium "I$^+$" donating reagents (*e.g.* Py_2IBF_4[4]) or "I$^+$" donating systems, wherein the reactive "I$^+$" species is formed *in situ* (*e.g.* $I_2/HCl/O_2$[5]). The most promising systems in terms of atom and waste economy use elementary iodine or iodide salts as an iodine atom source in combination with Lewis acid activation and environmentally benign oxidants, such as hydrogen peroxide or, even better, oxygen.[6] Much work has already been done in this research area,[6-7] but development of new methods, based on different approaches is an ongoing challenge as these may offer different selectivity and functional group tolerance. In contrast to the traditional polar reactivity manifolds, radical manifolds can be accessed by the use of visible-light photocatalysis.[8] Different light-driven halogenation reactions of arenes were reported before,[9] but to our knowledge no efficient direct visible-light promoted iodination has been reported so far.[10] Although catalytic use of molecular iodine[11] in visible-light photoredox chemistry is lately being exploited,[12] its use in combination with irradiation of photocatalysts is challenging and reports in this area are scarce.[13] The light absorption of iodine and its complexes often overlaps with the absorption bands of photocatalysts and photocatalytic reactions can therefore not be promoted effectively. Consequently, relatively high photocatalyst to iodine ratios are required and systems are limited to low concentrations.[13] In this work, we show how to circumvent iodine coloration issues and present an efficient photocatalytic system that utilizes a stoichiometric amount of iodine to iodinate electron-rich arenes.

Results and Discussion

Screening and optimization of reaction conditions

An iodination reaction is often accompanied by very coloured reaction solutions. Iodide salts (*e.g.* NEt_4I), a colourless iodine atom source, are redox active and get readily oxidized to iodine ($E_{ox} \approx 0.5$ V vs. SHE),[14] which forms coloured polyiodide ions (I_3^-) in the presence of residual iodide ions.[15] The build-up of polyiodide ions prevents any further photochemically promoted reactions, as these species strongly absorb light in an applicable range of the visible spectral region (**Figure 1a**). Another iodine atom source, molecular iodine (I_2), interacts with many commonly used solvents, causing blueshifting (400-510 nm) of the molecular iodine absorption band at 520 nm, or formation of a new charge-transfer (CT) complex band (240-350 nm).[16] The interaction of iodine with a solvent molecule reflects the solvent electron donating ability. In non-interacting solvents (DCM and DCE) or weakly interacting solvents (benzene), a spectral window at around 400 nm is observed (**Figure 1b**). The spectral window at the edge of the visible-light region can in principle be used to perform visible-light promoted reactions.

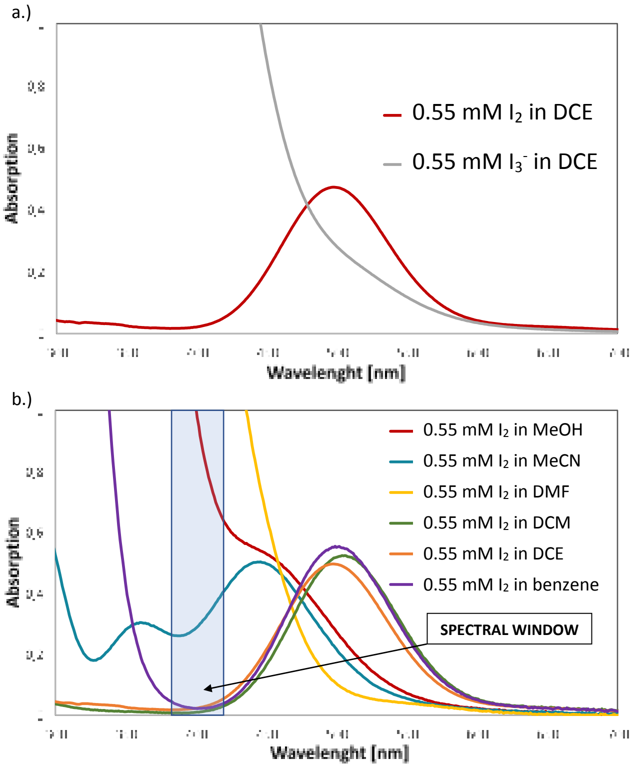
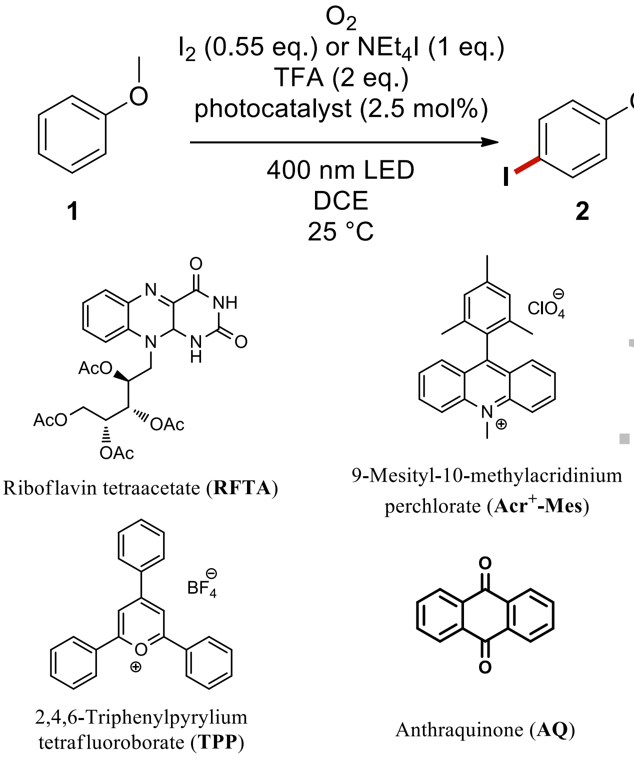


Figure 1: a.) UV-VIS spectra of iodine and NEt_4I_3 in DCE and b.) UV-VIS absorption of iodine solutions.

Based on these considerations, we attempted to develop a photoredox-catalyzed iodination system, via irradiation within the spectral window at around 400 nm (**Table 1**). We tested different photocatalysts with relatively high excited state oxidation potentials[17] that are capable of oxidizing anisole,[18] as well as an iodine atom source ($I^-/I_3^-/I_2$ to I_2/I^+).[14] Unsubstituted anthraquinone as photocatalyst provided the highest desired product yield among the tested metal-free dyes (entries **1-4**). The oxidation potential of anthraquinone was further enhanced by the addition of TFA,[19] resulting in a drastic increase of the reaction rate and yield of **2** (entry **5**). Solvent optimization (Table S1) at this stage revealed the highest reaction rate in benzene compared to other tested solvents (*vide infra* for mechanistic rationalization). Iodination in benzene proceeded with 96 % yield of **2** (Entry **6**) in only 0.5 h irradiation time. Addition of TFA, can on the other hand, also enhance electrophilicity of iodine molecules by its polarization and thereby trigger electrophilic iodination.

Table 1. Screening of the reaction conditions.



Riboflavin tetraacetate (**RFTA**)

9-Mesityl-10-methylacridinium perchlorate (**Acr$^+$-Mes**)

2,4,6-Triphenylpyrylium tetrafluoroborate (**TPP**)

Anthraquinone (**AQ**)

Entry	Iodine source	PC	TFA [eq.]	Reaction time	Yield of **2** [%]
1	I_2	RFTA	-	14 h	1
2	I_2	Acr$^+$-Mes	-	14 h	2
3	I_2	TPP	-	14 h	2
4	I_2	AQ	-	14 h	8
5	I_2	AQ	2.0	0.5 h	64
6[a]	I_2	AQ	2.0	0.5 h	96
7	I_2	TPP	2.0	2 h	3
8	I_2	-	2.0	2 h	2
9[b]	I_2	-	2.0	2 h	0
10[b]	I_2	AQ	2.0	2 h	0
11	NEt_4I	AQ	-	14 h	0
12	NEt_4I	AQ	2.0	14 h	0

General conditions: anisole (0.1 mmol), applied photocatalyst (2.5 mol%), trifluoroacetic acid (2 eq.) or without, indicated amount of iodine source in 1 mL of DCE. Irradiation with 400 nm LEDs under oxygen atmosphere. Given yields were determined by GC-FID analysis, using naphthalene as internal standard. [a] Benzene was used as a solvent. [b] No irradiation.

However, negative control experiments with another

essential role of the presence of light and photocatalyst for the reaction's progress. Reactions wherein iodide (in form of a soluble tetraalkyl ammonium salt) was used as iodine atom source did not yield any iodinated product (entries **11** and **12**). Other photocatalysts only provided trace amounts of product.

Synthetic scope and upscale of the reaction

Next, the synthetic scope of the reaction was explored. First, simple electron-rich iodoarenes (**2-14**) were prepared in good to excellent yields. The method showed high para-regioselectivity for the iodination of anisole yielding less than 4% of the ortho isomer of **2**, presumably due to a non-thermal activation step. For all other compounds a single regioisomer was observed.

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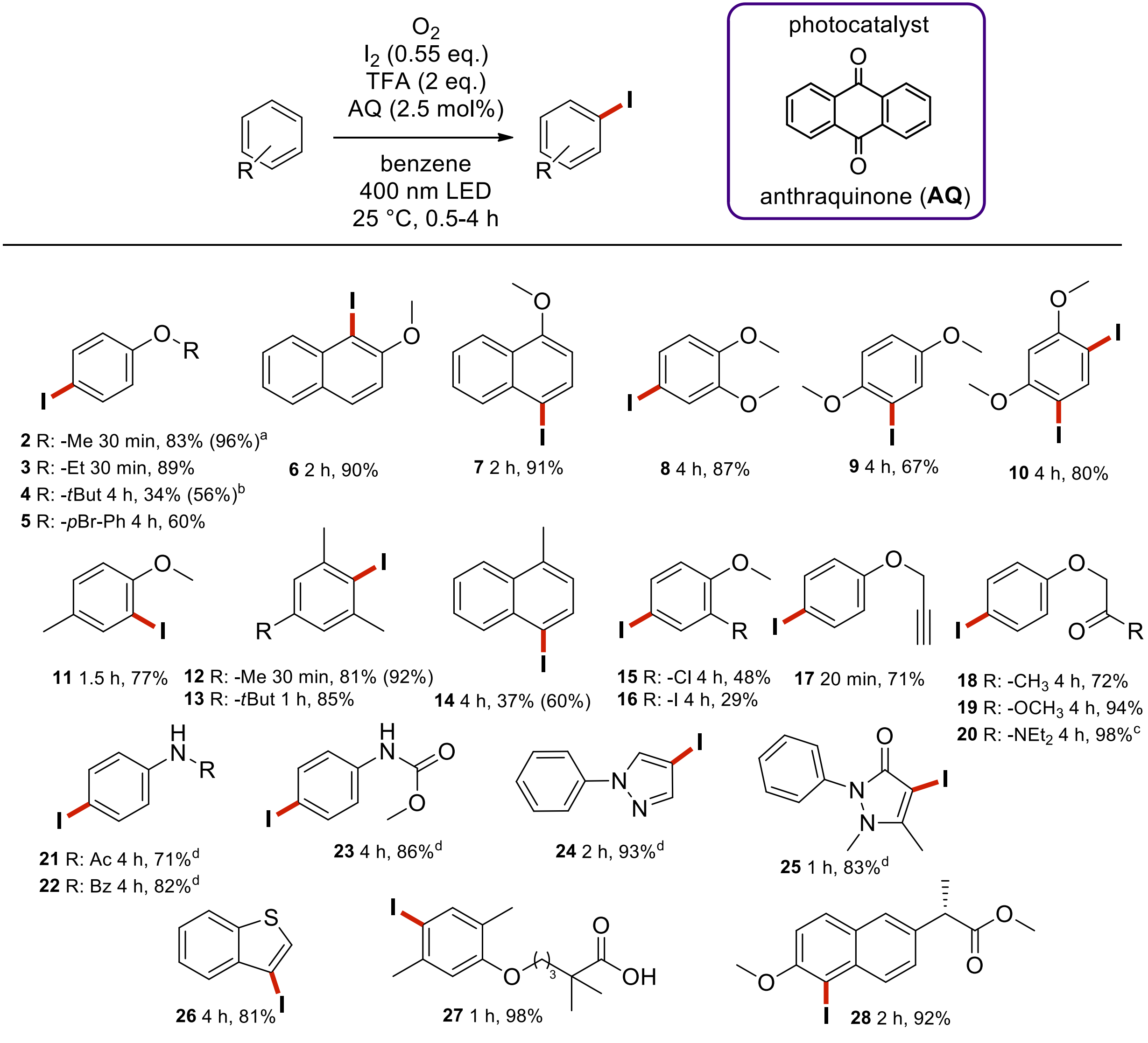
substituted arene **13**. Notably, no addition of iodine to triple bonds or α-carbonyl position was observed for arenes **17** and **18**, respectively. Despite the acidic conditions, the acid sensitive ester functionality in substrate **19** remained untouched, as there are no strong nucleophiles present in the system. Iodination of the amide derivative required one additional equivalent of acid to break complexes between amide and iodine (see Figures S8-9) and only then proceeded well, affording compound **20** in 98% yield. This approach was applied further for the iodination of other nitrogen containing compounds: protected anilines (**21-23**), phenyl pyrazole (**24**) and biologically active pyrazole derivative phenazone (**25**). The method was also applicable to the iodination of benzothiophene yielding **26**.

Scheme 1: Synthetic scope of the photocatalytic iodination.



2 R: -Me 30 min, 83% (96%)[a]
3 R: -Et 30 min, 89%
4 R: -*t*But 4 h, 34% (56%)[b]
5 R: -*p*Br-Ph 4 h, 60%
6 2 h, 90%
7 2 h, 91%
8 4 h, 87%
9 4 h, 67%
10 4 h, 80%
11 1.5 h, 77%
12 R: -Me 30 min, 81% (92%)
13 R: -*t*But 1 h, 85%
14 4 h, 37% (60%)
15 R: -Cl 4 h, 48%
16 R: -I 4 h, 29%
17 20 min, 71%
18 R: -CH_3 4 h, 72%
19 R: -OCH_3 4 h, 94%
20 R: -NEt_2 4 h, 98%[c]
21 R: Ac 4 h, 71%[d]
22 R: Bz 4 h, 82%[d]
23 4 h, 86%[d]
24 2 h, 93%[d]
25 1 h, 83%[d]
26 4 h, 81%
27 1 h, 98%
28 2 h, 92%

General conditions: 0.1 mmol of substrate, 2.5 mol% of AQ, 2 equiv. of TFA and 0.55 equiv. of I_2 were dissolved in 1 mL of benzene and irradiated at 400 nm for 0.5-4 h. Given yields are isolated. Yields in parenthesis are GC yields determined with naphthalene as an internal standard. [a] < 4% of ortho isomer was observed by ^1H NMR [b] In parenthesis is NMR yield determined with hexamethylbenzene as an internal standard. [c] 3 equiv. of TFA were used. [d] 4 eq. of TFA were used and the reaction was run in DCE.

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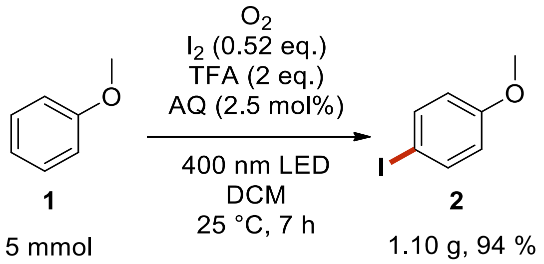
Late-stage iodination of biologically active gemfibrozil showed that the sterically hindered carboxylic group (**27**) can be tolerated in the reaction conditions. Notably, we also iodofunctionalized a bioactive naproxen ester derivative that possesses a chiral benzylic carbon atom. To our delight, we did not observe racemization and obtained this pharmacophore derivative **28** in 92% yield. The method gave lower yields for halogenated anisole derivatives **15** and **16,** as their oxidation potentials are probably on the limit of the anthraquinone excited state potential. Unfortunately, the method is not suitable for more electron-deficient arenes.

In the next step, we performed the reaction on a larger scale. DCM was used as solvent avoiding benzene on a larger scale (**Scheme 2**).

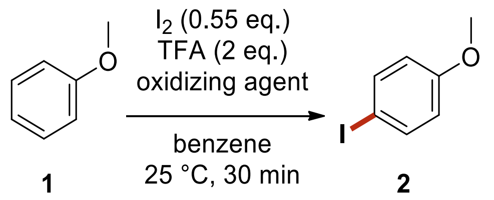


Scheme 2: Photocatalytic iodination in a gram scale reaction.

Mechanistic investigation

First, our system was compared with commonly used oxidants to test, if a similar reactivity can also be achieved by means of classic chemistry. An oxidative iodination of anisole **1** with excess of nitromethane, hydrogen peroxide[20] or peracetic acid[21] instead of oxygen and photocatalysts was investigated (**Table 2**). Classic oxidants gave only low yields (entries **2-4**) under the given conditions, while the photocatalytic conditions (entry **1**) enabled complete conversion of the starting material. The experiments show an advantage of photocatalytic oxidation over the classic oxidants and suggest that the light-driven iodination may operate via a different mechanism. Additionally, thioxanthene-9-one, a non-redox sensitizer with a similar triplet energy as anthraquinone (265 kJ/mol and 261 kJ/mol, respectively)[22] was tested (entry **5**). The latter experiment was performed to disprove singlet oxygen chemistry or other sensitization-driven reactions, as an important contribution to the reactivity of the system.

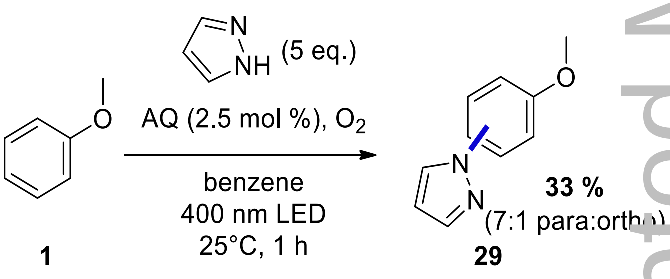
Table 2: Comparison of different oxidants.



Entry	Oxidizing agent	Yield of **2** [%]
1	O_2, AQ (2.5 mol%), 400 nm LED	96
2	30 % H_2O_2 (5 eq.)	5
3	30-40 % AcOOH in AcOH (5 eq.)	7
4	CH_3NO_2 (5 eq.)	0
5	O_2, thioxanthene-9-one (2.5 mol %), 400 nm LED	0

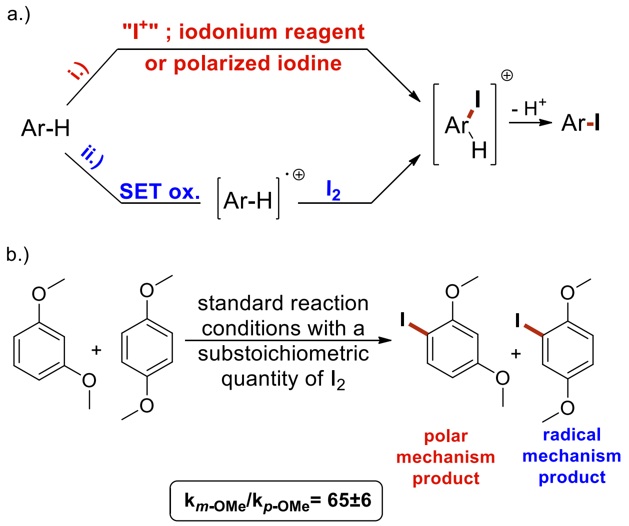
General conditions: 0.1 mmol anisole, 2 eq. TFA, 0.55 eq. I_2 and 2.5 mol% of applied photocatalyst or 5 eq. of applied oxidizing agent in 1 ml benzene. When photocatalyst was used, the solution was irradiated at 400 nm under oxygen atmosphere. Otherwise, the solutions were stirred in darkness for 30 min. Given yields were determined by GC-FID using naphthalene as an internal standard.

To probe whether the photocatalyst oxidizes the arene in the system, a literature reported trapping reaction with pyrazole as nucleophile[23] was performed in the absence of iodine (**Scheme 3**).[24] The isolated coupled product **29** strongly indicates in situ formation of an electrophilic arene radical-cation.



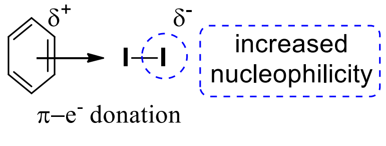
Scheme 3: Trapping of the arene radical-cation with pyrazole.

We conducted further mechanistic investigations to prove that the radical cation is an essential intermediate, through which the iodinated product is formed. Galli et al. addressed a similar question before[25] and developed a mechanistic probe that differentiates between a polar and a radical iodination mechanism (**Scheme 4**), based on intermolecular competition between 1,3-dimethoxybenzene (more nucleophilic, forms polar product) and 1,4-dimethoxybenzene (lower oxidation potential, forms radical product). The two compounds compete for the substoichiometric amount of iodinating reagent and the product distribution depends on the prevailing mechanism of the iodination. The obtained calculated ratio of the rate constants $k_{m\text{-OMe}}/k_{p\text{-OMe}}$ in our system is 65±6 (Table S3), while the literature value for classic “I^+” iodination is 1420±150[26] and for the only reported system wherein radical iodination was proposed is 210±20.[25c] The result indicates that the photocatalytic iodination might indeed proceed via iodination of the arene radical cation.



Scheme 4: a.) Possible polar and radical mechanism of iodination. b.) Competition experiment to distinguish between the two possible pathways.

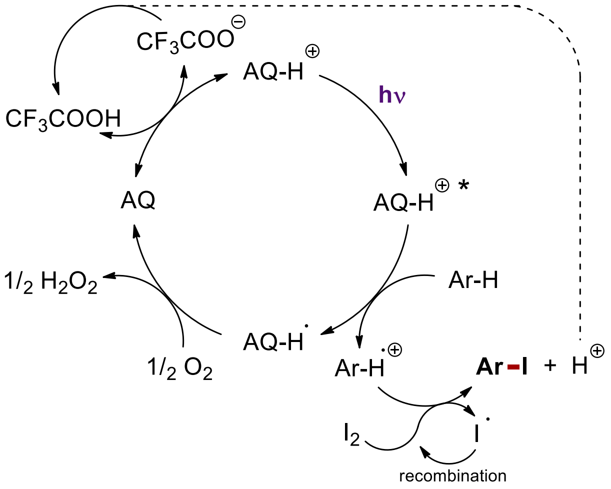
The observation of faster reaction rates in benzene compared to other tested solvents, is also in line with the obtained mechanistic evidence, supporting a radical mechanism. Benzene’s interaction with iodine is unique in a way, as it forms CT complexes, but does not cause strong blueshifting of the iodine band at 520 nm. This leaves a spectral window at 400 nm, despite the interaction with the solvent. In the iodine-benzene CT, benzene donates π-electrons to the iodine and thus makes the terminal iodine atom of the CT complex more nucleophilic (**Scheme 5**). Enhanced nucleophilicity of iodine is then reflected in a faster reaction with the electrophilic arene radical cations, leading to the iodinated product. Increased reactivity of iodine dissolved in interacting solvents (brown solutions) is a known phenomenon.[27]



Scheme 5: Iodine-benzene CT complex.

Evidently, the main role of acid is not polarization of iodine but rather altering the anthraquinone photoredox properties. A protonation of anthraquinone leads to enhanced absorption at 400 nm and facilitates reduction of anthraquinone (see figures S2-6).

Based on the previously reported mechanism[19] and our mechanistic investigation, we propose a mechanism (**Scheme 6**) for our photocatalytic oxidative iodination system, wherein protonated AQ acts as a photocatalyst whose excited form oxidizes the arene. The formed arene radical cation subsequently abstracts iodine atom from iodine molecule and forms the iodinated product. The coupled by-product of the reaction is the iodine radical ($I^{\cdot}$), which can recombine with another $I^{\cdot}$ to form I_2, leading to 100 % iodine economy of the reaction. The photocatalytic cycle is concluded with the regeneration of anthraquinone by oxygen. It should be noted that a polar mechanism wherein “I^+” species attacks an arene (**Scheme 4a** i) cannot be fully excluded especially with very electron-rich arenes.



Scheme 6: Proposed mechanism of the photocatalytic oxidative iodination reaction.

Conclusion

In conclusion, we reported an efficient light-driven method for the iodination of electron-rich aromatic compounds, using iodine, trifluoroacetic acid, inexpensive, unsubstituted anthraquinone photocatalyst, and oxygen as a terminal oxidant. The reactions proceed best in benzene, but also in DCM. The method is fast and shows high regioselectivity and tolerance towards many functional groups. The developed procedure was used on a gram scale reaction, as well as for the late-stage functionalization of bioactive molecules. Mechanistic investigations suggest that the system operates via the oxidation of an arene and subsequent reaction with molecular iodine.

The demonstrated approach of irradiation within the solvent dependent iodine spectral window might be important in the development of new light promoted iodination and iodine catalysed methods.

Experimental Section

For full experimental data see Supporting Information.

General procedure for photocatalytic iodination of electron-rich arenes.

The substrate (0.1 mmol) was weighed into a 5 mL crimp vial. A stirring bar, 1 ml of stock solution (0.5 mg AQ (0.0025 mmol) and 14.0 mg iodine (0.055 mmol) in 1 ml benzene) and 15.4 μL of TFA (0.2 mmol) were added and the vial was sealed with a crimp cap with a septum. Then an oxygen balloon was attached to the vial and the atmosphere inside the vial was purged three times with a 20 ml syringe. The reaction mixture was shaken briefly, and the vial was placed approximately 2 cm above a 400 nm LED and stirred under irradiation at 25 °C. Reaction progress was followed with visual inspection (colour change from dark brown to pink due to iodine consumption), TLC and GC-FID analysis. After completion of the reaction, the reaction mixture was poured into a 50 mL round bottom flask and diluted with DCM. Silica was added, the solvent was evaporated from the suspension and the residue was used as dry load for column chromatography on a Biotage® IsoleraTM Spektra. Petroleum ether and ethyl acetate were used as a mobile phase in all cases. A 10 g column was employed with silica gel of type 60 M (40-63 μm, 230-440 mesh) by Merck as a stationary phase.

Acknowledgements

This work was supported by the German Science Foundation (DFG) (GRK 1626, Chemical Photocatalysis), Slovenian Research Agency (P1-0134), bilateral project (BI-DE/18-19-013) and an Erasmus+ scholarship for RN. We thank Dr. Rudolf Vasold (University of Regensburg) for his assistance in GC-MS measurements, Dr. Melita Tramšek (Jožef Stefan Institute) for her assistance in Raman spectroscopy measurements and Regina Hoheisel (University of Regensburg) for her assistance in CV measurements.

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FULL PAPER

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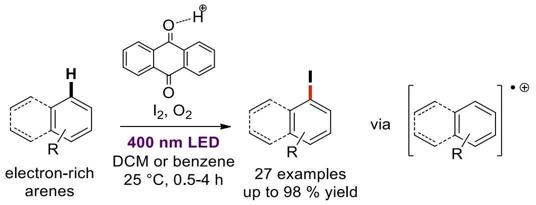

● visible light-driven iodination ● mechanistic investigation ● gram-scale reaction