

# Bromide Controlled Hydrazo Coupling of Phenols and Anilines via Organic Photocatalysis

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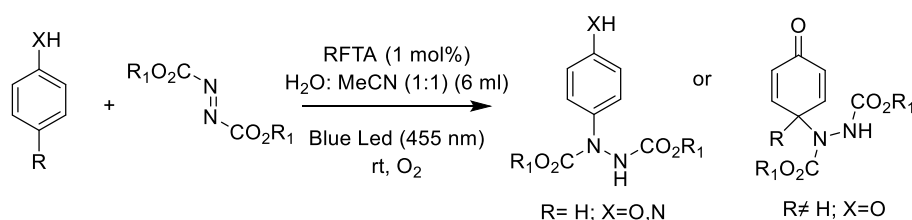
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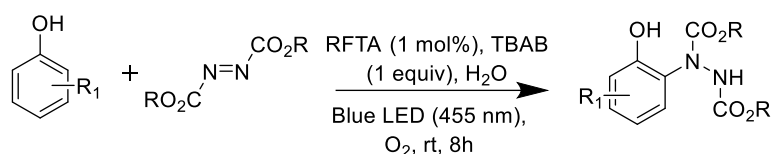
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Phenols and anilines are the most common and critical structural entities subsists in natural products, agro-materials, and bioactive compounds.<sup>1</sup> The *para*- selective cross aminative coupling in phenols or anilines is a significant demand as their *para*- amino derivatives occur in many essential drug molecules, dyes and natural products.

Here an efficient organic photocatalytic *para*- selective amination and aminative dearomatization of phenols and anilines with azodicarboxylates is developed. The formation of *para*- amino phenol or aniline and *para*- amino cyclohexadinone depends whether it has a *para*- substitution or not. The use of organic photocatalyst riboflavin tetraacetate (RFTA) is successfully demonstrated to avoid metal contamination. The reaction condition is simple and mild giving high selectivity with good to excellent yield. A broad substrate scope and nice functional group tolerance, with scalability and post functionalization makes the protocol worthy one.



The ortho selective amination of phenol was achieved with active participation of bromide anion (TBAB = tetrabutyl ammonium bromide) under same catalytic conditions.



**Keywords:** Phenol, Aniline, Azodicarboxylates, Organic photocatalysis, Riboflavintetraacetate

**References:** 1. a) M. Weber, M. Weber and M. Kleine-Boymann, *Ullmann's Encyclopedia of Industrial Chemistry*, 2000; b) J. H. P. Tyman, *Synthetic and natural phenols*, Elsevier, 1996; c) Z. Rappoport, *The chemistry of phenols*, John Wiley & Sons, 2004; d) S. Quideau, D. Deffieux, C. Douat-Casassus and L. Pouységu, *Angewandte Chemie International Edition*, 2011, **50**, 586.

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at

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**IIT, Indore**

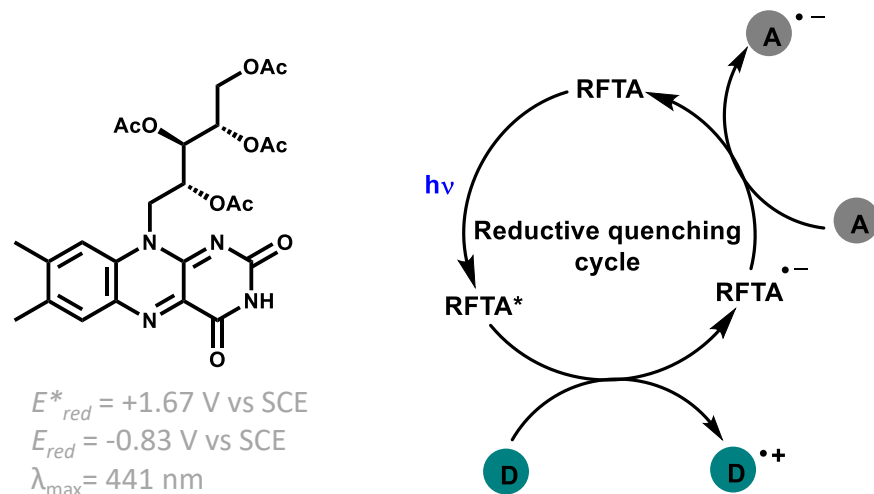


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- Introduction
- *para*-selective amination of phenols
- *ortho*-selective amination of phenols
- Conclusion
- Acknowledgement

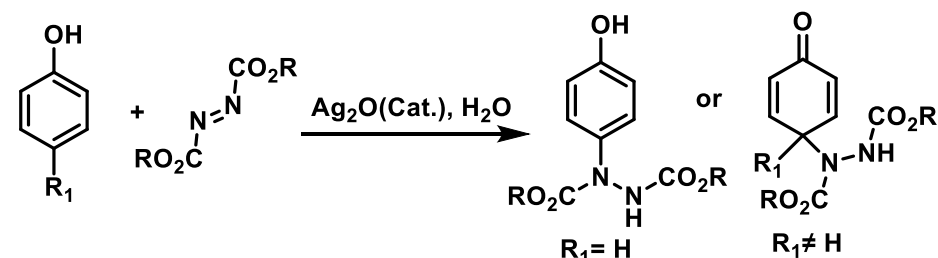
# Introduction

## ☐ Riboflavin Tetraacetate (RFTA)



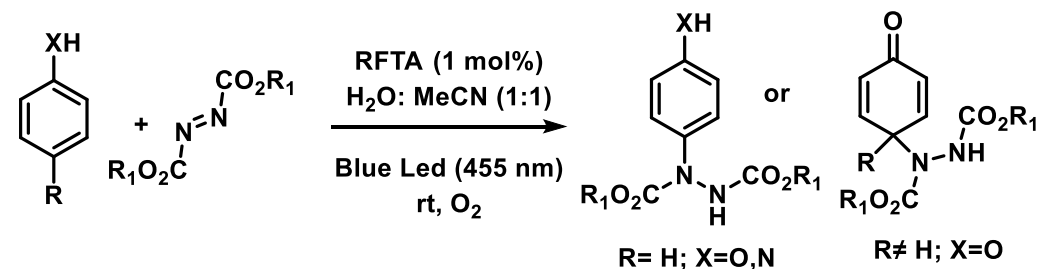
It can oxidise a wide range of organic molecules

## ☐ Hydrazo-coupling of Phenols

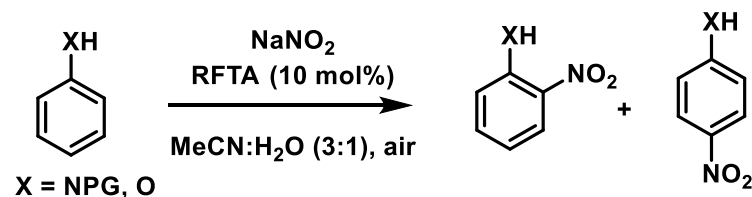


R Zhao, Z Zhou, J Liu, X Wang, Q Zhang, D Li *Org. Lett.* **2020**, *22*, 8144–8149

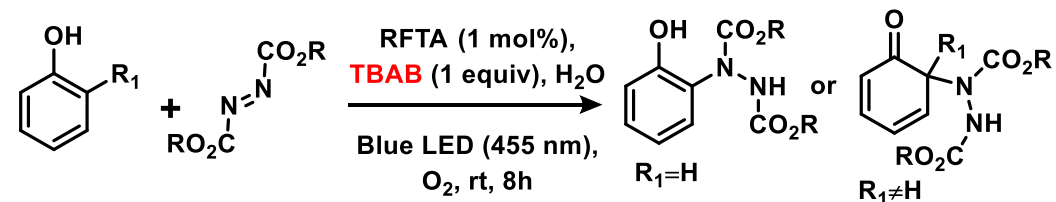
This work:



## ☐ RFTA Catalysed Nitration



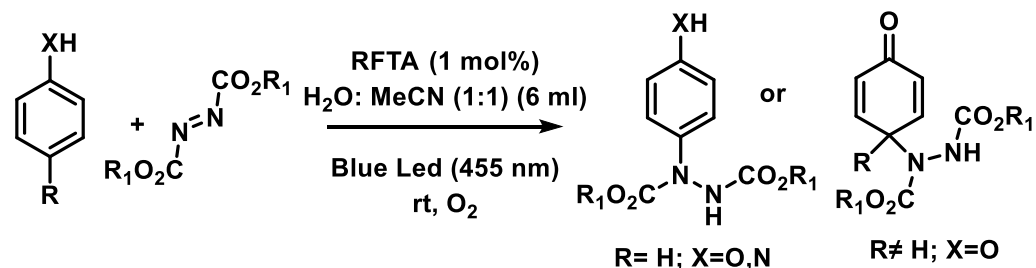
S.J.S Dusel, B. Konig *J. Org. Chem.* **2018**, *83*, 2802–2807



TBAB : Tetra butyl ammonium bromide



# para-selective amination of phenol

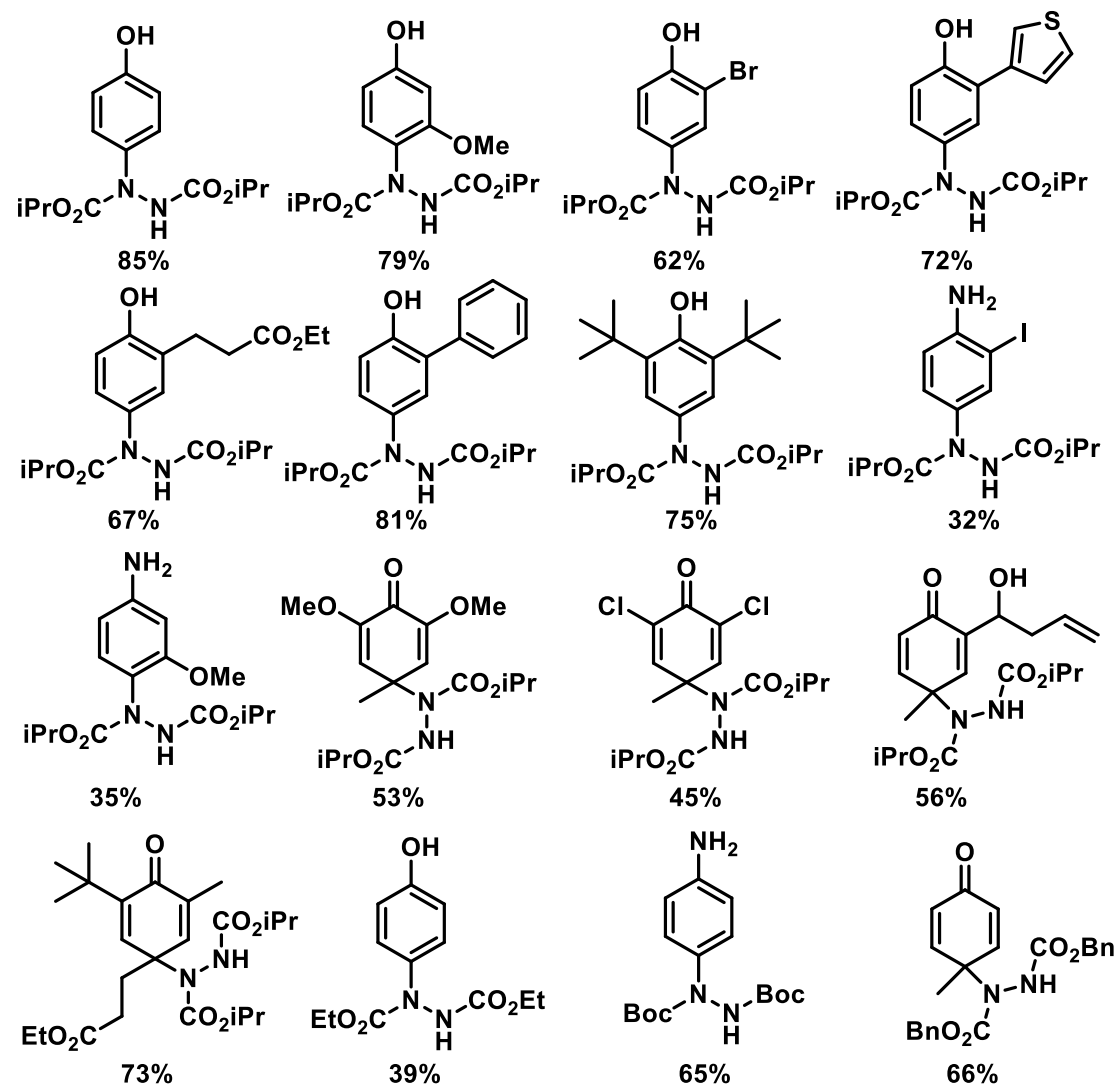


## Condition Optimization

Entry	Deviation from the standard condition <sup>a</sup>	Product Yield (%) <sup>b</sup>
1.	None	85
2.	Riboflavin instead of RFTA	trace
3.	4CzIPN (5 mol%) instead of RFTA	80
4.	[Ir(ppy) <sub>2</sub> (dtbbpy)]PF <sub>6</sub> (2 mol%) instead of RFTA	82
5.	H <sub>2</sub> O as solvent	53
6.	MeCH : H <sub>2</sub> O(1:4) as solvent	69
7.	Green LED instead of Blue LED	trace
8.	Sunlight instead of Blue LED	10
9.	No light	n.d
10.	No photocatalyst	trace

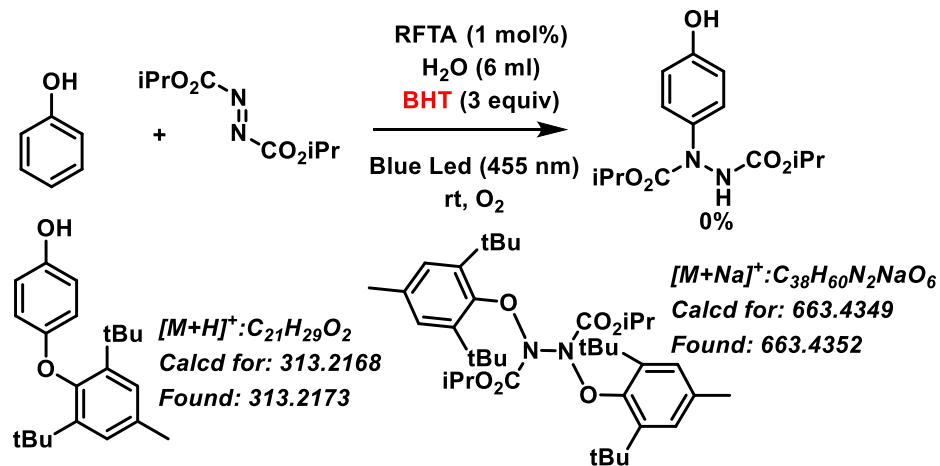
<sup>a</sup>Standard reaction conditions: Phenol (0.2 mmol), Diisopropyl azodicarboxylate (0.4 mmol), and RFTA (1 mol%) in MeCN-H<sub>2</sub>O mixture of 1:1 ratio (6 mL) irradiated with blue LED at room temperature for 1 hour under O<sub>2</sub> atmosphere. <sup>b</sup>Isolated yield.

## Substrate Scope

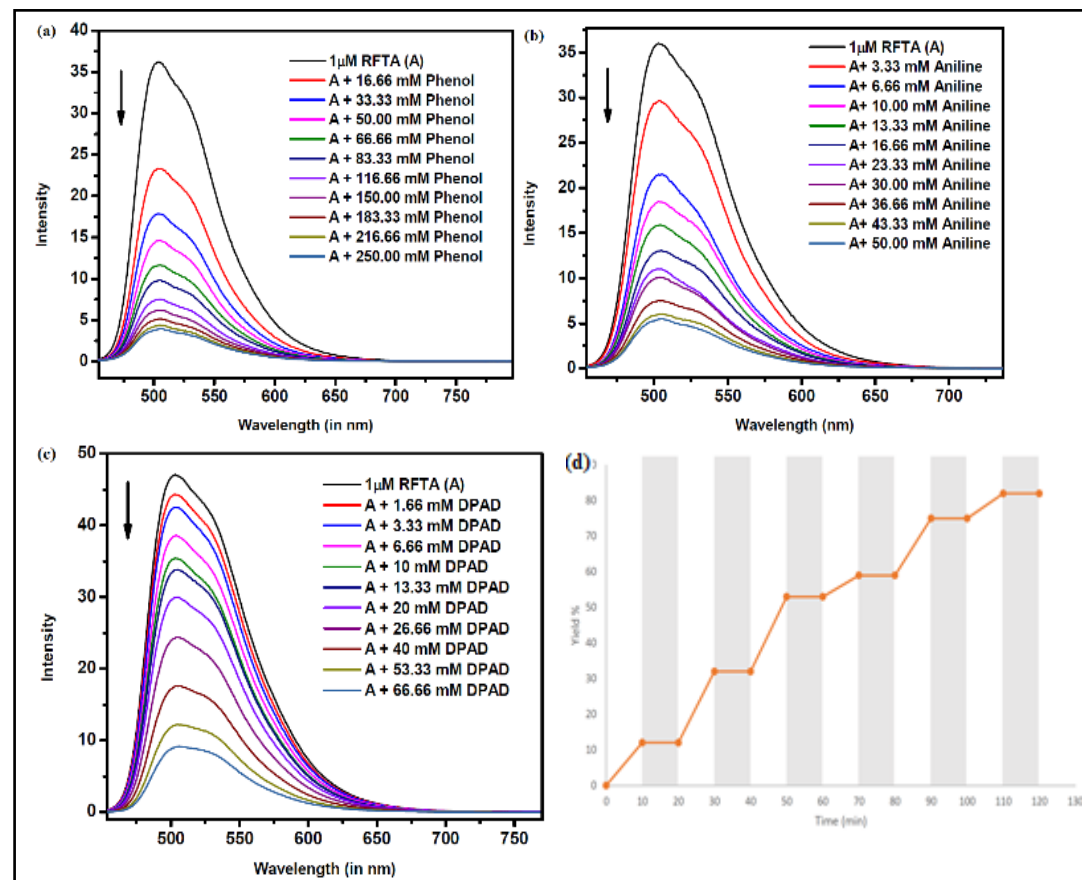


# *para*-selective amination of phenol

## □ Mechanistic Investigation



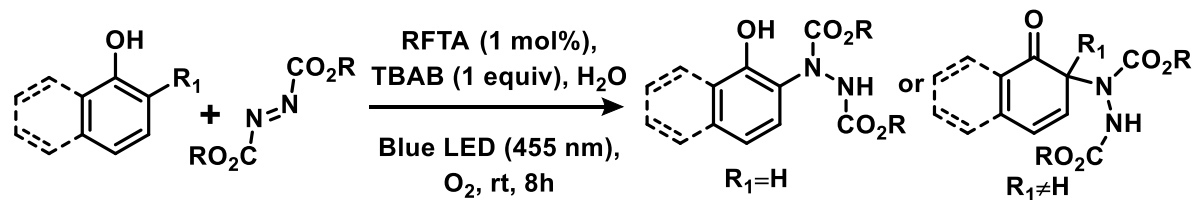
- Free radical mechanism
- RFTA (excited at 440 nm) got successfully quenched by phenol, aniline and diisopropylazodicarboxylate (DPAD) showing Stern-Volmer constant ( $K_{SV}$ ) of **105.4 M<sup>-1</sup>**, **32.5 M<sup>-1</sup>** and **52.2 M<sup>-1</sup>**.
- Light/dark experiment showed productive reaction need constant irradiation.
- The generation of H<sub>2</sub>O<sub>2</sub> was confirmed from starch/KI test.
- Quantum yield ( $\Phi$ ) for the reaction among phenol and DPAD was found to be **6.15**.
- Chain reaction process is occurring for very short period like second or sub-second time scale. <sup>a</sup>



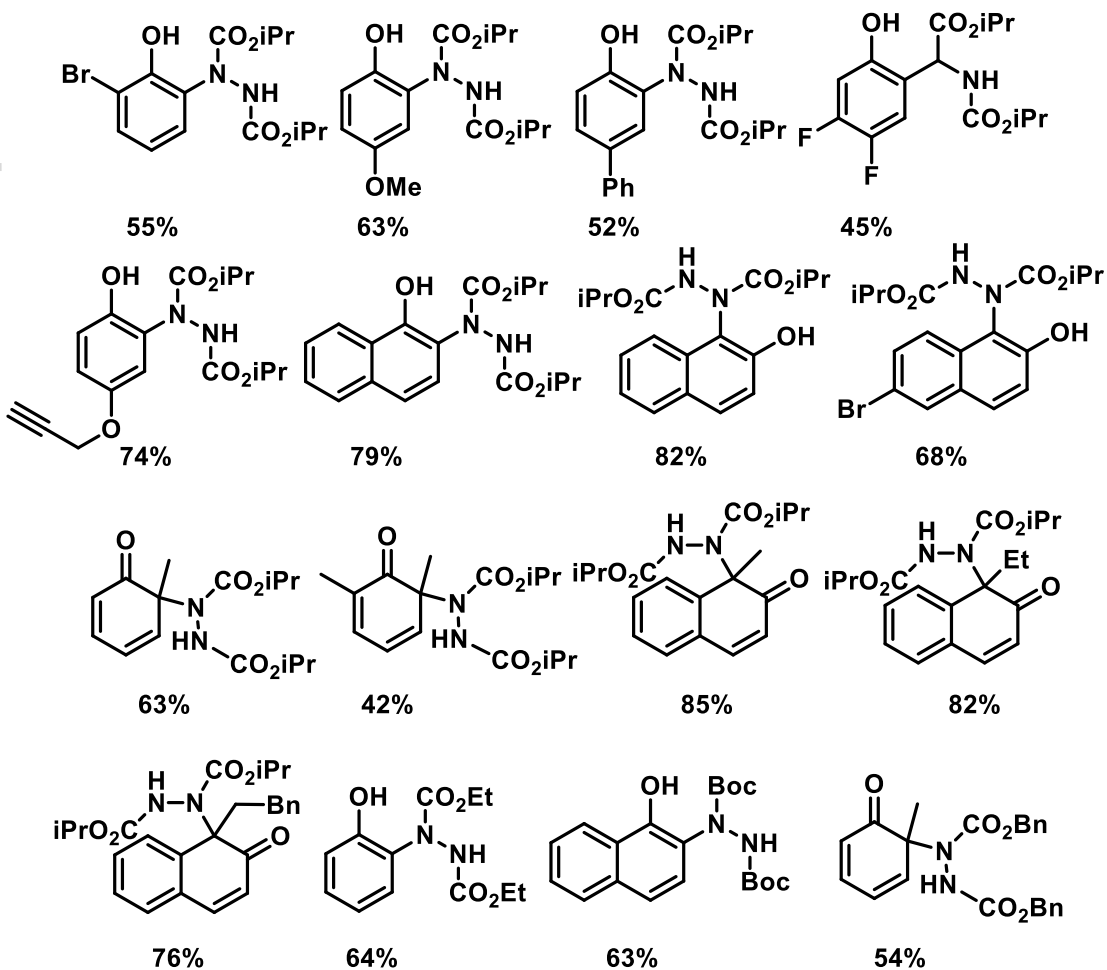
Fluorescence quenching of RFTA (1 μM in MeCN) upon titration with (a) phenol, (b) aniline and (c) DPAD; (d) Light/dark experiment



# ortho-selective amination of phenol



## Substrate Scope



## Reaction Condition Optimization

Entry	Deviation from the standard condition <sup>a</sup>	Yield (%) <sup>b</sup>
1.	None	76
2..	Riboflavin instead of RFTA	Trace
3.	4CzIPN (5 mol%) instead of RFTA	54
4.	MeCN : H <sub>2</sub> O(1:1) as solvent	70
5.	KBr instead of TBAB	23
6.	Br <sub>2</sub> instead of TBAB	n.d.
7.	Benzyl triethyl ammonium chloride instead of TBAB	35
8.	TBAI instead of TBAB	trace
9.	Sunlight instead of Blue LED	trace
10.	No light	n.d.
11.	No photocatalyst	n.d.

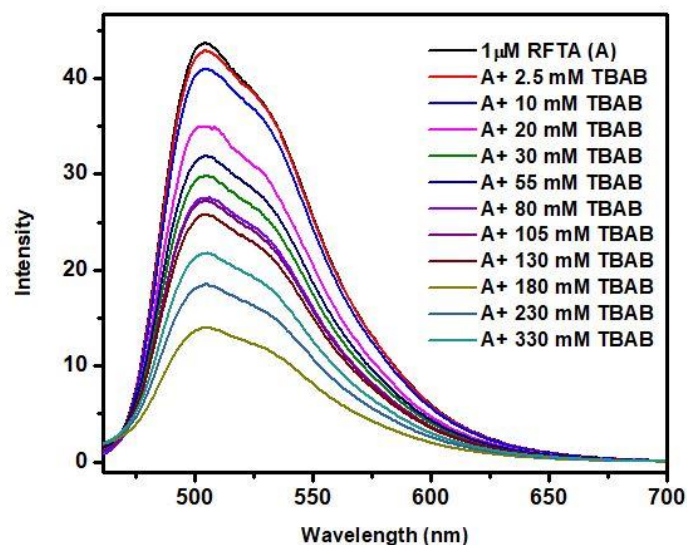
<sup>a</sup>Standard reaction conditions: **Phenol** (0.2 mmol), **DPAD** (0.4 mmol), RFTA (1 mol%) and TBAB (0.2 mmol) in H<sub>2</sub>O (6 mL) irradiated with blue LED at room temperature for 8 hour under O<sub>2</sub> atmosphere. <sup>b</sup>Isolated yield.



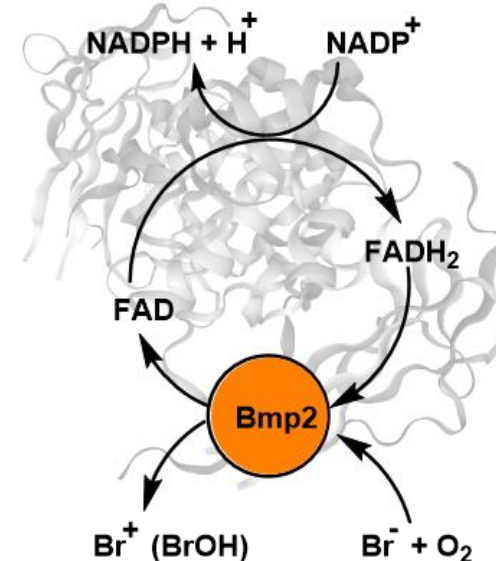
# ortho-selective amination of phenol

## □ Mechanistic Investigation

- The reaction do not proceed in presence of radical scavenger like BHT.
- RFTA successfully quenched by TBAB.
- Quantum yield ( $\Phi$ ) for the reaction among phenol and DPAD under the optimized condition was found to be **0.69 (69%)**.
- Generation of  $H_2O_2$  was confirmed from starch/KI test.
- The organic photo-catalytic process mimics the flavin dependent brominase (Bmp5, Bmp2)<sup>a</sup>.



Fluorescence quenching of RFTA (1  $\mu$ M in MeCN) upon titration with TBAB



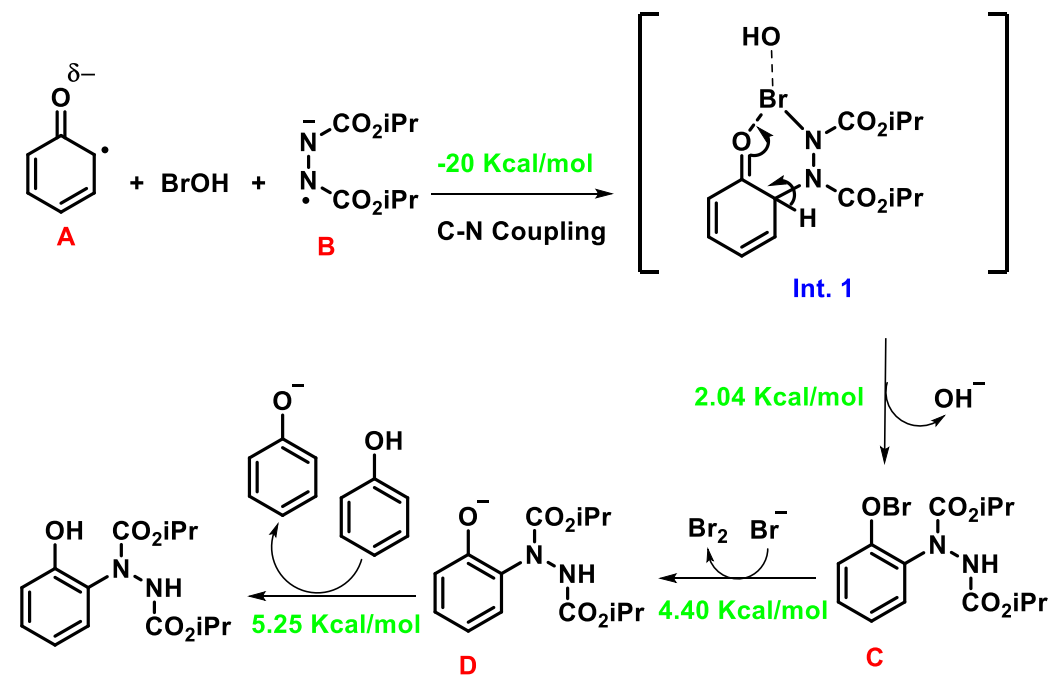
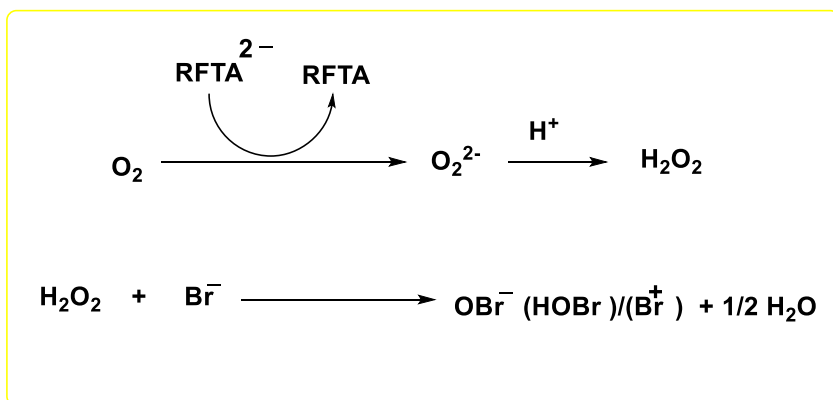
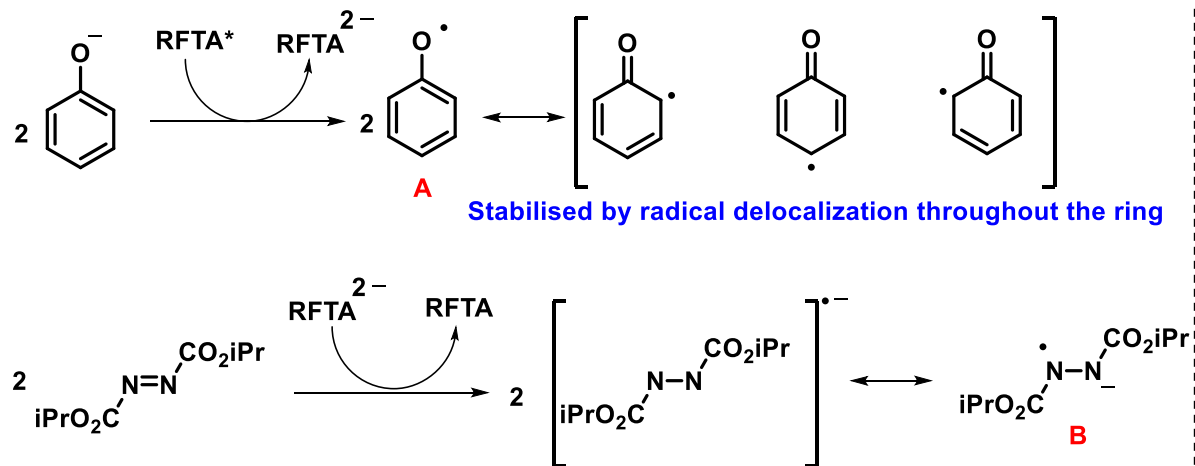
In vitro Formation of bromonium ion by Bmp2

<sup>a</sup> V. Agarwal, A. El Gamal, K. Yamanaka, D. Poth, *et. al. Nat. Chem. Biol.* **2014**, *10* (8), 640–647;

A. El Gamal, V. Agarwal *Proc. et. al. Natl. Acad. Sci. U. S. A.* **2016**, *113* (14), 3797-3802

# ortho-selective amination of phenol

## Plausible Mechanism

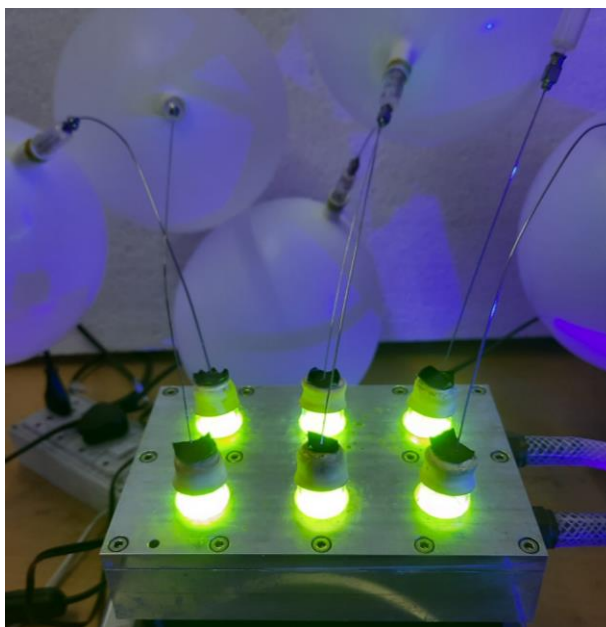


Every species involved has been fully optimized at the B3LYP-D3/6-31+G\*\*

# Conclusion

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- An organic photocatalytic process for *ortho*- or *para*-selective amination and aminative dearomatization of phenols and anilines is disclosed.
- The *ortho*- or *para*-selectivity is controlled by bromide salt (TBAB).
- The protocol uses mild conditions such as visible light, room temperature and water as solvent.



Reaction Set-up



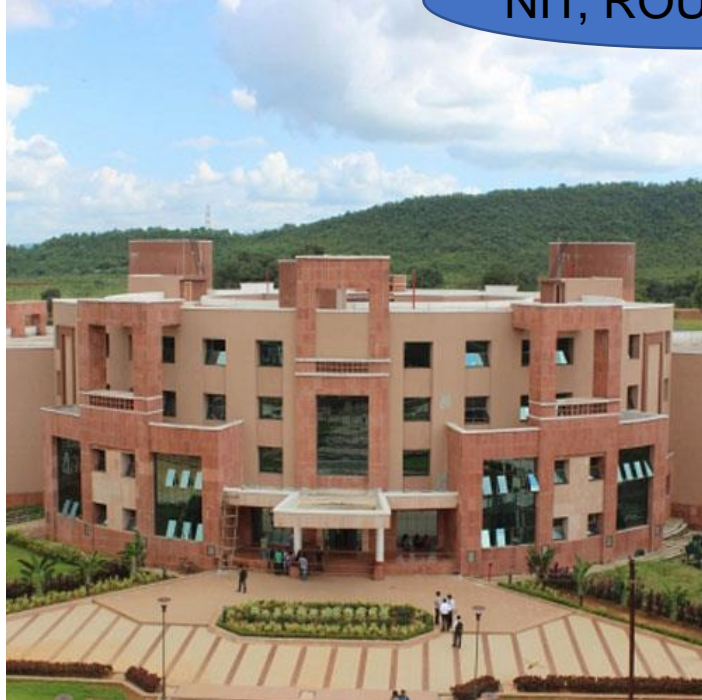
# Acknowledgement

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- I acknowledge my supervisor Dr. Debayan Sarkar for his sincere guidance.
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- I acknowledge all my lab mates seniors and juniors.
- I acknowledge NIT, Rourkela for providing research facility .
- I acknowledge The Almighty.

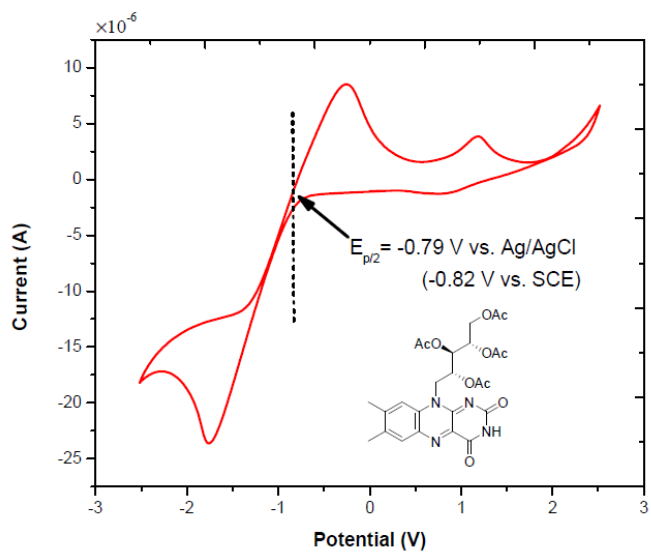
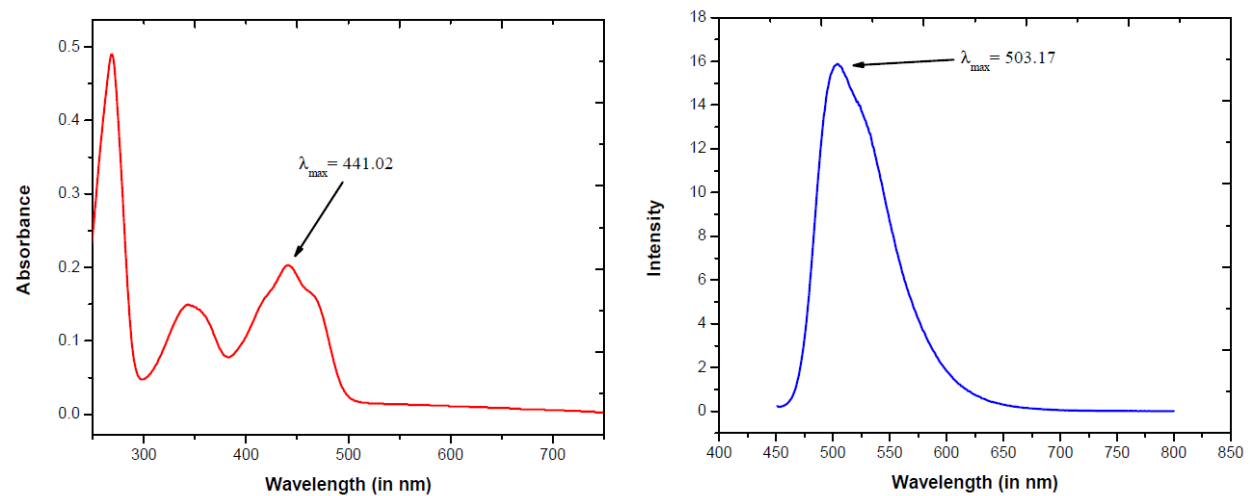


NIT, ROURKELA

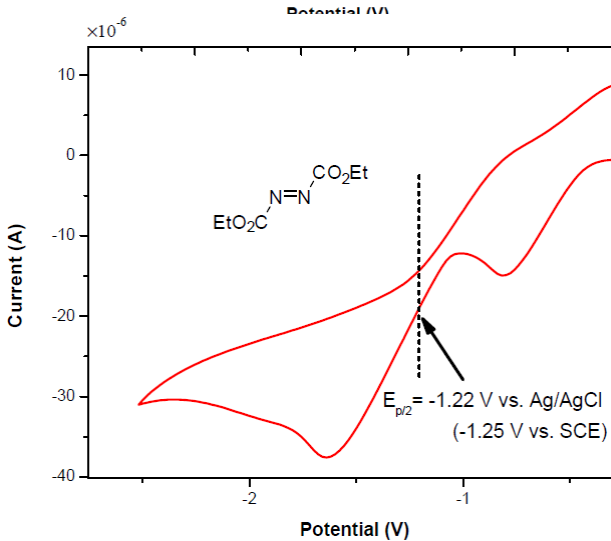
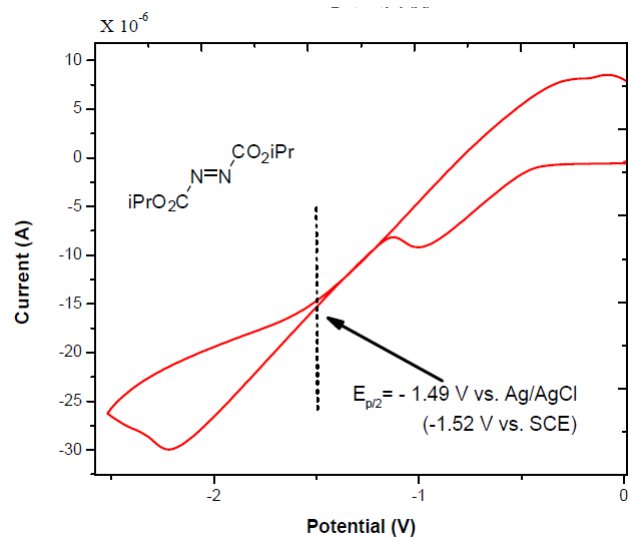
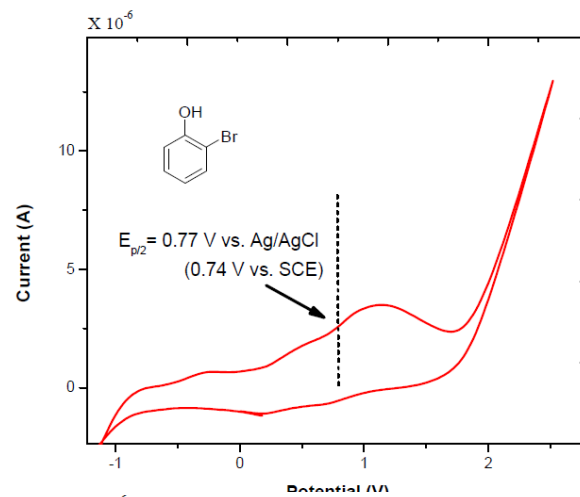
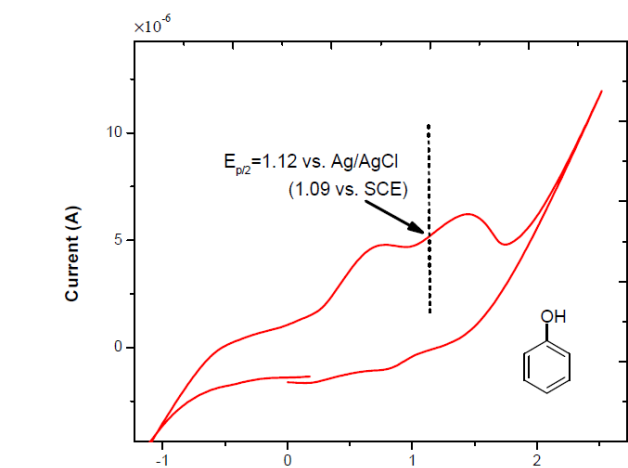


**THANK YOU**

## Characterization of RFTA

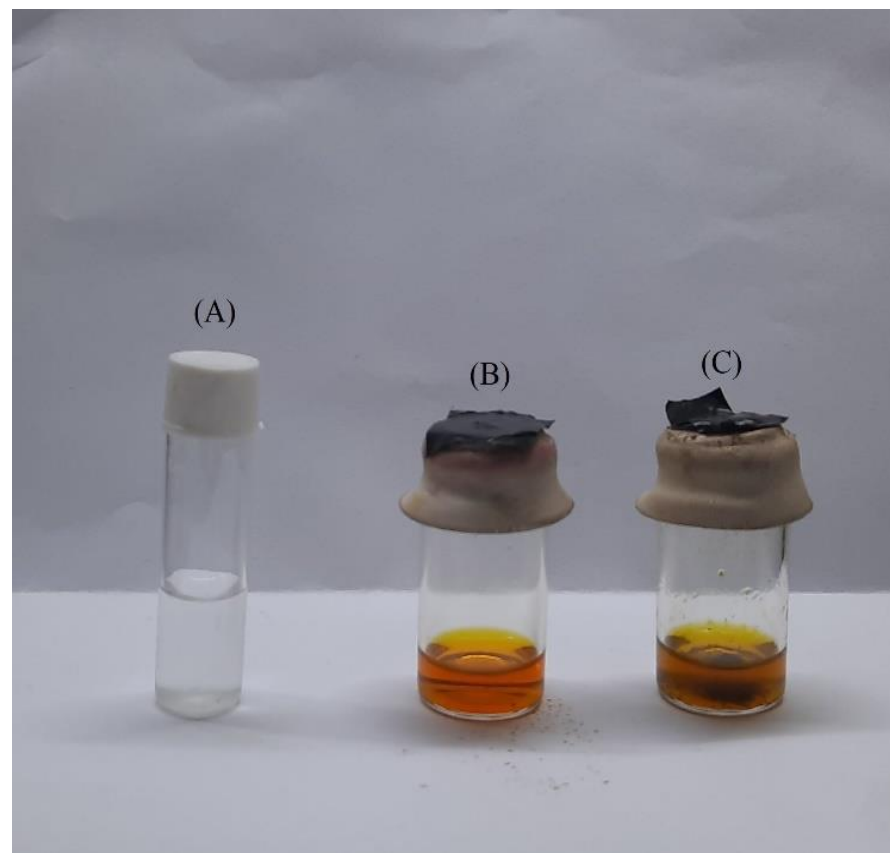


# CV Experiment



## □ Starch/KI Test

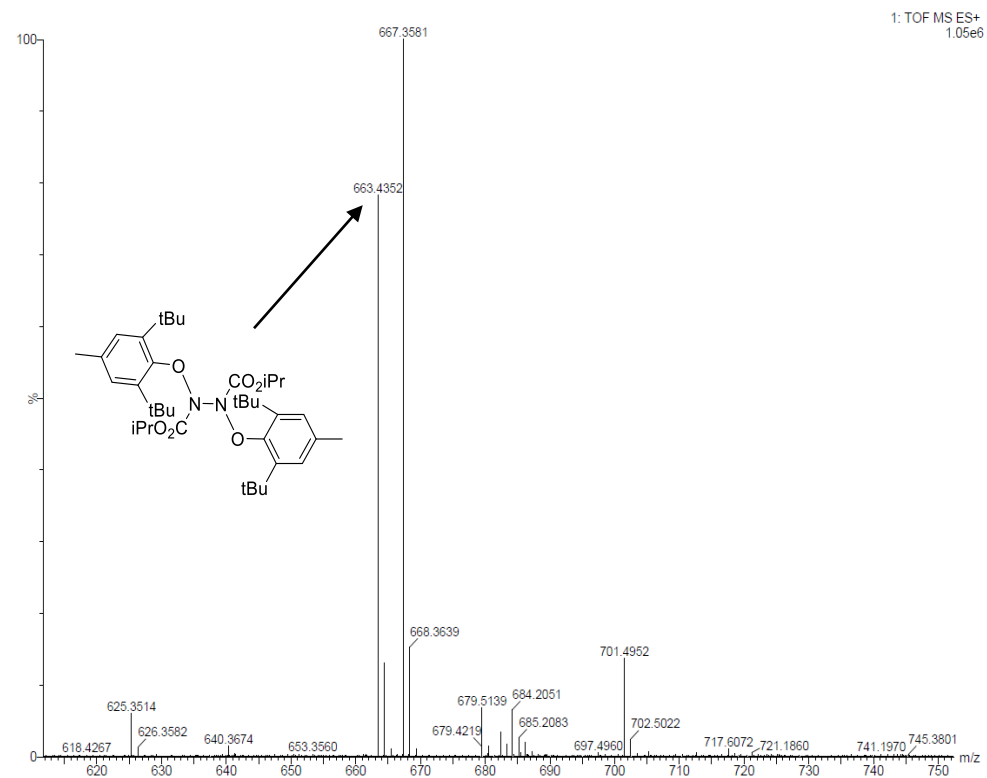
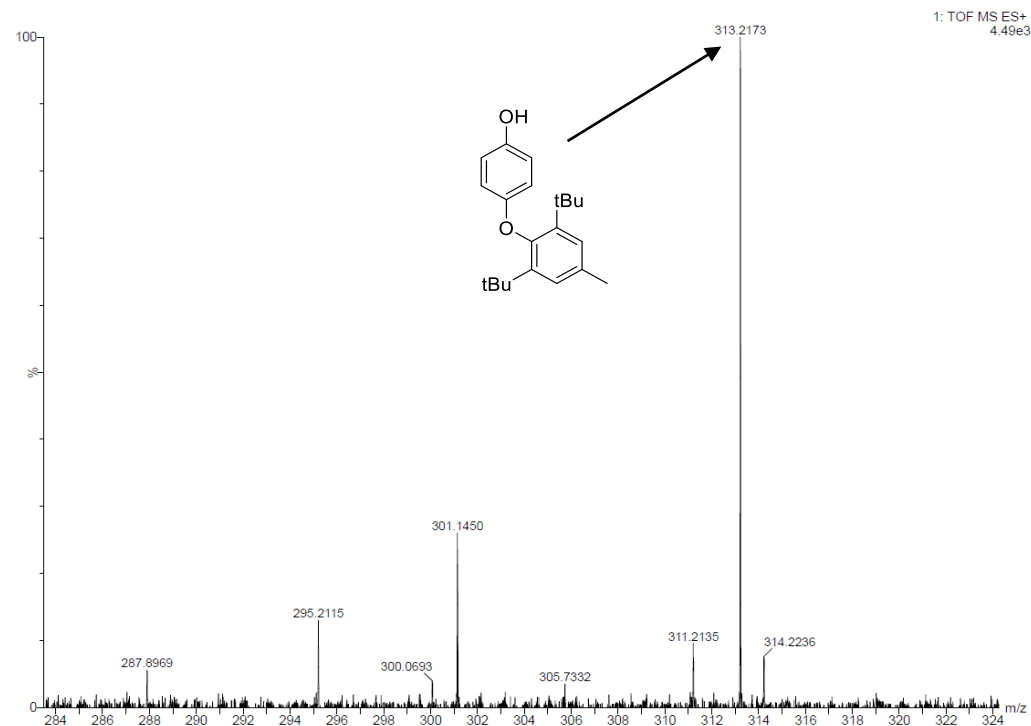
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(A) KI/Starch solution in  $H_2O$ , (B) The reaction mixture after completion of reaction (C) The mixture of reaction mixture after completion of reaction and 100  $\mu L$  of solution A



## Radical Trapping



## Quantum Yield Calculation

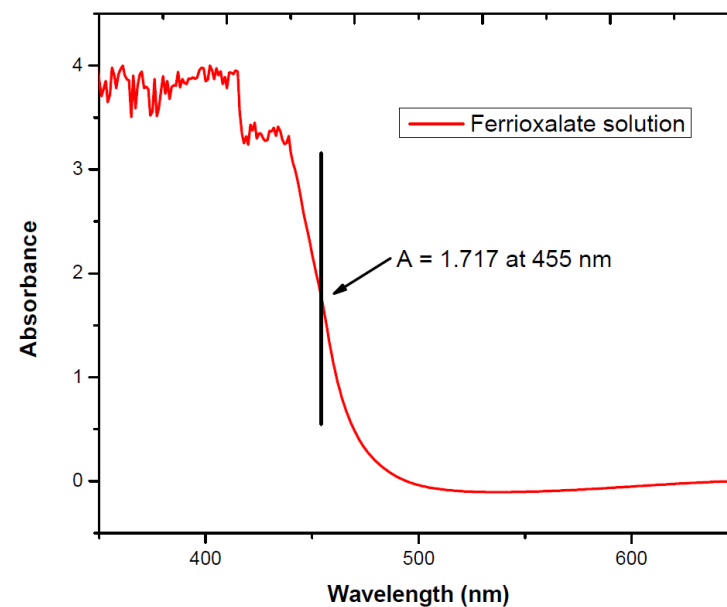
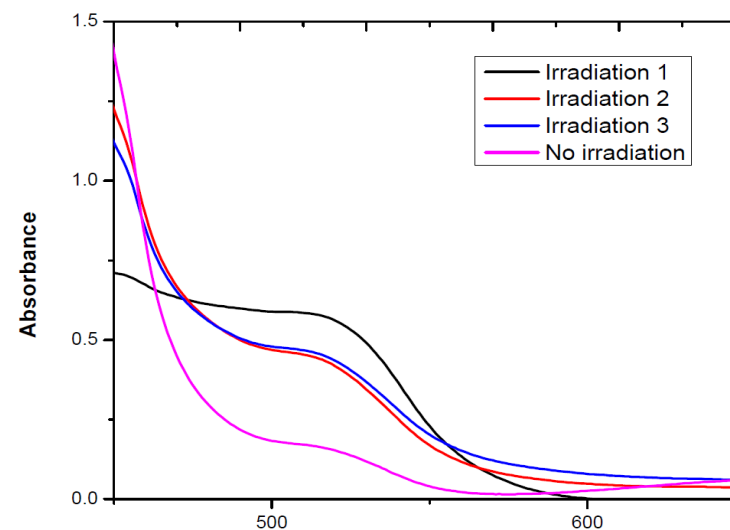
$$\text{photo flux} = \frac{\text{mol Fe}^{2+}}{\Phi \cdot t \cdot f} \quad (1)$$

$$\text{photo flux} = \frac{1.43 \times 10^{-7}}{0.84 \cdot 90.0 \text{ s} \cdot 0.98081} = 1.92 \times 10^{-9} \text{ einstein s}^{-1}$$

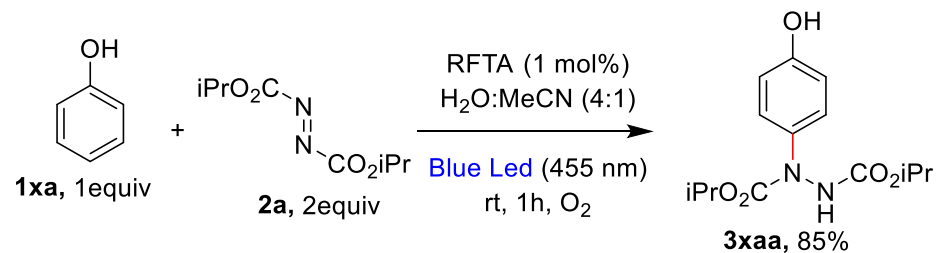
Where  $\Phi$  is the quantum yield for the ferrioxalate actinometer (0.84 for a 0.15 M solution at  $\lambda = 455 \text{ nm}$ )<sup>11</sup>,  $t$  is the time (90.0 s), and  $f$  (0.98081) is the fraction of light absorbed at 405 nm by the ferrioxalate actinometer. This value is calculated using eq 3 where  $A$  (1.717) is the absorbance of the ferrioxalate solution at 455 nm. The photon flux was calculated (average of three experiments) to be  $1.92 \times 10^{-9} \text{ einstein s}^{-1}$ .

$$f = 1 - 10^{-A} \quad (2)$$

$$f = 1 - 10^{-1.717} = 0.98081$$



## Quantum Yield Calculation



A reaction vessel was charged with **1x** (0.05 mmol, 1 equiv), **2a** (0.1 mmol, 2 equiv), RFTA (0.0005 mmol, 1 mol%), and 1.0 mL H<sub>2</sub>O-MeCN (1:1) mixture. The vial was then capped with a septum and purged with O<sub>2</sub>. The sample was stirred and irradiated ( $\lambda = 455$  nm, slit width = 0.5 mm) for 3600 s. After irradiation, the solution was passed through a silica plug. The yield of **3xaa** was determined to be 85% ( $4.25 \times 10^{-5}$  mol) by <sup>1</sup>H NMR using mesitylene as internal standard. **f** is fraction of incident light absorbed by RFTA and was calculated by eq4. The quantum yield ( $\Phi$ ) was determined using eq3 and found to be **6.15**.

$$\Phi = \frac{\text{mole product}}{\text{flux} \cdot t \cdot f} \quad (3)$$

$$\Phi = \frac{4.25 \times 10^{-5}}{1.9 \times 10^{-9} \cdot 3600 \cdot 0.999} = 6.15$$

$$\text{fraction of light absorbed (f)} = 1 - 10^{-2.969} = 0.999$$

