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Article

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Organocatalytic visible light enabled S_NAr of heterocyclic thiols: a Metal-free approach to 2-aminobenzoxazoles and 4-aminoquinazolines

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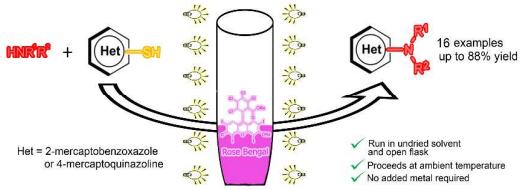


The direct amination reaction of heterocyclic thiols has been developed in the presence of the nonhazardous photocatalyst Rose Bengal under irradiation of visible light. The reaction provides a straightforward approach to pharmaceutically and synthetically useful to 2-aminobenzoxazole and 4-aminoquinazoline derivatives from the corresponding heterocyclic thiols with amines in good to excellent yields. Our photochemical reaction can be successfully adapted into continuous flow reactor which is applicable for large scale chemical industry. The key benefits of this reaction include the use of metal-free, low cost Rose Bengal catalyst and practical operation (ambient temperature, open flask and undried solvents).

KEYWORDS: Nucleophilic aromatic substitution; photochemistry; photoredox catalysis; Rose Bengal; Amination

1. Introduction

Amino heterocycle is a class of building block that attracts many interests in the pharmaceutical industry due to their broad spectrum of biological activities.[1] Many therapeutic agents in which amino group are attached to various *N*-heterocycles including benzoxazole and quinazoline are substructure for many therapeutically important molecules,[2] for example **1** (anti-HIV), Suvorexant (soporific drug), Gefitinib (EGFR inhibitor) and Prazosin (antihypertensive) (Figure 1).

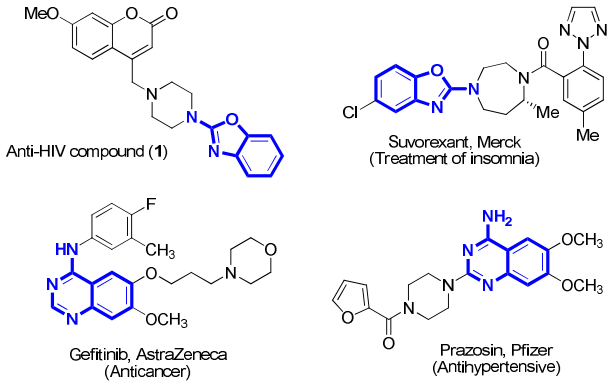


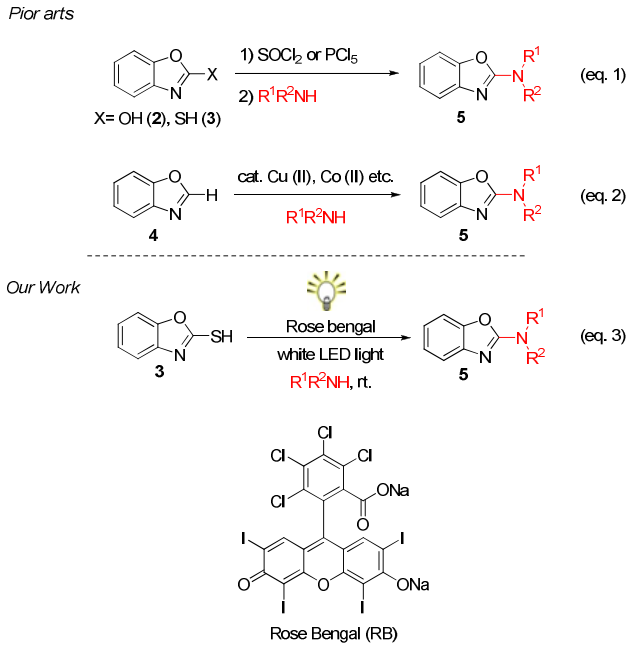
Figure 1. Selected examples of bioactive compounds with amino heterocycle scaffold.

Traditional methods to prepare such amino heterocycles involve the construction of C–N bonds from either corresponding hydroxyl/thiol derivatives or heterocycles. For example, 2-aminobenzoxazole (**5**)

can be synthesized from activation of either hydroxyl or thiol group in 2-hydroxyl (**2**) or mercaptobenzoxazole (**3**) respectively, into aryl halide followed by a S_NAr displacement with amines (Scheme 1, eq. 1). Even though those reactions are very efficient and straightforward but the use of toxic and acidic halogenating agents such as $SOCl_2$, $POCl_3$ and PCl_5 cannot be avoided.[3] If labile function is presented, an extra protection step is necessary. Recently, direct C–H amination of benzoxazole (**4**) into target amino compound (**5**) was introduced.[4] The use of transition metal such as Cu, Ag, Mn, Co and Fe[5] provided the amination product (**5**) in just one step (Scheme 1, eq. 2). Although this reaction is very atom economic, however, it needs high temperature, toxic metal or addition of co-oxidant. From process chemistry perspective, the use of hazardous reagent and toxic metal would increase operating cost in large-scale production of pharmaceuticals as extra safety protocols and metal removal step are needed. Therefore, a mild, scalable and metal-free approach for amino heterocycle synthesis would be highly desirable.

In recent years, photochemical reaction mediated by visible light has drawn a significant attention in the organic synthesis community. It provides a great tool for robust and environmentally friendly transformation.[6] Many photocatalytic reactions under visible light was able to transform thiols into a variety of organosulfur compounds via the formation of thiyl radical intermediate. For example, the construction of S–C bond was pioneered by Yoon via radical thiol-ene coupling reaction.[7] Oxidation of thiols using visible light photocatalytic reaction into disulfides[8] and sulfoxide[9] were reported. Also, oxidative cross-coupling reaction between thiols with diazonium,[6c] and organophosphate[10] were investigated.

Scheme 1. Synthetic approach to 2-aminobenzoxazole (**5**).



Taking an inspiration from the versatility of he thiol chemistry, we aim our attention to use heterocyclic thiols, for green conversion to heterocyclic amine by a photocatalytic S_NAr amination reaction. Many heterocyclic thiols are commercially available or easily prepared from thiolation of the corresponding heterocyclic alcohols with inexpensive and low toxicity reagents such as Lawesson's reagent or P_4S_{10}.[11] Herein, we present our development of metal-free amination of heterocyclic thiols for synthesis of amidine compounds in the presence of inexpensive and low toxic organic dye, Rose Bengal, as a photocatalyst with visible light irridiation (Scheme 1, eq.3). The reaction is also developed for continuous flow systhesis.

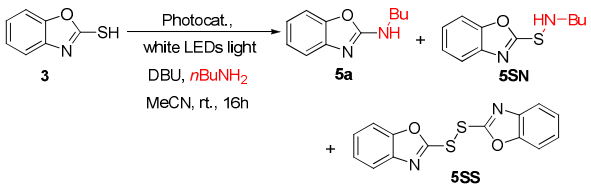
2. Result and discussion

2.1 Reaction optimization

We screened common photoredox catalysts in an amination reaction between 2-mercaptobenzoxazole (**3**) and *n*-butylamine under irradiation by white LED (Table 1). Carrying out the reaction in the presence of transition metal photoredox catalyst, $Ru(byp)_3Cl_2$ resulted in a low yield of desired amination product

5a (17%) with a significant amount of disulfide product (**5SS,** 10%) (Table 1, entry 1). Although there are many reports on efficient catalytic photoredox transformations with metal complex dyes, their high price and toxicity seem to limit their applications. Recent pursuit of environmentally benign photocatalyst has focused on commercially available and inexpensive metal-free organic dyes such as EosinY and Rose Bengal.[12] With the trend of more environmental friendly metal-free catalysis, it is thus advantageous to test some organic dyes as catalysts for this reaction. To our delight, both Rose Bengal and EosinY gave significantly higher yields of amine **5a** than that with $Ru(byp)_3Cl_2$ (Table 1). In comparison with EosinY, Rose Bengal gave a better yield without the formation of sulfenamide (**5SN**) side product.[13] When the reaction was performed in the absence of catalyst under LED irradiation, only starting material **3** was partially recovered. The result confirmed that the photoredox catalyst is essential for this substitution reaction.

Table 1. Screening of photocatalysts.[a]

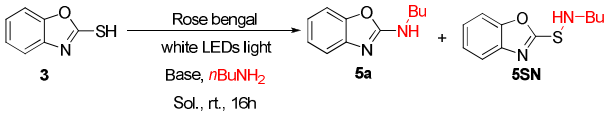


Entry	Photo-catalysts	Yield[b] (%)		
		5SN	**5a**	**5SS**
1	$Ru(byp)_3Cl_2$	-	17	10
2	EosinY	12	41	-
3	Rose Bengal	-	54	-
4c	No catalyst	-	-	-

[a]Reaction Conditions: 3 (1.00 equiv), nBuNH$_2$ (5.00 equiv.), DBU (5.00 equiv.) and catalyst (3 mol%) in MeCN (0.1 M) and stirred at rt. for 16 h. [b]Isolated yield with silica gel chromatography. [c]3 was recovered with 24% recovery.

With this promising results in hands, solvents, bases and amount of catalyst were examined in the presence of Rose Bengal as a photocatalyst (Table 2). Among the solvent screened, acetonitrile gave the best yield of amination product **5a** (Table 2, entries 1-4). In the absence of DBU, no sulfenamide product **5SN** was obtained and only amino **5a** and unreacted starting material **3** were isolated (Table 2, entry 5). The choice of bases is critical in the reaction selectivity and efficiency. DBU promote the formation of **5a** exclusively in 54% yield, while potassium carbonate (K_2CO_3) gave lower yield and diisopropylamine (DIPEA) also gave **5SN** side product (Table 2, entries 6-7). When the catalyst loading was increased to 10% mol, product **5a** was generated solely in 78% yield prompting us to use this as for further study (Table 2, entry 8). It is important to note that the reaction performed in degassed solvent under nitrogen atmosphere surprisingly, gave lower yield of the desired product **5a** along with the side product **5SN** (Table 2, entry 9). This result suggested that oxygen involved in the amination process.

Table 2. Optimization of the reaction conditions.[a]



Entry	Rose Bengal (mol %)	Base (eq.)	Solvent	Yield[b] (%)		
				5SN	**5a**	**3**
1	3	DBU (5.0)	MeCN	-	54	-
2	3	DBU (5.0)	Toluene	19	32	-
3	3	DBU (5.0)	^{i}PrOH	-	36	27
4	3	DBU (5.0)	H_2O:MeCN	-	37	17
5	3	-	MeCN	-	6	39
6	3	DIPEA (5.0)	MeCN	37	36	-
7	3	K_2CO_3 (5.0)	MeCN	-	31	-
8	10	DBU (3.0)	MeCN	-	78	-
9[c]	10	DBU (3.0)	MeCN	17	39	5

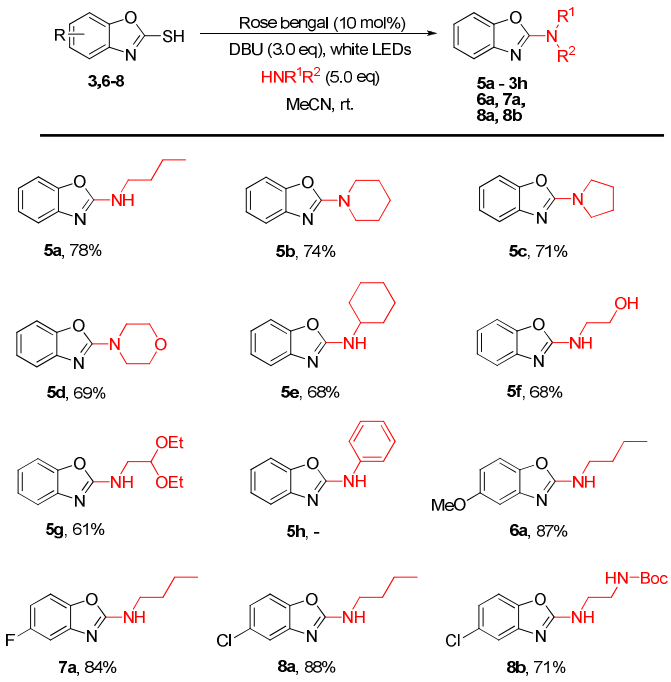
[a]Reaction Conditions: **3** (1.00 equiv), Rose Bengal, nBuNH$_2$ (5.00 equiv.) and base in solvent (0.1 M) at

rt. for 16 h. [b]Isolated yield. [c]Solvent was degassed and reaction was carried out in nitrogen atmosphere.

2.2 Functional group compatibility

With the optimum reaction conditions described above, the scope of the reaction was explored. Various amines were tested with 2-mercaptobenzoxazole (**3**) under the optimized condition (Scheme 2). Primary and secondary amines such as *n* -butylamine, piperidine, pyrrolidine and morpholine reacted smoothly with **3** under the optimized condition, giving desired products (**5a**-**d**) with good isolated yields (69-78%). Steric hindrance on amine had little effect on the reaction yield as cyclohexylamine gave **5e** in satisfactory yield (68%). For ethanolamine, which contains multiple nucleophilic atoms, C–N bond formation occurred selectively, giving product **5f** in 68% yield. Importantly, this transformation is suitable for acid labile functional group such as diethyl acetal group. The product **5g** was obtained in 61% yield as a sole product without any deprotection. Unfortunately, less reactive nucleophile such as aniline failed to react. With successful amination in 2-mercaptobenzoxazole **3**, we then extended the scope of this reaction to other substrates. 2-mercaptoenzoxazoles bearing substituents such as methoxy (**6**), fluoro (**7**) and chloro (**8**) groups were reacted with *n*-butylamine to provide desired products **6a-8a** in excellent yields, respectively. Moreover, the *N*-boc protecting group well tolerated this photoreaction condition as **8b** was obtained in 71% yield.

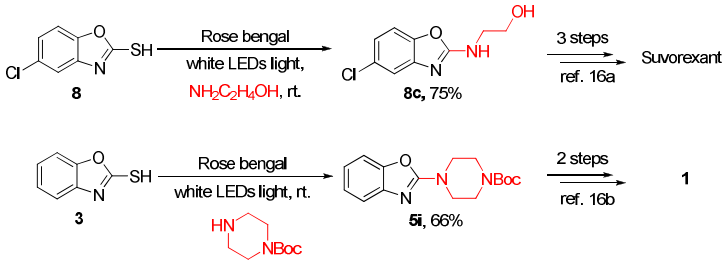
Scheme 2. Amination of benzoxazoles with various amines.



[a]Reaction Conditions: 2-mercaptobenzoxazole derivative (1.00 equiv), Rose Bengal (10 mol%), amine (5.00 equiv.) and DBU (3.00 equiv.) in MeCN (0.1 M) and stir at rt. for 16 h.

With these encouraging results in hand, we highlighted our amination promoted by visible light to perform the formal synthesis of two bioactive compounds containing amino-2-benzoxazole core such Suvorexant and **1** (Scheme 3). The former is a potent, brain-penetrant dual orexin receptor antagonist which is under phase III clinical trial from Merck &co[14] while the latter is a potent anti-HIV agent.[15] The key intermediates for Suvorexant and **1** were reported as compounds **8c** and **5i** respectively which were prepared from traditional S_NAr reaction of the corresponding halogenated benzoxazole derivatives.[16] Herein, using our method, we were able to prepare **8c** and **5i** smoothly in excellent yields from 2-mercaptobenzoxazoles **8** and **3** respectively. We would like to emphasize here that the use of thiol substrate as a starting material to perform direct amination does not only avoid the use of typical toxic halogenating agent but also the reaction condition is benign and convenient and can be performed at ambient temperature in an open flask system.

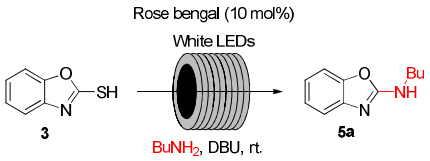
Scheme 3. Formal synthesis of Suvorexant and anti-HIV compound **1.**



2.3 Continuous flow reaction

In the past decade, flow chemistry has gained much attention in organic transformation in the aspect of green chemistry as it is safe, generate low waste, require less solvent and offer possibility of a continuous 24/7 production.[17] Importantly, combining flow chemistry with photoreaction will accelerate the reaction rate because the penetration ability of light increases by high surface area and minimal path length.[18] Due to this feature, we therefore performed the photocatalytic amination of 2-mercaptobenzoxazole **3** using a flow reactor. The mixture of **3**, DBU, *n*BuNH$_2$ and Rose Bengal were pumped into the transparent PFA tube which were surrounded with visible light source (Figure S2). To further understand of this transformation, we conducted a systematic study of two reaction variables: flow rate and reaction concentration (Table 3). Performing the amination of **5a** at 0.02 M concentration afforded 65% conversion at 120 min resident time (Table 3, entries 1). Lowering concentration to 0.01 M, a complete conversion within 60 min of residence time was achieved (Table 3, entries 2-4). Even though the concentration of the thiol crucially affected the reaction efficiency, the present catalytic visible light amination of thiol into amino in a flow reactor can lower the reaction time when compared to the batch reaction.

Table 3. Photocatalytic amination of 2-mercaptobenzoxazole **5a** using micro flow reactor.[a]



Entry	Conc. (M)	Flow rate	Residence	Conversion (%)[b]

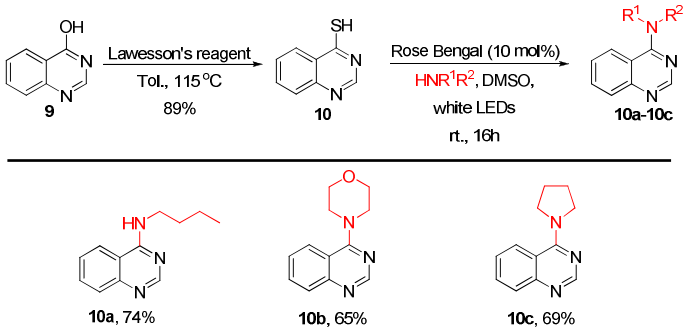
		(μL/min)	time (min)	
1	0.02	43.54	120	65
2	0.01	43.54	120	100
3	0.01	87.08	60	100
4	0.01	174.17	30	33

[a]Reaction were performed in transparent PFA tube (id = 0.8 mm, length = 2.60 meter, volume = 5,225 μL) equipped with white LEDs (1.5 Wx150 Fig. S2). [b]Determined by ^{1}H NMR.

2.4 Amination of 4-mercaptoquinazoline with various amines.

To extend the scope of this new amination method, we turned our attention to use our photoreaction to synthesize 4-aminoquinazolines, a class of compounds which has drawn considerable attention due to its various pharmaceutical effects (Scheme 4).[19] Traditional synthesis of 4-aminoquinazoline derivative often rely on 1) two-step protocol: halogenation of 4-hydroxyqunazoline (**9**) followed by S_NAr displacement with amine[20] or 2) one-step protocol: direct S_NAr of the 4-hydroxyquinazoline (**9**) mediated by phosphonium reagents such as BOP[21] and PyBOP[22]. Those methods however, require toxic and expensive reagents. Here, we first prepared 4-mercaptoquinazoline (**10**) from 4-hydroxyquinazoline (**9**) using Lawesson's reagent.[23] Even though an extra thiolation step is required, but the process is very efficient, no toxic and other additional reagents are required. With the 4-mercaptoquinazoline (**10**) in hands, the photocatalytic amination reaction proceeded smoothly with various amines such as *n*-butylamine, morpholine and pyrrolidine to provide **10a-10c** in good yields (65-74% yield).

Scheme 4. Direct amination of 4-mercaptoquinazoline **10**.

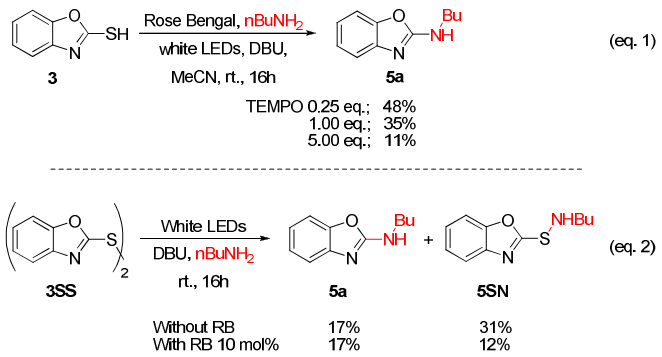


[a]Reaction Conditions: 4-mercaptoquinazoline (1.00 equiv), Rose Bengal (10 mol%), amines (5.00 equiv.) and DBU (3.00 equiv.) in DMSO (0.1 M) and stir at rt. for 16 h.

2.5 Proposed mechanism

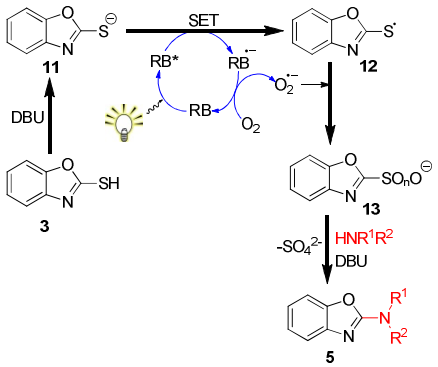
To shed light on the mechanism of this new visible-light-induced amination reaction, several mechanistic experiments were conducted (Scheme 5, eq. 1). When various amount of 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) as radical trapping agent was added to photocatalytic reaction of **3** under the identical reaction condition, the yield of **5a** significantly decreased upon increasing the amount of TEMPO (Scheme 5 eq. 1). Moreover, we carried out a set of electron paramagnetic resonance (EPR) experiment. In the absence of light, weak signal in EPR was observed while a sharp increase in the intensity of this signal was detected upon irradiation with white LED (Figure S3). Both experiments clearly indicated that this reaction is a radical process. We also suspected that disulfide **3SS** might be an intermediate in this transformation as it appeared as by-product in several reactions during optimization studies. Disulfide **5SS** were prepared via oxidation of corresponding thiol with hypervalent iodine based on our previous report.[13a] When subject **5SS** into photocatalytic amination with and without Rose Bengal catalyst, only small amino product **5a** (17% yield) and sulfenamide product **5SN** (12, 31% yield) were isolated. The poor yield of **5a** in this pathway could be explained from two main reasons. First, The S_NAr amination with **5SS** could gave the product but losing half amount of the starting material as it cannot be oxidized back into the original disulfide **5SS**. Second, competitive formation of sulfenamide **5SN** is also occurred.[13] With these observations, S_NAr amination via **5SS** as intermediate is perhaps not a major pathway in our photocatalytic reaction.

Scheme 5. Mechanistic experiments.



Based on above observation, we then proposed our visible-light-mediated amination of heterocyclic thiol mechanism as depicted in Scheme 6. First, 2-mercaptobenzoxazole (**3**) is deprotonated by DBU and transform into thiyl radical **12** via single electron transfer (SET) process catalyzed by Rose Bengal under visible light irradiation. Oxidative coupling between **12** and $O_2^{\cdot-}$ produce a peroxysulfur intermediate (**13**).[24] We hypothesized that **13** is indeed the key intermediate for S_NAr which was consequently attacked by the amine at the carbon atom at C–S bond to produce amino product **5** and liberate SO_4^{2-} as leaving group.

Scheme 6. Proposed reaction mechanism.



3. Conclusions

In summary, an efficient amination of heterocyclic thiols by photocatalytic reaction has been developed. We employed an inexpensive Rose Bengal as a photocatalyst and used commercial LED as a

light source. High functional group generality allowed us to produce various amino heterocycles such as 2-aminobenzoxazole and 4-aminoquinazoline derivatives in moderate to excellent yields in one-pot fashion. Our finding showed a new concept of utilizing the heterocyclic thiols as alternative substrate in S_NAr type reaction to construct C–N bond formation. This mild, cost effective, metal-free visible-light-enabled amination have clearly demonstrated an advantage over existing procedures. As these compounds are important pharmaceutical intermediates, our reaction should be of interest to the pharmaceutical industry. There is high potential for industrial scale up due to its compatibility with flow reactions, as demonstrated herein. Further studies on photocatalytic reaction promoted S_NAr in heterocyclic thiol, its application to more challenging and important amino heterocycles, as well as mechanistic investigations are currently on-going and will be reported in due course

4. Experimental Section

4.1 Materials and methods

All 2-mercaptobenzoxazole derivatives, photo-catalysts and amines were purchased from Sigma–Aldrich, Fluka (Switzerland) or Merck (Germany) and used without further purification. All reactions were carried out under an air atmosphere. MS (ESI) and HRMS (ESI) were obtained with a micrOTOF Bruker mass spectrometer. ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$, MeOD-d_4 and DMSO-d_6 at 400 MHz and 100 MHz, respectively, with a Varian Mercury 400 NMR or Bruker Avance 400 NMR spectrometers. Analytical thin-layer chromatography (TLC) was performed with precoated Merck silica gel 60 F_{254} plates (thick layer, 0.25 mm) and visualized by 254 nm using an ultraviolet lamp or by staining with aqueous potassium permanganate solution as the detecting agent. Column chromatography was performed using Merck silica gel 60 (70–230 mesh). LED reactors were made from a 1000 mL beaker lined with a commercial belt LED (1.5W × 150). EPR spectrometer from Bruker ELEXYS500. The frequency is in X-band. The modulation frequency is 100 kHz. The microwave power is 2.0 mW and modulation amplitude of 1.0 G.

4.2 General Procedure for the Synthesis of Amino Derivatives

A mixture of heterocyclic thiol (1.0 equiv.), Rose Bengal (0.1 equiv.), DBU (3.0 equiv.) and amine (1.5 equiv.) was suspended in MeCN or DMSO (0.1 M) in a pyrex glass tube (30 mL) and placed in the middle of beaker lined with a commercial belt LED (LED reactor (Figure S1)). The reaction mixture was stirred at room temperature for 16 h under white LEDs irradiation. The reaction mixture was quenched by H_2O (5 mL), extracted with EtOAc (3 × 20 mL). The combined extract was washed with brine (2 × 30 mL), dried with Na_2SO_4 and evaporated under reduced pressure to give the crude product, which was further purified by column chromatography (eluted with ethyl acetate/hexane) to afford the desired compound.

***N*-butylbenzo[*d*]oxazol-2-amine** (**5a**) [CAS: 21326-84-1]: Synthesized according to **General Procedure** using 2-mercaptobenzoxazole (**3**) (100 mg, 0.661 mmol), Rose Bengal (67.3 mg, 0.0661 mmol), DBU (297 μL, 1.98 mmol) and *n*-butylamine (402 μL, 3.30 mmol) in MeCN (6.60 mL) to afford **5a** (98.0 mg, 0.516 mmol, 78%) as an off-white solid; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.36 (d, J = 8.0 Hz, 1H, Ar-H), 7.23 (d, J = 8.0 Hz, 1H, Ar-H), 7.16 (t, J = 8.0 Hz, 1H, Ar-H), 7.02 (t, J = 8.0 Hz, 1H, Ar-H), 5.09 (brs, 1H, -NH), 3.49 (d, J = 4.0 Hz, 2H, -CH_2), 1.70-1.63 (m, 2H, -CH_2), 1.49-1.39 (m, 2H, -CH_2), 0.96 (t, J = 4.0 Hz, 3H, -CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 162.4, 148.7, 143.3, 124.1, 121.0, 116.5, 108.9, 43.2, 32.0, 20.1, 13.9; ESI-MS calculated for $C_{11}H_{15}N_2O$ $[M+H]^+$: 191.12, found at 191.12.

2-(piperidin-1-yl)benzo[*d*]oxazole (5b) [CAS: 2851-09-4]: Synthesized according to **General Procedure** using 2-mercaptobenzoxazole (**3**) (100 mg, 0.661 mmol), Rose Bengal (67.3 mg, 0.0661 mmol), DBU (297 μL, 1.98 mmol) and piperidine (326 μL, 3.30 mmol) in MeCN (6.60 mL) to afford **5b** (98.5 mg, 0.489 mmol, 74%) as a white solid; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.34 (d, J = 8.0 Hz, 1H, Ar-H), 7.23 (d, J = 8.0 Hz, 1H, Ar-H), 7.14 (t, J = 8.0 Hz, 1H, Ar-H), 6.99 (t, J = 8.0 Hz, 1H, Ar-H), 3.66 (s, 4H, -CH_2), 1.68 (s, 6H, -CH_2-); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 162.5, 148.7, 143.4, 123.8, 120.3, 116.0, 108.5, 46.6, 25.3, 24.1; ESI-MS calculated for $C_{12}H_{15}N_2O$ $[M+H]^+$: 203.12, found at 203.12.

2-(pyrrolidin-1-yl)benzo[*d*]oxazole (5c) [CAS: 111888-35-8]: Synthesized according to **General Procedure** using 2-mercaptobenzoxazole (**3**) (100 mg, 0.661 mmol), Rose Bengal (67.3 mg, 0.0661 mmol), DBU (297 μL, 1.98 mmol) and pyrrolidine (271 μL, 3.30 mmol) in MeCN (6.60 mL) to afford **5c** (88.3 mg, 0.469 mmol, 71%) as an off-white solid; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.36 (d, J = 8.0 Hz, 1H, Ar-H), 7.25 (d, J = 8.0 Hz, 1H, Ar-H), 7.15 (t, J = 8.0 Hz, 1H, Ar-H), 6.99 (t, J = 8.0 Hz, 1H, Ar-H), 3.66 (t, J = 8.0 Hz, 4H, α-CH_2 pyrrolidino), 2.04 (t, J = 8.0 Hz, 4H, β-CH_2 pyrrolidino); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 160.9, 149.0, 143.3, 123.9, 120.2, 115.9, 108.6, 47.5, 25.6; ESI-MS calculated for $C_{11}H_{13}N_2O$ $[M+H]^+$: 189.10, found at 189.10.

2-morpholinobenzo[*d*]oxazole (5d) [CAS: 21326-90-9]: Synthesized according to **General Procedure** using 2-mercaptobenzoxazole (**3**) (100 mg, 0.661 mmol), Rose Bengal (67.3 mg, 0.0661 mmol), DBU (297 μL, 1.98 mmol) and morpholine (285 μL, 3.30 mmol) in MeCN (6.60 mL) to afford **5d** (93 mg, 0.456 mmol, 69%) as an off-white solid; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.38 (d, J = 8.0 Hz, 1H, Ar-H), 7.27 (d, J = 8.0 Hz, 1H, Ar-H), 7.18 (t, J = 8.0 Hz, 1H, Ar-H), 7.05 (t, J = 8.0 Hz, 1H, Ar-H), 3.82 (t, J = 4.0 Hz, 4H, -$O(CH_2)_2$ morpholino), 3.70 (t, J = 4.0 Hz, 4H, -$N(CH_2)_2$ morpholino); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 162.0, 148.7, 142.5, 124.2, 121.1, 116.5, 108.9, 66.2, 45.8; ESI-MS calculated for $C_{11}H_{13}N_2O_2$ $[M+H]^+$: 205.10, found at 205.11.

***N*-cyclohexylbenzo[*d*]oxazol-2-amine (5e)** [CAS: 10450-11-0]: Synthesized according to **General Procedure** using 2-mercaptobenzoxazole (**3**) (100 mg, 0.661 mmol), Rose Bengal (67.3 mg, 0.0661 mmol), DBU (297 μL, 1.98 mmol) and cyclohexylamine (379 μL, 3.30 mmol) in MeCN (6.60 mL) to afford **5e** (97 mg, 0.449 mmol, 68%) as an off-white solid; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.36 (d, J = 8.0 Hz, 1H, Ar-H), 7.24 (d, J = 8.0 Hz, 1H, Ar-H), 7.16 (t, J = 8.0 Hz, 1H, Ar-H), 7.02 (t, J = 8.0 Hz, 1H, Ar-H), 5.08 (brs, 1H, NH), 3.76 (brs, 1H, -CH-), 2.12 (m, 2H, -CH_2), 1.77 (m, 2H, -CH_2), 1.66 (m, 1H, CH_2), 1.49-1.22 (m, 5H, -CH_2); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 161.2, 148.3, 142.6, 123.9, 120.8, 116.1, 108.7, 52.1, 33.4, 25.5, 24.7; ESI-MS calculated for $C_{13}H_{17}N_2O$ $[M+H]^+$: 217.13, found at 217.13.

2-(benzo[*d*]oxazol-2-ylamino)ethanol (**5f**) [CAS: 134704-32-8]: Synthesized according to **General Procedure** using 2-mercaptobenzoxazole (**3**) (100 mg, 0.661 mmol), Rose Bengal (67.3 mg, 0.0661 mmol), DBU (297 μL, 1.98 mmol) and ethanolamine (379 μL, 3.30 mmol) in MeCN (6.60 mL) to afford **5f** (97 mg, 0.449 mmol, 68%) as a white solid; ^{1}H NMR (MeOD-d_4, 400 MHz) δ 7.20 (m, 2H, Ar-H), 7.09 (d, J = 8.0 Hz, 1H, Ar-H), 6.97 (t, J = 8.0 Hz, 1H, Ar-H), 3.70 (t, J = 4.0 Hz, 2H, C$\underline{H}_2$-OH), 3.45 (t, J = 4.0 Hz, 2H, NH-C$\underline{H}_2$); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 164.4, 149.7, 143.6, 125.0, 122.0, 116.4, 109.7, 61.5, 46.2; ESI-MS calculated for $C_9H_{11}N_2O_2$ $[M+H]^+$: 179.08, found at 179.08.

***N*-(2,2-diethoxyethyl)benzo[*d*]oxazol-2-amine (5g)** : Synthesized according to **General Procedure** using 2-mercaptobenzoxazole (**3**) (100 mg, 0.661 mmol), Rose Bengal (67.3 mg, 0.0661 mmol), DBU (297 μL, 1.98 mmol) and aminoacetaldehyde diethyl acetal (480 μL, 3.30 mmol) in MeCN (6.60 mL) to afford **5g** (101 mg, 0.403 mmol, 61%) as a white solid; ^{1}H NMR (MeOD-d_4, 400 MHz) δ 7.18 (m, 2H, Ar-H), 7.07 (t, J = 8.0 Hz, 1H, Ar-H), 6.95 (t, J = 8.0 Hz, 1H, Ar-H), 4.65 (t, J = 4.0 Hz, 1H, C$\underline{H}$-$(OEt)_2$), 3.71-3.63 (m, 2H, O-C$\underline{H}_2$-CH_3), 3.57-3.49 (m, 2H, O-C$\underline{H}_2$-CH_3), 3.41 (d, J = 4.0 Hz, 2H, NH-C$\underline{H}_2$-CH), 1.12 (t, J = 8.0 Hz, 6H, (CH_2-C$\underline{H}_3$)$_2$); ^{13}C NMR (MeOD-d_4, 100 MHz) δ 164.3, 149.7, 143.6, 125.1, 122.1, 116.5, 109.7, 102.0, 63.96, 46.4, 15.6; HRMS calculated for $C_{13}H_{19}N_2O_3$ $[M+H]^+$: 251.1396, found at 251.1390.

***tert*-Butyl-4-(benzo[*d*]oxazol-2-yl)piperazine-1-carboxylate** (**5i**) [CAS: 195390-64-8]: Synthesized according to **General Procedure** using 2-mercaptobenzoxazole (**3**) (100 mg, 0.661 mmol), Rose Bengal (67.3 mg, 0.0661 mmol), DBU (297 μL, 1.98 mmol) and 1-boc-piperazine (614 mg, 3.30 mmol) in MeCN (6.60 mL) to afford **5i** (132 mg, 0.436 mmol, 66%) as a white solid; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.38 (d, J = 8.0 Hz, 1H, Ar-H), 7.27 (d, J = 8.0 Hz, 1H, Ar-H), 7.18 (t, J = 8.0 Hz, 1H, Ar-H), 7.05 (t, J = 8.0 Hz, 1H, Ar-H), 3.69 (t, J = 4.0 Hz, 4H, -CH_2-), 3.57 (t, J = 4.0 Hz, 4H, -CH_2-), 1.49 (s, 9H, -CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 161.9, 154.6, 148.7, 142.7, 124.2, 121.1, 116.5, 108.9, 80.4, 45.5, 28.4; ESI-MS calculated for $C_{16}H_{22}N_3O_3$ $[M+H]^+$: 304.16, found at 304.16.

***N*-butyl-5-methoxybenzo[*d*]oxazol-2-amine** (**6a**): Synthesized according to **General Procedure** using 5-methoxybenzoxazole-2-thiol (**6**) (100 mg, 0.552 mmol), Rose Bengal (56.2 mg, 0.0552 mmol),

DBU (248 μL, 1.66 mmol) and *n*-butylamine (273 μL, 2.76 mmol) in MeCN (5.50 mL) to afford **6a** (105 mg, 0.480 mmol, 87%) as a pale brown solid; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.11 (d, J = 8.0 Hz, 1H, Ar-H), 6.93 (d, J = 4.0 Hz, 1H, Ar-H), 6.59 (dd, J = 8.0, 4.0 Hz, 1H, Ar-H), 5.30 (brs, 1H, -NH), 3.80 (s, 3H, -OC$\underline{H}_3$), 3.47 (t, J = 8.0 Hz, 2H, CH_2), 1.66 (q, J = 8.0 Hz, 2H, -CH_2), 1.43 (m, 2H, -CH_2), 0.96 (t, J = 8.0 Hz, 3H, -CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 162.8, 157.1, 143.4, 142.9, 108.6, 107.3, 101.4, 55.9, 42.1, 31.8, 19.9, 13.7; HRMS calculated for $C_{12}H_{17}N_2O_2$ $[M+H]^+$: 221.1290, found at 221.1349.

***N*-butyl-5-fluorobenzo[*d*]oxazol-2-amine** (**7a**): Synthesized according to **General Procedure** using 5-fluorobenzoxazole-2-thiol (**7**) (100 mg, 0.591 mmol), Rose Bengal (60.1 mg, 0.0591 mmol), DBU (265 μL, 1.77 mmol) and *n*-butylamine (293 μL, 2.96 mmol) in MeCN (5.90 mL) to afford **7a** (103 mg, 0.496 mmol, 84%) as a pale-yellow brown solid; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.12 (dd, J = 8.0, 4.0 Hz, 1H, Ar-H), 7.02 (dd, J = 8.0, 4.0 Hz, 1H, Ar-H), 6.70 (t, J = 8.0 Hz, 1H, Ar-H), 5.79 (brs, 1H, NH), 3.47 (t, J = 8.0 Hz, 2H, -CH_2), 1.66 (q, J = 8.0 Hz, 2H, -CH_2), 1.43 (m, 2H, -CH_2), 0.96 (t, J = 8.0 Hz, 3H, -CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 163.6, 160.1 ($^1J_{CF}$ = 236.0 Hz), 144.7 ($^4J_{CF}$ = 1.0 Hz), 144.1 ($^3J_{CF}$ = 14.0 Hz), 108.5 ($^2J_{CF}$ = 11.0 Hz), 107.0 ($^3J_{CF}$ = 26.0 Hz), 103.3 ($^2J_{CF}$ = 26.0 Hz), 42.8, 31.8, 19.9, 13.7; HRMS calculated for $C_{11}H_{14}FN_2O$ $[M+H]^+$: 209.1090, found at 209.1150.

***N*-butyl-5-chlorobenzo[*d*]oxazol-2-amine** (**8a**) [CAS: 78096-47-6:]: Synthesized according to **General Procedure** using 5-chlorobenzo[*d*]oxazole-2-thiol (**8**) (122 mg, 0.661 mmol), Rose Bengal (67.3 mg, 0.0661 mmol), DBU (297 μL, 1.98 mmol) and *n*-butylamine (402 μL, 3.30 mmol) in MeCN (6.60 mL) to afford **8a** (130 mg, 0.581 mmol, 88%) as an white solid; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.30 (s, 1H, Ar-H), 7.13 (d, J = 8.0 Hz, 1H, Ar-H), 6.98 (d, J = 8.0, Hz, 1H, Ar-H), 5.62 (brs, 1H, -NH), 3.47 (t, J = 8.0 Hz, 2H, NH-C$\underline{H}_2$), 1.66 (m, 2H, -C$\underline{H}_2$-), 1.43 (m, 2H, -C$\underline{H}_2$-), 0.96 (t, J = 8.0 Hz, 3H, CH_2-C$\underline{H}_3$); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 163.0, 147.0, 144.0, 129.3, 120.6, 116.2, 109.2, 42.9, 31.7, 19.9, 13.7; HRMS calculated for $C_{11}H_{14}ClN_2O$ $[M+H]^+$: 225.0795, found at 225.0869.

***tert*-butyl-2-(5-chlorobenzo[*d*]oxazol-2-ylamino) ethylcarbamate** (**8b**) [CAS: 1144509-75-0:]: Synthesized according to **General Procedure** using 5-chlorobenzo[*d*]oxazole-2-thiol (**8**) (122 mg, 0.661

mmol), Rose Bengal (67.3 mg, 0.0661 mmol), DBU (297 μL, 1.98 mmol) and *N*-boc-ethylenediamine (522 μL, 3.30 mmol) in MeCN (6.60 mL) to afford **8b** (146 mg, 0.469 mmol, 71%) as an pale-yellow white solid; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.32 (d, *J* = 4.0 Hz, 1H, Ar-H), 7.14 (d, *J* = 8.0 Hz, 1H, Ar-H), 7.01 (dd, *J* = 8.0, 4.0 Hz, 1H, Ar-H), 5.07 (brs, 1H, -NH), 3.60 (t, *J* = 8.0 Hz, 2H, NH-C$\underline{H}_2$), 3.44 (m, 2H, NH-C$\underline{H}_2$), 2.39 (brs, 1H, -NH), 1.42 (s, 9H, (C$\underline{H}_3$)$_3$); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 162.6, 156.9, 146.9, 143.2, 129.5, 121.1, 116.2, 109.4, 80.0, 44.2, 40.2, 28.3; HRMS calculated for $C_{14}H_{19}ClN_3O_3$ $[M+H]^+$: 312.1115, found at 312.1214.

2-(5-chlorobenzo[*d*]oxazol-2-ylamino)ethanol (**8c**) [CAS: 1356342-15-8]: Synthesized according to **General Procedure** using 5-chlorobenzo[*d*]oxazole-2-thiol (**8**) (122 mg, 0.661 mmol), Rose Bengal (67.3 mg, 0.0661 mmol), DBU (297 μL, 1.98 mmol) and ethanolamine (200 μL, 3.30 mmol) in MeCN (6.60 mL) to afford **8c** (105 mg, 0.495 mmol, 75%) as an white solid; ^{1}H NMR (MeOD-d_4, 400 MHz) δ 7.21 (d, *J* = 8.0 Hz, 1H, Ar-H), 7.20 (s, 1H, Ar-H), 6.99 (d, *J* = 8.0 Hz, 1H, Ar-H), 3.75 (t, *J* = 4.0 Hz, 2H, C$\underline{H}_2$-OH), 3.50 (t, *J* = 4.0 Hz, 2H, NH-C$\underline{H}_2$); ^{13}C NMR (MeOD-d_4, 100 MHz) δ 165.4, 148.4, 145.3, 130.4, 121.6, 116.3, 110.5, 61.4, 46.2; HRMS calculated for $C_9H_{10}ClN_2O_2$ $[M+H]^+$: 213.0431, found at 213.0439.

quinazoline-4-thiol (**10**) [CAS: 3337-86-8]: A solution of 4-hydroxyquinazoline (**9**) (500 mg, 3.42 mmol) and Lawesson's reagent (2,075 mg, 5.13 mmol) in toluene (15 mL) was reflux at 115 ^{o}C overnight. After cooling, the reaction was added with water (100 mL) and filtered the precipitated yellow solid. Such a solid was re-dissolved by 3M NaOH solution (10 mL × 3). The aqueous solution was neutralized with 1M HCl solution (15 mL × 3) until complete precipitation occurred. After filtration compound **10** as yellow solid was rinsed with MeOH and dried until to afford **10** (493 mg, 3.04 mmol, 89%) as a yellow solid; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 13.8 (brs, 1H, SH), 8.52 (d, *J* = 8.0 Hz, 1H, Ar-H), 8.11 (s, 1H, Ar-H), 7.84 (d, *J* = 4.0 Hz, 1H, Ar-H), 7.67 (d, *J* = 8.0 Hz, 1H, Ar-H), 7.56 (t, *J* = 8.0 Hz, 1H, Ar-H).

***N*-butylquinazolin-4-amine** (**10a**) [CAS: 22754-07-0]: Synthesized according to **General Procedure** using quinazoline-4-thiol (**10**) (100 mg, 0.617 mmol), Rose Bengal (62.8 mg, 0.0617 mmol), DBU (326

μL, 1.85 mmol) and *n*-butylamine (305 μL, 3.09 mmol) in DMSO (6.10 mL) to afford **10a** (91 mg, 0.457 mmol, 74%) as a white solid; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.66 (s, 1H, Ar-H), 7.84 (d, *J* = 8.0 Hz, 1H, Ar-H), 7.73 (m, 2H, Ar-H), 7.46 (t, *J* = 8.0 Hz, 1H, Ar-H), 5.95 (brs, 1H, NH), 3.67 (d, *J* = 4.0 Hz, 2H, CH_2), 1.72 (t, *J* = 4.0 Hz, 2H, CH_2), 1.47 (q, *J* = 4.0 Hz, 2H, CH_2), 0.99 (t, *J* = 4.0 Hz, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 159.5, 155.3, 149.2, 132.5, 128.4, 125.9, 120.4, 114.9, 41.2, 31.4, 20.2, 13.8; ESI-MS calculated for $C_{12}H_{16}N_3$ $[M+H]^+$: 202.13, found at 202.13.

4)-quinazolin-4-yl)morpholine (**10b**) [CAS: 7471-81-0] Synthesized according to **General Procedure A** using quinazoline-4-thiol (**10**) (100 mg, 0.617 mmol), Rose Bengal (62.8 mg, 0.0617 mmol), DBU (326 μL, 1.85 mmol) and morpholine (267 μL, 3.09 mmol) in DMSO (6.10 mL) to afford **10b** (86 mg, 0.401 mmol, 65%) as a pale-yellow solid; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.75 (s, 1H, Ar-H), 7.94 (d, *J* = 8.0 Hz, 1H, Ar-H), 7.88 (d, *J* = 8.0 Hz, 1H, Ar-H), 7.75 (t, *J* = 8.0 Hz, 1H, Ar-H), 7.47 (t, *J* = 8.0 Hz, 1H, Ar-H), 3.90 (t, *J* = 4.0 Hz, 4H, -O($C\underline{H}_2$)$_2$ morpholino), 3.80 (t, *J* = 4.0 Hz, 4H, -N($C\underline{H}_2$)$_2$ morpholino); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 164.6, 153.8, 151.4, 132.7, 128.6, 125.7, 124.7, 116.4, 66.8, 50.3; ESI-MS calculated for $C_{12}H_{14}N_3O$ $[M+H]^+$: 216.11, found at 216.10.

4-pyrrolidin-1-yl)quinazoline (**10c**) [CAS: 81870-89-5] Synthesized according to **General Procedure** using quinazoline-4-thiol (**10**) (100 mg, 0.617 mmol), Rose Bengal (62.8 mg, 0.0617 mmol), DBU (326 μL, 1.85 mmol) and pyrrolidine (253 μL, 3.09 mmol) in DMSO (6.10 mL) to afford **10c** (85 mg, 0.426 mmol, 69%) as a pale-yellow solid; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.58 (s, 1H, Ar-H), 8.14 (d, *J* = 8.0 Hz, 1H, Ar-H), 7.82 (d, *J* = 8.0 Hz, 1H, Ar-H), 7.67 (t, *J* = 8.0 Hz, 1H, Ar-H), 7.37 (t, *J* = 8.0 Hz, 1H, Ar-H), 3.92 (t, *J* = 4.0 Hz, 4H, α-CH_2 pyrrolidino), 2.04 (t, *J* = 8.0 Hz, 4H, β-CH_2 pyrrolidino); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 159.8, 154.3, 151.1, 132.0, 127.9, 125.3, 124.4, 116.4, 51.0, 25.7; ESI-MS calculated for $C_{12}H_{14}N_3$ $[M+H]^+$: 200.12, found at 200.12.

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6. Supporting Information

Supporting Information is available free of charge on the ACS Publications website at DOI:XX. Reactor set up and NMR spectra (^{1}H and ^{13}C) for all products

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