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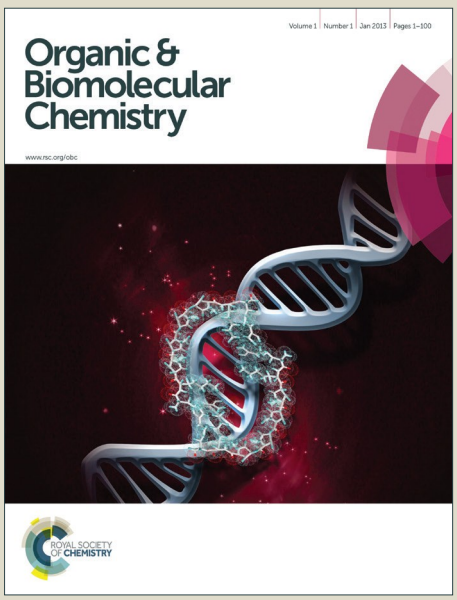

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PAPER

BODIPY Catalyzed Amide Synthesis Promoted by BHT and Air under Visible Light

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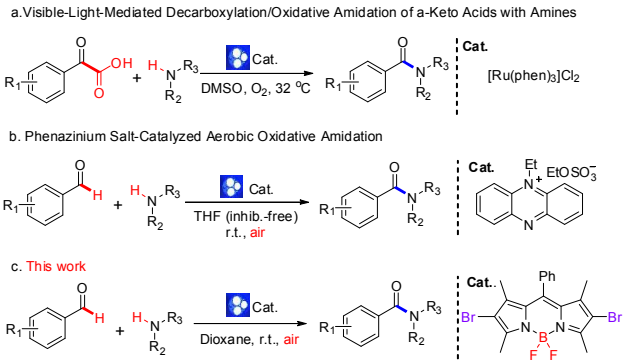
A novel and efficient protocol for the synthesis of amides is reported which employs a BODIPY catalyzed oxidative amidation reaction between aromatic aldehydes and amines under visible light. Compared with the known Ru or Ir molecular catalysts and other organic dyes, the BODIPY catalyst showed a higher reactivity toward this reaction. Mechanistic studies reveal that dioxygen could be activated through an ET and a SET pathway, forming the active peroxides in situ, which are vital for the key step of the reaction, i.e. the oxidation of hemiaminal to amide. The broad substrate scope and mild reaction conditions make this reaction practically useful and environmental friendly for the synthesis of amide compounds.

Introduction

The amide bond is not only the structural backbone of protein and peptides,[1] but also prevalent in natural products, pharmaceuticals, agrochemicals, materials and polymers.[2] The most used amide forming transformation is the coupling reaction of amines with acylating agents, such as acyl chlorides,[3] or with carboxylic acids in the presence of coupling agents.[4]From the view point of green chemistry, this protocol generates a copious amount of byproducts and chemical wastes and so needs to be improved or replaced.[5] Thus, "Amide formation avoiding poor atom economy reagents" is a big challenge and highly important in organic chemistry.[6] Another strategy for amide bond synthesis is the use of catalytic methods.[7] Synthetic reactions catalyzed by boronic acids,[8] *N*-heterocyclic carbenes,[9] and transition-metals[10–12] have shown potential applications in amide formation. In 2014, Lei[13] and Leow[14] reported elegant oxidative amidation of α-Keto acids and aromatic aldehydes with amines, providing a greener catalytic process for amide formation by photoredox catalysis (Scheme1).[15-18] Preliminary mechanistic studies reveal that O_2 activation under visible light irradiation might be the key step, and the photocatalysts $Ru(bpy)_3Cl_2$[13] and phenazinium salts[14] are vital for the reaction rate. The search for new metal-free photocatalysts with low cost, low toxicity and high efficiency for different organic reactions is a worthy endeavor in this area of research.

BODIPY derivatives are a class of privileged organic dyes, which are traditionally used as chemo sensors, labelling reagents, fluorescent switches and laser dyes. [19,20] Recently, the tandem oxidation/[3+2] cycloaddition,[21] cross-dehydrogenative-coupling reaction[22] and photo-oxidation[23] catalyzed by BODIPY derivatives has been reported,providing new example of promising metal-free photocatalysts with high stability and easy-to-modify structures, which would allow for easy optimization of their photocatalytic properties.[24] These BODIPY derivatives show strong absorption of visible light and long-lived excited triplet state, activating O_2 under visible light irradiation. However, the application of these catalysts in amide synthesis has not been reported. In continuing our work on photoredox catalysis driven by visible light,[25] herein we report a BODIPY-catalyzed aerobic oxidative amidation of aromatic aldehydes with low catalytic loading. Compared with the known Ru or Ir molecular catalysts and other organic dyes, the BODIPY catalyst showed higher reactivity toward this reaction. The broad substrate scope and mild reaction conditions make this reaction practically useful and environmental friendly for the synthesis of amide compounds.



Scheme 1 Oxidative Amidation of Aromatic acids and Aldehydes.

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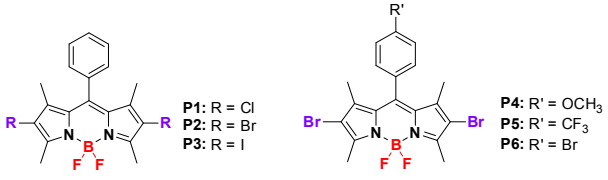
Results and discussion

Our initial investigation focused on the direct oxidative amidation of 4-bromobenzaldehyde (**1a**, 1 eq.) with pyrrolidine (**2a**, 3 equiv.) in the presence of 2 mol% of a photosensitizer under the irradiation of 3 W Blue LEDs in MeCN. As seen from Table 1, among the 15 photocatalysts that we had tested, nine of the readily available ones gave poor yields (Table 1, entries1-15). In contrast, the BODIPY derivatives P1-P6 gave better results (Table 1, entries 10-15), with the catalyst P2 furnishing the highest yield of 60% after 12h at room temperature (Table1, entry 11).[26] Light source was then investigated. We screened three light sources, 24 W Household bulbs, 3 W Blue LEDs and 3 W Green LEDs. Although BODIPY P2 shows strong absorption in much red-shifted region of 523 nm (Figure 1), 3 W Blue LEDs gave the highest yield (Table 1, entries 11, 17-18). The reason may be that the energy of blue light is higher than green light.

Table 1 Optimization of reaction conditions [a]

Entry	Cat.	Additive	Solvent	Yield[b]
1	$Ru(bpy)_3Cl_2$	-	MeCN	37%
2	$Ru(phen)_3Cl_2$	-	MeCN	46%
3	$Ru(phen)_3(PF_6)_2$	-	MeCN	42%
4	$Ir(dtbpy)(ppy)_2PF_6$	-	MeCN	44%
5	Phenazine Ethosulfate	-	MeCN	41%
6	Nile Red	-	MeCN	29%
7	Rhodamine B	-	MeCN	26%
8	Alizarin Red S	-	MeCN	22%
9	Methylene Blue	-	MeCN	16%
10	P1	-	MeCN	27%
11	P2	-	MeCN	60%
12	P3	-	MeCN	48%
13	P4	-	MeCN	47%
14	P5	-	MeCN	54%
15	P6	-	MeCN	56%
16[c]	P2	-	MeCN	9%
17[d]	P2	-	MeCN	50%
18[e]	P2	-	MeCN	37%
19	P2	-	H_2O	11%
20	P2	-	DMSO	30%
21	P2	-	THF	65%
22	P2	-	Dioxane	72%
23	P2	BHT (1 eq.)	Dioxane	85%
24	P2	BHT (2 eq.)	Dioxane	92%
25	P2	BHEB (2 eq.)	Dioxane	91%
26	no	BHT (2 eq.)	Dioxane	0
27[f]	P2	no	Dioxane	0
28	no	no	Dioxane	0



a: aldehyde **1a** (0.2 mmol, 1 eq.), pyrrolidine **2a** (3 equiv.), catalyst (2 mol%), irradiation with a 3 W Blue LEDs under air at room temperature for 12 h. b: Yield determined by ^{1}H NMR, 1,3,5-trimethoxylbenzene as internal standard. c: under argon. d: 24 W Household bulb. e: 3 W Green LEDs. f: No light.

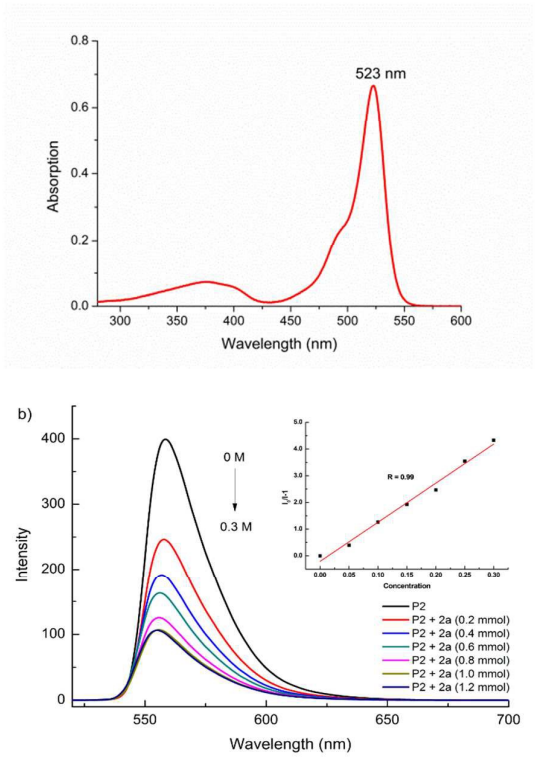


Figure 1 a) UV-Vis absorption spectra of BODIPY P2. c = 1.0 ×10^{-5} M in MeCN, 25 °C. b) Fluorescence spectra of BODIPY P2 at increasing concentration of **2a** (0, 0.2 mmol, 0.4 mmol, 0.6 mmol, 0.8 mmol, 1.0 mmol, 1.2 mmol) upon excitation at 438 nm. c = 1.0 × 10^{-3} M in MeCN, 25 °C. The inset represents the Stern-Volmer plot of BODIPY P2 *vs.* the concentration **2a**.

In addition, we found that the BODIPY P2 show strong fluorescence with a maximal peak at 558 nm in MeCN (Figure 1, b). The progressive addition of pyrrolidine **2a** quenched the fluorescence upon excitation of P2 with a quenching constant K = 14.6 M^{-1} in MeCN. These results suggested that the interaction of photoexcited BODIPY P2 with **2a** was strong. Next, solvents were screened and dioxane was found to be the best solvent for this reaction, affording the product in 72% yield (Table 1, entries 17-20). In an effort to probe whether or not radicals were involved in the reaction, the effect of radical inhibitors such as BHT (3, 5-di-tert-butyl-4-hydroxytoluene) and BHEB (2,6-di-tert-butyl-4-ethylphenol) were investigated (Table 1, entries 21-25). To our surprise, when two equivalents of BHT or BHEB were added to the reaction mixture, the yield was significantly improved to about 90% (Table 1, entries 22, 23). The Leow group[14] showed that inhibitor-free solvents give the best results foroxidative amidation reactions. Clearly, this

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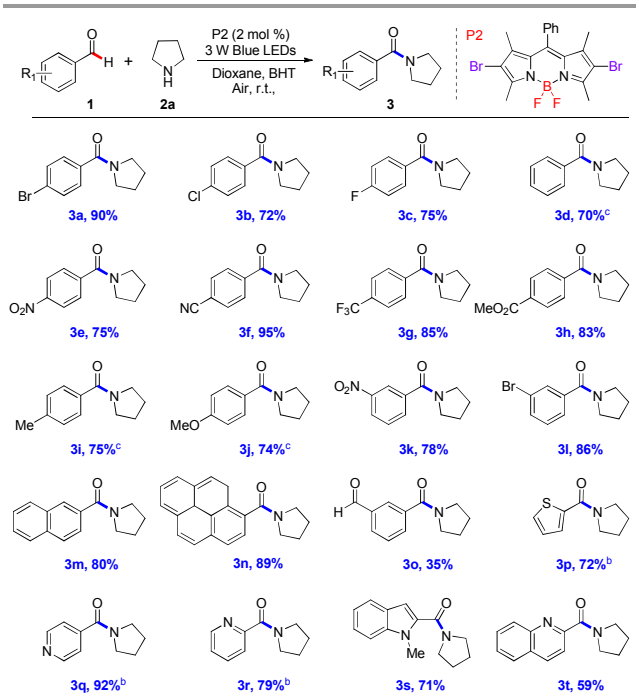
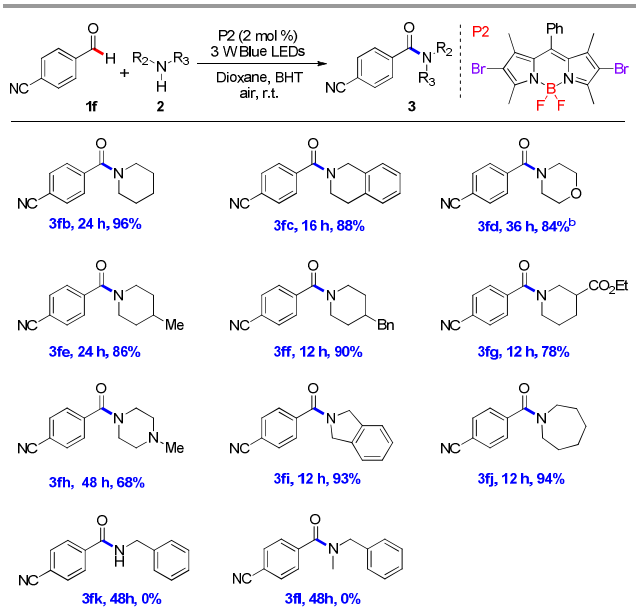
is different from our findings. It is reasonable to suspect that the BHT-OOH comes from the reaction of BHT with oxygen activated by the photocatalyst under the irradiation of the 3 W Blue LEDs. Careful study showedthat BHT peroxide, BHT-OOH, could be isolated underthe identical reaction conditionsin the absence of the substrates.The BHT-OOH compound showed higher reactivity than H_2O_2, and could serve as an oxidant for the reported oxidative amidation of aldehydes (vide infra).[26] Notably, the photocatalyst, oxygen and visible light are all essential for the amidation reaction (Table 1, entries 16, 27-28). In the absence of any of these components, no reaction occurred.



Scheme 2 Amidation of Aromatic Aldehydes with Pyrrolidine.
[a]Aldehydes **1** (0.2 mmol, 1 equiv.), pyrrolidine**2a** (3 equiv.), P2 (2 mol%), BHT (2 equiv.), under air, dioxane (2 mL), 3 W Blue LEDs irradiation at room temperature for 12 h. Isolated yield.[b] Reaction for 16 h.[c] Reaction for 24 h.

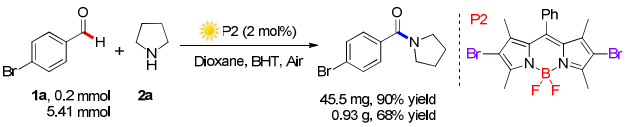
With the optimized reaction conditions in hand, a wide range of aromatic aldehydes (**1a-t**) were investigated to illustrate the reaction efficiency and scope in the presence of the photosensitizer P2 under an air atmosphere (Scheme 2). Generally, the desired amides (**3a-t**) were obtained in good to excellent yields via this BODIPY catalyzed oxidative amidation reaction under visible light. The aromatic aldehydes bearing electron-withdrawing or donating groups all underwent the amidation smoothly to give the desired amides in good toexcellent yields (**3a-3l**, 70%-95%). A wide range of useful functional groups attached to the aromatic aldehydes, such as CN, COOMe, Br, Cl, F, CF_3 and NO_2, were tolerated under the reaction conditions and are available for further functionalization. Furthermore, polycyclic and heterocyclic aromatic aldehydes also gave the desired products in 59-92% (**3m**-**3s**). In addition, the reaction of isophthalaldehyde with



Scheme 3 Amidation of Aromatic Aldehydes with Amines.
[a]4-Formylbenzonitrile **1f** (0.2 mmol, 1 equiv.), amine (3 equiv), P2 (2 mol%), BHT (2 equiv.), under air, dioxane (2 mL), 3 W Blue LEDs irradiation at room temperature.Isolated yield.[b] Amine (4 equiv.) and additional P2 (2 mol%) was added during reaction.

pyrrolidine afforded the mono-amidation product **3t** albeit with low yield. However, aliphatic aldehydes could not give the desired amide products under the optimized reaction conditions.

To further demonstrate the utility of this new protocol for amides synthesis, we run two direct oxidative amidation reactions of 4-bromobenzaldehyde with pyrrolidine (**2a**, 3 equiv.) under the irradiation of solar light outside the laboratory in the presence of 2 mol% P2, one at 0.2 mmol and the other at gram scale (Scheme 4). After 6 and 48 hours, the desired products were isolated in 90% and 68% yield, respectively. Compared with the reaction irradiated with 3 W LEDs, the solar light was more effective in promoting the reaction, showing the potential of application of this photocatalyst in “greener” organic synthesis.



Scheme 4 Oxidative Amidation Using Solar Light Irradiation.

Next, various amines were examined to explore the generality of the reaction conditions. Six- and seven-membered ring amines reacted with 4-formylbenzonitrile **1f** smoothly to give the corresponding amides in good yields (Scheme 3). Isoindoline and subsitituted six-memberred ring amines are also good substrates, affording the desired amides in 68%-96% yields. However, the reaction of **1f** with benzylamine and *N*-methylbenzylamine could not give the desired products (**3fk**, **3fl**) under the optimized reaction conditions, which ascribe to the easy generation of imines of

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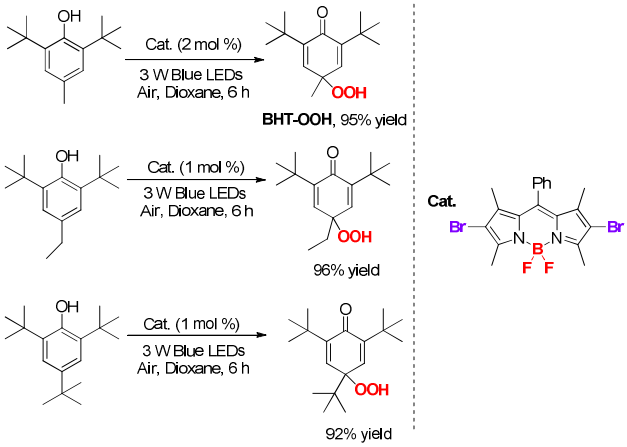
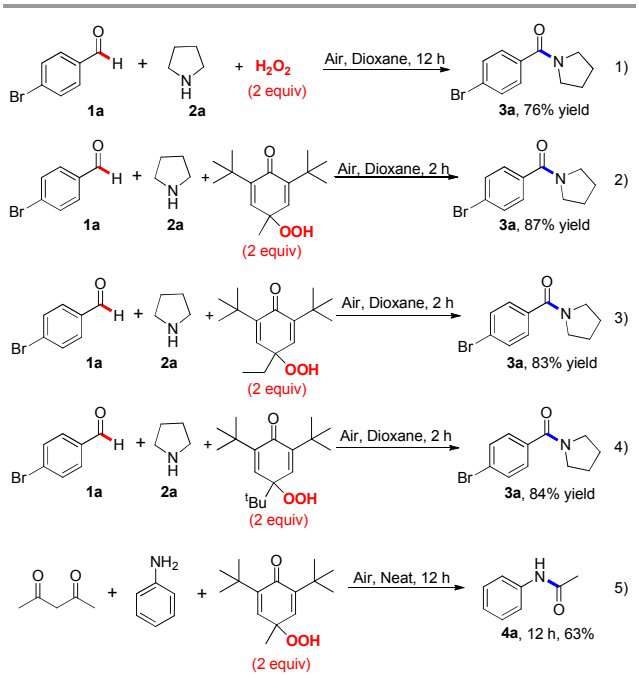
these two amines under the reaction conditions. In addition, the primary amines and aromatic amines could not give the desired amide products under the optimized reaction conditions.

In order to understand the effect of BHT on this reaction, the following studies were conducted. As showed in Scheme 5, when a solution of BHT in dioxane was irradiated under identical reaction conditions for 6 hours, a BHT hydroperoxide, BHT-OOH, was isolated with 95% yield. For the analogues of BHT, the corresponding hydroperoxide were also obtained with high isolated yields. These BHT-OOH compounds showed higher reactivity than H_2O_2 toward the oxidative amidation of 4-bromobenzaldehyde with pyrrolidine, affording the desired product with high yields[27] (Scheme 6). In addition, the BHT-OOH compound could promote the reaction between pentane-2, 4-dioneand aniline under solvent-free condition, affording amide **4a** in 63% yield (Scheme 6).[28] These results demonstrate that BHT-OOH can be easily formed in situ and most likely contributes to the amidation reaction, and it could be used as an easy-to-handle oxidant in oxidation reactions.



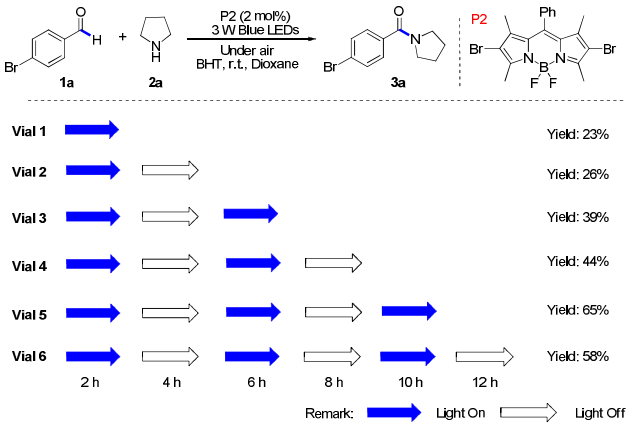
Scheme 5 The Reaction of BHT derivatives with oxygen.

To gain insight into the amidation mechanism, control experiments were performed. First, we conducted the radical chain probe experiment (scheme 7). When the reaction was irradiated with visible light, the reaction went well. However, the reaction stopped after the light was switched off. And the reaction worked again, when the light was turned on. The experiment of on-off switching of visible light suggested that the reaction is not a radical chain reaction. Then, the effect of photocatalyst was studied (the results are shown in the ESI). When H_2O_2 (1 equiv.) was added to the reaction of 4-bromobenzaldehyde (**1a**) with pyrrolidine (**2a**) in the absence of photocatalyst and visible light, the product **3a** was obtained only in 29% yield after 4 hours. However, when both the photocatalyst P2 (2 mol%) and H_2O_2 (1 equiv.) were added under the optimized reaction conditions, the product yield increased to 61% under visible light irradiation after 4 hours, suggesting that the amidation with H_2O_2 as oxidant was also promoted by light and photosensitizer P2 (see ESI, Table S4). These results are different from the findings reported by the



Scheme 6 The BHT-OOH Compound Promoted Oxidative Amidation

Leow group[14], which showed that when H_2O_2 was used as the oxidant, photocatalyst displayed no accelerating effect on the oxidative amidation under visible light irradiation. In the current study, H_2O_2 was detected in the reaction of 4-bromobenzaldehyde with pyrrolidine under visible light irradiation after 4 hours using P2 as photocatalyst (see ESI, Figure S4). These results suggest that the BHT-OOH compound or H_2O_2, which are generated in situ from O_2, are the real oxidants for this oxidative reaction.



Scheme 7 The Experiment of On-Off Switching of Visible Light

Based on our experiments[26] and the literature reports,[22, 24] a reaction mechanism for this oxidative amidation is suggested as shown in Scheme 8. Firstly, P2 is converted into a high-energy excited singlet $^1[P2]^*$ under visible light irradiation, which undergoes intersystem crossing (ISC) to produce a triplet $^3[P2]^*$[24]. Secondly, dioxygen is activated through two possible pathways. One is an energy transfer (ET) pathway

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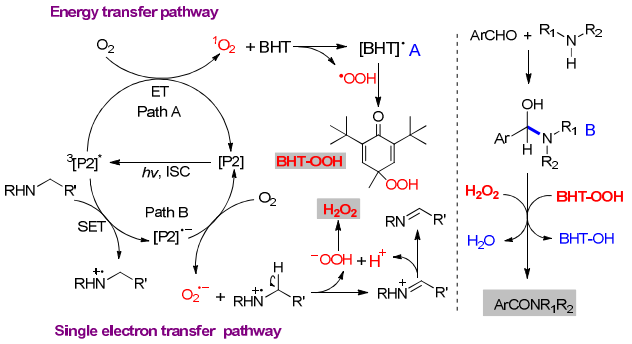
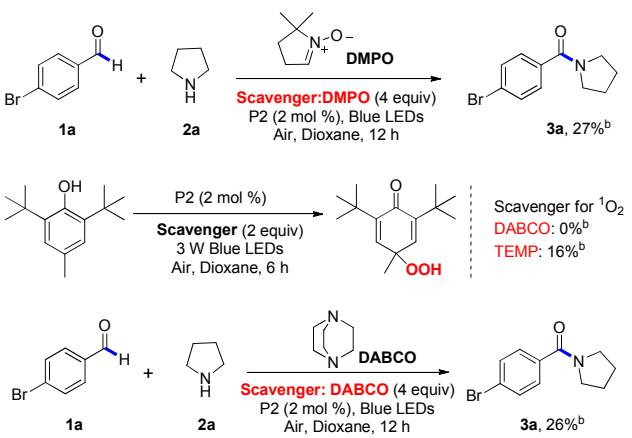
from $^3[P2]^*$ to O_2, regenerating the ground state P2 while producing the singlet oxygen ($^1O_2$). The latter then reacts with BHT, generating the hydroperoxide radical ·OOH and the BHT radical **A**, which combine to give rise to the BHT hydroperoxide BHT-OOH (Scheme 8).[26] Subsequently, the BHT-OOH compound oxidizes the α-hydroxy amine **B** to afford the amide



Scheme 8 Proposed Mechanism for the Aerobic Oxidative Amidation.

product and BHT-OH. On the other hand, dioxygen can also be activated through a single electron transfer (SET) pathway to form the superoxide radical $O_2^{\cdot-}$ from the radical anion $[P2]^{\cdot-}$, which is generated by SET from the amine to the excited state $^3[P2]^*$. Then, the active species $O_2^{\cdot-}$ produces H_2O_2 by reacting with the amine radical cation presumably via H-atom abstraction, which oxidizes **B** to afford the amide.



Scheme 9 The Capture of Reaction Intermediates.

[a]P2 (2 mol %), 4-bromobenzaldehyde **1a** (1 eq., 0.2 mmol), pyrrolidine**2a** (3 eq.), scavenger (4 equiv.) under air, 3 W Blue LEDs, dioxane (2 mL). [b]Yield determined by ^1H NMR, 1,3,5-trimethoxylbenzene as internal standard. DMPO = 5,5-dimethyl-1-pyrroline-N-oxide,DABCO = 1,4-Diazabicyclo[2.2.2]octane, TEMP = 2,2,6,6-tetramethylpiperidine.

The formation of the superoxide is supported by the observation that when an $O_2^{\cdot-}$ scavenger, 5, 5-dimethyl-1-pyrroline-N-oxide (DMPO), was added to reaction mixture under the optimized reaction conditions, the yield of desired product decreased to 27% (Scheme 9).[26] Similarly, when an $^1O_2$ scavenger, 1, 4-diazabicyclo [2.2.2] octane (DABCO), was added to the reaction mixture under the optimized reaction conditions, the yield of desired product decreased to 26% (Scheme 8).[26] These results support the proposal that the two possible pathways may operate in parallel in this reaction.

Conclusions

In summary, we have developed a novel protocol of amide synthesis, which involves the aerobic oxidative amidation of aromatic aldehydes with amines under the photoredox catalysis of a BODIPY. Experiments suggest that dioxygen could be activated through an ET and a SET pathway, forming the active oxidants in situ. The mild reaction conditions, broad substrate scope and air as oxidant make the protocol practically useful and environmentally friendly for the synthesis of compounds containing the amide motifs.

Experimental

General Information

All commercial reagents were used without further purification unless specified. Analytical thin layer chromatography (TLC) was performed on precoated silica gel 60 F_{254} plates and visualization on TLC was achieved by UV light (254 nm). Flash column chromatography was undertaken on silica gel (400 mesh) using a proper eluent. ^1H and ^{13}C NMR spectra were recorded on Bruker Avance 400 spectrometer in $CDCl_3$ using tetramethylsilane (TMS) as the internal standard. All spectra are referenced to $CDCl_3$ residual $CHCl_3$ peak (^1H NMR = 7.26 ppm; ^{13}C NMR = 77.1 ppm). All chemical shifts are quoted in parts per million (ppm), measured from the center of the signal except in the case of multiplets of more than one proton, which are quoted as a range. Splitting patterns are abbreviated as follows: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, and br = broad and combinations thereof. HRMS (ESI) were performed on a Fourier Transform Ion Cyclotron Resonance Mass Spectrometer. Melting points (MP) were determined uncorrected. IR spectra were recorded in KBr disks with a microscopic melting point X-5 spectrometer. Fluorescence measurements were conducted on a F-7000 Hitachi fluorescence spectrometer.

General Experimental Procedure for Preparation of Photosensitizers

5,5-Difluoro-1,3,7,9-tetramethyl-10-phenyl-5H-dipyrrolo[1,2-c:2',1'-f][1,3,2]diazaborinin-4-ium-5-uide (I).[29] Trifluoroacetic acid (25 µL, 0.33 mmol) in dry CH_2Cl_2 (1.5 mL) was added dropwise to a solution of benzaldehyde (0.27 mL, 2.5 mmol) and 2,4-dimethyl-1H-pyrrole (0.64 mL, 6.25 mmol) in dry CH_2Cl_2 (125 mL) at room temperature. The reaction mixture was stirred for 3 hours at room temperature, 2, 3-Dichloro-5, 6-dicyano-1, 4-benzoquinone (0.56 g, 2.5 mmol) was added under ice bath cooling and the mixture was stirred for 10 min. After stirring for an additional 1 hour at room temperature, NEt_3 (5 mL, 36 mmol) was added, followed by slow addition of $BF_3{\cdot}Et_2O$ (5 mL, 40.5 mmol). After 2 hours of stirring at room temperature, the reaction mixture was washed with saturated aqueous Na_2CO_3 solution (3 × 50 mL), dried over Na_2SO_4, and

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concentrated on a rotary evaporator. The brown, oily residue was purified by column chromatography on silica. The product fraction showing greenish fluorescence was dried to yield a red-brown solid.

2,8-Dihalogen-5,5-difluoro-1,3,7,9-tetramethyl-10-phenyl-5H-dipyrrolo[1,2-c:2',1'-f][1,3,2]diazaborinin-4-ium-5-uide(P1-P6).[30] A mixture of the 1,3,7,9-tetramethyl-BODIPY (0.5 mmol, 1 equiv.) and NXS (2.0 mmol, 4 equiv.,NXS = NCS or NBS or NIS) in CH_2Cl_2 (20 mL) was stirred overnight at room temperature. After completion of the reaction, the solvent was concentrated under reduced pressure. The crude product was further purified using column chromatography (petroleum ether/dichloromethane = 20:1) to afford the corresponding photosensitizers P1 to P6.

General Experimental Procedure for the Synthesis of Oxidation Amidation Compounds

A sealed tube was equipped with a magnetic stir bar and was charged with P2 (2 mg, 2 mol%), BHT (88 mg, 0.4 mmol, 2 equiv.), aldehydes (0.2 mmol, 1 equiv.), amines (0.6 mmol, 3 equiv.) and dioxane (2 mL) under air at room temperature. The reaction tube was placed at a distance of 5 cm from 3 W Blue LEDs and stirred for 12 hours (for substrates **1a**, **1b**, **1c**, **1e**, **1f**, **1g**, **1h**, **1k**, **1l**, **1m**, **1n**, **1o**, **1s**, **1t**, **2f**, **2g**, **2i**, **2j**), 16 hours (for substrates **1p**, **1q**, **1r**, **2c**), 24 hours (for substrates **1d**, **1i**, **1j**, **2b**, **2e**), 36 hours (for substrate **2d**) or 48 hours (for substrate **2h**). Thin layer chromatography (TLC) was used to monitor the progress of the reaction. After the reaction was completed, the reaction mixture was quenched with saturated aqueous Na_2SO_3 solution (20 mL) and extracted with EA (3 × 10 mL). The organic phase was dried over Na_2SO_4, and concentrated on a rotary evaporator. The crude product was further purified by column chromatography (petroleum ether/ ethyl acetate = 3:1) to give the desired products.

5,5-Difluoro-1,3,7,9-tetramethyl-10-phenyl-5H-dipyrrolo[1,2-c:2',1'-f][1,3,2]diazaborinin-4-ium-5-uide(I): Red-brown solid; 78% yield; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.40-7.39 (m, 3 H), 7.20-7.18 (m, 2 H), 5.90 (s, 2 H), 2.48 (s, 6 H), 1.29 (s, 6 H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 155.4, 143.2, 141.8, 135.0, 131.4, 129.1, 128.9, 128.0, 121.2, 14.6, 14.3 ppm.

2,8-Dichloro-5,5-difluoro-1,3,7,9-tetramethyl-10-phenyl-5H-dipyrrolo[1,2-c:2',1'-f][1,3,2]diazaborinin-4-ium-5-uide (**P1**): Red solid; 60% yield; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.53-7.51 (m, 3 H), 7.27-7.24 (m, 2 H), 2.59 (s, 6 H), 1.36 (s, 6 H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 152.5, 142.4, 138.0, 134.2, 129.7, 129.5, 129.4, 127.8, 122.6, 12.4, 11.9 ppm.

2,8-Dibromo-5,5-difluoro-1,3,7,9-tetramethyl-10-phenyl-5H-dipyrrolo[1,2-c:2',1'-f][1,3,2]diazaborinin-4-ium-5-uide (**P2**): Red solid; 83% yield; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.54-7.52 (m, 3 H), 7.26-7.24 (m, 2 H), 2.61 (s, 6 H), 1.36 (s, 6 H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 154.0, 142.1, 140.7, 134.4, 130.4, 129.6, 129.5, 127.8, 111.8, 13.7, 13.6 ppm; IR (KBr): 1533, 1459, 1348, 1180, 992, 720, 529 cm^{-1}; HRMS (*m/z*, ESI) Calcd. for $C_{19}H_{18}BBr_2F_2N_2^+$ $[M+H]^+$: 480.9892, found: 480.9897.

5,5-Difluoro-2,8-diiodo-1,3,7,9-tetramethyl-10-phenyl-5H-dipyrrolo[1,2-c:2',1'-f][1,3,2]diazaborinin-4-ium-5-uide (**P3**): Red solid; 69% yield; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.55-7.53 (m, 3 H), 7.27-7.25 (m, 2 H), 2.67 (s, 6 H), 1.40 (s, 6 H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 156.8, 145.3, 141.3, 134.7, 131.3, 129.5, 129.4, 127.7, 85.7, 16.9, 16.0 ppm.

2,8-Dibromo-5,5-difluoro-10-(4-methoxyphenyl)-1,3,7,9-tetramethyl-5H-dipyrrolo[1,2-c:2',1'-f][1,3,2]diazaborinin-4-ium-5-uide (**P4**): Red solid; 30% yield; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.14 (d, *J* = 8.5 Hz, 2 H), 7.03 (d, *J* = 8.5 Hz, 2 H), 3.89 (s, 3 H), 2.58 (s, 6 H), 1.42 (s, 6 H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 160.5, 153.7, 142.3, 140.6, 130.8, 129.1, 126.3, 114.8, 111.7, 55.4, 13.9, 13.7 ppm.

2,8-Dibromo-5,5-difluoro-1,3,7,9-tetramethyl-10-(4-(trifluoromethyl)phenyl)-5H-dipyrrolo[1,2-c:2',1'-f][1,3,2]diazaborinin-4-ium-5-uide (**P5**): Red solid; 35% yield; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.82 (d, *J* = 8.0 Hz, 2 H), 7.44 (d, *J* = 8.0 Hz, 2 H), 2.60 (s, 6 H), 1.34 (s, 6 H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 154.8, 140.3, 139.8, 138.3, 132.1 (q, J_{C-F} = 32.8 Hz, 1 C), 130.0, 128.7, 126.4 (q, J_{C-F} = 3.5 Hz, 1 C), 123.7 (q, J_{C-F} = 271 Hz, 1 C), 112.3, 13.9, 13.8 ppm.

2,8-Dibromo-10-(4-bromophenyl)-5,5-difluoro-1,3,7,9-tetramethyl-5H-dipyrrolo[1,2-c:2',1'-f][1,3,2]diazaborinin-4-ium-5-uide (**P6**): Red solid; 43% yield; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.68 (d, *J* = 8.4 Hz, 2 H), 7.15 (d, *J* = 8.4 Hz, 2 H), 2.61 (s, 6 H), 1.41 (s, 6 H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 154.4, 140.4, 133.3, 132.8, 130.2, 129.6, 123.9, 112.1, 112.0, 14.0, 13.7 ppm.

(4-bromophenyl)(pyrrolidin-1-yl)methanone (**3a**)[14]: White solid; 45.5 mg; 90% yield; mp: 78-80 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.50 (d, *J* = 8.4 Hz, 2 H), 7.37 (d, *J* = 8.4 Hz, 2 H), 3.60 (t, *J* = 6.8 Hz, 2 H), 3.38 (t, *J* = 6.6 Hz, 2 H), 1.97-1.90 (m, 2 H), 1.88-1.82 (m, 2 H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 167.5, 135.0, 130.4, 127.8, 123.1, 48.6, 45.3, 25.4, 23.4 ppm; IR (KBr): 2961, 1607, 1439, 1006, 841, 747 cm^{-1}; HRMS (*m/z*, ESI) Calcd. for $C_{11}H_{13}BrNO^+$ $[M+H]^+$: 254.0175, found: 254.0174.

(4-chlorophenyl)(pyrrolidin-1-yl)methanone (**3b**): Yellow solid; 30.2 mg; 72% yield; mp: 67-69 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.46 (d, *J* = 8.4 Hz, 2 H), 7.36 (d, *J* = 8.4 Hz, 2 H), 3.62 (t, *J* = 6.8 Hz, 2 H), 3.40 (t, *J* = 6.6 Hz, 2 H), 1.99-1.90 (m, 2 H), 1.89-1.84 (m, 2 H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 168.6, 135.8, 135.5, 128.7, 128.5, 49.6, 46.3, 26.4, 24.4 ppm;IR (KBr):2973, 1625, 1421, 1088, 850, 756 cm^{-1}; HRMS (*m/z*, ESI) Calcd. for $C_{11}H_{12}ClNNaO^+$ $[M+Na]^+$: 232.0499, found: 232.0496.

(4-fluorophenyl)(pyrrolidin-1-yl)methanone (**3c**): Yellow solid; 29.8 mg; 77% yield; mp: 79-82 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.55-7.51 (m, 2 H), 7.09-7.05 (m, 2 H), 3.63 (t, *J* = 6.8 Hz, 2 H), 3.42 (t, *J* = 6.6 Hz, 2 H), 1.99-1.92 (m, 2 H), 1.91-1.84 (m, 2 H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 168.7, 163.5 (d, J_{C-F} = 248 Hz, 1 C), 133.3 (d, J_{C-F} = 3.2 Hz, 1 C), 129.4 (d, J_{C-F} = 8.5 Hz, 1 C), 115.3 (d, J_{C-F} = 21.7 Hz, 1 C), 49.7, 46.3, 26.5, 24.4 ppm; IR (KBr): 2955, 1636, 1427, 1215, 850, 756 cm^{-1}; HRMS (*m/z*, ESI) Calcd. for $C_{11}H_{13}FNO^+$ $[M+H]^+$: 194.0976, found: 194.0970.

phenyl(pyrrolidin-1-yl)methanone (**3d**)[27]: Yellow oil; 24.5 mg; 70% yield; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.51-7.49 (m, 2 H), 7.39-7.37 (m, 3 H), 3.63 (t, *J* = 6.8 Hz, 2 H), 3.41 (t, *J* = 6.6 Hz, 2 H), 1.98-1.91 (m, 2 H), 1.89-1.82 (m, 2 H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 169.7, 137.3, 129.7, 128.2, 127.1, 49.6, 46.1, 26.4, 24.5 ppm; IR (KBr): 2960, 1622, 1421, 718 cm^{-1}; HRMS

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(*m/z*, ESI) Calcd. for $C_{11}H_{13}NNaO^+$ $[M+Na]^+$: 198.0889, found: 198.0885.

(4-nitrophenyl)(pyrrolidin-1-yl)methanone (**3e**): Light yellow solid; 33.5 mg; 75% yield; mp: 77-79 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 8.24 (d, *J* = 8.6 Hz, 2 H), 7.66 (d, *J* = 8.6 Hz, 2 H), 3.64 (t, *J* = 6.8 Hz, 2 H), 3.36 (t, *J* = 6.6 Hz, 2 H), 2.02-1.94 (m, 2 H), 1.93-1.87 (m, 2 H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 167.3, 148.4, 143.2, 128.1, 123.7, 49.4, 46.4, 26.4, 24.4 ppm; IR (KBr): 2958, 1621, 1521, 1430, 1351, 862, 721 cm^{-1}; HRMS (*m/z*, ESI) Calcd. for $C_{11}H_{13}N_2O_3^+$ $[M+H]^+$: 221.0920, found: 221.0918.

4-(pyrrolidine-1-carbonyl)benzonitrile (**3f**): Yellow oil; 38.3 mg; 95% yield; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.68 (d, *J* = 8.4 Hz, 2 H), 7.59 (d, *J* = 8.4 Hz, 2 H), 3.62 (t, *J* = 6.8 Hz, 2 H), 3.34 (t, *J* = 6.6 Hz, 2 H), 1.99-1.92 (m, 2 H), 1.91-1.83 (m, 2 H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 167.6, 141.4, 132.2, 127.8, 118.2, 113.5, 49.4, 46.3, 26.4, 24.3 ppm; IR (KBr): 2967, 2225, 1604, 1445, 862, 762 cm^{-1}; HRMS (*m/z*, ESI) Calcd. for $C_{12}H_{13}N_2O^+$ $[M+H]^+$: 201.1022, found: 201.1019.

pyrrolidin-1-yl(4-(trifluoromethyl)phenyl)methanone (**3g**): Yellow solid; 41.4 mg; 85% yield; mp: 75-77 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.66 (d, *J* = 8.2 Hz, 2 H), 7.61 (d, *J* = 8.2 Hz, 2 H), 3.64 (t, *J* = 6.8 Hz, 2 H), 3.38 (t, *J* = 6.6 Hz, 2 H), 2.00-1.94 (m, 2 H), 1.92-1.87 (m, 2 H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ_C168.2, 140.7, 131.6 (q, $J_{C\text{-}F}$ = 32.2 Hz, 1 C), 127.5, 125.4 (q, $J_{C\text{-}F}$ = 3.6 Hz, 1 C), 123.8 (q, $J_{C\text{-}F}$ = 271 Hz, 1 C), 49.5, 46.3, 26.4, 24.4 ppm; IR (KBr): 2958, 1610, 1448, 1324, 1130, 853 cm^{-1}; HRMS (*m/z*, ESI) Calcd. for $C_{12}H_{12}F_3NNaO^+$ $[M+Na]^+$: 266.0763, found: 266.0762.

methyl 4-(pyrrolidine-1-carbonyl)benzoate (**3h**): Yellow solid; 38.8 mg; 83% yield; mp: 96-98 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 8.04 (d, *J* = 8.3 Hz, 2 H), 7.54 (d, *J* = 8.3 Hz, 2 H), 3.90 (s, 3 H), 3.62 (t, *J* = 6.8 Hz, 2 H), 3.35 (t, *J* = 6.6 Hz, 2 H), 1.97-1.91 (m, 2 H), 1.89-1.82 (m, 2 H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 168.7, 166.4, 141.4, 131.1, 129.6, 127.0, 52.3, 49.4, 46.2, 26.4, 24.4 ppm; IR (KBr): 2955, 1716, 1621, 1421, 1280, 1103, 736 cm^{-1}; HRMS (*m/z*, ESI) Calcd. for $C_{13}H_{16}NO_3^+$ $[M+H]^+$: 234.1125, found: 234.1121.

pyrrolidin-1-yl(p-tolyl)methanone (**3i**): Yellow solid; 28.5 mg; 75% yield; mp: 73-75 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.42 (d, *J* = 8.0 Hz, 2 H), 7.18 (d, *J* = 8.0 Hz, 2 H), 3.63 (t, *J* = 6.8 Hz, 2 H), 3.43 (t, *J* = 6.6 Hz, 2 H), 2.36 (s, 3 H), 1.98-1.91 (m, 2 H), 1.88-1.82 (m, 2 H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 169.8, 139.9, 134.3, 128.8, 127.2, 49.7, 46.2, 26.4, 24.5, 21.4 ppm; IR (KBr): 2967, 1607, 1421, 839, 750 cm^{-1}; HRMS (*m/z*, ESI) Calcd: for $C_{12}H_{16}NO^+$ $[M+H]^+$: 190.1226, found: 190.1224.

(4-methoxyphenyl)(pyrrolidin-1-yl)methanone (**3j**): Yellow oil; 30.4 mg; 74% yield; mp: 71-73 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.51 (d, *J* = 8.8 Hz, 2 H), 6.89 (d, *J* = 8.8 Hz, 2 H), 3.82 (s, 3 H), 3.62 (t, *J* = 6.8 Hz, 2 H), 3.47 (t, *J* = 6.6 Hz, 2 H), 1.97-1.91 (m, 2 H), 1.89-1.84 (m, 2 H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 169.4, 160.8, 129.4, 129.2, 113.4, 55.3, 49.8, 46.3, 26.5, 24.5 ppm; IR (KBr): 2964, 1613, 1424, 1254, 1174, 1024, 847, 762 cm^{-1}; HRMS (*m/z*, ESI) Calcd. for $C_{12}H_{16}NO_2^+$ $[M+H]^+$: 206.1176, found: 206.1173.

(3-nitrophenyl)(pyrrolidin-1-yl)methanone (**3k**): Yellow solid; 34.5 mg; 78% yield; mp: 61-63 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 8.37 (t, *J* = 1.7 Hz, 1 H), 8.27-8.25 (m, 1 H), 7.86 (d, *J* = 7.6 Hz, 1 H), 7.60 (t, *J* = 8.0 Hz, 1 H), 3.66 (t, *J* = 6.8 Hz, 2 H), 3.43 (t, *J* = 6.6 Hz, 2 H), 2.02-1.95 (m, 2 H), 1.94-1.88 (m, 2 H) ppm; ^{13}C NMR (A100 MHz, $CDCl_3$): δ_C 166.9, 147.9, 138.7, 133.3, 129.6, 124.6, 122.3, 49.6, 46.5, 26.4, 24.4 ppm; IR (KBr): 2958, 1613, 1530, 1442, 1351, 824, 723 cm^{-1}; HRMS (*m/z*, ESI) Calcd. for $C_{11}H_{13}N_2O_3^+$ $[M+H]^+$: 221.0921, found: 221.0918.

(3-bromophenyl)(pyrrolidin-1-yl)methanone (**3l**): Yellow oil; 43.5 mg; 86% yield; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.64 (t, *J* = 1.6 Hz, 1 H), 7.54-7.51 (m, 1 H), 7.43-7.41(m, 1 H), 7.26 (t, *J* = 7.8 Hz, 1 H), 3.62 (t, *J* = 6.8 Hz, 2 H), 3.41 (t, *J* = 6.6 Hz, 2 H), 1.97-1.92 (m, 2 H), 1.90-1.86 (m, 2 H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 168.0, 139.1, 132.8, 130.2, 129.9, 125.6, 122.4, 49.6, 46.3, 26.4, 24.4 ppm; IR (KBr): 2958, 1625, 1430, 803, 747 cm^{-1}; HRMS (*m/z*, ESI) Calcd. for $C_{11}H_{13}BrNO^+$ $[M+H]^+$: 254.0175, found: 254.0174.

naphthalen-2-yl(pyrrolidin-1-yl)methanone (**3m**): Yellow oil; 36.2 mg; 80% yield; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 8.00 (s, 1 H), 7.86-7.83 (m, 3 H), 7.62-7.60 (m, 1 H), 7.53-7.48 (m, 2 H), 3.69 (t, *J* = 6.9 Hz, 2 H), 3.47 (t, *J* = 6.6 Hz, 2 H), 2.00-1.94 (m, 2 H), 1.89-1.83 (m, 2 H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 169.7, 134.5, 133.8, 132.6, 128.5, 128.1, 127.8, 127.0, 126.9, 126.5, 124.4, 49.7, 46.3, 26.4, 24.5 ppm; IR (KBr): 2970, 1607, 1421, 871, 765 cm^{-1}; HRMS (*m/z*, ESI) Calcd. for $C_{15}H_{15}NNaO^+$ $[M+Na]^+$: 248.1046, found: 248.1046.

pyren-1-yl(pyrrolidin-1-yl)methanone (**3n**): Yellow oil; 53.3 mg; 89% yield; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 8.21-7.97 (m, 9 H), 3.89 (t, *J* = 7.0 Hz, 2 H), 3.12 (t, *J* = 6.8 Hz, 2 H), 2.07-2.00 (m, 2 H), 1.85-1.79 (m, 2 H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ_C169.6, 132.6, 131.6, 131.1, 130.7, 128.6, 128.0, 127.1, 126.9, 126.2, 125.6, 125.4, 124.7, 124.6, 124.5, 124.1, 123.7, 48.6, 45.8, 26.0, 24.6 ppm; IR (KBr): 2960, 1621, 1418, 844, 718 cm^{-1}; HRMS (*m/z*, ESI) Calcd. for $C_{21}H_{18}NO^+$ $[M+H]^+$: 300.1383, found: 300.1381.

pyrrolidin-1-yl(thiophen-2-yl)methanone (**3o**): Yellow solid; 26.1 mg; 72% yield; mp: 57-59 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.50 (d, *J* = 3.6 Hz, 1 H), 7.45 (d, *J* = 5.0 Hz, 1 H), 7.06-7.04 (m, 1 H), 3.75 (t, *J* = 6.0 Hz, 2 H), 3.65 (t, *J* = 6.4 Hz, 2 H), 2.00-1.90 (m, 4 H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 161.8, 139.6, 129.5, 129.4, 127.1, 48.9, 47.3, 26.7, 24.1 ppm; IR (KBr): 2955, 1583, 1433, 829, 741 cm^{-1}; HRMS (*m/z*, ESI) Calcd. for $C_9H_{11}NNaOS^+$ $[M+Na]^+$: 204.0453, found: 204.0452.

pyridin-4-yl(pyrrolidin-1-yl)methanone (**3p**): Yellow oil; 32.4 mg; 92% yield; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 8.64 (s, 2 H), 7.34-7.33 (m, 2 H), 3.59 (t, *J* = 6.6 Hz, 2 H), 3.32 (t, *J* = 6.5 Hz, 2 H), 1.94-1.89 (m, 2 H), 1.87-1.84 (m, 2 H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 167.1, 150.1, 144.5, 121.2, 49.2, 46.2, 26.3, 24.3 ppm; IR (KBr): 2957, 1624, 1442, 835, 659 cm^{-1}; HRMS (*m/z*, ESI) Calcd. for $C_{10}H_{12}N_2O^+$ $[M+H]^+$: 177.1022, found: 177.1022.

pyridin-2-yl(pyrrolidin-1-yl)methanone (**3q**): Yellow oil; 27.8 mg; 79% yield; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 8.56 (d, *J* = 4.7 Hz, 1 H), 7.81-7.74 (m, 2 H), 7.33-7.30 (m, 1 H), 3.71 (t, *J* = 6.3 Hz, 2 H), 3.66 (t, *J* = 6.8 Hz, 2 H), 1.93-1.88 (m, 4 H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 166.5, 154.6, 148.0, 136.8, 124.6, 123.8, 49.1, 46.8, 26.6, 24.0 ppm; IR (KBr): 2961, 1627, 1448, 812, 753 cm^{-1}; HRMS (*m/z*, ESI) Calcd. for $C_{10}H_{12}N_2NaO^+$ $[M+Na]^+$: 199.0841, found: 199.0842.

(1-methyl-1H-indol-2-yl)(pyrrolidin-1-yl)methanone (**3r**): Yellow oil; 32.4 mg; 71% yield; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H

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7.63 (d, *J* = 8.0 Hz, 1 H), 7.36 (d, *J* = 8.2 Hz, 1 H), 7.32-7.28 (m, 1 H), 7.16-7.12 (m, 1 H), 6.75 (s, 1 H), 3.93 (s, 3 H), 3.72-3.67 (m, 4 H), 2.00-1.92 (m, 4 H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 162.4, 138.0, 132.8, 126.3, 123.5, 121.6, 120.1, 109.9, 104.6, 49.7, 46.2, 31.5, 26.4, 24.3 ppm; IR (KBr): 2958, 1616, 1524, 1462, 1342, 744 cm^{-1}; HRMS (*m/z*, ESI) Calcd. for $C_{14}H_{17}N_2O^+$ $[M+H]^+$: 229.1335, found: 229.1334.

pyrrolidin-1-yl(quinolin-2-yl)methanone (**3s**): Yellow oil; 27.1 mg; 59% yield; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 8.23 (d, *J* = 8.4 Hz, 1 H), 8.08 (d, *J* = 8.4 Hz, 1 H), 7.90 (d, *J* = 8.4 Hz, 1 H), 7.83 (d, *J* = 8.0 Hz, 1 H), 7.73 (t, *J* = 7.4 Hz, 1 H), 7.58 (t, *J* = 7.4 Hz, 1 H), 3.86 (t, *J* = 6.0 Hz, 2 H), 3.73 (t, *J* = 6.2 Hz, 2 H), 1.97-1.91 (m, 4 H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ_C166.5, 154.2, 146.5, 136.8, 129.8, 129.7, 128.2, 127.6, 127.5, 120.7, 49.2, 46.9, 26.6, 24.0 ppm; IR (KBr): 2964, 1627, 1410, 844, 771 cm^{-1}; HRMS (*m/z*, ESI) Calcd. for $C_{14}H_{15}N_2O^+$ $[M+H]^+$: 227.1178, found: 227.1179.

3-(pyrrolidine-1-carbonyl)benzaldehyde (**3t**): Yellow oil; 14.2 mg; 35% yield; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 10.04 (s, 1 H), 8.04 (s, 1 H), 7.93 (d, *J* = 7.5 Hz, 1 H), 7.80 (d, *J* = 7.5 Hz, 1 H), 7.59 (t, *J* = 7.6 Hz, 1 H), 3.67 (t, *J* = 6.7 Hz, 2 H), 3.44 (t, *J* = 6.5 Hz, 2 H), 2.00-1.96 (m, 2 H), 1.94-1.89 (m, 2 H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 191.5, 168.2, 138.2, 136.3, 133.0, 130.8, 129.2, 128.3, 49.6, 46.4, 26.4, 24.4 ppm; IR (KBr): 2923, 1698, 1621, 1450, 1191, 812, 741 cm^{-1}; HRMS (*m/z*, ESI) Calcd. for $C_{12}H_{14}NO_2^+$ $[M+H]^+$: 204.1019, found: 204.1020.

4-(piperidine-1-carbonyl)benzonitrile (**3fb**)[31]: Yellow solid; 41.1 mg; 96% yield; mp: 86-88 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.68 (d, *J* = 8.1 Hz, 2 H), 7.47 (d, *J* = 8.1 Hz, 2 H), 3.69 (br, s, 2 H), 3.26 (br, s, 2 H), 1.67 (br, s, 4 H), 1.50 (br, s, 2 H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 168.2, 140.9, 132.4, 127.5, 118.2, 113.2, 48.6, 43.2, 26.5, 25.5, 24.4 ppm; IR (KBr): 2931, 2228, 1627, 1448, 1271, 853 cm^{-1}; HRMS (*m/z*, ESI) Calcd. for $C_{13}H_{15}N_2O^+$ $[M+H]^+$: 215.1178, found: 215.1177.

4-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)benzonitrile (**3fc**): White solid; 46.1 mg; 88% yield; mp: 147-149 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.74-7.72 (m, 2 H), 7.56-7.55 (m, 2 H), 7.26-7.16 (m, 3.7 H, major), 6.91 (br, s, 0.4 H, minor), 4.89 (br, s, 1.1 H, major), 4.51 (br, s, 0.8 H, minor), 4.00 (br, s, 0.8 H, minor), 3.58 (br, s, 1.1 H, major), 3.00-2.87 (m, 2 H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 168.9 (major), 168.4 (minor), 140.5, 134.5, 133.4, 132.5 (major), 132.2 (minor), 129.2 (minor), 128.7 (major), 127.9 (minor), 127.6 (major), 127.3, 126.9 (major), 126.6 (minor), 125.8, 118.1, 113.7, 49.7 (minor), 45.2 (major), 44.8 (major), 40.7 (minor), 29.5 (major), 28.1 (minor) ppm; IR (KBr): 2919, 2225, 1627, 1445, 1259, 847, 756 cm^{-1}; HRMS (*m/z*, ESI) Calcd. for $C_{17}H_{15}N_2O^+$ $[M+H]^+$: 263.1178, found: 263.1177.

4-(morpholine-4-carbonyl)benzonitrile (**3fd**)[27c]: White solid; 36.3 mg; 84% yield; mp: 129-131 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.70 (d, *J* = 8.1 Hz, 2 H), 7.49 (d, *J* = 8.1 Hz, 2 H), 3.76 (br, s, 4 H), 3.60 (br, s, 2 H), 3.36 (br, s, 2 H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 168.3, 139.6, 132.5, 127.8, 118.0, 113.7, 66.7, 48.0, 42.5 ppm; IR (KBr): 2928, 2222, 1619, 1439, 1280, 1112, 1009, 847 cm^{-1}; HRMS (*m/z*, ESI) Calcd. for $C_{12}H_{13}N_2O_2^+$ $[M+H]^+$: 217.0971, found: 217.0970.

4-(4-methylpiperidine-1-carbonyl)benzonitrile (**3fe**): Yellow solid; 39.2 mg; 86% yield; mp: 83-85 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.68 (d, *J* = 7.6 Hz, 2 H), 7.46 (d, *J* = 7.6 Hz, 2 H), 4.63 (d, *J* = 11.4 Hz, 1 H), 3.53 (d, *J* = 11.7 Hz, 1 H), 3.00 (t, *J* = 11.8 Hz, 1 H), 2.78 (t, *J* = 11.8 Hz, 1 H), 1.78-1.58 (m, 5 H), 0.96 (d, *J* = 6.5 Hz, 3 H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 168.0, 140.8, 132.3, 127.4, 118.1, 113.1, 47.9, 42.5, 34.6, 33.6, 31.8, 30.9, 29.6, 22.6, 21.5, 14.0 ppm; IR (KBr): 2923, 2225, 1630, 1457, 1271, 1109, 853, 756 cm^{-1}; HRMS (*m/z*, ESI) Calcd. for $C_{14}H_{17}N_2O^+$ $[M+H]^+$: 229.1335, found: 229.1342.

4-(4-benzylpiperidine-1-carbonyl)benzonitrile (**3ff**): Yellow oil; 55.7 mg; 90% yield; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.65 (d, *J* = 8.1 Hz, 2 H), 7.44 (d, *J* = 7.6 Hz, 2 H), 7.23 (d, *J* = 7.0 Hz, 2 H), 7.17-7.14 (m, 1 H), 7.08 (d, *J* = 7.4 Hz, 2 H), 4.63 (d, *J* = 11.3 Hz, 1 H), 3.52 (d, *J* = 11.8 Hz, 1 H), 2.92 (t, *J* = 12.2 Hz, 1 H), 2.69 (t, *J* = 11.5 Hz, 1 H), 2.53 (t, *J* = 6.8 Hz, 2 H), 1.80-1.76 (m, 2 H), 1.57 (d, *J* = 11.4 Hz, 1 H), 1.27-1.21 (m, 1 H), 1.11-1.09 (m, 1 H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 168.1, 140.7, 139.6, 132.3, 129.0, 128.3, 127.5, 126.1, 118.1, 113.2, 47.8, 42.8, 42.4, 38.1, 32.5, 31.6 ppm; IR (KBr): 2918, 2228, 1627, 1448, 1283, 844, 700 cm^{-1}; HRMS (*m/z*, ESI) Calcd. for $C_{20}H_{21}N_2O^+$ $[M+H]^+$: 305.1648, found: 305.1649.

ethyl 1-(4-cyanobenzoyl)piperidine-3-carboxylate (**3fg**): Yellow oil; 44.6 mg; 78% yield; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.69 (d, *J* = 8.1 Hz, 2 H), 7.48 (d, *J* = 7.2 Hz, 2 H), 4.15 (br, s, 2 H), 3.59-3.46 (m, 1 H), 3.34-3.08 (m, 2 H), 2.59-2.43(m, 1 H), 2.10-2.08 (m, 1 H), 1.75 (s, 2 H), 1.61-1.45 (m, 1 H), 1.24 (s, 3 H), 0.86-0.82 (m, 1 H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 172.7, 172.3, 168.3, 140.2, 132.3, 127.5, 118.0, 113.3, 60.7, 48.8, 47.8, 43.9, 42.3, 41.4, 40.8, 27.1, 24.7, 23.5, 14.0 ppm; IR (KBr): 2926, 2228, 1724, 1639, 1436, 1274, 1182, 1091, 1026, 853, 765 cm^{-1}; HRMS (*m/z*, ESI) Calcd. for $C_{16}H_{19}N_2O_3^+$ $[M+H]^+$: 287.1390, found: 287.1391.

4-(4-methylpiperazine-1-carbonyl)benzonitrile (**3fh**): Yellow solid; 31.2 mg; 68% yield; mp: 91-93 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.71 (d, *J* = 8.4 Hz, 2 H), 7.50 (d, *J* = 8.4 Hz, 2 H), 3.81 (br, s, 2 H), 3.38 (br, s, 2 H), 2.51 (br, s, 2 H), 2.35-2.33 (m, 5 H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ_C168.2, 140.1, 132.4, 127.8, 118.1, 113.6, 55.1, 54.6, 47.5, 45.9, 42.1 ppm; IR (KBr): 2923, 2222, 1633, 1442, 1289, 1003, 841 cm^{-1}; HRMS (*m/z*, ESI) Calcd. for $C_{13}H_{16}N_3O^+$ $[M+H]^+$: 230.1287, found: 230.1290.

4-(isoindoline-2-carbonyl)benzonitrile (**3fi**): Light yellow solid; 46.2 mg; 93% yield; mp: 169-171 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.75 (d, *J* = 7.9 Hz, 2 H), 7.67 (d, *J* = 7.6 Hz, 2 H), 7.35-7.26 (m, 3 H), 7.17-7.15 (m, 1 H), 5.01 (s, 2 H), 4.72 (s, 2 H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 168.2, 140.7, 135.8, 132.4, 128.0, 127.7, 127.5, 122.9, 122.4, 118.0, 113.8, 54.7, 52.5 ppm; IR (KBr): 2912, 2225, 1615, 1424, 847, 759 cm^{-1}; HRMS (*m/z*, ESI) Calcd. for $C_{16}H_{12}N_2NaO^+$ $[M+Na]^+$: 271.0841, found: 271.0840.

4-(azepane-1-carbonyl)benzonitrile (**3fj**): Yellow solid; 42.9 mg; 94% yield; mp: 87-88 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.67 (d, *J* = 7.8 Hz, 2 H), 7.44 (d, *J* = 7.9 Hz, 2 H), 3.65 (t, *J* = 5.2 Hz, 2 H), 3.28 (t, *J* = 5.0 Hz, 2 H), 1.81-1.80 (m, 2 H), 1.69-1.57 (m, 6 H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 169.4 (major), 162.8 (minor), 141.6, 132.3, 127.1, 118.1, 112.8, 49.5 (major), 47.6 (minor), 46.3 (major), 43.3 (minor), 30.1 (minor), 29.3 (major), 27.8 (minor), 27.6 (major), 27.0 (major), 26.8 (minor), 26.7

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(minor), 26.3 (major) ppm; IR (KBr): 2926, 2228, 1630, 1427, 1280, 862 cm^{-1}; HRMS (*m/z*, ESI+) Calcd. for $C_{14}H_{17}N_2O^+$ $[M+H]^+$: 229.1335, found: 229.1334.

N-phenylacetamide (**4a**)[28]: White solid; 42.5 mg; 63% yield; mp: 99-101 °C; ^1H NMR (400 MHz, $CDCl_3$): δ_H7.86 (br, s, 1 H); 7.50 (d, *J* = 7.9 Hz, 2 H), 7.29 (t, *J* = 7.6 Hz, 2 H), 7.09 (t, *J* = 7.4 Hz, 1 H), 2.14 (s, 1 H) ppm; ^{13}C NMR (APT, 100 MHz, $CDCl_3$): δ_C 168.7, 138.0, 128.9, 124.2, 120.0, 24.4 ppm.

2,6-di-tert-butyl-4-hydroperoxy-4-methylcyclohexa-2,5-dienone (**BHT-OOH**): White solid; 95% yield; ^1H NMR (400 MHz, $CDCl_3$): δ_H 7.81(br, s, 1 H), 6.56 (s, 2 H), 1.36 (s, 3 H), 1.23 (s, 18 H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 186.2, 148.8, 140.0, 78.8, 34.8, 29.4, 23.9 ppm; HRMS (*m/z*, ESI) Calcd. for $C_{15}H_{24}NaO_3^+$ $[M+Na]^+$: 275.1617, found: 275.1615.

2,6-di-tert-butyl-4-ethyl-4-hydroperoxycyclohexa-2,5-dienone (**BHEB-OOH**): White solid; 96% yield; ^1H NMR (400 MHz, $CDCl_3$): δ_H 8.22 (br, s, 1 H), 6.50 (s, 2 H), 1.67 (q, *J* = 14.6 Hz, 7.3 Hz, 2 H), 1.22 (s, 18 H), 0.72 (t, *J* = 8.1 Hz, 3 H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 186.6, 149.9, 139.4, 82.6, 34.9, 29.5, 29.4, 7.9 ppm; HRMS (*m/z*, ESI) Calcd. for $C_{16}H_{27}O_3^+$ $[M+H]^+$: 267.1954, found: 267.1948.

2,4,6-tri-tert-butyl-4-hydroperoxycyclohexa-2,5-dienone (**TBP-OOH**): White solid; 92% yield; ^1H NMR (400 MHz, $CDCl_3$): δ_H 7.73 (br, s, 1 H), 6.71 (s, 2 H), 1.25 (s, 18 H), 0.96 (s, 9 H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 186.4, 150.2, 139.6, 85.9, 40.4, 35.2, 29.5, 26.0 ppm; HRMS (*m/z*, ESI) Calcd. for $C_{18}H_{31}O_3^+$ $[M+Na]^+$: 295.2267, found: 295.2266.

2,6-di-tert-butyl-4-hydroxy-4-methylcyclohexa-2,5-dienone (**BHT-OH**): White solid; ^1H NMR (400 MHz, $CDCl_3$): δ_H 6.55 (s, 2 H), 1.84 (br, s, 1 H), 1.41 (s, 3 H), 1.21 (s, 18 H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 186.1, 145.4, 143.2, 67.4, 34.5, 29.4, 28.0 ppm; HRMS (*m/z*, ESI) Calcd. for $C_{15}H_{24}NaO_2^+$ $[M+Na]^+$: 259.1668, found: 259.1670.

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