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Visible-Light Induced Regioselective Cycloaddition of Benzoyl Azides and Alkenes to Yield Oxazolines

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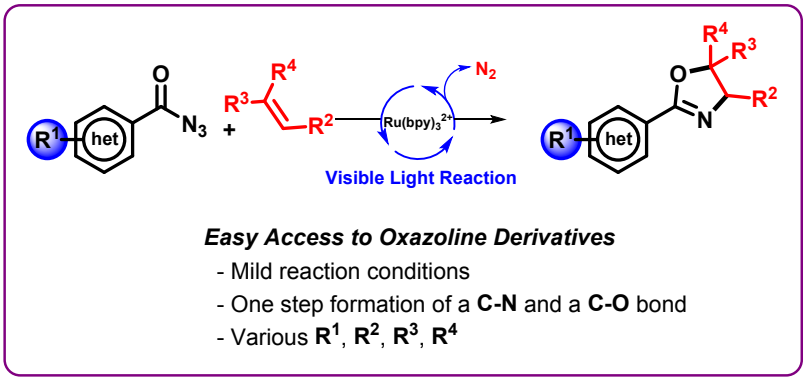
Supporting Information Placeholder



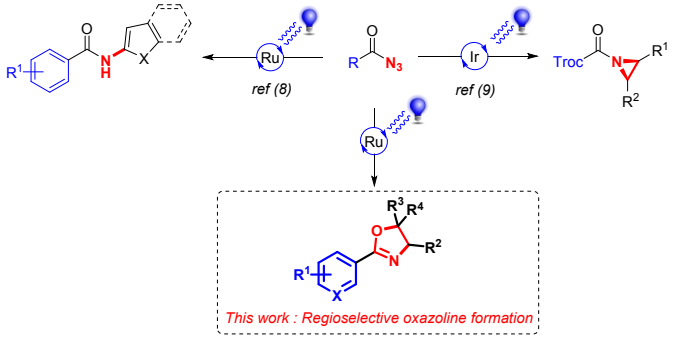
ABSTRACT: Visible-light catalysis allows the regioselective synthesis of oxazolines in high yields. The mild photosensitized manifold leverages the intermolecular formation of oxazolines with a wide functional group tolerance on both partners, benzoyl azides and alkenes. Mechanistic investigations suggest the sensitization of the azide moiety as the key activation step.

Introduction

Five-membered ring heterocycles represent one of the most prevalent subclasses of heterocycles.[1] Among them, the oxazoline core is an attractive target, because of its presence in many valuable synthetic and natural derivatives (*e.g.* patelamide A[2], useful in polymer material sciences[3] and as chiral ligands[4]). Despite the development of a plethora of strategies to build oxazolines, harsh conditions, intramolecular strategies and expensive catalysts are often required, thus limiting their applicability.[5] Consequently, innovative approaches to build the oxazoline core are to be sought.

Over the last decade, visible-light photocatalysis has emerged into a powerful tool for the formation of C-C, C-N or C-O bonds under mild conditions, using low energy light sources at room temperature. [6] Nevertheless, substantial efforts should be made in order to expand the scope of this tool and better understand the involved mechanisms. In particular visible-light sensitization mechanisms have remained relatively underdeveloped compared to photoredox ones. In this direction, we report the first visible-light sensitized reaction to build oxazolines. We aimed at avoiding highly pre-functionalized substrates as precursors by envisioning the use of easily accessible benzoyl azides derivatives to generate reactive nitrogen species. Under visible-light irradiation, dinitrogen was released as the only by-product. In particular, we wondered whether the *in-situ* generated acyl nitrene could cyclize on alkenyl partners to yield oxazolines. In this respect, only two UV-promoted examples, limited to fullerene or enolate derivatives as alkenyl partners have been reported.[7] In the former case – restricted to C_{60} systems – a two-steps

procedure involving an intermediate aziridine was used under high dilution conditions (11% yield),[7b] while in the latter synthetically useful yields were obtained on a severely limited selection of ortho-substituted aroyl-azides in the presence of cyclic enol-ethers.[7a]



Scheme 1: Visible-light activation of acyl azides.

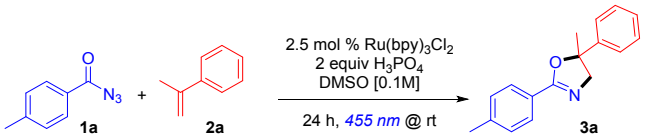
Analogously, reactions of acyl azides under visible-light catalysis are rare: to the best of our knowledge, only a photo-induced amidation reaction using benzoyl azides and electron-rich arenes (Scheme 1, top left),[8] the aziridination of alkenes using Troc-N_3 reagent from Yoon *et al.* (Scheme 1, top right)[9a] and a cascade cyclization towards oxindoles[9b] have been reported.

Herein, we disclose a distinctly new reactive pathway of benzoyl azides to selectively form oxazolines (Scheme 1, bottom). In contrast to the previous report by Nicewicz *et al.*,[10] this work represents the first general method to build the oxazoline nucleus *via* an intermolecular process under visible-light irradiation. The convergent nature of the strategy – as well as the straightforward synthesis of benzoyl azides from the corresponding benzoyl chloride or anhydride in the presence of sodium azide – make the process particularly appealing for the synthesis of highly-decorated structures. During the screening process of our previously reported C-H amidation reaction, the low-yielding cyclization of a putative carbenium ion was observed in two selected cases.[8] In this work, we systematically exploited the intermolecular cyclization to afford both carbocyclic and heterocyclic-decorated oxazolines.

Results and Discussion

We started our investigation using the following conditions: $Ru(bpy)_3Cl_2·6H_2O$ (2.5 mol %) as photocatalyst, H_3PO_4 (2 equiv) as an additive and 5 equivalents of the alkene in DMSO (0.1 M) under blue light irradiation (455 nm) at room temperature.[8] As a model reaction *p*-methylbenzoyl azide **1a** was reacted with *α*-methylstyrene **2a** in order to form the corresponding oxazoline derivative (5-methyl-5-phenyl-2-(*p*-tolyl)-4,5-dihydrooxazole **3a**). We were pleased to observe the total consumption of **1a** giving **3a** as the product in 78% yield (Table 1, entry 1). Intriguingly, no conversion of the starting material was observed under Yoon's aziridination conditions[9]. The same results were obtained using several different photocatalysts, such as *fac*-$Ir(ppy)_3$ (Entry 3) and Eosin Y (Entry 4). The ruthenium catalyst proved to be the only one able to perform the efficient sensitization of benzoyl azide **1a**. Decreasing the amount of catalyst from 2.5 mol% to 1 mol% caused a reduction of the yield to 58% (Entry 5).

Table 1: Optimization of the reaction conditions.



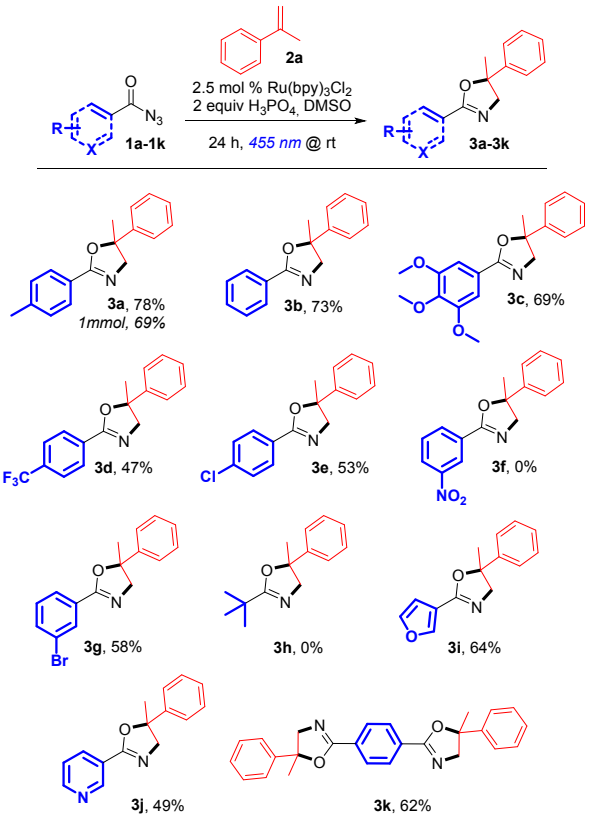
entry	variation from standard conditions [a]	yield [b]
1	**-**	**78%**
2	$[Ir(ppy)_2(dtbbpy)]^+$, Blue LED, CH_2Cl_2 [9]	0%
3	$Ir(ppy)_3$ instead of $Ru(bpy)_3Cl_2$	traces
4	Eosin Y instead of $Ru(bpy)_3Cl_2$	traces
5	1 mol % of $Ru(bpy)_3Cl_2$	58%
6	PTSA instead of H_3PO_4	25%
7	25 mol % of H_3PO_4	10%
8	Sunlight instead of Blue LED	65%[c]
9	No light	0%
10	No catalyst	0%
11	No H_3PO_4	0%
12	UV (254 nm) in MeCN @ 0°C	traces

[a] Standard conditions: reactions were performed with **1a** (0.31 mmol), **2a** (1.55 mmol), $Ru(bpy)_3Cl_2·6H_2O$ (2.5 mol %, 78 µmol), and H_3PO_4 (2 equiv, 0.62 mmol) in 3 mL of DMSO was irradiated with blue LED for 24 h. [b] isolated yields. [c] Sunlight irradiation without ruthenium catalyst led to a complex mixture.

Switching H_3PO_4 to other acids such as *p*-toluene sulfonic acid (PTSA) or diminishing the amount of H_3PO_4 (25 mol%) had a dramatic effect on the yield of the reaction (25% and 10%, respectively, Entries 6 and 7). Different control experiments confirmed that light, ruthenium catalysis and acid additive were crucial for the formation of the oxazoline **3a** (Entries 9, 10 and 11). Moreover, residual starting material was detected after reduced reaction times (12 h), while irradiation of 48 hours caused a slight decrease in the yields. Interestingly, the replacement of the LED irradiation with sunlight afforded the desired product in a good 65% yield (Entry 8), but only in the presence of the Ru-catalyst (Entry 8). Finally, a control experiment under the previously reported UV irradiation conditions (254 nm) was performed, but only traces of product can be detected, thus confirming the specific reactivity under visible-light conditions (Entry 12).

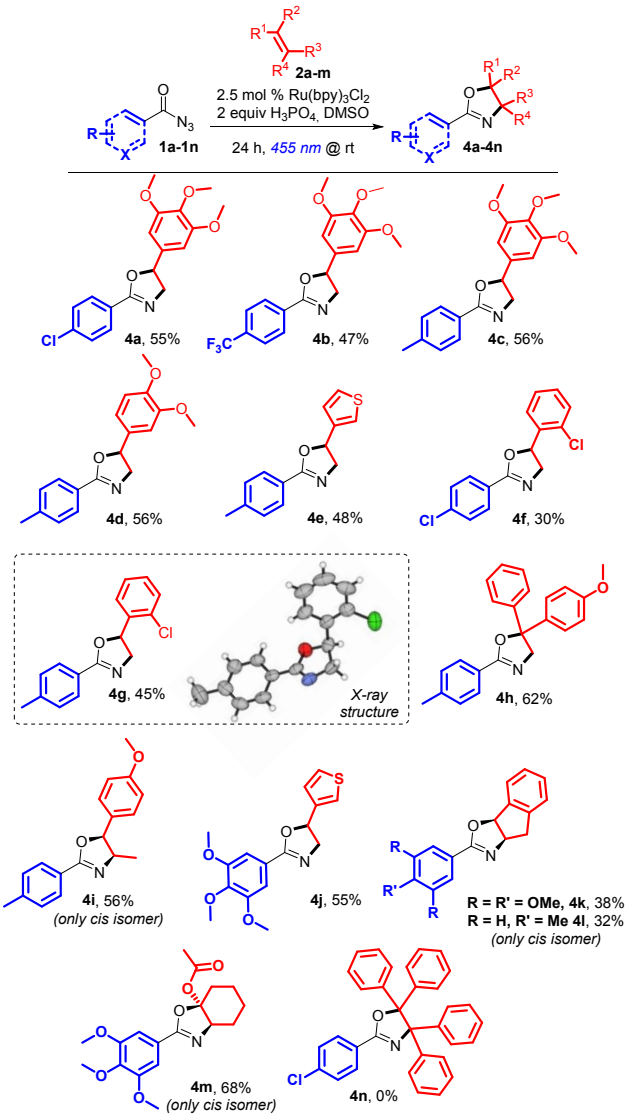
With these optimized conditions in hand (2.5 mol% of $Ru(bpy)_3Cl_2·6H_2O$, 2 equivalents of H_3PO_4 and 5 equivalents of alkene in DMSO (0.1 M) under blue light irradiation (~455 nm) at room temperature), we then investigated the scope of the synthetic manifold. At first, the substitution pattern on the benzoyl moiety was screened with both electron-donating and withdrawing groups (**Scheme 2**).

The parent benzoyl azide showed good conversion (Scheme 2, **3b**, 73%) and electron-donating groups, such as in *p*-methyl and 3,4,5-trimethoxy-derivatives **3a** and **3c** were tolerated (78% and 69% yield, respectively). Gratifyingly, compound **3a** was obtained in a good 69% yield when the reaction was performed on millimolar scale.



Scheme 2: Benzoyl azide scope of the photocatalyzed oxazoline formation. Reaction conditions: **1a–k** (0.34 mmol, 1 equiv), alkene (1.7 mmol, 5 equiv), H_3PO_4 (0.68 mmol, 2 equiv) and $Ru(bpy)_3Cl_2.6H_2O$ (8.5 µmol, 2.5 mol %) in dry DMSO (0.1 M) were irradiated with blue light under N_2. Isolated yield. All the compounds were obtained as racemic mixtures.

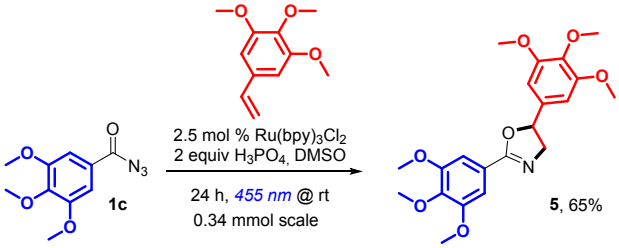
However, reaction of *o*-methylbenzoyl azide met with frustration, probably due to the steric hindrance of the methyl group. Electron-withdrawing groups on the benzoyl azides caused a decrease in reactivity towards *α*-methylstyrene, as observed for derivatives bearing a *p*-trifluoromethyl group **3d** (47%) or a *p*-chloro group **3e** (53%). 3-Bromobenzoyl azide provided product **3g** in 58%, which could be further functionalized using metal-catalyzed cross-coupling reactions. In the case of the *m*-nitro derivative, no formation of the desired product **3f** was observed. Also, pivaloyl azide did not react to provide **3h**, most likely due to a non-favourable energy transfer between the π-π systems. In particular, the available energy of the long-lived $[Ru(bpy)^3{}_{2+}]^*$ triplet state (46 kcal mol^{-1}) is presumably sufficient for energy transfer to aryl-acyl azides (E_{tr} = 41 kcal mol^{-1}), but not for alkyl-acyl azides.[8] Remarkably, heterobenzoyl azides were also efficient partners under the reaction conditions, providing the corresponding furyl-oxazoline **3i** or pyrido-oxazoline **3j** in 64 % and 49 % yield, respectively. This demonstrates that the reaction allows the synthesis of highly-decorated poly-heterocyclic scaffolds, which are highly prevalent in pharmaceutically-active compounds.[1] Finally, the terephthaloyl diazide **1k** reagent afforded compound **3k** in 62 % yield. Next, the alkenyl scope was investigated: mono-, di- and even tri-substituted alkenes bearing both electron-withdrawing and donating groups were found to be suitable coupling partners (**Scheme 3**).



Scheme 3: Scope of the alkenyl partner. Reaction conditions: **1a–n** (0.34 mmol, 1 equiv), alkene (1.7 mmol, 5 equiv), H_3PO_4 (0.68 mmol, 2 equiv) and $Ru(bpy)_3Cl_2.6H_2O$ (8.5 µmol, 2.5 mol %) in dry DMSO (0.1 M) were irradiated with blue light under N_2. Isolated yield. All the compounds were obtained as racemic mixtures.

Mono-substituted alkenes – such as 3,4,5-trimethoxystyrene – reacted with various benzoyl azides (*p*-Cl, *p*-CF_3, *p*-Me) yielding compounds **4a**, **4b** and **4c** in 43%, 47% and 56% yield, respectively. *p*-Methylbenzoyl

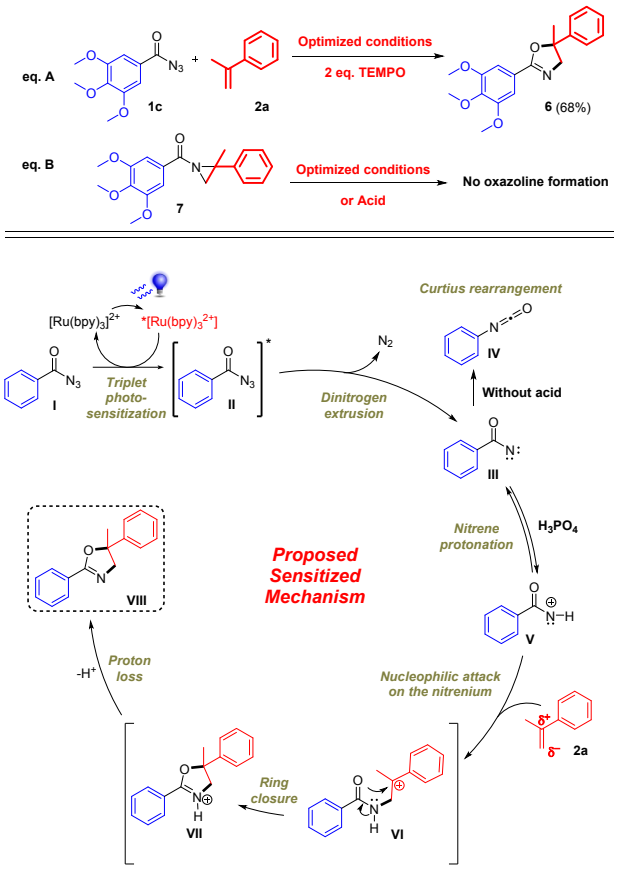
azide gave **4d** in 56% yield, as well as the derivative **4e** in 48% yield when coupled with 4,5-dimethoxystyrene and 3-vinylthiophene. Additionally, *p*-methylbenzoyl azide and 3,4,5-trimethoxybenzoyl azide produced respectively **4i** and **4j** in 56% and 55% yield. Moreover – electron-withdrawing groups were tolerated – as shown by using *o*-chlorostyrene, which was coupled with *p*-chloro benzoyl azide and *p*-methylbenzoyl azide giving products **4f** and **4g** in 30% and 45% yield. To our delight, the regiochemistry of the oxazoline formation was confirmed by the crystal structure of compound **4g** (highlighted in **Scheme 3**), allowing us to correct our previous report.[8] Then we focused our attention on *αα'* and in *αβ* disubstituted alkenes. First, we evaluated the reaction of a sterically-congested 1,1'-diarylethene with *p*-methylbenzoyl azide, which afforded the corresponding product **4h** (62% yield). *α,β*-disubstituted alkenes, such as anethole and indene, were also found to be compatible: *p*-methylbenzoyl azide **1a** afforded compound **4i** (56%) and indene gave products **4k** and **4l**, albeit in moderate yields. Cyclohex-1-en-1-yl acetate, a trisubstituted enol-ester, gave the corresponding product **4m** (68% yield), proving that aliphatic alkenes could also act as reaction partners. Notably, all *α,β* disubstituted alkenes coupled diastereoselectively with benzoyl azides, yielding exclusively the cis addition products (See S.I.). Finally, tetraphenyl ethene was tested in this reaction, but did not provide the desired product **4n**. Our reaction conditions have also been tested with alkynes (*i.e.* phenylacetylene, octyne, pentyne or propargyl alcohol) in order to reach oxazole derivatives. Unfortunately, alkynyl substrates were not reactive under the reaction conditions.



Scheme 4: Application to the synthesis of a bioactive compound

To demonstrate the synthetic applicability of the reported method, an anti-aggregant platelet agent was synthesized.[11] Trimethoxybenzoyl azide **1c** and the corresponding 3,4,5-trimethoxystyrene converted regioselectively under the reaction conditions to the desired product **5** in 65% yield (**Scheme 4**).

Based on literature data [6-11] and experiments, we propose the following mechanism. The presence of an acid additive was found to be crucial to obtain the desired products. Without acid, the slow conversion of the benzoyl azide into an isocyanate derivative was observed.[8] A sensitization pathway – rather than a radical mechanism – is supported by the absence of reaction inhibition upon addition of two equivalents of TEMPO (**Scheme 5**, upper, eq. A). Additionally, cyclic voltammetry and Stern-Volmer experiments corroborate this hypothesis.[8] We therefore suggest the following mechanistic manifold: benzoyl azide **I** is excited by the photocatalyst, providing the triplet benzoyl azide **II**, which loses dinitrogen to give the corresponding benzoyl nitrene **III**. This intermediate could then follow two pathways: without acid, **III** is readily converted into the isocyanate **IV** *via* Curtius rearrangement, whereas in the presence of acid the protonated benzoyl nitrene **V** is most likely formed.[13] Computational studies suggest that a triplet acyl-nitrenium is less prone towards the rearrangement than its singlet counterpart.[13b]



Scheme 5: Mechanistic investigations (upper) and proposed mechanism (lower).

The electron-rich alkene reacts regioselectively with the protonated intermediate **V** to give the carbocation intermediate **VI**. The formation of a stabilized benzylic carbenium intermediate – which spontaneously cyclizes to form the protonated oxazoline **VII** – could explain the observed regiochemistry. The intermediate **VII** – after loss of a proton – liberates the desired product **VIII**. Despite the fact that a catalytic amount of phosphoric acid was in principle needed, a sub-stoichiometric amount of acid caused the yield to drop from 78% to 10%. This may suggest that the excess of acid can inhibit the formation of side products, such as the isocyanate **IV**. Under Yoon's conditions (**Scheme 1**), the selective aziridine formation from troc-N_3 was observed for almost all alkenes; only a few electron-rich alkenes gave mixtures of aziridines and oxazolines, which may result from the acidic ring opening

reaction from aziridine to oxazoline.[14] Therefore – to exclude the involvement of an aziridine intermediate – our conditions were applied to an acyl-aziridine derivative **7** (**Scheme 5**, upper, eq. B). Interestingly – no oxazoline formation could be detected, while the starting aziridine was recovered – thus hinting against its involvement in the catalytic process.

In conclusion – a new synthetic access to the oxazoline skeleton *via* a regioselective visible-light photoinduced cyclization – yielding a wide range of polysubstituted oxazolines was reported. A protonated triplet nitrene – which reacts with the alkene *via* a formal 1,3-cycloaddition process – was proposed as an intermediate. Overall, our mechanistic investigations suggested a sensitization mechanism rather than a radical pathway *via* electron transfer. While we observed that electron-rich alkenes and benzoyl azide derivatives converted best in this reaction, a wide range of functional groups such as acetals, esters or halogen substituents, as well as heterocyclic scaffolds, proved to be compatible with our reaction conditions. We successfully applied our procedure to the synthesis of a biologically active compound and its wider use in synthetic chemistry may be easily envisaged.

EXPERIMENTAL SECTION

General Information

^{1}H NMR spectra were recorded on a Bruker Avance 300 or 400 MHz spectrometer in $CDCl_3$ or acetone-d_6. The residual non-deuterated solvent signal was used as reference, relative to the tetramethylsilane signal. ^{13}C NMR were recorded on a Bruker Avance 300 or 400 MHz (respective resonance frequency: 75 MHz and 101 MHz) under broadband ^{1}H decoupling in $CDCl_3$ or acetone-d_6. The residual non-deuterated solvent signal was used as reference, relative to the tetramethylsilane signal. In the case of ^{19}F spectra, the absolute referencing to the ^{1}H spectrum was used, as suggested by IUPAC. High resolution mass spectrometry (HRMS) analyses were performed at the mass spectrometry laboratory of UMR 8638 of the Faculty of Pharmacy, Université Paris Descartes. ^{1}H NMR data are reported as follows: chemical shift (ppm), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, quint = quintet, dd = doublet of doublets, ddd = doublet of doublet of doublets, td = triplet of doublets, qd = quartet of doublets, m = multiplet, br. s. = broad singlet), coupling constants (Hz) and number of protons.

All reactions were monitored by thin-layer chromatography using Merck silica gel plates 60 F_{254}; visualization was accomplished with short wavelength UV light (254 nm) and/or staining with appropriate stains (anisaldehyde, orthophosphomolybdic acid). Standard flash-chromatography was performed using Macherey-Naghel silica gel of particle size 40–63 μm according Still et al. $Ru(bpy)_3Cl_2{\cdot}6H_2O$ was purchased from Sigma Aldrich. All other commercially available reagents and solvents were used without further purification. Dry DMSO was stored in septum-sealed bottles in presence of 4Å MS as withdrawn using a syringe under a positive argon pressure.

The blue light irradiation was performed using high-power LEDs Philips LUXEON® Rebel (1W, λ_{max} = 450±10 nm, 145 lm @700mA). Irradiation occurred from the bottom of each vials at a distance of 2 cm. Each vial was cooled to 20°C by a cryostat plug connected to to a custom-made aluminum cooling block (see S.I.), equipped with a magnetic stirrer.

General procedure for the synthesis of benzoyl azides

The appropriate benzoyl chloride (5 mmol, 1.0 equiv) was dissolved in 7 mL of acetone. After cooling the reaction mixture to 0°C using ice bath, sodium azide (358 mg, 5.5 mmol, 1.1 equiv) in 7 mL of water is added dropwise at 0°C. The resulting mixture was stirred for 2 hours at 0°C, then transferred to a separating funnel. The organic layer was collected, dried on magnesium sulfate and evaporated under reduced pressure (temperature of the bath should not exceed 30°C) to give the corresponding acyl azide. **Caution: It is known that these reagents are potentially explosive and must be handle with care and store in the fridge. It is also recommended to prepare acyl azides at maximum 10 mmol scale to limit risks.**

General procedure for the reaction of benzoyl azide with alkenes

In a 5 mL snap vial, sealed with a PTFE septum and equipped with PTFE-coated magnetic stirring bar, $Ru(bpy)_3Cl_2{\cdot}6H_2O$, (6.4 mg, 8.5 μmol, 2.5 mol%), benzoyl azide **1a-m** (0.34 mmol, 1 equiv), H_3PO_4 (67 mg, 0.68 mmol, 2 equiv) and alkene (1.7 mmol, 5 equiv) were dissolved in dry DMSO (0.09 mmol/mL) and the resulting mixture was degassed by "freeze-pump-thaw" cycles (×2) via a syringe needle. The vial was irradiated through the flat bottom-side of the snap vial using blue LEDs. After 24 hours of irradiation (*the consumption of starting material was checked by TLC, using cyclohexane:AcOEt 8:2 as eluant*), the pressure in the vial is released by a needle and the reaction mixture was transferred to separating funnel, diluted with ethyl acetate (15 ml) and washed with 15 mL of water. The aqueous layer was extracted three times with ethyl acetate (15 ml each time). The combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. Purification of the crude product was achieved by flash column chromatography on silica using cyclohexane/ethyl acetate as eluent.

Compound **3a**: 5-methyl-5-phenyl-2-(*p*-tolyl)-4,5-dihydrooxazole. Yield: 78% (0.23 mmol, 56 mg), (69% on 1mmol scale of starting material giving 173mg of **3a**) R_f = 0.30 (cyclohexane:AcOEt 8:2). Physical aspect: yellow oil. Spectral data: ^{1}H NMR (300 MHz, acetone-d_6) δ 7.92 (d, J = 7.9 Hz, 2H), 7.48 (d, J = 8.5 Hz, 2H), 7.38 (t, J = 7.5 Hz, 2H), 7.34-7.24 (m, 3H), 4.13 (d, J = 14.9 Hz, 1H), 4.04 (d, J = 14.8 Hz, 1H), 2.40 (s, 3H), 1.77 (s, 3H). ^{13}C{^{1}H} NMR (75 MHz, acetone-d_6) δ 163.1, 147.2, 142.6, 130.1, 129.9, 129.5, 129.4, 129.0, 128.2, 125.3, 87.4, 70.0, 28.7, 21.7. HRMS (TOF ESI+) m/z: [M+H$^+$] Calcd. for $C_{17}H_{18}NO$ 252.1388; Found 252.1386.

Compound **3b**: 5-methyl-2,5-diphenyl-4,5-dihydrooxazole, Yield: 73% (0.20 mmol, 51 mg). R_f = 0.30 (cyclohexane:AcOEt 8:2). Physical aspect: yellow oil. Spectral data: ^{1}H NMR (300 MHz, acetone-d_6) δ 8.04 (d, J = 7.4 Hz, 2H), 7.54 – 7.46 (m, 5H),

7.39 (t, *J* = 7.5 Hz, 2H), 7.30 (d, *J* = 7.2 Hz, 1H), 4.15 (d, *J* = 14.7 Hz, 1H), 4.06 (d, *J* = 14.7 Hz, 1H), 1.78 (s, 3H). Spectral data are in agreement with the literature. [15]

Compound **3c**: 5-methyl-5-phenyl-2-(3,4,5-trimethoxyphenyl)-4,5-dihydrooxazole, Yield: 69% (0.21 mmol, 70 mg). R_f = 0.11 (cyclohexane:AcOEt 8:2). Physical aspect: yellow oil. Spectral data: ^{1}H NMR (300 MHz, acetone-d_6) δ 7.55-7.45 (m, 2H), 7.39 (t, *J* = 7.4 Hz, 2H), 7.32 (s, 2H), 7.30 – 7.22 (m, 1H), 4.13 (d, *J* = 14.7 Hz, 1H), 4.04 (d, *J* = 14.7 Hz, 1H) 3.89 (s, 6H), 3.87 – 3.74 (m, 3H), 1.78 (s, 3H). ^{13}C{^{1}H} NMR (75 MHz, acetone-d_6) δ 162.9, 154.4, 147.1, 142.2, 129.5, 128.2, 127.0, 125.3, 106.5, 87.7, 70.0, 60.8, 56.7, 28.5. HRMS (TOF ESI+) m/z: [M+Na$^+$] Calcd. for $C_{19}H_{21}NO_4Na$ 350.1368; Found 350.1364.

Compound **3d**: 5-methyl-5-phenyl-2-(4-(trifluoromethyl)phenyl)-4,5-dihydrooxazole, Yield: 47% (0.15 mmol, 45 mg). R_f = 0.30 (cyclohexane:AcOEt 9:1). Physical aspect: yellow oil. Spectral data: ^{1}H NMR (300 MHz, acetone-d_6) δ 8.25 (d, *J* = 7.6 Hz, 2H), 7.86 (d, *J* = 8.0 Hz, 2H), 7.55 – 7.46 (m, 2H), 7.46 – 7.36 (m, 2H), 7.35-7.25 (m, 1H), 4.21 (d, *J* = 15.2 Hz, 1H), 4.12 (d, *J* = 15.2 Hz, 1H), 1.87 – 1.79 (m, 3H). ^{19}F{^{1}H} NMR (282 MHz, acetone-d_6) δ -63.44 (s). ^{13}C{^{1}H} NMR (101 MHz, acetone-d_6) δ 161.9, 146.7, 133.1 (q, *J* = 32.3 Hz, C-CF_3), 129.6, 129.5, 128.4, 126.4 (q, *J* = 3.8 Hz, CH-C-CF_3), 125.2, 125.1 (q, *J* = 271.8 Hz, CF_3), 117.7, 88.2, 69.9, 28.6. HRMS (TOF ESI+) m/z: [M+Na$^+$] Calcd. for $C_{17}H_{14}F_3NONa$ 328.0925; Found 328.0916.

Compound **3e**: 2-(4-chlorophenyl)-5-methyl-5-phenyl-4,5-dihydrooxazole. Yield: 53% (0.17 mmol, 45 mg). R_f = 0.23 (cyclohexane:AcOEt 8:2). Physical aspect: yellow oil. Spectral data: ^{1}H NMR (300 MHz, acetone-d_6) δ 8.04 (d, *J* = 8.8 Hz, 2H), 7.54 (d, *J* = 8.4 Hz, 2H), 7.48 (d, *J* = 7.7 Hz, 2H), 7.39 (t, *J* = 7.4 Hz, 2H), 7.29 (t, *J* = 7.2 Hz, 1H), 4.16 (d, *J* = 14.9 Hz, 1H), 4.07 (d, *J* = 15.0 Hz, 1H), 1.78 (s, 3H). ^{13}C{^{1}H} NMR (101 MHz, acetone-d_6) δ 162.1, 146.9, 137.8, 130.6, 129.7, 129.5, 128.3, 128.2, 125.2, 87.9, 69.9, 28.6. HRMS (TOF ESI+) m/z: [M+H$^+$] Calcd. for $C_{16}H_{15}{}^{35}ClNO$ 272.0842; Found 272.0845.

Compound **3g**: 2-(3-bromophenyl)-5-methyl-5-phenyl-4,5-dihydrooxazole. Yield: 58% (0.18 mmol, 57 mg). R_f = 0.45 (cyclohexane:AcOEt 7:3). Physical aspect: yellow oil. Spectral data: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.14 (s, 1H), 7.93 (d, *J* = 7.7 Hz, 1H), 7.57 (d, *J* = 7.4 Hz, 1H), 7.44 – 7.11 (m, 6H), 4.10 (s, 2H), 1.74 (s, 3H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ 161.8, 145.2, 134.7, 134.3, 131.2, 130.0, 128.6, 127.5, 126.8, 124.3, 122.5, 87.2, 68.9, 28.2. HRMS (TOF ESI+) m/z: [M+H$^+$] Calcd. for $C_{16}H_{16}{}^{79}BrNO$ 316.0337; Found 316.0335.

Compound **3i**: 2-(furan-3-yl)-5-methyl-5-phenyl-4,5-dihydrooxazole. Yield: 64% (0.20 mmol, 46 mg). R_f = 0.50 (cyclohexane:AcOEt 6:4). Physical aspect: yellow oil. Spectral data: ^{1}H NMR (300 MHz, acetone-d_6) δ 8.14 (s, 1H), 7.67 (s, 1H), 7.45 (d, *J* = 7.8 Hz, 2H), 7.38 (t, *J* = 7.6 Hz, 2H), 7.28 (t, *J* = 7.1 Hz, 1H), 6.81 (s, 1H), 4.06 (d, *J* = 14.6 Hz, 1H), 3.97 (d, *J* = 14.6 Hz, 1H), 1.74 (s, 3H). Spectral data are in agreement with the literature. [16]

Compound **3j**: 5-methyl-5-phenyl-2-(pyridin-3-yl)-4,5-dihydrooxazole. Yield: 49% (0.15 mmol, 37 mg). R_f = 0.16 (cyclohexane:AcOEt 6:4). Physical aspect: yellow oil. Spectral data: ^{1}H NMR (300 MHz, acetone-d_6) δ 9.18 (s, 1H), 8.74 (d, *J* = 4.9 Hz, 1H), 8.33 (d, *J* = 8.0 Hz, 1H), 7.50 (d, *J* = 8.0 Hz, 3H), 7.40 (t, *J* = 7.5 Hz, 1H), 7.31 (t, *J* = 6.6 Hz, 1H), 4.19 (d, *J* = 14.9 Hz, 1H), 4.10 (d, *J* = 15.0 Hz, 1H), 1.81 (s, 3H). ^{13}C{^{1}H} NMR (75 MHz, acetone-d_6) δ 161.3, 153.1, 150.0, 146.7, 136.1, 129.6, 129.1, 128.3, 125.3, 124.4, 88.0, 69.8, 28.6. HRMS (TOF ESI-) m/z: [M-H$^-$] Calcd. for $C_{15}H_{13}N_2O$ 237.1028; Found 237.1018.

Compound **3k**: 1,4-bis(5-methyl-5-phenyl-4,5-dihydrooxazol-2-yl)benzene. Yield: 62% (0.20 mmol, 51 mg). R_f = 0.15 (cyclohexane:AcOEt 8:2). Physical aspect: yellow oil. Spectral data: ^{1}H NMR (300 MHz, acetone-d_6) δ 8.15 (s, 4H), 7.53 – 7.47 (m, 4H), 7.40 (t, *J* = 7.5 Hz, 4H), 7.30 (t, *J* = 7.2 Hz, 2H), 4.20 (d, *J* = 15.1 Hz, 2H), 4.11 (d, *J* = 15.1 Hz, 2H), 1.81 (s, 6H). ^{13}C{^{1}H} NMR (75 MHz, acetone-d_6) δ 162.4, 146.8, 131.8, 129.4, 129.0, 128.2, 125.1, 87.8, 69.8, 28.5. HRMS (TOF ESI+) m/z: [M+H$^+$] Calcd. for $C_{26}H_{25}N_2O_2$ 397.1916; Found 397.1913.

Compound **4a**: 2-(4-chlorophenyl)-5-(3,4,5-trimethoxyphenyl)-4,5-dihydrooxazole. Yield: 55% (0.17 mmol, 59 mg). R_f = 0.12 (cyclohexane:AcOEt 8:2). Physical aspect: yellow oil. Spectral data: ^{1}H NMR (300 MHz, acetone-d_6) δ 8.00 (d, *J* = 8.5 Hz, 2H), 7.52 (d, *J* = 8.5 Hz, 2H), 6.72 (s, 2H), 5.69 (dd, *J* = 9.6, 8.4 Hz, 1H), 4.43 (dd, *J* = 15.1, 10.1 Hz, 1H), 3.98 – 3.86 (m, 1H), 3.81 (s, 6H), 3.72 (s, 3H). ^{13}C{^{1}H} NMR (75 MHz, acetone-d_6) δ 163.0, 154.8, 137.8, 137.8, 130.7, 129.6, 127.9, 106.6, 104.2, 82.3, 64.0, 60.6, 56.6. HRMS (TOF ESI+) m/z: [M+Na$^+$] Calcd. for $C_{18}H_{18}NO_4{}^{35}ClNa$ 370.0822; Found 370.0825.

Compound **4b**: 2-(4-(trifluoromethyl)phenyl)-5-(3,4,5-trimethoxyphenyl)-4,5-dihydrooxazole. Yield: 47% (0.15 mmol, 57 mg). R_f = 0.18 (cyclohexane:AcOEt 6:4). Physical aspect: amorphous orange solid. Spectral data: ^{1}H NMR (300 MHz, acetone-d_6) δ 8.20 (d, *J* = 8.2 Hz, 2H), 7.84 (d, *J* = 8.2 Hz, 2H), 6.74 (s, 2H), 5.74 (t, *J* = 9.1 Hz, 1H), 4.48 (dd, *J* = 15.3, 10.1 Hz, 1H), 4.10 – 3.95 (m, 1H), 3.81 (s, 6H), 3.72 (s, 3H). ^{19}F{^{1}H} NMR (282 MHz, acetone-d_6) δ -63.5. ^{13}C{^{1}H} NMR (101 MHz, acetone-d_6) δ 162.7, 154.8, 139.3, 137.6, 132.8 (d, *J* = 32.5 Hz, C-CF_3), 132.7, 129.7, 126.4 (q, *J* = 3.8 Hz, CH-C-CF_3), 125.0 (q, *J* = 271.8 Hz, CF_3) 104.2, 82.5, 64.0, 60.6, 56.6. HRMS (TOF ESI+) m/z: [M+Na$^+$] Calcd. for $C_{19}H_{18}F_3NO_4Na$ 404.1086; Found 404.1070.

Compound **4c**: 2-(*p*-tolyl)-5-(3,4,5-trimethoxyphenyl)-4,5-dihydrooxazole. Yield: 56% (0.18 mmol, 57 mg). R_f = 0.30 (cyclohexane:AcOEt 8:2). Physical aspect: yellow oil. Spectral data: ^{1}H NMR (300 MHz, acetone-d_6) δ 7.89 (d, *J* = 7.8 Hz, 2H), 7.29 (d, *J* = 7.8 Hz, 2H), 6.71 (s, 2H), 5.65 (t, *J* = 8.9 Hz, 1H), 4.40 (dd, *J* = 14.9, 9.8 Hz, 1H), 3.88 (dd, *J* = 15.2, 8.2 Hz, 1H), 3.80 (s, 6H), 3.72 (s, 3H), 2.39 (s, 3H). ^{13}C{^{1}H} NMR (101 MHz, acetone-d_6) δ 163.8, 154.8, 142.5, 139.1, 138.2, 130.0, 129.0, 126.4, 104.1, 81.8, 64.0, 60.6, 56.6, 21.6 HRMS (TOF ESI+) m/z: [M+Na$^+$] Calcd. for $C_{19}H_{21}NO_4Na$ 350.1368; Found 350.1357.

Compound **4d**: 5-(3,4-dimethoxyphenyl)-2-(*p*-tolyl)-4,5-dihydrooxazole. Yield: 56% (0.18 mmol, 51.5 mg). R_f = 0.40 (cyclohexane:AcOEt 1:1). Physical aspect: yellow oil. Spectral data: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.89 (d, *J* = 8.2 Hz, 2H), 7.23 (d, *J* = 8.0 Hz, 2H), 7.04 – 6.71 (m, 3H), 5.78 – 5.44 (m, 1H), 4.43 (dd, *J* = 14.8, 10.1 Hz, 1H), 3.98 (dd, *J* = 14.8, 8.2 Hz, 1H), 3.87 (s, 3H), 3.85 (s, 3H), 2.39 (s, 3H). Spectral data are in accordance with the literature. [17]

Compound **4e**: 2-(4-methylphenyl)-4-(thiophen-3-yl)-4,5-dihydro-1,3-oxazole. Yield: 48% (0.15 mmol, 36 mg). R_f = 0.36 (cyclohexane:AcOEt 8:2). Physical aspect: amorphous yellow solid. Spectral data: ^{1}H NMR (300 MHz, acetone-d_6) δ 7.86 (d, *J* = 8.1 Hz, 2H), 7.50 (m, 2H), 7.28 (d, *J* = 8.0 Hz, 2H), 7.14 (dd, *J* = 4.7, 1.1 Hz, 1H), 5.81 (dd, *J* = 9.7, 7.6 Hz, 1H), 4.36 (dd, *J* = 14.8, 10.0 Hz, 1H), 3.93 (dd, *J* = 14.8, 7.4 Hz, 1H), 2.38 (s, 3H) . ^{13}C{^{1}H}

NMR (75 MHz, acetone-d_6) δ163.7, 143.6, 142.5, 130.0, 129.0, 128.2, 128.0, 126.4, 123.0, 77.96, 63.0, 21.6. HRMS (TOF ESI+) m/z: [M+H$^+$] Calcd. for $C_{14}H_{14}NOS$ 244.0796; Found 244.0784.

Compound **4f**: 5-(2-chlorophenyl)-2-(4-chlorophenyl)-4,5-dihydrooxazole. Yield: 30% (0.10 mmol, 26 mg). R_f = 0.60 (cyclohexane:AcOEt 9:1). Physical aspect: yellow oil. Spectral data: ^{1}H NMR (300 MHz, acetone-d_6) δ 8.04 (d, J = 8.4 Hz, 2H), 7.55 (d, J = 8.4 Hz, 2H), 7.52 – 7.42 (m, 2H), 7.42 – 7.31 (m, 2H), 6.02 (dd, J = 9.6, 8.1 Hz, 1H), 4.60 (dd, J = 15.2, 10.3 Hz, 1H), 3.82 (dd, J = 15.1, 7.3 Hz, 1H). ^{13}C{^{1}H} NMR (75 MHz, acetone-d_6) δ 162.9, 140.1, 138.0, 130.8, 130.7, 130.4, 129.8, 129.5, 128.5, 127.6, 127.1, 79.0, 63.5. HRMS (TOF ESI-) m/z: [M-H$^-$] Calcd. for $C_{15}H_{10}NO^{35}Cl_2$ 290.0139; Found 290.0153.

Compound **4g**: 5-(2-chlorophenyl)-2-(*p*-tolyl)-4,5-dihydrooxazole. Yield: 45% (0.14 mmol, 38 mg). R_f = 0.28 (cyclohexane). Physical aspect: Orange crystalline solid. Single crystals suitable for X-ray analysis were obtained by slow evaporation with acetone as solvent. Spectral data: ^{1}H NMR (300 MHz, acetone-d_6) δ 7.93 (d, J = 8.1 Hz, 2H), 7.52 – 7.42 (m, 2H), 7.39 – 7.34 (m, 2H), 7.32 (d, J = 8.0 Hz, 2H), 5.97 (dd, J = 10.2, 7.2 Hz, 1H), 4.57 (dd, J = 14.9 Hz, 10.2 Hz, 1H), 3.78 (dd, J = 14.9, 7.2 Hz, 1H), 2.41 (s, 3H). ^{13}C{^{1}H} NMR (75 MHz, acetone-d_6) δ 163.7, 142.8, 140.5, 131.8, 130.6, 130.5, 130.3, 130.1, 129.1, 128.5, 127.0, 126.1, 78.5, 63.5, 21.6. HRMS (TOF ESI+) m/z: [M+H$^+$] Calcd. for $C_{16}H_{15}NOCl$ 272.0842; Found 272.0833.

Compound **4h**: 5-(4-methoxyphenyl)-5-phenyl-2-(*p*-tolyl)-4,5-dihydrooxazole. Yield: 62% (0.20 mmol, 51 mg). R_f = 0.33 (cyclohexane:AcOEt 8:2). Physical aspect: yellow oil. Spectral data: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.99 (d, J = 8.0 Hz, 2H), 7.48 – 7.24 (m, 9H), 6.89 (d, J = 8.7 Hz, 2H), 4.69 (d, J = 14.6 Hz, 1H), 4.60 (d, J = 15.1 Hz, 1H), 3.81 (s, 3H), 2.43 (s, 3H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ 163.2, 159.2, 144.7, 142.0, 136.5, 129.3, 128.5, 128.4, 127.7, 127.6, 126.0, 125.2, 113.9, 90.1, 69.2, 55.4, 21.7. HRMS (TOF ESI+) m/z: [M+H$^+$] Calcd. for $C_{23}H_{22}NO_2$ 344.1651; Found 344.1655.

Compound **4i**: 5-(4-methoxyphenyl)-4-methyl-2-(*p*-tolyl)-4,5-dihydrooxazole. Yield: 56% (0.19 mmol, 53 mg). R_f = 0.10 (cyclohexane:AcOEt 8:2). Physical aspect: yellow oil. Spectral data: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90 (d, J = 8.2 Hz, 2H), 7.28 (d, J = 8.7 Hz, 2H), 7.22 (d, J = 8.0 Hz, 2H), 6.91 (d, J = 8.7 Hz, 2H), 5.03 (d, J = 7.9 Hz, 1H), 4.26 – 4.14 (m, 1H), 3.80 (s, 3H), 2.39 (s, 3H), 1.46 (d, J = 6.7 Hz, 3H. ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 162.9, 159.8, 141.8, 132.6, 129.1, 128.4, 127.3, 125.2, 114.2, 88.2, 70.7, 55.4, 21.6, 21.4. HRMS (TOF ESI+) m/z: [M+Na$^+$] Calcd. for $C_{18}H_{19}NO_2Na$ 304.1313; Found 304.1299.

Compound **4j**: 4-(thiophen-3-yl)-2-(3,4,5-trimethoxyphenyl)-4,5-dihydro-1,3-oxazole. Yield: 55% (0.19 mmol, 59 mg). R_f : 0.22 (cyclohexane:AcOEt 6:4). Physical aspect: orange oil. Spectral data: ^{1}H NMR (300 MHz, acetone-d_6) δ 7.55 – 7.47 (m, 2H), 7.26 (s, 2H), 7.19-7.12 (m, 1H), 5.83 (dd, J = 9.9, 7.5 Hz, 1H), 4.37 (dd, J = 14.8 Hz, 9.9 Hz, 1H), 3.93 (dd, J = 14.9, 7.6 Hz, 1H), 3.86 (s, 6H), 3.78 (s, 3H). ^{13}C{^{1}H} NMR (101 MHz, acetone-d_6) δ 163.6, 154.3, 143.5, 142.1, 128.0, 126.5, 124.3, 123.2, 106.5, 78.2, 63.0, 60.7, 56.6. HRMS (TOF ESI+) m/z: [M+Na$^+$] Calcd. for $C_{16}H_{17}NO_4SNa$ 342.0776; Found 342.0778.

Compound **4k**: 2-(3,4,5-trimethoxyphenyl)-3a,8b-dihydro-4H-indeno[2,1-d]oxazole. Yield 38% (0.12 mmol, 39 mg). R_f = 0.18 (cyclohexane:AcOEt 6:4). Physical aspect: yellow oil. Spectral data: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.54 (d, J = 7.2 Hz, 1H), 7.38 – 7.22 (m, 3H), 7.17 (d, J = 1.1 Hz, 2H), 6.03 (d, J = 8.0 Hz, 1H), 5.09 (td, J = 8.0, 1.9 Hz, 1H), 3.87 (s, 6H), 3.84 (s, 3H), 3.48 (dd, J = 17.2, 7.8 Hz, 1H), 3.29 (d, J = 17.2 Hz, 1H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ 162.9, 153.0, 142.1, 140.8, 139.5, 129.9, 127.3, 126.4, 125.7, 123.1, 105.6, 86.9, 70.0, 61.0, 56.3, 39.6. HRMS (TOF ESI+) m/z: [M+Na$^+$] Calcd. for $C_{19}H_{19}NO_4Na$ 348.1212; Found 348.1195.

Compound **4l**: 2-(*p*-tolyl)-3a,8b-dihydro-4H-indeno[2,1-d]oxazole. Yield 32% (0.10 mmol, 25 mg). R_f = 0.19 (cyclohexane:AcOEt 8:2). Physical aspect: yellow oil. Spectral data: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.86 (d, J = 8.2 Hz, 1H), 7.48-7.63 (m, 1H), 7.28-7.41 (m, 3H), 7.22 (d, J = 8.3 Hz, 1H), 6.08 (d, J=8.0 Hz, 1H), 5.14 (ddd, J = 8.0, 7.9, 2.1 Hz, 1H),3.53 (dd, J = 17.2, 7.9 Hz, 1H), 3.35 (dd, J = 17.2, 2.1 Hz, 1H),2.41 (s, 3H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ 163.2, 142.1, 141.7, 139.7, 129.7, 129.0, 128.3, 127.3, 126.3, 125.6, 125.0, 86.5, 70.0, 39.6, 21.3. HRMS (TOF ESI+) m/z: [M+Na$^+$] Calcd. for $C_{17}H_{15}NONa$ 272.1051; Found 272.1049.

Compound **4m**: 2-(3,4,5-trimethoxyphenyl)-4,5,6,7-tetrahydrobenzo[d]oxazol-7a(3aH)-yl acetate. Yield 68% (0.20 mmol, 51 mg). R_f = 0.15 (cyclohexane:AcOEt 7:3). Physical aspect: yellow oil. Spectral data: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.22 (s, 1H), 4.40 (t, J = 4.2 Hz, 1H), 3.91 (s, 6H), 3.88 (s, 3H), 2.10 (s, 2H), 1.91 – 1.83 (m, 4H), 1.62 (m, 2H), 1.58 – 1.46 (m, 4H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 184.7, 168.9, 154.7, 153.2, 151.7, 105.7, 61.0, 56.5, 27.9, 25.3, 24.0, 22.5, 21.5, 16.8, 16.1. HRMS (TOF ESI+) m/z: [M+H$^+$] Calcd. for $C_{18}H_{24}NO_6$ 350.1604; Found 350.1605.

Compound **5**: 2,5-bis(3,4,5-trimethoxyphenyl)-4,5-dihydrooxazole. Yield 65% (0.20 mmol, 81 mg). R_f = 0.16 (cyclohexane:AcOEt 6:4). Physical aspect: amorphous yellow solid. Spectral data: ^{1}H NMR (300 MHz, acetone-d_6) δ 7.28 (s, 2H), 6.72 (s, 2H), 5.66 (dd, J = 10.0, 8.6 Hz, 1H), 4.41 (dd, J = 14.9, 10.0 Hz, 1H), 3.95-3.90 (m, 1H), 3.87 (s, 6H), 3.82 (s, 3H), 3.79 (s, 3H), 3.73 (s, 3H). ^{13}C{^{1}H} NMR (101 MHz, acetone-d_6) δ 163.6, 154.8, 154.3, 142.1, 139.2, 138.0, 124.2, 106.4, 104.2, 82.1, 64.0, 60.7, 60.6, 56.6, 56.6. HRMS (TOF ESI+) m/z: [M+Na$^+$] Calcd. for $C_{21}H_{25}NO_7Na$ 426.1529; Found 426.1519.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information, containing full spectroscopic data for all new compounds, cyclovoltammetry data, Stern-Volmer analysis, X-ray crystallographic data and the corresponding CIF file is available free of charge on the ACS Publications website.

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The manuscript was written through contributions of all authors. / All authors have given approval to the final version of the manuscript. / ‡These authors contributed equally.

Notes

The authors declare no competing financial interest.

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