Room-Temperature Decarboxylative Cyanation of Carboxylic Acids Using Photoredox Catalysis and Cyanobenziodoxolones: Divergent Mechanism Compared to Alkynylation

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The one-step conversion of aliphatic carboxylic acids to the corresponding nitriles has been accomplished via the merger of visible light mediated photoredox and cyanobenziodoxolones (CBX) reagents. The reaction proceeded in high yields with natural and non-natural α-amino and α-oxy acids, affording a broad scope of nitriles with excellent tolerance of the substituents in the α position. The direct cyanation of dipeptides and drug precursors was also achieved.

The mechanism of the decarboxylative cyanation was investigated both computationally and experimentally and compared with the previously developed alkynylation reaction. Alkynylation was found to favor direct radical addition, whereas further oxidation by CBX to a carbocation and cyanide addition appeared more favorable for cyanation. A concerted mechanism is proposed for the reaction of radicals with EBX reagents, in contrast to the usually assumed addition elimination process.

1. Introduction

Nitriles are extremely useful building blocks in organic synthesis and material science, and especially in the synthesis of nitrogen containing heterocycles.1 Aliphatic nitriles in particular have found various applications in fine chemicals industry, both as building blocks and final products in natural and synthetic bioactive compounds.1b,2 For example, Anastrozole (1) is a blockbuster developed by AstraZeneca. It is the drug of choice in the treatment of breast cancer.3a Saxagliptin (2) is a classic drug for treating diabetes.3b Odanacatib (3), which is currently developed by Merck, is expected to be a top selling drug for osteoporosis and bone metastasis in the next few years (Figure 1).3c Nitriles often exhibit some bioactivity as bio-isosteres of carbonyl, halogens or other pharmacophores.2a Furthermore, the corresponding tetrazoles obtained after [3+2] cycloaddition with azides4 are also considered as bio-isosteres of the carboxylic acid group.5

As broadly available substrates, carboxylic acids are attractive starting materials (Scheme 1, C). Indeed, in nature, nitriles are synthesized through an enzymatic cascade starting from α-amino acids via a decarboxylative formation of aldoximes followed by dehydration.10 In synthetic chemistry, carboxylic acids have also been used to access nitriles. However, classical methods also involve multi-step procedures via the formation of amides or oximes followed by dehydration11 Consequently,
more efficient single step methods for the conversion of carboxylic acids to nitriles are needed.

In principle, a direct carboxylic acids-nitrile exchange would be a very efficient approach. However, this reaction occurs only at very high temperature (Scheme 2, A).\textsuperscript{12} It has been optimized by Klein in 1971 by heating carboxylic acids at 285 °C in the presence of α-methylglutaronitrile and phosphoric acid.\textsuperscript{12a} This method has been applied in continuous flow by Kappe and Cantillo in 2013.\textsuperscript{12b} An approach allowing milder reaction conditions is based on the radical decarboxylation of carboxylic acids followed by trapping of the in situ generated nucleophilic radical with a cyanation reagent. Barton and co-workers have developed a two steps visible light promoted decarboxylation via N-hydroxy-2-thiopyridone esters - the so-called “Barton Esters” (Scheme 2, B).\textsuperscript{13} Different reagents have been used to perform the cyanation of radicals, such as tosyl cyanide and organophosphoryl cyanides.\textsuperscript{13,14} Nevertheless, in this approach activation of the acids as Barton esters is required, leading to an additional synthetic step. A one-step decarboxylative cyanation of broadly available carboxylic acids would be therefore of high interest.

![Scheme 2](image)

In that regard, visible light mediated catalysis has emerged as a powerful method for the generation of radical with high chemoselectivity under mild conditions.\textsuperscript{15} In 2011, Rueping and co-workers reported a photoredox mediated oxidative Strecker reaction of tertiary amines using an iridium catalyst.\textsuperscript{16} In 2016, Opatz and co-workers were able to use an organic photocatalyst to promote this reaction.\textsuperscript{17} The same year, Xu and coworkers developed a cyanation of potassium alkyltrifluoroborates via photoredox catalysis using tosyl cyanide.\textsuperscript{18} The scope is limited to hydrocarbon-derived borates, and an excess of external oxidant and TFA is required. Recently, efficient photoredox-catalyzed decarboxylative transformations of carboxylic acids have been reported.\textsuperscript{19} In particular, the merger of photoredox catalysis and hypervalent iodine reagents for the decarboxylative alkynylation of aliphatic acids has been successfully and independently described by our group and the Xiao group.\textsuperscript{20} Key for success in this transformation was the use of ethynylbenziodoxolones (EBX reagents).

The corresponding cyanobenziodoxolone (CBX) reagent 4a was synthesized by Zhdankin and co-workers and used in the C-H cyanation of dialkylaryl amines.\textsuperscript{21} A radical pathway is probable for this transformation. Since then, cyanobenziodoxolones have been used successfully in the cyanation of nucleophiles,\textsuperscript{22} but have not yet been used in decarboxylative cyanation.\textsuperscript{23} Based on Zhdankin thermal cyanation with CBX and our previous decarboxylative alkynylation using EBX reagents and photoredox catalysis, we envisioned that CBX derivatives could be suitable reagents for the photoredox mediated cyanation of aliphatic acids using commercially available blue LEDs.

Herein, we report the successful implementation of this strategy using an iridium photoredox catalyst (Scheme 2, C). The scope of the decarboxylative cyanation is broad, allowing the functionalization of various α- amino and α-oxy acids. Valuable intermediates in the synthesis of drugs have been synthetized in good yield. Dipeptides are also suitable for this transformation. Finally, we investigated the mechanism of both the previously developed alkynylation and the new cyanation. Based on experimental and computational data, we proposed different mechanisms for the two reactions, involving radical or carboxatic anion intermediates for alkynylation or cyanation respectively. In the case of the alkynylation reaction, we further challenge the commonly accepted addition-elimination mechanism and propose that a concerted mechanism may be competitive.

2. Results and Discussion

Optimization of the decarboxylative cyanation

We started our investigations with the decarboxylative cyanation of protected proline 5a using the same conditions as we had reported for alkynyl transfer (with 1 mol% \textit{Ir}([dF(CF\textsubscript{3})\textsubscript{2}pp][dtbbpy])PF\textsubscript{6} \textit{(6)}, 3 equivalents CsOBz at room temperature in DCE, Table 1).\textsuperscript{20a} We were pleased to isolate 40% of the desired nitrile 7a after 4.5 h (Entry 1). The moderate yield was mostly due to the formation of alcohol 8 as a side product. The origin of the oxygen atom could be either dioxygen or water, but as the reaction was done in degassed DCE, we speculated that the most probable source was water. Indeed, the formation of alcohol 8 could be suppressed by the addition of 4 Å molecular sieves. Together with a lower amount of cesium benzoate (1.5 equiv instead of 3.0 equiv), this led to an improvement of yield (78%) as well as reproducibility (Entry 2). Decreasing the concentration to 0.05 M led to a decrease in yield to 46% (Entry 3), while a concentration of 0.10 M afforded 72% of 8 (Entry 4). Solubility issues started to be significant at 0.33 M, resulting in a lower yield (48%) (Entry 5). A strong effect of the solvent was also observed: highly polar solvent such as DMF or DMSO led only to decomposition, while acetoniitrile and toluene allowed the reaction to proceed only very slowly (Entries 6 and 7).

Performing the reaction in DCM did not affect the yield (Entry

![Scheme 2](image)
Finally, cyclic ethers such as THF and 1,4-dioxane were found to be the best solvents for this transformation (87 and 84% respectively, entries 9 and 10). Although small amounts of α-cyano-THF (9) could be isolated at the end of the reaction, the use of THF as solvent gave reproducibly better results. It is noteworthy that CsOAc and Cs₂CO₃ did not lead to formation of the product (results not shown). These results on cyclohexane showed the superiority of benziodoxolone reagents as a cyanide source. Furthermore, CBX (4a) is a user friendly reagent, as it is a crystalline solid with a high melting point.

The structure of the reagent is important, particularly the core of the five-membered ring. 1-Cyano-3,3-dimethyl-1,2-benziodoxole (CDBX, 4b) did not promote formation of 7a, and instead generated only THF 2-carbonitrile (9) (Scheme 3).

Electron withdrawing groups in benziodoxole (CDBX, 4a) did not promote formation of 7a, and instead generated only THF 2-carbonitrile (9) (Scheme 3).

Table 1 Optimization of the photoredox mediated decarboxylative cyanation of carboxylic acid 5a

<table>
<thead>
<tr>
<th>Entry</th>
<th>Concentration (M)</th>
<th>Solvent</th>
<th>Conversion (%)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.20</td>
<td>DCE</td>
<td>&gt; 95</td>
<td>40</td>
</tr>
<tr>
<td>2</td>
<td>0.20</td>
<td>DCE</td>
<td>&gt; 95</td>
<td>78</td>
</tr>
<tr>
<td>3</td>
<td>0.05</td>
<td>DCE</td>
<td>&gt; 95</td>
<td>46</td>
</tr>
<tr>
<td>4</td>
<td>0.10</td>
<td>DCE</td>
<td>&gt; 95</td>
<td>72</td>
</tr>
<tr>
<td>5d</td>
<td>0.33</td>
<td>DCE</td>
<td>&gt; 95</td>
<td>48</td>
</tr>
<tr>
<td>6</td>
<td>0.20</td>
<td>DMF / DMSO</td>
<td>&gt; 95</td>
<td>Decomp.</td>
</tr>
<tr>
<td>7</td>
<td>0.20</td>
<td>MeCN / DMSO</td>
<td>Low</td>
<td>Not isolated</td>
</tr>
<tr>
<td>8</td>
<td>0.20</td>
<td>DCM</td>
<td>&gt; 95</td>
<td>75</td>
</tr>
<tr>
<td>9</td>
<td>0.20</td>
<td>THF</td>
<td>&gt; 95</td>
<td>87</td>
</tr>
<tr>
<td>10</td>
<td>0.10</td>
<td>DCM</td>
<td>&gt; 95</td>
<td>84</td>
</tr>
</tbody>
</table>

*Reaction conditions: 0.10 mmol 5a (1 equiv), 0.15 mmol 4a (1.5 equiv), 1 μmol 6 (0.01 equiv) in DCE (0.5 mL) for 4.5 h at RT. The conversion of 5a by NMR is given.

Investigation of the reaction scope

We then turned our attention to the scope of the reaction with amino acids (Scheme 4). When the reaction was scaled up from 0.10 mmol to 0.30 mmol, nitrile 7a was obtained in 89% yield. In this case, 9% of side product 7b was also observed. While in the previously developed alkylation the reaction was sensitive to the substituent in α position of the amino acids, giving broadly varying yields, the decarboxylative cyanation is more general. In fact, both natural and unnatural α-amino acids can be functionalized in good yield in 5 to 18 hours under mild conditions. Different protecting groups, such as Cbz, Boc and Fmoc could be used, and cyanated proline derivatives 7a-c were obtained in excellent yield (86 – 92%). In the case of a less electron-withdrawing benzyl protecting group, cyanation still occurred, but only in 43% yield (product 7d). A free alcohol was tolerated to give 3-hydroxy proline derivatives 7e in 90% yield. Boc-protected piperidine 5f could be cyanated in 72% yield (product 7f). The reaction of Cbz-protected tetrahydroisoquinoline 3-carboxylic acid (5g) was site selective, yielding 65% of a single regioisomer 7g. From non-cyclic amino acids, primary, secondary and tertiary α-amino radicals can be generated and cyanated smoothly to furnish the corresponding nitrides 7h-j, although the yield is lower with tertiary radicals (51% for 7j). Valine, leucine and phenylalanine (5k-m) are suitable substrates (products 7k-m, 78-82%). For secondary radicals, the steric in α position did not have a strong influence on the outcome of the reaction. A benzyl ether was also tolerated in the transformation (7n, 80%). Protected glutamate, methionine and lysine 5o-q can be converted into the corresponding nitrides 7o-q in good to excellent yields (59-83%). The fact that the decarboxylative cyanation worked on methionine is especially noteworthy, as electrophilic cyanation reagents such as cyanogen bromide are known to react with this amino acid. Two dipeptides (Z-Gly-Pro-OH (5r) and Z-D-Ph-Pro-OH (5s)) could also be cyanated (products 7r and 7s). Cyanide 7s was obtained as a mixture of diastereoisomers. These preliminary results are promising for the cyanation of more complex amino acids. On the other hand, the reaction was not successful for tryptophan derivatives or when a sulfur atom was present in the β position (products 7t and 7u).
We then turned to other classes of substrates and were pleased to see that oxy-acids also underwent decarboxylative cyanation. Cyclic or acyclic compounds are both suitable for the reaction (products 7v-x). Lower yield was obtained with an acyclic phenol ether (product 7x). α-thio cyanide 7y could not be obtained under these reaction conditions. Furthermore, in contrast to the alkynylation reaction, only low yields were obtained in the case of carboxylic acids lacking the α-heteroatom (< 20%, results not shown). In this case, the major product obtained were the anhydrides resulting from the condensation of two carboxylic acids 5 or one carboxylic acid 5 and benzoic acid.

We then wondered if natural light could be used to promote the reaction. Indeed, after only four hours of sunlight irradiation, 7a was obtained in 90% yield (compared with 89% for blue LEDs, Scheme 5, A). The reaction can also be scaled up to 1 mmol using only 0.1 mol% of catalyst 6, with a slight decrease of yield, as 7a was obtained in 60% yield after 48 h of irradiation (corresponding to 600 turnovers, Scheme 5, C). To further highlight the utility of our methodology, 1,4-benzodioxan-2-carbonitrile (7v) was synthesized at the gram scale in 44% yield from the corresponding acid 5v (Scheme 5, C). The drop in yield is probably due to the less efficient irradiation on larger scale. Nitrile 7v is the common key intermediate in the synthesis of various types of receptor antagonists (calcium, imidazoline, α2-adrenoreceptor), such as commercialized Idazoxan (10) or lead compound WB-4101 (11) (Scheme 5). Another interesting application is the cyanation of carboxylic acid 5z, which can be obtained in one step from proline. Building block 7z can then be used to access the important antidiabetic drug Vildagliptin (12) in one step only. However, acid 5z contains a highly reactive α-chloro amide unit, which was unfortunately not compatible with our standard reaction conditions. We speculated that cesium benzoate was reacting with the substrate due to its high nucleophilicity. Indeed, when potassium benzoate was used as base, the desired product 7z could be obtained in 42% yield.

When comparing the results obtained in our previous work on alkynylation20a with the decarboxylative cyanation, the transformations appear very similar upon first look: Both reactions proceeded with the same catalyst and the benziodoxolone core of the hypervalent iodine reagents used was identical. Nevertheless, two important observations indicated that the reaction mechanism may be different:

1) The scope of the reaction was different: the alkynylation work with all classes of carboxylic acids. The presence of an α-heteroatom is beneficial, but not crucial for success. On the
other hand, the cyanation reaction had a broader scope than the alkynylation in the case of amino acids, but did not work well for simple aliphatic acids.

2) Side product 8 observed in the presence of moisture for the cyanation reaction was not observed in the case of the alkynylation reaction.

Taken together, these results seemed to indicate that the cyanation reaction may occur via an intermediate with higher carboxylation character. To support this speculation, we decided to study the reaction mechanism more in detail, both experimentally and via computation.

A speculative mechanism including different possible pathways is presented in Scheme 6. An important feature of this photoredox mediated Csp²-Csp coupling is the ability for carboxylic acids to undergo CO₂ extrusion (Scheme 6, A). It is now well established that Ir(df(CF₃)ppy)₂(dtbbpy)PF₆ (6) can generate the excited state *Ir(df(CF₃)ppy)₂(dtbbpy)PF₆ (6*) under visible light irradiation. This catalytic specie is strongly oxidizing (E₁/₂(IrIII/II) = +1.21 V vs SCE) and can lead to a thermodynamically favored single electron transfer (SET) with the in situ generated cesium carboxylate I (+0.95 V for Boc-Pro-OCS vs SCE), thus generating the strongly reducing Ir(II) complex 6red and the carboxyl radical which undergoes immediate decarboxylation to give nucleophilic radical II. Intermediate II can then react with the hypervalent iodine reagents to give iodine centered radical III. To close the catalytic cycle, we assume that radical III can be reduced by the strongly reducing Ir(II) complex 6red (E₁/₂(IrII/III) = -1.37 V vs SCE), thus regenerating the ground state photocatalyst Ir(df(CF₃)ppy)₂(dtbbpy)PF₆ (6).

Both the alkynylation and cyanation reactions were racemic, supporting the formation of either a radical or carbocation intermediate. To further support the existence of carbon centered radical II, we turned to radical clock and/or trapping experiments (Scheme 7). A radical clock experiment with cyclopropane 16 and EBX reagent 13b led to the formation of ring-opening product 17, confirming the intermediacy of radicals in the case of the alkynylation reaction. A similar experiment has also been done by Xiao and co-workers. In order to have a radical clock which could be used in both reactions, we then examined cyclopropyl amino acid 18. In the case of the alkynylation reaction, alkyne 19 could be isolated in 20% yield. This product probably resulted from the hydrolysis of the expected enamide 20. However, we were not able to isolate any product from the corresponding cyanation reaction. We therefore attempted a radical trap experiment with TEMPO in the cyanation reaction of protected proline 5a. In this case, the formation of the cyanation product was completely inhibited, and a mass corresponding to TEMPO-adduct 21 could be observed by high resolution mass spectroscopy. The presence of radical intermediate II is therefore strongly supported in the case of the alkynylation reaction. For the cyanation, it can be only considered as probable at this stage, as TEMPO can also act as a SET reagents and not only as a radical trap when photoredox catalytic cycles are considered.

After alkynylation or cyanation, the catalytic cycle would be closed by reduction of the formed radical III by iridium complex 6red. It is very challenging to gain further information about this catalytic step, due to the high reactivity of intermediate III. Nevertheless, recent computations performed by Chen and co-workers supported the fact that radical III is best described as a resonance structure including an iodine and an oxygen centered radical. The resulting enhanced stability may have several effects: First, it will make formation of the radical easier, and therefore accelerate the cyanation or alkynylation step. Second, it should make reduction more difficult, rationalizing the need for a photoredox catalyst with a relatively strong reduction potential. To support this hypothesis, we computed the reduction potential of complex 6red being known as -1.37 V vs SCE, the speculated catalytic step appears at least thermodynamically feasible. Third, decarboxylation to give an aryl radical becomes more difficult,
With a crude picture of the general mechanism in hand, we then turned to the investigation of the key alkylation/cyanation step (Scheme 6, B). Li and co-workers proposed α-addition followed by β-elimination as mechanism for the reaction of radicals with EBX reagents in their seminal work in 2012 (path a).33 This mechanism could also be proposed for the cyanation reaction. However, based on our work on the reaction of thiol anions and radicals with EBX and CBX reagents,22d,34 which highlighted a more complex mechanism picture, we wondered if other reaction pathways would also be accessible for carbon centered radicals. In particular, a one-step concerted α-addition/elimination mechanism could also be considered (path b). Furthermore, it is difficult to exclude directly a mechanism involving β-addition, followed by α-elimination and 1,2-shift (path c). Nevertheless, this mechanism appears less probable in the case of the cyanation reaction, as stable isonitrile products should have been isolated. However, none of these mechanisms would explain well the differences observed between the two classes of reagents, competition experiments were run between TIPS-EBX (13a) and CBX (4a) on proline derivative 5a. Cyanation was favored, showing the higher reactivity of CBX (4a). This result allowed us to exclude that formation of side product 8 was avoided by a faster reaction in the case of the alkylation reaction. To further support the intermediacy of an iminium intermediate, we ran the cyanation reaction in presence of C13 labelled potassium cyanide. Indeed, 2.2% C13 incorporation was observed. However, a control experiment showed that cyanide exchange was occurring directly on CBX (4a) under the reaction conditions. Consequently, this experiment cannot be used to further support the existence of an iminium intermediate.

Therefore, we turned to density functional theory (DFT) computations to further support two different mechanistic pathways (Figure 2). Both the alkylation and the cyanation of proline derivatives 5a with TIPS-EBX (13a) and CBX (4a) were computed at the PBE0-dDsC/TZ2P//M06/def2-SVP theoretical level (see computational details for additional information) for mechanistic paths b-d (Figure 2). In order to reproduce the solvent effect, an implicit continuum model for realistic solvents (COSMO-RS) was used, with DCE for the alkylation and THF for the cyanation. For both reactions, we were unable to locate a reaction intermediate corresponding to the frequently proposed radical intermediate a1 following path a. Therefore, only paths b-d are represented. For the alkylation reaction, both path b and c starts with a Van der Waals interaction complex b/c0, the formation of which is endothermic (Figure 2, A). From this intermediate, both a transition state bTS1 leading directly to the alkylation product 14a via concerted α addition and a transition state cTS1 leading to radical intermediate c1 via β-elimination could be located. The energies of both transition states are very close, indicating that the reaction could follow both pathways simultaneously. From radical c1, bond dissociation to generate radical III is followed by a barrierless 1,2-silicium shift to give alkylation product 14a. Finally, the SET pathway d was computed. For the steps involving electron-transfer, no energy barrier was determined for the outer sphere transfer mechanism.35 Electron-transfer from TIPS-EBX (13a) to radical II was found to be feasible, with only 11.3 kcal/mol required. However, the collapse of the radical anion to form radical III and an acetylide anion was found to be highly unfavorable, with an energy of 32.8 kcal/mol.

preventing potential side reactions resulting from these highly reactive species.

Scheme 7 Experiments supporting the existence of a carbon centered radical intermediate II

presence of a nucleophilic cyration reagent, but no product was obtained when the reaction was done in presence of KCN without CBX (4a). Furthermore, formation of alcohol 8 would have been expected independently of the used reagent, and it was observed only in the case of cyanation. Our working hypothesis was therefore that path d would be favored in case of CBX reagents, but not with EBX.

To gain further insight in the reactivity differences between the two classes of reagents, competition experiments were run between TIPS-EBX (13a) and CBX (4a) on proline derivative 5a.

### References


### Figures

- Figure 2: Mechanistic pathways for the alkylation and cyanation reactions.
- Figure 3: Electronic structures and geometries of key transition states and intermediates.
Figure 2. Reaction free energy profile at the [PBE0-dDsc/TZ2P//M06/def2-SVP] level for the alkynylation (A) and cyanation (B) of protected proline 5a for paths b-d.
Consequently, even if the SET transfer occur between TIPS-EBX (13a) and radical II, it is probably not contributing to the alkynylation reaction.

Pathways b-d were then examined for the cyanation reaction (Figure 2, B). α-addition via interaction complex b0 and transition state bTS occurred relatively easily, with a slightly lower transition state energy than the related alkynylation reaction (14.3 vs 17.2 kcal/mol). In contrast to the alkynylation reaction however, the β addition pathways was higher in energy (16.3 kcal/mol), in accordance with the fact that no isonitrile product had been observed. In this case, intermediate c1 could not be located, and formation of isonitrile c2 was directly observed. As expected, conversion of isonitrile c2 to the cyanation product 7a was predicted to be difficult, as the lowest energy pathway involved heterolytic bond cleavage with an activation energy of 34.5 kcal/mol. However, the major difference in the cyanation reaction appeared when the SET pathway d was computed. First, the oxidation of radical II by CBX (4a) is much easier than with TIPS-EBX (13a) (2.4 vs 11.3 kcal/mol). Second and most importantly, the collapse of the formed radical anion is again easy, as in this case the formation of the cyanide anion and radical III requires only 9.4 kcal/mol. Even if the assumption of a barrierless electron transfer could lead to an underestimation of the activation energy for this process, it appears plausible that the cyanation reaction could occur via a SET pathway, whereas this looks highly improbable for the alkynylation reaction.

The easier electron transfer to CBX (4a) when compared to TIPS-EBX (13a) could indicate a higher reduction potential. Both reagents were therefore examined by cyclic voltammetry. Although no defined reduction wave could be identified in the case of TIPS-EBX (13a), CBX (4a) showed an irreversible system with a clear reduction wave at -0.92 V vs SCE. This confirms that CBX is a relatively strong oxidant, which should be able to oxidize α-amino radicals to the corresponding iminium.

Conclusion
In summary, we have developed the one-step decarboxylative cyanation of α-amino and α-oxo acids using cyanobenziodoxolone (CBX, 4a). The reaction proceeded at room temperature under visible light irradiation using 0.1-1.5 mol % of an iridium catalyst. In particular, a broad range of amino acids could be cyanated using this methodology. Combined experimental and computational studies indicated that the favored mechanism is probably different from the previously developed decarboxylative alkynylation. Direct reaction of the radical formed by iridium-mediated decarboxylation was lower in energy for the alkynylation, whereas single electron transfer (SET) to form an iminium intermediate followed by cyanide addition was favored for cyanation. The cyanation reaction is expected to have high synthetic value for the synthesis of useful nitrile building blocks from biomass, whereas the discovery of different mechanism pathways for the reaction of radicals with benziodoxole reagents will set the bases for the development of further transformations based on the use of these versatile compounds.

Computational Details.
Geometries of minima and transition states were optimized using the M06-2X density functional with the def2-SVP basis set in Gaussian09. M06 computations uniformly employed the “Ultrafine” grid to remove known problems with integration grid size. Refined energy estimates that explicitly account for non-bonded interactions were obtained using a density dependent dispersion correction appended to the PBE0 functional (PBE0-dD). PBE0-dD single point computations used the TZ2P, as implemented in ADF. All free energies include the effects of solvation using the implicit continuum model for realistic solvents (COSMO-RS), as implemented in ADF, as well as unscaled free energy corrections derived from M06/def2-SVP computations. Reported reduction potentials were determined at the M06/def2-TZVPP level.

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Notes and references


(e) M. V. Vida, P. Caramenti and J. Waser, Org. Lett., 2015, 17, 5832; For recent review on hypervalent iodine reagents, see: (f) Y. Li, D. P. Hari, M. V. Vida and J. Waser, Angew. Chem., Int. Ed., 2016, 55, 4436;
23 During preparation of this manuscript, Xiao and co-workers reported the cyation of tertiary amines using cyanobenziodoxolones under photoredox conditions. In this work, two examples of decarboxylative cyation in moderate yields were also reported. However, the authors proposed a radical-based mechanism for this transformation: Q. Q. Zhou, D. Liu, W. J. Xiao and L. Q. Liu, Acta Chim. Sinica, 2016, in press, DOI: 10.6023/A16080414.
24 When cheaper organic dyes such as XX and XX were used, no product was obtained under the reaction conditions.
25 Determined by integration of the [H] NMR signals in the crude mixture.
30 Alternatively reduction of CBX (4a) by the iridium catalyst 6** to give radical III and cyanide could also be considered. To complete the catalytic cycle, radical III could recombine with the α-aminon radical II. The formed unstable hemiaminal could then give the iminium, which would react with the cyanide anion. Although this catalytic cycle cannot be excluded at this stage, it appears less probable, as the formation of the hemiacetal derived from 2-iodobenzoic acid was not observed during the reaction, and computation shows that radical II can react very fast with CBX (4a), present in stoichiometric amount.
31 In principle, a radical chain could also be initiated under the reaction conditions. However, the quantum yield of the reaction was determined to be 79% and 88% for alknylation and cyation respectively. In case of a chain reaction, quantum yield higher than 100% are more frequently observed. Furthermore, a catalytic cycle starting with electron-transfer from CBX (4a) to activated catalyst 6** was excluded by a Stern-Volmer analysis: excited state quenching was observed with carboxylate I, but not with CBX (4a). See Supporting Information for further details.
33 A value of 0.66 V was obtained for a simple benzylic radical. This higher oxidation potential is in agreement with the stabilization of radical III via resonance.
37 In principle, a more accurate reproduction of the free energy associated with outer sphere electron transfer could be determined, for example using molecular dynamics and explicit solvent to reproduce the reorganization energy. However, such computations are beyond the scope of the simplified mechanistic picture presented here.
38 See Figure S1 in the Supporting Information.
Graphical abstract:

Conversion of carboxylic acids to nitriles using photoredox catalysis and benziodoxolone reagents: divergent mechanism when compared to alkynylation!
Supporting Information for

Room-Temperature Decarboxylative Cyanation of Carboxylic Acids Using Photoredox Catalysis and Cyanobenziodoxolones: Divergent Mechanism Compared to Alkynylation

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1. Computational Details

The Cartesian coordinates of the structures are given in separate files.

**Table S1.** Electronic energies, free energy corrections, and solvation corrections for relevant species for the TIPS-EBX (13a) reaction pathways. PBE0-dDsC/TZ2P electronic energies were obtained from single point computations on M06/def2-SVP geometries. COSMO-RS solvation corrections were obtained at the PBE0-dDsC/TZ2P level in dichloroethane.

<table>
<thead>
<tr>
<th>Compound</th>
<th>M06/def2-SVP Electronic Energy (hartree)</th>
<th>M06/def2-SVP Free Energy Correction (hartree)</th>
<th>PBE0-dDsC/TZ2P Electronic Energy (hartree)</th>
<th>COSMO-RS Solvation Energy (kcal/mol)</th>
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<tr>
<td>TIPS-EBX (13а) (neutral)</td>
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¹ Note that ADF computes energies relative to atom fragments, which accounts for the magnitude differences between M06 and PBE0-dDsC electronic energies.
**Table S2.** Electronic energies, free energy corrections, and solvation corrections for relevant species for the CBX (4a) reaction pathways. PBE0-dDSC/TZ2P electronic energies\(^1\) were obtained from single point computations on M06/def2-SVP geometries. COSMO-RS solvation corrections were obtained at the PBE0-dDSC/TZ2P level in tetrahydrofuran.

<table>
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<tr>
<th>Compound</th>
<th>M06/def2-SVP Electronic Energy (hartree)</th>
<th>M06/def2-SVP Free Energy Correction (hartree)</th>
<th>PBE0-dDSC/TZ2P Electronic Energy (hartree)</th>
<th>COSMO-RS Solvation Energy (kcal/mol)</th>
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</table>
**Determination of computed reduction potentials.** Reported reduction potentials were determined using the Born-Haber cycle given in Scheme S1. Geometries of the different species were determined by optimization at the M06/def2-TZVPP level in implicit THF solvent using the SMD solvation model. Gas phase free energies were obtained from single point energy computations followed by frequency computations, as is standard procedure.\(^2\) The reduction potential is determined as: \( \Delta G^\circ (\text{soln}, \text{redox}) = \Delta G^\circ (\text{gas}, \text{redox}) + \Delta G^\circ (\text{solv}, \text{anion}) - \Delta G^\circ (\text{solv}, \text{radical}) \). The standard redox potential \( (E^0) \) is then obtained as: \( E^0 = -\frac{\Delta G^\circ (\text{soln}, \text{redox})}{ZF} \), where \( Z \) is the number of electrons transferred (one in this case) and \( F \) is Faraday’s constant (23.061 kcal per volt gram equivalent). The reference value of the SCE was taken as 4.522 V.\(^3\)

**Scheme S1.** Born-Haber cycle to calculate the reduction potential of radical species.

![Diagram of the Born-Haber cycle](attachment://born-haber-cycle.png)

**Table S3.** Computed free energies (at the M06/def2-TZVPP level) used to determine reduction potentials.

<table>
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<th>Species</th>
<th>Gas Phase</th>
<th>Solution Phase</th>
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<tr>
<td>Benzyol Anion</td>
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<td>-420.165561</td>
</tr>
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</table>

**Table S4.** Absolute and relative (to SCE) reduction potentials. SCE value taken as 4.522V.

<table>
<thead>
<tr>
<th>Species</th>
<th>Absolute Reduction Potential ( (E^0) )</th>
<th>Reduction Potential Relative to SCE</th>
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<tr>
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<tr>
<td>Benzyol Radical</td>
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2. General Methods

All reactions were carried out in oven dried glassware under an atmosphere of nitrogen, unless stated otherwise. For quantitative flash chromatography technical grade solvents were used. For flash chromatography for analysis, HPLC grade solvents from Sigma-Aldrich were used. THF, Et₂O, CH₃CN, toluene, hexane and CH₂Cl₂ were dried by passage over activated alumina under nitrogen atmosphere (H₂O content < 10 ppm, Karl-Fischer titration). NEt₃ and pyridine were distilled under nitrogen from KOH. The solvents were degassed by Freeze-Pump-Thaw method when mentioned. All chemicals were purchased from Acros, Aldrich, Fluka, VWR, Aplichem or Merck and used as such unless stated otherwise. All carboxylic acid starting materials were commercially available and used as received unless otherwise noted. Chromatographic purification was performed as flash chromatography using Macherey-Nagel silica 40-63, 60 Å, using the solvents indicated as eluent with 0.1-0.5 bar pressure. TLC was performed on Merck silica gel 60 F₂₅₄ TLC glass plates or aluminium plates and visualized with UV light, permanganate stain, CAN stain or Anisaldehyde stain. Melting points were measured on a Büchi B-540 melting point apparatus using open glass capillaries, the data is uncorrected. ¹H-NMR spectra were recorded on a Brucker DPX-400 400 MHz spectrometer in chloroform-d, DMSO-d₆ or CD₃OD, all signals are reported in ppm with the internal chloroform signal at 7.26 ppm, the internal DMSO signal at 2.50 ppm or the internal methanol signal at 3.30 ppm as standard. The data is being reported as (s = singlet, d = doublet, t = triplet, q = quadruplet, qi = quintet, m = multiplet or unresolved, br = broad signal, app = apparent, coupling constant(s) in Hz, integration, interpretation). ¹³C-NMR spectra were recorded with ¹H-decoupling on a Brucker DPX-400 100 MHz spectrometer in chloroform-d, DMSO-d₆ or CD₃OD, all signals are reported in ppm with the internal chloroform signal at 77.0 ppm, the internal DMSO signal at 39.5 ppm or the internal methanol signal at 49.0 ppm as standard. Infrared spectra were recorded on a JASCO FT-IR B4100 spectrophotometer with an ATR PRO410-S and a ZnSe prisma and are reported as cm⁻¹ (w = weak, m = medium, s = strong, br = broad). High resolution mass spectrometric measurements were performed by the mass spectrometry service of ISIC at the EPFL on a MICROMASS (ESI) Q-TOF Ultima API. Reactions were performed in test tubes (1.0 to 10 mL) which were hold using a rack for test tubes placed at the center of a crystallization flask, the latter was filled by water, in order to keep the temperature as constant as possible. On this flask were attached the blue LEDs (RUBAN LED 5MÈTRES - 60LED/M - 3528 BLEU - IP65 with Transformateur pour Ruban LED 24W/2A/12V, bought directly on RubanLED.com). The distance between the LEDs and the test tubes was approximatively 3-5 cm. Temperature ranged between 25 and 30°C, and long irradiation resulted in temperature increasing up to 34°C during overnight reactions.
3. Preparation of Reagents and Catalyst

The synthesis of reagents 4a-b and 13a-b had already been described before by our group. The procedures are taken from the indicated publications to facilitate reproduction of the results by having all data in the same file. Catalyst 6 is commercially available and was used as received; it was also synthesized as indicated below, affording comparable yields in the catalytic reactions.

1-Hydroxy-1,2-benziodoxol-3-(1H)-one (25)

Following a reported procedure,[4] NaIO₄ (7.24 g, 33.8 mmol, 1.05 equiv) and 2-iodobenzoic acid (24) (8.00 g, 32.2 mmol, 1.00 equiv) were suspended in 30% (v:v) aq. AcOH (48 mL). The mixture was vigorously stirred and refluxed for 4 h. The reaction mixture was then diluted with cold water (180 mL) and allowed to cool to rt, protecting it from light. After 1 h, the crude product was collected by filtration, washed on the filter with ice water (3 x 20 mL) and acetone (3 x 20 mL), and air-dried in the dark to give the pure product 25 (8.3 g, 31 mmol, 98%) as a colorless solid.

1H NMR (400 MHz, (CD₃)₂SO) δ 8.02 (dd, J = 7.7, 1.4 Hz, 1 H, ArH), 7.97 (m, 1 H, ArH), 7.85 (dd, J = 8.2, 0.7 Hz, 1 H, ArH), 7.71 (td, J = 7.6, 1.2 Hz, 1 H, ArH); 13C NMR (100 MHz, (CD₃)₂SO) δ 167.7, 134.5, 131.5, 131.1, 130.4, 126.3, 120.4; IR ν 3083 (w), 3060 (w), 2867 (w), 2402 (w), 1601 (m), 1585 (m), 1564 (m), 1440 (m), 1338 (m), 1241 (m), 1148 (m), 1018 (w), 834 (m), 798 (w), 740 (s), 694 (s), 674 (m), 649 (m); the reported values correspond to the ones in literature.[4]

1-Acetoxy-1,2-benziodoxol-3-(1H)-one (26)

Following a reported procedure,[5] 1-hydroxy-1,2-benziodoxol-3-(1H)-one (25, 10.3 g, 39.1 mmol, 1.00 equiv.) was suspended in acetic anhydride (35 mL) and heated to reflux for 30 minutes. The resulting clear, slightly yellow solution was slowly let to warm up to room

temperature and then cooled to 0 °C for 30 minutes. The white suspension was filtered and the filtrate was again cooled to 0 °C for 30 minutes. The suspension was once again filtered and the combined two batches of solid product were washed with hexane (2 x 20 mL) and dried in vacuo affording 26 (10.8 g, 35.3 mmol, 90%) as a white solid.

$^1$H NMR (CDCl$_3$, 400 MHz): δ 8.24 (dd, 1 H, $J = 7.6$, 1.6 Hz, ArH), 8.00 (dd, 1 H, $J = 8.3$, 1.0 Hz, ArH), 7.92 (ddd, 1 H, $J = 8.4$, 7.2, 1.6 Hz, ArH), 7.71 (td, 1 H, $J = 7.3$, 1.1 Hz, ArH), 2.25 (s, 3 H, COCH$_3$). $^{13}$C NMR (CDCl$_3$, 100 MHz): δ 176.5, 168.2, 136.2, 133.3, 131.4, 129.4, 129.1, 118.4, 20.4. The values of the NMR spectra are in accordance with reported literature data.[5]

**1-Cyano-1,2-benziodoxol-3-(1H)-one (4a)**

Following a reported procedure,[6] 1-acetoxy-1,2-benziodoxol-3-(1H)-one (26, 11.8 g, 38.6 mmol, 1.00 eq.) was dissolved under nitrogen in dry dichloromethane (200 mL). To the clear colorless solution was added via syringe trimethylsilyl cyanide (TMS-CN, 10 mL, 77 mmol, 2.00 eq.) over a five minute time period, then trimethylsilyl trifluoromethanesulfonate (TMS-OTf, 70 µL, 0.386 mmol, 0.01 equiv.). Precipitation occurred within 5 min and the reaction mixture was stirred at room temperature and under nitrogen for 30 min to ensure the completion of the reaction. The resulting thick white suspension was diluted with hexane (5 mL) before being filtered and the solid was washed with hexane (3 x 20 mL) and dried in vacuo affording 4a (10.3 g, 37.7 mmol, 98%) as a white solid.

$^1$H NMR (DMSO-$d_6$, 400 MHz): δ 8.29 (d, $J = 8.3$ Hz, 1 H, ArH), 8.13 (d, $J = 7.4$, 1.7 Hz, 1 H, ArH), 8.06-7.97 (m, 1 H, ArH), 7.88 (t, $J = 7.3$ Hz, 1 H, ArH). $^{13}$C NMR (DMSO-$d_6$, 100 MHz): δ 166.7, 136.5, 132.0, 131.9, 130.2, 127.8, 117.5, 87.9. IR ν 3157 (w), 3093 (w), 2160 (w), 1629 (s), 1562 (m), 1439 (m), 1321 (s), 1298 (s), 1148 (m), 839 (m), 747 (s). The characterization data is in accordance with reported literature values.[6]

**1-Acetoxy-3,3-dimethyl-3-(1H)-1,2-benziodoxole (28)**

Following a reported procedure,\(^7\) 1-chloro-3,3-dimethyl-3-(1H)-1,2-benziodoxole\(^8\) (27, 3.10 g, 10.5 mmol, 1.00 eq.) and silver acetate (1.83 g, 11.0 mmol, 1.05 eq.) were suspended under nitrogen in dry acetonitrile (30 mL). The mixture was stirred in the dark at room temperature for 15 hours. Filtration of the precipitated silver chloride followed by solvent removal in vacuo yielded compound 28 (2.98 g, 9.31 mmol, 89%) as a white solid. \(^1\)H NMR (CDCl\(_3\), 400 MHz): \(\delta\) 7.79 (dd, \(J = 8.0, 1.3\) Hz, 1 H, Ar\(H\)), 7.52-7.41 (m, 2 H, Ar\(H\)), 7.17 (dd, \(J = 7.4, 1.6\) Hz, 1 H, Ar\(H\)), 2.10 (s, 3 H, COC\(H_3\)), 1.52 (s, 6 H, C\(H_3\)). \(^1\)C NMR (CDCl\(_3\), 100 MHz): \(\delta\) 177.4, 149.4, 130.5, 130.0, 129.9, 126.3, 115.8, 84.6, 29.3, 21.6. The characterization data is in accordance with reported literature values.\(^7\)

1-Cyano-3,3-dimethyl-3-(1H)-1,2-benziodoxole (4b)

To a solution consisting of 1-acetoxy-3,3-dimethyl-3-(1H)-1,2-benziodoxole (28, 2.00 g, 6.25 mmol, 1.00 equiv.) and dry dichloromethane (15 mL) was added dropwise trimethylsilyl cyanide (TMS-CN, 1.71 mL, 12.5 mmol, 2.00 eq.) at room temperature under nitrogen. The clear colorless solution was stirred at room temperature for 20 hours. Solvent removal afforded a white solid, which was suspended in pentane (10 mL), filtered and dried in vacuo affording pure compound 4b (1.73 g, 6.03 mmol, 96%) as a white solid. \(R_f\) (pentane:EtOAc 7:3) = 0.54. \(^1\)H NMR (CDCl\(_3\), 400 MHz): \(\delta\) 8.05 (d, \(J = 8.3\) Hz, 1 H, Ar\(H\)), 7.62 (t, \(J = 7.3\) Hz, 1 H, Ar\(H\)), 7.58-7.49 (m, 1 H, Ar\(H\)), 7.33 (d, \(J = 7.5\) Hz, 1 H, Ar\(H\)), 1.48 (s, 6 H, C\(H_3\)). \(^1\)C NMR (CDCl\(_3\), 100 MHz): \(\delta\) 148.1, 131.7, 131.0, 128.3, 126.9, 111.6, 98.0, 80.4, 30.3. IR \(\nu\) 2974 (w), 2925 (w), 2139 (w), 1461 (m), 1436 (m), 1251 (m), 1160 (s), 1003 (w), 954 (s), 869 (m), 761 (s). The characterization data is in accordance with reported literature values.\(^9\)

5-Fluoro-1-Hydroxy-1,2-benziodoxol-3-(1H)-one (30)


\[^{[8]}\] This commercially available compound can also be synthesized following the practical procedure by V. Matousek, E. Pietrasiak, R. Schwenk, A. Togni, *J. Org. Chem.* 2013, 78, 6763.

Following a reported procedure,\textsuperscript{[10]} NaIO\textsubscript{4} (760 mg, 3.55 mmol, 1.05 equiv) and 5-fluoro-2-iodobenzoic acid (29) (900 mg, 3.38 mmol, 1.00 equiv) were suspended in 30\% (v:v) aq. AcOH (1.8 mL) / H\textsubscript{2}O (4.5 mL). The mixture was vigorously stirred and refluxed for 4 h. The reaction mixture was then diluted with cold water (180 mL) and allowed to cool to rt, protecting it from light. After 1 h, the crude product was collected by filtration, washed on the filter with ice water (3 x 10 mL) and acetone (3 x 10 mL), and air-dried in the dark to give the pure product 30 (908 mg, 3.22 mmol, 95\%) as a colorless solid.

\textsuperscript{1}H NMR (400 MHz, (CD\textsubscript{3})\textsubscript{2}SO) \(\delta\) 8.25 (bs, 1 H, O\textsubscript{H}), 7.90 – 7.78 (m, 2 H, ArH), 7.75 (dd, \(J = 8.4, 2.5\) Hz, 1 H, ArH). \textsuperscript{13}C NMR (100 MHz, (CD\textsubscript{3})\textsubscript{2}SO) \(\delta\) 166.7 (d, \(J = 2.6\) Hz), 164.0 (d, \(J = 248.3\) Hz), 134.2 (d, \(J = 7.5\) Hz), 128.5 (d, \(J = 8.7\) Hz), 121.98 (d, \(J = 23.9\) Hz), 117.4 (d, \(J = 23.6\) Hz), 114.4. The reported values correspond to the ones in literature.\textsuperscript{[10]}

**5-Fluoro-1-Acetoxy-1,2-benziodoxol-3-(1H)-one (38)**

Following a reported procedure,\textsuperscript{[5]} hypervalent iodine precursor 30 (800 mg, 2.84 mmol, 1.00 equiv.) was suspended in acetic anhydride (2.80 mL, 29.7 mmol, 10.5 equiv) and heated to reflux for 30 minutes. The resulting clear, slightly yellow solution was slowly let to cool down to room temperature and then cooled to 0 °C for 30 minutes. The white suspension was filtered and the filtrate was again cooled to 0 °C for 30 minutes. The suspension was once again filtered and the combined two batches of solid product were washed with hexane (2 x 20 mL) and dried in vacuo affording the corresponding OAc hypervalent iodine reagent 31 (825 mg, 2.55 mmol, 90\%) as a white solid.

\textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}) \(\delta\) 8.01 – 7.93 (m, 2H, ArH), 7.64 (ddd, \(J = 9.1, 7.7, 2.9\) Hz, 1H, ArH), 2.26 (s, 3H, OC(O)Me). \textsuperscript{13}C NMR (100 MHz, CDCl\textsubscript{3}) \(\delta\) 176.4, 166.7 (d, \(J = 2.9\) Hz), 165.0 (d, \(J = 254.5\) Hz), 131.7 (d, \(J = 8.0\) Hz), 131.0 (d, \(J = 8.1\) Hz), 123.7 (d, \(J = 24.0\) Hz), 120.0 (d, \(J = 24.3\) Hz), 111.2 (d, \(J = 2.3\) Hz), 20.2. The values of the NMR spectra are in

accordance with reported literature data, with small differences in chemical shifts for several signals.\textsuperscript{[11]}

5-Fluoro-1-Cyano-1,2-benziodoxol-3-(1H)-one (4c)

\[
\begin{array}{c}
\text{O} \quad \text{OAc} \\
\text{F} \\
\text{31} \\
\text{TMS-CN} \\
\text{1 mol\% TMSOTf}
\end{array}
\rightarrow
\begin{array}{c}
\text{O} \quad \text{CN} \\
\text{F} \\
\text{4c}
\end{array}
\]

Following a reported procedure,\textsuperscript{[6]} 5-Fluoro-1-acetoxy-1,2-benziodoxol-3-(1H)-one (31, 750 g, 2.31 mmol, 1.00 equiv.) was dissolved under nitrogen in dry dichloromethane (15 mL). To the clear colorless solution was added via syringe trimethylsilyl cyanide (TMS-CN, 0.62 mL, 4.6 mmol, 2.0 equiv.), over a five minute time period, then trimethylsilyl trifluoromethanesulfonate (TMS-OTf, 4.2 µL, 23 µmol, 0.010 equiv.). Precipitation occurred within 5 min and the reaction mixture was stirred at room temperature and under nitrogen for 30 min to ensure the completion of the reaction. The resulting thick white suspension was diluted with hexane (5 mL) before being filtered and the solid was washed with hexane (3 x 20 mL) and dried \textit{in vacuo} affording 4c (610 mg, 2.10 mmol, 91\%) as a white solid.

Mp: 181.1 – 184.1°C (decomp). \textsuperscript{1}H NMR (400 MHz, DMSO-\textit{d}_6) \( \delta \) 8.25 (dd, \( J = 8.9, 4.2 \) Hz, 1H, ArH), 7.99 – 7.75 (m, 2H, ArH). \textsuperscript{13}C NMR (100 MHz, DMSO-\textit{d}_6) \( \delta \) 165.3 (d, \( J = 2.4 \) Hz), 164.6 (d, \( J = 251.5 \) Hz), 133.1 (d, \( J = 7.7 \) Hz), 130.1 (d, \( J = 8.9 \) Hz), 123.8 (d, \( J = 24.5 \) Hz), 118.4 (d, \( J = 24.1 \) Hz), 111.4, 87.4. IR (solid) 3870 (s), 3740 (s), 3686 (s), 3620 (m), 3435 (w), 3335 (w), 3227 (w), 3109 (w), 2988 (w), 2914 (w), 2360 (m), 2162 (w), 2005 (w), 1926 (w), 1865 (w), 1739 (m), 1702 (m), 1647 (m), 1518 (s), 1457 (m), 1306 (m), 1141 (w), 1025 (s), 823 (w). HRMS (ESI) calcd for \( \text{C}_8\text{H}_4\text{FINO}_2^+ \) [M+H]\(^+\) 291.9265; found 291.9270.

2-Iodosyl-5-nitrobenzoic acid (30) and 2-iodosyl-3-nitrobenzoic acid (33)

\[
\begin{array}{c}
\text{24} \\
\text{H}_2\text{SO}_4, \text{HNO}_3
\end{array}
\rightarrow
\begin{array}{c}
\text{32} \\
\text{33}
\end{array}
\]

Following a reported procedure,\textsuperscript{[10]} fuming nitric acid (3.3 mL) was added to 2-iodobenzoic acid (24) (5.0 g, 20 mmol, 1.0 equiv) in concentrated \( \text{H}_2\text{SO}_4 \) (6.7 mL). The reaction was

equipped with a cooler and a nitrous vapor trap and was heated at 100 °C for 1 h. The reaction mixture was then poured in ice-water and filtered. A second crop of precipitate was filtered from the mother liquors. Both solids were combined, washed with acetone (10 mL) and dried under vacuum to afford 32 (2.19 g, 7.10 mmol, 36%). The mother liquors were reduced to one third and then kept at 4 °C, the resulting precipitate was filtered, washed with acetone (10 mL) and dried under vacuum to afford 33 (630 mg, 2.04 mmol, 10%).

32: 1H NMR (400 MHz, (CD3)2SO): δ 8.73 (dd, J = 8.8, 2.6 Hz, 1H, ArH), 8.58 (d, J = 2.4 Hz, 1H, ArH), 8.54 (br s, 1H, OH), 8.11 (d, J = 8.8 Hz, 1H, ArH). 33: 1H NMR (400 MHz, (CD3)2SO): δ 7.92 (dd, J = 7.9, 1.5 Hz, 1H, ArH), 7.79 (m, 1H, ArH), 7.67 (m, 1H, ArH). The reported values correspond to the ones in literature.[10]

5-Nitro-1-Acetoxy-1,2-benziodoxol-3-(1H)-one (34)

Following a reported procedure,[5] 5-nitro-1-hydroxy-1,2-benziodoxol-3-(1H)-one (32, 6.55 g, 21.2 mmol, 1.00 eq.) was suspended in acetic anhydride (18 mL) and heated to reflux for 30 minutes. The resulting clear, slightly yellow solution was slowly let to warm up to room temperature and then cooled to 0 °C for 30 minutes. The white suspension was filtered and the filtrate was again cooled to 0 °C for 30 minutes. The suspension was once again filtered and the combined two batches of solid product were washed with hexane (2 x 20 mL) and dried in vacuo affording 34 (5.88 g, 16.7 mmol, 79%) as a white solid.

1H NMR(400 MHz, Chloroform-d) δ 9.04 (d, J = 2.5 Hz, 1H, ArH), 8.71 (dd, J = 9.0, 2.5 Hz, 1H, ArH), 8.27 (d, J = 8.9 Hz, 1H, ArH), 2.30 (s, 3H, OC(O)Me).The values of the NMR spectra are in accordance with reported literature data.[5]

5-Nitro-1-Cyano-1,2-benziodoxol-3-(1H)-one (4d)

Following a reported procedure,[6] 1-acetoxy-1,2-benziodoxol-3-(1H)-one (34, 351 mg, 1.00 mmol, 1.00 eq.) was dissolved under nitrogen in dry dichloromethane (7.0 mL). To the clear
colorless solution was added via syringe trimethylsilyl cyanide (TMS-CN, 0.27 mL, 2.0 mmol, 2.00 eq.) over a five minute time period. then trimethylsilyl trifluoromethanesulfonate (TMS-OTf, 1.8 µL, 10 µmol, 0.01 equiv.). Precipitation occurred within 5 min and the reaction mixture was stirred at room temperature and under nitrogen for 30 min to ensure the completion of the reaction. The resulting thick white suspension was diluted with hexane (5 mL) before being filtered and the solid was washed with hexane (3 x 20 mL) and dried in vacuo affording 4d (273 mg, 0.859 mmol, 86 %) as a white solid. $^1$H NMR(400 MHz, DMSO-d6) δ 8.77 (dd, $J = 8.9, 2.7$ Hz, 1H, ArH), 8.64 (d, $J = 2.6$ Hz, 1H, ArH), 8.54 (d, $J = 8.9$ Hz, 1H, ArH). The characterization data is in accordance with reported literature values.$^{[6]}$

4,5-Dimethoxy-1-hydroxy-1,2-benziodoxol-3-(1H)-one (36)

Following a reported procedure,$^{[6]}$ NaIO$_4$ (840 mg, 3.95 mmol, 1.05 equiv) and 4,5-dimethoxy-2-iodobenzoic acid (35) (1.16 g, 3.76 mmol, 1.00 equiv) were suspended in 30% (v:v) aq. AcOH (1.8 mL in 4.5mL of H$_2$O). The mixture was vigorously stirred and refluxed for 4 h. The reaction mixture was then diluted with cold water (20 mL) and allowed to cool to rt, protecting it from light. After 1 h, the crude product was collected by filtration, washed on the filter with ice water (3 x 10 mL) and acetone (3 x 10 mL), and air-dried in the dark to give the pure product 36 (1.22 g, 3.76 mmol, >99%) as a colorless solid.

$^1$H NMR (400 MHz, (CD$_3$)$_2$SO) δ 7.99 (bs, 1 H, OH), 7.44 (s, 1 H, ArH), 7.22 (s, 1 H, ArH), 3.88 (bs, 6 H, OCH$_3$); $^{13}$C NMR (100 MHz, (CD$_3$)$_2$SO) δ 168.6, 154.1, 150.8, 124.3, 112.5, 110.9, 107.5, 56.2, 56.0. The reported values correspond to the ones in literature.$^{[6]}$

4,5-Dimethoxy-1-Acetoxy-1,2-benziodoxol-3-(1H)-one (37)

Following a reported procedure,$^{[7]}$ 4,5-dimethoxyl-1-hydroxy-1,2-benziodoxol-3-(1H)-one (36, 115 mg, 0.355 mmol, 1.00 eq.) was suspended in acetic anhydride (1.0 mL) and heated to reflux for 30 minutes. The resulting clear, slightly yellow solution was slowly let to warm up
to room temperature and then cooled to 0 °C for 30 minutes. The white suspension was filtered and the filtrate was again cooled to 0 °C for 30 minutes. The suspension was once again filtered and the combined two batches of solid product were washed with hexane (2 x 5 mL) and dried in vacuo affording 37 (108 mg, 0.295 mmol, 83 %) as a white solid.

\[^1\text{H}\] NMR (400 MHz, (CD\(_3\))\(_2\)SO) \(\delta\) 7.47 (s, 1H, ArH), 7.19 (s, 1H, ArH), 3.92 (s, 3H, OMe), 3.90 (s, 3H, OMe), 2.25 (s, 3H, OC(O)Me). \[^{13}\text{C}\] NMR (100 MHz, (CD\(_3\))\(_2\)SO) \(\delta\) 174.5, 167.7, 155.3, 151.2, 122.0, 112.9, 110.6, 109.2, 56.2, 56.1, 20.0. The values of the NMR spectra are in accordance with reported literature data.\[^6\]

**4,5-Dimethoxy-1-Cyano-1,2-benziodoxol-3-(1H)-one (4e)**

Following a reported procedure,\[^6\] 4,5-dimethoxy-1-acetoxy-1,2-benziodoxol-3-(1H)-one (37, 92 mg, 0.251 mmol, 1.00 equiv.) was dissolved under nitrogen in dry dichloromethane (2 mL). To the clear colorless solution was added via syringe trimethylsilyl cyanide (TMS-CN, 67 µL, 0.50 mmol, 2.00 equiv.) over a five minute time period, then trimethylsilyl trifluoromethanesulphonate (TMS-OTf, 0.90 µL, 5.03 µmol, 0.02 equiv.). Precipitation occurred within 5 min and the reaction mixture was stirred at room temperature and under nitrogen for 30 min to ensure the completion of the reaction. The resulting thick white suspension was diluted with hexane (5 mL) before being filtered and the solid was washed with hexane (3 x 20 mL) and dried in vacuo affording 4e (75 mg, 0.225 mmol, 90 %) as a white solid. \[^1\text{H}\] NMR (400 MHz, (CD\(_3\))\(_2\)SO) \(\delta\) 7.63 (s, 1H, ArH), 7.53 (s, 1H, ArH), 3.93 (s, 3H, OCH\(_3\)), 3.91 (s, 3H, OCH\(_3\)). \[^{13}\text{C}\] NMR (101 MHz, DMSO-d\(_6\)) \(\delta\) 166.6, 155.2, 151.9, 123.1, 112.7, 109.2, 107.0, 88.7, 56.2, 55.0. The characterization data is in accordance with reported literature values.\[^6\]

**3,5-Di(trifluoromethyl)phenyl(cyano)iodonium triflate (4f)**
Following a reported procedure,\textsuperscript{[12]} to a solution consisting of trifluoroacetic anhydride (TFAA, 20 mL) and dichloromethane (25 mL) was added dropwise at -50 °C aq. 30 wt% hydrogen peroxide (4.0 mL). After 10 minutes of stirring at -50 °C, a solution consisting of 1-iodo-3,5-bis(trifluoromethyl)benzene (38) (1.02 g, 3.00 mmol, 1.00 eq.) and dichloromethane (5.0 mL) was added dropwise. The reaction mixture was gradually warmed to 15 °C over a 14 hour time period. Next, the mixture was concentrated \textit{in vacuo}, affording the corresponding trifluoroacetate derivative (1.64 g, 2.90 mmol, 97%) as a white solid. The intermediate was dissolved in dry dichloromethane (10 mL) without additional purification and trimethylsilyl trifluoromethanesulfonate (TMS-OTf, 524 µL, 2.90 mmol, 1.00 eq.), followed by trimethylsilyl cyanide (TMS-CN, 388 µL, 2.90 mmol, 1.00 eq.), were added dropwise at room temperature. The resulting white suspension was diluted with dry dichloromethane (5.0 mL) and stirred at room temperature for 60 minutes, after which it was filtered. The white solid was washed with dichloromethane (2 x 10 mL), pentane (2 x 10 mL) and dried \textit{in vacuo} to afford the title compound 4f (1.46 g, 2.83 mmol, 98%) as a white solid. \textsuperscript{1}H NMR (CD\textsubscript{3}CN, 400 MHz): δ 8.97 (s, 2 H, Ar\textsubscript{H}), 8.45 (s, 1 H, Ar\textsubscript{H}). \textsuperscript{19}F NMR (CD\textsubscript{3}CN, 376 MHz): δ -63.6, -79.3. The values of the NMR spectra are in accordance with reported literature data.\textsuperscript{[12]}

\begin{center}
\begin{tabular}{c c c c}
 & & & \\
\textbf{25} & \textbf{TMS} & \textbf{TIPS} & \textbf{13a} \\
\hline
\textbf{39} & \textbf{CH\textsubscript{3}CN, rt} & & \\
\end{tabular}
\end{center}

Following a reported procedure,\textsuperscript{[13]} 2-iodosylbenzoic acid (25) (21.7 g, 82.0 mmol, 1.0 equiv) was charged in oven-dried three-neck 1L flask equipped with a magnetic stirrer. After 3 vacuum/nitrogen cycles, anhydrous acetonitrile (500 mL) was added via canula and cooled to 0 °C. Trimethylsilyl triflate (16.4 mL, 90.0 mmol, 1.1 equiv) was added dropwise via a dropping funnel over 30 min (no temperature increase was observed). After 15 min, (trimethylsilyl)(triisopropylsilyl)acetylene (39) (23.0 g, 90.0 mmol, 1.1 equiv) was added via canula over 15 min (no temperature increase was observed). After 30 min, the suspension became an orange solution. After 10 min, pyridine (7.0 mL, 90 mmol, 1.1 equiv) was added via syringe. After 15 min, the reaction mixture was transferred in a one-neck 1L flask and reduced under vacuum until a solid was obtained. The solid was dissolved in DCM (200 mL)

and transferred in a 1L separatory funnel. The organic layer was added and washed with 1 M HCl (200 mL) and the aqueous layer was extracted with CH₂Cl₂ (200 mL). The organic layers were combined, washed with a saturated solution of NaHCO₃ (2 x 200 mL), dried over MgSO₄, filtered and the solvent was evaporated under reduced pressure. Recrystallization from acetonitrile (ca 120 mL) afforded 13a (30.1 g, 70.2 mmol, 86%) as colorless crystals. Mp (Dec.) 170-176 °C. ¹H NMR (400 MHz, CDCl₃) δ 8.44 (m, 1 H, ArH), 8.29 (m, 1 H, ArH), 7.77 (m, 2 H, ArH), 1.16 (m, 21 H, TIPS). ¹³C NMR (100 MHz, CDCl₃) δ 166.4, 134.6, 132.3, 131.4, 126.1, 115.6, 114.1, 64.6, 18.4, 11.1. IR ν 2943 (m), 2865 (m), 1716 (m), 1618 (m), 1618 (m), 1604 (s), 1584 (m), 1557 (m), 1465 (m), 1439 (w), 1349 (m), 1291 (m), 1270 (w), 1244 (m), 1140 (m), 1016 (m), 999 (m), 883 (m), 833 (m), 742 (m), 702 (s), 636 (m); Characterization data of 13a corresponded to the literature values.[13]

1-[2-Bromophenylethynyl]-1,2-benziodoxol-3(1H)-one (13b)

Following a reported procedure,[14] trimethylsilyl triflate (1.0 mL, 5.5 mmol, 1.1 equiv) was added to a suspension of 2-iodosylbenzoic acid (25) (1.32 g, 5.00 mmol, 1 equiv) in CH₂Cl₂ (15 mL) at RT. The resulting suspension was stirred for 3 h, followed by the drop wise addition of ((2-bromophenyl)ethynl)trimethylsilane (40) (1.17 g, 5.50 mmol, 1.1 equiv). The resulting suspension was stirred for 6 h at RT. A saturated solution of NaHCO₃ (20 mL) was then added and the mixture was stirred vigorously for 30 minutes, the two layers were separated and the organic layer was washed with sat. NaHCO₃ (20 mL), dried over MgSO₄, filtered and evaporated under reduced pressure. The resulting solid was boiled in CH₃CN (20 mL). The mixture was cooled down, filtered and dried under high vacuum to afford 13b (1.50 g, 3.51 mmol, 70%) as a colorless solid.

Mp 174-177 °C (decomposition). ¹H NMR (400 MHz, CDCl₃) δ 8.44 (td, 2 H, J = 7.3, 2.1 Hz, ArH), 7.84 – 7.74 (m, 2 H, ArH), 7.68 (d, 1 H, J = 1.1 Hz, ArH), 7.61 (dd, 1 H, J = 7.6, 1.7 Hz, ArH), 7.36 (ddt, 2 H, J = 22.4, 7.5, 1.5 Hz, ArH). ¹³C NMR (101 MHz, CDCl₃)[15] δ

166.6, 135.2, 134.7, 133.0, 132.7, 131.8, 131.3, 127.6, 126.8, 126.4, 123.2, 116.5, 104.3, 55.4. IR ν 2358 (w), 2155 (w), 1638 (s), 1616 (m), 1585 (w), 1466 (w), 1316 (m), 1147 (w). HRMS (ESI) \( C_{15}H_{9}BrIO_{2}^+ \) [M+H]\(^+\) calc. = 426.8825; [M+H]\(^+\) obs. = 426.8828.

**Iridium catalyst (6)**

![](image.png)

Iridium photocatalyst 6 can be purchased from Sigma Aldrich, or it can also be synthetized following a reported procedure in two steps.\(^{[16]}\)

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4. Decarboxylative cyanation

Optimization of the reaction:

Dry degassed THF (0.5 mL) was added in a flame dried 1.5 mL test tube containing a teflon coated stirring bar, Cbz-Pro-OH (5a) (25 mg, 0.10 mmol, 1.0 equiv), CBX (4a) (41 mg, 0.15 mmol, 1.5 equiv), CsOBz (38 mg, 0.15 mmol, 1.5 equiv), 10 mg of heterogeneous powdered molecular sieves and Ir(dF(CF₃)ppy)₂(dtbbpy)PF₆ (6) (1.1 mg, 0.0010 mmol, 0.01 equiv) under N₂ (vacuum / N₂ exchange). The reaction mixture was again degassed by bubbling N₂ inside the test tube via syringe for 5 min before being irradiated using blue light LEDs for 4 h30 at rt.

The reaction mixture was filtered over silica, eluting with DCM, and evaporated under reduced pressure. Then the crude product was purified by preparative TLC (Heptane/Diethyl Ether 4/6) directly without any further work-up.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Base</th>
<th>Reagent</th>
<th>Solvent</th>
<th>Concentration (M)</th>
<th>Conversion[a] (%)</th>
<th>Yield[b] (%)</th>
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<td>4a</td>
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<tr>
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<td>Concentration</td>
<td>Yield (%)</td>
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<td>&gt;95</td>
<td>&lt;5</td>
</tr>
<tr>
<td>21</td>
<td>1.5 equiv CsOBz</td>
<td>4c</td>
<td>THF</td>
<td>0.20</td>
<td>&gt;95</td>
<td>75</td>
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<tr>
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<td>4d</td>
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<tr>
<td>23</td>
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<td>THF</td>
<td>0.20</td>
<td>&gt;95</td>
<td>52</td>
</tr>
<tr>
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<tr>
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</tr>
<tr>
<td>26</td>
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<td>&lt;10</td>
</tr>
<tr>
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<tr>
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<td>1.5 equiv CsOBz</td>
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<td>0.20</td>
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<td>&lt;5</td>
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<tr>
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<td>THF</td>
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<td>&lt;5</td>
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<td>THF</td>
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<td>Low</td>
<td>&lt;5</td>
</tr>
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</table>

[a] The conversion of 5a by NMR is given. [b] Isolated yield after preparative TLC. [c] Same conditions used for the decarboxylative alkynylation (3.0 equiv. CsOBz, no molecular sieves). [d] Using 1.1 equiv of CBX reagent. [e] Using 2.5 equiv of CBX reagent. [f] Solubility issue at 0.20 M. [g] In the dark. [h] Without photocatalyst. [i] Without base

**General procedure for decarboxylative cyanation.**

Dry degassed THF (1.5 mL) was added in a flame dried 4 mL test tube containing a teflon coated stirring bar, the carboxylic acid 5 (0.30 mmol, 1.0 equiv), CBX reagent (4a) (123 mg, 0.450 mmol, 1.5 equiv), CsOBz (114 mg, 0.450 mmol, 1.5 equiv), 30 mg of heterogeneous powdered molecular sieves (4 ångström) and Ir(dF(CF₃)ppy)₂(dtbbpy)PF₆ (6) (3 mg, 0.003 mmol, 0.01 equiv) under N₂ (vaccum / N₂ exchange). The reaction mixture was again degassed by bubbling N₂ inside the test tube via syringe for 5 min before being irradiated using blue light LEDs for 4h30 to 18 h at rt.

After completion of the reaction, the reaction mixture was filtered over silica, eluting with DCM, and evaporated under reduced pressure. The crude product was then dissolved in DCM, and washed 3 times with saturated aqueous solution of Na₂CO₃. The joined organic layers are then washed with brine, dried with MgSO₄, filtered and evaporated under reduced pressure.
pressure. Final purification was performed by column chromatography (Pentane/Ethyl Acetate) affording the corresponding nitrile.

NB: The mentioned work-up was not applied for N-Fmoc protected amino-acids, which were directly submitted to column chromatography.

**Benzyl 2-cyanopyrroldine-1-carboxylate (7a)**

Scope scale: Starting from 5a (75 mg, 0.30 mmol), the crude product was extracted following the previously described work-up prior to being purified by column chromatography (Pentane/Ethyl Acetate = 8:2) to afford 7a as colorless oil (61 mg, 0.27 mmol, 89%).

1 mmol scale: Starting from 5a (250 mg, 1.00 mmol), using 1.1 mg of Iridium catalyst 6 (0.1 mol%) and 48 h of irradiation, the crude product was extracted following the previously described work-up prior to being purified by column chromatography (Pentane/Ethyl Acetate = 8:2) to afford 7a as colorless oil (138 mg, 0.599 mmol, 60%).

Sunlight experiment: Starting from 5a (75 mg, 0.30 mmol), the reaction mixture was stirred for 4 h outdoors, under sunlight exposition instead of blue leds. The crude product was extracted following the previously described work-up prior to being purified by column chromatography (Pentane/Ethyl Acetate = 8:2) to afford 7a as colorless oil (62 mg, 0.27 mmol, 90%).

R_f: 0.35 (Pentane/Ethyl Acetate = 6:4). ^1H NMR (400 MHz, CDCl₃) δ 7.47 – 7.28 (m, 5H, ArH), 5.26 – 5.11 (m, 2H, OCH₂Ph), 4.58 (ddd, J = 7.3, 2.7 Hz, 1H, NCHCN), 3.58 (tdd, J =
10.7, 7.4, 3.4 Hz, 1H, NCH₂CH₂), 3.42 (ddd, J = 18.7, 9.7, 5.3 Hz, 1H, NCH₂CH₂), 2.34 – 1.96 (m, 4H, NCH₂CH₂CH₂CHCN). ¹³C NMR (100 MHz, CDCl₃) δ 154.2, 153.5, 135.9, 135.8, 128.5, 128.2, 128.0, 118.8, 118.6, 67.7, 67.5, 47.4, 46.9, 46.2, 45.8, 31.6, 30.67, 24.5, 23.6. IR 3607 (w), 3524 (w), 3410 (w), 3036 (w), 2960 (w), 2889 (w), 2244 (w), 1965 (w), 1706 (s), 1597 (w), 1540 (w), 1493 (w), 1410 (s), 1353 (s), 1266 (w), 1186 (m), 1120 (m), 1033 (w), 982 (w), 920 (w), 876 (w). HRMS (ESI) calcd for C₁₃H₁₄N₂NaO₂⁺ [M+Na]⁺ 253.0947; found 253.0962. The characterization data is in accordance with reported literature values.¹⁷

NB: Mixture of 2 rotamers with almost 1:1 ratio. They are not completely resolved.

The sunlight experiment took place in Lausanne (46º51’ Nm 6º57’ E), on April 19th 2016, from 14:00 to 18:00 with a light intensity of 400 to 800 W/m². Sun spectra during experiment:¹⁸

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**Tert-butyl-2-cyanopyrrolidine-1-carboxylate (7b)**

[Diagram of the molecule]

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¹⁸ Taken from: [http://www.meteolausanne.com/soleil-et-uv.html](http://www.meteolausanne.com/soleil-et-uv.html)
Starting from 5b (65 mg, 0.30 mmol), the crude product was purified by column chromatography (Pentane/Ethyl Acetate = 9:1) to afford 7b as colorless oil (50.7 mg, 0.258 mmol, 86%).

Rf: 0.40 (Pentane/Ethyl Acetate = 6:4). $^1$H NMR (400 MHz, CDCl$_3$) δ 4.62 – 4.35 (m, 1H, NCHCN), 3.59 – 3.41 (m, 1H, NCH$_2$), 3.33 (ddd, $J = 20.1, 14.3, 8.2$ Hz, 1H, NCH$_2$), 2.33 – 1.90 (m, 4H, NCH$_2$(CH$_2$)$_2$), 1.47 (s, 9H, $^t$Bu). $^{13}$C NMR (100 MHz, CDCl$_3$) δ 153.6 (m), 152.9 (major), 119.1, 81.4 (major), 80.9 (minor), 47.1 (major), 47.0 (minor), 45.9 (minor), 45.6 (major), 31.6 (major), 30.7 (minor), 28.2, 24.6 (minor), 23.7 (major). IR 2979 (w), 2889 (w), 2244 (w), 1703 (s), 1454 (w), 1391 (s), 1258 (w), 1167 (s), 1125 (m), 1036 (w), 982 (w), 921 (w), 872 (w).

The values of the NMR spectra are in accordance with reported literature data.\[19\]

NB: Mixture of 2 rotamers (major and minor) with a 1.5:1 ratio. They are not completely resolved.

(9H-fluoren-9-yl)methyl-2-cyanopyrrolidine-1-carboxylate (7c)

Starting from 5c (65 mg, 0.30 mmol), the crude product was purified by column chromatography (Pentane/Ethyl Acetate = 8:2) to afford 7c as colorless oil (88 mg, 0.28 mmol, 92%).

Rf: 0.35 (Pentane/Ethyl Acetate = 8:2). $^1$H NMR (400 MHz, CDCl$_3$) δ 7.78 (dd, $J = 7.4, 1.1$ Hz, 2H, ArH), 7.66 (t, $J = 6.8$ Hz, 1H), 7.59 (t, $J = 6.9$ Hz, 1H), 7.41 (t, $J = 7.5$ Hz, 2H, ArH), 7.34 (dd, $J = 7.4, 7.0$ Hz, 2H, ArH), 4.66 – 4.55 (m, 1H, NCHCN), 4.55 – 4.35 (m, 2H, OCH$_2$CHAr), 4.28 (app dt, $J = 20.0, 6.8$ Hz, 1H, OCH$_2$CHAr), 3.58 (ddd, $J = 15.1, 9.7, 7.2$, 3.1 Hz, 1H, NCH$_2$(CH$_2$)$_2$CHCN), 3.51 – 3.31 (m, 1H, NCH$_2$(CH$_2$)$_2$CHCN), 2.40 – 1.98 (m, 4H, NCH$_2$(CH$_2$)$_2$CHCN). $^{13}$C NMR (100 MHz, CDCl$_3$) δ 154.2, 153.7, 143.8, 143.7, 143.6, 143.5, 141.3, 141.2, 127.8, 127.2, 127.1, 125.0, 124.9, 124.9, 120.0, 118.8, 118.6, 68.1, 67.8, 47.5, 47.1 (probably superposition of 2 signals), 46.9, 46.3, 45.8, 31.8, 30.7, 24.6, 23.6. IR 3062 (w), 2959 (w), 2890 (w), 2249 (w), 1707 (s), 1446 (m), 1414 (s), 1350 (m), 1263 (w), 1188 (m), 1123 (m), 1034 (w), 985 (w), 917 (w), 876 (w). HRMS (ESI) caleld for C$_{20}$H$_{18}$N$_2$NaO$_2^+$ [M+Na]$^+$ 341.1260; found 341.1271.

NB: Mixture of 2 rotamers with almost 1:1 ratio. They are not completely resolved.

1-benzylpyrrolidine-2-carbonitrile (7d)

Starting from 5d (62 mg, 0.30 mmol), the crude product was purified by column chromatography (Pentane/Ethyl Acetate = 8:2) to afford 7d as colorless oil (24 mg, 0.13 mmol, 43%).

Rf: 0.32 (Pentane/Ethyl Acetate = 8:2). $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.39 – 7.26 (m, 5H, ArH), 3.92 (d, $J = 12.9$ Hz, 1H, NCH$_2$Ph), 3.73 – 3.63 (m, 2H, NCHCN + NCH$_2$Ph), 2.94 (ddd, $J = 9.5$, 8.1, 4.2 Hz, 1H, NCH$_2$CH$_2$CH$_2$), 2.59 (td, $J = 9.0$, 7.6 Hz, 1H, NCH$_2$CH$_2$CH$_2$), 2.24 – 2.07 (m, 2H, NCH$_2$CH$_2$), 1.93 (m, 2H, NCH$_2$CH$_2$).

$^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 137.6, 128.8, 128.5, 127.5, 118.0, 56.5, 53.2, 51.2, 29.5, 21.9. The values of the NMR spectra are in accordance with reported literature data.\(^{[20]}\)

**Tert-butyl (4R)-2-cyano-4-hydroxypyrroolidine-1-carboxylate (7e)**

Starting from 5e (69 mg, 0.30 mmol), the crude product was purified by column chromatography (Pentane/Ethyl Acetate = 6:4) to afford 7e as colorless solid (57 mg, 0.27 mmol, 90%, 2:1 dr).

**Major isomer:**

MP: 143.5 – 155.5°C. Rf: 0.2 (Heptane/Ethyl Acetate = 5:5) $^1$H NMR (400 MHz, CDCl$_3$, mixture of rotamers not fully resolved, about 2:1 major/Minor) $\delta$ 4.65 (d, $J = 7.2$ Hz, 0.4H, NCHCN + NCH$_2$CHOH), 4.61 – 4.50 (m, 1.6H, NCHCN + NCH$_2$CHOH), 3.59 (d, $J = 11.9$ Hz, 0.6H, NCH$_2$CHOH), 3.55 – 3.45 (m, 1.4H, NCH$_2$CHOH), 2.42 – 2.23 (m, 2H, NCH(CN)CH$_2$), 2.18 – 1.93 (bs, 1H, OH), 1.52 (s, 6H, tBu), 1.48 (s, 3H, tBu). $^{13}$C NMR (101 MHz, CDCl$_3$, mixture of rotamers not fully resolved) $\delta$ 153.6 (minor), 153.1 (major), 119.0, 81.9 (major), 81.4 (minor), 70.7 (minor), 69.6 (major), 54.7 (minor), 54.5 (major), 45.5 (major), 45.3 (minor), 39.3 (major), 38.8 (minor), 28.9. IR 3452 (w), 3292 (w), 2979 (w), 2939 (w), 2249 (w), 1697 (s), 1469 (w), 1402 (s), 1340 (w), 1260 (w), 1168 (s), 1126 (m), 1094 (w), 979 (w), 919 (w), 880 (w). HRMS (ESI) calcd for C$_{10}$H$_{16}$N$_2$NaO$_3$ $^+$ [M+Na]$^+$ 235.1053; found 235.1050.

**Tert-butyl 2-Cyanopiperidine-1-carboxylate (7f)**

Starting from 5f (69 mg, 0.30 mmol), the crude product was purified by column chromatography (Pentane/Ethyl Acetate = 8:2) to afford 7f as colorless solid (45 mg, 0.22 mmol, 72%).

Rf: 0.4 (Pentane/Ethyl Acetate = 8:2). \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 5.23 (bs, 1H, NCHCN), 4.05 (m, 1H, NCH\(_2\)), 2.93 (m, 1H, NCH\(_2\)), 1.93 (m, 1H, NCHCH\(_2\)), 1.86 – 1.76 (m, 1H, NCHCH\(_2\)), 1.77 – 1.61 (m, 3H, NCH\(_2\)CH\(_2\) + NCH\(_2\)CH\(_2\)CH\(_2\)), 1.47 (s, 10H, tBu + NCH\(_2\)CH\(_2\)C\(_4\)H\(_9\)). \(^{13}\)C NMR (101 MHz, CDCl\(_3\)) \(\delta\) 154.0, 117.8, 81.4, 44.0, 41.4, 28.5, 28.4, 24.5, 20.3. IR 2945 (w), 2864 (w), 2243 (w), 1704 (s), 1455 (w), 1401 (s), 1327 (w), 1268 (m), 1165 (s), 1088 (w), 1036 (w), 993 (w), 928 (w), 869 (w). HRMS (ESI) calcd for C\(_{11}\)H\(_{19}\)N\(_2\)O\(_2\)\([M+H]^+\) 211.1441; found 211.1442.

The values of the NMR spectra are in accordance with reported literature data.\(^{[21]}\)

**Benzyl 3-cyano-3,4-dihydroisoquinoline-2(1H)-carboxylate (7g)**

Starting from 5g (93 mg, 0.30 mmol), the crude product was purified by column chromatography (Pentane/Ethyl Acetate = 8:2) to afford 7g as colorless oil (57 mg, 0.20 mmol, 65%).

Rf: 0.40 (Heptane/Ethyl Acetate = 8:2). \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 7.44 – 7.33 (m, 5H, ArH), 7.32 – 7.22 (m, 2H, ArH), 7.22 – 7.09 (m, 2H, ArH), 5.71 – 5.32 (m, 1H, NCHCN), 5.24 (s, 2H, C(O)OC\(_2\)H\(_5\)Ph)), 4.89 (d, \(J = 16.6\) Hz, 1H, NCH\(_2\)Ar), 4.57 (d, \(J = 16.6\) Hz, 1H, NCH\(_2\)Ar), 3.26 (dd, \(J = 16.1, 5.8\) Hz, 1H, NCH\(_2\)Ar), 3.16 – 3.01 (m, 1H, NCHCH\(_2\)Ar). \(^{13}\)C NMR (101 MHz, CDCl\(_3\)) \(\delta\) 155.0, 135.6, 131.1, 129.6, 129.0, 128.6, 128.5, 128.3, 127.3, 126.4, 117.4, 68.4, 43.7, 42.1, 32.3. IR 3064 (w), 3037 (w), 2956 (w), 2854 (w), 2244 (w), 1967 (w), 1708 (s), 1597 (w), 1498 (w), 1454 (w), 1409 (s), 1327 (m), 1226 (m), 1166 (w), 1123 (m), 1093 (w), 999 (m), 910 (w), 822 (w). HRMS (ESI) calcd for C\(_{18}\)H\(_{17}\)N\(_2\)O\(_2\)\([M+H]^+\) 293.1285; found 293.1283.

**Tert-butyl (cyanomethyl)carbamate (7h)**

\[\text{BocH} – \equiv N\]

Starting from 5h (53 mg, 0.30 mmol), the crude product was purified by column chromatography (Pentane/Ethyl Acetate = 8:2) to afford 7h as colorless oil (31 mg, 0.20 mmol, 66%).

Rf: 0.35 (Pentane/Ethyl Acetate = 8:2). \( ^1 \)H NMR (400 MHz, CDCl\(_3\)) \( \delta \) 4.92 (bs, 1H, NH), 4.06 (bd, \( J = 6.1 \) Hz, 2H, \( CH_2 \)), 1.46 (s, 9H, \( tBu \)). \( ^{13} \)C NMR (100 MHz, CDCl\(_3\)) \( \delta \) 154.8, 116.5, 81.4, 34.1, 28.1. IR 3587 (w), 3355 (w), 2983 (w), 2939 (w), 2256 (w), 1704 (s), 1517 (s), 1374 (w), 1287 (s), 1255 (s), 1167 (s), 1052 (w), 941 (w), 859 (w). HRMS (ESI) calcd for C\(_7\)H\(_{13}\)N\(_2\)O\(_2\) [M+H]\(^+\) 157.0972; found 157.0970.

The values of the NMR spectra are in accordance with reported literature data.[22]

**Tert-butyl-(1-cyanoethyl)carbamate (7i)**

Starting from 5i (57 mg, 0.30 mmol), the crude product was purified by column chromatography (Pentane/Ethyl Acetate = 8:2) to afford 7i as colorless oil (44 mg, 0.26 mmol, 86%).

Rf: 0.29 (Pentane/Ethyl Acetate = 8:2). \( ^1 \)H NMR (400 MHz, CDCl\(_3\)) \( \delta \) 4.88 (bs, 1H, NH), 4.62 (bs, 1H, \( CH \)), 1.54 (d, \( J = 7.2 \) Hz, 3H, \( CH_3 \)), 1.46 (s, 9H, \( tBu \)). \( ^{13} \)C NMR (100 MHz, CDCl\(_3\)) \( \delta \) 154.1, 119.5, 81.2, 37.6, 28.2, 19.6. IR 3668 (w), 3319 (m), 2986 (m), 2947 (m), 2906 (w), 2795 (w), 2249 (w), 1684 (s), 1533 (s), 1451 (w), 1374 (m), 1335 (m), 1302 (m), 1259 (s), 1165 (s), 1074 (m), 1036 (m), 913 (w), 866 (m). HRMS (ESI) calcd for C\(_8\)H\(_{14}\)N\(_2\)NaO\(_2\) [M+Na]\(^+\) 193.0947; found 193.0947.

The values of the NMR spectra are in accordance with reported literature data.[23]

**Tert-butyl (2-cyanopropan-2-yl)carbamate (7j)**

Starting from 5j (61 mg, 0.30 mmol), the crude product was purified by column chromatography (Pentane/Ethyl Acetate = 8:2) to afford 7j as colorless oil (28 mg, 0.15 mmol, 51%).

Rf: 0.25 (Pentane/Ethyl Acetate = 8:2). \( ^1 \)H NMR (400 MHz, CDCl\(_3\)) \( \delta \) 4.79 (s, 1H, NH), 1.66 (s, 6H, NC(\( CH_3 \))\(_2\)CN), 1.48 (s, 9H, \( tBu \)). \( ^{13} \)C NMR (100 MHz, CDCl\(_3\)) \( \delta \) 153.6, 121.2, 81.3, 46.8, 28.2, 27.6. IR 3348 (m), 2982 (m), 2934 (w), 2246 (w), 1695 (s), 1515 (s), 1464 (w),

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1373 (m), 1281 (s), 1169 (s), 1088 (m), 960 (w), 861 (w). HRMS (ESI) calcd for C_{9}H_{16}N_{2}NaO_{2}^{+} [M+Na]^{+} 207.1104; found 207.1107.

**Tert-butyl-(1-cyano-2-methylpropyl)carbamate (7k)**

Starting from 5k (65 mg, 0.30 mmol), the crude product was purified by column chromatography (Pentane/Ethyl Acetate = 8:2) to afford 7k as colorless solid (48 mg, 0.24 mmol, 80%).

R_{f}: 0.35 (Pentane/Ethyl Acetate = 8:2). \(^{1}H\) NMR (400 MHz, CDCl\(_{3}\)) \(\delta\) 4.86 (br d, \(J = 9.5\) Hz, 1H, NH), 4.46 (t, \(J = 7.9\) Hz, 1H, BocNHCH), 2.11 – 1.91 (m, \(J = 6.7\) Hz, 1H, CHMe\(_{2}\)), 1.46 (s, 9H, tBu), 1.09 (d, \(J = 7.0\) Hz, 3H, CHMe\(_{2}\)), 1.07 (d, \(J = 7.0\) Hz, 3H, CHMe\(_{2}\)). \(^{13}C\) NMR (100 MHz, CDCl\(_{3}\)) \(\delta\) 154.4, 118.0, 81.1, 48.4, 31.8, 28.2, 18.5, 17.9. IR 3341 (m), 2976 (m), 2934 (w), 2248 (w), 1701 (s), 1519 (s), 1374 (m), 1255 (m), 1168 (s), 1019 (w), 916 (w), 869 (w). HRMS (ESI) calcd for C_{10}H_{18}N_{2}NaO_{2}^{+} [M+Na]^{+} 221.1260; found 221.1261.

The values of the NMR spectra are in accordance with reported literature data.\(^{[24]}\)

**(9H-fluoren-9-yl)methyl-(1-cyano-3-methylbutyl)carbamate (7l)**

Starting from 5l (106 mg, 0.30 mmol), the crude product was purified by column chromatography (Pentane/Ethyl Acetate = 10:2) to afford 7l as white solid (82 mg, 0.24 mmol, 82%).

R_{f}: 0.30 (Pentane/Ethyl Acetate = 8:2). \(^{1}H\) NMR (400 MHz, CDCl\(_{3}\)) \(\delta\) 7.77 (d, \(J = 7.5\) Hz, 2H, ArH), 7.57 (d, \(J = 7.5\) Hz, 2H, ArH), 7.41 (t, \(J = 7.5\) Hz, 2H, ArH), 7.32 (t, \(J = 7.4\) Hz, 2H, ArH), 5.16 – 5.05 (m, 1H, NH), 4.72 – 4.67 (m, 0.2H, CHCN), 4.63 (dd, \(J = 8.0\) Hz, 0.80H, CHCN), 4.49 (d, \(J = 6.7\) Hz, 2H, -OCH\(_{2}\)CH), 4.21 (t, \(J = 6.7\) Hz, 1H, -OCH\(_{2}\)CH), 1.87 – 1.58 (m, 3H, CH\(_{2}\)CHMe\(_{2}\)), 0.97 (d, \(J = 6.4\) Hz, 6H, CH\(_{2}\)CHMe\(_{2}\)). \(^{13}C\) NMR (100 MHz, CDCl\(_{3}\)) \(\delta\) 155.1, 143.4, 141.3, 127.8, 127.1, 124.8, 120.0, 118.7, 67.3, 47.0, 42.0, 41.2, 24.7, 22.1, 21.8. IR 3664 (w), 3326 (m), 3060 (w), 2961 (m), 2877 (w), 2249 (w), 1954 (w), 1918 (w), 1709 (s), 1525 (s), 1456 (m), 1326 (m), 1252 (s), 1168 (w), 1120 (w), 1041 (m), 916 (w), 866 (w). HRMS (ESI) calcd for C_{21}H_{22}N_{2}NaO_{2}^{+} [M+Na]^{+} 357.1573; found 357.1576

The values of the NMR spectra are in accordance with reported literature data, with small differences in chemical shifts.\(^{[25]}\)

NB: Mixture of rotamers not completely resolved.

**Benzyl-(1-cyano-2-phenylethyl)carbamate (7m)**

Starting from \(5m\) (90 mg, 0.30 mmol), the crude product was purified by column chromatography (Pentane/Ethyl Acetate = 10:2) to afford \(7m\) as white solid (66 mg, 0.24 mmol, 78%).

\(R_f: 0.37\) (Pentane/Ethyl Acetate = 8:2). \(^1^H\) NMR (400 MHz, CDCl\(_3\)) \(\delta\) 7.36 (m, 8H, ArH), 7.29 – 7.23 (m, 2H, ArH), 5.12 (s, 3H, OCH\(_2\)Ph + NH), 4.89 (dd, \(J = 7.3\) Hz, 1H, CHCN), 3.09 (dd, \(J = 13.8, 6.5\) Hz, 2H, NCHCH\(_2\)Ph). \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 154.9, 135.5, 133.5, 129.4, 129.0, 128.6, 128.5, 128.3, 128.0, 118.0, 67.7, 43.7, 38.9. IR 3322 (m), 3038 (w), 2963 (w), 2783 (w), 2245 (w), 1957 (w), 1887 (w), 1810 (w), 1701 (s), 1531 (s), 1451 (w), 1260 (s), 1151 (w), 1042 (m), 986 (w), 910 (w), 819 (w). HRMS (ESI) calcd for C\(_{17}\)H\(_{16}\)N\(_2\)NaO\(_2\)^+ [M+Na]^+ 303.1104; found 303.1113

The characterization data is in accordance with reported literature values.\(^{[26]}\)

**Tert-butyl (2-(benzyloxy)-1-cyanoethyl)carbamate (7n)**

Starting from \(5n\) (89 mg, 0.30 mmol), the crude product was purified by column chromatography (Pentane/Ethyl Acetate = 10:2) to afford \(7n\) as colorless oil (66 mg, 0.24 mmol, 80%).

\(R_f: 0.45\) (Pentane/Ethyl Acetate = 6:4). \(^1^H\) NMR (400 MHz, CDCl\(_3\)) \(\delta\) 7.44 – 7.29 (m, 5H, ArH), 5.31 (d, \(J = 9.0\) Hz, 1H, NH), 4.81 – 4.68 (m, 1H, NCHCN), 4.62 (s, 2H, OCH\(_2\)Ph), 3.72 (dd, \(J = 9.8, 3.6\) Hz, 1H, NCHCH\(_2\)O), 3.64 (dd, \(J = 9.7, 4.2\) Hz, 1H, NCHCH\(_2\)O), 1.46 (s, 9H, 'Bu). \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 154.3, 136.7, 128.6, 128.2, 127.8, 117.6, 81.3, 73.6, 69.0, 42.5, 28.2. IR 3659 (w), 3337 (w), 2979 (m), 2935 (w), 2875 (w), 2252 (w), 1711 (s), 1506 (s), 1464 (w), 1366 (m), 1289 (m), 1253 (m), 1165 (s), 1114 (m), 1022 (w), 913 (w), 871 (w). HRMS (ESI) calcd for C\(_{15}\)H\(_{20}\)N\(_2\)NaO\(_3\)^+ [M+Na]^+ 299.1366; found 299.1372

The characterization data is in accordance with reported literature values.\(^{[20]}\)


**Tert-butyl 4-(((9H-fluoren-9-yl)methoxy)carbonyl)amino)-4-cyanobutanoate (7o)**

Starting from 5o (128 mg, 0.300 mmol), the crude product was purified by column chromatography (Pentane/Ethyl Acetate = 8:2) to afford 7o as white solid (80 mg, 0.20 mmol, 66%).

Mp: 74-76°C. Rf: 0.25 (Pentane/Ethyl Acetate = 8:2). $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.77 (dt, $J = 7.6$, 0.9 Hz, 2H, ArH), 7.57 (d, $J = 7.5$ Hz, 2H, ArH), 7.45 – 7.36 (m, 2H, ArH), 7.36 – 7.28 (m, 2H, ArH), 5.66 (d, $J = 8.4$ Hz, 1H, NH), 4.68 (app q, $J = 7.5$ Hz, 1H, NCHCN), 4.47 (m, 2H, OCH$_2$CHAr), 4.21 (t, $J = 7.0$ Hz, 1H, OCH$_2$CHAr), 2.45 (m, 2H, BocCH$_2$CH$_2$), 2.12 (app q, $J = 6.9$ Hz, 2H, BocCH$_2$CH$_2$), 1.46 (s, 9H, tBu). $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 171.5, 155.6, 143.4, 141.3, 127.8, 127.1, 124.9, 120.0, 118.0, 81.7, 67.4, 47.0, 42.3, 31.1, 28.0, 27.9. IR 3331 (w), 2978 (w), 2253 (w), 1721 (s), 1524 (m), 1452 (m), 1374 (w), 1327 (w), 1250 (s), 1157 (s), 1047 (w), 952 (w), 849 (w). HRMS (ESI) calcd for C$_{24}$H$_{26}$N$_2$NaO$_4$ $^+$ [M+Na]$^+$ 429.1785; found 429.1798.

**Benzyl (1-cyano-3-(methylthio)propyl)carbamate (7p)**

Starting from 5p (85 mg, 0.30 mmol), the crude product was purified by column chromatography (Pentane/Ethyl Acetate = 8:2) to afford 7p as white solid (47 mg, 0.18 mmol, 59%).

Mp: 57-58°C. Rf: 0.15 (Pentane/Ethyl Acetate = 8:2). $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.43 – 7.31 (m, 5H, ArH), 5.37 (s, 1H, NH), 5.15 (s, 2H, OCH$_2$Ph), 4.85 (dd, $J = 8.1$, 7.7 Hz, 1H, NCHCN), 2.66 (t, $J = 6.9$ Hz, 2H, NCHCH$_2$CH$_2$S), 2.11 (m, 5H, NCHCH$_2$CH$_2$S + SMe). $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 155.0, 135.5, 128.6, 128.5, 128.3, 118.0, 67.8, 41.9, 32.1, 29.6, 15.5. IR 3321 (m), 3038 (w), 2924 (w), 2349 (w), 2250 (w), 1963 (w), 1712 (s), 1522 (s), 1444 (w), 1331 (w), 1250 (s), 1142 (w), 1053 (m), 974 (w), 914 (w). HRMS (ESI) calcd for C$_{13}$H$_{17}$N$_2$O$_4$S$^+ [M+H]$^+$ 265.1005; found 265.1009

**Benzyl tert-butyl (1-cyanopentane-1,5-diyl)dicarbamate (7q)**
Starting from 5q (114 mg, 0.300 mmol), the crude product was purified by column chromatography (Pentane/Ethyl Acetate = 6:2) to afford 7q as white solid (90 mg, 0.25 mmol, 83%).

Rf: 0.3 (Pentane/Ethyl Acetate = 6:2). 1H NMR (400 MHz, CDCl3) δ 7.40 – 7.28 (m, 5H, ArH), 5.16 (d, J = 8.6 Hz, 1H, BocNH), 5.09 (s, 2H, OCH2Ar), 4.90 (bs, J = 6.2 Hz, 1H, CbzNH), 4.50 (app q, J = 7.9 Hz, 1H, BocNHCHCN), 3.20 (m, 2H, CbzNHCH2), 1.81 (m, 2H, CbzNHCH2(CH2)2), 1.53 (m, 4H, CbzNHCH2(CH2)2), 1.45 (s, 9H, tBu). 13C NMR (100 MHz, CDCl3) δ 156.6, 154.4, 136.2, 128.1, 127.9, 66.9, 46.5, 45.4, 43.4, 29.8, 25.0. IR 3665 (w), 3327 (w), 2975 (w), 2941 (w), 2248 (w), 1698 (w), 1523 (s), 1455 (w), 1363 (s). The values of the NMR spectra are in accordance with reported literature data.\(^{[27]}\)

**Benzyl (2-(2-cyanopyrrolidin-1-yl)-2-oxoethyl)carbamate (7r)**

Starting from 5r (92 mg, 0.30 mmol), the crude product was purified by column chromatography (Full DCM to DCM/Acetone = 92:8) to afford 7r as yellowish oil (49 mg, 0.17 mmol, 56%).

Rf: 0.22 (DCM/Acetone = 95:5). 1H NMR (400 MHz, CDCl3, mixture of rotamers (major/minor)) δ 7.39 – 7.27 (m, 5H, ArH), 5.80 (s, 0.9H, NH (major)), 5.60 (s, 0.1H, NH (minor)), 5.14 (s, 0.2H, OCH2Ph (minor)), 5.11 (s, 1.8H, OCH2Ph (major)), 4.80 – 4.69 (m, 0.9H, NCHCN (major)), 4.66 (m, 0.1H, NCHCN (minor)), 4.18 (m, 0.1H, NC(O)CH2NHCbz (minor)), 4.11 – 3.87 (m, 1.9H, NC(O)CH2NHCbz, (major+minor)), 3.73 – 3.63 (m, 0.1H, NCH2(CH2)2CHCN (minor)), 3.63 – 3.54 (m, 0.9H, NCH2(CH2)2CHCN (major)), 3.49 (m, 0.1H, NCH2(CH2)2CHCN (minor)), 3.41 (m, 0.9H, NCH2(CH2)2CHCN (major)), 2.37 (m, 0.2H, NCH2(CH2)2CHCN (minor)), 2.34 – 2.04 (m, 3.8H, NCH2(CH2)2CHCN (minor+major)). 13C NMR (100 MHz, CDCl3, only major rotamer) δ 167.5, 156.3, 136.2, 128.4, 128.1, 127.9, 117.9, 66.9, 46.5, 45.4, 43.4, 29.8, 25.0. IR 3334 (w), 3037 (w), 2976 (w), 2248 (w), 1722 (s), 1664 (s), 1529 (m), 1442 (s), 1330 (w), 1250 (s), 1168 (w), 1055 (m), 905 (w), 849 (m), 795 (w), 736 (w), 711 (s), 665 (w), 625 (m), 589 (w), 553 (w).

992 (w), 916 (w), 832 (w). HRMS (ESI) calcd for C_{15}H_{17}N_{3}NaO_{3}^+ [M+Na]^+ 310.1162; found 310.1167.

The values of the NMR spectra are in accordance with reported literature data.\textsuperscript{28}

NB: Mixture of rotamers, NMR ratio of 10:1.

**Benzyl ((2R)-1-(2-cyanopyrrolidin-1-yl)-1-oxo-3-phenylpropan-2-yl)carbamate (7s)**

Starting from 5s (119 mg, 0.30 mmol), the crude product was purified by column chromatography (Full DCM to DCM/Acetone = 92:8) to afford 7s as colorless oil (62 mg, 0.16 mmol, 55%); obtained as a mixture of diastereoisomers (Major:minor = 1.2:1). The major diastereoisomer was generated as a mixture of inseparable rotamers (ratio: 56:44). The minor product could be partially isolated in ca. 95% purity.

R\textsubscript{f}: 0.22 (major) 0.20 (minor) (DCM/Acetone = 95:5). \textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}, signals are not fully resolved) \( \delta \) 7.37-7.29 (m, 5 H, (minor+major), ArH), 7.25 (m, 3.5 H, (minor + major), ArH), 7.21-7.14 (m, 1.5 H, (minor + major)), 5.69 (d, \( J = 8.5 \) Hz, 0.75 H, NH, (minor + major)), 5.45 (d, \( J = 7.8 \) Hz, 0.25 H, NH, major (rotamer 1)), 5.32 (d, \( J = 6.8 \) Hz, 0.25 H, major (rotamer 2)), 5.11 (m, 1.5 H, (minor + major)), 5.04-4.94 (m, 0.25 H, major), 4.68-4.62 (m, 1 H, (minor + major)), 4.58 (m, 0.25 H, (minor)), 4.50 (dd, \( J = 7.8 \), 2.1 Hz, 0.75 H, major), 3.60-3.50 (m, 0.75 H, major), 3.35 (m, 0.25 H, minor), 3.24 (dd, \( J = 14.0 \), 5.1 Hz, 0.25 H, major), 3.10-3.05 (m, 1 H, (minor + major)), 2.96 (m, 0.75 H, major), 2.58 (m, 0.25 H, minor), 2.50 (m, 0.75 H, major), 2.38-2.22 (m, 0.25 H, major), 2.18-2.07 (m, 1.25 H, (minor + major)), 2.00 (m, 1 H, (minor + major)), 1.94-1.87 (m, 0.25 H, minor), 1.82-1.68 (m, 1.25 H (minor + major) (overlap with impurity)). \textsuperscript{13}C NMR (101 MHz, Chloroform-d, signals are not fully resolved) \( \delta \) 171.1, 170.6, 170.4, 156.2, 155.6, 155.5, 136.1, 135.8, 135.4, 129.5, 129.4, 129.3, 128.8, 128.7, 128.5, 128.1, 128.0, 127.8, 127.3, 127.2, 127.1, 118.6, 117.8, 117.5, 67.1, 67.0, 54.2, 54.1, 47.4, 46.3, 46.1, 46.0, 40.0, 38.0, 32.2, 29.8, 29.7, 24.9, 24.6, 23.0. IR 3516 (w), 3307 (m), 3060 (w), 3033 (w), 2956 (w), 2887 (w), 2249 (w), 1961 (w), 1713 (s), 1651 (s), 1522 (m), 1439 (s), 1335 (m), 1249 (s), 1151 (w), 1053 (m), 914 (m). HRMS (ESI) calcd for C\textsubscript{22}H\textsubscript{23}N\textsubscript{3}NaO\textsubscript{3}^+ [M+Na]^+ 400.1632; found 400.1632.

Characterization data for the minor diastereoisomer:

\[ ^1H\text{ NMR (400 MHz, Chloroform-}d\text{)} \delta 7.34 (m, 7H, ArH), 7.30 – 7.16 (m, 3H, ArH), 5.69 (d, J = 8.6 Hz, 1H, NH), 5.19 – 5.00 (m, 2H, OCH}_2\text{Ph), 4.67 (dd, J = 7.9, 3.0 Hz, 1H, NCHCN), 4.58 (m, 1H, NC(O)CH/NHCBz), 3.36 (td, J }= 9.2, 6.9 \text{ Hz, 1H, NCH}_2\text{(CH}_2\text{)}_2\text{CHCN), 3.11 – 2.99 (m, 2H, NHCHCH}_2\text{Ph), 2.59 (m, 1H, NCH}_2\text{(CH}_2\text{)}_2\text{CHCN), 2.17 – 1.95 (m, 2H, NCH}_2\text{CH}_2\text{CH}_2\text{CHCN). }^{13}\text{C NMR (100 MHz, Chloroform-}d\text{)} \delta 170.6, 155.6, 136.1, 135.4, 129.5, 128.8, 128.5, 128.2, 128.0, 127.3, 117.3, 67.0, 54.1, 46.2, 46.0, 40.1, 29.7, 24.9. \text{IR 3534 (w), 3304 (w), 3060 (w), 3034 (w), 2957 (w), 2887 (w), 2249 (w), 1962 (w), 1714 (s), 1651 (s), 1526 (m), 1442 (s), 1335 (m), 1249 (s), 1154 (w), 1050 (m), 914 (w).}

2,3-Dihydrobenzo[b][1,4]dioxine-2-carbonitrile (7v)

Starting from 5v (54 mg, 0.30 mmol), the crude product was purified by column chromatography (Pentane/Ethyl Acetate = 9:1) to afford 7v as colorless solid (34 mg, 0.21 mmol, 70%).

Rf: 0.4 (Pentane/Ethyl Acetate = 8:2). \[ ^1H\text{ NMR (400 MHz, CDCl}_3\text{)} \delta 7.00 – 6.89 (m, 4H, ArH), 5.12 (dd, J = 3.7, 2.5 Hz, 1H, CHCN), 4.42 (dd, J = 11.8, 3.7 Hz, 1H, OCH}_2\text{CHCN), 4.35 (dd, J = 11.8, 2.6 Hz, 1H, OCH}_2\text{CHCN). }^{13}\text{C NMR (100 MHz, CDCl}_3\text{)} \delta 142.3, 140.4, 123.2, 122.6, 117.8, 117.7, 114.7, 64.6, 61.8. \text{IR 3656 (w), 3053 (w), 2980 (w), 2934 (w), 2885 (w), 2224 (w), 1764 (w), 1600 (w), 1496 (s), 1312 (m), 1260 (s), 1190 (w), 1118 (w), 1083 (s), 1018 (w), 931 (w), 883 (w), 832 (w).}

The values of the NMR spectra are in accordance with reported literature data. \[^{29}\]

Gram scale reaction

Starting from 5v (1.0 g, 5.6 mmol), the reaction was irradiated for 36h. Then the crude product was extracted following the previously described work-up prior to being purified by column chromatography (twice, Pentane/Ethyl Acetate = 9:1) to afford 7v as colorless solid (395 mg, 2.45 mmol, 44%).

2-(Benzyloxy)propanenitrile (7w)

Starting from 5w (54 mg, 0.30 mmol), the crude product was purified by column chromatography (Pentane/Ethyl acetate = 8:2) to afford 7w as colorless liquid (32 mg, 0.20 mmol, 66%).

Rf: 0.45 (Pentane/Ethyl Acetate = 8:2). \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 7.47 – 7.29 (m, 5H, Ar\(H\)), 4.85 (d, \(J = 11.6\) Hz, 1H, OCH\(_2\)Ph), 4.54 (d, \(J = 11.5\) Hz, 1H, OCH\(_2\)Ph), 4.26 (q, \(J = 6.8\) Hz, 1H, OCH\(_2\)CN), 1.59 (d, \(J = 6.8\) Hz, 3H, Me). \(^1\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 135.9, 128.6, 128.4, 128.2, 118.8, 72.1, 63.2, 19.8. IR 3068 (w), 3035 (w), 2998 (w), 2938 (w), 2875 (w), 2241 (w), 1967 (w), 1889 (w), 1754 (w), 1599 (w), 1498 (w), 1456 (w), 1386 (w), 1330 (w), 1259 (w), 1212 (w), 1071 (m), 1017 (m), 911 (w), 876 (w).

The values of the NMR spectra are in accordance with reported literature data.\[30\]

2-(4-(Tert-butyl)phenoxy)acetonitrile (7x)

Starting from 5x (62 mg, 0.30 mmol), the crude product was purified by column chromatography (Pentane/Ethyl Acetate = 8:2) to afford 7x as colorless oil (21 mg, 0.11 mmol, 37%).

Rf: 0.25 (Pentane/Ethyl Acetate = 9:1). \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 7.36 (d, \(J = 8.9\) Hz, 2H, Ar\(H\)), 6.92 (d, \(J = 8.9\) Hz, 2H, Ar\(H\)), 4.75 (s, 2H, OCH\(_2\)CN), 1.31 (s, 9H, tBu). \(^1\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 154.3, 146.0, 126.7, 115.3, 114.5, 53. 8, 34.2, 31.4.

The values of the NMR spectra are in accordance with reported literature data.\[31\]

Side product obtained in presence of water:
Benzy1 2-hydroxyypyrrolidine-1-carboxylate (8)

Isolated from the reaction mixture during the optimization (0.10 mmol scale). Reaction without molecular sieves furnished this side product in various amounts depending on the dryness of the reagents and the solvent. Purification by preparative TLC (Heptane/Ethyl Acetate = 6:4) afforded 8 as a colorless oil (10 mg, 90% purity, 0.041 mmol, 41%).

**Rt:** 0.20 (Heptane/Ethyl Acetate = 8:2). \(^1\)H NMR (400 MHz, Chloroform-\(d\), mixture of rotamers partially resolved, 2:1 ratio) \(\delta\) 7.42 – 7.29 (m, 5H, ArH), 5.52 (m, 1H, NCHOH), 5.17 (m, 2H, OCH\(_2\)Ph), 3.60 (m, 1H, NCH\(_2\)(CH\(_2\))\(_2\)), 3.35 (m, 1H, NCH\(_2\)(CH\(_2\))\(_2\)), 2.23 – 1.73 (m, 4H, NCH\(_2\)(CH\(_2\))\(_2\)). \(^1\)C NMR (101 MHz, Chloroform-\(d\)) \(\delta\) 155.8, 155.4, 136.4, 128.5, 128.1, 127.9, 82.2, 81.3, 67.1, 67.0, 46.2, 45.8, 33.6, 32.7, 22.8, 22.0. HRMS (ESI) calcd for C\(_{12}\)H\(_{15}\)NO\(_3\)Na: [M+Na] = 244.0950, found 244.0951. The values of the NMR spectra are in accordance with reported literature data.\(^{[32]}\)

**Labelling experiment with \(^{18}\)O-water \((^{18}\)O-labelled-8)\)**

![N-acetyl-8](image)

Dry degassed THF (1.0 mL) was added in a flame dried 4 mL test tube containing a teflon coated stirring bar, the Cbz-Pro-OH 5a (50 mg, 0.20 mmol, 1.0 equiv), CBX reagent (82 mg, 0.30 mmol, 1.5 equiv), CsOBz (76 mg, 0.30 mmol, 1.5 equiv) and Ir(dF(CF\(_3\))ppy\(_2\))(dtbbpy)PF\(_6\) (6) (2.2 mg, 0.0020 mmol, 0.01 equiv) under N\(_2\) (vaccum / N\(_2\) exchange). At this time, 36 \(\mu\)L of \(^{18}\)O-water (10 equiv, 97% atom \(^{18}\)O) was added by Hamilton syringe. The reaction mixture was degassed by freeze-pump-thaw cycle (3 times) before being irradiated using blue light LEDs for 10 h at rt.

After completion of the reaction, the reaction mixture was filtered using HPLC filter. An HRMS sample was diluted with dry acetonitrile.

Caution: classical filtration using silica gel leads to fast isotopic exchange of the hemiaminal. The labelled product was only observed when the reaction mixture was filtered using dry HPLC filter. NMR analysis showed formation of this side product in a 1:0.08 ratio in favor of nitrile 5a.


According to the HRMS spectra, the distribution between 8 and \(^{18}\)O-labelled-8 is 23:77, meaning incorporation is 77%.

**THF-2-carbonitrile (9)**

Observed as side product when reaction is performed in THF. For most of the reaction, a 10:1 NMR ratio between the nitrile product 7 and THF-2-carbonitrile (9) is observed in the crude mixture at the end of the reaction.

$^1$H NMR (400 MHz, Chloroform-$d$) $\delta$ 4.70 (dd, $J = 6.8, 4.9$ Hz, 1H, CHOCN), 4.07 – 3.88 (m, 2H, CH$_2$O), 2.29-2.23 (m, 2H, CH$_2$), 2.08-1.92 (m, 2 H, CH$_2$). The values of the $^1$H NMR spectra are in accordance with reported literature data.$^{[33]}$ The crude reaction spectrum is added in the spectra section.

5. Derivatization: Synthesis of a Vildagliptin precursor

(2-Chloroacetyl)-L-proline (5z)

Following a reported procedure,[34] In a 250 mL double-neck round bottom flask, the L-Proline (46) (10.0 g, 87.0 mmol) was dissolved in THF (100 mL), and chloroacetyl chloride (10.5 mL, 132 mmol) was slowly added for 15 min in ice-bath. After the addition, the reaction mixture was heated to 90 °C stirring for 2.5 h. After full conversion (controlled by TLC (25% MeOH-CH₂Cl₂)) the reaction was quenched with water (30 mL) and stirred for additional 20 min. Saturated brine (30 mL) and ethyl acetate (50 mL) were added and the organic layer was collected. The aqueous layer was extracted again with ethyl acetate (3x20 mL). The combined organic extracts were dried over anhydrous Na₂SO₄ and concentrated under vacuum. The honey-like residue was recrystallized in diisopropyl ether (30 mL) for 0.5 h at room temperature and the mixture was then cooled to 0 °C for 24 h. The precipitated crystalline white solid was filtered, washed with cold diisopropyl ether and dried at 50 °C under vacuum to obtain compound 5z (14.1 g, 73.4 mmol, 85 %); ¹H NMR (400 MHz, CDCl₃) δ 8.07 (bs, 1H, COOH), 4.58 (dd, J = 7.9, 3.6 Hz, 1H, NCHCOOH), 4.14 – 4.05 (m, 2H, CH₂Cl), 3.74 – 3.60 (m, 2H, NCH₂), 2.40 – 1.79 (m, 4H, NCH₂(CH₂)₂CHCOOH). The values of the NMR spectra are in accordance with reported literature data.[32]

1-(2-Chloroacetyl)pyrrolidine-2-carbonitrile (7z)

Dry degassed THF (1.5 mL) was added in a flame dried 4 mL test tube containing a teflon coated stirring bar, the carboxylic acid 5z (57 mg, 0.30 mmol, 1.0 equiv), CBX reagent (123 mg, 0.45 mmol, 1.5 equiv), KOBz (72 mg, 0.45 mmol, 1.5 equiv), 30 mg of heterogeneous powdered molecular sieves (4 ångström) and Ir(dF(CF₃)ppy)₂(dtbbpy)PF₆ (6) (7 mg, 0.006 mmol, 0.02 equiv) under N₂ (vaccum / N₂ exchange). The reaction mixture was again

degassed by bubbling N₂ inside the test tube via syringe for 5 min before being irradiated using blue light LEDs for 6 h at rt.

After completion of the reaction, the reaction mixture was filtered over silica, eluting with DCM, and evaporated under reduced pressure. Final purification was performed by column chromatography (Pentane/Ethyl Acetate = 1:1) affording the corresponding nitrile 7z (22 mg, 0.13 mmol, 42%).

Rf: 0.20 (Pentane/Ethyl Acetate = 1:1). ¹H NMR (400 MHz, CDCl₃) δ 4.86 (dd, J = 7.7, 2.2 Hz, 0.15H, NCHCN), 4.81 – 4.71 (m, 0.85H, NCHCN), 4.27 – 4.10 (m, 0.3H, CH₂Cl), 4.06 (d, J = 1.7 Hz, 1.7H, CH₂Cl), 3.76 – 3.74 (m, 0.15H, NCH₂(CH₂)₂), 3.74 – 3.68 (m, 0.85H, NCH₂(CH₂)₂), 3.66 – 3.55 (m, 0.85H, NCH₂(CH₂)₂), 3.57 – 3.47 (m, 0.15H, NCH₂(CH₂)₂), 2.42 (m, 0.15H, NCH₂(CH₂)₂), 2.37 – 2.26 (m, 1.85H, NCH₂(CH₂)₂), 2.26 – 2.17 (m, 1.85H, NCH₂(CH₂)₂), 2.17 – 2.08 (m, 0.15H, NCH₂(CH₂)₂). ¹³C NMR (100 MHz, CDCl₃) δ 165.2 (major), 164.8 (minor), 117.8 (not resolved), 47.0 (minor), 46.9 (major), 46.8 (minor), 46.5 (major), 41.5 (not resolved), 32.5 (minor), 30.0 (major), 25.2 (major), 22.8 (minor). IR 3513 (w), 2993 (w), 2959 (w), 2887 (w), 2247 (w), 1668 (s), 1421 (s), 1341 (w), 1274 (w), 1193 (w), 1155 (w), 1104 (w), 1048 (w), 1009 (w), 920 (w), 877 (w), 841 (w). HRMS (ESI) calcd for C₇H₁₀ClN₂O⁺ [M+H]⁺: 173.0476; found: 173.0474.

NB: Mixture of rotamers (major/minor ratio 1:0.2), which are not completely resolved.

The values of the NMR spectra are in accordance with reported literature data.[35]


**Procedure for radical trap experiment in the decarboxylative cyanation**

![Chemical structure diagram]

Dry degassed THF (0.5 mL) was added in a flame dried 1.5 mL test tube containing a teflon coated stirring bar, the carboxylic acid 5a (0.10 mmol, 1.0 equiv), CBX reagent 4a (0.15 mmol, 1.5 equiv), CsOBz (0.15 mmol, 1.5 equiv), TEMPO (0.60 mmol, 4.0 equiv) and Ir(dF(CF₃)ppy)₂(dtbbpy)PF₆ (6) (0.030 mmol, 0.30 equiv) under N₂. The reaction mixture was again degassed by bubbling N₂ inside the test tube via syringe for 5 min before being irradiated using blue light LEDs for 5 h at rt.

Then a small amount was filtered several times through HPLC filter, before being submitted to MS analysis. Nitrile was not found. TEMPO adduct 22 was found by mass.

Calculated for: [M+H] = 361.2475, found 361.2445.

**Procedure for cyclic voltammetry**

Cyclic voltammetric measurements were recorded in a glove box by a CHI760E electrochemical workstation that was connected to a glassy carbon working electrode (surface area = 0.07 cm²), a platinum wire auxiliary electrode, and an Ag/AgNO₃ (0.01 M) reference electrode filled with acetonitrile and [n-Bu₄][PF₆] (0.1 M). All potentials were referenced to Fe/Fe⁺ as internal standard.
Cyclic voltammogram of CBX (4a) (4 mM) recorded in CH$_3$CN solution at scan rate of 100 mV·s$^{-1}$; the potential is referenced to the ferrocene/ferrocnium couple

Cyclic voltammogram of TIPS-EBX (13a) (4 mM) recorded in CH$_3$CN solution at scan rate of 100 mV·s$^{-1}$; the potential is referenced to the ferrocene/ferrocnium couple

**Procedure for $^{13}$C-labelling experiment**

Dry degassed THF (1.5 mL) was added in a flame dried 4 mL test tube containing a teflon coated stirring bar, Cbz-protected L Proline (5a) (0.30 mmol, 1.0 equiv), CBX reagent (4a) (123 mg, 0.450 mmol, 1.5 equiv), K$^{13}$CN (39 mg, 0.60 mmol, 2.0 equiv), CsOBz (114 mg, 0.450 mmol, 1.5 equiv), 30 mg of heterogeneous powdered molecular sieves (4 ångström) and
Ir(dF(CF₃)ppy)₂(dtbbpy)PF₆ (6) (3 mg, 0.003 mmol, 0.01 equiv) under N₂ (vacuum / N₂ exchange). The reaction mixture was again degassed by bubbling N₂ inside the test tube via syringe for 5 min before being irradiated using blue light LEDs for 4h30 at rt.

After completion of the reaction, the orange reaction mixture was filtered over silica, eluting with DCM, and evaporated under reduced pressure. The crude product was then dissolved in DCM, and washed 3 times with saturated aqueous solution of Na₂CO₃. The joined organic layers are then washed with brine, dried with MgSO₄, filtered and evaporated under reduced pressure. Final purification was performed by column chromatography (Pentane/Ethyl Acetate = 8:2 to 6:4) affording the corresponding ¹³C-labelled nitrile 7a (30 mg, 0.13 mmol, 43%). Incorporation was calculated by ¹³C NMR integration (using peak at 135.9 ppm as internal standard), to be 2.2%.

Control experiment:
Dry degassed THF (1.5 mL) was added in a flame dried 4 mL test tube containing a teflon coated stirring bar, CBX reagent (4a) (123 mg, 0.450 mmol, 1.5 equiv) and K¹³CN (39 mg, 0.60 mmol, 2.0 equiv), under N₂ (vacuum / N₂ exchange). The reaction mixture was again degassed by bubbling N₂ inside the test tube via syringe for 5 min before being stirred in the dark for 4h30 at rt. Then, filtration led to the isolation of 140 mg of ¹³C-labelled reagent (unpure, some decompostiion occurred, and still KCN and ¹³C-KCN remaining). Incorporation was calculated by ¹³C NMR integrations (using peak at 118.5 as internal standard) to be 14.3%.

Procedure for radical clock experiments
1-bromo-2-(hex-5-en-1-yn-1-yl)benzene (17)

Dry degassed DCE (1.0 mL) was added in a flame dried 4 mL test tube containing a teflon coated stirring bar, cyclopropyl acetic acid 16 (19 µL, 0.20 mmol, 1.0 equiv), EBX reagent 13b (128 mg, 0.300 mmol, 1.5 equiv), CsOBz (152 mg, 0.600 mmol, 3.0 equiv), and Ir(dF(CF₃)ppy)₂(dtbbpy)PF₆ (6) (6.7 mg, 6.0 µmol, 0.03 equiv) under N₂ (vacuum / N₂ exchange / N₂ exchange). The reaction mixture was again degassed by bubbling N₂ inside the test tube via syringe for 5 min before being irradiated using blue light LEDs for 4h30 at rt. The reaction mixture was degassed by bubbling N₂ inside the test tube via syringe for 5 min before being stirred in the dark for 4h30 at rt. Then, filtration led to the isolation of 140 mg of ¹³C-labelled reagent (unpure, some decompostiion occurred, and still KCN and ¹³C-KCN remaining). Incorporation was calculated by ¹³C NMR integrations (using peak at 118.5 as internal standard) to be 14.3%.

S39
exchange). The reaction mixture was again degassed by bubbling N₂ inside the test tube via syringe for 5 min before being irradiated using blue light LEDs for 22 h at rt.

The reaction mixture was filtered over silica, eluting with ethyl acetate, and evaporated under reduced pressure (Crude NMR ratio 1:1 product remaining starting material). Then preparative TLC using heptane led to the isolation of 10 mg (about 21% yield, 90% pure) of the open product 17 as a colorless oil and no detection of the product formed after direct alkynylation.

\(^1\)H NMR (400 MHz, Chloroform-\(d\)) \(\delta\) 7.55 (dd, \(J = 8.0, 1.2\) Hz, 1H, ArH), 7.42 (dd, \(J = 7.7, 1.7\) Hz, 1H, ArH), 7.22 (td, \(J = 7.6, 1.3\) Hz, 1H, ArH), 7.12 (td, \(J = 7.8, 1.7\) Hz, 1H, ArH), 5.97 (ddt, \(J = 16.8, 10.2, 6.5\) Hz, 1H, ArCH₂CH₂CHCH₂), 5.15 (dd, \(J = 17.1, 1.7\) Hz, 1H, ArCH₂CH₂CHCH₂), 5.07 (dd, \(J = 10.2, 1.6\) Hz, 1H, ArCH₂CH₂CHCH₂), 2.56 (t, \(J = 7.1\) Hz, 2H, ArCH₂CH₂CHCH₂), 2.40 (m, 2H, ArCH₂CH₂CHCH₂).

The values of the NMR spectra are in accordance with reported literature data.\(^{[36]}\)

6-(2-Bromophenyl)hex-5-ynal (19)

\[
\begin{align*}
\text{BocH} & & \text{BocH} \\
\text{18} & \overset{13b, 3.0 \text{ equiv. CsOBz}}{\rightleftharpoons} & \text{Br} \\
3.0 \text{ mol \%} \text{ 6, DCE, 0.20 M blue led, 10 h, RT} & \rightarrow & \text{19, 20\%}
\end{align*}
\]

Dry degassed DCE (1.0 mL) was added in a flame dried 4 mL test tube containing a teflon coated stirring bar, cyclopropyl acetic acid 18 (43 mg, 0.20 mmol, 1.0 equiv), EBX reagent 13b (128 mg, 0.300 mmol, 1.5 equiv), CsOBz (152 mg, 0.600 mmol, 3.0 equiv), and Ir(dF(CF₃)ppy)₂(dtbbpy)PF₆ (6) (4.5 mg, 4.0 µmol, 0.02 equiv) under N₂ (vacuum / N₂ exchange). The reaction mixture was again degassed by bubbling N₂ inside the test tube via syringe for 5 min before being irradiated using blue light LEDs for 22 h at rt.

The reaction mixture was filtered over silica, eluting with ethyl acetate, and evaporated under reduced pressure. Then preparative TLC using heptane/diethyl ether (6:4) led to the isolation of 10 mg (20% yield) of the open product 19 as a colorless oil and the direct alkynylation product was not detected.

\(^1\)H NMR (400 MHz, Chloroform-\(d\)) \(\delta\) 9.86 (t, \(J = 1.4\) Hz, 1H, CHO), 7.56 (dd, \(J = 8.1, 1.4\) Hz, 1H, ArH), 7.42 (dd, \(J = 7.7, 1.7\) Hz, 1H, ArH), 7.22 (td, \(J = 7.6, 1.3\) Hz, 1H, ArH), 7.13 (td, \(J = 7.7, 1.7\) Hz, 1H, ArH), 2.73 (td, \(J = 7.3, 1.4\) Hz, 2H, ArCH₂CH₂CHCH₂), 2.56 (t, \(J = 6.8\) Hz,

2H, ArCH$_2$CH$_2$CH$_2$), 1.97 (p, $J = 7.0$ Hz, 2H, ArCH$_2$CH$_2$CH$_2$). $^{13}$C NMR (100 MHz, CDCl$_3$) δ 201.9, 133.3, 132.3, 128.9, 127.0, 125.6, 125.4, 93.8, 80.4, 42.7, 20.9, 18.9. IR 3677 (w), 3361 (w), 3064 (w), 2930 (w), 2853 (w), 2720 (w), 2239 (w), 1725 (s), 1676 (w), 1587 (w), 1511 (w), 1464 (m), 1432 (w), 1365 (w), 1251 (w), 1169 (w), 1112 (w), 1053 (w), 1028 (w), 916 (w), 866 (w). HRMS (ESI) calcd for C$_{12}$H$_{12}$BrO$^+$ [M+H]$^+$ 251.0066; found 251.0068.

Procedure for competitive experiment between CBX (4a) and TIPS-EBX (13a)

Using optimized conditions found for the decarboxylative alkynylation:
Dry degassed DCE (1.5 mL) was added in a flame dried 4 mL test tube containing a teflon coated stirring bar, Cbz-protected L Proline (5a) (75 mg, 0.30 mmol, 1.0 equiv), TIPS-EBX (13a) (96.0 mg, 0.225 mmol, 0.75 equiv), CBX (4a) (61.4 mg, 0.225 mmol, 0.75 equiv), CsOBz (0.23 g, 0.90 mmol, 3.0 equiv), and Ir(dF(CF$_3$)ppy)$_2$(dtbbpy)PF$_6$ (6) (3.4 mg, 3.0 µmol, 0.01 equiv) and under N$_2$ (vaccum / N$_2$ exchange). The reaction mixture was again degassed by bubbling N$_2$ inside the test tube via syringe for 5 min before being irradiated using blue light LEDs for 4h30 at rt.

The reaction mixture was filtered over silica, eluting with ethyl acetate, and evaporated under reduced pressure (Crude NMR showed remaining starting material, full conversion was not reached). Then purification by column chromatography starting from 9:1 to 6:4 heptane/ethyl acetate led to the isolation of the alkynylated product 14a (12 mg, 0.031 mmol, 10 % yield based on Cbz-Pro-OH (5a)) and the cyanated product 7a (17 mg, 0.074 mmol, 25% yield based on Cbz-Pro-OH (5a)).

Using optimized conditions found for the decarboxylative cyanation:
Dry degassed THF (1.5 mL) was added in a flame dried 4 mL test tube containing a teflon coated stirring bar, Cbz-protected L Proline (5a) (75 mg, 0.30 mmol, 1.0 equiv), TIPS-EBX (13a) (96.0 mg, 0.225 mmol, 0.75 equiv), CBX (4a) (61.4 mg, 0.225 mmol, 0.75 equiv), CsOBz (0.11 g, 0.45 mmol, 1.5 equiv), and Ir(dF(CF$_3$)ppy)$_2$(dtbbpy)PF$_6$ (6) (3.4 mg, 3.0 µmol, 0.01 equiv) and 4A molecular sieves (30 mg) under N$_2$ (vaccum / N$_2$ exchange). The reaction mixture was again degassed by bubbling N$_2$ inside the test tube via syringe for 5 min before being irradiated using blue light LEDs for 4h30 at rt.
The reaction mixture was filtered over silica, eluting with ethyl acetate, and evaporated under reduced pressure (Crude NMR showed remaining starting material, full conversion was not reached). Then purification by column chromatography starting from 9:1 to 6:4 heptane/ethyl acetate led to the isolation of the alkynylated product 14a (16 mg, 0.041 mmol, 14 % yield based on Cbz-Pro-OH (5a)) and the cyanated product 7a (39 mg, 0.17 mmol, 57% yield based on Cbz-Pro-OH (5a)).

Benzyl 2-((triisopropylsilyl)ethynyl)pyrrolidine-1-carboxylate (14a)

Rf: 0.28 (Pentane/Ethyl Acetate = 9:1). \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 7.46 – 7.27 (m, 5H, Ph), 5.16 (d, \(J\) = 3.2 Hz, 2H, CH\(_2\)-O), 4.67 – 4.51 (m, 1H, CH-C≡C), 3.64 – 3.49 (m, 1H, CH\(_2\)), 3.47 – 3.30 (m, 1H, CH\(_2\)), 2.21 – 1.98 (m, 3H, CH\(_2\)), 1.99 – 1.87 (m, 1H, CH\(_2\)), 1.11 – 0.93 (m, 21H, TIPS). \(^{13}\)C NMR (101 MHz, CDCl\(_3\))\[^{37}\] \(\delta\) 154.6, 136.9, 128.4, 127.8, 127.8, 127.6, 107.9, 82.6, 66.9, 66.7, 49.3, 48.8, 46.0, 45.5, 34.3, 33.4, 24.4, 23.6, 18.6, 11.1. IR 2943 (m), 2865 (m), 2170 (w), 1709 (s), 1464 (w), 1410 (s), 1356 (m), 1184 (m), 1119 (m), 1092 (m), 996 (w), 883 (m). HRMS (ESI) calcd for C\(_{23}\)H\(_{35}\)NNaO\(_2\)Si\(_2\) \([M+Na]^+\) 408.2329; found 408.2334.

Actinometry / Quantum yield

For this experiment, our light reactor gave only a very approximate value of the quantum yield because it is circular and therefore more difficult to calculate the amount of incident photons. For this purpose, a Kessil blue LED (40W) was used as light source, furnishing blue light from only one direction. Incident photon flux was measured using a calibrated photodiode from Thorlabs (S120VC), assuming all photons at the peak wavelength of the blue LED (465 nm). The latter was measured with a spectrometer from Ocean Optics (USB2000+XR1-ES).

Dry degassed THF (1.5 mL) was added in a flame dried 4 mL test tube containing a teflon coated stirring bar, Cbz-Pro-OH 5a (75 mg, 0.30 mmol, 1.0 equiv), CBX reagent (123 mg, 0.450 mmol, 1.5 equiv), CsOBz (114 mg, 0.450 mmol, 1.5 equiv), 30 mg of heterogeneous powdered molecular sieves and Ir(dF(CF\(_3\))ppy\(_2\))(dtbbpy)PF\(_6\) (3.3 mg, 3.0 \(\mu\)mol, 0.01 equiv).

\[^{37}\]\ Mixture of two rotamers, which are not completely resolved.
under N₂ (vacuum / N₂ exchange). The reaction mixture was again degassed by bubbling N₂ inside the test tube via syringe for 5 min before being irradiated using blue light Kessil LED (40W) for 40 min at rt. Air flow was used to keep the flask at room temperature during the irradiation. The reaction mixture was filtered over silica, eluting with DCM, and evaporated under reduced pressure. Then purification of the crude material leads to the isolation of 38 mg of the pure nitrile 7a (0.17 mmol, 55% yield).

Dry degassed DCE (1.5 mL) was added in a flame dried 4 mL test tube containing a teflon coated stirring bar, Cbz-Pro-OH 5a (75 mg, 0.30 mmol, 1.0 equiv), EBX reagent 13a (193 mg, 0.450 mmol, 1.5 equiv), CsOBz (229 mg, 0.900 mmol, 3.0 equiv), and Ir(dF(CF₃)ppy)₂(dtbbpy)PF₆ (6) (3.3 mg, 3.0 µmol, 0.01 equiv) under N₂ (vacuum / N₂ exchange). The reaction mixture was again degassed by bubbling N₂ inside the test tube via syringe for 5 min before being irradiated using blue light Kessil LED (40W) for 40 min at rt. Air flow was used to keep the flask at room temperature during the irradiation. The reaction mixture was filtered over silica, eluting with DCM, and evaporated under reduced pressure. Then purification of the crude material leads to the isolation of 57 mg of the pure alkyne 14a (0.15 mmol, 49% yield).

Using Planck-Einstein relation:
Photon energy at wavelength λ = 465 nm : E = h * c / λ
= 6.626 * 10⁻³⁴ * 2.998 * 10⁸ / (465 * 10⁻⁹)
= 4.27 * 10⁻¹⁹ [J]

Where h is Planck constant, c is the speed of light and λ is the wavelength of the LED.

Power density = light intensity measured / photodiode area
= 0.0065 / (π * (0.95/2)²) = 0.00917 [J s⁻¹ cm⁻²]

Photon density = Power density / Photon energy at wavelength λ=465 nm
= 0.00917 / 4.27 * 10⁻¹⁹
= 2.14758 * 10¹⁶ [photons s⁻¹ cm⁻²]

Error margin +/- 4 %

Finally quantum yield is calculated according to the following equation:
\[ \Phi_{\text{cyanation}} = \frac{\text{mol products}}{\text{mol incident photons}} = \frac{\text{mol products}}{\text{photon density} \times \text{t} \times f \times \text{area} / N_A} \]
\[ = \frac{0.166 \times 10^{-3}}{(2.14758 \times 10^{16} \times 2400 \times 0.9999 \times 2.2 / 6.022 \times 10^{23})} = 0.88 \]
\[ \Phi_{\text{alkynylation}} = \frac{\text{mol products}}{\text{photon density} \times \text{t} \times f \times \text{area} / 6.022 \times 10^{23}} \]
\[ = \frac{0.148 \times 10^{-3}}{(2.14758 \times 10^{16} \times 2400 \times 0.9999 \times 2.2 / 6.022 \times 10^{23})} = 0.79 \]

Where \( t \) is time of the irradiation in seconds (40 min = 2400 s); \( f = 1 - 10^A \) where \( A \) is absorbance. At 465 nm, absorbance was saturated at 1\( \mu \)M and about 0.31 at 5 nM. Concentration of photocatalyst under reaction conditions is 2.0 mM, meaning all the incident light is assumed to be absorbed by the photocatalyst \( \text{Ir(dF(CF}_3\text{)ppy)}_2(\text{dtbbpy})\text{PF}_6 \) (\( f > 0.9999 \)). And the irradiated test tube area can be calculated as a rectangle of 1cm wide and 2.2 cm high. Therefore the area is 2.2 cm\(^2\). And \( N_A \) is Avogadro number.

**Luminescence Quenching Experiments (Stern-Volmer Studies)**

Luminescence intensities were recorded using a Cary Eclipse SW fluorescence spectrophotometer from Varian. All solutions were excited at 380 nm and the emissions were detected at the 476 nm. Dry THF was degassed by three freeze-pump-thaw cycles. Samples were prepared as follow: to a degassed (\( \text{N}_2 / \text{Vacuum, 3 cycles} \)) glass cuvette capped with septa, was introduced stock solutions of photocatalyst and quencher (CBX or Z-Pro-OH) using Hamilton syringes, and the corresponding volume of THF to get a total volume of 1.0 mL. The concentration of \( \text{Ir(dF(CF}_3\text{)ppy)}_2(\text{dtbbpy})\text{PF}_6 \) was 4.96 x 10\(^{-6}\) M. As shown below, the cesium carboxylate is a good quencher whereas CBX doesn’t quench the excited state of the photocatalyst.
Determination of the enantiomeric excess of 14a and 7a

Samples were prepared in a 80/20 hexane/isopropanol mixture, before being submitted in chiral HPLC.

HPLC conditions for the alkyne 14a: Racemic mixture. Chiralcel IA, 99:1 Hexane/iPrOH, 1mL/min, 61min. $t_R^1 = 9.6$ min. $t_R^2 = 10.1$ min. $\lambda = 254$ nm.

**Signal 2: DAD1 B, Sig=210.4 Ref=360.100**

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**Totals:** 5923.26855 386.62047
HPLC conditions for the nitrile 7a: Racemic mixture. Chiralcel IA, 95:5 Hexane/iPrOH, 1mL/min, 61min. \( t_{R1} = 19.0 \) min. \( t_{R2} = 21.6 \) min. \( \lambda = 254 \) nm.

Signal 1: DAD1 A, Sig=254,4 Ref=360,100

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Totals: 945.93298  26.97804
7. Spectra of New Compounds
$^{1}$$H$-NMR (400 MHz, DMSO-$d_{6}$) of compound 4c

$^{13}$$C$-NMR (100 MHz, DMSO-$d_{6}$) of compound 4c
IR of compound 4c
$^1$H-NMR (400 MHz, DMSO-$d_6$) of compound 4a after $^{13}$C incorporation using $^{13}$C-KCN
$^{13}$C-NMR (100 MHz, DMSO-$d_6$) of compound 4d after $^{13}$C incorporation using $^{13}$C-KCN
\(^1\text{H-NMR}\) (400 MHz, CDCl\(_3\)) of compound 7a

\(^{13}\text{C-NMR}\) (100 MHz, CDCl\(_3\)) of compound 7a
$\textit{\textsuperscript{13}C-NMR}$ (100 MHz, CDCl$_3$) of compound 7a after $\textit{\textsuperscript{13}C}$ incorporation

IR of compound 7a
$^1$H-NMR (400 MHz, CDCl$_3$) of compound 7b

$^{13}$C-NMR (100 MHz, CDCl$_3$) of compound 7b
IR of compound 7b
$^1$H-NMR (400 MHz, CDCl$_3$) of compound 7c

$^{13}$C-NMR (100 MHz, CDCl$_3$) of compound 7c
IR of compound 7c
$^1$H-NMR (400 MHz, CDCl$_3$) of compound 7d

$^{13}$C-NMR (100 MHz, CDCl$_3$) of compound 7d
$^1$H-NMR (400 MHz, CDCl$_3$) of compound 7e (major isomer)

$^{13}$C-NMR (100 MHz, CDCl$_3$) of compound 7e (major isomer)
IR of compound 7e (major isomer)
$^1$H-NMR (400 MHz, CDCl$_3$) of compound 7f

$^{13}$C-NMR (100 MHz, CDCl$_3$) of compound 7f
IR of compound 7f
$^1\text{H-NMR}$ (400 MHz, CDCl$_3$) of compound 7g

$^{13}\text{C-NMR}$ (100 MHz, CDCl$_3$) of compound 7g
IR of compound 7g
$^1$H-NMR (400 MHz, CDCl$_3$) of compound 7h

$^{13}$C-NMR (100 MHz, CDCl$_3$) of compound 7h
IR of compound 7h
$\textbf{1}^\text{H-NMR} \ (400 \text{ MHz, CDCl}_3) \ of \ compound \ 7i$

$\textbf{1}^\text{3C-NMR} \ (100 \text{ MHz, CDCl}_3) \ of \ compound \ 7i$
IR of compound 7i
$^1$H-NMR (400 MHz, CDCl$_3$) of compound 7j

$^{13}$C-NMR (100 MHz, CDCl$_3$) of compound 7j
IR of compound 7j
$^1$H-NMR (400 MHz, CDCl$_3$) of compound 7k

$^{13}$C-NMR (100 MHz, CDCl$_3$) of compound 7k
IR of compound 7k
**$^1$H-NMR (400 MHz, CDCl$_3$) of compound 7l**

![NMR Spectrum for 7l]

**$^{13}$C-NMR (100 MHz, CDCl$_3$) of compound XX**

![NMR Spectrum for XX]
IR of compound 71
$^1$H-NMR (400 MHz, CDCl$_3$) of compound 7m

$^{13}$C-NMR (100 MHz, CDCl$_3$) of compound 7m
IR of compound 7m
$^1$H-NMR (400 MHz, CDCl$_3$) of compound 7n

$^{13}$C-NMR (100 MHz, CDCl$_3$) of compound 7n
IR of compound 7n
$^1$H-NMR (400 MHz, CDCl$_3$) of compound 7o

$^{13}$C-NMR (100 MHz, CDCl$_3$) of compound 7o
IR of compound 70
$^1$H-NMR (400 MHz, CDCl$_3$) of compound 7p

$^{13}$C-NMR (100 MHz, CDCl$_3$) of compound 7p
IR of compound 7p
$^1$H-NMR (400 MHz, CDCl$_3$) of compound 7q

$^{13}$C-NMR (100 MHz, CDCl$_3$) of compound XX
IR of compound 7q
$^1$H-NMR (400 MHz, CDCl$_3$) of compound 7r

$^{13}$C-NMR (100 MHz, CDCl$_3$) of compound 7r
IR of compound 7r
$^1$H-NMR (400 MHz, CDCl$_3$) of compound 7s (mixture)

$^{13}$C-NMR (100 MHz, CDCl$_3$) of compound 7s (mixture)
IR of compound 7s (mixture)
$^1$H-NMR (400 MHz, CDCl$_3$) of compound 7s (minor diastereoisomer)

$^{13}$C-NMR (100 MHz, CDCl$_3$) of compound 7s (minor diastereoisomer)
IR of compound 7s (minor diastereoisomer)
$^1$H-NMR (400 MHz, CDCl$_3$) of compound 7v

$^{13}$C-NMR (100 MHz, CDCl$_3$) of compound 7v
IR of compound 7v
$^{1}$H-NMR (400 MHz, CDCl$_3$) of compound 7w

$^{13}$C-NMR (100 MHz, CDCl$_3$) of compound 7w
IR of compound 7w
\(^1\)H-NMR (400 MHz, CDCl\(_3\)) of compound 7x

\(^{13}\)C-NMR (100 MHz, CDCl\(_3\)) of compound 7x
$^1$H-NMR (400 MHz, CDCl$_3$) of compound 7z

$^{13}$C-NMR (100 MHz, CDCl$_3$) of compound 7z
IR of compound 7z
$^1$H-NMR (400 MHz, CDCl$_3$) of compound 8

$^{13}$C-NMR (100 MHz, CDCl$_3$) of compound 8
$^1$H-NMR (400 MHz, CDCl$_3$) of crude NMR obtained for sunlight irradiation.
$^1$H-NMR (400 MHz, CDCl$_3$) of compound 19

$^{13}$C-NMR (100 MHz, CDCl$_3$) of compound 19
IR of compound 19