Catalytic Deprotection of Alkyne Dicobalt Hexacarbonyl Complexes using Near-Infrared Photocatalysis

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KEYWORDS: Photocatalysis, Alkyne Dicobalt Complexes, Near-Infrared, Catalytic Deprotection

ABSTRACT: Dicobalt hexacarbonyl complexes are well-known for their applications in Nicholas reaction or simply as protecting group for alkynes. To recover the alkyne, demetallation is necessary, which usually involves a stoichiometric amount of an oxidizing agent or a strong ligand. This article reports a demetallation methodology based on a photocatalytic process. This approach employs a photocatalyst under aerobic conditions and the optimal results were achieved using mild near-infrared irradiation. Mechanistic investigation is also presented to elucidate how the photocatalytic system promotes this deprotection. This tool is compatible with one-pot reaction and orthogonal deprotection of alkyne offering new perspectives for further applications.

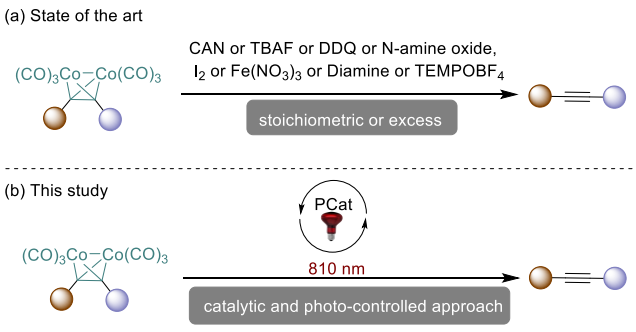
INTRODUCTION

Alkyne dicobalt hexacarbonyl complexes are relevant reagents that can be employed to functionalize a propargylic position through the Nicholas reaction.[1,2] This reaction has been applied to various structures, even in total synthesis of sophisticated natural coumpounds.[3] These cobalt-based complexes are also used as a rare protecting group for alkyne and is sometimes employed to stabilize fragile triple-bond[4] for specific applications such as click chemistry.[5] When a dicobalt hexacarbonyl complex is installed into biologically active molecules, their properties as a drug can be exacerbated as it was demonstrated in cancer treatment.[6] For most of these applications, the cobalt-complex is used as a transient group that needs to be demetalated to recover the original function. To do so, two main approaches are reported in the literature. First, a one-electron oxidizing reagent can be used to promote this deprotection like ceric ammonium nitrate (CAN),[7] 2,3-Dichloro-5,6-dicyano-1,4-benzoquinon (DDQ),[8] I_2,[9] or $Fe(NO_3)_3$.[10] Alternatively, a strong coordinating ligand (*N*-amine Oxide,[5a,5c] TBAF,[11] diamine[12] can be involved to substitute a carbonyl ligand on the cobalt center and promote the demetalation. Both strategies suffer from the same drawback because an over-stoichiometric amount of the deprotecting reagent is required to recover the triple-bond (Scheme 1). This is an important limitation since many of these reagents are toxic and not recyclable.

In parallel, the photocatalysis concept has recently emerged as a powerful tool to promote organic reactions via single electron transfer (SET)[13] or energy transfer (EnT) pathways.[14] In both cases, the photocatalyst (PCat) is promoted to its excited state through visible-light or near-infrared irradiation[15] providing new intermediates than can be used to triggered reaction. Thus, only a catalytic amount of PCat is engaged in achieving very complex transformations. To get a photocatalytic reaction even more renewable, O_2 can be used in some cases as a co-oxidant to close the catalytic cycle. Recent advancements in NIR-photocatalysis offer milder reaction conditions and present noteworthy benefits that should be taken into account for the development of new synthetic methodologies. Specifically, this light ($\lambda > 750$ nm) is lower in energy, penetrates deeper into solutions, and is biocompatible.

Herein, we report a new photocatalytic approach under aerobic conditions and near-infrared activation to demetalate of cobalt-alkyne complex. This strategy results in a photo-controlled reaction, facilitating the delivery of the alkyne function by simple light-activation.

Scheme 1. Demetallation of Alkyne Dicobalt Hexacarbonyl Complexes (a) State of the Art (b) Near-Infrared Photocatalysis Approach



RESULTS AND DISCUSSION

First, we screened potential photocatalysts that are able to perform the photodemetallation of complex **1a** bearing an internal alkyne with two *p*-methoxybenzyl groups (Figure 1a). Acetonitrile was chosen as solvent, as well as a catalytic loading of 8.0 mol% of photocatalyst and a reaction time of 4 h. Classical visible-light photocatalysts (4-CzIPN, $Ru(bpy)_3Cl_2$, Acr^+-Mes, $Ir(ppy)_3$, Eosin Y and Methylene Blue) were compared using the corresponding LEDs irradiation at their maximum of absorption (λ = 420 nm, λ = 565 nm, λ = 660 nm). To obtain comparable outcomes, the same irradiance range was used for the selected visible light LEDs.[16] Under visible light irradiation, this reaction can be performed catalytically with most of the photocatalysts but the deprotection efficiency is low to moderate. Indeed, the best result was obtained with the 4-CzIPN which allowed to isolate **2a** in 36% yield with a partial demetalation of **1a**. Even the very powerful oxidant, the Fukuzumi catalyst (Acr^+Mes^-, E^*_{red} = + 2.18 V vs SCE),[17] did not provide more than 32% yield. After recording the absorption spectrum of **1a** in MeCN, we observed a strong absorption band in UV (<400 nm), but also in the range 400-700 nm (Figure 1b). To anticipate a potential limitation due to visible wavelengths absorption, we compared these results with the Near Infrared-photocatalysts (NIR-photocatalysts) that we developed in our laboratory for various organic transformations: squaraine (**Sq687**)[18] and cyanines (**Cy746**, **Cy795**, **Cy997**, **Cy780**).[19] Above 700 nm, the complex **1a** should not overlap with the absorption of the photocatalyst. The reaction was run with **Sq687** as photocatalyst at 810 nm but any amelioration was observed since **2a** was isolated in 31% yield. However, two cyanines were efficient at 810 nm, both **Cy780** and **Cy795** afforded 68% yield with a partial conversion. To further optimize the reaction conditions, we selected the **Cy780** since less by-products were observed in the crude mixture.

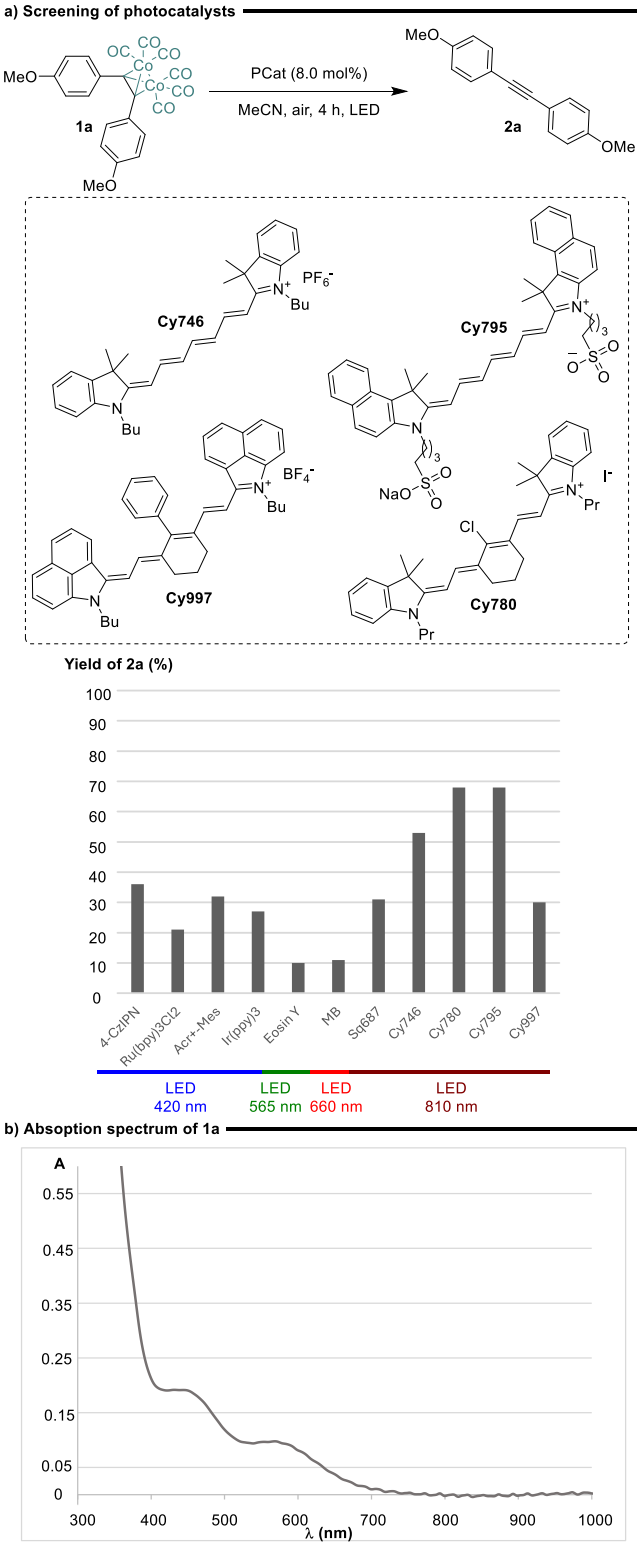


Figure 1. (a) Screening of photocatalysts. Reactions were run on 0.1 mmol in MeCN for 4 h, isolated yields are reported (b) Absorption spectrum of 1a in MeCN (C = 10^{-4}M)

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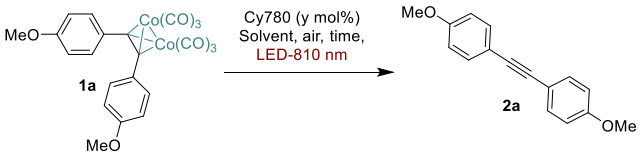
Table 1. Optimization Study

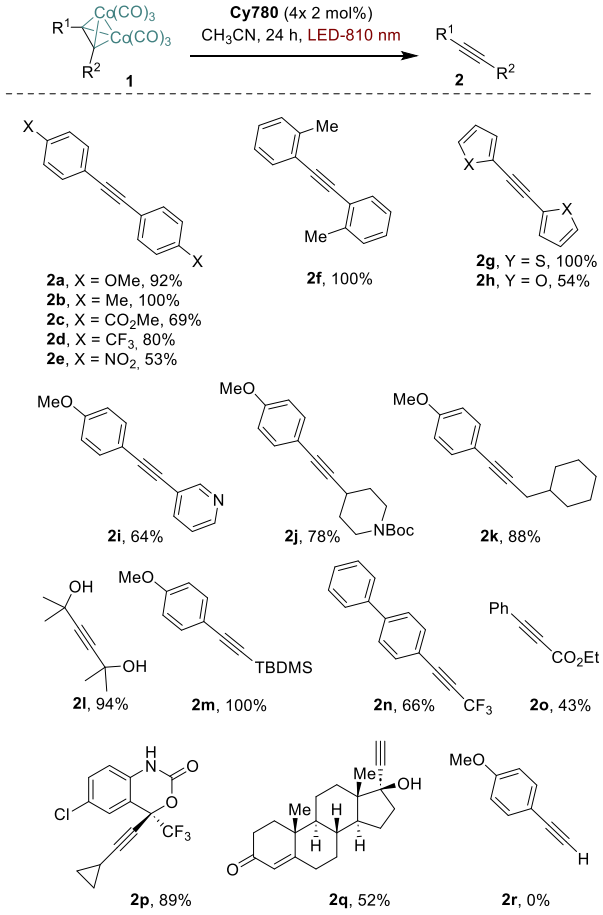


Entry	Parameter	Conditions[a]	Yield (%)[b]
1	Solvent	MeCN, 4 h, y = 8.0	68
2		DCE, 4 h, y = 8.0	25
3		DMSO, 4 h, y = 8.0	17
4		*i*PrOH, 4 h, y = 8.0	16
5	PCat loading	MeCN, 4 h, y = 5.0	46
6	Time	MeCN, 24 h, y = 8.0	60
7[c]	Cy780 Portionwise	MeCN, 24 h, y = 4 x 2.0	92
8[c]	Control	MeCN, 24 h, y = 4 x 2.0 In the dark	28
9		MeCN, 24 h, No PCat	20
10		MeCN, 24 h, No PCat In the dark	7

[a]Reactions were run on 0.1 mmol scale of **1a** in 1 mL of solvent at room temperature under air atmosphere. Irradiation with 2xLED-810 nm (2 x 23.7μW/mm^2). [b]Isolated yields obtained after column chromatography. [c]Portionwise addition was realized following the sequence: 4 x 2 mol% at t = 0 min, t = 3 h, t = 6 h, t = 9 h

Having found an efficient photocatalyst (**Cy780**), a series of experiments were started to optimize the reaction conditions (Table 1). A strong solvent effect was observed; the reaction was less efficient in DCE, DMSO and *i*PrOH (25%, 17% and 16 % yields respectively, entries 2-4). We tried to decrease the loading of photocatalyst to 5 mol% but in this case the conversion and yield were lower (46 % yield, entry 5). To push forward the full conversion, the reaction was set-up for 24 h of irradiation. Surprisingly, we did not observe any improvement of conversion, and a comparable yield was obtained (60%, entry 6). This result suggests that a degradation of the photocatalyst occurs during the reaction (see ESI pS3). A kinetic experiment shows that after 3 h, a plateau of conversion is reached and all the phototocalyst is photobleached (see ESI pS2). To circumvent this problem, we decided to add the photocatalyst in a portionwise manner (4 x 2.0 mol%). Thus, the reaction mixture is constantly refilled in fresh photocatalyst, and full conversion is obtained after 24 h and **2a** was isolated in 92 % yield (entry 7). This portionwise addition is technically simple since the reaction is achieved in open flask under aerobic conditions. Finally, control reactions were run. In the dark, we observed 28% of demetallation (entry 8), 20% without the photocatalyst (entry 9) and 7% when the complex **1a** is poured into CH_3CN in the dark for 24 h without photocalayst (entry 10). These results suggest that acetonitrile acts as a coordinating species promoting a slow decomposition of the cobalt complex, leading to a partial deprotection of the alkyne. This background reaction is not surprising, but the photocatalytic system is still important to accelerate the deprotection and reach the full conversion.

Scheme 2. Substrate scope and limitations for the NIR-photocatalytic demetallation of alkyne dicobalt hexacarbonyl complexes

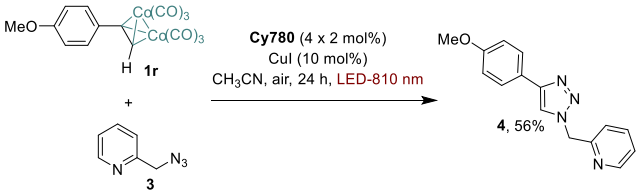


[a]Reaction conditions: 0.1 mmol of **1** and 4 x 2 mol% of **Cy780** in 1 mL of CH_3CN at room temperature under air atmosphere. Irradiation with 2 LED-810 nm (2x23.7 mW/mm^2). Isolated yields obtained after column chromatography.

Then, the optimal conditions were applied to explore the scope of alkyne dicobalt hexacarbonyl complexes (Scheme 2). By screening different para-substituted bis-aryl internal alkynes, we observed that it proceeds more efficiently with electrodonating groups such as methoxy (**2a,** 92% yield) or methyl (**2b**, 100% yield). For molecules containing electrowithdrawing groups (**2c-e**), we observed a significative erosion of the yields, ranging from 53% for nitro (**2e**) to 80% for the trifluoromethyl (**2d**). Surprisingly, the reactivity of bulkier alkyne **2f** with an ortho-methyl is still conserved and a quantitative yield was obtained for the deprotection. Heteroaromatic rings are also well tolerated since the bis-thiophene **2g** was obtained in 100% yield whereas the bis-furan **2h** was deprotected in 54%. The demetalation is still efficient for nitrogen-containing heterocycles such as pyridine and protected piperidine, the products **2i** and **2j**

were isolated in 64% and 78% yield respectively. Internal alkynes bearing alkyl groups are also compatible with these conditions of deprotection, as it was applied for the formation of **2k** (88% yield) and the sterically hindered **2l** (94% yield). The robustness of this photocatalyzed demetalation was also demonstrated using an alkynylsilane (tert-butyldimethylsilyl, TBDMS). Under optimized conditions, **2m** was obtained in quantitative yield. The deprotection of polarized alkynes was also achieved, the alkyne **2n** with the trifluoromethyl was isolated in 66% yield and the ester **2o** in 43% yield. These conditions also accommodated more complex molecules. For example, we deprotected the alkyne function within Efavirenz (**2p**), an HIV-1 reverse transcriptase inhibitor, with a remarkable yield of 89%. The efficient and selective demetalation of terminal alkynes is often more challenging since the deprotected alkyne is more reactive and able to undergo degradation during the process.[20] In our case, we observed that sterically hindered terminal alkynes are compatible with the developed conditions, as it was demonstrated with the deprotection of ethisterone (**2q**) in 52% yield. However, when less bulky terminal alkyne is considered such as **2r**, we only observed messy reaction with the formation of complex mixtures. It should be noted that similar result was obtained when we deprotected **2r** with CAN.

Scheme 3. One-pot tandem photodemetallation/CuAAC on terminal alkyne dicobalt hexacarbonyl complex



One solution to circumvent this problem is to use alkynylsilane derivatives (such as **2m**) and deliver the terminal alkyne after desilylation. However, this solution requires two steps. To provide another alternative, we aimed to determine whether a one-pot reaction could effectively trap the released terminal alkyne *in situ* before degradation. As a proof, a one-pot photodemetallation/copper-catalyzed azide-alkyne cycloaddition (CuAAC) was conducted between the complex **1r** and the azide **3** in presence of 10% of CuI (Scheme 3). Under these conditions, we obtained after purification, 56% of the triazole **4** for two steps. This result shows that sensitive non-bulky terminal alkynes can be photodemetaled but a second one-pot reaction is required to avoid their degradation.

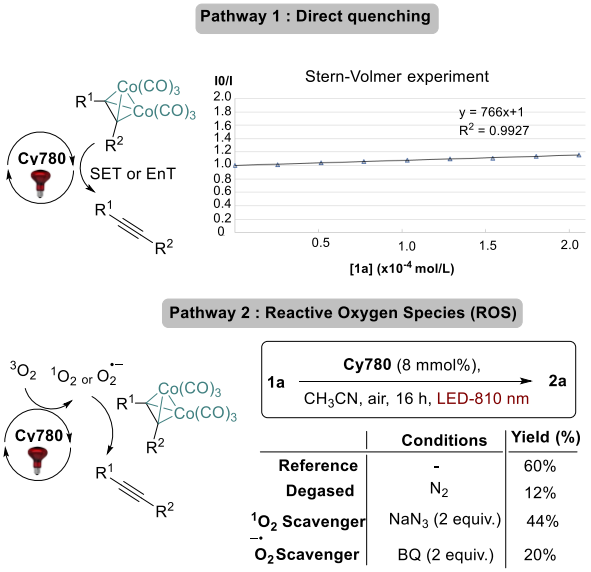
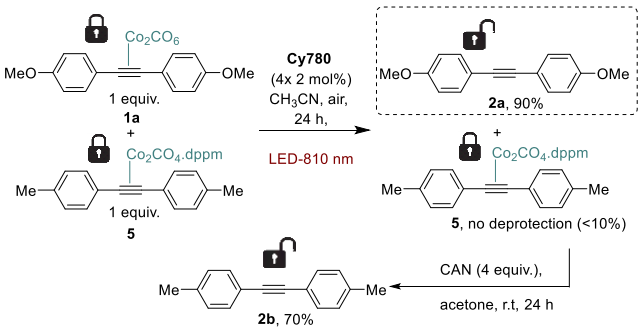


Figure 2. Mechanistic Investigation

We then explored the mechanism of the reaction, and two plausible pathways were considered (Figure 2). The pathway 1 involves a direct quenching of the photocatalyst at its excited state by the cobalt-complex to promote a SET or EnT. In principle, the one-electron oxidation of such complexes should be possible, the redox potential for alkyne dicobalt hexacarbonyl complexes are usually below +0.8 V vs SCE[21] whereas E^*_{red}(Cy780) =+0. 84 V vs SCE.[19b] However, the Stern-Volmer experiments revealed that no apparent quenching between **Cy780*** and the complex **1a** was observed and the low slope was attributed to the partial degradation of the photocatalyst. In addition, no EDA-complex between **Cy780** and **1a** was observed after recording the absorption spectra (see ESI pS4). The pathway 2 is related to the decomplexation of Co-complex by exchanging carbonyl ligands with reactive oxygen species (ROS) : singlet oxygen ($^1O_2$) or superoxide radical ($O_2^{\bullet-}$). The role of ROS in the demetalation of alkyne-Co_2CO_6 complexes has been studied in medicinal chemistry, where these complexes serve as CO-Releasing Molecules (CORMs) in cancer treatment.[22] The elevated ROS concentration in cancer cells leads to the release of CO and the alkyne moiety. Furthermore, it has been demonstrated that electron donor ligands can promote the heterolytic Co-Co cleavage and the subsequent liberation of alkyne.[23] Since cyanines are known to act as photosensitizer in photodynamic therapy (PDT), the formation of ROS under the reaction conditions is highly probable.[24] To verify this point, control reactions were run, using the deprotection of **1a** with 8 mmol% of **Cy780** in CH_3CN for 16 h of irradiation at 810 nm. In absence of dioxygen very low conversion was observed (12%), pointing the crucial role of O_2 in this reaction. In presence of sodium azide ($^1O_2$ scavenger) a partial erosion of the yield is notified starting from 60% for the reference conditions to 44%. The addition of benzoquinone (BQ) as $O_2^{\bullet-}$ scavenger provided a significative drop in conversion and yield (20%). In parallel, we also proved that **Cy780** is able to generate superoxide anion and $^1O_2$ by trapping these intermediates with hydroethidine and 9,10-dimethylanthracene (see ESI pS7). These combined experiments show that a plausible mechanism for this

demetalation involves ROS, generated by the NIR-photocatalyst.

Scheme 4. Orthogonal Deprotection of Alkyne Complexes



Finally, we explored the orthogonal deprotection of the alkyne dicobalt complexes. In the context of selective protection/deprotection of alkyne functions, we prepared the alkyne $Co_2(CO)_4$.dppm complex **5** (dppm, bis(diphenylphosphino)methane). This type of complexes is known to be more stable than the corresponding hexacarbonyl complexe and we expected to obtain a significative selectivity during the photodemetallation.[25] The mixture of **1a** and **5** in stoichiometric ratio was treated under the optimized conditions and we were pleased to observe a selective deprotection of **1a**, and **5** remained mainly untouched (Scheme 4). In addition, the deprotection of **5** was carried out in presence of 4 equivalents of CAN (70% of yield), demonstrating that these two complexes can be used as orthogonal protecting groups for alkynes based on selective deprotection methods. To secure this result, a control reaction was run with alkyne $Co_2(CO)_4$.dppm complex alone and we observed the same result (see ESI pS29). The NIR-photocatalytic deprotection of these complexes showed to be inefficient providing orthogonality for alkyne protection/deprotection.

CONCLUSION

In conclusion, the photo-demetalation of alkyne dicobalt hexacarbonyl complexes has been achieved using the near infrared photocatalysis driven by cyanines (**Cy780**). This approach shifts the paradigm from stoichiometric to photocatalytic since only 8% of photocatalyst is required to achieve the total deprotection. The reaction is quite versatile as it is compatible with various alkynes. For more reactive terminal alkynes, one-pot two-step procedures can be employed such as photodemetallation followed by CuAAC. The mechanistic study revealed that a direct quenching of **Cy780*** by dicobalt complex is not observed and a mechanism involving ROS is more favorable. Finally, the orthogonality between two different protecting groups alkyne-$Co_2(CO)_6$ complex and alkyne-$Co_2(CO)_4$.dppm complex has been demonstrated. The selective release of the alkyne-$Co_2(CO)_6$ cobalt complex under NIR-photocatalytic conditions could be advantageous for numerous applications, including the total synthesis of natural products.

EXPERIMENTAL SECTION

General Information. Unless otherwise stated, all the reagents are commercially available and were used without further purification. Tetrahydrofuran (THF) was distilled from sodium/benzophenone. Dichloromethane, toluene and acetonitrile were distilled over CaH_2. Anhydrous dimethyl sulfoxide (DMSO) was purchased from Sigma Aldrich.

Thin Layer Chromatography (TLC) was performed using Merck© silica gel 60 F254 Aluminum sheets. Column chromatography was performed using Merk© Geduran© Si 60 A° silica gel (0.040-0.063mm). Cyanines photocatalysts were purchased from TCI, Merk, ABCR or Few Chemicals (FC). ^{1}H, ^{13}C and ^{19}F NMR spectra were recorded on a Bruker 400 spectrometer or on a Bruker 500 spectrometer. Chemical shifts (δ) are given in ppm relative to the residual solvent peak. Data were treated with MestreNova software and are reported as follows: chemical shift, integration, multiplicity ((s = singlet, d = doublet, t = triplet, q = quartet, quint = quintet, sept = septet, hept = heptet, m = multiplet, br = broad signal) and coupling constant (Hz).

Infrared spectra were obtained on a Jasco FT/IR-4XLE FT/IR spectrometer using neat samples on a diamond ATR (PKS-D1 Diamond crystal kit). UV-vis absorption and fluorescence spectra were recorded on a SAFAS flx-Xenius XC spectrophotometer including wavelength extension unit (to 1100 nm) and using quartz cells (SAFAS, flx CELL QZ MACRO 10-S-45, Macro, TO 10, Volume 1000 à 3500 µl), at 20 °C (External temperature controller and cooling system).

High resolution mass spectrometry (HRMS) analysis was performed by the Mass Spectrometry Service at the University of Strasbourg. All the photocatalytic reactions were conducted using the following NIR-LED from Thorlabs: M810L4, light-emitting diode (LED, nominal wavelength: 810 nm, output power: 542 mW, irradiance: 23.7 µW/mm^2). The light source is placed in contact with the flask.

General Procedure D for the Photocatalytic Deprotection of Alkyne Dicobalt Hexacarbonyl Complexes.

A flask was charged with the complex **1** (0.1 mmol, 1 equiv.) and **Cy780** (1.4 mg, 0.002 mmol, 2 mol%). The mixture was dissolved in distilled MeCN (1 mL) and irradiated under 810 nm for 24 h (under air atmosphere). After 3 h, 6 h and 9 h, **Cy780** (1.4 mg, 0.002 mmol, 2 mol%) was added and the flask was turned by 1/8. The solvent was then evaporated in vacuo and a column chromatography afforded the title compound.

*1,2-bis(4-methoxyphenyl)ethyne (**2a**).* Prepared according to general procedure D on a 0.105 mmol scale, column chromatography (10% EtOAc in petroleum ether) afforded the title compound (23 mg, 0.097 mmol, 92%).^{1}H NMR (500 MHz, $CDCl_3$) δ 7.45 (d, *J* = 8.8 Hz, 4H), 6.87 (d, *J* = 8.8 Hz, 4H), 3.83 (s, 6H). ^{13}C{1H} NMR (126 MHz, $CDCl_3$) δ 159.5, 133.0, 115.9, 114.1, 88.1, 55.4. Data are consistent with those reported in the literature [26]

*1,2-di-p-tolylethyne (**2b**).* Prepared according to general procedure D on a 0.106 mmol scale, column chromatography (petroleum ether) afforded the title compound (22 mg, 0.106 mmol, 100%).^{1}H NMR (500 MHz, $CDCl_3$) δ 7.41 (d, *J* = 8.0 Hz, 4H), 7.15 (d, *J* = 8.0 Hz, 4H), 2.36 (s, 6H).^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 138.3, 131.6, 129.2, 120.5, 89.0,

21.7. Data are consistent with those reported in the literature. [27]

*Dimethyl 4,4'-(ethyne-1,2-diyl)dibenzoate (**2c**).* Prepared according to general procedure D on a 0.103 mmol scale, column chromatography (5% EtOAc in petroleum ether) afforded the title compound (21 mg, 0.071 mmol, 69%).^{1}H NMR (500 MHz, $CDCl_3$) δ 8.04 (d, *J* = 8.4 Hz, 4H), 7.61 (d, *J* = 8.4 Hz, 4H), 3.94 (s, 6H). $^{13}C\{^{1}H\}$ NMR (126 MHz, $CDCl_3$) δ 166.6, 131.8, 130.1, 129.7, 127.5, 91.5, 52.5. Data are consistent with those reported in the literature [26]

*1,2-bis(4-(trifluoromethyl)phenyl)ethyne (**2d**).* Prepared according to general procedure D on a 0.103 mmol scale, column chromatography (petroleum ether) afforded the title compound (26 mg, 0.083 mmol, 80%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.69 – 7.60 (m, 8H).$^{13}C\{^{1}H\}$ NMR (126 MHz, $CDCl_3$) δ 132.1, 130.6 (q, *J* = 32.7 Hz), 126.5, 125.5 (q, *J* = 3.8 Hz), 124.0 (q, *J* = 272.2 Hz), 90.3. ^{19}F NMR (471 MHz, $CDCl_3$) δ -62.9.[28]

*1,2-bis(4-nitrophenyl)ethyne (**2e**).* Prepared according to general procedure D on a 0.105 mmol scale, column chromatography (10% EtOAc in petroleum ether) afforded the title compound (15 mg, 0.056 mmol, 53%).^{1}H NMR (500 MHz, $CDCl_3$) δ 8.27 (d, *J* = 8.9 Hz, 4H), 7.72 (d, *J* = 8.9 Hz, 4H). $^{13}C\{^{1}H\}$ NMR (126 MHz, $CDCl_3$) δ 147.8, 132.8, 129.0, 124.0, 92.2. Data are consistent with those reported in the literature.[27]

*1,2-di-o-tolylethyne **(2f).*** Prepared according to general *procedure D* on a 0.106 mmol scale, column chromatography (petroleum ether) afforded the title compound (22 mg, 0.106 mmol, 100%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.52 (d, *J* = 7.3 Hz, 2H), 7.26 – 7.21 (m, 4H), 7.21 – 7.16 (m, 2H), 2.54 (s, 6H). $^{13}C\{^{1}H\}$ NMR (126 MHz, $CDCl_3$) δ 140.1, 132.0, 129.6, 128.4, 125.7, 123.5, 92.4, 21. Data are consistent with those reported in the literature.[29]

*1,2-di(thiophen-2-yl)ethyne (**2g**).* Prepared according to general *procedure D* on a 0.103 mmol scale, column chromatography (petroleum ether) afforded the title compound (20 mg, 0.103 mmol, 100%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.33 (dd, *J* = 5.1, 1.2 Hz, 2H), 7.30 (dd, *J* = 3.6, 1.2 Hz, 2H), 7.04 (dd, *J* = 5.1, 3.6 Hz, 2H). $^{13}C\{^{1}H\}$ NMR (126 MHz, $CDCl_3$) δ 132.3, 127.8, 127.3, 123.1, 86.3. Data are consistent with those reported in the literature [26]

*1,2-di(furan-2-yl)ethyne (**2h**).* Prepared according to general *procedure D* on a 0.106 mmol scale, column chromatography (petroleum ether) afforded the title compound (9 mg, 0.057 mmol, 54%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.45 (d, *J* = 1.9 Hz, 2H), 6.71 (d, *J* = 3.4 Hz, 2H), 6.43 (dd, *J* = 3.4, 1.9 Hz, 2H). $^{13}C\{^{1}H\}$ NMR (126 MHz, $CDCl_3$) δ 144.4, 136.6, 116.6, 111.3, 83.4. Data are consistent with those reported in the literature.[27]

*3-((4-methoxyphenyl)ethynyl)pyridine (**2i**).* Prepared according to general *procedure D* on a 0.105 mmol scale, column chromatography (20% EtOAc in petroleum ether) afforded the title compound (14 mg, 0.067 mmol, 64%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.90 (brs, 1H), 8.67 (brs, 1H), 7.77 (d, *J* = 7.9 Hz, 1H), 7.48 (d, *J* = 8.8 Hz, 2H), 7.40 – 7.28 (m, 1H), 6.89 (d, *J* = 8.8 Hz, 2H), 3.83 (s, 3H). $^{13}C\{^{1}H\}$ NMR (126 MHz, $CDCl_3$) δ 160.2, 152.5, 148.5, 138.5, 133.4, 124.3, 114.7, 114.3, 93.1, 85.0, 55.5. Data are consistent with those reported in the literature.[30]

*tert-butyl 4-((4-methoxyphenyl)ethynyl)piperidine-1-carboxylate (**2j**).* Prepared according to general *procedure D* on a 0.105 mmol scale, column chromatography (10% EtOAc in petroleum ether) afforded the title compound (26 mg, 0.082 mmol, 78%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.33 (d, *J* = 8.8 Hz, 2H), 6.81 (d, *J* = 8.8 Hz, 2H), 3.80 (s, 3H), 3.73 (ddd, *J* = 13.4, 6.6, 3.6 Hz, 2H), 3.23 (ddd, *J* = 13.4, 8.4, 3.4 Hz, 2H), 2.77 (tt, *J* = 8.1, 3.9 Hz, 1H), 1.84 (ddt, *J* = 13.4, 7.2, 3.4 Hz, 2H), 1.65 (dtd, *J* = 12.2, 8.1, 3.6 Hz, 2H), 1.46 (s, 9H). $^{13}C\{^{1}H\}$ NMR (126 MHz, $CDCl_3$) δ 159.3, 155.0, 133.1, 115.8, 114.0, 90.4, 81.8, 79.6, 55.4, 42.4, 31.7, 28.6, 27.7. Data are consistent with those reported in the literature.[31]

*1-(3-cyclohexylprop-1-yn-1-yl)-4-methoxybenzene (**2k**).* Prepared according to general *procedure D* on a 0.105 mmol scale, column chromatography (10% EtOAc in petroleum ether) afforded the title compound (21 mg, 0.092 mmol, 88%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.33 (d, *J* = 8.9 Hz, 2H), 6.81 (d, *J* = 8.9 Hz, 2H), 3.80 (s, 3H), 2.28 (d, *J* = 6.7 Hz, 2H), 1.90 – 1.83 (m, 2H), 1.74 (dt, *J* = 12.8, 3.3 Hz, 2H), 1.69 – 1.63 (m, 1H), 1.59 – 1.50 (m, 1H), 1.26 (tt, *J* = 12.7, 3.4 Hz, 2H), 1.17 (tt, *J* = 12.5, 3.3 Hz, 1H), 1.10 – 1.01 (m, 2H). $^{13}C\{^{1}H\}$ NMR (126 MHz, $CDCl_3$) δ 159.1, 133.0, 116.5, 113.9, 87.8, 81.2, 55.4, 37.7, 32.9, 27.4, 26.5, 26.3. Data are consistent with those reported in the literature.[32]

*2,5-dimethylhex-3-yne-2,5-diol (**2l**).* Prepared according to general *procedure D* on a 0.105 mmol scale, column chromatography (50% EtOAc in petroleum ether) afforded the title compound (14 mg, 0.099 mmol, 94%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.64 (s, 2H), 1.47 (s, 12H). $^{13}C\{^{1}H\}$ NMR (126 MHz, $CDCl_3$) δ 86.8, 65.0, 31.5. Data are consistent with those reported in the literature.[33]

*tert-butyl((4-methoxyphenyl)ethynyl)dimethylsilane (**2m**).* Prepared according to general *procedure D* on a 0.105 mmol scale, column chromatography (petroleum ether) afforded the title compound (26 mg, 0.106 mmol, 100%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.41 (d, *J* = 8.8 Hz, 2H), 6.82 (d, *J* = 8.8 Hz, 2H), 3.81 (s, 3H), 0.99 (s, 9H), 0.17 (s, 6H). $^{13}C\{^{1}H\}$ NMR (126 MHz, $CDCl_3$) δ 159.8, 133.6, 115.6, 113.9, 105.9, 90.8, 55.4, 26.3, 16.9, -4.4. Data are consistent with those reported in the literature.[34]

*4-(3,3,3-trifluoroprop-1-yn-1-yl)-1,1'-biphenyl (**2n**).* Prepared according to general *procedure D* on a 0.105 mmol scale, column chromatography (petroleum ether) afforded the title compound (17 mg, 0.069 mmol, 66%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.63 (s, 4H), 7.61 – 7.58 (m, 2H), 7.50 – 7.44 (m, 2H), 7.43 – 7.37 (m, 1H). $^{13}C\{^{1}H\}$ NMR (126 MHz, $CDCl_3$) δ 143.9, 139.8, 133.0 (d, *J* = 1.8 Hz), 129.1, 128.4, 127.4, 127.3, 117.3, 115.0 (q, *J* = 256.6 Hz), 86.7 (q, *J* = 6.4 Hz), 76.3 (q, *J* = 52.4 Hz). ^{19}F NMR (471 MHz, $CDCl_3$) δ -49.7. Data are consistent with those reported in the literature.[35]

*ethyl 3-phenylpropiolate (**2o**).* Prepared according to general *procedure D* on a 0.106 mmol scale, column chromatography (10% EtOAc in petroleum ether) afforded the title compound (8 mg, 0.046 mmol, 43%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.61 – 7.55 (m, 2H), 7.47 – 7.41 (m, 1H), 7.39 – 7.33 (m, 2H), 4.29 (q, *J* = 7.1 Hz, 2H), 1.35 (t, *J* = 7.1 Hz, 3H). $^{13}C\{^{1}H\}$ NMR (126 MHz, $CDCl_3$) δ 154.2, 133.1, 130.7, 128.7, 119.7, 86.1, 80.8, 62.2, 14.2. Data are consistent with those reported in the literature.[36]

*(S)-6-chloro-4-(cyclopropylethynyl)-4-(trifluoromethyl)-1,4-dihydro-2H-benzo[d][1,3]oxazin-2-one (Efavirenz) (**2p**).* Prepared according to general *procedure D* on a 0.103 mmol scale, column chromatography (20% EtOAc in petroleum ether) afforded the title compound (29 mg, 0.092 mmol,

89%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.16 (s, 1H), 7.49 (d, *J* = 2.3 Hz, 1H), 7.36 (dd, *J* = 8.5, 2.3 Hz, 1H), 6.83 (d, *J* = 8.5 Hz, 1H), 1.40 (tt, *J* = 8.3, 5.1 Hz, 1H), 0.97 – 0.82 (m, 4H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 149.1, 133.4, 131.9, 129.3, 128.0, 122.3 (q, *J* = 287.5 Hz), 116.3, 115.3, 96.1, 79.3 (q, *J* = 35.2 Hz), 66.3, 9.0 (d, *J* = 2.9 Hz), -0.5. ^{19}F NMR (471 MHz, $CDCl_3$) δ -80.9. Data are consistent with those reported in the literature.[37]

(8R,9S,10R,13S,14S,17R)-17-ethynyl-17-hydroxy-10,13-dimethyl-1,2,6,7,8,9,10,11,12,13,14,15,16,17-tetradecahydro-3H-cyclopenta[a]phenanthren-3-one (Ethisterone) ***(2q)***. Prepared according to general *procedure D* on a 0.104 mmol scale, column chromatography (30% EtOAc in petroleum ether) afforded the title compound (17 mg, 0.054 mmol, 52%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.73 (s, 1H), 2.57 (s, 1H), 2.44 – 2.25 (m, 5H), 2.07 – 1.97 (m, 2H), 1.93 (brs, 1H), 1.87 – 1.82 (m, 1H), 1.76 – 1.53 (m, 6H), 1.53 – 1.30 (m, 3H), 1.20 (s, 3H), 1.11 – 0.94 (m, 2H), 0.89 (s, 3H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 199.6, 171.1, 123.9, 87.2, 79.7, 74.2, 53.4, 49.9, 46.7, 38.9, 38.6, 36.2, 35.7, 34.0, 32.8, 32.4, 31.5, 23.1, 20.7, 17.4, 12.7. Data are consistent with those reported in the literature.[33]

ASSOCIATED CONTENT

Data Availability Statement

The data underlying this study are available in the published article and its Supporting Information

Supporting Information.

The Supporting Information is available free of charge.

Detailed experimental procedures, spectroscopic data, ^{1}H, ^{13}C and ^{19}F NMR spectra.

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JF, MC and JPG planned, ran and analyzed the experiments. MC and JPG designed, directed the project and wrote the manuscript with the help of JF. All the authors contributed to the discussions

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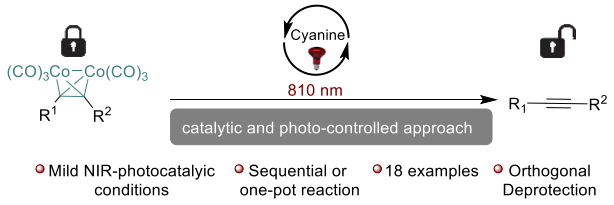
Cyanine
810 nm
catalytic and photo-controlled approach
Mild NIR-photocatalyic conditions
Sequential or one-pot reaction
18 examples
Orthogonal Deprotection