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Two-photon sensitive coumarinyl photoremovable protecting groups with rigid electron-rich cycles obtained by domino reactions initiated by a 5-*exo*-dig cyclocarbopalladation.

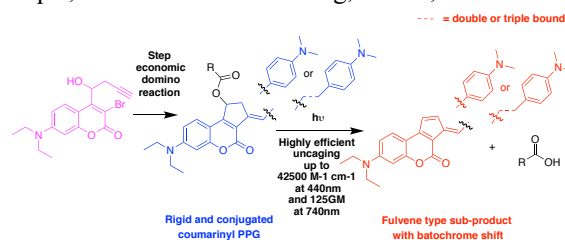
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ABSTRACT: We herein report the design, synthesis and photophysical characterization of extended and rigid coumarinyl derivatives showing large two-photon sensitivities ($\delta\alpha\Phi_u$ up to 125 GM) at 740 and 800 nm. To efficiently synthesize these complex PPGs, step-economic domino reactions were used. Moreover, those new coumarinyl PPGs display unique bathochromic shifts (≤ 100 nm) of the uncaging sub-products as a result of the formation of a more conjugated fulvene moiety.

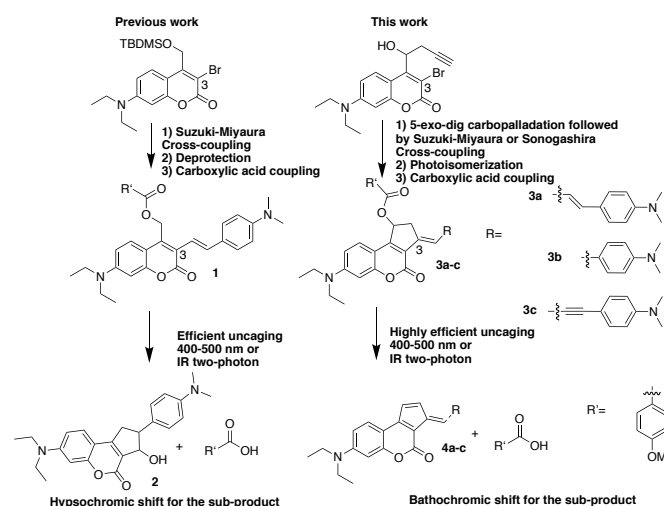
Photoremovable protecting groups (PPG) represent important tools in various fields of chemistry^{1,2} and biology.³ In particular, PPGs are used to mask the biological function of bioactive molecules, including peptides,⁴ proteins,⁵⁻⁷ nucleic acids,⁸ neurotransmitters⁹ and lipids (leading to so called caged-compounds).¹⁰ Therefore, a photolytic reaction can be used to induce a localized concentration jump of those bioactive molecules in order to rapidly initiate a wide range of dynamic biological processes. This strategy, which can be considered as seminal opto-pharmacology, was used to trigger biological responses in many fields of biology, such as neuroscience,⁹ cell biology,¹⁰ genetics or embryology.¹¹⁻¹² The development of new PPGs is largely driven by the challenge of enabling the use of visible, and red or even near-IR (NIR) light to initiate the photolytic reaction.² In this respect, PPGs sensitive to two-photon excitation (TPE) using NIR light have been introduced¹³⁻¹⁷ to allow more sophisticated uses of those phototriggers. The advantages of NIR light include deeper (1 cm) tissue penetration without the toxic effects induced by higher-energy light.¹⁸ Because TP absorption only occurs at the focal point of a focalized laser beam, intrinsic 3D spatial resolution of the photolysis area (it can be as little as 1 fL) can therefore be addressed. This technique requires to develop new photoremovable groups with larger molecular TP absorption cross-sections and higher uncaging quantum

yields.¹³⁻¹⁹ Molecular engineering of photoremovable protecting groups have been performed in order to increase TP absorption.¹³⁻²¹ Rigidity, aromatics connected by double or triple bonds, and decoration with electron-donor and -acceptor moieties were found to contribute to the TP absorption.²² Therefore, in this article we wish to explore the effect of the incorporation of a rigid Donor-Donor system on the two-photon uncaging efficiency.

Coumarinylmethyl PPGs are widely used phototriggers due to the rapid photolytic reaction (in the ns range).¹⁻² These latter caging groups have already been modified by π -extended electron-donating or electron-withdrawing moieties, leading to blue and green light-activatable PPGs.²³⁻²⁷ In most cases, those modifications lead to coumarinyl PPG with only modest uncaging quantum yields.^{2,28} In particular, Zhu and coworkers²⁵ introduced 7-diethylaminocoumarin (DEAC) analogues with electron-rich styryl appendages at the 3-position (**1**).

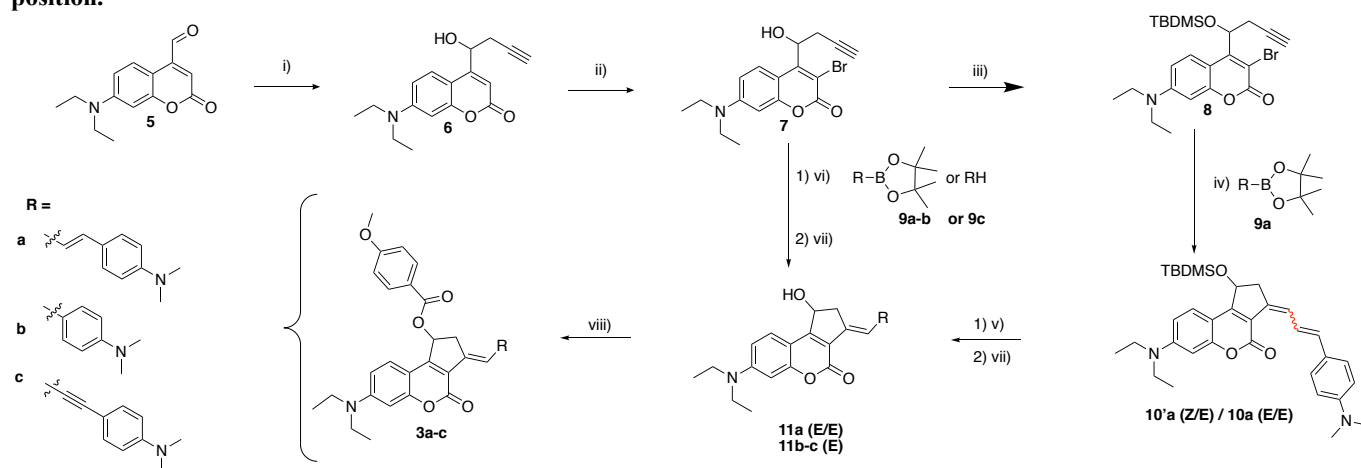
The styryl appendage allowed an efficient uncaging (both using one-photon excitation at 450 nm and TP IR excitation) and the photolytic reaction produced a lower conjugated by-product (**2**) through an intramolecular cyclization involving a light-generated carbocation intermediate.

Scheme 1. Recent evolution in the structure of electron-rich styryl appendages at the 3-position of DEAC PPGs and structures designed in the present work.



Herein, we developed π -extended and rigid coumarinyl PPGs (3a-c) at the 3-position in order to increase even further the TP absorption properties. To efficiently extend the conjugation of DEAC PPGs, we decided to exploit palladium-catalyzed cross-coupling domino reactions²⁹⁻³¹ in order to build fused polycyclic coumarinyl PPGs. Therefore, we explored the use of a 5-*exo*-dig cyclocarbopalladation reaction followed by a Suzuki-Miyaura or a Sonogashira cross-coupling reaction to form various π -extended rigid coumarinyl PPGs. Using such domino reactions, 3 different rigid coumarinyl PPGs have been efficiently synthesized. More importantly, those new PPGs showed enhanced uncaging properties and allowed the formation of highly conjugated sub-products (4a-c) leading to an interesting bathochromic shift.

The propargylated DEAC analogue **6** was obtained with 86% yield by treating the aldehyde **5** with freshly prepared **Scheme 2. Synthesis of coumarinyl photoremovable protecting groups 3a-c modified with rigid electron-rich cycles at the 3-position.**



i. propargylzinc bromide, THF, 1h30min, 0 °C to RT, 86%; ii. NBS, ammonium acetate, anhydrous acetonitrile, 30 min, RT, 93%; iii. TBDMSCl, imidazole, anhydrous DMF, 2 days, 50 °C with a heating block, 56%; iv. Compound 9a, K₂CO₃, Pd(PPh₃)₄, H₂O/DME, 45 min, microwave 105 °C, 77% (calculated yield), 53% (isolated yield); v. TBAF, THF, 30 min, RT, 41%; vi. Compound 9a-b, K₂CO₃, Pd(PPh₃)₄, H₂O/DME, 45 min, microwave 105 °C, 39%-23% (respectively for 11a and 11b) or compound 9c, diisopropylamine, PdCl₂(PPh₃)₂, CuI, 1h, microwave 120 °C, 47%; vii. 430 nm irradiation, CH₂Cl₂ or chloroform, 1h, RT, quant.; viii. *p*-methoxybenzoic acid, DMAP, DIC, CH₂Cl₂, 40.5 h up to 3.5 days, 0 °C to RT, 67%-20%-38% (respectively for 3a, 3b and 3c).

propargylzinc bromide as previously reported.³² Regioselective bromination of the 3-position of **6** was successfully performed by using *N*-bromosuccinimide in the presence of ammonium acetate as catalyst. In order to explore the efficiency of the planned domino reaction, i.e. a 5-*exo*-dig cyclocarbopalladation followed by a Suzuki-Miyaura cross-coupling, we decided to first explore this reaction pathway on the protected alcohol **8**. Therefore, compound **8** was synthesized in 56% yield. The domino reaction was performed on substrate **8** using **9a** (see Supporting Information for details), K₂CO₃, Pd(PPh₃)₄ (2 mol%) in a 3:1 mixture of DME/water at 105 °C under microwave activation for 45 minutes. Because of the mechanism involves an intramolecular *syn*-carbopalladation step, the domino reaction should only provide the Z/E diastereoisomer **10'a**, whereas an analytical HPLC analysis and NMR analysis of the crude revealed the formation of the two diastereoisomers (Z/E **10'a** and E/E **10a**) in an almost 8:2 ratio (see Supporting Information). Thus, we speculated that the formation of **10a** resulted from the Z to E photoisomerization of **10'a** under ambient light exposure. Both products showed a similar UV-Visible spectrum (maximum of absorption at 460 nm). It is noteworthy that, no trace of the product resulting from a direct Suzuki-Miyaura cross-coupling reaction was detected in the crude mixture. The use of an internal standard enabled us to determine by NMR analysis of the crude mixture that compound **10'a** was formed in 65% yield together with 12% yield of **10a**. After purification of the mixture, the two diastereoisomers (**10'a/10a**) were isolated as a 62:38 mixture with an overall 53% yield. This latter mixture of diastereoisomers was deprotected leading to the formation of diastereoisomers **11'a/11a** in 41% yield without altering the Z/E ratio. Remarkably, when the mixture of those two diastereoisomers was irradiated (at 430 nm), a complete conversion to the compound **11a** (E/E) was observed.

The stereochemistry of this compound was established by ¹H-NOESY experiments and by the analysis of the ¹H-¹H coupling constants related to the diene chain.

Beaucase TBDMS protection and deprotection are two steps with only modest reaction yields, we decided to explore the domino reaction directly on the key intermediate **7**, thus in a protecting group-free manner. As planned, the expected domino reaction again took place using **9a**, but also **9b**, as boron-based coupling partner, thus leading to the formation of compounds **11a** and **11b** in respectively 39% and 23% yields after a purification and a subsequent photoisomerization step using a 430 nm LED excitation. The stereochemistry of those compounds was again established by 1H-NOESY experiments and by the analysis of the 1H-1H coupling constants of relevance.

We also decided to explore the potential of a similar domino reaction, i.e., a 5-*exo*-dig cyclocarbopalladation followed here by a Sonogashira cross-coupling reaction, starting with **7** and the terminal alkyne **9c** as coupling partners. Under typical catalytic conditions, the desired compound **11c** was obtained in 47% yield after a photoisomerization step using a 430 nm LED excitation and followed by purification. The stereochemistry of this compound was established by 1D proton-coupled 13C NMR experiments (see Supporting Information). Finally, the *p*-methoxybenzoic acid (*p*-MBA) was chosen as model cargo and compounds **3a-c** were synthesized. Photophysical and photochemical characterizations and one-photon uncaging efficiencies of rigid and conjugated coumarinyl PPGs (**3a-c**) were characterized.

The photophysical properties of compounds **3a-c** (20 μ M) were studied in a 9:1 (v/v) mixture of MeOH/H₂O. These rigid PPGs show intense absorption in the visible and moderate fluorescence properties. It is noteworthy that compound **3b** is the only compound of the three that exhibits a hypsochromic shift of the absorbance peak (437 vs 446 nm) compared to the less rigid styryl analogue **1** described by Zhu and co-workers (Scheme 1).²⁵ More interestingly, the more conjugated compounds **3a** and **3c** induced a marked bathochromic shift in absorption as compared to **1**. Next, the photoinduced liberation of *p*-MBA from **3a-c** was monitored by UV-Visible spectroscopy and HPLC. Photolysis was carried out by irradiation of samples (20 μ M) at 430 nm (using a LUMOS 43 LED source from Atlas Photonics Inc.) in a 9:1 (v/v) mixture of MeOH/H₂O (Figure 1). During these photolysis experiments, compounds **3a-c** showed respectively a new broad absorbance at 557 nm, 534 nm and 550 nm whilst the initial absorbance at respectively 457 nm, 437 nm and 452 nm gradually diminished. The appearance of isobestic points at respectively 497 nm, 467 nm and 490 nm were also observed, indicating homogenous reactions. An almost quantitative ($\geq 98\%$) release of *p*-MBA was measured by

HPLC together with the formation of red shifted chromophores (**4a-c**) after complete photo-conversion of **3a-c**.

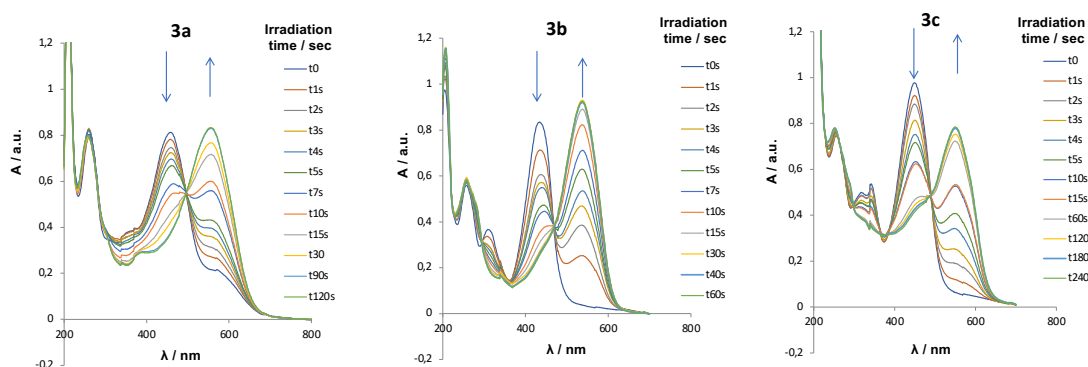
The hydrolytic stability was also explored by HPLC in MeCN /phosphate buffer (pH 7.4, 20 μ M) mixture (8:2, v/v) and in MeOH / H₂O mixture (9:1, v/v) at room temperature (in the dark) indicating no significant hydrolysis after 24 hours. Altogether, this agrees with an almost quantitative photolytic reaction according to the recognized photo-S_N1-dependent cleavage of coumarin-based PPGs.³³ However, and in sharp contrast with **1**, significant bathochromic shifts (up to 100 nm) were observed for the uncaging sub-products **4a-c** when tracking the UV-Vis absorption evolution of the photolysis process of our new PPGs (Figure 1). On the basis of the above results and the precedents in the literature, we can postulate a photolysis scenario for our new PPGs as shown in Scheme 3. In this scenario, we suggest as first step the formation of a free ion-pair (coumarin-based carbocation **12a-c** / conjugate base of *p*-MBA) via the reversible light-induced heterolytic cleavage of the corresponding C-O bond. Then, the so-formed carbocation intermediates **12a-c** evolve towards the fulvene-based products **4a-c**, via a simple irreversible deprotonation, the extension of conjugation being the driving force of the reaction. Thus, the photolytic reactions of our new coumarin-based PPGs **3a-c** are suggested to take place through a photo-E1-dependent mechanistic scenario.

The quantum yields for *p*-MBA release, as determined by competition with the *p*-MBA caged analogue **1** (R' = *p*-MBA, 20% uncaging quantum yield²⁵) as reference molecule, were 27%, 57% and 26% for **3a**, **3b** and **3c** respectively, indicating excellent photochemical efficiencies at wavelengths up to 500 nm. It is noteworthy that the clean photolytic reactions together with the important bathochromic shift of the uncaging sub-product allowed us to easily and unambiguously follow the rate of uncaging upon irradiation by UV-Visible spectroscopy. In particular, compound **3b** showed very interesting uncaging quantum yield leading to an uncaging efficiency (defined as $\epsilon_{\lambda_{max}} \cdot \Phi_{ij}$) of 24 200 M⁻¹.cm⁻¹. Altogether, the high photolytic efficiency and the quantitative release of *p*-MBA make those molecules remarkable PPGs for 400 to 500 nm uncaging experiments.

The photophysical and photochemical properties of all caged *p*-MBA analogues (**3a-c**) are summarized in Table 1.

In order to fully characterize the formation of the fulvene by-products (**4a**), 430 nm irradiation of **3a** was performed on preparative scale and the **4a** by-product formation was confirmed by mass spectroscopy and by ¹H and ¹³C NMR experiments.

Figure 1. Variation of UV absorbance after irradiation at 430 nm (using a LUMOS 43 LED source from Atlas Photonics Inc.) of 1.8 mL of 20 μ M solutions of **3a**, **3b** and **3c** in a 9:1 mixture of MeOH/H₂O.



It is noteworthy that this latter by-products was poorly soluble in the NMR solvent and some other diastereoisomers of **4a** were also observed after full irradiation. Therefore we decide to characterize compounds **4b** and **4c** only by mass spectroscopy. Unfortunately, all those fulvene type compounds did not show any useful fluorescent properties enabling the monitoring of the uncaging process by fluorescence.¹

The TP uncaging action cross section ($\delta_a\Phi_u$) of **3a-c** were determined at respectively 740 and 800 nm by two-photon excitation followed by UV-Visible spectroscopy and compared to *p*-MBA caged analogue **1** ($R'=p$ -MBA) as reference molecule. The TP photolysis kinetics of **3a-c** and **1** are presented in **Figure 2** (the quadratic dependency of the photolysis rate vs the laser power was confirmed at both wavelengths, see supporting information), showing that rigid and conjugated electron-rich cycles at the 3-position of coumarinyl PPGs can induce a 4 times higher efficiency than that of **1**. However, compound **3b** only showed a weak increase presumably due to the less conjugation caused by steric hindrance between *p*-dimethylaminobenzene part and $-CH_2-$ on five-membered ring. This study demonstrates that rigid and conjugated coumarinyl PPGs can indeed enhance both uncaging efficiency and 2PA properties. As a result, coumarin derivative **3c** shows unprecedented uncaging 2P sensitivity at 740 nm.

Scheme 3. Proposed mechanistic scenario for the photolytic reactions of compounds **3a-c**.

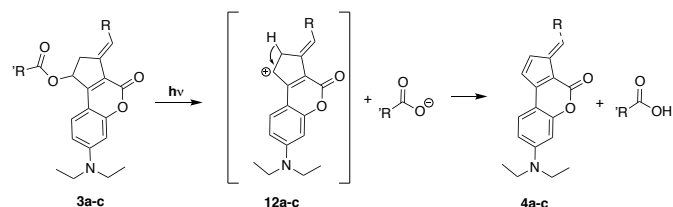
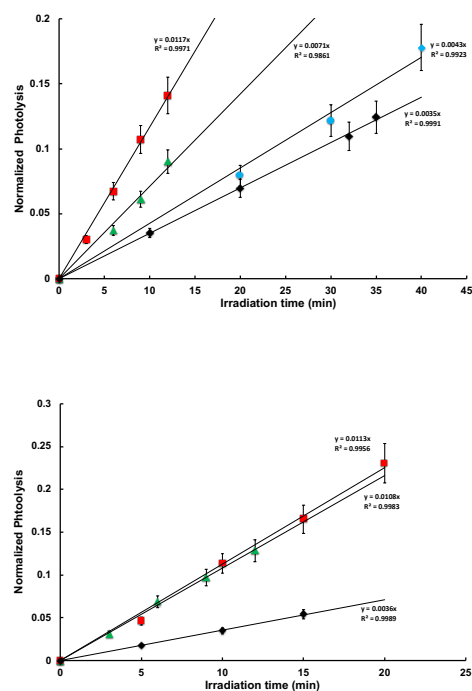


Table 1. Photophysical and photochemical properties of **1 and **3a-c** in MeOH / H₂O mixture (9:1, v/v) at 20°C, *estimated from **3a-c** full photolysis.**

Cpd.	Abs.	Fluo.	Sub-product Abs.	$\Phi_u^{[c]}$	$\delta_a\Phi_u$ 740/ 800 nm (GM)
	λ_{max} (nm)/ ϵ (M ⁻¹ cm ⁻¹)	λ_{max} (nm) / Φ			
1	446/41000	510/0.02	385/14000	0.2	32 / 8
3a	457/39000	609/0.016	557/45300*	0.27	63 / 23
3b	437/42500	588/0.042	534/44700*	0.57	42 / ND
3c	452/45800	556/0.018	550/36800*	0.26	125 / 29

Altogether, the use of step-economic domino reactions including cyclocarbopalladation allowed us to efficiently substitute coumarinyl PPGs by rigid and conjugated electron-rich cycles at the 3-position. This modification led to a significant improvement on the one-photon efficiency of the photolytic reaction (up to 57% quantum yield for one-photon photoconversion for compound **3b**). In addition, a very unique bathochromic shift (up to 100 nm) of the uncaging sub-products was observed for those type of coumarinyl PPGs as a result of the formation of a more conjugated fulvene product **4**. Most importantly, the incorporation of a rigid electron-rich and conjugated five-membered ring cycle at the 3-position of coumarinyl PPGs significantly increased the TP sensitivity, leading to an unprecedented TP uncaging action cross-section at 740 nm (up to 125 GM).

Figure 2. Two-photon excited photolysis of **3a-c at 740 nm (left) and 800 nm (right) followed by UV-Visible analysis and compared to the reference molecule **1**.**



1 : black diamond; **3a** : green triangle; **3b** : blue circle; **3c** : red square. The values were normalized regarding to the reference molecule for each experiments

The remarkable chemical and photophysical properties of those coumarinyl PPGs open the way for future developments using two-photon uncaging in neuroscience,⁹ cellular and molecular biology.⁴ But it should also be extremely beneficial for diverse applications in material sciences.³⁴

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

Experimental details, synthetic procedures, spectroscopic characterization and physical data determination (PDF).

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Author Contributions

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

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