Complexity-Building Photoinduced Cascade Involving C$_{sp2}$-C$_{sp3}$ Coupling of Aromatic Amides via [2+2] Reactivity of ESIPT-generated *o*-Azaxylylenes

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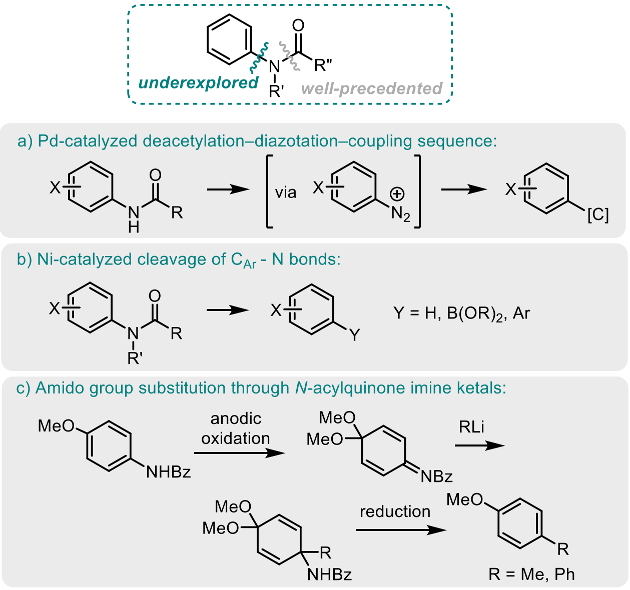
ABSTRACT: A new mode for complexity-building photochemical cascades which offer experimentally simple transition metal-free intramolecular C$_{sp2}$-C$_{sp3}$ cross coupling of aromatic amides attained via an unprecedented [2+2] reactivity of ESIPT-generated azaxylylenes. Coupled with short and straightforward post-photochemical modifications of the primary photoproducts, these cascades allow for a significant step-normalized growth of molecular complexity while accessing diverse and complex polyheterocyclic molecular architectures.

Recent renaissance in photoassisted organic chemistry drives modern synthetic method development and, at the same time, offers boundless opportunities for integrating the newly elaborated methods into complexity-building photochemical sequences. This is true for visible light photocatalysis,[1–5] and this is also true for photoinduced cascades triggered by the Excited State Intramolecular Proton Transfer (ESIPT), which yield complex polyheterocyclic molecular architectures via simple experimental procedures.

In this context, discovery of new C-C bond-forming reactions and their incorporation into such complexity-building photoinduced synthetic cascades is appealing on several levels. From the substrate perspective, one noticeable deficiency in synthetic approaches is the lack of direct methods to displace amido groups in ubiquitous anilides (or amido-heterocycles) with a carbon 'nucleophile.'

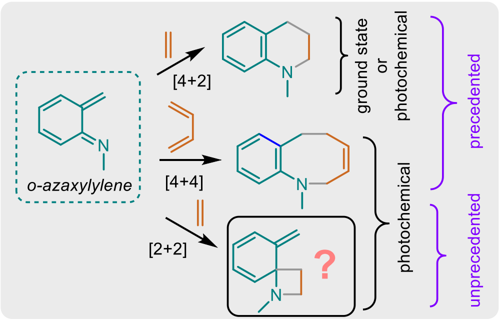
Scheme 1. Functionalization of anilides.



Most common workarounds are based on cross-coupling reactions involving transient arenediazonium salts (Scheme 1a),[6] although a number of catalytic reactions for cleavage of amide C(aryl)–N bonds are known (Scheme 1b).[7,8] A catalyst-free electrochemical redox addition-elimination approach was also suggested for the replacement of an amido group with C-nucleophiles (Scheme 1c).[9]

In this communication we disclose a transition metal-free formal C$_{sp2}$-C$_{sp3}$ cross-coupling in aromatic amides based on unprecedented [2+2] reactivity of *o*-azaxylylenes photogenerated via ESIPT and its application in synthesis of topologically novel complex polyheterocycles.

Scheme 2. General topological considerations.



As shown in Scheme 2, precedented ground state reactions of *o*-azaxylylenes follow inverse electron demand hetero-Diels Alder mode, yielding tetrahydroquinolines.[10–12] As we demonstrated in our prior work, with photogenerated azaxylylenes both [4+2] and [4+4] cycloadditions are also achievable.[13–17] Notice that, formally, azaxylylenes possess a conjugated C=NR (i.e. imine) moiety. This motivated us to explore an atypical reactivity for photogenerated azaxylylenes, namely the [2+2] imine cycloadditions in the exited state. We now report that this distinctive reaction topology indeed could be realized. Additionally, when paired with other photochemical and post-photochemical steps, it offers effective photoinduced complexity-building cascades for rapid access to novel polyheterocyclic cores.

Scheme 3 illustrates experimentally simple modular access to photoprecursors **4** by linking anilines (**1**) and aminothiophenes (**3**) with oxalyl amide tether. Irradiation of **4** with 365nm LEDs in DCM triggers their conversion to isoquinolinols **5**, which involves formal C_{sp2}-C_{sp3} cross-coupling between the anilide and thiophene moiety and is accompanied by substantial growth of complexity, as quantified by the Böttcher score[18–20] calculations.

The new photoinduced cascade has a broad scope as illustrated by Table 1. Reaction conditions were optimized by NMR scale experiments with acetone, DMSO, methanol, acetonitrile, DCM, and toluene. DCM was identified as the best solvent, with acetone being second best, performing marginally better in some of the cases. All reactions were run at ambient temperature and did not require temperature control. Structure of **5j** was confirmed by x-ray crystallography, while the rest of the products were characterized by NMR and corroborated computationally with DU8ML.[21]

Scheme 3. Modular access to photoprecursors **4** and the complexity-building photochemical cascade yielding isoquinolinols **5**.

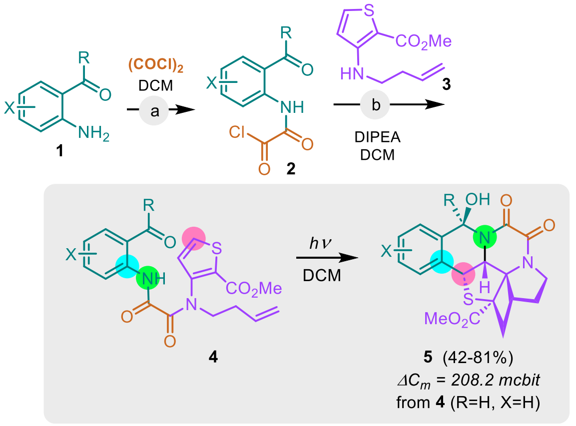
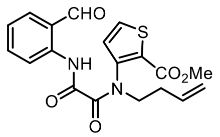
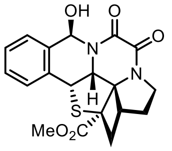
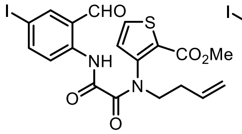
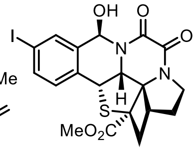
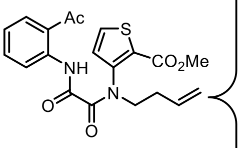
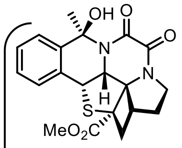
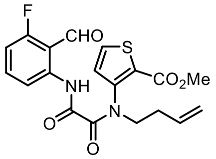
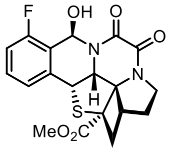
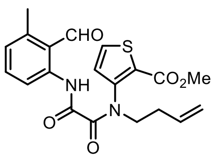
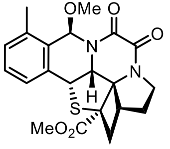
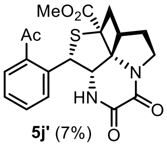
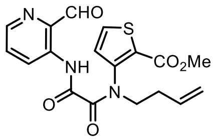
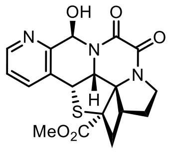
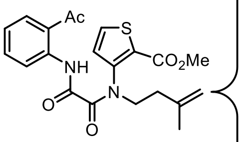
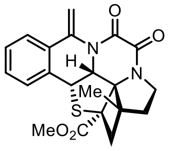
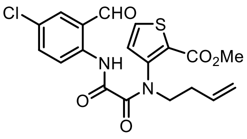
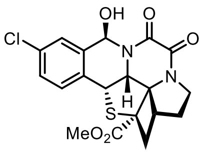
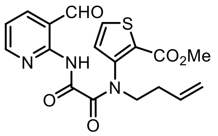
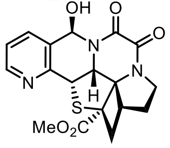
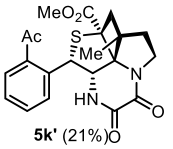
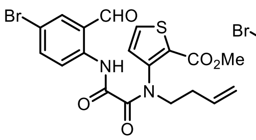
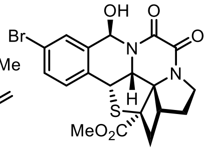
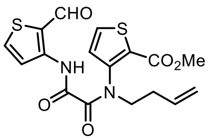
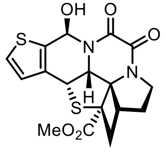
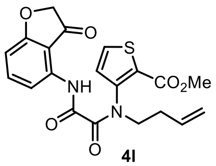
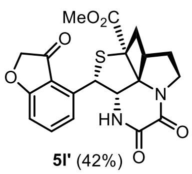


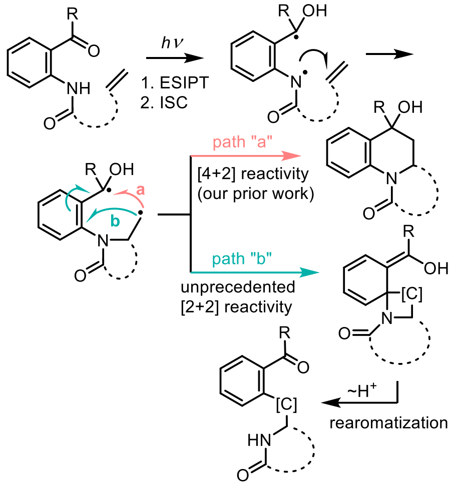
Table 1. Photoprecursors and fused isoquinolinol photoproducts (isolated yields).

Photoprecursor	Photoproduct	Photoprecursor	Photoproduct	Photoprecursor	Photoproduct
 **4a**	 **5a** (81%) ΔC_m = 208.2 mcbit	 **4e**	 **5e** (65%) ΔC_m = 208.2 mcbit	 **4j**	 **5j** (69%) x-ray ΔC_m = 230.0 mcbit
 **4b**	 **5b** (78%) ΔC_m = 208.2 mcbit	 **4f**	 **5f** (77%)* ΔC_m = 212.2 mcbit		 **5j'** (7%) ΔC_m = 149.9 mcbit
		 **4g**	 **5g** (78%) ΔC_m = 212.2 mcbit	 **4k**	 **5k** (59%) ΔC_m = 159.5 mcbit
 **4c**	 **5c** (84%) ΔC_m = 208.2 mcbit	 **4h**	 **5h** (57%) ΔC_m = 220.2 mcbit		 **5k'** (21%) ΔC_m = 155.5 mcbit
 **4d**	 **5d** (87%) ΔC_m = 208.2 mcbit	 **4i**	 **5i** (57%) ΔC_m = 208.2 mcbit	 **4l**	 **5l'** (42%) ΔC_m = 149.9 mcbit

* **5f** was isolated as methyl aminoacetals after column chromotography with methanol-chloroform eluent.

The formal mechanistic considerations are presented in Scheme 4. The initial attack of the N-centered terminus of azaxylylene's triplet on the tethered alkenic moiety yields a common 1,6-diradical which, after second intersystem crossing (ISC), could either collapse into quinolinol (*path a*, [4+2]), or undergo a novel [2+2] imine cycloaddition (*path b*, [2+2]) yielding a strained spiro-azetidine intermediate. Rearomatization of this intermediate via the amide elimination, plausibly accelerated by proton transfer, completes the reaction, which is formally a replacement of nitrogen by carbon. In this rearrangement, the *o*-ketone moiety is utilized as an auxiliary group to temporarily 'park' the NH proton.

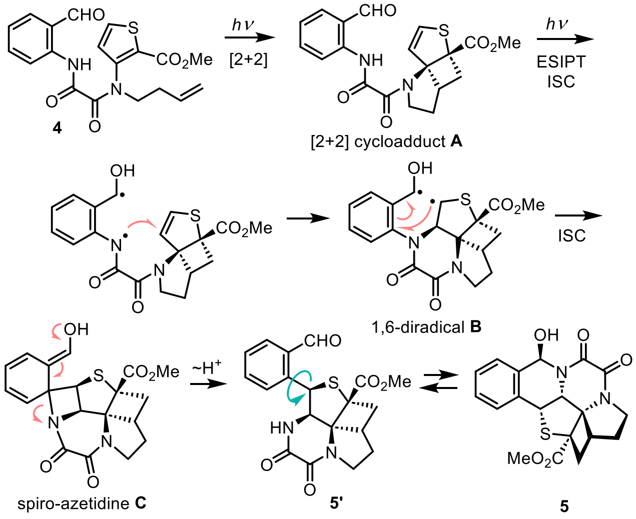
Scheme 4. Diverging typical [4+2] and alternative [2+2] reactivities of triplet azaxylylenes - formal mechanistic considerations.



It is evident that the partitioning in favor of *path b* is controlled by factors rendering the 1-6 collapse in the 1,6-diradical less favorable than 1-4 diradical recombination. *What are those factors?* Our prior work suggests that the oxalyl-tethered anilines or amino-heterocycles normally react with the *o*-azaxylylene photoactive cores in a [4+2] fashion. In this work, the serendipitous discovery was that the secondary unsaturated auxiliary group, i.e. the N-homoallyl, perturbed the typical flow of this reaction.

This hypothesis is detailed in Scheme 5. It is plausible that the initial excited state of the photoprecursor favors the shown [2+2] cycloaddition of the homoallylic moiety to aminothiophene, which occurs faster than the competing azaxylylene cycloaddition. This step yields a tricyclic dihydrothiophene cycloadduct **A** which is subsequently engaged with *o*-azaxylylene, ESIPT-generated in a secondary excitation. The difference from the previously studied topology is that the N-centered terminus of the azaxylylene triplet could only react with the dihydrothiophene pendant via a 6-membered transition state, yielding a topologically unique 1,6-diradical possessing the diketopiperazine moiety fused to thieno-cyclobutapyrrolidine.

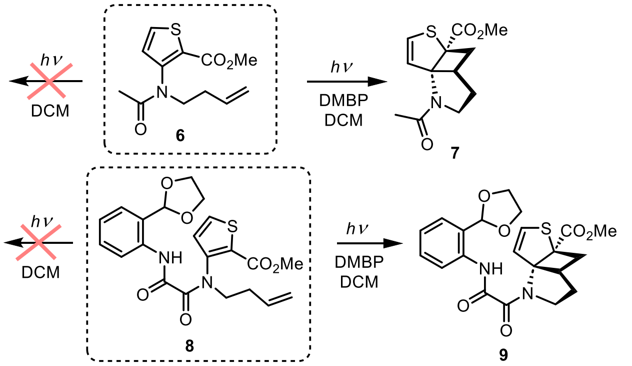
Scheme 5. Initial thiophene-homoallyl [2+2] cycloaddition biases the partitioning of 1,6-diradical **B** in favor of spiro-azetidine **C**.



We cannot fully rule out a possibility that each step in this dual (formal) [2+2] cascade occurs in a singlet excited state as a concerted reaction. However, two control experiments shown in Scheme 6 seem to support our mechanistic hypothesis.

Both, acetylated aminothiophene **6** and cyclic acetal **8** (i.e. acetal-protected photoprecursor **4a**) are unreactive upon direct irradiation in DCM, while sensitization with 4,4'-dimethoxybenzophenone (DMBP) yields the expected [2+2] cycloadducts **7** and **9**. It is plausible that azaxylylenes derived from photoprecursors **4** (in Scheme 3) act as triplet sensitizers for the initial thiophene-homoallyl [2+2] cycloaddition.

Scheme 6. Control experiments on direct and sensitized irradiation of truncated homoallyl-amidothiophenes, not capable of azaxylylene generation.

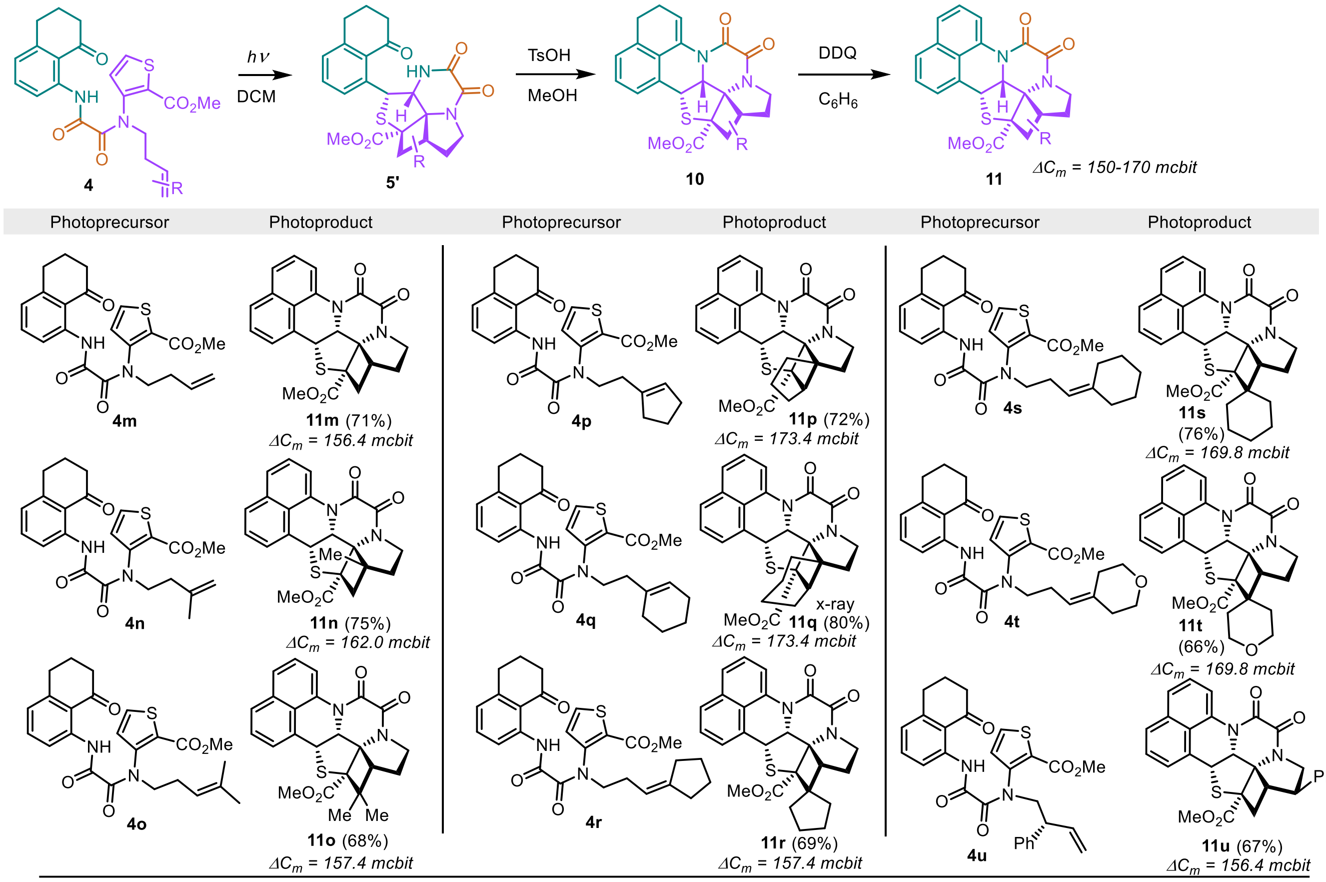


Additionally, the quantum yield for the formation of product **5b** is reduced with oxygen saturation, pointing to the involvement of the triplet state (for details see Supporting Information).

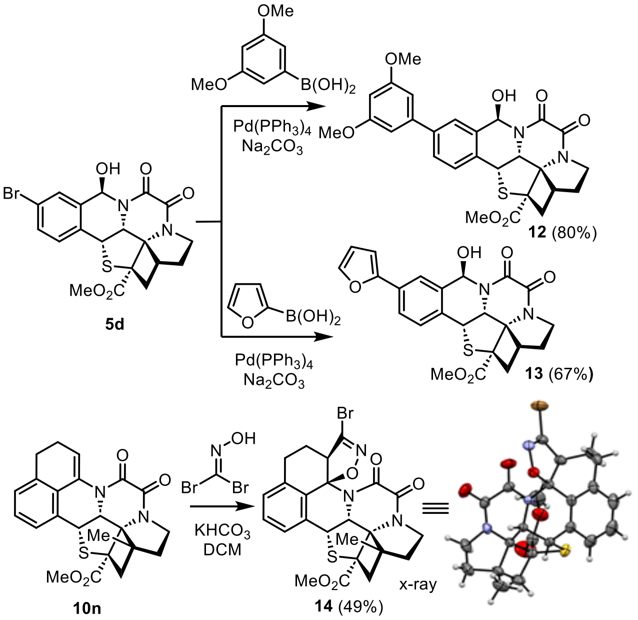
As seen in Table 1, occasionally hemiaminal photoproducts dehydrate to enamides, for example **5k**. This dehydration could be nearly quantitative in cyclic ketones, such as tetralone, especially under acid catalysis. Further, the tetralone enamide moiety could be fully aromatized under mild DDQ oxidation, giving access to complex fused benzo[de]quinolines, summarized in Table 2. These reactions also boast significant growth of molecular complexity as corroborated by the Böttcher scores.

The primary photoproducts could be introduced into simple yet advantageous post-photochemical transformations to further grow the core scaffold complexity and diversity, or to decorate the cores with various functionalities and (hetero)aromatic pendants. For example, the hemiaminal moiety in **5d** is tolerant of the Suzuki cross-coupling conditions, yielding biaryl **12** and arylfuran **13** in good yields, Scheme 7. The enamide moiety in **10n** lends itself to post-photochemical 1,3-dipolar cycloaddition furnishing **14**, which possesses a reactive bromoisoxazoline functionality and could be further modified. Even without subsequent potential transformations, the Böttcher complexity score for **14** is calculated at C_m = 742.7 mbit, which translates into step-normalized complexity increases of $\Delta\tilde{C}_m$ = 110.8 mbit in the three-step synthetic sequence starting from photoprecursor **4n**.

Table 2. Access to complex fused benzo[de]quinolines from aminotetralone-based photoprecursors (isolated yields).



Scheme 7. Post-photochemical modifications



In conclusion, we have elaborated a new mode for complexity-building photochemical cascades which offer experimentally simple transition metal-free C_{sp2}-C_{sp3} cross coupling of aromatic amides attained via an unprecedented [2+2] reactivity of ESIPT-generated azaxylylenes. Coupled with short and straightforward post-photochemical modifications of the primary photoproducts, these cascades allow for a significant step-normalized growth of molecular complexity while accessing diverse and complex polyheterocyclic molecular architectures.

ASSOCIATED CONTENT

Data Availability Statement. The data underlying this study are available in the published article and its supporting information.

Supporting Information. Experimental details, NMR spectra, x-ray data. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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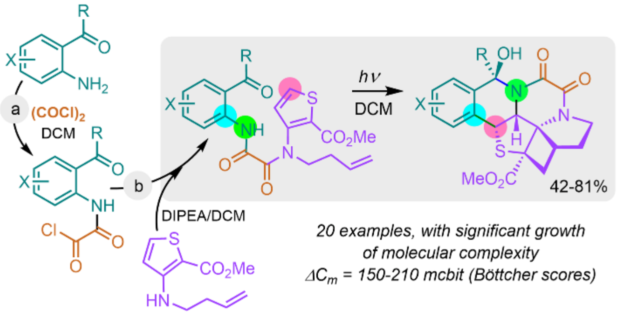
TOC GRAPHICS:



20 examples, with significant growth of molecular complexity ΔC_m = 150-210 mcbit (Böttcher scores)