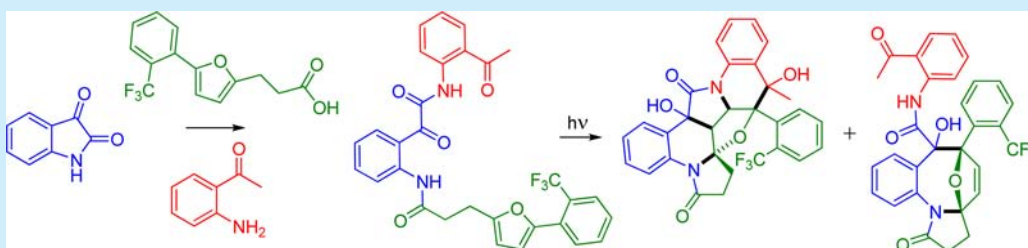


Photoinduced “Double Click” Cascade Offers Access to Complex Polyheterocycles from Readily Available Isatin-Based Photoprecursors

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S Supporting Information



ABSTRACT: The cascade photoassisted synthetic strategy for accessing complex N,O-polyheterocycles of unprecedented molecular architecture is developed. It is based on intramolecular cycloadditions of aza-*o*-xylylenes formed *in situ* via excited-state intramolecular proton transfer (ESIPT) of *o*-acylanilides. The photoprecursors are synthesized via a two-step one-pot method from readily available starting materials. The photochemical cascade (one experimentally simple step) results in the formation of four new heterocyclic rings with high control of diastereoselectivity.

Synthetic efficiency,¹ the coveted “ideal synthesis,”² and related concepts of step, atom, and redox economy have long been central to the philosophy of synthetic chemistry. Yet very few published syntheses could rival biochemical pathways in their spectacular efficiency and degree of chemo- and stereoselectivity.

Cascade reactions are one of the key strategies employed by nature,³ which are responsible for the deceptive, awe-inspiring simplicity with which the most complex molecules are assembled. Cascade polycyclizations,⁴ the reactions allowing for the single step formation of several rings from linear and sometimes achiral precursors, occupy a prominent place among them. Notable examples of such reactions include cationic cascades leading to polycyclic terpenes,^{5,6} nucleophilic cascades resulting in the formation of cyclic ether moieties,⁷ or pericyclic cascades leading to endiandric acids.⁸ These and similar biochemical sequences serve as constant inspiration for the synthesis of natural products.⁹ Such reactions are appealing not only in the context of the target-oriented synthesis but also as a potentially powerful tool in the biological and chemical space exploration. Rational design of polycyclizations is gaining momentum¹⁰ but still poses significant challenges. By their very nature the cascade reactions rely on the formation of highly reactive, short-lived intermediates in minute quantities without any spatial compartmentalization of sequential processes rendering control over the process difficult if not impossible.

Our strategy is based on photochemical generation of the aza-*o*-xylylene intermediates through the excited-state intramolecular proton transfer (ESIPT) in *o*-amido aldehydes and ketones and their [4 + 2] and [4 + 4] cycloadditions.¹¹ The

reaction is characterized by moderate to good yields, readily accessible photoprecursors, and significant growth of molecular complexity resulting from the process.

The [4 + 2] and [4 + 4] cycloadditions produce 2,5- or 3,4-dihydrofuran (DHF) intermediates, of which the most reactive 3,4-dihydrofuran can potentially be engaged in the second cascade step under the same irradiation conditions. Our previously reported photoassisted synthetic schemes involved the ground state postphotochemical transformations of the primary photoproducts via addition of reagents and changes in the reaction conditions. We recognized the synthetic potential of employing another sequential photochemical step, i.e. a photoinduced transformation of the primary photoproducts in a *photochemical cascade*.¹² As a result, we designed photoprecursors equipped with two *o*-acylanilide moieties, each capable of generating an azaxylylene moiety upon irradiation. Necessarily, such a potential photochemical “double click” cascade requires a (hetero)*dienic* pendant as a receptacle (Scheme 1).

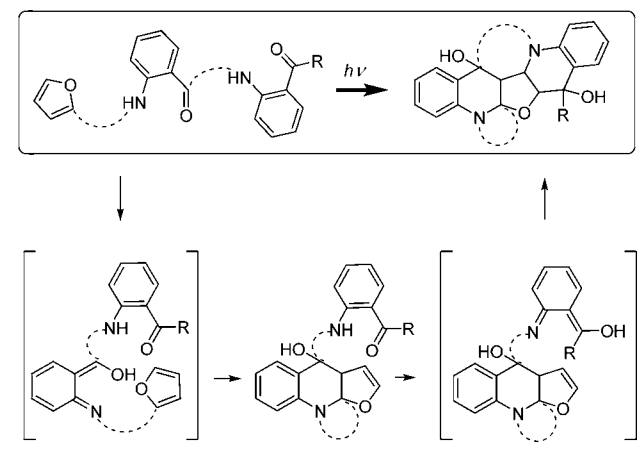
In this Letter, we report the development of a straightforward isatin-based multigram-scalable access to linear photoprecursors and the implementation of such photoinduced one-step double click cascades, offering rapid access to complex polyheterocycles containing four new heterocyclic moieties.

As shown in Scheme 2, photoprecursors 7a–d, 8 were synthesized by acylating commercial isatin (1) with furanpropanoic acids 2 or 3 followed by isatin’s ring opening with

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Scheme 1. Photochemical Cascade Design



anilines **6a–d**. This constituted a simple one-pot procedure for aromatic *o*-aminoketones, amino tetralone and acetophenone. *o*-Aminobenzaldehyde-based precursors **7a** and **8a** ($R' = H$) were synthesized from aminobenzyl alcohol **6a** and required an additional oxidation step with PCC.

Photoprecursors **7a–d**, **8** possess UV absorption maxima around 350–365 nm and can be irradiated in a Rayonet photoreactor equipped with RPR-3500 UV lamps (a broadband 300–400 nm UV source, with $\lambda_{\text{max}} \approx 350$ nm)¹³ or 365 nm UV LEDs, yielding photoproducts **10–12**, **14–16** in moderate yields. These photoinduced reactions of α -dicarbonyl

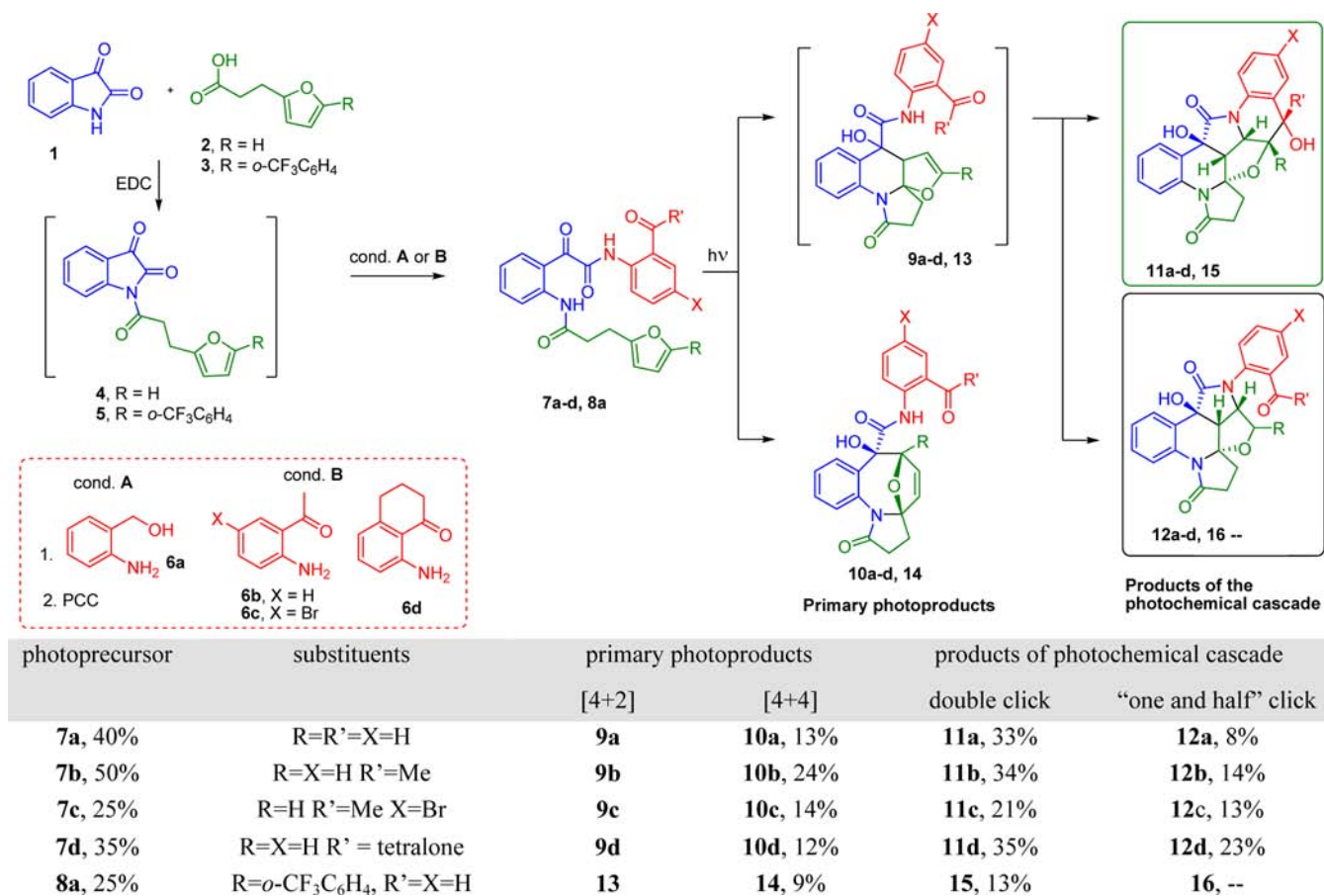
precursors were expectedly slower than the previously described “single click” cycloaddition reactions of simple aromatic amino-ketones or aldehydes. The relative quantum yield, calculated for the disappearance of the starting material, is approximately four times greater for the simple furanpropanamido-acetophenone as compared with isatin-based precursor **7a**.¹⁴

After the first “click” the resulting 2,5- or 3,4-dihydrofuran moiety is brought into spatial proximity of the second azaxylylene precursor which, upon excitation and ESIPT, could complete the cascade sequence with the second “click.” The overall combination of the reactivity and the mutual spatial arrangement of the remaining DHF double bond and the second photoactive core was much more favorable in the case of the [4 + 2] primary photoproducts **9a–d**, **13** (reactive 3,4-dihydrofurans), which proceeded to give the secondary products **11a–d**, **12a–d**, **15**. The [4 + 4] products, **10a–d** and **14** (containing a less reactive 2,5-dihydrofurans), proved unreactive.

A solution of a photoprecursor was irradiated until the primary [4 + 2] product was consumed. At this point the major component of the reaction mixture was the double click product (**11** or **15**), isolated after column chromatography with yields of up to 35%, along with unreactive primary [4 + 4] products, Scheme 2.

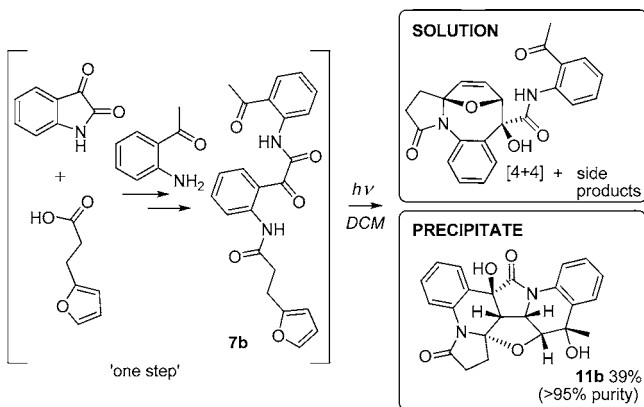
As some of the polyheterocyclic products were poorly soluble in dichloromethane (DCM), a simpler alternative procedure was developed for *in situ* generation of the photoprecursors and their irradiation until the double click

Scheme 2. Synthesis of Photoprecursors and Results of Their Irradiation



photoproduct precipitates from the reaction solution. Scheme 3 exemplifies this for photoprecursor **7b**, with the double click

Scheme 3. “One-Step” Reaction in DCM with Precipitated Double Click Product (No Chromatography Involved)

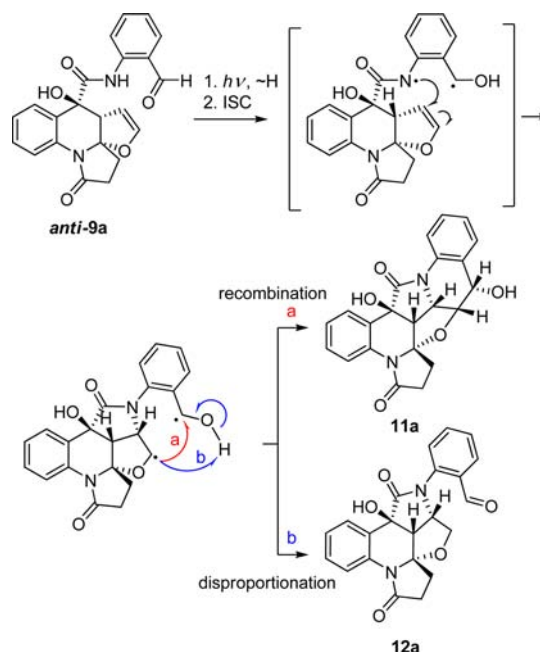


product **11b** isolated in 39% yield and >95% purity after washing with cold solvent. This procedure depends on solubility and is not universally applicable, but for the cases when it works, it offers an extremely simple one-step experimental route to rather complex polyheterocycles.

Previously, we demonstrated that the mechanism of these cycloadditions involve *triplet* diradicaloid species.¹⁵ The second “click” in the primary [4 + 2] photoproducts **9**, **13** occurs under imperfect structural arrangement and additional strain introduced with the formation of the first new three rings. In the past we did observe the products of radical disproportionation in the course of stepwise [4 + 2] processes. Reactions described here are no exception: such products of interrupted cycloaddition **12a–d** were isolated in 8–23% yields. Such “one and a half click” products still exemplify a considerable increase in complexity, exhibiting three new heterocyclic rings formed in a one-pot procedure.

The mechanistic rationale for the overall process is presented in Scheme 4. It is supported by NMR monitoring of these reactions. Initially the formation of the expected *syn*- and *anti*-[4 + 2] **9** (*syn* and *anti* are referring to the relative position of the newly formed benzylic hydroxyl-group and the dihydrofuran's oxygen) and [4 + 4] **10** products is observed. Compounds **9** and **10** have distinctive spin–spin coupling constants of the newly formed allylic fragment of dihydrofuran ring: $^3J_{\text{cis}} = 5.8$ Hz, $^3J = 2.0$ Hz, $^4J = 1.1$ Hz for the [4 + 4] cycloadduct and $^3J_{\text{cis}} = 3.1$ Hz, $^3J = 2.3$ Hz, $^4J = 2.6$ Hz for [4 + 2]. Upon continuous irradiation the initially formed *anti*-[4 + 2] adduct (*anti*-**9**) is observed to transform into the product that we termed “double click” **11** and “one-and-a-half click” **12**. Both of them arise from the initial excitation of the second *o*-formyl or *o*-acyl anilide moiety, resulting in ESIPT with the formation of transient azaxylylene, followed by the intersystem crossing onto the triplet manifold and the first addition of the formed N-radical to the vinyl ether moiety. The fate of the O-stabilized radical at this point diverges into two pathways: another intersystem crossing and radical recombination to form the “double click” product or hydrogen abstraction from OH-group re-forming the carbonyl group and furnishing the “one and a half click” product. The minor [4 + 2] adduct, *syn*-**9**, does not survive these conditions.

Scheme 4. Plausible Mechanistic Rationale for the Photochemical Cascade



Compounds **11** and **12** are easily distinguishable by NMR. Characteristic are the shifts of the protons of the newly formed tetrahydrofuran ring. In **11b**, H_a is the most downshift proton observed as a doublet of doublets, at 4.78 ppm ($J(H_a-H_c) = 7.5$ Hz, $J(H_a-H_b) = 4.6$ Hz). Both H_b and H_c are characterized by doublets at 4.61 and 3.26 ppm, respectively. To ascertain the stereochemistry of the compound we have conducted NOE experiments, Figure 1. In compound **11b** upon irradiation of the Me-group, a singlet at 1.48 ppm, the enhancement of H_b (2.2%) and H_a (0.8%) signals is observed. The irradiation of the OH-*b* proton, in contrast, does not produce the NOE effect on any of the protons. The irradiation of the OH-*a* proton, however, results in the enhancement of the H_c signal (3%).

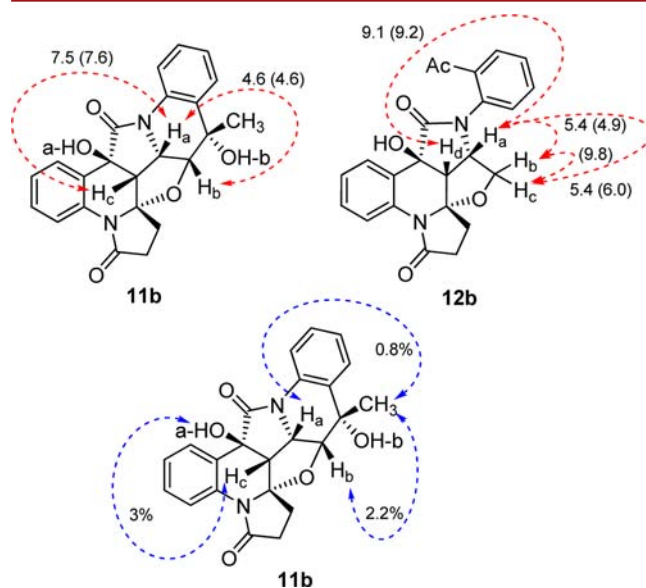


Figure 1. SSCCs for compounds **11b and **12a** (red arrows, calculated values are in parentheses); NOE difference for **11b** (blue arrows).**

This allowed us to postulate positioning of the CH₃, H_a, H_b, H_c, and OH-a groups on the same face of the molecule. In the case of compound **12b**, the structure was proven by the comparison of the calculated and experimental spin–spin coupling constants in the system. Proton H_a is observed as a doublet of triplets, $J(\text{H}_a\text{--H}_d) = 9.1 \text{ Hz}$, $J(\text{H}_a\text{--H}_b) = J(\text{H}_a\text{--H}_c) = 5.4 \text{ Hz}$. Both H_b and H_c are characterized by overlapping doublets of doublets at 3.91 ppm, and H_d is observed as a doublet at 3.69 ppm. The spin–spin coupling constants (SSCC) for compounds **11b** and **12b** are in excellent agreement with those calculated using the *relativistic force field* method (*rff*) developed in our laboratory.¹⁶

In conclusion, we have developed a new photochemical synthetic cascade which offers rapid access to complex polyheterocyclic molecular architectures from readily available isatin-based photoprecursors via tandem cycloadditions of ESIPT-photogenerated aza-*o*-xylylenes. The moderate yields are counterbalanced by extreme simplicity of the one-two step experimental procedures, with multigram-scalable synthesis of starting materials.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: [10.1021/acs.orglett.6b01775](https://doi.org/10.1021/acs.orglett.6b01775).

Experimental procedures and spectra (PDF)

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

- (1) (a) National Research Council, *Beyond the Molecular Frontier*; The National Academies Press: Washington, DC, 2003. (b) Pignataro, B., Ed. *Ideas in chemistry and molecular sciences*; Wiley-VCH: 2010; 333 pp.
- (2) (a) Gaich, T.; Baran, P. S. *J. Org. Chem.* **2010**, *75*, 4657. (b) Newhouse, T.; Baran, P. S.; Hoffmann, R. W. *Chem. Soc. Rev.* **2009**, *38*, 3010.
- (3) Jürjens, G.; Kirschning, A.; Candito, D. A. *Nat. Prod. Rep.* **2015**, *32*, 723.
- (4) Ueberbacher, B. T.; Hall, M.; Faber, K. *Nat. Prod. Rep.* **2012**, *29*, 337.
- (5) Stork–Eschenmoser hypothesis: (a) Stork, G.; Burgstahler, A. W. *J. Am. Chem. Soc.* **1955**, *77*, 5068. (b) Eschenmoser, A.; Ruzicka, L.; Jeger, O.; Arigoni, D. *Helv. Chim. Acta* **1955**, *38*, 1890.
- (6) Biomimetic synthesis: (a) Johnson, W. S.; Crandall, J. K. *J. Org. Chem.* **1965**, *30*, 1785. (b) Johnson, W. S.; Semmelhack, M. F.; Sultanbawa, M. U. S.; Dolak, L. A. *J. Am. Chem. Soc.* **1968**, *90*, 2994. (c) van Tamelen, E. E.; Seiler, M. P.; Wierenga, W. *J. Am. Chem. Soc.* **1972**, *94*, 8229.
- (7) For a review on biosynthetic hypotheses and their application in synthesis, see: (a) Vilotijevic, I.; Jamison, T. F. *Angew. Chem., Int. Ed.* **2009**, *48*, 5250. (b) de Maria, P. D.; van Gemert, R. W.; Straathof, A. J. J.; Hanefeld, U. *Nat. Prod. Rep.* **2010**, *27*, 370.
- (8) Biosynthetic hypothesis for the synthesis of the endiandric acid: (a) Bandaranayake, W. M.; Banfield, J. E.; Black, D. St. C. *J. Chem. Soc., Chem. Commun.* **1980**, 902. Biomimetic synthesis of the endiandric acid: (b) Nicolaou, K. C.; Petasis, N. A.; Zipkin, R. E.; Uenishi, J. *J. Am. Chem. Soc.* **1982**, *104*, 5555. (c) Nicolaou, K. C.; Petasis, N. A.; Uenishi, J.; Zipkin, R. E. *J. Am. Chem. Soc.* **1982**, *104*, 5557. (d) Nicolaou, K. C.; Zipkin, R. E.; Petasis, N. A. *J. Am. Chem. Soc.* **1982**, *104*, 5558. (e) Nicolaou, K. C.; Petasis, N. A.; Zipkin, R. E. *J. Am. Chem. Soc.* **1982**, *104*, 5560.
- (9) Anderson, E. A. *Org. Biomol. Chem.* **2011**, *9*, 3997.
- (10) For reviews of cascade reactions, see: (a) Nicolaou, K. C.; Chen, J. S. *Chem. Soc. Rev.* **2009**, *38*, 2993. (b) Nicolaou, K. C.; Edmonds, D. J.; Bulger, P. G. *Angew. Chem., Int. Ed.* **2006**, *45*, 7134. (c) Kim, J.; Movassaghi, M. *Chem. Soc. Rev.* **2009**, *38*, 3035. (d) Toure, B. B.; Hall, D. G. *Chem. Rev.* **2009**, *109*, 4439. (e) Juhl, M.; Tanner, D. *Chem. Soc. Rev.* **2009**, *38*, 2983. (f) Tietze, L. F., Ed. *Domino Reactions: Concepts for Efficient Organic Synthesis*; Wiley-VCH: 2014; 648 pp.
- (11) (a) Mukhina, O. A.; Kumar, N. N. B.; Arisco, T. M.; Valiulin, R. A.; Metzel, G. A.; Kutateladze, A. G. *Angew. Chem., Int. Ed.* **2011**, *50*, 9423. (b) Nandurkar, N. S.; Kumar, N. N. B.; Mukhina, O. A.; Kutateladze, A. G. *ACS Comb. Sci.* **2013**, *15*, 73. (c) Kumar, N. N. B.; Mukhina, O. A.; Kutateladze, A. G. *J. Am. Chem. Soc.* **2013**, *135*, 9608. (d) Cronk, W. C.; Mukhina, O. A.; Kutateladze, A. G. *J. Org. Chem.* **2014**, *79*, 1235. (e) Kumar, N. N. B.; Kuznetsov, D. M.; Kutateladze, A. G. *Org. Lett.* **2015**, *17*, 438. (f) Mukhina, O. A.; Kumar, N. N. B.; Cowger, T. M.; Kutateladze, A. G. *J. Org. Chem.* **2014**, *79*, 10956. (g) Umstead, W. J.; Mukhina, O. A.; Kutateladze, A. G. *Eur. J. Org. Chem.* **2015**, *2015*, 2205.
- (12) For recent examples of photochemical cascade reactions, see: (a) Basarić, N.; Horvat, M.; Mlinarić-Majerski, K.; Zimmermann, E.; Neudörfl, J.; Griesbeck, A. G. *Org. Lett.* **2008**, *10*, 3965. (b) Horvat, M.; Görner, H.; Warzecha, K.-D.; Neudörfl, J.; Griesbeck, A. G.; Mlinarić-Majerski, K.; Basarić, N. *J. Org. Chem.* **2009**, *74*, 8219 and the references cited therein.
- (13) Photolysis on a 1 mmol scale typically required 6–9 h.
- (14) (a) The absolute quantum yields for the ‘single’ click systems are found in ref 15. (b) The two weakly coupled chromophores in the photoprecursors have very similar UV absorption. The second ‘click’ happens only after the first, and therefore premature excitation of the ‘red’ aza-*o*-xylylene moiety wastes photons and lowers the quantum yield, unless there is an efficient intramolecular energy transfer from the ‘red’ to the ‘blue’ chromophore.
- (15) Mukhina, O. A.; Cronk, W. C.; Kumar, N. N. B.; Sekhar, M.; Samanta, A.; Kutateladze, A. G. *J. Phys. Chem. A* **2014**, *118*, 10487.
- (16) (a) Kutateladze, A. G.; Mukhina, O. A. *J. Org. Chem.* **2015**, *80*, 5218. (b) For the previous version of *rff*, see: Kutateladze, A. G.; Mukhina, O. A. *J. Org. Chem.* **2014**, *79*, 8397.