



HAL
open science

Photocatalyzed (3+2) Cycloaddition for the Dearomatization of Electron-Poor Arenes under Flow Conditions

Youssou Faye, Batoul Rkein, Antoine Bigot, Thierry Lequeux, Julien Legros, Isabelle Chataigner

► **To cite this version:**

Youssou Faye, Batoul Rkein, Antoine Bigot, Thierry Lequeux, Julien Legros, et al.. Photocatalyzed (3+2) Cycloaddition for the Dearomatization of Electron-Poor Arenes under Flow Conditions. Chemistry - A European Journal, 2023, 29 (49), pp.45-52. 10.1002/chem.202301567 . hal-04250204

HAL Id: hal-04250204

<https://hal.science/hal-04250204>

Submitted on 20 Oct 2023

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

Photocatalyzed (3+2) Cycloaddition for the Dearomatization of Electron-poor Arenes under Flow Conditions

Youssou Faye,^a Batoul Rkein,^a Antoine Bigot,^a Thierry Lequeux,^b Julien Legros^{*a} and Isabelle Chataigner^{*a,c}

Dedicated to Dr. Jean-Pierre Bégué on the occasion of his 85th birthday

[a] Y. Faye, Dr B. Rkein, A. Bigot, Dr. J. Legros, Prof. I. Chataigner

Univ Rouen Normandie, INSA Rouen Normandie, CNRS, Normandie Univ, COBRA, F-76000 Rouen, France

E-mail: julien.legros@univ-rouen.fr; isabelle.chataigner@univ-rouen.fr

[b] Prof. T. Lequeux

Normandie Univ., ENSICAEN, Unicaen, CNRS, LCMT, 14000 Caen, France.

[c] Prof. I. Chataigner

Sorbonne Université, CNRS, Laboratoire de Chimie Théorique, LCT UMR7616, 75005 Paris, France.

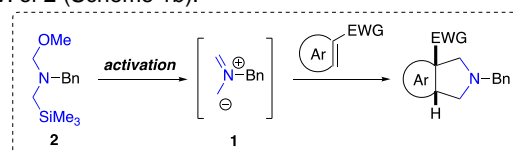
Supporting information for this article is given via a link at the end of the document.

Abstract: The photocatalyzed reaction between various electron-deficient aromatic compounds and a non-stabilized azomethine ylide is successfully performed in a flow system. Whereas the use of supported eosin as organic photocatalyst exhibited limited efficiency, turning to the soluble Rose Bengal allowed to transform a broad range of substrates from hetarenes (indole, benzofuran, quinoline, pyridine) to naphthalenes and benzenes. This photocatalyzed (3+2) dearomative cycloaddition under green light irradiation provides an efficient access to tridimensional scaffolds with a pyrrolidino moiety and can be performed in the friendly ethyl acetate. Computational studies support the mechanism involving azomethine ylide as reactive species toward the arene.

Introduction

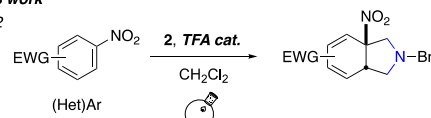
In the search for novel molecules with tridimensional structures,^[1,2] dearomative processes have become a hot topic due to the large number of starting materials available.^[3–7] Among them, electron-poor arenes are of interest since they are easily accessed through electrophilic aromatic substitution (S_EAr), and the presence of an electron-withdrawing group (such as a nitro or cyano group) can serve for post-functionalization.^[8–9] Thus, electron-deficient aromatic compounds have been shown to react as dipolarophiles in (3+2) cycloadditions,^[10–11] in particular by using the non-stabilized ylide **1** as dipole allowing construction of the popular pyrrolidino fragment (Scheme 1).^[12,13] Due to its ability to self-condense, **1** must be generated *in situ* in the presence of the dipolarophile. For this, a common source of **1** is the hemiaminal ether **2**, which decomposes, at room temperature, into the target ylide through acid,^[14,15] fluoride anion^[16] or transition metal catalysis^[17] (Scheme 1). However, it has been recently shown that this dipole could also be advantageously generated from the same starting chemical by using green light irradiation with eosin Y disodium salt as photosensitizer.^[18] Thus, from electron-poor (fluoro)olefins various pyrrolidines were obtained in good yields. Moreover, one single example of dearomatization of

the electrophilic 3-nitro-*N*-tosyl-indole **3**^[19,20] was reported with 2 equiv. of **2** (Scheme 1b).^[18]

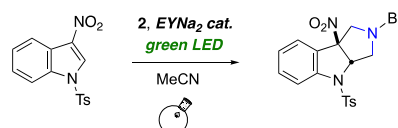


previous work

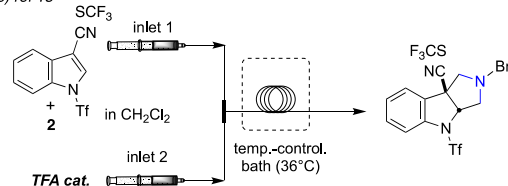
(a) ref 12



(b) ref 18

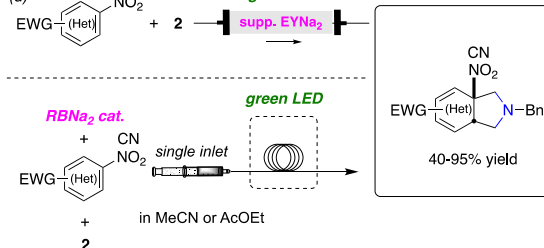


(c) ref 13



this work

(d)



Scheme 1. Generation of ylide **1** from **2**, and dearomative (3+2) cycloaddition under batch (a,b)^[12,18] and flow conditions (c,d)^[13]; acid- (a,c)^[12,13] and photocatalyzed reaction (b,d).^[18] EYNa₂ = eosin, RBNa₂ = rose bengal, both as disodium salts.

Visible-light photocatalysis is definitely an attractive way to promote reactions, and its combination with miniaturised flow

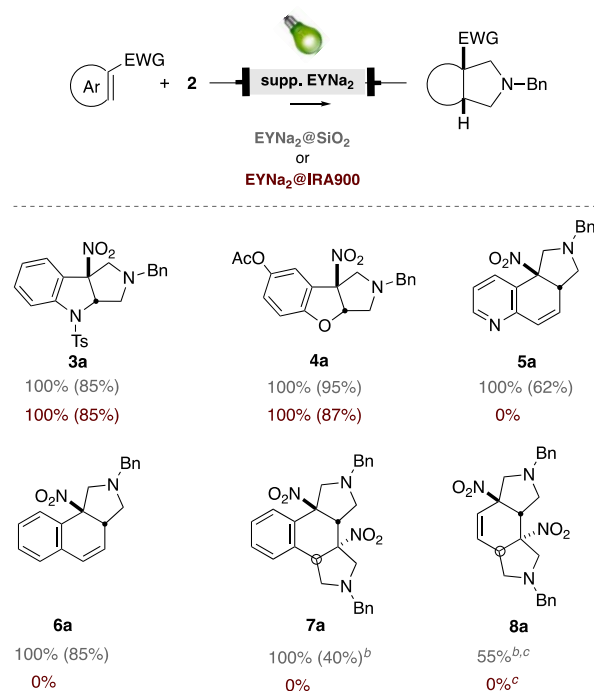
reactors provides a very effective synthetic tool.^[21–24] Not only the downsizing of the reactor brings an obvious decisive advantage for light absorption, but the operation in continuous flow may allow easier scale-up than under batch conditions, with significant gain in time, energy and reduction of effluents.^[25] Moreover, flow systems offer the possibility to handle and treat large volumes of chemicals –even hazardous– with reduced exposition of the operator.^[26–28] In this context, we recently showed that the reactive electron-poor indoles underwent smooth acid-catalyzed 1,3-dipolar cycloaddition under flow conditions (Scheme 1c).^[12,13] Herein, we report that the photocatalyzed dearomatization of structurally diverse electron-poor arenes, including the challenging benzenic derivatives, occurs by (3+2) cycloaddition under friendly flow conditions within less than 1 h, at room temperature (Scheme 1d).

Results and Discussion

Supported photocatalysts

The solubility of the eosin disodium salt (EYNa₂) is quite satisfactory in organic media to perform photocatalytic reactions in a classical stirred batch reactor. However, a direct transposition of the batch conditions to a simple flow system, consisting of a single inlet containing reagents and EYNa₂ feeding an irradiated reactor, is not so trivial since reproducibility/clogging issues are much likely to occur. Switching to the more soluble native form of EY was not an option since the catalyst contains a phenol function, potentially able to promote a competitive acid-catalyzed formation of **1**. Therefore, we oriented our investigations toward the use of a fixed-bed reactor containing supported eosin. For this, two solid supports were compared: silica^[29] and Amberlite IRA900 affording thus EY@SiO₂ and EY@IRA900, (catalyst loading = 5% w/w, see Supporting Information (S.I.) for details). Thus, we implemented a flow set-up consisting of a single inlet where a mixture of different nitroaromatic and hemiaminal ether **2** in MeCN were injected in a fixed bed reactor containing the supported eosin, and irradiated with green LED. The outlet was collected in a methanol solution to quench the reaction. Results are reported in Table 1. With EY@SiO₂ the reaction was quite efficient with full conversion of the standard *N*-tosyl-3-nitroindole starting material in only 1.5 minutes irradiation (85% yield for *cis*-fused **3a**). Delightfully, these conditions could be successfully applied to the dearomative cycloaddition of a variety of other nitroheteroarenes (benzofuran, quinoline) to afford products **4a** and **5a** (95% and 62% yield, respectively) but also to the less reactive nitronaphthalene (**6a**, 85% yield). With 1,3-dinitronaphthalene, the tricyclic adduct **7a** was obtained with a reasonable yield of 40% after 6 minutes. However, the 1,3-dinitrobenzene derivative was not fully converted (55%) into *bis*-cycloadduct **8a** under these conditions. This problem of reactivity can be explained with the stronger aromaticity of the 1,3-dinitrobenzene compared to the 1,3-dinitronaphthalene, rendering the corresponding substrate more stable and less reactive. Noteworthy, the diastereoselectivity of the process appeared to be complete and led, as previously observed under acidic catalysis,^[12] to the unique formation of the product with a *trans* relationship between the pyrrolidine rings.

Table 1. (3+2) Dearomative cycloaddition with supported photocatalyst eosin in a flow system.^a

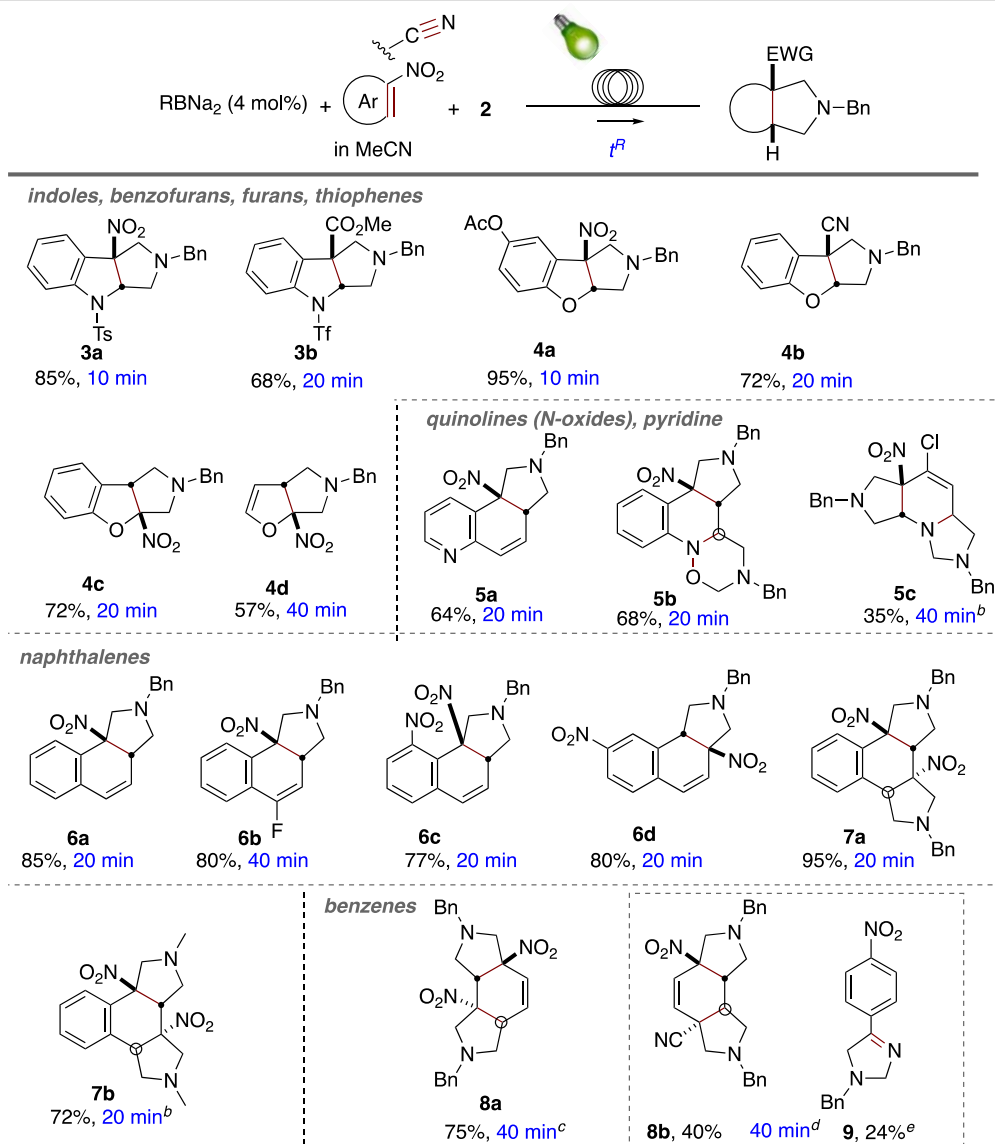


^a Reaction conditions: starting from nitroaromatic compound (0.2 mmol) and **2** (4 equiv.) in MeCN, injected at a flow rate = 0.050 mL·min⁻¹ (*t*^R = 1.5 min) under green light irradiation. ^b *t*^R = 6 min. ^c 9 equiv. of **2** were used.

Unfortunately, a pinkish colour was observed when collecting the product at the outlet of the flow system, indicating a leaching of eosin from silica. Therefore, the use of Amberlite IRA-900, containing an ammonium ending, could offer a much better material to support eosin through ionic interactions (EY@IRA900). In this case, the dearomatization of the reactive *N*-tosyl -nitroindole and -benzofuran fully proceeded within the same *t*^R as with the previous supported catalyst. However, all the other substrates remained unchanged with EY@IRA900, even at longer residence times. Based on these results, the following conclusions can be drawn. Whereas the use of supported catalyst is interesting for obvious reasons, the reaction occurs only at solid-liquid interface and most probably on surface (light penetration issue) with low efficiency as exhibited with EY@IRA900. In the case EY@SiO₂ the success of is probably connected to the leaching of eosin, the reaction taking place only in the liquid phase.

Homogeneous conditions

For these reasons, we turned our investigations toward fully liquid conditions with a more soluble photocatalyst exhibiting properties close to those of eosin: Rose Bengal (RBNa₂).^[30] Indeed, redox potential of EY and RB under their excited states (*E*_{red}^{T1}) are +0.83 and +0.81 V vs SCE, respectively.^[18] Thus, a simple flow set-up was implemented as follows: a mixture of electron-depleted aromatic, hemiaminal ether **2** (4 equiv) and Rose Bengal (4 mol%) was dissolved in MeCN and injected in a PFA tubing illuminated with a green LED. Results are reported in Table 2.

Table 2. Flow (3+2) Dearomative cycloaddition under homogeneous conditions.^a

^a Reaction conditions: starting from nitroaromatic compound (0.2 mmol), **2** (4 equiv.) and RBNa₂ (4 mol%), in MeCN, injected at a constant flow rate, under green light irradiation. ^b *N*-methoxymethyl-*N*-trimethylsilylmethylamine was used as dipole precursor. ^c 9 equiv. of **2** were used. ^d 100% conversion, **8b/9** 67:33. ^e Characterized as an imidazole adduct **10** after DDQ oxidation (see S.I. for details).

With these conditions, various electron-depleted arenes have been successfully dearomatized. Thus, *N*-protected indoles bearing a nitro or methoxycarbonyl group at position 3 afforded the expected products **3a** (85% yield) and **3b** (68%) within 10 to 20 minutes. Similarly, 3-nitro- and 3-cyano-benzofurans reacted well (**4a**, 95% and **4b**, 72%), as did the 2-nitro derivative (**4c**, 72%). 2-Nitrofuran led to the corresponding dearomatized cycloadducts in slightly lower yield (**4d**, 57%). Quinolines are also attractive heteroaromatic substrates and 5-nitroquinoline afforded **5a** in 64% yield. When reacting the 4-nitro-*N*-oxide quinoline, a double cycloaddition reaction occurred: a (3+2) cycloaddition onto the C=C bond bearing the NO₂, accompanied by a subsequent (3+3) formal cycloaddition on the *N*-oxide side, in a diastereoselective manner (**5b**, 68%). When starting from the strongly depleted 4-chloro-3-nitropyridine, a tricyclic adduct was formed through a

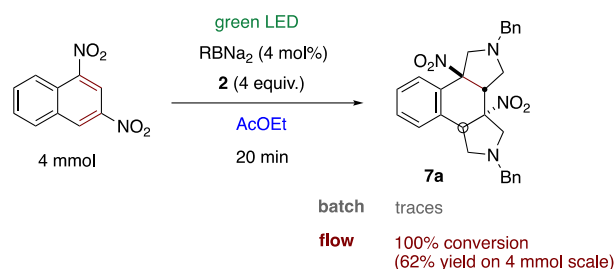
double (3+2) process where the second cycloaddition reaction occurred, in a chemo- and diastereo-selective manner, on the imine site. This furnished a fragile imidazolidine moiety (**5c**, 35%). The reduced yield was traced to the sensitivity of the product on silica. Interestingly, the chlorinated C=C bond did not react here, in line with previous observations.^[12]

Delightfully, these conditions were also effective with the more challenging naphthalene and benzene derivatives. Simple 1-nitronaphthalene nicely afforded **6a** (85%). The presence of an additional 4-fluoro- substituent was also tolerated, leading to the formation of an interesting scaffold **6b** in 80% yield. The fluorinated double bond thus proved resistant to both S_NAr and cycloaddition. Tricyclic structures **6c** and **6d** were also obtained starting from 1,8- and 2,7-dinitrothalenes (77% and 80% yield, respectively), with a single cycloaddition occurring in this case. In

contrast, a tetracyclic bis-cycloadduct **7a** was formed from 1,3-dinitronaphthalene (95%), arising from a bis-cycloaddition process. These results are in line with our previous observations in Diels-Alder reactions.^[31] Changing dipole was possible and the use of the *N*-methylated hemiaminal ether precursor led to the efficient formation bis-cycloadduct **7b** in a good 72% yield. Similarly, 1,3-dinitrobenzene afforded a cycloadduct resulting from a double reaction, **8a**, isolated in 75% yield, in a longer residence time ($t^R = 40$ min) for this more aromatic arene. Notably, 4-nitrobenzonitrile behaved differently towards **2**, giving two different cycloadducts **8b** and **9a** (ratio 75:25, and respective isolated yields of 40% and 24%). In this case, a competitive reaction on the C=C aromatic bonds (leading to **8b**) and on the CN group (**9a**) was observed. We previously demonstrated that benzonitriles bearing an additional electron-withdrawing group (CN, F, CF₃) could react as heterodipolarophiles, involving the CN group to create an imidazoline ring,^[32] but this result is in sharp contrast to the previously reported process in the presence of 3-nitrobenzonitrile, in acidic conditions, where only the C=C aromatic double bonds reacted as dipolarophile.^[12] The results gathered here show that this photocatalyzed dearomative (3+2) cycloaddition takes place with various types of (hetero)arenes, including the benzenic ones, bearing different types of electron-withdrawing groups.

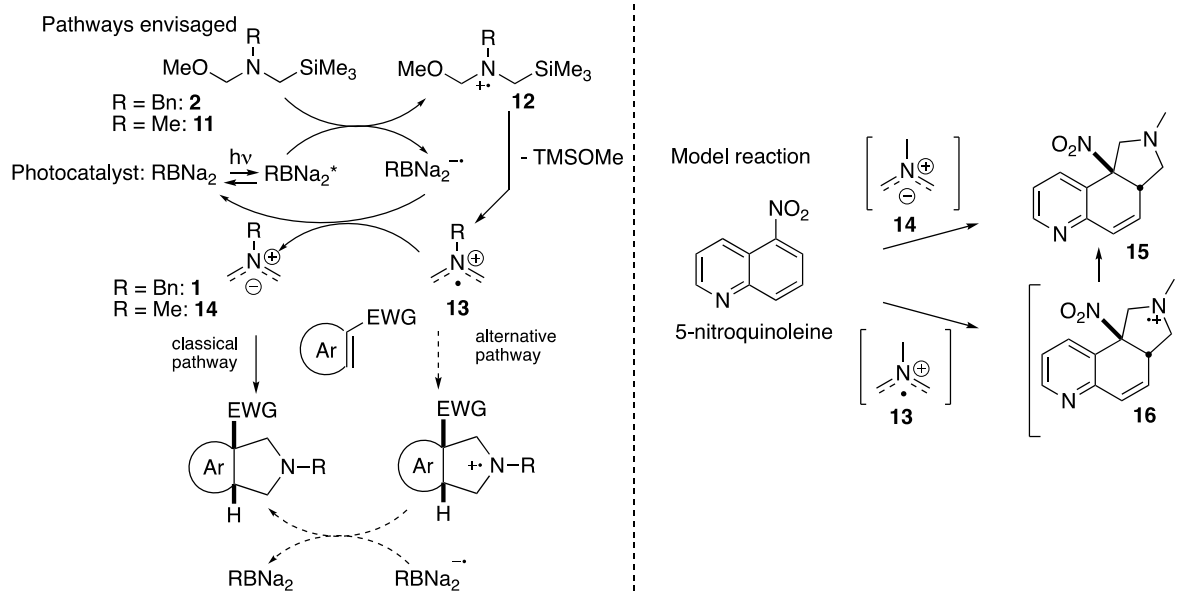
In the development of greener processes, not only the technology (such as photochemistry) plays an important role but also the chemicals, among which the solvent represents -by far- the biggest part.^[31-33] Whereas acetonitrile can be tolerated as polar aprotic solvent, its substitution by ethyl acetate is desirable.^[32] Therefore, whereas previous reactions were performed on 0.2 mmol scale of aromatic compound in MeCN, we

now assessed the dearomatization of 1,3-dinitronaphthalene on a 4 mmol scale in AcOEt (Scheme 2). Performed in a Vapourtec E-Series flow device, we were delighted to observe a full conversion within a similar 20 minutes residence time at this scale in this friendlier solvent. By comparison, in a classical flask, almost no conversion was obtained over this short reaction time.



Scheme 2. (3+2) Cycloaddition of 1,3-dinitronaphthalene with **2** in AcOEt.

In order to shed light on the mechanism of this photocatalyzed (3+2) cycloaddition, DFT calculations were then performed at the M062X/6-31+G(d,p) level considering an implicit solvation (SMD: CH₃CN) (for computational details, see S.I.). If the classical mechanism suggests the involvement of the azomethine ylide (AY) species **1** directly,^[18] another process, involving a reactive radical-cation type species and leading to the formation of the radical-cationic pyrrolidine can also be envisaged (Scheme 3, left part). Calculations were performed with *N*-methylated species as models of the *N*-benzylated used experimentally (AY **14** and AY⁺ **13**), and 5-nitroquinoline as electron-poor arene.

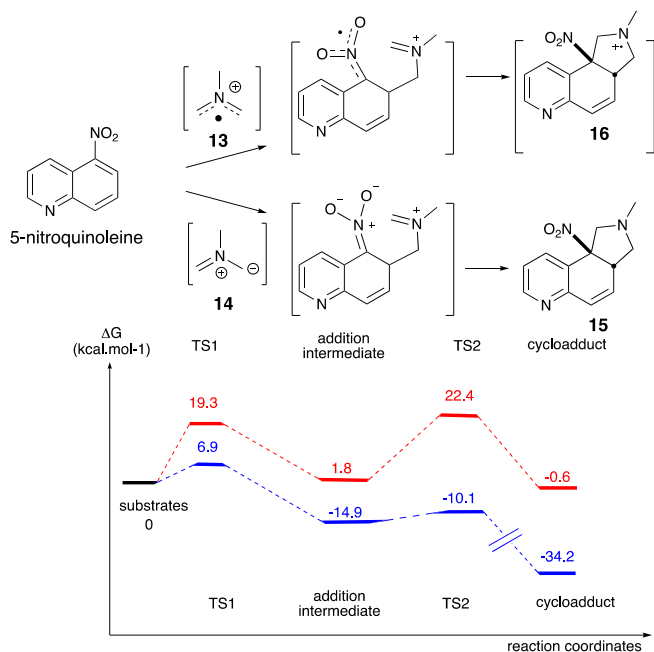


Scheme 3. Mechanistic pathways envisaged.

The isodesmic reaction (**14** + **16** → **13** + **15**) revealed a large negative energy value ($\Delta E_e = -35.8$ kcal.mol⁻¹), suggesting a much higher stability of **13** over **16**,^[34-35] probably because of the stabilizing delocalization possible with **13**. Quantitative evaluation of the preferred pathway on the activation energy was then

undertaken, considering that the reaction is under kinetic control. The transition state (TS) of the cycloadditions between 5-nitroquinoline and AY⁺ **13** or AY **14** were located, examining two approaches (*endo* and *exo*) in each case (Scheme 4 and S.I.). Expectedly, this revealed a preferred "classical" pathway ($\Delta\Delta G^\ddagger =$

12.4 kcal.mol⁻¹), with a slightly more favorable exo pathway ($\Delta\Delta G^\ddagger = 0.3$ kcal.mol⁻¹, see S.I.). More surprisingly, a stepwise cycloaddition reaction was disclosed, with formation of a zwitterionic intermediate, even if the determining step is unambiguously the first addition (Scheme 4).



Scheme 4. Energy profiles for the (3+2) cycloadditions between 5-nitroquinoline with 14 (blue) (“classical” pathway) and 13 (red) (alternative pathway), computed at the (SMD:CH₃CN) M062X/6-31+G(d,p) level of theory. Only the more favoured exo approach is depicted here. For more details, see S.I..

Conclusion

To conclude, we have developed an efficient dearomative photocatalyzed (3+2) cycloaddition in a flow system to access diversely functionalized polycyclic 3D-structures under non-acidic conditions. This reaction takes place between various electron-depleted aromatics and a non-stabilized azomethine ylide, photogenerated from a commercial hemiaminal ether through a radical cationic intermediate. Computational studies suggest a stepwise mechanism involving azomethine ylide **1** as the reactive species toward the arene. With supported eosin (silica, Amberlite) as organic photocatalyst either catalyst leaching occurred or poor efficiency was observed. In contrast, with the soluble Rose Bengal, a broad range of substrates from hetarenes (indole, benzofuran, quinoline, pyridine) to naphthalenes and benzenes were efficiently transformed into valuable 3D structures. This photocatalyzed (3+2) cycloaddition under green light irradiation can also advantageously be performed in the friendly ethyl acetate as solvent. An obvious next step is the extension of this methodology to an enantioselective version in the presence of a chiral photocatalyst, which will be undertaken in the near future.

Experimental section

General information

Structural identity was confirmed by ¹H and ¹³C NMR spectroscopy (300 MHz) in deuterated chloroform relative to (CH₃)₄Si. High-resolution mass spectra were recorded in S.I. operating in positive ion mode. IR spectra were recorded as films.

Experimental flow set-ups

Fluidic set-ups were made from PFA tubing (ID 1.6 mm) equipped with PEEK/ETFE connectors and ferrules (IDEX/Upchurch Scientific). Feed and collection lines consisted of PFA, equipped with PEEK/PTFE connectors and ferrules (IDEX/Upchurch Scientific). Solutions were injected with Elite Dual syringe pump from Harvard Apparatus.

Flow dearomative cycloaddition of nitroarenes with supported catalysts

A mixture of the requisite nitroarene (0.2 mmol) and the hemiaminal ether **2** (4 equiv.) were dissolved in MeCN under argon. The resulting solution was then injected at a constant flow rate ($Q = 0.05$ mL.min⁻¹; $t^R = 1.5$ min) in a packed-bed PFA reactor (ID = 1.6 mm, L = 8 cm) containing 100 mg of the required catalyst (EY@SiO₂ or EY@IRA900, 5% w/w) irradiated with green LED. The outlet was then collected in flask containing MeOH. Volatiles were then evaporated in vacuo and the crude product was purified by column chromatography on silica.

Flow dearomative cycloaddition of electron-poor arenes under homogeneous liquid conditions

A mixture of the electron-depleted arene (0.2 mmol), the hemiaminal ether **2** (4 equiv.) and the sodium salt of Rose Bengal (RBNa₂, 4 mol%) were dissolved in MeCN under argon. The resulting solution was injected, through a 2 mL loop, in the flow system, consisting of a PFA tube (L = 50 cm, ID = 1.6 mm) under green LED irradiation. The outlet was then collected in flask containing MeOH. Volatiles were then evaporated in vacuo and the crude product was purified by column chromatography on silica.

Gram-scale flow dearomative cycloaddition of 1,3-dinitronaphthalene in ethyl acetate solvent

A mixture of 1,3-dinitronaphthalene (4 mmol), the hemiaminal ether **2** (4 equiv.) and the disodium salt of Rose Bengal (RBNa₂, 4 mol%) were dissolved in 40 mL of AcOEt under argon. The resulting solution was injected at constant flow ($Q = 2$ mL.min⁻¹; $t^R = 20$ min) in the Vapourtec E-Series flow system ($P = 150$ W), through a PFA tube (ID = 1 mm, L = 3.2 m) under green LED irradiation. The outlet was then collected in flask containing MeOH. Volatiles were then evaporated in vacuo and the crude product was purified by column chromatography on silica to afford **7a** (62% yield).

Acknowledgements

The authors gratefully acknowledge the European France-(Manche)-England cross-border cooperation program INTERREG VA SmartT, co-financed by ERDF, for financial support. Labex SynOrg (ANR-11-LABX-0029), Carnot Institute I2C, graduate school for research XL-Chem (ANR-18-EURE-0020 XL CHEM), Région Normandie Rouen University, CNRS

and INSA Rouen are thanked for financial support as well as CRIANN (Saint Etienne du Rouvray, France) is kindly acknowledged for their generous allocation of computer time.

Keywords: Photocatalysis • Flow chemistry • (3+2) cycloaddition • Electron-poor Aromatics • Azomethine ylide

- [1] F. Lovering, J. Bikker, C. Humblet, *J. Med. Chem.* **2009**, *52*, 6752–6756.
- [2] F. Lovering, *Med. Chem. Commun.* **2013**, *4*, 515–519.
- [3] F. López Ortiz, M. J. Iglesias, I. Fernández, C. M. Andújar Sánchez, G. Ruiz Gómez, *Chem. Rev.* **2007**, *107*, 1580–1691.
- [4] S. P. Roche, J. A. Porco, *Angew. Chem. Int. Ed.* **2011**, *50*, 4068–4093.
- [5] Q. Ding, X. Zhou, R. Fan, *Org. Biomol. Chem.* **2014**, *12*, 4807–4815.
- [6] U. K. Sharma, P. Ranjan, E. V. V. der Eycken, S.-L. You, *Chem. Soc. Rev.* **2020**, *49*, 8721–8748.
- [7] C. Zheng, S.-L. You, *ACS Cent. Sci.* **2021**, *7*, 432–444.
- [8] See for instance: a) I. Chataigner, S. R. Piettre, *Org. Lett.* **2007**, *9*, 4159–4162. b) M. Andreini, F. Chapellas, S. Diab, K. Pasturaud, S. R. Piettre, J. Legros, I. Chataigner, *Org. Biomol. Chem.* **2016**, *14*, 2833–2839.
- [9] N. Kornblum, *Aldrich. Act.* **1990**, *23*, 71–78.
- [10] For a review on 3-nitroindoles reactivity with electron-rich species, see: a) B. Rkein, A. Bigot, L. Birbaum, M. Manneveau, M. De Paolis, J. Legros, I. Chataigner, *Chem. Commun.* **2021**, *57*, 27–44. See also b) H.-Z. Tian, S.-F. Wu, G.-W. Zhuang, G.-Q. Lin, X.-W. Sun, *Org. Biomol. Chem.* **2022**, *20*, 3072–3075. c) W.-C. Yuan, X.-M. Chen, J.-Q. Zhao, Y.-P. Zhang, Z.-H. Wang, Y. You, *Org. Lett.* **2022**, *24*, 826–831 For more recent publications on the reactivity of 3-nitroindoles in (3+2) cycloadditions/annulations
- [11] For reviews on the reactivity of other nitroarenes, see for instance: a) S. R. Nair, B. Baire, *Asian J. Org. Chem.* **2021**, *10*, 932–948. b) N. Wang, J. Ren, K. Li, *Eur. J. Org. Chem.* **2022**, ejoc.202200039.
- [12] a) S. Lee, I. Chataigner, S. R. Piettre, *Angewandte Chemie International Edition* **2011**, *50*, 472–476. b) S. Lee, S. Diab, P. Queval, M. Sebban, I. Chataigner, S. R. Piettre, *Chemistry – A European Journal* **2013**, *19*, 7181–7192.
- [13] a) M. Manneveau, S. Tanii, F. Gens, J. Legros, I. Chataigner, *Org. Biomol. Chem.* **2020**, *18*, 3481–3486. b) M. Manneveau, B. Rkein, D. Cahard, J. Legros, I. Chataigner, *J Flow Chem* **2022**, *12*, 141–145.
- [14] Y. Terao, H. Kotaki, N. Imai, K. Achiwa, *Chemical & Pharmaceutical Bulletin* **1985**, *33*, 896–898.
- [15] M. Baumann, I. Baxendale, S. Ley, *Synlett* **2010**, *2010*, 749–752.
- [16] A. Padwa, W. Dent, *J. Org. Chem.* **1987**, *52*, 235–244.
- [17] Z. Chen, Y. Zhou, T. Hu, H.-Y. Xiong, G. Zhang, *J. Org. Chem.* **2021**, *86*, 7714–7724.
- [18] T. Thierry, C. Lebargy, E. Pfund, T. Lequeux, *J. Org. Chem.* **2019**, *84*, 5877–5885.
- [19] B. Rkein, A. Bigot, L. Birbaum, M. Manneveau, M. D. Paolis, J. Legros, I. Chataigner, *Chem. Commun.* **2021**, *57*, 27–44.
- [20] B. Rkein, M. Manneveau, L. Noël-Duchesneau, K. Pasturaud, M. Durandetti, J. Legros, S. Lakhdar, I. Chataigner, *Chem. Commun.* **2021**, *57*, 10071–10074.
- [21] T. H. Rehm, *Chemistry – A European Journal* **2020**, *26*, 16952–16974.
- [22] L. Buglioni, F. Raymenants, A. Slattery, S. D. A. Zondag, T. Noël, *Chem. Rev.* **2022**, *122*, 2752–2906.
- [23] N. Emmanuel, C. Mendoza, M. Winter, C. R. Horn, A. Vizza, L. Dreesen, B. Heinrichs, J.-C. M. Monbaliu, *Org. Process Res. Dev.* **2017**, *21*, 1435–1438.
- [24] N. Emmanuel, P. Bianchi, J. Legros, J.-C. M. Monbaliu, *Green Chem.* **2020**, *22*, 4105–4115.
- [25] C. Wiles, P. Watts, *Green Chem.* **2014**, *16*, 55–62.
- [26] M. Movsisyan, E. I. P. Delbeke, J. K. E. T. Berton, C. Battilocchio, S. V. Ley, C. V. Stevens, *Chem. Soc. Rev.* **2016**, *45*, 4892–4928.
- [27] J.-C. Monbaliu, A. Cukalovic, C. V. Stevens, in *9. Safety Aspects Related to Microreactor Technology*, De Gruyter, **2014**, pp. 253–282.
- [28] J.-C. M. Monbaliu, J. Legros, *Lab Chip* **2023**, *23*, 1349–1357.
- [29] V. Blanchard, Z. Asbai, K. Cottet, G. Boissonnat, M. Port, Z. Amara, *Org. Process Res. Dev.* **2020**, *24*, 822–826.
- [30] N. A. Romero, D. A. Nicewicz, *Chem. Rev.* **2016**, *116*, 10075–10166.
- [31] B. Rkein, R. Coffinier, M. Powderly, M. Manneveau, M. Sanselme, M. Durandetti, M. Sebban, G. Hamdoun, H. Oulyadi, D. Harrowven, J. Legros, I. Chataigner, *Chem. Commun.* **2022**, *58*, 11807–11810.
- [32] M. Beuvin, M. Manneveau, S. Diab, B. Picard, M. Sanselme, S. R. Piettre, J. Legros, I. Chataigner, *Tetrahedron Letters* **2018**, *59*, 4487–4491.
- [33] R. A. Sheldon, *Green Chem.* **2017**, *19*, 18–43.
- [34] W. J. Hehre, R. Ditchfield, L. Radom, J. A. Pople, *J. Am. Chem. Soc.* **1970**, *92*, 4796–4801.
- [35] P. Muller, *Pure and Applied Chemistry* **1994**, *66*, 1077–1184.

