PAPER

Check for updates

Photocatalytic transformation of aliphatic heterocycles and electron-poor alkenes into functionalized heteroarenes

Lorenzo Di Terlizzi, [ID] *[a,b] Davide Ravelli [ID] [a] and Burkhard König [ID] [b]

We hereby describe the synthesis of functionalized heteroarenes (furans, pyrroles, thiophenes and indoles) thanks to the combination between tetrabutylammonium decatungstate (TBADT) photocatalysis and cobaloxime catalysis. The protocol makes use of aliphatic heterocycles and electron-poor alkenes, that are efficiently converted to the final products through a functionalization/aromatization sequence. Dedicated kinetic and deuteration studies allowed rationalization of the reaction mechanism. Overall, the process is characterized by a high atom economy, with hydrogen gas as the only coupled product.

Green foundation

1. Sustainable synthesis of functionalized heteroarenes *via* a dual (photo)catalytic strategy based on cheap decatungstate anion and cobaloxime complex, with 59 examples and up to 99% yield, with high atom economy and hydrogen gas as the only by-product.

2. Highly efficient and atom-economical preparation of functionalized heteroarenes from cheap and largely abundant starting materials, with hydrogen gas as the only coupled product. The efficiency of this protocol in the synthesis of complex and synthetically useful scaffolds avoids the requirement of known strategies relying on harsh conditions, high temperatures, purposely designed expensive catalysts and hazardous metals.

3. Reaction scale-up is expected to improve green metrics parameters and this is further substantiated by protocol robustness, as testified by the possibility to run the transformation in a telescoped fashion.

Introduction

Heteroaromatic rings such as furans,[1] pyrroles,[2] thiophenes[3] and indoles are substructures of molecules that find application in medicinal chemistry. Their derivatives show various biological effects, such as antitumoral, antipsychotic, antiinflammatory, antioxidant, antifungal, and antimicrobial activities. Furthermore, they are intermediates in organic synthesis with significant synthetic value.[4] Traditional approaches for the preparation of pyrrole, furan and thiophene scaffolds include the Paal–Knorr reaction, which involves an acid-mediated dehydrative cyclization of 1,4-diketone building blocks.[5] Drawbacks of this strategy relate to the difficult preparation of the required 1,4-dicarbonyl precursors and the long reaction times under reflux conditions in acid solution to realize the cyclization. Such severe reaction conditions are therefore not applicable to substrates containing acid-sensitive functional groups, thus limiting the scope of the reaction.[6] Regarding the synthesis of indoles, the oldest and most widely used approach is the Fischer synthesis, occurring through the acid-catalyzed or thermal sigmatropic rearrangement of *N*-aryl hydrazones to generate, after elimination of ammonia, the indole skeleton of interest.[7] Significant disadvantages of this synthesis include the use of toxic hydrazines and the need for elevated temperatures.

Synthetic chemists have long been attracted to such structural motifs and continuously seek new, straightforward methods for their preparation, possibly using abundant feedstocks under mild conditions. This still remains a challenging goal. Recently, powerful synthetic methodologies based on transition metal catalysis to forge functionalized heteroarenes have been investigated. Such approaches typically rely on the metal-catalyzed reduction of pre-functionalized starting materials[8] and involve harsh reaction conditions (high temperatures, hazardous metals).[9] In some instances, the use of purposely prepared ruthenium *N*-Heterocyclic Carbene (NHC) complexes[10] was required, while an alternative iodine-catalyzed process led to a mixture of di- and mono-functionalized structures.[11]

In parallel, photoredox catalysis has been widely applied for the synthesis of functionalized aromatic compounds. Along this line, most approaches decorate a pre-formed heteroaromatic core by C–H or C–X bond activation.[12] An alternative

aPhotoGreen Lab, Department of Chemistry, University of Pavia, Viale Taramelli 12, 27100 Pavia, Italy. E-mail: lorenzo.diterlizzi01@universitadipavia.it
bFakultät für Chemie und Pharmazie, Universität Regensburg, 93053 Regensburg, Germany

strategy uses partially saturated heterocycle precursors, which are functionalized and then aromatized under dihydrogen extrusion. Leonori's group developed such dehydrogenative strategies to prepare aromatic compounds (phenols, anilines, and aromatic aldehydes) from non-aromatic and easily available starting materials employing photocatalysis combined with cobalt as metal co-catalyst to orchestrate the dehydrogenative steps (Scheme 1a).[13] Recently, the synthesis of anilines was realized with the use of a heterogeneous photo-catalyst as well, namely mesoporous graphitic carbon nitride (mpg-CN) in combination with cobaloxime (Scheme 1b).[14] As a matter of fact, cobaloxime catalysis has recently gained attention for its versatile application in dual photocatalytic manifolds to trigger photo-dehydrogenative processes.[15,16]

Based on our expertise, we reasoned that the use of TBADT (tetrabutylammonium decatungstate, $(Bu_4N)_4[W_{10}O_{32}]$)[17] as a photocatalyst for the functionalization of organic substrates *via* C–H functionalization processes *via* a HAT manifold,[18] and its coupling with cobaloxime complexes[19] in a dual (photo) catalytic fashion, could produce $C(sp^2)$–$C(sp^3)$ bonds, in a Alk–H to Alk–C and then Ar–C sequence (where Alk and Ar are aliphatic and aromatic fragments, respectively), *via* a consecutive functionalization/aromatization protocol. Thus, we became interested in the synthesis of functionalized heteroarenes starting from non-aromatic, abundant, inexpensive, and readily available aliphatic heterocycles and electron poor alkenes (Scheme 1c).

Results

At the beginning of our investigation, we set out for the preparation of a furan scaffold starting from commercially available tetrahydrofuran **1a** (THF; 0.1 mmol) and dimethyl fumarate **2a** (0.11 mmol, 1.1 equiv.) in the presence of 7.5 μmol of TBADT (7.5 mol%), dimethylglyoxime (dmgH₂, 25 mol%) and cobalt benzoate (2.5 μmol, 2.5 mol%), all dissolved in dry acetonitrile. Irradiation was performed using a single high-power LED (3 W) with an emission peak centered at 365 nm for 24 hours. Under these conditions, product **3** was obtained in 89% NMR yield and 91% yield after purification *via* silica gel chromatography (entry 1, Table 1). Decreasing the quantity of TBADT reduced the yield of **3** to 70% (entry 2), while increasing the quantity of Co(OBz)₂ to 5 mol% decreased product formation in favor of the direct oxidation of THF to furan (entry 3). Different cobalt catalysts were also screened, which consistently furnished lower yields compared to Co(OBz)₂ (entries 4–7). If the reaction was instead performed with an irradiation wavelength centered at 395 nm, 385 nm or 405 nm, the amount of product formed decreased in all cases (entries 8–10). Finally, switching to dry acetone, dry dimethyl sulfoxide, or an acetonitrile/water mixture (9 : 1 ratio) lowered the obtained quantity of **3** to traces (entries 11–13). Moreover, TBADT and cobalt proved essential to observe the formation of the desired functionalized furan **3**: removing any of the two catalysts led to no product formation (entries 14 and 15), and the same outcome was observed in the dark (light omitted, entry 16). Further information about the optimization process is provided in the SI.

To have insight into the course of the present transformation, we then performed kinetic experiments on the model functionalization of **1a** with **2a** under standard conditions. As shown in Scheme 2, the reaction proceeds rapidly and can be considered completed after 4 hours of irradiation. Interestingly, after one hour, compound **2a** is almost fully con-
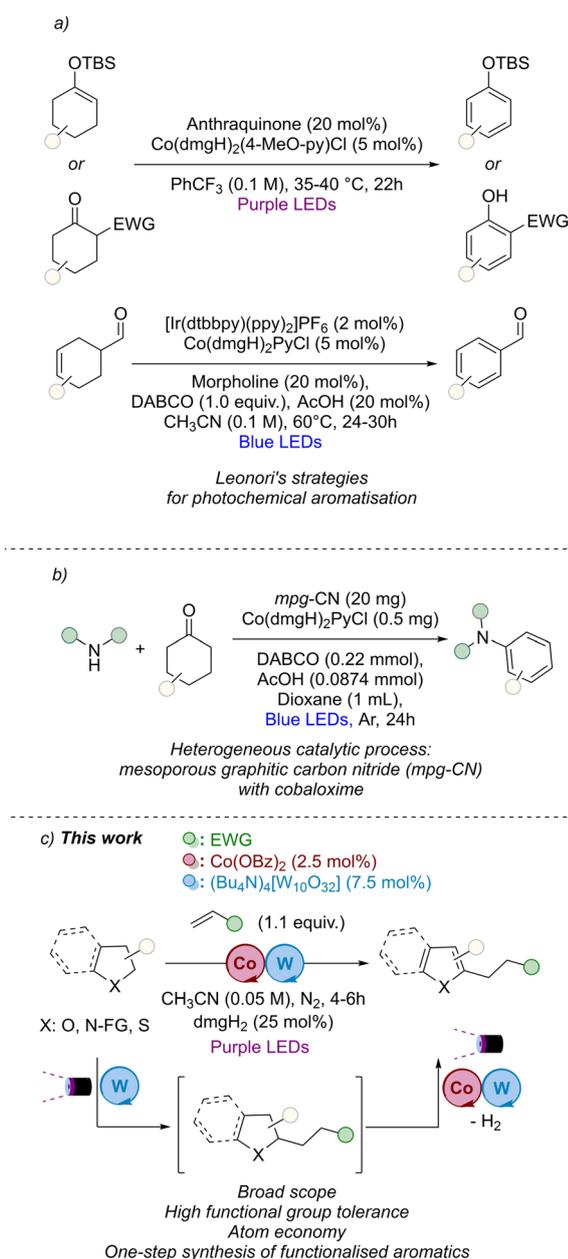

Scheme 1 Reported photochemical strategies for the synthesis of aromatic compounds employing cobaloxime-based catalysts under: (a) homogeneous and (b) heterogeneous conditions. (c) This work: one-pot synthesis of functionalized aromatic molecules employing TBADT and cobaloxime dual-catalysis.

Table 1 Optimization of reaction conditions for the synthesis of functionalized furan **3** [a]
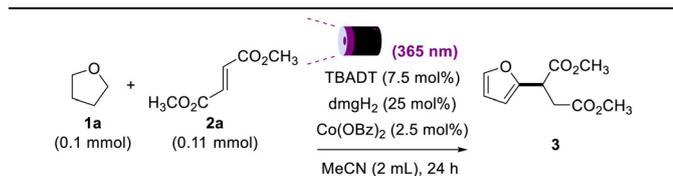
Entry	Deviation from standard conditions	Yield[b]
1	None	89 (91%)[c]
2	TBADT (5.0 mol%)	70%
3	Co(OBz)$_2$ (5.0 mol%)	69%[d]
4	CoBr$_2$ (2.5 mol%)	37%
5	CoI$_2$ (2.5 mol%)	39%
6	Co(OAc)$_2$ (2.5 mol%)	40%
7	Co^{II}(dmgh)$_2$Cl$_2$ (2.5 mol%)	30%
8	*hν* (395 nm)	45%
9	*hν* (385 nm)	66%
10	*hν* (405 nm)	33%
11	Dry acetone	25%
12	Dry DMSO	Traces
13	MeCN : H$_2$O (9 : 1)	31%
14	No TBADT	nd
15	No Co(OBz)$_2$	nd
16	No *hν* (365 nm)	nd

[a] Standard reaction conditions: irradiation carried out with a 365 nm LED (3 W) of 0.1 mmol of **1a**, 0.11 mmol of **2a**, 7.5 mol% TBADT, 2.5 mol% Co(OBz)$_2$ and 25 mol% of dmgH$_2$ dissolved in 2 mL of dry MeCN under nitrogen atmosphere and vigorous stirring. [b] Yields calculated by ^{1}H-NMR analysis employing CH$_2$Br$_2$ as standard. [c] Isolated yield. [d] Yield lowered by the formation of furan as side product.
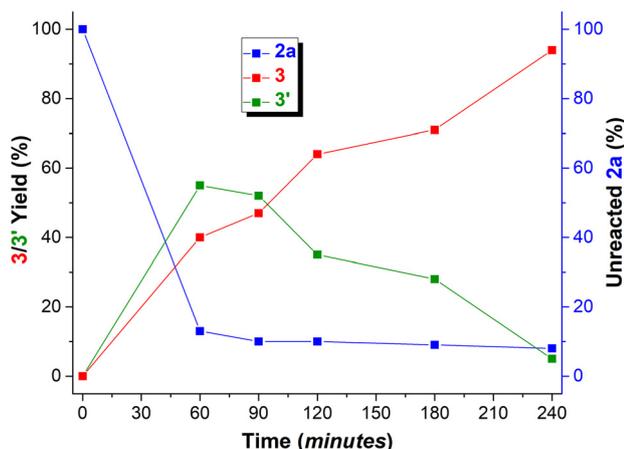
Scheme 2 Kinetic analysis of the photochemical reaction between THF **1a** and dimethyl fumarate **2a**.
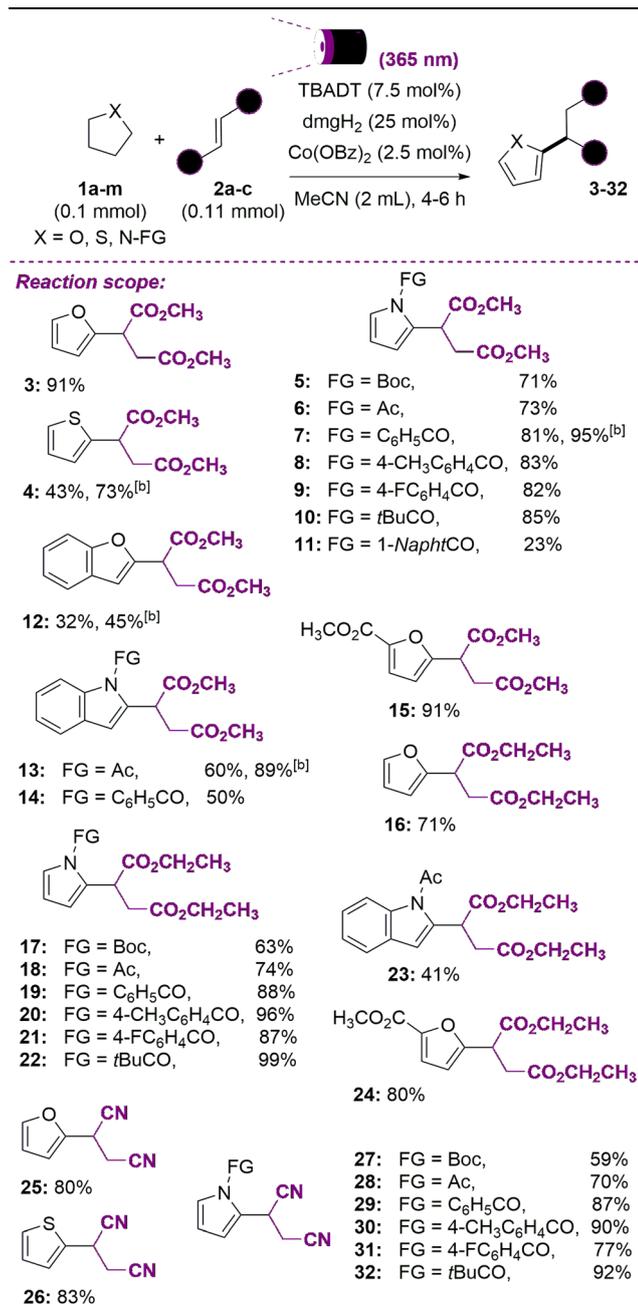
verted into a mixture of two different adducts. The most abundant one is product **3′** resulting from the hydroalkylation of the original double bond in **2a**, which is formed in 55% yield; at the same reaction time, the corresponding aromatized product **3** is generated in 40% yield. Longer irradiation times result in the gradual conversion of **3′** into **3**, indicating that the former is an intermediate compound on the route to the functionalized heteroarene of interest (Scheme 2).

With the optimized conditions in hand, we moved to study the substrate scope of the described transformation for the synthesis of differently functionalized heteroaromatic rings. Initially, we decided to employ symmetric electron-poor olefins to verify the H-donor scope: dimethyl fumarate **2a** was successfully functionalized using tetrahydrothiophene (THT) **1b**, and differently *N*-substituted pyrrolidines **1c–i** (Table 2). The reactions generally proceeded with good yield, affording various heteroaromatic scaffolds. The preparation of product **4** took place in a modest 43% yield. Analysis of the corresponding crude mixture after 2 hours of irradiation revealed the competitive formation of the unsubstituted heteroarene thiophene (see SI for further details). Accordingly, the reaction was also performed following a two-step telescoped approach. Such a strategy relied on the use of TBADT under irradiation to initially functionalize THT with the chosen olefin; subsequently, in the same vial dimethylglyoxime and cobalt benzoate were added, while irradiation of the reaction mixture was continued. This resulted in an increased yield of **4** (73%; see SI for further details). At the same time, the preparation of functionalized *N*-substituted pyrroles was carried out with excellent yields (ranging from 71% in the case of product **5** to 85% for molecule **10**). Pyrrole **7** was produced in 81% yield; however, by performing the reaction with the above-mentioned two-step telescoped approach, its formation increased to 95%. Molecule **11** was obtained in a rather poor yield of isolated product (23%), probably as a result of competitive light absorption by substrate **1i**, which hindered the desired photocatalytic transformation.

Functionalized benzofuran **12** and indoles **13–14** were synthesized as well in 32% (45% *via* the telescoped approach), 60% (89% *via* the telescoped approach) and 50% yield, respectively. Finally, compound **15** was prepared in 91% yield. The use of diethyl fumarate **2b** (instead of **2a**) did not influence the outcome of the reactions. Thus, most of the products were synthesized with comparable yields, including **18** (74%), **19** (88%), **20** (96%), **21** (87%), and **22** (99%). Finally, the functionalization of fumaronitrile **2c** proceeded smoothly, yielding differently functionalized heteroaromatic rings (products **25–32**), with yields ranging from 59% (for **27**) to 92% (for **32**).

Subsequently, non-symmetrical electron-poor olefins were reacted, such as acrylonitrile **2d**, methyl vinyl ketone **2e**, pent-1-en-3-one **2f**, differently substituted benzylidene malononitriles **2g–2k**, 3-benzylidenepentane-2,4-dione **2l** and acrylates **2m–2x**. As shown in Table 3, these radical traps were successfully employed to form new C(sp^2)–C(sp^3) bonds. In particular, the use of acrylonitrile **2d** enabled the preparation of products **33** and **34**. Molecule **33**, however, is highly volatile and was not isolated; nevertheless, its structure was confirmed by ^{1}H NMR

Table 2 Reaction scope for the preparation of functionalized heteroarenes using symmetric electron-poor olefins[a]

Reaction scope:

3: 91%

4: 43%, 73%[b]

12: 32%, 45%[b]

13: FG = Ac,   60%, 89%[b]
14: FG = C₆H₅CO,   50%

5: FG = Boc,   71%
6: FG = Ac,   73%
7: FG = C₆H₅CO,   81%, 95%[b]
8: FG = 4-CH₃C₆H₄CO, 83%
9: FG = 4-FC₆H₄CO,   82%
10: FG = tBuCO,   85%
11: FG = 1-NaphtCO,   23%

15: 91%

16: 71%

17: FG = Boc,   63%
18: FG = Ac,   74%
19: FG = C₆H₅CO,   88%
20: FG = 4-CH₃C₆H₄CO, 96%
21: FG = 4-FC₆H₄CO,   87%
22: FG = tBuCO,   99%

23: 41%

24: 80%

25: 80%

26: 83%

27: FG = Boc,   59%
28: FG = Ac,   70%
29: FG = C₆H₅CO,   87%
30: FG = 4-CH₃C₆H₄CO, 90%
31: FG = 4-FC₆H₄CO,   77%
32: FG = tBuCO,   92%

[a] Standard reaction conditions: irradiation carried out with a 365 nm LED (3 W) of 0.1 mmol of **1a–m**, 0.11 mmol of **2a–c**, 7.5 mol% TBADT, 2.5 mol% Co(OBz)₂ and 25 mol% of dmgH₂ dissolved in 2 mL of dry MeCN under nitrogen atmosphere and vigorous stirring. Isolated yields after silica gel chromatography purification. [b] Yield obtained following the two-step telescoped approach.

analysis of the crude reaction mixture. In the case of less volatile products **35–40**, the obtained yields were up to 76%. The adoption of methyl vinyl ketone **2e** and pent-1-en-3-one **2f** led to the preparation of a range of functionalized ketones (**41–50**) with applicability as key intermediates in organic synthesis.[4,8,9]

Table 3 Reaction scope for the preparation of functionalized heteroaromatics using electron-poor olefins[a]

Reaction scope:

33: 50%[b]

34: 61%[b]

35: FG = Boc,   60%
36: FG = Ac,   68%
37: FG = C₆H₅CO,   54%
38: FG = 4-CH₃C₆H₄CO, 74%
39: FG = 4-FC₆H₄CO,   70%
40: FG = tBuCO,   76%

41: FG = Boc,   78%
42: FG = C₆H₅CO,   45%
43: FG = 4-CH₃C₆H₄CO, 31%
44: FG = 4-FC₆H₄CO,   74%
45: FG = tBuCO,   85%

46: FG = Boc,   51%
47: FG = C₆H₅CO,   54%
48: FG = 4-CH₃C₆H₄CO, 53%
49: FG = 4-FC₆H₄CO,   63%
50: FG = tBuCO,   88%

59: 22%

60: 31%[c]

61: 34%[c]

51: FG = Boc,   X = H,   23%
52: FG = C₆H₅CO, X = H,   34%
53: FG = Boc,   X = Cl,   32%
54: FG = C₆H₅CO, X = Cl,   41%
55: FG = Boc,   X = F,   59%
56: FG = C₆H₅CO, X = F,   53%
57: FG = C₆H₅CO, X = Br,   31%
58: FG = C₆H₅CO, X = CH₃, 43%
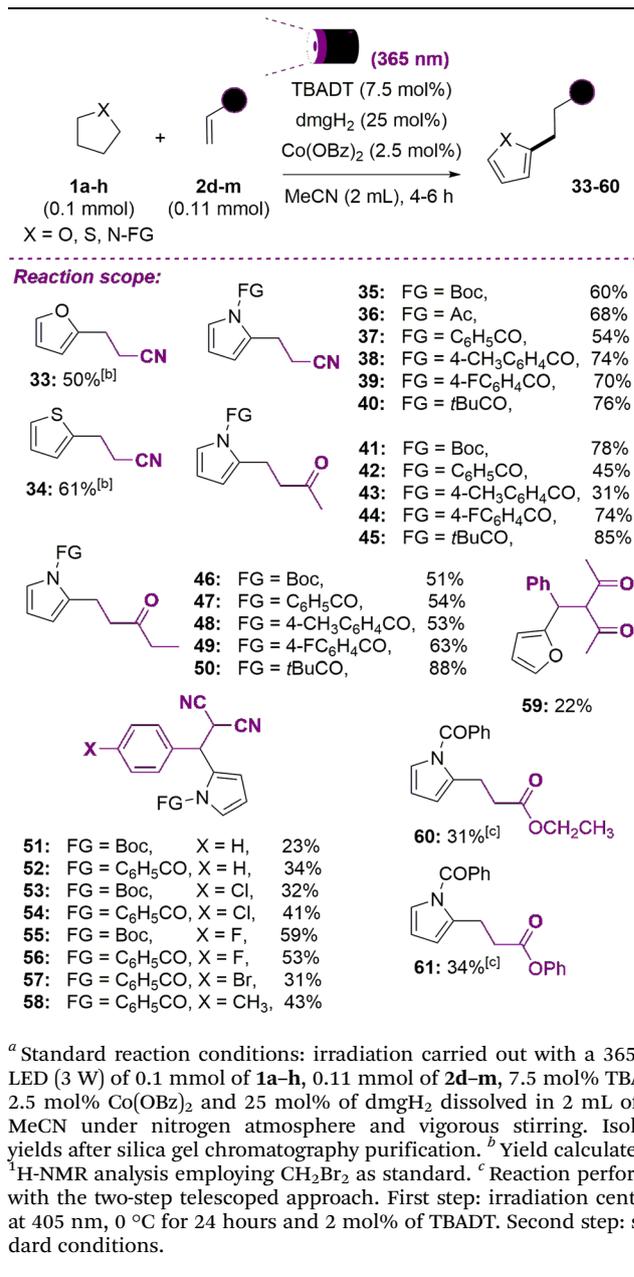
[a] Standard reaction conditions: irradiation carried out with a 365 nm LED (3 W) of 0.1 mmol of **1a–h**, 0.11 mmol of **2d–m**, 7.5 mol% TBADT, 2.5 mol% Co(OBz)₂ and 25 mol% of dmgH₂ dissolved in 2 mL of dry MeCN under nitrogen atmosphere and vigorous stirring. Isolated yields after silica gel chromatography purification. [b] Yield calculated by ¹H-NMR analysis employing CH₂Br₂ as standard. [c] Reaction performed with the two-step telescoped approach. First step: irradiation centered at 405 nm, 0 °C for 24 hours and 2 mol% of TBADT. Second step: standard conditions.

The yields of such products ranged from moderate in the case of molecule **43** (31%) to very good, as in the case of **41, 44, 45** and **50**, which were isolated in 74–88% yield in a single photochemical synthetic step. In the case of benzylidene malononitriles, diverse functionalized heteroarenes were successfully synthesized, although in variable yields, ranging from 23% (product **51**) to 59% (adduct **55**). Malononitriles with electron-withdrawing groups afforded the corresponding products with slightly higher yields, as in the case of the 4-chloro (**2h**) and 4-fluoro (**2i**) substituted starting materials. Furthermore, 3-benzylidenepentane-2,4-dione **2l** was successfully employed for the synthesis of molecule **59** in a serviceable yield (22%).

The functionalization of acrylates required the adoption of rather specific conditions, as they could undergo competitive polymerization. Therefore, to avoid this problem, the two-step telescoped approach was adopted, where some fine-tuning of reaction conditions was implemented in the first step: a lower amount of TBADT (2.0 mol%), a lower temperature (reaction performed at 0 °C), and an irradiation wavelength centered at 405 nm were employed to this end. Under these conditions, the first step enabled the complete conversion of the acrylate within 24 hours. Next, the missing reaction components (cobalt co-catalyst, dimethylglyoxime, and the remaining quantity of TBADT) were added to the crude reaction mixture, allowing for the formation of compounds **60–61** in moderate yields (Table 3).

Next, we performed our model reaction between deuterated tetrahydrofuran **1a-d_8** and dimethyl fumarate **2a** following the general procedure described. As a result, product **3-d_3** was isolated in 88% yield, offering the proof-of-concept that our strategy can be exploited for the preparation of functionalized, fully deuterated, heteroarenes (Scheme 3a). Instead, when the same reaction was performed by employing an equimolar mixture of **1a** and **1a-d_8**, products **3** and **3-d_3** were obtained after purification of the photolyzed reaction mixture in $a > 3:1$ ratio, highlighting a kinetic isotope effect (KIE) of 3.33 calculated by means of ^{1}H-NMR analysis (Scheme 3b; see also SI for further details). Finally, the reaction was performed in the presence of
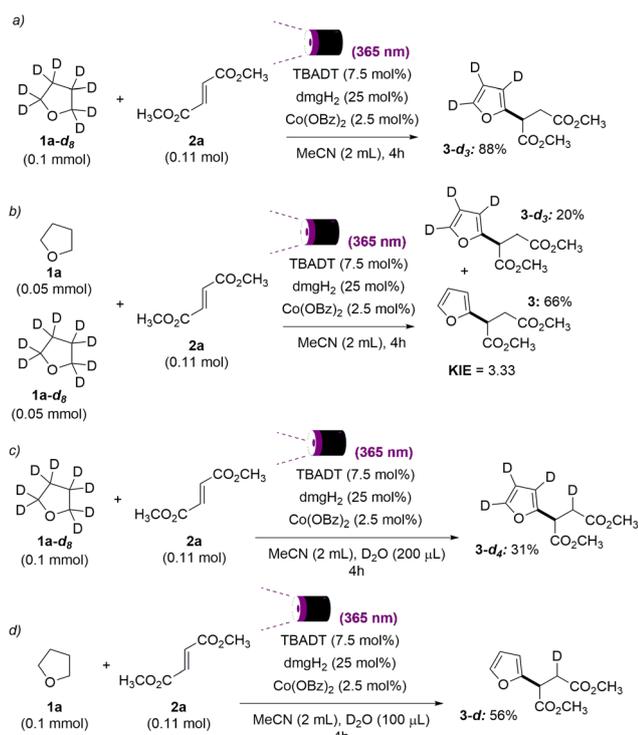

Scheme 4 Reaction scheme for the preparation of **3** on one-mmol scale, along with a picture of the obtained product. Two vials were employed to study the reproducibility of the method.

a partially deuterated reaction medium (up to 200 μL of D$_2$O were added). As a result, when the reaction was performed with **1a-d_8**, product **3-d_4** was isolated in 31% yield. On the other hand, when the reaction was performed with **1a**, product **3-d** was obtained in 56% yield. Both compounds were fully characterized by GC-MS and ^{1}H-NMR analysis, confirming the successful deuterium labelling (Scheme 3c and d). Finally, we also confirmed that hydrogen gas is formed as the only coupled product of the reaction *via* headspace GC analysis (see SI for further details). In this regard, it is important to stress that the liberated hydrogen gas could be conveniently employed in subsequent transformations, provided that the present protocol is carried out under proper conditions.[20]

The scalability of the process has been also investigated, starting from 1 mmol of **1a**, consistently employed in the reaction with dimethyl fumarate **2a**. To lower the amount of solvent, the reaction was performed with 5 mL of dry acetonitrile only. As depicted in Scheme 4, the reaction was completed after 16 hours of irradiation, delivering 180 mg of product **3** after purification (85% yield, average of two replicates). Green metric parameters were calculated to evaluate the sustainability character of our proposed method (see SI for further details). Thus, atom economy is almost quantitative (>98%): the starting materials are essentially converted into the targeted molecule with minimal loss of atoms, since the only coupled product is hydrogen gas. The calculated E-factor value is 83.2 kg kg^{-1} for the model reaction delivering **3** under standard conditions. Such value, however, can be significantly improved if the large scale (1 mmol) reaction is considered (E-factor drops to 23.7 kg kg^{-1}), showcasing the potential of the proposed process toward the design of environmentally friendly and efficient transformations.

Scheme 3 a) Reaction performed with **1a-d_8** for the synthesis of functionalized deuterated heteroarenes. (b) Kinetic Isotopic Effect (KIE) experiment carried out employing **1a-d_8** and **1a**. (c and d) Reactions performed in deuterated medium.

Conclusions

In conclusion, saturated heterocycles, such as THF, THT, various pyrrolidines, protected indolines and dihydrobenzofuran, smoothly underwent photocatalytic C–H cleavage and the corresponding *C*-centered radicals were trapped in Giese-type reactions with electron-poor alkenes as reaction partners. Thanks to the presence of a cobaloxime co-catalyst, the resulting intermediate adducts were directly aromatized to the corresponding heteroarene derivatives by elimination of hydrogen gas, either in a single-step fashion or through two subsequent telescoped steps (see Fig. S1 in the SI for the proposed

mechanistic scenario). The reported synthetic protocol offers an atom-economical approach for the preparation of functionalized heteroarenes in a robust and efficient fashion, which can also be easily scaled, while improving its green character (E-factor significantly decreases upon scale-up). Overall, this methodology allows for the synthesis of complex scaffolds useful in organic synthesis as key intermediates[21–23] in a versatile, straightforward and functional-group tolerant strategy, starting from abundant and cheap substrates.

Author contributions

Lorenzo Di Terlizzi: conceptualization, investigation, methodology, visualization, writing – original draft and editing. Davide Ravelli: supervision, visualization, writing – original draft and editing. Burkhard König: supervision, visualization, writing – original draft and editing.

Conflicts of interest

There are no conflicts to declare.

Data availability

The authors confirm that the data supporting the findings of this study are available within the article and its supplementary information (SI). Supplementary information: materials and methods, detailed experimental procedures, products characterization; ^{1}H, ^{13}C and ^{19}F-NMR spectra. See DOI: https://doi.org/10.1039/d5gc04418a.

Acknowledgements

References

1 H. Saeid, H. Al-sayed and M. Bader, *Alq. J. Med. App. Sci.*, 2023, **6**(1), 44–58.

2 (*a*) H. Kuznietsova, N. Dziubenko, I. Byelinska, V. Hurmach, A. Bychko, O. Lynchak and V. Rybalchenko, *J. Drug Targeting*, 2019, **28**(5), 547–563; (*b*) S. S. Gholap, *Eur. J. Med. Chem.*, 2016, **110**, 13–31; (*c*) V. Bhardwaj, D. Gumber, V. Abbot, S. Dhiman and P. Sharma, *RSC Adv.*, 2015, **5**, 15233–15266; (*d*) B. H. Ganesh, A. G. Raj, B. Aruchamy, P. Nanjan, C. Drago and P. Ramani, *ChemMedChem*, 2024, **19**, e202300447; (*e*) L. Borkotoky and R. A. Maurya, *Eur. J. Org. Chem.*, 2023, e202300822; (*f*) A. Nicolai, V. N. Madia, A. Messore, D. D. Vita, A. D. Leo, D. Ialongo, V. Tudino, E. Tortorella, L. Scipione, S. Taurone, T. Pergolizzi, M. Artico, R. D. Santo, R. Costi and S. Scarpa, *Pharmaceuticals*, 2021, **14**, 564; (*g*) B.-C. Ivan, S.-F. Barbuceanu, C. M. Hotnog, A. I. Anghel, R. Viorel Ancuceanu, M. A. Mihaila, L. I. Brasoveanu, S. Shova, C. Draghici, O. T. Olaru, G. M. Nitulescu, M. Dinu and F. Dumitrascu, *Int. J. Mol. Sci.*, 2022, **23**, 8854; (*h*) M. K. Scott, G. E. Martin, D. L. Di Stefano, C. L. Fedde, M. J. Kukla, D. L. Barrett, W. J. Baldy, R. J. Elgin, J. M. Kesslick, J. R. Mathiasen, R. P. Shank and J. L. Vaught, *J. Med. Chem.*, 1992, **35**, 552–558; (*i*) G. Campiani, S. Butini, C. Fattorusso, B. Catalanotti, S. Gemma, V. Nacci, E. Morelli, A. Cagnotto, I. Mereghetti, T. Mennini, M. Carli, P. Minetti, M. A. D. Cesare, D. Mastroianni, N. Scafetta, B. Galletti, M. A. Stasi, M. Castorina, L. Pacifici, M. Vertechy, S. D. Serio, O. Ghirardi, O. Tinti and P. Carminati, *J. Med. Chem.*, 2004, **47**, 143–157; (*j*) S. S. Fatahala, S. Hasabelnaby, A. Goudah, G. I. Mahmoud and R. H. A.-E. Hameed, *Molecules*, 2017, **22**, 461; (*k*) C. Battilocchio, G. Poce, S. Alfonso, G. C. Porretta, S. Consalvi, L. Sautebin, S. Pace, A. Rossi, C. Ghelardini, L. D. C. Mannelli, S. Schenone, A. Giordani, L. D. Francesco, P. Patrignani and M. Biava, *Bioorg. Med. Chem.*, 2013, **21**, 3695–3701; (*l*) P. D. MacLean, E. E. Chapman, S. L. Dobrowolski, A. Thompson and L. R. C. Barclay, *J. Org. Chem.*, 2008, **73**, 6623–6635; (*m*) G. M. Reddy, A. Camilo Jr and J. R. Garcia, *Bioorg. Chem.*, 2021, **106**, 104465; (*n*) R. H. A. El-Hameed, A. I. Sayed, S. M. Ali, M. A. Mosa, Z. M. Khoder and S. S. Fatahala, *J. Enzyme Inhib. Med. Chem.*, 2021, **36**, 2183–2198; (*o*) A. J. Castro, G. R. Gale, G. E. Means and G. Tertzakian, *J. Med. Chem.*, 1967, **10**, 29–32.

3 (*a*) X. Peng, G. Yin, K. Wu, G. Wu, J. Chen and Z. Wang, *Asian J. Org. Chem.*, 2024, **13**, e202300631; (*b*) D. Das, A. Das, S. Sutradhar, P. Sarkar and B. N. Ghosh, in *S-Heterocycles Retrospect, Prospects, and Biological Applications*, ed. S. Kulkarni, H. Akolkar, V. M. Khedkar and A. K. Haghi, Royal Society of Chemistry, 2024, 11, 317–351; (*c*) D. E. Kim, Y. Kim, D.-H. Cho, S.-Y. Jeong, S.-B. Kim, N. Suh, J. S. Lee, E. K. Choi, J.-Y. Koh, J. J. Hwang and C.-S. Kim, *Mol. Cells*, 2015, **38**, 138–144; (*d*) M.-L. Schweizer, J.-P. Furuno, A.-D. Harris and E.-N. Perencevich, *BMC Infect. Dis.*, 2011, **11**, 1–7; (*e*) C. Wu, E. R. Decker, N. Blok, H. Bui, T. J. You, J. Wang, A. R. Bourgoyne, V. Knowles, K. L. Berens, G. W. Holland, T. A. Brock and R. A. F. Dixon, Discovery, *J. Med. Chem.*, 2004, **47**, 1969–1986; (*f*) I. Jarak, M. Kralj, L. Suman, G. Pavlovic, J. Dogan, I. Piantanida, M. Zinic, K. Pavelic and G. Karminski-Zamola, *J. Med. Chem.*, 2005, **48**, 2346–2360; (*g*) M. Khalifa, E. Abdel-Latif and J. Gobouri, *Heterocycl. Chem.*, 2015, **52**, 674–680; (*h*) H. Ji and X. Zhang, Thiophene-Based Polymers: Synthesis and Applications, in *Sulfur–Containing Polymers: From Synthesis to Functional Materials*, ed. X.-H. Zhang and P. Theato, Wiley-VCH Gmbh, Weinheim, 2021, pp. 265–304.

4 (a) J. A. Law, D. P. Callen, E. L. Paola, G. Gomes and J. H. Frederich, *Org. Lett.*, 2022, **24**(36), 6499–6504; (b) Y. Hayashi, M. Nakamura, S. Nakao, T. Inoue and M. Shoji, *Angew. Chem., Int. Ed.*, 2002, **41**(21), 4079–4082; (c) A. Kouridaki, T. Montagnon, M. Tofi and G. Vassilikogiannakis, *Org. Lett.*, 2012, **14**(9), 2374–2377; (d) B. T. Sargent and E. J. Alexanian, *J. Am. Chem. Soc.*, 2016, **138**(24), 7520–7523; (e) P. La Manna, M. De Rosa, C. Talotta, A. Rescifina, G. Floresta, A. Soriente, C. Gaeta and P. Neri, *Angew. Chem., Int. Ed.*, 2020, **59**(2), 811–818.

5 (a) C. Paal, *Ber. Dtsch. Chem. Ges.*, 1884, **17**, 2756; (b) L. Knorr, *Ber. Dtsch. Chem. Ges.*, 1884, **17**, 2863.

6 S. Khaghaninejad and M. M. Heravi, Chapter Three - Paal–Knorr Reaction in the Synthesis of Heterocyclic Compounds, *Adv. Heterocycl. Chem.*, 2014, **111**, 95–146.

7 S. Wagaw, B. H. Yang and S. L. Buchwald, *J. Am. Chem. Soc.*, 1998, **120**(26), 6621–6622.

8 (a) S. R. Shengule, A. Willis and S. G. Pyne, *Tetrahedron*, 2012, **68**, 1207–1215; (b) J. Yun, D. Kim and H. Yun, *Chem. Commun.*, 2005, 5181–5183; (c) D. Kim, B.-M. Parka and J. Yun, *Chem. Commun.*, 2005, 1755–1757; (d) B. C. Ranu, J. Dutta and S. K. Guchhait, *Org. Lett.*, 2001, **3**(16), 2603–2605; (e) C. Campalani, M. Durai, W. Leitner and A. Bordet, *Green Chem.*, 2025, **27**, 2666–2671; (f) K. L. Luska, A. Bordet, S. Tricard, I. Sinev, W. Grünert, B. Chaudret and W. Leitner, *ACS Catal.*, 2016, **6**(6), 3719–3726.

9 (a) P. Jones and P. Knochel, *J. Chem. Soc., Perkin Trans. 1*, 1997, 3117–3118; (b) P. Andreetta, R. T. Martin, C. Souilah, Á. Rentería-Gómez, Z. Song, Y. K. Bayat, S. Ivlev, O. Gutierrez and A. Casitas, *Angew. Chem., Int. Ed.*, 2023, **62**, e202310129; (c) V. Korochantsev, A. Fatkulin, E. Podyacheva, A. Boldyrev, O. I. Afanasyev and D. Chusov, *Eur. J. Org. Chem.*, 2025, (4), e202401108; (d) B. Anxionnat, D. G. Pardo, G. Ricci and J. Cossy, *Org. Lett.*, 2011, **13**(15), 4084–4087.

10 S. Burling, B. M. Paine, D. Nama, V. S. Brown, M. F. Mahon, T. J. Prior, P. S. Pregosin, M. K. Whittlesey and J. M. J. Williams, *J. Am. Chem. Soc.*, 2007, **129**(7), 1987–1995.

11 B. Das, N. Chowdhury and K. Damodar, *Tetrahedron Lett.*, 2007, **48**, 2867–2870.

12 I. Ghosh, L. Marzo, A. Das, R. Shaikh and B. König, *Acc. Chem. Res.*, 2016, **49**(8), 1566–1577.

13 (a) H. P. Caldora, Z. Zhang, M. J. Tilby, O. Turner and D. Leonori, *Angew. Chem., Int. Ed.*, 2023, **62**, e202301656; (b) H. Zhao, H. P. Caldora, O. Turner, J. J. Douglas and D. Leonori, *Angew. Chem., Int. Ed.*, 2022, **61**, e202201870; (c) S. U. Dighe, F. Juliá, A. Luridiana, J. J. Douglas and D. Leonori, *Nature*, 2020, **584**, 75–81.

14 S. Zoltowska, S. Mazzanti, S. Stolfi, J. Xu, M. Huš, A. Oberlintner, M. Pavlin, P. Ghigna, B. Likozar, P. Torelli, L. Braglia, D. Ravelli, M. Fagnoni, I. Agirrezabal-Telleria, M. Antonietti, P. Giusto and O. Savateev, *ChemSusChem*, 2025, **18**, e202402439.

15 H. Zhao, A. J. McMillan, T. Constantin, R. C. Mykura, F. Juliá and D. Leonori, *J. Am. Chem. Soc.*, 2021, **143**(36), 14806–14813.

16 A. Mandal, M. Lim, L. Zhang, K.-W. Huang and S. U. Dighe, *ACS Catal.*, 2025, **15**(12), 9976–10004.

17 (a) L. Capaldo and D. Ravelli, *Org. Lett.*, 2021, **23**(6), 2243–2247; (b) A. Capucciati, L. Baraglia, E. Cassera, D. Merli, L. Capaldo and D. Ravelli, *Chem. – Eur. J.*, 2024, **30**, e202402986; (c) V. De Waele, O. Poizat, M. Fagnoni, A. Bagno and D. Ravelli, *ACS Catal.*, 2016, **6**(10), 7174–7182; (d) L. Capaldo, L. L. Quadri, D. Merli and D. Ravelli, *Chem. Commun.*, 2021, **57**, 4424–4427; (e) D. Ravelli, A. Albini and M. Fagnoni, *Chem. – Eur. J.*, 2011, **17**, 572–579; (f) Z. Wen, D. Pintossi, M. Nuño and T. Noël, *Nat. Commun.*, 2022, **13**, 6147; (g) D. Ravelli, M. Fagnoni, T. Fukuyama, T. Nishikawa and I. Ryu, *ACS Catal.*, 2018, **8**(1), 701–713; (h) A. Parodi, A. Jorea, M. Fagnoni, D. Ravelli, C. Samorì, C. Torri and P. Galletti, *Green Chem.*, 2021, **23**, 3420–3427; (i) A. Jorea, R. Chessa and D. Ravelli, *Adv. Synth. Catal.*, 2025, **367**, e202500012; (j) M. Leone, D. Arnaldi and M. Fagnoni, *Org. Chem. Front.*, 2025, **12**, 4970–4979.

18 (a) L. Capaldo, D. Ravelli and M. Fagnoni, *Chem. Rev.*, 2022, **122**(2), 1875–1924; (b) L. Capaldo and D. Ravelli, *Eur. J. Org. Chem.*, 2017, 2056–2071; (c) S. Protti, M. Fagnoni and D. Ravelli, *ChemCatChem*, 2015, **7**, 1516–1523; (d) L. Capaldo, L. L. Quadri and D. Ravelli, *Green Chem.*, 2020, **22**, 3376–3396; (e) M. Galeotti, M. Salamone and M. Bietti, *Chem. Soc. Rev.*, 2022, **51**, 2171–2223.

19 (a) B.-C. Hong and R. R. Indurmuddam, *Org. Biomol. Chem.*, 2024, **22**, 3799–3842; (b) P. P. Singh, S. Sinha, P. Gahtori, S. Tivari and V. Srivastava, *Org. Biomol. Chem.*, 2024, **22**, 2523–2538; (c) B. Sun, J. Wang, S. Zhou, J. Xu, X. Zhuang, Z. Meng, Y. Xu, Z. Zhang and C. Jin, *ACS Catal.*, 2024, **14**(14), 11138–11146; (d) Ritu, D. Kolb, N. Jain and B. König, *Adv. Synth. Catal.*, 2023, **365**, 605–611; (e) J. G. West, D. Huang and E. J. Sorensen, *Nat. Commun.*, 2015, **6**, 10093; (f) D. J. Abrams, J. G. West and E. J. Sorensen, *Chem. Sci.*, 2017, **8**, 1954–1959; (g) D. Kolb, A. A. Almasalma, M. Morgenstern, L. Ganser, I. Weidacher and B. König, *ChemPhotoChem*, 2023, **7**, e202300167; (h) D. Kolb, M. Morgenstern and B. König, *Chem. Commun.*, 2023, **59**, 8592–8595; (i) H. Cao, Y. Kuang, X. Shi, K. L. Wong, B. B. Tan, J. M. C. Kwan, X. Liu and J. Wu, *Nat. Commun.*, 2020, **11**, 1956.

20 SFMT (stop-flow microtubing) reactors have been successfully used in hydrogen-evolution protocols, enabling the proper management of volatile and gaseous reagents, intermediates and products; see: D.-S. Li, T. Liu, Y. Hong, C.-L. Cao, J. Wu and H.-P. Deng, *ACS Catal.*, 2022, **12**(8), 4473–4480.

21 (a) F. Jafarpour, H. Hazrati and M. Darvishmolla, *Adv. Synth. Catal.*, 2014, **356**, 3784; (b) A. Domagala, T. Jarosz and M. Lapkowski, *Eur. J. Med. Chem.*, 2015, **100**, 176–187; (c) P. Dydio, D. Lichosyt and J. Jurczak, *Chem. Soc. Rev.*, 2011, **40**, 2971–2985; (d) M. Movassaghi, D. S. Siegel and S. Han, *Chem. Sci.*, 2010, **1**, 561–566.

22 (a) C. O. Kappe, S. S. Murphree and A. Padwa, *Tetrahedron*, 1997, **53**, 14179–14233; (b) J. H. Rigby and F. C. Pigge, in *Organic Reactions*, ed. L. A. Paquette, Wiley & Sons,

New York, 1997; vol. 51, pp 351–478; (*c*) S. P. Tanis, E. D. Robinson, M. C. McMills and W. Watt, *J. Am. Chem. Soc.*, 1992, **114**, 8349–8362; F. Nuyttens, G. Appendino and P. J. DeClercq, *Synlett*, 1991, 526–528; (*d*) D. L. Wright, C. R. Whitehead, E. H. Sessions, I. Ghiviriga and D. A. Frey, *Org. Lett.*, 1999, **1**, 1535–1538; (*e*) K. D. Moeller, *Tetrahedron*, 2000, **56**, 9527–9554; (*f*) C. W. Bielawski and R. H. Grubbs, *Angew. Chem., Int. Ed.*, 2000, **39**, 2903–2906; (*g*) K. Paulvannan and J. W. Jacobs, *Tetrahedron*, 1999, **55**, 7433–7240; (*h*) D. S. Lee, J. K. Sello and S. L. Schreiber, *Org. Lett.*, 2000, **2**, 709–712; (*i*) L. Weber, K. Illgen and M. Almstetter, *Synlett*, 1999, 366–374.

23 (*a*) N. R. Deprez, D. Kalyani, A. Krause and M. S. Sanford, *J. Am. Chem. Soc.*, 2006, **128**, 4972–4973; (*b*) B. S. Lane, M. A. Brown and D. Sames, *J. Am. Chem. Soc.*, 2005, **127**, 8050–8057; (*c*) X. Wang, B. S. Lane and D. Sames, *J. Am. Chem. Soc.*, 2005, **127**, 4996–4997; (*d*) T. Ishiyama, Y. Nobuta, J. F. Hartwig and N. Miyaura, *Chem. Commun.*, 2003, 2924–2925; (*e*) J. Takagi, K. Sato, J. F. Hartwig, T. Ishiyama and N. Miyaura, *Tetrahedron Lett.*, 2002, **43**, 5649–5651.