Green Chemistry

PAPER

View Article Online
View Journal | View Issue

Cite this: *Green Chem.*, 2026, **28**, 4962

Turning light into carbinols: a metal-free radical strategy for pyridine based triaryl scaffolds

Matteo Leone * and Maurizio Fagnoni *

Triaryl carbinols are key building blocks in pharmaceuticals, agrochemicals, and functional materials, yet their synthesis typically relies on hazardous organometallic reagents or costly transition-metal catalysts. Here we report a metal-free, light-driven strategy for their preparation under mild and sustainable conditions. The method exploits the dual role of 2-propanol, which acts as a hydrogen donor in the photomediated HAT process with benzophenone, while the resulting ketyl radical selectively reduces 4-cyanopyridines *via* electron transfer, enabling a radical–radical coupling that furnishes triaryl carbinols in a single step. The protocol delivers excellent yields (up to 99%) across a broad substrate scope, encompassing diverse benzophenones and pyridines. Its robustness was demonstrated in batch, flow, and under simulated sunlight, and the methodology enabled the efficient synthesis of analogues of bioactive molecules of pharmaceutical relevance. Notably, the optimized protocol scores >80 on the EcoScale (indicating excellent sustainability in terms of reagent safety, energy input, and workup efficiency). This work establishes a versatile and greener platform for the synthesis of triaryl carbinols with strong potential for industrial and medicinal applications.

Received 23rd October 2025,
Accepted 16th February 2026

DOI: 10.1039/d5gc05657h

rsc.li/greenchem

Green foundation

1. This work advances green chemistry by introducing a metal-free, visible-light-driven synthesis of triaryl carbinols eliminating the need for hazardous organometallic reagents and costly transition-metal catalysts. The reaction proceeds under mild conditions, achieving excellent atom economy. Its scalability further underscores its practicality and low environmental impact. The preparation of analogues of bioactive compounds shows excellent results providing an efficient and user-friendly method.
2. Highly efficient (up to 99% yield) and atom-economical (AE = 93%) synthesis of triaryl carbinols was achieved from inexpensive and readily available starting materials. The protocol employs green solvents and harnesses light as a safe energy source. A high EcoScale score (86) underscores the superior sustainability of this method compared to traditional metal based protocols.
3. Triaryl carbinols obtained, particularly on a large scale, could be purified by simple crystallization, eliminating the need for extensive solvent use.

Introduction

The pursuit of greener methodologies for the synthesis of chemical products has been a central objective in recent decades.[1] In particular, the pharmaceutical and fine chemical sectors aim to reduce their carbon footprint by adopting lower-carbon fuels, improving energy efficiency, and employing catalytic processes.[2] Yet, many established transformations still rely heavily on organometallic reagents, which are hazardous, when handled in large quantities, but also raise significant environmental concerns due to the challenges associated with their disposal.[3] In this context, open-shell reactions offer valuable opportunities to access new reactivity modes and improve existing methods,[4] thereby contributing to more efficient synthesis of fine chemicals. Among these, light-mediated processes have emerged as powerful tools, promoting a wide range of transformations under mild conditions by harnessing photon energy as a green and traceless reagent.[5] Over the past decades, the scope of such reactions has expanded beyond academia, demonstrating considerable potential for application on an industrial scale.[6] Within this framework, we turned our attention to the synthesis of triaryl carbinols (TACs), a valuable class of compounds widely employed as key building blocks in pharmaceuticals, dyes, and functional materials.[7] Recent studies have underscored their broad potential, as TAC derivatives display significant biological activities, including antifungal (*e.g.* fenarimol),[8] anticancer,[9] and antiviral properties,[10] while also serving as essential intermediates in the preparation of commercially available drugs (Fig. 1a).[11] Their synthesis often makes use of benzophenones as reagents and typically relies on a limited number of strategies: (i) Grignard reactions of aryl bromides with benzophenones;[12] (ii) metal-mediated

PhotoGreen Lab, Department of Chemistry, University of Pavia, Viale Taramelli 12, 27100 Pavia, Italy. E-mail: maurizio.fagnoni@unipv.it

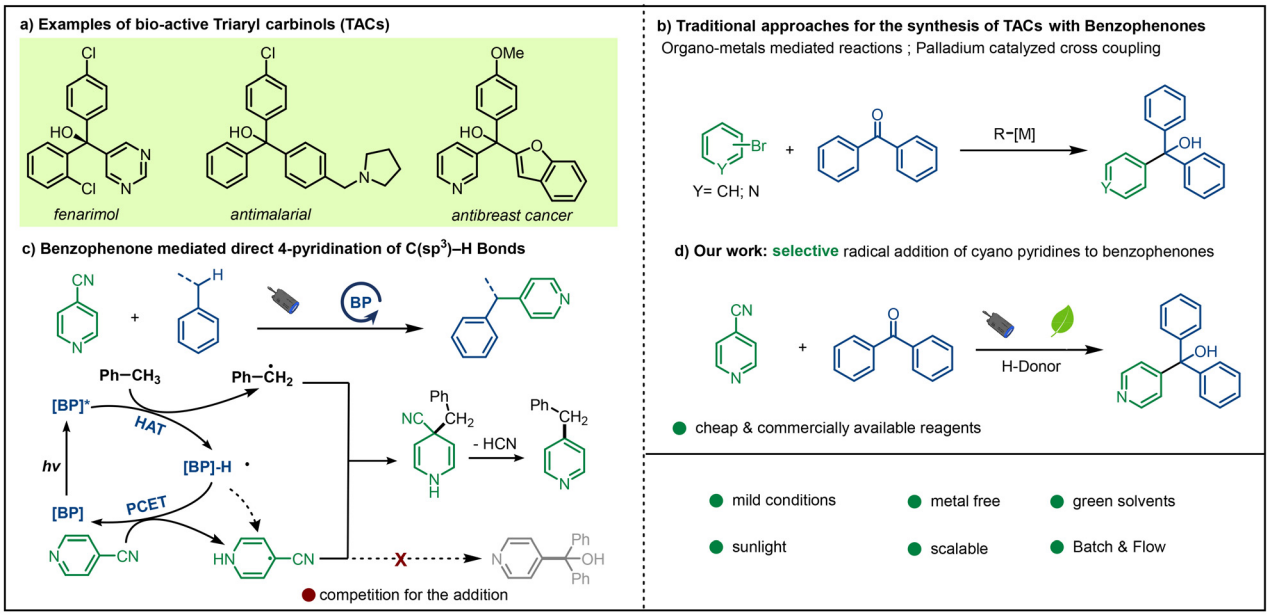


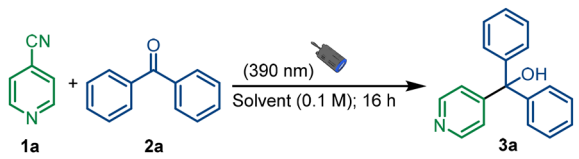
Fig. 1 (a) Bio-activity of various TACs (b) Polar approaches for the synthesis of TACs (c) application of benzophenone (**BP**) as photocatalyst for 4-pyridination of C(sp^3)–H bonds. (d) Our work.

reduction of cyanoarenes in the presence of benzophenones;[13] and (iii) transition-metal catalyzed addition of arylboronates to benzophenones (Fig. 1b).[14] To broaden the structural diversity and enhance the potential biological relevance of TACs, recent efforts have focused on incorporating heteroaromatic rings into their framework.[15] The introduction of such motifs is known to significantly influence physicochemical and pharmacological properties, often leading to improved bioactivity.[16] Developing an efficient and general strategy for their direct incorporation therefore remains highly desirable. Among the approaches reported for introducing heteroaromatic units,[17] heteroaromatic nitriles have emerged as particularly versatile building blocks in modern organic synthesis. Over the past decades, remarkable progress has been achieved in the decyanative cross-coupling of cyanoarenes, enabling the construction of a wide array of C(sp^2)–C and C(sp^2)–X (X = B, N, P, O, Si, S) bonds.[18] In this context, cyanopyridines have found extensive application in photocatalytic transformations, acting as optimal electron acceptors.[19] Of special interest is the well-established use of benzophenones as photocatalysts, acting as hydrogen-atom abstractors to generate nucleophilic radicals *via* C–H bond activation.[20] The corresponding benzophenone ketyl radical can then selectively reduce 4-cyanopyridines through a highly favorable proton-coupled electron transfer (PCET)[21] process, ultimately enabling efficient radical–radical coupling.[22] This reactivity has been largely restricted to couplings between benzylic radicals and cyanopyridines (Fig. 1c). To date, no approaches take advantage of benzophenones as both substrates and photoactive species. Building on these precedents, we envisioned that the intrinsic reactivity of benzophenones and cyanopyridines could be harnessed to develop a light-mediated radical–radical coupling between these two classes of building blocks (Fig. 1d). Surprisingly, no examples have been reported on the selective generation of TAC libraries under photo-mediated conditions. Although radical addition of 4-cyanopyridines to aromatic ketones has been described,[23] its broader application has been limited by competing side reactions such as benzopinacol formation[24] and undesired addition of competitive nucleophilic radicals in the presence of multiple C–H activation sites, which significantly reduce efficiency and practicality.[25] We envisioned that we could overcome these limitations choosing a suitable hydrogen donor capable of fulfilling multiple roles: (i) selective generating the benzophenone ketyl radical by HAT process (ii) reducing the 4-cyanopyridine by PCET or ET and (iii) avoid participating in undesired radical–radical coupling. Consequently, the choice of hydrogen donor plays a crucial role, since it is expected to suppress undesired side processes, thereby enabling selective access to the targeted TACs. This methodology not only would provide straightforward entry to a broad library of TACs but also holds promise for the scalable production of targeted compounds under mild, sustainable conditions, thereby reducing the environmental impact of such transformations. Moreover, the incorporation of pyridines, one of the most prevalent structural motifs in natural products and pharmaceuticals,[26] further underscores the synthetic relevance of this approach, possibly generating libraries of medicinally relevant compounds.

Results and discussion

Benzophenone has been widely employed as an efficient photocatalyst in net-reductive transformations.[27] In its excited

Table 1 Screening of optimal reaction conditions in batch



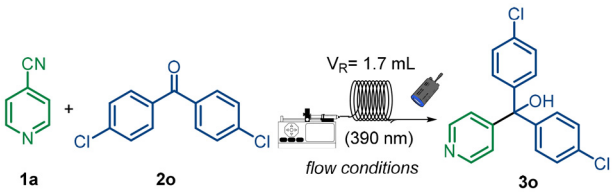
1a 2a 3a

Entry	1a (equiv.)	2a (equiv.)	H-Donor (equiv.)	Solvent (0.1 M)	Yield[a]
1	3	1	γ-Terpinene (10)	EtOAc	16%
2	3	1	Me_3N-BH_3 (2)	EtOAc	40%
3	3	1	2-Propanol (5)	EtOAc	45%
4	1	1.2	2-Propanol (5)	EtOAc	70%
5	**1**	**1.2**	**2-Propanol (10)**	**EtOAc**	**92% (90%)[b]**
6	1	1.2	2-Propanol (10)	MeCN	85%
7	1	1.2	2-Propanol (10)	MeCN/H_2O 9/1	72%
8	1	1.2	2-Propanol (10)	Acetone	61%
9[c]	1	1.2	2-Propanol (10)	2-MeTHF	10%
10[d]	1	1.2	2-Propanol (10)	EtOAc	0%
11	1	1.2	—	EtOAc	0%

Reaction conditions: reaction run on 0.2 mmol scale in 0.1 M of solvent under N_2. Reactions were irradiated with a 40 W Kessil lamp (390 nm) for 16 h. [a] Yield determined by GC-FID with the addition of biphenyl as an internal standard. [b] Isolated yield. [c] Competitive addition of the solvent onto cyanopyridine. [d] No light.

state, it readily abstracts a hydrogen atom from C–H bonds even with high bond dissociation energies (BDEs), generating the corresponding ketyl radical.[28] Owing to its oxidation potential (E_{ox} = −0.25 V *vs.* SCE),[29] this ketyl radical is capable of reducing 4-cyanopyridine (E_{red} = −0.67 V *vs.* SCE)[30] through a proton-coupled electron transfer (PCET) process. This strategy has been successfully exploited in a variety of transformations for the synthesis of substituted pyridines.[22] For our purposes, however, the coexistence of both the benzophenone-derived ketyl radical and the reduced cyanopyridine is essential to promote the desired radical–radical coupling. We therefore considered the possibility of generating the reduced cyanopyridine *via* electron transfer mediated by the radical adduct of the hydrogen donor. An ideal candidate fulfilling these requirements is 2-propanol: it features a relatively low BDE (91 kcal mol^{-1})[31] and can donate a hydrogen atom to excited benzophenone through a HAT process,[32] while the resulting α-hydroxyalkyl radical is sufficiently reducing (E_{ox} = −0.61 V *vs.* SCE)[33] to activate the cyanopyridine. Guided by these considerations and our previous experience,[34] we initiated optimization studies on the model reaction by screening different conditions (Table 1). Firstly, we screened different candidates as H-donors with low bond dissociation energies (BDEs)[31] and whose corresponding radicals are not highly nucleophilic (entries 1 and 2).[35] EtOAc was chosen as green media and despite obtaining promising results with γ-terpinene and M_3N–BH_3, they did not prove to be as efficient as 2-propanol (45% yield entry 3). With 2-propanol identified as the optimal donor, fine-tuning the stoichiometry of **1a**, as limiting reagent, and **2a** revealed that a slight excess of **2a** minimized waste while maintaining excellent reactivity (entry 4). Next, increasing the stochiometric amount of 2-propanol to 10 equivalents afforded the desired product **3a** in 90% isolated yield (entry 5). We also evaluated other green solvents,[36] including MeCN, H_2O, and acetone, which delivered **3a** in good to excellent yields (entries 6–8). In contrast, when 2-MeTHF was employed as the solvent, a competing addition onto **1a** was observed, resulting in a diminished yield of **3a**. Control experiments confirmed that no reactivity occurred in the absence of either light or the hydrogen donor recovering mostly starting materials (entries 10 and 11). To further enhance reaction efficiency, we likewise tested continuous-flow conditions. Compared to batch, flow offers superior heat and mass transfer, precise control over reaction parameters, and uniform light penetration, thereby enabling shorter reaction times, improved selectivity, and greater scalability under energy-efficient conditions.[37] With the aim of synthesizing drug analogues bearing chloro substituents, we considered optimizing the flow process using **2o** (Table 2). At a flow rate of 1.8 mL h^{-1}, complete conversion of the starting material was achieved, affording **3o** in 95% yield (90% in batch entry 2). Remarkably, the reaction could also be performed under more concentrated conditions (0.2 M EtOAc), which required a lower flow rate to ensure full conversion of **1a** (entry 4). These conditions not only enhanced the molar productivity but also reduced solvent consumption. With the optimized conditions in hand, we next investigated the radical addition of substituted benzophe-

Table 2 Screening of optimal reaction conditions in flow



1a 2o 3o

Entry	Flow rate	Solvent	RTD[a] (min)	Yield[b]	Productivity (mmol d^{-1})
1	2 mL h^{-1}	EtOAc (0.1 M)	51	80%	3.8
2	1.8 mL h^{-1}	EtOAc (0.1 M)	56	95% (90%)[c]	4.1
3	1.5 mL h^{-1}	EtOAc (0.2 M)	68	90%	6.5
4	**1.2 mL h^{-1}**	**EtOAc (0.2 M)**	**85**	**99% (98%)[d]**	**5.8**

Reaction conditions: **1a** (0.2 mmol 1.0 equiv.), **2o** (0.24 mmol, 1.2 equiv.), 2-propanol (2 mmol, 10 equiv.), EtOAc as solvent. Reactions were irradiated with two 40 W Kessil lamp (390 nm). [a] Ritention time distribution. [b] Yield determined by GC-FID with the addition of biphenyl as an internal standard. [c] Isolated yield for batch conditions. [d] Isolated yield.

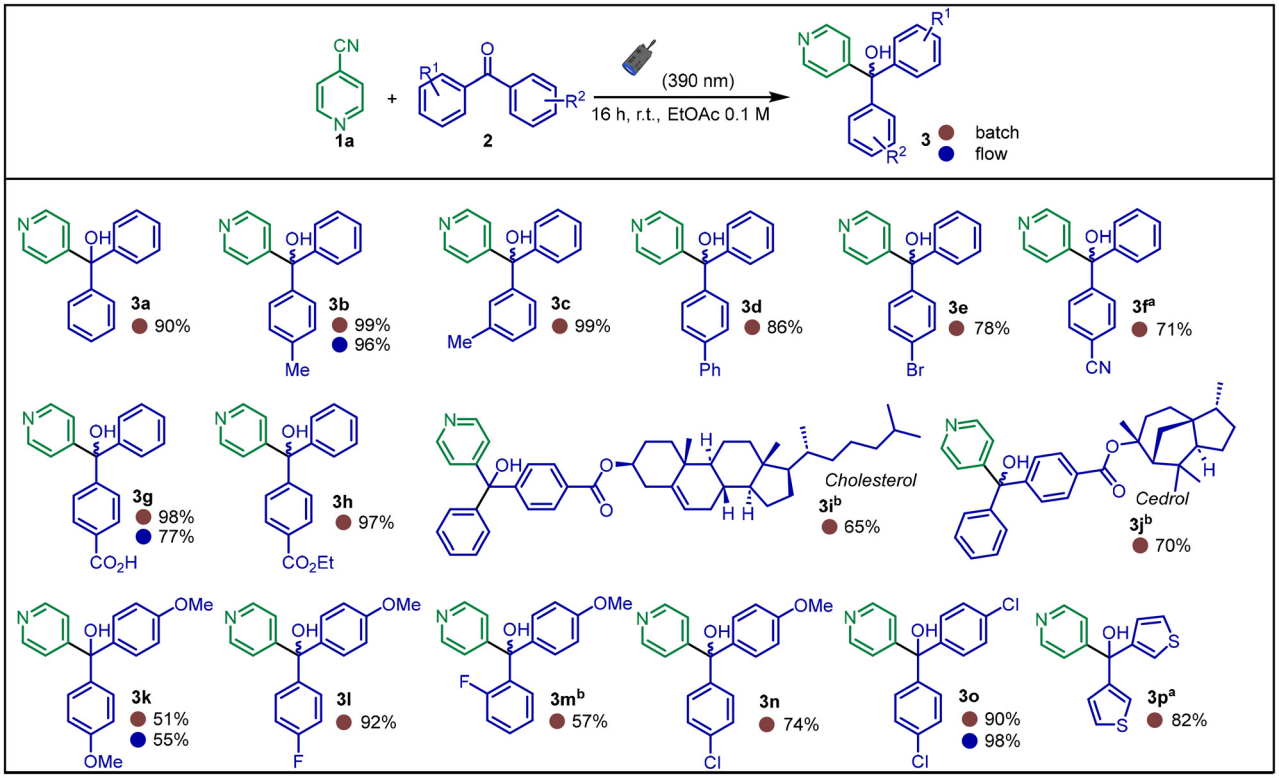


Fig. 2 Reaction conditions in batch: **1a** (0.2 mmol 1.0 equiv.) **2** (0.24 mmol 1.2 equiv.) 2-propanol (2 mmol 10 equiv.) EtOAc 2 mL (0.1 M); room temperature; 16 h Kessil 390 nm. Yields refered to chromatography pure compound. Reaction conditions in flow: **1a** (0.2 mmol 1.0 equiv.) **2** (0.24 mmol 1.2 equiv.) 2-propanol (2 mmol 10 equiv.) EtOAc 1 mL (0.2 M); room temperature; 16 h Kessil 390 nm. flow rate 1.2 mL h^{-1} V_r = 1.7 mL. Yields refered to chromatography pure compound. (a) 2 equiv. of **2** (b) DCM as additive (0.5 mL 0.5 M).

nones to 4-cyanopyridine (Fig. 2). The substrate scope was primarily examined in batch, with selected cases also evaluated under flow conditions. Guided by the results obtained for **3a** and **3o**, we first explored mono-substituted methylbenzophenones. *para*- (**2b**) and *meta*-substituted (**2c**) derivatives afforded the desired products **3b** e **3c** quantitatively, whereas the *ortho* analogue **2r** yielded only trace amounts, likely due to intramolecular quenching of the carbonyl excited state.[25] Comparable reactivity was observed for **3b** under flow conditions. We then examined *para*-substituted benzophenones with different electronic properties. Both electron-rich and electron-poor derivatives provided the corresponding products in good to excellent yields (**3d**–**3f**). Benzophenone **2f** showed a partial reduction to diaryl methanol, therefore for better reaction performances 2 equivalents of benzophenone were used. We screened also a free carboxylic acid which was remarkably well tolerated, affording **3g** in near-quantitative yield. Slightly diminished yields were obtained in flow, presumably due to the formation of insoluble salts in more concentrated reaction medium. Building on this robustness, the ester derivative **2h** furnished **3h** almost quantitatively. Importantly, the methodology also enabled late-stage functionalization of complex scaffolds, as demonstrated by the successful modification of cholesterol and cedrol derivatives, delivering **3i** and **3j** up to 70% yield. It is worth noting that, despite the presence of several C–H bonds susceptible to HAT in both substrates, the abstraction process was selectively directed to the chosen H-donor, thereby suppressing undesired side reactions. Next, we investigated bis-substituted benzophenones. The symmetric 4,4′-dimethoxybenzophenone **2k** afforded **3k** in moderate yield under both batch and flow conditions, whereas unsymmetrical derivatives (**2l**–**2n**) gave the desired products (**3l**–**3n**) in good to excellent yields. Interestingly, *ortho*-fluoro substitution slightly reduced reactivity, while **3o** was obtained in excellent yield both in batch and flow conditions. Finally, the feasibility of incorporating heteroaromatic scaffolds was demonstrated, with derivative **2p** affording **3p** in 82% yield. Encouraged by these results, we next investigated the reactivity of benzophenone **2o** with differently substituted cyanopyridines (Fig. 3). To the best of our knowledge, no systematic studies have explored the behavior of polysubstituted cyanopyridines in the presence of benzophenones;[22] previous reports have largely focused on the addition of nucleophilic radicals to 4-cyanopyridines. We attributed this limited exploration of cyanopyridine derivatization to two main factors: (i) the possible un-matching of redox potential of benzophenones, which may not align with that of substituted cyanopyridines;[38] and (ii) variations in spin density across the pyridine scaffold, which could lead to divergent reactivity at different C-positions and, consequently, to

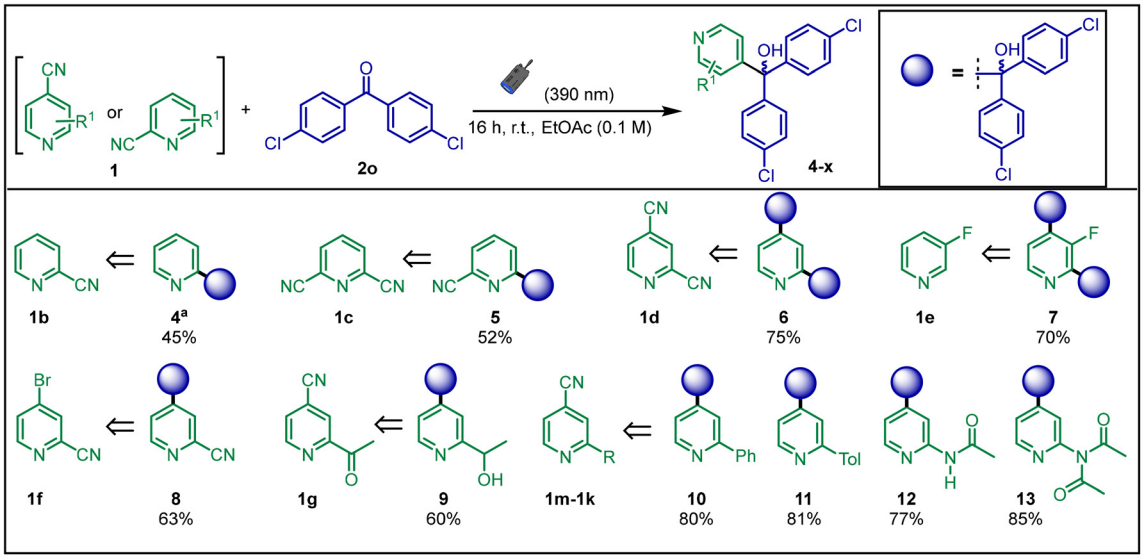


Fig. 3 Reaction conditions in batch: **1** 0.2 mmol (1 equiv.); **2o** 0.4 mmol (2.0 equiv.); 2-propanol 2 mmol (10 equiv.); EtOAc 2 mL (0.1 M); room temperature; 16 h 40 W Kessil (390 nm). Yields refered to chromatography pure compound. (a) **1b** 0.6 mmol (3.0 equiv.); **2o** 0.2 mmol (1.0 equiv.); 2-propanol 1 mmol (5.0 equiv.); EtOAc/HFIP/H_2O (4 : 2 : 1 v/v) (0.1 M); room temperature; 16 h 40 W Kessil (390 nm).

unpredictable outcomes.[39] We began our study with 2-cyanopyridine, which initially furnished only trace amounts of the desired product **4**, accompanied by significant formation of the corresponding diphenylmethanol derived from **2o**. This observation suggests that *ipso*-substitution at C-2 is less favorable than at C-4, rendering **2o** more prone to direct reduction.[40] Guided by this insight, we undertook reaction optimization (see SI section 4), ultimately isolating the desired product **4** in 45% yield. Notably, the addition of small amounts of water and performing the reaction under mildly acidic conditions significantly promoted the *ipso*-substitution pathway, by protonation of pyridine, thereby enhancing product formation.[41] We then evaluated 2,6-dicyanopyridine, whose electron-deficient core proved more reactive, readily undergoing ET to give the mono-substituted carbinol **5** in 52% yield showing better results using 2 equivalents of **2o**. Building on this, we investigated 2,4-dicyanopyridine and we were able to isolate the disubstituted product **6**, bearing carbinol units at both C-2 and C-4. Varying the equivalents of **2o** (0.5, 1.0, and 2.0 equiv.) consistently furnished **6** as the sole product. A similar outcome was observed with 3-fluoroisonicotinonitrile, which underwent double addition of **2o** at C-2 and C-4, affording **7** as the only detectable product. These findings indicate that, while *ipso*-substitution at C-4 is typically favored, in certain cases radical addition at C-2 can proceed with comparable activation barriers, leading to the formation of doubly substituted pyridines.[42] Next, we investigated the reactivity of a pyridine bearing a cyano group at C-2 and a good leaving group at C-4, such as a halide. As anticipated, *ipso*-substitution occurred preferentially at the *para* position, affording product **8** in 63% yield. This result highlights the potential to design pyridines with leaving groups beyond cyano, thereby enabling selective radical additions at C-2, C-4, or both positions depending on the substitution pattern. We then turned our attention to *ortho*-substituted 4-cyanopyridines. Pyridine **1g**, bearing an acetophenone moiety, underwent substitution with concurrent reduction of the ketone, mediated by **2o** itself.[43] Monitoring the reaction by ^{1}H NMR revealed that the addition of **2o** was accompanied by concomitant formation of the corresponding benzyl alcohol. Finally, C-2-substituted pyridines bearing either aryl groups or protected amines delivered the desired products in good yields (≈80%), underscoring the versatility of this methodology for diversifying pyridine scaffolds. To further demonstrate the practicality of our methodology, we scaled up the synthesis of **3o** to the gram scale using both batch and flow setups (Fig. 4a). In both cases, the reaction proceeded efficiently with no noticeable loss in yield, underscoring the robustness of the strategy and its suitability for scalable synthesis under mild conditions. Notably, compared to previously reported procedures,[15] this approach offers significant improvements in atom economy (AE) and Eco scale,[44] establishing it as a more sustainable and synthetically efficient alternative to conventional polar methodologies (see SI, section 10). Moreover, the reaction could be carried out under simulated solar irradiation (SolarBOX), affording **3o** in good yields (81% yield) and highlighting the potential of sunlight as a sustainable energy source (Fig. 4a).[45] We next explored the utility of this approach for the preparation of analogues of pharmaceutically and agrochemically relevant compounds. As a first example, we targeted fenarimol, a widely used fungicide commercialized under various tradenames and mostly applied for the control of powdery mildew.[46] Its analogue was obtained in a single step and in excellent yields in up to one millimolar scale, while avoiding the use of highly reactive *n*-BuLi and cryogenic conditions (−95 °C) required in traditional syntheses (Fig. 4b).[47] In a similar vein, we prepared

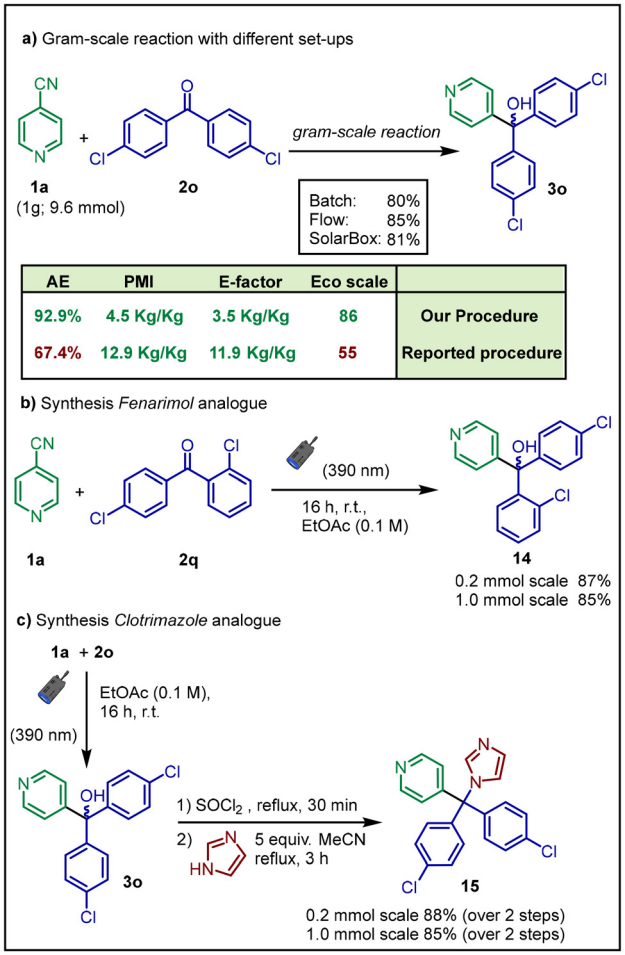


Fig. 4 (a) Grame scale reaction performed in batch, flow and solar box conditions. (b) Light-mediated synthesis of Fenarimol's analogue (c) light-mediated synthesis of clotrimazole's analogue.

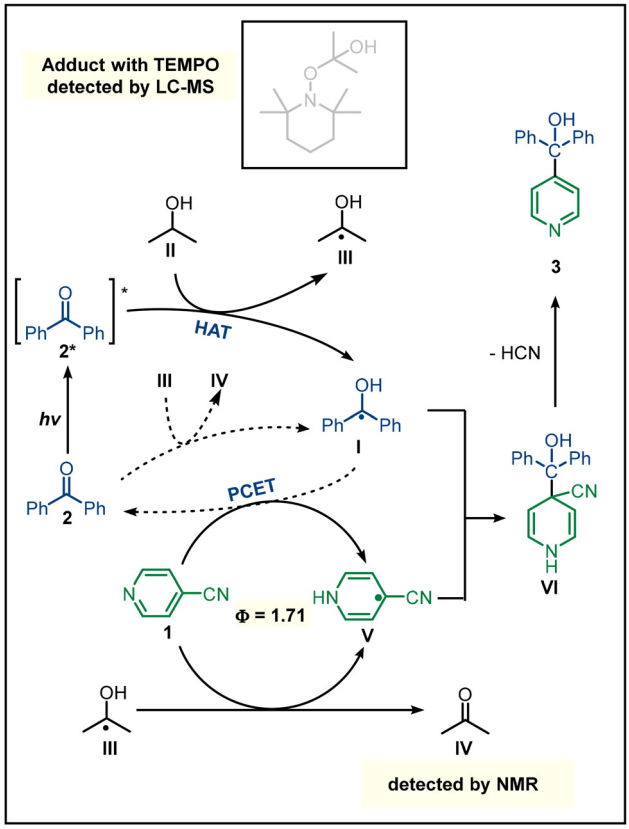


Fig. 5 Proposed mechanism.

an analogue of clotrimazole, a major antifungal active ingredient used in commercial formulations to treat vaginal yeast infections.[48]

In 2016, Canesten-brand clotrimazole was among the top-selling over-the-counter medications in Great Britain, with sales of £39.2 million.[49] Classical routes to clotrimazole involve the synthesis of the triaryl carbinol intermediate, typically employing organolithium reagents, followed by chlorination with $SOCl_2$ and subsequent nucleophilic substitution with imidazole.[50] In contrast, our strategy provided the target analogue under significantly milder conditions, delivering an overall yield above 80% over two steps on both small and millimolar scale (Fig. 4c).

Finally, to gain mechanistic insight, we carried out the reaction in the presence of TEMPO as a radical scavenger. The reaction was completely suppressed, and the formation of a TEMPO-2-propanol adduct was observed by LC-MS analysis, consistent with the involvement of a radical pathway (see SI). We then sought to investigate the fate of the ketyl radical generated from 2-propanol. To this end, the reaction was performed under the general conditions using CD_3CN as solvent, enabling direct NMR analysis of the crude mixture. This revealed the formation of acetone, supporting a possible electron transfer (ET) event between the cyanopyridine and the ketyl radical derived from 2-propanol. Further insight into the reaction pathway was obtained by determining the quantum yield for the consumption of **1a**, which gave ϕ = 1.71. This value indicates that both the benzophenone- and 2-propanol-derived ketyl radicals contribute to the reduction of cyanopyridine.

Therefore, based on these observations and previous reports, we propose the following mechanism (Fig. 5). Upon irradiation, benzophenone (**2**) is excited to its triplet state (**2***), it abstracts a hydrogen atom from 2-propanol (**II**).[31] This process generates the corresponding ketyl radicals (**I** and **III**), which are capable of reducing cyanopyridine **1** to the persistent radical (**V**).[51] The coexistence of radicals **I** and **V** in solution facilitates radical–radical coupling, and subsequent extrusion of HCN furnishes the triaryl carbinol (**3**) from intermediate **VI**. In addition, 2-propanol may play an auxiliary role, as it has been reported, to directly reduce benzophenone (**2**) to ketyl radical (**I**), although the associated rate constant ($k = 7 \times 10^4$ M^{-1} s^{-1}) is relatively low.[33a]

Conclusions

In summary, we have developed a metal-free, light-mediated strategy for the synthesis of triaryl carbinols from benzophe-

nones and cyanopyridines under mild and sustainable conditions. This approach avoids the use of hazardous organometallic reagents and costly transition-metal catalysts, while operating efficiently in green solvents. Central to the reactivity is the dual role of 2-propanol: as H-donor in a HAT process with benzophenone, while its corresponding radical reduces cyanopyridines, thus enabling the key radical–radical coupling that affords the target products.

The methodology grants straightforward access to a broad library of triaryl carbinols, and its robustness was demonstrated across different operational modes, including batch, flow, and gram-scale syntheses, as well as under solar-simulated irradiation. Furthermore, we showcased its applicability to the preparation of analogues of bioactive compounds of pharmaceutical and agrochemical relevance, highlighting its potential as a practical alternative to classical methods that rely on highly reactive organolithium reagents and harsh conditions.

Overall, this work establishes a versatile and scalable platform for the synthesis of pyridine based triaryl carbinols, with significant promise for future applications in industrial settings and medicinal chemistry.

Author contributions

This work was conceptualized by M. L., experimentation was performed by M. L. The first draft of the manuscript was prepared by M. L. and the final version was edited and revised by M. L. and M. F.

Conflicts of interest

There are no conflicts to declare.

Data availability

The data supporting this article have been included as part of the supplementary information (SI). Supplementary information is available. See DOI: https://doi.org/10.1039/d5gc05657h.

Acknowledgements

We acknowledge support from UniPV and MUR through the program 'Departments of Excellence' (2023-2027). We thank Elisa Girardi for preliminary experiments.

References

1 (*a*) P. T. Anastas, J. C. Warner and J. C. Warner, *Green Chemistry: Theory and Practice*, Oxford University Press, Oxford, 2000. 1. paperback; (*b*) *Encyclopedia of Green Chemistry*, ed. B. Török, Elsevier, Amsterdam Boston Heidelberg London New York Oxford Paris San Diego San Francisco Singapore Sydney Tokyo, 2025.

2 (*a*) R. S. Treptow, *J. Chem. Educ.*, 2010, **87**, 168–171; (*b*) D.-S. Chang, L.-T. Yeh and W. Liu, *Clean Technol. Environ. Policy*, 2015, **17**, 359–371; (*c*) J. Rissman, C. Bataille, E. Masanet, N. Aden, W. R. Morrow, N. Zhou, N. Elliott, R. Dell, N. Heeren, B. Huckestein, J. Cresko, S. A. Miller, J. Roy, P. Fennell, B. Cremmins, T. Koch Blank, D. Hone, E. D. Williams, S. De La Rue Du Can, B. Sisson, M. Williams, J. Katzenberger, D. Burtraw, G. Sethi, H. Ping, D. Danielson, H. Lu, T. Lorber, J. Dinkel and J. Helseth, *Appl. Energy*, 2020, **266**, 114848; (*d*) A. Estevez-Torres, F. Gauffre, G. Gouget, C. Grazon and P. Loubet, *Green Chem.*, 2024, **26**, 2613–2622.

3 (*a*) E. Dopp, L. M. Hartmann, A.-M. Florea, A. W. Rettenmeier and A. V. Hirner, *Crit. Rev. Toxicol.*, 2004, **34**, 301–333; (*b*) A. Majumdar, M. K. Upadhyay, M. Ojha, R. Biswas, S. Dey, S. Sarkar, D. Moulick, N. K. Niazi, J. Rinklebe, J.-H. Huang and T. Roychowdhury, *Sci. Total Environ.*, 2024, **951**, 175531.

4 (*a*) B. Halliwell and J. M. C. Gutteridge, *Free Radicals in Biology and Medicine*, Oxford University Press, 2015; (*b*) S. Z. Zard, *Radical Reactions in Organic Synthesis*, Oxford University PressOxford, 2003; (*c*) A. Studer, *Adv. Synth. Catal.*, 2020, **362**, 2074; (*d*) Z. X. Chen, Y. Li and F. Huang, *Chem*, 2021, **7**, 288–332; (*e*) D. P. Curran, B. Giese and N. A. Porter, *Stereochemistry of radical reactions: concepts, guidelines, and synthetic applications*, VCH, Weinheim New York, 1996; (*f*) M. Inoue, L. R. Malins and H. Renata, *Org. Lett.*, 2024, **26**, 7775–7777; (*g*) V. T. Perchyonok, I. N. Lykakis and K. L. Tuck, *Green Chem.*, 2008, **10**, 153–163.

5 (*a*) S. Crespi and M. Fagnoni, *Chem. Rev.*, 2020, **120**, 9790–9833; (*b*) M. D. Kärkäs, B. S. Matsuura and C. R. J. Stephenson, *Science*, 2015, **349**, 1285–1286; (*c*) D. Ravelli, S. Protti and M. Fagnoni, *Acc. Chem. Res.*, 2016, **49**, 2232–2242; (*d*) C. K. Prier, D. A. Rankic and D. W. C. MacMillan, *Chem. Rev.*, 2013, **113**, 5322–5363; (*e*) C. Michelin and N. Hoffmann, *Curr. Opin. Green Sustainable Chem.*, 2018, **10**, 40–45; (*f*) A. Quintavalla, D. Carboni and M. Lombardo, *ChemCatChem*, 2024, **16**, e202301225.

6 (*a*) L. Candish, K. D. Collins, G. C. Cook, J. J. Douglas, A. Gómez-Suárez, A. Jolit and S. Keess, *Chem. Rev.*, 2022, **122**, 2907–2980; (*b*) A. A. Adesina, *Catal. Surv. Asia*, 2004, **8**, 265–273; (*c*) M. Devi, S. Praharaj and D. Rout, in *Nanostructured Materials for Visible Light Photocatalysis*, Elsevier, 2022, pp. 535–567; (*d*) D. Lahiri, M. Nag and R. R. Ray, in *Photocatalytic Degradation of Dyes*, Elsevier, 2021, pp. 467–488; (*e*) P. Li, J. A. Terrett and J. R. Zbieg, *ACS Med. Chem. Lett.*, 2020, **11**, 2120–2130.

7 (*a*) S. Mondal and G. Panda, *RSC Adv.*, 2014, **4**, 28317–28358; (*b*) S. K. Sen Gupta and S. Mishra, *J. Phys. Chem. A*, 2011, **115**, 4616–4623; (*c*) S. Alhamed, J. Alnakhli, W. Boadi and R. Beni, *Open J. Med. Chem.*, 2019, **09**, 49–62; (*d*) J. De

Boer, in *Reviews of Environmental Contamination and Toxicology*, ed. G. W. Ware, Springer New York, New York, NY, 1997, vol. 150, pp. 95–106; (*e*) R. Beni, W. Boadi, K. Karim, J. Alnakhli and S. Alhamed, *Open J. Med. Chem.*, 2019, **09**, 37–47; (*f*) E. Kelderman, W. A. J. Starmans, J. P. M. Van Duynhoven, W. Verboom, J. F. J. Engbersen, D. N. Reinhoudt, L. Derhaeg, T. Verbiest, K. Clays and A. Persoons, *Chem. Mater.*, 1994, **6**, 412–417; (*g*) K. G. Rutherford, J. L. H. Batiste and J. M. Prokipcak, *Can. J. Chem.*, 1969, **47**, 4073–4076; (*h*) A. Bacchi, E. Bosetti, M. Carcelli, P. Pelagatti, G. Pelizzi and D. Rogolino, *CrystEngComm*, 2006, **8**, 233; (*i*) Y. Gong and F. F. Mulks, *Synthesis*, 2025, 1542–1550.

8 K. Oh, T. Matsumoto, A. Yamagami, T. Hoshi, T. Nakano and Y. Yoshizawa, *Int. J. Mol. Sci.*, 2015, **16**, 17273–17288.

9 M. R. Saberi, T. K. Vinh, S. W. Yee, B. J. N. Griffiths, P. J. Evans and C. Simons, *J. Med. Chem.*, 2006, **49**, 1016–1022.

10 S. Gemma, G. Campiani, S. Butini, G. Kukreja, B. P. Joshi, M. Persico, B. Catalanotti, E. Novellino, E. Fattorusso, V. Nacci, L. Savini, D. Taramelli, N. Basilico, G. Morace, V. Yardley and C. Fattorusso, *J. Med. Chem.*, 2007, **50**, 595–598.

11 (*a*) G. A. McNaughton-Smith, J. F. Burns, J. W. Stocker, G. C. Rigdon, C. Creech, S. Arrington, T. Shelton and L. De Franceschi, *J. Med. Chem.*, 2008, **51**, 976–982; (*b*) M. Keenan, M. J. Abbott, P. W. Alexander, T. Armstrong, W. M. Best, B. Berven, A. Botero, J. H. Chaplin, S. A. Charman, E. Chatelain, T. W. Von Geldern, M. Kerfoot, A. Khong, T. Nguyen, J. D. McManus, J. Morizzi, E. Ryan, I. Scandale, R. A. Thompson, S. Z. Wang and K. L. White, *J. Med. Chem.*, 2012, **55**, 4189–4204; (*c*) E. Zeiman, C. L. Greenblatt, S. Elgavish, I. Khozin-Goldberg and J. Golenser, *J. Parasitol.*, 2008, **94**, 280–286.

12 (*a*) J. E. Baldwin, R. M. Adlington, J. C. Bottaro, J. N. Kolhe, I. M. Newington and M. W. D. Perry, *Tetrahedron*, 1986, **42**, 4235–4246; (*b*) G. Cravotto, A. Procopio, M. Oliverio, L. Orio and D. Carnaroglio, *Green Chem.*, 2011, **13**, 2806; (*c*) M. Singh, J. T. Schott, M. A. Leon, R. T. Granata, H. K. Dhah, J. A. Welles, M. A. Boyce, H. S. Oseni-Olalemi, C. E. Mordaunt, A. J. Vargas, N. V. Patel and S. Maitra, *Bioorg. Med. Chem. Lett.*, 2012, **22**, 6252–6255; (*d*) Y. Wen, G. Chen, S. Huang, Y. Tang, J. Yang and Y. Zhang, *Adv. Synth. Catal.*, 2016, **358**, 947–957; (*e*) A. F. Quivelli, G. D'Addato, P. Vitale, J. García-Álvarez, F. M. Perna and V. Capriati, *Tetrahedron*, 2021, **81**, 131898.

13 (*a*) J. P. Wibaut and L. G. Heeringa, *Recl. Trav. Chim. Pays-Bas*, 1955, **74**, 1003–1020; (*b*) D. Seyferth, W.-L. Wang and R. C. Hui, *Tetrahedron Lett.*, 1984, **25**, 1651–1654; (*c*) D. Seyferth, R. C. Hui and W. L. Wang, *J. Org. Chem.*, 1993, **58**, 5843–5845; (*d*) J. A. D. Good, F. Wang, O. Rath, H. Y. K. Kaan, S. K. Talapatra, D. Podgórski, S. P. MacKay and F. Kozielski, *J. Med. Chem.*, 2013, **56**, 1878–1893; (*e*) X. Zeng, J. Cai and Y. Gu, *Tetrahedron Lett.*, 1995, **36**, 7275–7276; (*f*) M. Watanabe, M. Date, K. Kawanishi, M. Tsukazaki and S. Furukawa, *Chem. Pharm. Bull.*, 1989, **37**, 2564–2566.

14 (*a*) T. Maekawa, H. Sekizawa and K. Itami, *Angew. Chem., Int. Ed.*, 2011, **50**, 7022–7026; (*b*) C. Berini and O. Navarro, *Chem. Commun.*, 2012, **48**, 1538–1540; (*c*) Y.-X. Liao, C.-H. Xing and Q.-S. Hu, *Org. Lett.*, 2012, **14**, 1544–1547; (*d*) R. Akiyama, M. Sugaya, H. Shinozaki and T. Yamamoto, *Synth. Commun.*, 2019, **49**, 1193–1201; (*e*) Y. Okuda, M. Nagaoka and T. Yamamoto, *ChemCatChem*, 2020, **12**, 6291–6300; (*f*) J. Huang, X. Yan and Y. Xia, *Angew. Chem., Int. Ed.*, 2022, **61**, e202211080; (*g*) D. Lichte, N. Pirkl, G. Heinrich, S. Dutta, J. F. Goebel, D. Koley and L. J. Gooßen, *Angew. Chem., Int. Ed.*, 2022, **61**, e202210009; (*h*) S. Wu, X. Ye, Z. Wang and S. Shi, *ChemCatChem*, 2024, **16**, e202400633.

15 C. D. Jones, M. A. Winter, K. S. Hirsch, N. Stamm, H. M. Taylor, H. E. Holden, J. D. Davenport, E. V. Krumkalns and R. G. Suhr, *J. Med. Chem.*, 1990, **33**, 416–429.

16 (*a*) E. Kabir and M. Uzzaman, *Results Chem.*, 2022, **4**, 100606; (*b*) P. Ertl, S. Jelfs, J. Mühlbacher, A. Schuffenhauer and P. Selzer, *J. Med. Chem.*, 2006, **49**, 4568–4573; (*c*) H. V. Bossche, *J. Steroid Biochem. Mol. Biol.*, 1992, **43**, 1003–1021; (*d*) L. Banting, in *Progress in Medicinal Chemistry*, Elsevier, 1996, vol. 33, pp. 147–184; (*e*) I. A. S. De Borba, J. B. Peripolli, A. R. Joaquim and F. Fumagalli, *Organics*, 2025, **6**, 23.

17 (*a*) F. Minisci, R. Bernardi, F. Bertini, R. Galli and M. Perchinummo, *Tetrahedron*, 1971, **27**, 3575–3579; (*b*) C. Friedel and J. M. Crafts, *C. R. Chim.*, 1877, **84**, 1392; (*c*) N. Miyaura, K. Yamada and A. Suzuki, *Tetrahedron Lett.*, 1979, **20**, 3437–3440; (*d*) H. Nakahara, R. Shirai, Y. Nishimoto, D. Yokogawa and J. Yamaguchi, *Nat. Commun.*, 2025, **16**, 8998.

18 (*a*) S. Tong, K. Li, X. Ouyang, R. Song and J. Li, *Green Synth. Catal.*, 2021, **2**, 145–155; (*b*) R. Y. Peshkov, E. V. Panteleeva, W. Chunyan, E. V. Tretyakov and V. D. Shteingarts, *Beilstein J. Org. Chem.*, 2016, **12**, 1577–1584; (*c*) C. Berini and O. Navarro, *Chem. Commun.*, 2012, **48**, 1538–1540; (*d*) Y.-Y. Jiang, H.-Z. Yu and Y. Fu, *Organometallics*, 2013, **32**, 926–936; (*e*) E. C. Keske, T. H. West and G. C. Lloyd-Jones, *ACS Catal.*, 2018, **8**, 8932–8940; (*f*) J.-S. Zhang, T. Chen, Y. Zhou, S.-F. Yin and L.-B. Han, *Org. Lett.*, 2018, **20**, 6746–6749.

19 (*a*) A. McNally, C. K. Prier and D. W. C. MacMillan, *Science*, 2011, **334**, 1114–1117; (*b*) Z. Zuo, D. T. Ahneman, L. Chu, J. A. Terrett, A. G. Doyle and D. W. C. MacMillan, *Science*, 2014, **345**, 437–440; (*c*) D. Liu, C. Liu, H. Li and A. W. Lei, *Angew. Chem., Int. Ed.*, 2013, **52**, 4453–4456; (*d*) C. Yan, L. Li, Y. Liu and Q. Wang, *Org. Lett.*, 2016, **18**, 4686–4689; (*e*) M. M. Walker, B. Koronkiewicz, S. Chen, K. N. Houk, J. M. Mayer and J. A. Ellman, *J. Am. Chem. Soc.*, 2020, **142**, 8194–8202; (*f*) L.-J. Zhong, H.-Y. Wang, X.-H. Ouyang, J.-H. Li and D.-L. An, *Chem. Commun.*, 2020, **56**, 8671–8674; (*g*) G. Wang, J. Cao, L. Gao, W. Chen, W. Huang, X. Cheng and S. Li, *J. Am. Chem. Soc.*, 2017, **139**, 3904–3910.

20 (*a*) A. Beckett and G. Porter, *Trans. Faraday Soc.*, 1963, **59**, 2038–2050; (*b*) L. Capaldo, D. Ravelli and M. Fagnoni, *Chem. Rev.*, 2022, **122**, 1875–1924; (*c*) A. M. González-Cameno, M. Mella, M. Fagnoni and A. Albini, *J. Org. Chem.*, 2000, **65**, 297–303; (*d*) G. Campari, M. Fagnoni, M. Mella and A. Albini, *Tetrahedron: Asymmetry*, 2000, **11**, 1891–1906; (*e*) I. K. Sideri, E. Voutyritsa and C. G. Kokotos, *Org. Biomol. Chem.*, 2018, **16**, 4596–4614; (*f*) A. Pulcinella, S. Bonciolini, F. Lukas, A. Sorato and T. Noël, *Angew. Chem., Int. Ed.*, 2023, **62**, e202215374.

21 (*a*) E. C. Gentry and R. R. Knowles, *Acc. Chem. Res.*, 2016, **49**, 1546–1556; (*b*) R. Tyburski, T. Liu, S. D. Glover and L. Hammarström, *J. Am. Chem. Soc.*, 2021, **143**, 560–576; (*c*) M. H. V. Huynh and T. J. Meyer, *Chem. Rev.*, 2007, **107**, 5004–5064; (*d*) D. Shukla, W. G. Ahearn and S. Farid, *Photochem. Photobiol.*, 2006, **82**, 146; (*e*) R. I. Cukier and D. G. Nocera, *Annu. Rev. Phys. Chem.*, 1998, **49**, 337–369.

22 (*a*) T. Hoshikawa and M. Inoue, *Chem. Sci.*, 2013, **4**, 3118; (*b*) J. Xu, Y. Zhou and B. Liu, *J. Org. Chem.*, 2024, **89**, 15877–15883; (*c*) J. Xu and B. Liu, *Chem. – Eur. J.*, 2024, **30**, e202400612; (*d*) A. Bisoyi, A. Behera, A. R. Tripathy, V. K. Simhadri and V. R. Yatham, *J. Org. Chem.*, 2024, **89**, 17818–17823; (*e*) Y. Zhang and B. Liu, *Synlett*, 2025, 1064–1068.

23 B. M. Vittimberga, F. Minisci and S. Morrocchi, *J. Am. Chem. Soc.*, 1975, **97**, 4397–4398.

24 W. E. Bachmann, *Org. Synth.*, 1934, **14**, 8.

25 R. Bernardi, T. Caronna, S. Morrocchi and M. Ursini, *J. Heterocycl. Chem.*, 1996, **33**, 1137–1142.

26 (*a*) C. M. Marshall, J. G. Federice, C. N. Bell, P. B. Cox and J. T. Njardarson, *J. Med. Chem.*, 2024, **67**, 11622–11655; (*b*) S. De, A. Kumar, S. K. Ashok Kumar, S. K. Shah, S. Kazi, N. Sarkar, S. Banerjee and S. Dey, *RSC Adv.*, 2022, **12**, 15385–15406; (*c*) A. R. Dwivedi, S. Jaiswal, D. Kukkar, R. Kumar, T. G. Singh, M. P. Singh, A. M. Gaidhane, S. Lakhanpal, K. N. Prasad and B. Kumar, *RSC Med. Chem.*, 2025, **16**, 12–36.

27 (*a*) R. Mosca, M. Fagnoni, M. Mella and A. Albini, *Tetrahedron*, 2001, **57**, 10319–10328; (*b*) S. Wang, P. S. Singh and D. H. Evans, *J. Phys. Chem. C*, 2009, **113**, 16686–16693; (*c*) P. R. D. Murray, J. H. Cox, N. D. Chiappini, C. B. Roos, E. A. McLoughlin, B. G. Hejna, S. T. Nguyen, H. H. Ripberger, J. M. Ganley, E. Tsui, N. Y. Shin, B. Koronkiewicz, G. Qiu and R. R. Knowles, *Chem. Rev.*, 2022, **122**, 2017–2291; (*d*) A. Luridiana, D. Mazzarella, L. Capaldo, J. A. Rincón, P. García-Losada, C. Mateos, M. O. Frederick, M. Nuño, W. J. Buma and T. Noël, *ACS Catal.*, 2022, **12**, 11216–11225; (*e*) J. Lyu, M. Leone, A. Claraz, C. Allain, L. Neuville and G. Masson, *RSC Adv.*, 2021, **11**, 36663–36669.

28 A. M. Cardarelli, M. Fagnoni, M. Mella and A. Albini, *J. Org. Chem.*, 2001, **66**, 7320–7327.

29 P. Neta and L. K. Patterson, *J. Phys. Chem.*, 1974, **78**, 2211–2217.

30 U. Bruehlmann and E. Hayon, *J. Am. Chem. Soc.*, 1974, **96**, 6169–6175.

31 Y.-R. Luo, *Comprehensive Handbook of Chemical Bond Energies*, 1st edn, CRC Press, 2007.

32 G. O. Schenck, G. Koltzenburg and H. Grossmann, *Angew. Chem.*, 1957, **69**, 177–178.

33 (*a*) T. Lund, D. D. M. Wayner, M. Jonsson, A. G. Larsen and K. Daasbjerg, *J. Am. Chem. Soc.*, 2001, **123**, 12590–12595; (*b*) J. Lilie, G. Beck and A. Henglein, *Ber. Bunsenges. Phys. Chem.*, 1971, **75**, 458–465.

34 (*a*) M. Leone, D. Arnaldi and M. Fagnoni, *Org. Chem. Front.*, 2025, **12**, 4970–4979; (*b*) C. Manfrotto, M. Mella, M. Freccero, M. Fagnoni and A. Albini, *J. Org. Chem.*, 1999, **64**, 5024–5028.

35 (*a*) W. Tantawy and H. Zipse, *Eur. J. Org. Chem.*, 2007, **2007**, 5817–5820; (*b*) D. J. Van Hoomissen and S. Vyas, *J. Org. Chem.*, 2017, **82**, 5731–5742; (*c*) Y. Fu, Z. Wang, Y. Zhang, G. Shen and X. Zhu, *ChemistrySelect*, 2022, **7**, e202202625; (*d*) A. Gansäuer, L. Shi, M. Otte, I. Huth, A. Rosales, I. Sancho-Sanz, N. M. Padial and J. E. Oltra, in *Radicals in Synthesis III*, ed. M. Heinrich and A. Gansäuer, Springer Berlin Heidelberg, Berlin, Heidelberg, 2011, vol. 320, pp. 93–120; (*e*) M. Salamone, M. Galeotti, E. Romero-Montalvo, J. A. Van Santen, B. D. Groff, J. M. Mayer, G. A. DiLabio and M. Bietti, *J. Am. Chem. Soc.*, 2021, **143**, 11759–11776.

36 F. P. Byrne, S. Jin, G. Paggiola, T. H. M. Petchey, J. H. Clark, T. J. Farmer, A. J. Hunt, C. R. McElroy and J. Sherwood, *Sustainable Chem. Processes*, 2016, **4**, 7.

37 (*a*) L. Buglioni, F. Raymenants, A. Slattery, S. D. A. Zondag and T. Noël, *Chem. Rev.*, 2022, **122**, 2752–2906; (*b*) T. H. Rehm, *Chem. – Eur. J.*, 2020, **26**, 16952–16974; (*c*) A. I. Alfano, S. Pelliccia, G. Rossino, O. Chianese, V. Summa, S. Collina and M. Brindisi, *ACS Med. Chem. Lett.*, 2023, **14**, 672–680; (*d*) L. Capaldo, Z. Wen and T. Noël, *Chem. Sci.*, 2023, **14**, 4230–4247.

38 (*a*) W. J. Leigh, D. R. Arnold, R. W. R. Humphreys and P. C. Wong, *Can. J. Chem.*, 1980, **58**, 2537–2549; (*b*) A. Dewanji, P. E. Krach and M. Rueping, *Angew. Chem., Int. Ed.*, 2019, **58**, 3566–3570.

39 (*a*) E. Le Saux, E. Georgiou, I. A. Dmitriev, W. C. Hartley and P. Melchiorre, *J. Am. Chem. Soc.*, 2023, **145**, 47–52; (*b*) J. Zhang, G. Wu, Y. Zhao, X. Liu, H. Zhu, A. Studer, X. Qi and Q. Cheng, *Nat. Synth*, 2026, **5**, 27–35; (*c*) E. Georgiou, D. Spinnato, K. Chen, P. Melchiorre and K. Muñiz, *Chem. Sci.*, 2022, **13**, 8060–8064.

40 (*a*) W. D. Cohen and J. Böeseken, *Recl. Trav. Chim. Pays-Bas*, 1920, **39**, 243–279; (*b*) N. Filipescu and F. L. Minn, *J. Am. Chem. Soc.*, 1968, **90**(6), 1544–1547.

41 T. Caronna, S. Morrocchi and B. M. Vittimberga, *J. Heterocycl. Chem.*, 1980, **17**, 399–400.

42 (*a*) L. Gao, G. Wang, J. Cao, H. Chen, Y. Gu, X. Liu, X. Cheng, J. Ma and S. Li, *ACS Catal.*, 2019, **9**, 10142–10151; (*b*) E. Pu, Y. Zhu, S. Yang, P. Jiang, X. Li, H. Zhang and J. Chen, *Org. Lett.*, 2025, **27**, 10855–10861.

43 (*a*) S. Wang and B. König, *Angew. Chem., Int. Ed.*, 2021, **60**, 21624–21634; (*b*) C. Boeke, A. Mellott, G. Lahiri, H. Y. K. Huang and J. S. Cannon, *Tetrahedron Lett.*, 2024,

152, 155334; (*c*) B. A. Sandoval, S. I. Kurtoic, M. M. Chung, K. F. Biegasiewicz and T. K. Hyster, *Angew. Chem., Int. Ed.*, 2019, **58**, 8714–8718.
44 K. Van Aken, L. Strekowski and L. Patiny, *Beilstein J. Org. Chem.*, 2006, **2**, 3.
45 (*a*) S. Protti and M. Fagnoni, *Photochem. Photobiol. Sci.*, 2009, **8**, 1499–1516; (*b*) S. Choudhury, J.-O. Baeg, N.-J. Park and R. K. Yadav, *Green Chem.*, 2014, **16**, 4389; (*c*) S. Protti, D. Ravelli, M. Fagnoni and A. Albini, *Chem. Commun.*, 2009, 7351.
46 K. A. Lewis, J. Tzilivakis, D. J. Warner and A. Green, *Hum. Ecol. Risk Assess.*, 2016, **22**, 1050–1064.
47 H. M. Taylor, C. D. Jones, J. D. Davenport, K. S. Hirsch, T. J. Kress and D. Weaver, *J. Med. Chem.*, 1987, **30**, 1359–1365.
48 R. J. Holt, *Drugs*, 1975, **9**, 401–405.
49 D. Connelly, *Pharm. J.*, 2017, **298**, 7900.
50 J. Bartrolí, M. Algueró, E. Boncompte and J. Forn, *Arzneimittelforschung*, 1992, **42**, 832–835.
51 D. Leifert and A. Studer, *Angew. Chem., Int. Ed.*, 2020, **59**, 74–108.