Helvetica Chimica Acta

HELVETICA chimica acta

RESEARCH ARTICLE OPEN ACCESS

Photochemical Access to Trifluoromethylated Benzofuranols via 1,6-Hydrogen Atom Transfer

Abhilash Pedada | Johannes M. Wahl

Department Chemie, Johannes Gutenberg-Universität, Mainz, Germany

Correspondence: Johannes M. Wahl (wahl@uni-mainz.de)

Received: 25 September 2025 | **Revised:** 15 October 2025 | **Accepted:** 16 October 2025

Keywords: 1,6-hydrogen atom transfer | benzofurans | Norrish–Yang cyclization | photochemistry | trifluoroacetophenones

ABSTRACT

Ortho-alkoxy trifluoroacetophenones undergo efficient cyclization to benzofuranols under UV light irradiation (370 nm). Key to success is a 1,6-hydrogen atom transfer (1,6-HAT), which is enabled by the unique properties of the trifluoroacetophenone unit and strategic positioning of the methoxy group. The reaction proceeds best under dilute conditions, in polar aprotic solvents, and with high-intensity irradiation. Although triplet quenching and intermolecular HAT limit certain aromatic substitution patterns, the reaction still accommodates a diverse set of substrates, providing access to tertiary benzofuranols, including spirocyclic compounds (12 examples, up to 92% yield, up to 90:10 diastereomeric ratios [dr]). Subsequent dehydration provides trifluoromethyl-substituted benzofurans, offering a convenient route to these heterocycles.

1 | Introduction

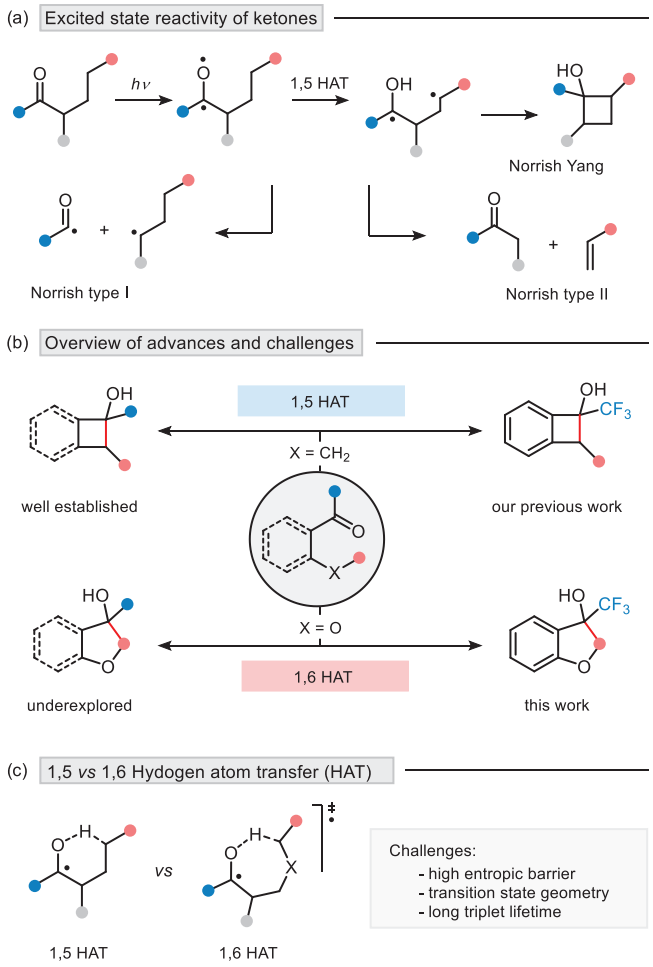
Irradiation of ketones populates their excited states, inducing radical behavior distinct from their ground-state reactivity [1]. A landmark example is the Norrish–Yang photocyclization to forge cyclobutanols (Scheme 1a) [2, 3]. This reaction is known to occur via an intramolecular 1,5-hydrogen atom transfer (1,5-HAT) followed by radical recombination. It has found significant applications in the synthesis of complex scaffolds and natural products, most likely due to its operational simplicity and catalyst-free nature (Scheme 1b, top) [4, 5]. However, the general sequence also offers the potential to access rings of different sizes, a possibility that remains less explored due to generally less favorable biradical generation [6, 7]. In particular, few strategies have targeted five-membered rings through 1,6-hydrogen atom transfer (1,6-HAT) pathways (Scheme 1b, bottom) [8, 9]. This scarcity arises because suitable ketones require long triplet lifetimes, as relatively high entropic barriers must be overcome to reach favorable transition-state geometries (Scheme 1c) [10, 11].

During a recent study on benzocyclobutenol synthesis, we noted that the unique excited state properties of trifluoroacetophenones for HAT processes (Scheme 1b, top right) [12]. We therefore envisioned that these motifs could enable the formation of five-membered analogs in the absence of γ-hydrogens via 1,6-HAT [13–16]. Thus, alkoxy-substituted trifluoroacetophenones would offer a convenient route to trifluoromethyl-substituted benzofuranols, which are difficult to access by other methods, with only few reported strategies [17, 18]. Moreover, trifluoromethyl-decorated heterocycles are of considerable interest in medicinal chemistry, providing further motivation to pursue the presented strategy [19–21].

2 | Results and Discussion

We commenced our survey using ortho-methoxy trifluoroacetophenone **1a** as a model substrate, which can be readily synthesized from commercially available 2-bromo anisole in one

This article is dedicated to *Armido Studer* on the occasion of the *Paracelsus* prize, in recognition of his outstanding contributions to chemistry.



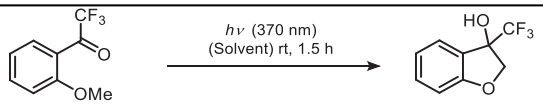
SCHEME 1 | (a) Excited state chemistry of ketones. (b) Overview of the developments for photochemical cyclization. (c) Challenges for using 1,6-hydrogen atom transfer (1,6-HAT) as a key step.

step. Initially, we employed our previously optimized conditions to excite the trifluoroacetophenone moiety of **1a** (Table 1, Entry 1). To our delight, the expected benzofuranol **2a** was obtained, but both conversion and yield were low. These results prompted a detailed optimization of the reaction parameters. The limited conversion suggested that a more efficient light source was required to effectively excite the substrate. When using a 40 W 370 nm Kessil lamp, full conversion was achieved, although the product yield remained low (Entry 2), indicating that factors beyond substrate excitation were limiting the efficiency of the reaction.

Next, we investigated the effect of solvent polarity. Switching from non-polar to polar solvents improved the yields, with acetonitrile performing best, affording benzofuranol **2a** in 49% yield (Entries 3–5). When reducing the light intensity of the Kessil lamp by 50%, lower conversion and diminished yields were witnessed (Entry 6). Finally, lowering the substrate concentration from 40 mM to 20 and 10 mM significantly minimized intermolecular side reactions and enhanced the yield of the desired product **2a** (Entries 7–8). When the reaction was performed on a 0.3 mmol scale, benzofuranol **2a** could be isolated in 83% yield using the optimized conditions (Entry 8).

We next sought to explore the scope of the reaction (Scheme 2). To enable a fair comparison of reaction yields, we extended the reaction times for some substrates beyond the optimized conditions to achieve complete conversion of the starting materials. Substituents on the aryl ring exhibited markedly different reactivity profiles compared to the model substrate. Fluorine substitution at the 4-position required 6 h reaction times, but afforded the desired product **2b** in good yield (Scheme 2a). We then shifted our focus to substitutions at the 3-position of the aryl ring. The trifluoromethyl derivative behaved comparably to the model substrate, whereas the 3-chloro analog required longer reaction times and was less efficient. Thus, benzofuranols **2c** and

TABLE 1 | Optimization conditions for the synthesis of trifluorodihydrofuranols.



1a **2a**

Entry	Solvent	Concentration (mM)	Conversion (%)	Yield (%)
1[a]	Benzene-d_6	40	<5	<5
2	Benzene-d_6	40	100	20
3	Cyclohexane	40	100	–[b]
4	Dichloroethane	40	100	–[b]
5	Acetonitrile-d_3	40	100	49
6[c]	Acetonitrile-d_3	40	58	30
7	Acetonitrile-d_3	20	100	67
8	Acetonitrile-d_3	10	100	91 (83)[d]

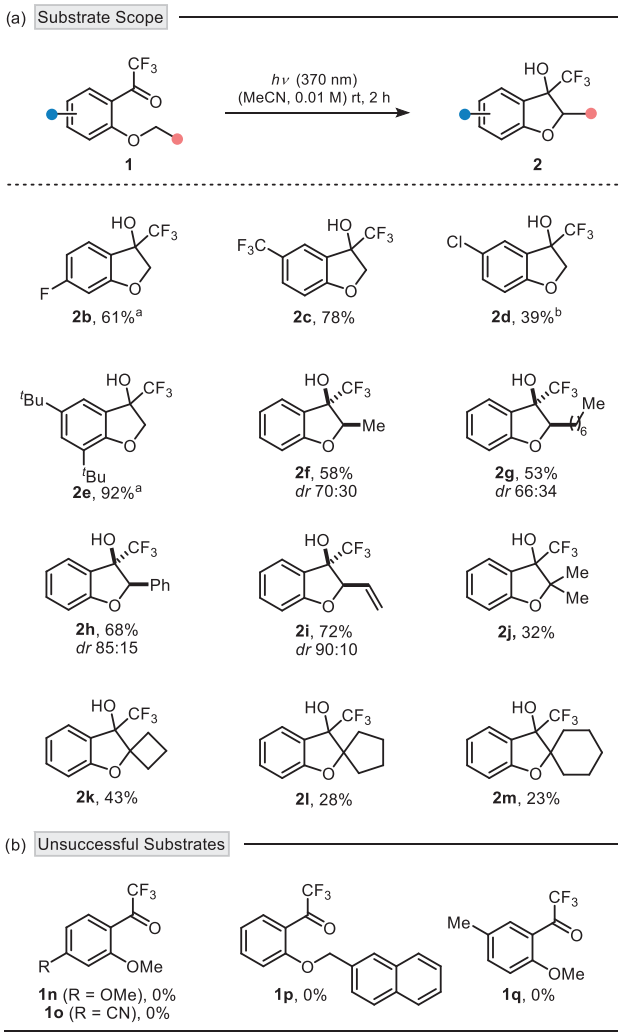
Note: Reactions were carried out in 0.5 mL of solvent in an NMR tube and irradiated with a Kessil lamp (370 nm). Conversions and yields were determined by ^{19}F NMR of the crude mixture using $PhCF_3$ as the internal standard.

[a]A LuzChem photoreactor with mercury lamps (355 nm) was used.

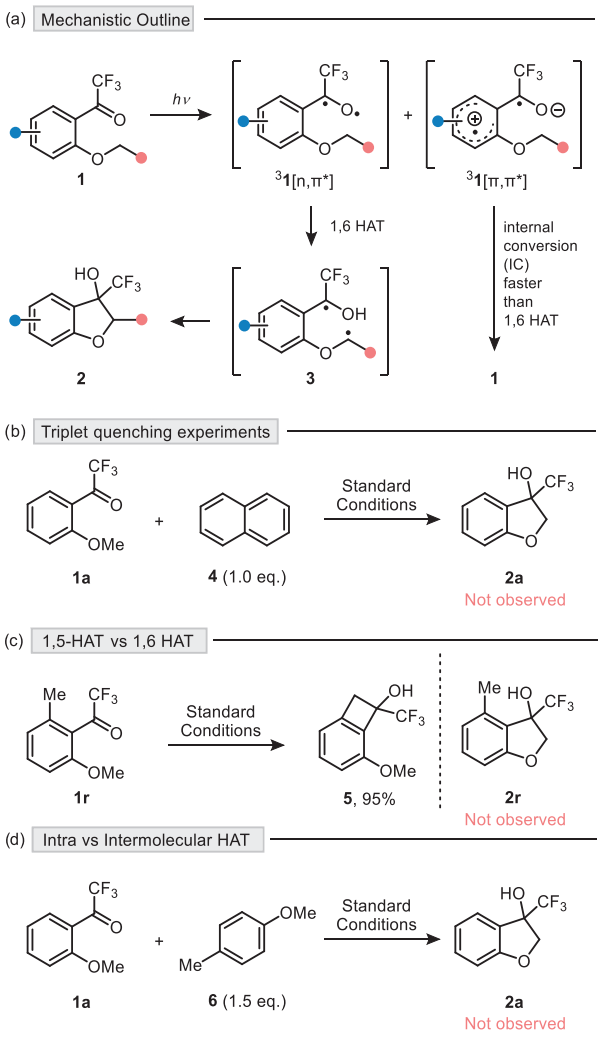
[b]A complex mixture of products was formed.

[c]The light intensity of the Kessil lamp was reduced by 50%.

[d]Isolated yield is given in parenthesis. The isolation reaction was run on a 0.3 mmol scale.



SCHEME 2 | Reactions were carried out on 0.3 mmol scale in 30 mL of solvent and irradiated for 2 h with a 40 W 370 nm Kessil lamp. (a) Reaction time is 6 h. (b) Reaction time is 5 h.

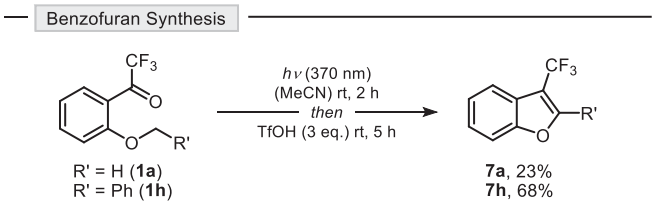


SCHEME 3 | For standard conditions, see Table 1, Entry 8. (a) Mechanistic outline. (b) Triplet quenching experiment. (c) Competition between the 1,5-hydrogen atom transfer (1,5-HAT) and 1,6-hydrogen atom transfer (1,6-HAT). (d) Competition between intramolecular and intermolecular HAT reactions.

2d could be isolated in 78% and 39% yield, respectively. In contrast, the 3,5-di-*tert*-butyl substituted acetophenone reacted smoothly and provided benzofuranol **2e** in 92% yield. We also examined the behavior of secondary and tertiary alkoxy substitution, as steric factors can influence both H-atom abstraction rates and the subsequent cyclization. Extension of the alkyl chain by ethyl and octyl groups afforded the desired products **2f-g** in moderate yields and dr, whereas allyl and benzyl groups generally provided superior results (**2h-i**), potentially due to better stabilization of the 1,5-biradical intermediate. We further explored secondary *O*-alkyl substituents to generate tertiary radical intermediates and assess the impact on reactivity. The isopropyl-substituted substrate afforded the product **2j** in low yield, although it can form a stable radical intermediate; however, steric hindrance likely hampers either H-atom abstraction or consecutive cyclization. Overall, these substrates yielded the corresponding spirocyclic compounds **2k-m** in moderate yields.

It needs to be noted that some substitutions at the aromatic ring(s) were not tolerated in the photocyclization reaction (Scheme 2b). Among them, acetophenones bearing 3-methoxy (**1n**) and 3-cyano (**1o**) groups remained unreacted. UV–Vis spectra revealed that their absorption profiles were nearly identical to the model substrate (see the Supporting Information for further information). In addition, 2-naphthylmethoxy trifluoroacetophenone (**1p**) showed no conversion, even after extended irradiation times. On the other hand, substrate **1q** bearing a 5-methyl substituent decomposed when subjected to the optimized reaction conditions.

To explain the unproductive reaction outcomes for such small structural changes, we had a closer look on the reaction mechanism (Scheme 3). Irradiation of aryl ketones is known to generate n,π^* and π,π^* triplet excited states of **1** that are energetically close to each other (Scheme 3a) [22, 23]. Population of the n,π^* state imparts radical character to the oxygen atom, enabling H-atom abstraction toward biradical **3**, whereas the π,π^* state imparts ionic character, which is inefficient for H-atom abstraction and likely reverts back to the starting material **1** by internal conversion (IC). We suspect that methoxy substituent leads to a preferred population of the π,π^* triplet state, explaining their unreactive



SCHEME 4 | Development of a one-pot sequence toward trifluoromethyl substituted benzofurans underlining the utility of the developed method.

nature due to insufficient 1,6-HAT [24]. On the other hand, naphthalene is known to be a competent triplet quencher. Thus, self-quenching of the n,π^* triplet excited state by the naphthyl group can be assumed [25]. We were able to confirm this hypothesis by the irradiation of model substrate **1a** in the presence of one equivalent (eq.) of naphthalene (**4**) (Scheme 3b). We were also able to show that 1,5-HAT is preferred over 1,6-HAT by using substrate **1r** bearing both a methyl and methoxy substituent in the two ortho positions of the trifluoroacetyl group (Scheme 3c). In this case, the benzocyclobutenol **5** was isolated in 95% as the sole product. The formation of benzofuranol **2r** was not observed. Interestingly, when 4-methylanisol (**6**) was added to the optimal photocyclization conditions for **1a**, full conversion but no formation of **2a** was observed, suggesting that intermolecular HAT may outcompete the required intramolecular version (Scheme 3d, see the Supporting Information for further details). This would also explain the decomposition of the tolyl-derived substrate **1q** (cf. Scheme 2b).

We envisioned that dehydration of the products could provide access to 3-trifluoromethyl-substituted benzofurans [26, 27]. Being aware of the challenge of generating a carbocation adjacent to a trifluoromethyl group, several reaction conditions were evaluated (see section 5.1 of the Supporting Information for further information). Among them, trifluoromethanesulfonic acid (TfOH) proved effective, affording the desired products **7a** and **7h** in acceptable yields when using a one-pot process (Scheme 4).

3 | Conclusion

In summary, we have established a photochemical cyclization strategy for the synthesis of trifluoromethyl-substituted furanols and furans from readily available trifluoroacetophenones. The transformation proceeds via a 1,6-HAT/radical recombination sequence that forges the key C—C bond and enables access to sterically demanding benzofuranols, including spirocyclic frameworks. In cases where diastereomeric products can be formed, the method provides moderate to good levels of selectivity (up to 90:10 dr). Ongoing efforts are directed toward extending this strategy to more complex, lipid-like molecules [28].

4 | Experimental Section

4.1 | General Procedure for Photocyclization Reaction

Ortho-methoxy-2,2,2-trifluoroacetophenone was dissolved in acetonitrile (0.01 M) and was irradiated using a 40 W 370 nm Gen 2 KSPR160L Kessil LED lamp for 2 h at room temperature. The solvent was removed under reduced pressure. The crude mixture was purified via flash column chromatography (SiO_2, hexane/EtOAc).

Author Contributions

A.P. and J.M.W. conceived the project. A.P. conducted all experimental work. J.M.W. provided supervision and secured funding. A.P. and J.M.W. contributed to the analysis and interpretation of the data and to the preparation of the manuscript.

Acknowledgments

Generous financial support by the Johannes Gutenberg-Universität Mainz and the Deutsche Forschungsgemeinschaft (CRC 1552, Project 465145163) is acknowledged.

Open access funding enabled and organized by Projekt DEAL.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The data that support the findings of this study are available in the supplementary material of this article.

References

1. J. W. Petr Klan, "Photochemistry of Organic Compounds," in *Chemistry of Excited Molecules* (Wiley VCH, 2009).

2. R. G. W. Norrish and C. H. Bamford, "Photo-Decomposition of Aldehydes and Ketones," *Nature* 140 (1937): 195–196, https://doi.org/10.1038/140195b0.

3. N. Yang and D.-D. H. Yang, "Photochemical Reactions of Ketones in Solution," *Journal of the American Chemical Society* 80 (1958): 2913–2914, https://doi.org/10.1021/ja01544a092.

4. C. Chen, "The Past, Present, and Future of the Yang Reaction," *Organic & Biomolecular Chemistry* 14 (2016): 8641–8647, https://doi.org/10.1039/C6OB01214K.

5. T. Bach and J. P. Hehn, "Photochemical Reactions as Key Steps in Natural Product Synthesis," *Angewandte Chemie International Edition* 50 (2011): 1000–1045, https://doi.org/10.1002/anie.201002845.

6. M. Nechab, S. Mondal, and M. P. Bertrand, "1,n-Hydrogen-Atom Transfer (HAT) Reactions in Which n≠5: An Updated Inventory," *Chemistry: A European Journal* 20 (2014): 16034–16059, https://doi.org/10.1002/chem.201403951.

7. S. Sarkar, K. P. S. Cheung, and V. Gevorgyan, "C-H Functionalization Reactions Enabled by Hydrogen Atom Transfer to Carbon-Centered Radicals," *Chemical Science* 11 (2020): 12974–12993, https://doi.org/10.1039/D0SC04881J.

8. D. Ravelli, S. Protti, and M. Fagnoni, "Carbon-Carbon Bond Forming Reactions via Photogenerated Intermediates," *Chemical Reviews* 116 (2016): 9850–9913, https://doi.org/10.1021/acs.chemrev.5b00662.

9. P. J. Wagner, "1,5-Biradicals and Five-Membered Rings Generated by .delta.-hydrogen Abstraction in Photoexcited Ketones," *Accounts of Chemical Research* 22 (1989): 83–91, https://doi.org/10.1021/ar00159a001.

10. A. E. Dorigo and K. N. Houk, "Transition Structures for Intramolecular Hydrogen-Atom Transfers: The Energetic Advantage of Seven-Membered Over Six-Membered Transition Structures," *Journal of the American Chemical Society* 109 (1987): 2195–2197, https://doi.org/10.1021/ja00241a056.

11. H. Ihmels and J. R. Scheffer, "The Norrish Type II Reaction in the Crystalline state: Toward a Better Understanding of the Geometric Requirements for γ-Hydrogen Atom Abstraction," *Tetrahedron* 55 (1999): 885–907, https://doi.org/10.1016/S0040-4020(98)01019-9.

12. H. Maag, M. Schmitz, A. Sandvoß, et al., "Photocyclization of Fluorinated Acetophenones Unlocks an Efficient Way to Solar Energy Storage," *Journal of the American Chemical Society* 146 (2024): 32701–32707, https://doi.org/10.1021/jacs.4c12249.

13. P. J. Wagner, M. A. Meador, and J. C. Scaiano, "Photocyclizations of o-(Benzyloxy)acetophenone and -Benzophenone: Effects of Variable Rotational Freedom on Biradical Behavior," *Journal of the American Chemical Society* 106 (1984): 7988–7989, https://doi.org/10.1021/ja00337a066.

14. S. Yamada, A. Iwaoka, Y. Fujita, and S. Tsuzuki, "Tetraalkylammonium-Templated Stereoselective Norrish-Yang Cyclization," *Organic Letters* 15 (2013): 5994–5997, https://doi.org/10.1021/ol4028732.

15. T. Horaguchi, C. Tsukada, E. Hasegawa, T. Shimizu, T. Suzuki, and K. Tanemura, "Photocyclization Reactions. Part 1. Synthesis of Dihydrobenzofuranols Using Photocyclization of 2-Alkoxybenzaldehydes, 2′-Alkoxyacetophenones, 2-Formylphenoxyacetic Acids and 2-Acetylphenoxyacetic Acids," *Journal of Heterocyclic Chemistry* 28 (1991): 1261–1272, https://doi.org/10.1002/jhet.5570280518.

16. C. B. DeZutter, J. H. Horner, and M. Newcomb, "Rate Constants for 1,5- and 1,6-Hydrogen Atom Transfer Reactions of Mono-, Di-, and Tri-Aryl-Substituted Donors, Models for Hydrogen Atom Transfers in Polyunsaturated Fatty Acid Radicals," *Journal of Physical Chemistry A* 112 (2008): 1891–1896, https://doi.org/10.1021/jp710750f.

17. B. Morandi and E. M. Carreira, "Expedient Preparation of Trifluoromethyl-Substituted Benzofuranols," *Organic Letters* 13 (2011): 5984–5985, https://doi.org/10.1021/ol202423s.

18. T. Kobatake, D. Fujino, S. Yoshida, H. Yorimitsu, and K. Oshima, "Synthesis of 3-Trifluoromethylbenzobfurans From Phenols via Direct Ortho Functionalization by Extended Pummerer Reaction," *Journal of the American Chemical Society* 132 (2010): 11838–11840, https://doi.org/10.1021/ja1030134.

19. C. Isanbor and D. O'Hagan, "Fluorine in Medicinal Chemistry: A Review of Anti-Cancer Agents," *Journal of Fluorine Chemistry* 127 (2006): 303–319, https://doi.org/10.1016/j.jfluchem.2006.01.011.

20. K. Müller, C. Faeh, and F. Diederich, "Fluorine in Pharmaceuticals: Looking Beyond Intuition," *Science* 317 (2007): 1881–1886.

21. S. Purser, P. R. Moore, S. Swallow, and V. Gouverneur, "Fluorine in Medicinal Chemistry," *Chemical Society Reviews* 37 (2008): 320–330, https://doi.org/10.1039/B610213C.

22. P. J. Wagner, M. A. Meador, and B. S. Park, "The Photocyclization of o-Alkoxy Phenyl Ketones," *Journal of the American Chemical Society* 112 (1990): 5199–5211, https://doi.org/10.1021/ja00169a031.

23. S. Rousseaux, J. Pearson, S. Dudra, et al., "Overriding Norrish Type II to Access Cyclopropanols," *Journal of the American Chemical Society* 147 (2025): 36890–36897, https://doi.org/10.1021/jacs.5c13001.

24. M. W. Wolf, R. E. Brown, and L. A. Singer, "Deactivation of Benzophenone Triplets via Exciplex Formation. Evidence for Dual Reaction Pathways," *Journal of the American Chemical Society* 99 (1977): 526–531, https://doi.org/10.1021/ja00444a036.

25. H. Satzger, B. Schmidt, C. Root, et al., "Ultrafast Quenching of the Xanthone Triplet by Energy Transfer: New Insight Into the Intersystem Crossing Kinetics," *Journal of Physical Chemistry A* 108 (2004): 10072–10079, https://doi.org/10.1021/jp047583+.

26. W. Liu, N. Chen, X. Yang, L. Li, and C.-J. Li, "Dehydrative Condensation of Carbonyls With Non-Acidic Methylenes Enabled by Light: Synthesis of Benzofurans," *Chemical Communications* 52 (2016): 13120–13123, https://doi.org/10.1039/C6CC07626B.

27. G. A. Kraus, P. J. Thomas, and M. D. Schwinden, "An Approach to Aflatoxins Using Type II Photocyclization Reactions," *Tetrahedron Letters* 31 (1990): 1819–1822, https://doi.org/10.1016/S0040-4039(00)98794-X.

28. R. Breslow and M. A. Winnik, "Remote Oxidation of Unactivated Methylene Groups," *Journal of the American Chemical Society* 91 (1969): 3083–3084, https://doi.org/10.1021/ja01039a043.

29. C. P. Rosenau, B. J. Jelier, A. D. Gossert, and A. Togni, "Exposing the Origins of Irreproducibility in Fluorine NMR Spectroscopy," *Angewandte Chemie International Edition* 57 (2018): 9528–9533, https://doi.org/10.1002/anie.201802620.

30. M. Matsui, T. Shiota, Y. Kubota, et al., "N-(2-Alkoxyphenyl)-Substituted Double Rhodanine Indoline Dyes for Zinc Oxide Dye-Sensitized Solar Cell," *Tetrahedron* 68 (2012): 4286–4291, https://doi.org/10.1016/j.tet.2012.03.060.

31. D. Albat, M. Reiher, J.-M. Neudörfl, and H.-G. Schmalz, "Improved Synthesis of MediPhos Ligands and Their Use in the Pd-Catalyzed Enantioselective N-Allylation of Glycine Esters," *European Journal of Organic Chemistry* 2021 (2021): 4237–4242, https://doi.org/10.1002/ejoc.202100748.

32. P. Hong, X. Zhu, X. Lai, Z. Gong, M. Huang, and Y. Wan, "Room-Temperature CuI-Catalyzed N-Arylation of Cyclopropylamine," *Journal of Organic Chemistry* 89 (2024): 57–67, https://doi.org/10.1021/acs.joc.3c01357.

33. S. O. Simonetti, E. L. Larghi, and T. S. Kaufman, "Alternate and Step-Economic Synthesis of the β-Methylstyrene Chelating Pre-Ligand of the Hoveyda-Grubbs' II Catalyst," *Organic Preparations and Procedures International* 47 (2015): 227–231, https://doi.org/10.1080/00304948.2015.1025021.

34. L. A. Böser and M. Oestreich, "Kinetic Resolution of BINOLs and Biphenols by Atroposelective, Cu-H-Catalyzed Si-O Coupling With Hydrosilanes," *Organic Letters* 26 (2024): 9531–9535.

35. K. M. Engle, S.-X. Luo, and R. H. Grubbs, "An S(N)Ar Approach to Sterically Hindered Ortho-Alkoxybenzaldehydes for the Synthesis of Olefin Metathesis Catalysts," *Journal of Organic Chemistry* 80 (2015): 4213–4220, https://doi.org/10.1021/acs.joc.5b00563.

36. M. Kirihara, K. Suzuki, K. Nakakura, et al., "Oxidation of Fluoroalkyl Alcohols Using Sodium Hypochlorite Pentahydrate," *Journal of Fluorine Chemistry* 243 (2021): 109719, https://doi.org/10.1016/j.jfluchem.2020.109719.

37. R. J. Wiles, J. P. Phelan, and G. A. Molander, "Metal-Free Defluorinative Arylation of Trifluoromethyl Alkenes via Photoredox Catalysis," *Chemical Communications* 55 (2019): 7599–7602, https://doi.org/10.1039/C9CC04265B.

38. W. Jud, S. Maljuric, C. O. Kappe, and D. Cantillo, "Cathodic C-H Trifluoromethylation of Arenes and Heteroarenes Enabled by an in Situ-Generated Triflyltriethylammonium Complex," *Organic Letters* 21 (2019): 7970–7975, https://doi.org/10.1021/acs.orglett.9b02948.

Supporting Information

Additional supporting information can be found online in the Supporting Information section.

Supporting file: hlca70023-sup-0001-SuppMat.pdf