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Catalytic vs. uncatalyzed [2 + 2] photocycloadditions of quinones with alkynes†

Alexander A. Fadeev and Martin Kotora *

Photoreactions of quinones with alkynes under catalytic and non-catalytic conditions were studied. In contrast to recent reports, simple irradiation with blue light is sufficient to trigger [2 + 2] photocycloadditions, which afford either fused cyclobutenes or reactive *para*-quinone methides (*p*-QMs) depending on the quinone structure. Revision of the chemo- and regioselectivity of the uncatalyzed photoreactions provided useful insight into their overlooked relatedness to the recently developed catalytic protocols. Experimental evidence indicates that the reactivity of the photochemically generated *p*-QMs is sufficient to perform uncatalyzed reactions with nucleophiles, which can help to explain the existing transformations and develop new cascade transformations involving quinones and alkynes.

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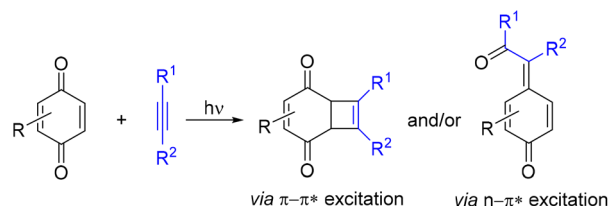
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1. Introduction

Photocatalytic reactions enable access to unique intermediates and products, inaccessible by classical chemical catalysis. The synergy between photochemistry and catalysis has created vast synthetic opportunities by establishing new reactivity modes, such as transition metal photoredox catalysis,¹ organic photoredox catalysis (photo-organocatalysis)² and metallaphotoredox catalysis.³ Photocatalytic approaches have been proven to be more general than purely photochemical methods by not requiring light absorption by reactants. On the other hand, purely photochemical reactions are ideally green, accessible and inexpensive and still remain a valuable synthetic tool.⁴

Quinones play an important role in chemistry and biology, largely due to their redox and photoredox properties. Since the discovery of [2 + 2] photodimerization of thymoquinone by Liebermann in 1877,⁵ the photochemistry of quinones has received considerable attention and continues to grow.⁶ Reactions of quinones with alkynes have attracted increased interest due to the accessibility of the starting materials and the structural diversity of the products, which was later broadened with the aid of catalysis.

Uncatalyzed photoreactions of quinones with alkynes have been reported since the 1960s, yielding either fused cyclobutenes or *p*-quinone methides (*p*-QMs) *via* π - π^* or n - π^* quinone triplet states, respectively (Scheme 1).⁷ The reaction outcome



Scheme 1 Possible products of uncatalyzed photoreactions of quinones with alkynes.

strongly depends on the electronic properties of the used quinone: electron-poor *p*-benzoquinones give *p*-QMs, while electronically richer methoxy-*p*-benzoquinones and naphthoquinones give cyclobutenes as main products. Notably, highly polar substrates reportedly react even in the absence of light.⁸ In recent years, such reactions have found application in the synthesis of push-pull chromophores and spiro-systems,⁸ caged compounds,⁹ and activators of mRNAs.¹⁰

Over the past decade, several catalytic photoreactions involving quinones and alkynes have been developed, enabling the synthesis of structurally diverse products: aryl ketones,^{11,12} indoles,¹³ naphthofurans¹⁴ and various carbonyl compounds with a sterically hindered quaternary stereocenter in the α -position.¹⁵ Given that these photocatalytic methods have already demonstrated high potential in diversity-oriented synthesis and target-oriented synthesis aimed at pharmaceuticals and their precursors, the development of purely photochemical versions of such processes may help to minimize the generated waste, synthesis costs, and the risks associated with product contamination by transition metals. To achieve this,

Department of Organic Chemistry, Faculty of Science, Charles University, Albertov 6, 128 43 Praha 2, Czech Republic. E-mail: kotora@natur.cuni.cz;

Fax: +420 221 951 053; Tel: +420 221 951 326

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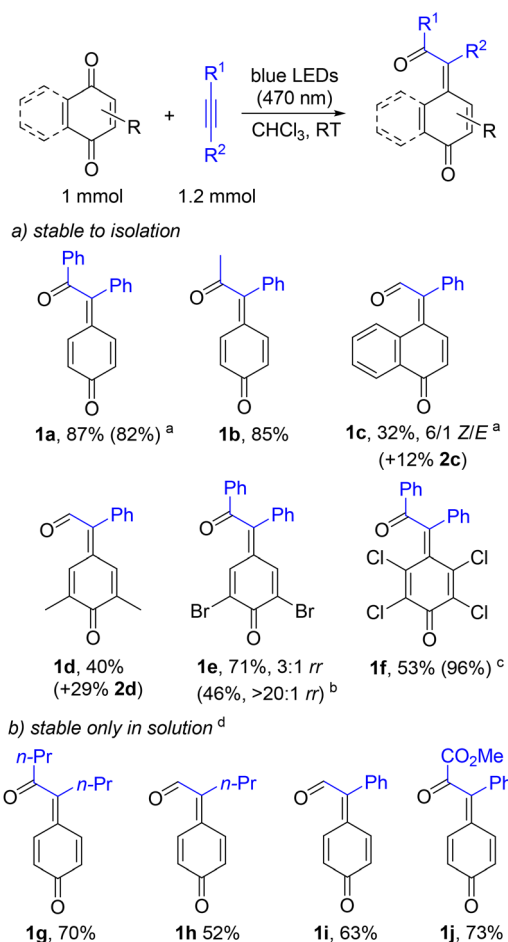
some of the aforementioned catalytic transformations relied on uncatalyzed photointeraction between quinones and alkynes to generate *p*-QMs as intermediates,¹⁵ although the subsequent uncatalyzed reactions with nucleophiles were found problematic.^{15a,ef} However, other reports excluded^{12,13} or did not consider^{11,14} such an interaction as part of the primary or secondary reaction pathway. Nevertheless, establishing pathways and conditions for product formation without a catalyst is important not only for the mechanistic understanding of such processes, but also for developing their enantioselective variants.^{15b,c}

Herein, we report the possibilities of uncatalyzed [2 + 2] photocycloadditions of quinones with alkynes, compare their chemo- and regioselectivity with the recent catalytic versions and revise the structures of three reported cycloaddition products. In addition, we establish the conditions for an efficient uncatalyzed addition of nucleophiles to the photochemically generated *p*-QMs, highlighting its reversibility and utility in the development of synthetically useful cascade transformations using easily accessible quinones and alkynes.

2. Results and discussion

2.1. Photoreactions leading to *p*-QMs

Initially, the high synthetic potential of *p*-QMs¹⁶ prompted us to study the structure and stability of those that can be obtained from readily available quinones and alkynes. We believed that the electron-withdrawing effect of the exocyclic carbonyl group in the expected products would benefit their stability and avoid the introduction of bulky stabilizing groups (*i.e.* aryl and *tert*-butyl^{7,15}), which may not be desired in further synthetic applications. First, a model reaction between *p*-benzoquinone and diphenylacetylene in acetonitrile under irradiation with blue light-emitting diodes (LEDs) showed that *p*-QM **1a** can be obtained in 82% isolated yield (Scheme 2). The yield was further improved to 87% by using chloroform as the solvent. Reacting *p*-benzoquinone with 1-phenyl-1-propyne under these conditions selectively provided **1b** in 85% yield. Electronically richer quinones exhibited higher reactivity of the C=C bonds. Thus, when phenylacetylene reacted with 1,4-naphthoquinone or with 2,6-dimethylbenzoquinone, *p*-QMs **1c** and **1d** were obtained in lower yields (32% and 40%) due to the concurrent formation of cyclobutenes **2c** and **2d** (12% and 29%). In fact, **1c** was obtained as a mixture of stereoisomers *Z*-**1c** and *E*-**1c** in a 6/1 ratio. Pure *Z*-**1c** (*Z/E* > 20/1) was obtained by crystallization of the isomeric mixture from DCM/hexanes and its structure was confirmed by X-ray diffraction analysis (see the ESI, Section 3†). Prolonged exposure of photosensitive *Z*-**1c** to blue light caused its isomerization into *E*-**1c** and aromatization of the latter.^{7d,10a} In contrast to electron-rich quinones, electron-poor tetrachloro-1,4-benzoquinone and 2,6-dibromo-1,4-benzoquinone reacted with diphenylacetylene chemoselectively to give *p*-QMs **1e** and **1f** as main products. Finally, several *p*-QMs were found to be unstable in the pure



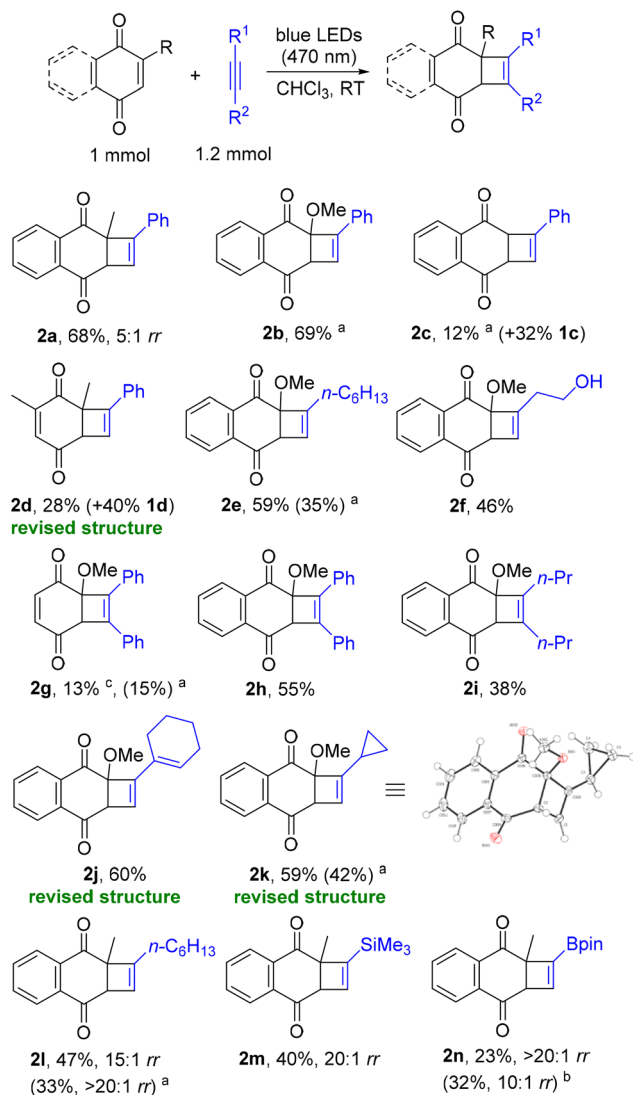
Scheme 2 Photoreactions leading to the predominant formation of *p*-QMs **1a–1j**. ^a MeCN was used as the solvent, ^b after subsequent purification by recrystallization, ^c yield in parentheses is based on the recovered diphenylacetylene, ^d NMR yields are given.

state but sufficiently stable in solution. For example, **1g** was generated in solution from *p*-benzoquinone and 4-octyne in 70% yield. Unsymmetrical alkynes, such as 1-pentyne, phenylacetylene, and methyl phenylpropiolate, regioselectively reacted with *p*-benzoquinone to give respective solutions of labile *p*-QMs **1h**, **1i** and **1j** in comparable yields.

2.2. Photoreactions leading to cyclobutenes

The synthesis of cyclobutenes by [2 + 2] photocycloaddition of quinones with alkynes does not typically require any additional reagents,^{7,10,15} although trifluoroacetic acid and potassium persulfate were recently reported as necessary additives for certain transformations of this type.¹² To evaluate the role of these reagents, we first attempted to perform [2 + 2] cycloadditions between such quinones and alkynes by the action of blue light alone (Scheme 3). All the reactions provided the cycloaddition products **2**, indicating that stoichiometric amounts of trifluoroacetic acid and potassium persulfate are not essential for such photoreactions to proceed. On





Scheme 3 Photoreactions affording fused cyclobutenes **2a–2n**.
^a MeCN was used as the solvent, ^b based on the ¹H NMR analysis of the crude mixture, ^c unreacted diphenylacetylene was recovered (56%).

the other hand, we did not observe an increase in the reaction's efficiency when these reagents were employed according to Shah's method.¹² To determine the reason for decreased yields in the catalyst-free photoreactions, we analyzed the reaction mixtures for possible byproducts. All the reactions proceeded with high conversion of quinones (>90%) and gave a similar outcome in acetonitrile and chloroform. 2-Methoxynaphthoquinone showed complete chemo- and regioselectivity in reactions with terminal alkynes, providing cyclobutenes **2b**, **2e**, **2f**, and **2h–2k** in 38–69% yields. A dimer of 2-methoxynaphthoquinone¹⁷ was formed in these reactions as the main byproduct (isolated in up to 22% yield when **2e** was synthesized in MeCN). Conversely, menadione was not only less prone to dimerization, but also less chemo- and regioselective. Thus, products arising from Paternò–Büchi reac-

tivity were detected in the crude mixtures, and cyclobutenes **2a** and **2l–2n** were formed as regioisomeric mixtures with the rr major/minor $\geq 5/1$. Some other possible photochemical side reactions can be found in the literature.^{7e,18}

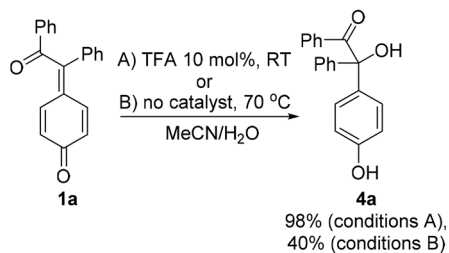
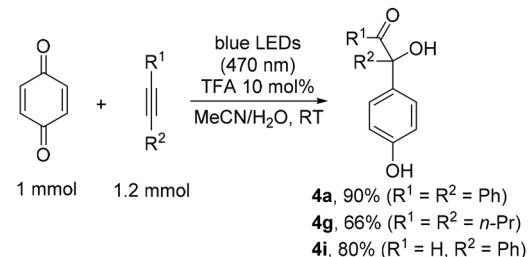
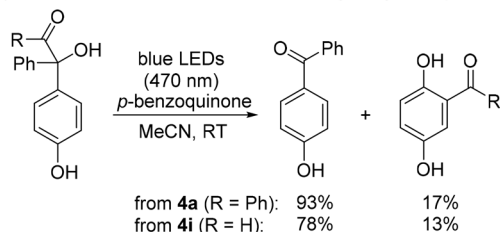
According to the earlier reports, photocycloadditions of terminal alkynes to monosubstituted quinone double bonds proceed regioselectively to give predominantly *syn*-products.^{7c,e} Shah, however, suggested an unusual reversal of regioselectivity in persulfate-mediated photoreactions of 2-methoxynaphthoquinone with cyclopropylacetylene and 1-ethynylcyclohexene based on the comparison of *J*-coupling in the ¹H NMR spectra.¹² When we conducted these photocycloadditions in a purely photochemical setup, the formed cyclobutenes **2j** and **2k** appeared spectrally identical to those reported by Shah *et al.* (the authors described cyclobutene hydrogens as singlets, yet we observed small *J*-coupling (<1 Hz)). To ascertain the structure, we obtained a single crystal of **2k**, X-ray diffraction analysis of which disproved the proposed *anti*-arrangement in favor of the *syn*-arrangement (see the ESI, Section 3†). Compiled NMR data of compounds **2** showed that the reversal of *syn*-selectivity in the reactions with other terminal alkynes is also unlikely (see the ESI, Table S2†). Besides that, analysis of NMR data revealed that the spectra of cyclobutene **2d** coincide with those of the recently reported 4-benzoyl-2,6-dimethylcyclohexa-2,5-dien-1-one¹¹ – a product of a copper-catalyzed photointeraction between phenylacetylene and *in situ* generated 2,6-dimethylbenzoquinone. However, the structure of this reported product entails a rapid equilibrium shift to the fully aromatic tautomer. More likely, this compound possesses the structure of cyclobutene **2d** and could be formed by the classical [2 + 2] photocycloaddition.

2.3. Product diversification using nucleophilic addition to *p*-QMs

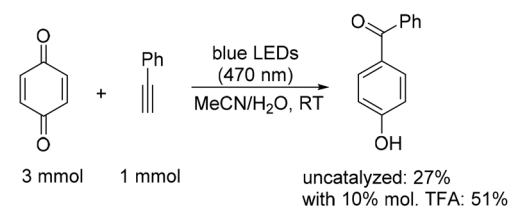
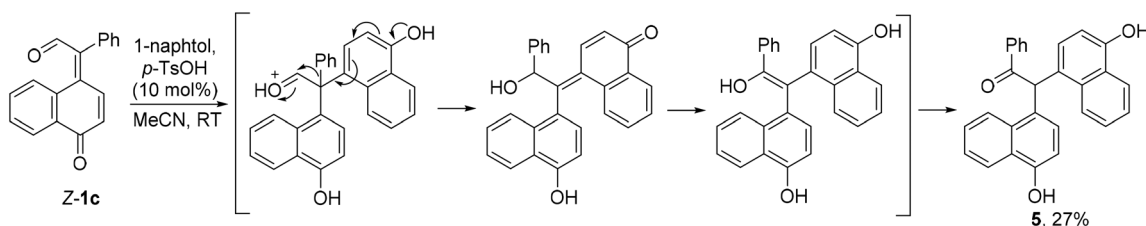
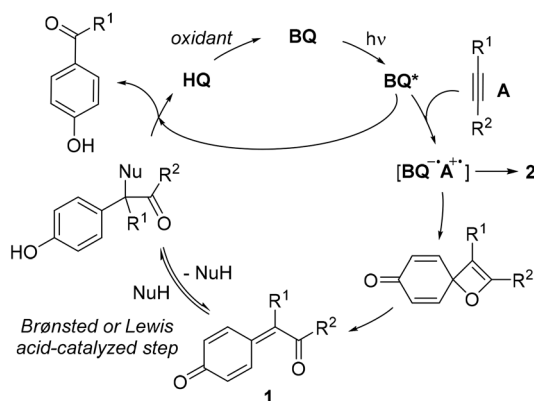
Recent studies have shown that [2 + 2] photocycloadditions of quinines with alkynes can work in tandem with catalytic 1,6-conjugate addition of nucleophiles to the *in situ* formed *p*-QMs.¹⁵ To address the less studied uncatalyzed addition, we first performed reactions of *p*-QM **1a** with carbon and heteroatom nucleophiles under catalyst-free conditions (Scheme 4). Thus, 1,6-conjugate addition of thiophenol and aniline proceeded rapidly at room temperature even in the absence of $\text{Zn}(\text{OTf})_2$,^{15a} providing adducts **3a**, its benzo analogue **3b**, and **3c** in high yields (**3c** was found to be unstable and isolated as the *O*-acetate derivative **3c'**). However, weaker nucleophiles reacted sluggishly at room temperature, and heating was found helpful. Thus, heating **1a** with imidazole at 70 °C afforded the *N*-alkylation product **3d** in nearly quantitative yield. Similarly, phosphonate **3e** was prepared in 66% yield from **1a** and triethyl phosphite in an Arbuzov-type reaction. The addition of indole became effective at 200 °C in a microwave reactor and furnished **3f** in 83% yield (for comparison, catalysis with $\text{Zn}(\text{OTf})_2$ ^{15a} afforded **3f** in a comparable yield of 87% at room temperature). Similarly, microwave-assisted addition of methanol to **1a** provided **3g** in 47% yield (98% based on recovered **1a**). Treatment of **1a** with potassium thio-





a) 1,6-conjugate addition of water to **1a**b) one-pot synthesis of alcohols **4a**, **4g** and **4i**c) oxidation of alcohols **4a** and **4i** into 4-hydroxybenzophenone

d) one-pot synthesis of 4-hydroxybenzophenone

**Scheme 5** Transformations based on nucleophilic addition of water to *p*-QMs **1a**, **1g** and **1i**.**Scheme 6** Unexpected outcome of the acid-catalyzed reaction of **Z-1c** with 1-naphthol and its plausible mechanism.**Scheme 7** Summarized mechanistic pathways for the uncatalyzed light-triggered reactions involving a quinone (BQ), a hydroquinone (HQ) and an alkyne (A).

formed without any additional reagents, (b) the subsequent 1,6-conjugate addition of nucleophiles to the photochemically generated *p*-QMs is reversible and can be efficiently achieved even without catalysis, and (c) the formation of *p*-hydroxyaryl ketones from quinones and alkynes can also proceed in an uncatalyzed fashion when an excess of quinone is used. Overall, uncatalyzed light-mediated reactions between quinones and alkynes offer milder and greener alternatives to their catalytic versions, yet allowing the preparation of diverse products from readily available starting materials. At the same time, we believe that understanding the uncatalyzed photo-reactivity may help to develop novel catalytic transformations with even broader synthetic applications.

Conflicts of interest

There are no conflicts to declare.

3. Conclusions

In conclusion, we reinvestigated the photochemical interaction between quinones and alkynes in both non-catalytic and catalytic protocols. We revised its chemo- and regioselectivity and showed that (a) such [2 + 2] photocycloadditions can be per-

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References

- (a) K. P. S. Cheung, S. Sarkar and V. Gevorgyan, *Chem. Rev.*, 2022, **122**, 1543–1625; (b) K. L. Skubi, T. R. Blum and T. P. Yoon, *Chem. Rev.*, 2016, **116**, 10035–10074.
- (a) N. A. Romero and D. A. Nicewicz, *Chem. Rev.*, 2016, **116**, 10075–10166; (b) D. Ravelli, M. Fagnoni and A. Albini, *Chem. Soc. Rev.*, 2013, **42**, 97–113; (c) M. J. Genzink, J. B. Kidd, W. B. Swords and T. P. Yoon, *Chem. Rev.*, 2022, **122**, 1654–1716.
- A. Y. Chan, I. B. Perry, N. B. Bissonnette, B. F. Buksh, G. A. Edwards, L. I. Frye, O. L. Garry, M. N. Lavagnino, B. X. Li, Y. Liang, E. Mao, A. Millet, J. V. Oakley, N. L. Reed, H. A. Sakai, C. P. Seath and D. W. C. MacMillan, *Chem. Rev.*, 2022, **122**, 1485–1542.
- (a) M. Oelgemöller, *Chem. Rev.*, 2016, **116**, 9664–9682; (b) M. D. Kärkäs, J. A. Porco, Jr. and C. R. J. Stephenson, *Chem. Rev.*, 2016, **116**, 9683–9747; (c) M. Tavakolian and M. Hosseini-Sarvari, *ACS Sustainable Chem. Eng.*, 2021, **9**, 4296–4323; (d) S. Protti, D. Ravelli and M. Fagnoni, *Trends Chem.*, 2022, **4**, 305–317.
- C. Liebermann, *Ber. Dtsch. Chem. Ges.*, 1877, **10**, 2177–2179.
- (a) J. M. Bruce, *Photochemistry of Quinones*, John Wiley & Sons Ltd, 1974; (b) K. Maruyama and A. Osuka, *Recent advances in the photochemistry of quinones*, John Wiley & Sons Ltd, 1988; (c) Y. Ando and K. Suzuki, *Chem. – Eur. J.*, 2018, **24**, 15955–15964.
- (a) H. E. Zimmerman and L. Craft, *Tetrahedron Lett.*, 1964, **5**, 2131–2136; (b) D. Bryce-Smith, G. I. Fray and A. Gilbert, *Tetrahedron Lett.*, 1964, **5**, 2137–2139; (c) S. P. Pappas and B. C. Pappas, *Tetrahedron Lett.*, 1967, **8**, 1597–1600; (d) S. P. Pappas and N. A. Portnoy, *J. Org. Chem.*, 1968, **33**, 2200–2203; (e) S. Farid, W. Kothe and G. Pfundt, *Tetrahedron Lett.*, 1968, **9**, 4147–4150; (f) E. Bosch, S. M. Hubig and J. K. Kochi, *J. Am. Chem. Soc.*, 1998, **120**, 386–395.
- (a) S. Kato, M. T. R. Beels, P. La Porta, W. B. Schweizer, C. Boudon, J.-P. Gisselbrecht, I. Biaggio and F. Diederich, *Angew. Chem., Int. Ed.*, 2010, **49**, 6207–6211; (b) C. Dengiz, O. Dumele, S. Kato, M. Zalibera, P. Cias, W. B. Schweizer, C. Boudon, J.-P. Gisselbrecht, G. Gescheidt and F. Diederich, *Chem. – Eur. J.*, 2014, **20**, 1279–1286; (c) C. Dengiz and T. M. Swager, *Synlett*, 2017, **28**, 1427–1431; (d) T. Shoji, J. Higashi, S. Ito, M. Yasunami and N. Morita, *Heterocycles*, 2011, **83**, 2271–2274; (e) B. A. Trofimov, L. N. Sobenina, Z. V. Stepanova, I. A. Ushakov, L. M. Sinegovskaya, T. I. Vakul'skaya and A. I. Mikhaleva, *Synthesis*, 2010, 470–476; (f) C. Dengiz, C. Prange, P. Gawel, N. Trapp, L. Ruhlmann, C. Boudon and F. Diederich, *Tetrahedron*, 2016, **72**, 1213–1224.
- J. Álvarez-García, V. Rubio-Pisabarro, C. Silva-López and M. M. Cid, *Org. Lett.*, 2020, **22**, 4527–4531.
- (a) X. Chen, C. Huang, W. Zhang, Y. Wu, X. Chen, C. Zhang and Y. Zhang, *Chem. Commun.*, 2012, **48**, 6432–6434; (b) S.-B. Tan, C. Huang, X. Chen, Y. Wu, M. Zhou, C. Zhang and Y. Zhang, *Bioorg. Med. Chem.*, 2013, **21**, 6124–6131.
- A. Sagadevan, V. P. Charpe, A. Ragupathi and K. C. Hwang, *J. Am. Chem. Soc.*, 2017, **139**, 2896–2899.
- S. Sultan, M. Bhat, M. A. Rizvi and B. A. Shah, *J. Org. Chem.*, 2019, **84**, 8948–8958.
- A. Sagadevan, A. Ragupathi and K. C. Hwang, *Angew. Chem., Int. Ed.*, 2015, **54**, 13896–13901.
- N. Chalotra, I. H. Shah, S. Raheem, M. A. Rizvi and B. A. Shah, *J. Org. Chem.*, 2021, **86**, 16770–16784.
- (a) A. Sharma, V. Dixit, S. Kumar and N. Jain, *Org. Lett.*, 2021, **23**, 3409–3414; (b) Z.-W. Qiu, L. Long, Z.-Q. Zhu, H.-F. Liu, H.-P. Pan, A.-J. Ma, J.-B. Peng, Y.-H. Wang, H. Gao and X.-Z. Zhang, *ACS Catal.*, 2022, **12**, 13282–13291; (c) L. Dai, J. Guo, Q. Huang and Y. Lu, *Sci. Adv.*, 2022, **8**, eadd2574; (d) J. Kumar, A. Ahmed, S. Kumar, S. Raheem, M. A. Rizvi and B. A. Shah, *New J. Chem.*, 2022, **46**, 10967–10973; (e) V. P. Charpe, A. Ragupathi, A. Sagadevan, Y.-S. Ho, M.-J. Cheng and K. C. Hwang, *Chem. – Eur. J.*, 2023, e202300110; (f) V. Dixit, A. Sharma, A. Jangid and N. Jain, *Adv. Synth. Catal.*, 2023, **365**, 892–899.
- For recent reviews, see: (a) A. Parra and M. Tortosa, *ChemCatChem*, 2015, **7**, 1524–1526; (b) C. G. S. Lima, F. P. Pauli, D. C. S. Costa, A. S. de Souza, L. S. M. Forezi, V. F. Ferreira and F. de C. da Silva, *Eur. J. Org. Chem.*, 2020, 2650–2692; (c) J.-Y. Wang, W.-J. Hao, S.-J. Tu and B. Jiang, *Org. Chem. Front.*, 2020, **7**, 1743–1778; (d) G. Singh, R. Pandey, Y. A. Pankhade, S. Fatma and R. V. Anand, *Chem. Rec.*, 2021, **21**, 4150–4173; (e) Y. Hussain, Tamanna, M. Sharma, A. Kumar and P. Chauhan, *Org. Chem. Front.*, 2022, **9**, 572–592.
- J. V. Ellis and J. E. Jones, *J. Org. Chem.*, 1975, **40**, 485–488.
- (a) F. A. L. Anet and D. P. Mullis, *Tetrahedron Lett.*, 1969, **10**, 737–740; (b) W. Kothe, *Tetrahedron Lett.*, 1969, **10**, 5201–5204.
- (a) S. M. McElvain, S. B. Mirviss and C. L. Stevens, *J. Am. Chem. Soc.*, 1951, **73**, 3807–3811; (b) L. Syper, *Tetrahedron*, 1987, **43**, 2853–2871; (c) T. Kataoka and T. Iwama, *Tetrahedron Lett.*, 1995, **36**, 245–248.
- For a recent example, see: L. J. Mitchell, W. Lewis and C. J. Moody, *Green Chem.*, 2013, **15**, 2830–2842.

