



Cite this: *Green Chem.*, 2020, **22**, 3539

Received 30th March 2020,
 Accepted 6th May 2020
 DOI: 10.1039/d0gc01135e
rsc.li/greenchem

Photochemical synthesis of acetals utilizing Schreiner's thiourea as the catalyst†

Nikoleta Spiliopoulou, Nikolaos F. Nikitas and Christoforos G. Kokotos  *

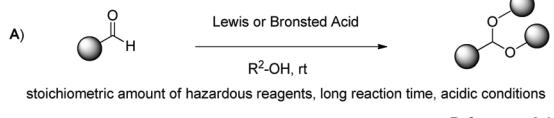
Acetalization of aldehydes is an area of great importance in Organic Chemistry for both synthetic and biological purposes. Herein, we report a mild, inexpensive and green photochemical protocol, where Schreiner's thiourea (*N,N'*-bis[3,5-bis(trifluoromethyl)-phenyl]-thiourea) is utilized as the catalyst and cheap household lamps as the light source. A variety of aromatic and aliphatic aldehydes were converted into acetals in good to high yields (23 examples, 36–96% yield) and an example of the synthesis of a cyclic acetal is provided. The reaction mechanism was also studied.

Introduction

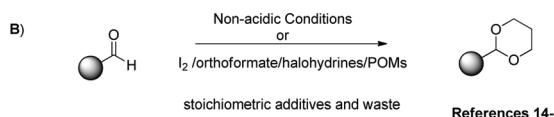
Compounds bearing the carbonyl moiety, such as aldehydes appear to have great synthetic interest and are classified among the most widely used functional groups in Organic Synthesis.¹ In some cases, its high reactivity towards nucleophilic, metal-hydride, alkyl and aryl reagents, constitutes an inhibiting factor that has to be confronted, in order to achieve the desired synthetic transformations. The protection of the carbonyl moieties into acetals with alcohols or diols is a widely employed method in pharmaceutical industry, such as drug design and also in other sectors.² The importance of acetals as carbonyl protecting groups lies in their stability in neutral and strongly basic conditions, which allows a wide spectrum of reactions to occur in their presence. Acetals, apart from their role as a protection group, can also behave as excellent intermediates in many synthetic transformations.³ Expanding their use, acetals are also considered as flavoring additives and aroma enhancers in cosmetic and food products⁴ or as anti-freezing additives in biodiesel fuels.⁵ Since aldehydes are one of the most frequently modifiable functional groups, a great variety of approaches have been reported for their conversion into acetals. The currently used methodologies include the use of strong mineral acids, such as HCl,⁶ solid acids,⁷ acidic polymers,⁸ metal catalysts,⁹ Lewis acids or organic acids^{10,11} (Scheme 1A). The reported synthetic strategies, where either the use of metal catalysts or stoichiometric amounts of acids are employed, raise many disadvantages and potential environ-

mental problems, such as corrosive conditions, long reaction times and usually poor selectivity.¹² In an effort to address these problems and comply with the principles of green and sustainable chemistry,¹³ alternative methods for the synthesis of acetals have been developed. Acetalization of carbonyl compounds can be also achieved utilizing basic¹⁴ or other non-acidic conditions employing hydroxylamine,¹⁵ iodine,¹⁶ trialkyl orthoformates,¹⁷ halohydrins¹⁸ or even catalytic amount of

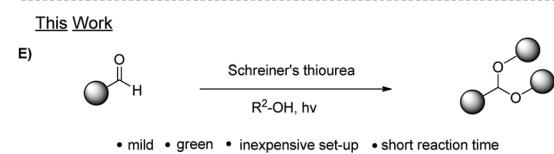
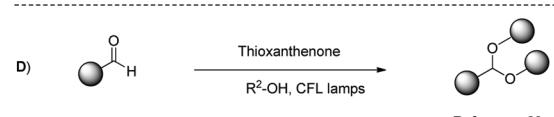
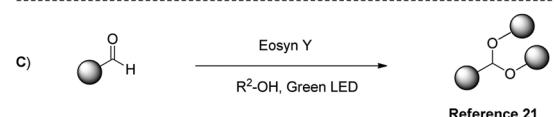
Previous Methods



References 6-11



References 14-19



Laboratory of Organic Chemistry, Department of Chemistry, National and Kapodistrian University of Athens, Panepistimiopolis 15771, Athens, Greece.
 E-mail: ckokotos@chem.uoa.gr

† Electronic supplementary information (ESI) available: Experimental data, ¹H, ¹³C and ¹⁹F NMR data, UV-Vis and mechanistic studies. See DOI: 10.1039/d0gc01135e

Scheme 1 Common synthetic pathways for the acetalization of aldehydes.



anionic metal-oxides as polyoxometalates (POMs)¹⁹ (Scheme 1B). Recently, a totally alternative approach for the synthesis of acetals, in line with the principles of photochemistry²⁰ was introduced in literature²¹ (Scheme 1C). The authors utilized Eosyn Y as the photocatalyst and green LED irradiation and succeeded in the acetalization of aldehydes in excellent yields. However, they did not clarify whether the acidic groups that Eosyn Y bear or the heat source that green LED emit, can be complementary or even the main factor in the completion of the reaction.

Being active for many years in the field of Photochemistry,²² our laboratory had successfully synthesized many different categories of compounds, utilizing a great variety of photocatalysts and studying simultaneously the mechanism of the reaction. Specifically, in 2019, our research group proposed a photochemical synthetic pathway for the acetalization of aldehydes with alcohols or diols, utilizing thioxanthone as the catalyst and common household lamps as the light source.²³ The synthesis of both aromatic and aliphatic acetals was achieved in satisfactory to high yields *via* this protocol (Scheme 1D). The only drawback of the method appeared to be the purification step, since thioxanthone (the catalyst) had a similar *R*_f with the product and a copious column chromatography was necessary. Every other attempt to purify the product by alternative means failed. Herein, exploiting the existing knowledge, we present a novel, mild, green, and fast photochemical synthesis of acetals from aldehydes, utilizing Schreiner's thiourea as the catalyst and cheap, commercially-available household lamps as the irradiation source (Scheme 1E). The driving idea in this work was initially the use of low-cost and environmentally friendly reagents, avoiding the production of hazardous by-products and time-consuming reactions. Working on this logic, we designed a photochemical protocol, where Schreiner's thiourea, an organic compound with a variety of properties (for example, hydrogen bonding with various classes of substrates),²⁴ is used as the catalyst. Its major feature is its ability to activate substrates *via* hydrogen bonding, a field that presents increasing interest in organic chemistry over the last two decades. Moreover, the cheap household lamps set-up or sunlight, which can be also employed, guarantee that no special apparatus or inert atmosphere are required. The reaction time varies from 3 to 18 h, depending on the substrate, and the product can be easily obtained *via* aqueous base extraction or evaporation, rendering this method intertwining with the principles of green chemistry.

Results and discussion

Bearing in mind that thioureas *via* their hydrogen bonding activation can behave similarly to Lewis acids,^{24b} we began our investigations with the evaluation of (thio)urea derivatives as the catalyst (Table 1).²⁵ A range of urea and thiourea catalysts were investigated, concluding that *N,N'*-bis[3,5-bis(trifluoromethyl)phenyl]-thiourea (**3a**) afforded higher yields *versus*

Table 1 Photochemical synthesis of acetal **2a** from aldehyde **1a**^a

Entry	Catalyst loading (mol%)	Catalyst	Yield ^b (%)	Reaction conditions	
				MeOH, <i>hν</i> , 18 h	MeOH, <i>hν</i> , 3 h
1	20		81		
2	10		59		
3 ^c	20		0		
4 ^d	20		13		
5	20		12		
6	20		20		
7	20		10		

^a All reactions were carried out with **1a** (0.50 mmol), catalyst (*x* mol%) in methanol (2 mL), under household bulb irradiation. ^b Yield of isolated product. ^c Reaction was kept in the dark. ^d Reaction took place at 50 °C, under dark.

simple urea and thiourea derivatives (Table 1, entry 1 *vs.* entries 5–7), confirming our initial hypothesis that the presence of the trifluoromethyl groups on the thiourea play a crucial role and *ortho*-CH is also important for the interactions in the catalyst–substrate complex. It has to be pinpointed that the product of the reaction is pure enough and purification can be achieved by just simple evaporation of the excess of methanol and aqueous base wash, without the need for column chromatography.²⁵ Decreasing the catalyst loading to 10 mol%, the yield of the desired acetal **2a** dropped to 59% (Table 1, entry 2). When the reaction was kept in dark, acetal **2a** was not formed (hydrogen bonding activation by itself is not enough for the catalysis, Table 1, entry 3). When the reaction was performed at 50 °C, the desired acetal was formed in 13% yield, verifying that light irradiation is the main factor for



Table 2 Methanol-solvent screening for the synthesis of acetal **2a** from aldehyde **1a**^a

Entry	Solvent	Yield ^b (%)
1	MeOH/MeCN (1 : 1)	24
2	MeOH/CHCl ₃ (1 : 1)	67
3	MeOH/EtOAc (1 : 1)	Traces
4	MeOH/Pet-ether (1 : 1)	61
5	MeOH/CH ₂ Cl ₂ (1 : 1)	63
6	MeOH/toluene (1 : 1)	50
7	MeOH/Et ₂ O (1 : 1)	50
8 ^c	MeOH	72
9 ^d	MeOH	50
10 ^e	MeOH	81

^a All reactions were carried out with **1a** (0.50 mmol), **3a** (20 mol%) and 1 : 1 mixture of solvents (2 mL), under household bulb irradiation.

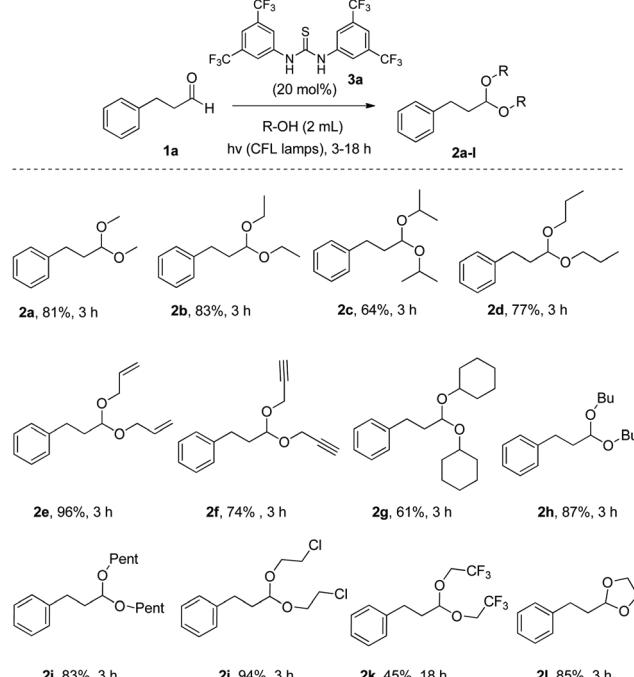
^b Yield of isolated product. ^c Blue LEDs instead of CFL lamps. ^d Green LEDs instead of CFL lamps. ^e Reaction time: 3 h.

the reaction outcome and the thermal pathway is minor (Table 1, entry 4). Furthermore, the irradiated reaction mixture in the absence of **3a** led to 9% yield.²⁵

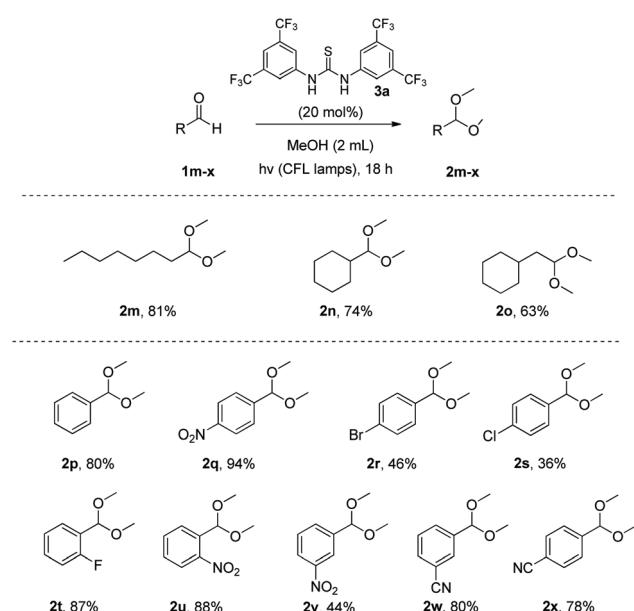
In an effort to further reduce the amount of the alcohol employed, we studied the behavior of the reaction in a 1 : 1 mixture of methanol and other solvents (Table 2, entries 1–7). Unfortunately, only in few occasions the yield of the desired product was good (Table 2, entries 2, 4 and 5), but still lower than when methanol was used alone. Attempts to alter the light source (blue and green LEDs) led to lower yields (Table 2, entries 8 and 9). Finally, the reaction time could be decreased to 3 h (Table 2, entry 10). Sunlight irradiation could efficiently replace household lamp irradiation.

Once the optimum reaction conditions were found, we diverted our attention into exploring the substrate scope (Schemes 2 and 3). Utilizing 3-phenyl-propanal (**1a**) as the starting material, a variety of alcohols were tested, providing the desired acetals in good to excellent yields (Scheme 2). Primary alcohols, alcohols bearing functional groups, such as -Cl or -CF₃ groups, or diols were utilized successfully, while secondary alcohols led to moderate yields, probably due to steric reasons, affording acetals **2a–2l**. Time reaction varied from 3 to 18 h, depending on substrate.

Subsequently, we explored the scope of the aldehydes with methanol (Scheme 3). Initially, other aliphatic aldehydes were tested. The desired products **2m–o** were obtained in good to excellent yields, even in the case of α,α -disubstituted aldehydes (like **1n**). In an effort to expand our method's application, we applied this method in a variety of aromatic aldehydes, bearing many different functional groups (**2p–x**) (Scheme 3). Aromatic substitution did not pose any problem for this methodology, since *para*-, *meta*- and *ortho*-substituted aromatic aldehydes afforded yields that varied from 36% to 94%. The crucial point is that substrates, that were problematic in pre-



Scheme 2 Substrate scope – alcohols.



Scheme 3 Substrate scope – aldehydes.

vious studies (like products **2q** and **2u–x**) that bear groups, like -CN or -NO₂, behaved excellently, providing a strong generality to our method.

Next, the reaction mechanism was studied. For better understanding of the hydrogen bonding activation that **3a** is providing, and having literature as a strong inspiration,^{26,27} we performed ¹H-NMR and ¹⁹F-NMR mechanistic experiments (Fig. 1).²⁵ Initially, the ¹H-NMR (in CDCl₃) of Schreiner's



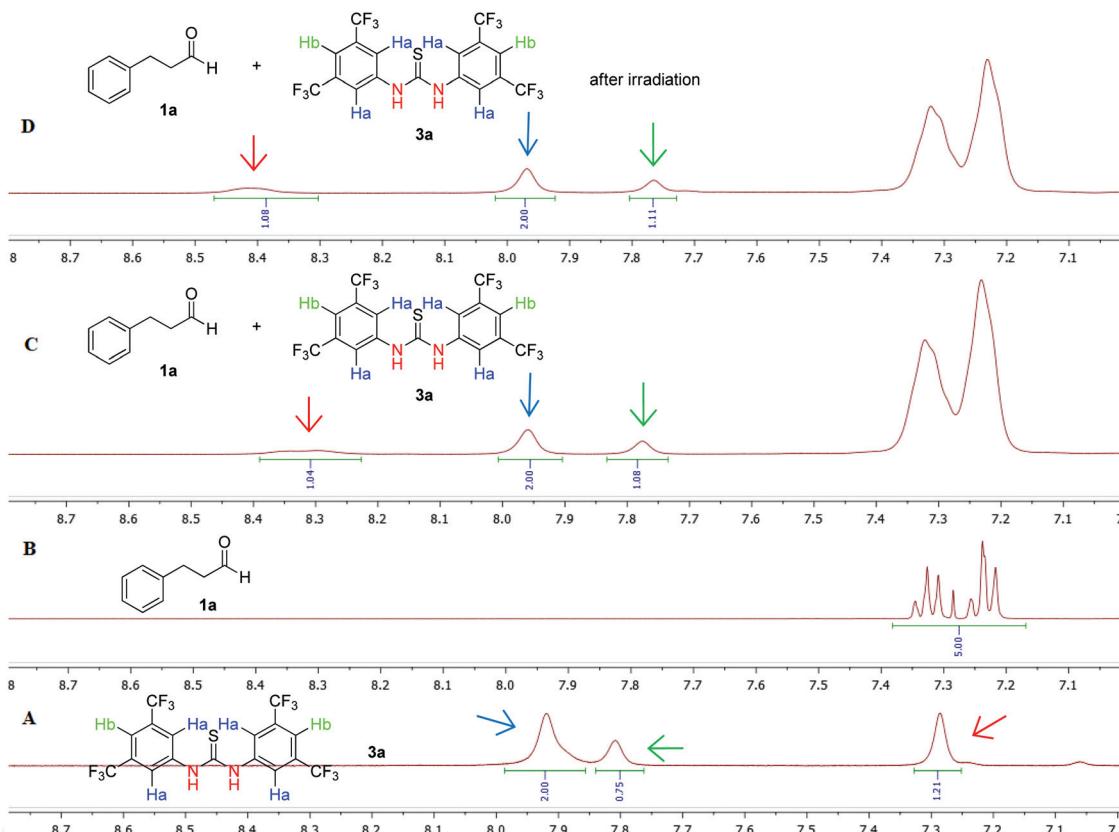


Fig. 1 Zoom in (8.70–7.00 ppm) of ^1H -NMR (in CDCl_3) of (A) Schreiner's thiourea **3a**, (B) 3-phenyl propanal (**1a**), (C) reaction mixture before irradiation and (D) reaction mixture after irradiation.

thiourea **3a** was recorded (Fig. 1A). Two sets of aromatic signals were recorded at 7.92 ppm and 7.81 ppm, while the *NH* appeared at 7.29 ppm. 3-Phenyl-propanal's (**1a**) ^1H -NMR spectrum is presented in Fig. 1B. The addition of 3-phenyl-propanal (**1a**) to a solution of thiourea **3a** in CDCl_3 , led to remarkable changes in ^1H -NMR chemical shifts of the catalyst, as expected (Fig. 1C). The peak at 7.92 ppm shifted downfield at 7.96 ppm, the peak 7.81 ppm shifted upfield at 7.78 ppm, while the *NH* protons shifted downfield from 7.29 ppm to 8.31 ppm. These results confirm the presence of hydrogen bonds between the substrate and the thiourea, supporting the formation of an aldehyde-catalyst complex. After irradiation, similar observations can be drawn (Fig. 1D).

Furthermore, the calculation of the quantum yield (ϕ) of the reaction was performed. According to Yoon and Cismenia,²⁸ the value of the quantum yield is critical for the reaction mechanism. The quantum yield (ϕ) of the photochemical reaction was measured: [$\phi = 46$ ($\phi > 1$)], indicating that a radical propagation mechanism is taking place.

Finally, UV-Vis absorbance studies were carried out (Fig. 2).²⁵ In literature, the presence of an electron donor-acceptor (EDA) complex has been postulated as key mechanistic point in selected photochemical reactions.^{29,30} The formation of an EDA complex is sometimes identified by the bathochromic shift in the UV-Vis absorbance spectrum, after

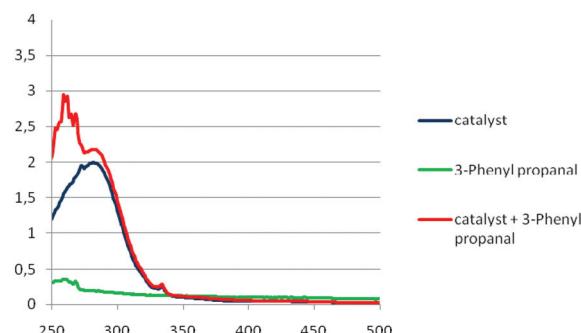
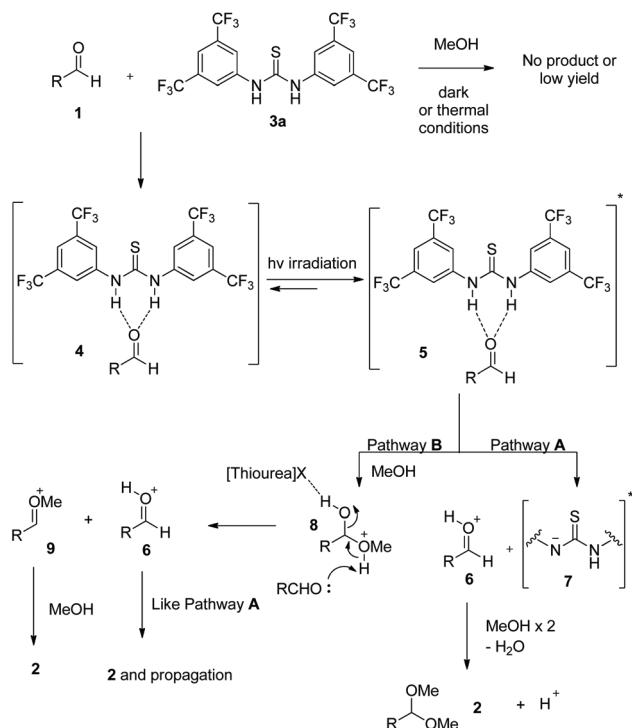


Fig. 2 UV-Vis absorbance of Schreiner's thiourea **3a** (6×10^{-5} M) in MeOH, 3-phenyl-propanal (**1a**) (1×10^{-3} M) in MeOH, and the reaction mixture (3-phenyl-propanal 1×10^{-3} M and Schreiner's thiourea 6×10^{-5} M) in MeOH.

mixing of the two reagents. Based on the UV-Vis absorbance spectra presented in Fig. 2, the absorption of Schreiner's thiourea **3a**, after the addition of aldehyde **1a** did not show any change (Fig. 2). Thus, an EDA-complex is not formed. The reaction was also performed open air and under argon atmosphere, without showing any significant differentiation, reinforcing the fact that oxygen does not participate in the reaction mechanism.





Scheme 4 Proposed reaction mechanism.

Collecting all these data, a possible mechanism can be proposed (Scheme 4). Initially, Schreiner's thiourea **3a** interacts with the aldehyde and *via* hydrogen bonding leads to aldehyde-catalyst complex **4**. Upon irradiation, **4** is excited to **5**. Herein, two possible pathways can be envisaged. Following literature precedent,^{24e,31} where a phenol or a thiourea can behave as a photoacid, complex **5** can lead to an *in situ*-generated acidic species, which leads to intermediates **6** and **7** (pathway A). Protonated intermediate **6** is intercepted by methanol, which after proton transfer, loss of water and another methanol addition leads to product **2** and regenerates the photogenerated acid. Alternatively (pathway B), one can assume a direct nucleophilic addition of methanol to **5**, leading to **8**, with or without a “loose” interaction with the thiourea moiety. Another molecule of aldehyde is activated by abstracting the proton from **8** leading to **6** and **9**, which afford the final product and ensure the propagation similarly to pathway A. A photo induced excited state proton transfer coupled electron transfer mechanism can not be completely excluded at the moment.

Conclusions

In conclusion, a green, inexpensive, mild, environmentally-friendly and fast photochemical synthetic protocol for the synthesis of acetals from aldehydes and alcohols was developed. Utilizing commercially available household lamps as the irradiation source and a simple catalyst, Schreiner's thiourea **3a**, which acts like hydrogen-bond donor, a variety of aromatic

and aliphatic acetals were isolated in good to excellent yields, either by solvent evaporation and aqueous basic extractions or column chromatography in some cases. Based on extensive mechanistic investigation, a proposed mechanistic pathway is presented.

Experimental

General procedure for the synthesis of acetals

In a glass vial with a screw cap containing *N,N'*-bis[3,5-bis(trifluoromethyl) phenyl]-thiourea (**3a**) (Schreiner's thiourea) (50 mg, 0.10 mmol) in alcohol (2 mL), aldehyde (0.50 mmol) was added. The vial was sealed with a screw cap and left stirring under household bulb irradiation (2 × 80 W household lamps) for 3–18 h. The desired product was isolated after base aqueous wash (when full consumption of aldehyde took place) or purification by column chromatography.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

The authors gratefully acknowledge the Hellenic Foundation for Research and Innovation (HFRI) for financial support through a grant, which is financed by 1st Call for H.F.R.I. Research Projects to Support Faculty Members & Researchers and the procurement of high-cost research equipment grant (grant number 655). N. S. would like to thank the Hellenic Foundation for Research and Innovation (HFRI) for financial support through a doctoral by the Hellenic Foundation for Research and Innovation (HFRI) under PhD Fellowship grant (Fellowship Number: 721). N. F. N. would like to thank the State Scholarships Foundation (IKY) for financial support through a doctoral fellowship, which is co-financed by Greece and the European Union (European Social Fund-ESF) through the Operational Programme “Human Resources Development, Education and Lifelong Learning” in the context of the project “Strengthening Human Resources Research Potential *via* Doctorate Research” (MIS-5000432), implemented by the State Scholarships Foundation (IKY). The authors would like to thank Costas Constantinou and Marios Constantinou (DIMCO) for access to the equipment for the measurement of the emission spectrum of the lamps. Also, COST Action C-H Activation in Organic Synthesis (CHAOS) CA15106 is acknowledged for helpful discussions.

Notes and references

- (a) P. S. Baran and J. M. Richter, *J. Am. Chem. Soc.*, 2004, 126, 7450–7451; (b) S. Krautwald, D. Sarlah, M. A. Schafroth and E. M. Carreira, *Science*, 2013, 340, 1065–1068;



(c) T. Sandmeier, S. Krautwald, H. F. Zipfel and E. M. Carreira, *Angew. Chem., Int. Ed.*, 2015, **54**, 14363–14367; (d) L. R. Malins, J. N. deGruyter, K. J. Robbins, P. M. Scola, M. D. Eastgate, M. R. Ghadiri and P. S. Baran, *J. Am. Chem. Soc.*, 2017, **139**, 5233–5241.

2 (a) D. M. Clode, *Chem. Rev.*, 1979, **79**, 491–513; (b) K. Bauer, D. Garbe and H. Surburg, *Common Fragrances and Flavor Materials: Preparation and Uses*, 4th edn, 2001, pp. 103–110; (c) P. G. M. Wuts and T. W. Greene, *Greene's Protective Groups in Organic Synthesis*, 4th edn, 2007, pp. 424–428.

3 For selected examples, see: (a) P. A. Bartlett, W. S. Johnson and J. D. Elliott, *J. Am. Chem. Soc.*, 1983, **105**, 2088–2089; (b) A. Mori and H. Yamamoto, *J. Org. Chem.*, 1985, **50**, 5444–5446; (c) T. Xu, Z. Yu and L. Wang, *Org. Lett.*, 2009, **11**, 2113–2116; (d) Z.-B. Zhu, Y. Wei and M. Shi, *Chem. – Eur. J.*, 2009, **15**, 7543–7548; (e) I. Suzuki, M. Yasuda and A. Baba, *Chem. Commun.*, 2013, **49**, 11620–11622; (f) Q. Yang, T. Xu and Z. Yu, *Org. Lett.*, 2014, **16**, 6310–6313.

4 H. Maarse, *Volatile Compounds I Foods and Beverages*, Marcel Dekker, Inc., New York, 1991.

5 P. H. R. Silva, V. L. C. Gonçalves and C. J. A. Mota, *Bioresour. Technol.*, 2010, **101**, 6225–6229.

6 (a) T. H. Fife and L. K. Jao, *J. Org. Chem.*, 1965, **30**, 1492–1495; (b) S. Sugai, T. Kodama, S. Akaboshi and S. Ikegami, *Chem. Pharm. Bull.*, 1984, **32**, 99–105; (c) R. A. Ugarte and T. W. Hudnall, *Green Chem.*, 2017, **19**, 1990–1998.

7 S. A. Patwardhan and S. Der, *Synthesis*, 1974, 348–349.

8 (a) L. Myles, R. Gore, M. Špulák, N. Gathergood and S. J. Connnon, *Green Chem.*, 2010, **12**, 1157–1162; (b) M. X. Tan, L. Gu, N. Li, J. Y. Ying and Y. Zhang, *Green Chem.*, 2013, **15**, 1127–1132.

9 (a) D. B. G. Williams and M. C. Lawton, *Green Chem.*, 2008, **10**, 914–917; (b) Z. Miao, L. Xu, H. Song, H. Zhao and L. Chou, *Catal. Sci. Technol.*, 2013, **3**, 1942–1954; (c) N. M. Leonard, M. C. Oswald, D. A. Freiberg, B. A. Nattier, R. C. Smith and R. S. Mohan, *J. Org. Chem.*, 2002, **67**, 5202–5207; (d) S. M. Patel, U. V. Chudasama and P. A. Ganeshpure, *J. Mol. Catal. A: Chem.*, 2003, **194**, 267–271; (e) J.-Y. Qi, J.-X. Ji, C.-H. Yueng, H.-L. Kwong and A. S. C. Chan, *Tetrahedron Lett.*, 2004, **45**, 7719–7721; (f) R. Kumar and A. K. Chakraborti, *Tetrahedron Lett.*, 2005, **46**, 8319–8323; (g) H. Mansilla and M. M. Afonso, *Synth. Commun.*, 2008, **38**, 2607–2618; (h) A. D. Chowdhury and G. K. Lahiri, *Chem. Commun.*, 2012, **48**, 3448–3450.

10 A. Thurkauf, A. E. Jacobson and K. C. Riee, *Synthesis*, 1988, 233–234.

11 B. Procuranti and S. J. Connnon, *Org. Lett.*, 2008, **10**, 4935–4938.

12 A. J. Showler and P. A. Darley, *Chem. Rev.*, 1967, **67**, 427–440.

13 P. T. Anastas and J. C. Warner, *Green Chemistry: Theory and Practice*, University Press, Oxford, New York, 1998.

14 J. Grabowski, J. M. Granda and J. Jureczak, *Org. Biomol. Chem.*, 2018, **16**, 3114–3120.

15 K. J. Mickelsen, C. M. Tajc, K. R. Greenwood and C. C. Browder, *Synth. Commun.*, 2012, **42**, 186–194.

16 (a) M. K. Basu, S. Samajdar, F. F. Becker and B. K. Banik, *Synlett*, 2002, 319–321; (b) B. Karimi and B. Golshani, *Synthesis*, 2002, 784–788.

17 K. Kumamoto, Y. Ichikawa and H. Kotsuki, *Synlett*, 2005, 2254–2256.

18 M. Barbasiewicz and M. Mąkosza, *Org. Lett.*, 2006, **8**, 3745–3748.

19 S. Zhao, Y. Jia and Y. F. Song, *Catal. Sci. Technol.*, 2014, **4**, 2618–2625.

20 For selected reviews, see: (a) C. K. Prier, D. A. Rankic and D. W. C. MacMillan, *Chem. Rev.*, 2013, **113**, 5322–5363; (b) D. Ravelli, S. Protti and M. Fagnoni, *Acc. Chem. Res.*, 2016, **49**, 2232–2242; (c) M. D. Kärkäs, J. A. Porco Jr. and C. R. J. Stephenson, *Chem. Rev.*, 2016, **116**, 9683–9747; (d) K. L. Scubi, T. R. Blum and T. P. Yoon, *Chem. Rev.*, 2016, **116**, 10035–10074; (e) N. A. Romero and D. A. Nicewicz, *Chem. Rev.*, 2016, **116**, 10075–10166; (f) D. Cambie, C. Bottecchia, N. J. W. Straathof, V. Hessel and T. Noel, *Chem. Rev.*, 2016, **116**, 10276–10341; (g) J. Schwarz and B. Konig, *Green Chem.*, 2018, **20**, 323–361; (h) I. K. Sideri, E. Voutyritsa and C. G. Kokotos, *Org. Biomol. Chem.*, 2018, **16**, 4596–4614.

21 H. Yi, L. Niu, S. Wang, T. Liu, A. K. Singh and A. Lei, *Org. Lett.*, 2017, **19**, 122–125.

22 (a) G. N. Papadopoulos, D. Limnios and C. G. Kokotos, *Chem. – Eur. J.*, 2014, **20**, 13811–13814; (b) G. N. Papadopoulos and C. G. Kokotos, *Chem. – Eur. J.*, 2016, **22**, 6964–6967; (c) G. N. Papadopoulos and C. G. Kokotos, *J. Org. Chem.*, 2016, **81**, 7023–7038; (d) N. Kaplaneris, A. Bisticha, G. N. Papadopoulos, D. Limnios and C. G. Kokotos, *Green Chem.*, 2017, **19**, 4451–4456; (e) D. Limnios and C. G. Kokotos, *Adv. Synth. Catal.*, 2017, **359**, 323–328; (f) G. S. Koutoulogenis, M. G. Kokotou, E. Voutyritsa, D. Limnios and C. G. Kokotos, *Org. Lett.*, 2017, **19**, 1760–1763; (g) I. Triandafyllidi, M. G. Kokotou and C. G. Kokotos, *Org. Lett.*, 2018, **20**, 36–39; (h) G. N. Papadopoulos, E. Voutyritsa, N. Kaplaneris and C. G. Kokotos, *Chem. – Eur. J.*, 2018, **24**, 1726–1731; (i) I. K. Sideri, E. Voutyritsa and C. G. Kokotos, *ChemSusChem*, 2019, **12**, 4194–4201; (j) N. F. Nikitas, D. I. Tzaras, I. Triandafyllidi and C. G. Kokotos, *Green Chem.*, 2020, **22**, 471–477; (k) E. Voutyritsa and C. G. Kokotos, *Angew. Chem., Int. Ed.*, 2020, **59**, 1735–1741.

23 N. F. Nikitas, I. Triandafyllidi and C. G. Kokotos, *Green Chem.*, 2019, **21**, 669–674.

24 (a) Z. Zhang and P. R. Schreiner, *Synlett*, 2007, 1455–1457; (b) P. R. Schreiner and A. Wittkopp, *Org. Lett.*, 2002, **4**, 217–220; (c) K. M. Lippert, K. Hof, D. Gerbig, D. Ley, H. Hausmann, S. Guenther and P. R. Schreiner, *Eur. J. Org. Chem.*, 2012, 5919–5927; (d) Z. Zhang, Z. Bao and H. Xing, *Org. Biomol. Chem.*, 2014, **12**, 3151–3162; (e) Z. M. Salem, J. Saway and J. J. Badillo, *Org. Lett.*, 2019, **21**, 8528–8532.

25 For more details, see ESI.†



26 M. Blain, H. Yau, L. Jean-Gerard, R. Auvergne, D. Benazet, P. R. Schreiner, S. Caillol and B. Andrioletti, *ChemSusChem*, 2016, **9**, 2269–2272.

27 S. Zhuo, T. Zhu, L. Zhou, C. Mou, H. Chai, Y. Lu, L. Pan, Z. Jin and Y. R. Chi, *Angew. Chem., Int. Ed.*, 2019, **58**, 1784–1788.

28 M. A. Cismesia and T. P. Yoon, *Chem. Sci.*, 2015, **6**, 5426–5434.

29 (a) R. S. Mulliken, *J. Phys. Chem.*, 1952, 801–822; (b) I. R. Gould and S. Farid, *Acc. Chem. Res.*, 1996, 522–528; (c) S. Farid, J. P. Dinnocenzo, P. B. Merkel, R. H. Young and D. Shukla, *J. Am. Chem. Soc.*, 2011, **133**, 4791–4801; (d) S. Farid, J. P. Dinnocenzo, P. B. Merkel, R. H. Young, D. Shukla and G. Guirado, *J. Am. Chem. Soc.*, 2011, **133**, 11580–11587; (e) M. Koch, G. Licari and E. Vaunthey, *J. Phys. Chem. B*, 2015, **119**, 11846–11857.

30 (a) E. Arceo, I. D. Junberg, A. Alvarez and P. Melchiorre, *Nat. Chem.*, 2013, **5**, 750–756; (b) L. Wozniak, J. J. Murphy and P. Melchiorre, *J. Am. Chem. Soc.*, 2015, **137**, 5678–5681; (c) M. Silvi, E. Arceo, I. D. Jurberg, C. Cassini and P. Melchiorre, *J. Am. Chem. Soc.*, 2015, **137**, 6120–6123; (d) J. J. Murphy, D. Bastida, S. Paria, M. Fagnoni and P. Melchiorre, *Nature*, 2016, **532**, 218–222; (e) A. Bahamonde and P. Melchiorre, *J. Am. Chem. Soc.*, 2016, **138**, 8019–8030; (f) M. L. Spell, K. Devenaux, C. G. Bresnahan, B. L. Bernard, W. Sheffield, R. Kumar and J. R. Ragains, *Angew. Chem., Int. Ed.*, 2016, **55**, 6515–6519; (g) R. Wang, L. Wang, Q. Xu, B. Y. Ren and F. Liang, *Org. Lett.*, 2019, **21**, 3072–3076.

31 (a) R. Iwata, K. Uda, D. Takahashi and K. Toshima, *Chem. Commun.*, 2014, **50**, 10695–10698; (b) N. Vallavoju, S. Selvakumar, S. Jockusch, M. P. Sibi and J. Sivaguru, *Angew. Chem., Int. Ed.*, 2014, **53**, 5604–5608; (c) T. Kimura, T. Eto, D. Takahashi and K. Toshima, *Org. Lett.*, 2016, **18**, 3190–3193; (d) C. Chen, L. Zhu, M. S. Baranov, L. Tang, N. S. Baleeva, A. Y. Smirnov, I. V. Yampolsky, K. M. Solntsev and C. Fang, *J. Phys. Chem. B*, 2019, **123**, 3804–3821.

