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Sunlight photocatalyzed regioselective β -alkylation and acylation of cyclopentanones[†]

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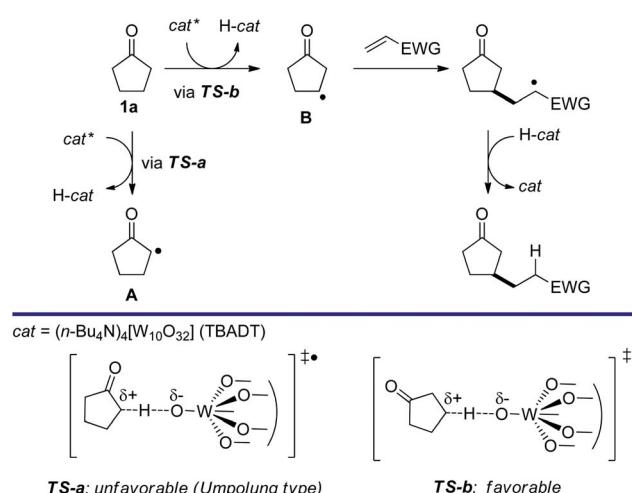
Sunlight-induced direct regioselective β -alkylation of cyclopentanones with electron-deficient alkenes was accomplished by using tetrabutylammonium decatungstate (TBADT) as the catalyst. The regiochemistry can be rationalized by a polar transition state for an S_{H2} reaction. In the presence of CO, the reaction gave the three-component β -acylation product in good yield.

Introduction

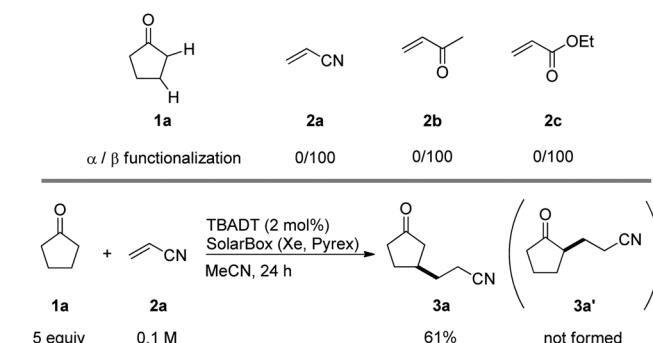
The site-selective conversion of sp^3 C–H bonds into C–C bonds remains a challenge in synthetic organic chemistry¹ and in recent years, much attention has been directed to both transition metal-catalyzed² and radical approaches to this goal.³ Of special note is a unique method to selectively convert β -C–H bonds (rather than α -C–H bonds) in ketones, reported by MacMillan and coworkers. This method employed radical generation from enamines formed *via* an organocatalytic reaction between the ketone and an amine.⁴ Alternatively, the ketone can be converted *in situ* to the corresponding α,β -unsaturated derivative and then functionalized.⁵

We hypothesized that a photocatalyzed radical approach⁶ based on the use of tetrabutylammonium decatungstate (TBADT) as the catalyst,^{7–9} would be promising to promote the β -regioselective alkylation of cyclopentanones. In cyclopentanone (**1a**), the α -C–H bond is weaker than the β -C–H bond.¹⁰ However, we reasoned that β -selective C–H bond cleavage would be promoted by polar effects¹¹ in a system requiring a highly polar S_{H2} (bimolecular homolytic substitution) transition state, as in the case of hydrogen abstraction by TBADT. When electronegative oxygen-centered radicals, such as those present in the excited decatungstate anion (cat^*), abstract hydrogen from C–H bonds, the transition state should be polar in order to balance the positively charged carbon atom. Therefore, **TS-a** (Scheme 1), leading to **A** *via* α -C–H cleavage from cyclopentanone, has to create an unstabilized electron-deficient α -carbon that can be

regarded as an Umpolung type,¹² rendering β -selective C–H bond cleavage to give **B** *via* **TS-b** more feasible. Thus, we assumed that regioselective C–H cleavage would be followed by



Scheme 1 Concept: photocatalyzed β -selective alkylation of cyclopentanone based on the radical polar effect.



Scheme 2 Regioselectivity in the TBADT-photocatalyzed C–H/C–C conversion in cyclopentanone (**1a**).

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Table 1 β -Alkylation of cyclopentanones using TBADT as the photocatalyst^a

Entry	1	Alkene 2	Method ^a	Product 3	Yield ^b (%)
1			A		61
2 ^c			A		41
3			B		58
4			A		46
5 ^d			A		51
6			A		61 (d.r. 1.1/1) ^e
7			B		70
8			B		73 (d.r. 1/1) ^f
9			B		55 (only <i>endo</i> -, d.r. 1.7/1) ^f
10			A		44 ^g
11			A		62 ^g

^a Method A: 1 (5 mmol), 2 (1 mmol), TBADT (2 mol%), MeCN (10 mL), irradiation by a SolarBox equipped with a 1.5 kW Xe lamp (500 W m⁻²) for 24 h. Method B: 1 (5 mmol), 2 (1 mmol), TBADT (2 mol%), MeCN (10 mL), irradiation by sunlight for 3–5 days (8 h per day; see ESI† for details).

^b Isolated yields by silica gel chromatography. If necessary, further purification was made by preparative HPLC. ^c TBADT (5 mol%), MeCN (5 mL), 12 h. ^d 12 h. ^e Determined by GC analysis. ^f Determined by ¹³C NMR and GC analysis. ^g Containing less than 5% of 4-alkylated product.



C–C bond formation which would be suitable for the straightforward β -C–H functionalization of cyclopentanone (**1a**). In this paper, we report that using TBADT as the photocatalyst, the reaction of cyclopentanones with electron-deficient alkenes proceeds with complete regioselectivity to give β -alkylated cyclopentanones. Interestingly, in most cases replacing artificial xenon light with sunlight irradiation led to similar or even better results. In addition, we also achieved TBADT-catalyzed β -acylation of cyclopentanone under CO pressurized conditions.

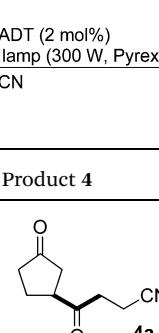
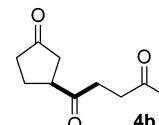
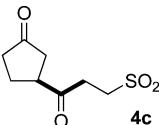
Results and discussion

We screened the reaction between cyclopentanone (**1a**) and several electron-deficient alkenes as radical acceptors, including acrylonitrile (**2a**), methyl vinyl ketone (**2b**) and ethyl acrylate (**2c**). All these reactions resulted in an exclusive selectivity for β -C–H/C–C conversion (Scheme 2). As an example, when an acetonitrile solution of **1a** (5 mmol), **2a** (1 mmol) and TBADT (2 mol%) was irradiated for 24 h using a SolarBox equipped with a 1.5 kW xenon lamp (500 W m⁻²), β -alkylated ketone **3a** was obtained in 61% yield. Not even trace amounts of **3a'** were detected in the ¹H NMR spectrum of the crude product.

With these favorable results in hand, we then examined the β -regioselective C–H/C–C reaction of cyclopentanones **1** with a variety of electron-deficient olefins **2**, and the results obtained are summarized in Table 1. The reaction of cyclopentanone (**1a**) with methyl vinyl ketone (**2b**) gave the expected 1,6-diketone **3b** in 41% yield after isolation by silica gel chromatography (entry 2). Interestingly, direct sunlight irradiation of the reaction mixture (3 days, *ca.* 24 h) gave **3b** in a higher yield (58%, entry 3). The reaction of **1a** with ethyl acrylate (**2c**) or *tert*-butyl acrylate (**2d**) gave moderate yields of keto esters **3c** and **3d**, respectively (entries 4 and 5). The reaction between **1a** and dibutyl maleate (**2e**) gave the corresponding ketone **3e** in 61% yield as a mixture of 1.1/1 diastereomers (entry 6). The direct sunlight-promoted reaction of **1a** with vinyl sulfone **2f** and fumaronitrile (**2g**) gave β -alkylated products **3f** and **3g** in 70 and 73% yield, respectively (entries 7 and 8). Reaction of **1a** with methylene norbornanone (**2h**) gave the corresponding 1,6-diketone **3h** exclusively as the *endo*-isomer in a 1.7/1 diastereomer ratio (entry 9). Gratifyingly, the reaction of 3-methylcyclopentanone (**1b**), which has one methine, one methyl, and three different methylene carbons, with **2b** proceeded with high selectivity for the abstraction of the β -methine C–H hydrogen, to afford 1,6-diketone **3i** having a quaternary carbon (entry 10). Similarly, **1b** reacted with vinyl sulfone **2f** to give **3j** in 62% yield (entry 11). We also examined the reaction of 2-methylcyclopentanone with **2b**; however, it yielded an inseparable 2 : 1 mixture of 4- and 3-alkylated products (see ESI†).

In our previous work, we have shown that radical carbonylations were feasible under TBADT-photocatalyzed conditions.⁹ Indeed, β -acylation of cyclopentanone (**1a**) under pressurized CO proceeded well. In this reaction the β -keto radical formed was trapped consecutively by CO and electron-deficient alkenes (Table 2).¹³ Thus, when an acetonitrile solution of **1a**, **2a** and TBADT (2 mol%) was irradiated for 20 hours under CO (200 atm) using a 300 W xenon lamp, the anticipated β -acylated

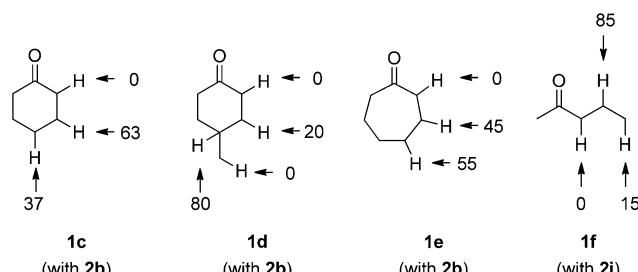
Table 2 Three-component β -acylation of cyclopentanone (**1a**) using TBADT as the photocatalyst^a

Entry	Alkene 2	Product 4	Yield ^b (%)
1	2a		58
2	2b		50
3	2f		61

^a **1a** (15 mmol), **2** (1 mmol), CO (200 atm), TBADT (2 mol%), MeCN (10 mL), irradiation by Xe lamp (300 W) for 20 h. ^b Isolated yield by silica gel chromatography.

product, diketo nitrile **4a**, was obtained in 58% yield (entry 1). Similarly, 1,4,7-triketone **4b** was obtained in 50% yield by a three-component reaction comprising **1a**, CO and **2b** (entry 2). The reaction with vinyl sulfone **2f** gave the corresponding diketo sulfone **4c** in 61% yield (entry 3).

For comparison, we examined the regioselectivities for cyclohexanone (**1c**), 4-methylcyclohexanone (**1d**) and cycloheptanone (**1e**) in the reaction with **2b** (Scheme 3). As a result, when both β - and γ -hydrogens were present, H-abstraction by TBADT showed a slight preference for γ -C–H cleavage (statistically corrected γ : β ratio *ca.* 1 : 0.8) with cyclohexanone (**1c**) and cycloheptanone (**1e**) and, as expected, no α -C–H/C–C conversion took place. On the other hand, the presence of a methine group in compound **1d** led to preferential selectivity (16 : 1, again statistically corrected) for the more hindered/labile γ -C–H



Scheme 3 Selectivity in the C–H photocatalyzed cleavage in cyclohexanone (**1c**), 4-methylcyclohexanone (**1d**), cycloheptanone (**1e**) and 2-pentanone (**1f**).



bond, despite the bulkiness of the photocatalyst. This behavior is quite similar to that observed above in the case of **1b**. In the reaction of 2-pentanone (**1f**) with methyl acrylate (**2i**), a selectivity for β -C–H over γ -methyl C–H was found (statistically corrected γ : β ratio *ca.* 1 : 8.5).

The approach described here compares favorably with related radical processes previously described for C–H functionalization in cycloalkanones. Sparse examples have been reported dealing with the reaction of ketones with hetero-atom radicals.¹⁴ Among them, there is only one report of selective β -chlorocarbonylation of carbonyl derivatives, which took place by irradiation in the presence of oxalyl chloride *via* hydrogen abstraction by chlorine (Cl[•]) radicals.^{14a}

A plausible mechanism is depicted in Scheme 4 for the photocatalyzed β -acylation of **1a**. We expected that excited polyoxotungstate anion $[\text{W}_{10}\text{O}_{32}]^{4-}\text{*}$ would have an electronegative oxygen character as the reactive site,¹⁵ and therefore the observed selectivity is in favor of β -C–H abstraction (at least for **1a**).¹⁶ The β -keto radical thus formed then undergoes consecutive addition to CO (when present) and to the electron-deficient olefin (*e.g.* acrylonitrile **2a**) to form an adduct radical. Back-hydrogen atom transfer from the reduced form of the tungstate anion to the latter radical gives the desired product **4a**, restoring the TBADT catalyst.

We can then assume that α -C–H abstraction in cyclic ketones is inefficient, as previously demonstrated in related studies on the reactivity of excited TBADT with acetone.¹⁷ In fact, acetone was safely used as a solvent in TBADT photocatalyzed reactions.^{8e,17}

The simplicity of the procedure is another advantage of the method, since it requires merely exposing the solution to the sun in a glass vessel on a window ledge (Fig. 1).^{8e} This 100% atom economical process has several benefits from the



Fig. 1 Pyrex glass vessel (20 mL capacity) used for the sunlight photocatalyzed β -C–H/C–C conversion of **1a**.

environmental point of view, because no artificial energy is required for irradiation, heating, cooling or stirring in order to carry out selective C–H/C–C conversion.¹⁸

Conclusions

In summary, we have developed a simple straightforward strategy for β -alkylation and acylation of cyclopentanones using electron-deficient alkenes as alkylating reagents under irradiation in the presence of TBADT as the catalyst. Interestingly, sunlight irradiation gave good results. The differentiation of favorable and unfavorable polar radical transition states has been exploited successfully in order to direct the regioselectivity. β -Acylation of cyclopentanone, which uses a three-component system comprising cyclopentanone, CO and electron-deficient alkenes, was also achieved. We believe that the radical polar effect provides a powerful strategy to induce selective catalytic C–H functionalization and we are now pursuing further studies along this line.

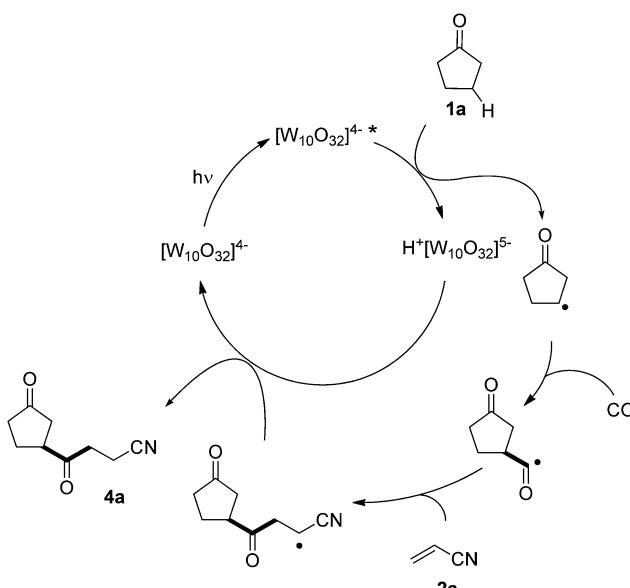
Experimental section

Typical procedure for β -alkylation of cyclopentanone (method A)

A magnetic stir bar and tetrabutylammonium decatungstate (TBADT, 66.4 mg, 0.02 mmol) were placed in a Pyrex flask. CH_3CN (10 mL), cyclopentanone (**1a**, 420.6 mg, 5 mmol) and acrylonitrile (**2a**, 53.1 mg, 1.0 mmol) were added to the reaction flask. The resulting solution was purged with nitrogen, then screw-capped and irradiated by a SolarBox (xenon lamp, 500 W m^{-2} , $53\text{ }^\circ\text{C}$) under stirring for 24 h. After the reaction, the solvent was evaporated under reduced pressure. The residue was purified by flash column chromatography on silica gel (hexane/ethyl acetate = 3/1) to give 83.7 mg of 3-(3-oxocyclopentyl)propanenitrile **3a** (61%).

Typical procedure for sunlight-induced β -alkylation of cyclopentanone (method B)

Tetrabutylammonium decatungstate (TBADT, 66.4 mg, 0.02 mmol) was placed in the Pyrex flask (Fig. 1). CH_3CN (10 mL),



Scheme 4 Proposed mechanism for the photocatalyzed β -C–H/C–C conversion in cyclopentanone and ensuing carbonylation.



cyclopentanone (**1a**, 420.6 mg, 5 mmol) and methyl vinyl ketone (**2b**, 70.1 mg, 1.0 mmol) were added to the reaction flask. The resulting solution was purged with nitrogen, then screw-capped and irradiated by exposing the reaction vessel to solar light on a window ledge of the Department of Chemistry of Pavia (Italy; 45° 10' 00" North, 9° 10' 00" East) in the July–September 2013 period for 8 h per day (from 9 a.m. to 5 p.m.). After the reaction, the solvent was evaporated under reduced pressure. The residue was purified by flash column chromatography on silica gel (hexane/ethyl acetate = 5/1) to give 89.4 mg of 3-(3-oxobutyl) cyclopentanone **3b** (58%).

Typical procedure for β -acylation of cyclopentanone

A magnetic stir bar, CH₃CN (10 mL), TBADT (66.4 mg, 0.02 mmol), cyclopentanone (**1a**, 1262 mg, 15 mmol) and acrylonitrile (**2a**, 53.1 mg, 1 mmol) were placed in a stainless steel autoclave equipped with a Pyrex glass liner to permit irradiation of the contents. The autoclave was closed, purged three times with carbon monoxide, pressurized with 200 atm of CO and then irradiated by a xenon arc lamp (300 W) with stirring for 20 h. After the reaction, excess CO was discharged at room temperature. The solvent was removed under reduced pressure. The residue was purified by flash column chromatography on silica gel (hexane/ethyl acetate = 1/2) to afford 95.8 mg of 4-oxo-4-(3-oxocyclopentyl)butanenitrile **4a** (58%).

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Notes and references

- For general reviews on C–H functionalization, see: (a) J.-Q. Yu and Z. Shi, *Top. Curr. Chem.*, 2010, **292**, 1–380; (b) G. Dyker, *Handbook of C–H Transformations*, Wiley-VCH, Weinheim, Germany, 2005.
- For recent reviews on transition metal-catalyzed C(sp³)-H functionalization, see: (a) G. Rouquet and N. Chatani, *Angew. Chem., Int. Ed.*, 2013, **52**, 11726; (b) O. Baudoin, *Chem. Soc. Rev.*, 2011, **40**, 4902; (c) R. Jazzaar, J. Hitce, A. Renaudat, J. Sofack-Kreutzer and O. Baudoin, *Chem.–Eur. J.*, 2010, **16**, 2654; (d) R. H. Crabtree, *J. Chem. Soc., Dalton Trans.*, 2001, 2437.
- For recent reports on radical mediated C(sp³)-H/C–C functionalization, see: (a) T. Hoshikawa and M. Inoue, *Chem. Sci.*, 2013, **4**, 3118; (b) A. P. Antonchick and L. Burgmann, *Angew. Chem., Int. Ed.*, 2013, **52**, 3267; (c) Z. Cui, X. Shang, X.-F. Shao and Z.-Q. Liu, *Chem. Sci.*, 2012, **3**, 2853.
- For C(sp³)-H functionalization at β -position of carbonyl compounds *via* enamine formation using organocatalyst, see: (a) M. T. Pirnot, D. A. Rankic, D. B. C. Martin and D. W. C. MacMillan, *Science*, 2013, **339**, 1593; (b) F. R. Petronijević, M. Nappi and D. W. C. MacMillan, *J. Am. Chem. Soc.*, 2013, **135**, 18323.
- For indirect approaches *via* α,β -unsaturated carbonyl compounds, see: (a) Z. Huang and G. Dong, *J. Am. Chem. Soc.*, 2013, **135**, 17747; (b) M. V. Leskinen, K.-T. Yip, A. Valkonen and P. M. Pihko, *J. Am. Chem. Soc.*, 2012, **134**, 5750; (c) P. Larini, C. E. Kefalidis, R. Jazzaar, A. Renaudat, E. Clot and O. Baudoin, *Chem.–Eur. J.*, 2012, **18**, 1932; (d) S.-L. Zhang, H.-X. Xie, J. Zhu, H. Li, X.-S. Zhang, J. Li and W. Wang, *Nat. Commun.*, 2011, **2**, 211; (e) Y. Hayashi, T. Itoh and H. Ishikawa, *Angew. Chem., Int. Ed.*, 2011, **50**, 3920; (f) A. Renaudat, L. Jean-Gérard, R. Jazzaar, C. E. Kefalidis, E. Clot and O. Baudoin, *Angew. Chem., Int. Ed.*, 2010, **49**, 7261.
- For selected recent reviews on photocatalysis, see: (a) M. Reckenthaler and A. G. Griesbeck, *Adv. Synth. Catal.*, 2013, **355**, 2727; (b) C. K. Prier, D. A. Rankic and D. W. C. MacMillan, *Chem. Rev.*, 2013, **113**, 5322; (c) D. Ravelli, M. Fagnoni and A. Albini, *Chem. Soc. Rev.*, 2013, **42**, 97; (d) J. Xuan and W.-J. Xiao, *Angew. Chem., Int. Ed.*, 2012, **51**, 6828; (e) L. Shi and W. Xia, *Chem. Soc. Rev.*, 2012, **41**, 7687; (f) D. Ravelli, D. Dondi, M. Fagnoni and A. Albini, *Chem. Soc. Rev.*, 2009, **38**, 1999; (g) M. Fagnoni, D. Dondi, D. Ravelli and A. Albini, *Chem. Rev.*, 2007, **107**, 2725.
- For reviews on decatungstate photocatalysis, see: (a) M. D. Tzirakis, I. N. Lykakis and M. Orfanopoulos, *Chem. Soc. Rev.*, 2009, **38**, 2609; (b) C. L. Hill, *J. Mol. Catal. A: Chem.*, 2007, **262**, 2; (c) C. Tanielian, *Coord. Chem. Rev.*, 1998, **178–180**, 1165; (d) C. L. Hill, *Synlett*, 1995, 127.
- For selected examples of synthetic applications using decatungstate photocatalyst, see: (a) H. Qrareya, D. Ravelli, M. Fagnoni and A. Albini, *Adv. Synth. Catal.*, 2013, **355**, 2891; (b) A. Molinari, A. Maldotti, A. Bratovic and G. Magnacca, *Catal. Today*, 2013, **206**, 46; (c) D. Ravelli, A. Albini and M. Fagnoni, *Chem.–Eur. J.*, 2011, **17**, 572; (d) M. Tzirakis and M. Orfanopoulos, *Angew. Chem., Int. Ed.*, 2010, **49**, 5891; (e) S. Protti, D. Ravelli, M. Fagnoni and A. Albini, *Chem. Commun.*, 2009, 7351; (f) M. D. Tzirakis and M. Orfanopoulos, *Org. Lett.*, 2008, **10**, 873; (g) R. F. Renneke, M. Pasquali and C. L. Hill, *J. Am. Chem. Soc.*, 1990, **112**, 6585.
- For TBADT photocatalyzed carbonylation of alkanes, see: (a) I. Ryu, A. Tani, T. Fukuyama, D. Ravelli, S. Montanaro and M. Fagnoni, *Org. Lett.*, 2013, **15**, 2554; (b) I. Ryu, A. Tani, T. Fukuyama, D. Ravelli, M. Fagnoni and A. Albini, *Angew. Chem., Int. Ed.*, 2011, **50**, 1869, also, see ref. 8g.
- F. G. Bordwell, T. Gallagher and X. Zhang, *J. Am. Chem. Soc.*, 1991, **113**, 3495.
- B. P. Roberts, *Chem. Soc. Rev.*, 1999, **28**, 25.
- B. T. Gröbel and D. Seebach, *Synthesis*, 1977, 357.
- For recent examples of radical carbonylation, see: (a) T. Fukuyama, N. Nakashima, T. Okada and I. Ryu, *J. Am. Chem. Soc.*, 2013, **135**, 1006; (b) T. Kippo, K. Hamaoka and I. Ryu, *J. Am. Chem. Soc.*, 2013, **135**, 632; (c) S. Sumino, T. Uji and I. Ryu, *Org. Lett.*, 2013, **15**, 3142.
- (a) A. Bashir-Hashemi and J. R. Hardee, *J. Org. Chem.*, 1994, **59**, 2132; (b) P. Dagaunt, T. J. Wallington, R. Liu and



M. J. Kurylo, *J. Phys. Chem.*, 1988, **92**, 4375; (c) R. Jaouhari, C. Filliatre and J. J. Villenave, *Can. J. Chem.*, 1983, **61**, 2295; (d) R. Jaouhari, B. Maillard, C. Filliatre and J. J. Villenave, *Tetrahedron*, 1983, **39**, 1559.

15 D. Dondi, D. Ravelli, M. Fagnoni, M. Mella, A. Molinari, A. Maldotti and A. Albini, *Chem.-Eur. J.*, 2009, **15**, 7949.

16 In the present system, α -C-H cleavage could occur in an equilibrium with back H-donation.

17 C. Tanielian, F. Cougnon and R. Seghrouchni, *J. Mol. Catal. A: Chem.*, 2007, **262**, 164.

18 The quantum yield of the process was estimated to be 0.04 based on an average flux of 30 W m^{-2} in the 295–400 nm range where the absorption of the photocatalyst is complete. This value is in agreement with that previously reported in the UV light-promoted activation of C–H hydrogens in cyclohexane (0.06, see: D. Dondi, M. Fagnoni and A. Albini, *Chem.-Eur. J.*, 2006, **12**, 4153).

