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Tetrabutylammonium Decatungstate-Photosensitized Alkylation of Electrophilic Alkenes: Convenient Functionalization of Aliphatic C–H Bonds

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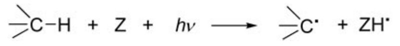
Abstract: Tetrabutylammonium decatungstate (TBADT, 2×10^{-3} M) is an effective photocatalyst for the alkylation of electrophilic alkenes (0.1 M, α,β-unsaturated nitriles, esters, ketones) by alkanes, alcohols, and ethers. The products are in most cases obtained in >70% isolated yields, through an experimentally very simple procedure. The kinetics of the radical processes following initial hydrogen abstraction by excited TBADT in deoxygenated MeCN have been studied. In the absence of a trap, back hydrogen transfer from reduced tungstate is the main pathway for alkyl radicals, while α-hydroxyalkyl radicals are oxidized to ketones by ground-state TBADT. With both radical types the reaction ceases at a few percent conversion. However, trapping by electrophilic alkenes is followed by reduction of the radical adduct and regeneration of the catalyst, which allows the alkylation to proceed up to complete alkene conversion with the mentioned good yields of products. With a nucleophilic (α-hydroxyalkyl) radical, alkylation is efficient (Φ = 0.58) and can also be carried out when degassing is omitted, the only difference being a short induction period. With a less reactive (cyclohexyl) radical, the quantum yield is lower (Φ = 0.06) and the reaction is considerably slowed in aerated solutions, but the chemical yield remains good.

Keywords: alkylation · C–H activation · photochemistry · photocatalysis · radicals

Introduction

The mild and selective functionalization of aliphatic C–H bonds remains a major goal in synthesis,[1] in particular in the context of current interest in sustainable methods that adhere to the principle of atom economy by minimizing the use of reagents and auxiliary agents and operate under mild, energy-saving conditions.[2] Catalysis by transition metal complexes is a promising possibility,[3] although metal complexation of compounds not containing π orbitals is less common than that of alkenes or aromatics, thus limiting the versatility of this approach. An appealing alternative would be a photochemical reaction. The photon is the ideal "green" reagent, since it leaves no residue and transfers large amounts of energy, while operating under mild and versatile conditions.[4] The excited states of alkanes and many simple aliphatic derivatives are high in energy and undergo unselective fragmentation, so photochemistry has little preparative value in this case. However, chemical activation through reaction with a photoexcited compound can be achieved under mild conditions and probably deserves more attention than it has received up to now. In this method, an activated intermediate is generated; in many instances this is a carbon-centered radical arising by hydrogen abstraction from a C–H bond [Eq. (1)].



(1)

These reactions include photoinduced radical chain processes (quantum yield ≫1, Scheme 1a), such as halogenation and related reactions. Other reactions, such as oxygenation, take place thermally following a chain course at high temperatures, but can be carried out photochemically at room temperature by stoichiometric generation and trapping of the radicals. A triplet ketone, a photogenerated acyl radical, or a photoexcited semiconductor can be used for the C–H bond activation. An excellent choice for a photoinitiator is a

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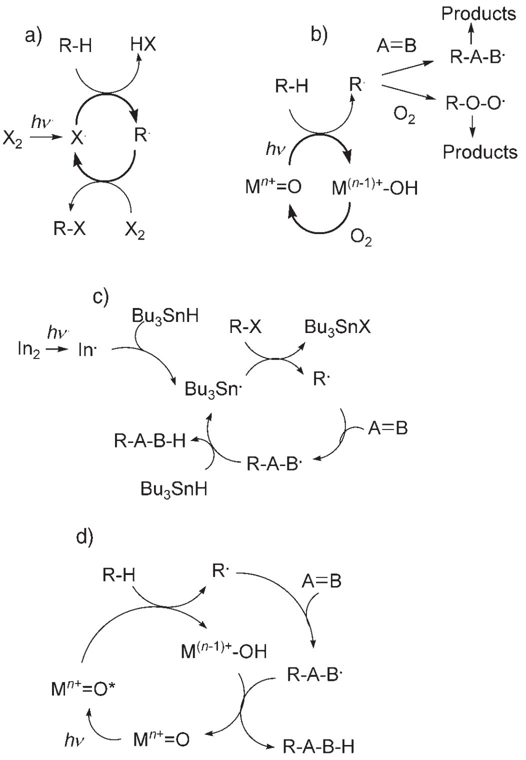


Scheme 1. Some of the different mechanisms for photoinduced reactions of aliphatic derivatives. a) (Photoinitiated) radical chain process. b) Non-chain photoreaction catalyzed by a polyoxometalate (M^{n+}=O). c) (Photoinitiated) radical chain alkyation reaction. d) Non-chain photocatalyzed alkylation reaction.

polyoxometalate (M^{n+}=O in Scheme 1 b),[5] provided that it is regenerated in the course of the reaction and functions as a photochemically activated catalyst (i.e., it is not consumed over several cycles), although the reaction of the organic compound is stoichiometric in terms of adsorbed photons.

Photocatalyzed oxygenation of alkanes with use of a polyoxometalate has been particularly well studied (sodium, potassium, or tetraalkylammonium decatungstate are most often used). Hydroperoxides or, under different conditions, ketones have been selectively obtained, sometimes with high levels of alkane conversion,[6] in contrast to the mixtures obtained under conventional (peroxide-initiated) autooxidation conditions. Under these conditions, the catalyst is reoxidized back by oxygen. Oxygenation may be taken as an example of radical addition to a multiple bond A=B (O=O in this case), but the extension of this concept to other reactions, in particular to addition to carbon–carbon multiple bonds, with the goal of achieving synthetically desirable C–C bond formation, has so far met with limited success. Radical addition of alkanes to alkenes and alkynes,[7a] or to CO,[7b] through polyoxometalate photocatalysis has been demonstrated but occurs only up to small degrees of conversion of the reagent (ca. 5–8 %), although good yields of nitriles and/or α-iminoesters have been obtained by addition to cyanoformates.[8,9]

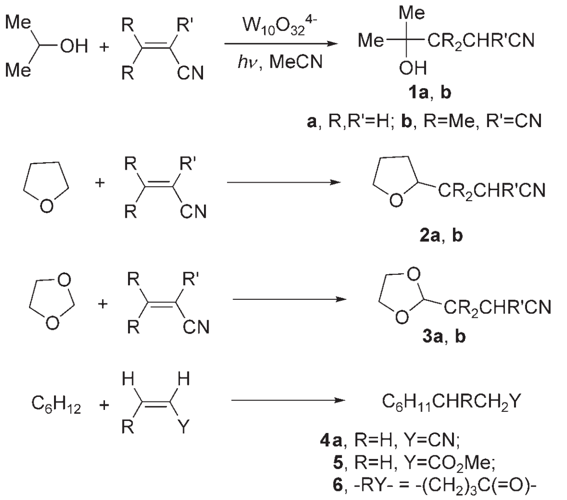
Addition to a C–C multiple bond, in contrast, is the most useful radical process in synthesis and occurs as a chain reaction (after initiation, in several cases photochemical), provided that an easily fragmentable precursor (R–X, with X = Br or, better, I) and a mediator, typically a tin derivative, are used (Scheme 1 c).[10] Extension of this principle to a chain radical process based on the cleavage of a strong bond such as a C–H one is out of the question. However, an appealing possibility is a non-chain, photocatalyzed process as shown in Scheme 1 d, involving H abstraction by the excited initiator, radical addition to a C–C π bond, and back hydrogen transfer to the radical adduct, leading to the regeneration of the photoinitiator. In comparison to Scheme 1 c, this path has the disadvantage of being a stoichiometric (in terms of photons; the oxometalate is a regenerated catalyst) rather than a chain process, but this shortcoming is counterbalanced by the excellent atom economy, since the reagents are 100 % incorporated in the products (unlike in Scheme 1 c, in which the atom or group X is lost). Furthermore, no mediator such as a tin derivative is used, conditions are mild, and toxic reagents are avoided. A first attempt to apply this concept—in the photocatalyzed addition of cycloalkanes to α,β-unsaturated nitriles—was successful[11] and we now report a study on the scope and mechanism of CH activation and C–C bond formation through radical alkylation of α,β-unsaturated compounds under photocatalytic conditions.

Results

Products studies: In this work, the easily prepared tetrabutylammonium decatungstate (TBADT) was used as the photocatalyst in acetonitrile, with alkanes, alcohols, ethers, and acetals serving as the radical precursors and electrophilic alkenes as radical traps. The reaction kinetics of radical generation and trapping were studied in detail in representative cases.

The photocatalyzed reactions were studied both in preparative experiments (100 mL argon-flushed solutions) for product isolation and characterization and in small-scale experiments (2 mL samples, deoxygenated by several freeze-degas-thaw cycles) for quantum yield measurements. TBADT was quite photostable when irradiated in oxygen-free MeCN, and under our conditions several hours were required for observable reduction to take place. Irradiation of this salt (0.002 M) in a nitrogen-flushed acetonitrile solution containing propan-2-ol (0.5 M), however, caused the development after a few minutes of the intense blue color characteristic of the reduced tungsten species. The only organic product was acetone, quantified by HPLC as its 2,4-dinitrophenylhydrazone.

When a similar solution containing acrylonitrile (AN, 0.1 M) was irradiated, the color was again apparent and persisted, but a new product besides acetone was formed and was identified after separation by distillation (isolated yield 72 % on the basis of the starting amount of AN) as 4-hydroxypentanenitrile (**1a**; see Scheme 2, Table 1). Similarly, photocatalysis of propan-2-ol in the presence of isopropylidenemalonitrile (IPMN, 0.1 M) under the same conditions gave the corresponding hydroxyalkylmalononitrile **1b** in a satisfactory yield (50%).



Scheme 2. Photoproducts arising from the irradiation of TBADT in the presence of various aliphatic derivatives and electrophilic alkenes.

Table 1. Isolated yields of TBADT-photocatalyzed (0.002 M) alkylation of electrophilic alkenes in acetonitrile (λ_{ir} 310 nm).

Donor [0.5 M]	Alkene [0.1 M]	Alkylated product (yield [%])
2-PrOH	CH_2=CHCN	**1a** (72)
	CMe_2=C(CN)$_2$	**1b** (50)
THF	CH_2=CHCN	**2a** (78)[a]
	CMe_2=C(CN)$_2$	**2b** (75)
DIOX	CH_2=CHCN	**3a** (76)
	CMe_2=C(CN)$_2$	**3b** (50)
C_6H_{12}	CH_2=CHCN	**4a** (63)[b]
	CH_2=$CHCO_2Me$	**5** (65)
	cyclohexen-2-one	**6** (43)

[a] Irradiation in MeCN containing 0.5% D_2O gave 2-[D_1]-**2a** (>90% specific deuteration). [b] MeCN containing 0.5% D_2O, 2-[D_1]-**4a** (>90% deuteration) was obtained.

Other alcohols, such as methanol, were oxidized under these conditions and similarly caused a fast development of the blue color. Tetrahydrofuran (THF) and 1,3-dioxolane (DIOX) were then examined as a representative ether and acetal, respectively. Irradiation of the tungstate in the presence of both substrates again gave the blue color, but no GC-detectable products. When the reactions were carried out in the presence of α,β-unsaturated nitriles, alkylation took place satisfactorily. Tetrahydrofuran thus gave 3-(2-tetrahydrofuranyl)propanenitrile (**2a**) from AN in 78% yield and dinitrile **2b** from IPMN in 75% yield. Similarly, the dioxolane gave the dioxolanylpropanenitrile **3a** in 76% yield with AN and dinitrile **3b** in 50% yield with IPMN.

We had previously reported that cyclohexane gave alkylated nitriles **4a** (63%) and **4b** (66%) in the presence of the above alkenes (see Table 1), while small amounts of bicyclohexyl and cyclohexyl methyl ketone (5% each) were formed in the absence of such additives.[11] Alkylation with cyclohexane was now extended to other electrophilic alkenes. In particular, alkylation of both methyl acrylate and cyclohexen-2-one was satisfactorily achieved, giving products **5** and **6**, respectively (Table 1). In contrast, attempted alkylation with amines was unsuccessful, irradiation of TBADT in the presence of Et_3N resulting in a rapid darkening of the solution, from which no products could be isolated.

As indicated, the above irradiations had been carried out after deoxygenation of the solutions. However, this step could be omitted. Thus, when carried out in an open tube, the irradiation of TBADT in the presence of propan-2-ol and AN gave product **1a** in a yield only slightly lower (64%) than had been obtained under air exclusion after the same irradiation time. The blue color was barely detectable in this case. The alkylation in air-equilibrated solution could also be carried out with cyclohexane, though in that case the required irradiation time was four times longer than under air exclusion.

The source of the β-hydrogen atom in the nitriles formed was tested by repeating the photocatalyzed addition of tetrahydrofuran to AN first in CD_3CN and then in CH_3CN containing 0.5% D_2O. No measurable deuteration resulted in the first case, while product **2a** was quantitatively obtained as the 2-[D_1] derivative under the latter set of conditions. Exactly the same result was obtained in the alkylation of AN with cyclohexane, which quantitatively gave the 2-[D_1] derivative of **4a** in the presence of 0.5% D_2O.

Monitoring the photoreaction: The above photocatalyzed reactions were conveniently carried out by irradiation at 310 nm, since TBADT absorbs strongly at this wavelength, where the blue reduced tungsten derivative that developed during the reaction absorbed poorly. The latter species corresponded, as previously determined, to a mixture of the one- and two-electron reduced decatungstate salts ($HW_{10}O_{32}^{4-}$/$H_2W_{10}O_{32}^{4-}$),[12–14] with the latter species predominating. Thanks to the 310 nm absorption of the residual catalyst, alkylation could be pursued up to virtually complete alkene conversion, though at a gradually decreasing rate. The course of the reaction was monitored and the time profiles for the formation of acetone from propan-2-ol and of product **1a** from the alcohol in the presence of AN are shown in Figure 1. These data can be compared with the moles of electrons accepted by the catalyst to form the tungstate reduced species, which were calculated from the known extinction coefficients of such compounds, as shown in Figure 2.

The reduction of the catalyst proceeded up to over 90% conversion in a few minutes. When it was the only additive, 2-PrOH was oxidized to acetone, reaching a 1×10^{-3} M concentration in the same time interval. Further irradiation produced only slow growth. When AN was also present, the rate of reduction of TBADT decreased to about two thirds of the previous value and that of formation of acetone to

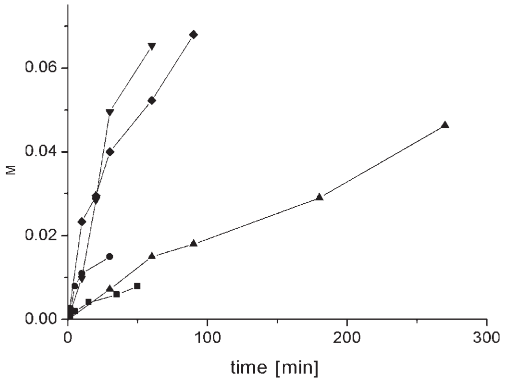


Figure 1. Products formed (M) upon irradiation of a degassed (except when noted) 2×10^{-3} M TBADT solution in MeCN in the presence of various reagents: (●) acetone (multiplied ×10 for better visibility) in the presence of 2-PrOH (0.5 M); (■) acetone (×10) and (◆) product **1a** in the presence of 2-PrOH (0.5 M) and AN (0.1 M); (▲) product **4a** in the presence of cyclohexane (0.5 M) and AN (0.1 M); (▼) product **1a** in the presence of 2-PrOH (0.5 M) and AN (0.1 M) in an air-equilibrated solution.

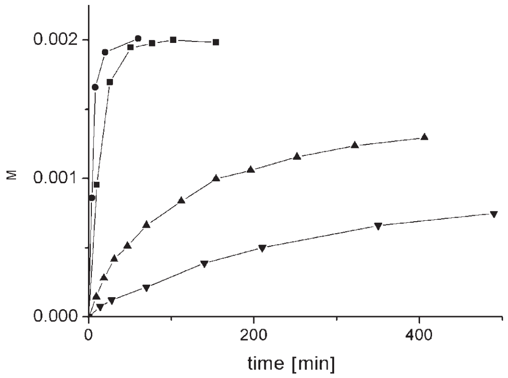


Figure 2. Electrons (M) accepted by the catalyst upon irradiation of a degassed 2×10^{-3} M TBADT solution in MeCN in the presence of various additives: (●) in the presence of 2-PrOH (0.5 M); (■) in the presence of 2-PrOH (0.5 M) and AN (0.1 M); (▼) in the presence of cyclohexane (0.5 M); (▲) in the presence of cyclohexane (0.5 M) and AN (0.1 M).

one third, while formation of product **1a** proceeded steadily, though at a gradually decreasing rate, even when 90 % of the catalyst had been reduced. The turnover number for **1a** (the ratio between the moles of product formed and the moles of electrons transferred to the catalyst) grew from ca. 12 in the initial phase to >35 at advanced conversion (see Figure 3). The same experiment in aerated solution showed an induction phase of a few minutes, but the amount of product **1a** formed later increased over that observed in degassed solution (as mentioned above, very little reduced TBADT was formed in this case).

With cyclohexane, reduction of the catalyst took place at a much slower pace, although it continued, reaching a plateau at which about 30 % of the starting amount had been reduced after 8 h. In contrast with the 2-PrOH case, the rate of TBADT reduction increased in the presence of AN, while alkylation proceeded effectively up to turnover numbers of 50 and above.

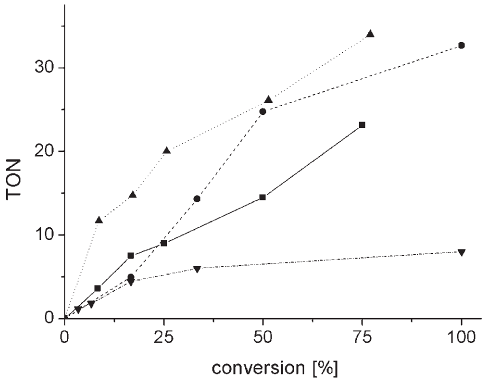


Figure 3. Turnover number of the photocatalyst for the formation of: 1) (▲) product **1a**, and 2) (▼) acetone (multiplied ×10) from a deaerated solution of 2-PrOH (0.5 M) and AN (0.1 M) in MeCN versus the AN conversion. (●) The same for product **1a** in air-equlibrated MeCN solution. (■) The same for product **4a** in deaerated MeCN in the presence of 0.5 M cyclohexane and 0.1 M AN.

The above reactions were carried out at a 0.5 M starting concentration of the hydrogen donors. The initial quantum yields for the above reactions were estimated by extrapolation of the curves in Figure 1 and Figure 2 and are reported in Table 2. Further experiments were carried out with lower concentrations of propan-2-ol and cyclohexane and the initial quantum yields of the TBADT reduction were likewise evaluated and are plotted in Figure 4 a and Figure 5 a.

Table 2. Initial quantum yields for the photochemical reduction of TBADT (Φ_r) and for photocatalyzed product formation (Φ_p) in MeCN and in the presence of AN ($\lambda_{ir} = 313$ nm).

R–H	Φ_r	Neat MeCN products (Φ_p)	Φ_r	0.1 M AN in MeCN products (Φ_p)
none	0.004			
2-PrOH	0.52	Me_2CO (0.31)	0.23	Me_2CO (0.09), **1a** (0.58)
C_6H_{12}	0.013	$(C_6H_{11})_2$ (0.008), $C_6H_{11}COMe$ (0.0065)	0.037	**4a** (0.06)
C_6H_{12}			0.004	**5** (0.05)[a]
MeOH	0.25		0.04	
THF	0.47		0.05	**2a** (0.20)
DIOX	0.36		0.04	**3a** (.38)

[a] In the presence of 0.1 M methyl acrylate.

The reaction course was also monitored by flash photolysis (FP). Previous studies by Hill et al.,[15,16] Giannotti et al.,[17] and Tanielian et al.[13] and others had found evidence of complex behavior after excitation of TBADT in MeCN. Picosecond transients preceded the reactive excited state (τ = 55 ns) and this gave the reduced polytungstate (first half-life ca. 700 ns), all of these species absorbing around 760 nm. In MeCN, the yield and the lifetime of the last species decreased in the presence of oxygen, and its lifetime was shortened, while addition of 2-PrOH (in air-saturated solution) increased the yield and made this species persistent over several hundred ns.

On repetition of the flash experiment in oxygen-free MeCN the above transient was observed (τ = 58±4 ns) with a small persistent component (>5 μs). The long-lived

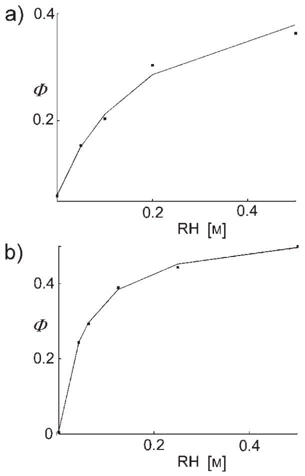


Figure 4. Initial quantum yields for photoinduced electron transfer to TBADT (2×10^{-3} M) by irradiation in MeCN in the presence of 2-PrOH as determined: a) by steady-state irradiation, and b) by flash photolysis.

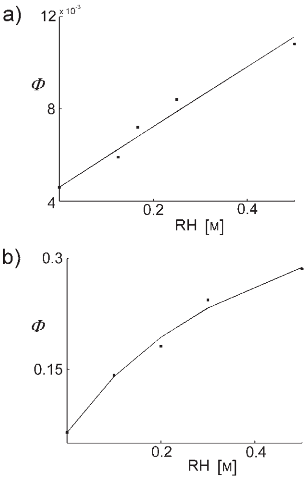


Figure 5. Initial quantum yields for photoinduced electron transfer to TBADT (2×10^{-3} M) by irradiation in MeCN in the presence of cyclohexane as determined: a) by steady-state irradiation, and b) by flash photolysis.

transient increased greatly and become dominant in the presence of increasing amounts of both cyclohexane and 2-PrOH (Figure 6). The addition of 0.1 M AN to these solutions caused no appreciable change.

The quantum yields for TBADT reduction under FP conditions were measured by use of benzophenone as actinometer. The results are plotted in Figure 4b and Figure 5b as a function of the additive concentration and the key parameters are reported in Table 2.

Discussion

Course of the reaction: The irradiation of TBADT in deoxygenated MeCN has been found to induce CH activation of various aliphatic derivatives and formation of dehydrogenated products. Thus, propan-2-ol is oxidized to acetone. As can be seen in Figure 1, the amount of this product formed reaches a plateau slightly above 1 mM. At this stage most of the catalyst (starting concentration 2 mM) is in the reduced form. The observed stoichiometry is fitted well by Equation (2).

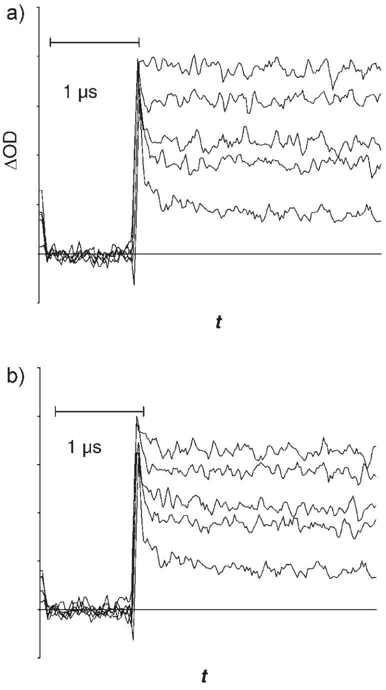


Figure 6. Time profile of the absorption at 760 nm after flashing of a 6×10^{-5} M solution of TBADT in MeCN in the presence: a) of propan-2-ol (0, 0.05, 0.1, 0.2 and 0.5 M, bottom-to-top), and b) of cyclohexane (0, 0.1, 0.2, 0.3, and 0.5 M). The curves were identical in the presence of 0.1 M AN.

$$\begin{aligned}&2\,W_{10}O_{32}^{4-} + Me_2CHOH\\&\rightarrow 2\,HW_{10}O_{32}^{4-}\ (\text{or } H_2W_{10}O_{32}^{4-}) + Me_2C{=}O\end{aligned}\qquad(2)$$

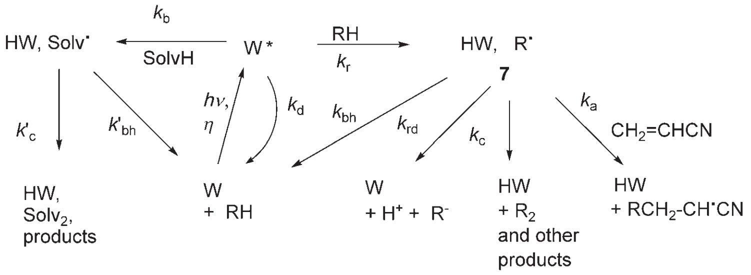
As for cyclohexane, this gives a little bicyclohexyl and cyclohexyl methyl ketone, but again a plateau is reached at a few percent conversion (not shown in the Figure 1).

The tungstate thus activates C–H bonds, but it behaves as a stoichiometric oxidant and accumulates in the inactive reduced state. Known reoxidation mechanisms are hydrogen evolution—demonstrated to occur, although inefficiently, in the presence of platinum[12]—or reaction with oxygen, which also traps the radicals to form peroxy derivatives.[6a]

In this work the reaction was carried out in the presence of electrophilic alkenes and alkylation was found to occur efficiently, overcoming the other photoinduced processes either for the major part (with propan-2-ol) or completely (with cyclohexane, THF, or DIOX). Under these conditions, TBADT is not a stoichiometric reagent, but rather a photocatalyst (TON > 35 at the end of the reaction). Although the rate of alkylation may vary considerably—the irradiation time required for converting propan-2-ol, for example, is much shorter than that for cyclohexane (by a factor of ca.

10)—the alkylation proceeds steadily in all cases, as shown by the regular increase in TON with conversion (see Figure 3).

Hydrogen abstraction: As mentioned in the Introduction, the nature and reactivity of the decatungstate's excited states and the primary events in the presence of several aliphatic derivatives have been clarified previously.[13,15–17] The reactive excited state of the $W_{10}O_{32}^{4-}$ ion, indicated simply as W* in Scheme 3, is characterized by a hole in a O-based MO and accordingly efficiently abstracts hydrogen from aliphatic derivatives to yield reduced $HW_{10}O_{32}^{4-}$ (indicated as HW in Scheme 3) and alkyl radicals. The discussion below on the early steps is very limited, because the current data essentially confirm previous work, while the subsequent radical reactions and their exploitation in synthesis are the target of this study and are discussed in some detail.



Scheme 3. Competing paths in the photocatalyzed activation of alkanes.

Reduced polytungstate is easily monitored by FP through the strong absorption in the visible region and, according to Scheme 3, the quantum yield associated with the reduction (Φ_{red}) is given by Equation (3), where η is the formation efficiency of the reactive excited state W* (from the literature η≈0.55[13]). Reduction of the tungstate involves two components: reaction with the hydrogen donor RH (k_r; see Scheme 3) and reaction with the solvent (k_b; this path includes any contribution to the reduction by the counter cation TBA^+ or by any impurity) in competition with decay of the excited state (k_d).

$$\Phi_{red} = \eta \frac{k_b + k_r[RH]}{k_d + k_b + k_r[RH]} \tag{3}$$

This can be expressed by means of the Stern–Volmer type Equation (4),[18] where $K = k_r/(k_d + k_b)$ and the value of Φ_{red} in neat acetonitrile [$\Phi^\circ = \eta k_b/(k_d + k_b)$], as well as the limiting value from extrapolation at growing [RH] ($\Phi_{lim} \equiv \eta$) are introduced.

$$\Phi_{red} = \frac{\Phi^o + \Phi_{lim} K[RH]}{1 + K[RH]} \tag{4}$$

The quantum yields of formation of (monoelectronic) reduced tungstate in the presence of either cyclohexane or propan-2-ol in FP experiments are plotted in Figure 4b and Figure 5b versus the hydrogen donor concentration. The lines connecting the experimental points were drawn according to Equation (4) and the values were obtained: $K = 5.3$ and $2.1\,\text{M}^{-1}$ for propan-2-ol and cyclohexane, respectively. These correspond to the rate constants $k_r = 10.1$ and $4.0\times10^7\,\text{M}^{-1}\,\text{s}^{-1}$ when account is taken of the measured TBADT lifetime in MeCN (58 ns; see Figure 6 and Table 3), close to the previously measured values ($k_r = 8$ and $3.7\times10^7\,\text{M}^{-1}\,\text{s}^{-1}$).[13] Some reduction occurs in neat MeCN ($\Phi^\circ = 0.09$), indicating that the solvent and the tetrabutylammonium counter cation contribute, although inefficiently, to the photoreduction (see Scheme 3). If such contribution were due to MeCN only, this would give $k'_r = 9\times10^4\,\text{M}^{-1}\text{s}^{-1}$. It may be noted that the rate of hydrogen abstraction by W* is about two orders of magnitude faster than by excited states of organic molecules similarly characterized by holes localized on oxygen, such as the ketone triplet state. As an example, benzophenone has $k_r = 7.5\times10^5$, 1.8×10^6, and $1.3\times10^2\,\text{M}^{-1}\,\text{s}^{-1}$ with cyclohexane, propan-2-ol, and MeCN.[19a–c] Similarly, TBADT has a much broader scope as a photocatalyst than titanium dioxide, to which it is often compared, since it is a stronger oxidant, able to activate alkanes and their simple derivatives, on which the latter is hardly active.[19d]

Table 3. Parameters for the TBADT-photoinduced activation of cyclohexane and propan-2-ol in MeCN.

Reagent	Φ_{lim}	K [M^{-1}]	k_q [$\text{M}^{-1}\,\text{s}^{-1}$]
C_6H_{12}[a]	0.52	2.1	4.0×10^7
C_6H_{12}[b]	0.52	0.024	
2-PrOH[a]	0.52	5.3	1.0×10^8
2-PrOH[b]	0.55	18.4	
	Φ(neat)		
MeCN[a,c]	0.09		9×10^4
MeCN[b]	0.004		

[a] From flash photolysis experiments. [b] From steady-state experiments. [c] Under the simplified assumption that the polytungstate is reduced only by the solvent; compare reference [13].

Radical reactions—neat solvent: As is apparent from comparison of Figure 4a,b and Figure 5a,b, the quantum yields for polytungstate reduction (Φ_{red}) in flash photolysis (FP) and in the steady-state (SS) experiments are different. The initial values of Φ_{red} (SS) with cyclohexane are much lower (about 2%) than the corresponding FP values at the same RH concentration, while Φ_{red} (SS) with propan-2-ol is larger than Φ_{red} (FP), about twice as much at low alcohol concentration. The quantum yield of reduction in neat MeCN—Φ° (SS)—is also much lower (4% of the FP value).

This is due to further reactions of the radicals formed in the primary step, in particular to paths leading to reoxidation of the catalyst (see Scheme 3). As it appears from Figure 6, the amount of reduced polytungstate remains unchanged over several μs. On a longer timescale, however, a further evolution takes place.[12] This involves disproportionation of the monoelectronic reduced anion $HW_{10}O_{32}^{4-}$ (HW) to yield the two-electron reduced polytungstate $H_2W_{10}O_{32}^{4-}$ ($k_{ds} = 9\times10^4\,\mathrm{M^{-1}s^{-1}}$).[12] Furthermore, HW is in part reoxidized by reaction with the alkyl radicals, either through back hydrogen transfer (k_{bh}) or through electron transfer to give a carbanion (k_{rd}; see Scheme 3). However, the alkyl radical $R^{\cdot}$ is also consumed through reactions not involving HW, which are typically quite fast ($k_c > 1\times10^9\,\mathrm{M^{-1}\,s^{-1}}$).[20] The unbalance of k_{ds} and k_c causes the progressive accumulation of reduced tungstate during the process and correspondingly the decrease of the alkyl radicals, since the $[HW]/[R^{\bullet}]$ ratio is determined by the reaction between the two species ($k_{bh} + k_{rd}$). This is a classical case of the persistent radical effect, as evidenced by Fischer et al.[21]

In the case of cyclohexane, the radicals undergo both dimerization to bicyclohexyl and disproportionation to cyclohexene and cyclohexane[16,20] [the latter reaction has not been specifically assessed here, but it obviously contributes to the observed Φ_{red} (SS)]. According to Scheme 3, the steady-state yield of reduced tungstate is a fraction of that initially formed, as expressed by the efficiency factor [Eq. (5)]; see Equation (6).

$$\alpha = \frac{k_c[R^{\cdot}]}{(k_{bh}[HW] + k_{rd}[HW] + k_c[R^{\cdot}]} \cong \frac{k_c[R^{\cdot}]}{\{(k_{bh} + k_{rd})[HW]\}} \quad (5)$$

$$\Phi_{red}\,(SS) = \eta\frac{k_b + \alpha k_r[RH]}{k_d + k_b + k_r[RH]} = \frac{\Phi^o + \alpha\Phi_{lim}K[RH]}{1 + K[RH]} \quad (6)$$

The Φ_{red} (SS) versus $[C_6H_{12}]$ plot (Figure 5 a) and comparison with Figure 5 b indicate that α is slightly over 1 %. The rate constant for the back reaction HW + $R^{\bullet}$ can be determined ($8\times10^9\,\mathrm{M^{-1}s^{-1}}$; see below) through the competition with addition to electrophilic alkenes. Hydrogen transfer (k_{bh}) is by far the main path in this reaction (Table 4), while formation of the cyclohexyl anion, as deduced from the proportion of cyclohexyl methyl ketone produced through trapping by MeCN, corresponds to about 5 % ($k_{rd} \approx 4\times10^8\,\mathrm{M^{-1}s^{-1}}$).[22] This relatively low value is reasonable, because electron transfer is largely endothermic as evaluated on the basis of the reduction potential of the *sec*-butyl radical [$E(R^-/R^{\bullet}) = -1.72$ V versus SCE;[23] compare $E(HW/W) = -0.97$ V[24].]

Table 4. Bimolecular rate constants (k, $\mathrm{M^{-1}s^{-1}}$) for the radical reactions in the TBADT photocatalytic processes in MeCN (see Scheme 3, Scheme 4).

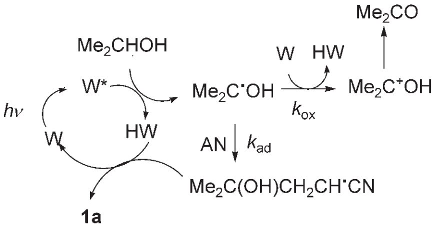
C_6H_{12}	2-PrOH
k_c 1×10^9	k_{ad} 1.5×10^8
k_{ad} 2×10^6	k_{ox} 2×10^{10}
k_{bh} 8×10^9	
k_{rd} 4×10^8	

Steady accumulation of HW causes a dramatic drop in the steady-state concentration of cyclohexyl radicals during the course of the process, and this actually becomes so low after a small (ca. 5 %) amount of conversion that formation of coupling products terminates. Such a limited conversion has been observed with other donors upon photocatalysis in the absence of oxygen.[5a]

Conversion back to MeCN is also important for the $^{\cdot}CH_2CN$ radicals formed by H abstraction from the solvent. Succinonitrile has been detected in small amounts under these conditions, but this is clearly a minor process.[12a] Actually, the steady-state value of Φ_{red} (SS) in neat MeCN is 0.004, 22 times smaller than the flash photolysis value, indicating that regeneration of TBADT and MeCN (rate constant k'_{bh}, see Scheme 3, right-hand side) efficiently competes with coupling of the cyanomethyl radicals ($k'_c = 1.2\times10^9\,\mathrm{M^{-1}\,s^{-1}}$).[25]

Unlike in the cyclohexane case, the steady-state quantum yield of tungstate reduction with propan-2-ol is larger than the flash photolysis value. Thus, at [2-PrOH] = 0.5 M, the initial value of Φ_{red} is 1.86 times larger than Φ_{red} (FP), and plotting of Φ_{red} (SS) versus the starting alcohol concentration (Figure 4 a) gives an apparent K value 3.4 times larger than the FP-derived value. As previously suggested,[12,21,26] but not quantitatively assessed, this is due to the oxidation of the α-hydroxyalkyl radical by the decatungstate (indicated as W) as shown in Scheme 4 and Equation (7).

$$Me_2C^{\cdot}OH + W \rightarrow Me_2CO + HW \quad (7)$$



Scheme 4. Competing paths in the photocatalyzed activation of propan-2-ol.

Indeed, at a low starting propan-2-ol concentration (= 0.1 M), Φ_{red} (SS)$\cong 2\times\Phi_{red}$ (FD), indicating that virtually every ketyl radical is oxidized. This is in accord with the easy oxidation of such radicals—$E(Me_2C^{\cdot}OH/Me_2C^{+}OH) = -0.61$ V versus SCE[27]—and, coupled with the rapid deprotonation of the cation to give acetone, supports electron transfer according to Equation (7) as a viable pathway.[19] The rate constant for radical reaction (k_{ox}) was again determined by competition with addition to electrophilic alkenes (see below). It may be noted that the excess of Φ_{red} (SS) over Φ_{red} (FP) diminishes with increasing alcohol concentration (compare Figure 4 a/b), reasonably because when a relatively high $Me_2C^{\bullet}OH$ concentration is generated, oxidation according to Equation (7) results in local depletion of the decatungstate and thus in incomplete oxidation of the radicals.[28a] As a result, the limiting value of Φ_{red} (SS) is only slightly larger than Φ_{red} (FP).

Figure 1 and Figure 3 show that the rather efficient oxidation of propan-2-ol to acetone (quantum yield 0.32 at 0.5 M alcohol starting concentration) stops when all of the starting amount of decatungstate has been reduced.[28b]

Thermal oxidation of the initially formed α-oxygen-substituted radicals may also occur with ethers and acetals such as tetrahydrofuran and 1,3-dioxolane, in view of the relatively accessible oxidation potentials of such species (oxidation potential of the 2-tetrahydrofuranyl radical = −0.35 V versus SCE, of the dioxolanyl radical = −0.9 V;[29] deprotonation, in this case from the α carbon, is a fast process).[30] In contrast, oxidation is excluded for alkyl radicals, for which the oxidation potential has a positive value versus SCE.[30] In the last case, oxidation (again coupled with deprotonation) occurs when a more easily reduced polyoxometalate (e.g., a phosphapolytungstate)is used.[24]

Radical reactions—trapping by electrophilic alkenes: As discussed above, with alcohols TBADT is a consumed reagent rather than a catalyst, whist with alkanes efficient back hydrogen transfer and HW accumulation severely limit the alkyl radical concentration. Thus, although for opposite reasons, the reactions stop at an early stage in both cases, depriving an otherwise promising (high rate constant for H abstraction; see above) method of photoinduced C–H bond activation of preparative interest. The reaction continues in oxygen-equilibrated solutions because molecular oxygen *regenerates* TBADT, thus maintaining the operation of the photocatalytic cycle, besides trapping the organic radical to give hydroperoxides.[6a,31] Under these conditions, Tanielian indeed found that a plot of the SS quantum yield of oxygen consumption versus cyclohexane concentration gave a value of K quite close to that obtained from the tungstate reduction in flash photolysis experiments.[13] Furthermore, the yield of hydroperoxides from cyclohexane corresponded to the amount of oxygen adsorbed, at least up to a certain level of conversion. Scheme 1b is therefore operative and reduced tungstate does not accumulate.

As the above data show, electrophilic alkenes are likewise efficient traps. Table 1 shows that α,β-unsaturated nitriles, dinitriles, esters and ketones (0.1 M) are smoothly alkylated under these condition up to *complete* conversion and, except for the case of cyclohexenone (where competitive light adsorption may have a negative effect), the *isolated* yields of the alkylation products are always >50 % and in most cases >70 %.

From the mechanistic point of view, the data show that trapping by AN contributes significantly to the decay of cyclohexyl radicals, which brings about an increase in accumulated HW (see Figure 2) due to the decreased contribution of back hydrogen transfer. Trapping is not complete, though, and the initial quantum yield of alkylation (0.06) corresponds to 22 % of the initial yield of radicals as determined by flash photolysis Φ_{red} (FP). The competition between trapping and back hydrogen transfer is expressed in Equation (8).

$$\frac{\Phi_{ad}}{\Phi_{red}\ (\mathrm{FP})} = \frac{k_{ad}[\mathrm{AN}]}{\{(k_{bh}+k_{rd})[\mathrm{HW}] + k_{ad}[\mathrm{AN}]\}} \tag{8}$$

This allows the rate of the latter process to be evaluated, since Φ_{red} is measured under the same conditions as Φ_{ad}. On the basis of the moderate rate of addition to AN (k_{ad} ca. $2\times10^6\,\mathrm{M}^{-1}\,\mathrm{s}^{-1}$),[32] this gives ($k_{bh}+k_{rd}$) = $8\times10^9\,\mathrm{M}^{-1}\mathrm{s}^{-1}$. In conjunction with the α value determined above, this gives a [HW]/[*cyclo*-$C_6H_{11}^{\cdot}$] ratio of 800 under steady-state conditions in neat MeCN in the early phase of the reaction (compare with [HW]/[*cyclo*-$C_5H_9^{\cdot}$] = 900, measured by EPR in the reaction with cyclopentane).[21] The proportion of reduced anion increases during the conversion, resulting in a decreased rate of alkylation, which nevertheless proceeds steadily and reaches a satisfactorily turnover number (Figure 3). The final step in the alkylation process is reduction of the adduct radical with regeneration of TBADT. This occurs by electron followed by proton transfer, as indicated by the experiments in 0.5 % D_2O/CH_3CN and in CD_3CN, in accord with the much easier reduction of α-cyano-substituted alkyl radicals (of known high electron affinity)[33] with respect to their unsubstituted counterparts. This is obviously a key step, both for allowing the catalytic role of the tungstate[34a] and for the reaction selectivity. As for the latter point, this introduces some limit to alkene concentration. Indeed, when a 1 M AN concentration is used, trapping of the radical adduct by the alkene (a relatively slow process, $k\approx1\times10^4\,\mathrm{M}^{-1}\,\mathrm{s}^{-1}$)[32] becomes competitive with electron transfer from HW and certain amounts of the dimeric and trimeric adducts are formed.[11]

In the case of propan-2-ol, initial H abstraction is much more efficient, resulting in fast accumulation of the reduced form HW.[34b] On the other hand, trapping by AN is also more efficient ($k_{ad}\approx1.5\times10^8\,\mathrm{M}^{-1}\mathrm{s}^{-1}$).[32] Since the alkylation cycle regenerates TBADT (Scheme 4), reduced HW is accumulated to a smaller extent with respect to neat solvent (see Figure 2), in contrast with what happens in the slow alkylation by cyclohexane, where the determining factor is back H transfer. The initial quantum yield of alkylation is somewhat larger than Φ_{red} (FP), while the quantum yield for the oxidation to acetone is 29 % of the value in the absence of the trap. These data confirm that oxidation is practically the only process from the α-hydroxyalkyl radical. The ratio between the quantum yield of acetone in the absence and in the presence of AN corresponds to the ratio $k_{ox}[\mathrm{W}]/(k_{ox}[\mathrm{W}] + k_{ad}\,[\mathrm{AN}])$ and allows calculation of $k_{ox} = 2\times10^{10}\,\mathrm{M}^{-1}\mathrm{s}^{-1}$. This high (diffusion-controlled) value is consistent with oxidation being the main process for the $Me_2C^{\cdot}OH$ radical under these conditions (k_{ox} [W] $\gg k_{bh}$ [HW]), as mentioned above. Other oxygen-substituted radicals such as those from tetrahydrofuran and dioxolane are likewise efficiently trapped. As with simple alkyl radicals, the final step is electron transfer to the (α-cyano) radical adduct, as established by deuteration experiments in the THF case.

It is interesting to compare the effects of oxygen and of alkenes on TBADT-photoinduced reactions. Both reagents are effective radical traps and the tungstate is regenerated in their presence, allowing conversion to proceed. The reaction with oxygen is complicated by the fact that the peroxy radical formed may give different reactions according to the substrate chosen and the conditions.[6b] Alcohols or ketones are thus formed from alkane hydroperoxides in different amounts. Trapping by unsaturated nitriles, esters, and ketones is a clean process, since it produces an electrophilic radical that is efficiently reduced by HW, avoiding competing processes. Furthermore, the alkylation can also be carried out in air-equilibrated solutions. As shown in Figure 1, in the case of propan-2-ol the alkylation efficiency actually becomes somewhat larger than under oxygen exclusion, after a short induction time, and reduced tungstate accumulates to a small degree. Dissolved oxygen ($[O_2] = 2\times10^{-3}\,\text{M}$, with $k_{O_2}\cong5\times10^9\,\text{M}^{-1}\,\text{s}^{-1}$)[35] competes with AN ($[\text{AN}] = 0.1\,\text{M}$, with $k_{\text{ad}}\approx1.5\times10^8\,\text{M}^{-1}\,\text{s}^{-1}$) for the short-lived radicals but on the other hand contributes to the reoxidation of HW, a persistent species, and thus to the overall efficiency of the process. The first effect causes the induction period, but the oxygen concentration then decreases, since equilibration with the atmosphere does not compensate for chemical consumption, and the alkylation proceeds under favorable conditions. With cyclohexane, on the other hand, alkylation is considerably slowed down (the rate becomes a quarter of its original value) in an aerated solution, consistently with the fact that the lower rate of addition to AN ($k_{\text{ad}}\approx2\times10^6\,\text{M}^{-1}\,\text{s}^{-1}$) makes trapping of the radicals by oxygen more important. Nevertheless, a good yield of the alkylated product is also obtained in this case, though after a longer irradiation time.

Conclusion

As mentioned in the Introduction, the wealth of data from previous research support the contention that the high reactivity of photoexcited decatungstates might make these materials highly suited for the mild activation of aliphatic C–H bonds. However, this rarely produces high chemical conversion, either because of a rapid drop in the alkyl radical concentration after a few percent conversion (due to reaction with the persistent reduced tungstate), or because of the catalyst consumption when an easily oxidized radical is used. Useful reactions are obtained when the radical is trapped efficiently by a path that regenerates the catalyst,[36] as is indeed the case for oxygenation, which can be carried out to a rather high level of conversion (>50%).[6] In the present case, the alkene serves the same function as oxygen: it *both* traps the radicals *and* regenerates the catalyst (in this case indirectly, via the radical adduct as shown in the cycle in Scheme 3). Competition between trapping by the above alkenes and the other available paths allows the key kinetic parameters for the reactions of the radicals generated by photocatalysis to be obtained. Neither oxygenation[31] nor alkylation[34a] are chain reactions, and the limiting quantum yield is in both cases about 0.5, close to the expected value $\Phi_{\text{lim}} = \eta$. As one might expect, alkylation is more efficient with more nucleophilic radicals—Φ_{ad} is 10 times larger with propan-2-ol than with cyclohexane, for example. This makes reaction with a "moderately activated" (α-hydroxy-substituted) alkyl derivative particularly convenient (e.g., it can also be carried out in air-equilibrated solution; indeed, it gives slightly better results under those conditions), but does not detract from the preparative value of alkylation with an alkane, since there are no significant competing processes and so a good chemical yield can be obtained, although after a longer irradiation time.

These results demonstrate that TBADT photocatalysis is a viable and rather general method for the mild functionalization of aliphatic C–H bonds, and that, besides for oxygenations, it can be conveniently used for C–C bond-forming reactions. Thermal analogy for such process is quite limited, variously involving the use of high temperature and pressure,[37a] the preparation and cleavage of peroxides,[37b] or a catalyzed process based on some sophisticate metal complex that requires a much more elaborate setup than the photochemical synthesis.[38,39] The reactions presented above are paradigmatic examples of 100% atom efficiency and the small amount of catalyst used, as well as the simple experimental setup, both during irradiation (e.g., no anhydrification or deoxygenation required) and during workup, make this method an example of "green" synthesis, comparing favorably with other approaches to CH functionalization.

Experimental Section

Materials: Tetrabutylammonium decatungstate (TBADT)[12a] and unsaturated dinitrile IPMN[41] were prepared by published procedures. The other materials and the solvents were of commercial origin.

Preparative irradiations: These were carried out in 1 cm diameter quartz tubes containing a solution (6 mL) of TBADT (40 mg, 0.002 M), the alkane (0.5 M), and the electrophilic alkene (0.1 M). These were purged with purified argon for 10 min, septum-capped, and irradiated for 15–20 h in a multilamp apparatus fitted with six 15-W phosphor-coated lamps (center of emission 310 nm). The irradiated solution was flushed with oxygen until colorless, passed through a 4-cm layer of neutral alumina, and concentrated. The residue was first examined by GC/MS and then chromatographed on silica gel with cyclohexane and cyclohexane/ethyl acetate 98:2 mixture as eluents. With IPMN essentially the same results were also obtained when degassing was omitted.

Compounds **1a**,[40,42] **2a**,[43] **3a**,[44] **4a**,[11] and **5**[45] had physical characteristics identical to those of the compounds prepared by alternative procedures as reported in the literature. Bicyclohexyl and cyclohexyl methyl ketone were recognized and determined by comparison of their GC/MS spectra with those of authentic samples.

2-Cyano-4-hydroxy-3,3,4-trimethylpentanenitrile (1b): Colorless crystals, m.p. 138–140 °C; ^{1}H NMR (300 MHz, CDCl$_3$, TMS): $\delta = 1.15$ (s, 6H), 1.3 (s, 6H), 4.4 (brs, each, 1H), 5.2 ppm (s, 1H); IR (KBr): $\tilde{\nu} = 3415$, 2170 cm^{-1}.

3-(2-Tetrahydrofuranyl)propanenitrile (2a) [D$_1$]-2: Oil that solidifies on standing; ^{1}H NMR (300 MHz, CDCl$_3$, TMS): $\delta = 1.5$ (m, 1H), 1.7–2.1 (m, 5H), 2.5 (m, 1H—2H in the non-deuterated analogue), 3.7–4.0 ppm (m, 3H); ^{13}C NMR (75 MHz, CDCl$_3$): $\delta = 13.9$ (t, $J = 20.6$ Hz, CHD), 25.6 (CH_2), 30.9 (CH_2), 31.1 (CH_2), 67.7 (CH_2), 77.0 (CH), 119.6 ppm (CN).

2-Cyano-3-methyl-3-(2-tetrahydrofuranyl)butanenitrile (2b): Oil that solidifies on standing; ^{1}H NMR (300 MHz, $CDCl_3$, TMS): $\delta = 1.15$ (s, 3H), 1.3 (s, 3H), 1.7 (m, 1H), 1.95 (m, 3H), 3.75–3.9 (m, 3H), 4.0 ppm (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 18.2$ (CH_3), 21.1 (CH_3), 26.1 (CH_2), 26.2 (CH_2), 32.8 (CH), 41.7 (C), 68.8 (CH_2), 81.5 (CH), 111.9 (CN), 112.3 ppm (CN); IR (KBr): $\tilde{\nu} = 2230$, 1070 cm^{-1}.

2-Cyano-3-[2-(1,3-dioxolanyl)]-3-methylbutanenitrile (3b): ^{1}H NMR (300 MHz, $CDCl_3$, TMS): $\delta = 1.25$ (s, 6H), 3.9 (s, 1H), 3.95–4.1 (AA'BB', 4H), 4.8 ppm (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 20.1$ (CH_3), 29.8 (CH), 41.3 (C), 65.5 (CH_2), 105.8 (CH_2), 111.6 ppm (CN); IR (KBr): $\tilde{\nu} = 2230$, 1070 cm^{-1}.

Steady-state measurements: Solutions (2 mL) of TBADT in MeCN (0.002 M) containing the appropriate additives in 1-cm optical path spectrophotometric cuvettes were degassed by five freeze–degas–thaw cycles (to 10^{-6} Torr). The samples were irradiated by means of a focalized Osram 150 W high-pressure mercury arc fitted with an interference filter at 313 nm or a band-pass filter (the former for quantum yield measurements, the latter for comparing reactivities). Light absorbed was determined by photometer and the light flux was measured by ferrioxalate actinometry. Formation of the alkylated products was determined by GC on the basis of calibration curves with use of benzophenone as internal standard). Formation of the two reduced forms of TBADT was monitored by spectroscopy in the visible region on the basis of the known molecular extinction coefficients of such molecules.[12,13b] Acetone was determined by HPLC by the method reported by Franco.[46]

Flash photolysis measurements: Flash photolysis measurements were carried out with an Applied Photophysics kinetic spectrometer and use of the fourth harmonic of a Nd-YAG Lumonics HY 200 laser. The quantum yield of transient formation was determined by comparison with the ketyl radical formed by excitation of benzophenone in propan-2-ol ($\varepsilon_{540} = 3220\,\text{M}^{-1}\,\text{cm}^{-1}$)[47] from benzophenone as the reference.

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