Perspective

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ACS Catal., **Just Accepted Manuscript** • DOI: 10.1021/acscatal.7b03354 • Publication Date (Web): 05 Dec 2017

Site-Selective C-H Functionalization by Decatungstate Anion Photocatalysis: Synergistic Control by Polar and Steric Effects Expands the Reaction Scope

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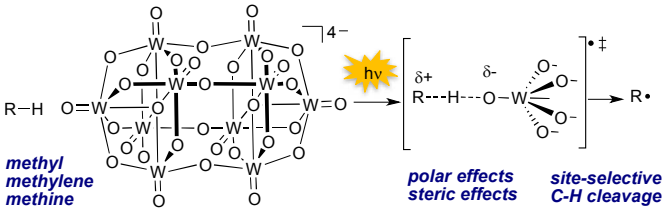
ABSTRACT: The synergistic control of the S_H2 transition states of hydrogen abstraction by polar and steric effects provides a promising strategy in achieving site-selective C(sp^3)-H functionalization under decatungstate anion photocatalysis. By using this photocatalytic approach, the C-H bonds of alkanes, alcohols, ethers, ketones, amides, esters, nitriles, and pyridylalkanes were functionalized site-selectively. In the remarkable case of a 2,4-disubstituted cyclohexanone bearing five methyl, five methylene, and three methine C-H bonds, one methine C-H bond in the isoamyl tether was selectively functionalized.

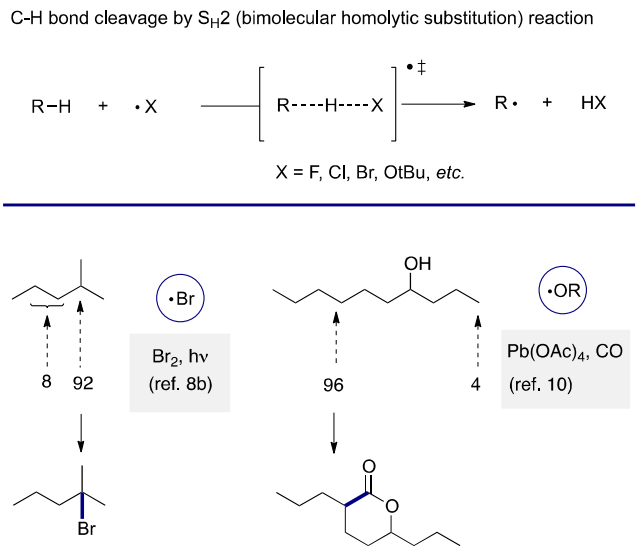


KEYWORDS "polar effects, steric effects, photocatalysis, decatungstate anion, C(sp^3)-H functionalization, alkanes, carbonyl compounds, nitriles"

INTRODUCTION

Catalytic C-H functionalization has recently become a mainstay of organic chemistry, and now there are many successful examples of directing group controlled methods.[1] Noteworthy is the progress of the direct functionalization of alkane C-H bonds,[2,3] in which a variety of transition metal complexes are used as the catalyst. Some of these are regarded as synthetic analogues of the natural P450 family of enzymes in which Fe- and Mn-centers are designed to function for C-H bond cleavage activity.[4,5] In particular, considerable effort has been directed at site-selective alkane C-H functionalization and remarkable examples[5] include a recent report on the enantioselective functionalization of C2-methylene of pentane by a Rh-carbene complex.[6]

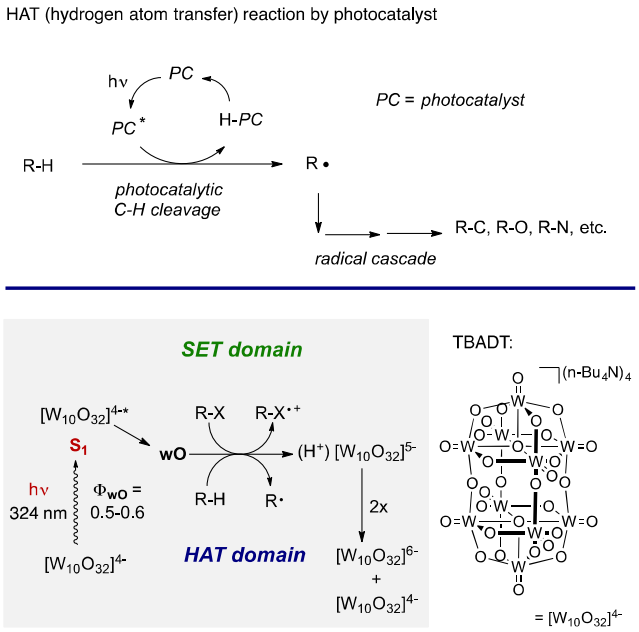
Alkane C-H bonds have long been recognized to be cleaved by hydrogen abstraction by a variety of radical species, such as halogen radicals, oxygen centered-radicals, and even carbon-centered radicals (Scheme 1, top equation).[7] In principle, such free radical-mediated S_H2 (homolytic bimolecular substitution)-type hydrogen abstraction has excellent potential to contribute to site-selective C(sp^3)-H functionalization, if powerful methodologies to control the site-selectivity are developed. A classic, yet useful example is the C-H bromination of alkanes, in which the weakest methine C-H bond is cleaved with good selectivity in the presence of methylene and methyl C-H bonds (Scheme 1, bottom left).[8] Similarly the well-known Barton nitrite reaction permits the site-selective C(sp^3)-H functionalization of saturated alcohols, in which the thermodynamic capability of alkoxy radicals to abstract hydrogen from alkyl C-H bonds at the δ-position is controlled by an entropically favorable intramolecular S_H2 process.[9] Examples include radical C-H carbonylation of secondary alcohols in the presence of lead tetraacetate, where the δ-methylene position is favored over δ-methyl.[10] For example, C-H carbonylation of 4-decanol results in a 96 to 4 ratio in favor of the weaker methylene C-H bond cleavage (Scheme 1, bottom right). The Hofmann-Löffler-Freytag reaction is an example of 1,5-H radical translocation from aminyl radicals to alkyl radicals.[11] Having a wider concept of 1,5-radical translocation,[12] synthetically useful methods for δ-site-selective C-H functionalization are now abundant.



Scheme 1. Examples of Site-selective C-H Functionalization by Br and Alkoxy Radicals

In recent years, photocatalytic radical approaches for C-H bond cleavage have attracted increasing attention as viable alternatives to thermal approaches.[13] The photocatalyst (PC) undergoes light absorption and, the PC in the excited state (PC*) may activate C-H bonds of alkanes by the direct cleavage through a hydrogen atom transfer (HAT) step (S_H2 reaction) to form an alkyl radical, which undergoes subsequent radical reactions to lead to C-H functionalized products (Scheme 2, top).[14] For many years, our groups have been involved in the development of C-H functionalization methodologies by photocatalytic protocols based on the decatungstate anion, routinely employed as the tetrabutylammonium salt (TBADT: tetrabutylammonium decatungstate, $(n\text{Bu}_4\text{N})_4[W_{10}O_{32}]$).[15,16]

The decatungstate anion is part of the large family of polyoxometalates (POMs).[17] POMs can be reduced in reversible one- or two-electron steps to give mixed-valence polyanions, called '*heteropoly blues*'.[18] This characteristic blue color is associated with the extra electrons on the metal centers,[19] originally present in their highest oxidation state. Accordingly, tracking the color change of the solution to blue is a valuable tool to monitor the system evolution.[19] Among the family of POMs,[20] the decatungstate anion has demonstrated an outstanding photochemical activity that motivated its use as a competent photocatalyst in the field of organic synthesis.[15,16] However, despite the first reports of its behavior dating back to the 1980s thanks to the pioneering work by Hill and coworkers,[21,22,23] the details of the processes involved in the activation of organic substrates have not been understood until recent experimental[23,24] and computational studies.[25]

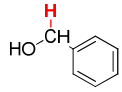


Scheme 2. Photocatalytic Action Modes of TBADT, $(n\text{Bu}_4\text{N})_4[W_{10}O_{32}]$, and the Use for C-H Functionalization

The absorption spectrum of the decatungstate anion shows a broad band centered at 324 nm (ε_{324} = 14100 $M^{-1}\cdot cm^{-1}$)[22] due to an allowed HOMO-LUMO transition with a marked LMCT character, where electrons are moved from oxygen centers to tungsten atoms (Scheme 2, bottom). The singlet excited state (S_1) initially formed, has a lifetime in the order of a few tens of picoseconds, however, it does not interact with organic substrates but rapidly decays to the actual reactive state (**wO**).[22,23] This is a relaxed excited state, probably of triplet multiplicity, that is formed with a quantum yield around 0.5-0.6. A recent report proposed that the population of **wO** from S_1 occurs through a reorganization of the singly occupied orbital centered on oxygen (not tungsten) atoms, leading to the formation of highly electrophilic oxygen centers with partial radical character.[25e] The interaction of **wO** with organic substrates present in solution can occur according to two different mechanisms, namely by a single electron transfer (SET), or by a hydrogen atom transfer (HAT), depending on the redox properties of the substrate. In a recent study, **wO** was predicted to have a redox potential E (**wO**/$[W_{10}O_{32}]^{5-}$) around + 2.44 V vs saturated calomel electrode (SCE),[25e] in good agreement with previous experimental investigations that measured the value to be in the range of + 2.26 to + 2.61 V vs SCE. Accordingly, when the substrate has an oxidation potential < + 2.44 V vs SCE, a SET event may take place, giving access to the radical cation of the starting substrate. By contrast, when the redox potential of the substrate does not match the above mentioned value, the generation of a $R^{\bullet}$ radical is feasible via HAT. Regardless of whether SET or HAT occurs, the oxidation process leads to the mono-reduced form of decatungstate, $[W_{10}O_{32}]^{5-}$, either protonated or not. On a longer timescale, $[W_{10}O_{32}]^{5-}$ spontaneously disproportionates, leading to the reduced form $[W_{10}O_{32}]^{6-}$ and the oxidized form of the cluster $[W_{10}O_{32}]^{4-}$. As

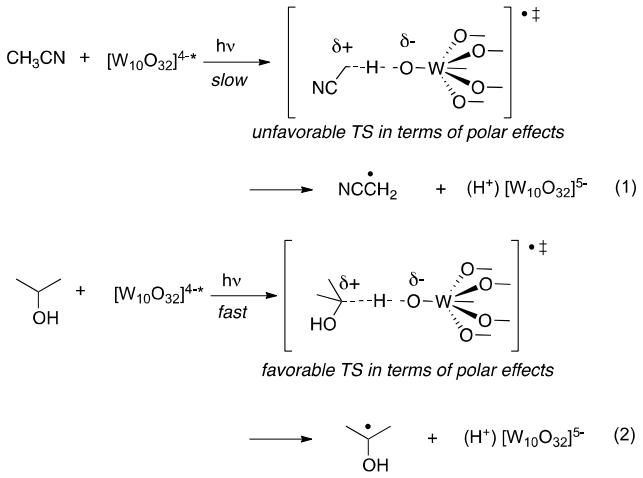
mentioned, following the color of the solution is a powerful tool to monitor the formation of oxidized substrate, since the blue color corresponds to reduced W centers and, accordingly, all of the above mentioned decatungstate species (S_1, **wO**, $[W_{10}O_{32}]^{5-}$ and $[W_{10}O_{32}]^{6-}$), with the exception of the original $[W_{10}O_{32}]^{4-}$, share characteristic absorptions in the red region of the visible spectrum. However, the extended overlap of the absorption spectra often prevents an unambiguous interpretation of the reaction course.

Table 1. Selected Rate Constants ($k_{R\text{-}H}$) for Hydrogen Abstraction from Various Hydrogen Donors by Excited Decatungstate Anions

hydrogen donor	$k_{R\text{-}H}$ ($M^{-1}\cdot s^{-1}$)	references
	6.5×10^4	24a
	2.5×10^6	24d
		
n = 1	2.4×10^7	24b
n = 2	4×10^7	28
n = 3	5.6×10^7	24b
	1.0×10^8	28
	2.8×10^8	29

[a] Measured in acetonitrile as solvent. Temperatures of the experiment were not reported with the exception of cyclohexane (298 K).

The rate of hydrogen abstraction ($k_{R\text{-}H}$) by the decatungstate anion heavily depends on the C-H bond, and the reported values span over 4 orders of magnitude (see Table 1). Bond dissociation energies are not necessarily reflected in the rate constants for C-H bonds substituted by functional groups. Indeed, low rate constants ($k_{R\text{-}H}$ < 2.5×10^6 $M^{-1}\cdot s^{-1}$) are reported on polar solvents, such as acetonitrile, [24a] acetone,[24a] dichloromethane, [24d] and chloroform,[24d] where the hydrogen has electrophilic character due to the attached polar substituent. This can be explained on the basis of polar effects.[26] The polar effects impact the transition state of hydrogen abstraction, where the electrophilic **wO** leads to unfavorable interactions with these compounds (Scheme 3, eq. 1). On the other hand, good H-donors (with $k_{R\text{-}H}$ > 10^7 $M^{-1}\cdot s^{-1}$) include alkanes, alcohols and alkylaromatics. The observed values for cycloalkanes lie in the 10^7-10^8 $M^{-1}\cdot s^{-1}$ range (Table 1) and generally speaking, alkylaromatics are better H-donors than pure aliphatic derivatives. However, in the case of toluene, it has been reported that activation occurs with partial charge-transfer character, at least in the first stages of the process.[27] Aliphatic alcohols are the best H-donors in the series, with values consistently in the 10^8 $M^{-1}\cdot s^{-1}$ range. This may be rationalized by favorable interaction between **wO** and the C-H bond adjacent to the OH functionality (Scheme 3, eq. 2).



Scheme 3. Postulated S_H2 TSs Exerted by Polar Effects with Decatungstate Anion

Decatungstate salts, when in the excited state, are very efficient in the homolytic cleavage of the C-H bonds as apparent from the data shown in Table 2, where the rate constant for hydrogen abstraction from cyclohexane was compared with those of other hydrogen acceptors. The TBADT* $k_{R\text{-}H}$ was two orders of magnitude higher with respect to excited ketones (ca. 10^7 versus 10^5 M^{-1} s^{-1}) and also compares favorably with oxygen centered radicals, such as *t*-butoxy and cumiloxy radicals (ca. 10^6 M^{-1} s^{-1}).

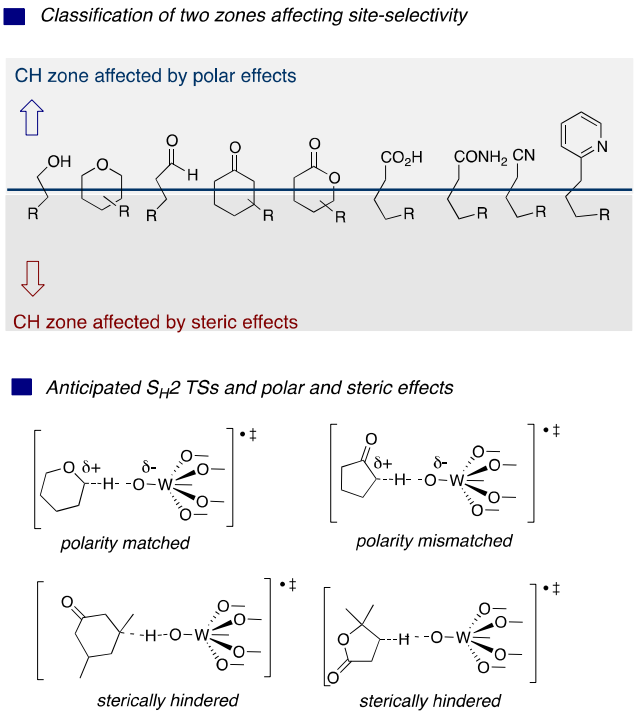
Table 2. Comparison of Rate Constants ($k_{R\text{-}H}$) for Hydrogen Abstraction from Cyclohexane[a]

hydrogen acceptor	$k_{R\text{-}H}$ ($M^{-1}\cdot s^{-1}$)	references
TBADT*	4×10^7	28
Ph_2CO*	7.2×10^5	30a
xanthone*	8.8×10^5	30b
*t*BuO$^\bullet$	9.6×10^5 [b]	30c
BnO$^\bullet$	1.3×10^6	30d
CumO$^\bullet$	$1.1\text{-}1.2\times10^6$	30d, 30e

[a] Measured in acetonitrile or benzene (*t*BuO•) as solvent at 298K.

Throughout our investigations we have noticed that the C-H functionalization of compounds containing a variety of functional groups occurs with site-selectivity, despite the high rate constants in the competing hydrogen abstraction reactions.

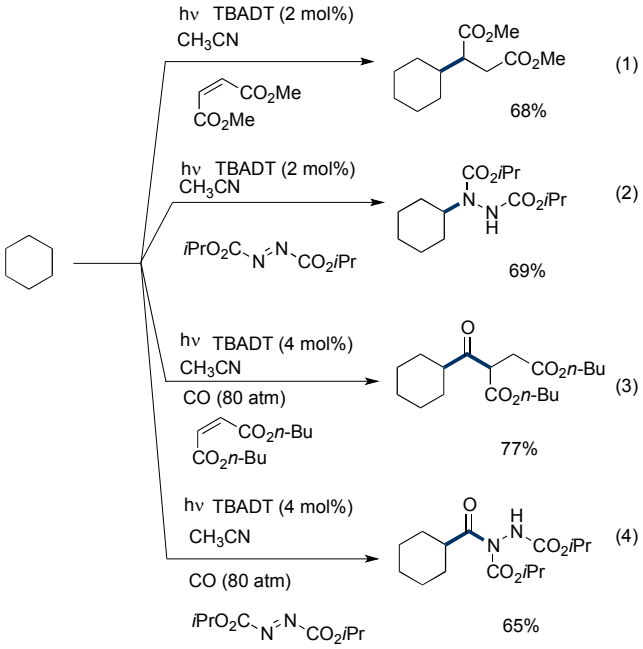
This is due to the control exerted by polar effects on the C-H cleavage step, which is associated with highly electrophilic oxygen centers of tungstate anions exhibiting radical character. In addition, since the decatungstate anion is a large molecule (MW of $[W_{10}O_{32}]^{4-}$ = 2350), steric effects also impact the site-selectivity in the S_H2 (HAT) transition states.[31] These two effects are important for site-selective C-H functionalization on their own, but if combined, these would work as a more powerful strategy applicable to functionalization of a wide range of complex organic molecules (Scheme 4). In this *Perspective*, we categorize C-H functionalization results obtained through the use of TBADT as the photocatalyst with a view to determine the origin of site-selectivity. We also examined how the concept of the synergistic strategy based on polar and steric effects applies to catalysis. It is important to note that Tungstate anions are not the sole reagent capable of site-selective C-H functionalization, however, they are particularly important due to the polar and steric effects in HAT processes for site-selective C-H functionalization which does not rely on the use of any directing groups.



Scheme 4. Synergistic Strategy Based on Polar and Steric Effects for Site-Selective C-H Functionalization

Alkanes ans Arylalkanes

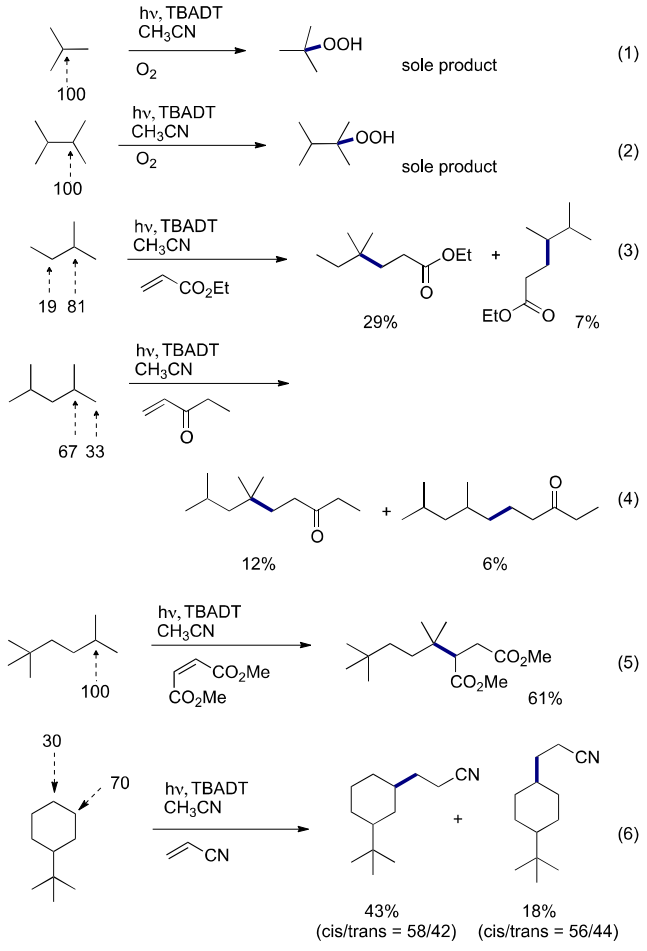
The capability of C-H cleavage by photo-excited decatungstate anion is so strong that even simple alkanes are converted to alkyl radicals. Alkyl radicals are derivatized to functionalized molecules through the formation of C-O, C-C, and C-N bonds by radical reactions. Under aerobic conditions, the decatungstate anion catalyzes oxidation of cycloalkanes. For example, cyclohexane is converted to a mixture of cyclohexanol and cyclohexanone.[32] Generally a xenon lamp is used as the light source, however, reactions also proceed under sunlight irradiation.[32a,b] Recent results show that heterogeneous catalysis, using immobilized decatungstate anion on an ion-exchange organic resin or on a carbon support, is also possible.[32c] A cooperative dual catalysis was examined for the synthesis of cycloalkenes from cycloalkanes, in which cobaloxime pyridine chloride was responsible for the abstraction of a second hydrogen atom from the cycloalkyl radical.[33] Since alkyl radicals have nucleophilic character, they undergo smooth addition onto electron-deficient alkenes (Scheme 5, eq. 1).[34] The C-H addition reaction can be extended to unsaturated esters, ketones, sulfones, and nitriles.[34b] The reaction is also possible under continuous flow photo-irradiation.[34d] Azodicarboxylates serve as an efficient radical trap, which lead to the preparation of substituted hydrazides (Scheme 5, eq. 2).[35] In the presence of pressurized CO, alkyl radicals add to CO to give acyl radicals, which undergo addition to electron-deficient alkenes to provide unsymmetrical ketones in good yields (Scheme 5, eq. 3).[36,37] Similarly, with CO and azodicarboxylates, the corresponding carboxylic acid amides are obtained in good yield (Scheme 5, eq. 4).[35] These radical reactions show the utility of decatungstate anion catalyzed C-H functionalization.



Scheme 5. C-H Functionalization Reactions of Cyclohexane by Decatungstate Photo-Catalysis

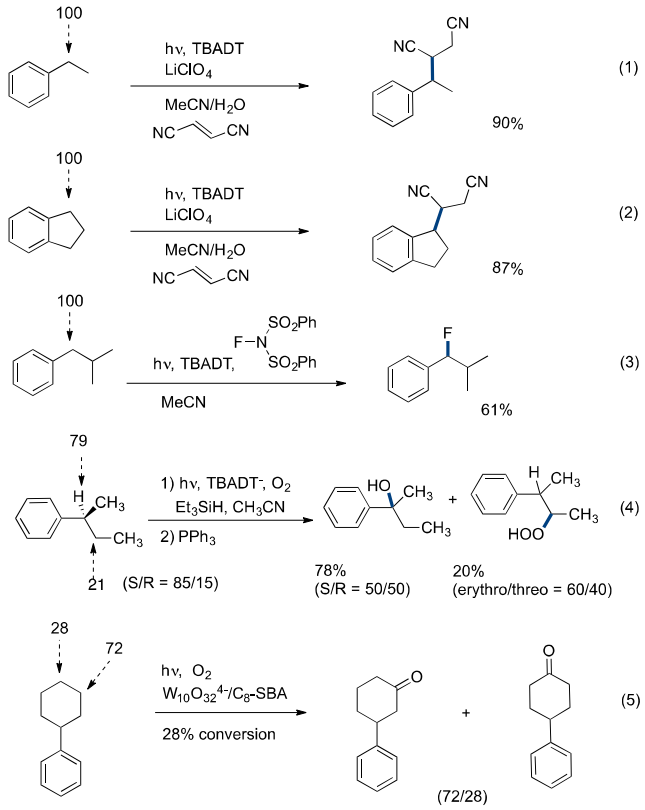
Site-selective cleavage of methine C-H bonds over methyl C-H bonds in alkanes is often observed by the formation of a C-O bond under aerobic conditions using decatungstate anion as the photocatalyst.[31a,38] For example, oxidation of isobutane proceeds site-selectively at the methine C-H bond, leading to TBHP in almost quantitative yield (Scheme 6, eq 1).[38a] The photo-catalyzed reaction of 2,3-dimethylbutane resulted in a

site-selective C-H cleavage at the methine C-H bond to give the corresponding hydroperoxide exclusively (Scheme 6, eq. 2).[38b] However, the presence of a tertiary carbon does not always leave to a selective process. In the case of adamantane, after reduction, both 1-adamantanol and 2-adamantanol are formed together with adamantanone. The reaction was quite efficient, with a quantum yield of 0.11.[38e] Similarly, the TBADT-catalyzed reaction of isopentane with ethyl acrylate gave a mixture of two products, derived from methine C-H and methylene C-H cleavage (Scheme 6, eq. 3).[39] In the case of 2,3-dimethylpentane, both methine and methylene groups are sterically congested and as a result, methyl C-H functionalization competes (Scheme 6, eq. 4). On the other hand, the methine C-H bond of 2,2,5-trimethylhexane, which is located remote to the *t*-Bu group was selectively functionalized (Scheme 6, eq. 5). In general the bulky *t*-Bu group strongly affects the site-selectivity due to steric effects. In the case of *t*-butylcyclohexane, the methine hydrogen is completely shielded by the bulky *t*-Bu group and the same holds for the methylene hydrogens present in the 2-position (Scheme 6, eq. 6).[31a] As a result, in the reaction with acrylonitrile, C-H cleavage took place at the 3- and 4-positions to give a mixture of two positional isomers.



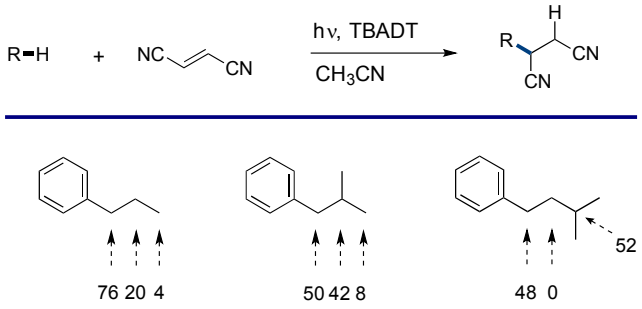
Scheme 6. Site-selectivity in Decatungstate-Catalyzed C-H Functionalization of Isobutane, 2,3-Dimethylbutane, Isopentane, 2,4-Dimethylpentane, 2,2,5-Trimethylhexane, and t-Butylcyclohexane

The presence of a more labile benzylic hydrogen in alkylaromatics generally drives the selective formation of benzyl radicals. The process was particularly clean when toluene, ethylbenzene (Scheme 7, eq. 1), indane (Scheme 7, eq. 2), and cumene were used.[27,40] Site-selective fluorination of the benzylic position was achieved by the TBADT photocatalysis in combination with *N*-fluorobenzenesulfonimide as the fluorine source.[41] Thus, isobutylbenzene was converted into fluoroisobutylbenzene under flow irradiation conditions (Scheme 7, eq 3). Selective benzylic oxidation of cumene[42] and 9-substituted fluorene[43] was also reported. However, the C-H functionalization of benzylic hydrogens is not always exclusive as we see an example of eq. 4 in Scheme 7. Thus, the photooxygenation of (*S*)-*sec*-butylbenzene with triethylsilane as the hydrogen donor gives racemic benzylic alcohols as major products (78% yield) and the secondary hydroperoxide is formed in 20% yield.[44] The C-H oxidation of cyclohexylbenzene is reported to be affected by steric effects, when decatungstate-supported mesoporous silica is used.[45] In this case the steric effects, enhanced by the cyclic structure, hamper the usual benzylic and homo-benzylic functionalization, which leads to a mixture of 3-oxo and 4-oxo phenylcyclohexanes (Scheme 7, eq. 5). The observed selectivity resembles that described for *tert*-butylcyclohexane in Scheme 6, eq. 6.



Scheme 7. Site-selectivity in Decatungstae-Catalyzed C-H Functionalization of Ethylbenzene, Indane, Isobutylbenzene, *sec*-Butylbenzene, and Cyclohexylbenzene

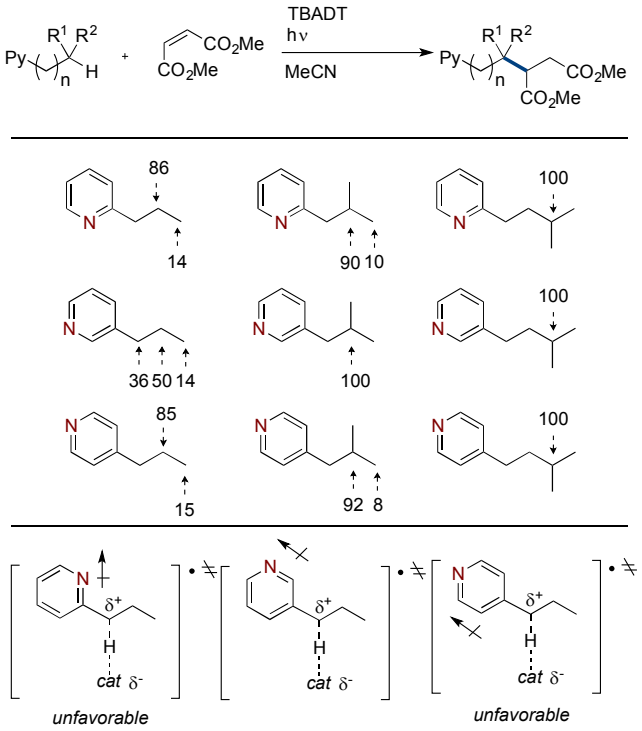
To obtain further insights into the site-selectivity by TBADT catalysis, we investigated alkylbenzenes having an elongated alkyl chain (Scheme 8).[46] The reaction of propylbenzene with fumaronitrile predominantly gave α-alkylated product along with β- and γ-alkylated products (α/β/γ = 76/20/4). In the cases of isobutylbenzene and isopentylbenzene having a methine C-H bond, alkylation at the benzylic C-H bond competed with alkylation at the methine C-H bond.



Scheme 8. Site-selectivity in Decatungstate-Catalyzed C-H Alkylation of Propylbenzene, Isobutylbenzene, and Isopentylbenzene

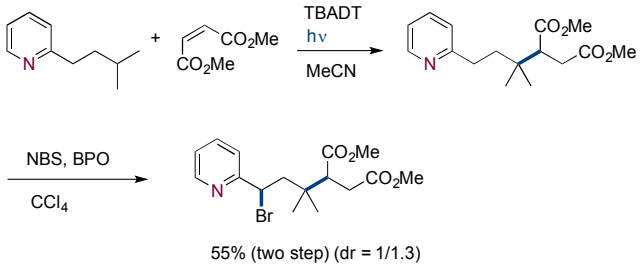
Alkylpyridines

TBADT photocatalyzed C-H alkylation of alkylpyridines was investigated systematically in terms of the radical polar effects (Scheme 9), and shows strong reluctance to α-C-H functionalization.[46] For example, the reaction of 2-propylpyridine gave the β-alkylated product in the majority, and no alkylation at the benzylic position took place. C-H functionalization of 2-isobutylpyridine and 2-isopentylpyridine took place at the methine C-H bond preferentially or exclusively, and no formation of the α-alkylated product was observed. The absence of C-H abstraction at the α-position is rationalized by an inductive effect of the pyridine ring influencing the S_H2 transition states. Among nine alkylpyridines examined one exception was found, 3-propylpyridine, which gave a mixture of α-, β-, and γ-alkylated products in a ratio of 36/50/14. This result is presumably due to weakened inductive polar effects of the 3-pyridyl group as compared with those of the 2- or 4-pyridyl group.



Scheme 9. Site-Selectivity in C-H Alkylation of Alkylpyridines and Possible TSs

Consecutive site-selective C-H functionalization of 2-isopentylpyridine is successful (Scheme 10).[46] The TBADT photocatalyzed C-H alkylation took place at γ position. The subsequent treatment of the C-H alkylation product with *N*-bromosuccinimide (NBS) in the presence of benzoyl peroxide (BPO) gave α-bromination product.

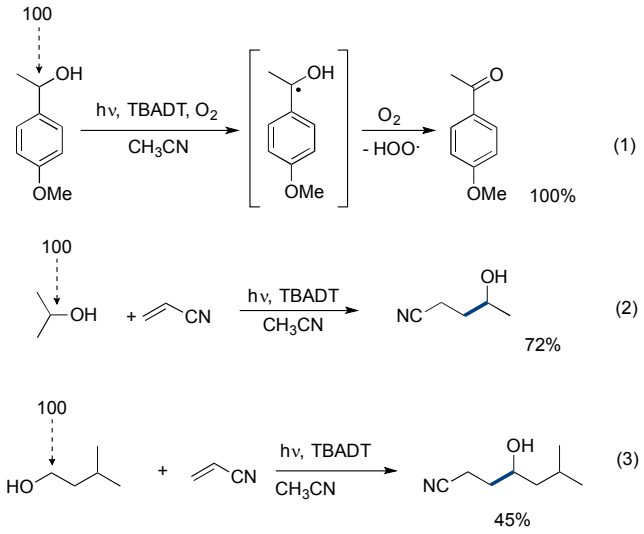


Scheme 10. Consecutive Double C-H Functionalization of 2-Isopentylpyridine

Alcohols and Ethers

In the case of aliphatic saturated alcohols, the decatungstate anion is able to induce site-selective C-H cleavage of the most labile C-H bond adjacent to the oxygen atom to form the corresponding α-hydroxyalkyl radical.[28,35,47,48] The HAT transition states are well accommodated to those stabilized by polar

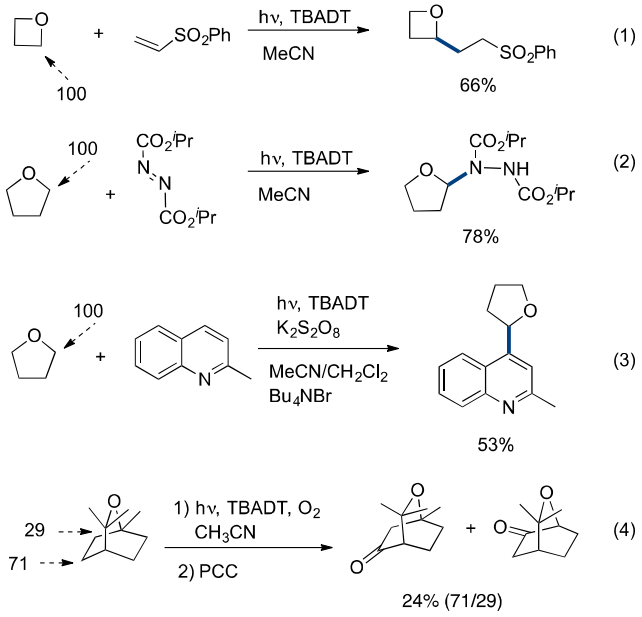
effects, as demonstrated with isopropanol as discussed earlier (Scheme 3, eq. 2). In addition, benzylic hydrogens of 1-aryl alkanols are easily cleaved,[29,47g,47h,47i] and the facile oxidation of the radicals formed gave the corresponding aldehydes or ketones even in the absence of oxygen. The reaction was particularly clean when applied to aryl methyl carbinols under an oxygen atmosphere (Scheme 11, eq. 1). The presence of a cobalt-based co-catalyst accelerates the oxidation leading to carbonyls, even when starting from aliphatic secondary alcohols.[33] Selectivity for the secondary alcohol was also observed for the oxidation of diols[48a] and glycerol.[48b] For example, a 90% yield of 4-hydroxy-2-butanone was formed from 1,3-butanediol by using silica-bound decatungstate anion under heterogeneous conditions.[48a] When isopropanol was added to acrylonitrile in the presence of the TBADT catalyst, the corresponding γ-hydroxynitrile was formed in a 72% yield (Scheme 11, eq. 2).[28] Similarly, isopentanol was reacted with acrylonitrile and C-H bond cleavage took place site-selectively α to the hydroxyl group and no functionalization at methine C-H bond was observed (Scheme 11, eq. 3).[39,49] On the other hand, the reaction of 4-methyl-2-pentanol proceeded poorly to give a 66:34 mixture of products via α and γ attack. This suggested that increased steric hindrance would have retarded the H-abstraction from the secondary alcoholic portion.



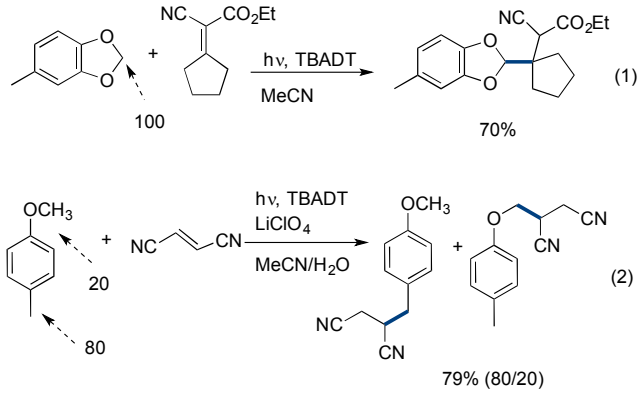
Scheme 11. Site-Selectivity in C-H Functionalization of Alcohols

Analogous with alcohols, the C-H bond adjacent to the oxygen atom of ethers is also cleaved easily. The resulting α-oxy radicals have been employed in C-C or C-N bond formation.[32b,c,d,35,50-53] For example, the methyl hydrogen of anisole is smoothly abstracted by decatungstate anion and is able to functionalize C_{60}.[51] Similarly crown ethers are suitable substrates for the synthesis of [60]fullerene/crown ether conjugates,[52] and polyethylene glycol (PEG) was added to carbon nanotubes in order to improve their water solubility.[53] Site-selectivity is also observed with oxygen-containing heterocycles (Scheme 12). 2-Substituted oxetane is formed selectively by reaction of oxetane with vinyl sulfone in good yield (Scheme 12, eq. 1).[50a] THF is selectively functionalized with an azodicarboxylate via formation of a new C-N bond (Scheme 11, eq. 2).[35] Recently we reported the photocatalytic Minisci reaction using TBADT and persulfate anions,[54] which proceeds selectively with THF (Scheme 12, eq. 3). In the case of eucalyptol, there is no possibility to form an α-oxy radical, and therefore hydrogen abstraction takes place at the methylene C-H bonds of the ring (Scheme 12, eq. 4). Following oxidation by PCC, two keto ethers were isolated in a 71 : 29 ratio, in which the ratio is likely to be a reflection of steric effects.[55]

C-H functionalization of 1,3-benzodioxoles also takes place with the selective formation of the α,α-dioxyalkyl radical (Scheme 13, eq. 1).[50b] The complete site-selectivity is attributed to the presence of the two adjacent oxygen atoms, since the C-H functionalization of *p*-methylanisole was not selective (Scheme 13, eq. 2).[27]



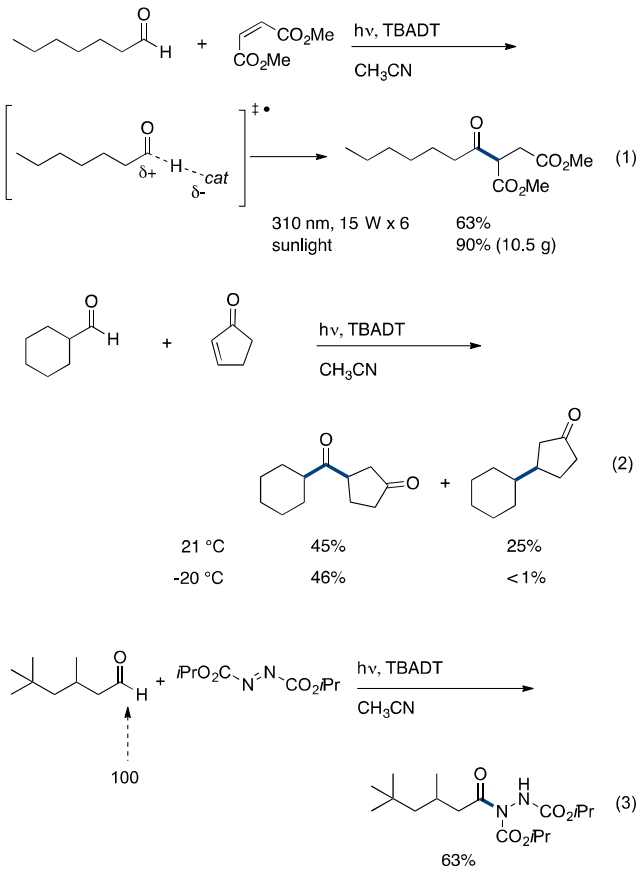
Scheme 12. Site-Selectivity in C-H Functionalization of Ethers



Scheme 13. C-H Functionalization of Aromatic Ethers

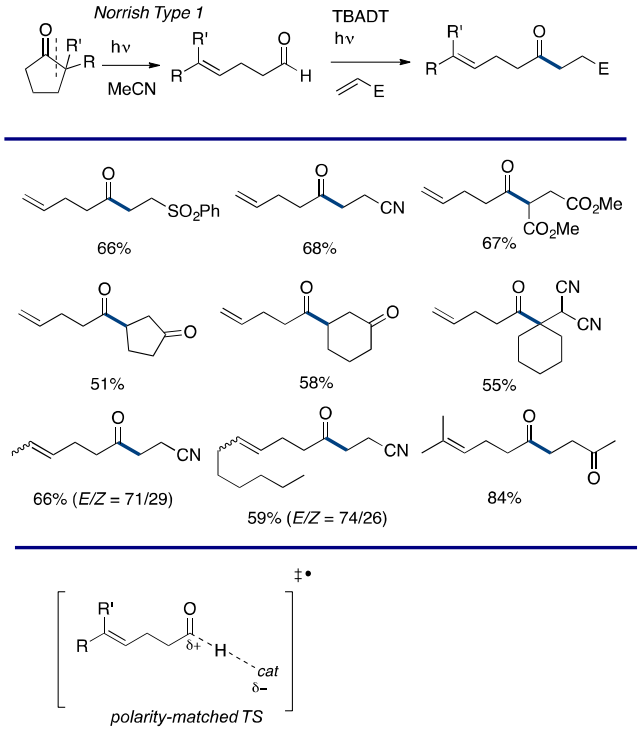
Aldehydes

Formyl group is known to have a weak C-H bond, which can be selectively abstracted by TBADT under irradiation to generate acyl radicals. The S_H2 transition state for formyl C-H cleavage by decatungstate anion would be stabilized by partial positive charge on the carbonyl carbon, which provides a beneficial polar effect.[56] The reaction of heptanal with dimethyl maleate in the presence of TBADT under irradiation proceeds smoothly to give the corresponding unsymmetrical ketone in good yield (Scheme 14, eq. 1).[57] These photocatalyzed reactions were scalable, and when carried out under sunlight irradiation with 100 mL solution (surface area: 10 cm^2, thickness: 1 cm), the alkylated products were obtained in up to 10 g after several days.[34b] In this system, no artificial energy, no light source, no heating/cooling, and no stirring are required. In the reaction of secondary and tertiary aldehydes, decarbonylation of the acyl radical intermediates often competes. The undesired side reaction was suppressed by reaction at lower temperature (Scheme 14, eq. 2) or under a CO atmosphere.[57] The formyl C-H alkylation was extended to aromatic and heteroaromatic aldehydes and can be used in the synthesis of amides.[58] The reaction of aldehydes with diisopropyl azodicarboxylate in the presence of TBADT proceeded well to give amides in good yields.[35] In the example given in eq. 3 (Scheme 14), C-H cleavage took place site-selectively at the formyl C-H and no side product formed from methine C-H cleavage was observed. TBADT photocatalyzed acylation of fullerene by aldehydes via formyl hydrogen abstraction has been reported and gave acyl functionalized fullerenes.[59]

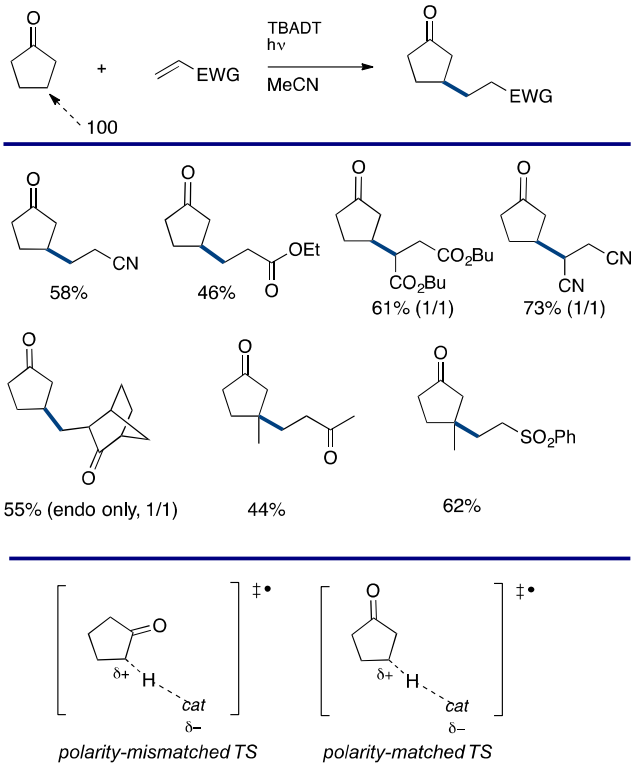


Scheme 14. Site-Selective Functionalization of Formyl C-H Bond

The TBADT photocatalyzed site-selective C-H functionalization was successfully combined with a Norrish Type 1 reaction of ketones to achieve a one-pot synthesis of homoallyl ketones (Scheme 15).[60] When cyclopentanone was irradiated, in the absence of TBADT catalyst, 4-pentenal was obtained in 98% yield. Following this first reaction, electron-deficient alkenes and TBADT catalyst were added to the reaction mixture and the resulting solution was irradiated with the same light source, which gave homoallyl ketones in good yields. In these reactions an enal is formed in situ and there is an allylic C-H bond which could undergo C-H functionalization. However, no such reaction is observed. This is probably due to the more favorable polar effects in the S_H2 TS of formyl-H abstraction (Scheme 15, bottom).



Scheme 15. One-pot Synthesis of γ,δ-Unsaturated Ketones via Sequential Norrish Type 1 Reaction and Formyl C-H Alkylation

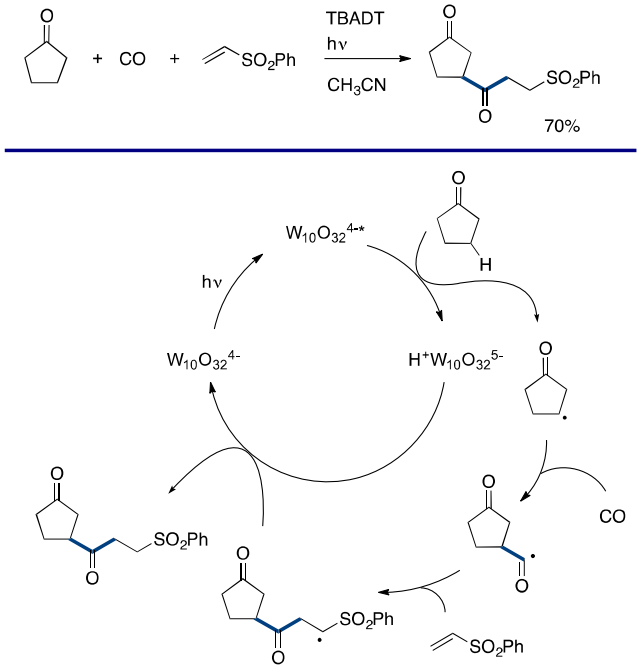


Scheme 16. β-Site-Selective C-H Alkylation of Cyclopentanones

Ketones

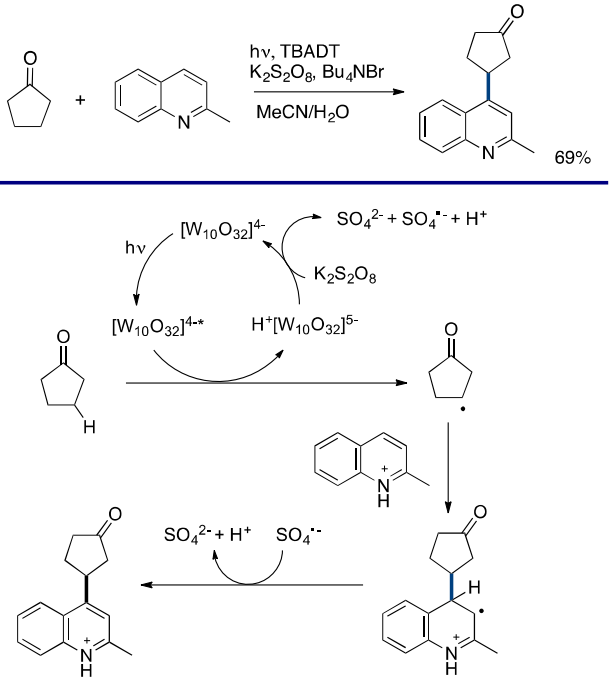
Cyclopentanone has two types of methylene C-H bonds. In terms of bond dissociation energy, the α-C-H bond is weaker than the β-C-H bond. However, inspection of the S_H2 transition state leading to the α-radical does not make a polarity matched TS because decatungstate anion is electrophilic. In contrast, the S_H2 transition state leading to the β-radical can make a polarity matched TS, and therefore the site-selective C-H bond cleavage at the β-C-H bond is expected to occur. Indeed, the photo-irradiation reaction of cyclopentanone with electron-deficient alkenes in the presence of TBADT gave only β-alkylated products (Scheme 16).[61] β-Selective alkylation of cyclopentanone was also promoted by sunlight irradiation, however the reaction took longer to go to completion.

Alkylation of 3-methylcyclopentanone preferentially proceeded at the methine C-H bond to give the alkylated product at the 3-position with 95 : 5 selectivity. β-Site-selective C-H acylation was achieved by combination of the alkylation methodology with radical carbonylation.[37] For example, the reaction of cyclopentanone with electron deficient alkenes under pressurized CO (200 atm) proceeded well to give 1,4-diketones in good yields (Scheme 17).[61] The catalytic cycle, including radical cascade, is given in Scheme 17.



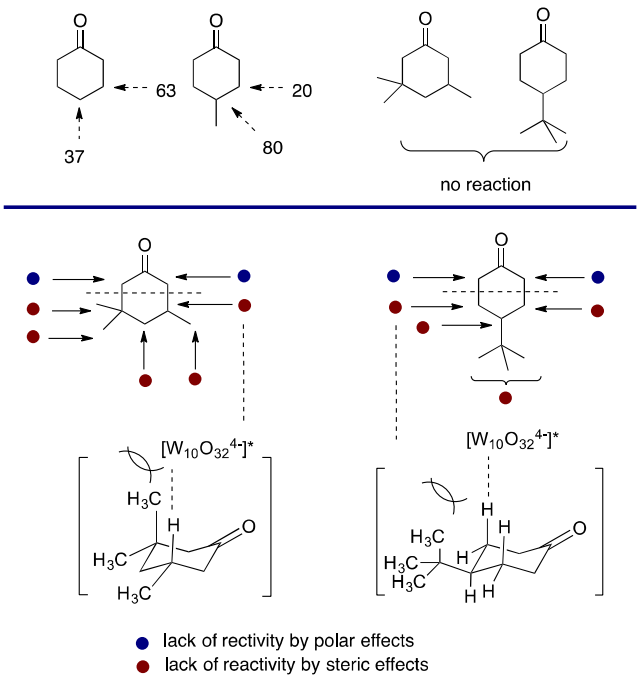
Scheme 17. β-Site-Selective C-H Acylation of Cyclopentanone and the Related Catalytic Cycle Including Radical Cascade

β-Site-selective C-H functionalization of cyclopentanone can also be employed in TBADT-catalyzed Minisci reactions. As shown in Scheme 18, the reaction of cyclopentanone with 2-methylquinoline took place in the presence of the TBADT photocatalyst and persulfate as oxidant to afford β-arylated cyclopentanones.[54] A possible mechanism is depicted in Scheme 18, bottom. In this case, excited TBADT is able to homolytically cleave the C-H bond β to the carbonyl group. The reduced form of the photocatalyst ($H^+[W_{10}O_{32}]^{5-}$) is oxidized by $K_2S_2O_8$, liberating an equivalent of acid along with an oxidant ($SO_4^{\bullet-}$) to regenerate $[W_{10}O_{32}]^{4-}$. The β-carbonyl radical is trapped by the protonated heterocycle, and subsequent one-electron oxidation of the adduct radical affords β-arylated cyclopentanone.



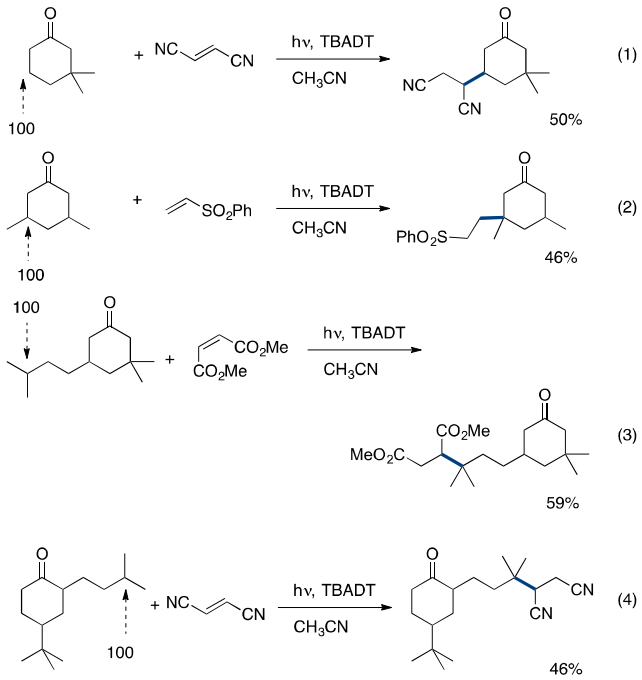
Scheme 18. β-Site-Selective C-H Arylation of Cyclopentanone and the Related Mechanism

TBADT-catalyzed C-H alkylation of cyclohexanone gave two products via β- and γ-functionalization, whereas no α-functionalization took place (Scheme 19).[61] 4-Methylcyclohexanone preferentially gave γ-alkylated product via methine C-H functionalization, in which the ratio of γ-methine to β-methylene was 80 : 20 (16 : 1, statistically corrected for 1H). In contrast, C-H functionalization of 3,3,5-trimethylcyclohexanone and 4-*tert*-butylcyclohexanone did not take place, even though both substrates have a weak methine C-H bond.[49] The lack of reactivity of these substrates is rationalized by steric effects between substituents and the large decatungstate anion. This effect can be represented as shown in Scheme 19, in which blue circles indicate the sites deactivated by polar effects and red circles those deactivated by steric effects.[49]



Scheme 19. Experimental Results and Analysis of Available Reaction Sites of Cyclohexanones

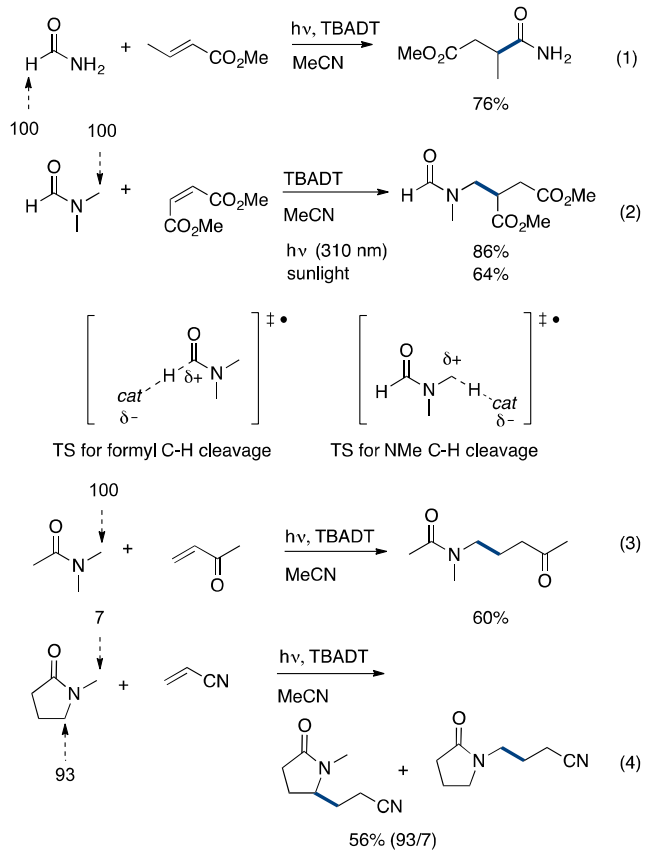
As both polar and steric effects individually impacted the site-selectivity of the C-H functionalization, next a synergistic strategy was tested employing two dimethyl-substituted cyclohexanones (Scheme 20, eqs 1 and 2).[49] The C-H alkylation of 3,3-dimethylcyclohexanone proceeded site-selectively at the β-methylene C-H bond (Scheme 20, eq. 1). C-H alkylation of 3,5-dimethylcyclohexanone also took place site-selectively at the methine C-H bond (Scheme 20, eq. 2). On the other hand, two methine carbons are present in 3,3-dimethyl-5-isopentyl cyclohexanone, however, C-H alkylation took place site-selectively at the methine carbon in the tether, which is located in less congested surroundings (Scheme 20, eq. 3). The reaction of 2-isoamyl-4-*tert*-butylcyclohexanone, which has three methine C-H bonds, also proceeded selectively at the methine located at the isoamyl tether (Scheme 20, eq. 4).



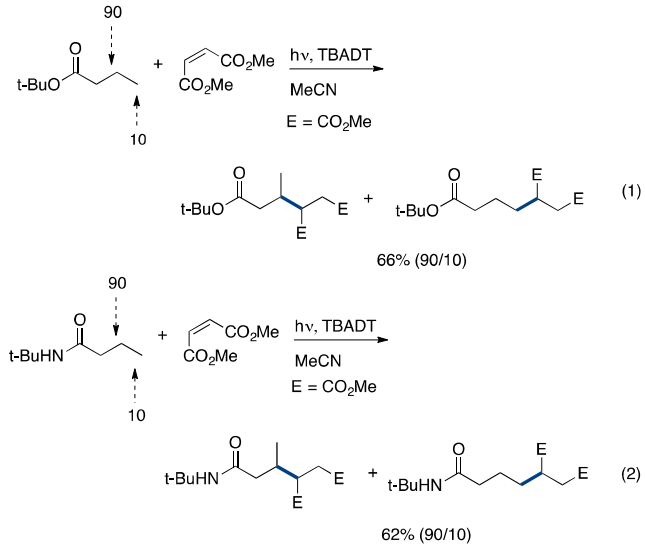
Scheme 20. Site-Selective Alkylation of Substituted Cyclohexanones

Carboxylic Acid Amides, Esters, and Nitriles

Decatungstate anion catalyzed C-H alkylation of formamide with electron-deficient alkenes proceeds to give carboxylic acid amides in good yields (Scheme 21, eq. 1).[62] In contrast, C-H functionalization of *N*,*N*-dimethyl formamide took place at the *N*-methyl group preferentially (Scheme 21, eq. 2). Both TSs appear to have favorable polar effects, however it may be more advantageous for H-abstraction to occur from the *N*-methyl C-H bond. Similarly, C-H functionalization of *N*,*N*-dimethyl acetamide took place site-selectively at the *N*-methyl group (Scheme 21, eq. 3). The lack of the reactivity α to the carbonyl is similar to that observed for ketones. C-H functionalization of γ-butyrolactam preferentially proceeded at the inner *N*-methylene C-H rather than the *N*-methyl C-H (Scheme 21, eq. 4).

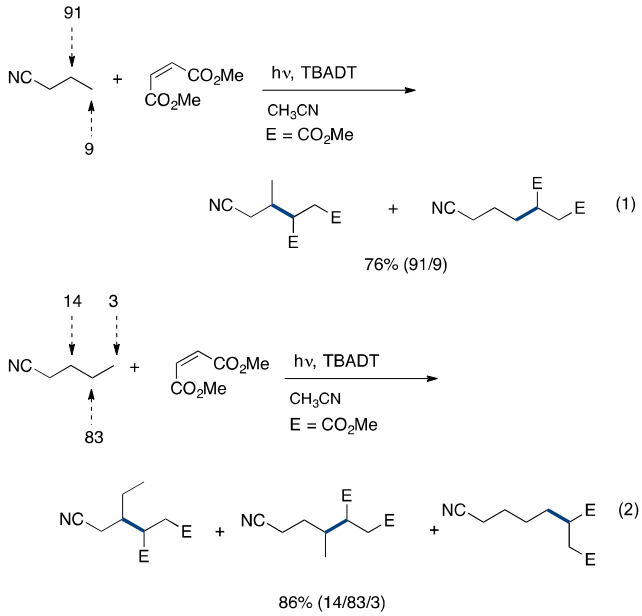


Scheme 21. Site-Selective Alkylation of Carboxylic Acid Amides



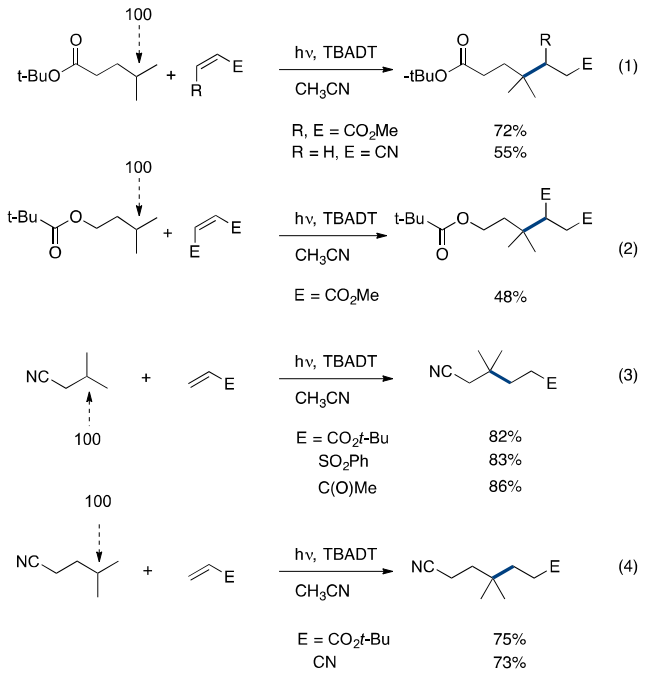
Scheme 22. Site-Selectivity for the Alkylation of Butyric Acid Ester and Amide

In the reactions of butyric acid *tert*-butyl ester and butyric acid *tert*-butyl amide, α-alkylation did not take place, which is consistent with polar effects being exerted in the S_H2 transition states (Scheme 22).[49] In these cases, C-H functionalization proceeded mainly at the β-methylene groups (90% selectivity) with a small amount of by-product obtained via γ-methyl C-H functionalization. Butyronitrile exhibited a quite similar tendency (Scheme 23, eq. 1).[63] Interestingly, in the case of valeronitrile, C-H alkylation took place at the γ-position preferentially (Scheme 23, eq. 2).[63] This result suggests that the inductive effect of the cyano group influences C-H cleavage at the β-position, which destabilizes the transition state.[64] A similar γ-preference was also observed in the reaction of *tert*-butyl pentanoate.[49]



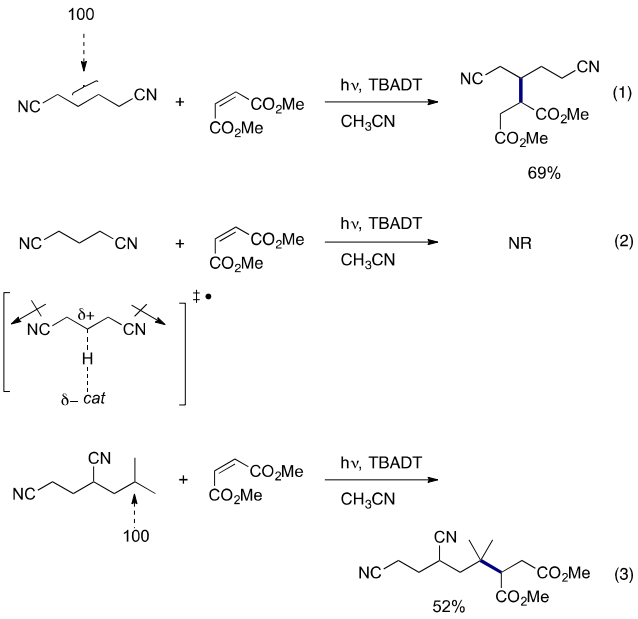
Scheme 23. Site-Selectivity for the Alkylation of Butyronitirile and Valeronitrile

In the reaction of aliphatic esters and nitriles with a branched alkyl chain, alkylation took place at the methine C-H bond selectively.[49,63] For example, *tert*-butyl-4-methylpentanoate reacted with dimethyl maleate and acrylonitrile to give only the corresponding alkylated products via methine C-H functionalization (Scheme 24, eq. 1).[49] In sharp contrast to the reaction of isopentanol (Scheme 10, eq. 3), when isopentyl pivalate was reacted with dimethyl maleate, no functionalization at α to oxygen took place, and as a result methine C-H was selectively functionalized (Scheme 24, eq. 2).[49] Presumably hydrogen abstraction at the α position is suppressed by the bulky pivalate group. Similarly, the reaction of isovaleronitrile and isocapronitrile gave products derived from methine C-H functionalization (Scheme 24, eqs. 3 and 4).[63]



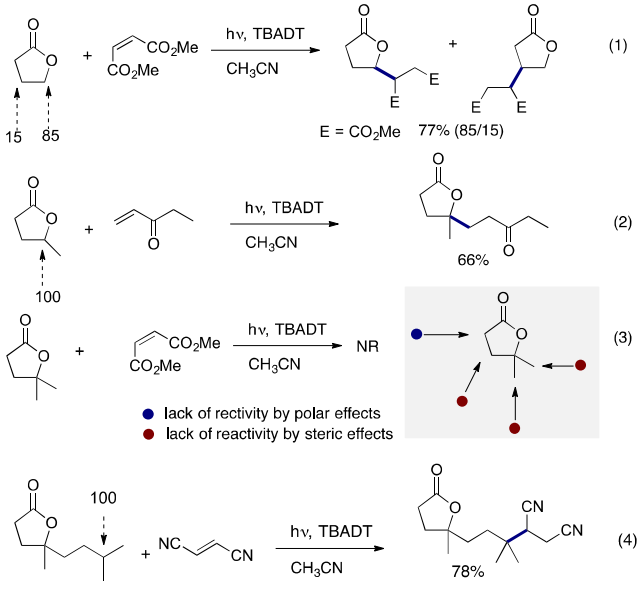
Scheme 24. Site-Selective Alkylation of Branched Aliphatic Carboxylic Acid Esters and Nitriles

Site-selectivity of the reaction with dinitriles is highly dependent on the structures. Whereas the reaction of adiponitrile with dimethyl maleate took place selectively at the β-methylene carbon to give the alkylated product in good yield, the reaction of glutaronitrile did not proceed (Scheme 25, eqs. 1 and 2 respectively).[63] The lack of reactivity for glutaronitrile could be explained by strong inductive-destabilization of the S_H2 transition state by the two β-cyano groups. Taking advantage of the propensity, the dinitrile compound containing three methylene groups and two methine groups was reacted with dimethyl maleate, which proceeded selectively at the remote methine carbon (Scheme 25, eq. 3).[63]



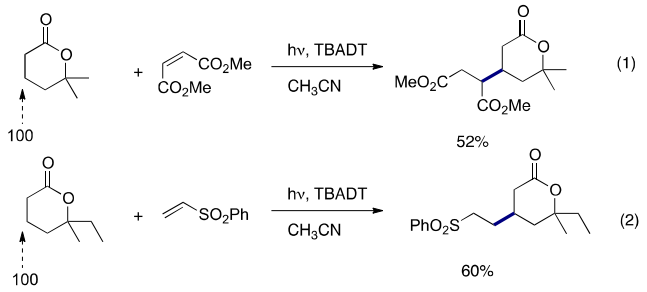
Scheme 25. Site-Selective Alkylation of Dinitriles

TBADT-catalyzed C-H alkylation of γ-butyrolactone took place predominantly at the γ-position (β/γ = 15/85) (Scheme 26, eq. 1).[49] Introduction of a methyl group at the γ-position resulted in selective C-H alkylation at the methine C-H bond (Scheme 26, eq. 2).[50] When the dimethyl-substituted butyrolactone was tested, no reaction took place (Scheme 26, eq. 3).[49] The lack of reactivity is likely due to steric effects originating from the bulky dimethyl substituents, as indicated using red circles. When the lactone had an isoamyl tether, the methine C-H of the isoamyl chain was selectively functionalized. In this case reaction of the carbonyl α-methylene and three other methylene groups was suppressed by polar and steric effects, respectively (Scheme 26, eq. 4).[49]



Scheme 26. β-Site-Selective Alkylation of γ-Lactones

We predicted that δ-dimethyl-substituted δ-lactones would also undergo selective β-alkylation due to polar and steric effects. Indeed, this proved to be the case, and the replacement of one methyl group by an ethyl group still gave the product via β-alkylation selectively (Scheme 27, eq. 1 and 2 respectively). [49]



Scheme 27. β-Site-Selective Alkylation of δ-Lactones

Conclusions and Perspective

Decatungstate anion, upon photoexcitation, is capable of abstracting a hydrogen atom from C(sp^3)-H bonds. The hydrogen abstraction from cyclohexane to form the cyclohexyl radicals is known to proceed with a rate constant around 10^7 $M^{-1}s^{-1}$ at room temperature. However, in functionalized and more complex molecules, such as substituted cyclohexanes and cyclohexanones, the reaction efficiencies are markedly different. This is closely associated with highly electrophilic oxygen centers of the tungstate anion exhibiting partial radical character which demands the S_H2 type HAT transition states to be significantly polar. Steric congestion surroundings the target C-H bonds greatly slows down or even hampers the HAT process catalyzed by the decatungstate anion. This is attributed to the decatungstate anion being a relatively large molecule (MW of $[W_{10}O_{32}]^{4-}$ = 2350) and thus, the synergistic control of polar effects and steric effects is key to achieving site-selective C(sp^3)-H functionalization through radical reactions. As for steric effects, a larger size of POMs may have further possibilities. Optimism for future progress lies in the fact that the photocatalytic radical strategy shows much promise for more complex molecules.

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ACKNOWLEDGMENT

We thank Dr. Sara Kyne (University of Lincoln, UK) for comments that improved the manuscript. We also thank Dr. Megumi Okada, Mr. Keiichi Yamada, Ms. Saki Fujii, Mr. Luca Capaldo, Mr. Mattero. C. Quattrini, and all co-workers for their experimental and intellectual contributions. IR thanks a Grants-in-Aid for Scientific Research (A) (26248031) from JSPS for financial support of this work.

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REFERENCES

(1) (a) Murai, S.; Kakiuchi, F.; Sekine, S.; Tanaka, Y.; Kamatani, A.; Sonoda, N.; Chatani, N. *Nature* **1993**, 366, 529. (b) Murai, S. *Activation of Unreactive Bonds and Organic Synthesis,* Topics in Organometallic Chemistry, Vol. 3, Springer-Varlag Berline, 1999. For recent reviews, see: (c) Lyons, T. W.; Sanford, M. S. *Chem. Rev.* **2010**, *110*, 1147. (d) Rouquet, G.; Chatani, N. *Angew. Chem., Int. Ed.* **2013**, *52*, 11726. (e) Huang, Z.; Lim, H. N.; Mo, F.; Young, M. C.; Dong, G. *Chem. Soc. Rev.* **2015**, *44*, 7764. (f) Shul'pin, G. B. *Catalysts* **2016**, *6*, 50. (g) Dixneuf, P. H.; Doucet, H. *C-H Bond Activation and Catalytic Functionalization I and II*, Topics in Organometallic Chemistry, Vols. 55 and 56, Springer Cham, 2016.

(2) For reviews, see: (a) Zhou, M.; Crabtree, R. H. *Chem. Soc. Rev.* **2011**, *40*, 1875. (b) Che, C.-M. Lo, V. K.-Y.; Zhou C.-Y.; Huang, J.-S. *Chem. Soc. Rev.* **2011**, *40*, 1950. (c) Brückl, T.; Baxter, R. D.; Ishihara, Y.; Baran, P. S. *Acc. Chem. Res.* **2012**, *45*, 826. (d) Liu, W.; Groves, J. T. *Acc. Chem. Res.* **2015**, *48*, 1727. (e) Hartwig, J. F.; Larsen, M. A. *ACS. Cent. Sci.* **2016**, *2*, 281. (f) Yu, J.-Q.; Shi, Z, *C-H Activation*, Topics in Current Chemistry,Vol. 292. Springer Heidelberg, 2010.

(3) For selected recent papers on C(sp^3)-H functionalization, see: (a) Adams, A. M.; Du Bois, J.; Malik, H. A. *Org. Lett.* **2015**,*17*, 6066. (b) Cuthbertson, J. D.; Macmillan, D. W. C. *Nature* **2015**, *519*, 74. (c) Lee, M.; Sanford, M. S. *J. Am. Chem. Soc.* **2015**, *137*, 12796. (d) Miao, J. Yang. K.; Kurek. M.; Ge, H. *Org. Lett.* **2015**, *17*, 3738. (e) Huang, X.; Groves, J. T. *ACS Catal.* **2016**, *6*, 751. (f) Chu, J. C. K.; Rovis, T. *Nature* **2016**, *539*, 272. (g) Kawamata, Y.; Yan, M.; Liu, Z.; Bao, D.-H.; Chen, J.; Starr, J. T.; Baran P. S. *J. Am. Chem. Soc.* **2017**, *139*, 7448. (h) Mbofana, C. T.; Chong, E.; Lawniczak, J.; Sanford, M. S. *Org. Lett.* **2016**, *18*, 4258. (i) Liu Y.; Ge, H. *Nature Chem.* **2017**, *9*, 26. (j) Nanjo, T.; de Lucca, E. C. Jr. White, M. C. *J. Am. Chem. Soc.* **2017**, *139*, 14586.

(4) (a) Barton, D. H. R.; Doller, D. *Acc. Chem. Res.* **1992**, *25*, 504. (b) Barton, D. H. R. *Tetrahedron* **1998**, *54*, 5805. (c) Perkins, M. J. *Chem. Soc. Rev.* **1996**, 229.

(5) (a) White, C. *Science*, **2012**, *335*, 807. (b) Liu, W.; Groves, J. T. *Acc. Chem. Res.* **2015**, *48*, 1727. (c) Costas, M. *Coord. Chem. Rev.* **2011**, *255*, 2912. (d) Sharma, A.; Hartwig, J. F. *Nature* **2015**, *517*, 600. (e) Osberger, T. J.; Rogness, D. C.; Kohrt, J. T.; Stepan, A. F.; White, M. C. *Nature*, **2016**, *537*, 214. (f) Frost, J. R.; Huber, S. M.; Breitenlechner, S.; Bannwarth, C.; Bach, T. *Angew. Chem. Int. Ed.* **2015**, *54*, 691. (g) Milan, M.; Bietti, M.; Costas, M. *ACS Cent. Sci.* **2017**, *3*, 196.

(6) Liao, K.; Negretti, S.; Musaev, D. G.; Bacsa, J.; Davies, H. M. L. *Nature* **2016**, *533*, 230.

(7) (a) Egloff, G.; Schaad, R. E.; Lowry, C. D. *Chem. Rev.*, **1931**, *8*, 1. (b) Folkin, A.; Schreiner, P. R. *Chem. Rev.*, **2002**, *102*, 1551. (c) Yi, H.; Zhang, G.; Wang, H.; Huang, Z.; Wang, J.; Singh, A. K.; Lei, A. *Chem. Rev.* **2017**, *117*, 9016. For selected recent (d) Matcha, K.; Antonchick, A. P. *Angew. Chem. Int. Ed.* **2013**, *52*, 2082. (e) Amaoka, Y.; Nagatomo, M.; Watanabe, M.; Tao, K.; Kamijo, S.; Inoue, M. *Chem. Sci.* **2014**, *5*,

4339. (f) Chu, X. Q.; Meng, H.; Zi, Y.; Xu, X. P.; Ji, S. J. *Chem. Commun*. **2014**, *50*, 9718. (g) Narayan, R.; Antonchick, A. P. *Chem. Eur. J*. **2014**, *20*, 4568. (h) Zhao, J.; Fang, H.; Qian, P.; Han, J.; Pan, Y. *Org. Lett*. **2014**, *16*, 5342. (i) Zhou, W.; Qian, P.; Zhao, J.; Fang, H.; Han, J.; Pan, Y. *Org. Lett*. **2015**, *17*, 1160. (j) Huang, H. Y.; Wu, H. R.; Wei, F.; Wang, D.; Liu, L. *Org. Lett*. **2015**, *17*, 3702. (k) Ji, J.; Liu, P.; Sun, P. *Chem. Commun*. **2015**, *51*, 7546. (l) Mukherjee, S.; Maji, B.; Tlahuext-Aca, A.; Glorius, F. *J. Am. Chem. Soc*. **2016**, *138*, 16200. (m) Le, C.; Liang, Y.; Evans, R. W.; Li, X.; MacMillan, D. W. C. *Nature* **2017**, *547*, 79.

(8) For C-H bromination, see: (a) Kharasch, M. S.; Hered, W.; Mayo, F. R.; *J. Org. Chem*. **1941**, *6*, 818. (b) Russell, G. A.; Brown, H. C. *J. Am. Chem. Soc*. **1955**, *77*, 4025. (c) Jiang, X.; Shen, M.; tang, Y.; Li, C. *Tetrahedron Lett*. **2005**, *46*, 487. (d) Manabe, Y.; Fukase, K.; Matsubara, H.; Hino, Y.; Fukuyama, T.; Ryu, I. *Chem. Eur. J*. **2014**, *20*, 12750. (e) For remote C-H chlorination and bromination, see: (e) Wiedenfeld, D.; Breslow, R. *J. Am. Chem*. Soc. **1991**, *113*, 8977. (f) Quinn, R. K.; Könst, Z. A.; Michalak, S. E.; Schmidt, Y.; Szklarski, A. R.; Flores, A. R.; Nam, S.; Horne, D. A.; Yanderwal, C. D.; Alexanian, E. J. *J. Am. Chem. Soc*. **2016**, *138*, 696. (g) Czaplyski, W. L.; Na, C. G. Alexanian, E. J. *J. Am. Chem. Soc*. **2016**, *138*, 13854.

(9) For remote functionalization of alcohols based on 1,5-HAT, see: (a) Barton, D. H. R. *Pure Appl. Chem*. **1968**, *16*, 1. (b) Majetich, G.; Wheless, K. *Tetrahedron* **1995**, *51*, 7095. (c) Dorigo, A. E.; Houk, K. N. *J. Am. Chem. Soc*. **1987**, *109*, 2195.

(10) (a) Tsunoi, S.; Ryu, I.; Sonoda, N. *J. Am. Chem. Soc*. **1994**, *116*, 5473. (b) Tsunoi, S.; Ryu, I; Okuda, T.; Tanaka, M.; Komatsu, M.; Sonoda, N. *J. Am. Chem. Soc*. **1998**, *120*, 8692.

(11) (a) Wolff, M. E. *Chem. Rev*. **1963**, *63*, 55. Also see a recent review: (b) Chiba, S.; Chen, H. *Org. Biomol. Chem*. **2014**, *12*, 4051.

(12) (a) Curran, D. P.; Shen, W. *J. Am. Chem. Soc*. **1993**, *115*, 6051. (b) Zhang, J.; Li, Y.; Zhang, F.; Hu, C.; Chen, Y. *Angew. Chem. Int. Ed*. **2016**, *55*, 1872. (c) Wang, C.; Harms, K.; Meggers, E. *Angew. Chem. Int. Ed*. **2016**, *55*, 13495. (d) Choi, G. J.; Zhu, Q.; Miller, D. C.; Gu, C. J.; Knowles, R. R. *Nature* **2016**, *539*, 268.

(13) For selected recent reviews on photocatalysis, see: (a) Fagnoni, M.; Dondi, D.; Ravelli, D.; Albini, A. *Chem. Rev*. **2007**, *107*, 2725. (b) Ravelli, D.; Dondi, D.; Fagnoni, M.; Albini, A. *Chem. Soc. Rev*. **2009**, *38*, 1999. (c) Shi, L.; Xia, W. Chem. *Soc. Rev*. **2012**, *41*, 7687. (d) Xuan, J.; Xiao, W. J. *Angew. Chem. Int. Ed*. **2012**, *51*, 6828. (e) Ravelli, D.; Fagnoni, M.; Albini, A. *Chem. Soc. Rev*. **2013**, *42*, 97. (f) Prier, C. K.; Rankic, D. A.; Macmillan, D. W. C. *Chem. Rev*. **2013**, *113*, 5322. (g) Reckenthaler, M.; Griesbeck, A. G. *Adv. Synth. Catal*. **2013**, *355*, 2727. (h) Twilton, J.; Le, C.; Zhang, P.; Shaw, M. H.; Evans, R. W.; MacMillan, D. W. C. *Nature Rev. Chem*. **2017**, *1*, Article Number 0052.

(14) (a) Protti, S.; Fagnoni, M.; Ravelli, D. *ChemCatChem* **2015**, *7*, 1516. (b) Capaldo, L.; Ravelli, D. *Eur. J. Org. Chem*. **2017**, *2017*, 2056.

(15) Tzirakis, M. D.; Lykakis, I. N.; Orfanopoulos, M. *Chem. Soc. Rev*. **2009**, *38*, 2609.

(16) Ravelli, D.; Protti, S.; Fagnoni, M. *Acc. Chem. Res*. **2016**, *49*, 2232.

(17) (a) Borrás-Almenar, J. J.; Coronado, E.; Mueller, A. Polyoxometalate Molecular Science, Kluwer Academic Publisher, Dordrecht, 2003. (b)Pope, M. T.; Müller, A. *Angew. Chem. Int. Ed*. **1991**, *30*, 34. (c) Long, D.L.; Burkholder, E.; Cronin, L. *Chem. Soc. Rev*. **2007**, *36*, 105. (d) Dupré, N.; Rémy, P.; Micoine, K.; Boglio, C.; Thorimbert, S.; Lacote, E.; Hasenkonpf, B.; Malacria, M. *Chem. Eur. J*. **2010**, *16*, 7256. (e) Wang, S.-S.; Yang, G. Y. *Chem. Rev*. **2015**, *115*, 4893.

(18) Pope, M. T. *Heteropoly Blues in Mixed-Valence Compounds. Theory and Applications in Chemistry, Physics, Geology, and Biology*, Part of the NATO Advanced Study Institutes Series book series, Brown, D. B. Ed. **1980**, 58, pp. 365-386.

(19) Ravelli, D.; Dondi, D.; Fagnoni, M.; Albini, A.; Bagno, A. *Phys. Chem. Chem. Phys*. **2013**, *15*, 2890.

(20) (a) Renneke, R. F.; Pasquali, M.; Hill, C. L. *J. Am. Chem. Soc*. **1990**, *112*, 6585. (b) Jaynes, B. S.; Hill, C. L. *J. Am. Chem. Soc*. **1995**, *117*, 4704.

(21) Hill, C. L. *Synlett* **1995**, *1995*, 127. and references therein.

(22) Duncan, D. C.; Netzel, T. L.; Hill, C. L. *Inorg. Chem*. **1995**, *34*, 4640.

(23) Tanielian, C. *Coord. Chem. Rev*. **1998**, *178-180*, 1165.

(24) (a) Tanielian, C.; Cougnon, F.; Seghrouchni, R. *J. Mol. Catal. A: Chem*. **2007**, *262*, 164. (b) Duncan, D. C.; Fox, M. A. *J. Phys. Chem. A* **1998**, *102*, 4559. (c) Ermolenko, L. P.; Delaire, J. A.; Giannotti, C. *J. Chem. Soc., Perkin Trans. 2* **1997**, 25. (d) Texier, I.; Delaire, J. A.; Giannotti, C. *Phys. Chem. Chem. Phys*. **2000**, *2*, 1205.

(25) (a) Awad, M. K.; Anderson, A. B. *J. Am. Chem. Soc*. **1990**, *112*, 1603. (b) Jen, S. F.; Anderson, A. B.; Hill, C. L. *J. Phys. Chem*. **1992**, *96*, 5658. (c) Ravelli, D.; Dondi, D.; Fagnoni, M.; Albini, A.; Bagno, A. *J. Comput. Chem*. **2011**, *32*, 2983. (d) Ravelli, D.; Dondi, D.; Fagnoni, M.; Albini, A.; Bagno, A. *Phys. Chem. Chem. Phys*. **2013**, *15*, 2890. (e) De Waele, V.; Poizat, O.; Fagnoni, M.; Bagno, A.; Ravelli, D. *ACS Catal*. **2016**, *6*, 7174.

(26) (a) Minisci, F.; Recupero, F.; Cecchetto, A.; Gambarotti, C.; Punta, C. Faletti, R.; Paganelli, R.; Pedulli, G. F. *Eur. J. Org. Chem*. **2004**, 109. (b) D'Alfonso, C.; Bietti, M.; DiLabio, G. A.; Lanzalunga, O.; Salamone, M. *J. Org. Chem*. **2013**, *78*, 1026. (c) Pitts, C. R.; Bloom, S.; Woltornist, R.; Auvenshine, D. J. Ryzhkov, L. R.; Siegler, M. A.; Lectka, T. *J. Am. Chem. Soc*. **2014**, *136*, 9780. (d) Salamone, M.; Bietti, M. *Acc. Chem. Res*. **2015**, *48*, 2895.

(27) Qrareya, H.; Ravelli, D.; Fagnoni, M.; Albini, A. *Adv. Synth. Catal*. **2013**, *355*, 2891.

(28) Dondi, D.; Fagnoni, M.; Albini, A. *Chem. Eur. J*. **2006**, *12*, 4153.

(29) Tanielian, C.; Lykakis, I. N.; Seghrouchni, R.; Cougnon, F.; Orfanopoulos, M. *J. Mol. Catal. A: Chem*. **2007**, *262*, 170.

(30) (a) Giering, L.; Berger, M.; Steel, C. *J. Am. Chem. Soc*. **1974**, *96*, 953. (b) Coenjarts, C.; Scaiano, J. C. *J. Am. Chem. Soc*. **2000**, *122*, 3635. (c) Weber, M.; Fischer, H. *J. Am. Chem. Soc*. **1999**, *121,* 7381. (d) Bietti, M.; Martella, R.; Salamone, M. *Org. Lett*. **2011**, *13*, 6110. (e) Avila, D. V.; Brown, C. E.; Ingold, K. U.; Lusztyk, J. *J. Am. Chem. Soc*. **1993**, 115, 466.

(31) (a) Dondi, D.; Ravelli, D.; Fagnoni, M.; Mella, M.; Molinari, A.; Maldotti, A.; Albini, A. *Chem. Eur. J*. **2009**, *15*, 7949. For chemoselective esterification using bulky polyoxometalate as the catalyst, see: (b) Bosco, M.; Rat, S.; Dupré, N.; Hasenknopf, B.; Lacote, E.; Malacria, M.; Rémy, P.; Kovensky, J.; Thorimbert, S.; Wadouachi, A. *ChemSusChem* **2010**, *3*, 1249.

(32) (a) Giannotti, C.; Richter, C. *Int. J. Photoenergy* **1999**, *1*, 69. (b) Texier, I.; Giannotti, C.; Malato, S.; Richter, C.; Ouazzani, J.; Delaire, J. *J. Chim. Phys*. **1999**, *96*, 430. (c) Fornal, E.; Giannotti, C. *J. Photochem. Photobiol. A: Chem*. **2007**, *188*, 279. (d) Wu, W.; Fu, Z.; Tang, S.; Zou, S.; Wen, X.; Meng, Y.; Sun, S.; Deng, J.; Liu, Y.; Yin, D. *Appl. Catal. B-Environ*. **2015**, *164*, 113.

(33) West, J. G.; Huang, D.; Sorensen, E. J. *Nat. Commun*. **2015**, *6*, 10093.

(34) (a) Dondi, D.; Fagnoni, M.; Molinari, A.; Maldotti, A.; Albini, A.*Chem. Eur. J*. **2004**, *10*, 142. (b) Protti, S.; Ravelli, D.; Fagnoni, M.; Albini, A. *Chem. Commun*., **2009**, 7351. (c) Ravelli, D.; Montanaro, S.; Zema, M.; Fagnoni, M.; Albini, A. *Adv. Synth. Catal*. **2011**, *353*, 3295. (d) Bonassi, F.; Ravelli, D.; Protti, S.; Fagnoni, M. *Adv. Synth. Catal*. **2015**, *357*, 3687.

(35) Ryu, I.; Tani, A.; Fukuyama, T.; Ravelli, D.; Montanaro, S.; Fagnoni, M. *Org. Lett*. ***2013****, 15,* 2554.

(36) Ryu, I.; Tani, A.; Fukuyama, T.; Ravelli, D.; Fagnoni, M.; Albini, A. *Angew. Chem. Int. Ed*., **2011**, *50*, 1869.

(37) For reviews on radical carbonylations, see: (a) Ryu, I.; Sonoda, N. *Angew. Chem. Int. Ed*. **1996**, *35*, 1050. (b) Ryu, I.; Sonoda, N.; Curran, D. P. *Chem. Rev*. **1996**, *96*, 177. (c) Ryu, I. C*hem. Soc. Rev*. **2001**, *30*, 16. (d) Sumino, S.; Fusano, A.; Fukuyama, T.; Ryu, I. *Acc. Chem. Res*. **2014**, *47*, 1563. Also see recent work: (e) Fukuyama, T.; Nakashima,

N.; Okada, T.; Ryu, I. *J. Am. Chem. Soc.* **2013**, *135*, 1006. (f) Kawamoto, T.; Sato, A.; Ryu, I. *Chem. Eur. J.* **2015**, *21*, 14764.

(38) (a) Chambers, R. C.; Hill, C. L. *Inorg. Chem.* **1989**, *28*, 2509. (b) Renneke, R. F.; Pasquali, M.; Hill, C. L. *J. Am. Chem. Soc.* **1990**, *112*, 6585. (c) Renneke, R. F.; Kadkhodayan, M.; Pasquali, M.; Hill, C. L. *J. Am. Chem. Soc.* **1991**, *113*, 8357. (d) Ermolenko, L. P.; Giannotti, C. *J. Chem. Soc., Perkin Trans. 2* **1996**, 1205. (e) Giannotti, C.; Richter, C. *Trends in Photochemistry & Photobiology* **1997**, *4*, 43.

(39) Fukuyama, T.; Yamada, K.; Nishikawa, T.; Ravelli, D.; Fagnoni, M.; Ryu, I. *Chem. Lett. accepted.*

(40) For TBADT catalyzed benzylation of C_{60}, see: Tzirakis, M. D.; Orfanopoulos, M. *Org. Lett.* **2008**, *10*, 873.

(41) Nodwell, M. B.; Bagai, A.; Halperin, S. D.; Martin, R. E., Knust, H.; Britton, R. *Chem. Commun.* **2015**, *51*, 11783.

(42) Lykakis, I. N.; Orfanopoulos, M. *Tetrahedron Lett.* **2004**, *45*, 7645.

(43) Lykakis, I. N.; Orfanopoulos, M. *Tetrahedron Lett.* **2005**, *46*, 7835.

(44) Lykakis, I. N.; Orfanopoulos, M. *Curr. Org. Chem.* **2009**, *13*, 1737.

(45) Ni, L.; Ni, J; Lv, Y.; Yang, P.; Cao, Y. *Chem. Commun.* **2009**, 2171.

(46) Fukuyama, T.; Nishikawa, T.; Yamada, K.; Ravelli, D.; Fagnoni, M.; Ryu, I. *Org. Lett.* Article ASAP. DOI: 10.1021/acs.orglett.7b03339

(47) (a) Yamase, T.; Takabayashi, N.; Kaji, M. *J. Chem. Soc., Dalton Trans.* **1984**, 793. (b) Nomiya, K.; Sugie, Y.; Miyazaki, T.; Miwa, M. *Polyhedron* **1986**, *5*, 1267. (c) Nomiya, K.; Miyazaki, T.; Maeda, K.; Miwa, M. *Inorg. Chim. Acta* **1987**, *127*, 65. (d) Nomiya, K.; Matsubara, S.; Yamashita, K.; Miwa, M. *Polyhedron* **1987**, *6*, 1919. (e) Hill, C. L.; Renneke, R. F.; Combs, L. A. *New J. Chem.* **1989**, *13*, 701. (f) Mylonas, A.; Hiskia, A.; Androulaki, E.; Dimotikali, D.; Papaconstantinou, E. *Phys. Chem. Chem. Phys.* **1999**, *1*, 437. (g) Lykakis, I. N.; Tanielian, C.; Orfanopoulos, M. *Org. Lett.* **2003**, *5*, 2875. (h) Lykakis, I. N.; Tanielian, C.; Seghrouchni, R.; Orfanopoulos, M. *J. Mol. Catal. A: Chem.* **2007**, *262*, 176. (i) Tzirakis, M. D.; Lykakis, I. N.; Panagiotou, G. D.; Bourikas, K.; Lycourghiotis, A.; Kordulis, C.; Orfanopoulos, M. *J. Catal.* **2007**, *252*, 178.

(48) (a) Maldotti, A.; Molinari, A.; Bigi, F. *J. Catal.* **2008**, *253*, 312. (b) Molinari, A.; Maldotti, A.; Bratovcic, A.; Magnacca, G. *Catal. Today* **2013**, *206*, 46.

(49) Yamada, K.; Fukuyama, T.; Fujii, S.; Ravelli, D.; Fagnoni, M.; Ryu, I. *Chem. Eur. J.* **2017**, *23*, 8615.

(50) (a) Ravelli, D.; Zoccolillo, M.; Mella, M.; Fagnoni, M. *Adv. Synth. Catal.* **2014**, *356*, 2781. (b) Ravelli, D.; Albini, A.; Fagnoni, M. *Chem. Eur. J.* **2011**, *17*, 572.

(51) Tzirakis, M. D.; Orfanopoulos, M. *Org. Lett.* **2008**, *10*, 873.

(52) Tzirakis, M. D.; Orfanopoulos, M. *Angew. Chem. Int. Ed.* **2010**, *49*, 5891.

(53) Ravelli, D.; Montanaro, S.; Tomasi, C.; Galinetto, P.; Quartarone, E.; Merli, D.; Mustarelli, P.; Fagnoni, M. *ChemPlusChem* **2012**, *1*, 210.

(54) Quattrini, M. C.; Fujii, S.; Yamada, K.; Fukuyama, T.; Ravelli, D.; Fagnoni, M.; Ryu, I. *Chem. Commun.* **2017**, *53*, 2335.

(55) Zakrzewski, J.; Giannotti, C. *J. Photochem. Photobiol. A: Chem.* **1992**, *63*, 173.

(56) (a) Roberts, B. P. *Chem. Soc. Rev.* **1999**, *28*, 25. Also see a recent work by bromine radical: (b) Kippo, T.; Kimura, Y.; Ueda, M.; Fukuyama, T.; Ryu, I. *Synlett.* **2017**, *28*, 1733.

(57) Esposti, S.; Dondi D.; Fagnoni, M.; Albini, A. *Angew. Chem. Int. Ed.* **2007**, *46*, 2531.

(58) Ravelli, D.; Zema, M.; Mella, M.; Fagnoni, M.; Albini, A. *Org. Biomol. Chem.* **2010**, *8*, 4158.

(59) Tzirakis, M. D. Orfanopoulos, M. *J. Am. Chem. Soc.* **2009**, *131*, 4063.

(60) Okada, M.; Yamada, K.; Fukuyama, T.; Ravelli, D.; Fagnoni, M.; Ryu, I. *J. Org. Chem.* **2015**, *80*, 9365.

(61) Okada, M.; Fukuyama, T.; Yamada, K.; Ryu, I.; Ravelli, D.; Fagnoni, M. *Chem. Sci*, **2014**, *5*, 2893.

(62) Angioni, S.; Ravelli, D.; Emma, D.; Dondi, D.; Fagnoni, M.; Albini, A. *Adv. Synth. Catal.* **2008**, *350*, 2209.

(63) Yamada, K.; Okada, M.; Fukuyama, T.; Ravelli, D.; Fagnoni, M.; Ryu, I. *Org. Lett.* **2015**, *17*, 1292.

(64) For γ-preference to β in hydrogen abstraction of tetrahydropyran by *t*-butoxy radical. See, Jenkins, I. D. *J. Chem. Soc., Chem. Commun.* **1994**, 1227.