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Letter

Coupling Reaction between Aldehydes and Non-Activated Hydrocarbons via the Reductive Radical-Polar Crossover Pathway

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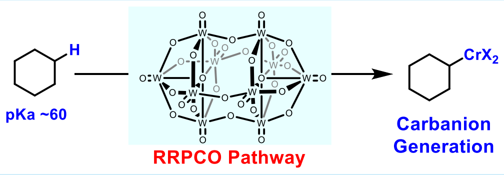
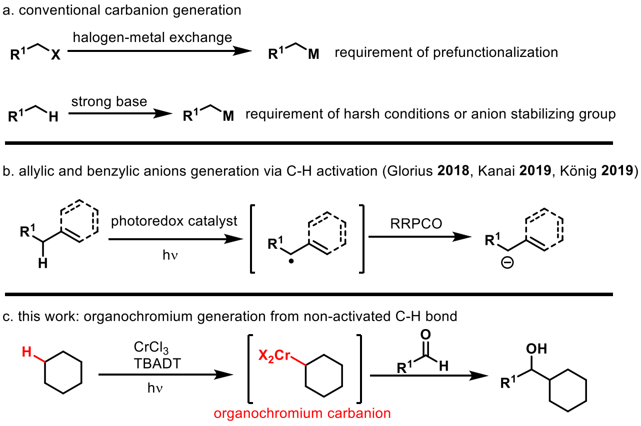
ABSTRACT: Herein, we describe the generation of an organochromium-type carbanion species from a non-activated C−H bond and its nucleophilic addition to aldehydes. The catalytic carbanion generation occurred through formal deprotonation of a non-activated C−H bond under mild conditions and did not need the prefunctionalization or anion stabilizing group. Carbon radical intermediates generated by decatungstate photocatalyst-mediated hydrogen abstraction were captured by a chromium salt with the reductive radical-polar crossover reaction to produce organochromium carbanions.



The addition of carbon nucleophiles to carbonyls plays a key role in C−C bond formation. Among the nucleophiles used, organometallic reagents in particular have contributed to the development of organic synthesis.[1] However, despite the usefulness of organometallic reagents, methods for their preparation are limited. In most cases, preparation of the organometallic reagent requires prefunctionalization, such as halogenation for halogen−metal exchange, or stannylation for tin−lithium exchange. Although direct deprotonation from a C−H bond is one of the most straightforward methods for generating organometallics, strongly basic conditions or anion stabilizing groups such as carbonyl groups, sulfur atoms, or sp carbons are required (Scheme 1a). Recently, reductive radical-polar crossover (RRPCO) reactions have emerged as a powerful method for the generation of carbanions. RRPCO has enabled the generation of anions from various prenucleophiles, such as carboxylic acids, olefins, ammonium, etc.[2] Glorius and Kanai independently reported the generation of allylchromium nucleophiles via RRPCO of allyl radicals, which were formed through allylic C−H activation by photoredox catalysts (Scheme 1b).[3] König developed the generation of benzylic anions from benzylic C−H bonds by using the RRPCO pathway.[4] In these reports, the RRPCO process enabled the mild and catalytic preparation of carbanions from allylic and benzylic C−H bonds. However, the formation of carbanions from less acidic non-activated C−H bonds, which are hard to deprotonate selectively under conventional basic conditions, is still challenging.

Scheme 1. Methods for the Preparation of Carbanions



The decatungstate anion, typically utilized as the tetrabutylammonium salt [TBADT, tetrabutylammonium decatungstate, $(nBu_4N)_4[W_{10}O_{32}]$], has been recognized as a unique photocatalyst that enables non-activated C−H bond functionalization through a hydrogen atom transfer mechanism.[5] TBADT is a highly active photocatalyst with excellent site selectivity. Although a wide range of reactions have been developed using TBADT, most reports have focused on radical reactions, such as addition to unsaturated bonds, fluorination, and oxidation. We report herein that the combination of TBADT and a chromium salt generated organochromium compounds from non-activated C−H bonds under mild conditions (Scheme 1c).

We chose the coupling between cyclohexane **1a** and benzaldehyde **2a** as a standard reaction for the optimization of the reaction conditions (Table 1). Chromium(III) trichloride was found to be the best chromium source among those tested[6] (entries 1−3). The yield was further improved by increasing the amount of TBADT, cyclohexane,

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Table 1. Reaction Optimization[a]

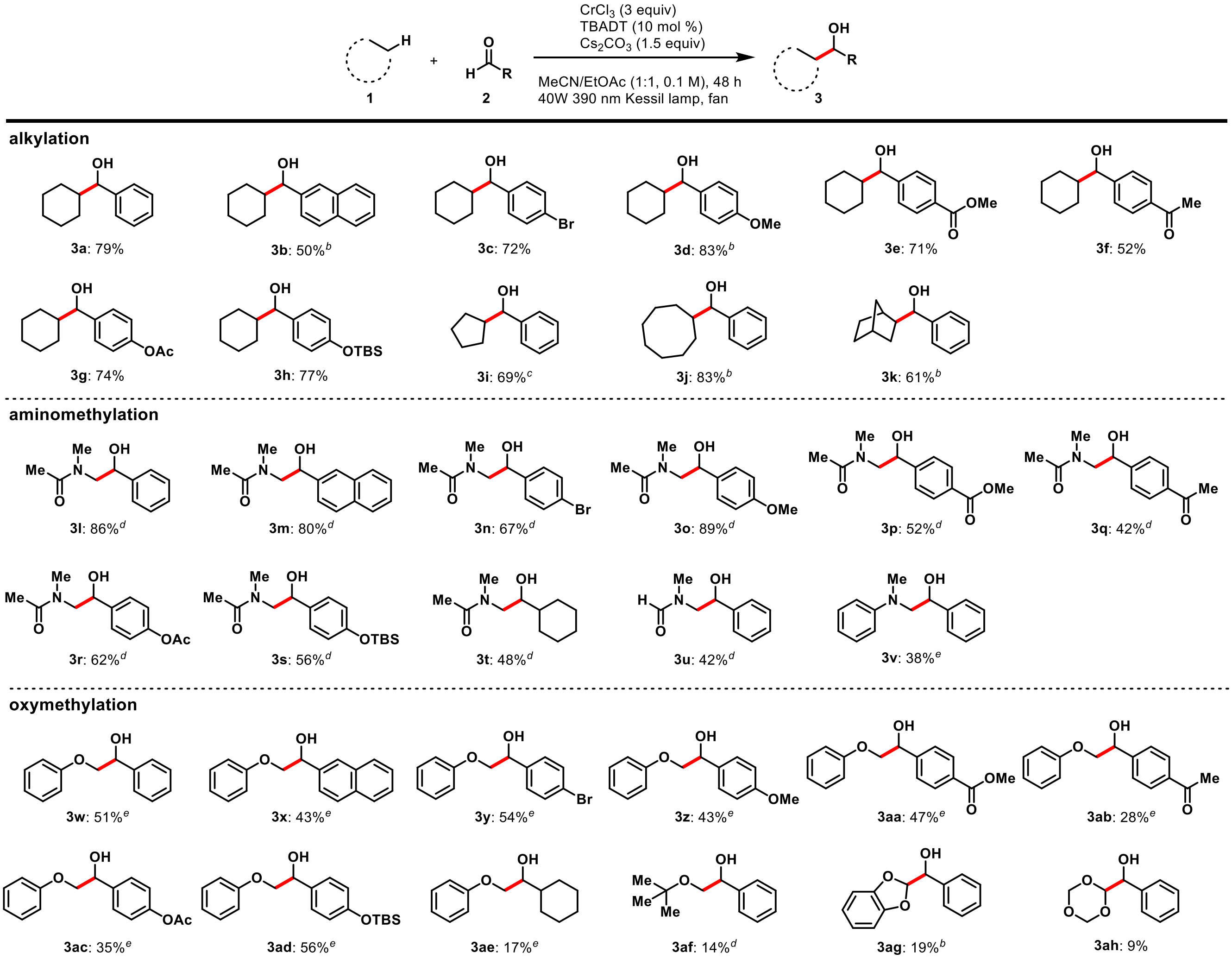
entry	Cr salt	TBADT (mol %)	**1a** (equiv)	yield[b] (%)
1	$CrCl_2$ (2 equiv)	3	20	2
2	$CrCl_3$·3THF (2 equiv)	3	20	9
3	$CrCl_3$ (2 equiv)	3	20	20
4	$CrCl_3$ (2 equiv)	10	20	50
5	$CrCl_3$ (3 equiv)	10	20	69
6	$CrCl_3$ (3 equiv)	10	30	75 (79)
7[c]	$CrCl_3$ (3 equiv)	10	20	64
8[d]	$CrCl_3$ (3 equiv)	10	30	42

[a] Standard conditions: **2a** (0.20 mmol), $CsCO_3$ (1.5 equiv), MeCN/EtOAc (1:1, 0.1 M), 40 W 390 nm Kessil lamp, fan, 48 h. [b] NMR yield. Isolated yield shown in parentheses. [c] A 40 W 370 nm Kessil lamp was used instead of a 390 nm lamp. [d] No Cs_2CO_3 was added.

and $CrCl_3$ (entries 4–6, respectively). Removing the base resulted in a decreased yield (entry 7). Changing the wavelength from 390 to 370 nm had little influence on the results (entry 8).

With the optimized conditions in hand, we then explored the substrate scope of this coupling reaction (Scheme 2). Bromo and methoxy substituents did not affect the results (**3c** and **3d**). Because of the high chemoselectivity of the organochromium anion, aldehyde groups were preferentially alkylated in the presence of ester and ketone functional groups, and no alkylation of the ketone or ester was observed (**3e** and **3f**). Protecting groups such as *tert*-butyldimethylsilyl (TBS) and acetyl were also tolerated under the reaction conditions (**3g** and **3h**). In addition, carbanion nucleophiles were prepared from cyclopentane, cyclooctane, and norbornane and reacted with **2a** to give products in good yields (**3i–3k**). Furthermore, the developed method could be applied to the generation of functionalized carbanions as follows. Utilization of *N*,*N*-dimethylacetamide (DMA), dimethylformamide, and *N*,*N*-dimethylaniline (**1b**)[7] enabled the aminomethylation of aldehydes to produce 1,2-aminoalcohol derivatives in good

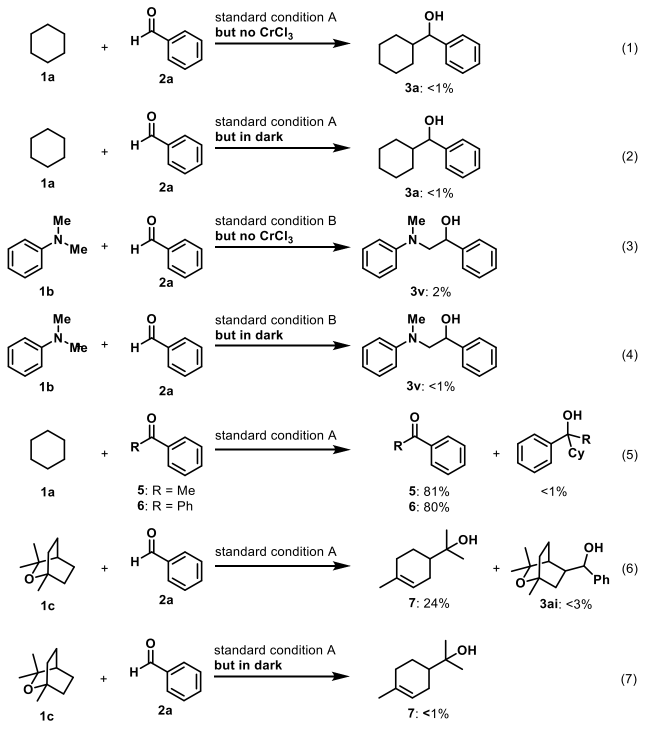
Scheme 2. Substrate Scope for Aldehyde Alkylation[a]



[a] Standard conditions: **2** (0.20 mmol, 1 equiv), **1** (30 equiv), Cs_2CO_3 (1.5 equiv), $CrCl_3$ (3 equiv), TBADT (10 mol %), MeCN/EtOAc (1:1, 0.1 M), 40 W 390 nm Kessil lamp, fan, 48 h. Isolated yield. [b] **1** (20 equiv) was used. [c] **1** (40 equiv) was used. [d] **1** was used as the solvent: **2** (0.80 mmol), Cs_2CO_3 (1.5 equiv), $CrCl_3$ (3 equiv), TBADT (10 mol %), MeCN/EtOAc/**1** (2:1:3, 0.067 M), two 40 W 390 nm Kessil lamps, fan, 48 h. [e] **1** was used as the solvent: **2** (0.80 mmol), Cs_2CO_3 (1.5 equiv), $CrCl_3$ (3 equiv), TBADT (10 mol %), MeCN/**1** (2:3, 0.08 M), two 40 W 390 nm Kessil lamps, fan, 48 h.

yields (**3l**–**3v**). In the case of DMA, formal deprotonation of the *N*-methyl group, the hydrogen of which is much less acidic than the carbonyl α-proton, proceeded selectively due to the unique site selectivity of TBADT-mediated hydrogen abstraction. Aliphatic cyclohexanecarboxaldehyde was also aminomethylated in good yield (**3t**). By using anisole, the oxymethylation of aldehydes was also possible (**3w**–**3ae**). *tert*-Butyl methyl ether also gave the desired product (**3af**), but the yield was lower. Acetals could be used as alternatives to 1,3-dithiane,[8] although the yields were low (**3ag** and **3ah**).

Scheme 3. Mechanistic Studies[a]



[a]Standard condition A: aldehyde or ketone (0.20 mmol), **1** (30 equiv), Cs_2CO_3 (1.5 equiv), $CrCl_3$ (3 equiv), TBADT (10 mol %), MeCN/EtOAc (1:1, 0.1 M), 40 W 390 nm Kessil lamp, fan, 48 h. Standard condition B: **2a** (0.80 mmol), Cs_2CO_3 (1.5 equiv), $CrCl_3$ (3 equiv), TBADT (10 mol %), MeCN/**1b** (2:3, 0.08 M), two 40 W 390 nm Kessil lamps, fan, 48 h.

Control experiments were carried out to gain mechanistic insight into this reaction (Scheme 3). No product was observed for reactions between **1a** and **2a** without the chromium salt or without light (eqs 1 and 2). Although the reaction between **1b** and **2a** is known to proceed by a radical-ketyl radical coupling mechanism under irradiation at 300 nm,[7] only 2% of **3v** was observed in the NMR spectrum of the crude reaction mixture using the standard reaction conditions but without $CrCl_3$ (eq 3). Changing **2a** to acetophenone (**5**) or benzophenone (**6**) resulted in the recovery of the starting material in 80% and 81% yields, respectively (eq 5), and the coupling products were observed in the NMR spectrum of the crude reaction mixture in <1% yield. These results eliminate the possibility of the formation of bonds between the alkyl radical and ketyl radical that are generated from carbonyl groups by irradiation.[7,9] Moreover, the reaction between **2a** and eucalyptol (**1c**) gave only trace amounts of coupling product **3ai**, but instead, α-terpineol (**7**) was obtained as the major product (eq 6).[10] On the other hand, only a trace amount (<1%) of **7** was observed when the reaction was conducted in the dark (eq 7). The generation of **7** is evidence of the formation of the anionic intermediate, which triggered the β-alkoxy elimination to form **7**.

From the control experiments described above, we propose the reaction mechanism as depicted in Figure 1. First, abstraction of hydrogen from a non-activated C–H bond by photoexcited decatungstate **B** generates carbon radical intermediate **D** and reduced decatungstate **C**. Reduced decatungstate **C** [$E([W_{10}O_{32}]^{4-}/[W_{10}O_{32}]^{5-}$ = −0.97 V vs SCE],[11] reduces $CrCl_3$ to $CrCl_2$ [$E(Cr^{3+}/Cr^{2+})$ = −0.65 V vs SCE].[12] The resulting $CrCl_2$ captures radical intermediate **D** to form organochromium carbanion **E**. Carbanion **E** reacts with aldehydes with high chemoselectivity to give final product **F**.

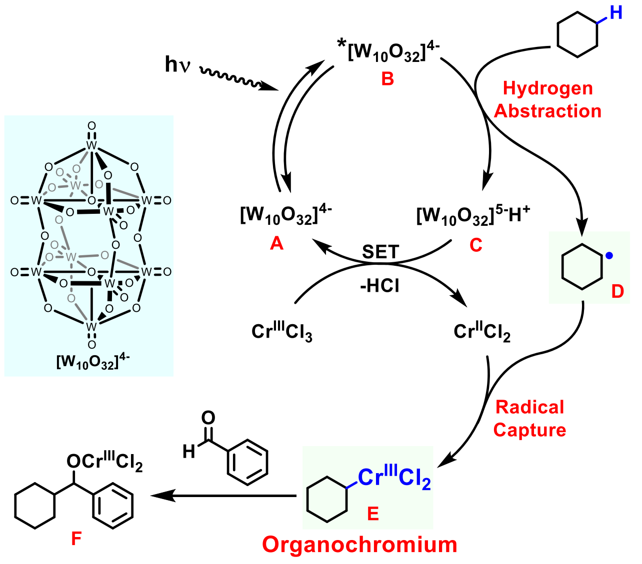


Figure 1. Proposed mechanism.

In summary, we have developed the formal generation of a catalytic carbanion from a non-activated C–H bond via decatungstate-catalyzed hydrogen abstraction followed by RRPCO radical capture with a chromium salt. The method could be applied to a wide range of substrates, including cycloalkanes, amides, and ethers, with high site selectivity and chemoselectivity, and the organochromium carbanions generated then reacted with aldehydes. By using DMA and anisole as nucleophile precursors, novel synthetic routes to vicinal aminoalcohol and diol derivatives, which are useful building blocks for pharmaceutical and materials chemistry, were possible. Mechanistic studies supported the generation of carbanion intermediates.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c00096.

Experimental Procedures and spectral data for all new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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REFERENCES

(1) Schlosser, M., Ed. *Organometallics in Synthesis Third Manual*; John Wiley & Sons, Inc.: Hoboken, NJ, 2013.

(2) For a review, see: Pitzer, L.; Schwarz, J. L.; Glorius, F. *Chem. Sci.* **2019**, *10*, 8285.

(3) (a) Schwarz, J. L.; Schäfers, F.; Tlahuext-Aca, A.; Lückemeier, L.; Glorius, F. Diastereoselective Allylation of Aldehydes by Dual Photoredox and Chromium Catalysis. *J. Am. Chem. Soc.* **2018**, *140*, 12705. (b) Mitsunuma, H.; Tanabe, S.; Fuse, H.; Ohkubo, K.; Kanai, M. Catalytic asymmetric allylation of aldehydes with alkenes through allylic C(cp^3)-H functionalization mediated by organophotoredox and chiral chromium hybrid catalysis. *Chem. Sci.* **2019**, *10*, 3459.

(4) Meng, Q.-Y.; Schirmer, T. E.; Berger, A. L.; Donabauer, K.; König, B. *J. Am. Chem. Soc.* **2019**, *141*, 11393.

(5) (a) Dondi, D.; Cardarelli, A. M.; Fagnoni, M.; Albini, A. Photomediated synthesis of β-alkylketones from cycloalkanes. *Tetrahedron* **2006**, *62*, 5527. (b) Dondi, D.; Fagnoni, M.; Albini, A. Tetrabutylammonium Decatungstate-Photosensitized Alkylation of Electrophilic Alkenes: Convenient Functionalization of Aliphatic C-H Bonds. *Chem. - Eur. J.* **2006**, *12*, 4153. (c) Ravelli, D.; Zema, M.; Mella, M.; Fagnoni, M.; Albini, A. Benzoyl radicals from (hetero)-aromatic aldehydes. Decatungstate photocatalyzed synthesis of substituted aromatic ketones. *Org. Biomol. Chem.* **2010**, *8*, 4158. (d) Ravelli, D.; Albini, A.; Fagnoni, M. Smooth Photocatalytic Preparation of 2-Substituted 1,3-Benzodioxoles. *Chem. - Eur. J.* **2011**, *17*, 572. (e) Ravelli, D.; Montanaro, S.; Zema, M.; Fagnoni, M.; Albini, A. A Tin-Free, Radical Photocatalyzed Addition to Vinyl Sulfones. *Adv. Synth. Catal.* **2011**, *353*, 3295. (f) Ryu, I.; Tani, A.; Fukuyama, T.; Ravelli, D.; Fagnoni, M.; Albini, A. Atom-Economical Synthesis of Unsymmetrical Ketones through Photocatalyzed C-H Activation of Alkanes and Coupling with CO and Electrophilic Alkenes. *Angew. Chem., Int. Ed.* **2011**, *50*, 1869. (g) Montanaro, S.; Ravelli, D.; Merli, D.; Fagnoni, M.; Albini, A. Decatungstate As Photoredox Catalyst: Benzylation of Electron-Poor Olefins. *Org. Lett.* **2012**, *14*, 4218. (h) Ryu, I.; Tani, A.; Fukuyama, T.; Ravelli, D.; Montanaro, S.; Fagnoni, M. Efficient C−H/C−N and C−H/C−CO−N Conversion via Decatungstate-Photoinduced Alkylation of Diisopropyl Azodicarboxylate. *Org. Lett.* **2013**, *15*, 2554. (i) Halperin, S. D.; Fan, H.; Chang, S.; Martin, R. E.; Britton, R. A Convenient Photocatalytic Fluorination of Unactivated C−H Bonds. *Angew. Chem., Int. Ed.* **2014**, *53*, 4690. (j) Okada, M.; Fukuyama, T.; Yamada, K.; Ryu, I.; Ravelli, D.; Fagnoni, M. Sunlight photocatalyzed regioselective β-alkylation and acylation of cyclopentanones. *Chem. Sci.* **2014**, *5*, 2893. (k) Bonassi, F.; Ravelli, D.; Protti, S.; Fagnoni, M. Decatungstate Photocatalyzed Acylations and Alkylations in Flow *via* Hydrogen Atom Transfer. *Adv. Synth. Catal.* **2015**, *357*, 3687. (l) West, J. G.; Huang, D.; Sorensen, E. Acceptorless dehydrogenation of small molecules through cooperative base metal catalysis. *Nat. Commun.* **2015**, *6*, 10093. (m) Murphy, J. J.; Bastida, D.; Paria, S.; Fagnoni, M.; Melchiorre, P. Asymmetric catalytic formation of quaternary carbons by iminium ion trapping of radicals. *Nature* **2016**, *532*, 218. (n) Quattrini, M. C.; Fujii, S.; Yamada, K.; Fukuyama, T.; Ravelli, D.; Fagnoni, M.; Ryu, I. Versatile cross-dehydrogenative coupling of heteroaromatics and hydrogen donors *via* decatungstate photocatalysis. *Chem. Commun.* **2017**, *53*, 2335. (o) Fukuyama, T.; Nishikawa, T.; Yamada, K.; Ravelli, D.; Fagnoni, M.; Ryu, I. Photocatalyzed Site-Selective C(sp^3)−H Functionalization of Alkylpyridines at Non-Benzylic Positions. *Org. Lett.* **2017**, *19*, 6436. (p) Fukuyama, T.; Yamada, K.; Nishikawa, T.; Ravelli, D.; Fagnoni, M.; Ryu, I. Site-selectivity in TBADT-photocatalyzed C(sp^3)−H Functionalization of Saturated Alcohols and Alkanes. *Chem. Lett.* **2018**, *47*, 207. (q) Ravelli, D.; Fagnoni, M.; Fukuyama, T.; Nishikawa, T.; Ryu, I. Site-Selective C−H Functionalization by Decatungstate Anion Photocatalysis: Synergistic Control by Polar and Steric Effects Expands the Reaction Scope. *ACS Catal.* **2018**, *8*, 701. (r) Perry, I. B.; Brewer, T. F.; Sarver, P. J.; Schultz, D. M.; DiRocco, D. A.; MacMillan, D. W. C. Direct arylation of strong aliphatic C−H bonds. *Nature* **2018**, *560*, 70. (s) Yuan, Z.; Yang, H.; Malik, N.; Čolović, M.; Weber, D. S.; Wilson, D.; Bénard, F.; Martin, R. E.; Warren, J. J.; Schaffer, P.; Britton, R. Electrostatic Effect Accelerate Decatungstate-Catalyzed C−H Fluorination Using [^{18}F]- and [^{19}F]NFSI in Small Molecules and Peptide Mimics. *ACS Catal.* **2019**, *9*, 8276. (t) Fukuyama, T.; Nishikawa, T.; Ryu, I. Site-Selective C(cp^3)−H Functionalization of Fluorinated Alkanes Driven by Polar Effects Using a Tungstate Photocatalyst. *Eur. J. Org. Chem.* **2019**, DOI: 10.1002/ejoc.201901135.

(6) See the Supporting Information for details.

(7) A coupling reaction between aldehydes and **1b** with 300 nm UV irradiation was reported previously: Kim, S. S.; Mah, Y. J.; Kim, A. R. A facile preparation of ethanolamines by direct irradiation of some carbonyl compounds in *N,N*-dimethylaniline. *Tetrahedron Lett.* **2001**, *42*, 8315.

(8) For a review, see: (a) Gröbel, B.-T.; Seebach, D. Umpolung of the Reactivity of Carbonyl Compounds Through Sulfur-Containing Reagents. *Synthesis* **1977**, *1977*, 357. (b) Corey, E. J.; Seebach, D. Carbanions of 1,3-Dithianes. Reagents for C−C Bond Formation by Nucleophilic Displacement and Carbonyl Addition. *Angew. Chem., Int. Ed. Engl.* **1965**, *4*, 1075. (c) Corey, E. J.; Seebach, D. Synthesis of 1,n-Dicarbonyl Derivates Using Carbanions from 1,3-Dithianes. *Angew. Chem., Int. Ed. Engl.* **1965**, *4*, 1077. (d) Seebach, D.; Wilka, E.-M. Alkylation of 2-Lithio-1,3-dithianes with Arenesulfonates of Primary Alcohols. *Synthesis* **1976**, *1976*, 476.

(9) (a) Petronijević, F. R.; Nappi, M.; MacMillan, D. W. C. Direct β-Functionalization of Cyclic Ketones with Aryl Ketones via the Merger of Photoredox and Organocatalysis. *J. Am. Chem. Soc.* **2013**, *135*, 18323. (b) Hager, D.; MacMillan, D. W. C. Activation of C−H Bonds via the Merger of Photoredox and Organocatalysis: A Coupling of Benzylic Ethers with Schiff Bases. *J. Am. Chem. Soc.* **2014**, *136*, 16986.

(c) Jeffrey, J. L.; Petronijević, F. R.; MacMillan, D. W. C. Selective Radical−Radical Cross-Couplings: Design of a Formal β-Mannich Reaction. *J. Am. Chem. Soc.* **2015**, *137*, 8404. (d) Uraguchi, D.; Kinoshita, N.; Kizu, T.; Ooi, T. Synergistic Catalysis of Ionic Brønsted Acid and Photosensitizer for a Redox Neutral Asymmetric α-Coupling of *N*-Arylaminomethanes with Aldimines. *J. Am. Chem. Soc.* **2015**, *137*, 13768. (e) Wang, C.; Qin, J.; Shen, X.; Riedel, R.; Harms, K.; Meggers, E. Asymmetric Radical−Radical Cross-Coupling through Visible-Light-Activated Iridium Catalysis. *Angew. Chem., Int. Ed.* **2016**, *55*, 685. (f) Fava, E.; Millet, A.; Nakajima, M.; Loescher, S.; Rueping, M. Reductive Umpolung of Carbonyl Derivatives with Visible-Light Photoredox Catalysis: Direct Access to Vicinal Diamines and Amino Alcohols via a-Amino Radicals and Ketyl Radicals. *Angew. Chem., Int. Ed.* **2016**, *55*, 6776. (g) Li, W.; Duan, Y.; Zhang, M.; Cheng, J.; Zhu, C. A photoredox catalyzed radical−radical coupling reaction: facile access to multi-substituted nitrogen heterocycles. *Chem. Commun.* **2016**, *52*, 7596. (h) Ding, W.; Lu, L.-Q.; Liu, J.; Liu, D.; Song, H.-T.; Xiao, W.-J. Visible Light Photocatalytic Radical−Radical Cross-Coupling Reactions of Amines and Carbonyls: A Route to 1,2-Amino Alcohols. *J. Org. Chem.* **2016**, *81*, 7237. (i) Xia, Q.; Tian, H.; Dong, J.; Qu, Y.; Li, L.; Song, H.; Liu, Y.; Wang, Q. *N*-Arylamines Coupled with Aldehydes, Ketones, and Imines by Means of Photocatalytic Proton-Coupled Electron Transfer. *Chem. - Eur. J.* **2018**, *24*, 9269. (j) Berger, A. L.; Donabauer, K.; König, B. Photocatalytic Barbier reaction − visible-light induced allylation and benzylation of aldehydes and ketones. *Chem. Sci.* **2018**, *9*, 7230. (k) Liu, Y.; Liu, X.; Li, J.; Zhao, X.; Qiao, B.; Jiang, Z. Catalytic enantioselective radical coupling of activated ketones with N-aryl glycines. *Chem. Sci.* **2018**, *9*, 8094. (l) Vu, M. D.; Das, M.; Guo, A.; Ang, Z.-E.; Đokić, M.; Soo, H. S.; Liu, X.-W. Visible-Light Photoredox Enables Ketone Carbonyl Alkylation for Easy Access to Tertiary Alcohols. *ACS Catal.* **2019**, *9*, 9009.

(10) In TBADT-mediated reactions, **1c** is known to be transformed into C−H-functionalized products, not **7** (see refs 5q and 9c).

(11) (a) Renneke, R. F.; Pasquali, M.; Hill, C. L. Polyoxometalate Systems for the Catalytic Selective Production of Nonthermodynamic Alkanes. Nature of Excited-State Deactivation Processes and Control of Subsequent Thermal Processes in Polyoxometalate Photoredox Chemistry. *J. Am. Chem. Soc.* **1990**, *112*, 6585. (b) Waele, V. D.; Poizat, O.; Fagnoni, M.; Bagno, A.; Ravelli, D. Unraveling the Key Features of the Reactive State of Decatungstate Anion in Hydrogen Atom Transfer (HAT) Photocatalysis. *ACS Catal.* **2016**, *6*, 7174.

(12) Wrona, P. K. Electrochemical behavior of Cr(II) and Cr(III) ions in weakly acidic solutions. *J. Electroanal. Chem.* **1992**, *322*, 119.