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Visible-Light Photocatalytic Preparation of 1,4-Ketoaldehydes and 1,4-Diketones from α-Bromoketones and Alkyl Enol Ethers

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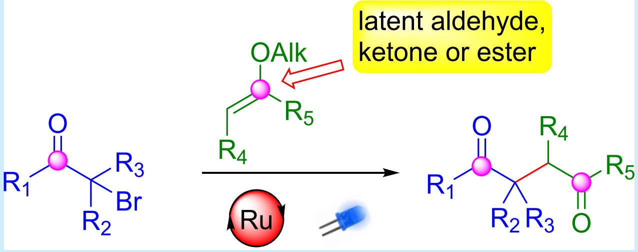
Supporting Information

ABSTRACT: A Ru^{2+}-photocatalyzed, visible-light-mediated ATRA reaction for the straightforward preparation of 1,4-ketoaldehydes, 1,4-diketones, and 1,4-ketoesters, which are of difficult access by other means, is reported herein. This method employs readily accessible α-bromoketones and alkyl vinyl ethers as starting materials, allowing the construction of secondary, tertiary, and challenging quaternary centers. In addition, the synthetic usefulness of this method is illustrated by applying it to the construction of substituted pyrroles.



The dicarbonyl moiety is present in many natural products, and it is also employed as a precursor for the synthesis of heterocyles. In particular, 1,4-dicarbonyl compounds are the direct starting materials for the construction of pyrroles,[1] furans,[2] thiophenes,[3] and cyclopentenones.[4] Interestingly, while many methods for the preparation of diketones[5] have been reported, introducing an acetaldehyde fragment at the α position of a ketone remains a challenging transformation. Thus, the number of methods described so far for the synthesis of 1,4-ketoaldehydes remains scarce; Pan[6] reported an organocatalytic isomerization of allylic alcohols (Scheme 1a); Jiang and Loh[7] utilized the bond cleavage of a cyclopropane intermediate derived from enaminones (Scheme 1b); Fagnoni[8] performed a conjugate radical addition of an acetal derived radical (Scheme 1c); and very recently, Yu and co-workers[9] reported a radical hydroacylation of enals, although the latter method is limited to the use of cinnamaldehydes as radical acceptors (Scheme 1d). On the other hand, our group[10] and Reiser[11] developed radical-ionic sequences based on the use of esters, amides, and nitriles as radical precursors. Despite these advances, the development of general procedures is still highly desirable. Recently, the photoredox radical reactions[12] have emerged as an alternative for the development of clean, atom-economic and modulable reactions, which can be applied to atom transfer radical additions (ATRA).[13] In this context, here we report an ATRA-based, light-mediated photocatalytic procedure for the preparation of 1,4-ketoaldehydes, 1,4-diketones, and 1,4-ketoesters.

In this work, we envisaged that, in the presence of the appropriate photocatalyst (PC), an α-bromoketone radical precursor **1** would add to an enol ester or enol ether **2**, which would serve as an electron-rich radical acceptor, generating, after the halogen-atom transfer, an unstable geminal halohydrine **4**. According to our previous work,[10] the latter would collapse to generate the carbonyl moiety, affording the expected dicarbonyl compound **5** (Scheme 1e).

We started our study by evaluating the conversion of 2-bromoacetophenone **1a** into its corresponding 1,4-ketoaldehyde **5a**, and the representative results are presented in Table 1.[14] Initially, we selected vinyl pivalate **2a** (4 equiv) as the radical acceptor, 2 mol % of $[Ru(bpy)_3]Cl_2$ (**3a**) as the photocatalyst (PC), and DIPEA (4 equiv) as the stoichiometric reducing agent in DMF/H_2O (4:1, v/v, 0.25 M, entry 1). Under these conditions, the desired product **5a** was isolated in 5% yield. Changing the PC to $[Ir(dtbbpy)(ppy)_2]PF_6$ (**3b**, entry 2) or switching the acceptor to the less hindered vinyl acetate (entry 3) also led to a low yield of **5a**. Different solvents were tested, such as DCM, DMSO, and CH_3CN. The latter showed a slight improvement in the yield (19%, entry 4). Other reducing agents were examined; sodium ascorbate was the most effective, improving the yield up to 53% (entry 5). Intriguingly, when ethylvinyl ether (**2c**) was used as the acceptor, a similar yield of **5a** was observed (46%, entry 6), but switching back to DIPEA as reductant increased the yield to 79% (entry 7), and the same result was obtained with catalyst **3b** (entry 8). The amelioration of the yield with ethyl vinyl ether can be attributed to the fact that **2c** is more electron-rich than **2a** or **2b**, favoring the polar effects and making the radical addition more efficient. Finally, we conducted some control experiments. When the reaction was performed without any additive, traces of **5a** were observed (entry 9). In addition, when the reaction was performed in the dark, the starting material remained unchanged (entry 10).

Subsequently, we evaluated which halogen would serve as the best radical precursor. Thus, 2-chloroacetophenone (**1b**) and 2-iodoacetophenone (**1c**) were tested with the optimized reaction conditions. As seen in Scheme 2, **1b** reacted very slowly, obtaining **5a** in traces, along with 28% of reduction product (**6a**) and starting material (65%). On the other hand,

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Scheme 1. Methods for the Synthesis of 1,4-Ketoaldehydes

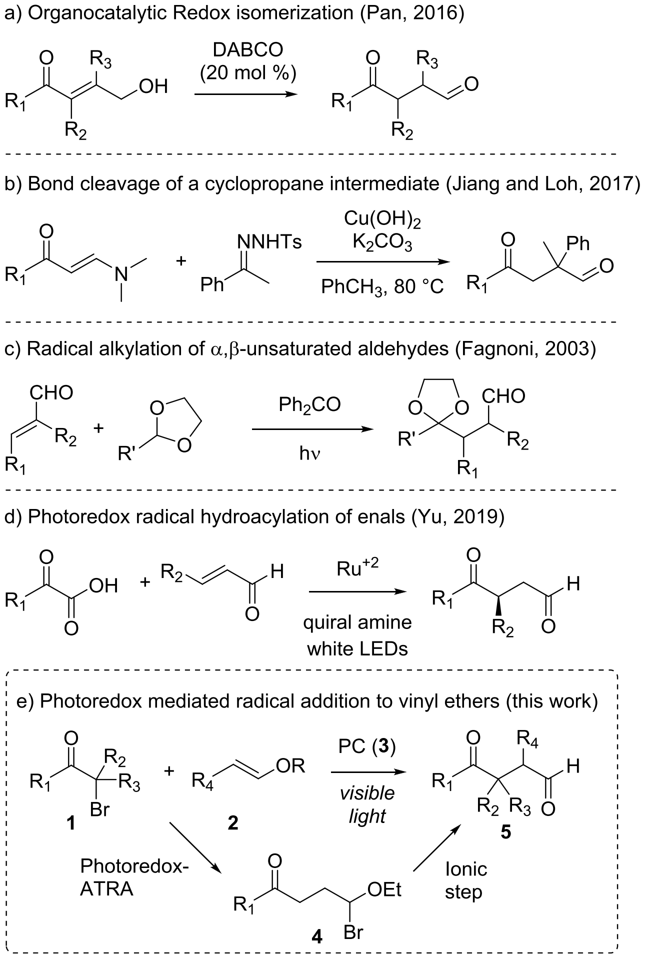
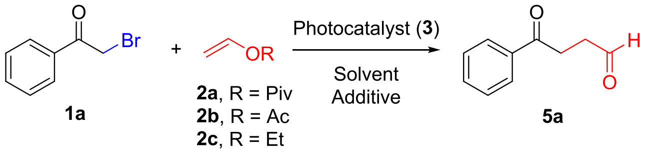


Table 1. Screening of the Reaction Conditions[a]

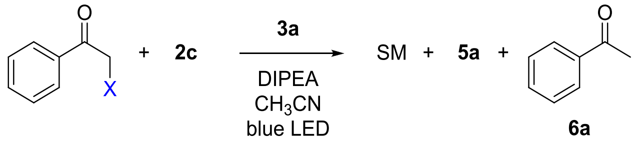


Photocatalyst (PC): [Ru(bpy)$_3$]Cl$_2$ (**3a**)
[Ir(dtbbpy)(ppy)$_2$]PF$_6$ (**3b**)

entry	acceptor	PC	additive	solvent	yield (%)
1	**2a**	**3a**	DIPEA	DMF/H$_2$O	5
2	**2a**	**3b**	DIPEA	DMF/H$_2$O	5
3	**2b**	**3a**	DIPEA	DMF/H$_2$O	5
4	**2a**	**3a**	DIPEA	CH$_3$CN	19
5	**2a**	**3a**	sodium ascorbate	CH$_3$CN	53
6	**2c**	**3a**	sodium ascorbate	CH$_3$CN	46
7	**2c**	**3a**	DIPEA	CH$_3$CN	79
8	**2c**	**3b**	DIPEA	CH$_3$CN	79
9	**2c**	**3a**		CH$_3$CN	traces
10[b]	**2c**	**3a**	DIPEA	CH$_3$CN	NR

[a] Reaction conditions: a degassed mixture of **1a** (1 equiv), **2a–c** (4 equiv), **3a** or **3b** (2 mol %) and additive (4 equiv) in the indicated solvent (0.25 M) was irradiated with blue LED strips for 1 h at rt. [b] Reaction was carried out in the dark.

Scheme 2. Evaluation of the Halogen Atom in the Radical Precursor



	SM	5a	6a
1a, X = Br	Trace	79%	Trace
1b, X = Cl	65%	Trace	28%
1c, X = I	0%	10%	81%

the starting material was completely consumed when the more reactive 2-iodoacetophenone **1c** was employed, but the major product formed was acetophenone **6a** in 81% yield. This inefficiency of α-iodoketones to form radicals had been already observed in our group[15] and explained by Curran[16] in terms of the facile formation of I$_2$ and the corresponding enolate through an ionic mechanism.

With the optimized conditions in hand, we evaluated the scope of the reaction (Figure 1). Primary acetophenones afforded the corresponding ketoaldehydes **5b–f** in good yields (68–76%) without any interference of the aromatic ring substituents. Secondary α-bromoketones also worked with efficiency. For example, tetralone derivatives **5h** and **5i** were obtained in 78 and 75% yields, respectively, whereas **5j** was prepared in 76% yield from 2-bromo-4-chromanone. For the latter, it is worth mentioning that the reaction was scaled up to 1 g (4.4 mmol) of precursor, without a significant detriment of the yield (70%). Aliphatic bromoketones were successfully employed as well as substrates. Thus, cyclopentanone (**5k**), cyclohexanone (**5l**), and cycloheptanone (**5m**) derivatives were synthesized in 60–63% yields. Notably, amirine analogue **5n** was obtained in 72% yield as a 6:1 mixture of diastereoisomers from its corresponding α-bromoketone without alteration of the internal double bond. Remarkably, this methodology worked for tertiary substrates, rendering compound **5o** in 52% yield. Although the yield is lower in the latter case, the construction of quaternary centers is worth it.

Next, we changed the radical acceptor in order to prepare 1,4-diketones. Figure 2 shows the results when 2-methoxypropene (**2d**) was used as the radical acceptor. Applying the same reaction conditions as before, 1,4-diketones **7a–j** were obtained in good yields. Once again, no interference was observed with other potential radical precursors like chlorine (**7b**), as well as different substitution patterns in the aromatic cycle (**7c–f**). Secondary α-bromoketones were also employed as starting material, giving α-tetralone derivatives **7g** and **7h** in 72 and 67% yields, respectively. α-Bromocyclopentanone and α-bromocyclohepatnone served also as aliphatic radical precursors, giving rise to **7i** and **7j** in 61 and 63% yields, respectively. As can be noted, the yields are quite similar for acceptors **2c** and **2d**, showcasing the generality of the procedure.

Furthermore, we prepared more elaborated methyl enol ethers such as **2e**[17] and **2f**[18] according to known procedures in order to test its reactivity. When **2e** was subjected to the optimized reaction conditions with **1b** and **1j**, diketones **8** (33%) and **9** (22%, dr 2:1) were obtained in moderate yields. This is probably due to the higher stability of the generated benzylic radicals, occasioning a less efficient bromine-atom transfer.[19] Although the yields for the latter experiments are moderate, the construction of more complex dicarbonyl compounds like **8** or **9** by other means is not trivial and would require long routes and complex starting materials.[20] On

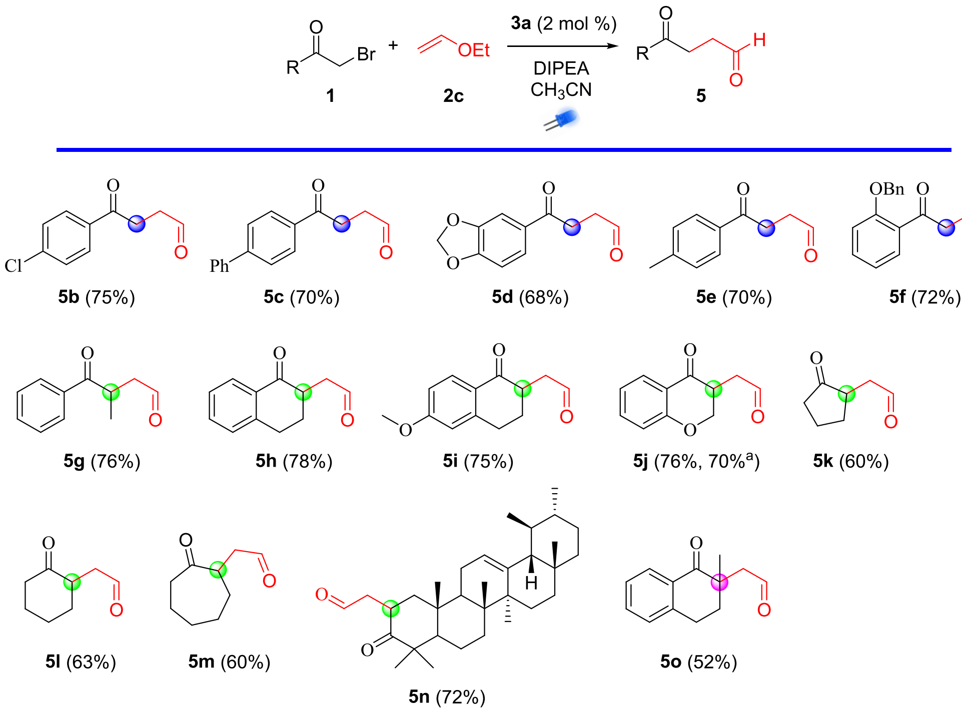


Figure 1. Scope of the radical precursor. All reactions were run with 50 mg of precursor (**1a**−**p**). Reaction conditions: a degassed solution of **1** (1 equiv), **2c** (4 equiv), **3a** (2 mol %), and DIPEA (4 equiv) in CH$_3$CN (0.25 M) was irradiated by blue LED strips for 1−24 h at room temperature. (a) The reaction was performed on a 1g (4.4 mmol) scale.

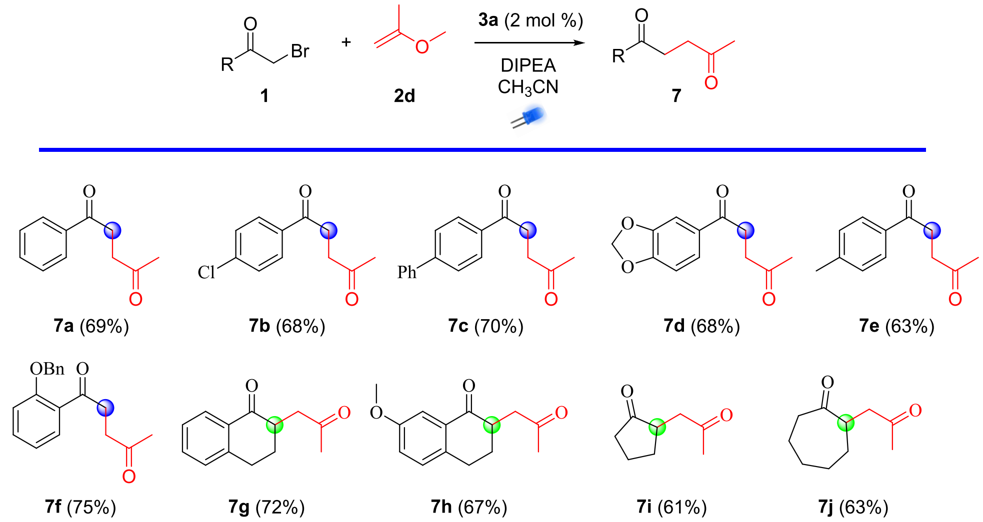


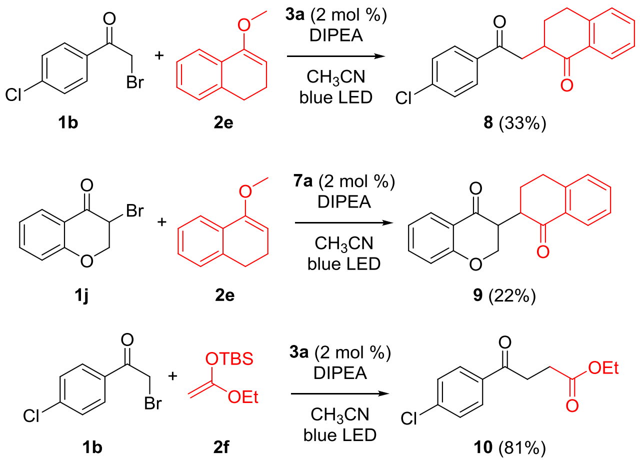
Figure 2. Preparation of 1,4-diketones. All reactions were run with 50 mg of precursor (**1a**−**p**). Reaction conditions: a degassed solution of **1** (1 equiv), **2d** (4 equiv), **3a** (2 mol %), and DIPEA (4 equiv) in CH$_3$CN (0.25 M) was irradiated by blue LED strips for 1−8 h at room temperature.

the other hand, acceptor **2f** was highly efficient and afforded **10** in 81% yield, showing that this procedure can be expanded to the synthesis of ketoesters (Scheme 3).

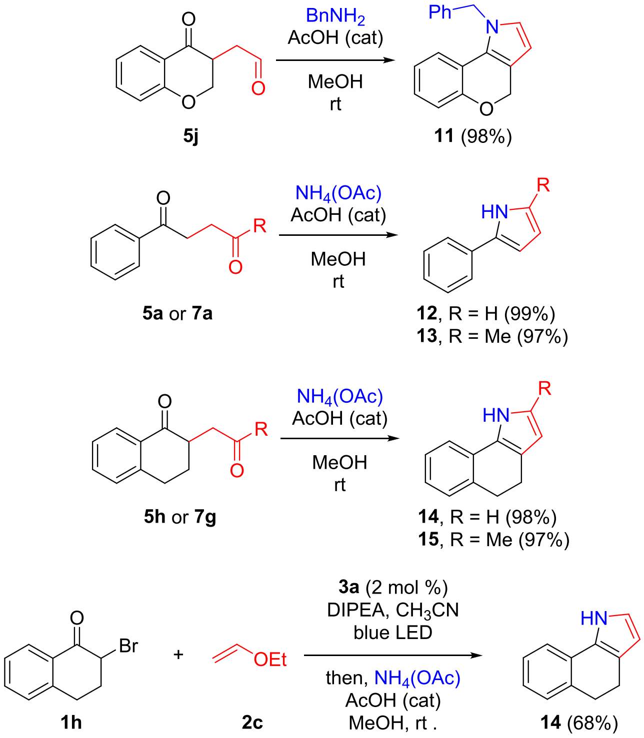
As mentioned before, 1,4-ketoaldehydes are valuable starting materials for the construction of heterocycles, such as pyrroles. To showcase this application, we treated compound **5j** with benzylamine and a catalytic amount of acetic acid, producing pyrrole **11** in 98% yield. This reaction was equally efficient when ammonium acetate was employed as the nitrogen source, generating compound **12**[21] from **5a** in almost quantitative yield. In the same way, disubstituted pyrroles **13**[22] and **14**[23] were prepared in 97 and 98% yields, respectively, whereas trisubstituted pyrrole **15**[24] was straightforwardly forged from **7g** in nearly quantitative yield (97%). Compound **14** was also prepared in a *one-pot* protocol: initially, a mixture of **1h** and **2c** was treated under the described photoredox conditions. Then, when **1h** was completely consumed (monitored by TLC), the solvent was switched to methanol and the reaction was directly treated with NH$_4$(OAc) and AcOH. Under these conditions, pyrrole **12** was isolated in 68% overall yield (from **1h**). This last sequence shows that our protocol can be a direct and efficient way to prepare heteropolycyclic compounds (Scheme 4).

A plausible mechanism of our transformation is depicted in Scheme 5. Photoexcitation of Ru^{2+} catalyst with blue LED light should generate *Ru^{2+} species, which are reduced by DIPEA,

Scheme 3. Dicarbonyl Compounds from Elaborated Acceptors

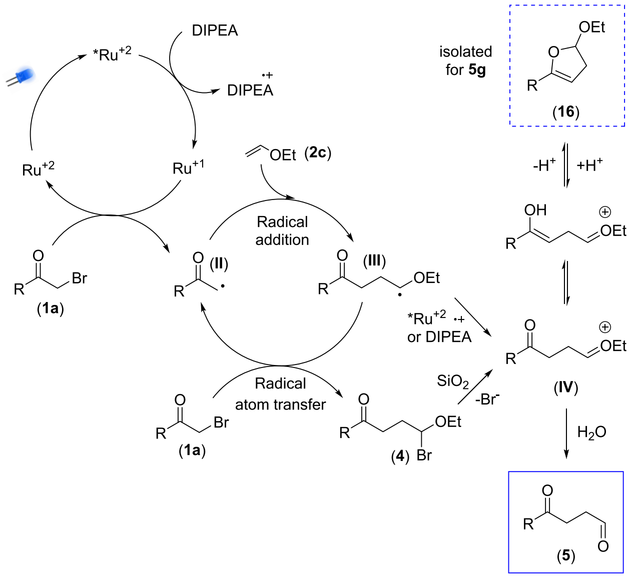


Scheme 4. Synthetic Transformations of Dicarbonyl Compounds



serving as the sacrifice amine, to Ru^{1+}. The latter can perform an electron transfer to starting material (**1a**), giving rise to radical **II** and regenerating Ru^{2+}. Once the radical **II** is formed, the mechanism follows a typical ATRA path, i.e., radical addition to **2c** to produce **III**, which transfers the bromine atom from **1a**, giving **II** and ATRA adduct **4**. During column chromatography, **4** can collapse to produce the isolated dicarbonyl compound. Alternatively, radical **III** is oxidized to oxonium **IV** by either $^{*}Ru^{2+}$ or $DIPEA^{\bullet+}$, and hydrolysis of oxonium ion **IV** produces **5**. It is worth noting that both adduct **4** and acetal **16** were observed along with **5** during the reaction (TLC) and in the ^{1}H NMR crude spectrum. In addition, **16** was isolated in small amounts for compound **5g** (see the SI for details and characterization); however, after purification, only **5** was recovered.

Scheme 5. Plausible Mechanism for the formation of 5



In conclusion, herein we report an efficient photocatalytic method for the synthesis of 1,4-ketoaldehydes, 1,4-diketones, and 1,4-ketoesters from readily accessible starting materials, which would be difficult to obtain by other routes. Our method is quite general, allowing the construction of secondary, tertiary, and quaternary carbons, and it shown to be a practical way for the synthesis of substituted pyrroles.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b01275.

Experimental procedures, characterization and copies of ^{1}H and ^{13}C NMR spectra for new compounds (PDF)

FID files (ZIP)

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Notes

The authors declare no competing financial interest.

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REFERENCES

(1) (a) Bean, G. P. In *The Chemistry of Heterocyclic Compounds*; Jones, R. A., Ed.; Wiley-VCH, 1990; Vol. *48*, pp 105−294. (b) Ferreira, V. F.; de Souza, M. C. B. V.; Cunha, A. C.; Pereira, L. O. R.; Ferreira, M. L. G. *Org. Prep. Proced. Int.* **2001**, *33*, 411. (c) Fuchs, P. J. W.; Zeitler, K. *J. Org. Chem.* **2017**, *82*, 7796.

(2) (a) Rao, H. S. P.; Jothilingam, S. J. *J. Org. Chem.* **2003**, *68*, 5392. (b) Khaghaninejad, S.; Heravi, M. M. *Adv. Heterocycl. Chem.* **2014**, *111*, 95.

(3) Mortensen, D. S.; Rodríguez, A. L.; Carlson, K. E.; Sun, J.; Katzenellenbogen, B. S.; Katzenellenbogen, A. J. *J. Med. Chem.* **2001**, *44*, 3838.

(4) (a) Paterson, I.; Xuan, M.; Dalby, S. M. *Angew. Chem., Int. Ed.* **2014**, *53*, 7286. (b) An, J.; Bagnell, L.; Cablewski, T.; Strauss, C. R.; Trainor, R. W. *J. Org. Chem.* **1997**, *62*, 2505. (c) Geraghty, N. W. A.; Morris, N. M. *Synthesis* **1989**, 603.

(5) (a) Cowherd, F. G.; Doria, M.-C.; Galeazzi, E.; Muchowski, J. M. *Can. J. Chem.* **1977**, *55*, 2919. (b) Shimizu, M.; Akiyama, T.; Mukaiyama, T. *Chem. Lett.* **1984**, *13*, 1531. (c) Miyashita, M.; Yanami, T.; Kumazawa, T.; Yoshikoshi, A. *J. Am. Chem. Soc.* **1984**, *106*, 2149. (d) Kitahara, H.; Tozawa, Y.; Fujita, S.; Tajiri, A.; Morita, N.; Asao, T. *Bull. Chem. Soc. Jpn.* **1988**, *61*, 3362. (e) Fiandanese, V.; Marchese, G.; Naso, F. *Tetrahedron Lett.* **1988**, *29*, 3587. (f) Lu, X.; Ji, J.; Ma, D.; Shen, W. *J. Org. Chem.* **1991**, *56*, 5774. (g) Echavarren, A. M.; Pérez, M.; Castaño, A. M.; Cuerva, J. M. *J. Org. Chem.* **1994**, *59*, 4179. (h) Miyashita, A.; Matsuoka, Y.; Numata, A.; Higashino, T. *Chem. Pharm. Bull.* **1996**, *44*, 448. (i) Yuguchi, M.; Tokuda, M.; Orito, K. *Chem. Lett.* **2004**, *33*, 674. (j) Sauthier, M.; Castanet, Y.; Mortreux, A. *Chem. Commun.* **2004**, 1520. (k) Nishiyama, Y.; Kobayashi, A. *Tetrahedron Lett.* **2006**, *47*, 5565. (l) Enders, D.; Han, J.; Henseler, A. *Chem. Commun.* **2008**, 3989. (m) Setzer, P.; Beauseigneur, A.; Pearson-Long, M. S. M.; Bertus, P. *Angew. Chem., Int. Ed.* **2010**, *49*, 8691. (n) Xuan, J.; Feng, Z.-J.; Chen, J.-R.; Lu, L.-Q.; Xiao, W.-J. *Chem. - Eur. J.* **2014**, *20*, 3045. (o) Kwon, Y.; Schatz, D. J.; West, F. G. *Angew. Chem., Int. Ed.* **2015**, *54*, 9940. (p) Yin, H.; Nielsen, D. U.; Johansen, M. K.; Lindhardt, A. T.; Skrydstrup, T. *ACS Catal.* **2016**, *6*, 2982. (q) Miao, C.-B.; Zeng, Y.-M.; Shi, T.; Liu, R.; Wei, P.-F.; Sun, X.-Q.; Yang, H.-T. *J. Org. Chem.* **2016**, *81*, 43. (r) Geibel, I.; Christoffers, J. *Eur. J. Org. Chem.* **2016**, *2016*, 918. (s) Yang, J.; Mei, F.; Gu, Y. *Green Chem.* **2018**, *20*, 1367.

(6) Mondal, K.; Mondal, B.; Pan, S. C. *J. Org. Chem.* **2016**, *81*, 4835.

(7) Ni, M.; Zhang, J.; Liang, X.; Jiang, Y.; Loh, T.-P. *Chem. Commun.* **2017**, *53*, 12286.

(8) Dondi, D.; Caprioli, I.; Fagnoni, M.; Mella, M.; Albini, A. *Tetrahedron* **2003**, *59*, 947.

(9) Zhao, J.-J.; Zhang, H.-H.; Shen, X.; Yu, S. *Org. Lett.* **2019**, *21*, 913.

(10) Peralta-Hernández, E.; Blé-González, E. A.; Gracia-Medrano-Bravo, V. A.; Cordero-Vargas, A. *Tetrahedron* **2015**, *71*, 2234.

(11) Föll, T.; Rehbein, J.; Reiser, O. *Org. Lett.* **2018**, *20*, 5794.

(12) For recent reviews on photocatalytic radical reactions, see: (a) Angnes, R. A.; Li, Z.; Correia, C. R. D.; Hammond, G. B. *Org. Biomol. Chem.* **2015**, *13*, 9152. (b) Goddard, J.-P.; Ollivier, C.; Fensterbank, L. *Acc. Chem. Res.* **2016**, *49*, 1924. (c) Shaw, M. H.; Twilton, J.; MacMillan, D. W. C. *J. Org. Chem.* **2016**, *81*, 6898. (d) Lee, K. N.; Ngai, M.-Y. *Chem. Commun.* **2017**, *53*, 13093. (e) Matsui, J. K.; Lang, S. B.; Heitz, D. R.; Molander, G. A. *ACS Catal.* **2017**, *7*, 2563. (f) Xie, J.; Jin, H.; Hashmi, S. K. *Chem. Soc. Rev.* **2017**, *46*, 5193. (g) Khalid, M.; Mohammed, S. *Asian J. Chem.* **2019**, *31*, 25.

(13) (a) Nguyen, J. D.; Tucker, J. W.; Konieczynska, M. D.; Stephenson, C. R. J. *J. Am. Chem. Soc.* **2011**, *133*, 4160. (b) Wallentin, C.-J.; Nguyen, J. D.; Finkbeiner, P.; Stephenson, C. R. J. *J. Am. Chem. Soc.* **2012**, *134*, 8875. (c) Pirtsch, M.; Paria, S.; Matsuno, T.; Isobe, H.; Reiser, O. *Chem. - Eur. J.* **2012**, *18*, 7336. (d) Gu, X.; Li, X.; Qu, Y.; Yang, Q.; Li, P.; Yao, Y. *Chem. - Eur. J.* **2013**, *19*, 11878. (e) Arceo, E.; Montroni, E.; Melchiorre, P. *Angew. Chem., Int. Ed.* **2014**, *53*, 12064. (f) Knorn, M.; Rawner, T.; Czerwieniec, R.; Reiser, O. *ACS Catal.* **2015**, *5*, 5186. (g) Huang, M.; Li, L.; Zhao, Z.-G.; Chen, Q.-Y.; Guo, Y. *Synthesis* **2015**, *47*, 3891. (h) Courant, T.; Masson, G. *J. Org. Chem.* **2016**, *81*, 6945. (i) Magagnano, G.; Gualandi, A.; Marchini, M.; Mengozzi, L.; Ceroni, P.; Cozzi, P. G. *Chem. Commun.* **2017**, *53*, 1591. (j) Triandafillidi, I.; Kokotou, M. G.; Kokotos, C. G. *Org. Lett.* **2018**, *20*, 36−39.

(14) See the Supporting Information for the full and comprehensive optimization.

(15) Peralta-Hernández, E.; Cortezano-Arellano, O.; Cordero-Vargas, A. *Tetrahedron Lett.* **2011**, *52*, 6899.

(16) Curran, D. P.; Guthrie, D. B.; Geib, S. J. *J. Am. Chem. Soc.* **2008**, *130*, 8437.

(17) (a) Bonvallet, P. A.; Todd, E. M.; Kim, Y. S.; McMahon, R. J. *J. Org. Chem.* **2002**, *67*, 9031. (b) Liu, J.-L.; Zhu, Z.-F.; Liu, F. *Org. Lett.* **2018**, *20*, 720.

(18) Wenzel, A. G.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2002**, *124*, 12964.

(19) Quiclet-Sire, B.; Zard, S. Z. *J. Am. Chem. Soc.* **2015**, *137*, 6762.

(20) (a) Mu, X.-J.; Zou, J.-P.; Wang, Z.-T.; Zhang, W. *Tetrahedron Lett.* **2005**, *46*, 4727. (b) Lin, Q.; Li, Y.; Das, D. K.; Zhang, G.; Zhao, Z.; Yang, S.; Fang, X. *Chem. Commun.* **2016**, *52*, 6459.

(21) Yamamoto, H.; Sasaki, I.; Mitsutake, M.; Karasudani, A.; Imagawa, H.; Nishizawa, M. *Synlett* **2011**, *2011*, 2815.

(22) Cho, H.; Madden, R.; Nisanci, B.; Török, B. *Green Chem.* **2015**, *17*, 1088.

(23) Ivanov, A. V.; Shcherbakova, V. S.; Mikhaleva, A. I.; Trofimov, B. A. *Russ. J. Org. Chem.* **2014**, *50*, 1775.

(24) Tsutsui, H.; Kitamura, M.; Narasaka, K. *Bull. Chem. Soc. Jpn.* **2002**, *75*, 1451.

DOI: 10.1021/acs.orglett.9b01275