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Recent Progress in Visible-Light Photoredox-Catalyzed Intermolecular 1,2-Difunctionalization of Double Bonds via an ATRA-Type Mechanism

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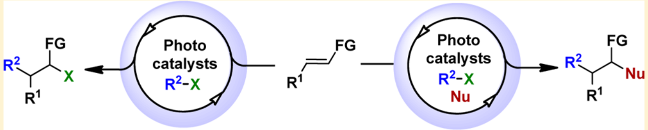
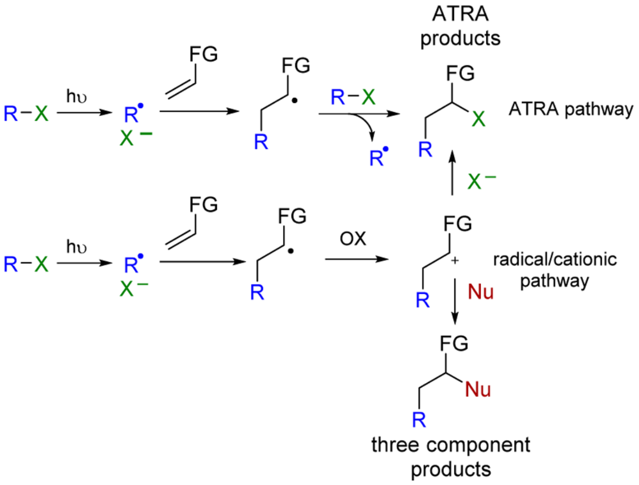


ABSTRACT: Radical difunctionalizations of alkenes constitute an efficient method for the construction of complex organic molecules. This synopsis focuses on visible-light catalysis, a recent and very promising technological refinement of this class of transformations. Examples taken from the literature illustrate the use of a variety of (metallic or nonmetallic) systems, which allow us to leverage the energy of readily available visible-light radiation to efficiently create some of the most commonly looked for types of bonds (C–X, C–O, C–N, and C–C) under mild conditions and starting from unsaturated substrates.

Intermolecular vicinal difunctionalization of alkenes that proceeds via radical addition has long been recognized as a convenient method for elaborating highly *α*,*β*-functionalized compounds. Over the past decade, atom-transfer radical addition onto alkenes (ATRA) has had a tremendous impact on these fields.[1] Popularized by the work of Kharasch,[2] these reactions have found wide applications in industry and academic research laboratories. As in every other field of chemistry, once the feasibility of a new kind of reaction has been shown, concerns about production of avoidable waste, use of unfriendly (such as toxic) reagents, and the efficiency of the process in terms of atoms or energy required to conduct it arise. These concerns initiate a quest for more robust, simple to implement, selective, green, and atom-economic processes. In this context, catalytic processes, and in particular photoredox catalysis in our case, appear to be suitables candidate to improve the overall performance of this kind of reaction compared to classic radical initiation conditions. Indeed, the principle of photoredox chemistry, based on decades of studies on radical chemistry, led to the possibility of converting photon energy to "chemical" energy to give mild conditions and avoiding the use of toxic metals, opening new perspectives to chemists.[3]

In this JOCSynopsis, we highlight recent advances in the field of photocatalyzed redox intermolecular tandem vicinal difunctionalization of alkenes and the different approaches developed. We also give an overview of functionalization of various alkenes and in particular reactions featuring three-component tandem vicinal difunctionalization. All of these transformations can be seen as particular cases of one of the two general sequences depicted in Scheme 1.

Scheme 1. General Sequences



Early reports of photoredox catalysis were published in the 1970s, and first developments of this field were concentrated around generation of free radicals from various precursors using $Ru(bpy)_3^{2+}$ as catalyst.[3,4] However, since the emergence of other metal-based and metal-free catalysts, we witnessed an explosion of the number of publications concerning photoredox catalysis but also an expansion of the field of applications of such processes.[3,5]

ATOM GROUP TRANSFER RADICAL ADDITIONS

Selenide Group Transfer Radical Addition. The earliest report of a photoredox process[4e,6] resulting in the direct functionalization of an alkene can be attributed to Barton in 1994 (Scheme 2).[7] In this pioneering work, a tosyl radical generated by one-electron reduction of Se-phenyl *p*-toluenese-

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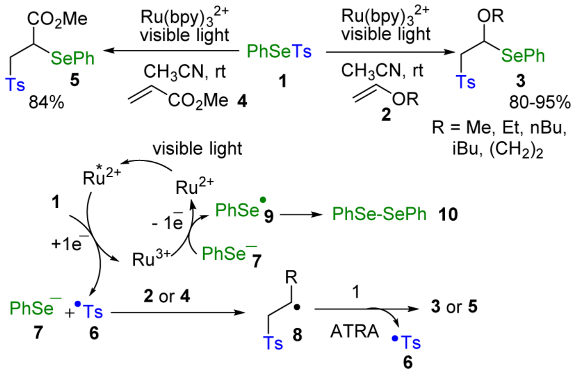
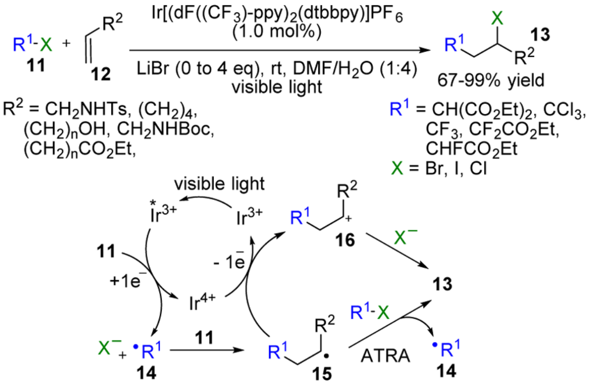
Scheme 2. Photoinitiated ATRA Reactions Developed by Barton et al.[7]



lenosulfonate (TsSePh, **1**) by Ru(bpy)$_3^{2+}$ directly added to the electron-rich β-position of an enol ether **2** as well as the electron-poor position β-position of an acrylate **4**. The resulting α-radical **8** could then add to a second molecule of **1** continuing the radical chain and forms phenylselenyl **3** or **5**. The proposed mechanism of such transformation (Scheme 1). Visible-light irradiation of Ru(bpy)$_3^{2+}$ to form a strongly reducing species *Ru(bpy)$_3^{2+}$, which performs a single-electron transfer (SET) to generate sulfonyl radical **6** and phenylselenoate **7** from TsSePh **1**. Subsequent addition of **6** to olefins **2** or **4** furnishes radical **8**. The latter species can be directly trapped by **7** from **1**, leading to the desired β-phenylselenosulfones **3** or **5** and sulfonyl radical **6**. Then, photocatalyst Ru(bpy)$_3^{2+}$ is regenerated by oxidation of **7** into radical **9**, which dimerizes to yield diphenyl diselenide **10**.

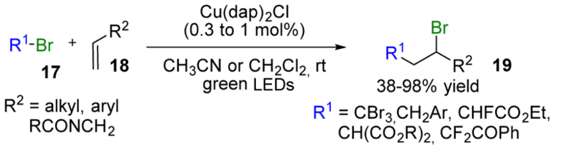
Halogen-Atom Transfer Radical Addition. This reaction, known as the Kharasch addition,[2] is one of the most efficient ways to introduce a halogen atom starting from olefinic substrates. While the use of photoactivable catalysts represents a good alternative to the use of toxic reagents and harsh conditions, photoredox-mediated halogen ATRA reaction has only recently been reported. The first example was published by Stephenson et al. using an iridium-based photoinitiator with transfer of the halogen atom from an ester halide **11** to an alkene **12** (Scheme 3).[8] In this work, haloalkylated products **13** were obtained with yields between 67 and 99% under mild conditions. A variety of functional groups were tolerated, such as esters, alcohols, and carbamates. The presence of a soft Lewis acid, such as LiBr, was often required to assist the direct monoelectronic reduction of the alkyl halide into the corresponding radical. Similarly to Barton's work, the authors envisaged a radical chain mechanism, with the Ir-based catalyst functioning as the photoinitiator. However, an alternative mechanism has been suggested in which the oxidation of radical **15** by Ir^{4+} produces carbocation **16**, regenerating a ground-state Ir^{3+} catalyst. Final addition of halide furnishes the desired ATRA product **13**. An interesting application of this reaction has been achieved by Hawker et al. in a living radical polymerization of methacrylate derivatives.[9]

Scheme 3. Photoinitiated ATRA Reactions Developed by Stephenson et al.[8]



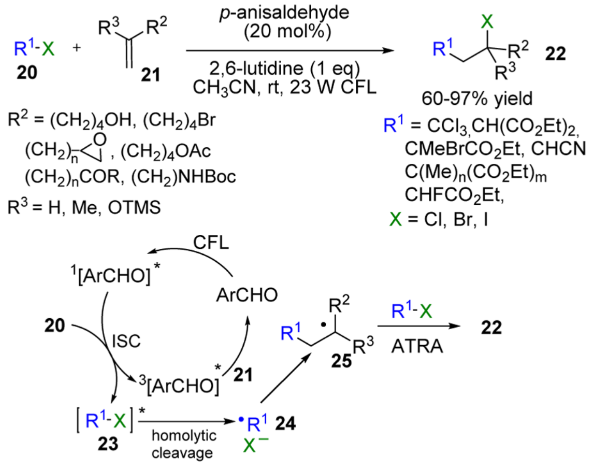
One year later, the copper photocatalyst Cu(dap)$_2$Cl was successfully used by Reiser et al. for ATRA of CBr$_4$, bromomalonate, and α-bromoacetophenone **17** to various olefins **18**.[10] High yields of the ATRA adducts **19** were obtained with unactivated alkenes but were lower for more reactive double bonds such as styrenes (Scheme 4). This photoredox-catalyzed ATRA strategy was later efficiently extended to other haloalkanes **17** such as bromobenzyl[10b] and adapted to be run under continuous flow irradiation providing similar or better yields.[11]

Scheme 4. ATRA Reactions Developed by Reiser et al.[10]



In 2014, Melchiorre et al.[12] described an elegant photochemical approach where *p*-anisaldehyde irradiated by a compact fluorescent lamp (CFL) catalyzed the ATRA of electron-deficient haloalkanes **20** to various alkenes **21** in high yields (Scheme 5). In a plausible mechanism, *p*-anisaldehyde (ArCHO) absorbs a photon to reach an excited, singlet state ^{1}[ArCHO]*. After rapid intersystem crossing (ISC) to the triplet state ^{3}[ArCHO]*, an energy transfer to the haloalkane **20** takes place, which regenerates ground-state photocatalyst **A**. Then, photosensitized haloalkane **23** undergoes a homolytic cleavage leading to the electron-deficient alkyl radical **24** which then adds to **21**. Finally, this resulting radical **25** propagates the ATRA reaction.

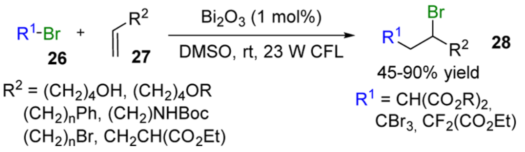
Scheme 5. ATRA Reactions Developed by Melchiorre et al.[12]



An inexpensive photocatalyst, bismuth oxide (Bi$_2$O$_3$), was successfully used by Pericàs et al. for bromine-ATRA of olefins

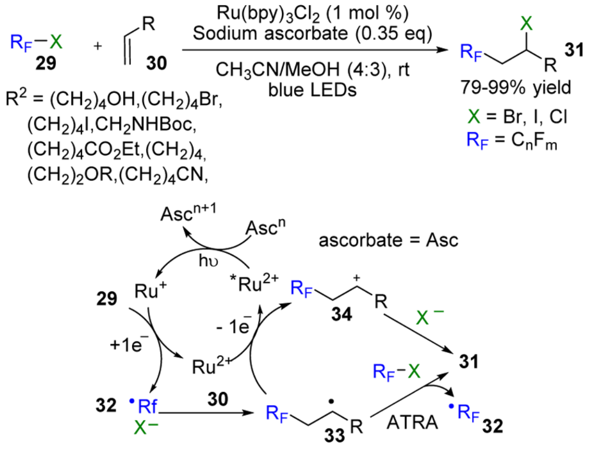
27 under the irradiation of a 23 W CFL.[13] This recyclable catalyst was employed with various organobromides **26** to give rise to the corresponding ATRA products **28** in moderate to good yields (Scheme 6).

Scheme 6. ATRA Reactions Developed by Pericàs et al.[13]



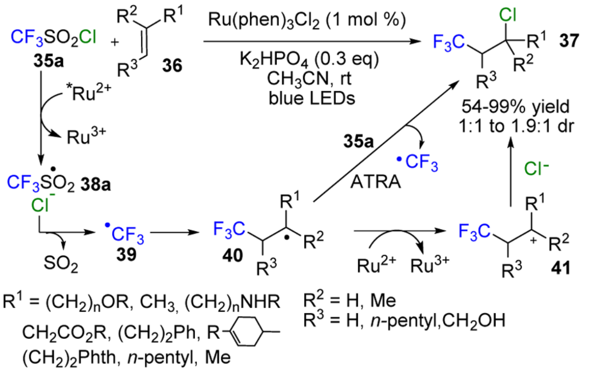
Atom-Transfer Radical Trifluoromethylation Reactions. The inclusion of fluorinated functional groups into structures has a strong impact on biological properties and bioaviability of bioactive compounds.[14] However, the easy introduction of this motif in a chemo- and regioselective manner is a long-standing challenge, and many attempts to achieve this goal have been reported.[14,15] The photoredox-catalyzed ATRA reaction has proved to be an effective method to incorporate a (per)fluoroalkyl moiety onto alkenes. Such a reaction was first reported by Stephenson et al. in 2011 (Scheme 3).[8a] Although this synthetic approach was effective for the preparation of a range of perfluorohalogenated substrates from unactivated alkenes, there are some limitations in its application to perfluoroalkyl iodides **29** as ATRA reagents. The same group reported a solution to this problem by using the $Ru(bpy)_3^{2+}$ as the photocatalyst combined with sodium ascorbate as an electron donor (Scheme 7).[8b] In this case, the mechanism involves the reductive quenching of the excited state of $*Ru^{2+}$ by sodium ascorbate to produce the reducing Ru^+ species. Then, perfluoroalkyl radical **32**, formed by the Ru^+-mediated monoelectronic reduction of **29**, reacts with alkene **30** to provide radical **33**, which could be rapidly oxidized into cation **34** either by single-electron transfer SET from $*Ru^2$ or by iodine atom transfer. Thus, various unactivated alkenes **30** were found to perform well in the iodoperfluoroalkyaltion under these new conditions.

Scheme 7. Iodofluoroalkylation developed by Stephenson et al.[8b]



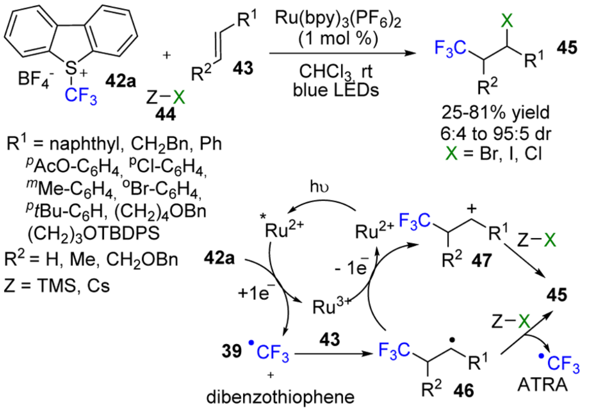
A similar transformation also providing halotrifluoromethylated product was achieved by Jung, Han et al.[16] using trifluoromethanesulfonyl chloride **35a** as the trifluoromethyl source[17] and visible light in the presence of a ruthenium photocatalyst (Scheme 8). Using this protocol, the chlorotrifluoromethylation of a variety of substrates including mono-, di-, and trisubstituted unactivated alkenes could be performed in good to excellent yields. Here, the excited Ru^{2+} complex first generates the CF_3SO_2 radical **38a**, which eliminates SO_2 to afford the CF_3 radical **39**. Addition to the alkene provides radical **40**, which is oxidized by Ru^{3+} into carbocation **41** and trapped by a chloride anion. Even though strong experimental evidence supports such a mechanism, a radical chain transfer mechanism may also be operative.

Scheme 8. Chlorotrifluoromethylation Developed by Han et al.[16]



In 2015, our group developed an alternate multicomponent method for the halotrifluoromethylation of styrenes and alkenes[18] by using Umemoto's reagent (**42a**)[19] as a source of the trifluoromethyl radical in combination with cheap sources of halogens (Scheme 9). The reaction proceeds first via single-electron reduction of Umemeto's reagent by the photoexcited $Ru(bpy)_3(PF_6)_2$ catalyst under irradiation by a blue LED device with a wavelength of 425 nm. Reduction induces fragmentation of **42a** to generate the desired trifluoromethyl radical **39** and dibenzothiophene. Addition of CF_3 radical **39** to alkenes **43** gives stabilized α-aryl radical **46**, which can be oxidized by $Ru(bpy)_3)^{3+}$ to the corresponding α-aryl cation **47**. Alternatively, **45** may regenerate CF_3 radical **39** from another equivalent of Umemoto's reagent **42** in a radical propagation step to give **45**. Suitable halogen ions (Cl^-, Br^-, or I^-) can then be used to trap this cation **47** to deliver the desired difunctionalized alkene product **45**. A range of terminal and

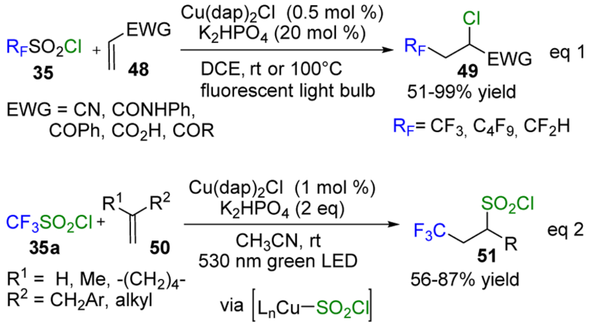
Scheme 9. Halotrifluoromethylation Developed by Masson et al.[18]



internal styrenes **43** could be obtained with yields going up to 77%, and non-activated alkene derivatives were obtained with 45% and up to 55% yields, respectively. Moderate to excellent diastereoselectivity (up to 95:5) was found.

Although a wide variety of alkenes were suitable substrates under the conditions reported above, no example of halotrifluoromethylation of electron-poor alkenes was studied. This limitation was, however, overcome when Dolbier et al.[20] described a $[Cu(dap)_2]Cl$-catalyzed chlorotrifluoromethylation of α,β-unsaturated amides and esters (Scheme 10, eq 1). Under visible-light irradiation, the ATRA reaction of CF_3SO_2Cl **35a** as well as other (per)fluoroalkylsulfonyl chlorides **35** proceed smoothly to afford a series of chloroperfluorated alkanes **49** in good to excellent yields. After this report, Reiser et al.[21] disclosed an elegant trifluoromethylchlorosulfonylation of unactivated alkenes under similar conditions but in which no SO_2 was lost from CF_3SO_2Cl **35a** (Scheme 10, eq 2). This reaction was achieved with $Cu(dap)_2Cl$ as the photocatalyst under irradiation with green LEDs to afford the trifluoromethyl chlorosulfonylated products **51** in 56−87% yields. This unusual reactivity was accounted for by an inner sphere mechanism where the copper catalyst is assumed to weakly coordinate SO_2Cl, thus preventing SO_2 loss.

Scheme 10. Trifluoromethylation Developed by Dolbier and Reiser[20,21]

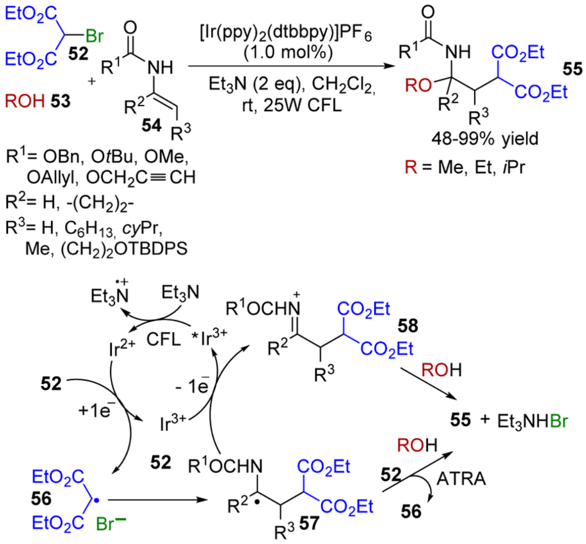


■ ATOM TRANSFER RADICAL MULTICOMPONENT REACTIONS

In the photoredox-ATRA olefin difunctionalizations described above, carbocations are among the various kinds of reactive intermediates generated, thus giving potential access to large libraries of vicinal difunctionalized compounds by catering to a subsequent nucleophilic addition step in the process.[22]

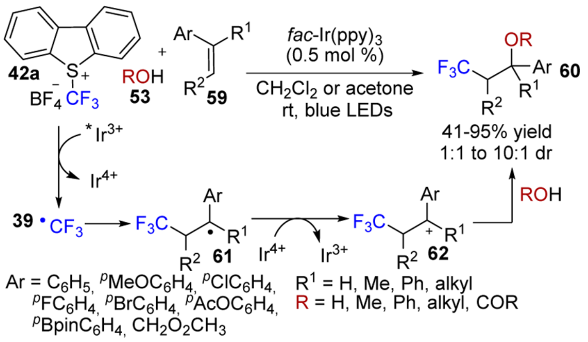
Atom Transfer Radical Multicomponent Oxyalkylation Reactions. In this context, our group developed in 2012 an efficient, three-component oxyalkylation reaction of enecarbamates **54** with diethyl bromomalonate **52** and alcohols **53** via a visible light catalyzed ATRA approach (Scheme 11).[23] Using $Ir(ppy)_2(dtb\text{-}bpy)\ (PF_6)$ as the photocatalyst under irradiation with a 25 W CFL, diethyl malonate radical **56** was generated from bromomalonate **52** via single-electron reduction. Two alternative pathways regarding the succession of oxidation states ($Ir^{4+}/{}^*Ir^{3+}$ and Ir^{3+}/Ir^{2+}) through which the iridium center passes for the reduction of **52** were envisioned. Since 2 equiv of a tertiary amine is required for the success of this difunctionalization, hypotheses were oriented toward a pathway where photoactivated Ir^{3+} would oxidize triethylamine and then reductively generate alkyl radical **56** under its Ir^{2+} form. Addition of this electrophilic radical **56** to the β-position of enecarbamates **54** provides α-amido radicals **57** which upon single-electron oxidation (or radical propagation) and addition of alcohols results in the formation of β-alkylated α-carbamidoethers **55** as stable imine precursors in good to excellent yields. This transformation was found to be compatible with a wide range of enecarbamates, including β-branched as well as several carbamate protecting groups such as Cbz, Alloc, Boc, and amide.

Scheme 11. Photocatalyzed Three-Component Oxyalkylation of Enecarbamates by Masson et al.[23]



In the same year, Koike, Akita et al. reported photoredox-catalyzed three-component oxytrifluoromethylation of styrenes using Umemoto's reagent **42** and various *O*-nucleophiles **53**, such as water, alcohols, and carboxylic acids (Scheme 12).[24]

Scheme 12. Photocatalyzed Three-Component Oxytrifluoromethylation of Styrenes by Koike, Akita et al.[24]



Upon reductive fragmentation of Umemoto's reagent **41** with excited *fac*-$Ir(ppy)_3$, trifluoromethyl radical **39** undergoes addition to the β-position of styrene to generate benzylic radical **61**, which is oxidized and trapped by oxygen nucleophile **53** to give a wide variety of oxytrifluoromethylated products **60** in good yield. This process is highly regioselective for both terminal and internal alkenes and also shows moderate to good diastereoselectivity. The authors have subsequently shown that this strategy could be extended to the synthesis of β-trifluoromethyl ketones via the attack of DMSO as another *O*-nucleophile on photoredox-generated carbocations.[25] Very recently, they have reported a very efficient photocatalytic

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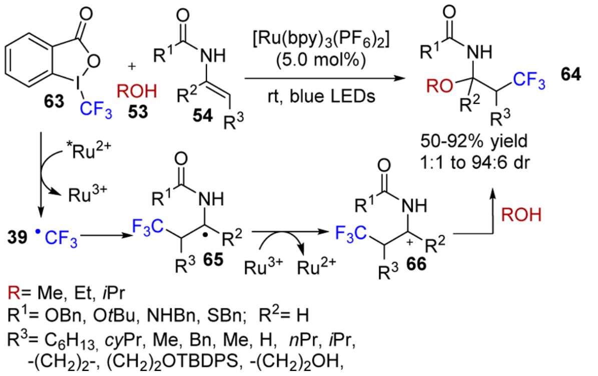
oxidifluoromethylation of alkenes using *N*-tosyl-*S*-(difluoromethyl)-*S*-phenylsulfoximine as a CF_2H group source.[26]

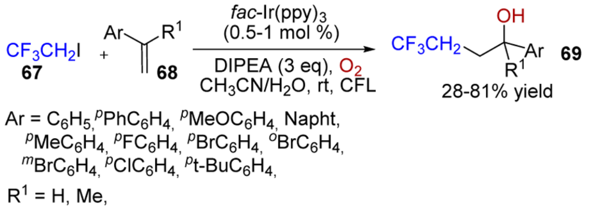
Two years later, we described a three-component oxytrifluoromethylation of enecarbamates **54**[27] leading to important *β*-aminotrifluoromethylated products **64** (Scheme 13).[28] Similar to our previous work, the electrodeficient CF_3 radical **39** selectively adds to the *β*-position to give the *α*-amido radical **65**, which is subsequently oxidized and trapped by alcohol **53**. While Umemoto's reagent **42** did not afford the desired addition product, Togni's reagent **63**[29] and 5% mol of photocatalyst $Ru(bpy)_3(PF_6)_2$ gave the desired products **64** in good yields with moderate diastereoselectivity. A broad reaction scope was demonstrated with good functional group tolerance.

Scheme 13. Three-Component Oxytrifluoromethylation of Enecarbamates by Magnier and Masson et al.[27]



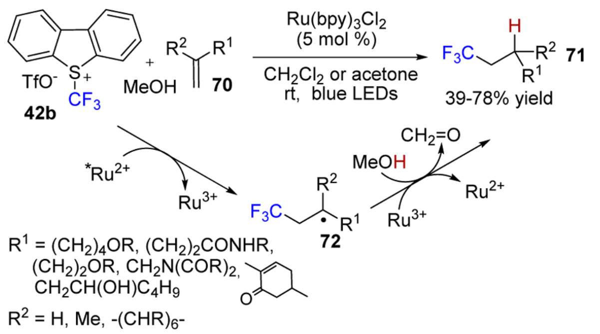
Recently, Chen, Guo et al. disclosed a novel photocatalytic hydroxytrifluoroethylation of styrenes **68** leading to *γ*-trifluoromethylalcohols **69** in moderate to excellent yields (Scheme 14).[30] This reaction was achieved with CF_3CH_2I **67** as the fluoroalkylating reagent and *fac*-$Ir(ppy)_3$ as the photoredox catalyst in a mixture of CH_3CN/water under an air atmosphere. Preliminary mechanistic investigations indicated that the oxygen atom present in the resulting hydroxytrifluoroethyl adduct comes from O_2 and not water.

Scheme 14. Photocatalyzed Hydroxytrifluoromethylation of Styrenes by Chen, Guo et al.[30]



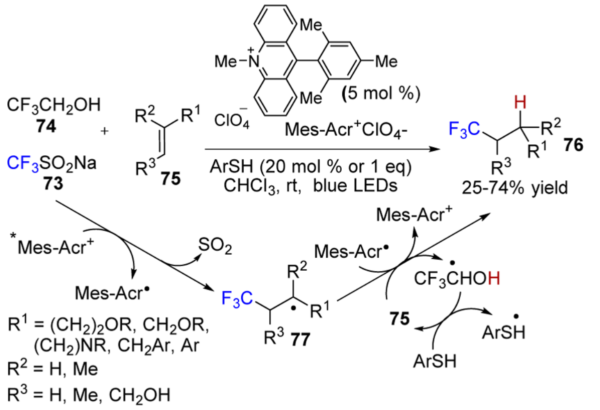
Atom Transfer Radical Multicomponent Hydroalkylation Reactions. Three-component radical/cationic reactions are not limited to oxyalkylation. For instance, hydroalkylation was described by Gouverneur et al. in a $Ru(bpy)_3Cl_2$-photocatalyzed three-component reductive hydrotrifluoromethylation of unactivated alkenes with Umemoto's reagent **42b** and MeOH (Scheme 15).[31] In contrast to the work described above, MeOH serves only as a source of hydrogen in this process. In this reaction, the second radical intermediate **72** generated in the reaction abstracts a hydrogen atom from alcohol to give hydrotrifluoromethylated products **71** in good yields and with excellent regioselectivity. This approach has subsequently been extended to the synthesis of hydrodifluoroalkylation and hydroperfluoalkylation of alkenes by using THF, DBU, or TMEDA as the H atom donor.[32]

Scheme 15. Photocatalyzed Three-Component Hydrotrifluoromethylation of Alkenes by Gouverneur et al.[31]



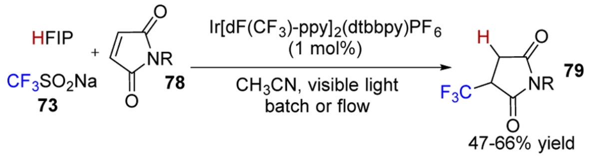
Shortly thereafter, Nicewicz et al. disclosed a metal-free photoredox reductive hydrotrifluoromethylation of terminal and internal unactivated alkenes with Langlois reagent, CF_3SO_2Na **73**[33] as the CF_3 source and 2,2,2-trifluoroethanol (TFE, **74**) as the H atom donor (Scheme 16).[34] In this case, the organic photoredox catalyst, 9-mesitylacridinium perchlorate (Mes-Acr$^+$$ClO_4^-$), promoted the single electron photooxidation of Langlois reagent **73** and subsequent addition onto the alkenes **75**. It was found that the presence of a catalytic or stoichiometric amount of thiophenol (ArSH) was required to allow an efficient regeneration of the photocatalyst.

Scheme 16. Photo-organocatalyzed Three-Component Hydrotrifluoromethylation of Alkenes by Nicewicz et al.[34]



Very recently, Lefebvre, Hoffmann, and Rueping reported an efficient photocatalytic hydrotrifluoromethylation of dedicated alkenes with Langlois reagent as CF_3 source and iridium photocatalyst, performed in a batch or flow system (Scheme 17).[35] The reaction proceeded best with hexafluoro-2-propanol

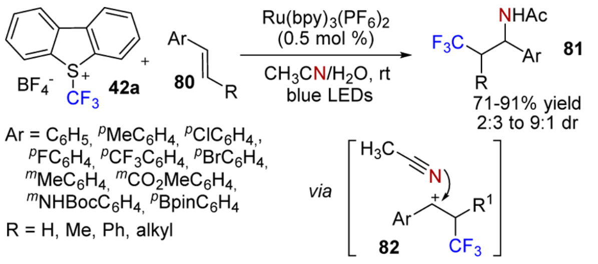
Scheme 17. Continuous-Flow Photocatalyzed Three-Component Hydrotrifluoromethylation of Maleimides by Lefebvre, Hoffmann, and Rueping[35]



(HFIP) as cosolvent, which is proposed to act as the H atom donor in this reaction. A wide range of *N*-alkylated maleimide derivatives **78** are compatible with these conditions. Thanks to this protocol, the reaction could be performed in a larger scale and with a decreased reaction time.

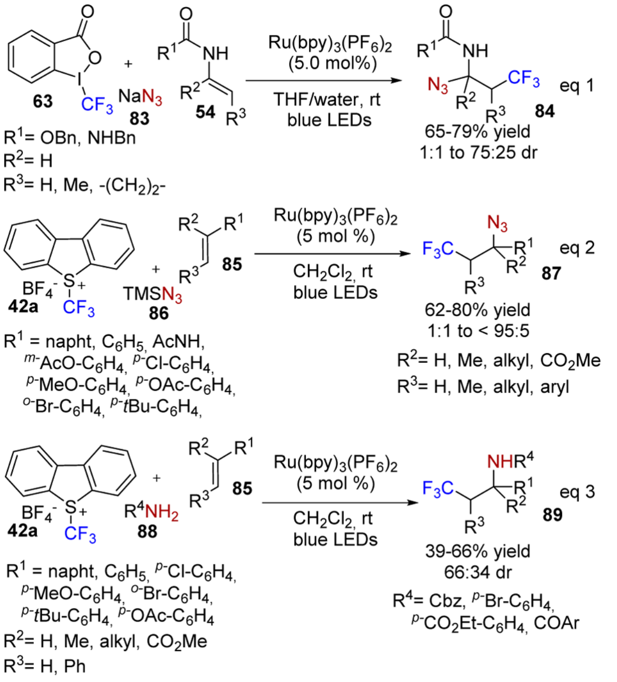
Atom Transfer Radical Multicomponent Aminoalkylation Reactions. Atom transfer radical multicomponent aminoalkylation reactions of alkenes are interesting methods to provide direct access to *β*-aminotrifluoromethylated products, which are useful synthetic intermediates in the synthesis of biologically active compounds.[28] Nevertheless, this is a quite challenging process due to the potential problem of oxidation of the amine component via reductive quenching of the photocatalysts.[3] Koike, Akita, et al. have reported a solution to this problem by employing CH_3CN as the nitrogen nucleophile (Scheme 18).[36] In this case, the benzylic trifluoromethylated radical intermediate **82** is trapped by the nitrile group via a Ritter-type reaction, yielding **81** in high yields with moderate to good diastereoselectivity. Moreover, complex structures like steroids were found to be suitable partners for alkene difunctionalization reactions yielding bioinspired products.

Scheme 18. Three-Component Aminotrifluoromethylation by Koike, Akita et al.[36]



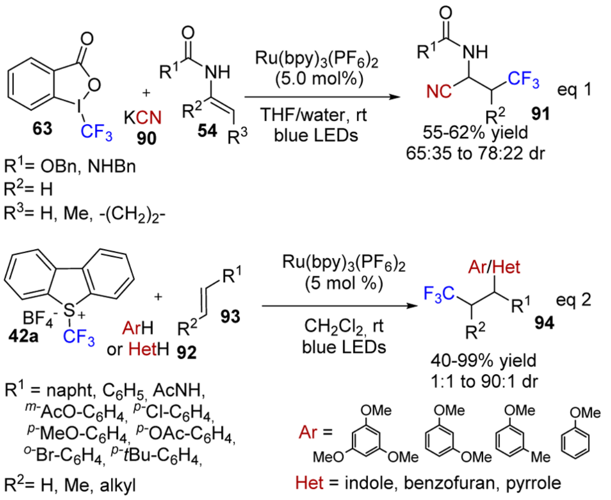
Based on our previous work, we developed a novel three-component procedure for the azidotrifluoromethylation of enecarbamates **54** where sodium azide **83** was used as an amine precursor (Scheme 19, eq 1).[27] The conditions described in Scheme 13 were slightly modified using a THF/water mixture instead of nucleophilic alcohol solvents. Later, we extended this visible light catalyzed azidotrifluoromethylation strategy to various alkenes such as styrenes, unactivated alkenes, and enol ethers **85**.[37] Various trifluoromethyl radical sources and azide nucleophiles were screened here, and Umemoto's reagent **42a** and azidotrimethylsilane **86** were found to be the reagents of choice for the three-component reaction. Again, this protocol enjoys a reasonably broad substrate scope with terminal and internal styrene derivatives, enols, and limonenes (Scheme 19, eq 2). In addition, the first example of a photoredox-catalyzed aminotrifluoromethylation employing deactivated anilines or amide **88** as direct source of nitrogen atom was also reported in this work.[37] A variety of 1,1-disubstituted, 1,2-disubstituted, and 1,1,2-trisubstituted alkenes could be converted into aminotrifluoromethylation products **89** smoothly in 39−81% yield (Scheme 19, eq 3).

Scheme 19. Three-Component Aminotrifluoromethylation by Magnier, Masson et al.[37]



Atom Transfer Radical Multicomponent Carboalkylation Reactions. Unlike oxy-, hydro-, and aminoalkylation, examples of intermolecular carboalkylation reactions of alkenes via ATRA-type reactions are very scarce. The first case of photoredox-catalyzed carbotrifluoromethylation reaction of activated alkenes was developed by us.[27] Thus, treatment of various enecarbamates **54** with Togni's reagent **63** and potassium cyanide **90** as the *C*-nucleophile under visible-light irradiation allowed for the synthesis of cyano-*β*-trifluoromethyl carbamates **91** in good yields (Scheme 20, eq 1). Our group reported a novel visible light photocalyzed arylation with concomitant trifluoromethylation.[38] In this work, $Ru(bpy)_3(PF_6)_2$ was used as photocatalyst to generate the desired trifluoromethyl radical **39** from **42a**. Electron-rich aryl 1,3,5-trimethoxybenzene (TMB) was used as model reactant to perform the aryltrifluoromethylation, and the reaction proceeded smoothly against various styrene derivatives giving desired *gem*-diaryl products **94** with yields between 51 and 67% (Scheme 20, eq 2). Interestingly, the electron richness of the aryl reactant was found to have a strong effect on addition to the cation, and dimethoxybenzene or anisidine gave slightly

Scheme 20. Three-Component Carbotrifluoromethylation by Masson et al.[38]



lower yields (44−65%). In addition, electron-rich heteroaromatics such as indole, pyrrole, or benzofuran derivatives were found to be perfectly suitable for the reaction in a regioselective way.

■ CONCLUSION

Photoredox catalysis applied to the double functionalization of alkenes is a versatile and efficient process to facilitate the construction of various structural motifs with many potential applications. Due to their catalytic nature, these processes can generally be conducted under mild conditions and yield products with a high selectivity.

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Notes

The authors declare no competing financial interest.

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Géraldine Masson received her Ph.D. in 2003 from Joseph Fourier University under the supervision of Dr. Sandrine Py and Prof. Yannick Vallée. In the years 2003−2005 she was a Marie Curie postdoctoral research fellow with Prof. Jan van Maarseveen and Prof. Henk Hiemstra at the University of Amsterdam. In 2005, she joined the research group of Prof. Jieping Zhu at the Institut de Chimie des Substances Naturelles (ICSN) as a CNRS researcher before initiating her independent career in 2011. Her group's research activities are directed toward the development of new organocatalytic enantioselective reactions and novel synthetic methodologies and photoredox catalysis and its application in the synthesis of diverse natural and unnatural molecules displaying biologically activities.

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■ REFERENCES

(1) Recent reviews: Pintauer, T.; Matyjaszewski, K. *Chem. Soc. Rev.* **2008**, *37*, 1087.

(2) (a) Kharasch, M. S.; Jensen, E. V.; Urry, W. H. *Science* **1945**, *102*, 128. (b) Kharasch, M. S.; Jensen, E. V.; Urry, W. H. *J. Am. Chem. Soc.* **1945**, *67*, 1626.

(3) Recent reviews: (a) Xi, Y.; Yi, H.; Lei, A. *Org. Biomol. Chem.* **2013**, *11*, 2387. (b) Yoon, T. P. *ACS Catal.* **2013**, *3*, 895. (c) Prier, C. K.; Rankic, D. A.; MacMillan, D. W. C. *Chem. Rev.* **2013**, *113*, 5322. (d) Koike, T.; Akita, M. *Synlett* **2013**, *24*, 2492. (e) Schultz, D. M.; Yoon, T. P. *Science* **2014**, *343*, 1239176. (f) Hopkinson, M. N.; Sahoo, B.; Li, J.-L.; Glorius, F. *Chem. - Eur. J.* **2014**, *20*, 3874. (g) Meggers, E. *Chem. Commun.* **2015**, *51*, 3290. (h) Kärkäs, M. D.; Matsuura, B. S.; Stephenson, C. R. J. *Science* **2015**, *349*, 1285. (i) Cao, M.-Y.; Ren, X.; Lu, Z. *Tetrahedron Lett.* **2015**, *56*, 3732. (j) Ravelli, D.; Protti, S.; Fagnoni, M. *Chem. Rev.* **2016**, DOI: 10.1021/acs.chemrev.5b00662. (k) Skubi, K. L.; Blum, T. R.; Yoon, T. P. *Chem. Rev.* **2016**, DOI: 10.1021/acs.chemrev.6b00018.

(4) (a) Hedstrand, D. M.; Kruizinga, W. H.; Kellogg, R. M. *Tetrahedron Lett.* **1978**, *19*, 1255. (b) Pac, C.; Ihama, M.; Yasuda, M.; Miyauchi, Y.; Sakurai, H. *J. Am. Chem. Soc.* **1981**, *103*, 6495. (c) Pac, C.; Ishitani, O.; Sakurai, H. *J. Org. Chem.* **1984**, *49*, 26. (d) Goren, Z.; Willner, I. *J. Am. Chem. Soc.* **1983**, *105*, 7764. (e) Cano-Yelo, H.; Deronzier, A. *J. Chem. Soc., Perkin Trans. 2* **1984**, 1093. (f) Hironaka, K.; Fukuzumi, S.; Tanaka, T. *J. Chem. Soc., Perkin Trans. 2* **1984**, 1705.

(5) (a) Ischay, M. A.; Anzovino, M. E.; Du, J.; Yoon, T. P. *J. Am. Chem. Soc.* **2008**, *130*, 12886. (b) Nicewicz, D. A.; MacMillan, D. W. C. *Science* **2008**, *322*, 77. (c) Narayanam, J. M. R.; Tucker, J. W.; Stephenson, C. R. J. *J. Am. Chem. Soc.* **2009**, *131*, 8756.

(6) First applications of photoredox catalysis using Ruthenium photocatalyst: (a) Cano-Yelo, H.; Deronzier, A. *J. Chem. Soc., Faraday Trans. 1* **1984**, *80*, 3011. (b) Cano-Yelo, H.; Deronzier, A. *Tetrahedron Lett.* **1984**, *25*, 5517. (c) Cano-Yelo, H.; Deronzier, A. *New J. Chem.* **1987**, *11*, 479. (d) Cano-Yelo, H.; Deronzier, A. *J. Photochem.* **1987**, *37*, 315.

(7) Barton, D. H. R.; Csiba, M. A.; Jaszberenyi, J. C. *Tetrahedron Lett.* **1994**, *35*, 2869.

(8) (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.

(9) Fors, B. P.; Hawker, C. J. *Angew. Chem., Int. Ed.* **2012**, *51*, 8850.

(10) (a) Pirtsch, M.; Paria, S.; Matsuno, T.; Isobe, H.; Reiser, O. *Chem. - Eur. J.* **2012**, *18*, 7336. (b) Paria, S.; Pirtsch, M.; Kais, V.; Reiser, O. *Synthesis* **2013**, *45*, 2689. (c) Knorn, M.; Rawner, T.; Czerwieniec, R.; Reiser, O. *ACS Catal.* **2015**, *5*, 5186.

(11) Tucker, J. W.; Zhang, Y.; Jamison, T. F.; Stephenson, C. r. J. *Angew. Chem., Int. Ed.* **2012**, *51*, 4144.

(12) Arceo, E.; Montroni, E.; Melchiorre, P. *Angew. Chem., Int. Ed.* **2014**, *53*, 12064.

(13) Riente, P.; Pericàs, M. A. *ChemSusChem* **2015**, *8*, 1841.

(14) (a) Gakh, A. A.; Shermolovich, Y. *Curr. Top. Med. Chem.* **2014**, *14*, 952. (b) Sodeoka, M.; Egami, H. *Pure Appl. Chem.* **2014**, *86*, 1247. (c) Meyer, F. *Chem. Commun.* **2016**, *52*, 3077. (d) Kirsch, P. *Modern Fluoroorganic Chemistry: Synthesis, Reactivity, Applications*, 2nd completely revised and enlarged ed.; Wiley: New York, 2013.

(e) Furuya, T.; Kamlet, A. S.; Ritter, T. *Nature* **2011**, *473*, 470. (f) Tomashenko, O. A.; Grushin, V. V. *Chem. Rev.* **2011**, *111*, 4475. (g) Wu, X.-F.; Neumann, H.; Beller, M. *Chem. - Asian J.* **2012**, *7*, 1744. (h) Wang, J.; Sánchez-Roselló, M.; Aceña, J. L.; del Pozo, C.; Sorochinsky, A. E.; Fustero, S.; Soloshonok, V. A.; Liu, H. *Chem. Rev.* **2014**, *114*, 2432.

(15) (a) Koike, T.; Akita, M. *Top. Catal.* **2014**, *57*, 967. (b) Merino, E.; Nevado, C. *Chem. Soc. Rev.* **2014**, *43*, 6598. (c) Egami, H.; Sodeoka, M. *Angew. Chem., Int. Ed.* **2014**, *53*, 8294. (d) Alonso, C.; Martínez de Marigorta, E.; Rubiales, G.; Palacios, F. *Chem. Rev.* **2015**, *115*, 1847. (e) Barata-Vallejo, S.; Bonesi, S. M.; Postigo, A. *Org. Biomol. Chem.* **2015**, *13*, 11153. (f) Yang, X.; Wu, T.; Phipps, R. J.; Toste, F. D. *Chem. Rev.* **2015**, *115*, 826.

(16) Oh, S. H.; Malpani, Y. R.; Ha, N.; Jung, Y.-S.; Han, S. B. *Org. Lett.* **2014**, *16*, 1310.

(17) For the trifluoromethylation initiated by the reduction of CF_3SO_2Cl, see: Nagib, D. A.; MacMillan, D. W. C. *Nature* **2011**, *480*, 224.

(18) Carboni, C.; Dagousset, G.; Magnier, E.; Masson, G. *Synthesis* **2015**, *47*, 2439.

(19) Umemoto, T. *Chem. Rev.* **1996**, *96*, 1757 and references cited therein.

(20) Tang, X.-J.; Dolbier, W. R., Jr. *Angew. Chem., Int. Ed.* **2015**, *54*, 4246.

(21) Bagal, D. B.; Kachkovskyi, G.; Knorn, M.; Rawner, T.; Bhanage, B. M.; Reiser, O. *Angew. Chem., Int. Ed.* **2015**, *54*, 6999.

(22) Representative examples on radical and radical−ionic multicomponent reactions: (a) Godineau, E.; Landais, Y. *Chem. - Eur. J.* **2009**, *15*, 3044. (b) Ryu, I.; Sonoda, N.; Curran, D. P. *Chem. Rev.* **1996**, *96*, 177.

(23) Courant, T.; Masson, G. *Chem. - Eur. J.* **2012**, *18*, 423.

(24) Yasu, Y.; Koike, T.; Akita, M. *Angew. Chem., Int. Ed.* **2012**, *51*, 9567.

(25) Tomita, R.; Yasu, Y.; Koike, T.; Akita, M. *Angew. Chem., Int. Ed.* **2014**, *53*, 7144.

(26) Arai, Y.; Tomita, R.; Ando, G.; Koike, T.; Akita, M. *Chem. - Eur. J.* **2016**, *22*, 1262.

(27) Carboni, A.; Dagousset, G.; Magnier, E.; Masson, G. *Org. Lett.* **2014**, *16*, 1240.

(28) (a) Mita, T.; Kudo, Y.; Mizukoshi, T.; Hotta, H.; Maeda, K.; Takii, S. WO2004018410, 2004. (b) Mita, T.; Kudo, Y.; Mizukoshi, T.; Hotta, H.; Maeda, K.; Takii, S. JP2005272452, 2005. (c) Kawai, H.; Yuan, Z.; Kitayama, T.; Tokunaga, E.; Shibata, N. *Angew. Chem., Int. Ed.* **2013**, *52*, 5575.

(29) (a) Eisenberger, P.; Gischig, S.; Togni, A. *Chem. - Eur. J.* **2006**, *12*, 2579. (b) Kieltsch, I.; Eisenberger, P.; Togni, A. *Angew. Chem., Int. Ed.* **2007**, *46*, 754.

(30) Li, L.; Huang, M.; Liu, C.; Xiao, J.-C.; Chen, Q.-Y.; Guo, Y.; Zhao, Z.-G. *Org. Lett.* **2015**, *17*, 4714.

(31) Mizuta, S.; Verhoog, S.; Engle, K. M.; Khotavivattana, T.; O'Duill, M.; Wheelhouse, K.; Rassias, G.; Médebielle, M.; Gouverneur, V. *J. Am. Chem. Soc.* **2013**, *135*, 2505.

(32) (a) Lin, Q.-Y.; Xu, X.-H.; Qing, F.-L. *Org. Biomol. Chem.* **2015**, *13*, 8740. (b) Park, S.; Joo, J. M.; Cho, E. J. *Eur. J. Org. Chem.* **2015**, *2015*, 4093.

(33) Langlois, B. R.; Laurent, E.; Roidot, N. *Tetrahedron Lett.* **1991**, *32*, 7525.

(34) Wilger, D. J.; Gesmundo, N. J.; Nicewicz, D. A. *Chem. Sci.* **2013**, *4*, 3160.

(35) Lefebvre, Q.; Hoffmann, N.; Rueping, M. *Chem. Commun.* **2016**, *52*, 2493.

(36) Yasu, Y.; Koike, T.; Akita, M. *Org. Lett.* **2013**, *15*, 2136.

(37) Dagousset, G.; Carboni, A.; Magnier, E.; Masson, G. *Org. Lett.* **2014**, *16*, 4340.

(38) Carboni, A.; Dagousset, G.; Magnier, E.; Masson, G. *Chem. Commun.* **2014**, *50*, 14197.

DOI: 10.1021/acs.joc.6b01058
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