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## Organic &amp; Biomolecular Chemistry

## Review

## The past, present, and future of the Yang reaction†

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Photoexcited ketones have diradical characteristics and are functionally similar to high-spin metal-oxo species that are frequently used to catalyze C–H oxidation. First discovered by Yang in 1958, photoexcited ketones can abstract a hydrogen atom from hydrocarbons inter- or intramolecularly. Coupling with atom-transfer, group-transfer, or radical addition, the Yang reaction can be used to achieve various types of C–H functionalization. We provide in this article an overview of triplet ketone-mediated or catalyzed C–H functionalization reactions.

Norrish–Yang cyclization is a well-known photochemical process that generates cyclobutanols from  $\gamma$ -hydrogen-bearing ketones. This intramolecular C–H functionalization reaction works by UV-irradiation of ketone to generate a diradical species that abstracts a  $\gamma$ -hydrogen to create a reactive site for cyclization (Fig. 1A). In contrast to Norrish type II cleavage wherein the diradical intermediate fragments into enol and olefin, combination of the radicals provides a cyclobutane ring. Shortly after N. C. Yang started his career at the University of Chicago, he reported in 1958 the discovery of this cyclization reaction with his wife and scientific collaborator D.-D. H. Yang.<sup>1</sup> They showed that photoexcitation of ketone **1** in cyclohexane gave cyclobutanol **2** along with the Norrish type II cleavage products acetone (**3**) and 1-pentene (**4**) (Fig. 1B).

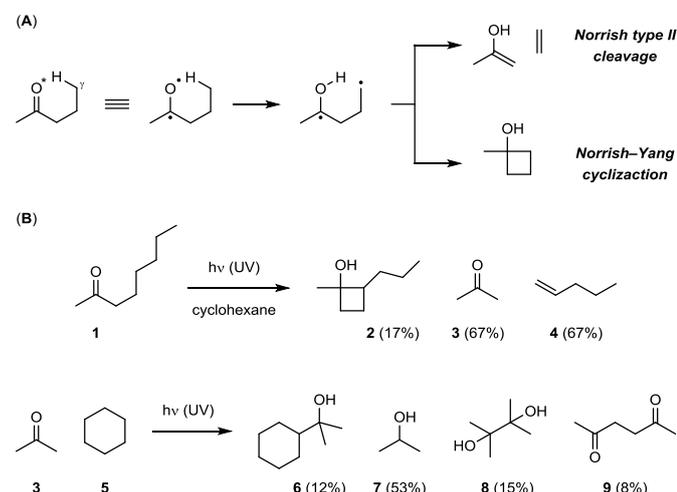


Fig. 1. (A) The general reactions of Norrish type II cleavage and Norrish–Yang cyclization. (B) The Norrish–Yang cyclization and Yang C–H functionalization reactions reported by D.-D. H. Yang and N. C. Yang in 1958.

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† Dedicated to Professor Tien-Yau Luh on the occasion of his 70th birthday

However, Norrish–Yang cyclization was an intramolecular variation of a more general reaction that the Yangs discovered. In the same report, they also described that UV-irradiation of a 1:8 mixture of acetone (**3**) and cyclohexane (**5**) afforded 2-cyclohexylpropan-2-ol (**6**), 2-propanol (**7**), pinacol (**8**), 2,5-hexadione (**9**), and a small amount of methane and carbon monoxide, the Norrish type I cleavage products of acetone. They further proposed that photoexcited acetone (**3\***) abstracted a hydrogen atom from **5** to give cyclohexyl radical and acetone ketyl radical. Combination of these two radical species then yielded **6**. It is somewhat surprising that the intermolecular Yang reaction was largely ignored despite the wide application of Norrish–Yang cyclization.

Photolytic C–H abstraction by ketones was generally regarded as photoreduction of triplet ketones.<sup>2</sup> Both C–H and S–H are effective hydrogen donors.<sup>3–6</sup> Through a series of careful kinetic studies, Walling concluded that triplet ketone has reactivity similar to that of *tert*-butoxy radical.<sup>4</sup> He also found that UV-irradiation of a mixture of **5** and benzophenone (**10**) in carbon tetrachloride gave nearly quantitative yields of cyclohexyl chloride (**11**), benzopinacol (**12**), and hexachloroethane (**13**) based on consumed **5** (Fig. 2).<sup>7</sup> Chlorination of 2,3-dimethylbutane (**14**) also proceeded with excellent regioselectivity to give chloride **15**. However, there had been no further development of triplet ketone-mediated C–H halogenation reactions until recently.

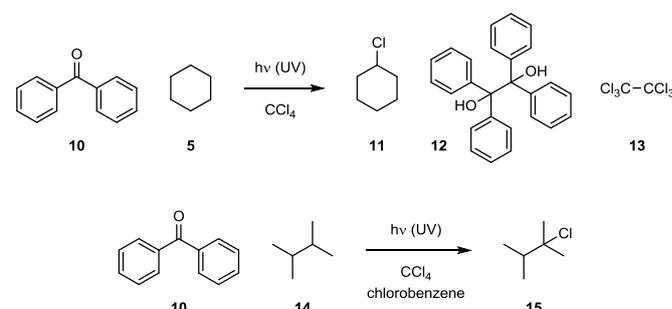


Fig. 2. Performing Yang reaction in carbon tetrachloride led to the formation of C–H chlorination products.

The power of the Yang reaction has been recognized by Breslow.<sup>8</sup> In a series of work on remote C–H oxidation,<sup>9</sup> he showed that fatty alcohols and steroids could be functionalized selectively at unactivated positions by a triplet benzophenone attached to a remote position of the molecule. For example, C–H abstraction of the C14-fatty alcohol derivative **16** occurred predominantly at the C12 position (Fig. 3).<sup>10</sup> Oxidation of the steroid derivative **20** was also remarkably selective giving **21** as the only product.<sup>11</sup> Here, combination of radicals generated from the initial C–H abstraction at the C14 position was prohibited due to the rigid structure of the intermediate. Consequently, hydrogen transfer from C15 to the ketyl radical occurred to yield an olefin.

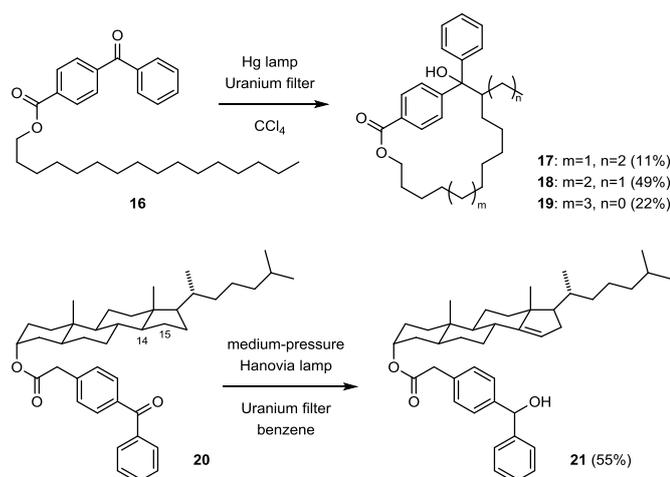


Fig. 3. Breslow's remote C–H oxidation reactions.

Ethereal C–H abstraction/radical addition is arguably the most explored Yang-type reaction. However, it was developed independent of Yang's work and rooted in Ciamician's discovery that exposure of benzophenone (**10**) in ethanol to sunlight (UV-visible light) gave benzopinacol (**12**).<sup>12</sup> Schenck reported in 1957 that UV-irradiation of a mixture of **10**, isopropanol (**22**), and maleic acid (**23**) gave tertiary alcohol **24** (Fig. 4), and offered a correct mechanistic interpretation for this coupling reaction.<sup>13</sup> Unfortunately, Schenck's work did not catch much attention either. Following the cue of Pedersen,<sup>14</sup> Elad studied ketone-initiated photoaddition of cyclic ethers to terminal olefins in 1964.<sup>15–17</sup> He found that photoexcited acetophenone (**25**) could abstract an ethereal C–H from tetrahydrofuran (**26**). The resulting radical could then add to dimethyl maleate (**27**) to give adduct **28** after back-hydrogen transfer. Similarly, exposure of a mixture of acetone (**3**), 1,3-dioxolane (**29**) and 1-decene (**30**) to sunlight yielded protected undecanal **31**.

It should be noted that ketones in these reactions were at times referred to as photosensitizers. However, as Elad noted, the term sensitizer should only be used when "a compound initiates a photochemical process through light absorption and does not undergo a chemical change itself."<sup>16</sup> In other words, sensitizers transfer triplet energy to the substrate without undergoing chemical transformations. Here, the photoexcited ketone should not be considered as a sensitizer because it

abstracts a hydrogen atom from the substrate and is often consumed quickly due to facile Ciamician coupling. As a result, a substoichiometric to excess amount of ketone is typically required for this radical addition reaction.

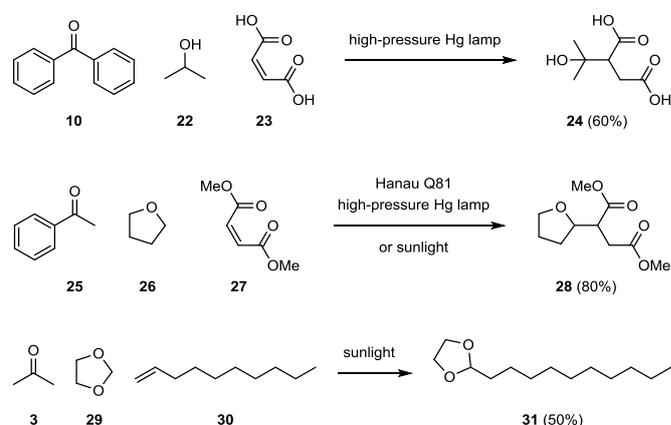


Fig. 4. Schenck and Elad's photochemical ethereal C–H functionalization/radical addition reactions.

Fraser-Reid demonstrated in 1972 that only a catalytic amount of benzophenone (**10**) was required to promote the coupling of alcohols and enones.<sup>18</sup> He later achieved the synthesis of pillarose with this C–H functionalization reaction.<sup>19</sup> UV-irradiation of enone **32** in the presence of 16 mol % of **10** and a large excess of ethylene glycol gave  $\delta$ -lactone **33** (Fig. 5). Subsequent C6-deoxygenation and C7-oxidation afforded ethyl pillarose (**34**). Fraser-Reid has also provided evidence that **10** served as a C–H abstraction catalyst instead of a triplet energy-transfer photosensitizer in these coupling reactions.<sup>20</sup>

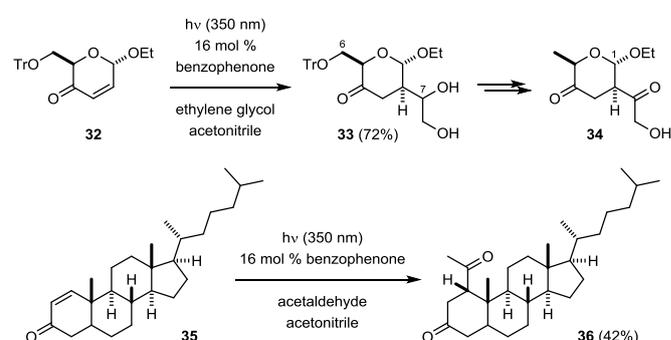


Fig. 5. Fraser-Reid's photochemical radical conjugate addition reactions.

Fraser-Reid further found that photoexcited benzophenone could catalyze conjugate addition of aldehydes to enones.<sup>21</sup> For example, irradiation of 1-cholesten-3-one (**35**) with 16 mol % of **10** and a large excess of acetaldehyde gave ketone **36**. However, this reaction is not mechanistically related to the Yang reaction because **10** worked as a photosensitizer to transfer its triplet energy to acetaldehyde. The triplet aldehyde then underwent Norrish type I cleavage to give a carbonyl radical that added to enone.<sup>22</sup> Over the past decades, the scope of photochemical C–H abstraction/radical addition has been expanded to include amines and alkanes as radical donors and alkynes as acceptors.<sup>23–27</sup> In addition, other than

the ester group, nitro, sulfone, amide, nitrile, and aldehyde groups can all be used as activating groups for the radical acceptors.<sup>28-32</sup>

Addition of radicals to substituted butenolides has also been shown to proceed with good diastereoselectivity.<sup>33-36</sup> For example, Mann reported in 1994 that irradiation of butenolide **37** with **10** in methanol gave  $\gamma$ -lactone **38** as the only diastereomeric product (Fig. 6).<sup>34</sup> Additionally, Hoffmann showed that 4,4'-dimethoxybenzophenone is an effective catalyst for the coupling of *N*-methylpyrrolidine (**39**) and butenolide **40**.<sup>35</sup> The  $\alpha$ -radical of **39** approached **40** from its less hindered face to yield **41** selectively.

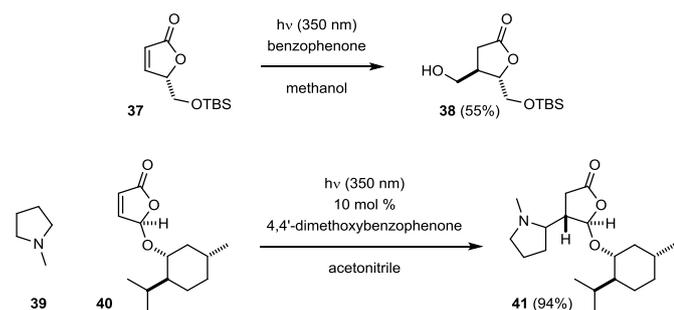


Fig. 6. Diastereoselective radical addition to butenolides.

Various tandem processes has also been developed to elaborate the conjugate addition products. For example, Guzmán showed in 1981 that the coupling of isopropanol (**22**) and dihydropyranone **42** gave  $\delta$ -lactone **43** that rearranged to  $\gamma$ -lactones **44** under the reaction conditions (Fig. 7).<sup>37</sup> Gómez also found that photolysis of enone **45** with **10** in isopropanol (**22**) provided bicyclic lactone **46** through C–H abstraction of **22**, conjugate addition to **45**, 6-exo-trig cyclization, and back-hydrogen transfer.<sup>38</sup>

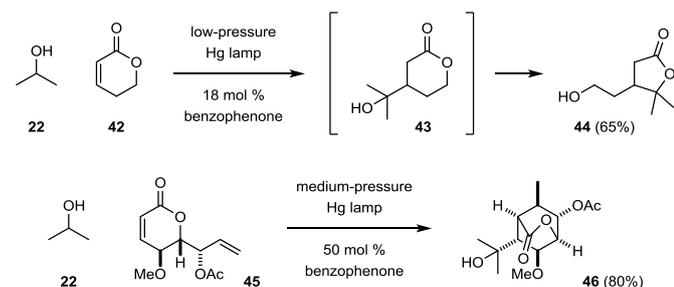


Fig. 7. Tandem reactions involving photochemical radical addition to dihydropyranone.

A significant advancement in this field of research is the development of photochemical group-transfer reactions by Inoue.<sup>39-42</sup> Inoue first showed in 2011 that C–H carbamoylation of tetrahydrofuran (**26**) could be achieved by irradiation of **26** with pentafluorophenyl isocyanate (**47**) in the presence of **10** (Fig. 8).<sup>39</sup> The use of an electron-deficient isocyanate is important to the efficient formation of amide **48**. He then showed that C–H cyanation of *N*-Boc-L-proline methyl ester (**49**) by tosyl cyanide (**50**) could be promoted by **10**\* to deliver *trans*-cyanoproline derivative **51** with excellent regio- and diastereoselectivity.<sup>41</sup>

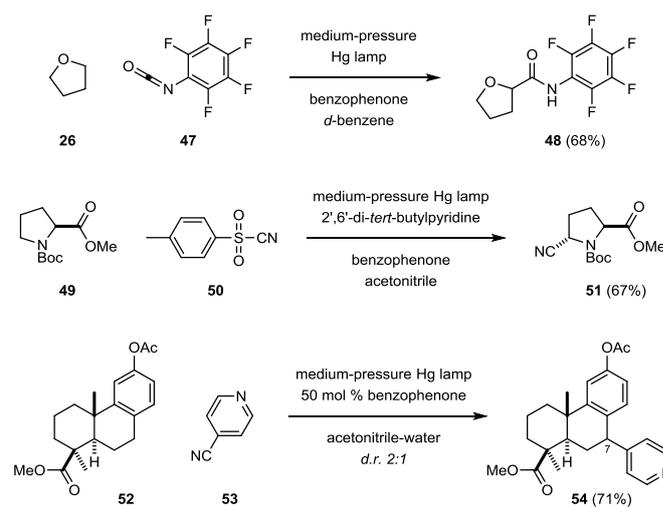


Fig. 8. Inoue's C–H carbamoylation, cyanation, and 4-pyridination reactions.

Inoue also demonstrated in 2013 that C–H pyridination of methyl *O*-acetyl podocarpate (**52**) could be realized by irradiation of **52** with 4-cyanopyridine (**53**) in the presence of **10**.<sup>42</sup> Unlike the Gif-type Minisci reaction,<sup>43</sup> the addition of the benzylic radical of **52** to **53** was highly regioselective. The 4-pyridination product **54** was obtained as a 2:1 mixture of C7-diastereomers without 2-pyridination.

Although Walling has shown that the Yang reaction could be intercepted with chlorination, the development of a Yang-type C–H halogenation reaction did not occur until 2012.<sup>44</sup> As a serendipity during the study of vanadium-catalyzed C–H fluorination, Chen found that irradiation of 4-ethylacetophenone (**55**) with light generated from a household compact fluorescent lamp (CFL) led to the formation of benzylic radical **56** that could be fluorinated to provide benzylic fluoride **57** (Fig. 9). This reaction proceeded through intermolecular hydrogen abstraction of **55** by **55**\* to give **56** and ketyl radical **58**. After Selectfluor (**59**) donated a fluorine atom to **56**, the resulting aminium radical cation **60** abstracted a hydrogen atom from **58** to turn over **55** and yield ammonium **61**.

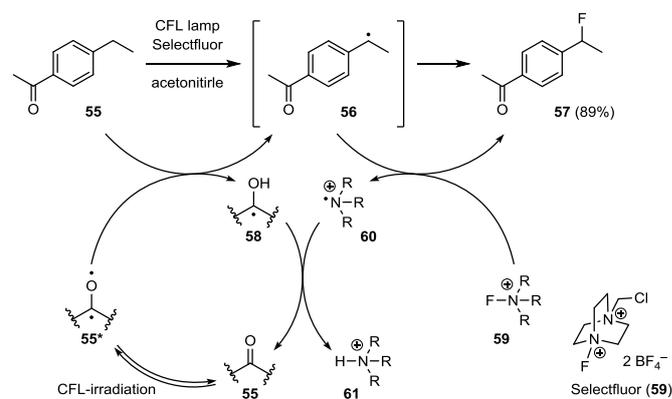


Fig. 9. Chen's discovery of a Yang-type C–H fluorination reaction.

Unlike most Yang reactions, fluorination of **55** by **59** was particularly efficient giving no Ciamician coupling product.

Chen hypothesized that dimerization of **58** did not occur because of a facile hydrogen transfer from **58** to the highly energetic aminium radical cation **60**, which quickly turned over to **55**. It was thus possible to use a low loading of exogenous ketone to catalyze C–H fluorination. Indeed, CFL-irradiation of ethylbenzene (**57**) in the presence of 5 mol % of acetophenone (**25**) yielded benzylic fluoride **58** (Fig. 10).<sup>45</sup> The efficiency of this reaction was further improved when using **10** or 9-fluorenone (**60**) as the catalyst as both **10** and **60** absorb visible light much more efficiently than **55**. C–H chlorination could also be achieved by replacing **59** with *N*-chlorosuccinimide (NCS) under otherwise the same reaction conditions.<sup>44</sup>

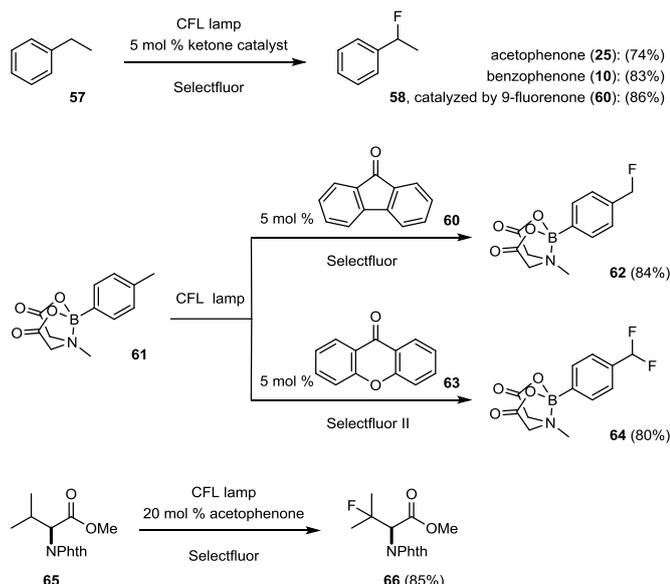


Fig. 10. Chen's tripte ketone-catalyzed C–H fluorination reactions.

Because the  $n/\pi^*$  energy gap can be tuned by changing the substituent groups of ketone, the reactivity and selectivity of triplet ketone can be modulated easily. In general, diarylketones are more effective benzylic C–H fluorination catalysts whereas monoarylketones are more reactive toward unactivated C–H. Selective formation of the mono- or difluorination products can also be achieved through catalyst-control. For example, 9-fluorenone (**60**) catalyzed benzylic C–H monofluorination of boronate **61** to give **62**; xanthone (**63**) catalyzed benzylic C–H difluorination to yield **64**. De Frutos and Kappe have further shown that the reaction efficiency could be significantly improved with flow chemistry and black-light irradiation.<sup>46</sup>

Intriguingly, acetophenone (**25**), with a larger  $n/\pi^*$  gap, is a colorless oil and has only a trace amount of absorption in the visible light region. However, CFL-irradiation can activate **25** to abstract unactivated C(sp<sup>3</sup>)–H groups effectively presumably through residual absorption of light between 380 and 400 nm.<sup>47</sup> Thus, C–H fluorination of *N*-phthaloyl-L-valine methyl ester **65** could be achieved under very mild conditions to give  $\beta$ -fluoro  $\alpha$ -amino ester **66** with excellent regioselectivity. Chen has also demonstrated that CFL-irradiation could drive other photoreactions of monoarylketones and enones that have no

apparent absorption above 380 nm.<sup>47</sup> For example, CFL-irradiation induced Norrish type II cleavage and Norrish–Yang cyclization of valerophenone (**67**) to give acetophenone (**25**), propene (**68**), and cyclobutanols **69** and **70** (Fig. 11). The coupling of cyclopentenone (**71**) and 2-propanol (**22**) also proceeded smoothly to give adduct **72** under CFL-irradiation. Residual absorption has also been used by Melchiorre to induce aldehyde-catalyzed atom-transfer radical addition of haloalkanes to olefins.<sup>48</sup>

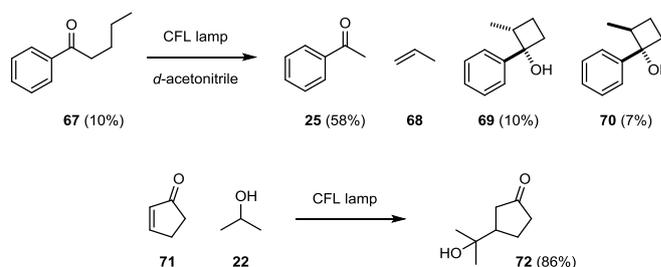


Fig. 11. Chen's demonstration of photoreactions driven by residual absorption.

Tan has reported the development of an interesting photochemical C–H fluorination in 2014.<sup>49</sup> Although the reaction conditions were similar to that reported by Chen, a different mechanism of C–H abstraction was involved. He showed that fluorination of Boc-protected 1-admantylamine (**73**) by **59** to give fluoride **74** could be achieved by CFL-irradiation of **73** in the presence of a catalytic amount of anthraquinone (**75**) (Fig. 12). This result is in sharp contrast to Chen's fluorination wherein no reaction occurred in the presence of an N–H group. The selectivity of triplet **75** was also quite different from that of triplet **60**. Kinetic and computational studies strongly support the hypothesis that photoexcited **75**<sup>\*</sup> transferred its triplet energy to **59** to generate **59**<sup>\*</sup> that donated its fluorine atom to **75**. The resulting aminium radical dication **76** abstracted a hydrogen atom from **73** to yield 3-admantyl radical that incorporated a fluorine atom from [**75**–F]<sup>\*</sup> to yield **74**.

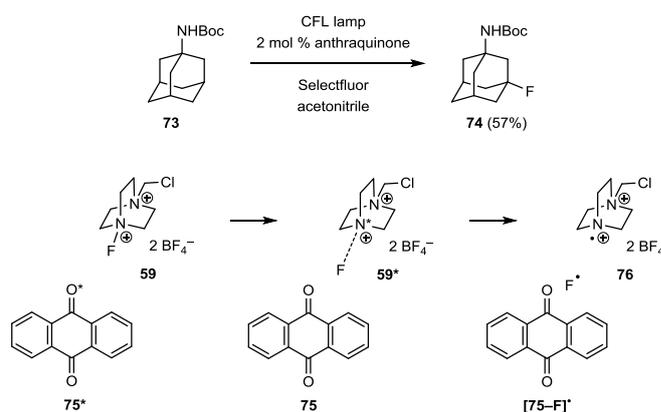


Fig. 12. Tan's photochemical C–H fluorination reaction.

Li has extended the utility of Yang reaction from functionalization of C(sp<sup>3</sup>)–H to C(sp<sup>2</sup>)–H in 2016.<sup>50</sup> He showed that the Yang C–H functionalization could be used to introduce

a trifluoromethyl group to caffeine (**77**) via radical adduct **78** to give the 8-substituted product **79** selectively (Fig. 13). This reaction started with single-electron oxidation of Langlois' reagent (**80**) by triplet acetone (**3\***) to generate trifluoromethanesulfinyl radical (**81**) and ketyl radical anion **82**. Subsequent decomposition of **81** yielded trifluoromethyl radical (**83**) and sulfur dioxide (**84**). Radical addition of **83** to **77** then provided **78**. Abstraction of the *ipso*-hydrogen of **78** by **82** afforded **79** and alkoxide **85**. Li also found that using diacetyl (**86**) as a co-solvent allowed for initiation of this photochemical process by visible light. Thus, trifluoromethylation of arene **87** could be achieved under very mild conditions to give **88**.

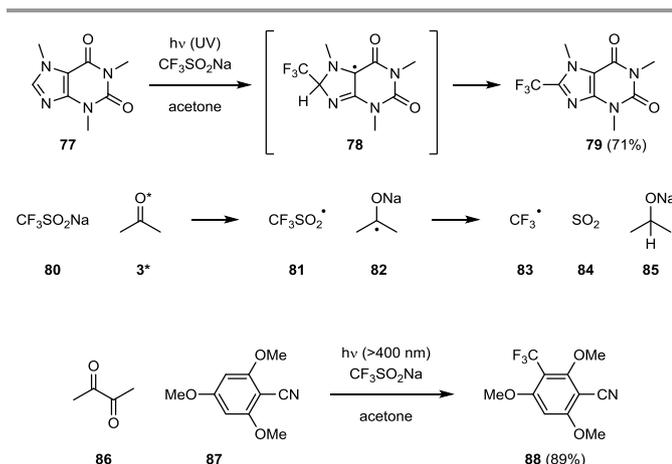


Fig. 13. Li's photochemical C-H trifluoromethylation reactions.

The past decade has witnessed rapid advancement in C-H functionalization and radical chemistry is an important branch in this research field.<sup>51-81</sup> Using photochemical methods to induce radical reactions has also regained popularity recently. The diradical characteristics of triplet carbon-oxo (carbonyl) make photoexcited ketones functionally equivalent to high-spin metal-oxo species,<sup>82-90</sup> the major C-H oxidation catalysts in nature. Similar to the ligands of metal-oxo complexes, the substituent groups of ketones can modulate the reactivity and selectivity of the catalyst. Since the discovery of the Yang C-H functionalization reaction more than fifty years ago, triplet ketones have been used to initiate a variety of atom-transfer, group-transfer, and radical addition reactions. The scope of Yang reaction has gone beyond enzymatic C-H functionalization; however, the selectivity and efficiency are still far from ideal. In particular, the regioselectivity of hydrogen abstraction largely depends on the stereoelectronic properties of the substrates, making it hard to achieve complete catalyst-controlled selectivity that overwrites the innate C-H reactivity. There is also no good strategy to establish a transit interaction between the catalyst and certain functional groups of the substrate to direct C-H abstraction. A list of ketones with different excitation wavelengths allowing for selective activation of the catalyst with narrow-band or laser excitation in the presence of multiple chromophores is also yet to be compiled. We hope that these challenges will inspire future endeavours that enable "precision chemical reactions".

## Acknowledgements

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