*Saarland University, Organic Chemistry, Building C4.2, 1st floor, room 1.01, GER-66123 Saarbruecken

Email: peter.huy@uni-saarland.de; Homepage: peterhuylab.de, ORCID: orcid.org/0000-0002-5099-5988

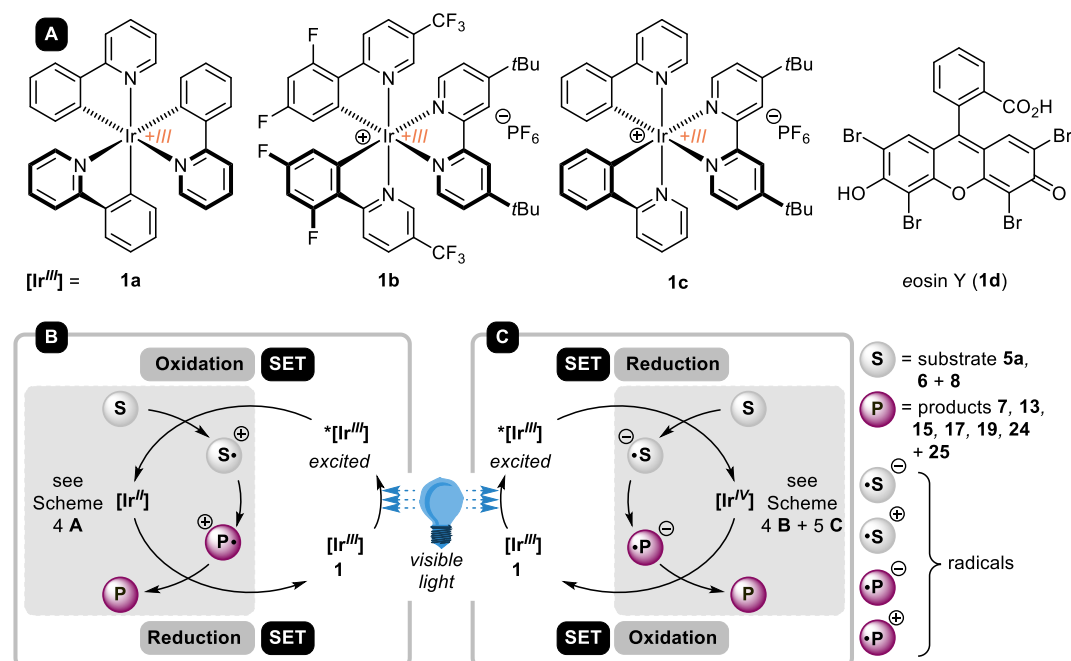# Light Promoted Radical Formation – Toolbox for the Construction of Complex Molecules

Abstract

Radicals can be generated at room temperature by means of visible light, when certain catalysts are engaged. Conventional protocols are mainly limited to the formation of radicals that are stabilized by adjacent electron withdrawing groups. Novel methods also enable the formation of non-stabilized radicals from naturally abundant alcohols and amines.

Radicals allow for reaction modes that are often contrary to charged intermediates with paired electrons. Conventionally, radical reactions require high reaction temperatures such as reflux in an organic solvent, radical initiators or irradiation with energy-rich ultraviolet light (wavelength λ < 380 nm). Due to the harsh reaction conditions many functional group are not compatible. Therefore, structurally complex target molecules are frequently not accessible by this means.

Photoredox catalysis with low-energy visible light enables radical transformations already at room temperature.[1] Suitable catalysts are iridium complexes of the oxidation state *+III* such as **1a-c** (= **[Ir^{III}]**), ruthenium complexes of the oxidation level *+II* and organic dyes like Eosin Y (**1d**) (Scheme 1 **A**). The energy difference of the highest occupied molecular orbital (HOMO) and the lowest unoccupied molecular orbital (LUMO) of these compounds is low. Electron transition between these frontier orbitals are facilitated by means of visible light (λ = 380-520 nm). Most organic molecules do not absorb light in the visible spectral range. Thus, the catalyst is excited selectively.

Scheme 1. A Examples for photoredox catalysts, **B** and **C** simplified mechanism of photoredox catalyzed reactions.

A

Whilst irradiation with blue light effects electron shifts in iridium complexes **1a-c**, excitation of Eosin Y (**1d**) affords green light. Subsequently, the excited photocatalyst (e.g. ***[Ir^{III}]**) facilitates the conversion of substrate molecules **S** to reactive radical intermediates through a single electron transfer (SET, Scheme 1 **B+C**).[2] In this step one electron is transferred either from the intermediate ***[Ir^{III}]** to the starting molecule **S** (Scheme 1 **B**) or vice versa (Scheme 1 **C**).
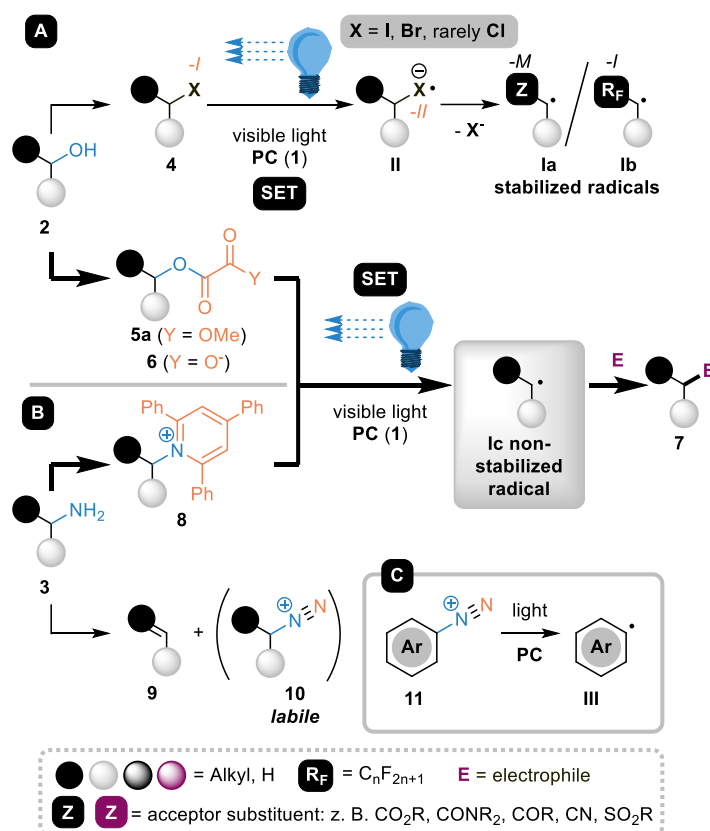
In the former case, the starting material is oxidized to the radical cation **•S$^+$**, while the activated iridium complex is reduced to **[Ir^{II}]**. In the latter instance, the substrate is reduced to the anionic radical **•S$^-$**, whereas the complex ***[Ir^{III}]** is simultaneously oxidized to species **[Ir^{IV}]**. Therefore, the photocatalyst in the activated state can serve as oxidant and reductant.

The resulting intermediates containing an unpaired electron react further to the radical species **•P$^+$** or **•P$^-$**, which are derived from the product **P.** Often these processes involve other reactants and consist of several steps. Subsequently, a final electron transfer from **[Ir^{II}]** to **•P$^+$** and **•P$^-$** to **[Ir^{IV}]**, respectively, allows to regenerate the photocatalyst **[Ir^{III}]** and gives rise of the product **P.**

Since the photocatalyst donates and acceptes one electron, these transformations are overall redoxneutral. In analogy to protons in *Brønsted* acid catalysis, electrons can be regarded as catalysts.[3]

Light Induced Radical Formation

Alcohols **2** and amines **3** are of high natural abundance. Therefore, the development of methods for the transformation of these functional groups into alkyl radicals of type **I** constitutes a highly attractive target (Scheme 2). Indeed, alkyl radicals **I** are formed upon visible light irradiation from alkyl halides of type **4** (Scheme 2 **A**). This conversion is initiated by means of a SET from the excited photocatalyst (e.g. ***[Ir^{III}]**) to the σ*-orbital of the C-X bond of **4**, which furnishes radical anion intermediate **II** (comparable to **•S$^-$**). Nevertheless, this reduction step is in general only possible, when alkyl

Scheme 2. Strategies for formation of alkyl radicals.

iodides and bromides are used that are carrying electron withdrawing groups **Z** like carbonyl, heteroaryl and perfluorinated alkyl portions. The electron poor substituents facilitate the reduction of **4** yielding **II**. Even in the excited state photocatalysts are not capable to reduce alkyl halides without electron-deficient functions. In addition, negative mesomeric (-*M*) and inductive (-*I*) effects are crucial for the stabilization of the radicals **Ia** and **Ib**, which emerge from the homolysis of the C-X bond of radical **II**.[4]

Nevertheless, non-stabilized radicals of type **Ic** are accessible via oxalic acid derivatives **5a** and **6**, which are deduced from alcohols **2**. Typically, type **Ic** radicals are subsequently quenched with electrophilic molecules. Reactions of aryl diazonium salts **11**, which are readily synthesized from aromatic amines, under photoredox catalysis delivers aryl radicals of type **III** (Scheme 2 **C**). However, analogous aliphatic diazonium salts **10** are labile and decompose to alkenes **9** (Scheme 2 **B**). As consequence, non-aromatic diazonium salts are no feasible precursors for radicals. In contrast, generation of

non-stabilized radicals **Ic** has been accomplished through visible light activation of pyridinium salts of type **8**, which are easily synthesized from amines **3**. Interestingly, intermediates **Ic** can also be accessed by means of light induced decarboxylation from carboxylic acids.[1,4]

Radicals Derived from Alcohols

The groups of *Overman* and *MacMillan* developed a method for the visible light promoted transformation of caesium and potassium oxalates **6** into alkyl radicals **Ic** based on iridium complex **Ib** (Scheme 3 **A**). Further reaction with electron-poor olefins **12** delivered products **13**. Thereby, the salts **6** are produced from alcohols **2** by reaction with oxalyl chloride (COCl)$_2$ or MeO(C=O)(C=O)Cl and subsequent saponification. Moreover, visible light facilitates the conversion of **6** with electron-poor dienes **14** to the *E*-configured alkenes **15** under kinetic control.[5c]

Iridium catalyst **1b** also enables radical substitutions with heteroarenes **16**.[5d] Recently, *Studer* and co-workers synthesized alkylboronates of type **19** utilizing biscatecholdiboronate **18** in conjunction with alkyl methyl oxalates **5a**.[6] Worthy of note, boronic acid esters such as **19** constitute essential starting materials for *Suzuki* cross

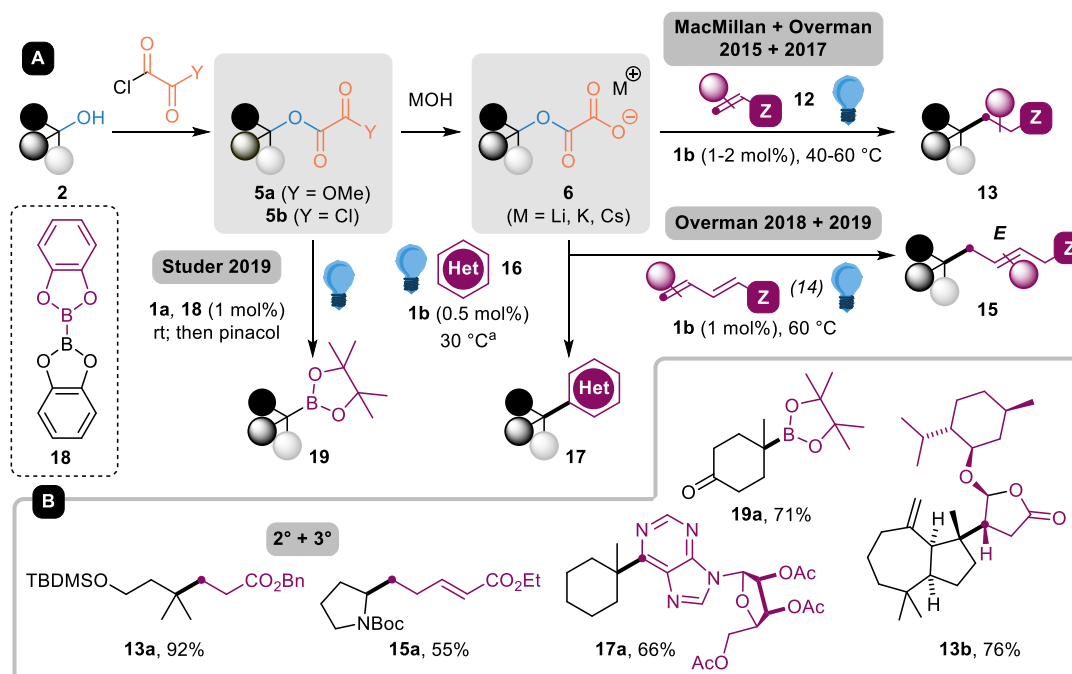couplings for the versatile construction of C-C-bonds. A related method has been established by the group of *Opatz*.[7] Therein, caesium oxalates **6** were coupled with aryl cyanides under decarboxylation. Phenanthen was applied as photocatalyst, excitation was achieved with ultraviolet or even sun light.

In particular tertiary (3°) alcohols **2** are feasible for the production of radicals (Scheme 3 **B**). Usage of secondary (2°) substrates diminishes yields (example **15a**). This outcome is due to a decrease of the stability of alkyl radicals in the order 3° > 2° > 1°. As highlighted in Scheme 3 **B**, levels of functional group compatibility are high. Even acid-labile Boc-carbamates and silyl ethers are tolerated (examples **13a** and **15a**).

Remarkably, visible light mediated radical additions allow for the synthesis of structurally complex natural products. Transformation of the lacton **13b** in four further steps yielded the terpenoid *Cheloviolen A*.[5b]
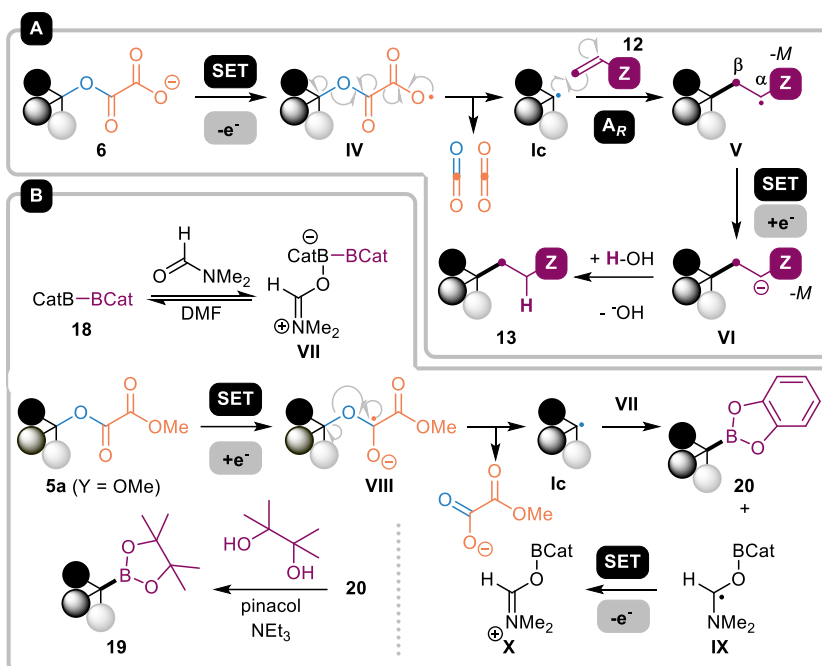
Oxidation or Reduction?

Conversions of substrate **6** (**S** in Scheme 1 **B**) are induced by an electron transfer onto the excited iridium complex *[Ir^{III}]* (Scheme 4 **B**).

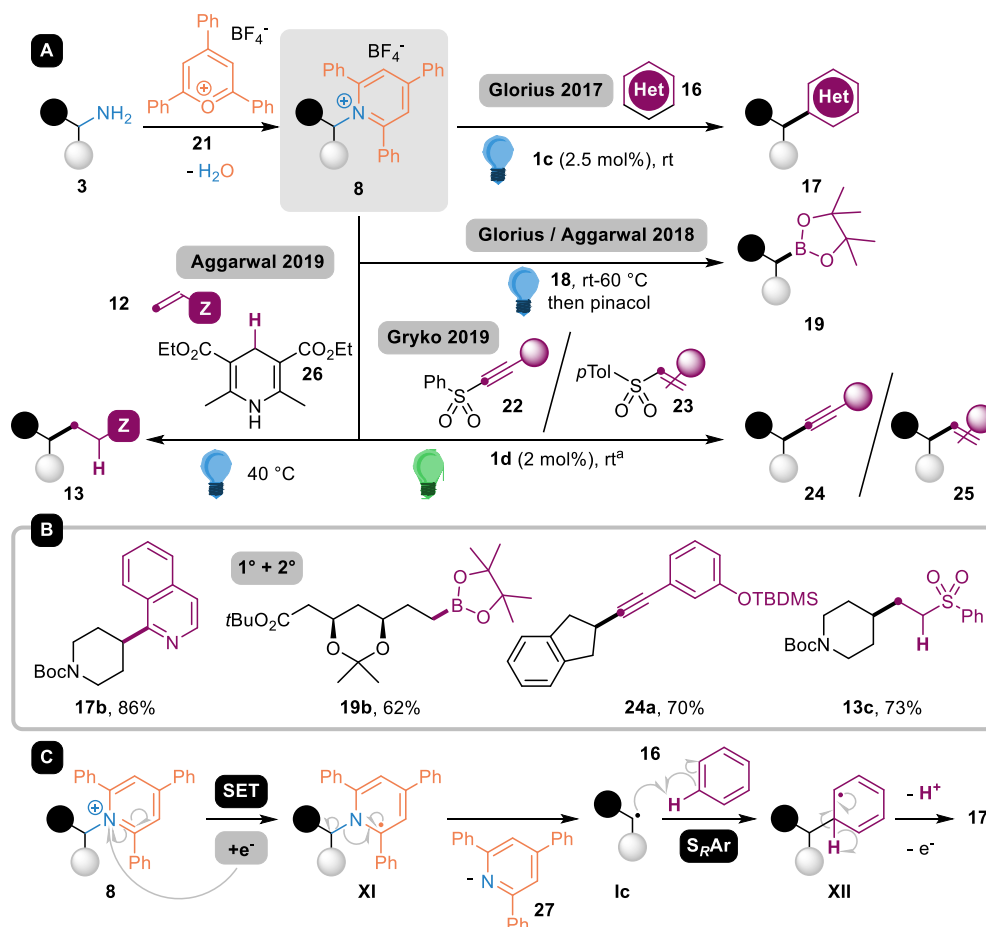**Scheme 3. A** Transformations of alcohols **2** via alkyl radicals and **B** representative products prepared. a. With (NH$_4$)$_2$S$_2$O$_8$. TBDMS = *tert*-butyldimethylsilyl, Boc = *tert*-butyloxycarbonyl, Ac = acetyl.

C

The resulting neutral, resonance stabilized O-centred radical **IV** (= **•S⁺**) undergoes homolytic cleavage, out of which C-centred radical **Ic** arises. **Ic** in turn surpasses radical addition (A$_R$) onto electron-deficient alkene **12**. The formed radical intermediate **V** is stabilized by conjugation with the acceptor substituent **Z**, which explains the regioselective addition to the β-position of **12**. Thereby, intermediate **V** corresponds to the product deduced radical **•P⁺** in Scheme 1 **B**. Reduction via a SET from the reduced photocatalyst **[Ir^{II}]** results in closed-shell anion **VI**, which is resonance stabilized by means of the substituent **Z**.

Scheme 4. Strategies for formation of alkyl radicals. Cat = catechol

Protonation through water, which is present in the reaction mixture, eventually leads to product **13**.

Scheme 5. A Transformations of amines proceeding through carbon-centred radicals, **B** selected products and **C** mechanism for the radical formation in the case of products of type **17**. a. With di-*iso*-propylethyl amine to reduce [Ir^{IV}]. *p*Tol = *para*-tolyl.

D

In contrary, fragmentation of alkyl methyl oxalate **5a** is commenced by a reductive SET from excited state photocatalyst *__[Ir^III^]__ (Scheme 4 **B**). Afterwards, homolysis of the C-O single bond between one carbonyl group and the alkyl residue affords non-stabilized radical **1c**. In fact, the solvent DMF reacts with diboronate **18** in an equilibrium to *Lewis* acid base complex **VII**. Next, radical **1c** abstracts a boryl moiety from **VII** under cleavage of the B-B bond. Then, oxidation of resulting radical **IX** through complex **[Ir^IV^]** yields DMF adduct **X** as by-product (and **[Ir^III^]**). In the end, transesterification of boronate **20** using pinacol delivers boronic acid ester **19**, which is less prone towards hydrolysis than **20**.

Radicals Deduced from Amines

The group of *Glorius* produced alkyl radicals in the presence of catalyst **1c** from *Katritzky´s* salts **8**[8] using blue light (Scheme 5 **A**).[9a] Pyridinium salts **8** on the other hand are accessible with ease through condensation of primary amines **3** with aromatic pyrilium heterocycles **21**. In addition, the groups of *Glorius*[9b] and *Aggerwal*[10a] simultaneously reported methods for the light promoted synthesis of boronic acid esters **19** without the need of a photocatalyst. Thereby, diboronate **18** initially forms a π-complex with pyridinium cation **8**. Visible light irradiation facilitates an SET from one electron rich catechol residue of **18** to the electron deficient pyridinium heterocycle **8**.

The working group of *Gryko* presented a protocol for the production of type **24** and **25** alkynes and alkenes, respectively.[11] Noteworthy, metal-free Eosin Y (**1d**) has been harnessed as photocatalyst. Without the necessity of a catalyst, *Aggarwal* and co-workers described a procedure for the addition of alkyl radicals to *Michael*-acceptors **12**.[10b] The 1,4-dihydropyridine **26** induces this radical reaction via SET onto heteroarene **8** and provides an H-atom for the formation of product **13**. Related protocols for the synthesis of alkenes have been disclosed by *Glorius*,[9c] *Wang* and *Uchiyama*.[12]

The substrate scope of the mentioned approaches comprises primary and secondary amines (Scheme 5 **B**). Due to steric constraints, triphenyl-pyridinium salts with tertiary *N*-alkyl groups are not accessible. Hence, the methods for amine to radical transformations are complementary to the previously discussed procedures engaging alcohols (*vide supra*). Again, high levels of functional group tolerance can be attested.

In terms of mechanism, the synthesis of heteroarenes **17** is launched via a reductive single electron transfer from the photocatalyst *__[Ir^III^]__ to electron-poor pyridinium cation **8** (Scheme 5 **C**).[9a] In the following, homolytic cleavage of the C-N single bond in **XI** results in formation of non-stabilized alkyl radical **1c** and triphenylpyridine **27**. Subsequently, addition of **1c** to heteroarene **16** provides π-radical **XII**. Deprotonation by means of pyridine **27** and SET to metal complex **[Ir^IV^]** eventually completes the radical aromatic substitution (S_RAr), out of which alkylated arene **17** arises.

Recent further developments even enable the formation of tertiary alkyl fluorides, which are elsewise difficult to access, from alcohols via non-stabilized radicals of type **Ic**.[13]

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Peter Huy, born 1980, is leading a young researcher´s group as a *Liebig* fellow at the Saarland University since 2014. He performed his PhD thesis in organic chemistry in the group of Prof. Hans-Guenther Schmalz at the University of Cologne. Subsequently, he joined the group of Prof. Ari Koskinen at the Aalto University in Helsinki and the group of Prof. Ben List at the Max-Planck Institute for Carbon Research in Muehlheim at Ruhr as a postdoctoral researcher. His research interests are committed towards homogenous catalysis and natural product synthesis.