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Review

Toolbox Review | *Very Important Paper* | SPECIAL ISSUE

A Retrosynthetic Approach for Photocatalysis

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Abstract: Visible-light-mediated chemical reactions have become very popular within the last 15 years. Many excellent reviews have summarized reaction principles and recent results in photochemistry and photocatalysis. However, despite their popularity photochemistry and photoredox catalysis are not regular parts of the bachelor and master curriculum of chemistry education. As a consequence, most chemists will use in synthesis planning classic retrosynthetic disconnections and only rarely consider photocatalytic steps. The aim of this article is to be a useful tool for synthetic chemists, that are interested in the synthetic aspects of photocatalysis and looking for a specific retrosynthetic disconnection. Not only are informative schemes provided but also are the availability of the catalysts and reagents as well as the functional group tolerance of the respective method briefly discussed.

Introduction

Visible-light-mediated chemical reactions have become very popular within the last 15 years. Photons, which were already predicted to play a vital part in the future of chemistry at the beginning of the 20th century, were rediscovered as traceless reagents in organic synthesis.[1] Technical progress made selective and intensive light sources available, photo-flow reactors allow the upscaling of the reaction and a broad range of newly developed photocatalysts enables a manifold of formerly unknown chemical transformations or improving classic reactions adapting photocatalytic conditions.[2] Photocatalysis is not anymore a merely academic field of research, finding its way increasingly into applications in the chemical and pharmaceutical industry.[3]

Many excellent reviews have summarized reaction principles and recent results in photochemistry and photocatalysis.[4] However, despite their popularity photochemistry and photoredox catalysis are not regular parts of the bachelor and master curriculum of chemistry education. As a consequence, most chemists will use in synthesis planning classic retrosynthetic disconnections and only rarely consider photocatalytic steps.[5]

The goal of this project is to provide chemists with a chemical review tool in form of a digital, extendable and updatable collection summarizing photochemical and photocatalytic transformations from a retrosynthetic perspective.

The reader is able to search for the desired bond-disconnection in the interlinked article, which will provide selected examples of reported photocatalytic methods. Omitting the discussion of principles or individual reaction mechanisms the retrosynthetic disconnections for different types of bonds are given as a condensed excerpt of the published literature (Table 1). We

Table 1. Overview of photocatalytically accessible, retrosynthetic C–C and C-X bond disconnections.

	C-sp^3	**C-sp^2**	**C-sp**	**F**	**Cl**	**Br**	**I**	**B**	**N**	**O**	**P**	**S**
C-sp^3	sp^3-sp^3	sp^3-sp^2	*n.c.*	C-F	C-Cl	C-Br	C-I	C-B	C-N	C-O	C-P	C-S
C-sp^2	sp^3-sp^2	sp^2-sp^2	sp^2-sp									
C-sp	*n.c.*	sp^2-sp	*n.c.*									

[a] n.c.: not covered.

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Table 2. Retrosynthetic overview of the compound classes covered in this review.

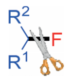
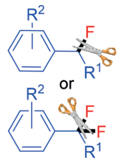
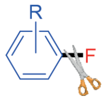
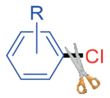
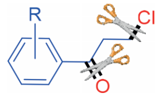
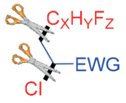
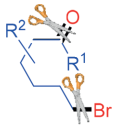
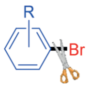
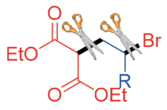
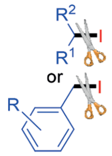
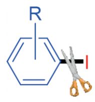
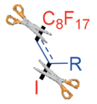
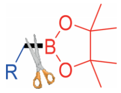
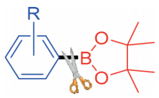
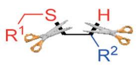
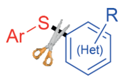
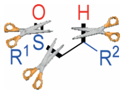
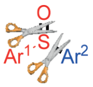
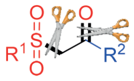
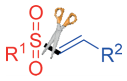
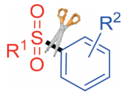
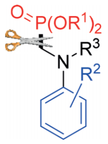
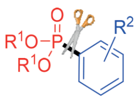
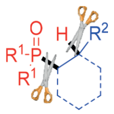
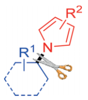
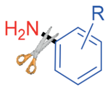
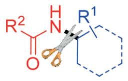
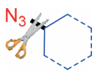
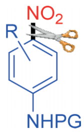
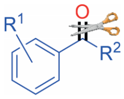
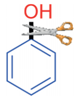
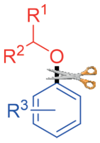
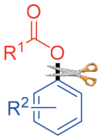
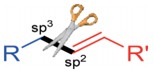
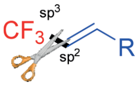
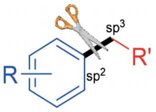
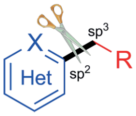
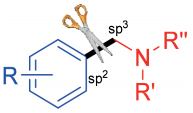
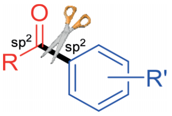
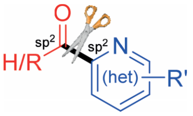
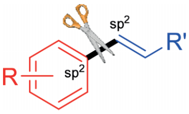
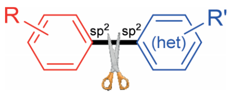
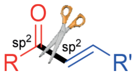
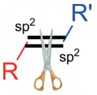
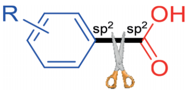
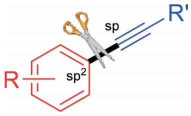
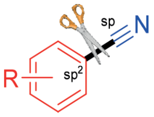
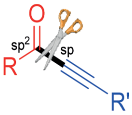
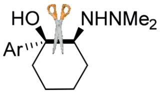
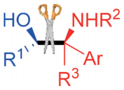
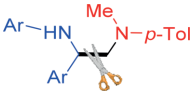
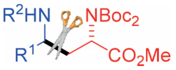
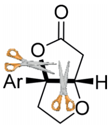
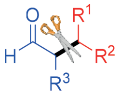
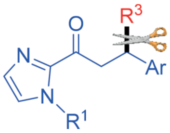
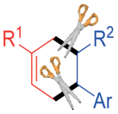
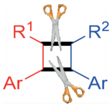
C-F	 **alkyl fluorides**	 **benzyl mono- / difluorides**	 **aryl fluorides**	
C-Cl	 **alkyl chlorides**	 **aryl chlorides**	 **β-chloro ketones**	 **ATRA products**
C-Br	 **alkyl bromides**	 **bromo ketones (remote)**	 **aryl bromides**	 **ATRA products**
C-I	 **alkyl- / benzyl iodides**	 **aryl Iodides**	 **ATRA products**	
C-B	 **alkyl boronates**	 **aryl boronates**		
C-S	 **alkyl thioethers**	 **aryl thioethers**	 **alkyl sulfoxides**	 **aryl sulfoxides**
	 **alkyl sulfones**	 **vinyl sulfones**	 **aryl sulfones**	
C-P	 **alkyl phosphonates**	 **aryl phosphonates**	 **alkyl phosphine oxides**	 **aryl phosphine oxides**
C-N	 **aliphatic amines / amides**	 **aryl amines**	 **amides**	 **aliphatic azides**
	 **nitroarenes**			

Table 2. (*Continued.*)

C-O	 **(benzylic)ketones**	 **phenol**	 **ethers**	 **anhydrides**
	 **esters**			
C-C sp^2-sp^3	 **alkyl ketones**	 **substituted alkenes**	 **trifluoromethyl alkenes**	 **substituted arenes**
	 **substituted heteroarenes**	 **α-aminoalkyl substituted arenes**	 **aliphatic carboxylic acids**	
C-C sp^2-sp^2	 **aryl ketones/aldehydes**	 ***N*-heteroaryl ketones/aldehydes**	 **arylated alkenes**	 **bi(hetero)aryls**
	 **alkenyl carbonyls**	 **alkenes**	 **aromatic carboxylic acids**	 **α,β-unsaturated carboxylic acids**
C-C sp^2-sp	 **arylated alkynes**	 **cyanoarenes**	 **ynones**	
C-C sp^3-sp^3	 **cyclic α-amino alcohols**	 **linear α-amino alcohols**	 **1,2-diamines**	 **1,3-diamines**
	 **γ-lactones**	 **α-alkylated carbonyls**	 **β-alkylated carbonyls**	 **cyclohexenes**
	 **cyclobutanes**			

present all reactions in the same style and include the target structure, the corresponding retrosynthetic synthon, and the required starting materials as published in the reference. To illustrate the scope of the method the functional group tolerance and a few selected examples with yields are given. Additionally, the reaction conditions, additives, photocatalyst and light source are provided to summarize the required equipment and chemicals. Finally, we briefly discuss the transformation and highlight e.g. commercial availability of important reagents or catalysts. If multiple procedures for a similar disconnection exist, they are given with notes about the differences to the method highlighted in the scheme.

It is not possible to cover comprehensively all disconnections in this tool and not every reference can be provided for a given transformation. Instead, we wish to demonstrate the diverse photocatalytic strategies for a certain bond formation. Typically, more than one method exists for a single problem, which ensures a broad synthetic scope and good reproducibility. We apologize to researchers that do not find their reported reaction in this document, but a selection was unavoidable. Updates of the collection may include further references. It is noteworthy that C–H bond-forming reactions (formal defunctionalizations) are not covered since the retrosynthetic utility of this transformation is very limited. However, this section might be added in a later version of the review. C-sp-C-sp/C-sp^3 disconnections are not covered as well due to the limited number of examples available.

At the core of this survey are the following disconnection tables: Table 1 and Table 2. Intuitive clicking on the bond that should be formed will lead to a corresponding set of schemes and references that describe suitable photocatalytic transformations. The references are directly linked to the publisher's homepage to assure fast access to the original and full information.

In conclusion, during the compilation of this review, we realized that photochemistry and photocatalysis offer already a rich variety of solutions for common retrosynthetic disconnection problems. Moreover, many new, synthetic transformations that were not known or elusive by traditional thermal/polar reactivity are now covered by this new area of organic chemistry. But despite its versatility, some disconnections remain to be developed. We hope that this survey will be applied as a regular work tool for organic chemists, but also help to identify potential "white spots" on the map of photocatalysis and fuel future discoveries.

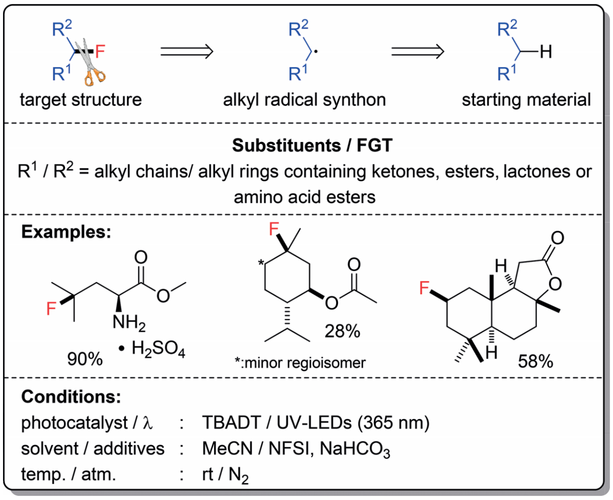
1. C–F Bond

Fluorinated organic molecules play an important role in bioactive compounds e.g. pharmaceuticals and pesticides.[6] Currently, more than 25 % of all pharmaceutical drug candidates contain at least a single fluorine atom due to its effect on drug metabolism and protein stabilization.[6a] Further applications of fluorine-containing molecules include medicinal diagnostics with ^{18}F labeled PET tracers and polyfluorination of organic compounds.[7] Many methods for the introduction of fluorine atoms into small molecules on both lab and industrial scale have been developed, relying mainly on the use of extremely reactive elemental F_2, toxic HF or unreactive fluoride salts.[7] There is still a demand for new, selective and mild procedures particular for late-stage modifications of bioactive compounds.[8] In this respect, photocatalysis provides retrosynthetic synthons to the toolbox of the organic chemist by supplying both new methods for direct C–H fluorinations and for directed decarboxylative fluorinations.

1.1 Generation of Aliphatic C–F Bonds

Strategy 1

The selective fluorination of aliphatic C–H bonds is still a grand challenge of organic chemistry. One photocatalytic solution was provided by the group of Britton who developed a strategy for the fluorination of simple molecules (Scheme 1).[9] The reaction required irradiation with 365 nm LEDs for 16 h in the presence of commercially available photocatalyst, tetrabutylammonium decatungstate (TBADT), and the fluorination reagent *N*-fluorobenzenesulfonimide (NFSI). Although the isolated yields were generally moderate (40–60 %) and the functional group tolerance was rather low, since mostly only ketones, esters, lactones, and protonated amino acid esters worked, this method was adopted by Merck & Co for the remote fluorination of leucine methyl ester which was a precursor for the (now ceased) Anticancer agent odanacatib.[10] After transfer of the reaction into flow and another optimization cycle, the yield could be increased to 90 % in a 45 g scale reaction which illustrated the utility of this method for the selective fluorination of tertiary C–H bonds.



Substituents / FGT

R^1 / R^2 = alkyl chains/ alkyl rings containing ketones, esters, lactones or amino acid esters

Conditions:

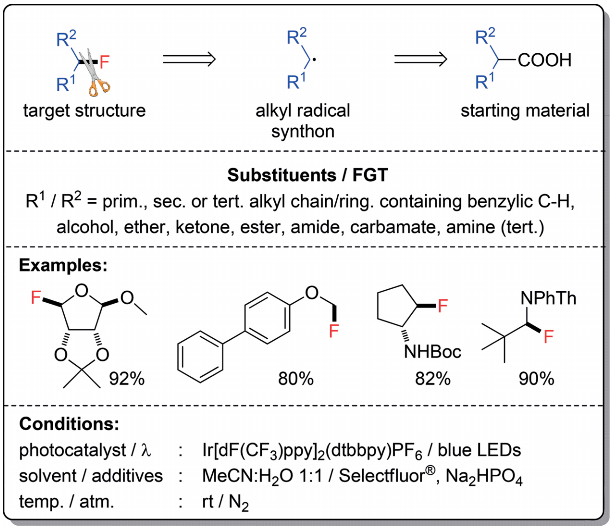
photocatalyst / λ : TBADT / UV-LEDs (365 nm)
solvent / additives : MeCN / NFSI, $NaHCO_3$
temp. / atm. : rt / N_2

Scheme 1. Alkyl-halide disconnection for the direct fluorination of secondary and tertiary aliphatic C–H bonds.[9]

Alternative strategies for this disconnection employed either tetracyanobenzene[11] or anthraquinone[12] as photosensitizers and provided a similar substrate scope. Further alternative methods used ketones as directing groups recommending these strategies particularly for the fluorination of steroids.[13] Hamashima and co-workers demonstrated that also phthalimides could act as directing groups for selective fluorinations.[14] Finally, even a uranium catalyzed method was described by Sorensen and co-workers.[15]

Strategy 2

Carboxylic acids are among the most abundant functional groups in both natural products and fine chemicals. Therefore, the MacMillan group developed a viable, photoredox-catalytic strategy for the decarboxylative fluorination of aliphatic carboxylic acids (Scheme 2).[16] The method employed commercially available Ir[dF(CF_3)ppy]$_2$(dtbbpy)PF_6 as the photocatalyst, Selectfluor® as the fluorine source and Na_2HPO_4 as the base. The reaction mixture was irradiated with blue LEDs for 1 h to 15 h leading to the fluorinated products in generally very good yields (70–90 %). The functional group tolerance includes alcohols, ethers, ketones, esters, and protected amines.



Substituents / FGT

R^1 / R^2 = prim., sec. or tert. alkyl chain/ring. containing benzylic C-H, alcohol, ether, ketone, ester, amide, carbamate, amine (tert.)

Conditions:

photocatalyst / λ : Ir[dF(CF_3)ppy]$_2$(dtbbpy)PF_6 / blue LEDs
solvent / additives : MeCN:H_2O 1:1 / Selectfluor®, Na_2HPO_4
temp. / atm. : rt / N_2

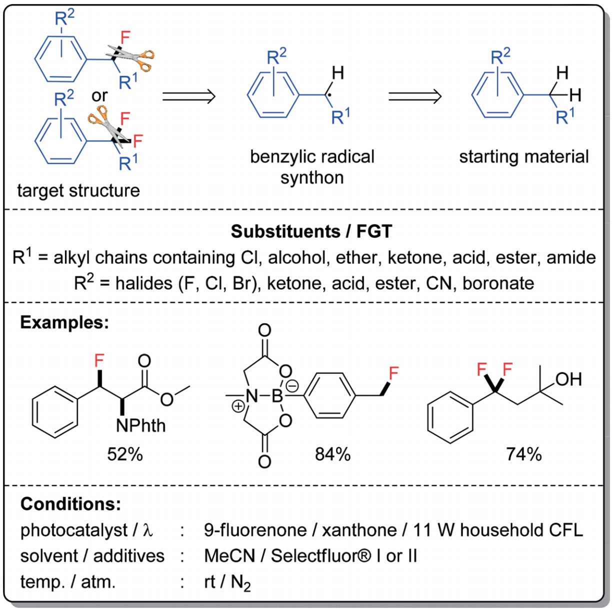
Scheme 2. Alkyl-halide disconnection for the decarboxylative fluorination of aliphatic carboxylic acids.[16]

Many alternative decarboxylative fluorination procedures were published complementing the substrate scope of MacMillan's method e.g. by Paquin and co-workers who used α-oxo carboxylic acids as starting materials and the cheaper Ru(bpy)$_3$Cl$_2$ as photosensitizer or by Ye and co-workers who used an organic dye instead of transition metals.[17] Hammond published an alternative method with a smaller scope using a heterogeneous photosensitizer.[18] A new strategy for the decarboxylative fluorination of heteroarenes was realized by Tang and co-workers.[19] However, the method is limited to electron-rich heteroarenes and suffers from dimerization of the heteroaryl radical intermediate lowering the overall yield. Jamison and co-workers developed a visible-light-mediated strategy using SF_6 for aliphatic fluorination starting from allylic alcohols rather than carboxylic acids.[20] Finally, MacMillan and co-workers published another strategy for this transformation starting from alcohols rather than carboxylic acids.[21]

1.2 Generation of Benzylic C–F Bonds

Fluorinated organic molecules play an important role in bioactive compounds e.g. pharmaceuticals and pesticides.[6] Currently, more than 25 % of all pharmaceutical drug candidates contain at least a single fluorine atom due to its effect on drug metabolism and protein stabilization.[6a] Further applications of fluorine-containing molecules include medicinal diagnostics with ^{18}F labeled PET tracers and polyfluorination of organic compounds.[7] Many methods for the introduction of fluorine atoms into small molecules on both lab and industrial scale have been developed, relying mainly on the use of extremely reactive elemental F_2, toxic HF or unreactive fluoride salts.[7] There is still a demand for new, selective and mild procedures particular for late-stage modifications of bioactive compounds.[8] In this respect, photocatalysis provides retrosynthetic synthons to the toolbox of the organic chemist by supplying both new methods for direct C–H fluorinations and for directed decarboxylative fluorinations.

Since the benzylic position is typically easily metabolized in biomolecules, Chen and co-workers developed a specific method for the mono or double fluorination of benzylic C–H bonds depending on the catalyst and fluorination reagent used (Scheme 3).[22] Both catalysts, 9-fluorenone and xanthone are cheap and commercially available, as are the fluorination reagents Selectfluor® I and II. The reaction mixture was irradiated for 6 h to 96 h with an 11 W fluorescent light bulb. The yields ranged typically from 60 % to 80 % and the functional group tolerance of the method comprises aromatic halides (F, Cl, Br), ketones, esters, aromatic carboxylic acids, and protected amino groups.



Substituents / FGT

R^1 = alkyl chains containing Cl, alcohol, ether, ketone, acid, ester, amide
R^2 = halides (F, Cl, Br), ketone, acid, ester, CN, boronate

Conditions:

photocatalyst / λ : 9-fluorenone / xanthone / 11 W household CFL
solvent / additives : MeCN / Selectfluor® I or II
temp. / atm. : rt / N_2

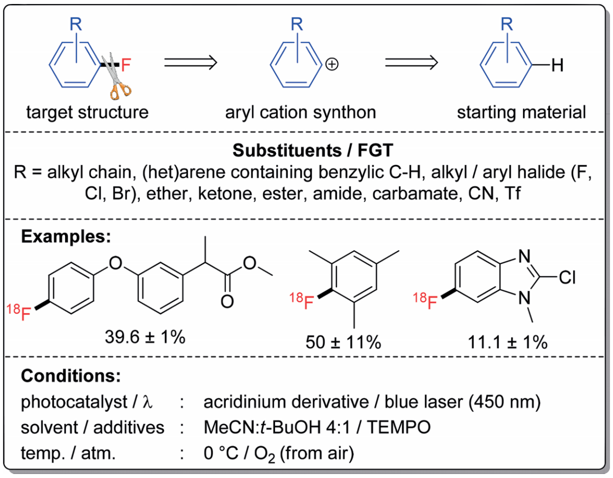
Scheme 3. Alkyl-halide disconnection for the direct mono or double fluorination of benzylic C–H bonds.[22]

Alternative strategies for the monofluorination of benzylic C–H bonds were reported by Lectka and co-workers who employed tetracyanobenzene as photocatalyst and by Wu and co-workers who used Fukuzumi's catalyst.[23]

1.3 Generation of Aromatic C–F Bonds

Fluorinated organic molecules play an important role in bioactive compounds e.g. pharmaceuticals and pesticides.[6] Currently, more than 25 % of all pharmaceutical drug candidates contain at least a single fluorine atom due to its effect on drug metabolism and protein stabilization.[6a] Further applications of fluorine-containing molecules include medicinal diagnostics with ^{18}F labeled PET tracers and polyfluorination of organic compounds.[7] Many methods for the introduction of fluorine atoms into small molecules on both lab and industrial scale have been developed, relying mainly on the use of extremely reactive elemental F_2, toxic HF or unreactive fluoride salts.[7] There is still a demand for new, selective and mild procedures particular for late-stage modifications of bioactive compounds.[8] In this respect, photocatalysis provides retrosynthetic synthons to the toolbox of the organic chemist by supplying both new methods for direct C–H fluorinations and for directed decarboxylative fluorinations.

Recently, groups of Li and Nicewicz reported the first photocatalytic, direct fluorination of aromatic C–H bonds using radioactive ^{18}F (Scheme 4).[24] The method employs 9-mesityl-3,6-di-*tert*-butyl-10-phenylacridinium perchlorate as the photocatalyst, tetrabutylammonium-^{18}F as fluoride source as well as TEMPO and air as oxidants. The reaction mixture was irradiated with a blue laser (450 nm) for 30 to 60 min. The radiochemical yields (RCYs) were generally low ranging from 5–50 % but many functional groups including alkyl chains, (hetero)arenes, halides (F, Cl, Br) ethers, ketones, esters, amides, carbamates, nitriles, and triflates were tolerated.



Substituents / FGT
R = alkyl chain, (het)arene containing benzylic C-H, alkyl / aryl halide (F, Cl, Br), ether, ketone, ester, amide, carbamate, CN, Tf

Conditions:
photocatalyst / λ : acridinium derivative / blue laser (450 nm)
solvent / additives : MeCN:*t*-BuOH 4:1 / TEMPO
temp. / atm. : 0 °C / O_2 (from air)

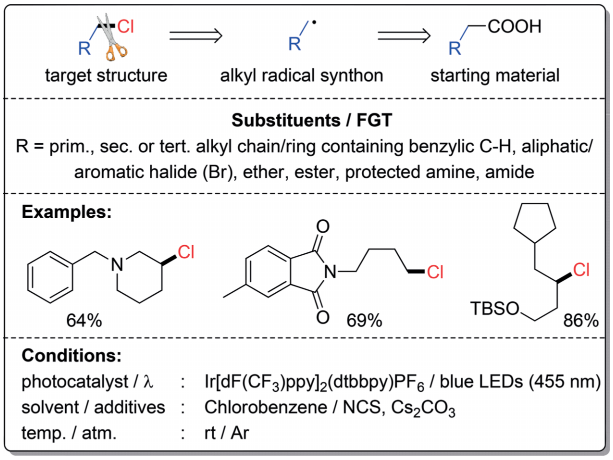
Scheme 4. Aryl-halide disconnection for the direct fluorination of aromatic C–H bonds in electron-rich arenes.[24]

2. C–Cl/Br/I Bonds

Aliphatic and aromatic halides (Cl, Br, I) are valuable synthetic intermediates in organic synthesis, accessible by many standard textbook reactions.[25] However, new halogenation strategies are still developed. The main goal is to find milder and more selective conditions, to enable stereoselective halogenation or to perform late-stage functional group interconversions converting bioactive molecules into complex building blocks.[26] Visible-light-mediated methods offer radical and polar reactivity and ATRA (atom transfer radical addition) reactions lead to a diverse product scope.

2.1 Generation of Aliphatic C–Cl Bonds

Glorius and co-workers published a silver-free procedure for a Hunsdiecker-type decarboxylative halogenation of the readily available feedstock of aliphatic carboxylic acids (Scheme 5).[27] The method employed $[Ir(dF(CF_3)ppy)_2(dtbbpy)]PF_6$ as photocatalyst and the common laboratory chemicals: *N*-chlorosuccinimide (NCS) as chlorine source and cesium carbonate as the base. The reaction mixture was irradiated with blue LEDs (455 nm) for 14 h providing the corresponding chlorinated products in generally very good yields (70–90 %). The reported functional group tolerance comprises bromides, ethers, esters, protected amines, and amides. It is noteworthy that, the method could not only be applied to decarboxylative chlorinations, but also for brominations and iodinations if either diethyl bromomalonate or *N*-iodosuccinimide (NIS), were used as halide sources.



Substituents / FGT
R = prim., sec. or tert. alkyl chain/ring containing benzylic C-H, aliphatic/ aromatic halide (Br), ether, ester, protected amine, amide

Conditions:
photocatalyst / λ : $Ir[dF(CF_3)ppy]_2(dtbbpy)PF_6$ / blue LEDs (455 nm)
solvent / additives : Chlorobenzene / NCS, Cs_2CO_3
temp. / atm. : rt / Ar

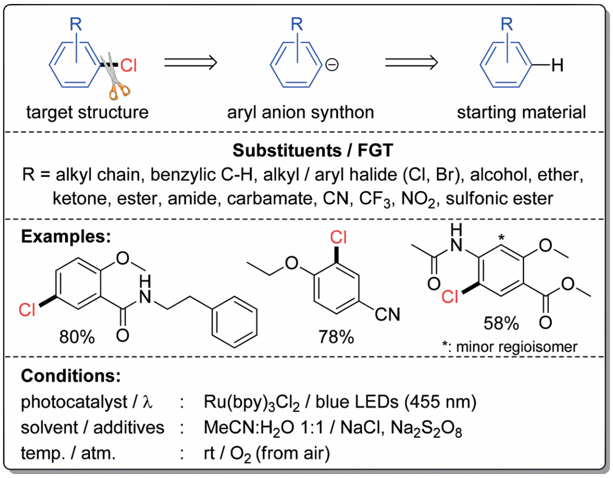
Scheme 5. Alkyl-halide disconnection for the decarboxylative chlorination of aliphatic carboxylic acids.[27]

Direct, photocatalytic chlorination of aliphatic C–H bonds was developed by Chen and co-workers who employed benzo- or acetophenone as photocatalysts and NCS as chlorine source providing a broader functional group tolerance but limited to benzylic C–H bonds or offering only low selectivity if molecules without benzylic C–H bonds were used.[28]

2.2 Generation of Aromatic C–Cl Bonds

Aliphatic and aromatic halides (Cl, Br, I) are valuable synthetic intermediates in organic synthesis, accessible by many standard textbook reactions.[25] However, new halogenation strategies are still developed. The main goal is to find milder and more selective conditions, to enable stereoselective halogenation or to perform late-stage functional group interconversions converting bioactive molecules into complex building blocks.[26] Visible-light-mediated methods offer radical and polar reactivity and ATRA (atom transfer radical addition) reactions lead to a diverse product scope.

Oxidative electrophilic aromatic substitutions use NaCl rather than $Cl_2/AlCl_3$ as the source for Cl^+. Hu and co-workers reported in 2017 the photocatalytic chlorination of electron-rich arenes (Scheme 6).[29] NaCl, sodium persulfate and ruthenium trisbipyridine ($Ru(bpy)_3Cl_2$) as photosensitizer and irradiation with blue LEDs for 24 h led to the corresponding chlorinated arenes in excellent yields (60–90 %) albeit only moderate ortho/para regioselectivity as expected from the Cl^+ reactivity. Many functional groups were tolerated including halides (Cl, Br), alcohols, esters, amides, CN, CF_3 and NO_2 groups but the method failed to chlorinate very electron-deficient arenes e.g. nitrobenzene or trifluoromethoxybenzene.



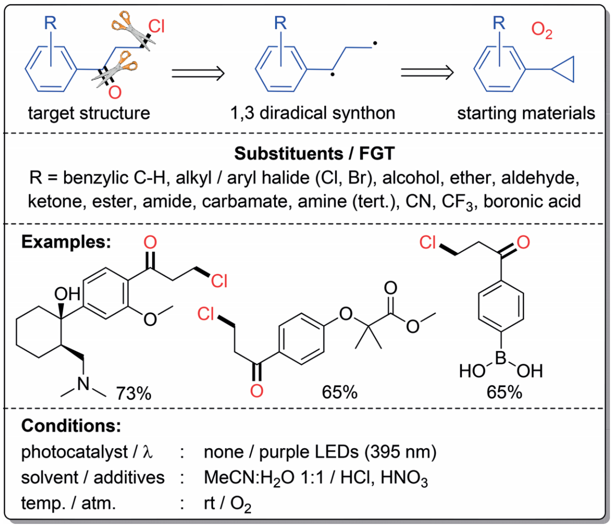
Scheme 6. Aryl-halide disconnection for the direct chlorination of aromatic C–H bonds in electron-rich arenes.[29]

Alternatively, two transition-metal-free, photocatalytic chlorination methods were developed by our group giving similar yields and showing the same functional group tolerance.[30]

2.3 Generation of β-Chloro Ketones

Aliphatic and aromatic halides (Cl, Br, I) are valuable synthetic intermediates in organic synthesis, accessible by many standard textbook reactions.[25] However, new halogenation strategies are still developed. The main goal is to find milder and more selective conditions, to enable stereoselective halogenation or to perform late-stage functional group interconversions converting bioactive molecules into complex building blocks.[26] Visible-light-mediated methods offer radical and polar reactivity and ATRA (atom transfer radical addition) reactions lead to a diverse product scope.

Our group reported the visible-light-mediated oxychlorination of aryl cyclopropanes (Scheme 7).[31] No photocatalyst, only diluted HCl and HNO_3, as well as irradiation with a high power 395 nm LED for 2 h were required to promote the reaction giving the corresponding β-chloro ketones in generally good yields (50–70 %). The functional group tolerance includes halides (F, Cl, Br), alcohols, ethers, aldehydes, esters, amides, CN and CF_3 groups and boronic acids. Electron-rich starting materials gave better yields than electron-deficient ones. It is noteworthy that, if sodium anthraquinone-2-sulfonate was used as a photosensitizer, other nucleophiles than chloride could be used (e.g. bromide, H_2O or MeOH) expanding the scope of the method.

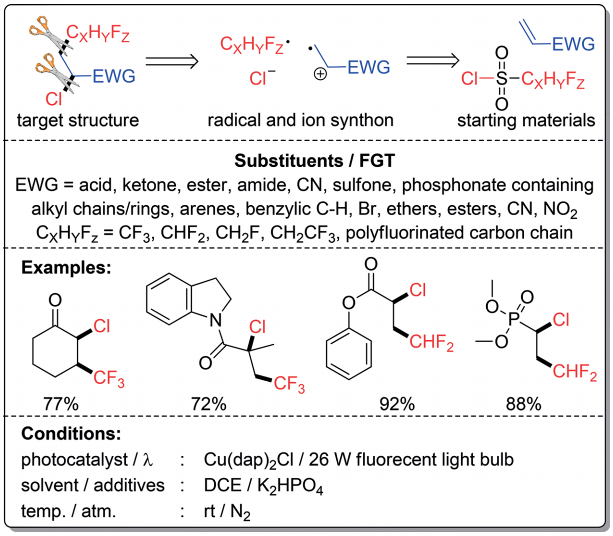


Scheme 7. Alkyl-halide/oxygen disconnection for the oxochlorination of aryl cyclopropanes.[31]

2.4 ATRA Reactions Generating Chlorinated Products

Aliphatic and aromatic halides (Cl, Br, I) are valuable synthetic intermediates in organic synthesis, accessible by many standard textbook reactions.[25] However, new halogenation strategies are still developed. The main goal is to find milder and more selective conditions, to enable stereoselective halogenation or to perform late-stage functional group interconversions converting bioactive molecules into complex building blocks.[26] Visible-light-mediated methods offer radical and polar reactivity and ATRA (atom transfer radical addition) reactions lead to a diverse product scope.

The group of Dolbier developed a strategy for an atom transfer radical addition (ATRA) of fluorinated sulfonyl chlorides to Michael acceptors (Scheme 8).[32] The method employed $Cu(dap)_2Cl$ as the photocatalyst, the fluorinated sulfonyl chloride as ATRA precursor and K_2HPO_4 as a base. The reaction mixture was irritated with a 26 W fluorescent light bulb for 12–24 h giving the ATRA products in yields of 70–90 %. The functional group tolerance comprises different electron-withdrawing groups and many fluorinated sulfonyl chlorides.



Substituents / FGT

EWG = acid, ketone, ester, amide, CN, sulfone, phosphonate containing alkyl chains/rings, arenes, benzylic C-H, Br, ethers, esters, CN, NO_2

$C_xH_yF_z$ = CF_3, CHF_2, CH_2F, CH_2CF_3, polyfluorinated carbon chain

Conditions:

photocatalyst / λ : $Cu(dap)_2Cl$ / 26 W fluorecent light bulb
solvent / additives : DCE / K_2HPO_4
temp. / atm. : rt / N_2

Scheme 8. Alkyl-halide/perfluoroalkyl disconnection for the synthesis of 2-chlorofluorinated alkyl chains.[32]

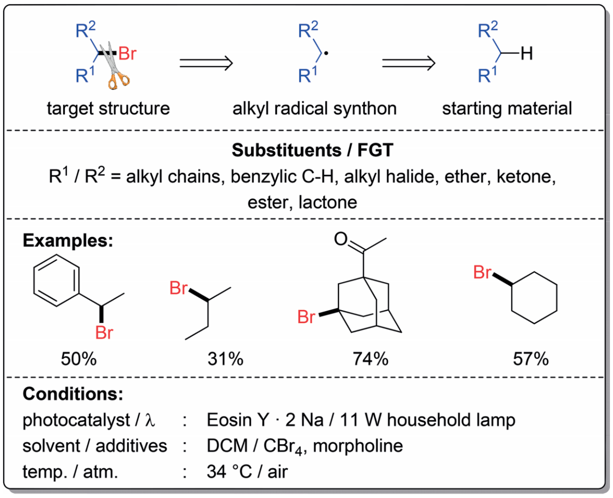
An alternative ATRA chlorotrifluoromethylation was developed by Han and co-workers using $Ru(phen)_3Cl_2$ as photocatalyst providing similar yields and functional group tolerance.[33] Reiser and co-workers reported an ATRA chlorination with sulfonyl chlorides and managed to preserve the SO_2 in the product leading to chlorinated sulfones.[34] It is noteworthy that, this method is not limited to Michael acceptors; electron-rich and poor double- as well as triple bonds react. Finally, the Magnier group managed to perform this ATRA reaction with *N*-chlorinated sulfoximines adding both the sulfoximine and Cl to the double bond.[35]

2.5 Generation of Aliphatic Bromides

Aliphatic and aromatic halides (Cl, Br, I) are valuable synthetic intermediates in organic synthesis, accessible by many standard textbook reactions.[25] However, new halogenation strategies are still developed. The main goal is to find milder and more selective conditions, to enable stereoselective halogenation or to perform late-stage functional group interconversions converting bioactive molecules into complex building blocks.[26] Visible-light-mediated methods offer radical and polar reactivity and ATRA (atom transfer radical addition) reactions lead to a diverse product scope.

Strategy 1

In addition to the chlorination, several photocatalytic strategies for the bromination of aliphatic C–H bonds were published. Tan and co-workers employed the commercially available disodium salt of Eosin Y as photocatalyst and CBr_4 as bromine source, as well as morpholine as the sacrificial electron donor (Scheme 9).[36] The reaction mixture was irradiated with an 11 W household lamp for 24 h providing the corresponding brominated products in yields of 50–70 %. The reported functional group tolerance included only alkyl halides (Cl, Br), ethers, ketones, and esters.



Substituents / FGT

R^1 / R^2 = alkyl chains, benzylic C-H, alkyl halide, ether, ketone, ester, lactone

Conditions:

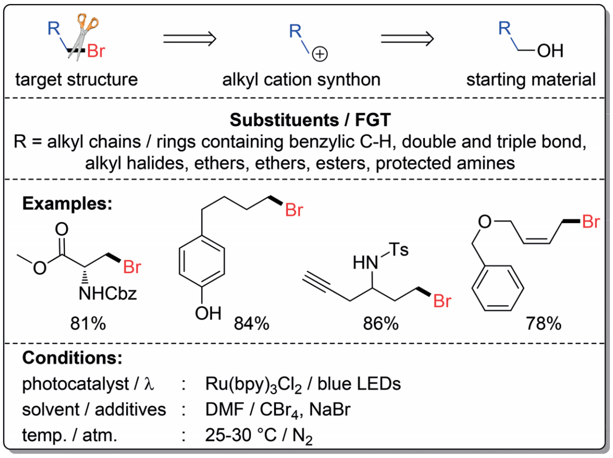
photocatalyst / λ : Eosin Y · 2 Na / 11 W household lamp
solvent / additives : DCM / CBr_4, morpholine
temp. / atm. : 34 °C / air

Scheme 9. Alkyl-halide disconnection for the direct bromination of secondary or tertiary aliphatic C–H bonds.[36]

An alternative procedure with a similar substrate scope was published by Lu and co-workers using KBr and $NaNO_2$ as a bromination system.[37] Another strategy was published by Franzén and co-workers employing NBS as the bromine source.[38] The authors proposed that a trityl-cation as Lewis acid together with simple hood light promoted an efficient bromination of the benzylic position of electron-rich arenes.

Strategy 2

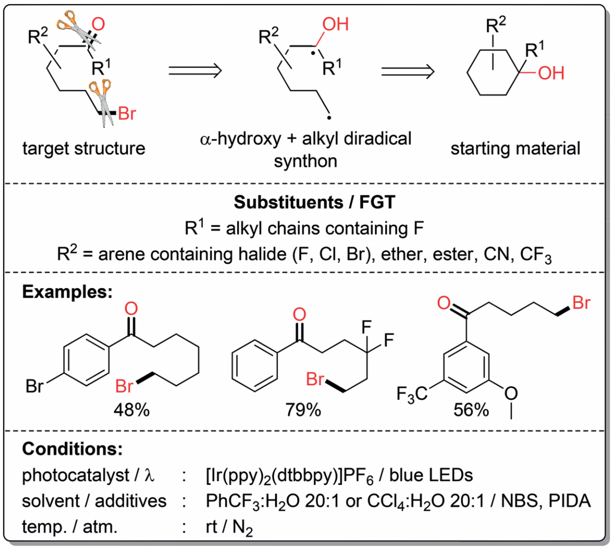
Another textbook bromination is the Appel reaction which turns aliphatic alcohols into the corresponding halides.[40] However, a significant disadvantage is the generation of stoichiometric amounts of triphenylphosphinoxide as side product which is often hard to separate.[41] Therefore, Stephenson and co-workers developed an elegant method for a photocatalytic Appel reaction which completely avoids the generation of triphenylphosphinoxide (Scheme 10).[39] The strategy required $Ru(bpy)_3Cl_2$ as the photocatalyst, a mixture of CBr_4 and NaBr as bromine sources as well as DMF as the solvent. The reaction mixture was illuminated with blue LEDs for 5–15 h giving the corresponding deoxobrominated products in yields from 70 to 90 %. The reported functional group tolerance comprises double and triples bonds, ethers, esters and protected amines. It is noteworthy that, also iodinations could be performed if iodoform and NaI instead of CBr_4 and NaBr were used.



Scheme 10. Alkyl-halide disconnection for the deoxygenative bromination of aliphatic alcohols.[39]

Strategy 3

Zhu and co-workers developed a photocatalytic, oxidative ring-opening bromination of unstrained, cyclic, benzylic, tertiary alcohols (Scheme 11).[42] The procedure used $[Ir(ppy)_2(dtbbpy)]PF_6$ as the photocatalyst, NBS as bromine source and phenyliodine(III) diacetate (PIDA) as hypervalent iodine species. The reaction mixture was irradiated with blue LEDs giving the corresponding, remotely brominated ketones in yields of 50–70 %. The functional group tolerance comprises aromatic halides (F, Cl, Br), ethers, esters, CN and CF_3 groups. The reaction times were very long ranging from 12 h to 100 h.

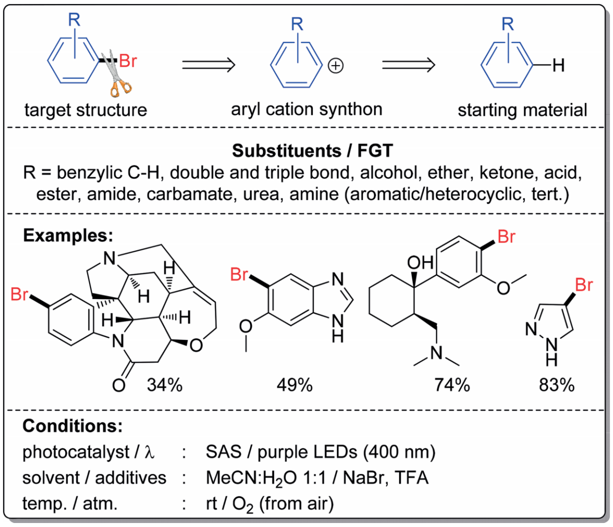


Scheme 11. Alkyl-halide disconnection for the remote, oxidative bromination of cyclic, aliphatic alcohols.[42]

2.6 Generation of Aromatic Bromides

Aliphatic and aromatic halides (Cl, Br, I) are valuable synthetic intermediates in organic synthesis, accessible by many standard textbook reactions.[25] However, new halogenation strategies are still developed. The main goal is to find milder and more selective conditions, to enable stereoselective halogenation or to perform late-stage functional group interconversions converting bioactive molecules into complex building blocks.[26] Visible-light-mediated methods offer radical and polar reactivity and ATRA (atom transfer radical addition) reactions lead to a diverse product scope.

The direct bromination of electron-rich arenes and heteroarenes was achieved using sodium anthraquinone-2-sulfonate (SAS) as an inexpensive and commercially available photocatalyst with NaBr and TFA (Scheme 12).[43] The reaction mixture was irradiated with a 400 nm LED for 4 h giving the brominated products in yields from 60–80 %. The functional group tolerance comprises double and triple bonds, halides, alcohols, acids, esters, and free amines, but the procedure failed to brominate electron-deficient arenes e.g. chlorobenzene.



Substituents / FGT
R = benzylic C-H, double and triple bond, alcohol, ether, ketone, acid, ester, amide, carbamate, urea, amine (aromatic/heterocyclic, tert.)

Conditions:
photocatalyst / λ : SAS / purple LEDs (400 nm)
solvent / additives : MeCN:H_2O 1:1 / NaBr, TFA
temp. / atm. : rt / O_2 (from air)

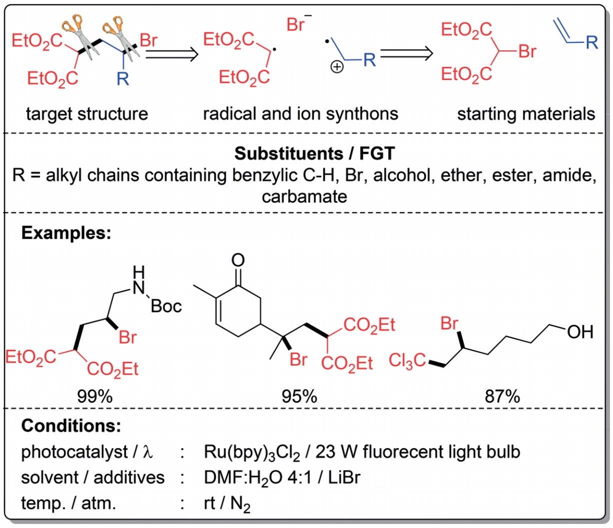
Scheme 12. Aryl-halide disconnection for the direct bromination of aromatic C–H bonds in electron-rich arenes.[43]

An alternative method published by Lamar uses NBS as the bromine source extending the substrate scope to phenols and free amine groups.[44] The groups of Fukuzumi and Zhang published visible-light-mediated methods for the oxidative bromination of arenes, however with more limited substrate scope.[45]

2.7 ATRA Reactions Generating Brominated Products

Aliphatic and aromatic halides (Cl, Br, I) are valuable synthetic intermediates in organic synthesis, accessible by many standard textbook reactions.[25] However, new halogenation strategies are still developed. The main goal is to find milder and more selective conditions, to enable stereoselective halogenation or to perform late-stage functional group interconversions converting bioactive molecules into complex building blocks.[26] Visible-light-mediated methods offer radical and polar reactivity and ATRA (atom transfer radical addition) reactions lead to a diverse product scope.

Stephenson and co-workers published a visible-light-mediated ATRA reaction of diethyl bromomalonate with alkenes (Scheme 13).[46] The method employed $Ru(bpy)_3Cl_2$ as the photocatalyst, diethyl bromomalonate as ATRA precursor and LiBr. The reaction mixture was irradiated with a fluorescent light bulb for 24 h giving the ATRA reaction products in yields of 70–90 %. The functional group tolerance includes alcohols, ethers, esters, amides, and carbamates. However, the authors demonstrated that also many other ATRA precursors instead of just diethyl bromomalonate could be used e.g. CF_2BrCO_2Et or CCl_3Br providing the corresponding products also in excellent yields.



Substituents / FGT
R = alkyl chains containing benzylic C-H, Br, alcohol, ether, ester, amide, carbamate

Conditions:
photocatalyst / λ : $Ru(bpy)_3Cl_2$ / 23 W fluorecent light bulb
solvent / additives : DMF:H_2O 4:1 / LiBr
temp. / atm. : rt / N_2

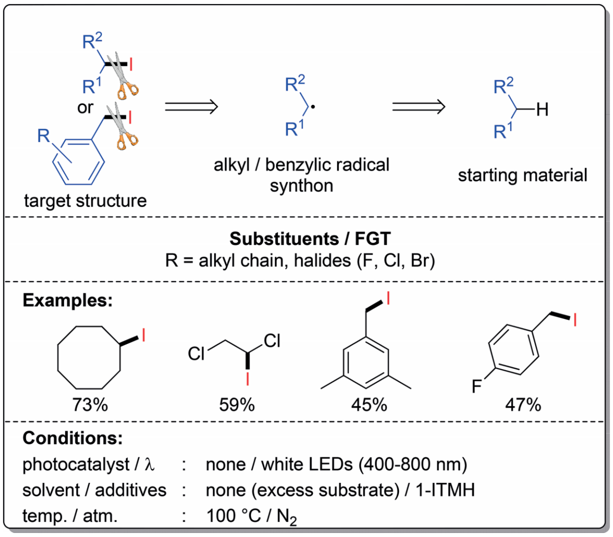
Scheme 13. Alkyl-halide disconnection for the ATRA reaction between diethyl bromomalonate and alkenes.[46]

Many alternative methods for this transformation were published e.g. by Pericàs using Bi_2O_3 as heterogeneous photocatalyst[47] or by Reiser using $Cu(dap)_2Cl$ instead of $Ru(bpy)_3Cl_2$.[48]

2.8 Generation of Aliphatic Iodides

Aliphatic and aromatic halides (Cl, Br, I) are valuable synthetic intermediates in organic synthesis, accessible by many standard textbook reactions.[25] However, new halogenation strategies are still developed. The main goal is to find milder and more selective conditions, to enable stereoselective halogenation or to perform late-stage functional group interconversions converting bioactive molecules into complex building blocks.[26] Visible-light-mediated methods offer radical and polar reactivity and ATRA (atom transfer radical addition) reactions lead to a diverse product scope.

The direct, visible-light-mediated iodination of benzylic and secondary C–H bonds was realized by Gandelmann and co-workers (Scheme 14).[49] The method did not require a photocatalyst and used 1-iodo-3,5,5-trimethylhydantoin (1-ITMH) which was activated by white light (400–800 nm) and high temperatures (100 °C). The yields of the iodinated products were moderate (40–60 %) and the reaction was unselective towards alkyl chains. The functional group tolerance included only chloride and fluoride; the reaction time was short (0.5–2 h).



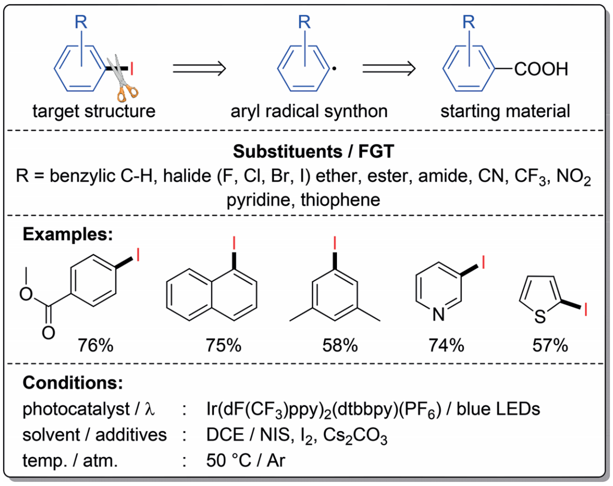
Scheme 14. Alkyl-halide disconnection for the direct iodination of secondary or benzylic aliphatic C–H bonds.[49]

Additional methods for the generation of aliphatic iodides were developed by Glorius and co-workers focusing on the decarboxylative iodination of aliphatic carboxylic acids[27] (see 2.1 for details) and by Stephenson and co-workers enabling the deoxygenative iodination of aliphatic alcohols (see 2.5 for details).[39]

2.9 Generation of Aromatic Iodides

Aliphatic and aromatic halides (Cl, Br, I) are valuable synthetic intermediates in organic synthesis, accessible by many standard textbook reactions.[25] However, new halogenation strategies are still developed. The main goal is to find milder and more selective conditions, to enable stereoselective halogenation or to perform late-stage functional group interconversions converting bioactive molecules into complex building blocks.[26] Visible-light-mediated methods offer radical and polar reactivity and ATRA (atom transfer radical addition) reactions lead to a diverse product scope.

Fu and co-workers published a procedure for the decarboxylative aromatic iodination (Scheme 15).[50] They used Ir(dF(CF$_3$)ppy)$_2$(dtbbpy)(PF$_6$) as the commercially available photocatalyst, *N*-iodosuccinimde (NIS) in combination with I_2 as iodine source and cesium carbonate as a base. The reaction mixture was illuminated with blue LEDs for 24–36 h giving the products in yields of 60–80 %. The functional group tolerance was broad including both electron-donating and electron-withdrawing substituents (halides, ethers, CN and NO_2 group) as well as pyridine and thiophene as heterocycles.



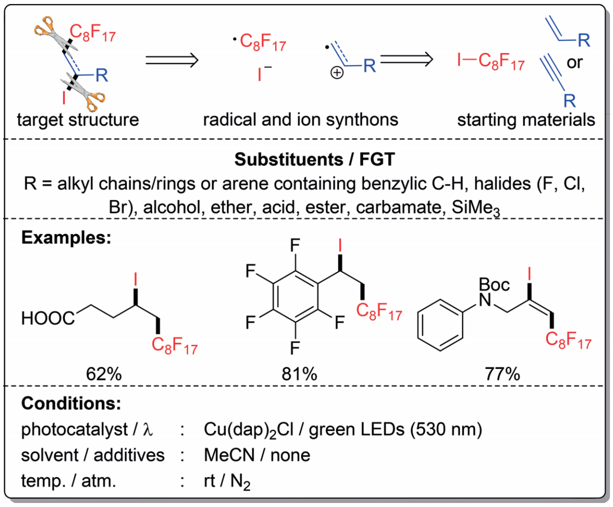
Scheme 15. Aryl-halide disconnection for the decarboxylative iodination of aromatic carboxylic acids.[50]

Another method, which did not require a photocatalyst, was published by Li and co-workers and started from aryl triflates instead of carboxylic acids providing similar yields and functional group tolerance.[51] Finally, our group developed a method for the direct C–H iodination of electron-rich arenes.[52]

2.10 ATRA Reactions Generating Iodinated Products

Aliphatic and aromatic halides (Cl, Br, I) are valuable synthetic intermediates in organic synthesis, accessible by many standard textbook reactions.[25] However, new halogenation strategies are still developed. The main goal is to find milder and more selective conditions, to enable stereoselective halogenation or to perform late-stage functional group interconversions converting bioactive molecules into complex building blocks.[26] Visible-light-mediated methods offer radical and polar reactivity and ATRA (atom transfer radical addition) reactions lead to a diverse product scope.

Reiser and co-workers developed a visible-light-mediated ATRA reaction between perfluoroalkyl iodides and alkenes or alkynes (Scheme 16).[53] The method employed Cu(dap)$_2$Cl as the photocatalyst, perfluorinated octyl iodide and did not require any other additives. The reaction mixture was irradiated with green LEDs for 12–42 h giving the ATRA products in yields of 60–80 %. The functional group tolerance was good including halides, alcohols, ethers, esters, acids, carbamates and silanes.



Scheme 16. Alkyl-halide disconnection for the ATRA reaction between perfluoroalkyl iodides and alkenes/alkynes.[53]

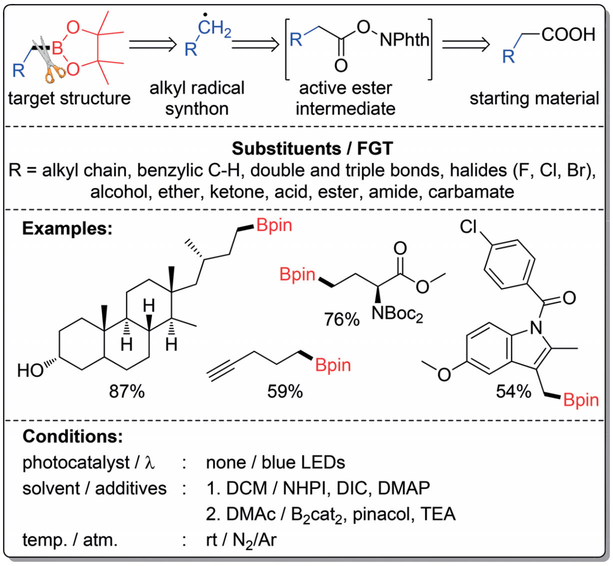
Alternative methods focusing on other fluorinated alkyl iodides were published by Stephenson[46] (e.g. CF_3I) and Guo[54] (CF_3CH_2I) providing similar yields and functional group tolerance.

3. C–B Bond

3.1 Generation of Alkyl Boronates

Since the discovery of the Suzuki coupling, organoboron compounds gained more and more attention as important intermediates in organic synthesis.[55] But in addition to their popularity as reagents, the pharmaceutical industry discovered that the boronic acid acts as bioisostere for carboxylic acids which increased the demand for more versatile and mild methodologies to introduce boron into organic molecules.[56]

Aggarwal and co-workers reported the visible-light-mediated synthesis of alkyl boronic esters (Scheme 17).[57] The reaction does not require a photocatalyst but with *N*-hydroxyphthalimide (NHPI) prefunctionalized alkyl carboxylic acids (can also be done as one-pot procedure), bis(catecholato)diboron (B_2cat_2), pinacol and triethylamine. The reaction mixture was irradiated with blue LEDs for 14 h giving the corresponding pinacolates after transesterification in generally good yields (50–70 %). The functional group tolerance was broad including alkyl chains and (hetero)aromatic rings containing double and triple bonds, halides (F, Br), alcohols, ethers, esters, and carbamates.



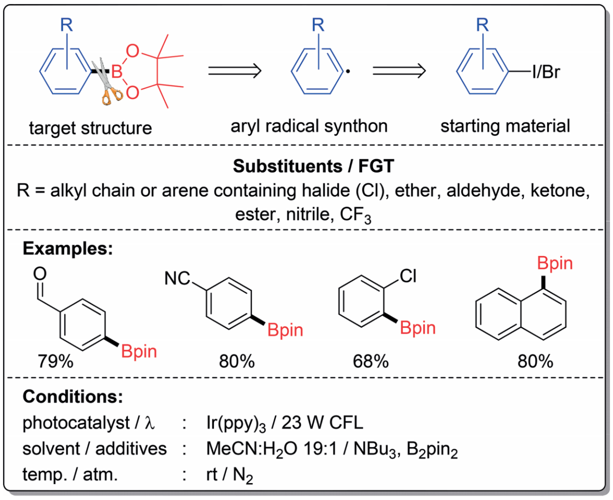
Scheme 17. Alkyl-boron disconnection for the synthesis of alkyl boronic esters.[57]

Alternative procedures were reported by Li and co-workers who employed directly B_2pin_2 and [Ir(ppy)$_2$(dtbpy)]PF$_6$ as photocatalyst[58] and by Glorius and co-workers who started from Katritzky salts rather than carboxylic acids.[59]

3.2 Generation of Aryl Boronates

Since the discovery of the Suzuki coupling, organoboron compounds gained more and more attention as important intermediates in organic synthesis.[55] But in addition to their popularity as reagents, the pharmaceutical industry discovered that the boronic acid acts as a bioisoster for carboxylic acids which increased the demand for more versatile and mild methodologies to introduce boron into organic molecules.[56]

Fu and co-workers developed the visible-light-mediated borylation of aryl halides (Scheme 18).[60] The method required Ir(ppy)$_3$ as the commercially available photocatalyst, tributylamine (NBu$_3$) as electron donor and bis(pinacolate)diboron (B$_2$pin$_2$) as boron source. The reaction mixture was irradiated for 24–36 h with a 23 W CFL giving the borylated products in generally very good yields (70–90 %). The functional group tolerance was moderate including alkyl groups, phenyl rings, halides (Cl), ethers, aldehyde, ketones, esters, and nitriles.



Conditions:
photocatalyst / λ : Ir(ppy)$_3$ / 23 W CFL
solvent / additives : MeCN:H$_2$O 19:1 / NBu$_3$, B$_2$pin$_2$
temp. / atm. : rt / N$_2$

Scheme 18. Aryl-boron disconnection for the synthesis of aryl boronic esters.[60]

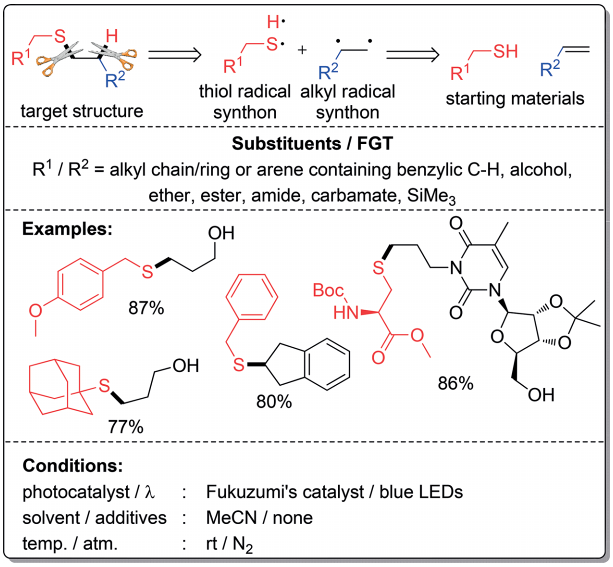
Alternative procedures were reported by Yan and co-workers starting from diazonium salts rather than bromides/iodides[61] and from Li and co-workers starting from triflates or mesylates rather than bromides/iodides.[51] Another alternative was published my Marder et al. utilizing a new rhodium based photocatalyst combined with nickel dual catalysis for the borylation of polyfluorinated arenes.[62] Furthermore, Glorius and co-workers reported the decarboxylative borylation of NHPI activated aryl carboxylic acids.[63] Finally, Beller[64] and Mankad[65] independently reported the visible-light-mediated direct C–H borylation using either iron or rhodium complexes but with very limited substrate scopes.

4. C–S Bond

4.1 Generation of Aliphatic Thioethers

Organosulfur compounds belong to the most versatile building blocks in organic chemistry.[66] Due to the variety of accessible oxidation states of sulfur many different compound classes can be prepared and find application in pesticides, pharmaceuticals as well as fine chemicals and materials. Especially the addition of sulfur centered radicals to double bond, known as thiol-ene reaction, has been studied extensively and depending on the reaction conditions sulfides, sulfoxides or sulfones are accessible.

Wang and co-workers reported the visible-light-mediated thiol-ene reaction between thiols and alkenes (Scheme 19).[67] The method employed 9-mesityl-10-methylacridinum tetrafluoroborate (Fukuzumi's catalyst) as photocatalyst and does not require further additives. The reaction mixture was irradiated with blue LEDs for 6 h to give the corresponding products in generally very good yields (70–90 %). The functional group tolerance was moderate including alcohols, ethers, esters, amide, carbamates and trimethylsilyl groups.



Conditions:
photocatalyst / λ : Fukuzumi's catalyst / blue LEDs
solvent / additives : MeCN / none
temp. / atm. : rt / N$_2$

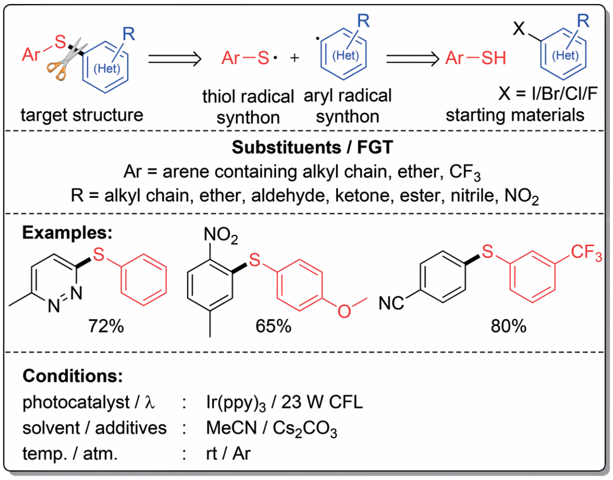
Scheme 19. Alkyl-sulfur disconnection for the synthesis of aliphatic thioethers.[67]

Many alternative procedures with similar substrate scopes were developed varying mostly in the catalyst used: phenylglyoxylic acid,[68] benzophenone,[69] Ru(bpz)$_3$,[70] Bi$_2$O$_3$[71] and TiO$_2$[72] to name some representative examples. Additionally, Glorius and co-workers reported a biocompatible procedure starting from disulfides rather than free thiols.[73]

4.2 Generation of Aromatic Thioethers

Organosulfur compounds belong to the most versatile building blocks in organic chemistry.[66] Due to the variety of accessible oxidation states of sulfur many different compound classes can be prepared and find application in pesticides, pharmaceuticals as well as fine chemicals and materials. Especially the addition of sulfur centered radicals to double bond, known as thiol-ene reaction, has been studied extensively and depending on the reaction conditions sulfides, sulfoxides or sulfones are accessible.

Fu and co-workers developed the visible-light-mediated thiolation of aryl halides (iodides, bromides, chlorides, and fluorides) (Scheme 20).[74] The method employed Ir(ppy)$_3$ as commercially available photocatalyst and cesium carbonate as base. The reaction mixture was irradiated with a 23 W CFL for 6–24 h giving the corresponding products in generally very good yields (70–90 %). The reported functional group tolerance was moderate including alkyl chains, ethers, aldehydes, ketones, esters, nitriles, and nitro groups. It is noteworthy that also many electron-deficient heteroarenes reacted well under the reaction conditions.



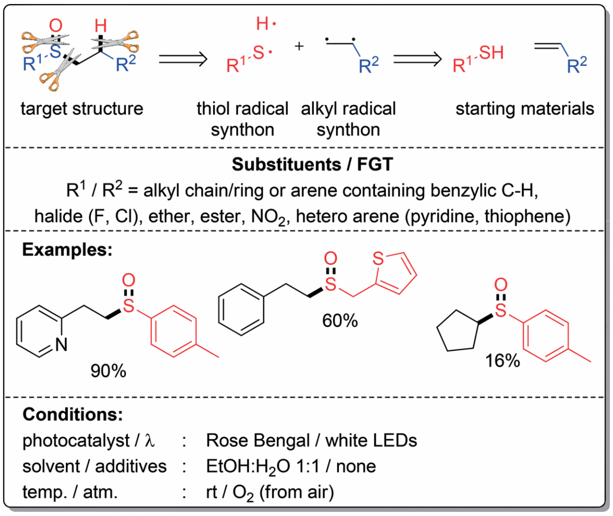
Scheme 20. Aryl-sulfur disconnection for the synthesis of aromatic thioethers.[74]

Many alternative thiolations of arenes were reported e.g. starting from diazonium salts rather than halides[75] or amines (via in situ conversion to diazonium salts)[76] Moreover, the direct thiolation of indoles was reported starting either from thiols[77] or sulfonyl chlorides[78] as well as the direct thiolation of benzimidazoles starting either from thiols[79] or sulfinic acids.[80]

4.3 Generation of Aliphatic Sulfoxides

Organosulfur compounds belong to the most versatile building blocks in organic chemistry.[66] Due to the variety of accessible oxidation states of sulfur many different compound classes can be prepared and find application in pesticides, pharmaceuticals as well as fine chemicals and materials. Especially the addition of sulfur centered radicals to double bond, known as thiol-ene reaction, has been studied extensively and depending on the reaction conditions sulfides, sulfoxides or sulfones are accessible.

Wang and co-workers reported the visible-light-mediated thiol-ene reaction with simultaneous oxidation of the sulfur atom to give sulfoxides (Scheme 21).[81] The method employed Rose Bengal as photocatalyst and O$_2$ from air as oxidant. The reaction mixture was irradiated with white LEDs for 2 h giving the corresponding products in generally good yields (50–70 %). The reported functional group tolerance was moderate including benzylic C–H bonds, halides (F, Cl), ethers, esters, and nitro groups.



Scheme 21. Alkyl-sulfur disconnection for the synthesis of sulfoxides.[81]

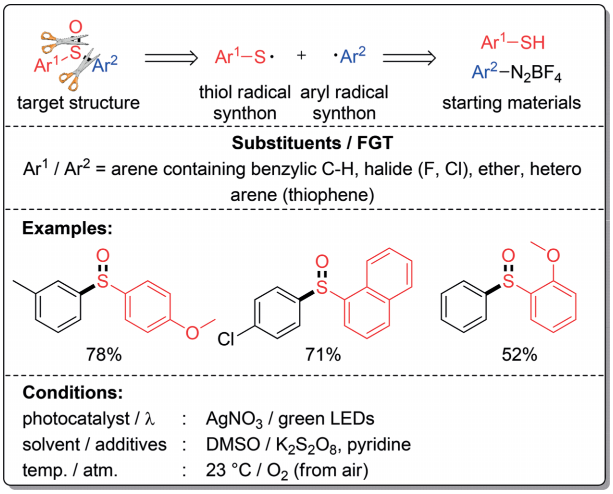
Alternative procedures used either Eosin Y[82] or *N*-hydroxyphthalimide (NHPI)[83] as photocatalysts showing similar yields and functional group tolerance. Another strategy using also Eosin Y as the photocatalyst leads to oxidation of both the sulfur atom and the double bond giving β-keto sulfoxides.[84]

4.4 Generation of Aromatic Sulfoxides

Organosulfur compounds belong to the most versatile building blocks in organic chemistry.[66] Due to the variety of accessible oxidation states of sulfur many different compound classes can be prepared and find application in pesticides, pharmaceuticals as well as fine chemicals and materials. Especially the addition of sulfur centered radicals to double bond, known as thiol-ene reaction, has been studied extensively and depending on the reaction conditions sulfides, sulfoxides or sulfones are accessible.

Strategy 1

Lee and co-workers reported the visible-light-mediated sulfoxidation of aryl diazonium salts (Scheme 22).[85] The method employed a silver salt as catalyst, persulfate, and O_2 from air as oxidants and pyridine as base. The reaction mixture was irradiated with green LEDs for 15 h giving the corresponding products in generally good yields (60–80 %). The reported functional group tolerance was rather low including only benzylic C–H bonds, halides (F, Cl) and ethers.

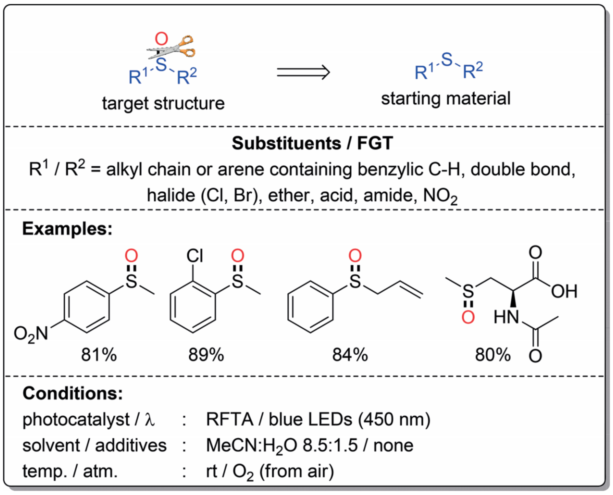


Scheme 22. Aryl-sulfur disconnection for the synthesis of sulfoxides.[85]

An alternative, catalyst-free procedure was developed by our group starting from sulfinamides rather than thiols which were coupled with electron-rich (hetero)arenes e.g. pyrroles or indoles.[86]

Strategy 2

Chibulka and co-workers reported the visible-light-mediated oxidation of aromatic and aliphatic thioethers (Scheme 23).[87] The method employed riboflavin tetraacetate (RFTA) as the photocatalyst, and O_2 from air as oxidant. The reaction mixture was irradiated with blue LEDs (450 nm) for 1 to 480 min depending on the substrate giving the corresponding products in generally very good yields (70–90 %). The reported functional group tolerance was moderate including benzylic C–H and double bonds as well as halides (Cl, Br), ethers, acids, amides, and nitro groups.



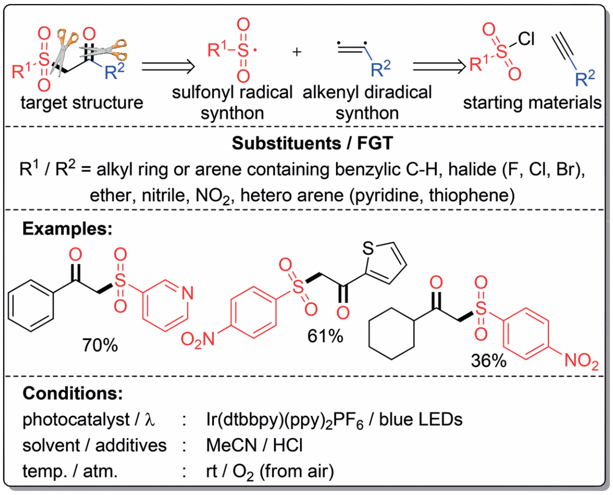
Scheme 23. Sulfur-oxygen disconnection for the synthesis of sulfoxides.[87]

Many alternative procedures with similar substrate scopes but different photocatalyst were developed e.g. using Rose Bengal,[88] a thioxanthone derivative,[89] Pt/$BiVO_4$[90] or heterogeneous TiO_2.[91]

4.5 Generation of Alkyl Sulfones

Organosulfur compounds belong to the most versatile building blocks in organic chemistry.[66] Due to the variety of accessible oxidation states of sulfur many different compound classes can be prepared and find application in pesticides, pharmaceuticals as well as fine chemicals and materials. Especially the addition of sulfur centered radicals to double bond, known as thiol-ene reaction, has been studied extensively and depending on the reaction conditions sulfides, sulfoxides or sulfones are accessible.

Ni and co-workers reported the visible-light-mediated oxosulfonylation of aromatic and aliphatic terminal alkynes (Scheme 24).[92] The method employed commercially available Ir(dtbbpy)(ppy)$_2$PF$_6$ as photocatalyst, HCl and O_2 from air as oxidant. The reaction mixture was irradiated with blue LEDs for 8 h giving the corresponding products in generally good yields (60–80 %). The reported functional group tolerance was moderate including benzylic C–H bonds, halides (F, Cl, Br), ethers, nitriles, and nitro groups as well as some heteroarenes (thiophene, pyridine).



Substituents / FGT

R^1 / R^2 = alkyl ring or arene containing benzylic C-H, halide (F, Cl, Br), ether, nitrile, NO$_2$, hetero arene (pyridine, thiophene)

Conditions:

photocatalyst / λ : Ir(dtbbpy)(ppy)$_2$PF$_6$ / blue LEDs
solvent / additives : MeCN / HCl
temp. / atm. : rt / O_2 (from air)

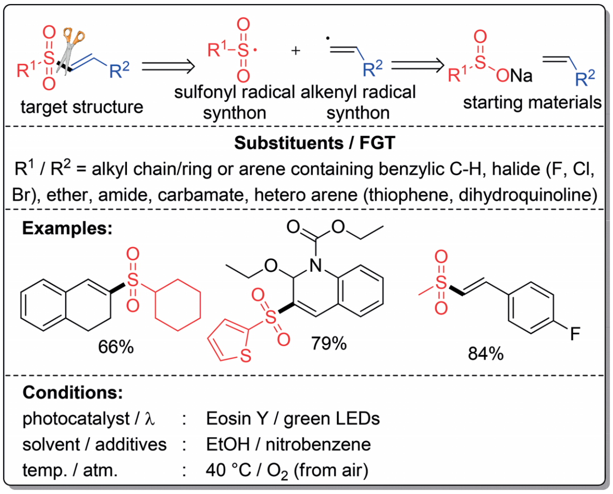
Scheme 24. Alkyl-sulfur disconnection for the synthesis of sulfones.[92]

An alternative procedure was developed by Huang and co-workers starting from sulfonylhydrazines rather than sulfonyl chlorides.[93] In addition to the previous method also electron-rich arenes/electron-donating substituents were tolerated. Another alternative method was published by Wang and co-workers starting from sulfinic acids and alkenes rather than sulfonyl chlorides and alkynes showing a similar substrate scope/functional group tolerance as the previous two methods.[94]

4.6 Generation of Vinyl Sulfones

Organosulfur compounds belong to the most versatile building blocks in organic chemistry.[66] Due to the variety of accessible oxidation states of sulfur many different compound classes can be prepared and find application in pesticides, pharmaceuticals as well as fine chemicals and materials. Especially the addition of sulfur centered radicals to double bond, known as thiol-ene reaction, has been studied extensively and depending on the reaction conditions sulfides, sulfoxides or sulfones are accessible.

Our group reported the visible-light-mediated sulfonylation of alkenes (Scheme 25).[95] The method employed commercially available Eosin Y as photocatalyst as well as nitrobenzene and O_2 from air as oxidants. The reaction mixture was irradiated with green LEDs for 18 h giving the corresponding products in generally good yields (60–80 %). The reported functional group tolerance was moderate including benzylic C–H bonds, halides (F, Cl, Br), ethers, amides, and carbamates as well as some heteroarenes (thiophene, dihydroquinoline).



Substituents / FGT

R^1 / R^2 = alkyl chain/ring or arene containing benzylic C-H, halide (F, Cl, Br), ether, amide, carbamate, hetero arene (thiophene, dihydroquinoline)

Conditions:

photocatalyst / λ : Eosin Y / green LEDs
solvent / additives : EtOH / nitrobenzene
temp. / atm. : 40 °C / O_2 (from air)

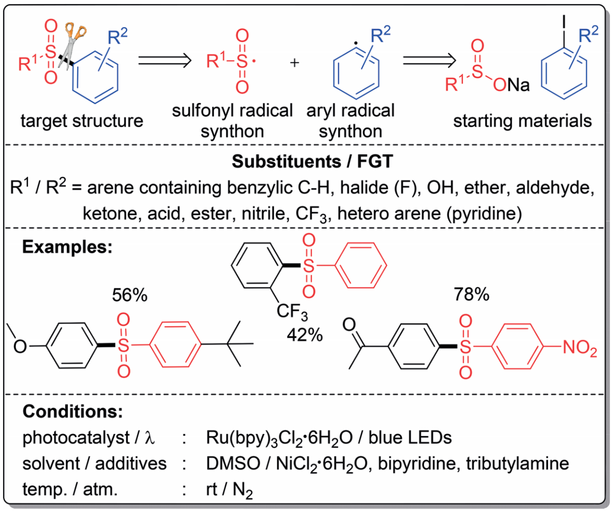
Scheme 25. Alkyl-sulfur disconnection for the synthesis of sulfones.[95]

Later, it could be demonstrated that this transformation could also be realized with a heterogeneous photocatalyst giving similar yields.[96] An extension of this method was published by Zhang and co-workers who focused on enamides as starting materials rather than alkenes.[97] An alternative, oxidant free procedure with a similar substrate scope and functional group tolerance was published by Lei and co-workers who replaced nitrobenzene with a cobalt complex.[98]

4.7 Generation of Aryl Sulfones

Organosulfur compounds belong to the most versatile building blocks in organic chemistry.[66] Due to the variety of accessible oxidation states of sulfur many different compound classes can be prepared and find application in pesticides, pharmaceuticals as well as fine chemicals and materials. Especially the addition of sulfur centered radicals to double bond, known as thiol-ene reaction, has been studied extensively and depending on the reaction conditions sulfides, sulfoxides or sulfones are accessible.

Manolikakes and co-workers reported the visible-light-mediated sulfonylation of aryl iodides by photoredox dual catalysis (Scheme 26).[99] The method employed commercially available $Ru(bpy)_3Cl_2{\cdot}6H_2O$ as the photocatalyst, $NiCl_2{\cdot}6H_2O$ as co-catalyst, bipyridine as ligand as well as tributylamine as base. The reaction mixture was irradiated with blue LEDs for 24 h giving the corresponding products in generally moderate yields (50–70 %). The reported functional group tolerance was broad including benzylic C–H bonds, halides (F), alcohols, ethers, aldehydes, ketones, esters, acids, nitriles, and CF_3 groups as well as some heteroarenes (e.g. pyridine).



Scheme 26. Alkyl-sulfur disconnection for the synthesis of sulfones.[99]

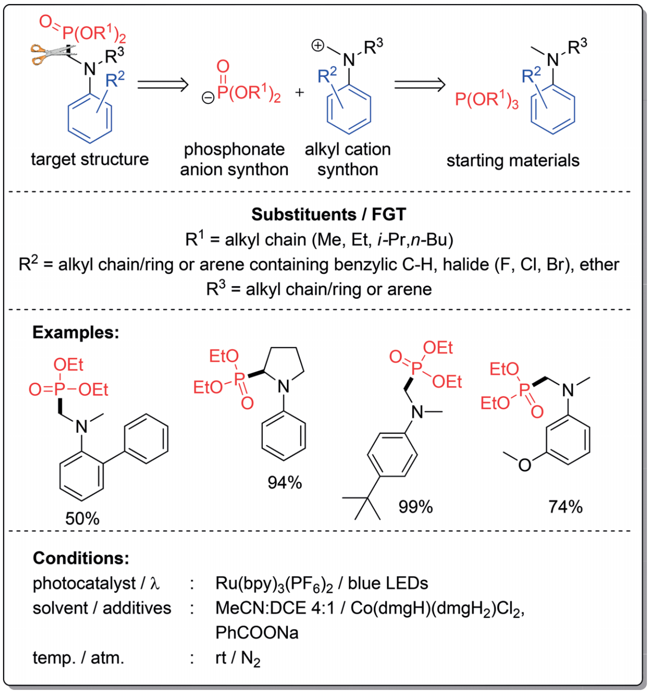
Many alternative procedures for the synthesis of aryl sulfones were developed e.g. by the group of Lee starting from thiols and diazonium salts.[85] More specialized procedures were developed for the sulfonylation of electron-rich heteroarenes (e.g. pyrroles and indoles) by the Reiser group[100] and for the sulfonylation of anilines by Willis and co-workers.[101] Another interesting approach for the synthesis of C-3 sulfonylated pyrrole derivatives was developed by Rueping and co-workers starting from *N*-protected pyrrolidines under oxidative conditions.[102]

5. C–P Bond

5.1 Generation of Aliphatic Phosphonates

Organophosphorus compounds are important motifs in organic chemistry and find many different applications e.g. in pesticides but also in pharmaceuticals or as ligands for transition metals.[103] The traditional synthesis of these compounds can be achieved in many ways e.g. by nucleophilic substitution or addition as well as transition metal catalysis.[104] Many of these methods require forcing conditions like the Michaelis–Arbuzov reaction.[105] By use of photoredox catalysis much milder reaction conditions are accessible which enables the broad applicability of these methods e.g. for late-stage functionalization of complex molecules.

Lei and co-workers reported the visible-light-mediated oxidant free phosphonylation of *N*,*N*-disubstituted anilines by photoredox dual catalysis (Scheme 27).[106] The method employed commercially available $Ru(bpy)_3(PF_6)_2$ as the photocatalyst, $Co(dmgH)(dmgH_2)Cl_2$ as co-catalyst, and sodium benzoate as additive. The reaction mixture was irradiated with blue LEDs for 24 h giving the corresponding products in generally very good yields (70–90 %). The reported functional group tolerance was low including benzylic C–H bonds, halides (F, Cl, Br), ethers.



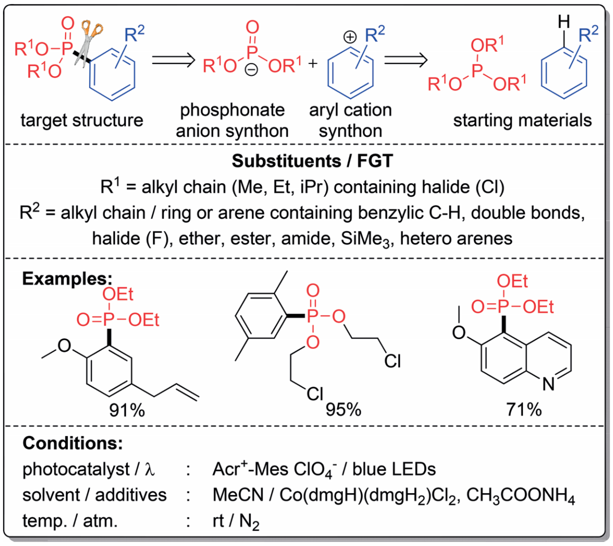
Scheme 27. Alkyl-phosphor disconnection for the synthesis of alkyl phosphonates.[106]

An alternative method was developed by Rueping and co-workers focusing on tetrahydroisoquinolines.[107] This method was modified by Kobayashi and co-workers using a polymer immobilized iridium catalyst.[108]

5.2 Generation of Aromatic Phosphonates

Organophosphorus compounds are important motifs in organic chemistry and find many different applications e.g. in pesticides but also in pharmaceuticals or as ligands for transition metals.[103] The traditional synthesis of these compounds can be achieved in many ways e.g. by nucleophilic substitution or addition as well as transition metal catalysis.[104] Many of these methods require forcing conditions like the Michaelis–Arbuzov reaction.[105] By use of photoredox catalysis much milder reaction conditions are accessible which enables the broad applicability of these methods e.g. for late-stage functionalization of complex molecules.

Lei and co-workers reported the visible-light-mediated oxidant free phosphonylation of electron-rich arenes by photoredox dual catalysis (Scheme 28).[109] The method employed commercially available 9-mesityl-10-methylacridinum perchlorate (Acr$^+$-Mes ClO_4^-) as the photocatalyst, Co(dmgH)(dmgH$_2$)Cl$_2$ as co-catalyst, and ammonium acetate as additive. The reaction mixture was irradiated with blue LEDs for 24 h giving the corresponding products in generally good yields (60–80 %). The reported functional group tolerance was broad including benzylic C–H bonds, double bonds, halides (Cl), ethers, esters, amides, SiMe$_3$ groups as well as some heteroarenes (e.g. thiophene).



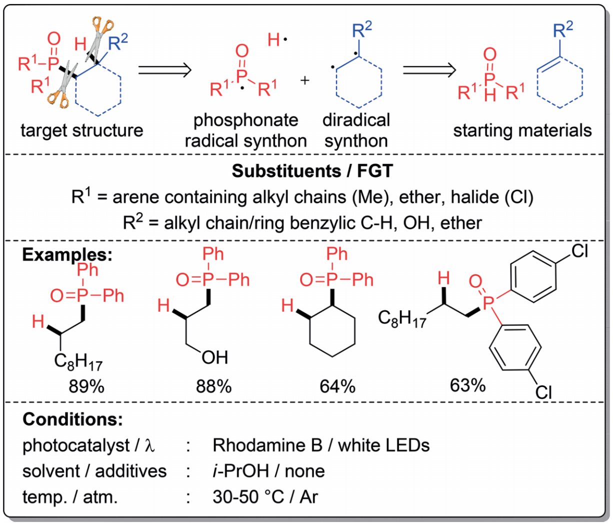
Scheme 28. Aryl-phosphor disconnection for the synthesis of aryl phosphonates.[109]

Many alternative procedures for the synthesis of aryl phosphonates were developed e.g. by our group using [Ru(bpz)$_3$][PF$_6$]$_2$ as the photocatalyst and ammonium persulfate as the terminal oxidant,[110] or by Lakhdar and co-workers starting from diaryliodonium salts.[111] In addition to the oxidative pathways also reductive phosphonylations were reported e.g. by our group starting from electron-deficient aryl halides,[112] by Toste and co-workers starting from aryl diazonium salts[113] and by Xia and co-workers starting from *N*-benzamidebenzotriazoles.[114] Finally, Yu and co-workers reported a dual catalyzed procedure for the phosphinylation of sp^2 hybridized aryl and alkyl triflates expanding previous procedures to olefins.[115]

5.3 Generation of Aliphatic Phosphine Oxides

Organophosphorus compounds are important motifs in organic chemistry and find many different applications e.g. in pesticides but also in pharmaceuticals or as ligands for transition metals.[103] The traditional synthesis of these compounds can be achieved in many ways e.g. by nucleophilic substitution or addition as well as transition metal catalysis.[104] Many of these methods require forcing conditions like the Michaelis–Arbuzov reaction.[105] By use of photoredox catalysis much milder reaction conditions are accessible which enables the broad applicability of these methods e.g. for late-stage functionalization of complex molecules.

Kobayashi and co-workers reported the visible-light-mediated hydro-phosphinylation of olefins by photoredox catalysis (Scheme 29).[116] The method employed commercially available Rhodamine B as the photocatalyst and did not require any other additives. The reaction mixture was irradiated with white LEDs for 24 h giving the corresponding products in generally good yields (60–80 %). The reported functional group tolerance was low including only benzylic C–H bonds halides (Cl), hydroxy groups and ethers.



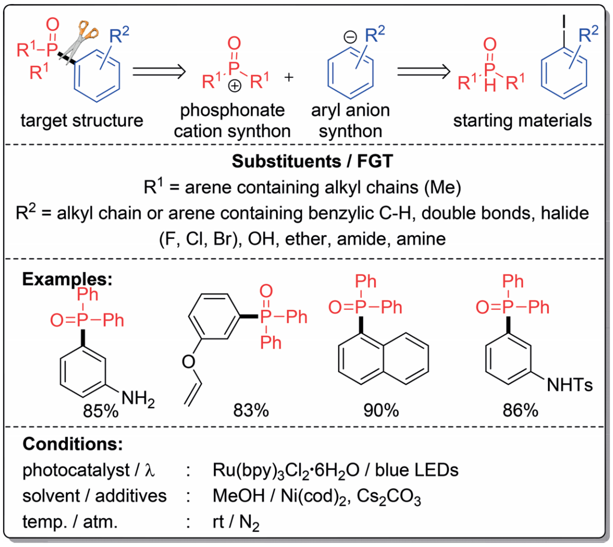
Scheme 29. Alkyl-phosphor disconnection for the synthesis of alkyl phosphine oxides.[116]

An alternative procedure was developed by Cai and co-workers starting from aryl alkynes instead of olefins under air atmosphere yielding beta-keto phosphine oxides.[117] Another interesting method was developed by Lakhdar and co-workers for the synthesis of benzo[b]phosphole oxides starting from disubstituted alkynes.[118]

5.4 Generation of Aromatic Phosphine Oxides

Organophosphorus compounds are important motifs in organic chemistry and find many different applications e.g. in pesticides but also in pharmaceuticals or as ligands for transition metals.[103] The traditional synthesis of these compounds can be achieved in many ways e.g. by nucleophilic substitution or addition as well as transition metal catalysis.[104] Many of these methods require forcing conditions like the Michaelis–Arbuzov reaction.[105] By use of photoredox catalysis much milder reaction conditions are accessible which enables the broad applicability of these methods e.g. for late-stage functionalization of complex molecules.

Xiao and co-workers reported the visible-light-mediated phosphinylation of aryl iodides by photoredox dual catalysis (Scheme 30).[119] The method employed commercially available $Ru(bpy)_3Cl_2{\cdot}6H_2O$ as photocatalyst, $Ni(cod)_2$ as co-catalyst, and cesium carbonate as base. The reaction mixture was irradiated with blue LEDs for 24 h giving the corresponding products in generally very good yields (70–90 %). The reported functional group tolerance was broad including benzylic C–H bonds, double bonds, halides (F, Cl, Br), ethers, amides as well as free hydroxy groups and amines.



Substituents / FGT

R^1 = arene containing alkyl chains (Me)

R^2 = alkyl chain or arene containing benzylic C-H, double bonds, halide (F, Cl, Br), OH, ether, amide, amine

Conditions:

photocatalyst / λ : $Ru(bpy)_3Cl_2{\cdot}6H_2O$ / blue LEDs
solvent / additives : MeOH / $Ni(cod)_2$, Cs_2CO_3
temp. / atm. : rt / N_2

Scheme 30. Aryl-phosphor disconnection for the synthesis of aryl phosphine oxides.[119]

Alternative procedures for the synthesis of heterocyclic aryl phosphates by direct C–H functionalization were developed e.g. by Wu and co-workers for the phosphorylation of 8-hydroxyquinolines[120] or 8-aminoquinolines[121] and by Hong and co-workers for the phosphinylation of coumarins.[122] Finally, Wu and co-workers developed a method for the C–H phosphinylation of thiazoles.[123]

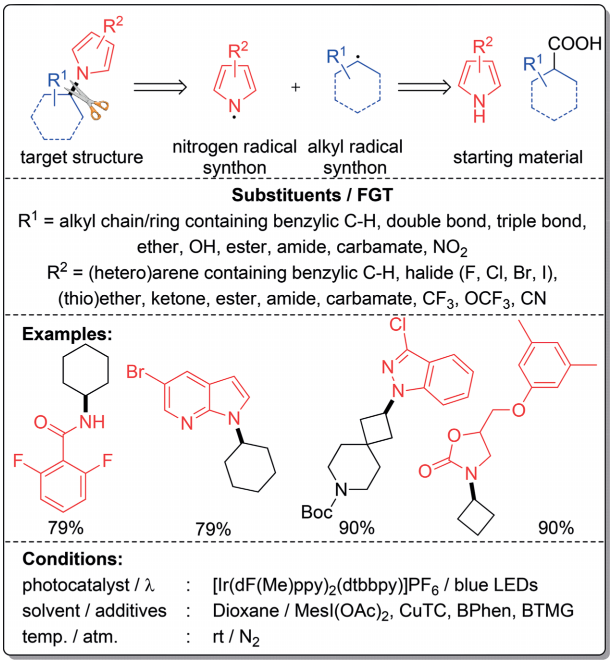
6. C–N Bond

6.1 Generation of (Cyclic) Aliphatic Amines/Amides

Nitrogen-containing molecules belong to the most important compound classes due to their ubiquitous presence in fine chemicals, pharmaceuticals and, of course, natural products. Many thermal (and some electrochemical) methods for the formation of C–N bonds were developed and extensively reviewed.[124] In addition to those methods many photochemical and photocatalytic processes were developed giving rise to previously elusive transformations.

Strategy 1

MacMillan and co-workers reported the visible-light-mediated synthesis of aliphatic amines by photoredox catalysis (Scheme 31).[125] The method employed commercially available $[Ir(dF(Me)ppy)_2(dtbbpy)]PF_6$ as the photocatalyst, CuTC (copper(I) thiophene-2-carboxylate) as cocatalyst as well as bathophenanthroline as ligand for the copper catalyst and BTMG (2-*tert*-butyl-1,1,3,3-tetramethylguanidine) as base. The reaction mixture was irradiated with blue LEDs for 1 h giving the corresponding products in generally good yields (60–90 %). The reported functional group tolerance was broad including benzylic C–H bonds, double and triple bonds, halides (F, Cl, Br, I), (thio)ethers, ketones, esters, amides, carbamates, as well as NO_2, CF_3, OCF_3, and CN groups. It is noteworthy that not only heteroaryl nitrogen nucleophiles could be used but also amides, sulfonamides, carbamates, and urea derivatives.



Substituents / FGT

R^1 = alkyl chain/ring containing benzylic C-H, double bond, triple bond, ether, OH, ester, amide, carbamate, NO_2

R^2 = (hetero)arene containing benzylic C-H, halide (F, Cl, Br, I), (thio)ether, ketone, ester, amide, carbamate, CF_3, OCF_3, CN

Conditions:

photocatalyst / λ : $[Ir(dF(Me)ppy)_2(dtbbpy)]PF_6$ / blue LEDs
solvent / additives : Dioxane / $MesI(OAc)_2$, CuTC, BPhen, BTMG
temp. / atm. : rt / N_2

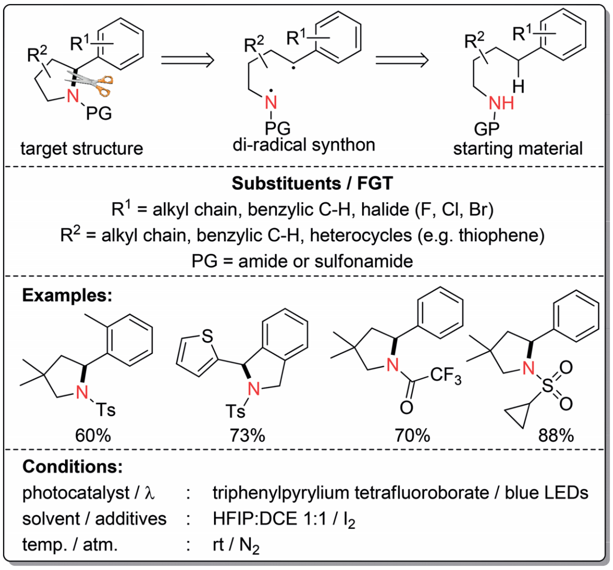
Scheme 31. Alkyl-nitrogen disconnection for the synthesis of aliphatic amines and amides.[125]

An extension of this method was published by Hu and co-workers starting from active esters (NHPI esters) instead of performing an in-situ pre-functionalization with $MesI(OAc)_2$.[126]

Alternative methods were published by Fu and co-workers starting from alkyl iodides and carbazole derivatives[127] or aliphatic amines[128] and by Molander and co-workers starting from aryl aldehydes instead of carboxylic acids and aliphatic amines via a photocatalyzed reductive amination.[129] Another alternative was reported by Zuo and co-workers who realized the direct C–H amination of methane and other short-chained aliphatic molecules by cerium photocatalysis.[130]

Strategy 2

Muñiz and co-workers reported the visible-light-mediated synthesis of cyclic amines by photoredox catalysis (Scheme 32). The method employed commercially available triphenylpyrylium tetrafluoroborate as the photocatalyst and I_2 as cocatalyst.[131] The reaction mixture was irradiated with blue LEDs for 18 h giving the corresponding products in generally good yields (60–80 %). The reported functional group tolerance was low including benzylic C–H bonds, halides (F, Cl, Br), as well as amides, sulfonamides and heterocycles (e.g. thiophene).



Substituents / FGT
R^1 = alkyl chain, benzylic C-H, halide (F, Cl, Br)
R^2 = alkyl chain, benzylic C-H, heterocycles (e.g. thiophene)
PG = amide or sulfonamide

Examples:

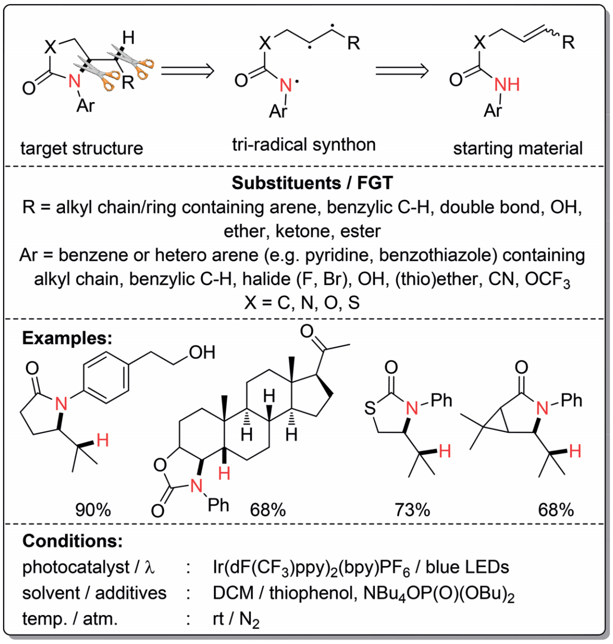
Conditions:
photocatalyst / λ : triphenylpyrylium tetrafluoroborate / blue LEDs
solvent / additives : HFIP:DCE 1:1 / I_2
temp. / atm. : rt / N_2

Scheme 32. Alkyl-nitrogen disconnection for the synthesis of cyclic amines and amides.[131]

A similar procedure for the synthesis of pyrrolidines was reported by Nagib and co-workers who used potassium iodide and (diacetoxyiodo)benzene instead of a photocatalyst.[132] Muñiz and co-workers also reported an alternative procedure using only I_2 and stoichiometric amounts of NBS without an additional photocatalyst for the synthesis of piperidines rather than pyrrolidines.[133]

Strategy 3

Stephenson and co-workers reported the visible-light-mediated synthesis of cyclic amides, carbamates or urea derivatives by photoredox catalysis (Scheme 33).[134] The method employed commercially available $Ir(dF(CF_3)ppy)_2(bpy)PF_6$ as the photocatalyst and thiophenol as well as a tetrabutylammonium phosphate derivative as cocatalysts. The reaction mixture was irradiated with blue LEDs for 12–72 h giving the corresponding products in generally very good yields (70–90 %). The reported functional group tolerance was broad including benzylic C–H bonds, halides (F, Br), OH, ethers, ketones, esters, CN and OCF_3 groups.



Substituents / FGT
R = alkyl chain/ring containing arene, benzylic C-H, double bond, OH, ether, ketone, ester
Ar = benzene or hetero arene (e.g. pyridine, benzothiazole) containing alkyl chain, benzylic C-H, halide (F, Br), OH, (thio)ether, CN, OCF_3
X = C, N, O, S

Examples:

Conditions:
photocatalyst / λ : $Ir(dF(CF_3)ppy)_2(bpy)PF_6$ / blue LEDs
solvent / additives : DCM / thiophenol, $NBu_4OP(O)(OBu)_2$
temp. / atm. : rt / N_2

Scheme 33. Alkyl-nitrogen disconnection for the synthesis of cyclic amides.[134]

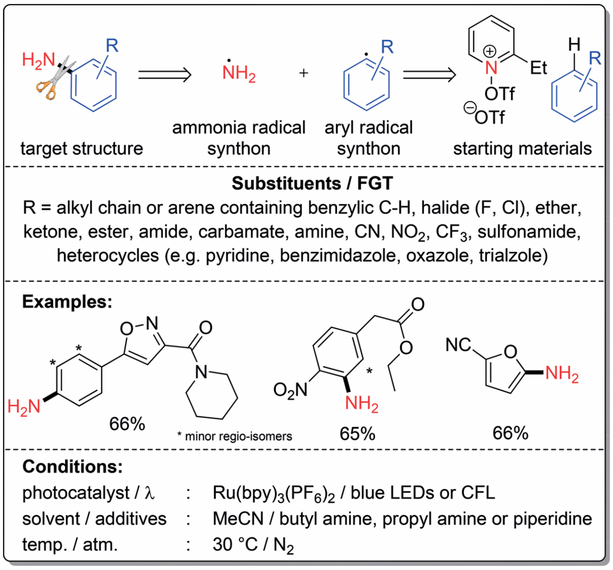
Knowles and co-workers extended the method by adding Michael-acceptors (e.g. acrylates) instead of hydrogen leading to more complex structures.[135] Another extension was reported by Molander and co-workers adding arenes instead of Michael-acceptors to the double bond.[136] In addition, Jamison and co-workers developed an intermolecular version of this method for the synthesis of indolines starting from 2-iodo anilines by use of Nickel/photoredox dual catalysis.[137]

6.2 Generation of Aromatic Amines

Nitrogen-containing molecules belong to the most important compound classes due to their ubiquitous presence in fine chemicals, pharmaceuticals and, of course, natural products. Many thermal (and some electrochemical) methods for the formation of C–N bonds were developed and extensively reviewed.[124] In addition to those methods many photochemical and photocatalytic processes were developed giving rise to previously elusive transformations.

Strategy 1

Ritter and co-workers reported the visible-light-mediated amination of arenes by photoredox catalysis (Scheme 34).[138] The method employed commercially available $Ru(bpy)_3(PF_6)_2$ as the photocatalyst and either butylamine propylamine or piperidine as the base in the second reaction step. The reaction mixture was irradiated with blue LEDs for 15–90 min or with a CFL for 24 h giving the corresponding products in generally good yields (60–80 %). The reported functional group tolerance was broad including benzylic C–H bonds, halides (F, Cl), ethers, ketones, esters, amides, carbamates, amines, nitriles, nitro, and CF_3 groups as well as sulfonamides and various heterocycles.



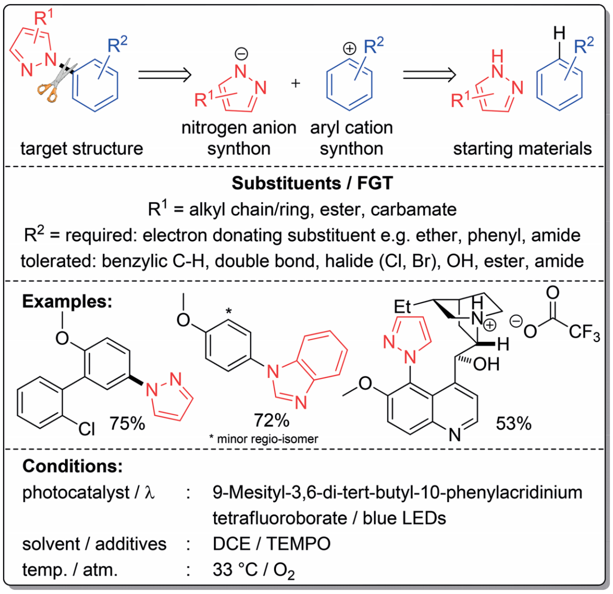
Scheme 34. Aryl-nitrogen disconnection for the synthesis of aromatic amines.[138]

An alternative procedure for the synthesis of arylamines was simultaneously developed by Carreira and co-workers using basically the same reaction conditions.[139] Furthers alternatives were developed by Liu and co-workers starting from aryl azides,[140] Sanford and co-workers who started from phthalimide trifluoroacetamides instead of pyridinium triflates yielding aryl phthalimides[141] and by Leonori and co-workers who started from *O*-dinitroaryl hydroxylamines yielding arylamines (e.g. piperidines).[142] In addition to this method, Leonori and co-workers recently contributed another procedure for the direct amination of arenes starting from simple, unfunctionalized secondary amines.[143]

A more specialized procedure was developed by Wang and co-workers focusing on the amination of quinoxalinones.[144] An alternative procedure for the amination of heteroarenes (indoles, pyrroles, furans, benzofurans) was developed by Yu and co-workers starting from benzene sulfonylated hydroxylamines as amine source.[145]

Strategy 2

Nicewicz and co-workers reported the visible-light-mediated amination of arenes by photoredox catalysis (Scheme 35).[146] The method employed commercially available 9-mesityl-3,6-di-*tert*-butyl-10-phenylacridinium tetrafluoroborate as the photocatalyst and TEMPO as additive. The reaction mixture was irradiated with blue LEDs for 24–72 h giving the corresponding products in generally good yields (60–80 %). The reported functional group tolerance was moderate requiring an electron-donating substituent on the arene coupling partner and tolerating benzylic C–H bonds, halides (Cl, Br), OH, ethers, esters, amides, carbamates, amines.

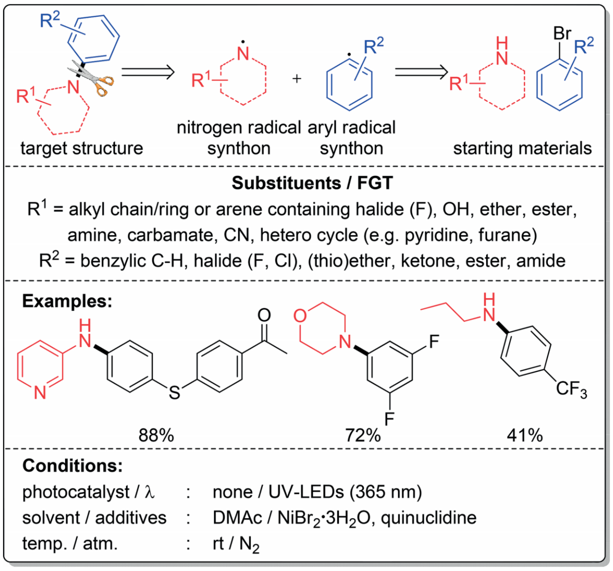


Scheme 35. Aryl-nitrogen disconnection for the synthesis of aromatic amines.[146]

Xia and co-workers expanded the procedure using diphenylamines instead of pyrazoles and phenols as coupling partner.[147] Moreover, in a follow-up publication, Nicewicz and co-workers expanded their procedure from *N*-heterocycles (e.g. pyrazole) as amine coupling partner to aliphatic amines e.g. amino acids.[148] Again, this procedure was expanded by Zhou and co-workers using a cobalt-based cocatalyst so that no oxygen was required.[149] Finally, our group reported the addition of amides to electron-deficient arenes complementing the previously mentioned procedures.[150]

Strategy 3

Miyake and co-workers reported the visible-light-mediated amination of arenes by photoredox catalysis (Scheme 36).[151] The method did not require a special photocatalyst but only employed $NiBr_2 \cdot 3H_2O$ as the catalytically active component as well as quinuclidine as sacrificial base. The reaction mixture was irradiated with blue LEDs for 3–15 h giving the corresponding products in generally good yields (60–80 %). The reported functional group tolerance was broad including benzylic C–H bonds, halides (F, Cl), OH, (thio)ethers, ketones, esters, amides, carbamates, amines, nitriles as well as some heterocycles (e.g. pyridine or furan).



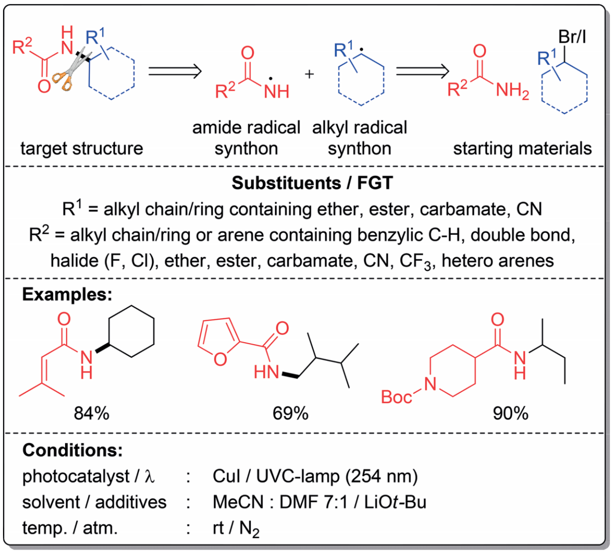
Scheme 36. Aryl-nitrogen disconnection for the synthesis of aromatic amines.[151]

MacMillan and co-workers reported a similar procedure using an additional iridium based photocatalyst and blue light instead of only the nickel complex.[152] Our group was able to realize this transformation using a heterogeneous photocatalyst instead of an iridium-based one.[153] Johannes and co-workers expanded MacMillan's procedure from alkylamines to monoarylamines.[154] In addition to that, MacMillan and co-workers also published the sulfonamidation of arenes starting from aryl halides and sulfonamides.[155]

6.3 Generation of Amides

Nitrogen-containing molecules belong to the most important compound classes due to their ubiquitous presence in fine chemicals, pharmaceuticals and, of course, natural products. Many thermal (and some electrochemical) methods for the formation of C–N bonds were developed and extensively reviewed.[124] In addition to those methods many photochemical and photocatalytic processes were developed giving rise to previously elusive transformations.

Fu and co-workers reported the UV-light mediated amidation of alkyl bromides and iodides by photoredox catalysis (Scheme 37).[156] The method employed commercially available copper iodide as the photocatalyst and lithium *tert*-butylate as the base. The reaction mixture was irradiated with a 254 nm UVC-lamp light source for 24 h giving the corresponding products in generally good yields (60–80 %). The reported functional group tolerance was broad including double bonds, halides (F, Cl), ethers, esters, carbamates, CN and CF_3 groups as well as heteroarenes (e.g. pyridine or furan).



Scheme 37. Alkyl-nitrogen disconnection for the synthesis of amides.[156]

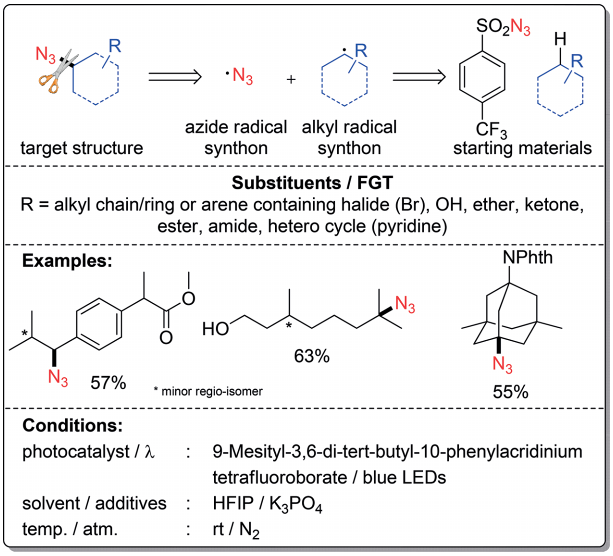
An alternative procedure was developed by Leow who reported an oxidative coupling between aromatic aldehydes and secondary amines to forge amides using phenazine-ethosulfate as commercially available photocatalyst.[157] Moreover, Laha and co-workers realized the amidation of the benzylic position by C–H activation using commercially available dicyanoanthracene as the photocatalyst and *N*-methoxy amides as starting materials.[158] Finally, Stephenson and co-workers reported the aryl-amidation of double bonds starting from aryl sulfonacetamides. In this reaction, the aryl sulfonacetamide splits, loses SO_2 and both the acetamide and the aryl residue add to the double bond.[159]

In addition to the amidation of aliphatic amines also amidations of anilines were reported. Tan and co-workers developed a method using potassium salts of thio acids as carbonyl source and simple anilines as amine source.[160] The reported functional group tolerance was broad including halides (F, Cl), OH, ethers, acids, esters, carbamates, and CN groups. Moreover, our group contributed the amidation of heterocycles (e.g. pyrroles and furans) starting from acyl azides[161] and the sulfonamidation of heterocycles starting from *N*-alkylsulfonamides.[162]

6.4 Generation of Aliphatic Azides

Nitrogen-containing molecules belong to the most important compound classes due to their ubiquitous presence in fine chemicals, pharmaceuticals and, of course, natural products. Many thermal (and some electrochemical) methods for the formation of C–N bonds were developed and extensively reviewed.[124] In addition to those methods many photochemical and photocatalytic processes were developed giving rise to previously elusive transformations.

Alexanian and co-workers reported the visible-light-mediated azidation of aliphatic compounds by photoredox catalysis (Scheme 38).[163] The method employed commercially available 9-mesityl-3,6-di-*tert*-butyl-10-phenylacridinium tetrafluoroborate as the photocatalyst and K_3PO_4 as the base. The reaction mixture was irradiated with blue LEDs for 20 h giving the corresponding products in generally good yields (60–80 %). The reported functional group tolerance was moderate including halides (Br), OH, ethers, ketones, esters, amides, heterocycles (e.g. pyridine).



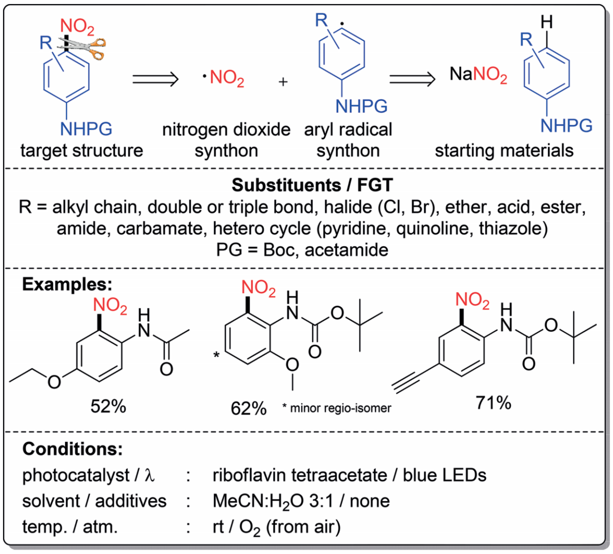
Scheme 38. Alkyl-nitrogen disconnection for the synthesis of aliphatic azides.[163]

A similar procedure was reported by Chen and co-workers using $Ru(bpy)_3Cl_2$ as photocatalyst and Zhdankin's Reagent as azide source.[164] An alternative procedure for the synthesis of benzylic azides by C–H functionalization was developed by Greaney and co-workers using a copper-based photocatalyst and Zhdankin's Reagent as azide source.[165] Moreover, Leonori and co-workers developed a method for the azidation of α-amino acids giving α-amino azides after decarboxylative azidation catalyzed by Rhodamine 6G.[166] Another alternative procedure was developed by Reiser and co-workers who reported a copper-catalyzed oxo-azidation of vinyl arenes to give α-azido-ketones.[167] A similar procedure was developed by Lu and co-workers yielding α-azido alcohols instead of ketones.[168]

6.5 Generation of Nitroarenes

Nitrogen-containing molecules belong to the most important compound classes due to their ubiquitous presence in fine chemicals, pharmaceuticals and, of course, natural products. Many thermal (and some electrochemical) methods for the formation of C–N bonds were developed and extensively reviewed.[124] In addition to those methods many photochemical and photocatalytic processes were developed giving rise to previously elusive transformations.

Our group reported the visible-light-mediated acid-free nitration of protected anilines by photoredox catalysis (Scheme 39).[169] The method employed commercially available riboflavintetraacetate (RFTA) as the photocatalyst without further additives. The reaction mixture was irradiated with blue LEDs for 1–24 h giving the corresponding products in generally moderate yields (50–70 %). The reported functional group tolerance was moderate including double and triple bonds, halides (Cl, Br), ethers, acids, esters, amides, carbamates and heterocycles (e.g. pyridine, or thiazole).



Scheme 39. Aryl-nitrogen disconnection for the synthesis of nitroarenes.[169]

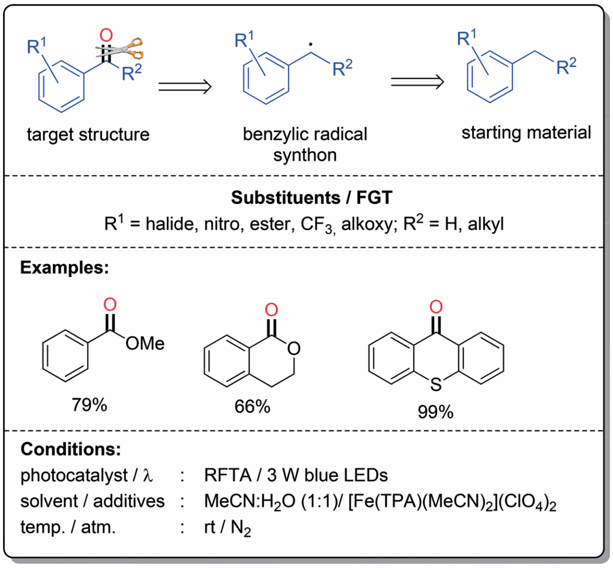
7. C–O Bond

7.1 Generation of Ketones

Ketones are versatile building blocks of functional chemicals and pharmaceuticals. Traditionally stoichiometric amount of heavy metals like Cr, Mn, Fe, etc. in presence of an excess amount of oxidant were used for benzylic oxidation of alkyl arenes.[170] In a metal-free version, a stoichiometric amount of hypervalent iodine was used for this purpose.[171] Alternatively, photoredox catalysis may offer a milder approach in this direction.

Strategy 1

Recently Pandey and co-workers showed C–O bond formation via benzylic sp^3 C–H bond activation (Scheme 40). They used $Ir[dF(CF_3)ppy]_2(dtbbpy)PF_6$ as photocatalyst for benzylic oxidation of various alkyl aryls to corresponding carbonyl compounds with moderate to good yield (60–80 %).

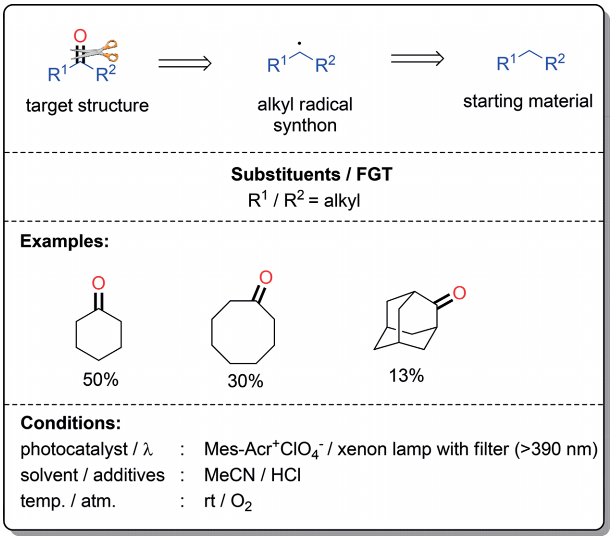


Scheme 40. Alkyl-oxygen disconnection for the synthesis of benzylic ketones.[172]

König and co-workers showed C–H oxygenation of alkyl benzene using riboflavintetraacetate (RFTA) as photocatalyst and $Sc(OTf)_2$ as an additive.[172] But the substrate scope was limited. Later, Wolf and co-workers improved the protocol by a dual catalyst system consisting of RFTA and $[Fe(TPA)(MeCN)_2](ClO_4)_2$ (TPA=tris(2-pyridylmethyl)amine). They were able to perform benzylic oxidation with both electron-donating and withdrawing groups. Moreover, the procedure tolerated many functional groups. Yields are 60–99 %.[173] Lei and co-workers also performed photooxygenation of benzylic sp^3 C–H bond using an organic dye, 9-mesityl-10-methylacridinium ion as photocatalyst and air as oxidant. The yield was moderate (50–70 %) and the substrate scope was not broad.[174] This organic photocatalyst suffers from deactivation due to the presence of nucleophiles. To enhance catalytic performance, Fukuzumi and co-workers showed that the addition of $[(tris(2\text{-}pyridylmethyl)amine)Cu^{II}](ClO_4)_2$ increased the catalytic durability of an organic photocatalyst, 9-mesityl-10-methyl acridinium ion (Acr$^+$-Mes).[175] In a different approach, Alemán, Mancheño, and co-workers designed acridinium-based organo-photocatalysts bearing an imide group at the C9-position and showed better performance for photo-oxygenation.[176] Another method was reported by Yadav and co-workers using CBr_4 as catalyst with the bromine radical as the catalytic active species.[177]

Strategy 2

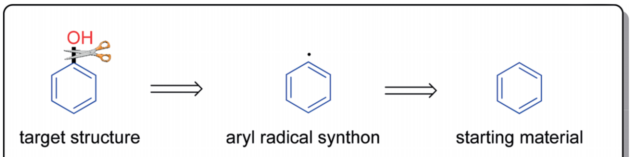
The selective activation of C(sp^3)–H bonds of alkanes without directing groups is still a challenge. Although not on a preparative scale, Fukuzumi and co-workers reported a method to synthesize cyclohexanol and cyclohexanone using 9-mesityl-10-methyl acridinium ion as photoredox catalyst and dioxygen as oxidant (Scheme 41).[178] Yields are poor (below 50 %) and always formed with alcohol as a side-product. A more elaborate strategy was reported by Noel and co-workers using tetrabutylammonium decatungstate (TBADT) as the photocatalyst in a micro-flow reactor yielding the benzylic and alkyl ketones in generally good yields.[179]



Scheme 41. Alkyl-oxygen disconnection for the synthesis of aliphatic ketones.[178]

7.2 Generation of Phenol

Phenol is an important bulk chemical for the industry. In 2011, Fukuzumi and co-workers showed the first example of photooxygenation of benzene with oxygen and water to phenol under ambient conditions by using the 3-cyano-1-methylquinolinium ion as a photocatalyst, although the yield was poor (30 %) (Scheme 42).[180] Almost two years later, they reported the use of DDQ as a photoredox catalyst of this reaction with an improved yield (93 %).[181] The stoichiometric amount of DDQ produced $DDQH_2$ as reduction product. The use of TBN (*tert*-butyl nitrite) allows the use of DDQ in a catalytic amount. Notably, no phenol was observed to be oxidized further because of fast back-electron-transfer of the phenol radical cation, although it is well known that phenol is more readily oxidized than benzene. Inspired by Fukuzumi's results, the Wu group developed the transformation of benzene to phenol without any external oxidant in the presence of a cobaloxime complex.[182] They were able to reach >95 % yield over 5 hours. In a preparative scale, after irradiation for 26 h, a 41 % yield was obtained if 2 mL of benzene (22.3 mmol) were used.



Conditions:

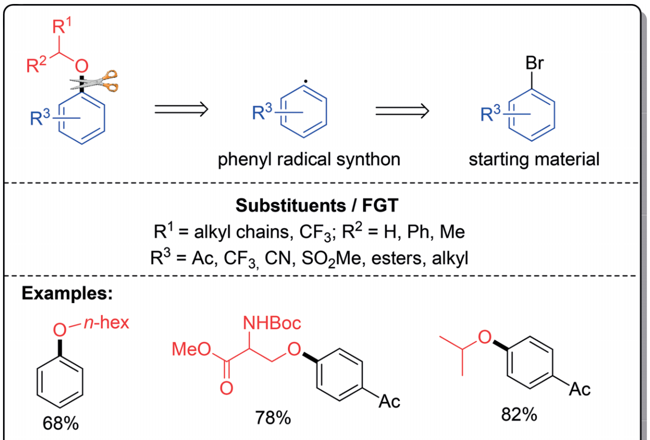
photocatalyst / λ : DDQ / Xenon lamp with filter (>365 nm)
solvent / additives : Water / TBN
temp. / atm. : rt / O_2

Scheme 42. Aryl-oxygen disconnection for the synthesis of phenol.[180]

7.3 Generation of Ethers

Strategy 1

MacMillan and co-workers used a combination of $NiCl_2$ and the iridium catalyst to form aryl ethers starting from an array of aryl bromides (Scheme 43).[184] Both electron-withdrawing and electron-donating substituents were successfully coupled with primary and secondary alcohols. In a different approach, the direct alkoxylation of benzene was developed by the Fukuzumi[183] and Wu[185] groups using alcohol as nucleophile. Chroman could be constructed using this method via intramolecular alkoxylation. For heteroarenes scope, the C-3 etherification of imidazopyridine was also reported by Hajra and co-workers.[186] They used rose Bengal as a photocatalyst and primary and secondary alcohol as nucleophile.



Substituents / FGT

R^1 = alkyl chains, CF_3; R^2 = H, Ph, Me
R^3 = Ac, CF_3, CN, SO_2Me, esters, alkyl

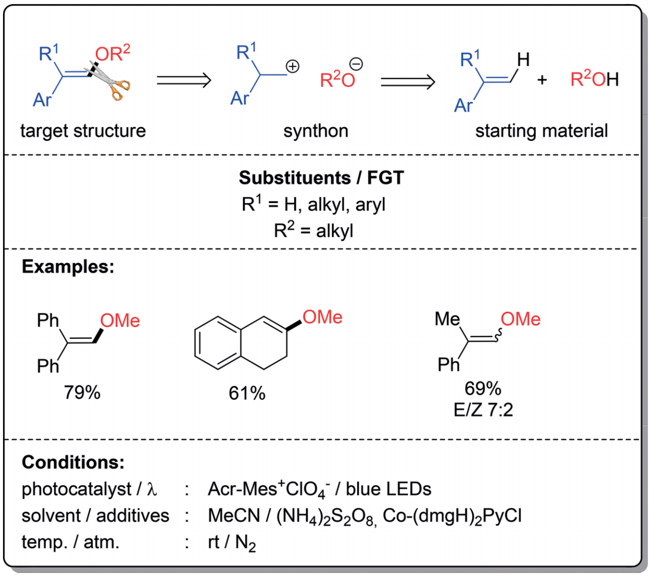
Conditions:

photocatalyst / λ : $Ir[dF(CF_3)ppy]_2(dtbbpy)PF_6$ / blue LEDs
solvent / additives : MeCN / K_2CO_3, quinuclidine, $NiCl_2$·glyme
temp. / atm. : rt / N_2

Scheme 43. Aryl-oxygen disconnection for the synthesis of ethers.[184]

Strategy 2

Lei and co-authors reported the synthesis of enol ethers using the strategy of photocatalytic dehydrogenative coupling of alkenes and alcohols (Scheme 44).[187] The reaction scope of alkenes is somewhat limited as only styrene derivatives can be used. However, the choice of alcohol is flexible, as many aliphatic alcohols can be used. Yields are generally good (60–80 %).

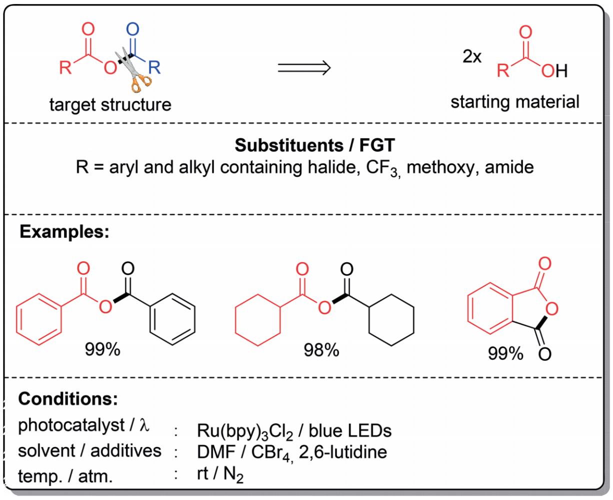


Scheme 44. Alkene-oxygen disconnection for the synthesis of enol ethers.[187]

7.4 Generation of Anhydrides

Strategy 1

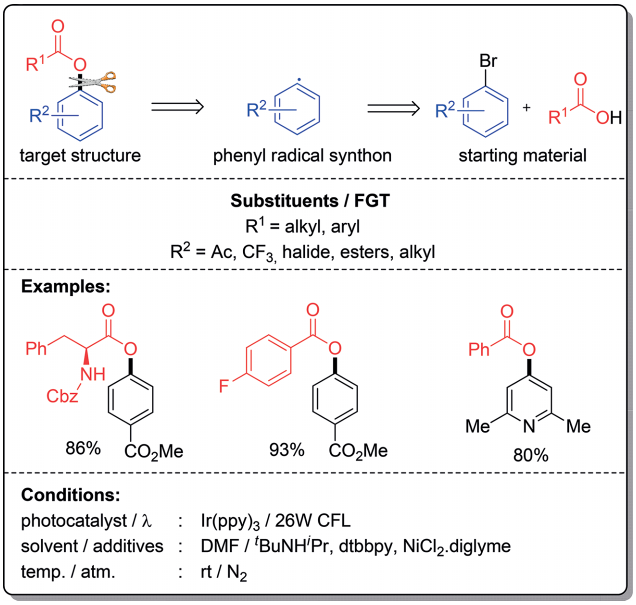
Stephenson and co-workers developed the method for anhydride formation via activation of C–O bonds by the Vilsmeier–Haack reagent formed by Ru(bpy)$_3$Cl$_2$ and CBr$_4$ in DMF (Scheme 45).[188] All products were obtained in very good yield (>90 %). In a preparative scale, they scaled up the reaction of 4-*tert*-butylbenzoic acid (2.5 g) with a lower catalyst loading (0.2 mol-%). The product yield was 85 % yield after work-up. Additionally, when the reaction of 4-*tert*-butylbenzoic acid was conducted in a flow reactor, the reaction time was shortened, providing the anhydride in 97 % yield.



Scheme 45. Carbonyl-oxygen disconnection for the synthesis of anhydrides.[188]

7.5 Generation of Esters

MacMillan and co-workers developed a cross-coupling reaction between carboxylic acids and aryl bromides for the synthesis of O-aryl esters (Scheme 46).[189] By using $NiBr_2$•diglyme (5 mol-%) and $[Ir(ppy)_3]$(2 mol-%) as the photosensitizer under irradiation with visible light, a variety of aromatic compounds could be coupled with alkyl and aryl carboxylic acids to afford the corresponding esters in good yields (62–95 %).



Substituents / FGT
R^1 = alkyl, aryl
R^2 = Ac, CF_3, halide, esters, alkyl

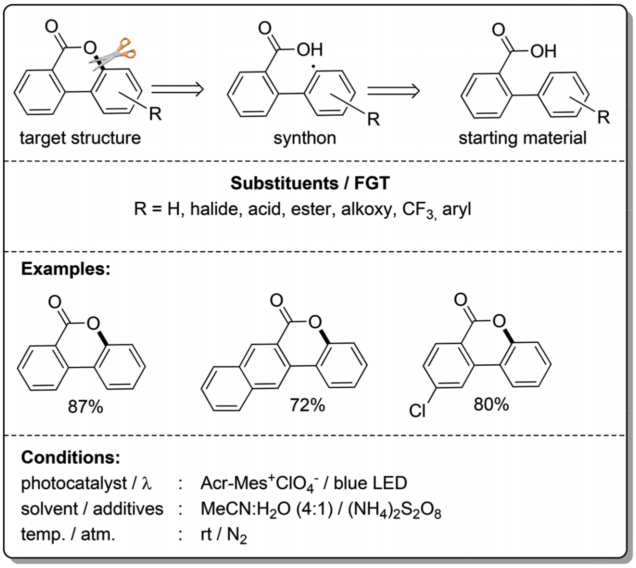
Examples:

Conditions:
photocatalyst / λ : $Ir(ppy)_3$ / 26W CFL
solvent / additives : DMF / ^{t}BuNH^{i}Pr, dtbbpy, $NiCl_2$.diglyme
temp. / atm. : rt / N_2

Scheme 46. Aryl-oxygen disconnection for the synthesis of aromatic esters.[189]

Strategy 2

Gonzalez-Gomez et al. used 9-mesityl-10-methyl acridinium ion as photocatalyst with $(NH_4)_2S_2O_8$ as an external oxidant (Scheme 47).[190] Zhu and Xie et al. used the same photocatalyst with a cobalt co-catalyst.[191] They found that the use of sodium benzoate as a base was paramount for improving yields.



Substituents / FGT
R = H, halide, acid, ester, alkoxy, CF_3, aryl

Examples:

Conditions:
photocatalyst / λ : Acr-Mes$^+$ClO$_4^-$ / blue LED
solvent / additives : MeCN:H_2O (4:1) / $(NH_4)_2S_2O_8$
temp. / atm. : rt / N_2

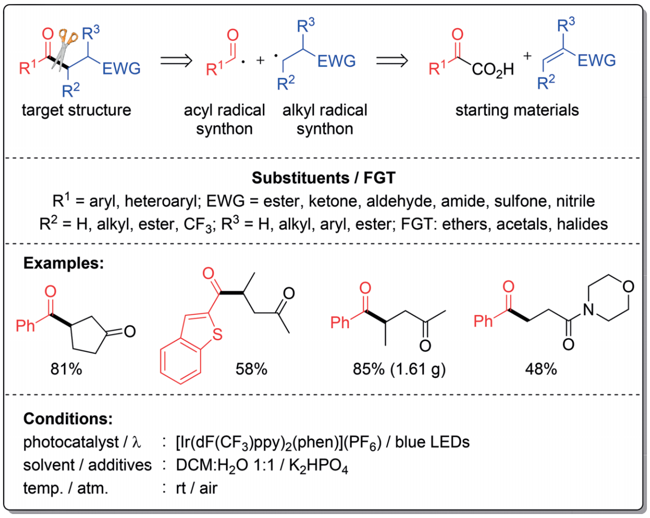
Scheme 47. Aryl-oxygen disconnection for the synthesis of lactones.[190]

8. C–C Bond: sp^2-sp^3 Disconnection

8.1 Generation of Alkyl Ketones

One retrosynthetic approach to ketones involves the disconnection between the carbonyl group and the α-carbon atom. Recent reports show the principle realized in photocatalytic synthesis. The reported methods typically rely on the generation of acyl radicals from suitable precursors and their addition to electron-poor olefins.

The strategy reported by Shang and Fu used aromatic α-oxocarboxylic acids as the source of acyl radicals and Michael acceptors such as α,β-unsaturated esters, ketones, amides, nitriles, sulfones or aldehydes (Scheme 48). Acyl radicals were generated in a photooxidative manner using commercially available $[Ir(dF(CF_3)ppy)_2(phen)](PF_6)$ photocatalyst under blue light irradiation. On the olefin side, the reaction tolerated alkyl and electron-withdrawing substituents (R^2 and R^3) and was limited to mono-β-substituted olefins. Aryl substituents were only tolerated at the α position (R''). The typical yields were in the range of 50–90 % and benzaldehyde was identified as the main side product. Additionally, the reaction can be scaled-up to over one gram of substrate. α-Oxocarboxylic acids were also used as the source of acyl radical for the addition to α-trifluoromethyl alkenes, which upon β-fluorine elimination yielded γ,γ-difluoroallylic ketones.[193] Importantly, this strategy was not limited to aromatic α-oxocarboxylic acids, but alkyl- and amino-substituted ones can also be used (R^1 = alkyl, aryl or amine).



Substituents / FGT
R^1 = aryl, heteroaryl; EWG = ester, ketone, aldehyde, amide, sulfone, nitrile
R^2 = H, alkyl, ester, CF_3; R^3 = H, alkyl, aryl, ester; FGT: ethers, acetals, halides

Examples:

Conditions:
photocatalyst / λ : $[Ir(dF(CF_3)ppy)_2(phen)](PF_6)$ / blue LEDs
solvent / additives : DCM:H_2O 1:1 / K_2HPO_4
temp. / atm. : rt / air

Scheme 48. Acyl-alkyl disconnection for the synthesis of alkyl ketones.[192]

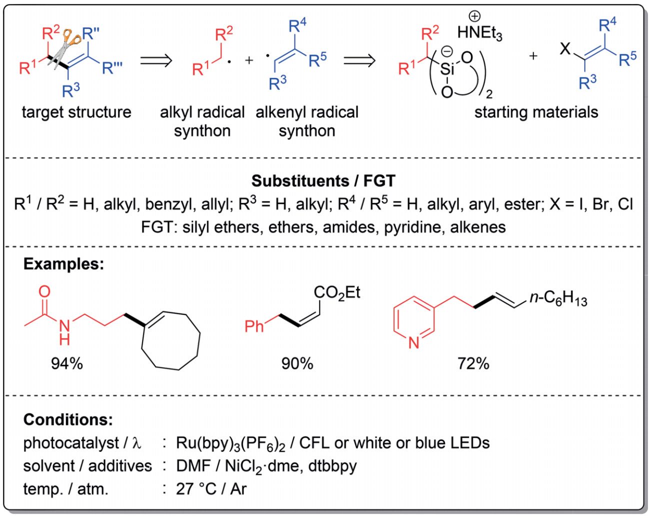
Other recent reports show that acyl radicals, suitable for the synthesis of alkyl ketones, can be accessed from acylsilanes,[194] anhydrides,[195] 4-acyl-1,4-dihydropyridines,[196] 2-(*S*)-pyridyl thioesters,[197] or – after carbonylation with CO - from organosilicates.[198] Alternatively, the synthesis of alkyl ketones through reaction of photogenerated alkyl radicals with carbonyl compounds has been reported.[199]

8.2 Generation of Substituted Alkenes

Strategy 1

Substituted alkenes are not only important functional groups in many natural products, but also serve as convenient starting materials for various late-stage functionalization procedures. Alkyl-substituted arenes and alkenes are accessible by photo-nickel dual catalysis. The method exploits the affinity of organonickel species for sp^3-centered carbon radicals and consequently enables the coupling to various aryl and alkenyl halides.

Molander et al. reported alkyl silicates as the source of primary and secondary sp^3-radicals (Scheme 49).[200] Starting materials were prepared by the authors from the corresponding alkyl trimethoxysilanes and were isolated without the need for chromatographic purification. Electron-rich, -neutral and –deficient alkenyl halides: iodides, bromides, and chlorides, were used as cross-coupling partners giving the desired olefins in 50–90 % isolated yields. The method was compatible with diverse functional groups, but unprotected alcohols and amines were not tolerated well. Gram-scale synthesis was shown. Importantly, the geometry of the double bond was fully retained during the reaction. The oxidation potentials of alkylsilicates (E = +0.75 V vs. SCE, on average) allowed for the use of readily available $[Ru(bpy)_3(PF_6)_2]$ photocatalyst in the photoredox cycle and the Ni(II) complex was used as pre-catalyst for the cross-coupling cycle. The choice of light source had no influence on the reaction and both CFL or LED (white or blue) lamps were used.



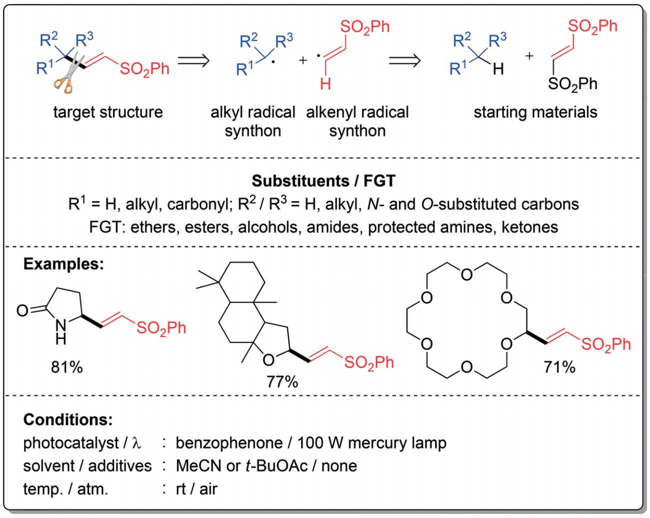
Scheme 49. Alkenyl-alkyl disconnection for the synthesis of substituted alkenes.[200]

Similarly, dual catalysis has been employed for alkene synthesis starting from other alkyl radical precursors such as trifluoroborate salts,[201] 4-alkyl-1,4-dihydropyridines,[202] α-amino acids,[203] *N*-arylamines,[203] carboxylic acids[204] or even unactivated alkyl bromides.[205]

Strategy 2

Photocatalytic synthesis of olefins can be also achieved without resorting to dual catalysis and in some cases in completely metal-free conditions. The retrosynthetic analysis leads to the precursors of alkyl radicals and olefins bearing a good radical leaving group (e.g. arylsulfonyl).

In 2014, Kamijo and Inoue reported the direct alkenylation of aliphatic $C(sp^3)$–H bonds with *trans*-1,2-bis(phenylsulfonyl)-ethylene (Scheme 50).[206] Benzophenone upon the excitation with UV light served as a hydrogen-atom-transfer mediator to generate carbon radicals, which upon addition to the olefin and elimination of a sulfonyl radical gave (*E*)-sulfonylalkenes. The alkenylation occurred preferably at the most electron-rich C–H bonds adjacent to heteroatoms such as nitrogen or oxygen, but also the functionalization of inert aliphatic C–H bonds was achieved. The obtained yields usually exceeded 70 %, even for complex starting materials such as methyl deoxycholate. MeCN or *t*BuOAc were used as solvents and the reaction mixtures were irradiated at room temperature with 100 W mercury lamp. A clear advantage of the method stems from the fact that all of the reaction components are commercially available. The synthetic utility was further demonstrated by converting the derived sulfonylalkenes to prenyl- and pyrrole-derivatives.

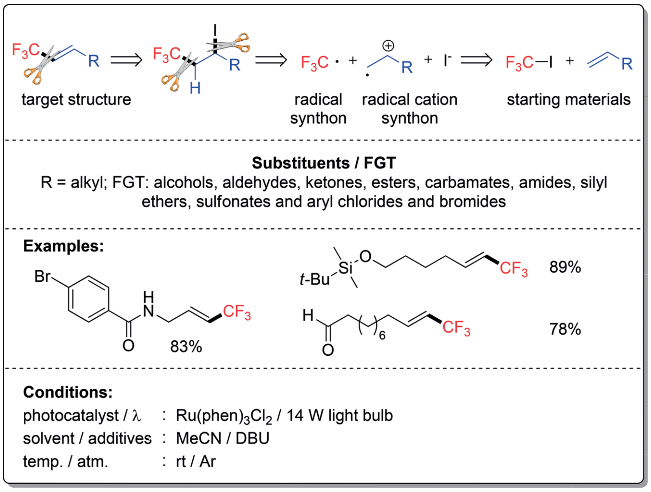


Scheme 50. Alkenyl-alkyl disconnection for the synthesis of substituted alkenes.[206]

The above-mentioned studies were limited to the *trans*-1,2-bis(phenylsulfonyl)ethylene on the olefin scope. However, numerous other photocatalytic methods have been developed, allowing to introduce a broad range of alkenyl fragments via alkyl radical coupling.[207]

8.3 Generation of Trifluoromethyl Alkenes

CF_3 groups are important structural motifs in pharmaceutically active compounds.[208] A convenient visible-light-induced strategy to this class of compounds involves photoinduced ATRA reactions of alkenes with trifluoroiodomethane, followed by elimination of hydrogen halide (Scheme 51).



Substituents / FGT
R = alkyl; FGT: alcohols, aldehydes, ketones, esters, carbamates, amides, silyl ethers, sulfonates and aryl chlorides and bromides

Conditions:
photocatalyst / λ : $Ru(phen)_3Cl_2$ / 14 W light bulb
solvent / additives : MeCN / DBU
temp. / atm. : rt / Ar

Scheme 51. Alkenyl-CF_3 disconnection for the synthesis of trifluoromethyl alkenes.[209]

Cho et al. developed a method for trifluoromethylation of alkenes, employing visible light-induced photocatalysis, CF_3I and a base.[209] It allowed for functionalization of a variety of terminal alkenes in 80–95 % isolated yields and displayed remarkable selectivity towards (*E*)-stereoisomers. Although $Ru(phen)_3Cl_2$ was a photocatalyst of choice, other commercially available Ru- and Ir complexes also proved effective. Importantly, the required catalyst loading was very low (0.01 mol-%). DBU was used as both the quencher for the photocatalyst and the base for hydrogen iodide elimination. It allowed selective elimination of more acidic hydrogen atoms in α-position to the CF_3 group, minimizing the formation of allyl-products. The method tolerated a variety of functional groups including alcohol, unprotected aldehydes and ketones, esters, carbamates, amides, silyl ethers, sulfonates, and aryl halides. It was not limited to terminal alkenes, however, the internal ones displayed low regio- and stereoselectivity, giving the mixtures of isomers.

Alternatively, visible-light-induced methods for the synthesis of trifluoromethyl alkenes have been reported e.g. with the use of 1-trifluoromethyl-1,2-benziodoxol-3(1H)-one (Togni reagent)[210] or photoreduced trifluoromethyl iodide.[211]

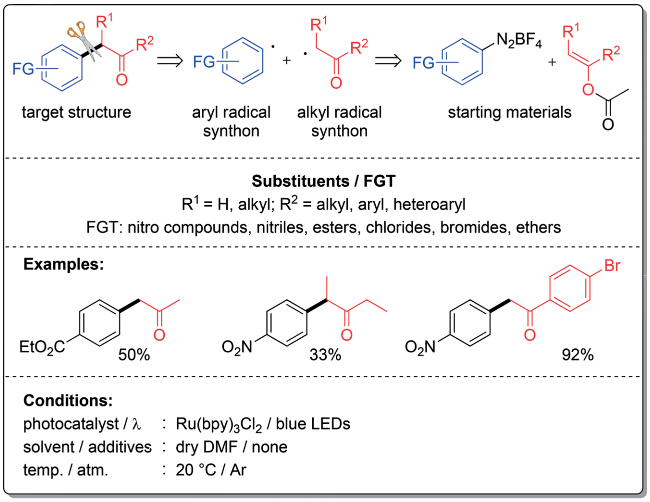
8.4 Generation of Substituted Arenes

The sp^2-sp^3 disconnection is a logical approach to alkyl-substituted arenes. Two retrosynthetic strategies can be considered leading either to precursors of sp^2 radicals and suitable coupling partners (Meerwein-type arylation), or, as in the case of substituted alkenes, sp^3 radicals often supported by dual photocatalysis with nickel.

Methods for the direct C–H functionalization of heteroarenes are described in Section 8.5.

Strategy 1

In the first of the abovementioned strategies, aryldiazonium salts or hypervalent iodine compounds can be considered as convenient precursors of aryl-sp^2 centered radicals.[212,213] These compounds react efficiently with enol acetates, providing β-aryl ketones (Scheme 52). The reaction proceeds at room temperature and is compatible with various functional groups such as NO_2, CF_3, CN, esters, halides or heteroarenes. The best results (yields 75–90 %) were obtained with terminal olefins, while β-substituted ones give more moderate yields (30–35 %). The process is redox-neutral and does not require any additives. Although the ruthenium complex was reported as a photocatalyst of choice, the reaction proceeds also in the presence of organic dyes: Eosin Y, Eosin B, and Rose Bengal. The method can be used for the synthesis of β-aryl aldehydes, although in this case yields below 30 % were obtained.



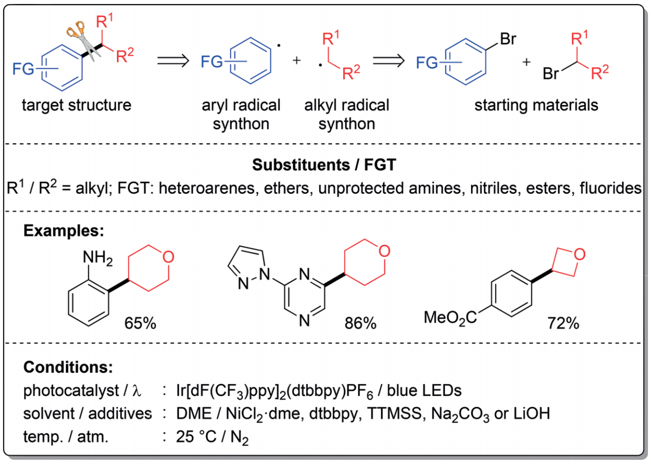
Substituents / FGT
R^1 = H, alkyl; R^2 = alkyl, aryl, heteroaryl
FGT: nitro compounds, nitriles, esters, chlorides, bromides, ethers

Conditions:
photocatalyst / λ : $Ru(bpy)_3Cl_2$ / blue LEDs
solvent / additives : dry DMF / none
temp. / atm. : 20 °C / Ar

Scheme 52. Aryl-alkyl disconnection for the synthesis of substituted arenes.[212]

Strategy 2

The second approach towards alkyl-substituted arenes relies on the formation and reactivity of C(sp^3) radicals. The groups of MacMillan, Molander, Doyle, and Fensterbank showed that, similar to substituted alkene synthesis, such radicals can be accessed from organoboron-compounds, 1,4-dihydropyridines, bis-catecholato silicates, and amino acids.[214] However, the use of non-activated alkyl halides for this purpose was more challenging. A solution to this challenge has been reported by MacMillan in 2016.[215] They developed a cross-electrophile coupling method between alkyl and aryl halides, employing nickel dual catalysis and tris(trimethylsilyl)silane as additive (Scheme 53).



Scheme 53. Aryl-alkyl disconnection for the synthesis of substituted arenes.[215]

The activation of alkyl bromides is realized via halogen abstraction by a silyl radical and results in the formation of the alkyl radical. It enters the Ni-catalytic cycle and upon reductive elimination forms a new C(sp^2)–C(sp^3) bond. Primary, secondary, and tertiary alkyl bromides react with isolated yields ranging from 50 to over 90 %. On the aryl bromide scope, the reaction tolerates both electron-donating and electron-withdrawing substituents, as well as heteroarenes. All of the coupling partners are readily available or can be easily obtained from the corresponding alcohols. The reaction is compatible with functional groups including unprotected amines, esters, nitriles, 3- and 4-membered rings and more. Different conditions for the same type of transformation were developed by Lei et al. They succeeded in coupling primary and secondary alkyl bromides with the strongly reducing Ir(dtbby)(ppy)$_2$PF$_6$ complex and the addition of MgCl$_2$.[216]

Along with the growing interest in hydrogen-atom-transfer photocatalysis, the use of non-prefunctionalized alkyl radical precursors has been extensively studied and several cross-coupling reactions with aryl halides have been developed.[217]

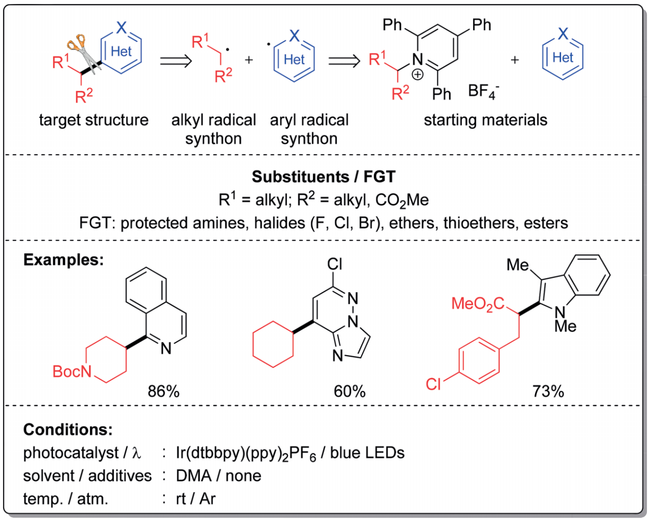
8.5 Generation of Substituted Heteroarenes

Heteroarenes constitute the backbone of a vast number of natural products, medicinally valuable compounds, and agrochemicals. Hence, late-stage functionalization of these structural motifs receives growing interest as a preferred strategy for diversification of compound libraries. Electron-deficient aromatic compounds react with alkyl radicals via Minisci-type alkylation. The photocatalytic variants of these reactions received a lot of attention in recent years and numerous protocols have been reported.[218]

Other methods for the synthesis of alkyl-substituted arenes are described in Section 9.5.

Strategy 1

Glorius reported a deaminative strategy for the generation of alkyl radicals and reactions with nitrogen-containing heteroarenes (Scheme 54).[219] Abundant and inexpensive primary amines have been activated by converting into Katritzky pyridinium salts and used as starting materials. The synthesis requires condensation of an amine with 2,4,6-triphenylpyrylium tetrafluoroborate, typically without chromatographic purification. The photocatalytic reaction gave alkylated quinolones, isoquinolines, imidazopyridazine, phenanthridine and phenanthroline derivatives in yields from 60 to 90 %. Commercially available [Ir(dtbbpy)(ppy)$_2$]PF$_6$ was used as photocatalyst and a reaction time of 48 h was required. Katritzky salts derived from natural and unnatural amino acid methyl esters were used in the reaction. Due to the more electrophilic nature of alkyl radicals, these compounds were treated with more electron-rich heteroarenes, giving products in yields of 30–70 %.

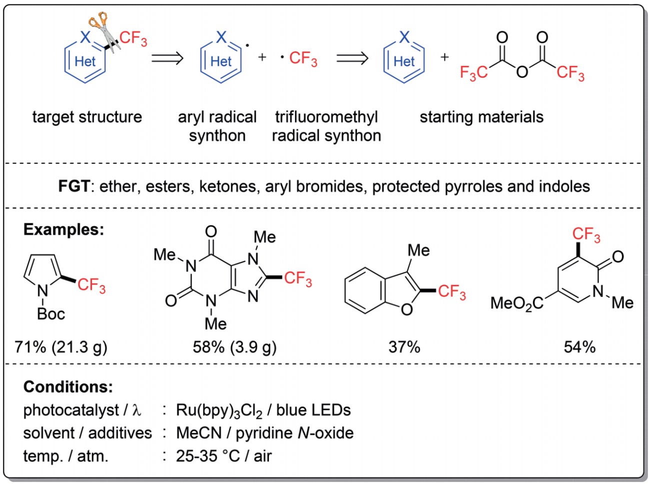


Scheme 54. Heteroaryl-alkyl disconnection for the synthesis of substituted heteroarenes.[219]

Many other alkyl-radical precursors have been applied in photocatalytic Minisci-type reaction. These include carboxylic acids, borates, and boronic acids, *N*-(acyloxy)phthalimides, alkyl halides, alcohols, ethers, alkanes and more.[130,220] A variant of C(sp^3)-H heteroarylation utilizing 1,5-hydrogen atom transfer has also been developed.[221]

Strategy 2

Electrophilic CF_2X radicals react with electron-rich arenes and heteroarenes and allow for late-stage tri- and difluoromethylation. In 2015, Stephenson developed a strategy that employs pyridine *N*-oxide for the generation of CF_3 radicals from cheap and available trifluoroacetic anhydride (Scheme 55).[222] The reaction proceeds under blue light irradiation and requires a loading of 0.1–1 mol-% of $[Ru(bpy)_3]Cl_2$ photocatalyst. Various C–H trifluoromethylated heteroarenes and arenes were obtained in yields from 25 to 65 %. The reaction tolerated the presence of air and moisture. Trifluoromethylation of *N*-Boc-pyrrole was scaled-up to 18 g in both batch- and flow-mode giving the product in 57 % and 71 %, respectively. Through a collaboration with Eli Lilly this scale was increased to 1.2 kg in a continuous flow system (50 % yield).[223] The methodology was later on expanded to radical perfluoroalkylation and chloro-difluoromethylation of (hetero)arenes.[224]



Scheme 55. Heteroaryl-trifluoromethyl disconnection for the synthesis of substituted electron-rich heteroarenes.[222]

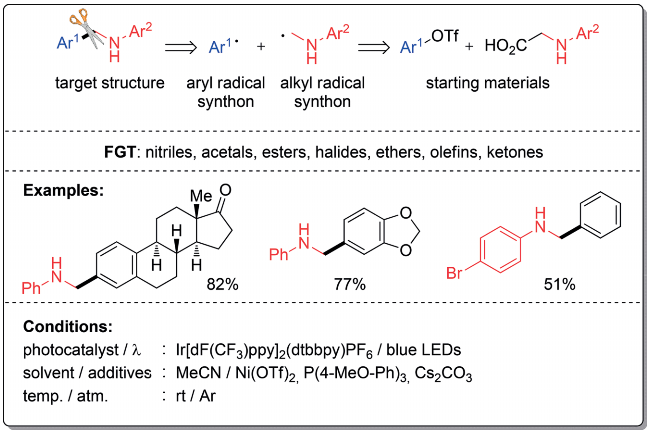
Other methods for visible-light-induced synthesis of trifluoromethylated heteroarenes have been reported. MacMillan accessed trifluoromethyl radical species by reducing trifluoromethanesulfonyl chloride,[225] while the groups of Fukuzumi, Cho, and You used platinum(II) acetylacetonate as a photosensitizer to reduce trifluoromethyl iodide.[211]

8.6 Generation of α-Aminoalkyl-Substituted Arenes

α-Arylamines are motifs present in many biologically active compounds.[226] Photocatalytic methods towards this class of compounds utilize either α-aminoalkyl radical chemistry or iminium ions.

Strategy 1

The affinity of α-aminoalkyl radicals to Ni(0) complexes has been exploited by Rueping, who developed a nickel dual catalytic approach towards benzylamines starting from aryl sulfonates and α-amino acids (Scheme 56).[227] Generation of the α-aminoalkyl radical was achieved via single electron-oxidation by the excited state of Ir(III) complex, followed by deprotonation and decarboxylation. Although most of the presented examples utilized triflates as the source of aryl fragments, mesylates, tosylates, and bromides can also be used, while chlorides display much lower activity. The desired cross-coupling products were formed in isolated yields from 50 to 95 %. The methods functional group tolerance includes esters, halides, protected aldehydes, olefins, and ketones.



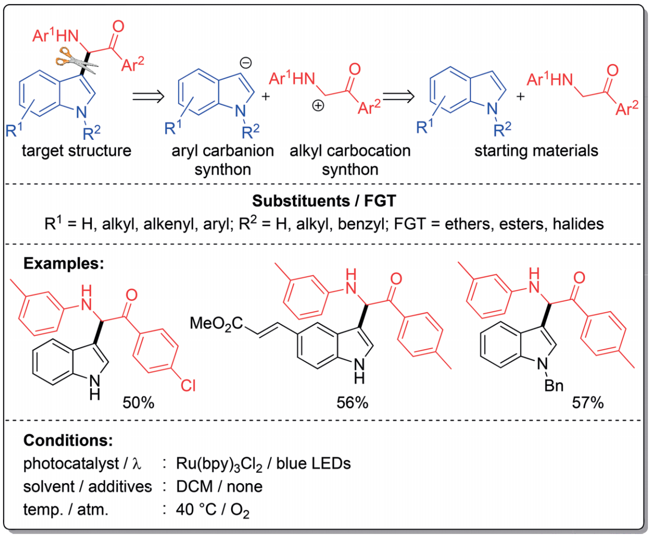
Scheme 56. Aryl-(α-aminoalkyl) disconnection for the synthesis of substituted arenes.[227]

Other arylation reactions of α-aminoalkyl radicals have been developed by the group of MacMillan. Their work covers both decarboxylative transformations of α-amino acids or direct C–H activation of amines for coupling in either purely photocatalytic or dual/triple catalytic manner.[214b,217b,228] Very recently Shang, Fu et al. reported enantioselective Minisci-type decarboxylative α-aminoalkylation of heterocycles mediated by triphenylphosphine and sodium iodide,[210c] while Phipps achieved the same goal by employing iridium-photocatalyst and chiral Brønsted acids.[229]

Strategy 2

Oxidative generation of iminium cations is a convenient and well-established way for functionalization of amines in α-position.[230] Photocatalysis allows for the oxidation of amines in very mild conditions, often using O_2 as electron acceptor.

Li et al. applied this reactivity for the construction of functionalized indoles (Scheme 57).[231] α-Amino ketones and indole derivatives were used as starting materials, giving the desired products in 40 to 75 % yields. Free-, *N*-methyl- and *N*-benzyl protected indoles were tolerated, while *N*-acyl species gave only trace amounts of product. Rueping et al. developed an alternative method, targeting a similar type of product with α-aminoesters instead of α-amino ketones as starting materials. They achieved yields of 40 to 85 % by taking advantage of combined visible-light photoredox and Lewis acid catalysis to activate the imine intermediate.[232] The reaction displayed functional group tolerance to aryl halides, nitriles, esters, ethers, as well as free-, *N*-methyl- and *N*-TBS protected indoles, Stephenson et al. reported Friedel–Crafts alkylation of electron-rich arenes with iminium cations derived from dialkylamides.[233] The photocatalytic approach was presented along with its thermal alternative occurring at 55 °C.



Scheme 57. Aryl-(α-aminoalkyl) disconnection for the synthesis of substituted arenes.[231]

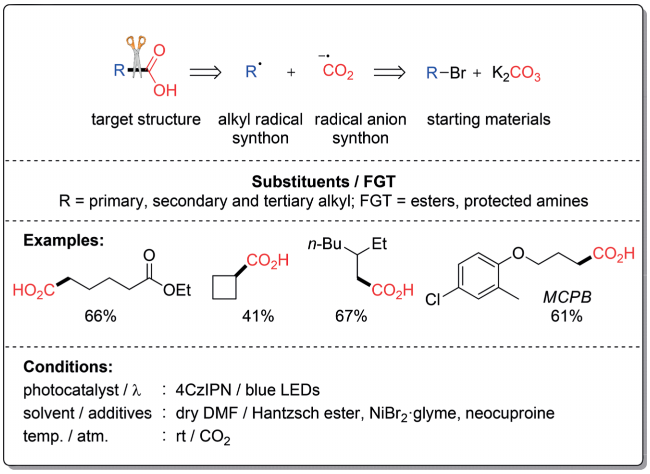
8.7 Generation of Aliphatic Carboxylic Acids

Due to the abundance, low cost, and nontoxicity of CO_2, its fixation is arguably the most important approach for photocatalytic synthesis of carboxylic acids. It is also directly inspired by natural photosynthesis, which uses the energy of visible light to transform CO_2 into valuable chemicals. For these reasons, recent years witnessed immense development of photocatalytic carboxylation processes.[234]

Strategy 1

König et al. presented the application of dual nickel-photoredox catalysis for the carboxylation of aliphatic bromides with CO_2 derived in situ from K_2CO_3 (Scheme 58). They used 4CzIPN as an organic photocatalyst, $NiBr_2$•glyme, and neocuproine as co-catalyst and Hantzsch ester as a terminal electron donor. The reaction was irradiated with standard blue LEDs. It allowed transforming non-activated primary, secondary and tertiary alkyl bromides into corresponding carboxylic acids and the reported yields were in the range of 40–70 %. Additionally, functional groups such as ester, chloride, or Boc-protected amine were tolerated. The practical application of the protocol was demonstrated in the synthesis of biologically active 4-(4-chloro-o-tolyloxy)butyric acid (MCPB).

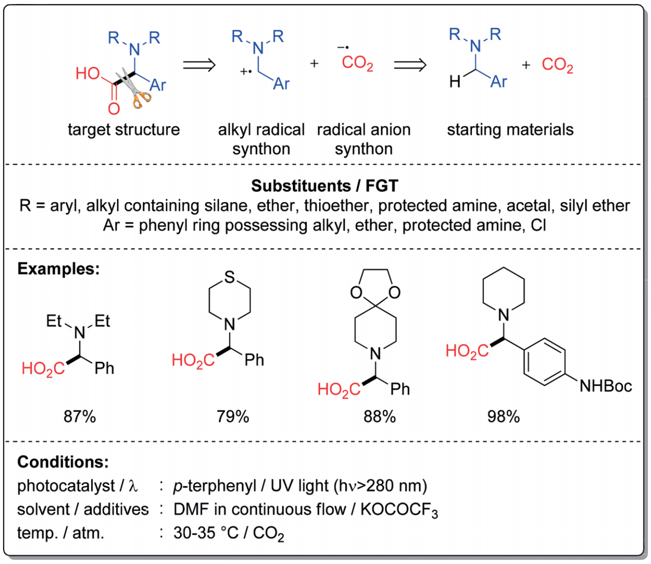
Other methods for the synthesis of aliphatic carboxylic acids through the addition of CO_2 to activated substrates involve the reactions with alkenes[236] and direct C(sp³)-H activation.[237]



Scheme 58. Alkyl-carbonyl disconnection for the synthesis of aliphatic carboxylic acids.[235]

Strategy 2

An alternative strategy towards aliphatic carboxylic acids is the activation of CO_2 itself. One-electron-reduction leads to a reactive radical anion, which may then couple with organic substrates, forming a C–C bond. In 2016 Jamison et al. took this approach to achieve the photocatalyzed synthesis of amino acids in continuous flow (Scheme 59).[238] Gaseous CO_2 and benzylamines were used as substrates. The application of UV light with *p*-terphenyl as a photocatalyst allowed to combine the photooxidation of amines to radical cations and reduction of carbon dioxide, followed by radical-radical coupling of the two species. The reaction displayed high regioselectivity, providing the carboxylation at benzylic position. The typical yields were in the range of 60–95 %. The scope of the reaction was further expanded on non-benzylic amine (*N*-cyclohexylpiperidine), although lower yield of 43 % was obtained.



Substituents / FGT
R = aryl, alkyl containing silane, ether, thioether, protected amine, acetal, silyl ether
Ar = phenyl ring possessing alkyl, ether, protected amine, Cl

Conditions:
photocatalyst / λ : *p*-terphenyl / UV light (hν>280 nm)
solvent / additives : DMF in continuous flow / $KOCOCF_3$
temp. / atm. : 30-35 °C / CO_2

Scheme 59. Alkyl-carbonyl disconnection for the synthesis of aliphatic carboxylic acids through CO_2 activation.[238]

The continuous flow photoredox catalysis approach allowed the same authors to perform direct β-selective hydrocarboxylation of styrenes.[239] Along with organic photocatalysts, CO_2 reductive activation with metal complexes and semiconductors have been extensively studied.[234a]

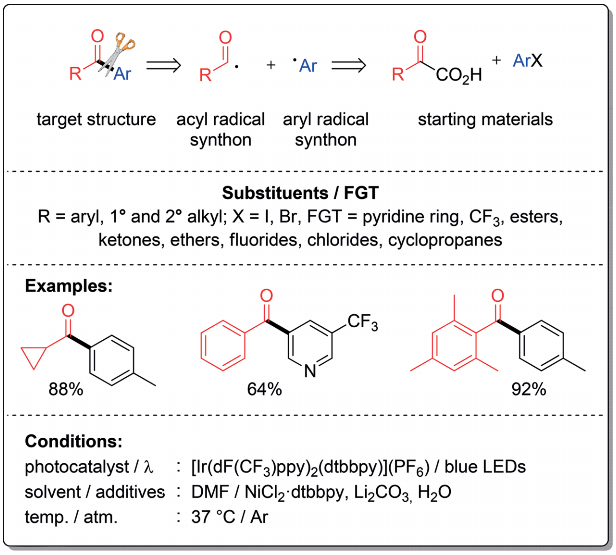
9. C–C Bond: sp^2-sp^2 Disconnection

9.1 Generation of Aryl Ketones

Strategy 1

One retrosynthetic approach to ketones involves the disconnection between the carbonyl group and the α-carbon atom. Recent reports show this principle operating in photocatalytic synthesis as well. The reported methods typically rely on the generation of acyl radicals from suitable precursors and their coupling to arenes.

One of the best-established methods for the generation of acyl radicals involves oxidative decarboxylation of α-oxoacids. They can be used for *ipso*-substitution in aryl halides or aryl boronic acids, activated by Pd- or Ni complexes.[241] MacMillan developed a dual catalytic strategy based on commercially available $[Ir(dF(CF_3)ppy)_2(dtbbpy)]PF_6$ photocatalyst, $NiCl_2$•dtbbpy complex under blue light irradiation (Scheme 60).[240] It allowed transforming aryl bromides and iodides into aryl ketones, using various ketoacids as second reagents. On the halide side, the reaction tolerated alkyl and acyl substituents, chlorides and fluorides, as well as the presence of electron-withdrawing groups and pyridine ring. In the case of α-oxoacids, both alkyl- and aryl- substituents could be appended to the carbonyl group. The typical yields were in the range of 60–90 %. The authors reported the facilitating effect of strong 34 W blue LED lamp on the yield of the product, compared to the standard LED strips. Importantly, the usefulness of the strategy was demonstrated in the synthesis of fenofibrate – a pharmaceutically important agent.



Substituents / FGT
R = aryl, 1° and 2° alkyl; X = I, Br, FGT = pyridine ring, CF_3, esters, ketones, ethers, fluorides, chlorides, cyclopropanes

Conditions:
photocatalyst / λ : $[Ir(dF(CF_3)ppy)_2(dtbbpy)](PF_6)$ / blue LEDs
solvent / additives : DMF / $NiCl_2$·dtbbpy, Li_2CO_3, H_2O
temp. / atm. : 37 °C / Ar

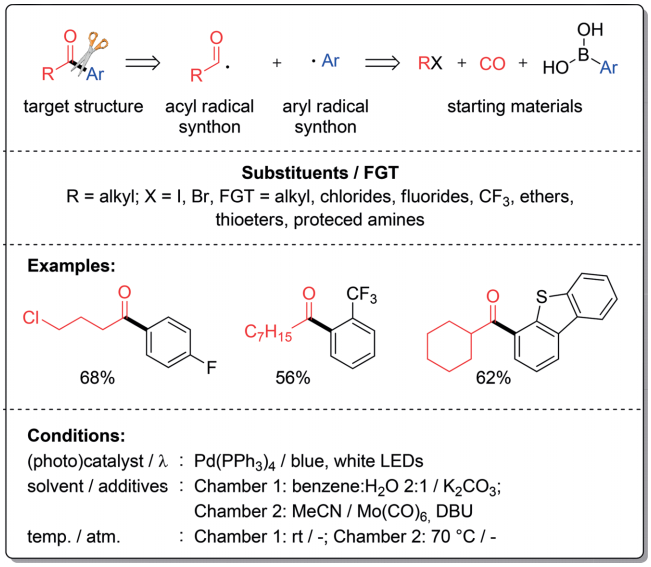
Scheme 60. Acyl-aryl disconnection for the synthesis of aryl ketones.[240]

Alternatively to nickel-species, palladium complexes can also be used in the dual catalytic approach towards aryl ketones. Shang, Fu et al. showed the use of $Pd(Nixantphos)Cl_2$ in the synthesis of aryl ketones from α-oxocarboxylicacids and aryl amides from oxalate monoamides.[242] In a similar fashion, palladium-based catalyst provided also access to aryl aldehydes from glyoxylic acid, though in this case the organic photocatalyst - 4CzIPN – was used.[243]

Strategy 2

α-Oxoacids are not the only sources of acyl radical intermediates in the photocatalytic synthesis of aryl ketones. Aldehydes serve this purpose as well, provided the HAT (hydrogen-atom-transfer) step is involved in the overall process. This approach has been demonstrated by MacMillan, in the triple catalysis with quinuclidine as a HAT catalyst.[244]

Another possibility is the consecutive generation of alkyl radicals and their carbonylation with CO. Odell et al. reported carbonylative Suzuki–Miyaura coupling of unactivated alkyl halides and aryl boronic acids, leading to aryl ketones (Scheme 61).[245]



Substituents / FGT
R = alkyl; X = I, Br, FGT = alkyl, chlorides, fluorides, CF_3, ethers, thioeters, proteced amines

Conditions:
(photo)catalyst / λ : $Pd(PPh_3)_4$ / blue, white LEDs
solvent / additives : Chamber 1: benzene:H_2O 2:1 / K_2CO_3; Chamber 2: MeCN / $Mo(CO)_6$, DBU
temp. / atm. : Chamber 1: rt / -; Chamber 2: 70 °C / -

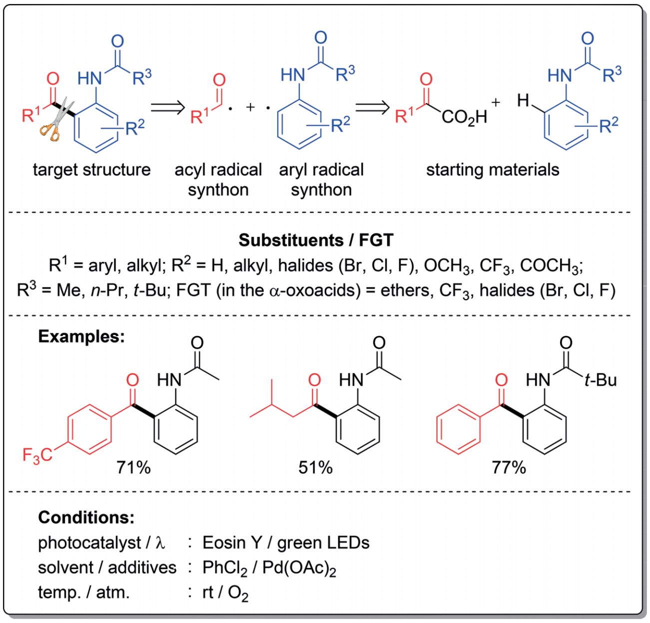
Scheme 61. Acyl-aryl disconnection for the synthesis of aryl ketones.[245]

The reaction was catalyzed exclusively by $Pd(Ph_3)_4$ with 1 mol-% catalyst loading. It has been proposed that, along with the coupling of boronic acids, it is directly responsible for single electron transfer (SET) or photosensitization of alkyl halides, with no additional photocatalyst required. The reaction set-up comprised two chambers: one for the generation of CO of relatively low pressure (≈ 2.5 bar) from $Mo(CO)_6$, and the second one for the catalytic reaction. The procedure allowed for the synthesis of various aryl ketones and the yields range was typically 60–70 % for alkyl iodides and 30–50 % for alkyl bromides. Primary and secondary alkyl halides were tolerated. In the case of tertiary ones, the adamantly-substituted substrates reacted smoothly, while *tert*-butyl bromide and iodide gave no desired product. Excellent chemoselectivity for the iodide center was observed in the presence of chlorine atom. Limitations on the boronic acid side included the presence of aryl bromide, nitroarene, and pyridine ring. The application of the method was demonstrated in the synthesis of the antipsychotic drug, melperone.

Strategy 3

Direct C–H acylation of arenes can also be performed, provided the Pd co-catalyst is used together with the photocatalyst, and the directing group is present in the substrate.

Li, Wang et al. reported decarboxylative *o*-acylation of acetanilides with α-oxocarboxylic acids as an acyl radical source (Scheme 62).[246] Eosin Y (3 mol-%) was used for photo-oxidation of α-oxocarboxylic, and O_2 as sacrificial oxidant. The presence of an amide-directing group in combination with $Pd(OAc)_2$ allowed the *ortho*-C–H activation of the aryl substrate. The reaction proceeded under green light irradiation at room temperature. It was carried out for 15 hours, typically giving isolated yields of the desired *o*-acylacetanilides in the 70–80 % range. The use of alkyl-substituted α-oxocarboxylic acids is tolerated, but the yields of the products are lower (50–60 %). Except for acetanilides, the use of other directing groups (*N*-phenylbutyramide and *N*-phenylpivalamide) instead of acetanilide also provided desired *ortho*-acylation in 82 % and 77 % yields, respectively. Various functional groups such as halides (Br, Cl, F), ethers, ketones, or the CF_3 group were tolerated. This also included small substituents (Me, Cl, F) in *ortho*-position to the acetanilides, but the more sterically demanding *o*-substituents such as *i*Pr o *t*Bu groups inhibited the reaction.



Substituents / FGT
R^1 = aryl, alkyl; R^2 = H, alkyl, halides (Br, Cl, F), OCH_3, CF_3, $COCH_3$;
R^3 = Me, *n*-Pr, *t*-Bu; FGT (in the α-oxoacids) = ethers, CF_3, halides (Br, Cl, F)

Conditions:
photocatalyst / λ : Eosin Y / green LEDs
solvent / additives : $PhCl_2$ / $Pd(OAc)_2$
temp. / atm. : rt / O_2

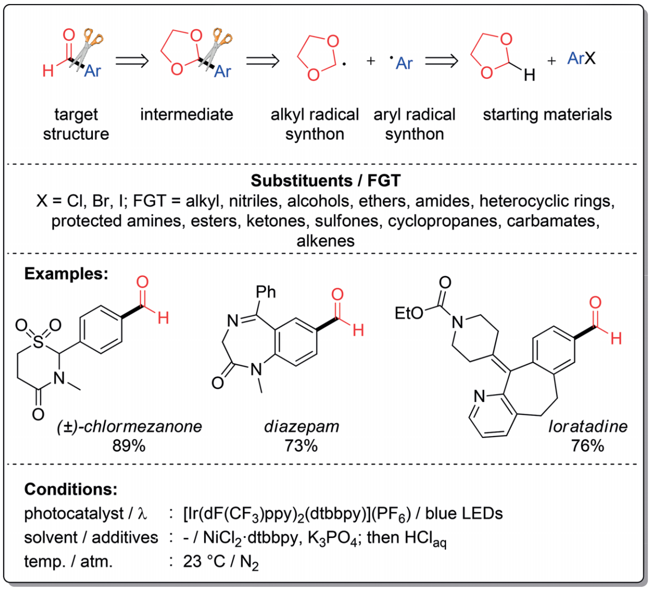
Scheme 62. Acyl-aryl disconnection for the synthesis of aryl ketones.[246]

Another report showed similar reactivity with azobenzene moiety as the directing group and Mes-Acr$^+$ as the photocatalyst.[247] Furthermore, the intramolecular acylation was achieved starting from mixed anhydrides (synthesized in-situ).[248] In this case, no palladium-catalyst nor directing group was required.

Strategy 4

Aromatic aldehydes are important chemical intermediates and various methods of their synthesis have been developed over the years.[249] Recently, the spectrum of catalytic protocols has been extended to photocatalytic formylation of aromatic compounds, providing a photochemical alternative towards such classical reactions as e.g. Vilsmeier–Haack, Reimer–Tiemann, and Duff.

Doyle et al. reported a dual nickel-photoredox approach for redox-neutral formylation of aryl chlorides with 1,3-dioxolane (Scheme 63).[250] The reaction exploits the ability of Ni(III)–Cl bond to undergo photolysis, producing a chlorine radical, which then activates 1,3-dioxolane through selective hydrogen-atom-abstraction. Aryl acetals, which form in the reaction can be easily hydrolyzed, yielding the desired aldehydes. A typical set of reaction conditions involved $[Ir(dF(CF_3)ppy)_2(dtbbpy)]PF_6$ photocatalyst, $NiCl_2$•dtbbpy, K_3PO_4 as a base and blue light irradiation. The reaction time was 72 h. It provided a series of aryl and heteroaryl aldehydes, involving examples of biologically relevant compounds such as fenofibrate, loratadine, diazepam, etc. Typical yields were in the range of 60–80 %. Both electron-deficient and electron-rich aryl chlorides were tolerated, although the former ones gave generally higher yields. Additionally, the method proved applicable to aryl bromides and iodides.



Substituents / FGT
X = Cl, Br, I; FGT = alkyl, nitriles, alcohols, ethers, amides, heterocyclic rings, protected amines, esters, ketones, sulfones, cyclopropanes, carbamates, alkenes

Conditions:
photocatalyst / λ : $[Ir(dF(CF_3)ppy)_2(dtbbpy)](PF_6)$ / blue LEDs
solvent / additives : - / $NiCl_2$·dtbbpy, K_3PO_4; then HCl_{aq}
temp. / atm. : 23 °C / N_2

Scheme 63. Formyl-aryl disconnection for the synthesis of aryl aldehydes.[250]

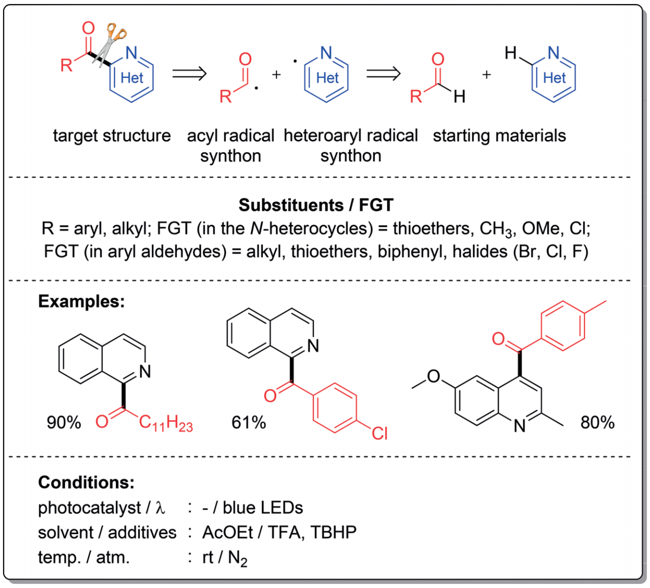
The alternative protocol that also exploits aryl halides has been developed by Mariano, Wang et al.[251] Aromatic aldehydes were obtained via dual catalytic formylation with diethoxyacetic acid as a formyl group source.

9.2 Generation of Heteroaryl Ketones/Aldehydes

Strategy 1

N-heteroarenes can be acylated directly, without resorting to dual catalysis. Ravelli, Ryu et al. reported the use of excited tetrabutylammonium decatungstate (TBADT) to generate acyl radicals directly from aldehydes and formamides. Their Minisci-type addition to protonated quinaldine leads to the formation of heteroaryl ketones.[220j]

Lei et al. obtained acylated *N*-heterocycles using both aromatic and aliphatic aldehydes under photocatalyst-free conditions (Scheme 64).[252] The process required, however, the presence of *tert*-butyl hydroperoxide (TBHP), which was postulated to form the photoactive complex with the protonated heterocycle. TFA was used as the second additive and the reaction was run under the blue light irradiation and an atmosphere of nitrogen for 24 h. The typical yields were in the range of 50–90 %. *para*-Substituted aryl aldehydes gave higher yields then *ortho*-derivatives. More sterically demanding aldehydes e.g. mesitaldehyde were also tolerated. On the *N*-heterocycle side, substituted quinolones, isoquionolines and quinoxaline have been used. The applicability of the method was further demonstrated in a 2 gram-scale synthesis of acylated isoquinoline.



Substituents / FGT
R = aryl, alkyl; FGT (in the *N*-heterocycles) = thioethers, CH_3, OMe, Cl; FGT (in aryl aldehydes) = alkyl, thioethers, biphenyl, halides (Br, Cl, F)

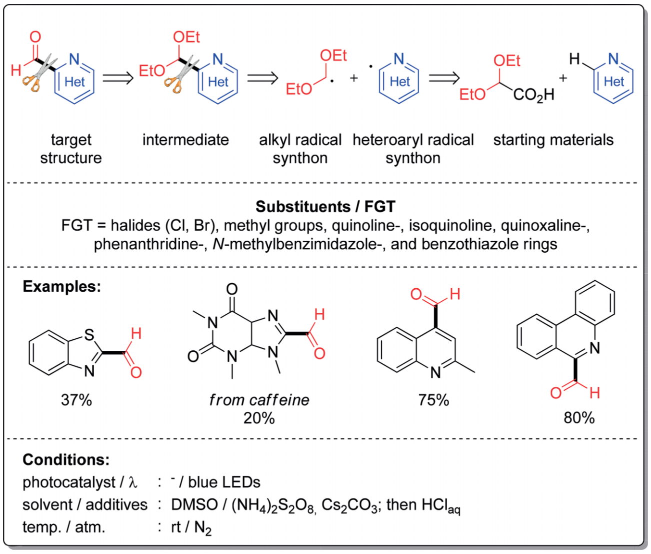
Conditions:
photocatalyst / λ : - / blue LEDs
solvent / additives : AcOEt / TFA, TBHP
temp. / atm. : rt / N_2

Scheme 64. Acyl-heteroaryl disconnection for the synthesis of heteroaryl ketones.[252]

Strategy 2

Along with acylation, which leads to aryl ketones, formylation of *N*-heteroaromatic compounds has been developed. It provides access to heteroaryl aldehydes and is a photocatalytic alternative towards such classical reactions as e.g. Vilsmeier–Haack, Reimer–Tiemann, and Duff.

Yang and Xia reported a visible-light-induced, C–H formylation of *N*-heterocycles with 2,2-diethoxyacetic acid (Scheme 65).[253] The reaction was carried out without any photocatalyst, in the presence of ammonium persulfate as the oxidant and cesium carbonate as the base. In the standard reaction conditions, the mixture was irradiated with 15 W blue LEDs and quenched by HCl to hydrolyze the acetal intermediate. The proposed mechanism involves the formation of the nucleophilic 2,2-diethoxymethine radical, which adds to the *N*-heterocycle. The method provides various formylated heterocycles, starting from such substrates as substituted quinolines, isoquinolines, quinoxaline, phenanthridine, *N*-methylbenzimidazole, and benzothiazole. The typical yields were in the range of 40–70 %. The applicability of the method was further demonstrated in a synthesis of formylated caffeine, although lower yield (20 %) was obtained.



Substituents / FGT
FGT = halides (Cl, Br), methyl groups, quinoline-, isoquinoline, quinoxaline-, phenanthridine-, *N*-methylbenzimidazole-, and benzothiazole rings

Conditions:
photocatalyst / λ : – / blue LEDs
solvent / additives : DMSO / $(NH_4)_2S_2O_8$, Cs_2CO_3; then HCl_{aq}
temp. / atm. : rt / N_2

Scheme 65. Formyl-heteroaryl disconnection for the synthesis of heteroaryl aldehydes.[253]

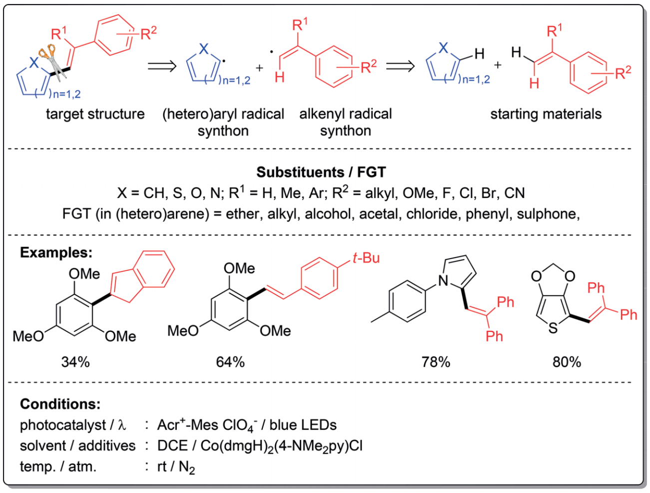
Additionally, the authors explored their method in the C–H acylation of heteroaromatic compounds with α-oxocarboxylic acids. A number of other photocatalytic acylation reactions exploiting α-oxocarboxylic as acyl radical source have also been published.[254]

9.3 Generation of Arylated Alkenes

Strategy 1

Arylated alkenes can be traditionally prepared by cross-coupling reactions catalyzed by transition metals such as Pd or Ni.[255] In this approach, the C(sp^2)–C(sp^2) bond between an aryl and alkenyl moieties is formed, providing the desired structural motif. Thanks to the recent developments in photocatalysis, the same disconnection analysis may now lead to visible-light induced reactions, which do not require a laborious prefunctionalization of the starting materials and in many cases may be advantageous alternatives.

Zhang, Lei et al. reported a photoinduced, dehydrogenative C–H/C–H cross-coupling of arenes and alkenes in a dual catalytic system comprising acridinium photocatalyst and a cobaloxime proton-reducing catalyst (Scheme 66).[256] The process was carried out under the blue light irradiation at room temperature and required no other oxidants. It was postulated that it occurs via oxidation of arenes and subsequent radical addition to the olefin. However alternative mechanistic pathway, in which the activation of the olefin occurs first, cannot be ruled out. Various substituted arylated alkenes were obtained and the typical yields were in the range of 50–90 %. Both electron-rich and electron-deficient styrenes could be employed in the transformation. However, no reaction was observed with aliphatic olefins. On the arene side, only electron-rich compounds proved reactive.



Substituents / FGT
X = CH, S, O, N; R^1 = H, Me, Ar; R^2 = alkyl, OMe, F, Cl, Br, CN
FGT (in (hetero)arene) = ether, alkyl, alcohol, acetal, chloride, phenyl, sulphone,

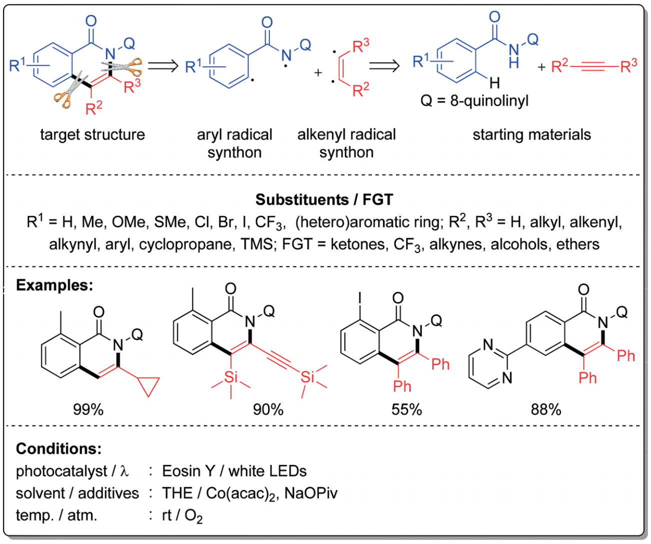
Conditions:
photocatalyst / λ : Acr^+-Mes ClO_4^- / blue LEDs
solvent / additives : DCE / $Co(dmgH)_2(4\text{-}NMe_2py)Cl$
temp. / atm. : rt / N_2

Scheme 66. Aryl-alkenyl disconnection for the synthesis of arylated alkenes.[256]

Alternative, photocatalytic methods for arylation of alkenes with aryl diazonium salts[257] or via directing-group-promoted C–H activation[258] have also been reported.

Strategy 2

The synthesis of a C(sp^2)–C(sp^2) bond between aryl and alkenyl moieties can lead to the formation of a new ring. Rueping, Sundararaju et al. used dual cobalt-photoredox catalysis to transform benzamides and alkynes into isoquinolones (Scheme 67).[259]



Scheme 67. Aryl-alkenyl disconnection for the synthesis of isoquinolones.[259]

The benzamide substrates possess an 8-quinolinyl directing group appended to the nitrogen atom. Eosin Y was used as a photocatalyst for stepwise oxidation of Co(I) to Co(III) complex and dioxygen was a terminal electron acceptor. The reaction was carried out under white light irradiation in 2,2,2-trifluoroethanol. The developed method provided a broad library of isoquinolones, starting from benzamides with different substituents at *ortho*-, *meta*-, and *para*-positions. These also included moieties with strongly chelating properties such as thienyl, pyrazolyl, pyridinyl, pyrimidyl, and 7-azaindolyl. Internal and terminal alkynes can be used, as well as diynes. Functional groups e.g. hydroxy, silyl, and ethynyl were well tolerated. The typical yields were in the range of 70–90 %.

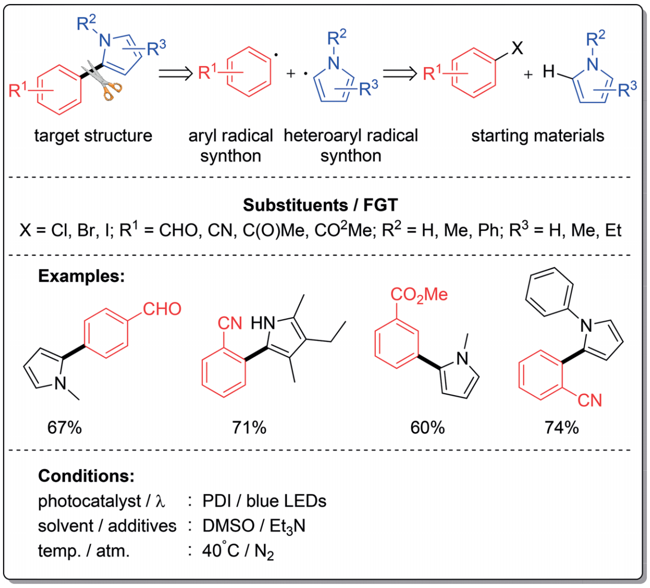
More annulation reactions involving aryl-alkenyl bond formation were published by König,[260] Fu,[261] Zhou[262] or Rueping.[263] Different examples of the synthesis of phenanthridine derivatives from biphenyl isocyanides and alkyl radical precursors were also reported.[264]

9.4 Generation of Bi(hetero)aryls

Strategy 1

The disconnection analysis of C(sp^2)–C(sp^2) bonds between two aryl or heteroaryl moieties often recommends transition metal-catalyzed reactions as the preferred synthetic approach. However, resorting to photocatalytic methods to realize such transformations, provides certain advantages. In many cases, cheap and non-toxic organic dyes can be used as photocatalysts and the reaction usually proceeds at room temperature.

König et al. reported a photoreductive activation of aryl halides and their coupling to substituted pyrroles (Scheme 68).[265] The reaction utilized the ability of perylenebisimide (PDI), which was used as a photocatalys, to accumulate the energy of two visible light photons in a consecutive photoinduced electron-transfer (conPET) process. Thereby an excited state of higher energy can be generated, which allows for the reduction of redox-demanding aryl bromides and chlorides to carboanions which, after the C-X bond cleavage, give aryl radicals, prone to form C–C bonds with electron-rich pyrroles. The reaction proceeded at 40 °C under blue light irradiation. Triethylamine (8 equiv.) was used as a terminal electron donor. The desired biaryl products were formed in yields ranging from 55 % to 75 %. Functional groups such as aldehyde-, keto-, ester-, or nitrile group were well tolerated.



Scheme 68. Aryl-aryl disconnection for the synthesis of biaryls.[265]

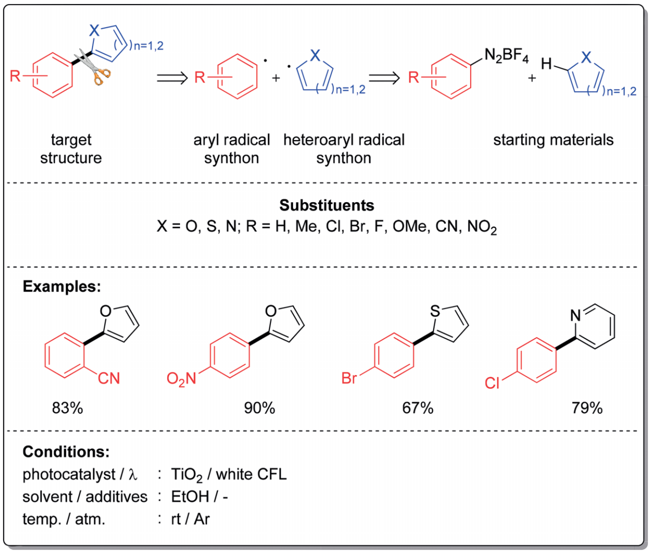
The same authors reported the use of operationally more convenient and readily available Rhodamine 6G for the activation and C(sp^2)-C(sp^2) coupling of stable aryl halides.[266] They also developed a sensitization-initiated approach, in which the required reducing power is generated through the absorption of visible light by Ru(bpy)$_3$Cl$_2$ photocatalyst and subsequent energy transfer to polycyclic aromatic hydrocarbons.[267]

Strategy 2

The C(sp^2)-C(sp^2) disconnection between two aryl groups can also lead to arenediazonium salts and non-functionalized arenes as starting materials.[268] The same is true for retrosynthetic photocatalysis and the light-induced variants of the Gomberg–Bachmann reaction have been reported. The reaction can proceed through the formation of colored charge-transfer complexes between the substrate or can be mediated by the photocatalyst.

The pioneering examples of photoredox-catalysed synthesis of biaryls with arenediazonium salts were reported by Cano-Yelo and Deronzier, who obtained phenanthrenes through the photocatalyzed Pschorr reaction.[270]

Rueping et al. used TiO_2 to mediate the intermolecular coupling between arenediazonium salts and heteroaromatics (Scheme 69).[269] They found that the reaction proceeds through formation of TiO_2-azoethers, which undergoes excitation upon the visible light irradiation. The reaction required a large excess of heteroarenes, which were used in the 1:1 volume ratio to the solvent (EtOH). 11 W CFL bulb was used as the light source and the amount of TiO_2 varied from 0.1 to 1 equiv. Both electron-rich and electron-poor substrates could be applied in this transformation, and the yields of the desired products were in the range of 55–95 %. The practical application of the method was demonstrated in the synthesis of a muscle relaxant – dantrolene.



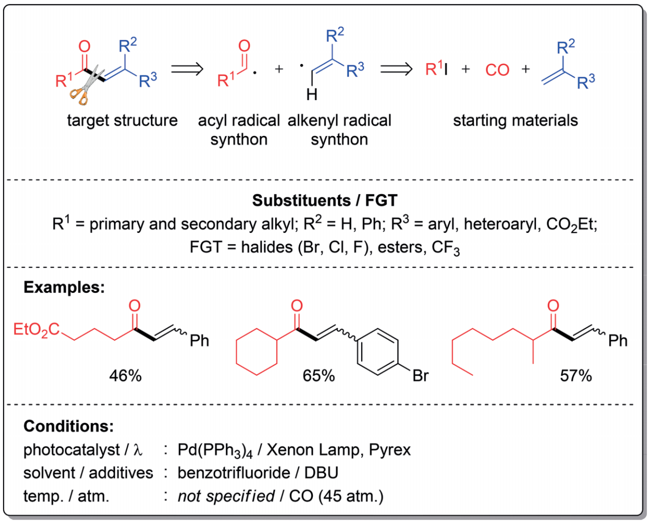
Scheme 69. Aryl-aryl disconnection for the synthesis of biarenes.[269]

The authors reported also a continuous-flow version of this reaction, with TiO_2 immobilized in the microchannels of a continuous flow reactor.[271] Other known methods use alternative photocatalysts such as different semiconductors,[272] ruthenium complexes,[273] iodo-BODIPY compounds,[274] organic dyes,[275] porphyrins,[276] etc.

9.5 Generation of Alkenyl Carbonyls

α,β-Unsaturated carbonyl compounds are key intermediates for organic synthesis. They are substrates in such classical transformations as Michael addition, Diels-Alder reaction or Heck reaction. The α,β-unsaturated carbonyl functionality is also present in various natural products, drugs, and fine chemicals.[277] However, the photocatalytic synthesis of this class of compounds, based on the disconnection between the carbonyl and α-carbon atoms, proved to be challenging.

Ryu et al. reported the synthesis of α,β-unsaturated ketones via carbonylative Mizoroki–Heck reaction of alkyl iodides with alkenes (Scheme 70).[278] The reaction exploited the formation of alkyl radicals from halides, upon the photoinduced single-electron-transfer, and their subsequent carbonylation with CO, which gave the carbonyl radicals. $Pd(PPh_3)_4$ was used as a photocatalyst and xenon lamp provided the required light energy. The use of DBU as a base allowed for deprotonation of intermediate β-carbonyl radical, paving the way for α,β-unsaturated products. A library of enones was synthesized, with typical yields in the range of 40–65 %, as a mixture of *E*/*Z*-isomers. Both primary and secondary iodoalkanes were competent in the reaction. On the olefin side, electron-withdrawing substituents were tolerated, while electron-rich alkenes displayed much lower reactivity.



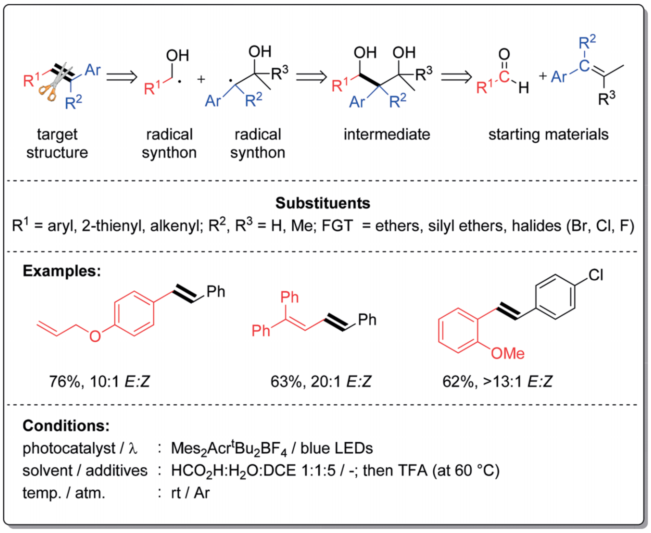
Scheme 70. Alkenyl-carbonyl disconnection for the synthesis of α,β-unsaturated carbonyl compounds.[278]

Another example of photocatalytic, acyl radical alkenylation was recently reported recently by Zhu et al.[279] The authors used C2-acyl-substituted benzothiazolines as acyl radical precursors and 1,1-dicyano-1-alkenes, in the presence of hypervalent iodine reagents to obtain β,β-dicyanoenones in 50–80 % yield. Additionally, few examples involving acylation of alkynes, followed by subsequent cyclization, were reported.[280]

9.6 Generation of Alkenes

Alkenes are omnipresent in natural compounds and bioactive molecules. They are also useful functional groups for further chemical transformations. When considering the construction of C–C double bonds, the olefin metathesis is among the most important methods, both in academical research and in industry. Various modes of activating the reaction have been developed, which employ chemical,[281] mechanochemical,[282] and thermal energy,[283] or alternatively, the energy of light.[284]

Glorius et al. reported a visible-light-induced carbonyl–olefin metathesis through the 1,3-diol formation and fragmentation sequence (Scheme 71).[285] A series of electron-rich aromatic aldehydes was converted into olefins, typically in 40–85 % yields and with high selectivity for the *E* isomer. Functional groups such as protected alcohols, halides or heteroarenes were tolerated. Both α- and β-substituted styrenes were competent substrates in the reaction. Additionally, an example of intramolecular ring-closing carbonyl-olefin metathesis was also reported. The addition of water was necessary to introduce the 1,3-diol motif. Therefore, a 3-component solvent mixture comprising formic acid, water, and dichloroethane was proposed, to promote all the reaction steps and enable efficient phase diffusion. The addition of TFA after the reaction assured the complete fragmentation of 1,3-diol intermediate. Additionally, the authors introduced a new acridinium-based photocatalyst, which is less prone to radical or nucleophilic decomposition, and described its synthesis and characterization.



Substituents

R^1 = aryl, 2-thienyl, alkenyl; R^2, R^3 = H, Me; FGT = ethers, silyl ethers, halides (Br, Cl, F)

Conditions:

photocatalyst / λ : $Mes_2Acr^tBu_2BF_4$ / blue LEDs
solvent / additives : HCO_2H:H_2O:DCE 1:1:5 / -; then TFA (at 60 °C)
temp. / atm. : rt / Ar

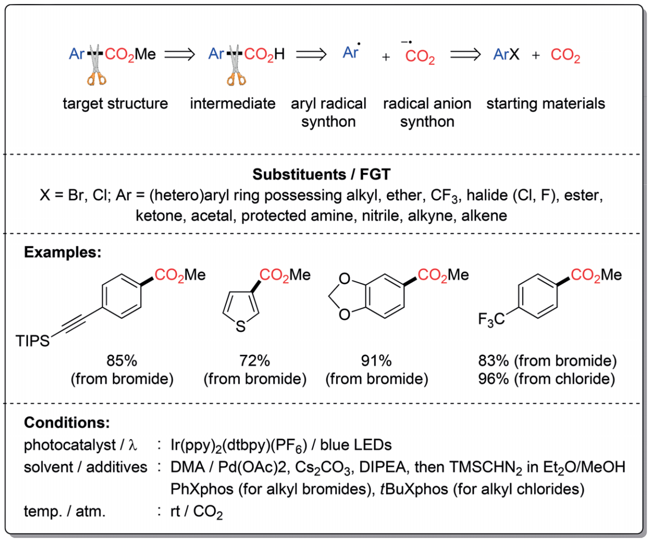
Scheme 71. C(sp^2)-C(sp^2) disconnection for the synthesis of alkenes.[285]

Recently, König, Gschwind et al. reported a photoinduced carbonyl-metathesis (McMurry reaction), starting from aromatic aldehydes.[286] To tackle the challenge of transferring 4 electrons in one catalytic cycle, they used bis(pinacolato)diboron as terminal reductant and oxygen trap, $[Ir(FCF_3ppy)_2dtbbpy]PF_6$ as a photocatalyst and 4-Me-BnSH as an additional electron shuttle. It allowed for obtaining a diverse range of symmetrical and unsymmetrical alkenes with typical yields in the range of 40–70 % for homo-coupling and 40–60 % for cross-coupling.

9.7 Generation of Aromatic Carboxylic Acids

Due to the abundance, low cost, and nontoxicity of CO_2, its fixation is arguably the most important approach for photocatalytic synthesis of carboxylic acids. It is also directly inspired by natural photosynthesis, which uses the energy of visible light to transform CO_2 into valuable chemicals. For these reasons, recent years witnessed immense development of photocatalytic carboxylation processes.[234]

Aromatic carboxylic acids can be conveniently synthesized from corresponding aryl halides with the aid of photocatalysis. One of the strategies, that operates also for aliphatic acids, has been described in the Section 8.7. Another method was introduced in 2017 by Iwasawa et al. who reported dual palladium-photoredox catalysis for carboxylation of aryl bromides and chlorides (Scheme 72).[287] The authors used $Pd(OAc)_2$ as the source of Pd(0) and *t*BuXphos as the ligand to enable oxidative addition of halides followed by the subsequent CO_2 insertion. $Ir(ppy)(dtbbpy)(PF_6)$ was used as the photocatalyst and DIPEA as the terminal electron donor. The reaction mixture was irradiated with blue LEDs. The procedure involved subsequent esterification with trimethylsilyldiazomethane ($TMSCHN_2$). Both electron-rich and electron-deficient aryl bromides were converted into esters and typical yields were in the range of 70–90 %. To expand the reaction scope to aryl chlorides, the use of more electron-rich *t*BuXphos phosphine ligand was required. Recently the same authors, as well as the groups of Jana and Jiang showed that similar carboxylation can be achieved with aryl triflates.[288]



Substituents / FGT

X = Br, Cl; Ar = (hetero)aryl ring possessing alkyl, ether, CF_3, halide (Cl, F), ester, ketone, acetal, protected amine, nitrile, alkyne, alkene

Conditions:

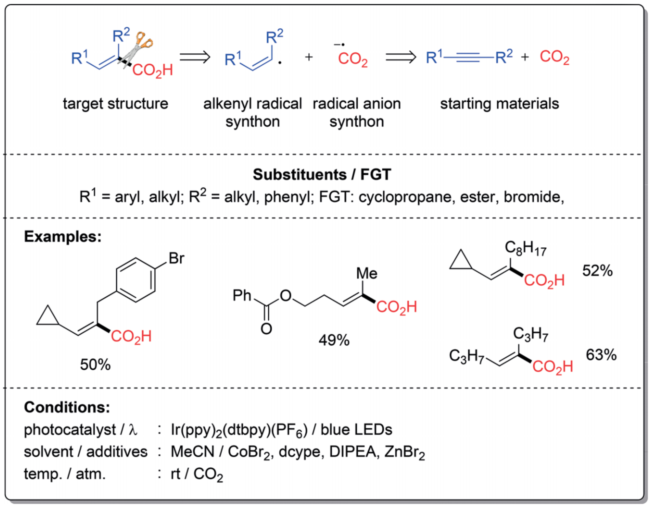
photocatalyst / λ : $Ir(ppy)_2(dtbpy)(PF_6)$ / blue LEDs
solvent / additives : DMA / Pd(OAc)2, Cs_2CO_3, DIPEA, then $TMSCHN_2$ in Et_2O/MeOH
PhXphos (for alkyl bromides), *t*BuXphos (for alkyl chlorides)
temp. / atm. : rt / CO_2

Scheme 72. Aryl-carbonyl disconnection for the synthesis of aromatic carboxylic acids.[287]

9.8 Generation of α,β-Unsaturated Carboxylic Acids

Due to the abundance, low cost, and nontoxicity of CO_2, its fixation is arguably the most important approach for photocatalytic synthesis of carboxylic acids. It is also directly inspired by natural photosynthesis, which uses the energy of visible light to transform CO_2 into valuable chemicals. For these reasons, recent years witnessed immense development of photocatalytic carboxylation processes.[234]

In 2018, Zhao, Wu et al. reported the synthesis of α,β-unsaturated carboxylic acids via visible-light-driven alkyne hydrocarbocarboxylation with CO_2 (Scheme 73).[289] They applied cobalt-photoredox dual catalysis with Ir(ppy)(dtbbpy)(PF_6) as a photocatalyst and $CoBr_2$ as a co-catalyst. Furthermore, bis(dicyclohexylphosphino)ethane (dcype) was used as a ligand, DIPEA as a sacrificial electron donor and $ZnBr_2$ as an additive. Aryl and alkyl-substituted internal alkynes were competent substrates and the typical yields of hydrocarboxylation products were in the range of 50–60 %. Importantly, CO_2 insertion occurred preferentially at the alkyl-substituted site. Although the presented scope of this reaction was small, the process was further developed towards the one-pot hydrocarboxylation/alkene isomerization/cyclization sequence, giving various heterocycles such as coumarins, 2-quinolones, 2-benzoxepinones, 2-pyrones, and γ-hydroxybutenolides.



Scheme 73. Alkenyl-carbonyl disconnection for the synthesis of α,β-unsaturated carboxylic acids.[289]

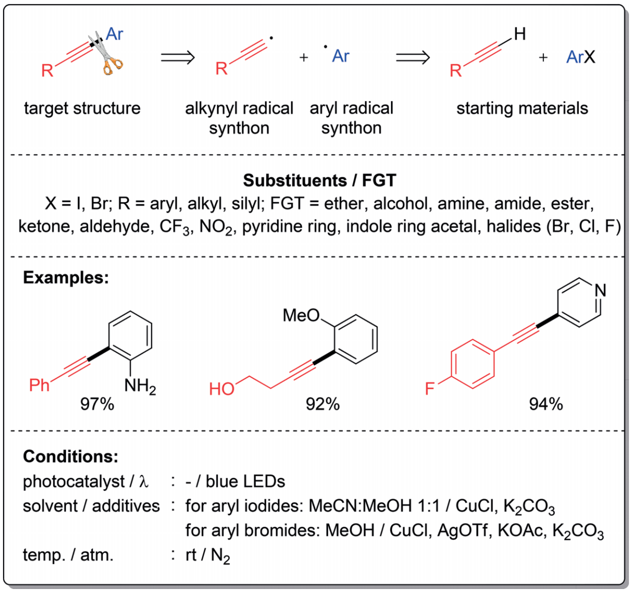
An alternative method for the photocatalytic synthesis of α,β-unsaturated carboxylic acids was recently reported by Iwasawa et al., who used dual palladium-photoredox catalysis for carboxylation alkenyl triflates[288a]

10. C–C Bond: sp^2-sp Disconnection

10.1 Generation of Arylated Alkynes

Alkynes are arguably one of the most important and versatile functional groups in organic synthesis. A plethora of methods exists, which allow for their transformations and late-stage functionalization.[290] Consequently, alkynes are useful intermediates in both academic and industrial synthesis. Among them, aryl acetylenes, which possess a triple C(sp^2)-C(sp) bond, are of particular importance, as they find application in the widespread molecular electronics.[291]

In 2012 Hwang et al. developed a synthesis of arylated alkynes via photo-induced Sonogashira reaction (Scheme 74).[292] They utilized the ability of simple copper(I) chloride to form copper phenylacetylides with alkynes, which can be then photoexcited with blue light, providing electron-deficient acetylene moiety. They were coupled to various electron-poor and electron-rich aryl halides. Two separate sets of conditions were developed for aryl iodides and aryl bromides. In the former case, K_2CO_3 was used as a base and the reaction was run in MeCN/MeOH solvent mixture. For aryl bromides, KOAc and MeOH were used. Additionally, the reaction required 2 mol-% of AgOTf. Both aryl- and alkyl-substituted acetylenes could be used in the reaction and typical yields were in the range of 85–95 %. The method displayed broad functional group tolerance, which included e.g. non-protected amines, alcohols, aldehydes, heteroaromatic rings, etc.



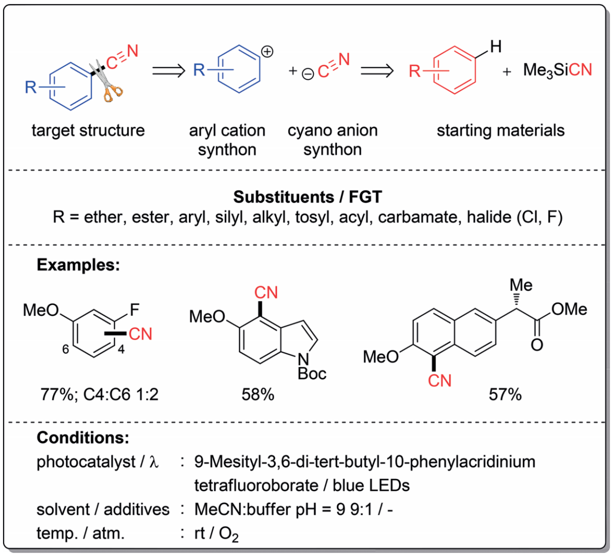
Scheme 74. Aryl-alkynyl disconnection for the synthesis of arylated alkynes.[292]

Alternatively, other catalysts mediating alkyne-aryl coupling have been developed. This includes e.g. mixed Pd-Ru$(bpy)_3(PF_6)_2$[293] and Au-Ru$(bpy)_3(PF_6)_2$[294] systems, metal nanoparticles,[295] mesoporous composites,[296] BODIPY-Pd(II) complexes,[297] as well as metal-free methods.[298]

10.2 Generation of Cyanoarenes

The cyanoarene structural motif is present in various natural products and pharmacologically active compounds. They are also useful synthetic intermediates for late-stage transformation into benzoic acids,[299] benzaldehydes,[300] esters,[301] aryl ketones,[302] amides,[303] or amines.[304] In recent years photocatalysis responded to the need for a mild and metal-free synthesis of cyanoarenes from readily available aryl compounds.

Nicewicz et al. reported a direct C–H cyanation of arenes under blue light irradiation (Scheme 75).[305] Strongly oxidizing 3,6-di-*tert*-butyl-9-mesityl-10-phenylacridinium tetrafluoroborate was used to transform electron-rich arenes into radical cations, reactive towards trimethylsilyl cyanide. The reaction required basic media (a buffer pH = 9 was used in a mixture with acetonitrile). The typical yields of the products (often as a mixture of regioisomers) were in the range of 50–80 %. Electron-rich heteroaromatic compounds were also competent substrates and provided desired products in 40–60 % yield. Furthermore, the applicability of the method was demonstrated in the late-stage functionalization of bioactive compounds: methyl esters of naproxen, gemfibrozil, fenoprofen, as well as *N*-Boc-melatonin.



Substituents / FGT
R = ether, ester, aryl, silyl, alkyl, tosyl, acyl, carbamate, halide (Cl, F)

Conditions:
photocatalyst / λ : 9-Mesityl-3,6-di-tert-butyl-10-phenylacridinium tetrafluoroborate / blue LEDs
solvent / additives : MeCN:buffer pH = 9 9:1 / -
temp. / atm. : rt / O_2

Scheme 75. Aryl-CN disconnection for the synthesis of cyanoarenes.[305]

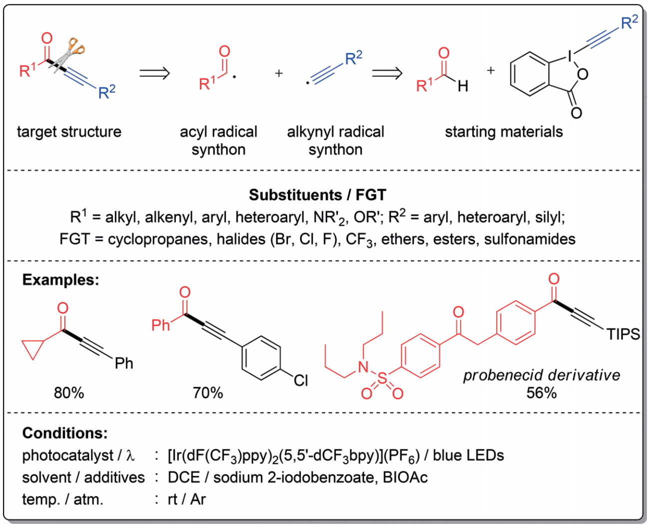
Very recently, the same group developed the photocatalytic synthesis of cyanoarenes from methoxyarenes through cation-radical accelerated-nucleophilic aromatic substitution. In this case, acetone cyanohydrin could be used as a cheap and readily available source of cyanide.[306] Furthermore, our group reported the use of mesoporous graphitic carbon nitride (mpg-CN) photocatalyst as an operationally simple strategy for arene C–H and C-X functionalization, including the cyanation of arenes.[153]

10.3 Generation of Ynones

Strategy 1

Ynones possess the C(sp^2)-C(sp) bond, which bridges the carbonyl group and alkynyl fragment. Similar to many other unsaturated organic compounds, they are present as structural motifs in various molecules of biological importance and serve as versatile intermediates in organic synthesis.[307]

In 2017 Glorius et al. reported the synthesis of ynones from aldehydes (Scheme 76).[308] Photoredox-mediated hydrogen-atom transfer under blue light irradiation provided access to acyl radicals. Ethynylbenziodoxolones were used as the source of the alkynyl fragment. The reaction required the presence of $[Ir(dF(CF_3)ppy)_2(5,5'\text{-}dCF_3bpy)](PF_6)$ photocatalyst, sodium 2-iodobenzoate and BIOAc (BI = benziodoxolone). Primary, secondary and tertiary aliphatic aldehydes could be used in the transformation, as well as alkenyl and aryl aldehydes. The latter ones included also complex biomolecules such as derivatives of probenecid, lithocholic acid, cholesterol, and adapalen. On the ethynylbenziodoxolones side, various aryl and TIPS substituted compounds were competent substrates. The typical yields of the products were in the range of 70–80 %. Furthermore, the examples of alkynylation of formamides and formates were reported.



Substituents / FGT
R^1 = alkyl, alkenyl, aryl, heteroaryl, NR'$_2$, OR'; R^2 = aryl, heteroaryl, silyl;
FGT = cyclopropanes, halides (Br, Cl, F), CF_3, ethers, esters, sulfonamides

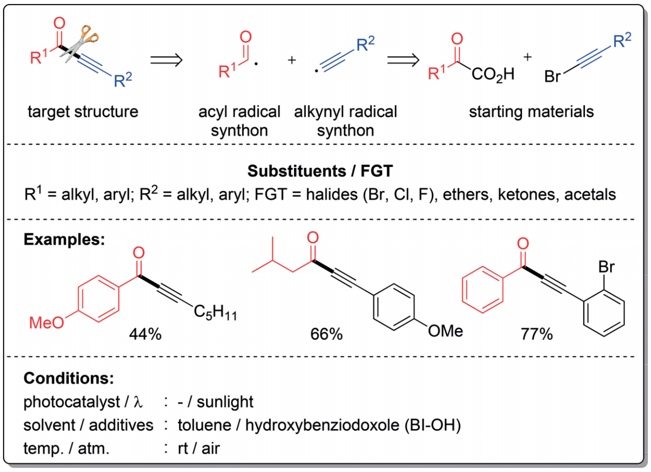
Conditions:
photocatalyst / λ : $[Ir(dF(CF_3)ppy)_2(5,5'\text{-}dCF_3bpy)](PF_6)$ / blue LEDs
solvent / additives : DCE / sodium 2-iodobenzoate, BIOAc
temp. / atm. : rt / Ar

Scheme 76. Alkynyl-carbonyl disconnection for the synthesis of ynones.[308]

Other compounds able to act as acyl group donors for ynones have also been described. These include α-keto-acids,[309] aldehydes,[308] benzothiazolines,[279] β-carbonyl alcohols,[310] and (provided the consecutive carbonylation with CO) alkyl carboxylic acids.[311]

Strategy 2

The hyper-valent iodine(III) species bearing the alkyne fragment do not necessary need to be provided in equimolar amounts. Li, Wang et al. reported a decarboxylative alkynylation of α-keto acids, in which hyper-valent iodine(III) reagents are generated in situ from the suitable bromoacetylenes and catalytic amount of hydroxybenziodoxole (Scheme 77).[312]



Substituents / FGT

R^1 = alkyl, aryl; R^2 = alkyl, aryl; FGT = halides (Br, Cl, F), ethers, ketones, acetals

Conditions:

photocatalyst / λ : - / sunlight
solvent / additives : toluene / hydroxybenziodoxole (BI-OH)
temp. / atm. : rt / air

Scheme 77. Alkynyl-carbonyl disconnection for the synthesis of ynones.[312]

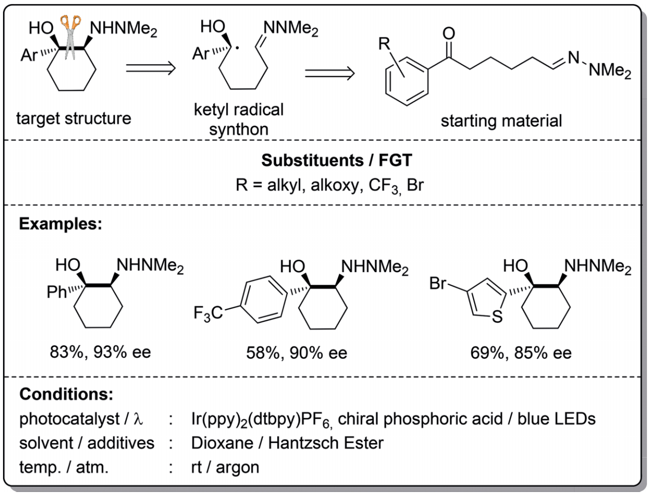
The reaction did not require the presence of any additional photocatalyst. Although blue light was shown to be responsible for the desired reactivity, the process proceeded also well under sunlight instead of LED irradiation. Various alkyl- and aryl-substituted α-keto acids and aryl-substituted bromoacetylenes were transformed into ynones. The typical yields were in the range of 60–75 %. Bromoacetylenes with electron-withdrawing groups on the benzene rings gave generally higher yields than those with electron-donating groups. Additionally, an exemplary reaction of 2-alkylbromoacetylene was demonstrated.

11. C(sp^3)-C(sp^3) Disconnection

The development of new stereoselective methods to form C(sp^3)-C(sp^3) bonds has attracted much interest in the scientific community and many reactions have been developed over the years. However, milder and more selective conditions are still in demand to perform late-stage functionalizations. Visible-light-mediated methods are attractive to form C(sp^3)-C(sp^3) bonds in an enantioselective manner through sp^3-carbon-centered radicals as the key intermediates.

11.1 Generation of Cyclic α-Amino Alcohols

Knowles and co-workers applied a method using commercially available Ir(ppy)$_2$(dtbbpy)PF$_6$ as photocatalyst, (R,R)-dinaphtho-[2,1-d:1′,2′-f][1,3,2]dioxaphosphepin,4-hydroxy-2,6-bis(triphenylsilyl)-,4-oxide as chiral phosphoric acid and Hantz'sch Ester (HEH) as reductant. The reaction mixture was irradiated with blue LEDs for 3 h giving the corresponding cyclic α-amino alcohols in yields of 60–80 % and enantioselectivities >85 % ee via a coupling reaction between ketyl radicals and a hydrazine moiety present in the molecule (Scheme 78).[313] The reported functional group tolerance includes bromides, ethers, and CF$_3$ groups.



Substituents / FGT

R = alkyl, alkoxy, CF$_3$, Br

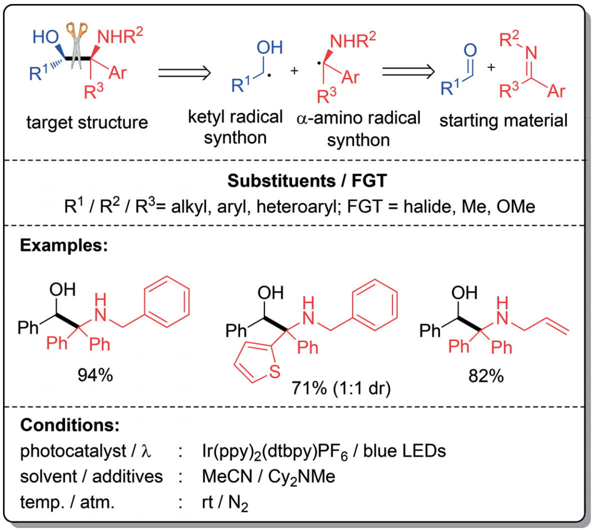
Conditions:

photocatalyst / λ : Ir(ppy)$_2$(dtbpy)PF$_6$, chiral phosphoric acid / blue LEDs
solvent / additives : Dioxane / Hantzsch Ester
temp. / atm. : rt / argon

Scheme 78. Amino alcohol disconnection for the synthesis of cyclic α-amino alcohols.[313]

11.2 Generation of Acyclic α-Amino Alcohols

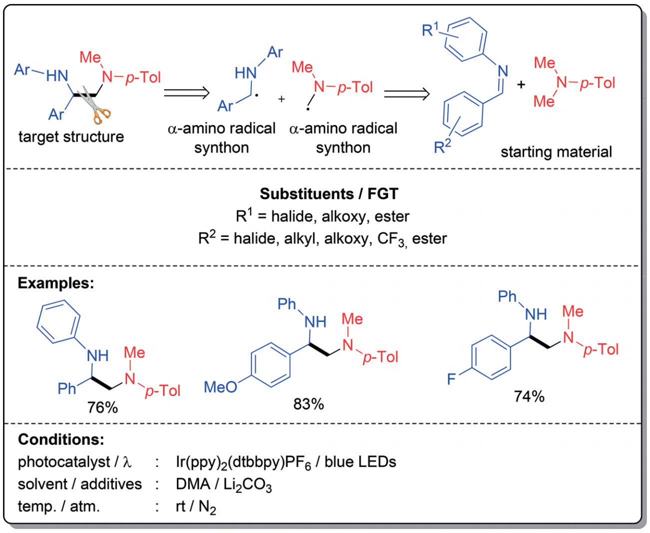
Fan, Walsh, and co-workers used chemoselective cross-electrophile couplings between aldehydes and ketimines to furnish amino alcohols with yields of 70–94 % (Scheme 79).[314] They used the Umpolung reactivity of ketimines to avoid a homocoupling side reaction. Commercially available Ir(ppy)$_2$(dtbpy)PF$_6$ was used as photocatalyst and dicyclohexylmethylamine (Cy$_2$NMe) as base. The reaction mixture was irradiated with blue light for 20 h; the reported functional group tolerance was limited to halide, methyl and methoxy groups.



Scheme 79. C(sp^3)-C(sp^3) bond disconnection for the synthesis of acyclic α-amino alcohols.[314]

11.3 Generation of 1,2-Diamines

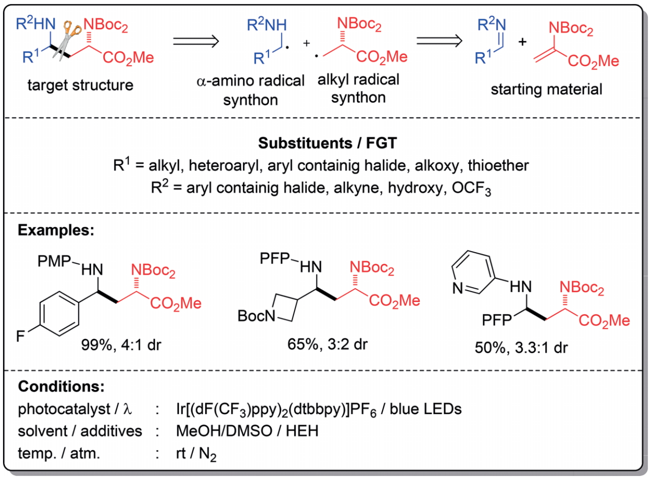
Rueping and co-workers synthesized unsymmetrical 1,2-diamines with reductive SET Umpolung of an aldimine as the key step (Scheme 80).[315a] They used Ir(ppy)$_2$(dtbpy)PF$_6$ as photocatalyst and lithium carbonate as a base under blue light irradiation in an inert atmosphere. The corresponding products were obtained in 70–97 % and the reported functional group tolerance included halides (F, Br), ethers, esters, and CF$_3$ groups. Gilmore and co-workers showed that symmetrical 1,2-diamines can be synthesized in 54–82 % yield.[315b] Coupling of liquid ammonia and aldehydes/ketones allows the generation of primary amines without the need for protecting groups. The intermediates were transformed into diamines by a formal dimerization. They used Ru(bpy)$_3$Cl$_2$•6H$_2$O as photocatalyst and liquid ammonia or NH$_3$ gas as ammonia source.



Scheme 80. C(sp^3)-C(sp^3) bond disconnection for the synthesis of 1,2-di-[315a]

11.4 Generation of 1,3-Diamines

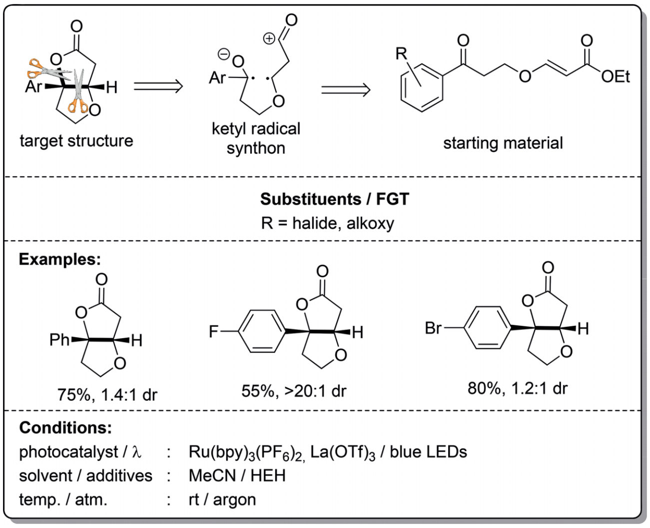
Dixon and co-workers showed a one-pot Umpolung coupling of imines and dehydroalanine derivatives for the diastereoselective construction of 1,3-diamine products in 50–99 % yield and 3:1 to 7:2 diastereoselectivity (Scheme 81).[316] They used Ir[(dF(CF$_3$)ppy)$_2$(dtbbpy)]PF$_6$ as photocatalyst and a Hantz'sch ester as reductant. The reported functional group tolerance comprises aryl halides and ethers as well as alkynes, esters and protected amines. Twofold Boc protection of the starting material was necessary for the reaction to proceed.



Scheme 81. C(sp^3)-C(sp^3) bond disconnection for the synthesis of 1,3-diamines.[316]

11.5 Generation of γ-Lactones

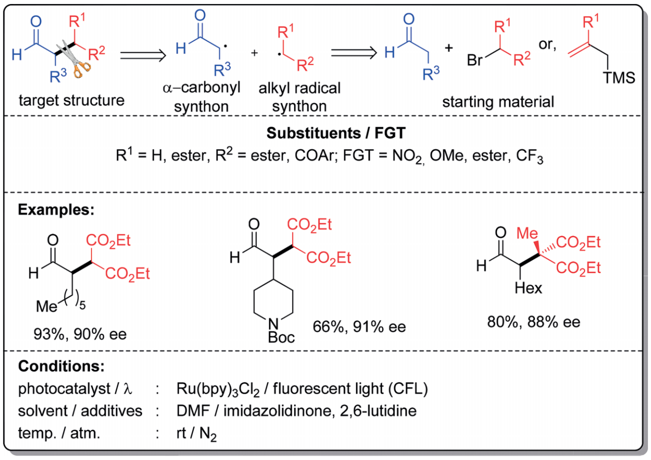
Cannon and co-workers applied an intramolecular addition of ketyl radicals to vinylogous carbonates to provide polysubstituted tetrahydrofurans (Scheme 82).[317] They used Ru(bpy)$_3$(PF$_6$)$_2$ as photocatalyst in the presence of Lewis acid (La(OTf)$_3$) and Hantz'sch ester as a reductant under blue light irradiation. The diastereoselectivity of the C–C bond formation was 1.4–5:1 after 48 h; the minor diastereomers were converted to 2,6-dioxabicyclo[3.3.0]-octan-3-ones by a Lewis acid-mediated epimerization cascade in yields from 60 to 80 %. The reported functional group tolerance includes halides (F, Br) and ethers.



Scheme 82. C(sp^3)-C(sp^3) and C(sp^3)-O bonds disconnection for the synthesis of γ-lactones.[317]

11.6 Generation of α-Alkylated Carbonyl Compounds

Nicewicz and MacMillan used dual organo-photoredox catalysis for the enantioselective α-alkylation of aldehydes with α-bromocarbonyl compounds (Scheme 83).[318] They obtained yields from 63 to 93 % and enantioselectivities of 88–96 % ee. Later, they extended the scope of the reaction to trifluoromethylations,[319] cyano-alkylations,[320] and benzylations[321] They combined different photocatalysts and organocatalysts for this purpose e.g. Ru(bpy)$_3$Cl$_2$ and imidazolidinone for the addition of diethyl malonate. The reported functional group tolerance includes nitro, ester, CF$_3$, and methoxy. Melchiorre and co-workers showed that a similar type of stereoselective C–C bond formation is possible without any photocatalyst under visible light irradiation.[322] They found that enamines formed by the condensation of a chiral catalyst and an aldehyde react with benzyl bromides under irradiation with visible light overall achieving an enantioselective α-alkylation of aldehydes. In a different approach, Meggers and co-workers have designed new chiral iridium complexes that act simultaneously as photoredoxcatalysts and as chiral Lewis acids for asymmetric induction in the formation of C–C bonds.[323]



Substituents / FGT

R^1 = H, ester, R^2 = ester, COAr; FGT = NO$_2$, OMe, ester, CF$_3$

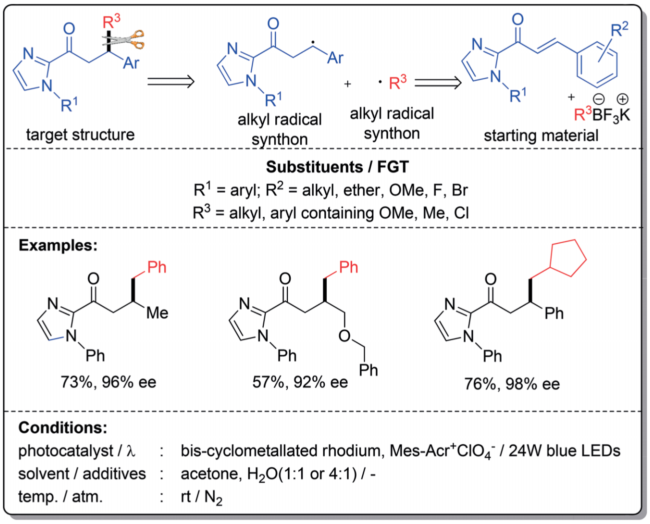
Conditions:

photocatalyst / λ : Ru(bpy)$_3$Cl$_2$ / fluorescent light (CFL)
solvent / additives : DMF / imidazolidinone, 2,6-lutidine
temp. / atm. : rt / N$_2$

Scheme 83. C(sp^3)-C(sp^3) bond disconnection for the α-alkylation of carbonyl compounds.[318]

11.7 Generation of β-Alkylated Carbonyl Compounds

Meggers and co-workers have designed chiral rhodium complexes that act simultaneously as photoredox catalysts and as chiral Lewis acids for asymmetric induction in the formation of C–C bonds (Scheme 84).[324] They obtained the products in yields of 60–90 % and enantioselectivity of >92 %ee. Functional group tolerance comprises halides (F, Cl, Br), methoxy and methyl. Melchiorre and co-workers used a commercially available amino-catalyst, (2R)-pyrrolidine,2-[bis [3,5-bis(trifluoromethyl)phenyl][(trimethylsilyl)oxy]methyl] under household bulb, 23 W compact fluorescent light (CFL), in the absence of any external photoredox catalyst for this reaction.[322b] Yields range from 29 to 83 %; enantioselectivity reaches up to 90 % ee and functional groups such as halides (F, Cl, Br), methoxy and methyl are tolerated.



Substituents / FGT

R^1 = aryl; R^2 = alkyl, ether, OMe, F, Br
R^3 = alkyl, aryl containing OMe, Me, Cl

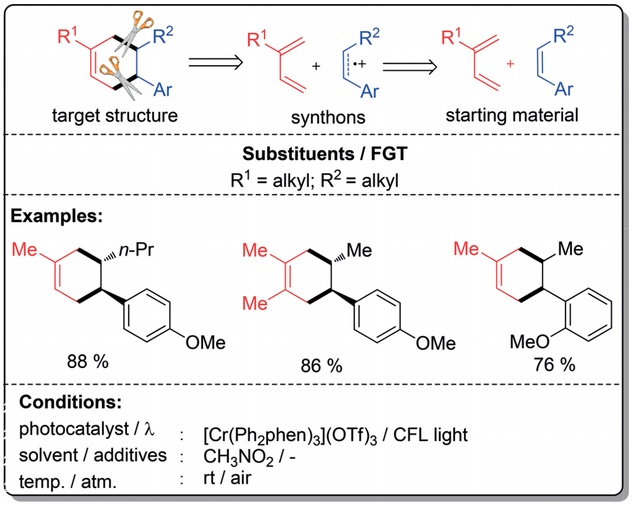
Conditions:

photocatalyst / λ : bis-cyclometallated rhodium, Mes-Acr$^+$ClO$_4^-$ / 24W blue LEDs
solvent / additives : acetone, H$_2$O(1:1 or 4:1) / -
temp. / atm. : rt / N$_2$

Scheme 84. C(sp^3)-C(sp^3) bond disconnection for β-alkylation of carbonyl compounds.[324]

11.8 Generation of Cyclohexenes

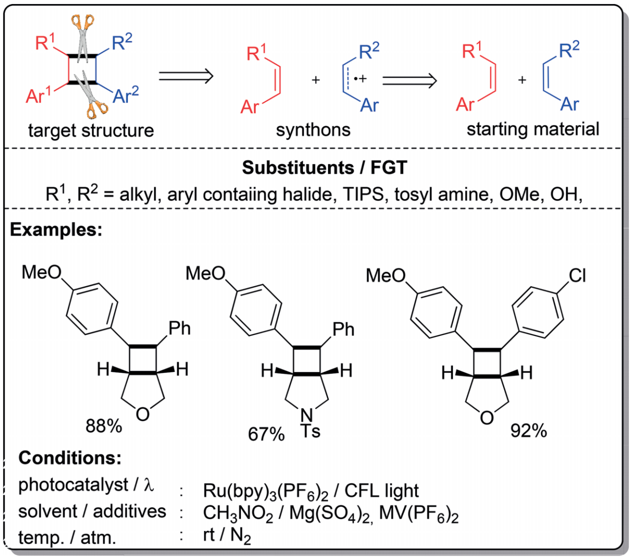
Ferreira and co-workers synthesized cyclohexenes by cycloadditions using $[Cr(Ph_2phen)_3](OTf)_3$ as photocatalyst and irradiation with a compact fluorescent light bulb (CFL) (Scheme 85).[326] Yields are 70–90 % with diastereoselectivities from 6:1 to 19:1. Functional group tolerance was not reported. Yoon and co-workers showed that ruthenium(II) polypyridyl photocatalysis enables Diels-Alder reactions with electron-rich dienophiles.[325]



Scheme 85. C(sp^3)-C(sp^3) bond disconnection for the synthesis of cyclohexenes.[325]

11.9 Generation of Cyclobutanes

Cyclobutanes are typically synthesized by [2+2] cycloadditions. $Ru(bpy)_3Cl_2$ photocatalysis enables the cycloaddition of both electron-rich and electron-deficient olefins to cyclobutanes (Scheme 86).[327,328] The obtained yields range from 54 to 88 %. Functional group tolerance comprises halides (F, Br), tosylamine, TIPS, methoxy, and hydroxyl. The method is applicable to gram-scale synthesis at ambient sunlight. Cibulka and co-workers used flavin as a photocatalyst in acetonitrile under argon atmosphere. They obtained yields between 60 to 90 % with diastereoselectivities >10:1 for most cases.[329] Functional group tolerance comprises methoxy, bromo, and CF_3. Using similar activation modes the intermolecular [2+2] homocoupling[330] of styrenes, cinnamates, and chalcones, as well as the heterocoupling between cinnamates and 1,1-diarylethylenes is possible.[331] Bach and co-workers used chiral xanthone and thioxanthone for inter- and intramolecular [2+2] photocycloaddition reactions at 366 nm.[332] Alternatively, [2+2] cycloadditions can be achieved by an energy-transfer process under UV irradiation with sensitizers such as benzophenones.[333]



Scheme 86. C(sp^3)-C(sp^3) bond disconnection for the synthesis of cyclobutane.[327]

Acknowledgments

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Keywords: Homogeneous catalysis · Photocatalysis · Photoredox catalysis · Retrosynthesis · Synthetic methods

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