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Decarboxylative photocatalytic transformations

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Photocatalytic decarboxylation of carboxylic acids or their redox active esters has become an important strategy in organic chemistry. Using catalytic amounts of metal-based or organic photocatalysts, normally under visible light irradiation, these substrates generate carbon centered radicals, which have been applied to a broad range of C–C and C–heteroatom bond forming reactions. Addition reaction to electron-deficient alkenes, hydroalkylation of unsaturated C–C bonds and addition to C–heteroatom multiple bonds have been extensively studied. Cross-coupling reactions such as arylation, alkylation, allylation, vinylation, alkynylation, acylation, cyanation and C–H functionalization reactions are also successfully performed. In the case of C–heteroatom bond forming reactions, C–halogen, C–oxygen, C–sulfur, C–nitrogen, C–phosphorus, C–boron and C–silicon are fundamental functionalization processes. Hydro- and deuterodecarboxylation reactions allow the substitution of the carboxylic group by a hydrogen or a deuterium atom regioselectively. Finally, decarboxylative elimination reactions, such as olefination reactions for the synthesis of alkenes and decarboxylative C–C bond cleavage of cyclic carboxylic acids, give 1,*n*-dicarbonyl compounds. These photoredox transformations, a renaissance in organic chemistry, starting from readily accessible carboxylic acids widely available in Nature and the pharma industry with a great structural diversity occur under mild and simple reaction conditions with excellent efficiency and clean energy input.

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1. Introduction

Decarboxylative reactions performed under photoredox catalysis have gained much interest in the last decade as versatile strategies in organic synthesis.[1–18] Carboxylic acids are suitable starting materials that can be mainly obtained from renewable

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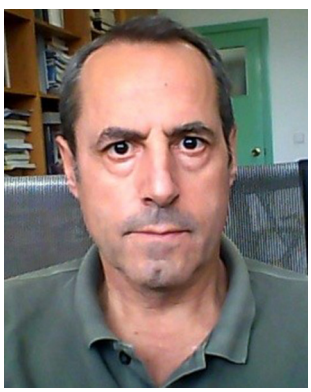


Francisco Foubelo

Francisco Foubelo was born in 1961 and studied Chemistry at the University of Oviedo where he received his BS (1984), MS (1986) and PhD (1989) degrees, under the direction of Professors J. Barluenga, M. Yus and F. J. Fañanás. He then joined the laboratory of Professor M. F. Semmelhack at Princeton University as a Fulbright postdoctoral fellow, and, in 1991, the group of Professor M. Yus at the University of Alicante, where he became an associate professor in 1995 and a full professor in 2002. His current research interests are focused on the development of new synthetic methodologies involving chiral sulfinyl imines and on metal-promoted functionalization of alkenes and alkynes.

Carmen Nájera

Professor Carmen Nájera was born in Nájera (La Rioja, 1951) and studied chemistry at the University of Zaragoza (1973) and PhD at the University of Oviedo (1979). After postdoctoral stays at the ETH, Oxford, Harvard and Uppsala University, she became an Associate Professor (1985) at the University of Oviedo and a Full Professor (1993) at the University of Alicante. She is the coauthor of more than 400 papers (25 000+ citations, h 76), 6 patents and 30 book chapters and has supervised 50 PhD students. In 2016–2017 she was named the ChemPubSoc Europe Fellow and in 2012 the full Member of the Royal Spanish Academy of Sciences.

feedstocks and possess a broad structural diversity, especially amino acids, fatty acids or sugar acids. The formation of an electrophilic radical occurs by single electron oxidation of a carboxylate ion using photocatalysts able to form excited state units as oxidants. On the other hand, under redox neutral decarboxylation conditions nucleophilic radicals are formed. These radicals can be used in a range of C–C and C–heteroatom bond formation reactions with appropriate acceptors. Alternatively, mainly *N*-(acyloxy)phthalimide (NHPI) esters can be used as redox-active esters (RAEs) in decarboxylative transformations under mild reaction conditions.[1,14,19–22] In this case, the RAE (NHPI ester) is reduced by a photocatalyst, by accepting an electron, generating the corresponding radical after decarboxylation and formation of the phthalimidyl anion. This review covers the synthetic applications of decarboxylative transformations starting from carboxylic acids and their derivatives reported in the last seven years.

2. C–C bond-forming reactions

In this section, addition reactions of electrophilic olefins (Giese reactions), unactivated alkenes, alkynes, carbonyl compounds and imines will be considered (Sections 2.1–2.3). Cross-coupling reactions by arylation, alkylation, allylation, alkenylation, alkynylation, acylation, cyanation, C–H bond functionalization and cyclization processes will be subsequently treated (Sections 2.4–2.12).

M. Gracia Retamosa

Maria de Gracia Retamosa is a Senior Research fellow of the University of Alicante (CIDEGENT program of the G. Valenciana). She received her PhD in 2008 at the University of Alicante (Spain) under the guidance of Prof. Carmen Nájera and José Miguel Sansano. She is the coauthor of 45 articles and 5 patents. She did several postdoctoral stays [Prof. Michael Greaney at the University of Edinburgh (UK, 2009), Prof. Jesús M. Sanz at the University Miguel Hernández (Elche, Spain, 2009–2011) and Prof. Fernando P. Cossío at the University of the Basque Country and Donostia International Physics Center (Spain, 2012–2016)]. Recently, she has joined the group of Prof. Rosario Fernández and José M. Lassaletta as a postdoctoral researcher [CSIC (Sevilla, Spain)]. Her current research interests include asymmetric metal and organocatalysis and synthesis of compounds of pharmacological interest.

José M. Sansano

Professor José Miguel Sansano was born in Rojales (Alicante), studied chemistry at the University of Alicante, where he obtained his BSc and PhD degrees in 1988 and 1994, respectively. His thesis was supervised by Prof. C. Nájera and dealt about sulfone chemistry. After spending a two-year postdoctoral stay at the University of Leeds (UK) with Prof. R. Grigg, he joined the University of Alicante in 1996, where he was appointed Associate Professor in 2001. In 2010 he was promoted to Full Professor in the same University. He was an invited visiting Professor at Chuo University in 2014 and at the UFRJ (Brazil). He is the coauthor of more than 200 articles and he has supervised 13 PhD students.

Ana Sirvent

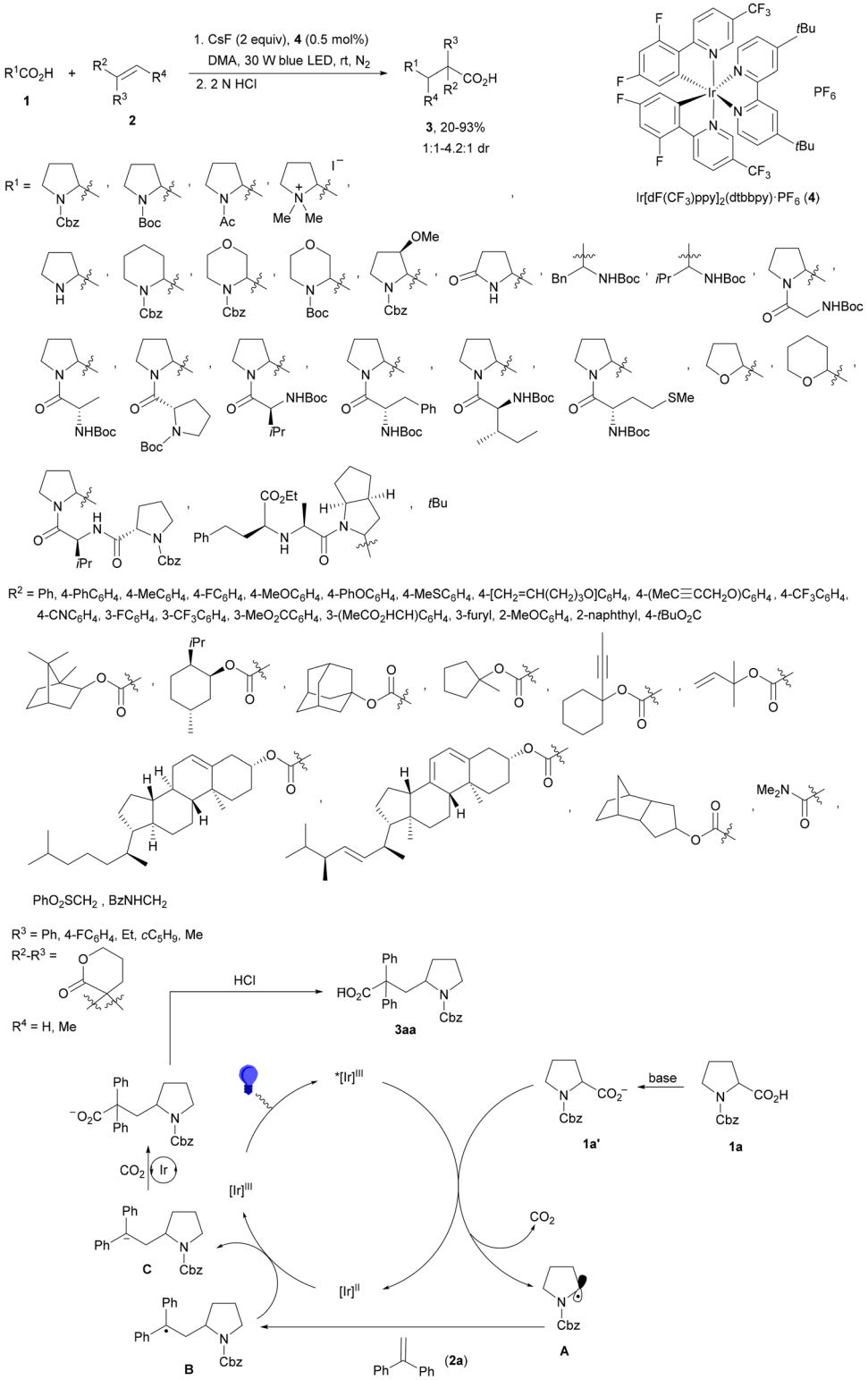
Ana Sirvent received her BSc (2015), MSc (2016) and PhD degrees (2021) from the University of Alicante (Spain) under the supervision of Prof. Francisco Foubelo and Prof. Miguel Yus. During her PhD studies, in 2019, she conducted a short research stay in the group of Prof. Jonathan A. Ellman at Yale University (USA). In 2021, she joined the group of Prof. Nuno Maulide at the University of Vienna (Austria) as a postdoctoral researcher. Since 2024, she has been a postdoctoral researcher at the University of Alicante.

Miguel Yus

Professor Miguel Yus was born in Zaragoza (1947) and received his BSc (1969), MSc (1971) and PhD (1973) degrees from the University of Zaragoza. After two years at Max Planck Institut für Kohlenforschung (Mülheim/Ruhr) he returned to the University of Oviedo, becoming associate professor (1977) and full professor (1987). In 1988 he went to the University of Alicante, being a visiting professor at ETH-Zentrum, Oxford, Harvard, Uppsala, Marseille, Tucson, Okayama, Paris, Strasbourg, Bolognia, Sassari, Tokyo and Kyoto. He has published 600+ papers, supervised 62 doctoral theses, getting 35 000+ citations and an h-index of 84. He has been in the Advisory-Board of 30+ journals.

2.1. Addition reactions of electron-deficient alkenes

Decarboxylative Giese reactions (DGRs) have been recently carried out under photocatalysis and have been covered by Kanegusuku and Roizen[23] and by Lee and co-workers[14] until 2021. Carbon-centered radicals, generated from NHPI esters or from carboxylic acids, added to Michael acceptors through a regioselective conjugate pathway under mild and environmentally benign photocatalytic conditions. Overman and co-workers[24,25] employed

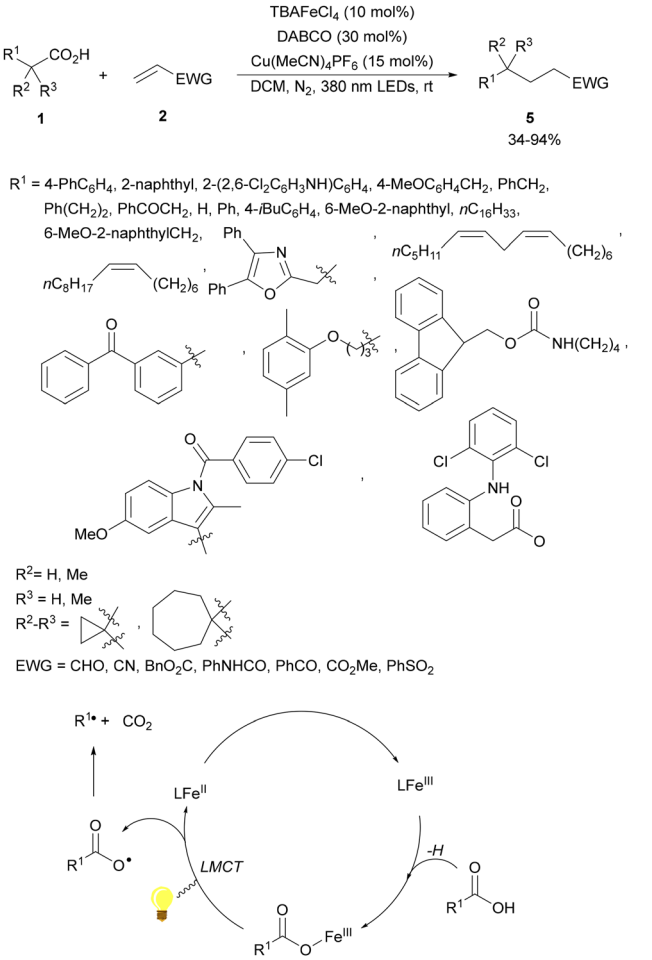


Scheme 1 Carbocarboxylation of alkenes **2** with carboxylic acids **1** under Ir photocatalysis.

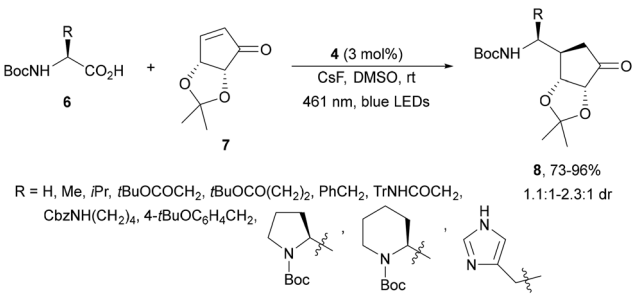
NHPI esters for the synthesis of natural products under $Ru(bpy)_2(BF_4)_2$ metallaphotocatalysis. König and co-workers[26] carried out the DGR of *N*-Boc-protected α-amino acids (AAs) and fatty acids using the abundant dye Eosin Y as the photocatalyst. Oxidative decarboxylation of carboxylic acids was described by MacMillan and co-workers[27,28] using K_2HPO_4 as base and an iridium photocatalyst. Carboxylic acids with a secondary or tertiary α-carbon, as well as primary α-substituted carboxylic acids bearing oxygen or nitrogen atoms at the α-position, were also used.[29–43] Instead of iridium photocatalysts, organic dyes have been employed, such as 9-mesityl-10-methylacridinium perchlorate [Acr-Mes]ClO_4 in aqueous acrylonitrile, allowing the use of a wide range of substrates.[44] Other organic photocatalysts have been employed for DGRs.[45–49] Titanium oxide was able to promote the DGRs by photoexcitation with 390 nm light.[50]

Recent advances in photomediated decarboxylative Giese reactions of carboxylic acids are focused on metallaphotocatalysis[15] and organocatalysis.[51] Concerning metallaphotocatalysis, iridium, ruthenium, titania and iron have been mainly employed. In the case of carboxylic acids, the corresponding radicals are generated by a radical decarboxylation mechanism with extrusion of CO_2. However, Yu and co-workers[52] reported a carbon-economical and sustainable carbocarboxylation of alkenes. They employed carboxylic acids **1**, including α-amino acids, peptides, terpenoids and alkyl carboxylic acids, for DGRs on activated alkenes **2** under Ir photocatalysis to obtain carbon radicals. Such radicals were reduced to carbanions that were able to react with the *in situ* generated CO_2 affording γ-amino butyric acid derivatives (GABAs) **3** in the case of AAs (Scheme 1). This is the only example of carbocarboxylation of alkenes allowing the recycling of CO_2. The most efficient metallaphotocatalyst was $Ir[dF(CF_3)(ppy)]_2(dtbbpy)\cdot PF_6$ (**4**), with CsF as a base in *N*,*N*-dimethylacetamide (DMA) under 1 atm N_2 and 30 W blue LED irradiation at room temperature. The gram-scale reaction of 1,1-diphenylethylene with *N*-Cbz-Pro was carried out under sunlight irradiation, obtaining **3aa** in 74% yield with only 0.1 mol% of the photocatalyst (PC). Mechanistic studies based on control and kinetic experiments indicate that the initial single-electron transfer (SET) between the photoexcited $*[Ir]^{III}$ and the carboxylate ion **1a′**, generated by deprotonation of **1a** with the base, formed the α-amino radical **A** and CO_2. Radical addition of **A** to **2a** produces radical **B**, which undergoes SET reduction by $[Ir]^{II}$ to provide the carbanion **C**. The final reaction of **C** with CO_2 furnishes carboxylate ion **D**, which after protonation affords **3aa**.

A dual catalytic system developed by merging iron/copper catalysis has been employed by the Li and Zeng group[53] for the decarboxylative alkylation of electron-deficient alkenes with alkyl carboxylic acids. An iron catalyst, tetrabutylammonium tetrachloroferrate(III) (TBAFeCl_4), and $Cu(MeCN)_4PF_6$ as a cocatalyst and 1,4-diazabicyclo[2.2.2]octane (DABCO) as a base in dichloromethane (DCM) and a N_2 atmosphere at room temperature produced the desired products **5** by irradiation with a 390 nm LED lamp (Scheme 2). Several carboxylic acids including various types of drugs or natural products, such as diclofenac, oxaprozin, ibuprofen, naproxen, linoleic acid, oleic acid, carbamic acid, gemfibrozil, indomethacin, aceclofenac, ketoprofen and stearic acid, were used. As olefinic counterparts,

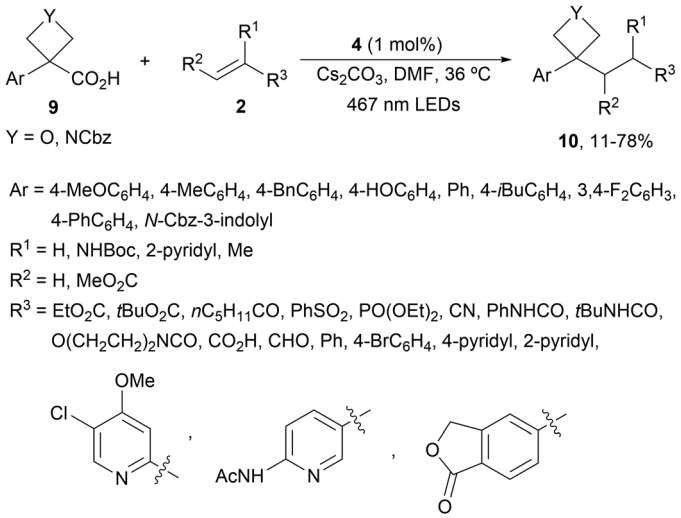


Scheme 2 Decarboxylative Giese reaction of carboxylic acids and electron-deficient alkenes under Fe/Cu photocatalysis.



Scheme 3 Decarboxylative Giese reaction of AAs with enone **7** under Ir photocatalysis.

acrolein, acrylodinitrile, acrylonitrile, methyl acrylate, acrylamide, phenyl vinyl ketone and vinyl sulfone were employed. Mechanistic studies supported a ligand-to-metal change transfer (LMCT)[54,55] pathway of the iron catalyst, whereas the copper catalyst here might act as a Lewis acid activating the electron-deficient olefin and inhibiting the potential polymerization. The carbon radical was formed through the LMCT of the iron catalyst followed by decarboxylation.



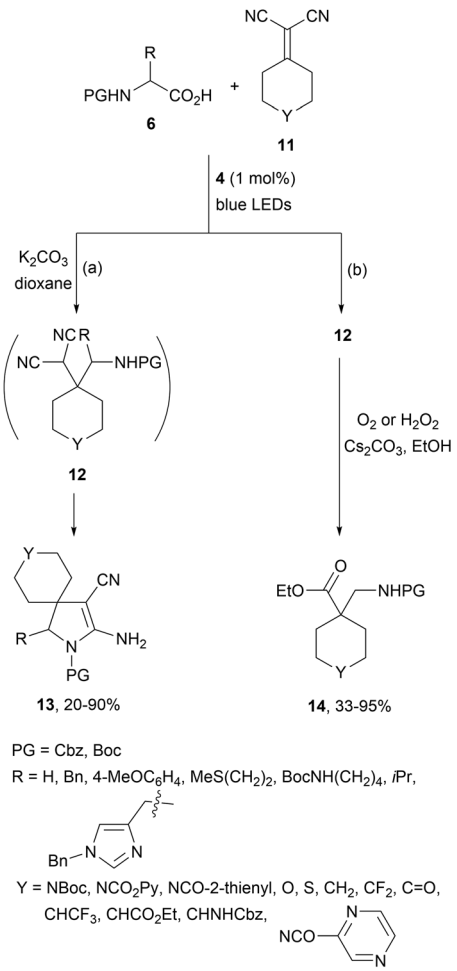
Scheme 4 Decarboxylative Giese reaction of oxetane and azetidine carboxylic acids **9** and electron-poor alkenes **2** under Ir photocatalysis.

Jung and co-workers[56] performed the photoreductive β-aminoalkylation of an α,β-unsaturated carbasugar mimic **7** driven by blue LEDs light using **4** as an Ir photocatalyst (Scheme 3). Different *N*-Boc α-amino acids **6** reacted with the cyclopentenone derivative **7** in DMSO at room temperature to provide γ-amino ketones **8** with very good yields and moderate diastereoselectivity. The resulting products **8** were transformed into 5′-amino carbasugar nucleoside analogues for *S*-adenosyl methionine-based methyltransferase inhibitors.

Four membered heterocyclic carboxylic acids **9** bearing an aryl group generate benzyl radicals using the Ir photocatalyst **4** (Scheme 4).[57] Oxetane and azetidine carboxylic acids **9** reacted with electron-poor alkenes **2** in DMF at 36 °C to provide products **10** in moderate to good yields due to the formation of secondary products. Experimental and computational studies revealed that only oxetane and azetidine substrates favored the DGR pathway and minimized dimer formation.

Gómez-Suárez and co-workers[58] have described a two-step procedure for the DGR generating *in situ* **11** as electron-poor alkenes. Starting from malononitrile and cyclic ketones the corresponding alkenes **11** were generated by Knoevenagel condensation followed by a domino DGR/base-mediated cyclization. Intermediate **12** was formed using Ir complex **4** as a photocatalyst and after cyclization the resulting spirocyclic products **13** were isolated in modest to good yields (Scheme 5a). The same group[59] recently reported a two-step procedure based on a domino DGR/oxidative functionalization to obtain β^2- and α-quaternary $\beta^{1,2}$-amino acid derivatives **14** in good yields (Scheme 5b). In this case, the aminoalkylation DGR was also carried out in the presence of $Ir[dF(CF_3)ppy_2(dtbbpy)]PF_6$ (**4**). This strategy has been scaled up *via* continuous-flow technology.

Decarboxylative 1,4-addition of α-oxo carboxylic acids to α,β-unsaturated carbonyl compounds gives the corresponding 1,4-dicarbonyl compound derivatives by intermediacy of acyl radicals. Ir-derived complexes have been mainly used as metallaphotocatalysts.[60–62] Recently, Tunge and co-workers[63]

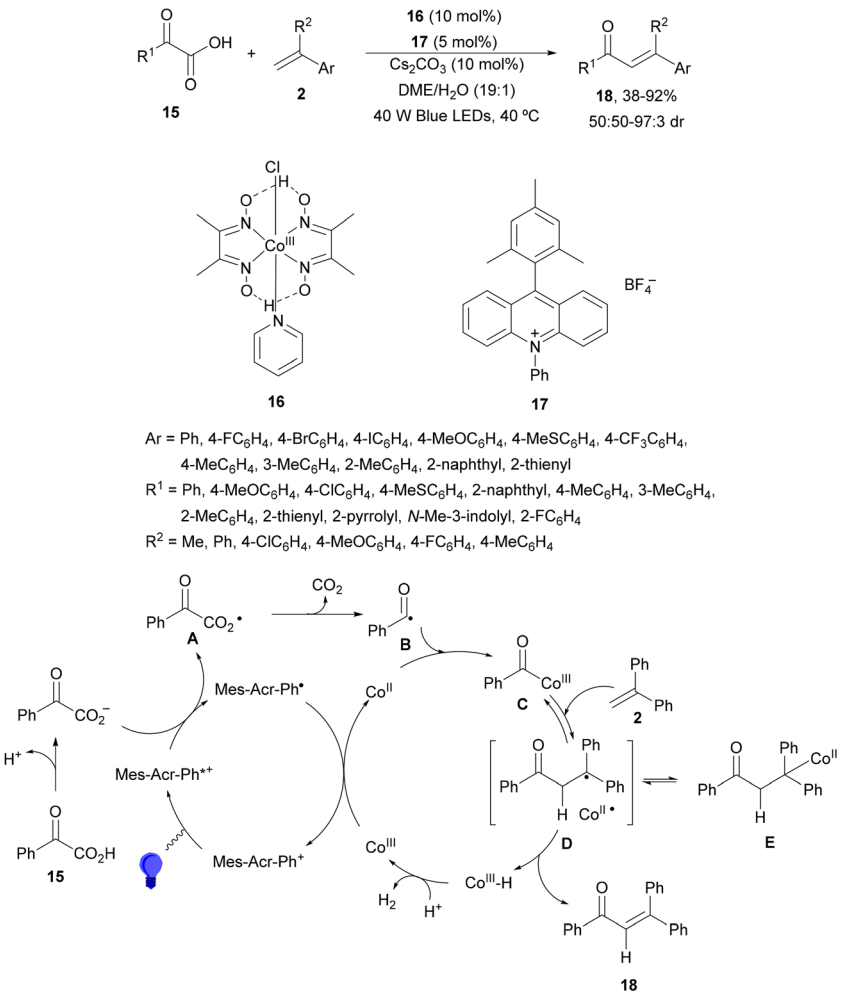


Scheme 5 Two-step DGR/cyclization and DGR/oxidative functionalization between alkylidenemalononitriles and AAs under Ir photocatalysis (a, b).

reported the aroylation of alkenes **2** with α-keto acids **15** using cobaloxime **16** and organophotocatalyst **17** (Mes-Acr-Ph$^+$) as a cooperative catalyst. This method allowed access to chalcone cores **18** in moderate to good yields and diastereoselectivities (Scheme 6). In the proposed mechanism photocatalyst (PC) **17** gave upon irradiation Mes-Acr-Ph^{+}* [$E_{1/2}$ (PC*/PC) = +2.17 V]. A SET from the deprotonated α-keto acid would generate the carboxy radical intermediate **A**, which after decarboxylation afforded acyl radicals **B**. The reduced PC Mes-Acr-Ph$^{\bullet}$ can be oxidized by the Co(III) catalyst to close the catalytic cycle. The generated Co(II) species would react with the acyl radical **B** to give intermediate **C**, which undergoes a radical addition with **2** forming intermediate **D**. Homolytic cleavage of the Co–C bond results in a Co(II) species **E**. Final hydrogen atom transfer provides product **18** and Co(III)–H, which can react with a proton from another molecule of α-keto acid **15** to evolve H_2 gas and return Co to its catalytic cycle.

Organophotoredox catalysis has been expanded in the past few years as a cheaper alternative to Ir-based photocatalysis.[15,51,64] The family of organophotoredox catalysts are composed of (a) arenes coupled with dicyanoarenes (DCAs), (b) carbazolyldicyanobenzene (CDCB) derivatives, (c) dicyanopyrazines (DPZs), (d) flavins (FLs), (e) thioxanthones (TXs), (f) pyrimidopteridine *N*-oxides (PPTNOs), (g) acridinium derivatives, (h) 2,2′-bipyridine and (i) potassium–carbon nitride (Fig. 1). All of them have been used as PCs in the DGR of carboxylic acids including α-keto acids.

Recent applications of some of these organocatalysts will be considered. In the case of an arene as a photocatalyst and a dicyanoarene (DCA) as a redox mediator, Yoshimi and co-workers have reported the DGRs of aliphatic[65,66] and aromatic[67] carboxylic acids. In the first case, experiments conducted using phenanthrene (Phen) as the electron-donor (ED) and 1,4-dicyanobenzene as the electron-acceptor (EA) demonstrate photoinduced electron transfer (PET) from the ED to the EA, generating the radical cation of the ED, which oxidizes the alkyl carboxylate ion to form the carboxy radical able to generate the alkyl radical (Scheme 7A). When aromatic carboxylic acids are used, the EDs such as biphenyl (BP) and the EAs such as 1,4-dicyanonaphthalene (DCN) or 9,10-dicyanoanthracene (DCA) were used as photoredox catalysts (Scheme 7B). In the first case, the EA$^{\bullet-}$ undergoes back electron transfer (BET) to radical **A** generating anion **B**. In the second case, two BET processes occur in the oxidation of ED$^{\bullet-}$ to ED and of the carboxy radical to the anion.



Scheme 6 Decarboxylative Giese reaction of α-oxo acids **15** with styrenes **2** under cobaloxime **16** and Mes-Acr-Ph$^+$ (**17**) dual photocatalysis.

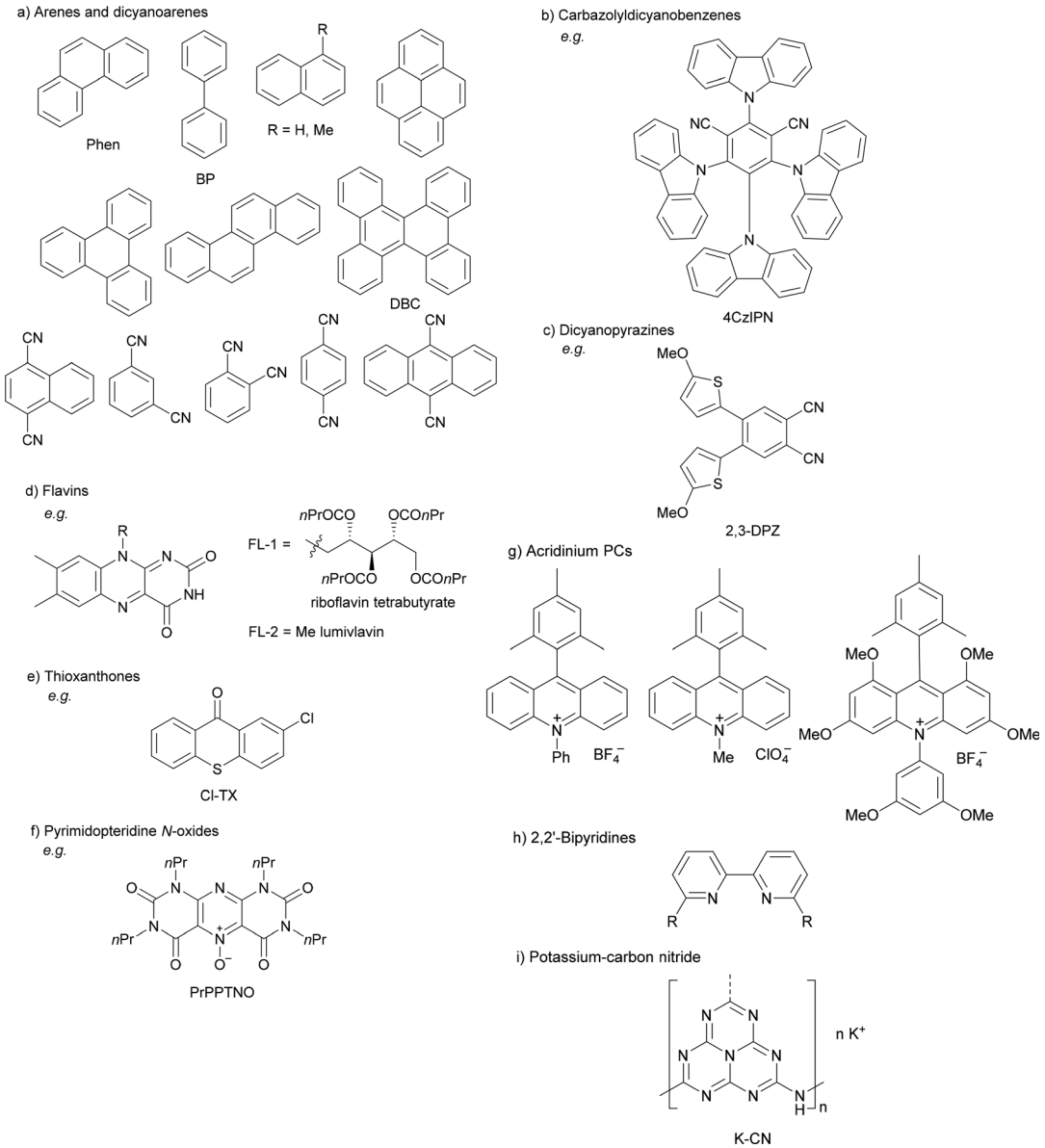
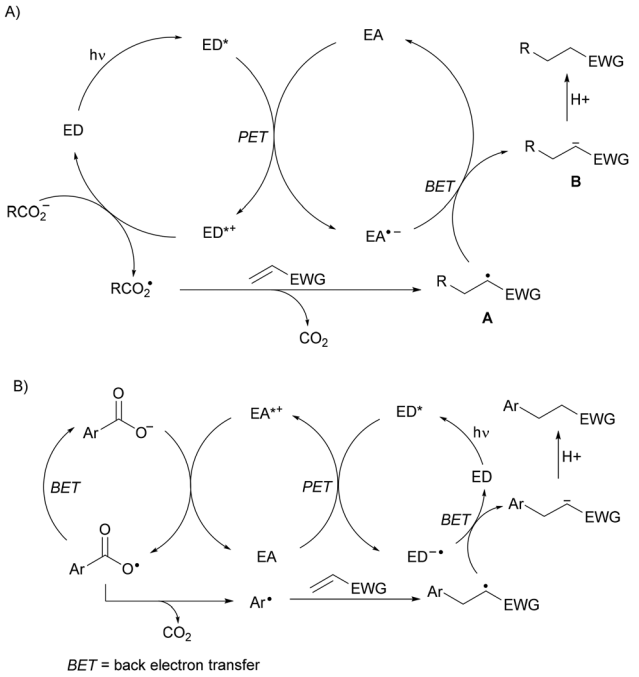


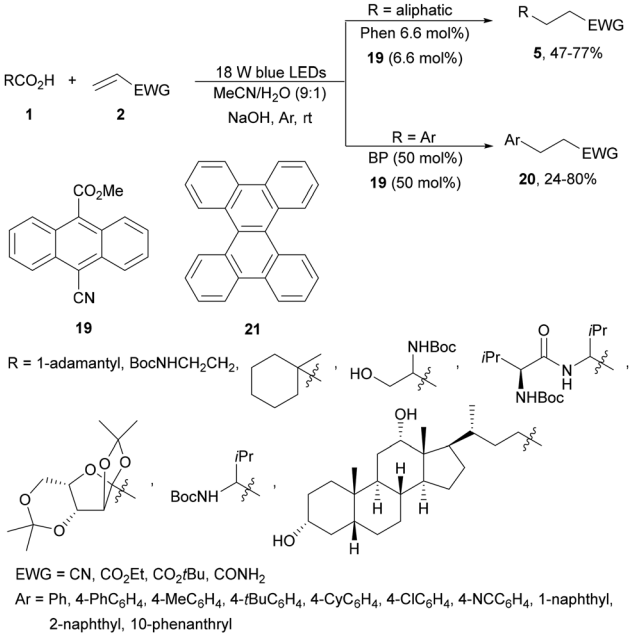
Fig. 1 Representative organophotocatalysts (a–i) for decarboxylative Giese reaction of carboxylic acids.

Yoshimi and co-workers[68] recently reported the use of 9-cyano-10-methoxycarbonylanthracene **19** as the EA instead of 9,10-dicyanoanthracene (DCA), because of its better solubility, and BP in a two-molecule photoredox system for the DGR of aromatic and aliphatic carboxylic acids. For aromatic acids, BP/**19** in aqueous MeCN as solvent and NaOH as a base were employed whereas for the aliphatic ones Phen/**19** induced DGR under visible light (Scheme 8). The replacement of Phen by BP allowed a facile tuning of the oxidation potential of these electron donor molecules. Products **5** and **20** were obtained in moderate to good yields using visible light (405 nm) under an argon atmosphere at room temperature. The same group[69] described that the EA **19** together with Phen or BP as the ED is slightly unstable and studied the modification of these EDs. Dibenzo[*g*,*p*]chrysene **21** absorbs blue LED light (405 nm) with a 0.10×10^3 molar extinction coefficient with an oxidation potential of 1.7 eV. Working with only **21**/1,4-DCB (6.6 mol%) and KOH as a base in aqueous MeCN, aliphatic carboxylic acids gave DGR products **5** in higher yields (30–94%). In the case of aromatic carboxylic acids, the same group[70] studied **19** as the EA and the effects of different EDs and of NaOH or KOH as bases. The influence of the counter-cation (Na^+ or K^+) was relatively minor. Additionally, the dependence of the oxidation ability of the radical cation on the ED allowed estimation of the oxidation potential of the benzoate ions.

Primary carboxylic acids, such as L-glutamic acid and L-aspartic acid methyl esters **22**, showed a low rate of decarboxylation as in the case of aromatic carboxylic acids due to the high oxidation potential of the carboxylate ion and the weak donating ability of the primary alkyl radical.[71] The reaction of compounds **22** with acrylate and acrylamide derivatives **2** took place with BP/DCN and with Phen/CMA (**19**) under visible light



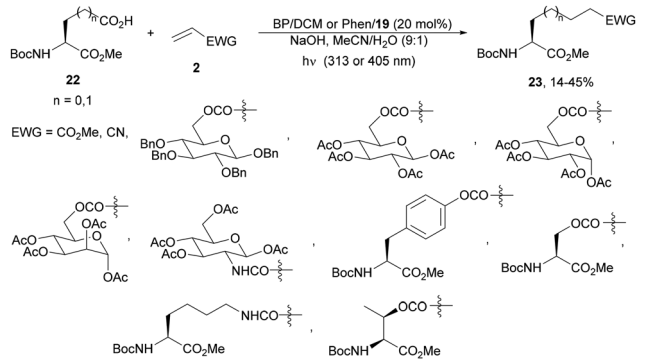
Scheme 7 Plausible mechanisms (A, B) for decarboxylative Giese reactions using two organic photocatalysts.



Scheme 8 Decarboxylative Giese reaction of aliphatic and aromatic acids with electron-deficient alkenes under two organic photoredox systems.

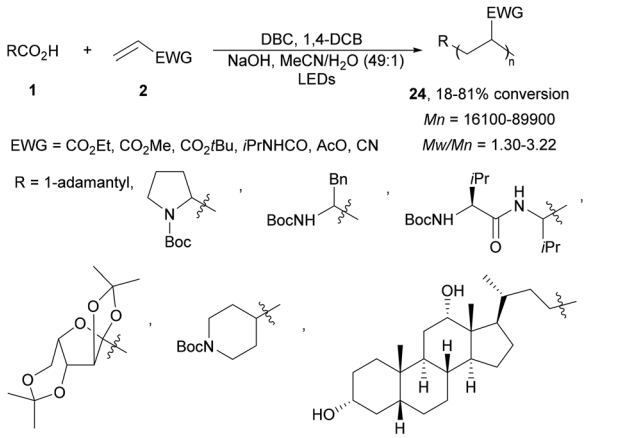
(405 nm) or UV (313 nm) to give products **23** in moderate yields with complete retention of the configuration of the AA unit (Scheme 9). This method was used for the preparation of substrates with carbohydrates, amino acids and peptides.

Recently, this photoinduced decarboxylation of carboxylic acids was applied to the radical polymerization under visible



Scheme 9 Decarboxylative Giese reaction of L-glutamic and L-aspartic acid methyl esters **22** with electron-deficient alkenes under two organic photoredox systems.

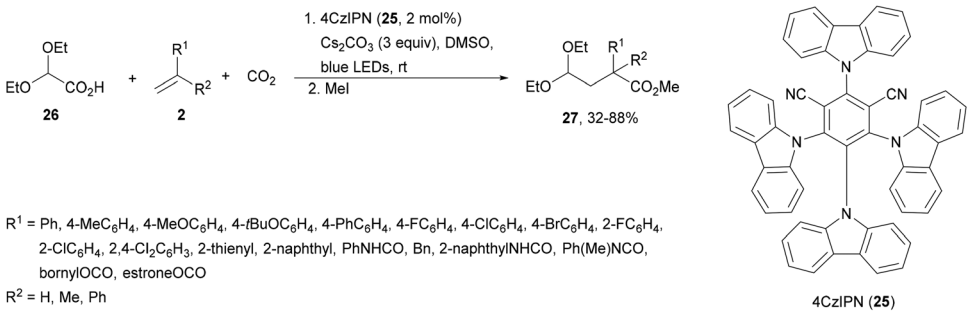
light.[72] Various carboxylic acids and electron-withdrawing



Scheme 10 Decarboxylative co-polymerization of carboxylic acids and electron-poor alkenes under two organic photoredox systems.

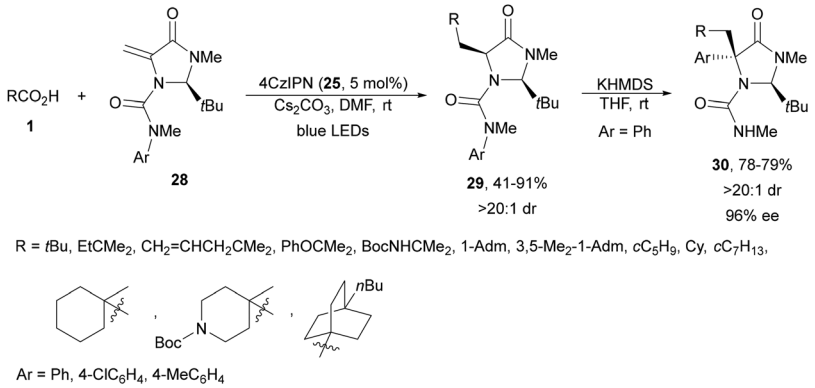
alkenes afforded block copolymers **24** with number-average molecular weight (M_n) and polydispersity (M_w/M_n) depending on both the concentration of ED/EA and the carboxylic acid (Scheme 10).

Carbazolyldicyanobenzenes (CDCBs) are structural derivatives of cyanoarenes with the phenyl core as an electron acceptor and the carbazole units as electron donor structures. They are characterized by a high singlet energy and therefore high oxidation potentials. The HOMO is mainly delocalized over the four carbazolyl moieties and the LUMO is centered on the dicyanobenzene ring. In addition, due to steric hindrance between the carbazolyl and nitrile groups, a large dihedral angle (about 60°) is observed, limiting torsional flexibility and reducing nonradiative decay. Therefore, these PCs exhibit bimodal redox properties both in their ground and excited states, which can be tuned by modification of both structural units.[15,51,64] Generally, 1,2,3,5-tetrakis-(carbazol-9-yl)-4,6-dicyanobenzene (4CzIPN, **25**) is the most used organocatalyst of this family.[73] Zhang and Schubert[74] demonstrated that 4CzIPN is a similar photocatalyst to Ir **4**[75] for the DGR of carboxylic acids and dehydroalanine derivatives. In a recent

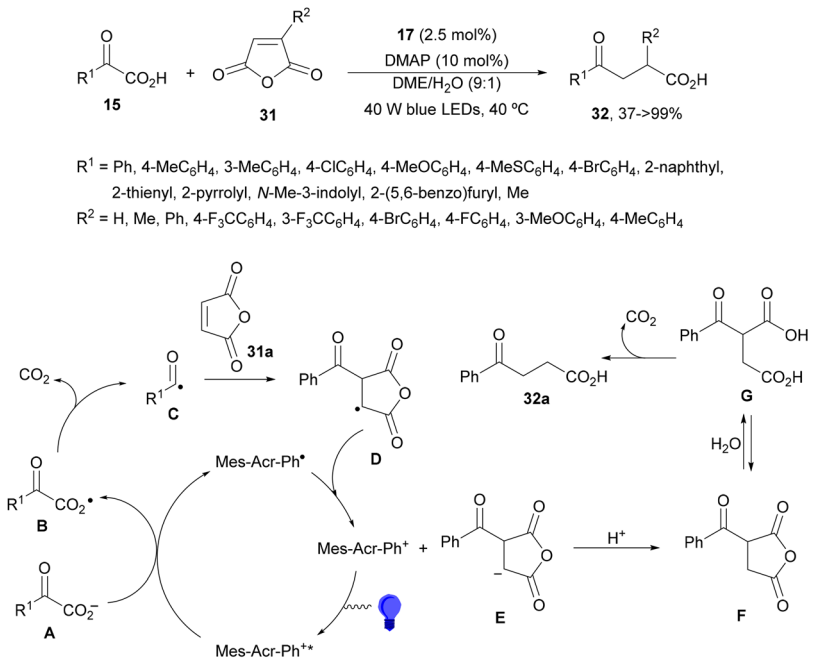


Scheme 11 Formyl/carboxylation of activated alkenes **2** with diethyl glyoxylic acid acetal **26** and CO_2.

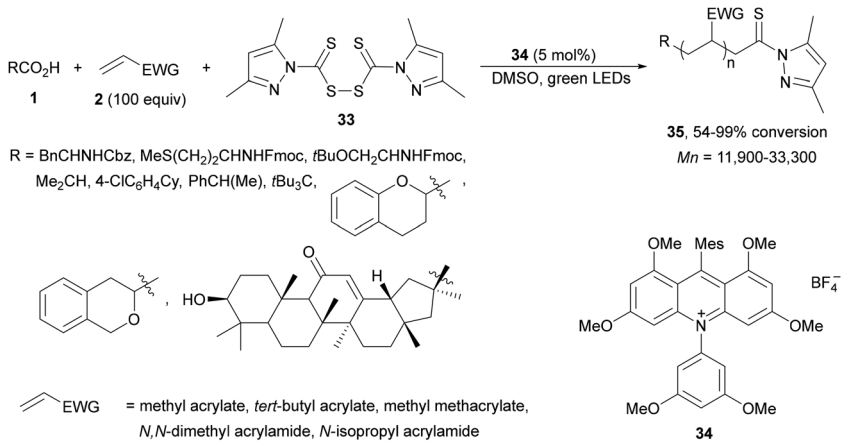
publication, 2,2-diethoxy acetic acid **26** has been employed by Sun and co-workers[76] as a formyl radical equivalent in the sequential formyl/carboxylation of alkylated alkenes **2** and CO_2 using 4CzIPN **25** as the photocatalyst (Scheme 11). Adducts **27** were obtained after methylation of intermediate carboxylate ions in moderate to good yields. On the other hand, the acetal group can be further



Scheme 12 Decarboxylative Giese reaction of dehydroalanines **28** and aliphatic carboxylic acids under 4CzIPN (**25**) photocatalysis and subsequent Clayden rearrangement.



Scheme 13 Decarboxylative Giese reaction of α-keto acids **15** and maleic anhydrides **31** using $[Mes\text{-}Acr\text{-}Ph]^+BF_4^-$ (**17**) as the photocatalyst.



Scheme 14 Decarboxylative RAFT polymerization of carboxylic acids and acrylates using acridinium salt **34** as a photocatalyst.

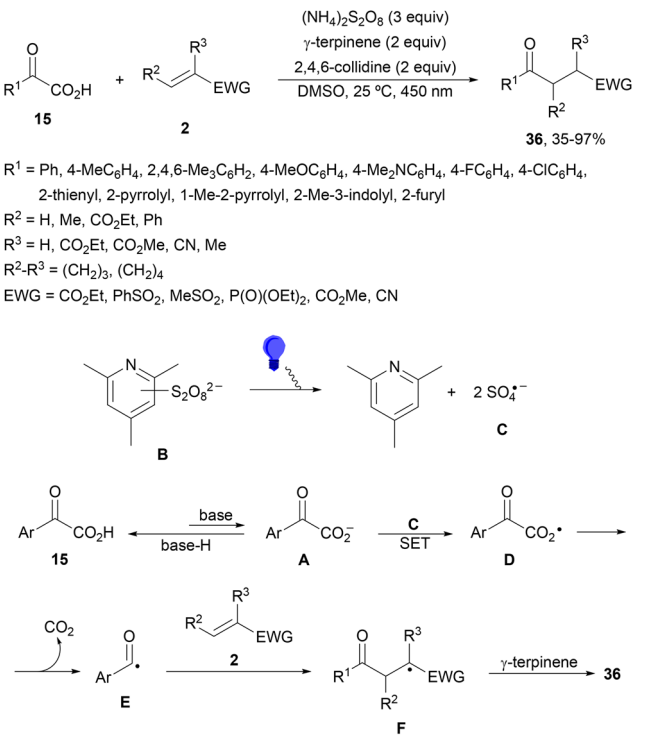
hydrolyzed to an aldehyde or transformed into diverse functionalized compounds.

Wang and co-workers[77] performed a DGR using carboxylic acids and imidazolidinone-derived dehydroalanines **28** as Michael acceptors. Under irradiation with blue LEDs using 4CzIPN (**25**) as a PC in the presence of Cs_2CO_3 as a base in DMF at room temperature, products **29** were isolated with good yields (Scheme 12). These compounds **29** were subjected to a Clayden rearrangement[78,79] to deliver products **30** as precursors of chiral quaternary α-aryl amino acid derivatives with high diastereoselectivity *via* memory of chirality.

Ionic photocatalysts such as acridinium salts[15,51,64] are excellent alternatives to metal-based PCs, because of high oxidative and reducing power and more favorable electron-transfer between the ED and the PC excited state than metallacatalysts. A recent work of Tunge and co-workers[80] employed 9-mesityl-10-phenylacridinium tetrafluoroborate (**17**) as a PC for the DGR of α-keto acids **15** with maleic anhydrides **31** as traceless synthons of acrylic acid (Scheme 13). A dual decarboxylative procedure resulted in γ-keto acids **32** in good yields working with 4-dimethylaminopyridine (DMAP) as a base in aqueous dimethoxyethane (DME) and 40 W blue LED irradiation at −40 °C. This process can be carried out for instance in aqueous methanol as solvent to obtain the corresponding methyl γ-keto esters. On the other hand, when acrylic acid or maleic acid **31a** was used as a Michael acceptor the resulting products **32** were obtained in low yields. In the general proposed mechanism, Mes-Acr-Ph$^+$ is excited to Mes-Acr-Ph^{+}*, which after a SET from the carboxylate ion **A** generates the carboxy radical **B** intermediate. Subsequent decarboxylation of **B** gives the acyl radical **C**, which undergoes Giese addition into the maleic anhydride generating intermediate **D**. The reduced PC will return to its ground state *via* a SET process to **D** affording enolate **E**. Protonation of **E** by a new molecule of α-keto acid and subsequent hydrolysis of the maleic anhydride **F** unit gives intermediate **G**, which undergoes decarboxylation to furnish the γ-keto acid **32a**.

Radical polymerization by a reversible addition-fragmentation chain-transfer (RAFT) from carboxylic acids and acrylic derivatives has been recently performed using acridinium salts as PCs by Hooper and co-workers.[81] In the presence of a thiocarbonyl disulfide **33** used as the RAFT agent under green light and the acridinium salt **34** polymers **35** were isolated with low dispersity (1.12–1.58) and an M_n of 11 900 to 33 300 g mol^{-1} determined by NMR (Scheme 14). In contrast, the use of Ir catalyst **4** gave poorer results. Different carboxylic acids such as AAs, secondary and tertiary ones were more effective than the corresponding primary ones.

Light-mediated DGR without a PC has been described by Lu and coworkers[82] using α-keto acids **15** and Michael acceptors **2**. This procedure was carried out under oxidative conditions in

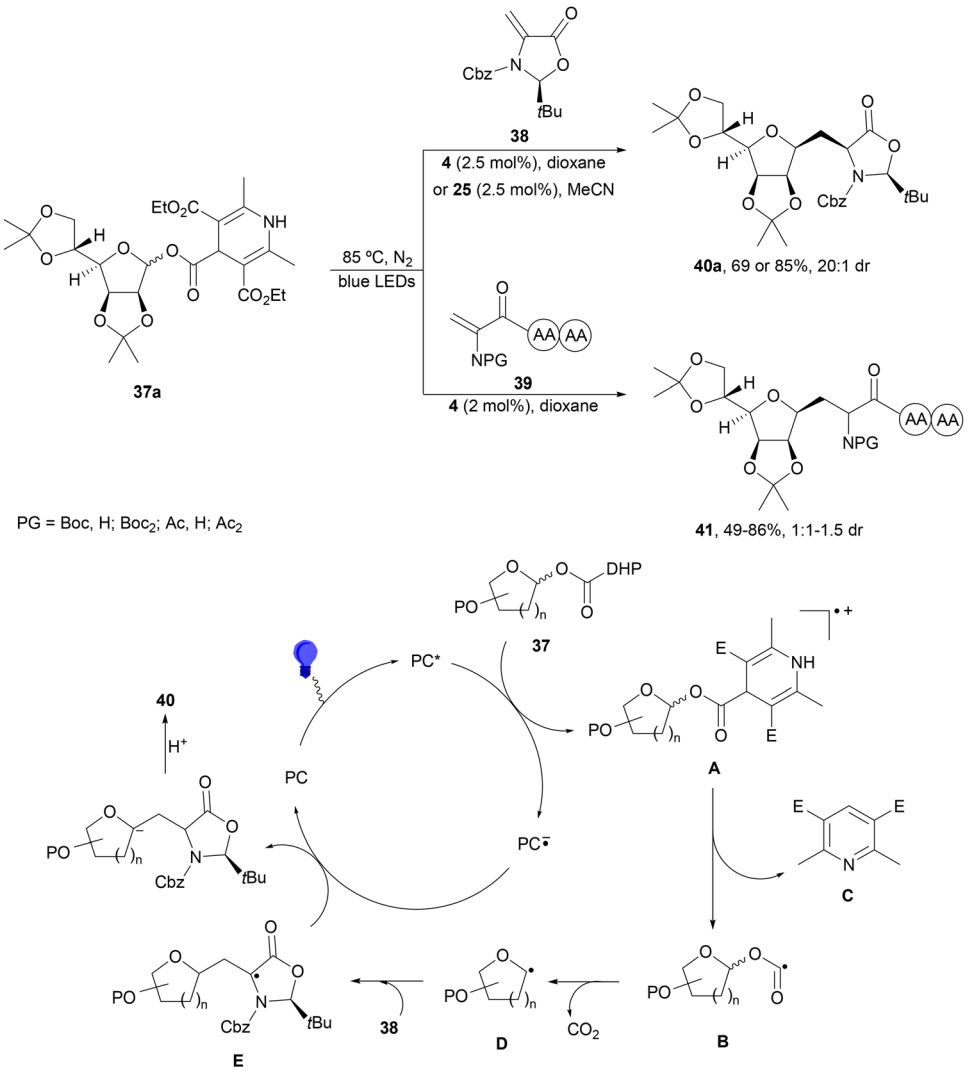


Scheme 15 Light-mediated DGR of α-keto acids **15** and Michael acceptors under oxidative conditions without a photocatalyst.

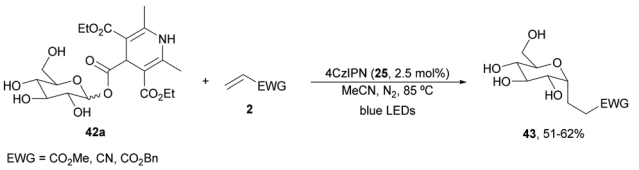
the presence of ammonium persulfate, γ-terpinene as a hydrogen atom transfer (HAT) source and 2,4,6-collidine as a base (Scheme 15). Products **36** were obtained in better yields under light-mediated than that under thermal (50 °C) reaction conditions. In the proposed mechanism, $SO_4^{\bullet -}$ (**C**) is formed by photodecomposition of the combination of 2,4,6-collidine and $S_2O_8^{2-}$ (**B**). Upon formation of **C**, SET between **C** and glyoxylate anion **A** can occur to provide radical **D**, which decarboxylates to the acyl radical **E**. Subsequent Giese addition to **2** forms radical **F**, which undergoes HAT from γ-terpinene to yield product **36**.

In conclusion, the two-molecule photoredox system employs inexpensive, stable and neutral organic molecules and allows the modulation of the back electron transfer from the radical anion of the EA and the replacement of the ED with the same EA facilitating a change in the oxidation potential maintaining the same EA. This modification is impossible for the one-molecule photoredox catalysis. However, 4CzIPN has shown very good photocatalytic properties being easily modified at the carbazole and dicyanobenzene units.

1,4-Dihydropyridine (DHP)-derived glycosyl esters **37** have been employed as redox-active ester (RAE) precursors of glycosyl radicals *via* anomeric C(sp^3)–O bond homolysis and subsequent decarboxylation in DGRs.[83] For instance, ester **37a** reacted with oxazolidinone-derived dehydroalanine **38** and dehydroalanine peptides **39** using Ir complex **4** or 4CzIPN (**25**) as a photocatalyst under blue LED irradiation in MeCN or 1,4-dioxane at 85 °C to provide products **40** and **41**, respectively (Scheme 16). A wide range of glycosyl DHP esters derived from monosaccharides and oligosaccharides were used to give products **40** in moderate to good yields (up to 87%) and good to excellent stereoselectivities (up to >20:1 dr). In the case of starting compounds **39**, containing dipeptides and tripeptides, the corresponding mannofuranosyl peptides **41** were obtained in 34–65% yields with excellent anomeric selectivity. According

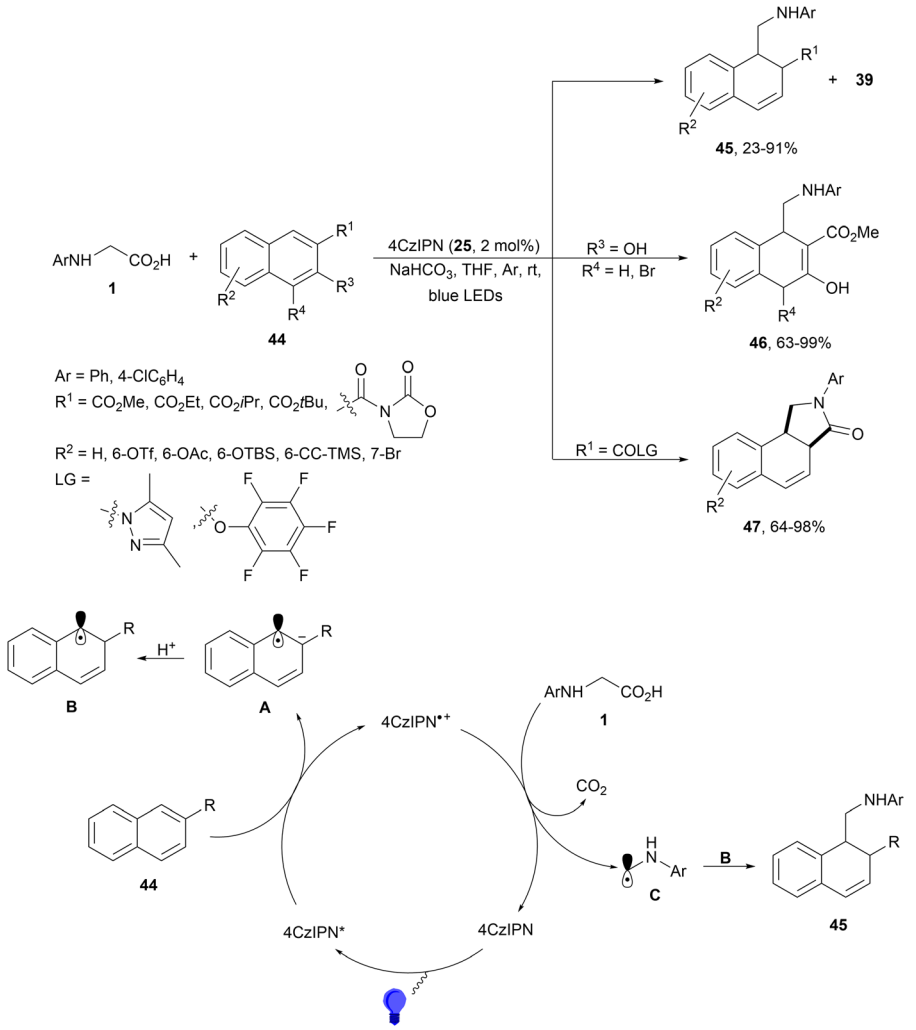


Scheme 16 Decarboxylative Giese reaction of glycosyl DHP esters **37** with dehydroalanine-derivatives **38** and **39** under Ir **4** or 4CzIPN (**25**) photocatalysis.

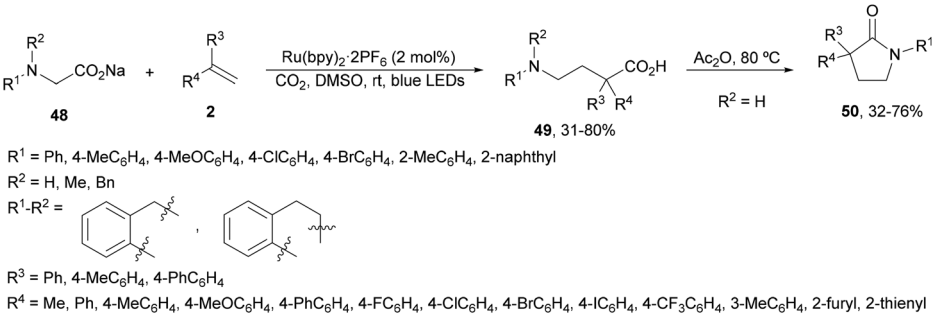


Scheme 17 Decarboxylative Giese reaction of unprotected glycosyl DHP esters **42** and Michael acceptors under 4CzIPN (**25**) photocatalysis.

to mechanistic studies a proposed mechanism is depicted in Scheme 16. The excited PC* promotes the SET oxidation of ester **37** to intermediate **A** followed by homolysis to the alkoxycarbonyl radical **B** and Hantzsch pyridine **C**. After decarboxylation of **B**, glycosyl radical **D** is formed, which adds to **38** giving radical **E**. Radical **E** undergoes SET with the reduced $PC^{\bullet -}$ to yield, after protonation, product **40**.



Scheme 18 1,2-Hydroalkylation of naphthalene derivatives **44** with *N*-arylglycines under 4CzIPN (**25**) photocatalysis.

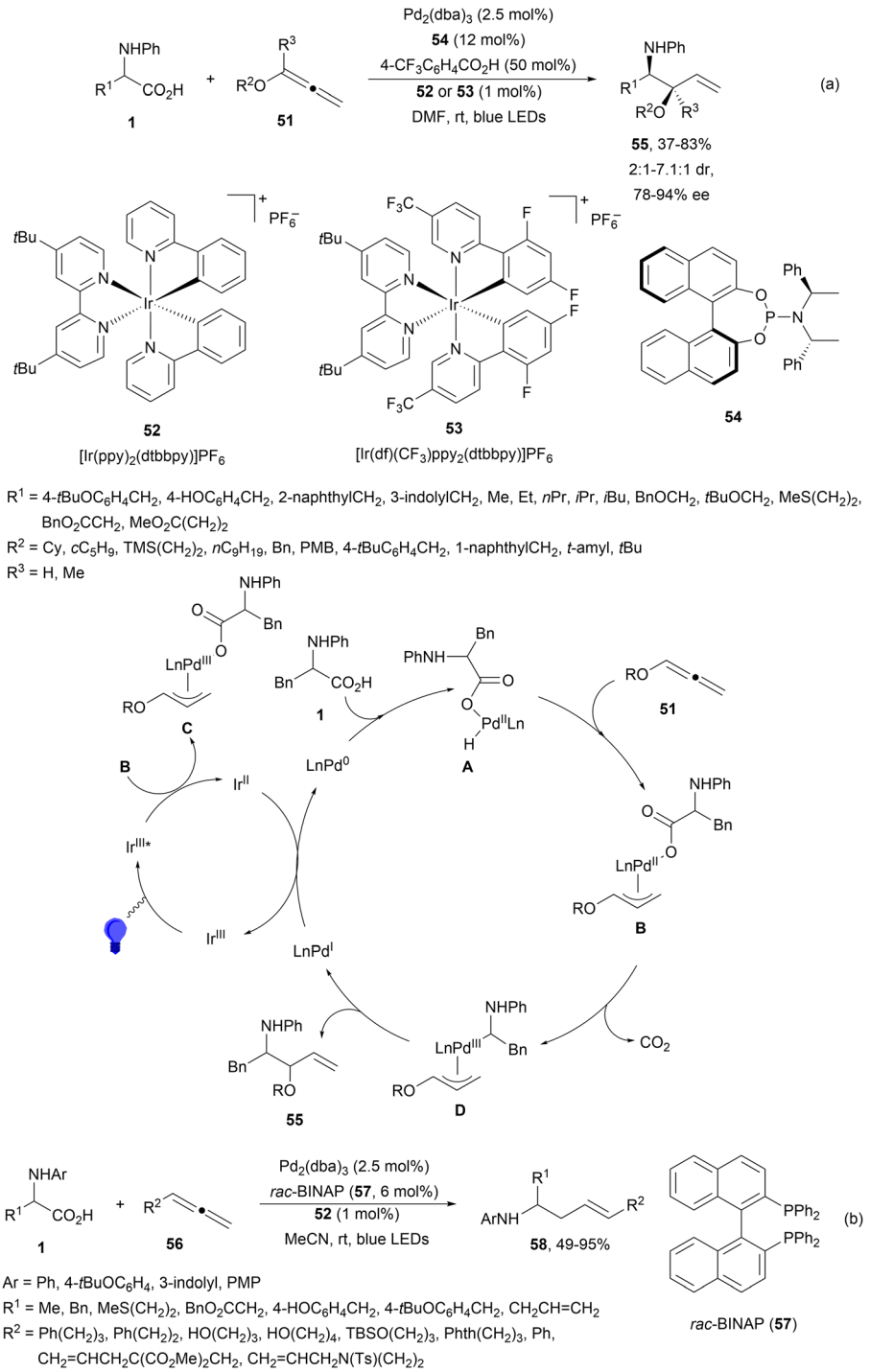


Scheme 19 Aminomethylation/carboxylation of styrenes with sodium glycinates **48** and CO_2 under $Ru(bpy)_2{\cdot}2PF_6$ photocatalysis.

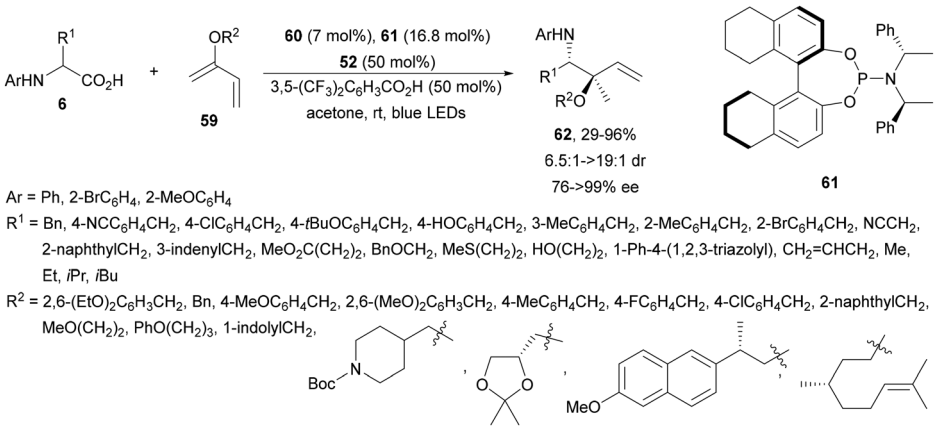
Recently, Fairbanks and co-workers[84] described the DGR of unprotected glycosyl DHP esters **42** using 4CzIPN (**25**) as a PC in dry MeCN under blue LED irradiation at 85 °C (Scheme 17). Using acrylates as Michael acceptors and glucose DHP ester **42a** products **43** were obtained in 51 to 62% yields. The reaction could be applied to mannose and galactose DHP esters, as well as to maltose and lactose DHP esters.

2.2. Addition to electron-rich alkenes

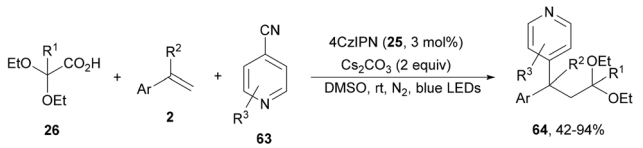
Decarboxylative hydroalkylation of C–C double bonds has been performed with substituted naphthalene derivatives **44** and α-amino acids **1** using different PCs.[85] This 1,2-hydroalkylation is a formal dearomatization carried out under redox-neutral conditions and using 4CzIPN (**25**) as a more efficient PC than Ir or Ru complexes. Substituted 1,2-dihydronaphthalenes **45** were

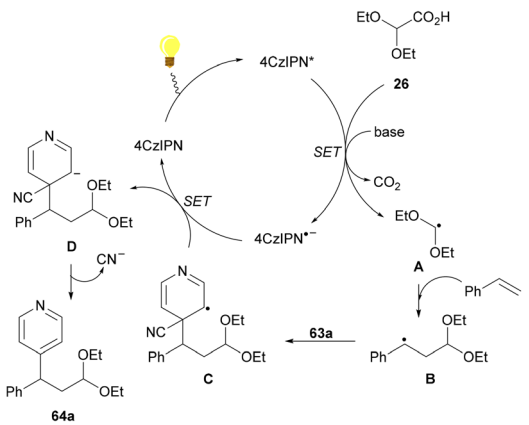


Scheme 20 Decarboxylative hydrofluoroalkylation of allenes **51** (a) and **56** (b) with *N*-aryl AAs under Pd/Ir complex photocatalysis.

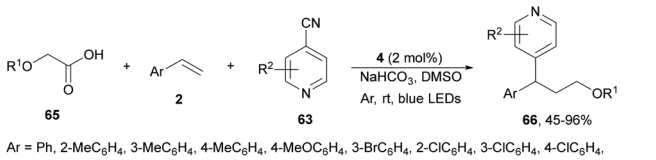


Scheme 21 Decarboxylative hydroalkylation of dienol ethers **59** with *N*-aryl AAs under Pd/Ir complex photocatalysis.





Scheme 22 Three-component acetalation–pyridylation of styrene derivatives with diethoxyacetic acids (**26**) and cyanopyridines **63** under 4CzIPN (**25**) photocatalysis.

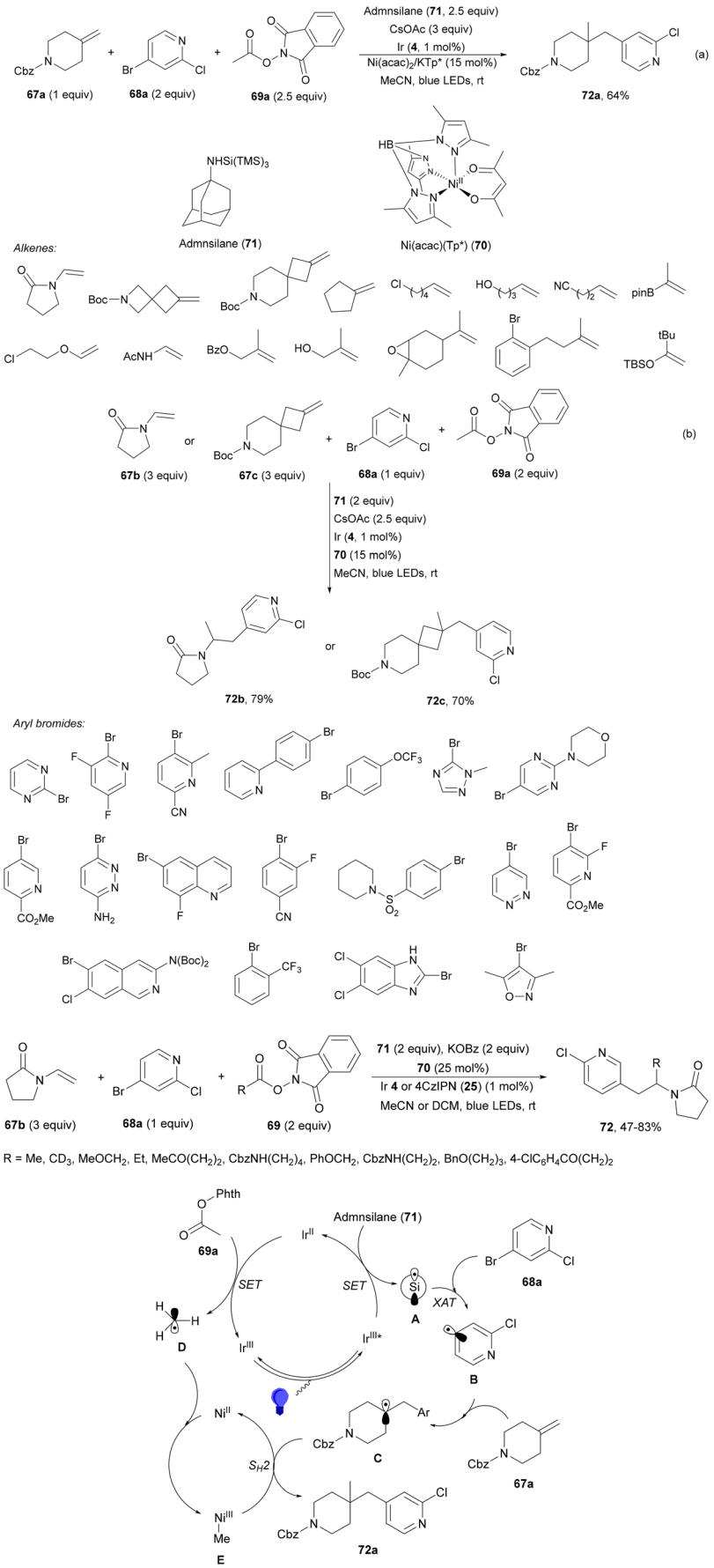


Scheme 23 Three-component alkoxymethylation-pyridylation of styrene derivatives with α-alkoxy acetic acids **65** and cyanopyridines **63** under Ir photocatalysis.

obtained in good yields under visible light (Scheme 18). When an ester group was incorporated at the 2-position of naphthalene **44**, tricyclic lactam-fused products **47** were also obtained. These compounds **47** were exclusively formed when the substituent at the 2-position of naphthalene was changed to *N*-acyl pyrazole or pentafluorophenyl ester with excellent diastereoselectivity. In the case of 3-hydroxy-2-methoxycarbonylnaphthalenes, products **46** were exclusively obtained with 63–99% yields. In the proposed mechanism, naphthalene **44** is transformed into the radical anion **A** by oxidation with the photoexcited species 4CzIPN* to deliver 4CzIPN$^{+\bullet}$. Protonation of **A** gives radical **B** and *N*-arylglycine undergoes single-electron oxidation by 4CzIPN$^{+\bullet}$ to provide after decarboxylation radical **C**. Final recombination of radical **B** and **C** gives products **45–47**.

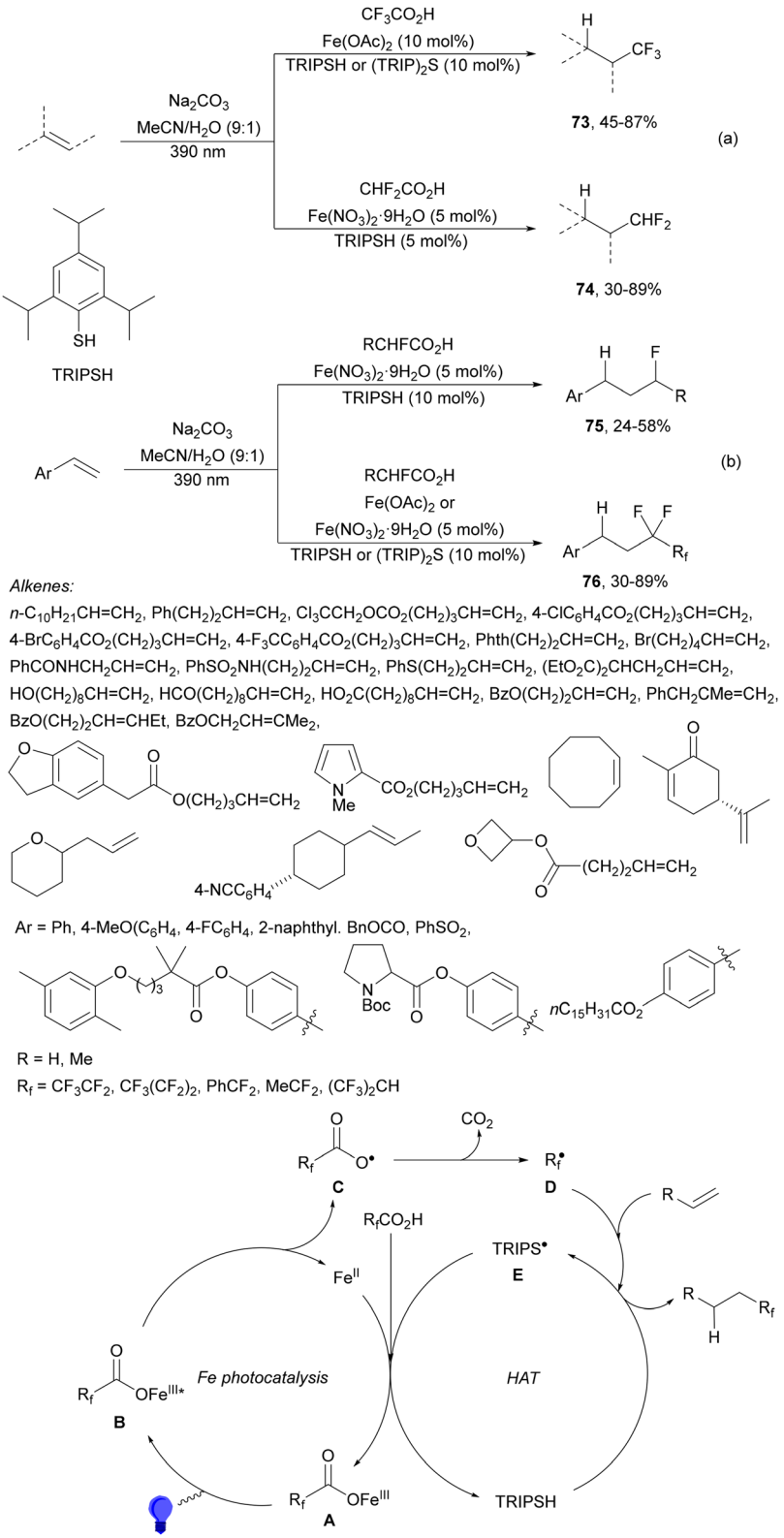
Tandem aminomethylation/carboxylation of styrenes with sodium glycinates **48** has been developed under Ru(bpy)$_3$·2PF$_6$ photocatalysis using CO_2 (1 atmosphere) in DMSO at room temperature (Scheme 19).[86] This methodology afforded α,α-disubstituted γ-amino acids **49** in moderate to good yields. In some cases Ir complex **4** was also used in place of the Ru complex. When the resulting products **49** were treated with acetic anhydride the corresponding γ-lactams **50** were obtained in moderate to good yields. This procedure represents a step forward in the development of atom-economical decarboxylative reactions.

In the case of allenes, a dual Pd/photoredox-catalyzed regio- and enantioselective decarboxylative hydroalkylation with *N*-aryl AAs has been recently reported by Breit and co-workers.[87] When 1-alkoxyallenes **51** were hydroalkylated using Ir complexes **52** or **53** in the presence of 4-CF$_3$C$_6$H$_4$CO$_2$H and Feringa's phosphoramidite **54** as a chiral ligand *syn*-1,2-amino ethers **55** were obtained in good yields with good diastereo- and enantioselectivities under blue LED irradiation (Scheme 20a). The Ir catalyst gave better results than 4CzIPN. This transformation starts by oxidative addition of Pd(0) to the AA giving the palladium hydride species **A**. Migratory insertion of **A** into the allene forms the π-allyl palladium species **B**, which *via* a



Scheme 24 Aryl-alkylation of unactivated alkenes **67** with aryl bromides **68** and NHPI esters **69** using Admnsilane **71**, Ir **4** and Ni (**70**) complexes as photoredox catalysts.

reductive quenching process of the excited Ir(III)* complex provides intermediate **C**. Subsequent SET from the carboxylate ion to Pd facilitates the decarboxylation step resulting in intermediate **D**. Final reductive elimination forms the product and the Pd(I) species, which is reduced by the Ir(II) complex. With monosubstituted allenes **56** linear decarboxylative hydroalkylation took



Scheme 25 Decarboxylative hydrofluoroalkylation (a, b) of alkenes under $Fe(OAc)_2$ or $Fe(NO_3)_3$ and TRIPSH photocatalysis.

place with *N*-aryl AAs using *rac*-BINAP (**57**) as a ligand for Pd to provide homoallyl amines **58** with good yields and regio- and *E*/*Z*-diastereoselectivities (Scheme 20b).

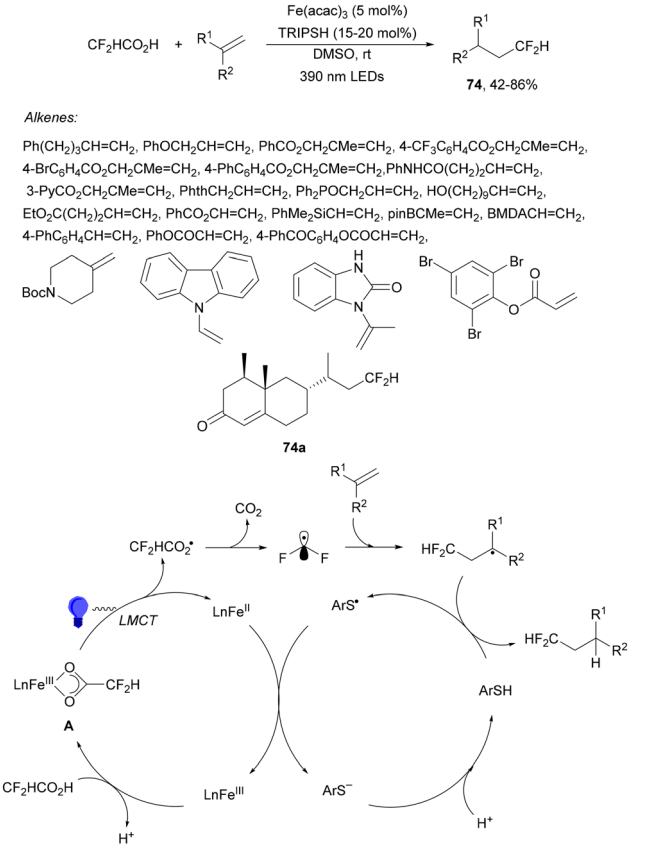
Breit and co-workers[88] performed the enantioselective hydroalkylation of dienol ethers **59** with AAs **6** using dual Pd/Ir photoredox catalysis. The decarboxylative 1,2-Markovnikov addition was carried out with an (η^3-cinnamyl)PdCp complex (**60**) and the chiral phosphoramidite **61** and [Ir(ppy)$_2$(dtbbpy)]PF$_6$ (**52**) in acetone at room temperature under blue LED irradiation to provide products **62** up to >19:1 dr and up to >99% ee (Scheme 21). Mechanistic studies suggest a reversible hydropalladation as the key step.

Zhang and co-workers[89] have reported a three-component acetalation–pyridylation of alkenes using 4CzIPN (**25**) as an organophotocatalyst and Cs_2CO_3 as a base. Diethoxyacetic acids **26**, cyanopyridines **63** and styrene derivatives **2** provided difunctional products **64** with very good yields and regioselectivities (Scheme 22). According to experimental results a plausible mechanism was proposed in which excited 4CzIPN* by irradiation of **25** with blue LED generates the formyl radical equivalent **A** and CO_2. Hydroalkylation of styrene by intermediate **A** forms radical **B**, which reacts with 4-cyanopyridine **63** to generate radical **C**. Subsequent reduction of **C** by 4CzIPN$^{-\bullet}$ forms anion **D**, which evolves to product **64a**. Some products showed favorable *in vitro* antitumor activity.

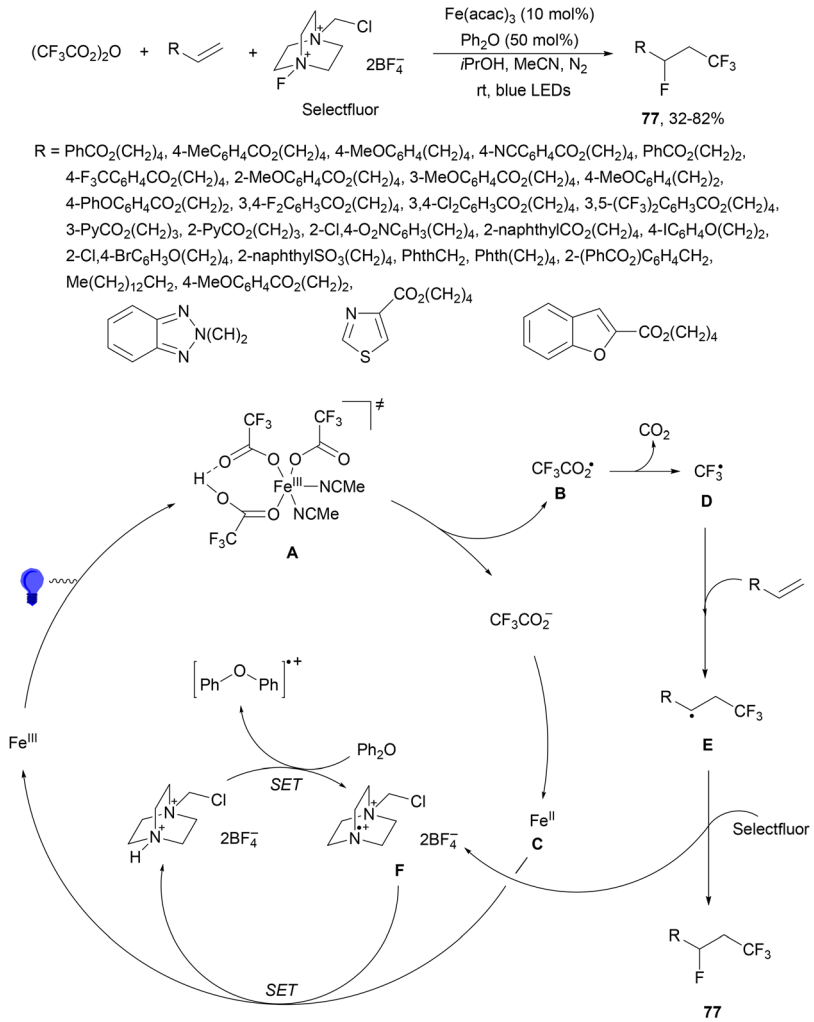
Recently, a similar three-component decarboxylative coupling reaction of α-aryloxyacetic acids **65**, cyanopyridines **63** and styrene derivatives **2** provided pyridines **66** with good yields (Scheme 23).[90] In this case, Ir complex **4** was the best PC, with $NaHCO_3$ as a base in DMSO at room temperature under blue LED irradiation. This process was carried out in a gram-scale.

Aryl-alkylation of unactivated alkenes has been recently described by MacMillan and co-workers.[91] This process took place by reaction of alkenes **67** with aryl bromides **68** and NHPI esters **69** under Ir complex **4** or **25** and Ni complex **70** photocatalysis in the presence of adamantylaminosupersilane (Admnsilane **71**) and CsOAc as a base under blue LED irradiation (Scheme 24). By a triplet radical sorting mechanism of an aryl radical and a primary radical from the RAE **69** the corresponding products **72** resulted in good yields. Different unactivated alkenes **67** reacted with 4-bromo-2-chloro-pyridine **68a** and NHPI **69a** to provide products **72** in 59–79% yields (Scheme 24a). Different aryl bromides **68** were allowed to react with alkenes **67b** and **67c** and NHPI ester **69a** giving products **72** in 41–72% yields (Scheme 24b). The scope of NHPI esters **69** was studied with *N*-vinylpyrrolidone **67b** and 4-bromo-2-chloropyridine **68a** to obtain products **72** in 47–83 yields using 4CzIPN (**25**) or Ir complex **4** as a photocatalyst (Scheme 24c). A proposed mechanism for the alkene aryl-alkylation is shown in Scheme 24: blue light excites the Ir photocatalyst **4** to the long-lived triplet excited state Ir(III)*, which is reductively quenched by Admnsilane (**71**). After aza-Brook rearrangement the silane radical **A** is formed, which undergoes a halogen atom transfer (XAT) with aryl bromide **68a** to give an aryl radical **B**. Addition of **B** to alkene **67a** results in the hindered alkyl radical **C**. To close the photoredox catalytic cycle Ir(II) reduces an NHPI ester **69a** to provide the primary alkyl radical **D** after decarboxylation. This species is captured by the S_H2 radical-sorting Ni catalyst **70** to afford complex **E**, which reacts with radical **C** providing product **72a**.

Recently, several studies on iron-catalyzed hydrofluorination have been reported.[92–94] West and co-workers[92] published hydrofluoroalkylation of alkenes with fluoroalkylcarboxylic acids under mild conditions using Fe and redox-active thiol catalysis. Unactivated alkenes reacted with trifluoroacetic acid or difluoroacetic acid with Fe(OAc)$_2$ and 2,4,6-triisopropylbenzenethiol (TRIP thiol) (or its disulfide) as catalysts, Na_2CO_3 as a base, aqueous MeCN at room temperature under 390 nm Kessil blue LED irradiation to furnish product **73** or **74**, respectively, with good yields (Scheme 25a). These hydrotrifluoromethylation and hydrodifluoromethylation reactions have been applied to APIs and natural products. Non-steroidal and anti-inflammatory drugs such as ibuprofen, flurbiprofen and ioxoprofen provided the corresponding fluorinated products with 62–82% yields. Sulfonamide-containing probenecid and naproxen were trifluoromethylated in 89 and 43% yields, respectively. (−)-Borneol, L-menthol, oleic acid, monosaccharides, flavone and others were hydrofluoroalkylated with good yields. *N*-Boc-proline, estrone, 18β-glycyrrhetinic acid and pregnenolone derivatives gave useful conversions. Hydromonofluoroalkylation of styrene derivatives and hydro(polyfluoro)alkylation were performed under similar reaction conditions to provide products



Scheme 26 Decarboxylative hydrofluoromethylation of alkenes with CF_2HCO_2H under Fe(acac)$_3$ and TRIPSH photocatalysis.

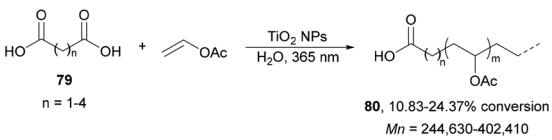


R = $PhCO_2(CH_2)_4$, 4-$MeC_6H_4CO_2(CH_2)_4$, 4-$MeOC_6H_4(CH_2)_4$, 4-$NCC_6H_4CO_2(CH_2)_4$, $PhCO_2(CH_2)_2$, 4-$F_3CC_6H_4CO_2(CH_2)_4$, 2-$MeOC_6H_4CO_2(CH_2)_4$, 3-$MeOC_6H_4CO_2(CH_2)_4$, 4-$MeOC_6H_4(CH_2)_2$, 4-$PhOC_6H_4CO_2(CH_2)_2$, 3,4-$F_2C_6H_3CO_2(CH_2)_4$, 3,4-$Cl_2C_6H_3CO_2(CH_2)_4$, 3,5-$(CF_3)_2C_6H_3CO_2(CH_2)_4$, 3-$PyCO_2(CH_2)_3$, 2-$PyCO_2(CH_2)_3$, 2-Cl,4-$O_2NC_6H_3(CH_2)_4$, 2-naphthyl$CO_2(CH_2)_4$, 4-$IC_6H_4O(CH_2)_2$, 2-Cl,4-$BrC_6H_3O(CH_2)_4$, 2-naphthyl$SO_3(CH_2)_4$, $PhthCH_2$, $Phth(CH_2)_4$, 2-$(PhCO_2)C_6H_4CH_2$, $Me(CH_2)_{12}CH_2$, 4-$MeOC_6H_4CO_2(CH_2)_2$,

Scheme 27 Decarboxylative fluorotrifluoromethylation of alkenes using $Fe(acac)_3$, Selectfluor and Ph_2O under photocatalysis.

75 and **76** (Scheme 25b). In the proposed mechanism, photochemical formation of a disulfide or thiyl radical enables oxidation of Fe(II) to Fe(III), which promotes the homolysis of the acids through an LMCT process[54,55] of the Fe(III)-carboxylate. In the Fe photocatalysis cycle carboxylate ion **A** is transformed into **B** after LED irradiation, which evolves into Fe(II) and the carboxy radical **C**. Decarboxylation of **C** forms the fluorinated radical **D**. Subsequent radical addition onto the alkene provided the corresponding carbon centered radical, which reacts with the thiol as the HAT reagent to give the product, and the thiyl radical **E** will reoxidize the Fe(II) and receive a proton from the acid or from water closing both catalytic cycles.

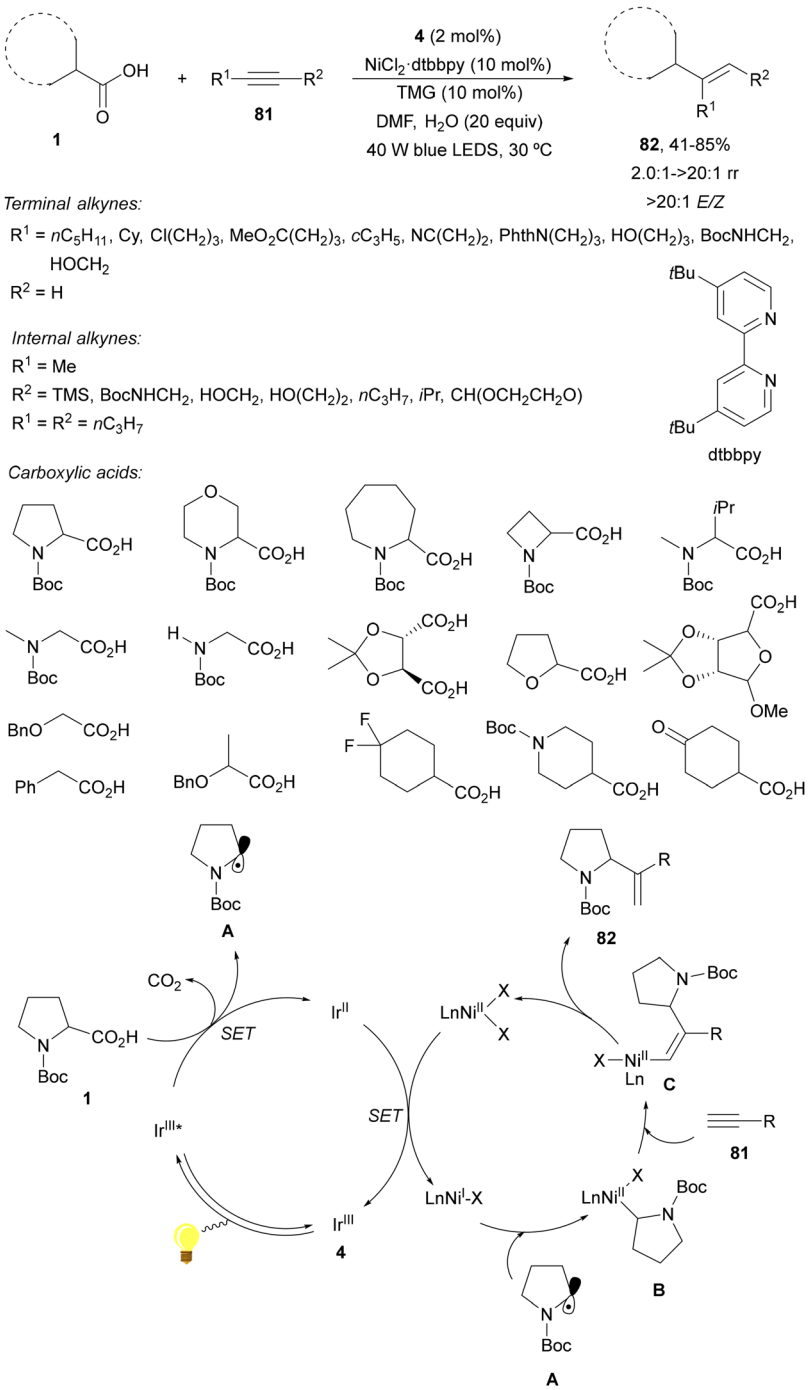
Guo, Xia and co-workers[93] have reported photoinduced decarboxylative hydrodifluoromethylation of alkenes. In this case, terminal alkenes reacted with α,α-difluoroacetic acid using $Fe(acac)_3$ and TRIPS as catalysts, with DMSO as solvent at room temperature under 390 nm LED irradiation to give products **74** with moderate to good yields (Scheme 26). These reaction conditions were also applied to APIs and natural products used in the pharmaceutical industry. In the presence



Scheme 28 Photopolymerization of vinyl acetate initiated by carboxylic acids **79** under TiO_2 NP photocatalysis.

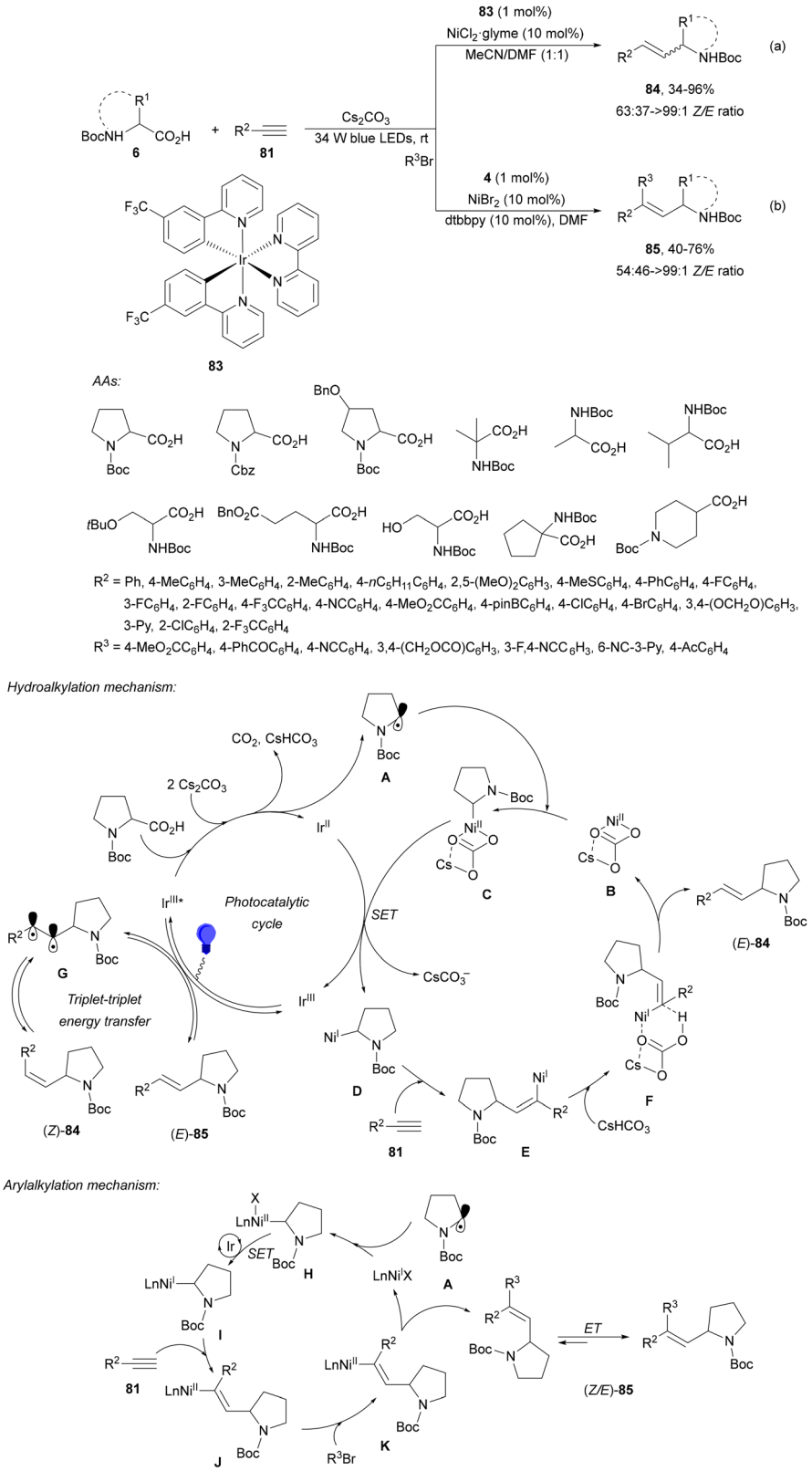
of D_2O, it was possible to perform deuteriodifluoromethylation of alkenes with >91% deuterium incorporation. Gram-scale experiments were carried out in continuous-flow in the synthesis of (+)-nootkalone to obtain 0.89 g of product **74a** with 82% yield and 1 : 1 dr. In the proposed catalytic cycles, a LMCT process[54,55] takes place through the iron complex **A**, providing similar intermediates to that shown in Scheme 25. Under similar reaction conditions, the Giese reaction of electron-deficient alkenes with aliphatic carboxylic acids using $FeCl_3$ (10 mol%) and DABCO as a base in MeCN at room temperature under 390 nm LED irradiation occurs.

In the presence of a Brønsted acid, the formation of iron LMCT[54,55] was facilitated for the activation of haloalkylcarboxylates ($C_nX_mCO_2^-$, X = F or Cl) to produce C_nX_m radicals.[94] Unactivated terminal alkenes reacted with trifluoroacetic anhydride, Selectfluor, diphenyl ether and Fe(acac)$_3$ as a catalyst in isopropanol and MeCN under a N_2 atmosphere and blue light irradiation to form products **77** with moderate to good yields (Scheme 27). A wide variety of APIs were subjected to this Brønsted acid-unlocked iron LMCT photocatalysis. According to mechanistic studies, the photodecomposition of *in situ*-generated Fe$(CF_3CO_2)_3$ occurred only under acidic conditions. In the proposed mechanism, the Fe(III) photoactive species, after irradiation through TS **A**, gives CF_3CO_2 radical **B** and Fe(II) intermediate **C**. After decarboxylation of **B**, the desired CF_3 radical **D** is trapped by the alkene to form radical **E**, which is fluorinated by Selectfluor to give product **77**. The generated *N*-radical cation **F** required the regulation by the redox buffer diphenyl ether to avoid the formation of C–N bonds.



Scheme 29 Decarboxylative hydroalkylation of unactivated alkynes **81** and carboxylic acids under Ir/Ni photoredox catalysis.

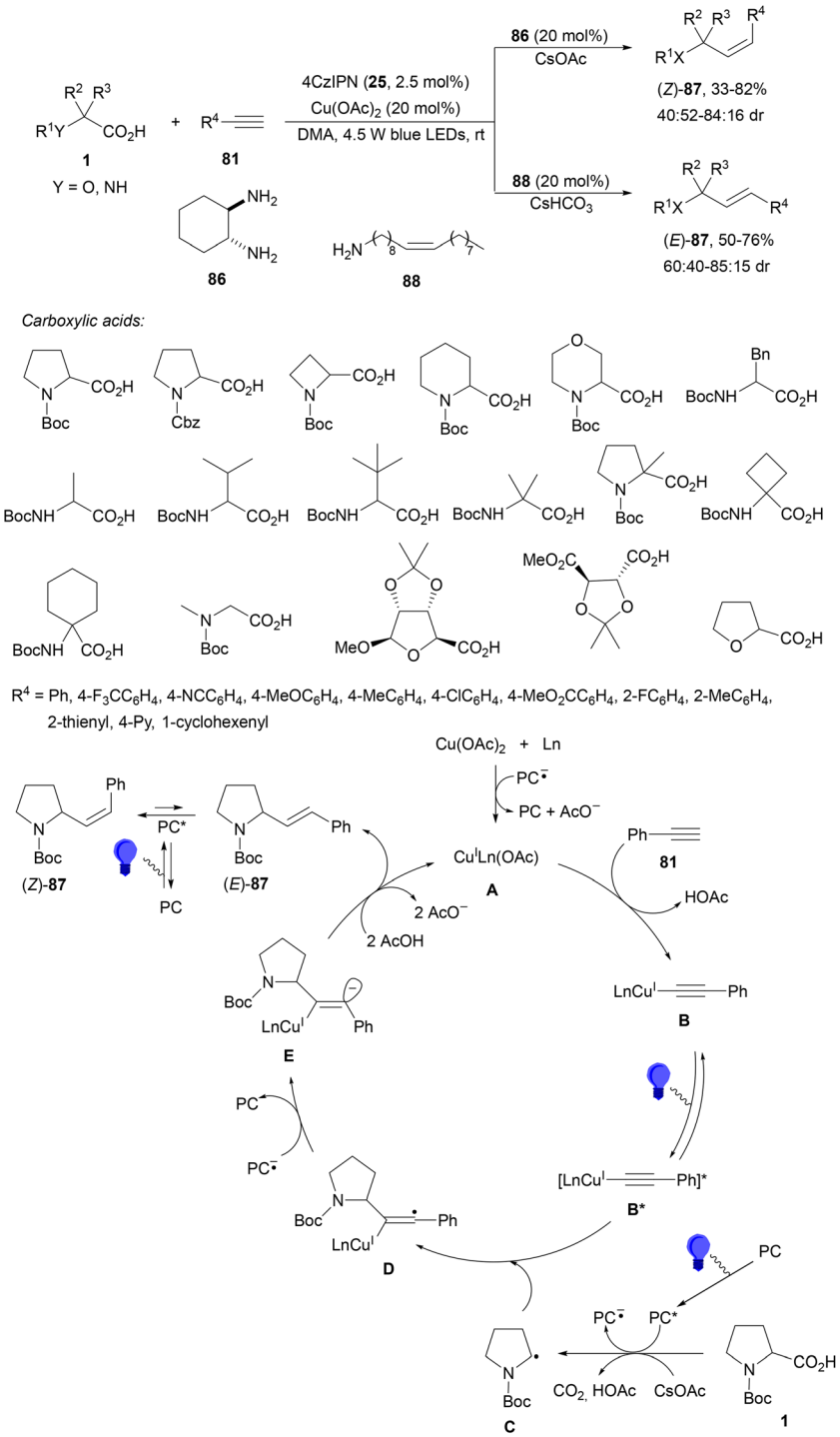
Radical polymerization of alkenes initiated by photocatalytic decarboxylation of carboxylic acids has been performed by Liao and Ni[95] using titanium oxide nanoparticles (NPs) as a photocatalyst. The polymerization of vinyl acetate was achieved with carboxylic diacids **79** in aqueous media (Scheme 28). The rate of this polymerization depends strongly on the diacid



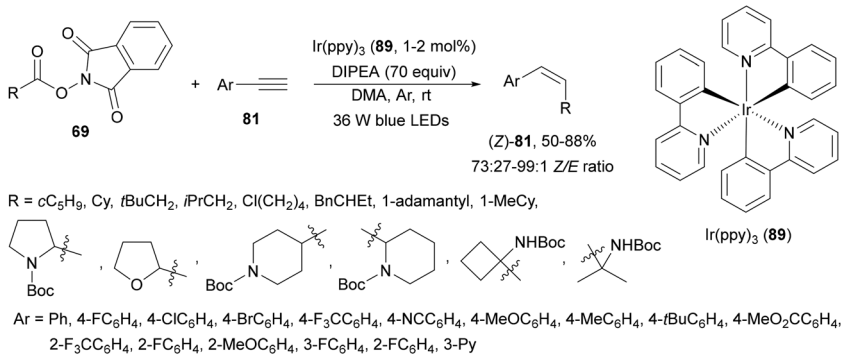
Scheme 30 Decarboxylative hydroalkylation and arylalkylation of terminal alkynes **81** (a, b) with AAs under Ir/Ni dual photocatalysis.

structure and it was found that diacids with an even carbon number polymerized faster. This process was carried out in a reactor using a mercury vapor lamp at a frequency of 365 nm during 3 hours with 0.2% wt of TiO_2. The number average molecular weight (M_n) of PVAc **80** ranges from 240 to 400 kDa and the molecular weight distribution ranges from 1.96 to 2.63.

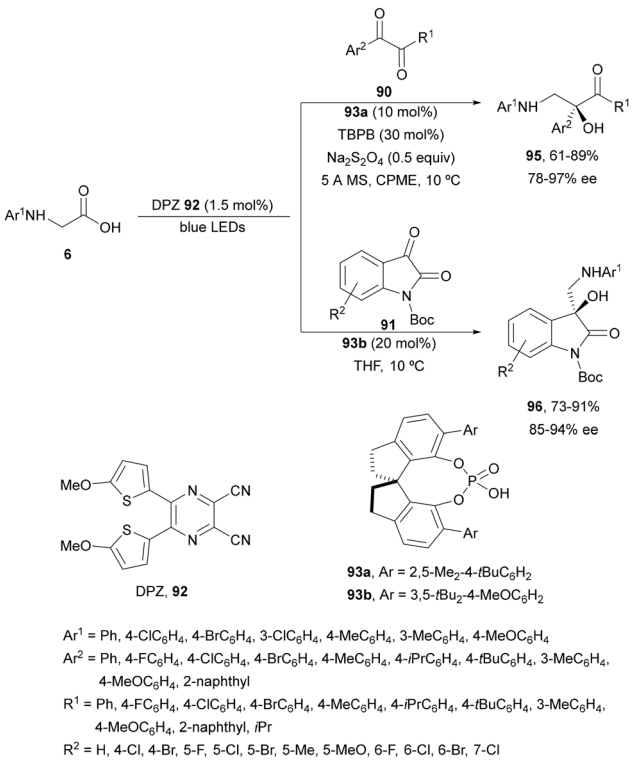
Naphthalene derivatives, styrenes, allenes and dienes can be hydroalkylated by photochemical decarboxylation of carboxylic acids under very different reaction conditions. Recently, iron-catalyzed hydrofluoroalkylation has been developed as an inexpensive process. In addition, three-component processes between carboxylic acids, styrenes, alkenes and cyanopyridines can be performed using 4CzIPN or Ir complexes as photocatalysts.

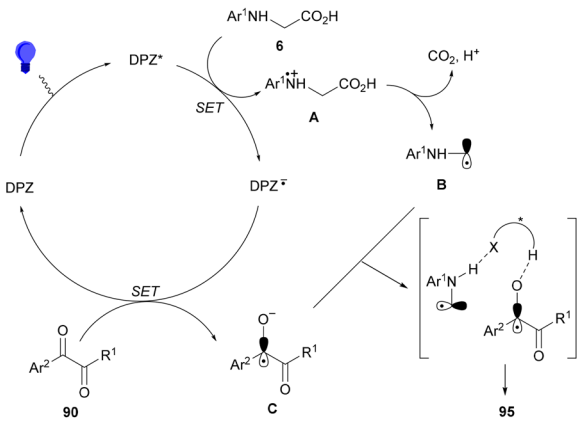


Scheme 31 Decarboxylative hydroalkylation of terminal alkynes with carboxylic acids under Cu/4CzIPN (**25**) photocatalysis.



Scheme 32 Decarboxylative alkylation of terminal arylalkynes **81** with NHPI esters **69** using Ir complex **89** as a photocatalyst.





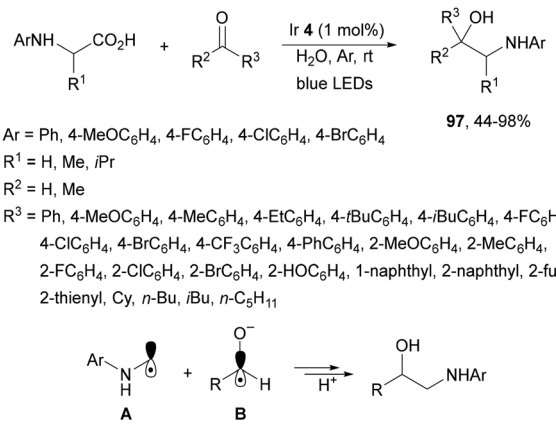
Scheme 33 Enantioselective decarboxylative addition of *N*-arylglycines to 1,2-dicarbonyl compounds **90** or to isatins **91** under dual DPZ **92** and CPA **93** photocatalysis.

Radical photopolymerization of alkenes has been efficiently carried out under TiO_2 NP irradiation.

2.3. Addition reaction to alkynes

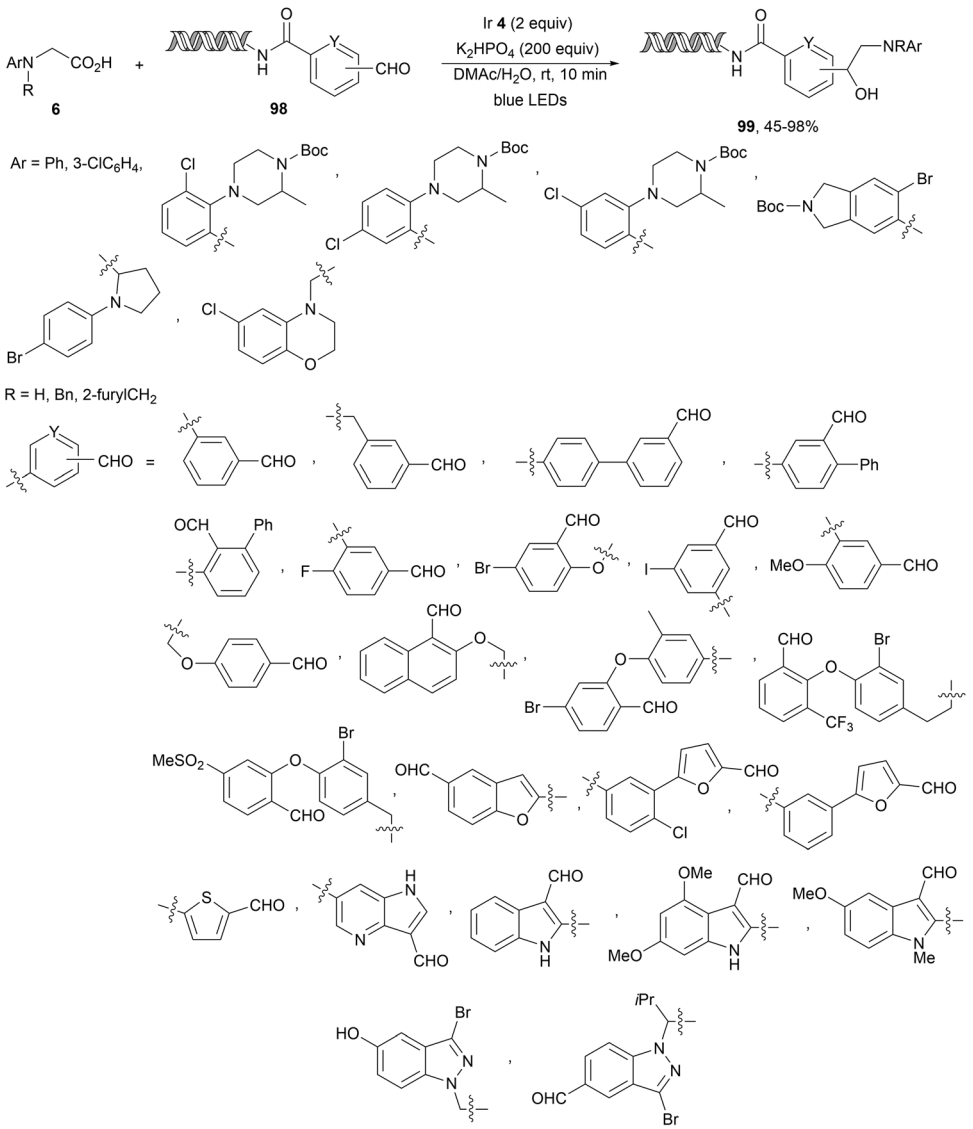
Decarboxylative hydroalkylation of unactivated alkynes was reported by MacMillan and co-workers[96] using metallaphotoredox catalysis.[15] This procedure involves photocatalytic decarboxylative radical generation from carboxylic acids and the Ir complex **4** and oxidative radical capture by low valent nickel species to form and alkyl-Ni(II) complex **B**, which undergoes a migratory insertion coupling step with the alkyne generating a vinyl-nickel complex **C** *via cis*-carbometallation. Terminal and internal alkynes **91** and carboxylic acids **1** reacted in the presence of Ir complex **4** and 5,5′-di*tert*butylbipyridine (dtbbpy)·$NiCl_2$ as dual catalysts and 1,1,3,3-teramethylguanidine (TMG) as a base in aqueous DMF under visible light to provide stereoselective products **92** in good yields (Scheme 29). In the case of terminal alkynes, branched products were regioselectively obtained instead of linear ones, indicating that the nickel-mediated pathway is exclusively operative. The proposed metallaphotoredox dual catalytic cycle supports the observed regio- and stereochemical outcomes.

Rueping and co-workers[97] have reported the anti-Markovnikov dual catalyzed hydroalkylation of terminal alkynes **81** using *N*-protected AAs **6** and the Ir complex **83** and $NiCl_2$·glyme as a

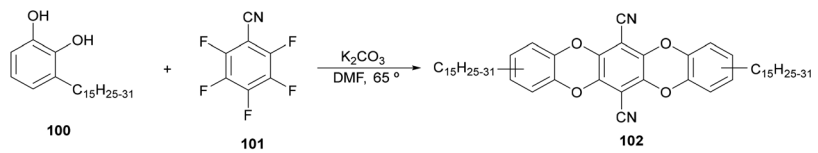


Scheme 34 Decarboxylative radical addition of *N*-aryl amino acids to aldehydes or ketones in water under Ir **4** photocatalysis.

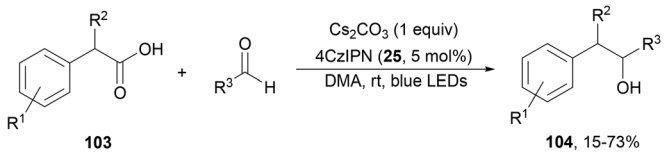
catalyst under blue LED irradiation. Products **84** were obtained with moderate to complete *Z*/*E* diastereoselectivities and yields using Cs_2CO_3 as a base and a 1 : 1 mixture of MeCN and DMF at room temperature (Scheme 30a). In addition, arylalkylation of alkynes *via* a photoredox/nickel dual catalyzed three-component cross-coupling was achieved by changing the reaction conditions. Terminal alkynes **81**, AAs **6** and aryl bromides were subjected to photoredox/nickel dual catalysis using Ir complex **4** and $NiBr_2$·dtbbpy with Cs_2CO_3 as a base in DMF at room temperature to obtain products **85** with moderate diastereoselectivity (Scheme 30b). Control experiments for both processes and DFT calculations support the proposed mechanisms. In the case of hydroalkylation of alkynes, the Ir(III) complex **83** gives a triplet excited state Ir(III)* complex after absorption of visible light. Oxidation of the carboxylic acid and subsequent CO_2 extrusion generates the alkyl radical intermediate **A**, which is trapped by the Ni(II) complex **B** to afford Ni(II) intermediate **C**. Reduction of **C** by an Ir(II) complex gives Ni(I) intermediate **D**,



Scheme 35 Decarboxylative coupling of α-amino acids with DNA-conjugated aldehydes under Ir **4** photocatalysis.

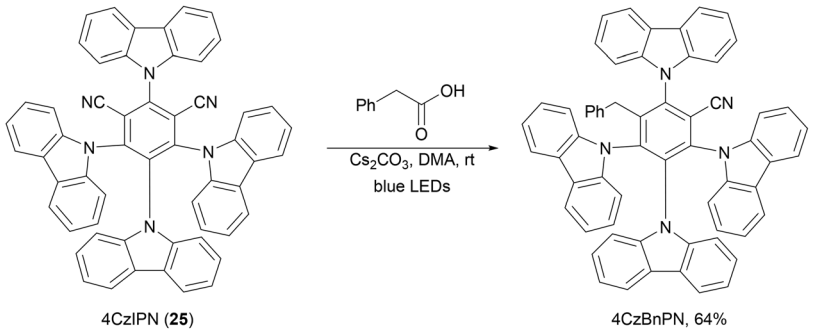


Scheme 36 Synthesis of PC **102** derived from urushiol (**100**).

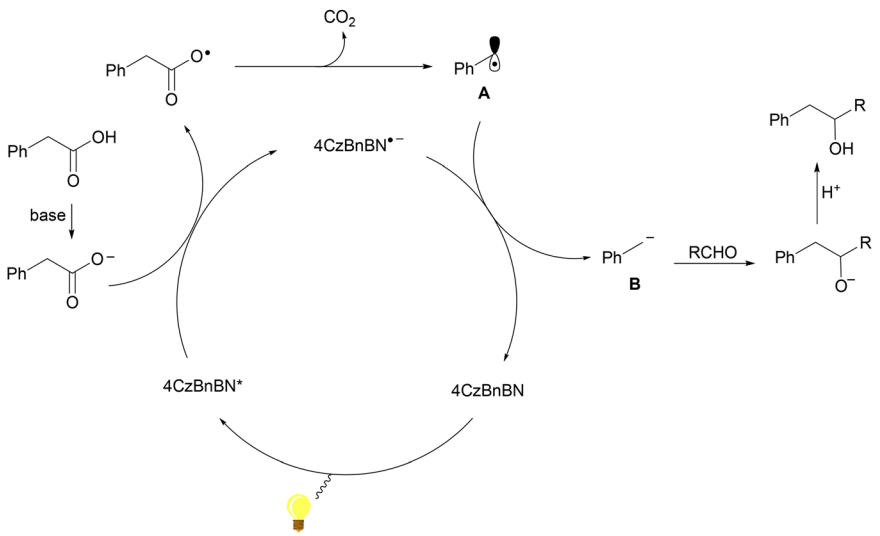


103 104, 15-73%

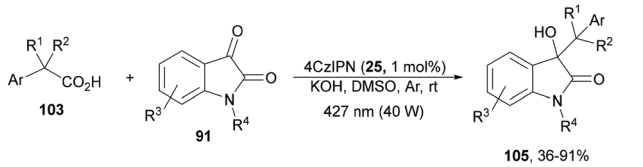
R^1 = H, 4-F, 4-Cl, 4-Br, 3-F, 3-Br, 2-Br, 4-CF_3, 4-Me, 3-Me, 2-Me. 4-Ph, 2-naphthyl, 1-naphthyl, 4-BocNH, 4-MeO, 3,4-(OCH_2O), 2-thienyl, 4-*t*Bu
R^2 = H, Me, Me_2, Ph, CH_2=CH
R^3 = *n*-C_4H_9, Et, *n*-$C_{11}H_{23}$, $Ph(CH_2)_2$, *i*Pr, *i*Bu, Me_3CCH_2, Me_2



4CzIPN (25) 4CzBnPN, 64%



Scheme 37 Decarboxylative addition of arylacetic acids **103** with aliphatic aldehydes under 4CzIPN photocatalysis.



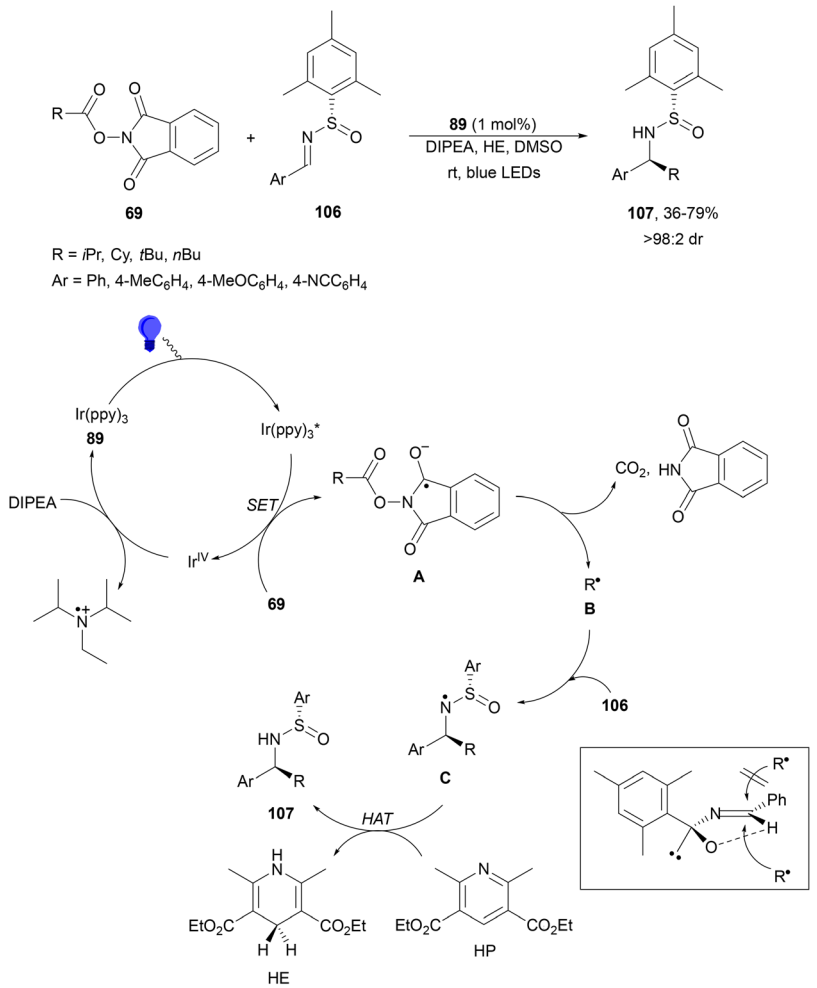
103 91 105, 36-91%

Ar = Ph, 4-MeC_6H_4, 4-EtC_6H_4, 4-$MeOC_6H_4$, 4-$HO(CH_2)_2C_6H_4$, 4-ClC_6H_4, 4-BrC_6H_4, 3-EtC_6H_4, 4-*t*BuC_6H_4, 3-$PhCOC_6H_4$, 6-MeO-2-naphthyl
R^1 = H, Me
R^2 = Me
R^1-R^2 = $(CH_2)_4$
R^3 = H, 4-Me, 4-Cl, 5-Me, 5-*i*Pr, 5-MeO, 5-F. 5-Cl, 5-CO_2Me, 5-CF_3O, 6-MeO, 6-Cl, 7-Me, 7-Cl, 7-CF_3O, 5,7-Me_2
R^4 = H, Me

Scheme 38 Decarboxylative coupling of arylacetic acids **103** with isatins **91** under 4CzIPN photocatalysis.

which after alkyne 1,2-migratory insertion forms the Ni(I) intermediate **E**. Final protonation of **E** *via* intermediate **F** provides product (*E*)-**84** and Ni complex **B**. The (*Z*)-isomer **84** is formed *via* intermediate **G** through an energy transfer pathway. In the second catalytic cycle, the proposed mechanism for the arylalkylation of alkynes is as follows: the Ni(II) intermediate **H** *via* a SET process gives Ni(I) intermediate **I**, which after addition to the alkyne and oxidative addition of an aryl bromide provides intermediates **J** and **K**, respectively. Final reductive elimination of **K** delivers the *anti*-addition three-component coupling product *anti*-**85**. The *syn*-addition product **85** is obtained *via* an energy transfer (ET) pathway.

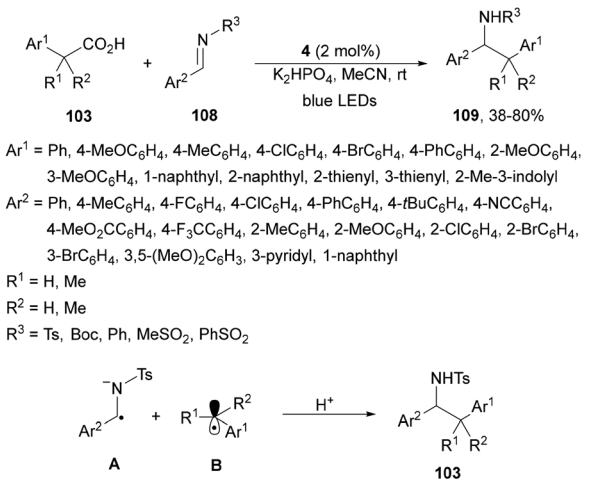
Pericàs and co-workers[98] performed the decarboxylative stereodivergent[99] hydroalkylation of alkynes using copper instead of nickel and 4CzIPN (**25**) instead of an Ir complex as a photoredox



Scheme 39 Decarboxylative asymmetric addition of NHPI esters **69** to mesityl-substituted *N*-sulfinimines **106** under Ir(ppy)$_3$ (**89**) photocatalysis.

catalyst. By a multivariate high-throughput experimentation (HTE) approach different carboxylic acids, including AAs and α-oxy acids, reacted with terminal alkynes **81** using Cu(OAc)$_2$, diamine **86** as a ligand, CsOAc as a base and DMA as solvent and blue LED at room temperature (Scheme 31). The resulting (*Z*)-alkenes **87** were obtained with moderate stereoselectivity. On the other hand, (*E*)-alkenes **87** were formed by changing ligand **86** to oleylamine (**88**) and using $CsHCO_3$ as a base. In the proposed mechanism, upon irradiation of the PC the Cu(II) complexes were reduced to Cu(I) **A** and also the carboxylate ion was oxidized to radical **C**, which underwent decarboxylation. The Cu(I) complex **A** generates acetylide **B**, which after photoexcitation gives the species **B*** with a depletion of charge on the alkyne moiety through ligand-to-metal charge transfer (LMCT)[54,55] accelerating the attack of the radical **C** to form the vinyl radical **D**. Subsequent oxidation of $PC^{-\bullet}$ by **D** provides vinyl anion **E**, which after protonation and protodemetallation of the Cu–C bond gives enriched (*E*)-**87**, generating the Cu(I) species. Isomerization of (*E*)-**87** *via* energy transfer (ET) mediated by the PC provides (*Z*)-**87**.

Decarboxylative hydroalkylation of terminal acetylenes **81** using NHPI esters **69** has been performed by Luo, Tang and co-workers[100] using an Ir(ppy)$_3$ (**89**) complex as a photocatalyst and blue LED irradiation. A wide range of primary, secondary and tertiary carboxylate ions as well as α-amino and α-oxy acid-derived esters **69** reacted with terminal arylalkynes **81** to



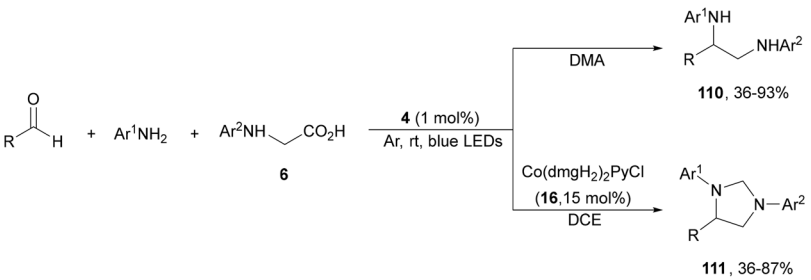
Scheme 40 Decarboxylative coupling of arylacetic acids **103** with aldimines **108** under Ir complex **4** photocatalysis.

provide alkenes **88** with good yields and *Z*/*E*-diastereoselectivities (Scheme 32). This process took place at room temperature under an Ar atmosphere with DIPEA as a base and DMA as solvent without the requirement of metal activation.

The photocatalytic hydroalkylation of alkynes with carboxylic acids must be carried out under Ni or Cu co-catalysis and under Ir photocatalysis in the case of NHPI esters with good diastereoselective control of the obtained alkenes.

2.4. Addition to C–heteroatom multiple bonds

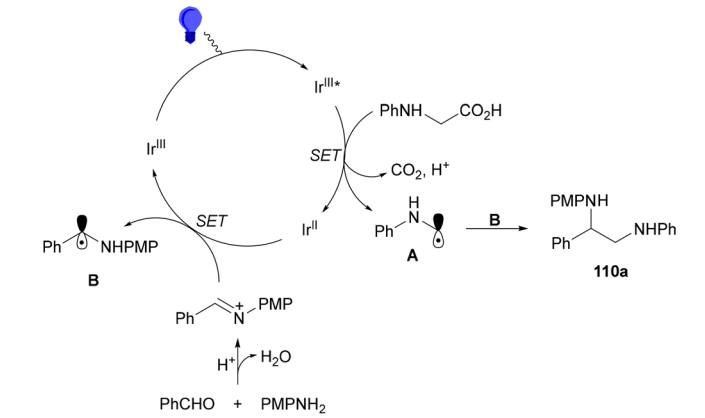
Decarboxylative addition of benzylic radicals to carbonyl groups was initially carried out with arylacetic acids[101] and 9-fluorenone[102] or *N*-methylphthalimides[103] under photocatalytic conditions. Jiang and co-workers[104] reported the enantioselective radical addition to 1,2-diketones **90** and isatins **91** of *N*-acylglycines **6** using a visible light dual catalytic system dicyanopyrazine photocatalyst DPZ **92** and a chiral phosphoric acid (CPA), SPINOL **93a** or **93b** (Scheme 33). This reaction was performed in the presence of tetra-*n*-butylphosphonium bromide (TBPB) and $Na_2S_2O_4$ in cyclopentyl methyl ether (CPME) at 10 °C to provide products **95** in good yields and up to 97% ee. In the case of isatins **94**, SPINOL **93b** was the best CPA and THF was used as solvent to obtain 3-hydroxy-3-aminomethylindolyn-2-ones **96** in good yields and ees. DPZ is able to generate intermediate **A**, which after decarboxylation forms the α-amino radical **B**. $DPZ^{-\bullet}$ reduces the 1,2-diketone giving intermediate **C**. Both radicals **B** and **C** are

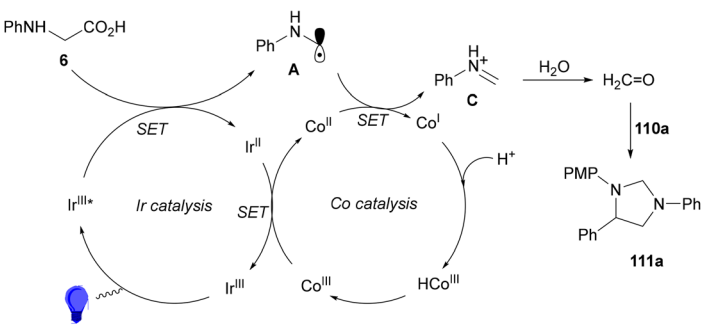


R = Ph, 4-MeC$_6$H$_4$, 4-EtC$_6$H$_4$, 4-MeOC$_6$H$_4$, 4-EtOC$_6$H$_4$, 4-FC$_6$H$_4$, 4-ClC$_6$H$_4$, 4-BrC$_6$H$_4$, 4-NCC$_6$H$_4$, 4-F$_3$CC$_6$H$_4$, 4-PhC$_6$H$_4$, 3-MeC$_6$H$_4$, 3-FC$_6$H$_4$, 2-naphthyl, 2-MeC$_6$H$_4$, 2-FC$_6$H$_4$, 2-HOC$_6$H$_4$, 2-furyl, 2-thienyl, *n*Bu, *i*Bu, *n*C$_5$H$_{11}$, Cy

Ar^1 = 4-MeOC$_6$H$_4$, Ph, 4-MeC$_6$H$_4$, 4-*t*BuC$_6$H$_4$, 4-FC$_6$H$_4$, 4-ClC$_6$H$_4$, 4-BrC$_6$H$_4$, 4-indolyl, 2-benzothiazolyl

Ar^2 = Ph, 4-MeOC$_6$H$_4$, 4-FC$_6$H$_4$, 4-ClC$_6$H$_4$





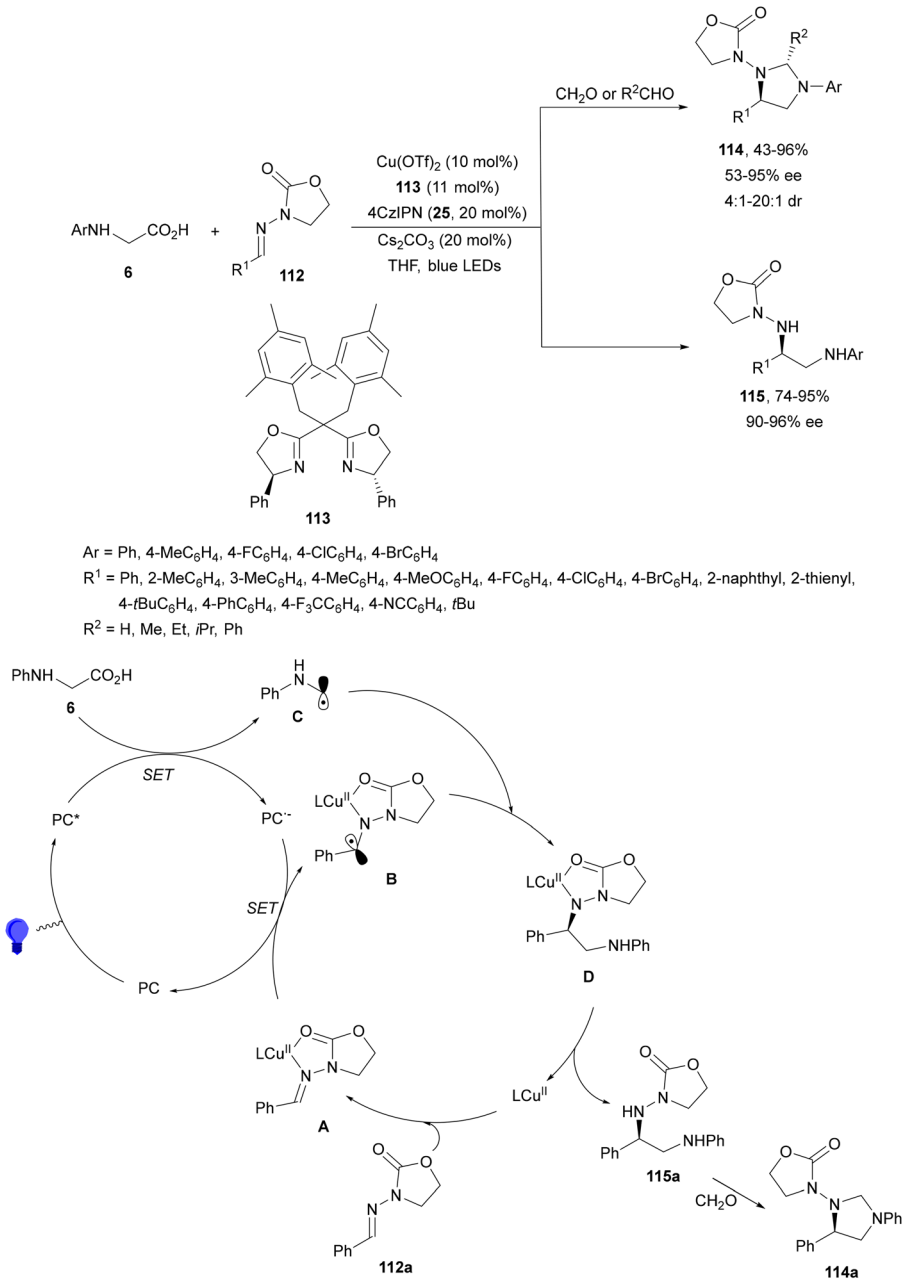
Scheme 41 Decarboxylative radical coupling of aldehydes, amines and *N*-aryl glycines under Ir complex **4** photocatalysis.

activated by the CPA by hydrogen bonding favoring their coupling to provide 1,2-aminoalcohols **95**.

Decarboxylative addition of *N*-aryl amino acids to aldehydes or ketones has been described under visible-light in water at room temperature using Ir complex **4** as a photocatalyst (Scheme 34).[105] The corresponding 1,2-amino alcohols **97** were obtained in very good yields and the reaction of *N*-phenyl glycine and 4-$MeOC_6H_4CHO$ was carried out on a gram scale. According to experimental studies the α-amino radical **A** reacts with the alcoholate radical **B** to provide the product.

In the case of DNA-conjugated aldehydes **98**, the photoredox-mediated decarboxylative coupling with α-amino acids provided DNA-encoded 1,2-amino alcohols **99** (Scheme 35).[106] This reaction proceeded for a wide range of aldehydes but also for ketones with conversions >50% using Ir complex **4** as a PC and K_2HPO_4 as a base in aqueous DMAc at room temperature in only 10 minutes irradiation time.

For the synthesis of 1,2-amino alcohols by decarboxylative coupling of α-amino acids with aldehydes an urushiol derivative **102** has been used as a photocatalyst by Zhang and co-workers.[107] This PC was prepared from urushiol **100** and 2,3,5,6-tetrafluoroterephthalonitrile (**101**) in the presence of K_2CO_3 (Scheme 36). Due to the photoredox properties of **102** it was used in MeCN as solvent with $NaHCO_3$ as a base at room temperature under blue



Scheme 42 Decarboxylative asymmetric coupling of *N*-aryl glycines and hydrazones **112** under Cu/4CzIPN photocatalysis.

LED irradiation to obtain 1,2-amino alcohols **97** with modest to high yields (16–93%). This biomass-based PC exhibits absorption in the visible region (λ_{max} = 426 nm) and its half-wave potentials were +1.17 and −1.24 V, which can be assigned to **102**$^{-\bullet}$/**102** and **102**/**102**$^{-\bullet}$, respectively, according to cyclic voltammetry measurements.

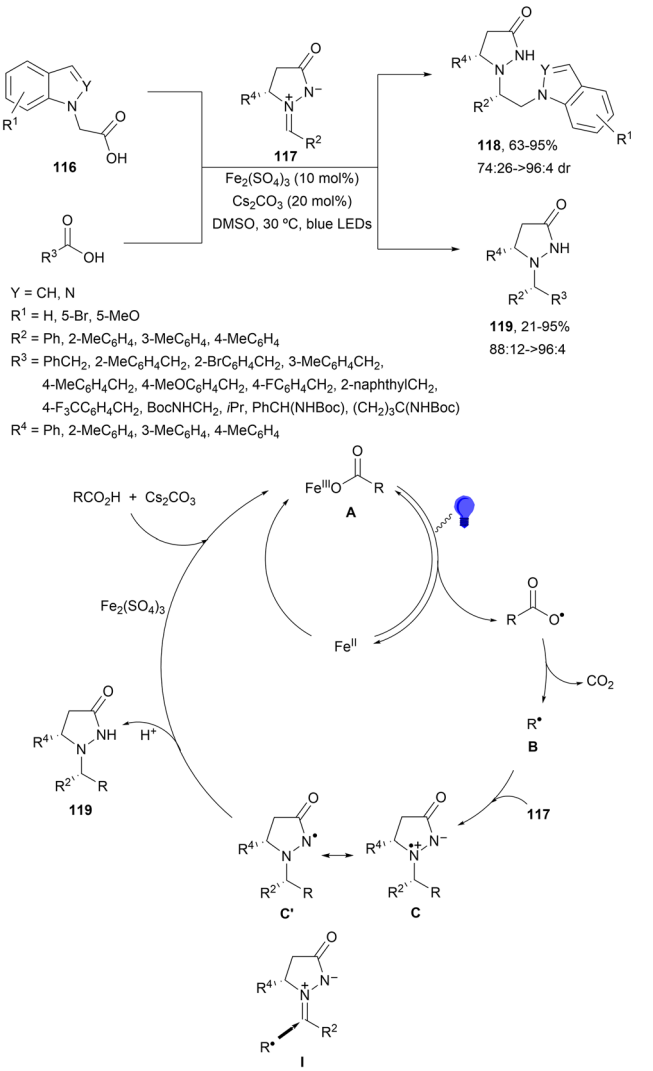
König and co-workers[108] have reported a redox-neutral procedure for benzylate aliphatic aldehydes *via* the photocatalytic generation of benzyl carbanions[109] from arylacetic acids **103**. Different carboxylic acids **103** reacted with aldehydes using Cs_2CO_3 as a base, 4CzIPN (**25**) as a PC and DMA as solvent at room temperature to provide alcohols **104** in moderate to good yields (Scheme 37). Deuterium labeling experiments suggest the formation of an anion intermediate with D_2O as an electrophile. Considering experimental and computational studies, the following mechanism is proposed: after deprotonation of the carboxylic acid the carboxylate ion is oxidized by the excited 4CzBnBN*. Actually, this organophotocatalyst 4CzBnBN has been formed by reaction of 4CzIPN with the benzyl anion **B** (generated from phenylacetic acid) through an E1cb mechanism. Radical **A** is converted into anion **B** by 4CzBnPN$^{-\bullet}$, which adds to aldehyde forming the corresponding alcoholate, which suffers protonation to yield the final product **104**.

Recently, the addition of arylacetic acids to aromatic aldehydes has been described[110] just changing Cs_2CO_3 by CsF as a base using DMF as solvent. The corresponding alcohols **104** (R^3 = Ar, heteroaryl) were obtained with 50–96% yields and this process was performed on a gram-scale for the reaction of α,α-diphenylacetic acid with 4-fluorobenzaldehyde. Isatins **91** reacted with arylacetic acids **103** to provide 3-hydroxy-3-alkyloxindoles **105** using 4CzIPN as a PC, KOH as a base and DMSO as solvent at room temperature under two 40 W 427 nm Kessil tuna blue lamp irradiation (Scheme 38).[111] The reaction of isatin (R^3 = R^4 = H) with α,α-dimethylphenylacetic acid was carried out on a gram-scale to obtain the corresponding oxindole **105** in 71% yield. In this case, mechanistic studies demonstrate that the process involves cross-coupling between a persistent ketyl radical and a transient alkyl radical from the carboxylic acid.

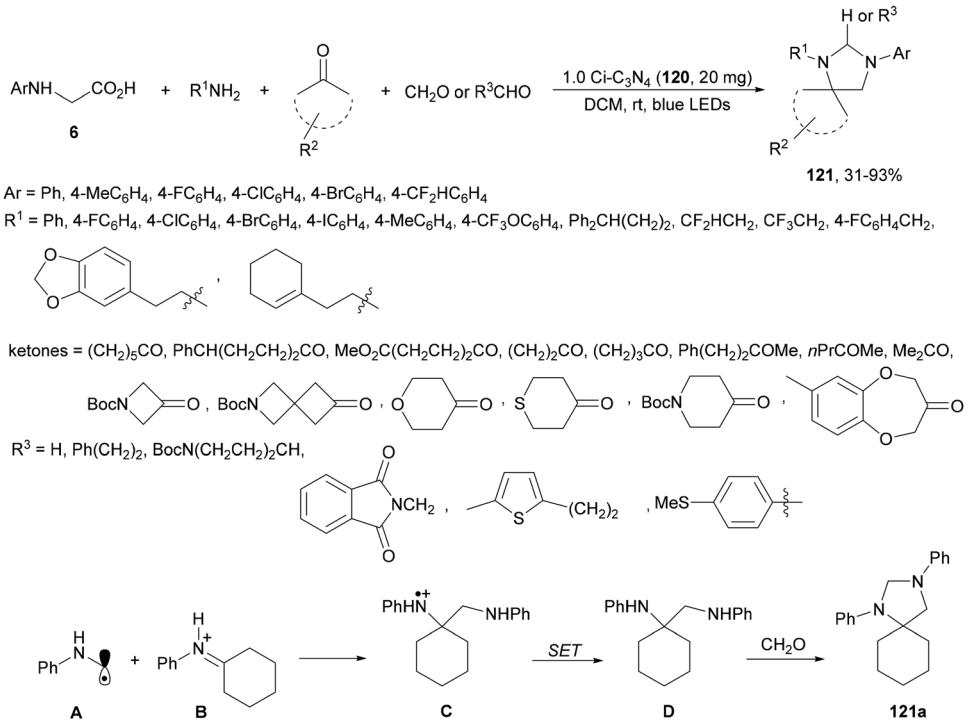
The reaction of carboxylic acids with carbonyl compounds under photocatalyzed decarboxylation takes place by cross-coupling of ketyl radicals and alkyl radicals from the carboxylic acid. However, in the case of arylacetic acids and aldehydes, the mechanism involves the addition of benzylic anions to the carbonyl group.

Decarboxylative radical addition to C=N double bonds under photocatalytic conditions has been studied with imines, nitrones and isocyanates. Maestro, Alemán and co-workers[112] described the enantioselective addition of alkyl radicals to chiral *N*-sulfinimines **106** (Scheme 39). They used NHPI esters **69**, Ir(ppy)$_3$ (**89**) as a PC, DIPEA as a base, visible light and DMSO as solvent in the presence of 1.5 equivalents of Hantzsch ester (HE) to provide products **107** with good diastereoselectivities. The best results were obtained with mesityl-substituted *N*-sulfinimines and secondary or tertiary alkyl groups. In the proposed mechanism, the photoexcited catalyst generates, through a SET process, the radical anion **A** from the NHPI ester by an oxidative pathway. Reductive elimination of the phthalimide group leads to decarboxylation and formation of radical **B**, which undergoes radical addition to *N*-sulfinimine to form radical **C**. Finally, HE donates hydrogen through hydrogen atom transfer (HAT) to **C** giving rise to product **107** and HP. The approach of the radical to **106** takes place by the less hindered *Si*-face of the imine explaining the *S* configuration of the new stereocenter.

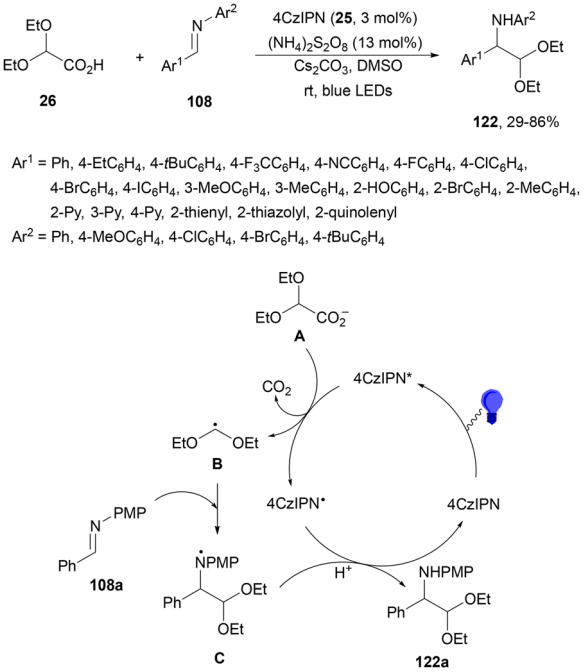
A visible-light-mediated decarboxylative benzylation of *N*-protected aldimines **108** with arylacetic acids **103**[101] has been reported by Weng, Lu and co-workers.[113] This process took place using Ir complex **4** as PC, K_2HPO_3 as a base in MeCN at room temperature under blue LED irradiation to give rise to *N*-protected amines **109** with good yields (Scheme 40). In the proposed mechanism the excited Ir(III)* species forms the α-amino radical anion **A**, which combines with the benzylic



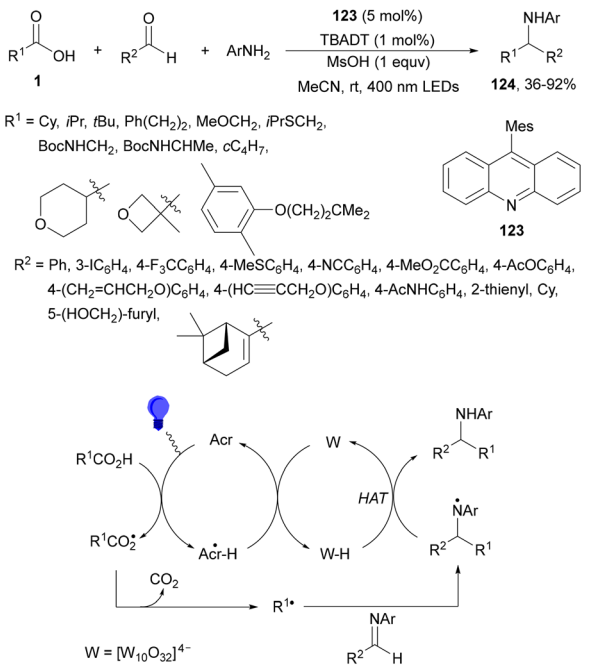
Scheme 43 Decarboxylative radical addition of carboxylic acids to chiral azomethine imines **117** under $Fe_2(SO_4)_3$ photocatalysis.



Scheme 44 Decarboxylative four-component reaction of *N*-aryl glycines, amines, ketones and aldehydes under carbon nitride **120** photocatalysis.



Scheme 45 Decarboxylative radical addition of 2,2-diethoxyacetic acid **26** to aldimines **108** under 4CzIPN (**25**) photocatalysis.



Scheme 46 Decarboxylative radical addition of carboxylic acids to *in situ* generated imines under acridine **123**/TBADT photocatalysis.

radical **B** by a radical-radical coupling pathway giving after protonation products **109**.

Zhong, Zeng and co-workers[114] applied the decarboxylative radical coupling of *N*-aryl amino acids with aldehydes[105] to imines. In this case, a three-component reaction between aromatic amines, aldehydes or acetophenone and *N*-aryl glycines **6** using the Ir complex **4** as a PC, DMA as solvent under Ar provided 1,2-diamines **110** in modest to high yields (Scheme 41). Under the

same blue LED irradiation and using Co(dmgH$_2$)PyCl (**16**) as an oxidant, imidazolines **111** were obtained in moderate to good yields. These reactions were scaled-up for products **110a** and **111a**, using benzaldehyde, anisidine and *N*-phenyl glycine, which were obtained on a gram-scale with 79 and 55% yields, respectively. According to control experiments two plausible mechanisms were proposed. Under the former reaction conditions, *N*-phenyl glycine is reduced by Ir(III)* to produce Ir(II) and the α-amino radical **A** after CO_2 elimination. The intermediate imine is reduced by Ir(II) to generate Ir(III) and the radical **B**, which undergoes a radical coupling reaction with **A** to form the diamine **110a**. In the case of product **111a**, Co(III) can be reduced by Ir(III) to generate Co(II), which can be reduced by radical **A** to Co(I) and the iminium ion **C**. Subsequent oxidation of Co(I) to Co(III) can be performed by coordination with H^+ followed by H_2 elimination. Diamine **110a** can be cyclized by formaldehyde, which was generated by hydrolysis of iminium ion **C** in the presence of water, and the corresponding imidazoline **111a** is then produced.

The same group achieved the asymmetric synthesis of imidazolidines by a three-component process involving a decarboxylative radical coupling/cyclization reaction of *N*-aryl glycines **6**, aldehydes and hydrazones **112** under copper and visible light-induced photoredox catalysis (Scheme 42).[115] This process took place using Cu(OTf)$_2$ and chiral bisoxazoline **113** as a ligand, 4CzIPN (**25**) as a PC, and Cs_2CO_3 as a base in THF at 0 °C to room temperature to furnish imidazolidines **114** with good yields and up to 95% ee. When this reaction was performed in the absence of an aldehyde, chiral diamines[116] **115** can be obtained with high yields and enantioselectivities. In the proposed reaction mechanism intermediate **A** is formed by the ligand exchange between the hydrazone **112a** and the chiral copper catalyst [L-Cu(II)], which has been reduced to radical **B** by a SET of $PC^{-\bullet}$. Subsequently, radical **B** reacts with the α-amino carbonyl radical **C** to produce **D**, which after protonation and ligand exchange gives rise to diamine **115** and regenerates intermediate **A**. Diamine **115a** can be cyclized with the aldehyde to give imidazolidine **114a**.

Recently, an iron catalyzed decarboxylative radical addition of *N*-indole acetic acid and related compounds **116** or carboxylic acids to chiral azomethine imines **117**[117] upon visible light irradiation was reported.[118] In the presence of $Fe_2(SO_4)_3$ (10 mol%) and Cs_2CO_3 in DMSO at 30 °C under blue LED irradiation the corresponding adducts **118** or **119** were obtained with good yields and diastereoselectivities (Scheme 43). In the proposed catalytic cycle, a LMCT process[54,55] occurs upon irradiation of the *in situ* formed iron(III) carboxylate **A** with subsequent decarboxylation to provide radical R$^\bullet$ (**B**), followed by addition of this radical **B** to the less shielded face of the chiral azomethine imine **117** *via* model **I**. The generated Fe(II) would be re-oxidized into Fe(III) during the facile reduction of cation intermediate **C**, or the amidyl **C′** derived thereof. Final protonation gives the addition product **118** or **119**.

Spiro-imidazolidines **121** have been synthesized by a four-component method under carbon nitride photocatalysis.[119] Starting from primary amines, cyclic ketones, *N*-aryl glycines **6** and aldehydes in dry dichloromethane at room temperature under visible light mediated photocatalysis, the corresponding products **121** were isolated with moderate to good yields (Scheme 44). The heterocatalyst carbon nitride 1.0 Ci–C_3N_4 **120** was prepared from melamine and glyoxal and can be recovered and recycled in multiple runs without loss of activity and was used in a gram-scale synthesis in a continuous photo flow fashion. In the proposed mechanism an α-amino radical intermediate **A** is formed from *N*-phenyl glycine. In the meantime, primary amine and ketone condensed to generate the iminium ion species **B**, which undergoes a free radical addition to give the radical adduct **C**. Subsequent reduction of **C** provides diamine **D**, which by reaction with formaldehyde gives rise to the corresponding spiro-imidazolidine **121a**.

Hong and co-workers[120] employed 4CzIPN (**25**) as an organic PC for the decarboxylative radical addition of the 2,2-diethoxyacetic acid **26** derived radical to imines **108** using $(NH_4)_2S_2O_8$ as an oxidant in catalytic amounts under visible-light irradiation (Scheme 45). α-Amino acetals **122** were obtained in the presence of Cs_2CO_3 as a base in DMSO at room temperature with modest to good yields. In the proposed mechanism, the excited state of 4CzIPN* undergoes reductive quenching by $(EtO)_2CHCO_2^-$ (**A**), which after decarboxylation forms a diethoxymethyl radical **B**. Addition of **B** to imine **108a** gives the nitrogen centered radical **C**, which by reduction and protonation affords product **122a**.

Dual acridine **123** and tetra-*n*-butylammonium decatungstate (TBADT) photocatalysis have been employed in the radical addition of alkyl carboxylic acids with *in situ* generated imines from aldehydes and aromatic amines.[121] This three-component reaction allowed the preparation of amines **124** in the presence of methanesulfonic acid (MsOH) and MeCN under 400 nm LED irradiation (Scheme 46). The role of TBADT is to facilitate the turnover of acridine PC by means of hydrogen atom transfer. In

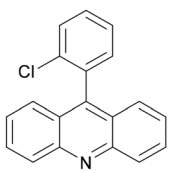


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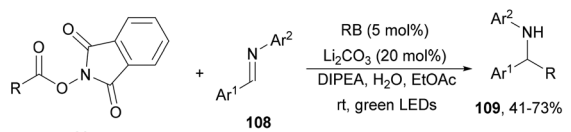
Fig. 2 Acridine **125** used as a PC in the three-component reaction of carboxylic acids, aldehydes and amines.



69 **108** **109**, 41-73%

R = $Ph(CH_2)_3$, $Ph(CH_2)_2$, nC_6H_{13}, Et, *n*BuCHMe$(CH_2)_2$, $nC_{13}H_{27}$, Cy, *t*Bu, $MeO_2C(CH_2)_7$
Ar^1 = Ph, 4-$MeO_2CC_6H_4$, 4-FC_6H_4, 4-ClC_6H_4, 4-BrC_6H_4, 2-FC_6H_4, 4-MeC_6H_4, 2-thienyl 3-Py, 4-$MeOC_6H_4$
Ar^2 = Ph, 4-ClC_6H_4, 4-$MeOC_6H_4$, 3-$F_3CC_6H_4$

Scheme 47 Decarboxylative coupling of NHPI esters **69** with aldimines **108** under rose Bengal photocatalysis.

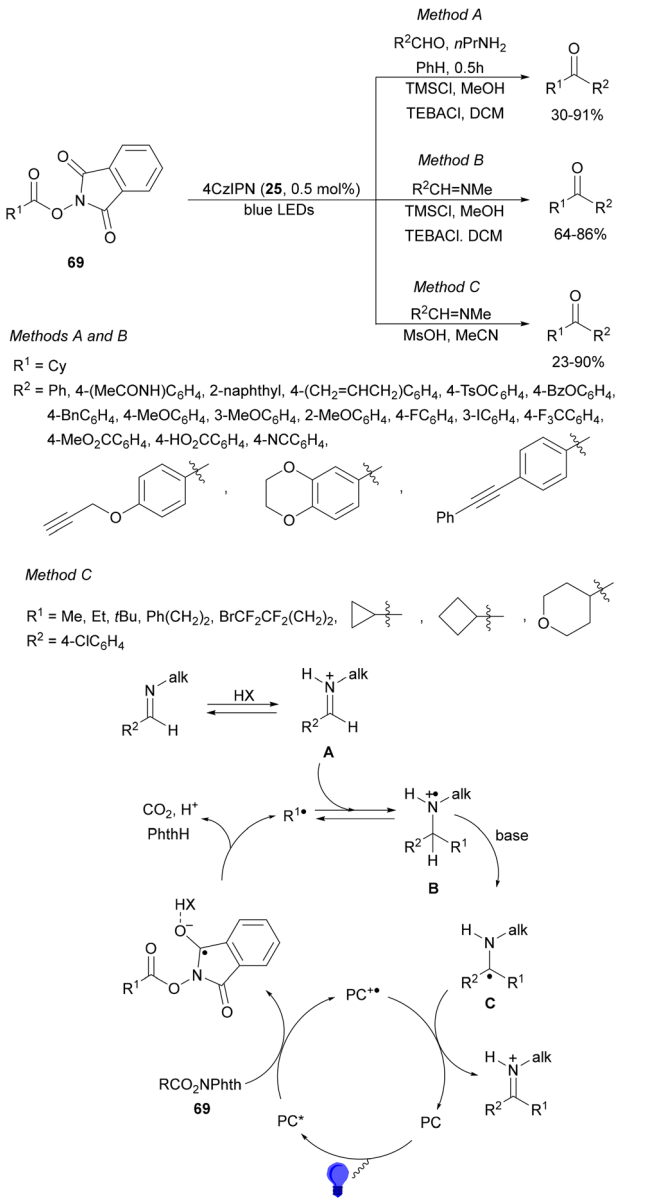
the case of using a stoichiometric amount of MsOH, it is for the generation of iminium species, which are more susceptible to radical addition. Other azomethine substrates such as hydrazones and nitrones were successfully alkylated.

A similar three-component transformation has been described by Larionov and co-workers[122] using acridine **125** (8 mol%) (Fig. 2), $Cu(MeCN)_4BF_4$ (8 mol%), TsOH (8 mol%) and MeCN as solvent. The corresponding amines **124** were obtained in high yields (63–98%) employing secondary and tertiary carboxylic acids.

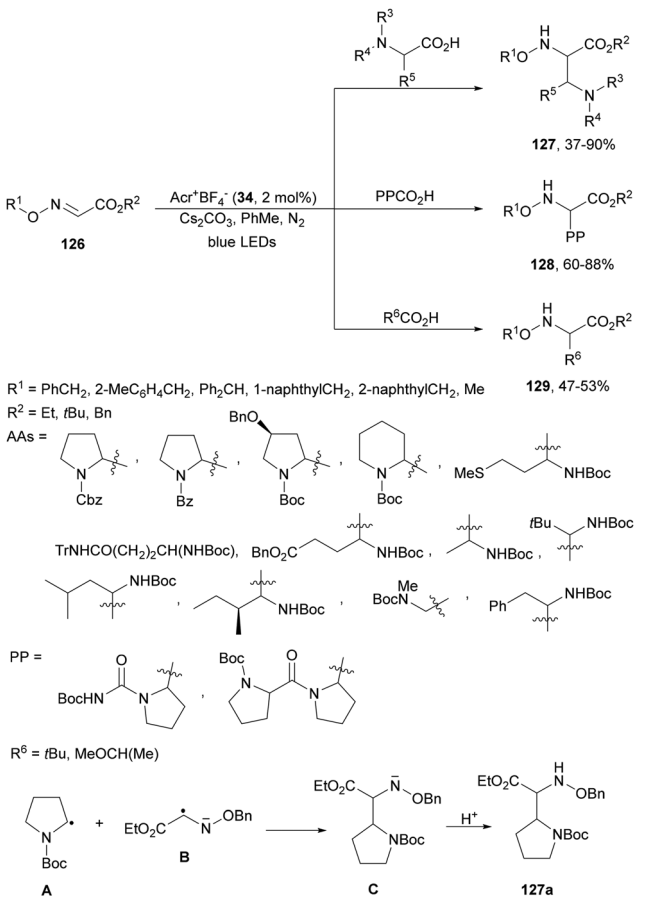
Reductive coupling of imines **108** with NHPI esters **69** has been achieved using rose Bengal (RB) as a photocatalyst by Rueping and co-workers.[123] Working with Li_2CO_3 and DIPEA in aqueous EtOAc at room temperature under green LED irradiation, the corresponding amines **109** were obtained in good yields (Scheme 47).

Dilman and co-workers[124] reported the one-pot transformation of aldehydes to ketones by preliminary formation of aldimines, which reacted with alkyl radicals generated from NHPI esters **69** under photoredox conditions (Scheme 48). Starting from aldehydes in the presence of *n*-propylamine followed by addition of TMSCl in methanol, TEBACl and 4CzIPN (**25**) as a PC in DCM under blues LED irradiation, the corresponding ketones were obtained in 30–91% yields (Method A). On the other hand, starting from *N*-methyl imines under the same reaction conditions the resulting ketones were isolated in 64–86% yields (Method B). These procedures worked with NHPI esters to generate secondary and tertiary radicals. However, with esters **69** leading to less stable radicals such as primary or cyclopropyl, $MeSO_3H$ in acetonitrile was used instead of MeOH for the activation of imines to provide ketones in 32–96% yields (Method C). In the proposed mechanism, iminium ion **A** reacts with radical $R^{1\bullet}$ giving radical cation **B**. Loss of proton in **B** leads to the formation of a carbon centered imine precursor of ketones after acidic work-up with 1 M HCl in EtOH.

Glyoxylic oxime esters **126** underwent radical coupling with α-AA derivatives under photoredox decarboxylative conditions using acridinium salt **34** as a photocatalyst (Scheme 49).[125]



Scheme 48 Decarboxylative radical addition of NHPI esters **69** to imines under 4CzIPN (**25**) photocatalysis.

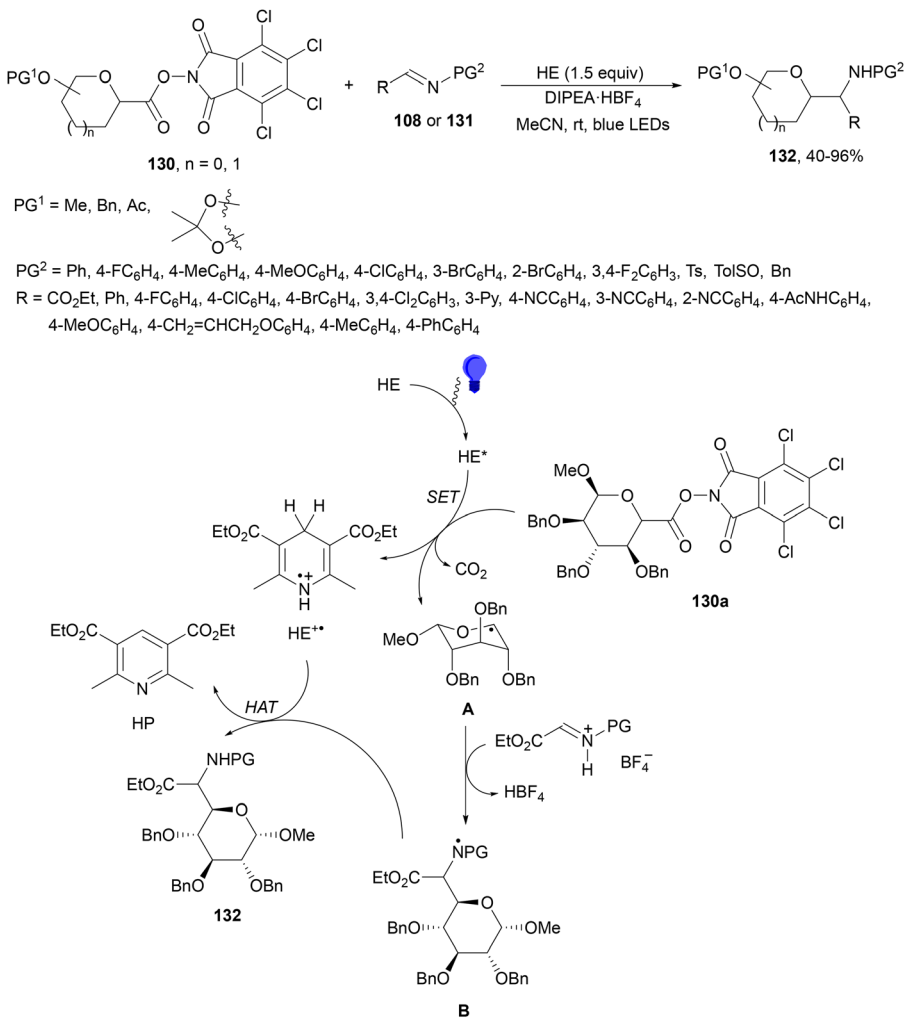


Scheme 49 Decarboxylative coupling of glyoxylic oxime esters **126** with AAs, dipeptides and carboxylic acids under acridinium **34** photocatalysis.

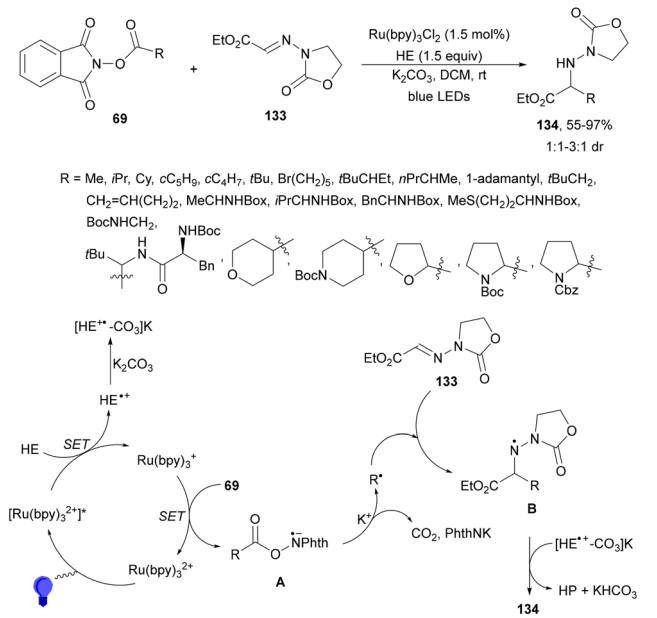
Cyclic and chain AAs, dipeptides and aliphatic acids were used as alkyl radical sources to provide α,β-diamino esters **127**, multi-amino esters **128** and α-AA derivatives **129**, respectively. Two possible mechanisms have been proposed: (a) the addition of radical **A**, formed from the acid after decarboxylation, to glyoxylic oxime ester **126** and (b) the coupling of radical **A** with **B**, which was reduced by $Acr^{-\bullet}$* to give anion **C**, which after protonation afforded product **127a**.

Mariano, Wang and co-workers[126] performed the synthesis of *C*-glycosyl amino acids **132** by reaction of imines **108** and imino esters **131** with RAE of saccharides **130**. This visible-light-promoted coupling took place in the absence of PC, using HE and DIPEA·HBF_4 in acetonitrile at room temperature to form products **132** in moderate to good yields (Scheme 50). Pentoses and hexoses preserved the configuration of the anomeric carbon atom. In the proposed mechanism, HE in acetonitrile absorbs in the visible region to give excited HE*, which serves as a SET donor to glycosyl *N*-hydroxydichlorophthalimide (TCNHPI) ester **130a** to provide after decarboxylation intermediate **A** and $HE^{+\bullet}$. Radical **A** reacts with protonated imino ester (**131**$H^+BF_4^-$) to form radical **B** and HBF_4. Subsequent HAT of **B** by $HE^{+\bullet}$ releases product **132** and the pyridine derivative (HP) of HE.

Photoredox radical alkylation of glyoxylic ester-derived hydrazones **133** with NHPI esters **69** has been carried out by Shen and co-workers.[127] Under visible-light irradiation, in the presence of $Ru(bpy)_3Cl_2$ and HE using K_2CO_3 as a base in DCM at room temperature, α-amino ester derivatives **134** were obtained with high yields (Scheme 51). In addition to hydrazones **133**, *O*-benzyl oximes and *N*-benzoyl hydrazones can be employed as radical acceptors. With respect to NHPI esters, the oleanolic acid derivative was obtained in 98% yield and the chenodeoxycholic acid derivative was obtained in 82% and 81% yields, respectively. Experimental studies suggest that the *N*-centered radical **B** after decarboxylation of radical **A** and addition to **133** would abstract a hydrogen atom from $HE^{+\bullet}$ species. DFT calculations also suggest that K_2CO_3 has important beneficial functions in stabilizing HE intermediates facilitating HAT processes. Therefore, [HE^{+}*–CO_3]K has been postulated to produce product **134**.



Scheme 50 Decarboxylative radical addition of redox-active esters of saccharides **130** to imines **108** and imino esters **131** using Hantzsch ester under visible light.

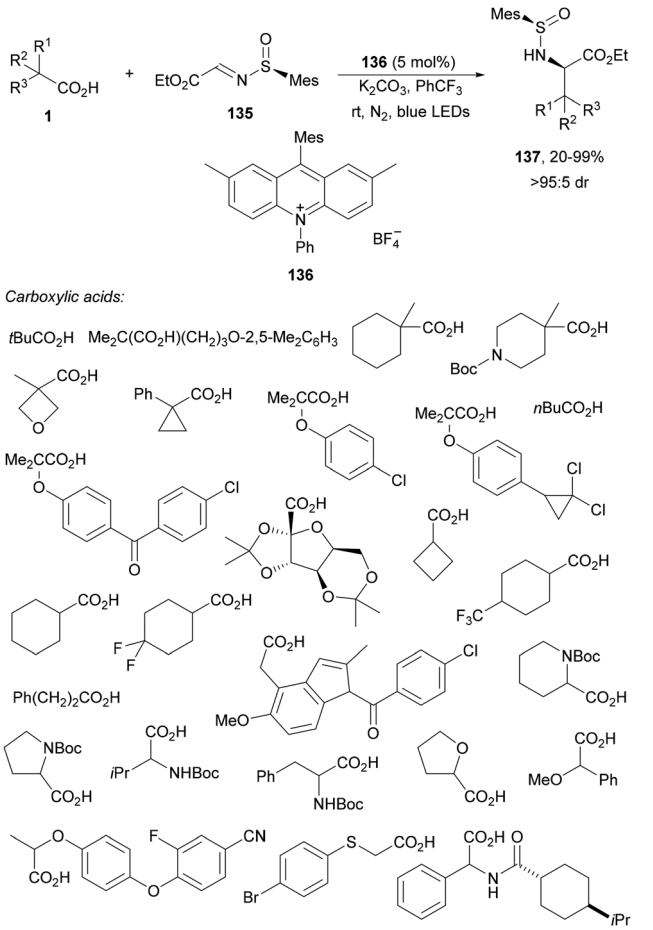


Scheme 51 Decarboxylative addition of NHPI esters **69** to glyoxylic ester-derived hydrazones **133** under $Ru(bpy)_3Cl_2$ photocatalysis.

Kärkäs and co-workers[128] reported the synthesis of amino acid derivatives **137** by reaction of chiral glyoxylate derived sulfinyl imines **135** with carboxylic acids through photoredox catalysis with an acridinium-based PC **136** (Scheme 52). As in the case of Alemán's group[112] (Scheme 39) this process allows the asymmetric synthesis of amines but as α-amino acid derivative **137** with modest to high yields and diastereoselectivities (>95 : 5 dr). In the proposed mechanism the radical from the carboxylic acid decarboxylation adds to the *N*-sulfinyl imine **135**.

Noël and co-workers[129] reported recently a decarboxylative cross-coupling of NHPI esters **69** derived from α-AAs and sulfonyl hydrazones **138** (Scheme 53a). This process took place with ethyl glyoxylate-derived 4-trifluoromethylphenyl sulfonyl hydrazones **138** as the radical acceptor HE as a reductive quencher and disodium Eosin Y ($EYNa_2$, **139**) as a PC under blue LED irradiation. The obtained adducts were subjected to cleavage conditions in ethanol providing esters **140**. This approach can be considered as a C1 homologation of carboxylic esters, a safer alternative to the traditional Arndt–Eistert reaction, and has been extended to peptides on a solid phase. In addition, aromatic and aliphatic *N*-sulfonyl hydrazones **141** were transformed into β-aryl ethylamines **142** with good yields (Scheme 53b). Mechanistic investigation suggests that excited $EYNa_2$* is reductively quenched by the sacrificial electron donor HE to generate $HE^{+\bullet}$. Subsequently, the NHPI ester is reduced by $EYNa_2^{-\bullet}$ giving the alkyl radical, after decarboxylation. Addition of $R^\bullet$ to the sulfonyl hydrazone **141** provides the hydrazinyl radical **A**, which after HAT from $HE^{+\bullet}$ or neutral HE generates the product and the pyridinium **B**.

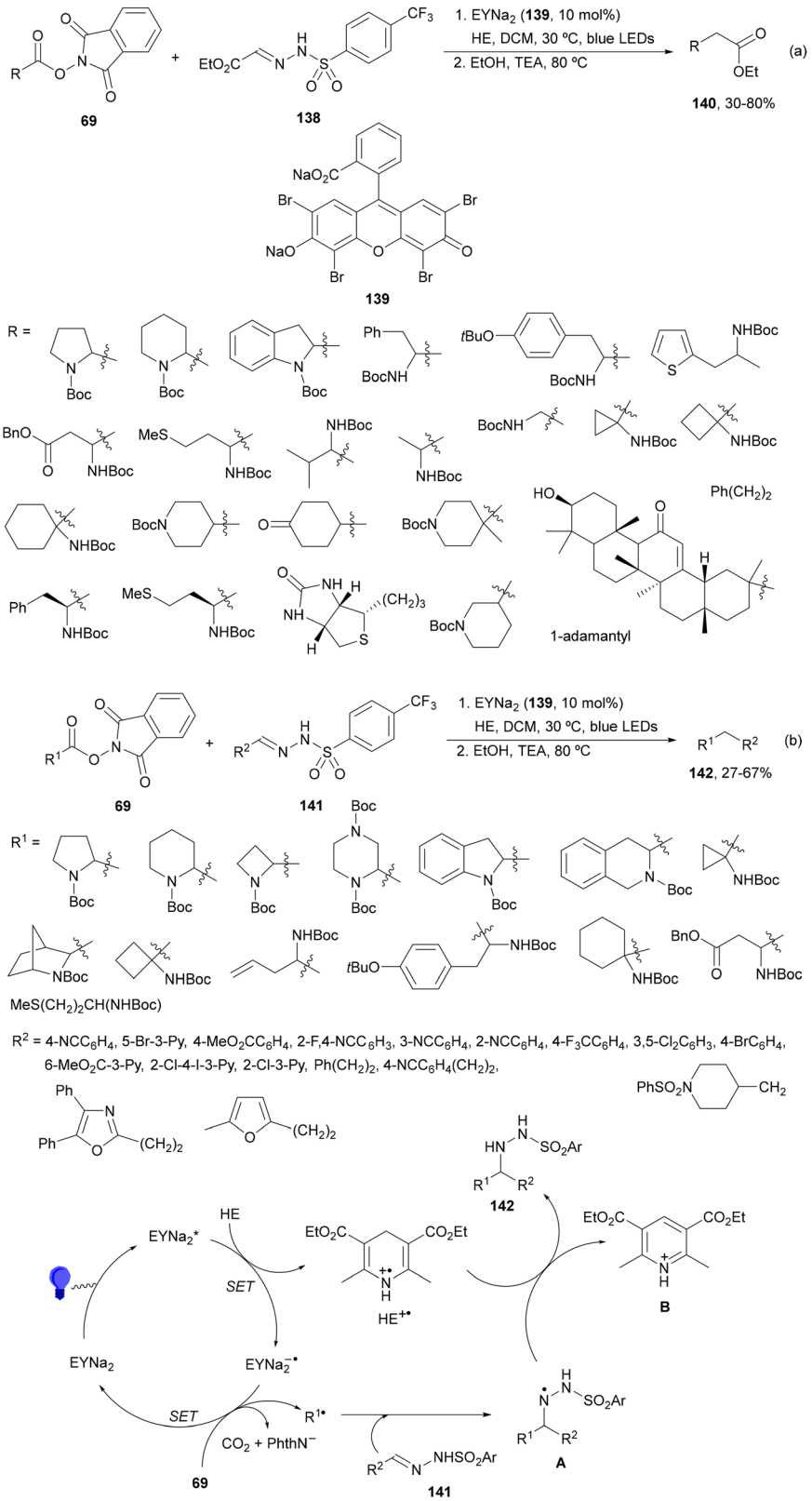
N-Acyl imines have been generated *in situ* by decarboxylation of *N*-acyl α-amino acid derived NHPI esters **143** under visible-light photoredox conditions.[130] By merging Ir complex **4** and



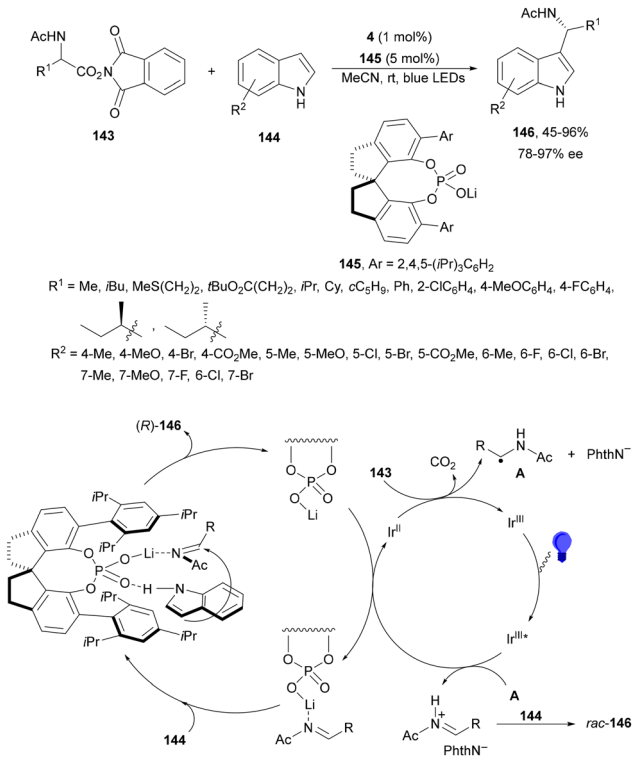
Scheme 52 Decarboxylative asymmetric radical addition of carboxylic acids to chiral *N*-sulfinyl imines **135** under [Mes-Me_2Acr-Ph]BF_4 (**136**) photocatalysis.

chiral phosphate **145**, NHPI esters **143** reacted with indoles **144** to form 3-substituted indoles **146** in up to 96% yield and up to 97% ee (Scheme 54). This asymmetric Friedel-Crafts reaction could take place by generation of an α-aminoalkyl radical **A** and Ir(III). Irradiation of Ir(III) with blue LEDs forms Ir(III)*, which oxidizes **A** to *N*-acyl imine **B**. The chiral phosphate acts as a bifunctional catalyst by activation of the *N*-acyl imine and hydrogen bonding with indole favoring indole attack on the *Si* face of the imine to afford **146** with R configuration. The removal of the *N*-acyl group from products **146** can be achieved by treatment with the Schwartz reagent (Cp_2ZrHCl).[131]

Maruoka and co-workers[132] employed *N*-protected α-amino acid derived NHPI esters **143** as precursors of *N*-protected imines. In the presence of ester-stabilized phosphonium ylides **147**, $Ir(ppy)_3$ (**89**) as a PC and $ZnCl_2$ as a Lewis acid under blue LED irradiation provided β-amino phosphonium ylides **148** with good yields (Scheme 55). These products **148** were further subjected to *in situ* photocatalytic transformations such as: (a) reduction with ascorbic acid or deuteration with trifluoroacetic acid in $MeCN/D_2O$ to form β-AAs **149** or **150** in high yields; (b) alkylation reaction with alkenes giving products **151** with modest diastereoselectivity; (c) (hetero)arylation by using



Scheme 53 Decarboxylative radical addition of NHPI esters **69** to sulfonyl hydrazones **138** (a) and **141** (b) under Eosin Y (**139**) photocatalysis.



Scheme 54 Decarboxylative generation of *N*-acyl imines from *N*-acyl α-amino acid derivatives NHPI esters **143** and enantioselective addition of indoles **144** under Ir **4** and chiral phosphate **145** photocatalysis.

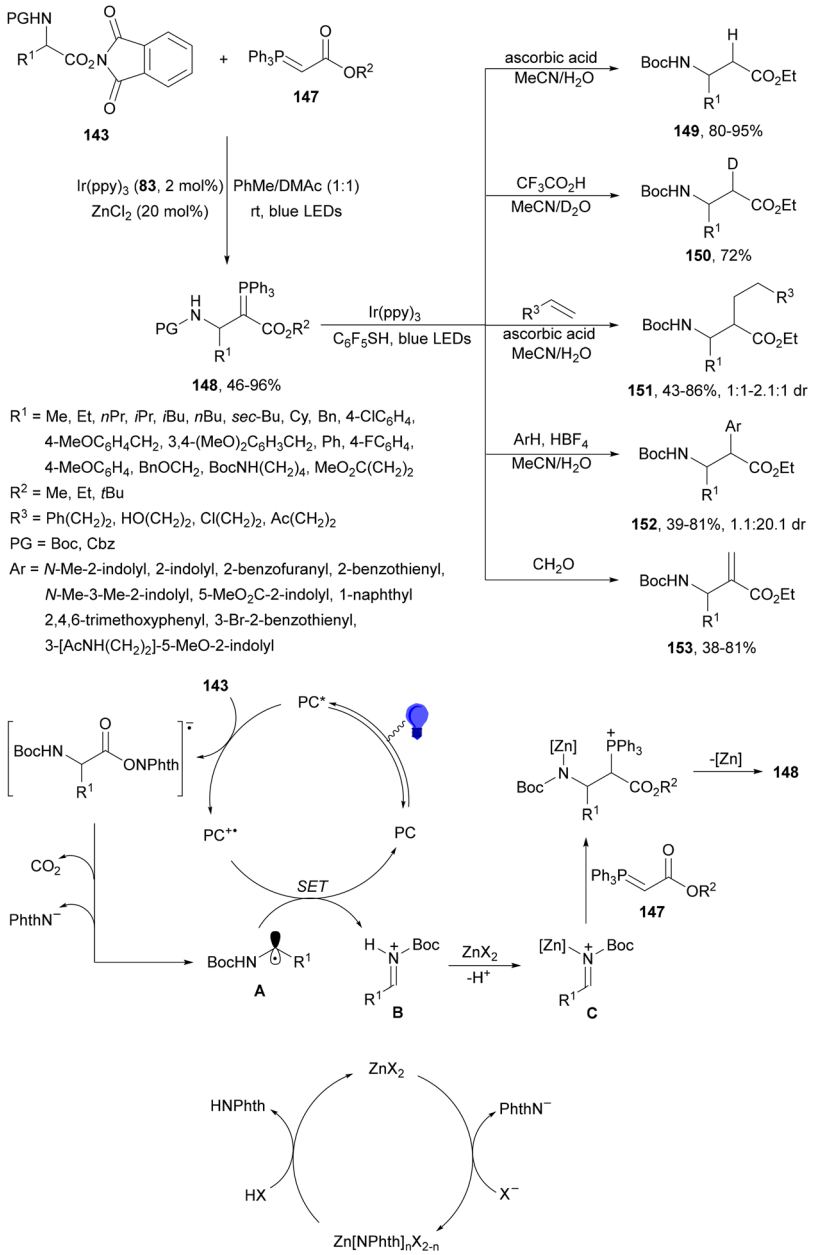
electron-rich hetero(arenes) and HBF_4 as Brønsted acid, resulting in product **152** with moderate dr; and (d) Wittig olefination without isolation of **148** with formaldehyde afforded products **153** with moderate to good yields. Concerning the first decarbonylative photoredox reaction, in the proposed mechanism the *N*-acyl iminium intermediate **B** is generated from **143** *via* a radical-polar crossover process of the amino radical **A**. The role of $ZnCl_2$ is the capture of the phthalimide anion by complexation and also accelerating the formation of a C–C bond by coordination of **B**, forming intermediate **C**, which after reaction with **147** facilitates the proton transfer from the α-position of the phosphonium ion to the nitrogen atom providing ylide **148**.

Seidel and co-workers[133] recently reported the decarboxylative alkylation of cyclic imine-BF_3 **154** with carboxylic acids under acridine (**154**)-copper dual catalysis to provide α-alkyl substituted azacycles **156** with good yields (Scheme 56a). This addition was carried out using $Cu(OTf)_2$·toluene and acridine **155** in DCM at room temperature or in DCE at 70 °C when primary radicals are involved. In the proposed catalytic cycle, acridine **155** forms a photoactive H-bonded complex with carboxylic acid **1**, which after excitation with purple light (395 nm) undergoes decarboxylation to the alkyl radical and acridinyl radical **155H•**. The alkyl radical **A** reacts with **154a** in the presence of Cu(II) species to provide intermediate **B**. Acridinyl radical **155H•** is oxidized to $\mathbf{155H}^+$ by Cu(II) species $LnCu(OTf)_2$. Protonation of **B** by $\mathbf{155H}^+$ furnished complex $\mathbf{156H}^+$-BF_3 regenerating acridine **155**. A three-component reaction of complexes **154**, [1.1.1]propelane (**157**) and carboxylic acids under similar reaction conditions, in the absence of Cu(II), afforded products **158** in good yields (Scheme 56b). In this case, the initially formed radical **A** reacts with [1.1.1]propelane (**157**) to give radical **C**, which after addition to **154** leads to aminyl radical **D**. Acridinyl radical **155H•** reduces aminyl radical **D** to generate intermediate **E** and acridinium $\mathbf{155H}^+$. Finally, protonation of **E** provides product–BF_3 complex $\mathbf{158H}^+$–BF_3.

Decarboxylative addition of acid derived radicals to nitrones was previously described by Zheng, Huang and co-workers[134] earlier than Dilman's group.[121] In this case, α-AAs were used as α-aminoalkyl radical precursors and acyclic **159** and cyclic nitrones **160** as radical acceptors to provide acyclic **161** and cyclic **162** β-amino hydroxylamines with good yields and moderate to good diastereoselectivities (Scheme 57a). This process took place using Ir complex **4** as a PC and Li_2CO_3 as a base in DMF under blue LED irradiation at room temperature. The antihistamine drug mepyramine was prepared from nitrone **159a** and *N*,*N*-dimethylglycine followed by N–O bond cleavage of **161a** with Zn and Pd-catalyzed *N*-alkylation with 2-chloropyridine (Scheme 57b).

Aryl isocyanates **162** can be transformed into amides **163** by a Ce(III)-photocatalyzed addition of radicals from carboxylic acids. Primary, secondary and tertiary aliphatic carboxylic acids reacted with isocyanates **162** using catalytic amounts of $CeCl_3$ and TBACl in MeCN at room temperature under blue LED irradiation (Scheme 58).[135] A wide range of amides were obtained with up to 93% yield and on a gram scale. In the proposed mechanism, $CeCl_3$ was oxidized by isocyanate **162** to a Ce(IV) complex, which underwent a photoinduced ligand-to-metal charge-transfer (LMCT)[54,55] to generate the Ce(III) complex and Cl•. The reaction of Cl• with the carboxylic acid forms radical **A** and HCl. Decarboxylation of **A** gives the alkyl radical **B**, which was then added to isocyanate **162** to provide radical **C**. After reduction of radical **C** by the Ce(III) complex, anion **D** and the Ce(III) complex are formed. Additionally, the coupling of radical anion **E** and radical **A** could also produce anion **D**. Finally, protonation of anion **D** gives product **163**. Moreover, the HAT process between radical **D** and carboxylic acid **1** to give amide **163** cannot be ruled out. When the reaction was carried out in darkness at higher temperatures the yield increased smoothly with the temperature. Therefore, the thermal reaction pathway should coexist, but the radical addition pathway should be the main pathway.

Cross-coupling of arylacetic acids and α-AAs with imines or *in situ* generated imines takes place using Ir complex **4** as a PC to give amines and 1,2-diamines, respectively. When organic PCs, such as 4CzIPN or acridine, are used as PCs an additional oxidant must be used. However, active NHPI esters react with imines using rose Bengal or 4CzIPN through a radical addition mechanism. Imine derivatives of glycosylic esters react with carboxylic acids to give α-AA derivatives and with α-AAs to provide α,β-diamino acids using acridinium salts as PCs. In

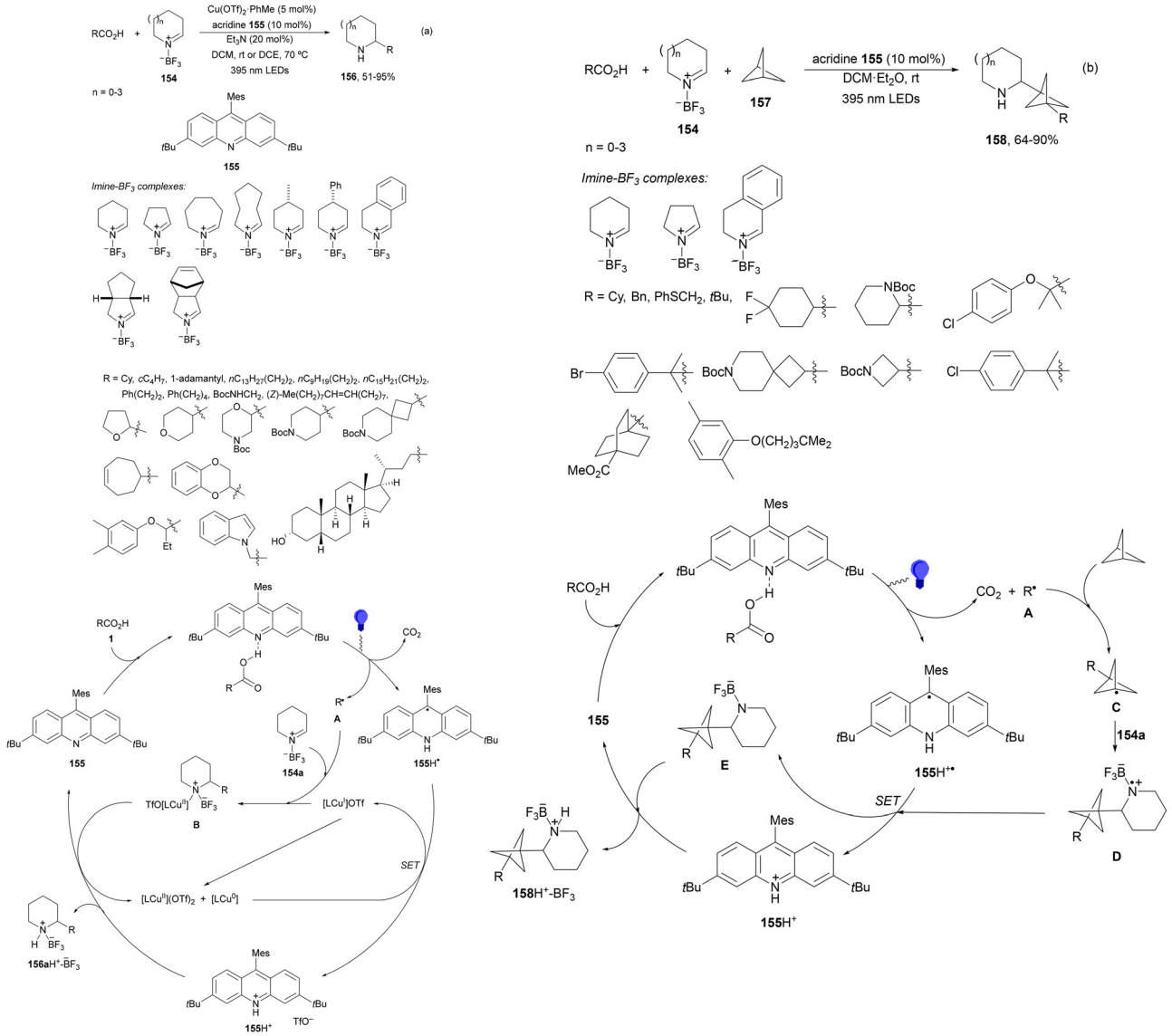


Scheme 55 Decarboxylative generation of *N*-protected imines from NHPI esters **143** and addition of phosphonium ylides **147** under $Ir(ppy)_3$ (**89**) photocatalysis.

the case of NHPI esters α-AA derivatives are formed by addition reaction under $Ru(bpy)_3Cl_2$ catalysis and Hantzsch ester (HE) as a radical acceptor or with disodium Eosin Y as a PC. *N*-Protected α-amino NHPI esters generate *N*-protected imines under Ir catalysis, which are able to react with indoles in the presence of chiral phosphate to provide chiral 3-substituted indoles. When these NHPI esters are allowed to react with phosphonium ylides β-amino phosphonium ylides are formed, which can be further transformed in a one-pot process into β-amino ester derivatives. Other radical acceptors such as cyclic imine-BF_3, nitrones and isocyanates react with carboxylic acids to provide cyclic amines, diamines and amides, respectively.

2.5. Arylation reactions

$C(sp^2)$–$C(sp^3)$ cross-coupling of aromatic halides with aliphatic carboxylic acids or derivatives by photoredox decarboxylation processes is an excellent alternative to transition metal-catalyzed cross-coupling reactions. Metallaphotoredox decarboxylation arylation was reported by MacMillan and Doyle in 2014 using $NiCl_2$ and Ir complexes as PCs.[136] This nickel/photoredox dual catalysis is a general tool for the cross-coupling of carboxylic acids and aromatic electrophiles.[137] It has been found that the presence of oxygen is important for catalyst activation when air-stable Ni(II) precatalysts were used to promote rapid reduction of Ni(II) to Ni(0) by Ir(II).[138] A wide range of secondary, benzylic,

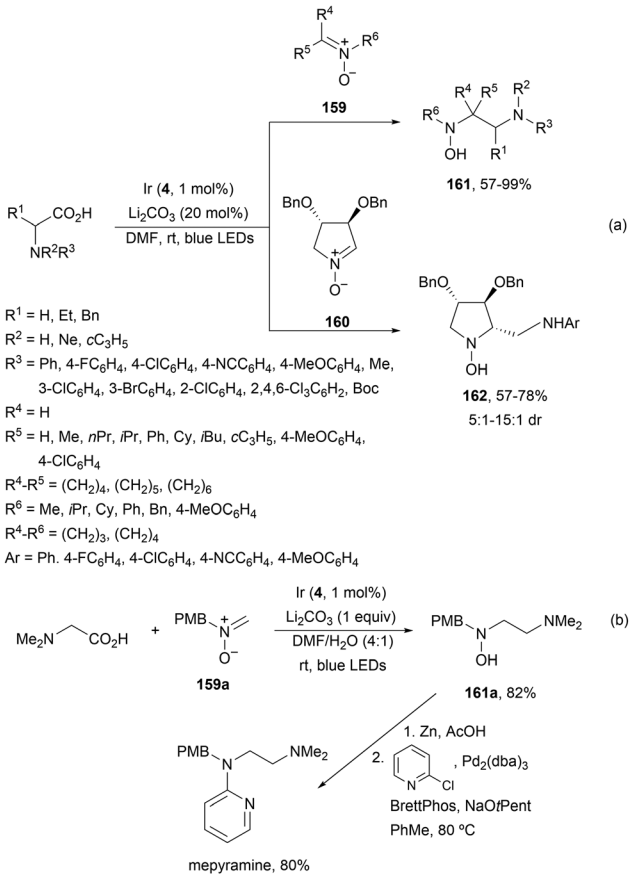


Scheme 56 Decarboxylative radical alkylation of cyclic imine-BF_3 complexes **154** with carboxylic acids (a) and propellane (b) **157** under acridine **155** photocatalysis.

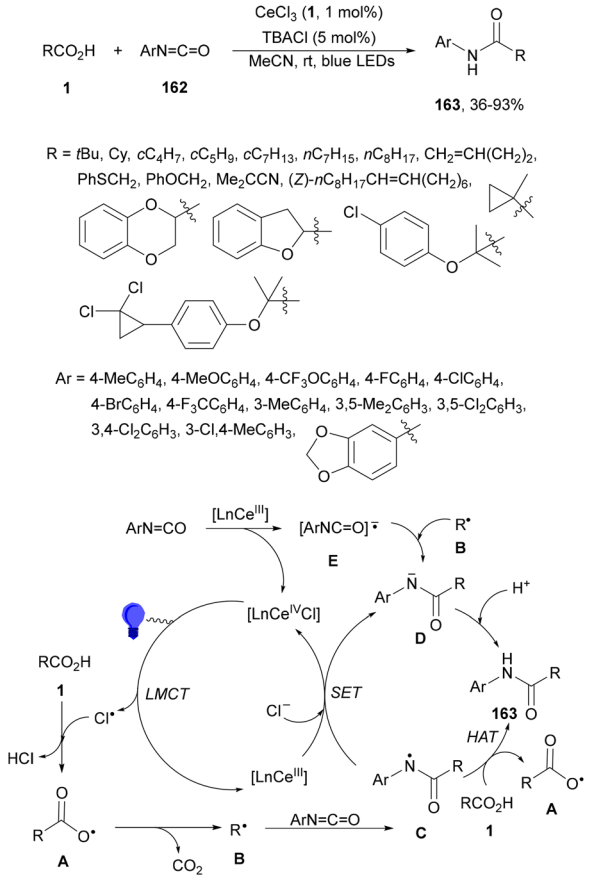
α-amino and α-oxy carboxylic acids reacted with aryl iodides, bromides and chlorides under metallaphotoredox conditions. Notably, an enantioselective arylation of α-AAs by employing bis-oxazoline **164** as a chiral ligand was reported by MacMillan, Fu and co-workers.[139] Starting from racemic α-AAs and aryl bromides an enantioconvergent[140] arylation provided chiral benzylic amines **165** with good yields and up to 93% ee (Scheme 59).

Luo and Zhang[141] employed 4CzIPN (**25**) instead of Ir complexes as a PC for the cross-coupling of AAs with aryl halides *via* Ni/photoredox dual catalysis. Under this class of catalysis an enantioconvergent[140] cross-coupling of α-heterocyclic carboxylic acids **166** with aryl bromides has been described (Scheme 60).[142] In the presence of catalytic amounts of 4CzIPN (**25**), $NiBr_2$·DME and chiral ligand **164**, with Cs_2CO_3 as a base in acetone under blue LED irradiation the corresponding *N*-benzyl heterocycles **167** were obtained in modest to good yields. The presence of a directing group at the C2 position in the heterocyclic carboxylic acid increased the enantioselectivity from up to 58% ee to 88% ee. Hypothetical chelation of the alkyl radical to Ni in intermediate **A** increasing the rigidity of the complex has been postulated.

Recently, Itami and co-workers[143] reported the cross-coupling of *N*-protected glycines **168** with aryl bromides to obtain *N*-protected primary benzylamines **169** under 4CzIPN (**25**) photoredox conditions (Scheme 61). This decarboxylative process was performed with $NiCl_2$·DME and 2,2′-bipyridine (bpy) as a ligand and Cs_2CO_3 as a base in DMF under blue LED irradiation to provide *N*-protected benzylamines **169** with up to 73% yield. Only *N*-tosyl glycine failed to react.



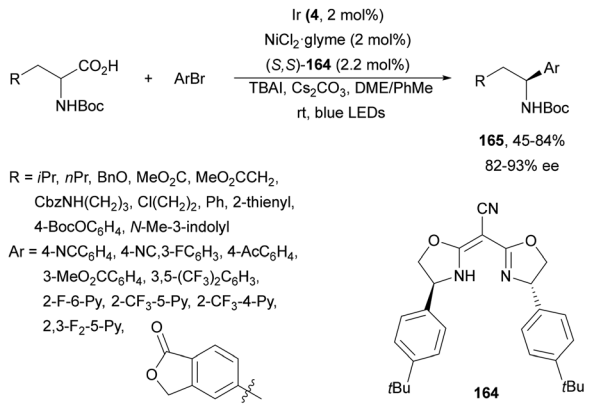
Scheme 57 Decarboxylative radical addition to nitrones **159** and **160** of radicals from α-AAs under Ir photocatalysis (a). Synthesis of mepyramine (b).



Scheme 58 Decarboxylative radical addition of carboxylic acids to isocyanates **162** under Ce(III)-photocatalysis.

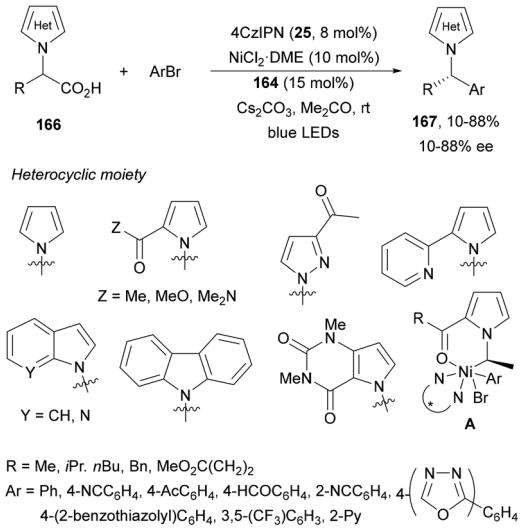
Formylation of aryl halides and triflates under 4CzIPN (**25**)/Ni photocatalysis was carried out by Mariano, Wang and co-workers[144] using diethoxy acetic acid **26** as a source of radical $(EtO)_2CH^{\bullet}$. Using 20 mol% of **25** and 5 mol% of $NiCl_2 \cdot 6H_2O$ as catalysts and 4,4′-di-*tert*-Bu-2,2′-bipyridine (dtbbpy, 24 mol%) as a ligand and Cs_2CO_3 as a base under blue LED irradiation, aromatic aldehydes were obtained after acetal deprotection in 45–85% yield. Direct decarboxylative formylation of aryl and hetaryl iodides with glyoxylic acid was carried out by Shang, Fu and co-workers.[145] Dual photoredox conditions with 4CzIPN (**25**) as an organic PC and Pd(Xantphos)Cl_2 instead of Ni as a metallaphotocatalyst and CsOAc as a base in DMF at room temperature under blue LED irradiation afforded directly aromatic aldehydes with good yields (Scheme 62). In this case, the aryl iodide is firstly added to a Pd(0) catalyst to produce the Pd(II) intermediate **A**. Subsequent addition of the formyl radical affords the Pd(III) intermediate **B**, which after a SET process with $4CzIPN^{-}$ produces the Pd(II) intermediate **C** and 4CzIPN. Final reductive elimination of intermediate **C** generates the aromatic aldehyde. The presence of an excess of CsOAc (150 mol%) is crucial for the *in situ* generation of the active cesium salt CsO_2C–CHO.

Ribosyl and deoxyribosyl acids **170** underwent Ni/photoredox decarboxylative cross-coupling reaction with aryl/heteroaryl

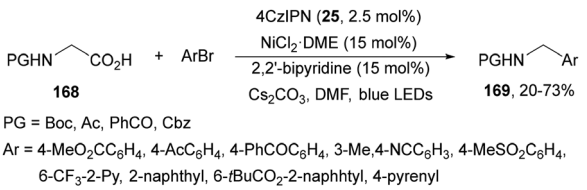


Scheme 59 Enantioconvergent decarboxylative arylation of AAs under Ir/Ni photocatalysis.

bromides to give aryl/heteroaryl-*C*-nucleosides **171** (Scheme 63).[146] This process was performed using 4CzIPN as an organocatalyst, $NiBr_2$ with bpy as a ligand, K_2CO_3 as a base in DMF at 30 °C under blue LED irradiation. Products **171** were isolated in moderate to good yields and high stereoselectivity. In the proposed mechanism, the initial excitation of 4CzIPN produces photoexcited (4CzIPN)*, which promotes the photooxidative



Scheme 60 Enantioconvergent decarboxylative arylation of heterocyclic carboxylic acids **166** under 4CzIPN (**25**)/Ni photocatalysis.

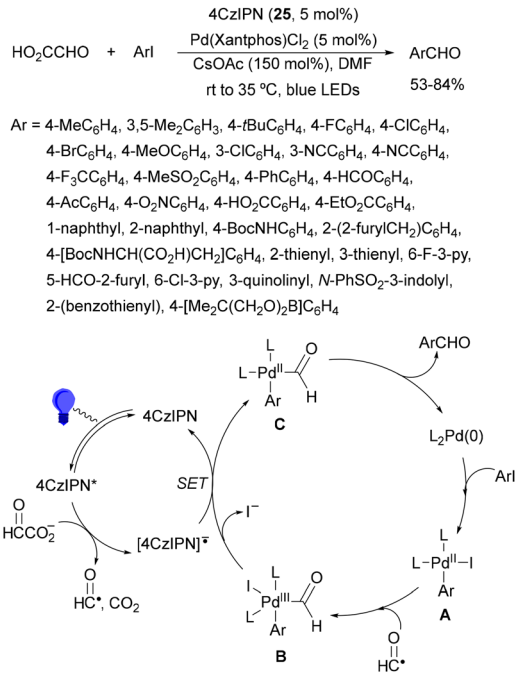


Scheme 61 Decarboxylative arylation of *N*-protected glycines **168** with aryl bromides under 4CzIPN (**25**)/Ni photocatalysis.

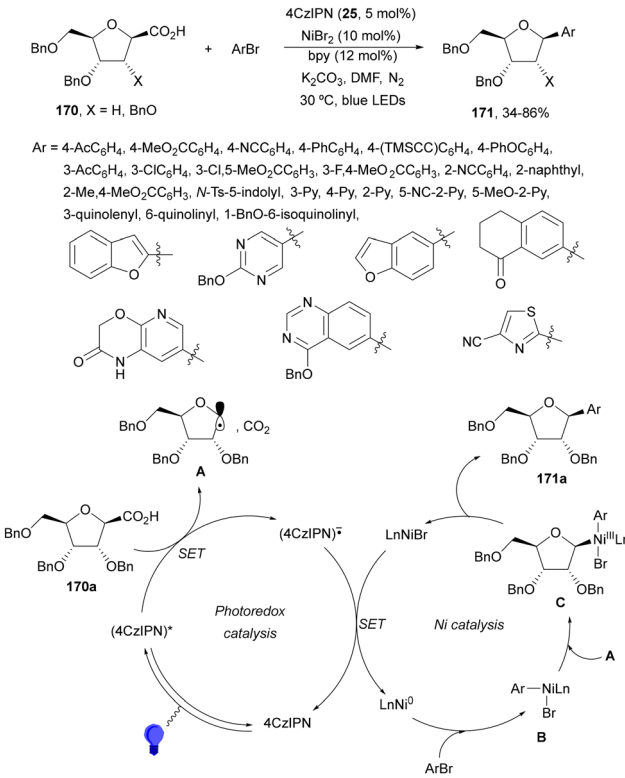
decarboxylation of **170a** to form the anomeric radical **A.** In the Ni catalytic cycle the active LnNi(0) species is generated *via* two SET reduction processes of Ni(bpy)Br_2 by the PC. This Ni(0) species undergoes oxidative addition to the aryl bromide forming the Ni(II) intermediate **B**, which reacts with radical **A** to generate a Ni(III) complex **C**. Reductive elimination of **C** produces product **167** and the Ni(I) complex Ni(bpy)Br, which is reduced by $(4CzIPN)^{-\bullet}$ to the Ni(0) species.

Molander and co-workers[147,148] reported the cross-coupling of DNA-encoded libraries (DELs), conjugates with aromatic groups **172**, with AA derivatives under Ir/Ni photocatalysis. Coupling with aryl bromides and aryl iodides enabled satisfactory incorporation of alkyl groups to provide compounds **173** (Scheme 64). This process was carried out in partially aqueous DMSO as solvent (23 : 77), with 1,1,3,3-tetramethylguanidine (TMG) as a base during 10 minutes irradiation under blue LED irradiation using Ir complex **4** as a PC and Ni(II) bis(2,2,6,6)tetramethyl-3,5-heptanedioate (TMHD). In this case, Ir complex **4** gave better results than 4CzIPN (**25**).

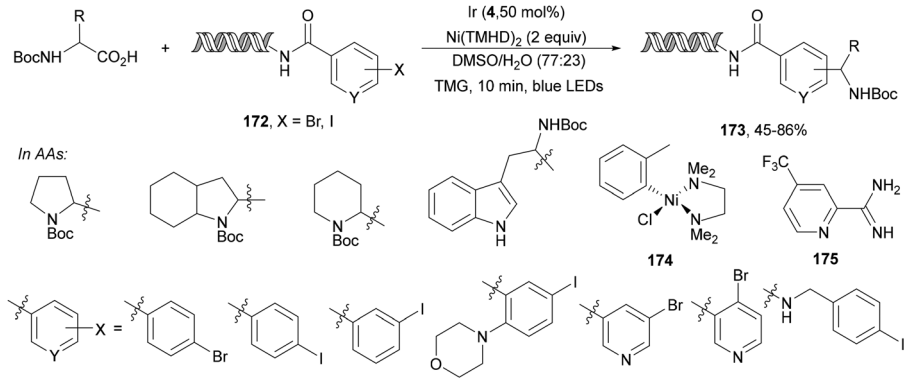
Kölmel, Flanagan and co-workers[149] simultaneously described this transformation in DMSO/H_2O (40 : 60) using DNA-tagged and heteroaryl iodides **172** and *N*-Boc AA derivatives **6** in the presence of Ir complex **4**/Ni complex **174** and 4-CF_3-2-pyridyl carboxamidine **175** (Scheme 64) as a ligand. This cross-coupling occurred



Scheme 62 Decarboxylative formylation of aryl halides with glyoxylic acid under 4CzIPN (**25**)/Pd(0) photocatalysis.



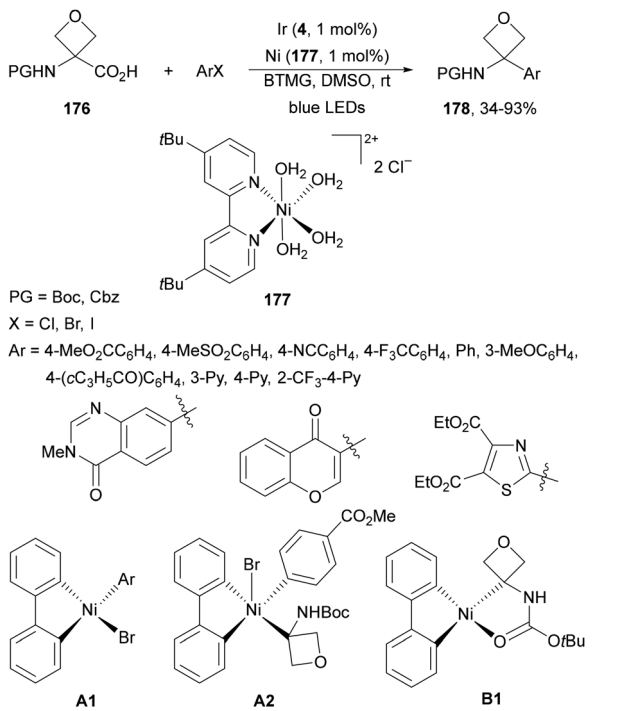
Scheme 63 Decarboxylative arylation of ribosyl/deoxyribosyl acids **170** under 4CzIPN (**25**)/Ni photocatalysis.



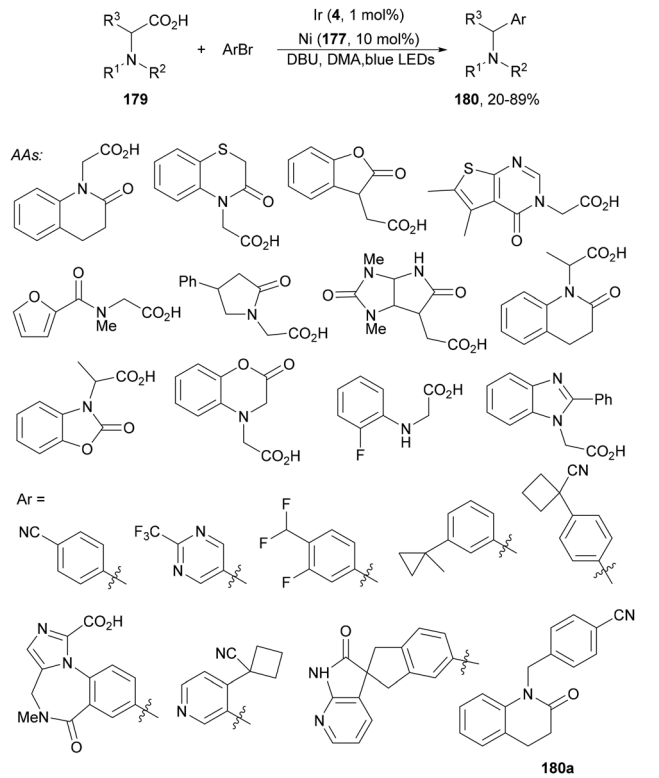
Scheme 64 Decarboxylative cross-coupling of DNA-encoded library **172** with AA derivatives **6** under Ir/Ni photocatalysis.

in the presence of K_2HPO_4 as a base at room temperature during 40 minutes blue LED irradiation to afford products **173** in 9–93% yields. Recently, Chheda and co-workers[150] reported the cross-coupling of DELs, **172** bromides, with carboxylic acids using Ir complex **4** and $NiCl_2$·dtbbpy in DMSO in the presence of phthalimide as an additive[151] and Barton base [2-*tert*-butyl-1,1,3,3-tetramethylguanidine, (BTMG)] under a N_2 atmosphere and blue LED irradiation. In this process, DNA-cationic surfactant complexation enables dissolution and reaction on-DNA in anhydrous organic solvents. Products of type **173** were obtained with 12–96% yields.

Photoredox Ir/Ni dual catalyzed decarboxylative arylation cross-coupling has been translated from the batch to the continuous flow reactor using a 'microslug' screening platform by Jensen, Robinson and co-workers.[152] The group of Merck[153] has applied cross-coupling reactions under Ir/Ni photoredox catalysis to 18 pharmaceutical relevant aryl halides using an integrated photoreactor. This integrated photoreactor improves the success rate and reduces the reaction time with excellent results in its discovery programs. Using a microscale high-throughput experimentation (HTE), MacMillan and co-workers[154] were able to perform a rapid optimization of several photoredox reactions including cross-couplings. This approach has been translated to several commercial flow reactors. Gesmundo and co-workers[155] developed chemical-coated glass beads (Chembeads) as a parallel bead dispenser to expedite HTE processes namely $C(sp^2)$–$C(sp^3)$ decarboxylative cross-couplings and libraries under Ir/Ni photoredox conditions.



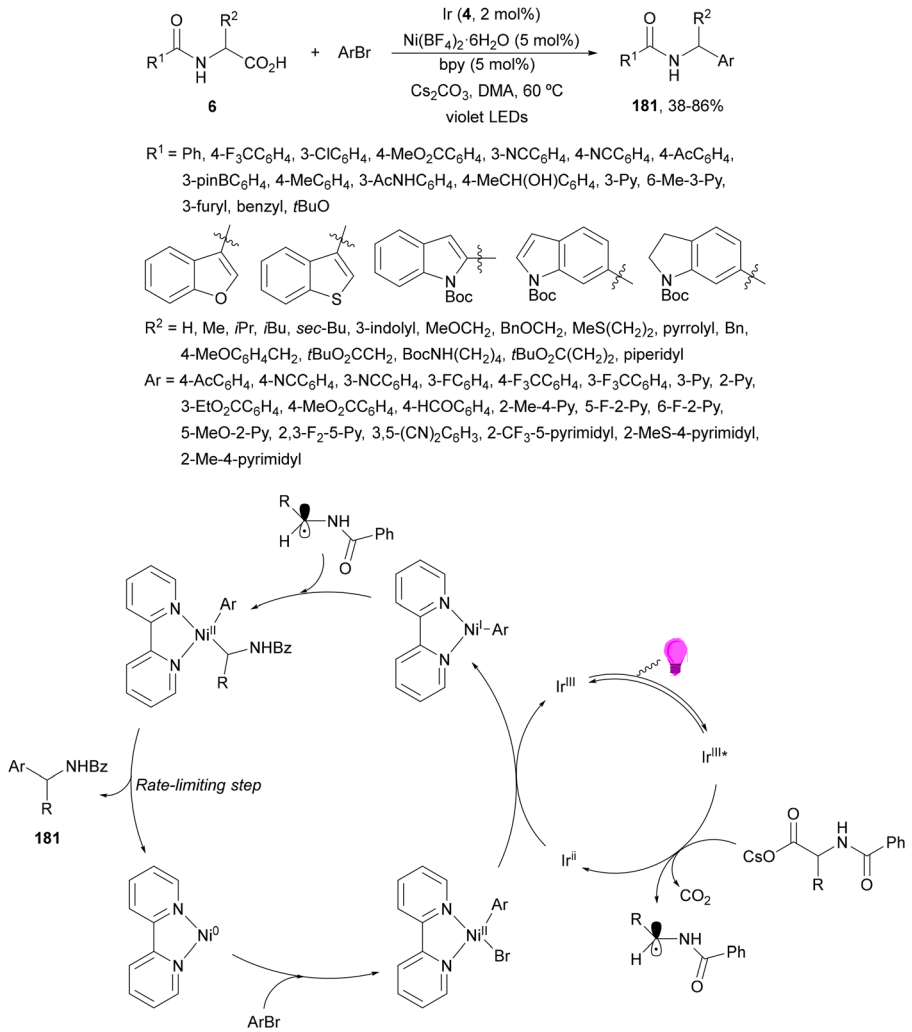
Scheme 65 Decarboxylative oxetanylation of aryl halides with oxetanyl amino acids **176** under Ir (**4**)/Ni (**177**) dual photocatalysis.



Scheme 66 Decarboxylative arylation of α-amino acids **179** with aryl bromides under Ir/Ni (**177**) dual photocatalysis.

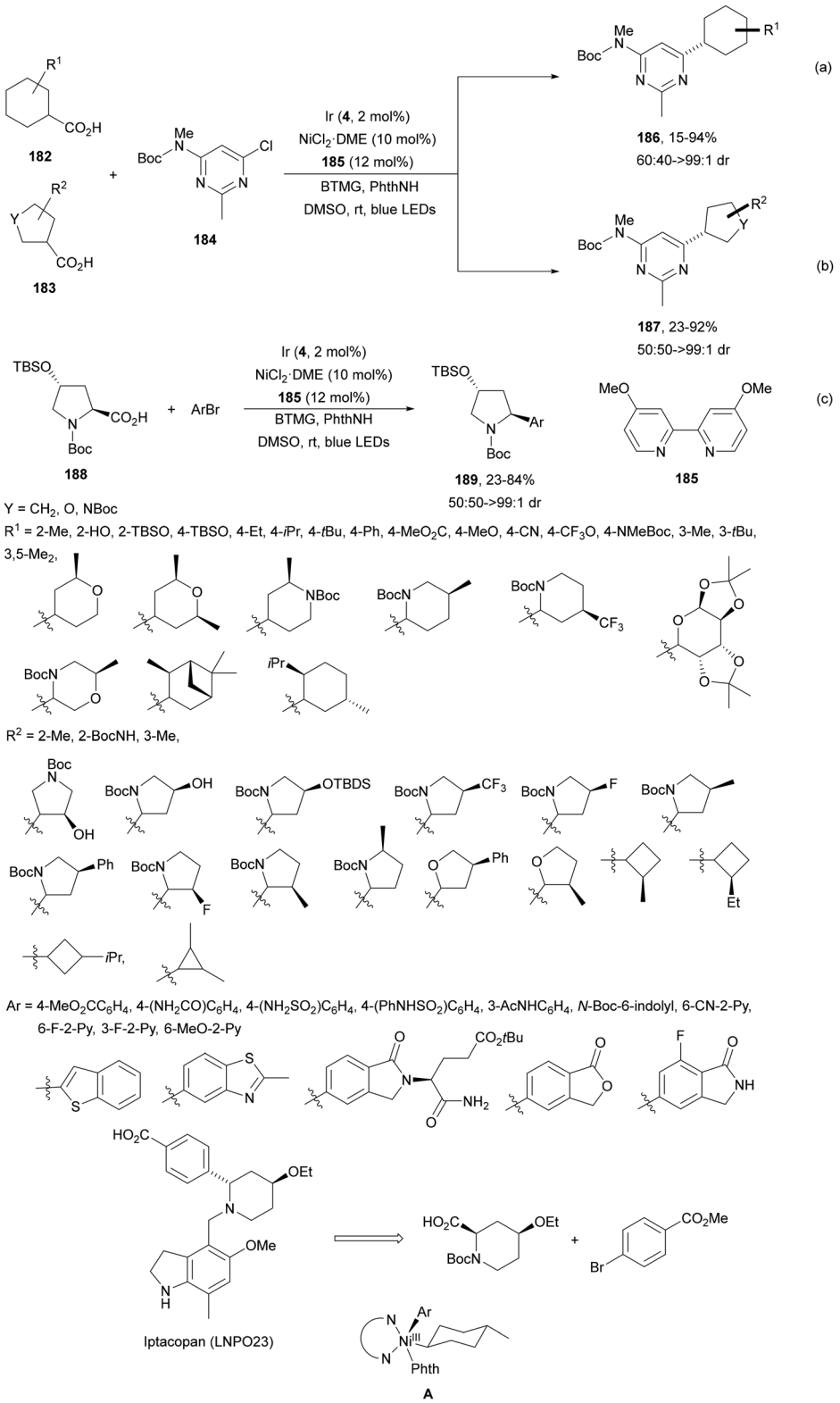
Oxetanes are employed in medicinal chemistry as carbonyl or *gem*-dimethyl bioisosteres. On the other hand, 1-amino-3-oxetanes can function as amide replacement in druglike molecules and exhibits comparable pK_a values.[156] In addition, they are also employed as surrogates to *gem*-dimethyl groups with a similar molecular volume but significant increase of solubility being liponeutral. Terrett, Huestis and co-workers,[157] through the combination of an Ir/Ni dual photoredox catalyzed strategy, accomplished the synthesis of aryl aminooxetanes **176** by arylation of oxetanyl amino acids **176**. Aryl halides reacted with AAs **178** using Ir complex **4** and $[Ni(dtbbpy)(H_2O)_4]Cl_2$ (**177**) as catalysts and Barton's base (BTMG) in anhydrous DMSO at room temperature under blue LED irradiation to provide products **174** in moderate to good yields (Scheme 65). Intermediate tertiary radicals coupled more efficiently than other tertiary acids such as 1-(Boc-amino)cyclobutanecarboxylic acid or cyclopropane derived α-amino acid or 1-(Boc-amino)-3,3-difluorocyclobutanecarboxylic acid. DFT calculations of two possible pathways A and B for the aminooxetanyl radical suggested that the initial oxidative addition of the aryl halide to Ni(0) to give intermediate **A1** ($\Delta G^{\neq}$ = 11.8 kcal mol^{-1}) becomes the turnover-limiting step. Subsequent radical addition to Ni(II) forms intermediate **A2**. However, in path B – typical of benzylic radicals – a higher barrier of oxidative addition to the Ni(I)-oxetanyl species to form intermediate **B1** was calculated to be 23.9 kcal mol^{-1}, higher than that for intermediate **A1**.

The synthesis of benzylamines by alkylation with benzyl halides and electron-deficient amines suffers from a lack of commercial availability of these electrophiles. However, using easily accessible aryl bromides as electrophiles in decarboxylative cross-coupling metallaphotoredox reactions should allow the synthesis of *N*-benzylamine derivatives. Hopkins and co-workers[158] at Merck have described the cross-coupling of AAs **179** with aryl bromides under Ir/Ni photoredox conditions (Scheme 66). A great diversity of *N*-benzylic derivatives **180** were obtained in moderate to good yields using DBU as a base in DMA under blue LED irradiation. Working in a continuous flow photoreactor, the representative product **180a** was obtained on a gram-scale with 70% yield.

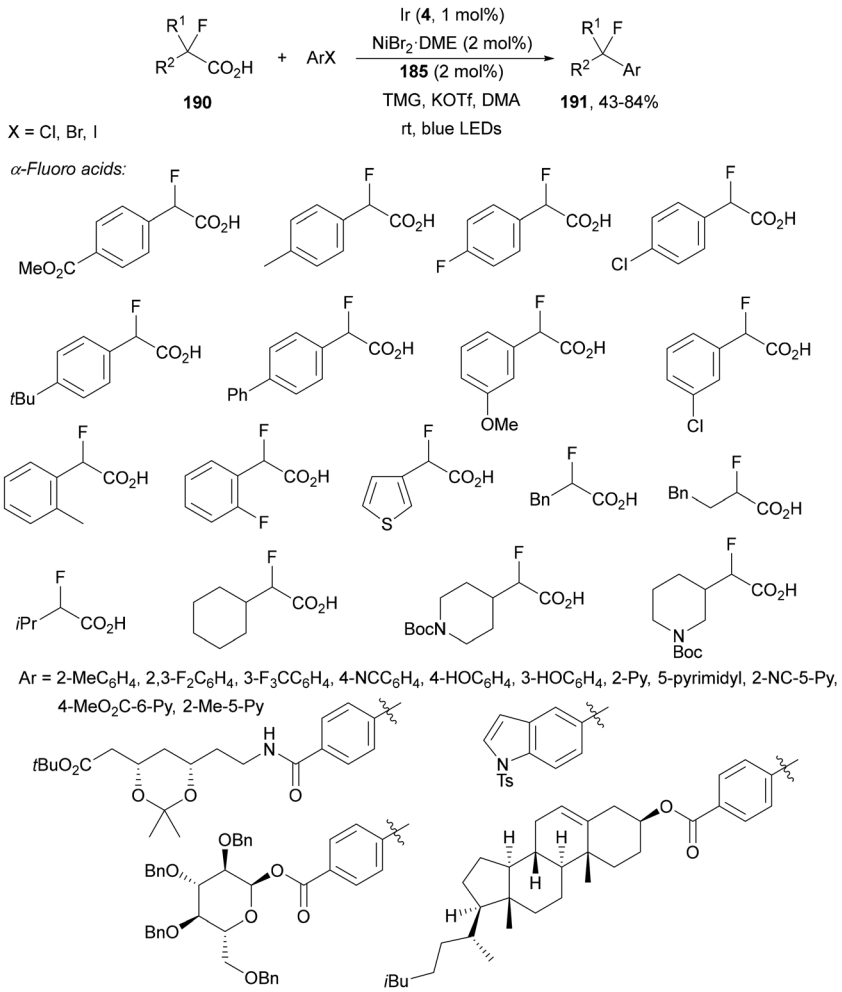


Scheme 67 Decarboxylative arylation of *N*-acylamino acids with aryl bromides under Ir/Ni photocatalysis.

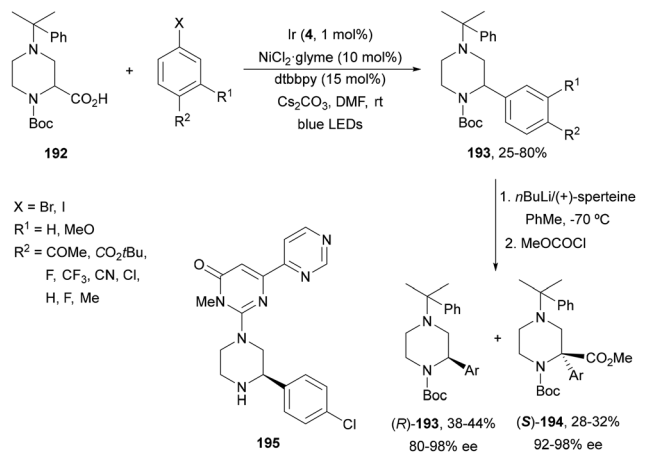
Oderinde and co-workers[159] have extensively studied the synthesis of amides **181** by decarboxylative arylation of *N*-benzoylamino acids of type **6** under Ir/Ni metallaphotoredox conditions (Scheme 67). A wide range of AAs and aryl bromides were applied to the synthesis of *N*-aryl amides **181** in good yields using Cs_2CO_3 as a base and DMA as a solvent under violet



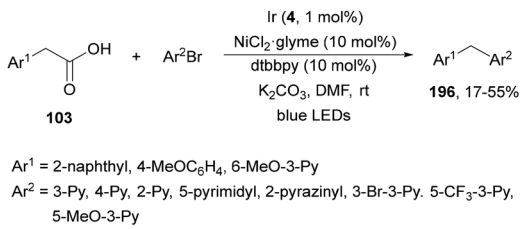
Scheme 68 Decarboxylative arylation of cyclic carboxylic acids **182** (a), **183** (b) and **188** (c) under Ir/Ni metallaphotocatalysis.



Scheme 69 Decarboxylative cross-coupling of aryl halides with α-fluoro carboxylic acids **190** under Ir (**4**)/$NiBr_2$·**185** dual photocatalysis.



Scheme 70 Decarboxylative arylation of 2-piperazine carboxylic acid **192** under Ir/Ni photocatalysis and subsequent kinetic resolution.



Scheme 71 Decarboxylative arylation of (hetero)aryl acetic acids with (hetero)aryl bromides under Ir (**4**)/Ni photocatalysis.

LED irradiation (400 nm). They observed that only one electron-poor aryl bromide participated in the cross-coupling conditions as it was also observed by MacMillan's group.[136,139] The presence of phthalimide[151] as an additive with electron-rich aryl bromides gave low yields or no product formation. Mechanistic investigations and DFT calculations revealed that in the Ni catalytic cycle reductive elimination *via* a Ni(II) species, rather than *via* a Ni(III) species, is thermodynamically favorable and also the reduction of Ni(II)ArBr to Ni(I)Ar by Ir(II). This alternative mechanism is outlined in Scheme 67.

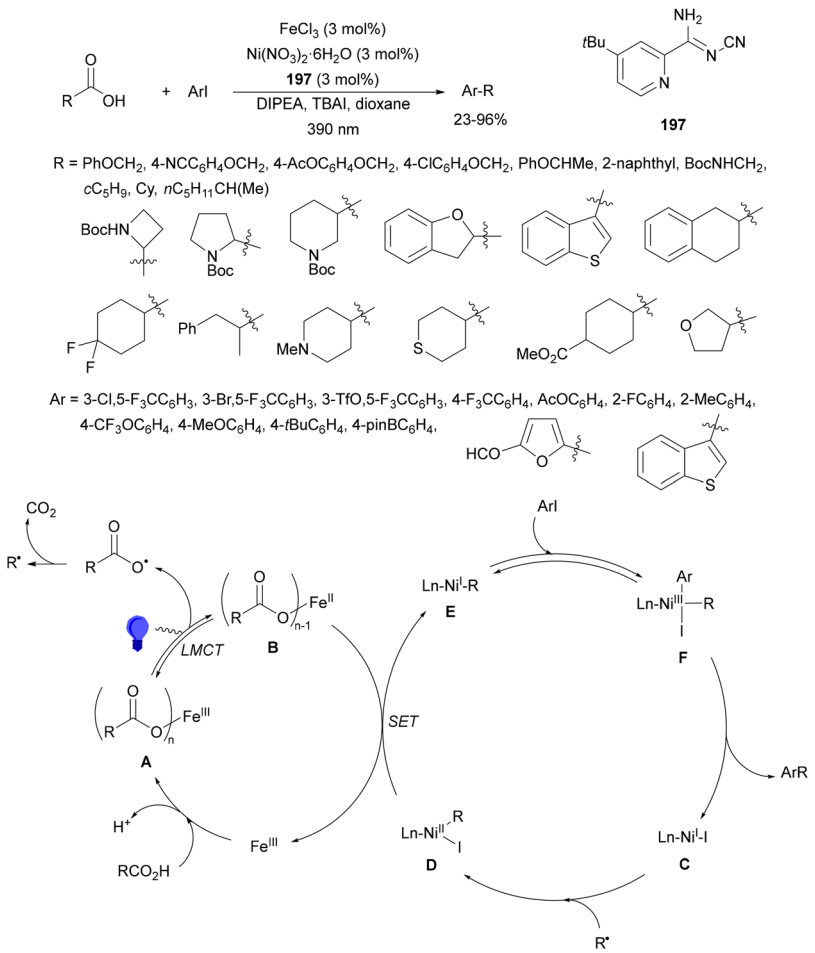
The same group recently reported the stereoselectivity aspects of Ir/Ni metallaphotoredox decarboxylative arylation of substituted cyclic carboxylic acids with aryl bromides and

chlorides.[160] This process with acids **182** and **183** with aryl chloride **184** took place with Ir (**4**) as a PC, $NiCl_2$·DME and 4,4′-dimethoxybipyridine (**185**) as a ligand, BTMG as a base, phthalimide as an additive[161] in DMSO at room temperature and under blue LED irradiation to furnish products **186** and **187**, respectively, as *trans*-diastereomers with in general good yields and up to 99 : 1 dr (Scheme 68a and b). In the case of aryl bromides, hydroxyproline derivative **188** was transformed into *trans*-pyrrolidines **189** with 23–84% yields and up to > 99 : 1 dr (Scheme 68c). This methodology was applied to the synthesis of iptacopan, LNPO23, a recently approved drug prescribed to adults with C3G, PNH and IgA nephropathy.[161] It was prepared enantioselectively on a 200 mmol scale in flow in only 4 steps. In this case, DFT calculations supported that the $L_2ArXNi(III)R$ species **A** is the diastereodetermining intermediate and undergoes reductive elimination to afford *trans*-products.

For the synthesis of secondary and tertiary fluorides **191** an efficient decarboxylative cross-coupling of α-fluoro carboxylic acids **190** with aryl halides was developed by Gutierrez, Koh and co-workers.[162] In the presence of catalytic amounts of Ir complex **4**, $NiBr_2$·DME and ligand **185** in DMA with TMG and KOTf as bases at room temperature under blue LED irradiation, fluorides **191** were obtained in good yields (Scheme 69). DFT calculations rationalized the less effective decarboxylative cross-coupling for α-fluoro carboxylic acids than that for the nonfluorinated carboxylic acids due to the higher energy barrier for the formation of α-fluoroalkyl radicals.

Coldham and co-workers[163] have prepared orthogonally protected 2-arylpiperazines **193** by decarboxylative arylation of piperazine carboxylic acid **192** with aryl bromides and iodides under Ir (**4**)/$NiCl_2$·dtbbpy photocatalysis in moderate to good yields (Scheme 70). These products were subjected to kinetic resolution with *n*-BuLi/(+)-sparteine as a chiral ligand for lithiated intermediates to provide a mixture of (*R*)-**193** and (*S*)-**194** by reaction with methyl chloroformate. This methodology has been applied to the synthesis of glycogen synthase kinase (GSK)-3β inhibitor **195**. The direct C–H lithiation of the piperazine ring followed by Negishi coupling to give 2-aryl piperazines was very low-yielding.[164]

Decarboxylative arylation of aryl acetic acids **103** *via* metallaphotoredox catalysis has been employed for the synthesis of heterodiarylmethanes **196** (Scheme 71).[165] Different substituted aryl and hetaryl bromides reacted with aryl acetic acids **103** using Ir (**4**)/$NiCl_2$·dtbbpy as catalysts and K_2CO_3 as a base in



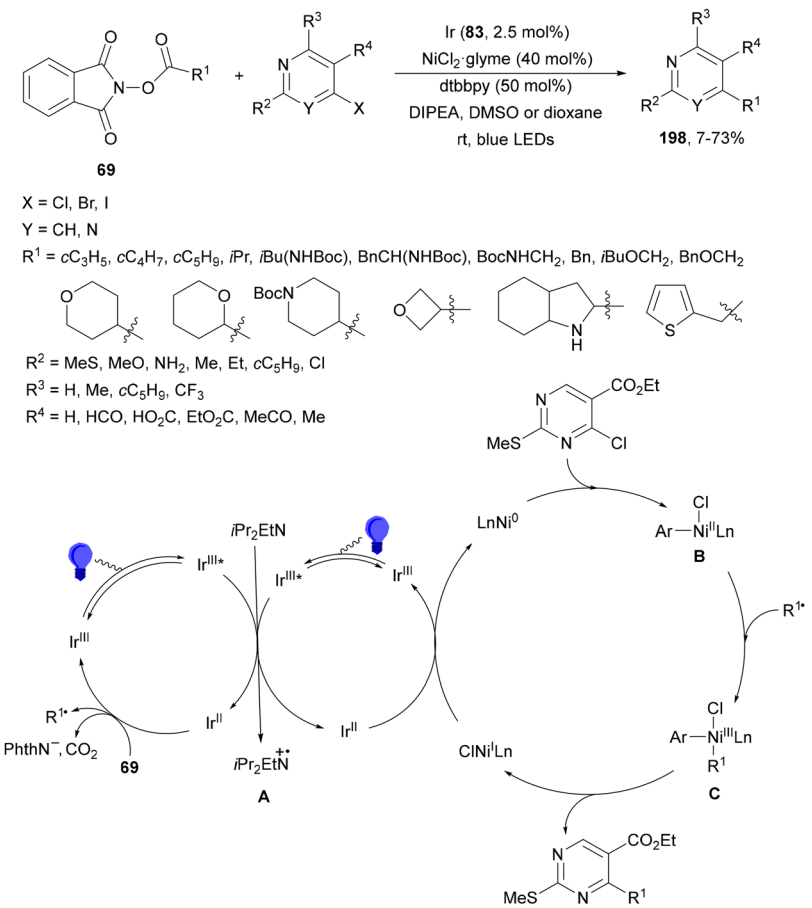
Scheme 72 Decarboxylative arylation of aliphatic carboxylic acids under Fe/Ni metallaphotocatalysis.

DMF under blue LED irradiation in the presence of air to provide heterodiarylmethanes **196** in moderate yields.

Noël and co-workers[166] employed heterogeneous semiconductor graphite carbon nitride (gCN) **120** as a PC instead of Ir complex **4** for decarboxylative cross-coupling of (hetero)aryl acetic acids **103** with aryl bromides to obtain (hetero)diarylmethanes **196**. In this case, 2.5 mg mL^{-1} of gCN, 5 mol% of $NiBr_2$·glyme and 4,4′-diphenylbipyridyl ligand (7.5 mol%) were used as catalysts. Moreover, phthalimide (1 equivalent)[151] was added in order to accelerate the rate of decarboxylative coupling, Cs_2CO_3 was employed as a base, and MeCN was employed as solvent at 43 °C under 390 nm irradiation. A wide range of products **196** were isolated in 23–96% yield and gCN could be easily recovered and reused multiple times without a loss in reactivity.

Inexpensive $FeCl_3$ as metallaphotoredox, $Ni(NO_3)_2·6H_2O$ and piperidine carboxamidine **197** ($^{4t\mathrm{Bu}}$PyCam$^{\mathrm{CN}}$) have been used in decarboxylative cross-coupling of a wide range of aliphatic carboxylic acids **1** with aryl iodides.[167] The corresponding products were obtained in the presence of DIPEA as a base and TBAI in dioxane at 390 nm under Ar at room temperature with modest to good yields (Scheme 72). In the proposed catalytic cycles, firstly Fe carboxylate complex **A** can be formed, which under irradiation undergoes an LMCT process[54,55] giving a carboxy radical and Fe(II) species **B**. Decarboxylation of the carboxy radical gives R•, which adds to LnNi(I)X (**C**) to form LnNi(II)RX intermediate **D**. This species **D** undergoes SET by **B** or **C** to give intermediate **E**. Reversible oxidative addition of ArI forms **F**, which by reductive elimination forms the product and regenerates **C**.

Redox-active esters[19–21] such as NHPI esters have been used as alkylating reagents in cross-coupling decarboxylative arylations under Ir/Ni metallaphotoredox conditions as an alternative to carboxylic acids. Aliphatic NHPI esters **69** reacted with pyrimidine and pyridine heterocyclic chlorides, bromides and iodides using Ir complex **83**, $NiCl_2$·glyme and dtbbpy as a ligand, DIPEA as a base in DMSO or dioxane at room temperature under blue LED irradiation (Scheme 73).[168] The corresponding alkylated heterocycles **198** were obtained with modest to good yields. In the plausible mechanism, three catalytic cycles were proposed, the radical generation cycle by an Ir(III) PC, the photoexcited Ir(III)* species is reduced by the Hünig's base to generate a *N*-centered radical cation **A** and Ir(II) species able to transform the NHPI ester to a C-centered radical, $PhthN^-$ and CO_2. The initial Ni(0) species undergoes oxidative addition to heteroaryl halides to form the Ni(II) complex **B**,

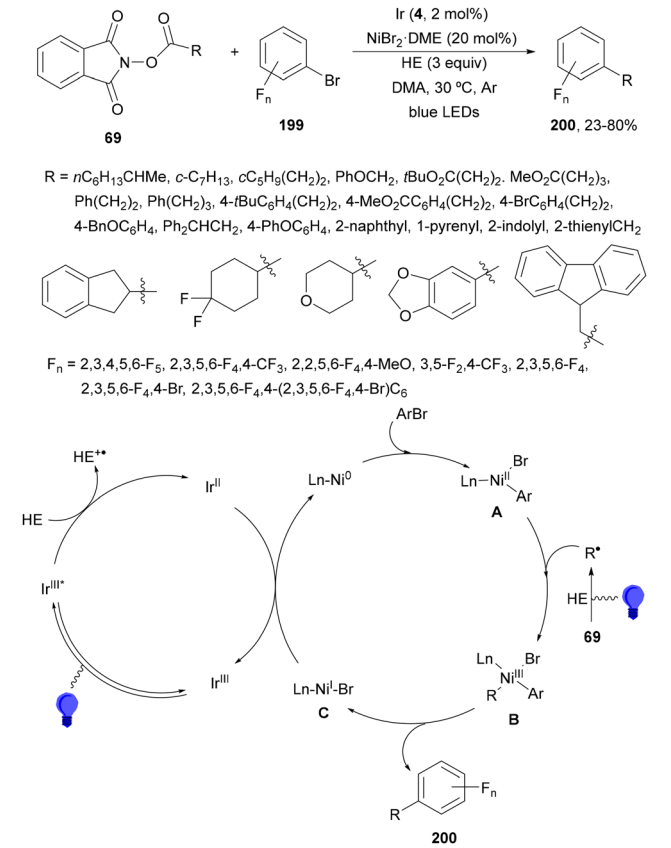


Scheme 73 Decarboxylative cross-coupling of NHPI esters **69** with heteroaryl halides under Ir/Ni metallaphotocatalysis.

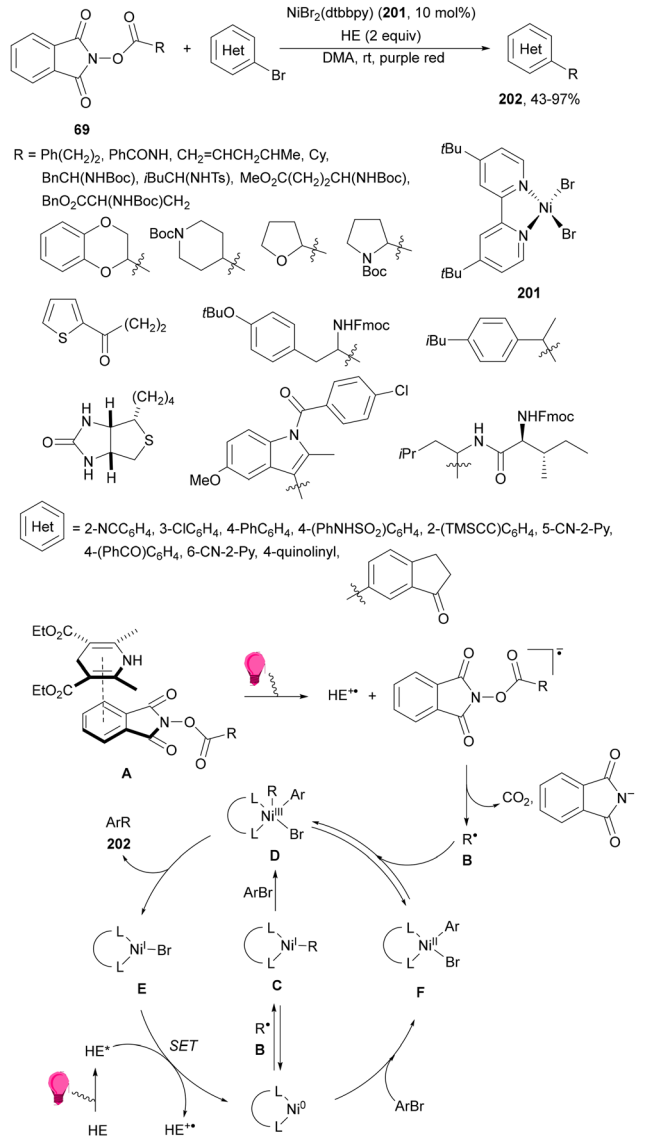
which reacts with R^1 to provide the Ni(III) intermediate **C**. Subsequent reductive elimination gives the alkylated heterocycle and Ni(I) species which is reduced by Ir(II) species.

Decarboxylative coupling of NHPI esters **69** with bromopolyfluoroarenes **199** has been carried out through the synergetic action of Hantzch ester (HE), Ir complex **4** as a PC and $NiBr_2$·DME in DMA at 30 °C under blue LED irradiation to obtain products **200** with good yield (Scheme 74).[169] This method was applied not only to primary and secondary alkyl carboxylic NHPI esters but also to unnatural AAs and drug molecules like isoxepac, indomethacin and chlorambucil. In the proposed mechanism, the NHPI ester reacts with HE under blue irradiation to give $R^{\bullet}$, which reacts with the Ni(II) species **A** to give the Ni(III) species **B**. Subsequently, reductive elimination provides the product and the Ni(I) species **C**. Final SET from Ir(II), obtained by reductive quenching of Ir(III) with HE, to Ni(I) species provides the Ni(0) species able to react by oxidative addition of ArBr to yield intermediate **A**.

Molander and co-workers[170] reported the arylation of NHPI esters **69** with (hetero)aryl bromides using HE and $NiBr_2$·dtbbby (**201**) for the decarboxylative cross-coupling reaction. Under light irradiation at 390 nm (purple light) the HE promoted the radical generation through electron donor–acceptor (EDA) complex activation of the NHPI ester. Primary, secondary, benzylic, α-oxy and α-amino acid carboxylic acid derived NHPI esters were transformed into the corresponding arylated products **202** in DMA as solvent with good yields (Scheme 75). Based on experiments, the irradiation of colored EDA complex **A** triggers an intra-coupling SET process generating a dihydropyridine radical cation and a phthalimide radical anion. Subsequently decarboxylation yields radical **B**, which by reaction with the Ni(0) species gives the Ni(I) intermediate **C**. Oxidative addition of aryl halide to **C** produces the Ni(III) species **D**, which undergoes reductive elimination to form the product the Ni(I) species **E**. This intermediate **E** gives by a SET process from excited HE* the Ni(0) species. A process involving oxidative addition of ArBr to Ni(0) to give intermediate **F** cannot be ruled out.



Scheme 74 Decarboxylative arylation of NHPI esters **69** with bromopolyfluoroarenes **199** under Ir/Ni metallaphotocatalysis.



Scheme 75 Decarboxylative cross-coupling of NHPI esters **69** with (hetero)aryl bromides under Hantzsch ester and $NiBr_2$(dtbbpy) **201** photocatalysis.

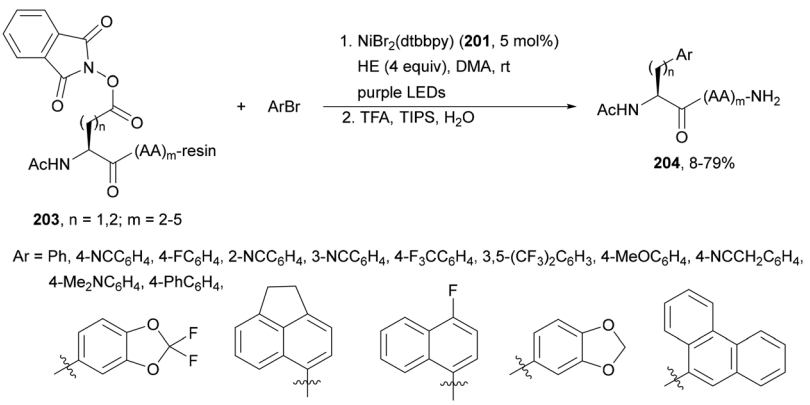
Peptides on a solid phase (Rink amide resin) bearing a NHPI ester derived from aspartic or glutamic acid **203** have been arylated under the same reaction conditions than those from Molander's group.[170] By avoiding multistep solution-phase AA synthesis, this greener alternative was applicable to differently supported di-, tri-, tetra- and pentapeptides, which after cross-coupling decarboxylation and hydrolysis provided free C-terminus peptides **204** (Scheme 76).[171] These peptides were obtained in good yields considering that the process started from the allyl ester resin-linked peptide.

Rovis and co-workers[172] recently reported a low-energy orange-light absorbing Ir(III) photocatalyst **205**, which can be used in Ir/Ni metallaphotoredox catalysis in both carboxylic acids and NHPI esters. This PC **205** showed complementary modes of dual oxidative and reductive decarboxylative arylation. Aliphatic α-amino carboxylic acids react with aryl bromides to furnish cross-coupled products **202** with good yields using **205**/$NiBr_2$(dtbbpy) **201** as a catalyst and BTMG as a base in DMF at 55 °C (Scheme 77a). In the case of carboxylic acids without the α-heteroatom the reaction failed. However, NHPI esters **69** derived from secondary and tertiary carboxylic acids could be arylated even generating *in situ* these esters with a coupling reagent. In the presence of DIPEA as a base this cross-coupling gave products **202** in very good yields (Scheme 77b). The proposed catalytic cycles, oxidative and reductive pathways, are depicted in Scheme 77. The oxidative activation of the carboxylic acid to carboxy radical followed by decarboxylation gives the C-centered radical $R^{\bullet}$. Subsequent oxidative addition of aryl bromide to Ni(II) and reaction with the radical gives the Ni(III) complex, which by reductive elimination affords the product **202** and a Ni(I) species. In the reductive pathway DIPEA acts as a sacrificial reductant to quench Ir(III)* after irradiation. The resulting Ir(II) species reduces the NHPI ester to liberate the alkyl radical. The Ni cycle proceeds as before for the oxidative pathway.

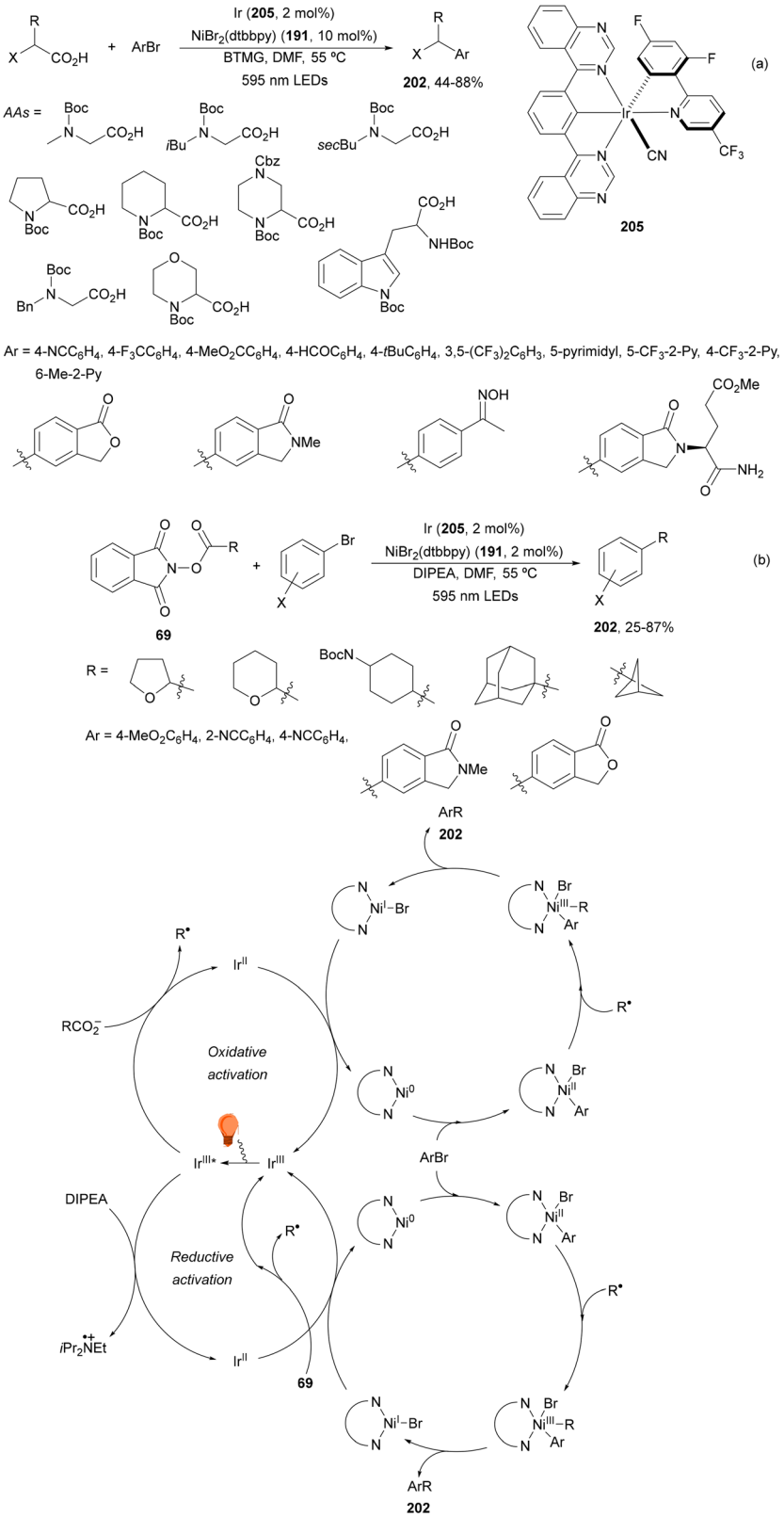
1,4-Dialkylbenzene and derivatives **207** can be prepared from 1,4-diiodobenzene analogues **206** by decarboxylative arylation photoredox cross-coupling with NHPI esters **69** under mild reaction conditions (Scheme 78a).[173] Zhang and co-workers employed HE as a donor and *in situ* prepared Ni(II) complex **201**, $NaHCO_3$ as a base and NHP as solvent at 30 °C under 390–395 nm purple LED irradiation. Products **207** were obtained in moderate yields and 3,6-dialkylcarbazole analogues **209**, useful optoelectronic and medicinal materials, were prepared from 3,6-diiodocarbazoles **208** in modest yields (Scheme 78b).

Arylation of carbohydrates can be carried out by cross-coupling of DHP-derived esters **37** with aryl bromides under 4CzIPN (**25**) and Ni(II) dual photocatalysis. Diao and co-workers[174,175] prepared aryl *C*-glycosides **211** using Na_2CO_3 as a base in dioxane at 84 °C under blue LED irradiation with in general good yields and moderate to high diastereoselectivity (Scheme 79). Furanoses and pyranoses were transformed into dihydropyridine derived esters **37** by reaction with DHP acid **210** using diisopropyl carbodiimide (DIC). In the proposed mechanism oxidation of **37** with 4CzIPN* followed by deprotonation affords intermediate **A**, which by subsequent fragmentation gives radical **B** and HE. Upon ejection of CO_2, **B** was transformed into glycoxyl radical **C**, which enters in the Ni catalytic cycle Ni(0) → Ni(I) → Ni(II) → Ni(III) to give the cross-coupling product with the aryl bromide. D-Mannofuranose derivatives gave mainly the α-anomeric glycosides. D-Ribofuranoses with common protecting groups, such as benzyl, silyl and benzoyl, gave mainly the β-anomers except D-galactofuranose and D-arabinofuranose, which favored the α-anomer due to the dominating effect of the C2 substituent. 2-Deoxy-D-ribofuranoses gave mixtures of α and β anomers. Pyranoses provided mainly α-selectivity due to the kinetic anomeric effect.

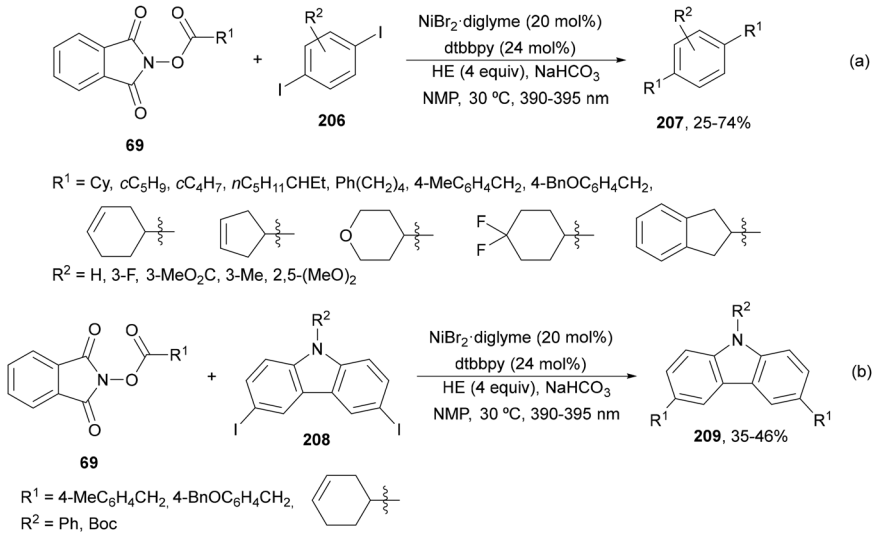
Wang and co-workers[176] reported the arylation of α-AAs **179** and α-oxy carboxylic acids **65** with aryl nitriles **63** using only 3-aminofluorene-2,4-dicarbonitrile (AFDC, **212**) as acceptor–donor PC like 4CzIPN (**25**). Upon light excitation, the photoexcited state of these compounds showed both strong oxidative and reductive capabilities even higher than Ir complexes and organic dyes. This arylation process was performed in the absence of Ni(II) complexes using CsF in DMSO at room temperature under 390–395 nm LED irradiation to afford arylated products **180** and **213**, respectively, with good yields (Scheme 80). In the proposed mechanism, the excited PC* oxidizes the α-AA to



Scheme 76 Decarboxylative arylation of supported peptides **203** bearing a NHPI ester in the C-terminus under HE/$NiBr_2$(dtbbpy) (**201**) photocatalysis.



Scheme 77 Decarboxylative arylation of carboxylic acids (a) and NHPI esters (**69**) (b) under Ir (**205**)/Ni (**201**) low-energy-light photocatalysis.



Scheme 78 Decarboxylative cross-coupling of diiodoarenes **206** (a) and **208** (b) with NHPI esters (**69**) under HE/Ni **201** photocatalysis.

form the carboxy radical, which after decarboxylation generates the α-amino radical intermediate **A**. The reduced $PC^{-\bullet}$ reacts with the aryl nitrile to give by a SET process radical anion **B** followed by regeneration of the PC. Radical–radical coupling of **A** with **B** and subsequent aromatization with release of cyanide deliver the benzylic amine **180**.

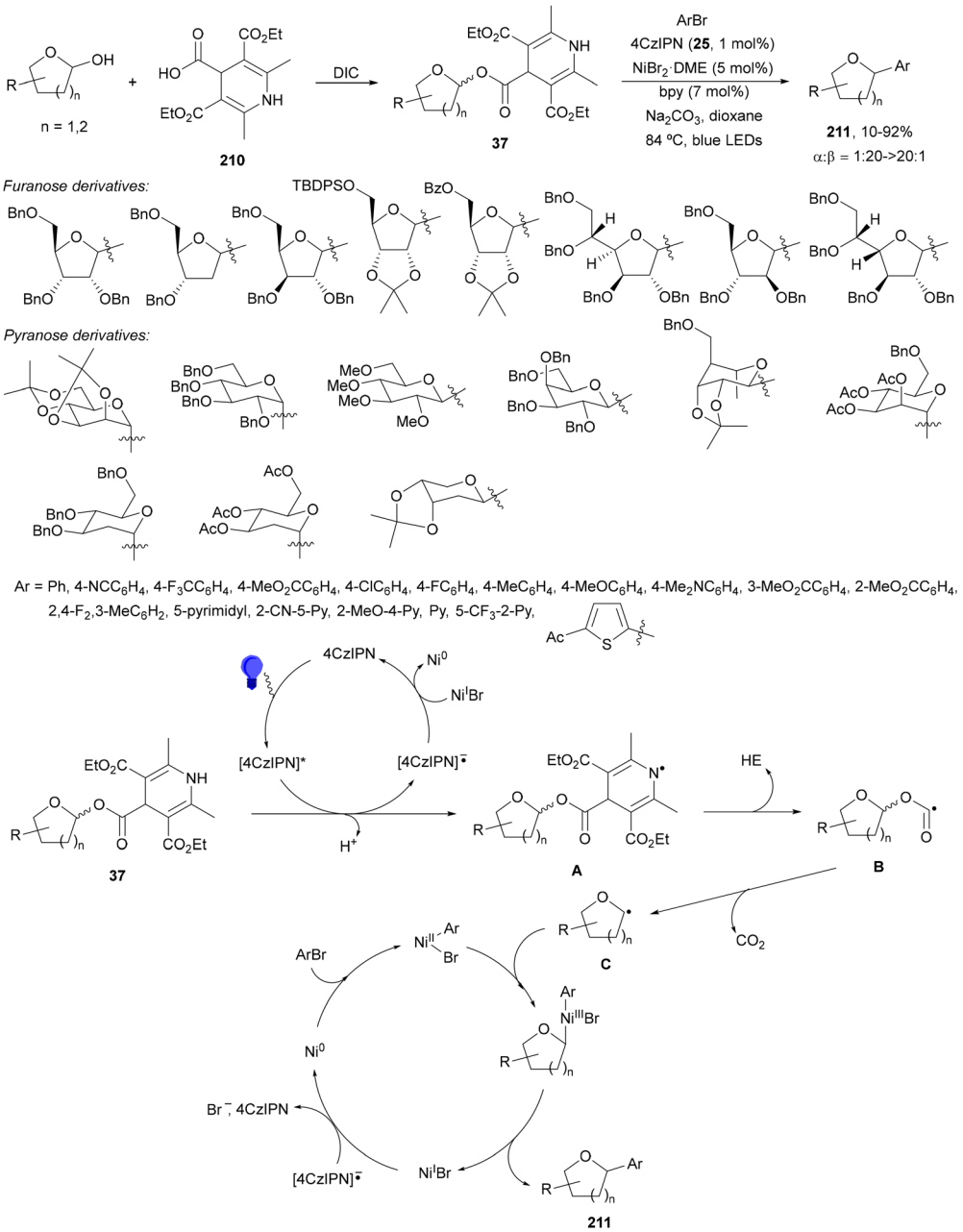
Decarboxylative cross-coupling of aryl halides with alkyl carboxylic acids under metallaphotoredox catalysis has become a general method for the construction of $C(sp^2)$–$C(sp^3)$ bonds. Ir(III) complexes as photocatalysts and Ni complexes converted into Ni(0) species by SET events are able to undergo oxidative addition with aryl halides. The resulting Ni-aryl species undergoes oxidative radical capture, from the decarboxylation of the carboxylate ion by a photoexcited Ir(III) complex, resulting in a Ni(III))–aryl–alkyl complex, which undergoes reductive elimination to give the coupled product. This methodology has been extensively applied to the synthesis of benzylamines from α-AAs and DNA-encoded libraries, α-fluorinated benzylic alkanes from α-fluoro carboxylic acids and heterodiarylmethanes from aryl acetic acids. NHPI esters can be used alternatively for the generation of alkyl radicals and have been employed in the presence of stoichiometric amounts of Hantzsch ester or under Ir(III)/Ni(II) metallaphotoredox catalysis under mild reaction conditions. Several processes have been implemented in continuous flow reactors. In addition it has been applied to the synthesis of pharmaceuticals such as GSK-3β inhibitors, iptacopan (LNPO23), arylated peptides and arylated glycosides. These reaction conditions are compatible with enantioselective processes using chiral bisoxazoline ligands for Ni(II) complexes.

2.6. Alkylation reactions

Decarboxylative cross-coupling of carboxylic acids and NHPI esters with alkyl electrophiles under photoredox conditions is a direct method for $C(sp^3)$–$C(sp^3)$ carbon bond formation. MacMillan and co-workers reported in 2016[177] the decarboxylative alkylation of aliphatic carboxylic acids with alkyl halides by merging photoredox and Ni catalysis. As shown in Section 2.4 for this metallaphotoredox catalysis, the first SET process transformed the carboxylic acid into CO_2 and the alkyl radical **A** by excited Ir(III)* and the other SET process generated a Ni(0) species. This Ni(0) complex reacts with the radical **A** to produce an alkyl–Ni(I) intermediate **B**, which by subsequent oxidative addition with alkyl halide forms the Ni(III) species **C**. Final reductive elimination creates a $C(sp^3)$–$C(sp^3)$ bond and the Ni(I) species **D**, which after a SET process regenerates Ni(0) species (Scheme 81).

Gutierrez, Koh and co-workers[162] employed α-fluoro carboxylic acids **190** in decarboxylative cross-coupling reactions with aryl halides (Scheme 69) and also alkyl chlorides. Under the same reaction conditions and in the presence of KOTf, the corresponding fluorinated products **214** were obtained in up to 60% yield and moderate diastereoselectivity (Scheme 82).

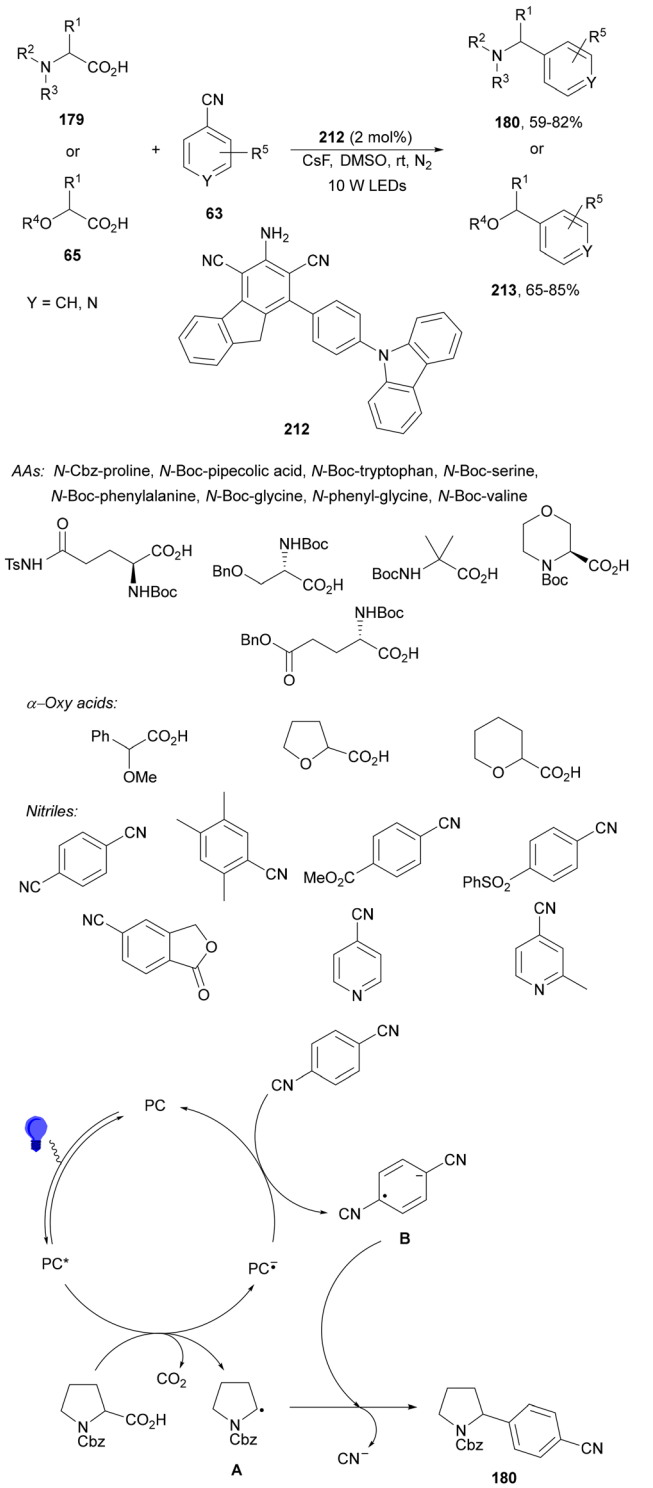
C–Alkyl glycosides are particularly important for the synthesis of glycopeptide analogues and drugs.[178] Glycosyl carboxylic acids **170** have been used as sources of glycosyl radicals by Ni/photoredox decarboxylative cross-coupling with aryl bromides using 4CzIPN (**25**) as a PC (Scheme 63).[146] Recently, *C*-alkyl glycosides **216** have been prepared by Ir/Ni metallaphotocatalytic decarboxylative cross-coupling of acids **170** with alkyl bromides (Scheme 83).[179] In this case, $Ru(bpy)_2Cl_2$ or 4CzIPN (**25**) failed as photocatalysts. However, in the presence of Ir (**4**), $NiCl_2$·DME and ligand dMebpy (**215**), K_2CO_3 as a base in aqueous MeCN under blue LED irradiation, *C*-glycosides **216** were obtained with moderate yields mainly as β-diastereomers. A wide variety of alkyl bromides were employed including those bearing drug molecules or natural product fragments. On the other hand, only uronic acid forms of furanoses were suitable as substrates for this cross-coupling reaction. However, other furanosyl and pyranosyl carboxylic acids failed. Under gram-scale conditions product **216a** was obtained in 42% yield



Scheme 79 Decarboxylative arylation of DHP-derived glycosyl esters **37** under 4CzIPN (**25**)/$NiBr_2$ photocatalysis.

instead of 63% yield for the millimole scale. In the proposed catalytic cycle, based on DFT calculations, Ni(0) species reacts firstly with alkyl bromide to give intermediate **A**, which after reaction with anomeric radical generates Ni(III) species **B**.

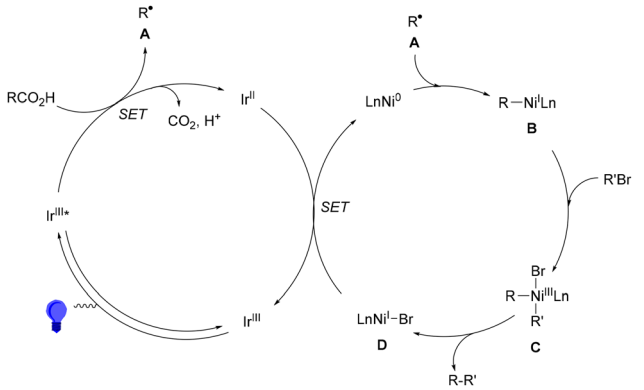
Asymmetric photoredox cross-coupling has been studied by Jiang and co-workers[180] by enantioconvergent[140] substitution of α-bromo ketones **217** with *N*-aryl α-AAs. Single-electron reductive debromination of racemic α-bromo ketones generates achiral alkyl radicals, which participate in asymmetric $C(sp^3)$–$C(sp^3)$ bonds forming cross-coupling with α-amino radicals (Scheme 84a). This process took place under metal-free conditions using the dicyanopyrazine-derived chromophore (**92**, DPZ) as a PC and SPINOL **218** as CPA. Similar reaction conditions were used by the same group[104] in the enantioselective decarboxylative reaction of *N*-aryl glycines with 1,2-dicarbonyl compounds **90** and to isatins **91** (Scheme 33). Products **219** were obtained under blue LEDs irradiation at 0 °C in 1,2-dimethoxyethane with good yields and up to 97% ee. This enantioconvergent cross-coupling was applied to α-bromo-α-fluorophenones **220** to obtain fluorinated β-amino phenones **221** in up to 80% yield and up to 94% ee (Scheme 84b). Tertiary α-bromo ketones **222** were transformed into β-amino phenones **224** using SPINOL CPA **93b**, **145** or **223** as chiral catalysts (Scheme 84c). In Scheme 33, the role of the CPA as a



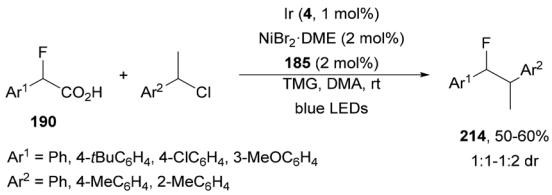
Scheme 80 Decarboxylative arylation of α-AAs and α-alkoxy acids with aryl nitriles under 3-amino-fluorene-2,4-dicarbonitrile **212** photocatalysis.

bifunctional H-bonding catalyst in the cross-coupling of radicals **A** and **B** is depicted.

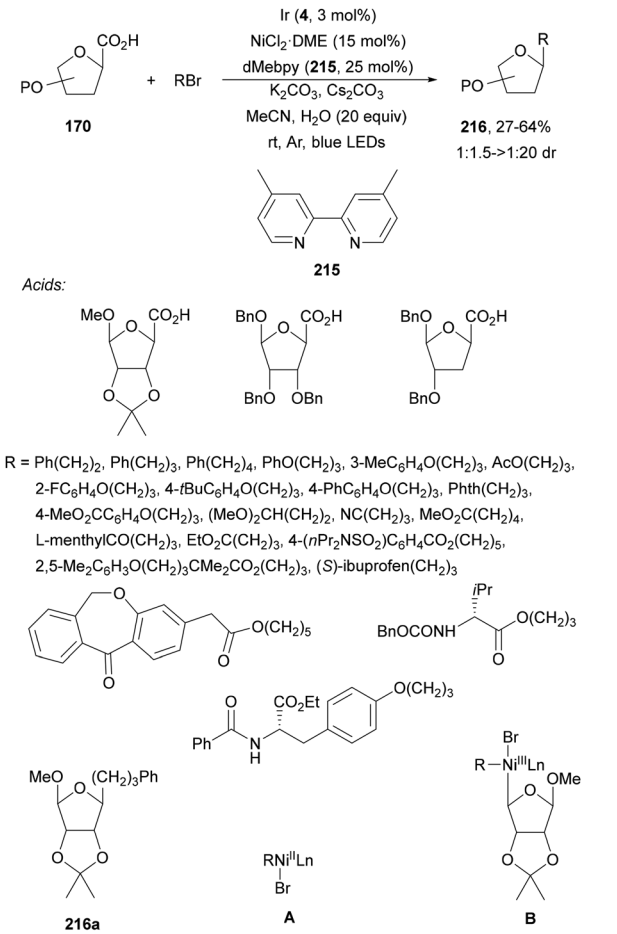
Zhao, Jiang and co-workers[181] applied the enantioconvergent[140] substitution with *N*-aryl glycines to 3-chloroindoles under visible light irradiation. A cooperative catalysis using DPZ



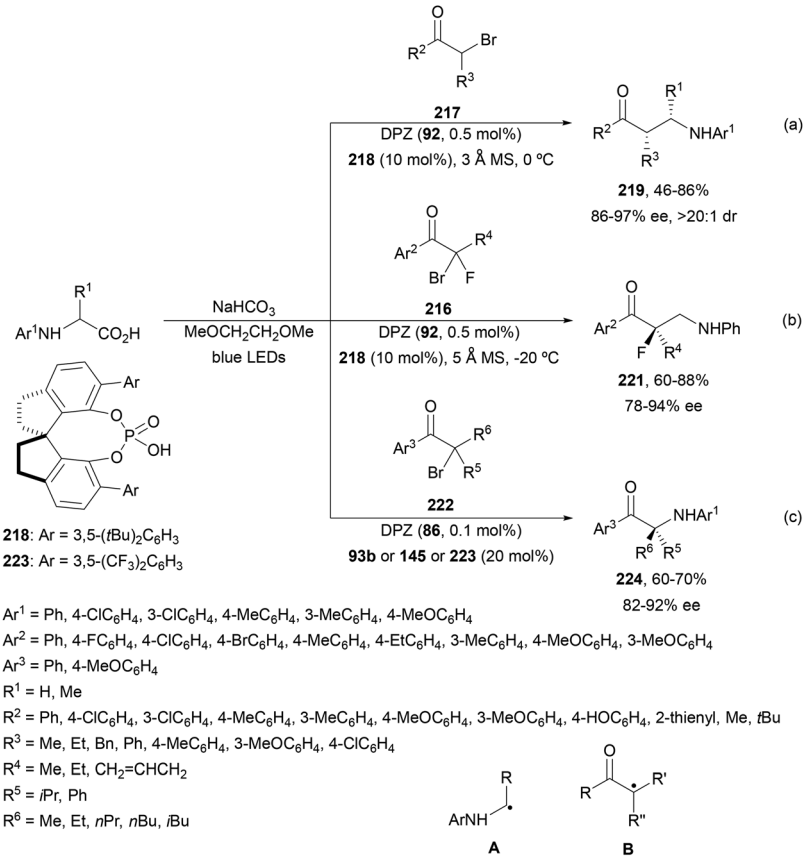
Scheme 81 Proposed mechanism for the metallaphotoredox cross-coupling of carboxylic acids with alkyl bromides.



Scheme 82 Decarboxylative alkylation of α-fluoro carboxylic acids **190** under Ir (**4**)/$NiBr_2$·**185** dual catalysis.



Scheme 83 Decarboxylative alkylation of glycosyl carboxylic acids **170** under Ir/Ni dual photocatalysis.



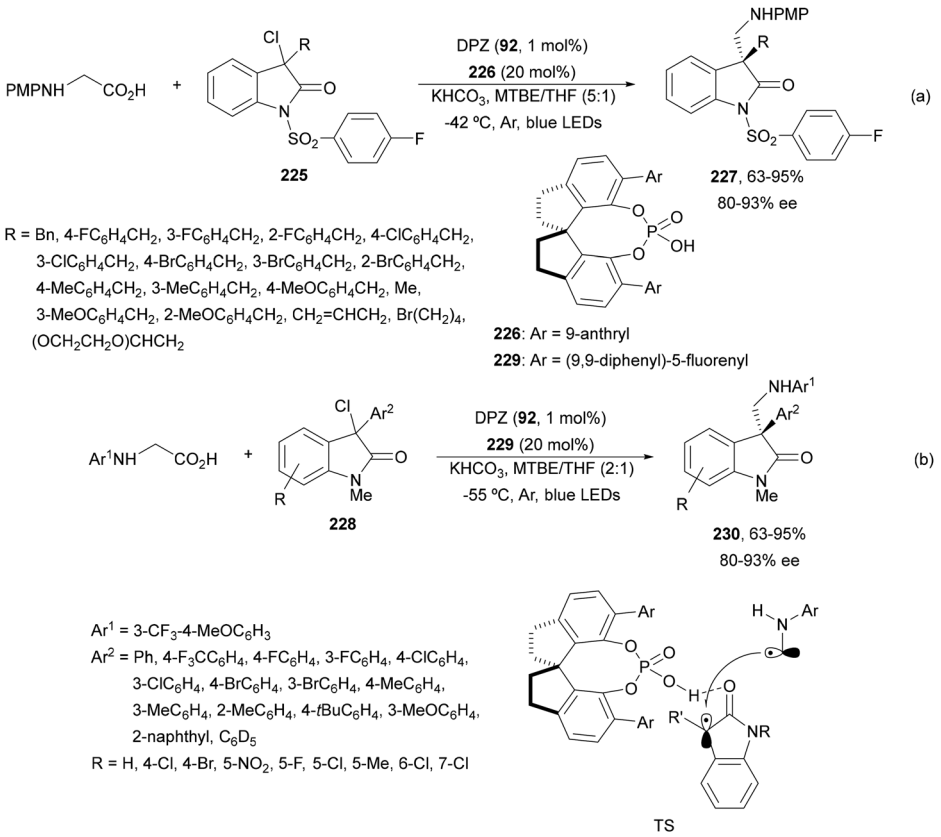
Scheme 84 Enantioconvergent decarboxylative alkylation of α-bromo ketones **217** (a), **220** (b) and **222** (c) with *N*-aryl AAs under DPZ (**92**)/SPINOL-CPA (**93b**, **145**, **218**, and **223**) photocatalysis.

(**92**) and SPINOL (**226**) as chiral Brønsted acid was employed for this cross-coupling reaction between 3-chlorooxindoles **225** and *N*-aryl glycines working in a 5 : 1 mixture of MTBE/THF at −42 °C under Ar to give chiral 3-aminomethylene-3-alkyl oxindoles **227** in up to 95% yield and up to 93% ee (Scheme 85a). When 3-aryl-substituted oxindoles **228** were allowed to react with *N*-aryl glycines in the presence of DPZ (**92**) as a photoredox and SPINOL-CPA **229** as a chiral Brønsted acid in a 2 : 1 mixture of MTBE/THF at −55 °C under Ar, the corresponding 3-aminomethylene-3-aryl oxindoles **230** were obtained in up to 97% yield and up to 95% ee (Scheme 85b). A ternary TS for the formation of the C–C bond has been proposed.

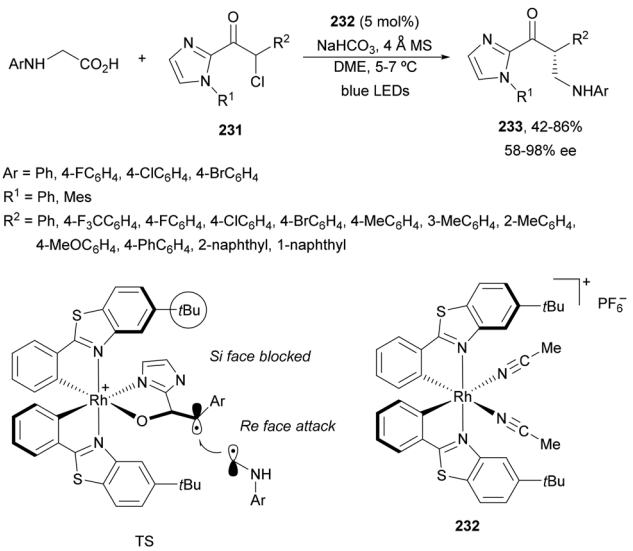
Meggers and co-workers[182] reported an enantioconvergent[140] cross-coupling of α-chloro imidazol-2-yl ketones **231** with *N*-aryl glycines photocatalyzed by chiral bis-cyclometalated chiral-at-Rh **232** in the presence of 4 Å MS, $NaHCO_3$ as a base in DME at 5–7 °C to provide products **233** in up to 80% yield and up to 98% ee (Scheme 86). In the proposed TS, the complex formed by *N*,*O*-bidentate coordination of 2-acyl imidazole substrate to Rh catalyst gives the corresponding radical, which reacted with the aminomethyl radical to give the product.

Decarboxylative trifluoromethylation of aliphatic carboxylic acids has been achieved by MacMillan and co-workers[183] by combination of Ir/Cu dual photocatalysis. Togni's reagent **234** reacted with primary, secondary and tertiary carboxylic acids in the presence of Ir complex **4**, CuCN, bathophenanthroline (Bphen) as a ligand, BTMG as a base in aqueous EtOAc at room temperature under blue LED irradiation to furnish alkyl-CF_3 products **235** in moderate to good yields (Scheme 87). According to experimental studies, formation of $CuCF_3$ was not detected and a copper-mediated decarboxylation is likely operative. Therefore, the carboxylate ion would ligate the Cu(II) catalyst and by a SET from intermediate **A** to Ir(III)* would deliver the Cu(III) carboxylate **B**. The dissociated form of **B** gives a carboxy radical and Cu(III) complex **C**. Extrusion of CO_2 generates an alkyl radical and Cu(II) **D**, which recombines to form the Cu(III) species **E**. A second SET process between **E** and the reduced Ir(II) affords an alkylcopper(II) species **F**. Subsequent reaction of **F** with Togni's reagent delivers an alkyl-CF_3 product **229** *via* reductive elimination and complex **G**, which undergoes ligand exchange with the acid to give intermediate **A**. Several medicinal agents and natural products were decarboxylative trifluoromethylated by this protocol (Scheme 87).

Decarboxylative cross-coupling of alcohols and carboxylic acids through dual combination of N-heterocyclic carbenes (NHC)-mediated deoxygenation and hypervalent iodine-mediated decarboxylation has been achieved by Sakai and MacMillan[184] to form $C(sp^3)$–$C(sp^3)$ bonds. Firstly, carboxylic acid was premixed with



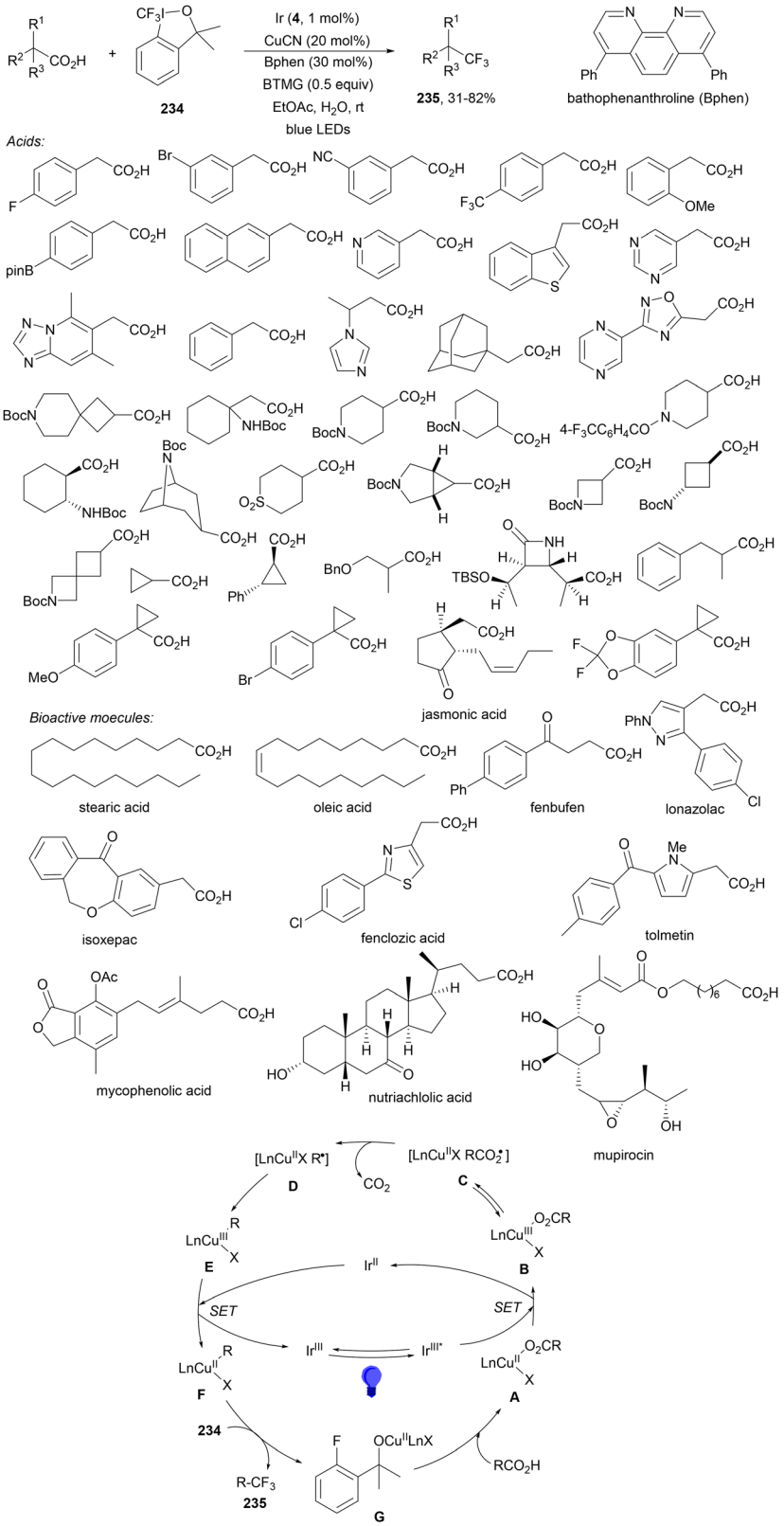
Scheme 85 Enantioconvergent decarboxylative alkylation of 3-chloro substituted oxindoles **225** (a) and **228** (b) with *N*-aryl glycines under DPZ (**92**)/SPINOL-CPAs (**226** and **229**) photocatalysis.



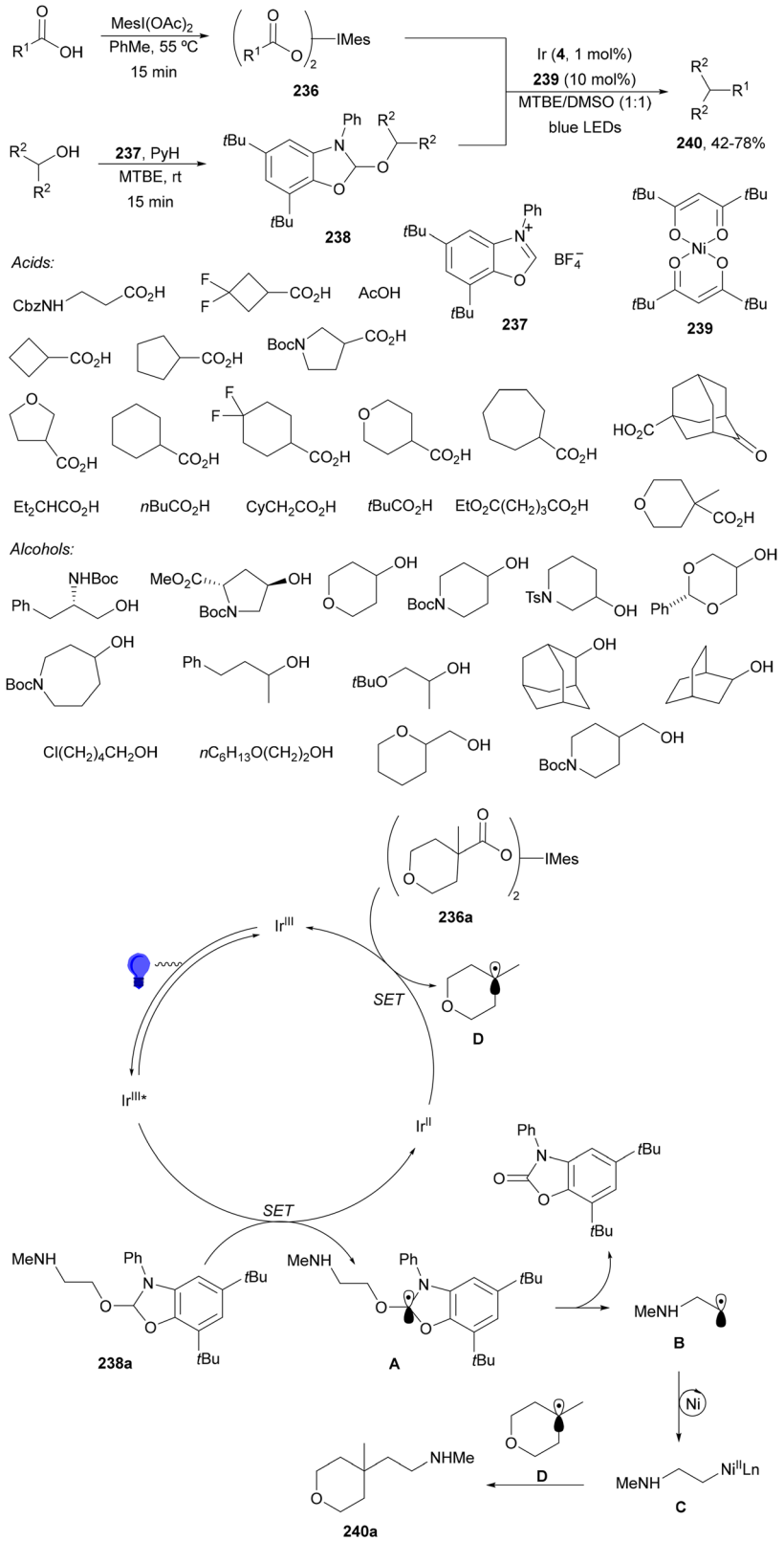
Scheme 86 Enantioconvergent decarboxylative alkylation of α-chloro imidazolyl ketones **231** with *N*-aryl glycines under chiral Rh complex **232** photocatalysis.

iodomesitylene diacetate to afford the activated iodonium dicarboxylate **236**, which was used without additional purification. The alcohol was allowed to react with benzoxazolinium salt **237** to form the activated NHC–alcohol adduct **238** under basic conditions. Visible light irradiation of **230**/**232**, using Ir complex **4** and the Ni complex **239** as catalysts gave coupled products **240** (Scheme 88). These alkyl-alkyl cross-coupled products include highly congested quaternary carbon centers. This methodology has been applied to functionalization of D-glucopyranose, isoandrosterone, cedrol and gemfibrozil. In the proposed catalytic cycle, Ir(III)* oxidized adduct **238a** to give intermediate **A**, which after β-scission liberated the alkyl radical **B**, which was trapped by Ni catalyst **239** to form the Ni-alkyl intermediate **C**. Concurrently, reduction of the iodonium dicarboxylate **236a** by Ir(II) gives radical **D** after CO_2 extrusion and MesI, and regenerates the Ir(III) catalyst. Finally, Ni-catalyzed bond formation of radicals **B** and **C** gives product **240a** and regenerates the Ni(II) catalyst.

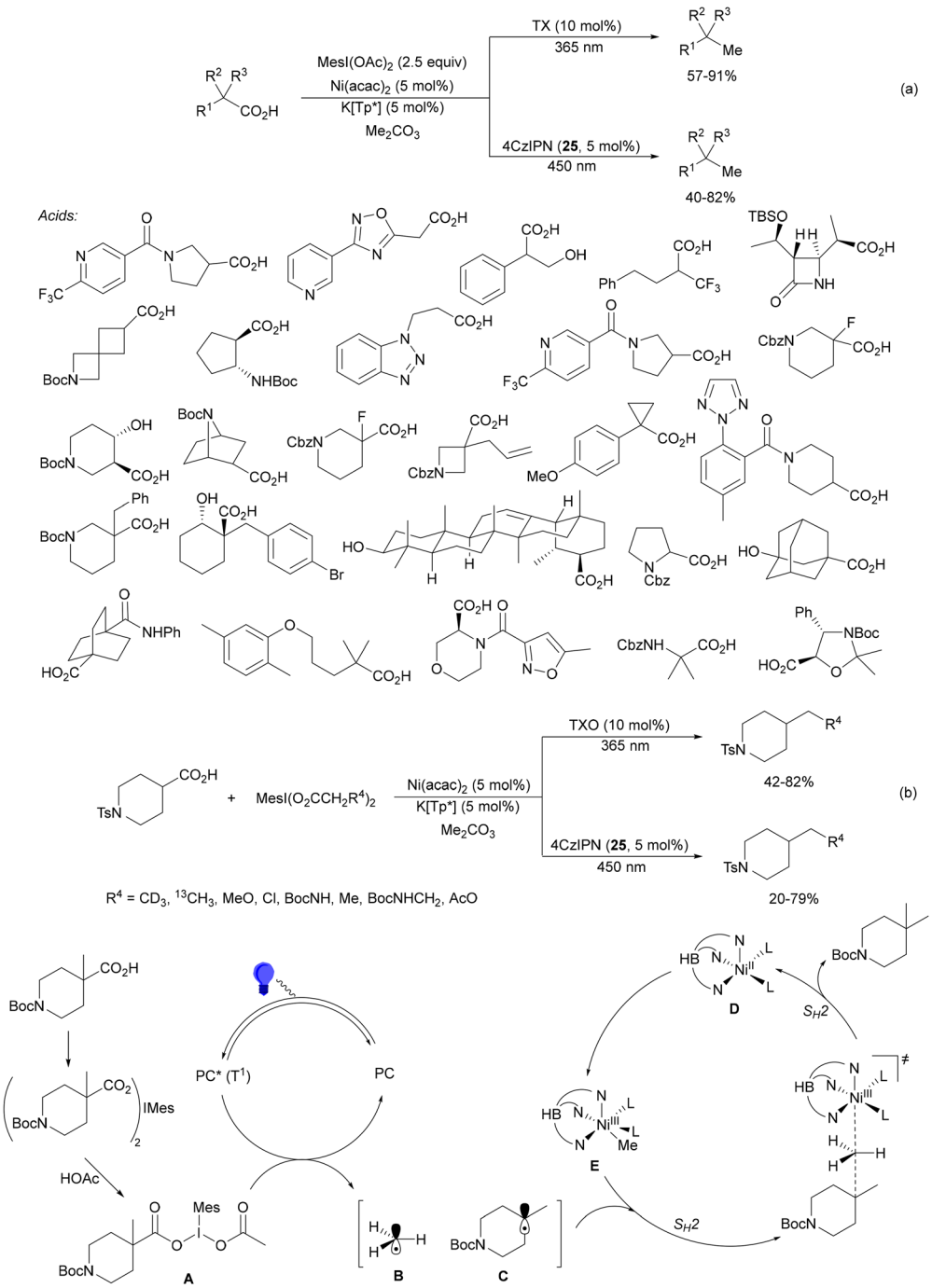
Double decarboxylative cross-coupling of aliphatic carboxylic acids *via* a complementary sequence involves free radical generation, radical sorting by selective binding to Ni(II) and bimolecular homolytic substitution (S_H2) at a Ni(III) alkyl complex. MacMillan and co-workers[185] have achieved this elusive transformation by reaction of different primary, secondary and tertiary acids with $MesI(OAc)_2$ to form *in situ* iodonium dicarboxylate **236**, $Ni(acac)_2$, potassium tri-(2,5-dimethyl-1-pyrazolyl) borohydride (K[Tp*]) as the ligand under 365 nm UV irradiation with thioxanthone (TX) as a sensitizer (Scheme 89a). A second protocol



Scheme 87 Decarboxylative trifluoromethylation of aliphatic carboxylic acids with Togni's reagent **234** under dual Ir/Cu photocatalysis.



Scheme 88 Decarboxylative cross-coupling of alcohols and carboxylic acids under Ir/Ni photocatalysis.



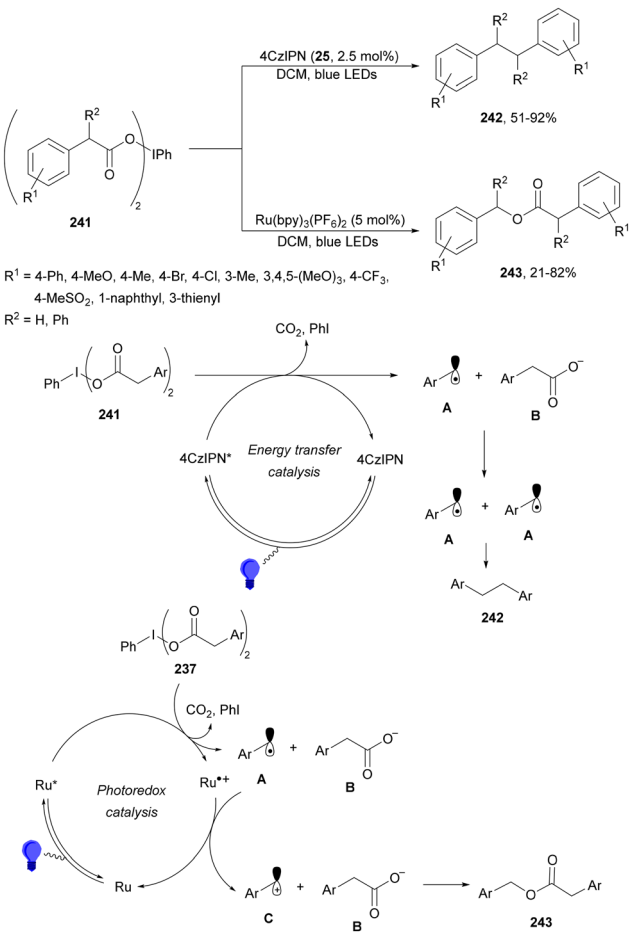
Scheme 89 Double decarboxylative cross-coupling of aliphatic acids (a, b) under TX or 4CzIPN (**25**) and Ni(acac)$_2$ photocatalysis.

was set up for substrates which decomposed upon UV irradiation. For these reaction conditions, 450 nm light with 4CzIPN (**25**) as a PC was used. Apart from acetic acid other preactivated small alkyl carboxylic acids as iodomesitylene dicarboxylates were also employed to provide cross-coupled products with *N*-tosyl-4-pipecolic acid in 44–82% yields (Scheme 89b). In the photosensitization catalytic cycle, after irradiation with UV or visible light of TX or 4CzIPN, respectively, a long-lived, high energy triplet state is formed (2.8 or 2.6 eV, respectively) able to transfer energy to the hypervalent iodine(III) species **A** with a mixture of both carboxylate ions. After I–O homolysis and extrusion of CO_2 two alkyl radicals **B** and **C** are formed. At this point, Ni(II) complex **D** would capture the less substituted radical **B** generating Ni(III) alkyl complex **E**, which undergoes S_H2 homolytic substitution with radical **C** to yield the cross-coupled product and regenerates the Ni(II) catalyst **D**.

Murakami and co-workers[186] recently performed a decarboxylative homocoupling of iodonium dicarboxylates **241**, prepared

from aryl acetic acids and phenyliodine(III) diacetate (PIDA), using 4CzIPN (**25**) as a PC under blue LED irradiation (Scheme 90). This process works as an energy transfer pathway to form 1,2-diarylethanes **242** with good yields. This radical homocoupling occurs thanks to the high reduction ability of 4CzIPN (**25**), giving two benzyl radicals **A** by decarboxylation, which reacted to give products **242**. On the other hand, when $[Ru(bpy)_3]2PF_6$ was used as a PC, esters **243** were obtained through a SET pathway, which generated firstly a carboxylate ion **B** and a benzyl radical **A**. Subsequent single-electron oxidation of **A** gives cation **C**, which reacts with carboxylate ion **B** forming esters **243**.

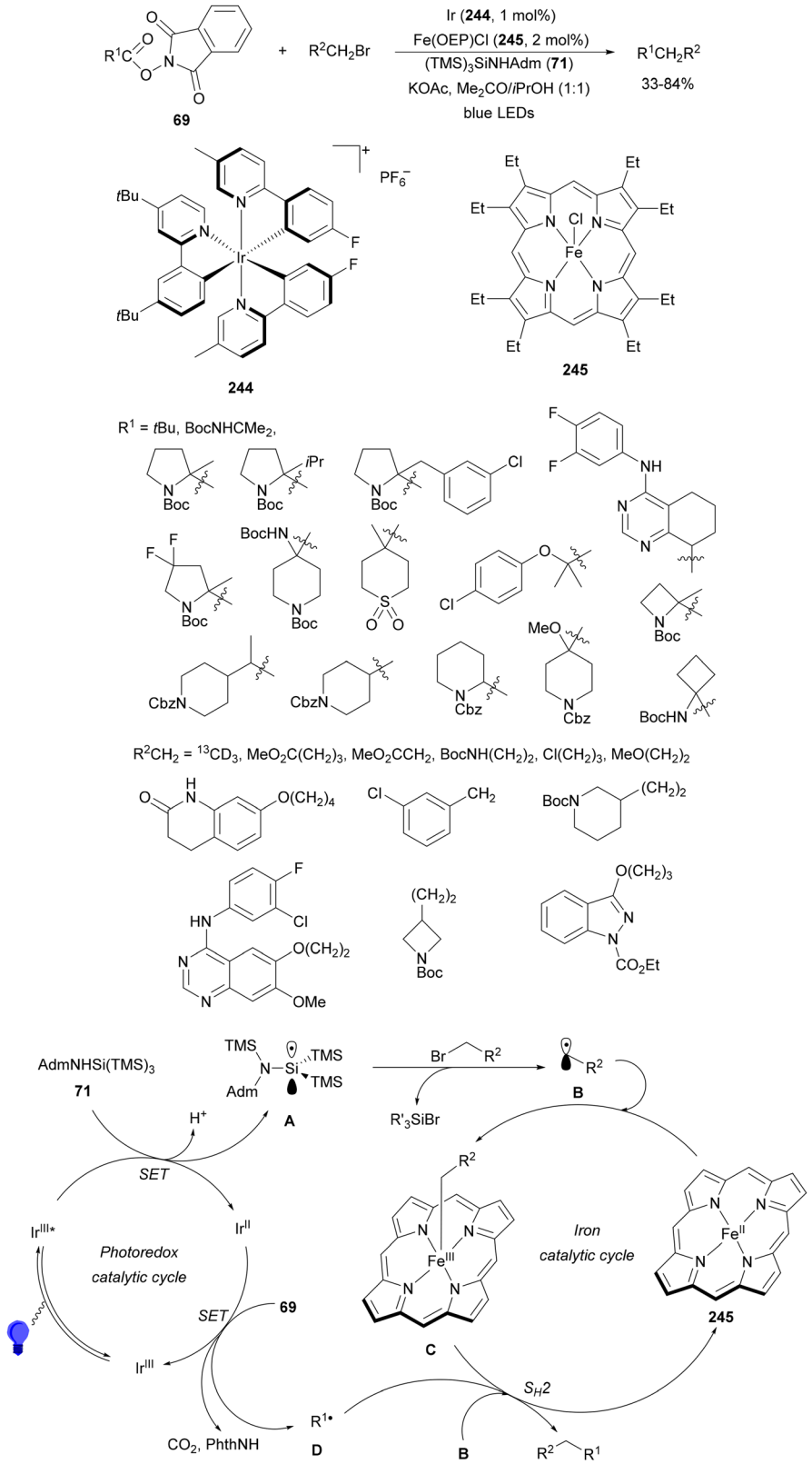
Redox active tertiary NHPI esters **69** have been coupled with alkyl bromides *via* iron porphyrin catalysis. This biomimetic $C(sp^3)$–$C(sp^3)$ bond formation was reported by MacMillan and co-workers[187] *via* dual photoredox and iron catalysis. The reaction of esters **69** derived from AAs and α-oxy acids and primary alkyl bromides was performed with Ir complex **244** as a PC, Fe(OEP)Cl (**245**), amino silane **71**, KOAc as a base in acetone/iPrOH (1 : 1) under blue LED irradiation to furnish cross-coupled products with good yields (Scheme 91). In the proposed mechanism, after irradiation of **244** this oxidizing Ir complex undergoes SET with the amino silane **71** to give a reduced Ir(II) complex. The oxidized silane reagent generates a silyl radical **A**, which abstracts a bromine atom from the alkyl bromide to give a primary alkyl radical **B**. This radical is captured by Fe(II) porphyrin **245** to furnish intermediate **C**. The Ir(II) complex reduces the NHPI ester *via* a SET to provide the tertiary radical **D** upon extrusion of CO_2 and phthalimide. Intermediate **C** and radical **D** led to an S_H2 reaction, giving the cross-coupled product and regenerating the Fe(II) catalyst.



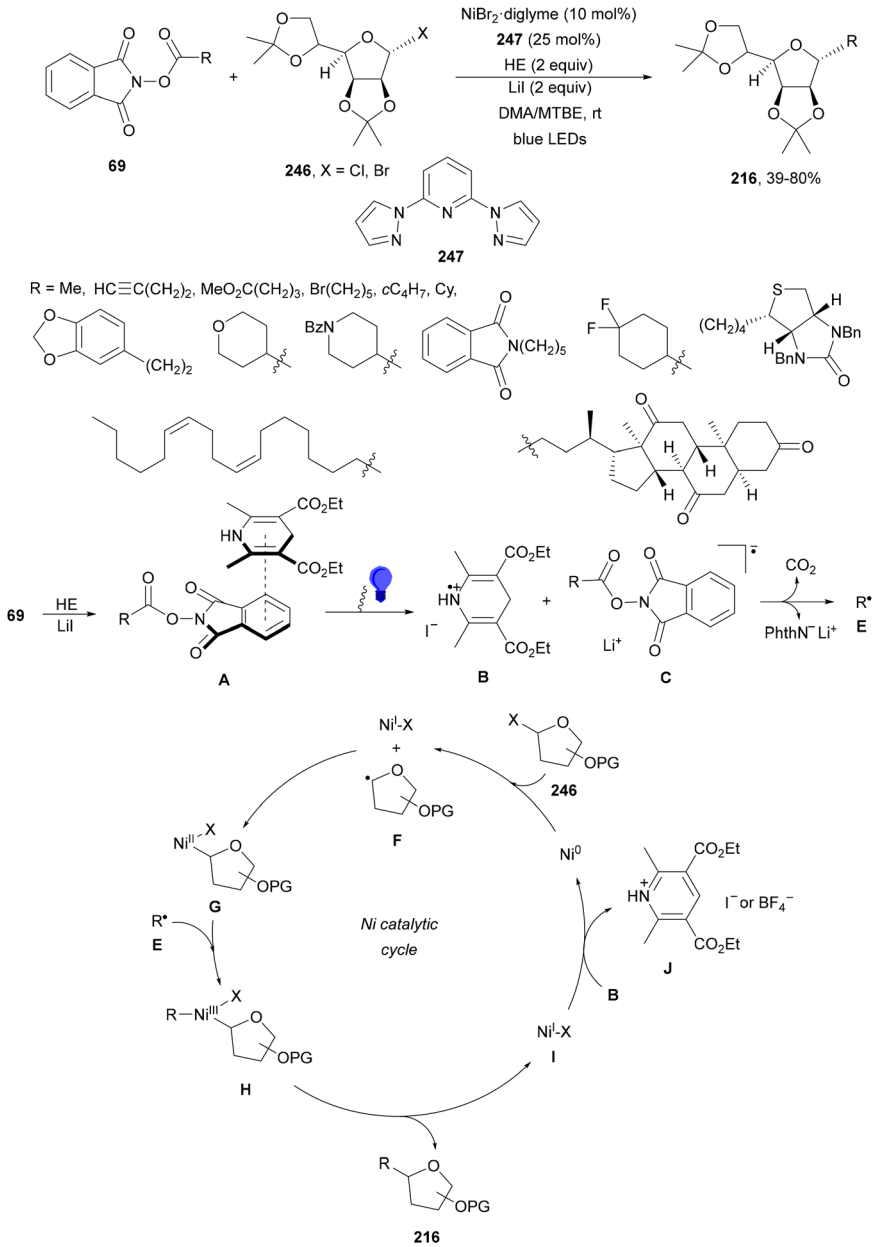
Scheme 90 Decarboxylative homocoupling of iodonium dicarboxylates **241** under 4CzIPN (**25**) photocatalysis and esterification under $Ru(bpy)_3(PF_6)_2$ photocatalysis.

An umpolung strategy (see Scheme 83) for the synthesis of *C*-alkyl glycosides **216** has been developed based on a Ni-catalyzed cross-coupling of glycosyl halides **246** and aliphatic NHPI esters **69** in the presence of HE and LiI (Scheme 92).[188] In this case, $NiBr_2$·diglyme and ligand **247** were used in DMA/MTBE as solvents at room temperature under blue LED irradiation to give glycosides **216** with moderate to good yields. As glycosyl halides, D-mannofuranose, D-ribofuranose, D-galactofuranose and L-rhamnopyranose derivatives were employed to give after reaction with 3,4-$(OCH_2O)C_6H_4CH_2CH_2NHPI$ the corresponding glycosides **216** in 39–80% yields and moderate to excellent control of diastereoselectivity. Based on previous disclosures by Molander[170] (Scheme 75), a tentative mechanism was proposed for the photoinduced Ni-catalyzed glycosylation reaction. NHPI esters in the presence of HE and LiI generates an EDA complex **A**. Upon blue LED irradiation **B** and **C** species were formed. Intermediate **C** suffers decarboxylative fragmentation to afford **D** and radical species **E**. In the Ni-catalyzed cycle, Ni(II) reacts with glycosyl halide to deliver **F** and a glycosyl radical, which reassociates with the Ni centre to generate the Ni(II)-species **G**. Radical **E** is trapped by **G** to the Ni(III)-species **H**, which after reductive elimination provides the Ni(I)-species **I** and the *C*-alkyl glycoside product. Ni(I)-species **I** regenerates the Ni(0)-species by reaction with **B** to form the pyridine by-product **J**.

Photoredox Cu-catalyzed decarboxylative $C(sp^3)$–$C(sp^3)$ cross-coupling of aliphatic NHPI esters **69** with diborylalkyl organometallic reagents **248** provided *gem*-diborylalkanes **249** (Scheme 93).[189] This process was carried out using Ir complex **4**. CuCl, DBU as a base in DCE at room temperature and (diborylalkyl)lithium **248** were allowed to react *in situ* with $ZnBr_2$ to form the corresponding (diborylalkyl)zinc species. Products **249** were obtained with moderate to good yields for primary, secondary and tertiary carboxylic acid derivatives **69**, including bioactive molecules such as pharmaceuticals and natural compounds, namely, gemfibrozil, enoxolom, oleanolic acid, betulinic acid and lithocholic and dehydrocholic acids, and APIs such as isoxepac, tolmetin, oxaprozin, indomethacin and gabapentin derivatives have been successfully employed. The prepared *gem*-diborylalkanes are valuable building blocks in organic synthesis, especially in cross-coupling transformations. Based on mechanistic experiments, two catalytic cycles have been proposed to explain this photocatalytic cross-coupling. Diborylmethylzinc halide reagents react with Cu(I) to form diborylmethylcopper(I) complex **A** by a transmetallation process. Subsequently, *via* SET with PC* **A** gives the Cu(II) intermediate **B** and $PC^{-\bullet}$. SET from $PC^{-\bullet}$ to NHPI ester **69** gives the alkyl radical **C**, which can be trapped by **B** to generate the Cu(III) intermediate **D**. Final reductive elimination affords the *gem*-diboryl product.



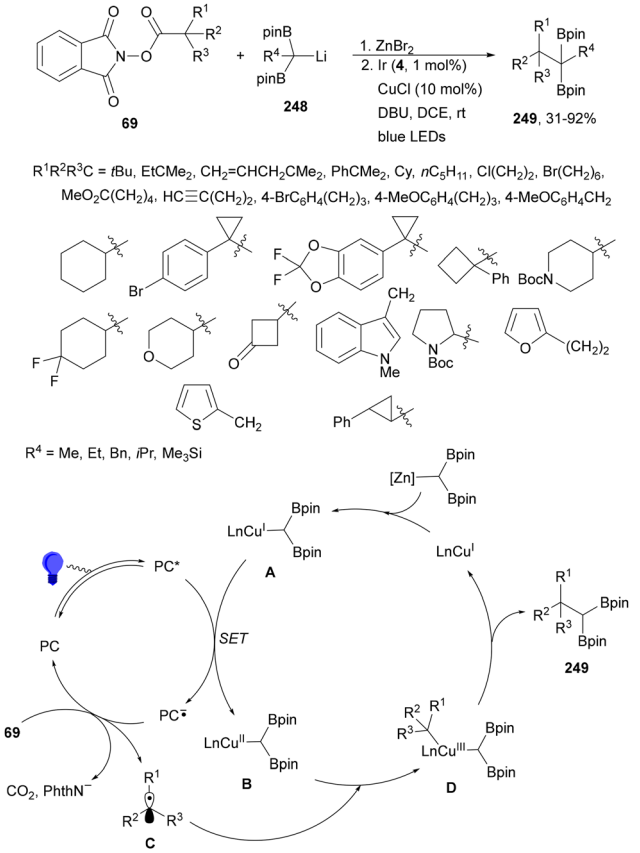
Scheme 91 Decarboxylative cross-coupling of NHPI esters **69** with alkyl bromides under Ir (**244**)/Fe porphyrin (**245**) photocatalysis.



Scheme 92 Decarboxylative cross-coupling of NHPI esters **69** with D-mannofuranose derivative **246** under HE and $NiBr_2$·**247** photocatalysis.

Liu and co-workers[190] recently reported enantioselective decarboxylative difluoromethylation of aliphatic NHPI esters **69** under Ir/Ni dual photocatalysis. As a nucleophile, $(DMPU)_2Zn(CF_2H)_2$ (**250**)[191] was used for difluoromethylation of the Ni(II) catalyst. Under blue LED irradiation, $Ni(ClO_4)_2{\cdot}6H_2O$, chiral oxazoline ligand **251** and Ir complex **4** as a PC enable enantioconvergent[140] preparation of cross-coupled products **252** with up to 89% yield and >99% ee (Scheme 94). This asymmetric difluoromethylation protocol was applied to the synthesis of fluorinated analogues of bioactive molecules. Difluoromethylation of dipeptides, tripeptides and the pentapeptide Leu-enkephalin afforded the corresponding fluorinated derivatives. Other drug analogues of lisdexafematine, dobutamine and ixazomib were difluoromethylated. In the proposed mechanism, the Ir catalytic cycle generates the alkyl radical **A** from the NHPI ester. In the Ni-catalytic cycle, complex **B** reacts with **250** to give a Ni(I)–CF_2H species **C**, which by oxidation with Ir(IV) provides a Ni(II)–CF_2H complex **D**. Oxidative substitution of **D** by the alkyl radical **A** produces a high-valent alkylNi(III)–CF_2H species **E**. Reductive elimination of the product and regeneration of the Ni(I) catalyst **B** closes the catalytic cycle. An alternative pathway, involving the quenching of Ir(III)* by Ni(I) species, cannot be ruled out.

Decarboxylative alkylation of 1,3-dicarbonyl compounds with NHPI esters **69** has been carried out under photoredox/Fe/chiral primary amine triple catalysis. This enantioconvergent[140] process



Scheme 93 Decarboxylative C(sp^3)–C(sp^3) cross-coupling of aliphatic esters **69** with diborylalkyl organozinc compounds under Ir/Cu photocatalysis.

employed Ir complex **4**, iron porphyrin **245** and (*S*)-**253** as a chiral primary amine in a 1 : 1 mixture of MTBE and $PhCF_3$ at 20 °C under blue LED irradiation to provide products **254**, bearing a quaternary stereocenter with good yields and enantioselectivities (Scheme 95).[192] Different functionalized NHPI esters **69** were compatible with these reaction conditions. In the case of 1,3-dicarbonyl compounds, 2-oxocycloalkyl esters and 2-oxocyclopentanecarboxamides were appropriate nucleophiles and also acyclic β-keto esters. In the proposed mechanism, the reaction commences by formation of the enamine **A** between the β-keto ester and the primary amine (*S*)-**253**, which is transformed into radical species **B** by a SET from Ir(III)* and Ir(II). This Ir(II) reduces the NHPI ester to give after decarboxylation the primary alkyl radical **C**, which is captured by porphyrin Fe(II) **D** to give alkyl–Fe(OEP). Then, an outer-sphere radical rebound takes place between **B** and **E** to form imine **F** and Fe(II) complex **D**. Finally, hydrolysis of **F** yields the corresponding product.

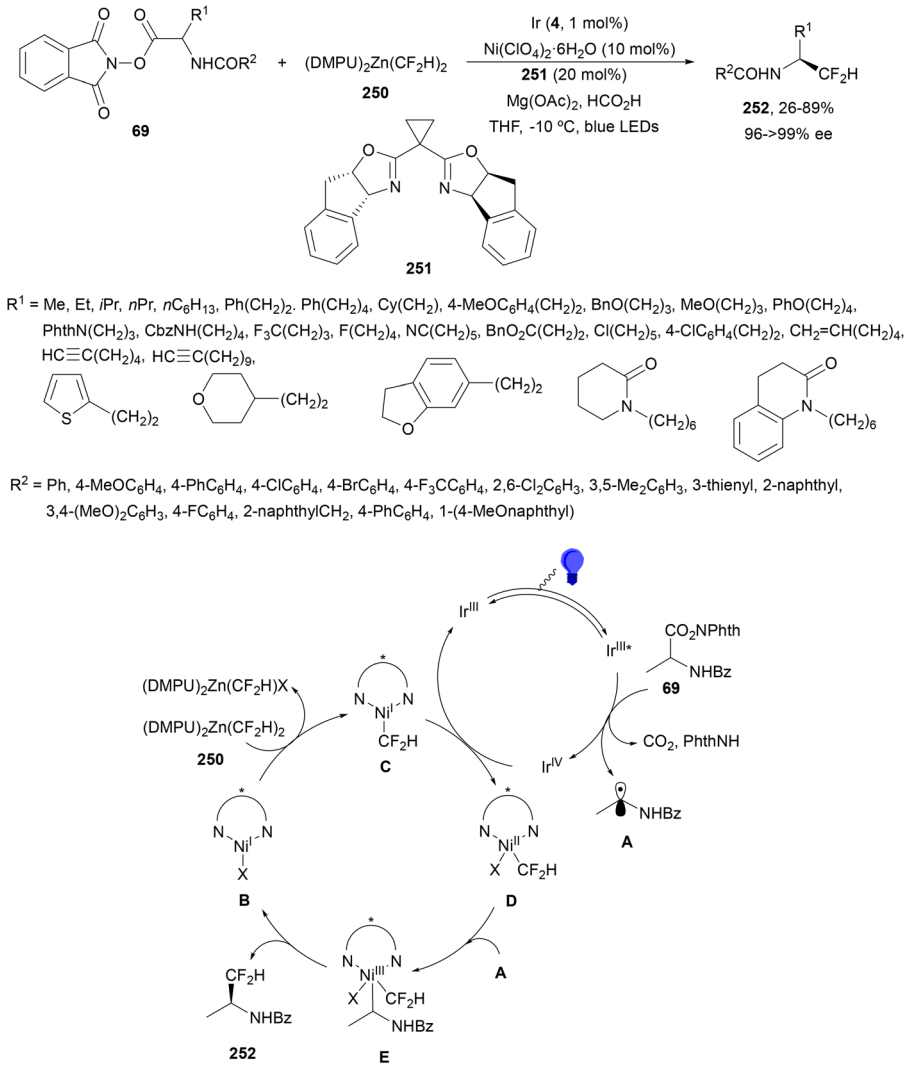
Silyl enol ethers **255** can also be alkylated with aliphatic NHPI esters **69** under photocatalytic decarboxylation with a combination of triphenylphosphine and sodium iodide.[193] α-Alkylated phenones **256** were obtained with good yields using 20 mol% of PPh_3 and 150 mol% of NaI in MeCN at room temperature under blue LED irradiation (Scheme 96). This metal-free, low-cost catalytic system is appealing for a large-scale synthesis. DFT calculations and natural bond orbital analysis suggest that complexation to give a charge transfer complex (CTC) **A**, of NHPI ester, NaI and PPh_3 is endergonic (-3.8 kcal mol^{-1}) but after irradiation, the favorable formation of the Ph_3P–$I^{\bullet}$ (**B**) radical is 11.9 kcal mol^{-1} exergonic. In the catalytic cycle, radical **C**, from the NHPI ester, reacts with silyl enol ether to give radical **D**, which after SET provides cationic intermediate **E**, a precursor of product **256**.

Decarboxylative alkylation of difluoroenoxysilanes **257** with NHPI esters using Ir photocatalyst **89** gave α,α-difluoro phenones **258**.[194] This transformation has been carried out in DMF at 60–65 °C under blue LED irradiation giving products **258** with very good yields even on a gram-scale (Scheme 97). In the case of cyclopropanecarboxylic acid derivatives, both *trans*- and *cis*-1-phenyl-2-carboxycyclopropanes gave *trans*-alkylated products. In the proposed catalytic cycle, radical **A** formed by photocatalysis of NHPI esters reacts with difluoroenoxysilane **257** to form radical **B**, which after SET gives cationic species **C**, the precursor of product **258**.

Decarboxylative cross-coupling of aliphatic carboxylic acids with alkyl halides has been achieved under Ni/Ir dual photoredox catalysis. Enantioconvergent processes have been carried out between amino acids and α-bromo ketones or 3-chloro isoindoles using DPZ and SPINOL as CPA. In the case of α-chloro imidazolyl ketones a chiral Rh complex was employed. Hypervalent iodine reagents were used as intermediates for the trifluoromethylation of carboxylic acids under Ir/Cu photocatalysis. For the alkylation of alcohols and for the double decarboxylation Ni/organocatalyst have been used. In the case of homocoupling of iodonium dicarboxylates 4CzIPN or a Ru complex were employed as photocatalysts. Concerning cross-coupling of aliphatic NHPI esters with alkyl halides, iron porphyrin or $NiBr_2$/Hantzsch ester has been used as a PC. Difluoromethylation of NHPI esters has been performed with organozinc reagents under Ni photocatalysis. Enantioconvergent alkylation of 1,3-dicarbonyls with aliphatic NHPI esters was achieved with Ir/Fe porphyrin as a catalyst in the presence of a chiral primary amine. Silyl enol ethers have been alkylated with NHPI esters with PPh_3/NaI or an Ir complex as a PC.

2.7. Allylation and benzylation reactions

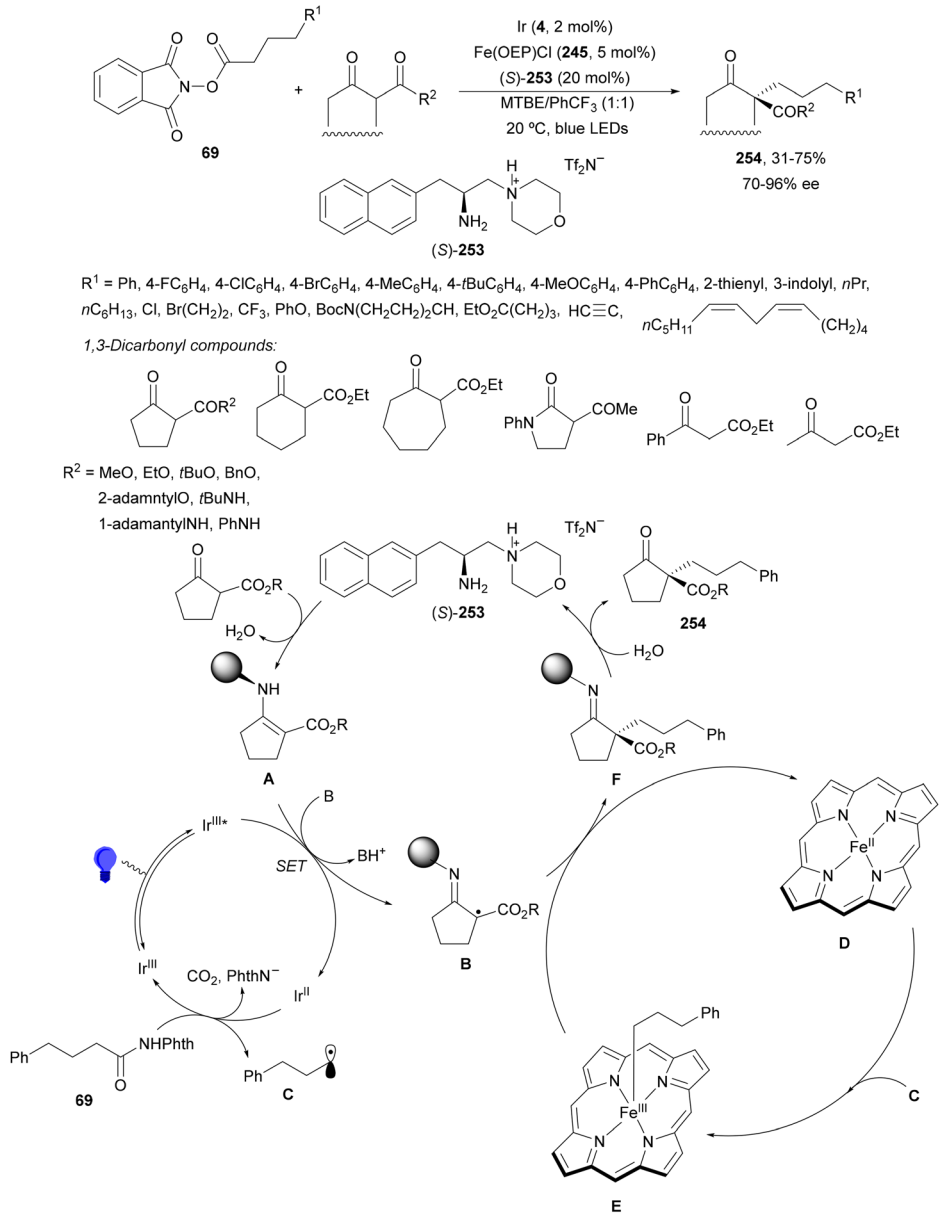
Decarboxylative allylation by photoredox catalysis is a direct strategy to build C(sp^3)–allyl bonds from aliphatic carboxylic acids. Zhu and co-workers[195] reported in 2017 a redox-neutral process under mild reaction conditions based on the allylation of *N*-aryl AAs with allyl sulfone **259**, acting as a radical acceptor, under visible light irradiation. This process was carried out using Ir complex **260** and Cs_2CO_3 as a base in aqueous MeCN at room temperature to give products **261** with in general good yields (Scheme 98). In the proposed mechanism, Ir(III)* promotes a SET process to *N*-aryl glycine, which upon loss of H^+ and CO_2 delivers the α-amino radical **A** and Ir(II). Radical addition/fragmentation processes of radical **A** and the allyl sulfone provides the product and sulfinyl radical **B**, which after oxidation of Ir(II) completes the catalytic cycle.



Scheme 94 Enantioconvergent decarboxylative difluoromethylation of NHPI esters **69** under Ir/Ni photocatalysis.

Dual catalytic decarboxylative allylation and benzylation methods employing carbonates as π-electrophiles have been performed using Pd(0) and 4CzIPN (**25**) as catalysts by Cartwright and Tunge.[196] A variety of carboxylic acids such as acyclic and cyclic AAs, α-alkoxy acids, aryl acetic acids and other aliphatic carboxylic acids reacted with carbonate **262** to give the corresponding allylated products **263** with good yields under blue LED irradiation (Scheme 99a). Branched acyclic allylic carbonates **265** were allowed to react with *N*-Boc AA **264** to provide stereoselectively products **266** with good yields (Scheme 99b). In the case of styryl carbonates **267**, a mixture of *Z*/*E* diastereoisomers **268** were obtained (Scheme 99c). Decarboxylative benzylation worked with benzylic carbonates **269** bearing an extended conjugation to provide products **270** in moderate yields (Scheme 99d). The proposed catalytic cycle for allylation proceeds *via* a reductive quenching pathway in which the excited 4CzIPN* is quenched by a π–allylPd carboxylate species **A**. SET from the carboxylate ion to Pd gives species **B**, which by decarboxylation forms a carbon radical. Rebound of this radical with the π–allylPd species results in the formation of an allylated product and Pd(I), which can be reduced by $4CzIPN^{\bullet -}$ to complete the cycle.

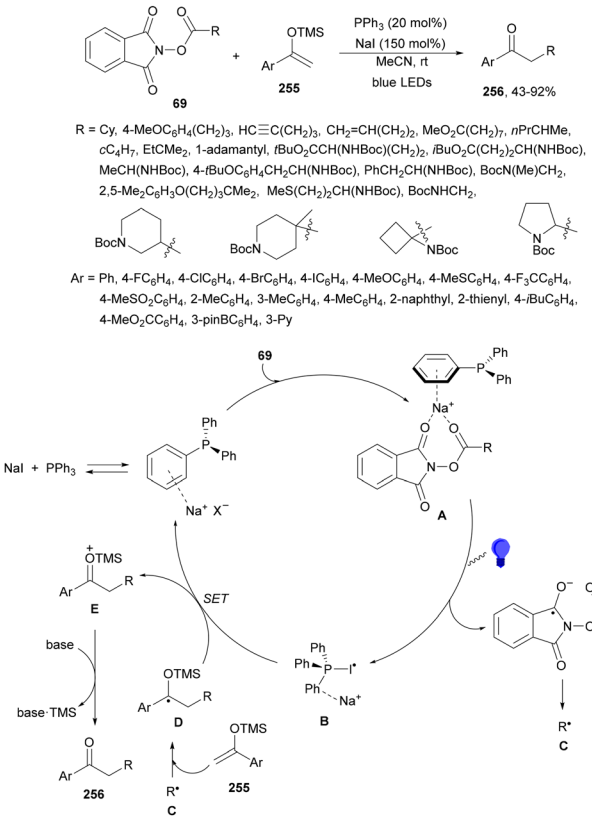
Regio- and enantioconvergent[140] allylation of aryl acetic acids has been performed under dual Pd/Ir photoredox catalysis.[197] Allylic acetates **271** reacted with aryl acetic acids **103** in the presence of $Pd_2(dba)_3$ and chiral ligand **273** with $Ir(dFMeppy)_2(dtbbpy)PF_6$ (**272**) as a PC and K_2CO_3 as a base in DMA as solvent to furnish products **274** with good yields and up to 94% ee (Scheme 100a). This decarboxylative allylation took place with regioselectivity but other carboxylic acids did not undergo this AAA. Vinyl epoxides **275** were benzylated under the same photocatalytic conditions using MeO-biphep (**276**) as a chiral ligand and Cs_2CO_3 as a base in MeCN, affording homoallylic alcohols **277** bearing all-carbon quaternary stereocenters in moderate to good yields with good regio- and enantioselectivities (Scheme 100b). In the proposed plausible pathway, the aryl acetic acid is



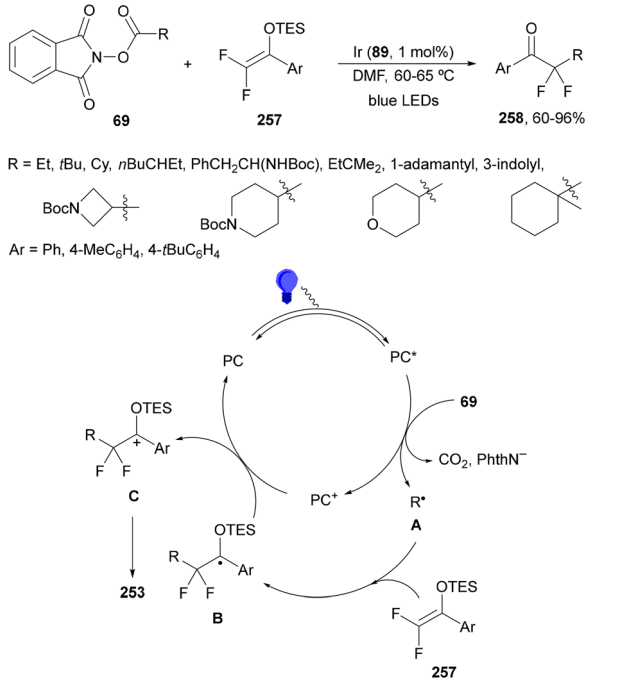
Scheme 95 Enantioconvergent decarboxylative alkylation of 1,3-dicarbonyl compounds with NHPI esters **69** under photoredox/Fe/chiral amine **253** triple catalysis.

reduced by the excited PC to give the benzyl radical **A** and CO_2. In the Pd catalytic cycle, oxidative addition between Pd(0) and allylic acetate **271** leads to π–allylPd intermediate **B.** Trapping of radicals **A** and **B** produces the Pd(III) species **C**, which after reductive elimination gives product **274** and Pd(I) species **D**. Finally, the Ir(II) complex reduced **D** to Pd(0) and also regenerated the PC.

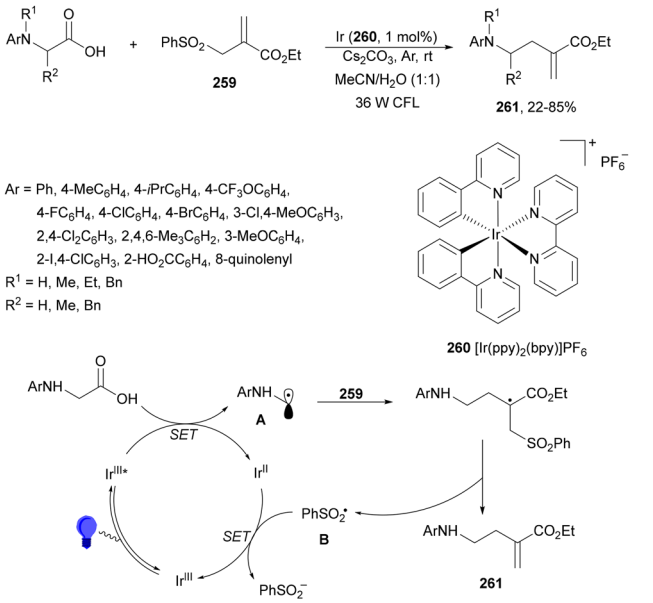
Breit and co-workers[198] studied decarboxylative allylation of *N*-aryl AAs with allylic carbonates using dual Ni/Ir photoredox catalysis. Homoallylic amines **279** were obtained by reaction of *N*-aryl AAs with allylic carbonates **278** in the presence of $NiCl_2$·glyme and 2,2′-bipyridine as a ligand, $Ir(ppy)_2(dtbbpy)PF_6$ (**52**) as a PC, Cs_2CO_3 as a base in MeCN at room temperature under blue LED irradiation (Scheme 101a). Compounds **279** were isolated with, in general, very good yields and up to >95 : 5 dr. When carbonates **280** derived from cinnamyl alcohol and derivatives were allowed to react with *N*-aryl AAs, branched products **281** were prepared in moderate yields and excellent diastereoselectivities (Scheme 101b). These homoallylic amines were further subjected to cyclization reactions to obtain five- and six-membered rings. Control experiments and DFT calculations supported the proposed mechanism depicted in Scheme 101. After generation of radical **A** from *N*-aryl AA, the Ni(0) complex **B** reacts with allylic carbonate **278** to give by oxidative addition the σ-allyl species **C** in equilibrium with the π–allyl intermediate **D.** Radical capture of **C** forms the Ni(II)



Scheme 96 Decarboxylative alkylation of silyl enol ethers **255** with NHPI esters **69** under PPh_3/NaI photocatalysis.



Scheme 97 Decarboxylative alkylation of difluoroenoxysilanes **257** with NHPI esters **69** under $Ir(ppy)_3$ (**89**) photocatalysis.

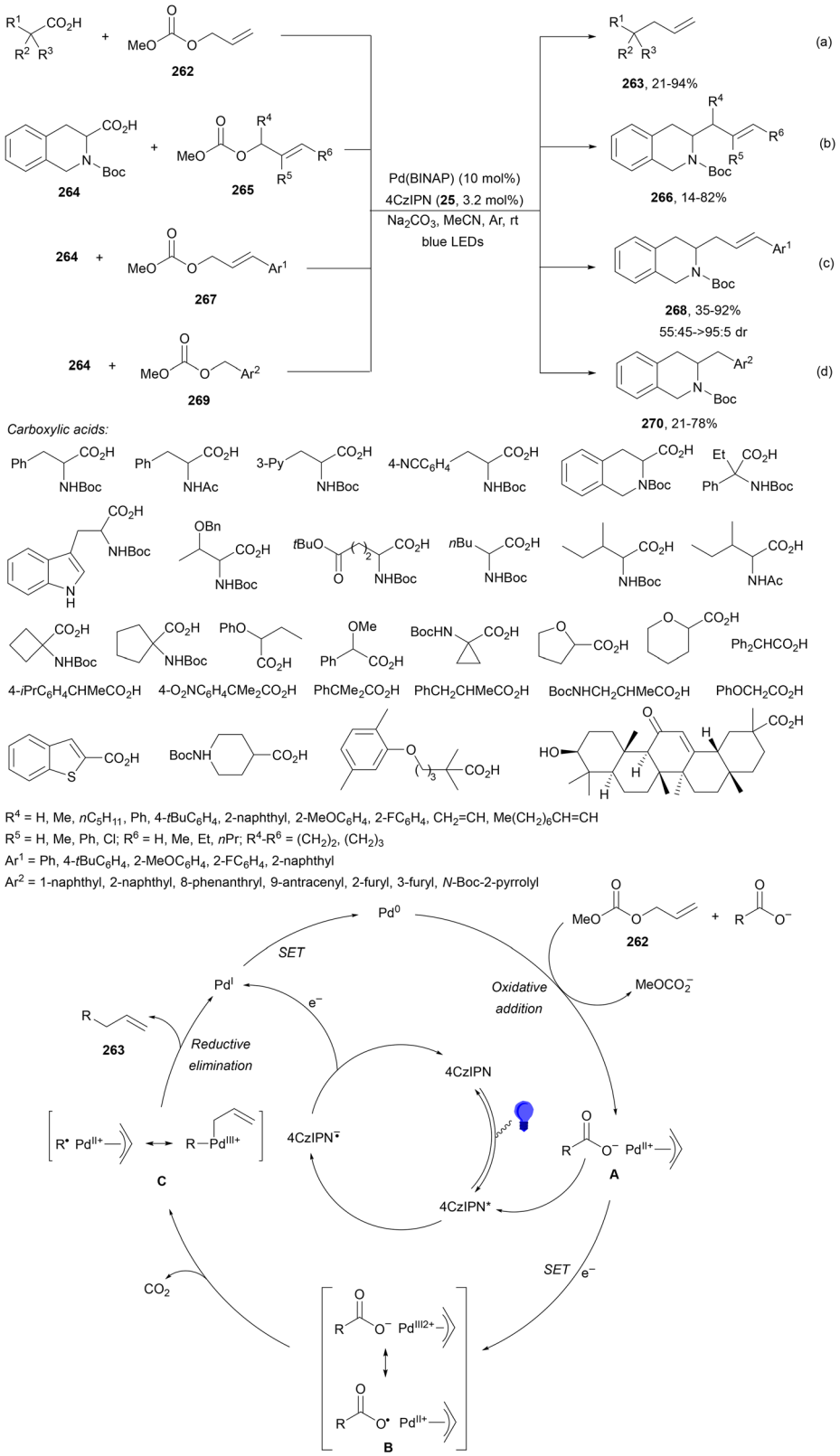


Scheme 98 Decarboxylative allylation of *N*-aryl AAs with allylsulfone **259** under $[Ir(ppy)_2(bpy)]PF_6$ (**260**) photocatalysis.

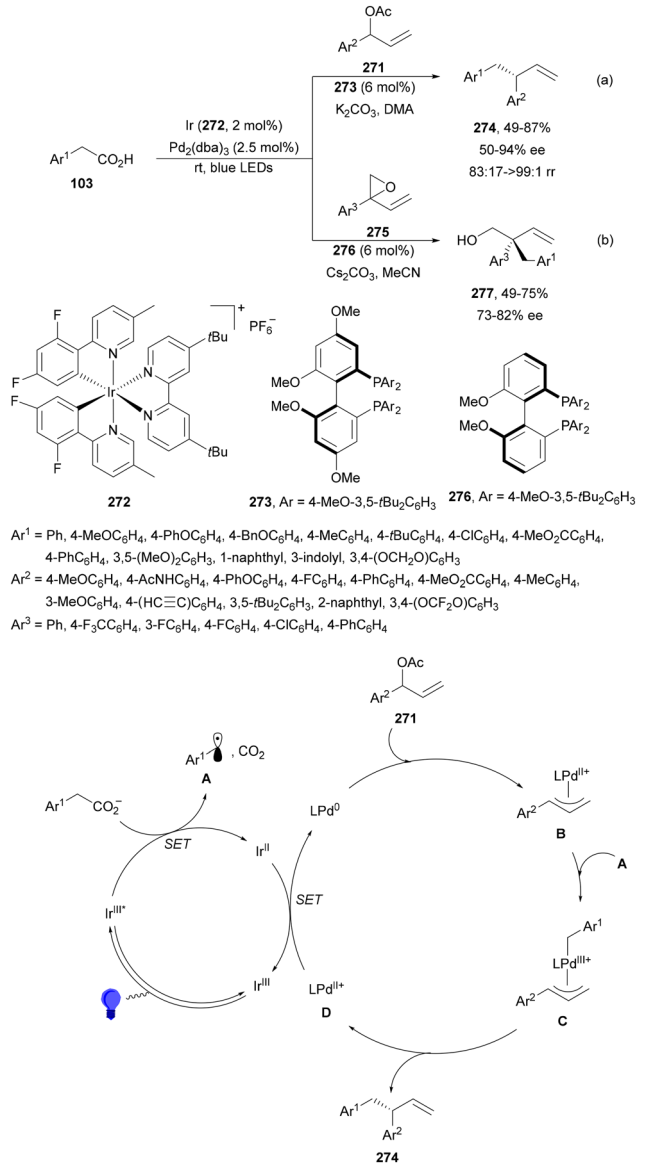
intermediate **E**, which by an oxidative proton coupled electron transfer (PCET) process, the α-amino radical is oxidized to an imine, whereas Ni(II) is reduced to Ni(I) species **F**. Subsequently, a nucleophilic attack from the Ni-bound allylic moiety at the imine occurs to lead to intermediate **G** through an eight-membered ring TS. Afterward, the product is liberated and the Ni(I) species **H** is reduced to Ni(0) by the PC.

Decarboxylative allylation of carboxylic acids with vinyl cyclopropanes **282** has been reported by Sureshkumar and co-workers[199] under Ir complex **4** photocatalysis. Different aliphatic carboxylic acids including α-AAs reacted with vinyl cyclopropanes **282** using Cs_2CO_3 as a base in DCE under blue LED irradiation to give products **283** with 48–94% yields (Scheme 102). The resulting γ,δ-unsaturated diesters and homoallyl amino acid derivatives were obtained mainly as *E*-diastereomers. A plausible mechanism is proposed, which starts with the formation of radical **A** after oxidation by photo-excited Ir(III)*. This radical **A** reacts with **282** to form the radical species **B**, which after ring-opening affords radical **C**, which undergoes a SET process to form Ir(II) and anionic intermediate **D**. Finally, protonation of **D** gives product **283**.

Recently, Yang, Xia and co-workers[200] reported photoinduced ligand-to-copper charge transfer for decarboxylative allylation of aromatic carboxylic acids. Different allyl sulfones **259** reacted with aromatic carboxylic acids to give allyl arenes **284** in moderate to good yields using $Cu(OTf)_2$ under 390 nm LED irradiation (Scheme 103). In the plausible mechanism, the carboxylic acid coordinates Cu(II) to give the complex **A** by LMCT[54,55] providing after irradiation the carboxy radical **B** and reduced Cu(I). Radical **B** undergoes decarboxylation to release an aryl radical **C**, which is captured by the allyl sulfone to give radical **D**, Finally, radical **D** loses the sulfonyl radical to yield the allylated product **284**.



Scheme 99 Decarboxylative allylation and benzylation of aliphatic carboxylic acids (a–d) with allylic and benzylic carbonates under Pd/4CzIPN (**25**) dual photocatalysis.



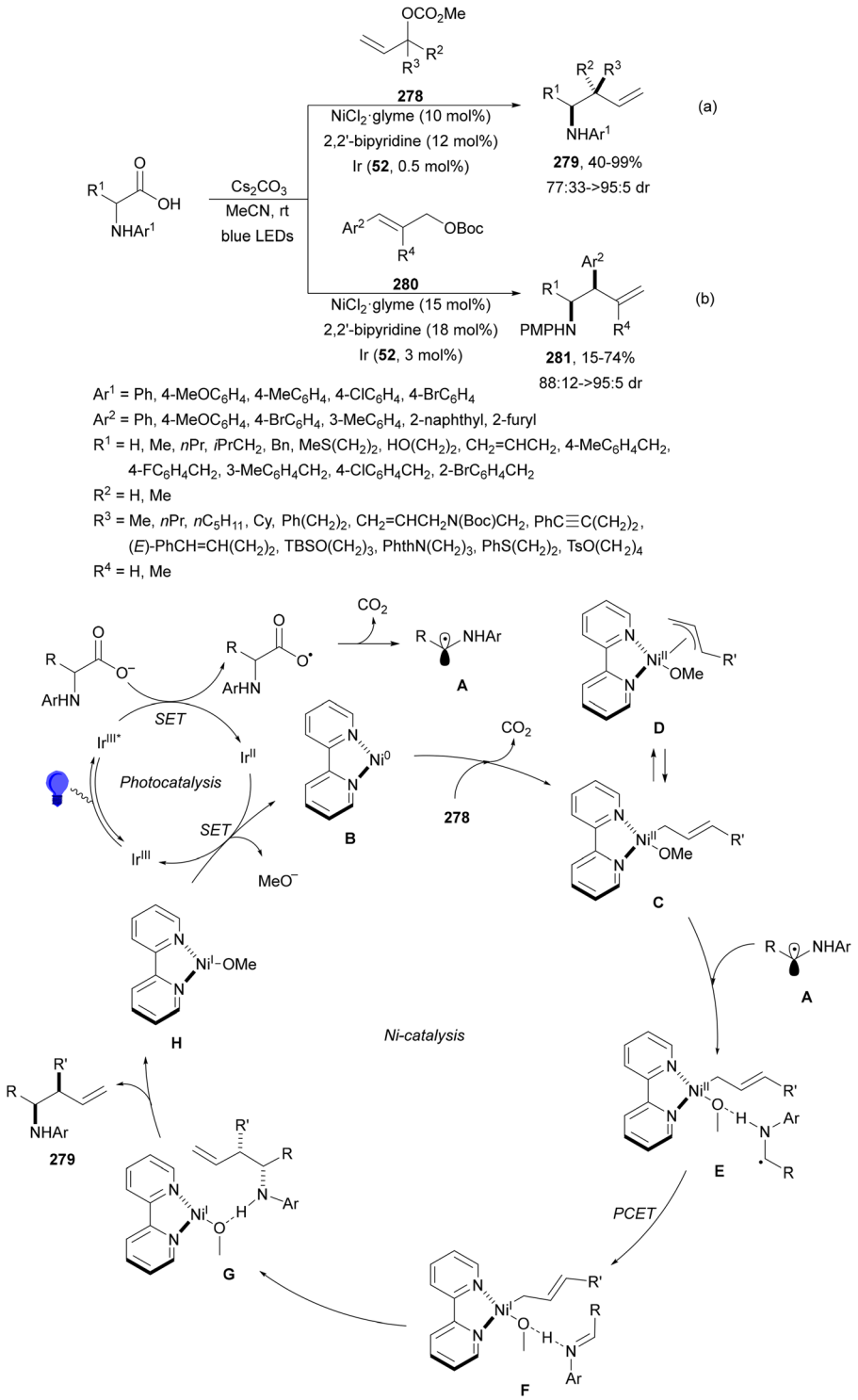
Scheme 100 Decarboxylative enantioconvergent allylation of aryl acetic acids with allylic acetates **271** (a) and vinyl epoxides **275** (b) under dual Pd/Ir (**272**) photocatalysis.

Morita–Baylis–Hillman (MBH) acetates **286** have been recently employed in allylation reactions of aliphatic carboxylic acids by decarboxylative photoredox processes. Xie, Loh and co-workers[201] reported an organophotoredox/DABCO catalytic system for the radical–radical coupling of MBHAs **286** with sodium α-fluor and α,α-difluoro carboxylate ions **285** (Scheme 104a). In the presence of Mes-Acr^{+}Ph $(BF_4)^-$ **287** and DABCO under blue LED irradiation the corresponding mono- and difluoro homoallylic compounds **288** were obtained with good yields and in general high *E*/*Z*-diastereoselectivities. Several bioactive molecules, FDA-approved drugs and AA derivatives were transformed into the corresponding fluorine-containing molecules. In the proposed mechanism, after oxidation of **286** by PC* under a SET process, radical **A** is formed after decarboxylation to give PC$^{-\bullet}$. MBHA reacts with DABCO producing the allylic ammonium salt **B**, which is reduced by PC$^{\bullet-}$ to provide radical **C** regenerating PC and DABCO. Radical–radical coupling of **A** and **C** gives product **288**. However, because the reaction can be performed in the absence of DABCO, an alternative mechanism has been proposed. Radical **A** can be added to MBHA delivering intermediate **D**, which is reduced by PC$^{\bullet-}$ to give anion **E**. Finally, the elimination of the acetate group yields product **288**. The same group[202] performed the same allylation using *N*-Boc AAs **6** and MBHAs **286** in the presence of Mes-Acr^{+}Ph $(BF_4)^-$ **287** as an organophotocatalyst and 2.5 equivalents of Na_3PO_4 as a base in DCE at room temperature under Ar (Scheme 104b). The corresponding homoallylic amines **289** were isolated in good yields with mainly the *E*-configuration. This method was applied to biologically active peptides such as anserine, triglyceride and acetyltetrapeptide-11. In the proposed mechanism, the α-amino alkyl radical **A′** from the *N*-Boc AA reacts with MBHA **286** to give radical **D′**, which after reduction by PC$^{\bullet-}$ and acetate elimination of anion **E′** affords product **289**.

Allylic alkylation of carboxylic acids with MBHAs **286** under visible light has been recently achieved by Akondi and co-workers[203] under photoinduced LMCT[54,55] using $Fe(OTf)_2$/2,4,6-collidine as a catalyst. Trisubstituted alkenes **290** having mainly the *E*-configuration have been obtained with moderate to very good yields (Scheme 105). The proposed mechanism involves a similar pathway to that shown in Scheme 104 for *N*-Boc AAs except the initial oxidation of Fe(II) to Fe(III) and the formation of Fe(III)-carboxylate complex, which upon irradiation with blue LEDs gives the carboxy radical and Fe(III) by a LMCT process. A similar transformation was further described by Loh and co-workers[204] using $FeBr_3$ as a photocatalyst, K_3PO_4 as a base in MeCN at room temperature under 390 nm LED irradiation to give alkenes **290** in 31–96% yields and up to 19 : 1 *E*/*Z*-diastereoselectivity.

When NHPI esters **69** were used instead of carboxylic acids their allylation with MBHAs **286** took place under very mild reaction conditions in the presence of rose Bengal (RB) as a PC, DIPEA (2 equivalents) as a sacrificial reagent in aqueous DCE at room temperature under blue LED irradiation.[205] The corresponding substituted alkyl acrylates **290** were isolated with, in general, good yields and up to $>99:1$ *E*/*Z*-diastereoselectivity (Scheme 106). In the proposed mechanism photoexcited RB* is reductively quenched by DIPEA to give DIPEA$^{+\bullet}$ and RB$^{-\bullet}$, which reduced NHPI ester to form radical anion **A** and RB. After N–O bond splitting of intermediate **A**, radical **B** is formed as well as CO_2 and PhthN$^-$. Radical **B** undergoes radical addition to MBHA **286** to form radical **C**, which after β-acetoxy radical elimination gives product **290**.

Decarboxylative allylation and benzylation of aliphatic carboxylic acids can be carried out under Pd/organophotocatalysis with carbonates. Allylic carbonates have also been employed using Ni/Ir as a dual photocatalyst and only Ir in the case of vinyl cyclopropanes. Allylic sulfones are appropriate allylic reagents of aromatic carboxylic acids under Cu photoinduced LMCT. Recently, Morita–Baylis–Hillman acetates (MBHAs) have

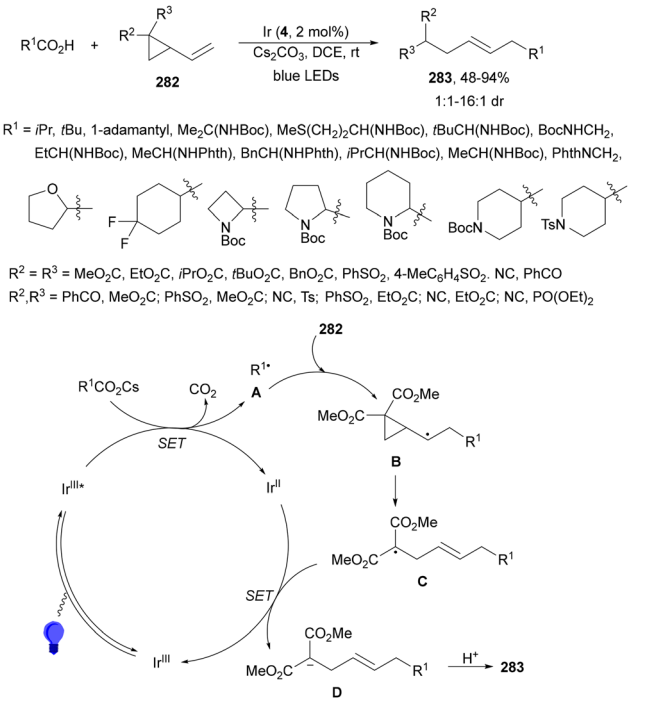


Scheme 101 Decarboxylative allylation of *N*-aryl AAs with allylic carbonates **278** (a) and **280** (b) under Ni/Ir (**52**) photocatalysis.

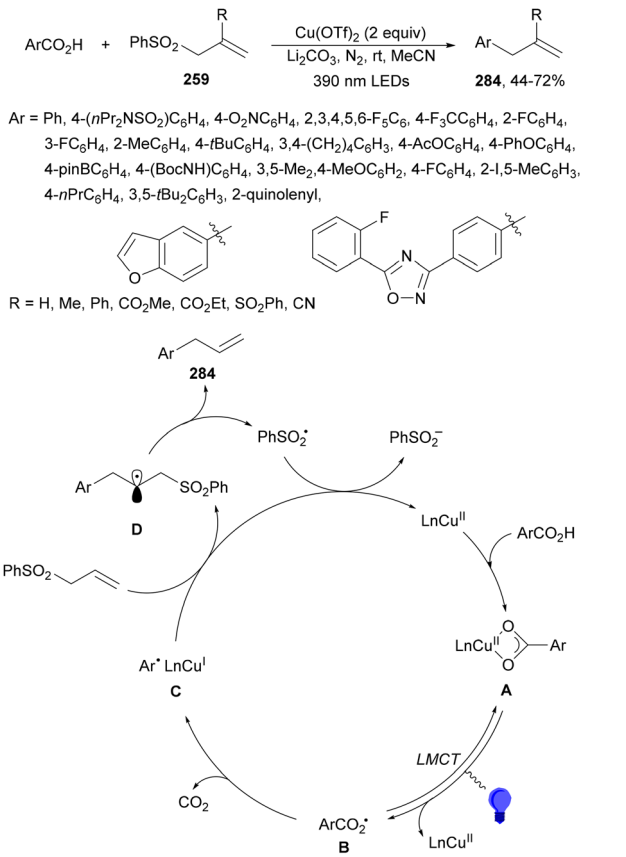
been used as allylation reagents using Mes-Acr^{+}Ph $(BF_4)^{-}$ as an organophotocatalyst or $Fe(OTf)_2$ in a LMCT process. In the case of NHPI esters and MBHAs, rose Bengal under aqueous conditions was used to perform the corresponding allylation with high *E*-diastereoselectivity.

2.8. Alkenylation reactions

Initial studies about decarboxylative vinylation of carboxylic acids were described by MacMillan and co-workers by reaction with vinyl sulfones[206] under Ir photocatalysis and also by cross-coupling with vinyl halides[207] under Ir/Ni dual photocatalysis.



Scheme 102 Decarboxylative allylation of aliphatic carboxylic acids with vinyl cyclopropanes **282** under Ir (**4**) photocatalysis.



Scheme 103 Decarboxylative allylation of aromatic carboxylic acids with allylic sulfones **259** under Cu photoinduced LMCT.

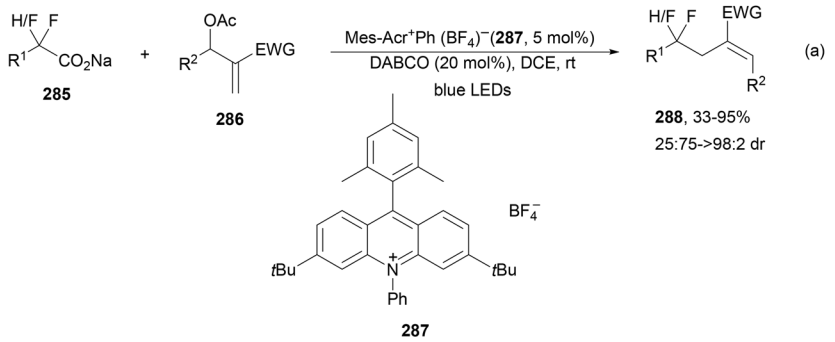
Fu and co-workers[208] employed *gem*-difluoroalkenes **291** for decarboxylative monofluoroalkylation of α-AAs using Ir complex **4** as a PC and a compact fluorescent light (CFL) bulb to obtain products **292** (Scheme 107). This alkenylation reaction took place with Li_2CO_3 as a base, in DMSO at room temperature under an Ar atmosphere giving products **292** with, in general, good yields and moderate diastereoselectivity. In the proposed mechanism, once the α-aminoalkyl radical **A** is generated by a SET process followed by decarboxylation, *gem*-difluoroalkene is reduced by Ir(II) *via* a SET to a radical anion, which decomposes to radical **B** and the fluoride anion regenerating Ir(III). Finally, radical–radical cross-coupling between **A** and **B** affords product **292**.

Formylation of vinyl bromides **293** was carried out by Mariano, Wang and co-workers[144] using diethoxyacetic acid **26** by Ni/4CzIPN (**25**)-mediated photoredox reaction. This cross-coupling vinylation took place with $NiCl_2$/4,4′-$(MeO)_2$bpy (**185**) and the organocatalyst 4CzIPN (**25**) under blue LED irradiation in DMF at room temperature to furnish, after HCl deprotection, the corresponding α,β-unsaturated aldehydes **294** (Scheme 108). A plausible mechanism has been proposed in which the oxidation of diethoxyacetic acid by 4CzIPN* gives CO_2 and radical **A**. Reduction of the Ni(I) intermediate by SET forms Ni(0) species, which reacts with radical **A** to provide intermediate **B**. Oxidative addition of vinyl bromide **293** to **B** generates the Ni(III) complex **C**. Final reductive elimination of intermediate **C** produces acetal **D** and Ni(I)-species. Aqueous acidic work-up converts acetal **D** into aldehyde **294**.

Decarboxylative alkenylation of aliphatic carboxylic acids with vinyl sulfones was also carried out in the presence of an organic photocatalyst instead of Ir as it was previously described by MacMillan.[206] In this case, riboflavin tetraacetate (RFTA) **296** was used as a PC for the reaction of carboxylic acids with styryl sulfones **295** under blue LED irradiation (Scheme 109).[209] The resulting (*E*)-alkenes **297** were regio- and diastereoselectively obtained with moderate to good yields. This process can be explained by addition of radical **A**, formed by decarboxylation of the carboxy radical, to styryl sulfone to form radical **B** followed by β-elimination of the sulfonyl radical under thermodynamic control.

Recently, a decarboxylative photocatalytic alkenylation of carboxylic acids with styryl sulfones **295** *via* iron LMCT[54,55] activation has been reported.[210] Aliphatic carboxylic acids reacted with styryl sulfone **295a** (Ar = Ph) using $Fe(NO_3)_3$, ligand **298**, Na_2CO_3 as a base in DCM at room temperature under 390 nm LED irradiation to provide alkenes **297** with moderate yields and total *E*-diastereoselectivity (Scheme 110). In this case, the iron carboxylate converts after irradiation to the corresponding photoexcited state **A**, which by a fragmentation process generates the carboxy radical **B** and Fe(II) species. Subsequent decarboxylation to **C** and addition to styryl sulfone followed by β-elimination of the sulfonyl radical gives the product.

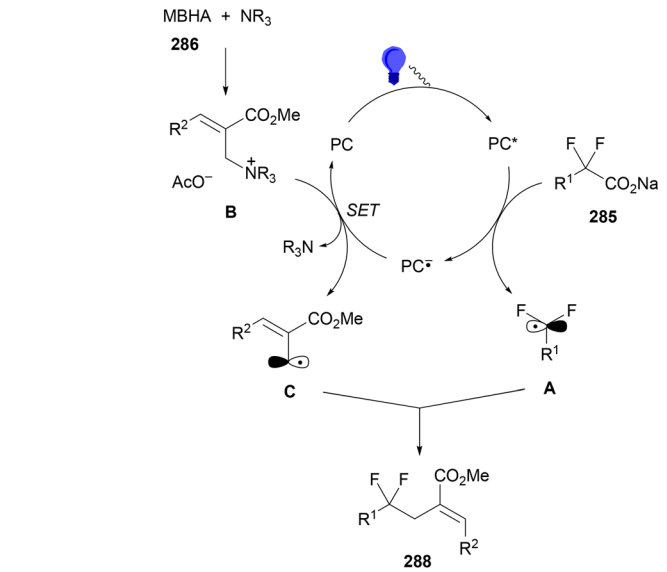
Vinyl sulfonium salts **299** have been used as radical acceptors for decarboxylative alkenylation of NHPI esters **69** in the presence of Eosil Y **139** as an organophotocatalyst.[211] A broad range of primary, secondary and tertiary carboxylic acid derivatives **69**

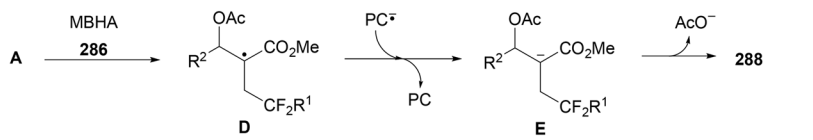


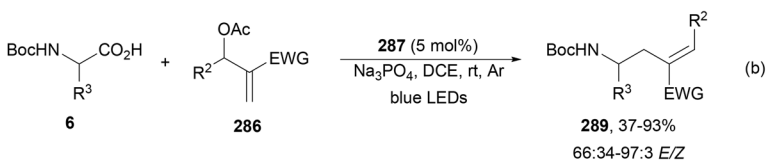
R^1 = Ph, 4-FC_6H_4, 4-ClC_6H_4, 4-BrC_6H_4, 4-NCC_6H_4, 4-$F_3CC_6H_4$, 4-PhC_6H_4, 4-*t*BuC_6H_4, 4-$MeOC_6H_4$, 3-BrC_6H_4, 2-BrC_6H_4, 2,4,6-$Me_3C_6H_2$, *N*-Boc-5-indolyl, 4-$AcHNC_6H_4$, 4-$MeO_2C_6H_4$, H, Me

R^2 = Ph, 4-ClC_6H_4, 4-BrC_6H_4, 4-NCC_6H_4, 4-$HCOC_6H_4$, 4-$O_2NC_6H_4$, 4-$MeOC_6H_4$, 4-*t*BuC_6H_4, 2-FC_6H_4, 2-ClC_6H_4, 1-naphthyl, 4-(TMSC≡C)C_6H_4, Cy, *n*Pr, H

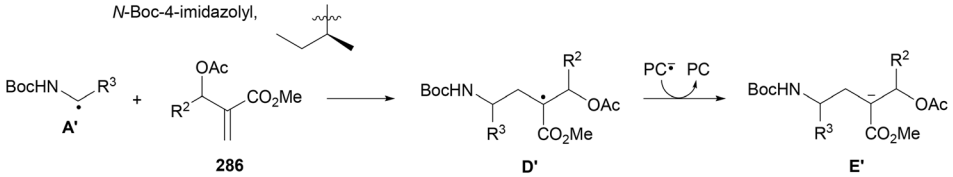
EWG = MeO_2C, NC



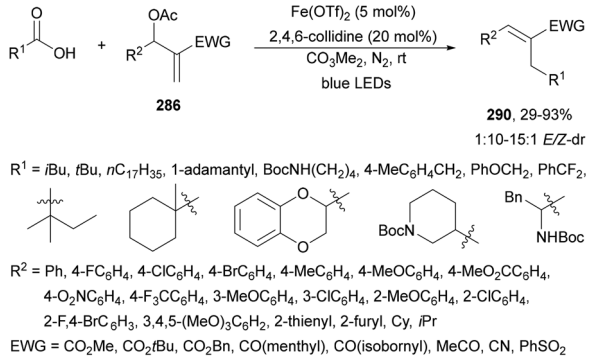




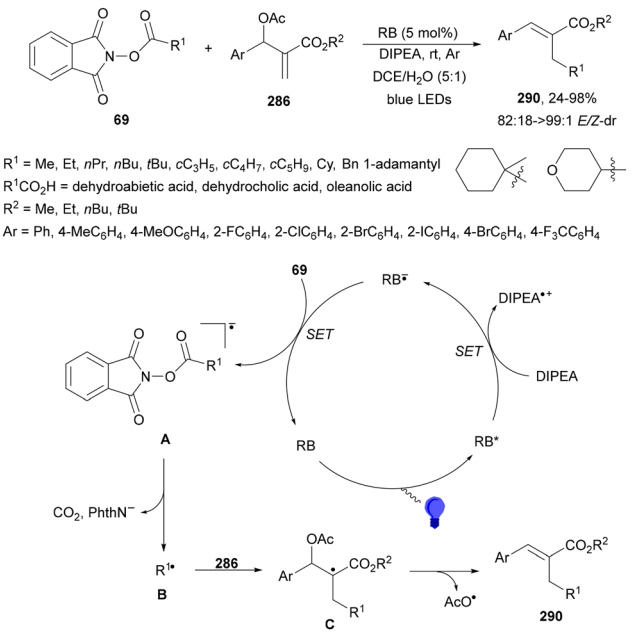
R^3 = H, Me, Bn, *i*Pr, *i*Bu, $HOCH_2$, $HO_2C(CH_2)_2$, $BocHN(CH_2)_4$, $MeS(CH_2)_2$, 4-$HOC_6H_4CH_2$, *N*-Boc-2-indolyl, *N*-Boc-4-imidazolyl,



Scheme 104 Decarboxylative allylation of sodium mono- and difluoro carboxylate (a) and *N*-Boc AAs (b) with MBHAs **286** under MesAcr$^+$Ph (BF_4^-) **287** photocatalysis.



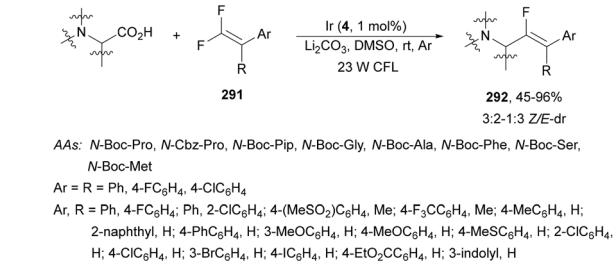
Scheme 105 Decarboxylative allylation of aliphatic carboxylic acids with MBHAs (**286**) under $Fe(OTf)_2$/2,4,6-collidine photocatalysis.

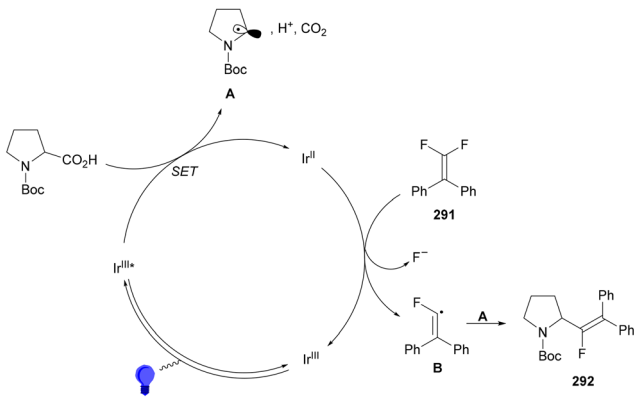


Scheme 106 Decarboxylative allylation of aliphatic NHPI esters **69** with MBHAs **286** under RB photocatalysis.

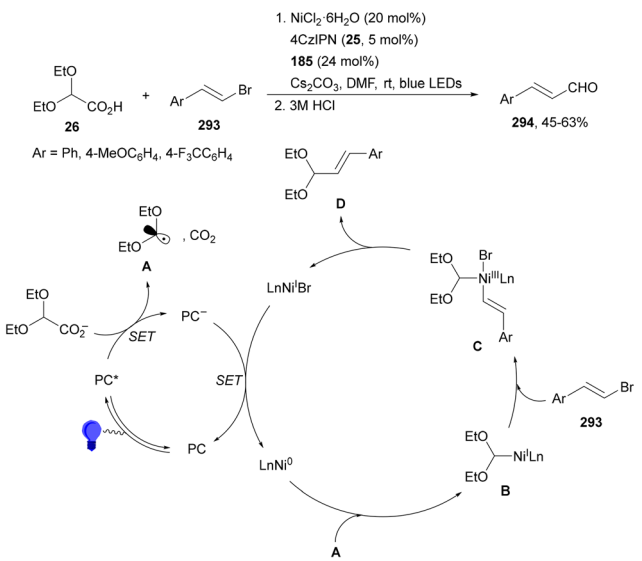
reacted with vinyl sulfonium salts **299** under mild conditions to give alkenes **297** with moderate to good yields and *E*-configuration (Scheme 111). In this procedure, radical **A** obtained by decarboxylation of the NHPI ester adds at the α-position of the vinyl sulfonium salts to provide intermediate **B**. Subsequently, $DIPEA^{+\bullet}$ transforms radical **B** into anion **C**, which undergoes β-elimination to afford **297**.

Aliphatic carboxylic acids have been utilized in a Heck process by a photoredox/Pd catalysis with vinyl arenes.[212] A *cis*-selective decarboxylative alkenylation of tertiary and secondary aliphatic carboxylic acids with styrenes occurred in the presence of Ir complex **4** as a PC, $Pd(OAc)_2$, 3,4,7,8-tetramethyl-1,10-phenanthroline (TMP, **300**) as a ligand, K_2HPO_4 as a base in chlorobenzene as solvent under Ar and blue LED irradiation to deliver β-alkylated styrenes **297** with *Z*-selectivity (Scheme 112). The observed stereoselectivity is attributed to the Ir PC, which



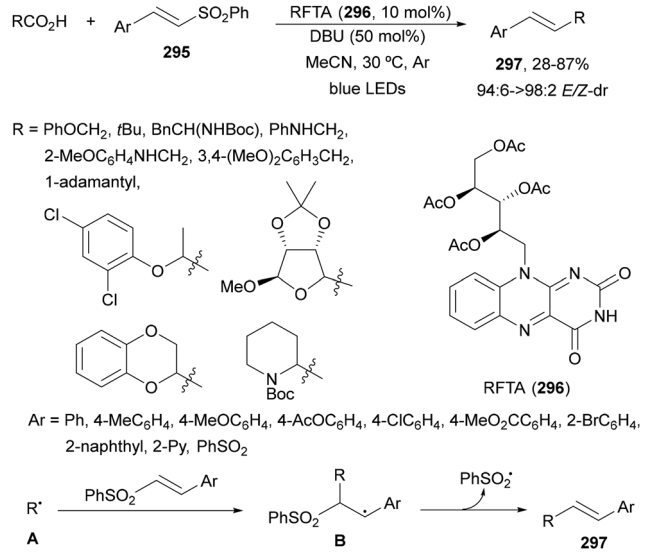


Scheme 107 Decarboxylative vinylation of α-AAs with *gem*-difluoroalkenes **291** under Ir (**4**) photocatalysis.

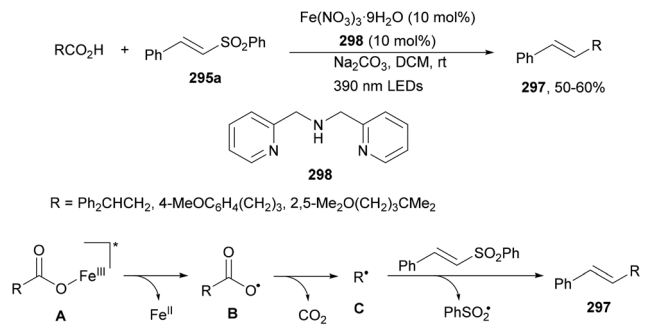


Scheme 108 Decarboxylative alkenylation of diethoxyacetic acid **26** with vinyl bromides **293** under Ni/4CzIPN (**25**) photocatalysis.

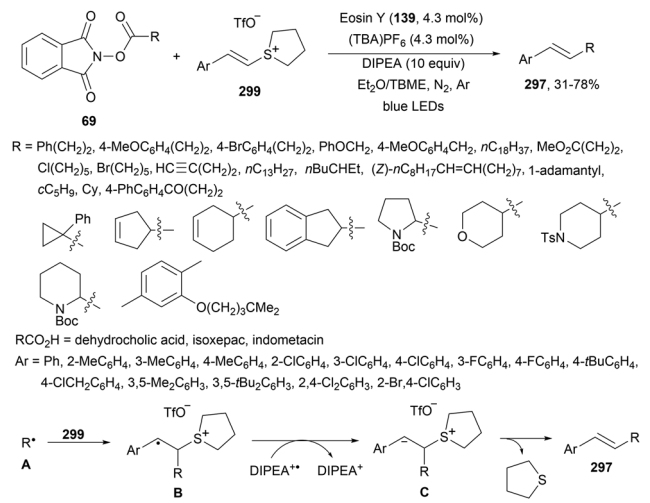
promotes a SET and energy-transfer to sensitize *E*-olefin to its triplet state isomerizing *E*-olefin to its thermodynamically less favored *Z*-isomer. Products *Z*-**297** were isolated in up to 84% yield and up to 99 : 1 dr. In the proposed mechanism, according to experimental studies, the phenanthroline-supported Pd(II) catalyst reacts with the alkyl radical **A** and styrene to give a benzylic Pd(III) species **B**. Oxidation of Ir(II) by **B** regenerates Ir(III) and gives Pd(II) species **C**, which by β-H elimination delivers product *E*-**297** and Pd(II)–H species **D**. This intermediate



Scheme 109 Decarboxylative alkenylation of aliphatic carboxylic acids with styryl sulfones **295** under RFTA **296** photocatalysis.



Scheme 110 Decarboxylative alkenylation of aliphatic carboxylic acids with styryl sulfone **295a** under Fe(III) LMCT photocatalysis.



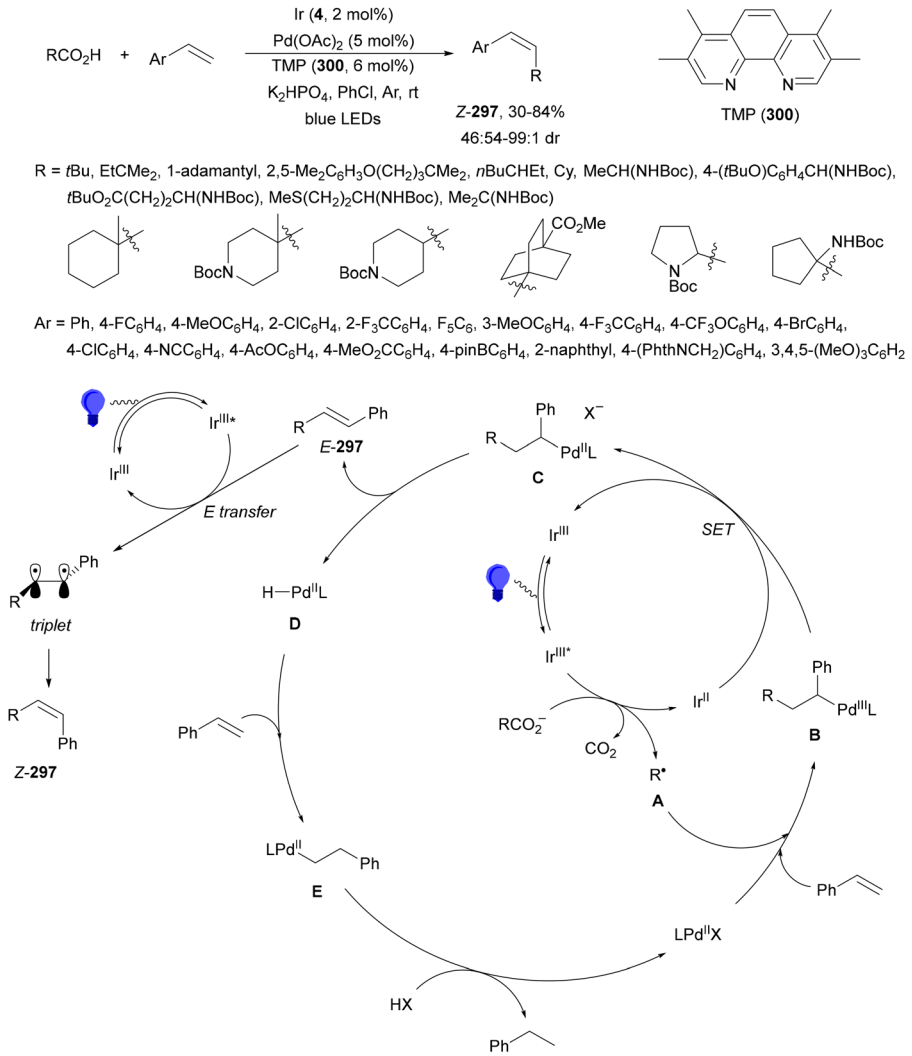
Scheme 111 Decarboxylative alkenylation of NHPI esters **69** with vinyl sulfonium salts **299** under Eosin Y **139** photocatalysis.

D inserts into an excess of styrene, as a hydrogen acceptor, to give complex **E**, which after protonation forms ethylbenzene and regenerates LPd(II)X. Simultaneously, Ir(III)* in its triplet state sensitizes *E*-**297** to *Z*-**297**.

Decarboxylative Heck-type reaction of aliphatic carboxylic acids with styrenes, vinyl silanes and vinyl boronates in the absence of external oxidants was carried out in the presence of Mes-Acr$^+$ClO$_4^-$ **301** as an organophotocatalyst and cobaloxime catalyst **302**.[213] The corresponding alkenes, 1,3-dienes and conjugated enynes were obtained with good yields (Scheme 113a). However, β-substituted styrenes and aliphatic alkenes gave very low yields (<10%). In the case of vinyl silanes and boronates, they were efficiently transformed into substituted vinyl silanes and boronates **303** (Scheme 113b). A tentative mechanism has been proposed: in the photoredox catalytic cycle the carboxylate ion was oxidized by [Mes-Acr$^+$]* to deliver radical **A**, which reacts with styrene to form benzylic radical **B**. The reduced PC (Mes-Acr$^•$) can be oxidized by Co(III) catalyst **302** to complete this catalytic cycle. The generated Co(II) can capture radical **B** to form a Co(III) intermediate **C**, which delivers the product and LnCo(III)–H. Finally, this LnCo(III)–H may react with a H$^+$ or another molecule of Co(III)–H to release H_2 and regenerate the catalyst. A multicomponent coupling of aliphatic carboxylic acids, acrylates and styrenes was achieved using the same reaction conditions (Scheme 113c). In this case, the alkyl radicals derived from carboxylic acids reacted firstly with the acrylate to give an α-acyl radical, which then added to the vinyl arene to provide products **304** with moderate yields and high *E*-diastereoselectivity.

Decarboxylative Heck-type reaction of aliphatic NHPI esters **69** and styrenes was initially studied by Fu[214] and Glorius[215] groups independently using Pd as a catalyst under photoredox conditions. The Chinese group[214] employed Pd(PPh$_3$)Cl$_2$ (5 mol%) and Xantphos (6 mol%) as a ligand and K_2CO_3 as a base in aqueous DMA at room temperature under blue LED irradiation to obtain compounds **297** with good yields and diastereoselectivities (Scheme 114a). In the case of Glorius and co-workers,[215] Pd(PPh$_3$)$_4$ (5 mol%) in THF at room temperature under blue LED irradiation afforded products *E*-**297** with good yields (Scheme 114b). They proposed a catalytic cycle[215] initiated by photoexcitation of Pd(0) followed by SET to NHPI ester, which forms the corresponding alkyl radical **A** upon release of CO_2 and PhthN$^-$. Addition of this radical to styrene gives the benzylic radical **B**, which after β-hydride elimination releases the product and Pd(II)–H species. Reductive elimination of phthalimide regenerates the catalyst.

Iridium complexes were used as PCs in decarboxylative Heck-type reactions with alkyl NHPI esters **69** with styrenes. Gao, Ye and co-workers[216] employed Ir(ppy)$_3$ (**89**) as a photocatalyst in the presence of TfOH and DMSO as solvent at room temperature under blue LED irradiation to give the corresponding alkenes **297** with moderate to high yields (Scheme 115). The plausible mechanism involves the formation of the alkyl radical **A** by means of photoexcited Ir(III)* and subsequent addition to styrene gives radical **B**, which is oxidized to a carbocation **C** by Ir(IV). In the presence of TfOH, β-elimination of a proton affords alkene **297**.

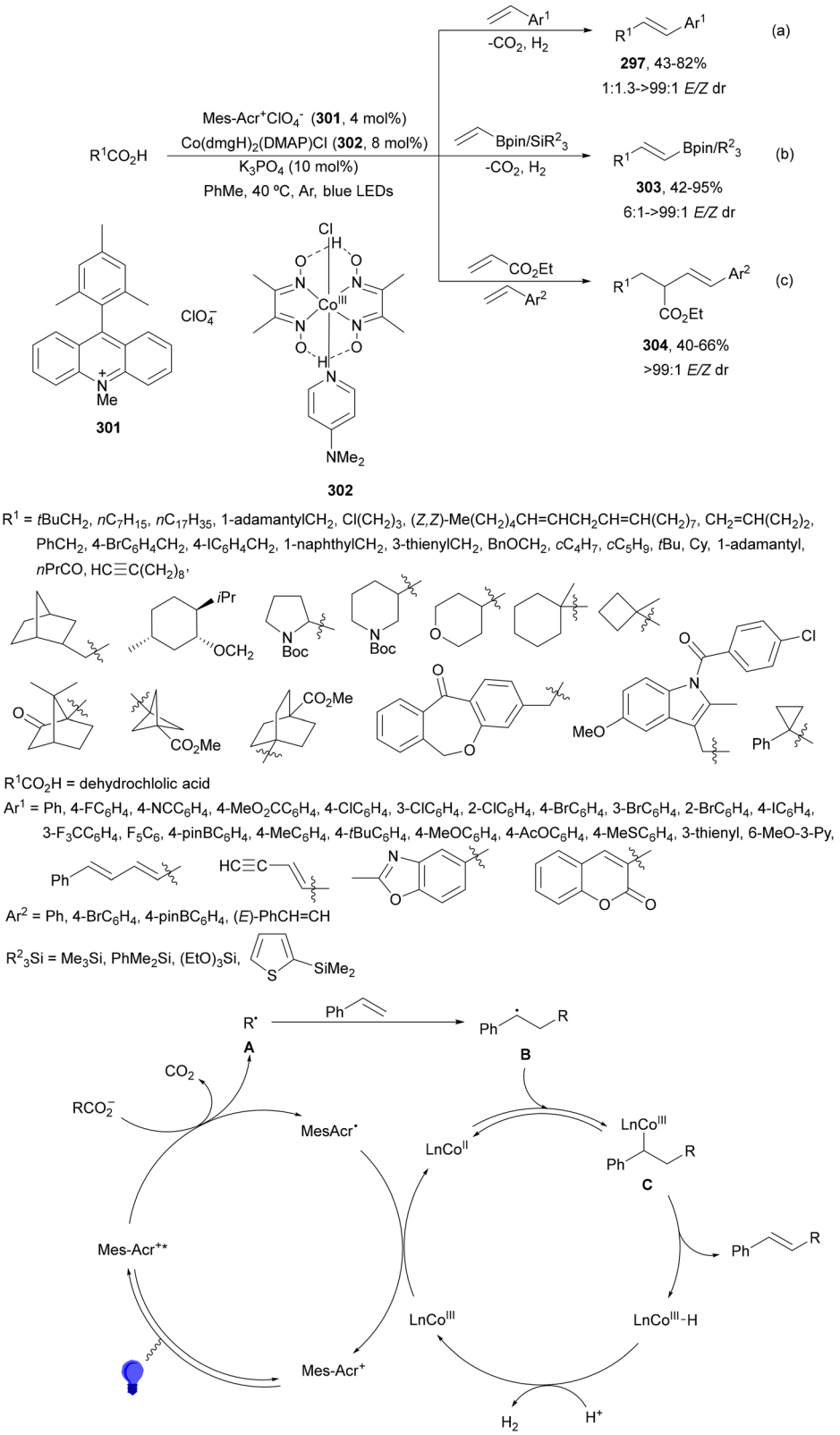


Scheme 112 Decarboxylative Heck-type reaction of aliphatic carboxylic acids with styrenes under Ir/Pd photocatalysis.

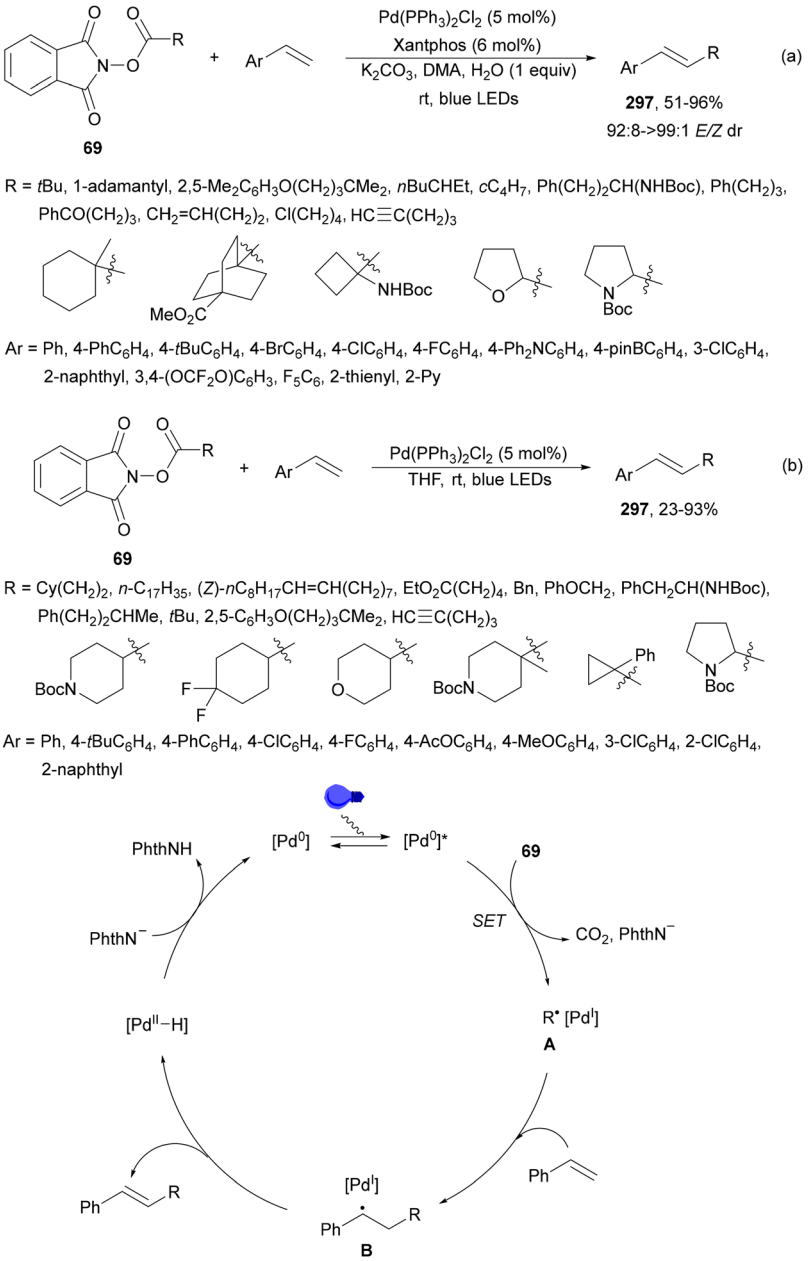
Zhao, Loh and co-workers[217] performed decarboxylative Heck-type reaction of alkyl NHPI esters **69** with enamides **305** using $Ir(ppy)_3$ (**89**) as a PC (Scheme 116). This process was carried out in DMF at room temperature under blue LED irradiation to provide β-alkylated enamides **306** with good yields and excellent *E*-diastereoselectivities. In the proposed mechanism, the alkyl radical **A** from the NHPI ester adds to the enamide to give the α-aminoalkyl radical **B**, which is oxidized by $Ir(III)^+$ species to form cationic intermediate **C**. Finally, deprotonation of **C** gives the product. The resonance form of **C** gives the iminium ion **D** with two possible conformers **D** and **D′**. Conformer **D** explains the observed stereochemistry.

Sodium iodide and triphenylphosphine have been used as PCs for decarboxylative Heck-type reaction of NHPI esters **69** with 1,1-diarylethylenes[217] and with enamides **305**.[218] Sang, Fu and co-workers[217] employed NHPI esters derived from α-AAs, α-alkoxy acids and thioglycolic acid with 1,1-diarylethylenes in acetone at room temperature under blue LED irradiation to obtain allylic products **307** (Scheme 117a). In the case of Fu and co-workers,[218] alkyl NHPI esters including α-AA derivatives reacted with enamides **305** to give enamides **306** in good yields and *E*-diastereoselectivity (Scheme 117b). The proposed mechanism[193] for the PPh_3/NaI photoredox process is depicted in Scheme 96.

A third strategy for $C(sp^2)$–$C(sp^3)$ bond formation through decarboxylative vinylation reactions under photoredox conditions used α,β-unsaturated carboxylic acids.[219] Duan and co-workers[220] reported a dual decarboxylative coupling of α,β-unsaturated carboxylic acids with alkyl NHPI esters **69** using $Ir(ppy)_3$ (**89**) as a PC and $Mg(ClO_4)_2$ as an additive in NMP at room temperature under 23 W fluorescent light (CFL) bulb irradiation. A broad range of substituted alkenes **297** were obtained with, in general, good yields and *E*-diastereoselectivity (Scheme 118). A plausible mechanism was proposed involving the formation of the radical **A** from the NHPI ester by Ir(III)* and subsequent attack on the C=C bond of the α,β-unsaturated carboxylic acids to give radical **B**. This is followed by deprotonation of **B** by the phthalimide anion from radical-carboxylate **C**, which might be



Scheme 113 Decarboxylative Heck-type reaction of aliphatic carboxylic acids and terminal alkenes (a–c) under Mes-Acr$^+$ClO$_4$ (**301**) and cobaloxime **302** photocatalysis.



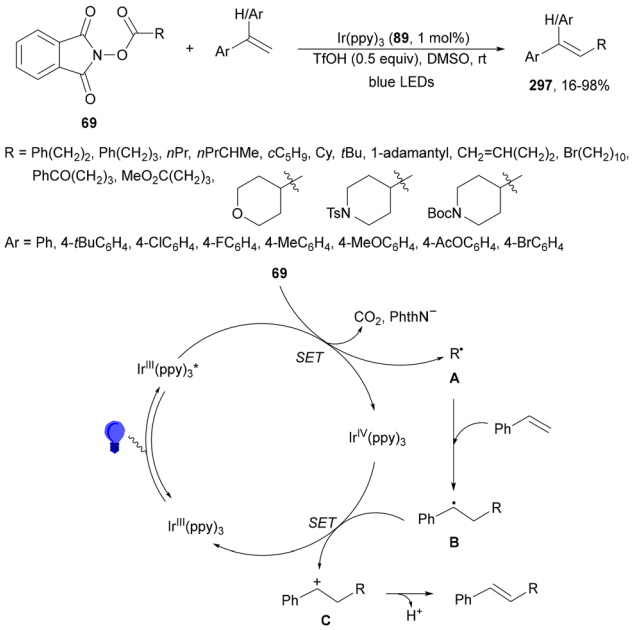
Scheme 114 Decarboxylative Heck-type reaction of aliphatic NHPI esters **69** with styrenes under Pd photocatalysis (a, b).

oxidized by PC* to radical **D**. This radical **D** delivers CO_2 and the final product.

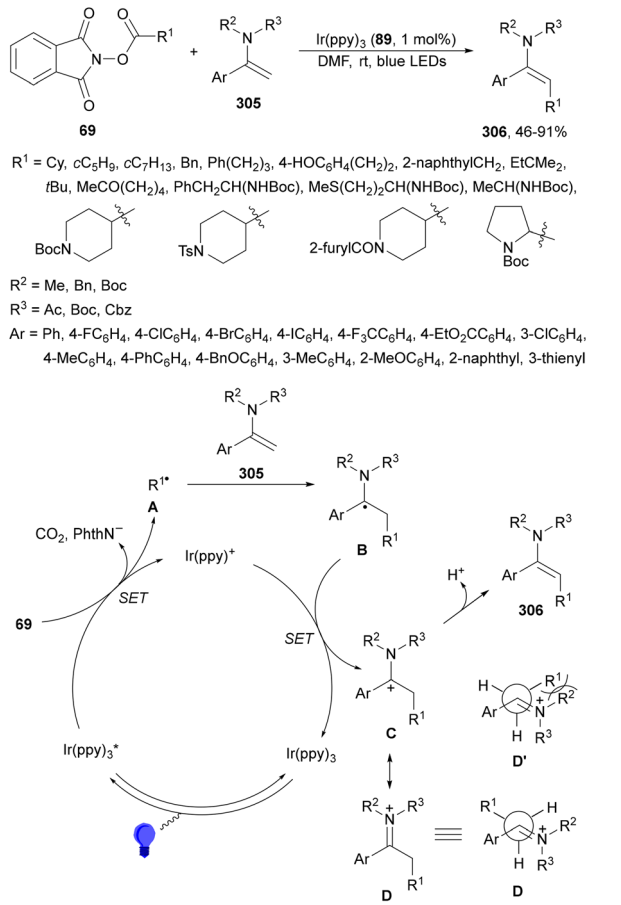
Under similar reaction conditions described for the Heck-type reaction of 1,1-diarylethylenes with NHPI esters using NaI/PPh_3 as a PC[217] (Scheme 117a), a vinylation of NHPI esters with cinnamic acids (Scheme 119) was carried out. Working with *N*-Boc-protected phenylalanine and α,β-unsaturated carboxylic acids, the corresponding allylic amines **67** were obtained with good yields and *E*-diastereoselectivity.[217]

Lu and co-workers[221] reported the synthesis of monofluoroalkenes **309** *via* dual decarboxylative cross-coupling of α-fluoro acrylic acids **308** with alkyl NHPI esters **69** using $Ir(ppy)_3$ (**89**) as a PC and DABCO as a base in DMAc at room temperature under blue LED irradiation. Starting from *Z*/*E* mixtures of α-fluoro acrylic acids **308**, the corresponding products **309** were obtained with good yields and high *Z*-diastereoselectivity (Scheme 120). Primary, secondary and tertiary NHPI esters as well as biologically active molecules containing carboxylic acids or α-fluoro acrylic acids **308** were successfully employed. In the proposed mechanism, radical **B** resulting from the addition of radical **A** to **308** is transformed by SET into cation **C**, which undergoes decarboxylation to form product **309**.

The same group[222] recently reported a photoinduced decarboxylative difluoroalkylation and perfluoroalkylation of α-fluoro



Scheme 115 Decarboxylative Heck-type reaction of alkyl NHPI esters **69** with styrenes under $Ir(ppy)_3$ photocatalysis.



Scheme 116 Decarboxylative Heck-type reaction of aliphatic NHP esters **69** with enamides **305** under $Ir(ppy)_3$ photocatalysis.

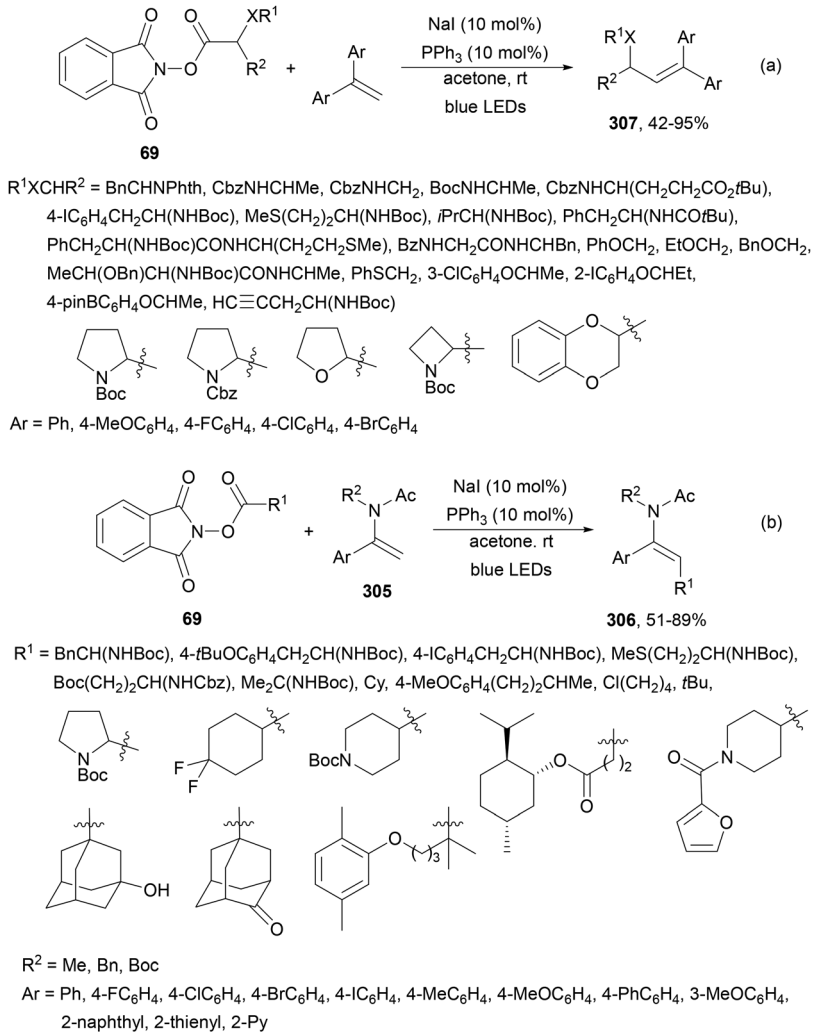
acrylic acids **308**. Using $Ru(bpy)_3Cl_2{\cdot}6H_2O$ as a PC and DABCO as a base in DMAc at room temperature under blue LED irradiation, *tert*-butyl 2-bromo-2,2-difluoroacetate **310** gave difluoromethylene-substituted monofluoroalkenes **311** with moderate yields (37–68%) and good *Z*-diastereoselectivity (Scheme 121a). When bromodifluoro acetamides **312** were employed as alkylating agents, the corresponding products **313** were isolated in 53–63% yields and $>20:1$ dr (Scheme 121b). Moreover, the reaction was expanded to polyfluoroalkyl bromides **314** to obtain polyfluoroalkylated monofluoroalkenes **315** (Scheme 121c). In the proposed catalytic cycle, photoexcited $Ru(bpy)_3^{2+*}$ species is reduced by DABCO yielding $Ru(bpy)_3^{+}$, able to reduce bromodifluoroacetate to radical **A** through a SET. This radical **A** adds to the α-fluoroacetic acid anion to form radical **B**, which after oxidation by $DABCO^{+\bullet}$ leads to the formation of cation **C**. Final decarboxylation of **C** generates product **311**.

Alcohols have been used as alkylating agents of α-fluoroacrylic acids **308** under photoinduced decarboxylative cross-coupling by Lu and co-workers.[223] In this case, $Ir(ppy)_3$ (**89**) was used as a PC, DABCO as a base and an electron mediator, and *tert*-butyl peroxybenzoate (TBPB) as an oxidant in MeCN at room temperature under blue LED irradiation to furnish allylic alcohols **316** in 40 to 75% yields and up to 30 : 1 *Z*/*E* diastereoselectivity (Scheme 122). In the proposed catalytic cycle, reduced Ir(II)$(ppy)_3$ was oxidized by TBPB through a SET to generate Ir(III)$(ppy)_3$ and the *tert*-butyloxy radical, which abstracts the α-hydrogen of the alcohol to form radical **A**. Addition of radical **A** to the α-fluoroacrylate anion generates radical **B**, which gives an electron to $DABCO^{+\bullet}$ to afford cationic intermediate **C** and DABCO. Finally, decarboxylation of **C** gives the thermodynamically more stable *Z*-product **316**.

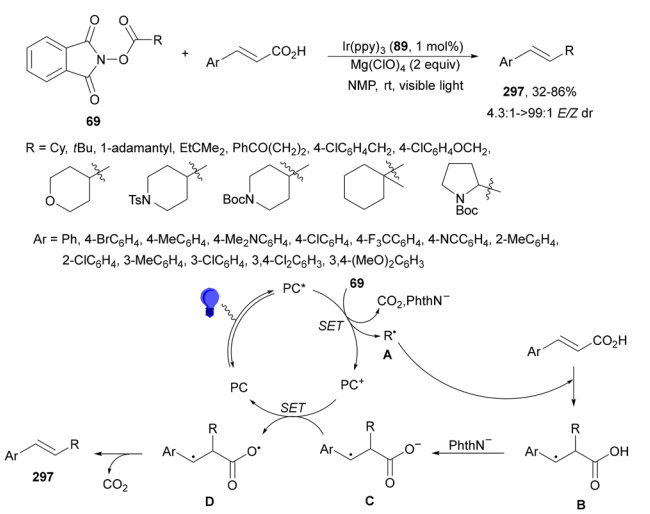
Three main strategies can be used for decarboxylative alkenylation reactions of alkyl carboxylic acids and derivatives under photoredox conditions: (a) vinyl halides or vinyl sulfones as alkenylation agents, (b) Heck-type alkylation of styrenes and enamides, and (c) α,β-unsaturated carboxylic acids as alkenylating reagents of NHPI esters or alkyl halides or alcohols, In the first case, Ir complexes, $NiCl_2$/4CzIPN, $Fe(NO_3)_2$ and organophotocatalysts such as riboflavin tetraacetate and Eosin Y have been used. Heck-type processes with carboxylic acids react in the presence of Ir/Pd or Mes-Acr^{+}/cobaloxime as a dual catalyst, whereas with NHPI esters they have been alkenylated under Pd or Ir or NaI/PPh_3 photocatalysis. Cinnamic acids and derivatives react with NHPI esters under Ir or NaI/PPh_3 photocatalysis, whereas for the reaction with 2-bromo-2,2-difluoro carboxylate derivatives a Ru complex or an Ir complex for alcohols in the presence of DABCO has been employed as a photocatalyst.

2.9. Alkynylation reactions

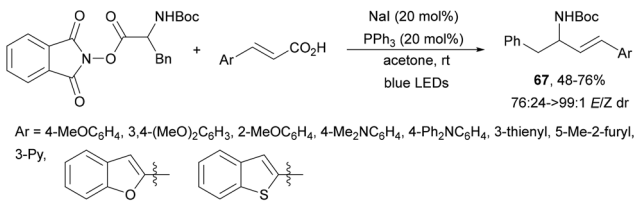
Photoredox-mediated decarboxylative alkynylation of aliphatic carboxylic acids has been carried out using hypervalent iodine reagents,[224,226] alkynyl sulfones or bromides and terminal alkynes. In 2015, Jiao[227] and Waser[228] groups reported independently alkynylation of alkyl carboxylic acids with hypervalent iodine reagents such as ethynylbenziodoxolone (EBX) using Ir complex **4** as a PC. In 2016, Li, Chen and co-workers[229]



Scheme 117 Decarboxylative Heck-type reaction of NHPI esters with 1,1-diarylethylenes (a) or enamides **305** (b) under PPh_3/NaI photocatalysis.



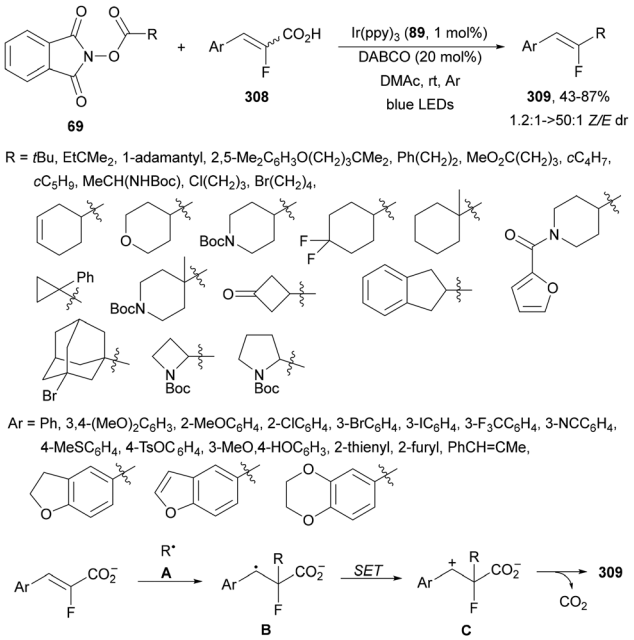
Scheme 118 Decarboxylative alkenylation of alkyl NHPI esters **69** with cinnamic acids under Ir(ppy)$_3$ (**89**) photocatalysis.



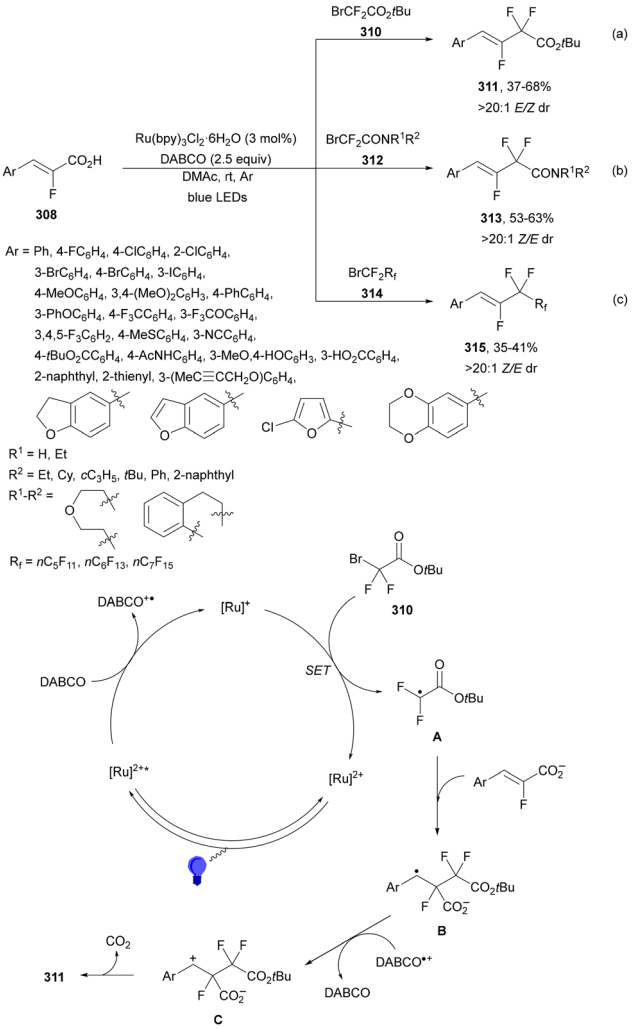
Scheme 119 Decarboxylative alkenylation of a NHPI ester with α,β-unsaturated carboxylic acids under NaI/PPh_3 photocatalysis.

employed 9,10-dicyanoantreacene (DCA) as an organophotocatalyst also under blue LED irradiation.

Alkyl nitrile radicals generated from carboxylic acid derived oxime ethers **317** have been alkynylated with R–EBX **318** by Waser and co-workers[230] using 4ClCzIPN **319** as a PC to provide nitriles **320** under blue LED irradiation (Scheme 123). Azetidinone, cyclobutanone and cyclopentanone oxime ethers **317** gave the corresponding alkynyl nitriles **320** in moderate to good yields. A one-pot protocol started from cyclobutanone



Scheme 120 Decarboxylative alkenylation of alkyl esters **69** with α-fluoro acrylic acids **308** under Ir(ppy)$_3$ (**89**) photocatalysis.



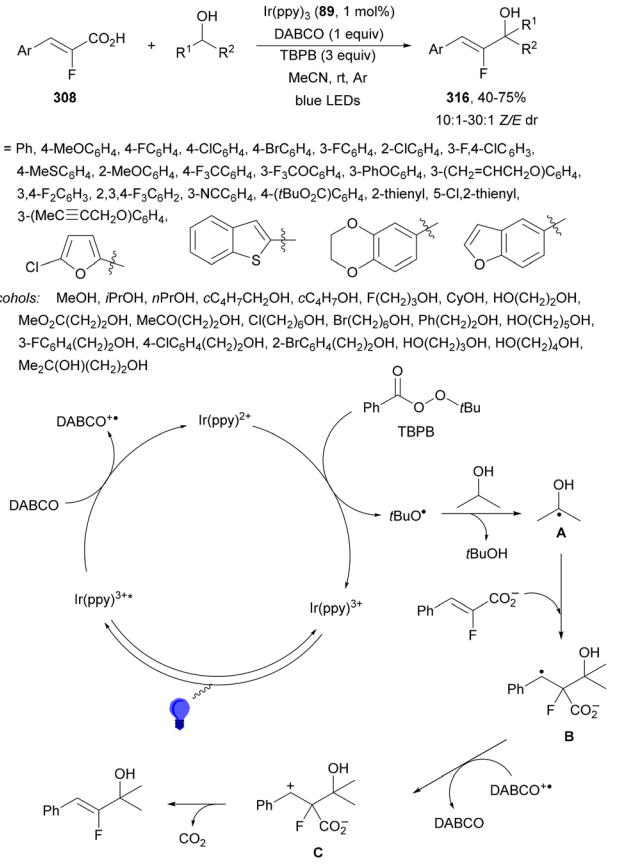
Scheme 121 Decarboxylative alkenylation of 2-bromo-2,2-difluoro-alkane derivatives **310** (a), **312** (b) and **314** (c) with α-fluoroacrylic acids **308** under Ru(bpy)$_3$Cl$_2$·6H$_2$O photocatalysis.

and the hydroxylamine derivative; after condensation, two equivalents of Ph–EBX and 5 mol% of **319** were added followed by 1 hour irradiation delivering 6-phenyl-5-hexynenitrile in 71% yield instead of 79% by isolation of the oxime ether. It was proposed that the reaction starts by oxidation of potassium carboxylate by the excited state of the organophotocatalyst **319** to give carboxy radical **A** and PC$^{-\bullet}$. Decarboxylation of **A** releases the α-oxy radical **B**, which can either lead to iminyl radical **C** after acetone extrusion or can be trapped by the EBX reagent forming **D**. The iminyl radical **C** fragments into alkyl nitrile radical **E**, which reacts with EBX to give, through TS in a concert mechanism, the product and radical **F**. Final reduction of **F** by PC$^{\bullet-}$ allows the generation of PC and potassium carboxylate **G**.

Waser and co-workers[231] performed alkynylation of peptides **321** with R–EBX **318** using 4CzIPN (**25**) as a PC and K_2HPO_4 as a base in degassed aqueous DMF at room temperature under blue LED irradiation (Scheme 124). Arylated R–EBX **318** gave the best results providing alkynylated peptides at the C-terminus **322** in moderate to high yields. Di-, tetra- and hexapeptides even unprotected peptides were efficiently alkynylated as well as in the presence of carboxylic acid side chains except tryptophan, which needed to be protected. According to the previously described proposed mechanism,[228] after decarboxylation of the peptide by photoexcited **25**, the resulting radical **A** adds to R–EBX at the α-position to the iodine radical leading to adduct **B**. Subsequently, β-elimination of iodine radical **C** gives also the alkynylated product. This radical **C** will be reduced by 4CzIPN$^{\bullet-}$ to give 2-iodobenzoate **D**. This methodology was applied to vinylation reactions using vinyl-benziodoxolane as the reagent.

Alkynylation of different glycosylic acids **323** by decarboxylative photoredox reaction with EBXs **318** took place in the presence of Ir complex **324** to provide alkynyl *C*-glycosides **325** in up to 95% yield (Scheme 125).[232] Under visible-light, acids **323** reacted with EBXs in the presence of K_2CO_3 at 40 °C with excellent diastereoselectivity, except for deoxyribosylic acid, which gave a mixture of β : α = 1/2 anomers. In the proposed catalytic cycle, the glycosyl radical adds to **318** followed by radical elimination to give products **325**.

Decarboxylative alkynylation of aliphatic carboxylic acids with R–EBX **318** under 4CzIPN (**25**) photocatalysis has been implemented in batch and continuous flow.[233] Under both reaction conditions α-AAs and dipeptides were alkynylated using DBU as a base in DMSO at room temperature to give products **326** with similar moderate to high yields (Scheme 126a). Scale-up under flow conditions for the reaction of *N*-Boc-Pro with Ph–EBX provided the corresponding product in 88% yield. Aliphatic and α-oxy carboxylic acids were decarboxylative alkylated *via* batch



Scheme 122 Decarboxylative alkenylation of alcohols with α-fluoroacrylic acids **308** under $Ir(ppy)_3$ (**89**) photocatalysis.

conditions in the presence of Cs_2CO_3 as a base to give products **327** in moderate to good yields (Scheme 126b).

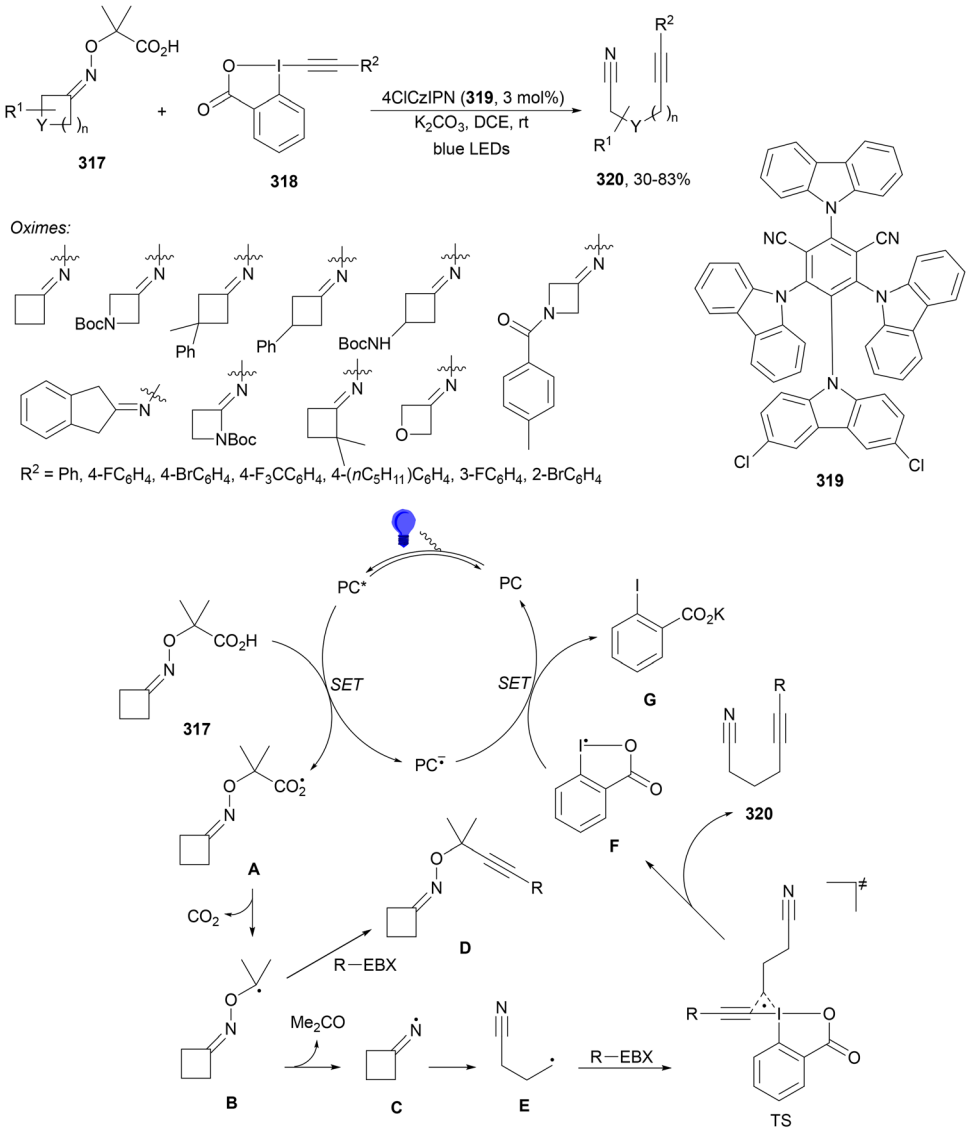
Along this manuscript it has been shown that unsaturated sulfones are excellent SOMO-philes to trap alkyl radicals.[209] Recent applications of alkynyl sulfones in decarboxylative photoredox processes have been described by Wei, Hu and co-workers[210] using $Fe(NO_3)_3$ *via* a LMCT[54,55] mechanism (Scheme 110). They reported a couple of examples using alkynyl sulfone **328** and alkyl carboxylic acids under similar reaction conditions to that for styryl sulfones **295a** to provide products **327** in moderate yields (Scheme 127).

Zhao, Xia and co-workers[234] recently reported an iron-catalyzed LMCT photoredox *via* fragmentation–alkynylation of carboxylic acid derived oxime ethers **317** to give alkynes **320** using alkynyl sulfones **329** as reagents (Scheme 128). The resulting products **320** were obtained in the presence of $Fe(acac)_3$ as a PC and KOH as a base in toluene under N_2 at 30 °C and 390 nm LED irradiation. This procedure was performed under batch conditions and a gram-scale reaction was carried out using cyclobutanone derived oxime **317a** and methyl phenylethynyl sulfone to give 6-phenyl-5-hexynenitrile in 75% yield. A plausible mechanism involves the photoexcitation of a carboxylate-iron(III) complex **B**, which by the LMCT event produces the reduced Fe(II) complex and an aroyloxy radical **C**. Subsequent decarboxylation of **C** releases a radical intermediate **D**, which generates after fragmentation the iminyl radical **E** followed by a radical transposition to radical **F**. Addition of radical **F** to alkynyl sulfone gives radical **G**, which after methylsulfonyl radical elimination leads to product **320**. This methodology has been applied to styryl sulfones and allyl sulfones to obtain the corresponding unsaturated nitriles.

Alkynyl bromides **330** reacted with glyoxylic acid acetal **26** in the presence of 4CzIPN (**25**) as a PC and Cs_2CO_3 as a base in a mixture of DMF/MeCN at room temperature under blue LED irradiation to give alkynyl acetal products **331** with moderate yields (Scheme 129).[235] Radical intermediate **A** can lose CO_2 to form acetal radical **B**, which adds to alkynyl bromide **330** to give radical **C** which forms the product and a bromine radical. This protocol can be applied to the synthesis of acetylenic aldehydes by acid hydrolysis.

Alkynyl *C*-nucleosides **325** have been directly prepared by decarboxylative alkynylation of ribosyl carboxylic acids **323** with terminal alkynes under Ir/Cu dual photocatalysis by Zhu and Messaoudi.[236] This coupling was carried out using CuOAc and 4,4′-di-*t*Bu-bpy **322** as a ligand, Ir complex **4** as a PC, and CsOAc as a base in DMA at room temperature under air and blue LED irradiation to furnish products **325** with, in general, good yields and high diastereoselectivity (Scheme 130). Aryl-substituted alkynes with electron-withdrawing and electron-donating groups successfully reacted under these reaction conditions as well as heteroaromatic alkynes. Challenging aliphatic alkynes afforded the corresponding products in yields ranging from 52 to 93%. With respect to carboxylic acid protecting groups, benzoyl and acetonide produced products **325** in an α,β ratio of 4 : 1, whereas benzyl protected 2-deoxy-D-ribose gave **325** in a 6 : 1 α,β ratio. On the other hand, OBn-protected glucopyranosyl acid failed. The presence of oxygen inhibits the competitive decarboxylative hydroalkylation of the alkyne under dual copper-photoredox catalysis.[98] In the proposed mechanism, the photocatalytic cycle generates the anomeric radical **A** and the reduced Ir(II) complex. In the copper-catalyzed cycle the monomeric Cu(I)-acetylide complex **B** is formed, which by a SET gives the Cu(II)-complex **C**. At this stage, two possible pathways may be involved: (a) oxidation of the Cu(I) complex by oxygen, or (b) photoexcitation of LCu(I) to LCu(I)* followed by SET. Subsequently, the anomeric radical **A** can be captured by Cu(II) complex **C** to form the Cu(III)-species **D**, which after reductive elimination delivers product **325** and regenerates the Cu(I) catalyst. Reoxidation of the Ir(II) complex by a molecule of dioxygen regenerates the Ir PC and closes the catalytic cycle.

Double decarboxylative coupling of alkynoic acids **333** and alkyl carboxylic acids has been reported by Lee and co-workers[237] to obtain the corresponding internal alkynes **327** (Scheme 131). This process was carried out with $Fe(NO_3)_3{\cdot}9H_2O$ or $FeCl_2$/tris(2-pyridylmethyl)amine (TPA) as a catalyst and $PhI(OAc)_2$ as an oxidizing agent in MeCN at room temperature under blue LED irradiation. Initial studies were performed with different alkynoic acids **333** and 2,3-dihydro-1,4-benzodioxine-2-carboxylic acid **334** to afford products **327** with good yields (Scheme 131a). However, when diverse alkyl carboxylic acids were allowed to react with

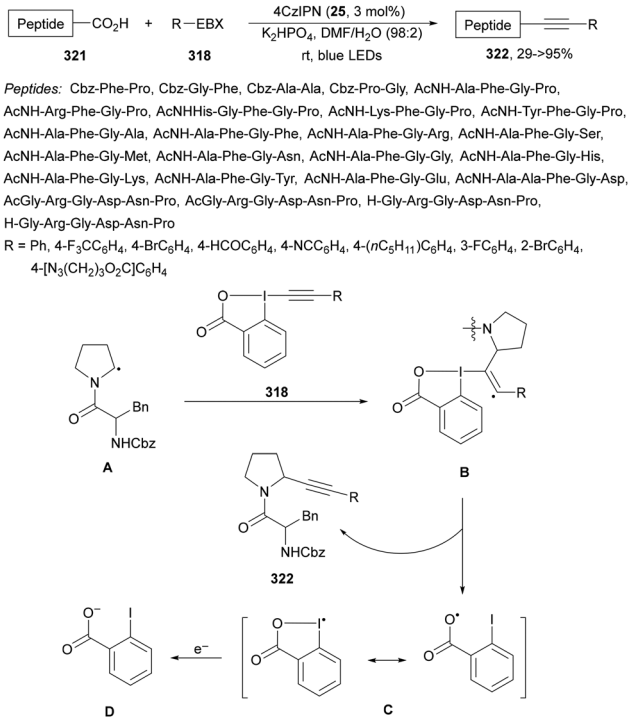


Scheme 123 Decarboxylative alkynylation of oxime ethers **317** with R–EBX (**318**) under 4ClCzIPN (**319**) photocatalysis.

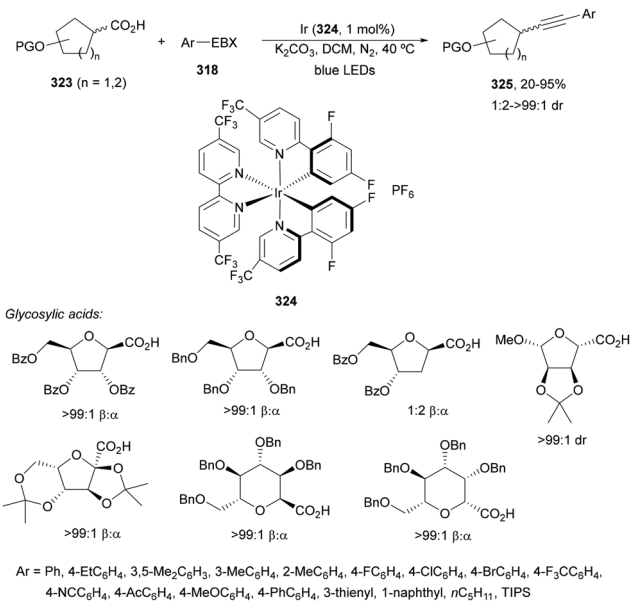
phenyl propiolic acid the corresponding alkynes **327** were isolated with good yields (Scheme 131b). According to control experiments a plausible mechanism was proposed. Initially, the alkyl carboxylic acid reacts with $PhI(OAc)_2$ to give intermediate **A**, which reacts with the photoactivated Fe(III)* or Fe(II)* catalyst by SET to give after decarboxylation the radical anion species **B**. This intermediate evolves to radical **C**, which adds to the alkynoic acid to form radical **D**. Sequential SET and deprotonation of **D** provides intermediate **E**, which after decarboxylation affords the acetylenic product **327**. The formation of radical **C** by a LMCT[54,55] pathway has been also postulated.

Decarboxylative alkynylation of NHPI esters **69** has been performed using alkynyl sulfones or directly terminal alkynes under mild reaction conditions. Under visible light irradiation alkynyl sulfones **329** reacted with NHPI esters using different photocatalysts such as $Ru(bpy)_3(PF_6)_2$.[226,238–241] Recently, Xu, Song and co-workers[242] described the alkynylation of *gem*-borylsilyl NHPI ester **334** with alkynyl sulfones **328** using $Ir(ppy)_3$ as a PC, Hantzsch ester (HE) as a reductant, and DIPEA as a base in DCM at room temperature under Ar and blue LED irradiation to obtain alkynes **335** with good yields (Scheme 132). In the proposed mechanism, the Ir(II) complex, formed by reduction of Ir(III)* in the presence of HE *via* a SET process, reduced NHPI ester **334** to give the β-borylsilyl radical **A** releasing CO_2 and $PhthN^-$. This intermediate **A** adds to alkynyl sulfone **328** affording radical **B**. Final β-elimination of the sulfonyl radical provides the product. The same process was carried out with allyl sulfones to furnish the corresponding allylated products.

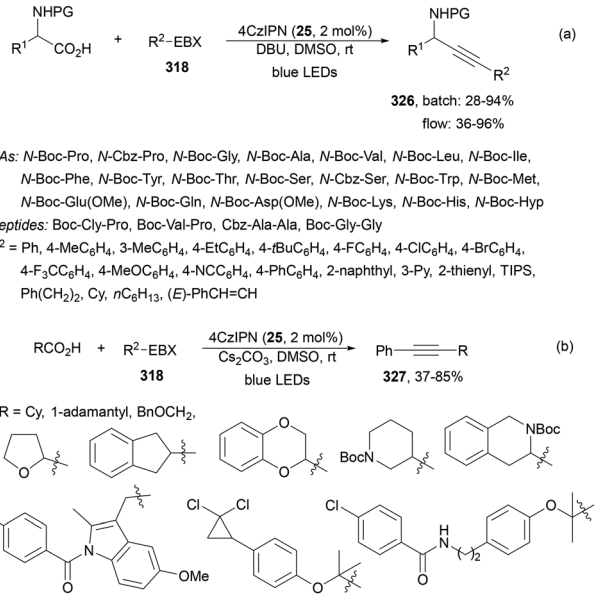
Decarboxylative alkynylation of NHPI esters **69** with terminal alkynes, as in the case of carboxylic acids, has been carried out under copper catalysis. Fu and co-workers[243] employed $Ru(bpy)_2Cl_2$/CuI and visible light at room temperature with α-AAs to give the corresponding propargyl amines in good yields. Later, Zhang and Zhang[244] reported the use of CuI (10 mol%) and a tridentate



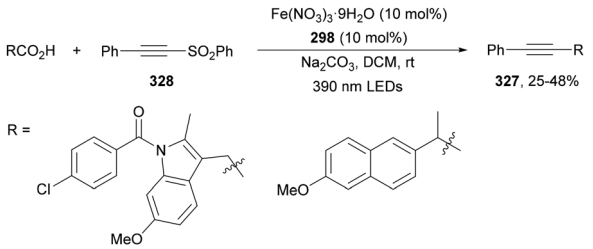
Scheme 124 Decarboxylative alkynylation of peptides **321** with alkynylbenziodoxolones (**318**) under 4CzIPN (**25**) photocatalysis.



Scheme 125 Decarboxylative alkynylation of glycosylic acids **323** with Ar–EBX **318** under Ir complex **324** photocatalysis.



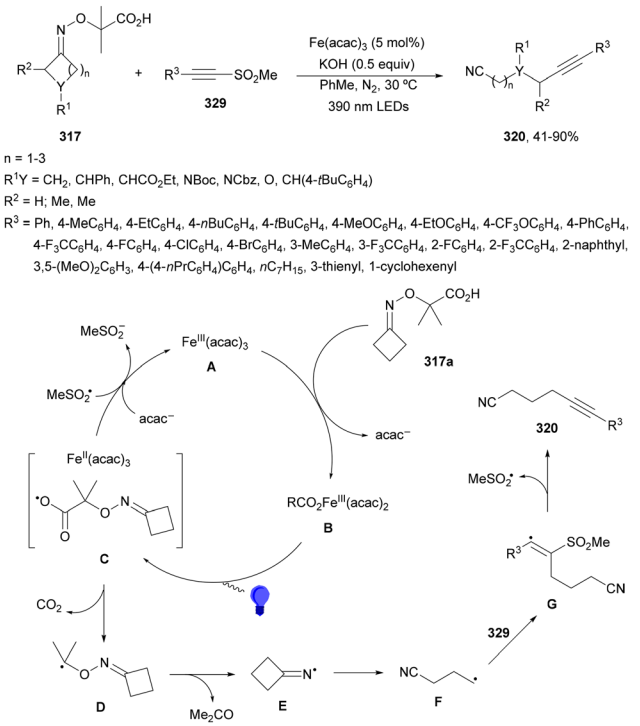
Scheme 126 Decarboxylative alkynylation of α-AAs, peptides (a), α-oxy acids and aliphatic carboxylic acids (b) with R–EBX (**318**) under 4CzIPN (**25**) photocatalysis under batch and flow conditions.



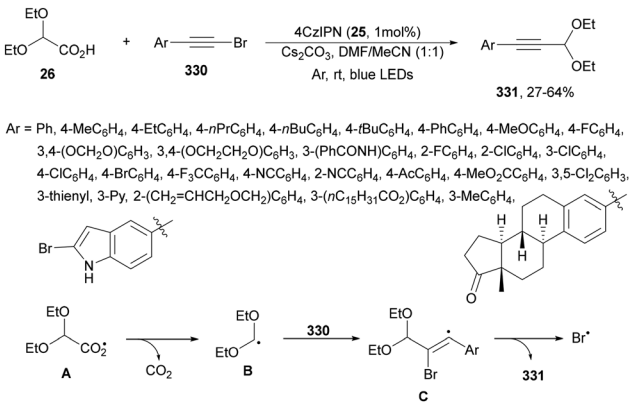
Scheme 127 Decarboxylative alkynylation of aliphatic carboxylic acids with alkynyl sulfone **328** under $Fe(NO_3)_3$ photocatalysis.

ligand **336** for the alkynylation of NHPI and *N*-hydroxytetrachlorophthalimide (TCNHPI) esters derived from primary, secondary and tertiary carboxylic acids with terminal alkynes to give internal alkynes **327** with good yields (Scheme 133). Experimental studies reveal that the Cu–acetylide **A** gives after irradiation excited complex **B**, which by a SET to the NHPI ester generates complex **C** and radical **D**. Both intermediates **C** and **D** form the Cu(III) species **E**, which undergoes reductive elimination to furnish the product.

Wang, Liang, Ni and co-workers[245] reported the same alkynylation process using CuCl and $Cu(acac)_2$ as catalysts in the presence of Et_3N as a ligand in THF at room temperature under Ar and blue LED irradiation. The corresponding internal alkynes **327** were obtained in 26–76% yields with a wide range of carboxylic acid derivatives and terminal alkynes (Scheme 134a). Cyclohexanecarboxylic acid was allowed to react with *N*-hydroxyphthalimide using DCC in DCM and the formed NHPI ester was alkynylated *in situ* with $4\text{-MeC}_6\text{H}_4\text{C}{\equiv}\text{CH}$ under the above reaction conditions providing the corresponding alkyne in 70% yield. For the coupling of non-aryl alkynes, 10% of $\text{PhC}{\equiv}\text{C–Cu}$ should be added giving products **327** in 45–98% yield (Scheme 134b). Experimental and theoretical DFT calculations supported a reaction mechanism which starts by formation of complex **A** by reaction of CuCl with Et_3N. Subsequently, complex



Scheme 128 Decarboxylative alkynylation of carboxylic acid derived oxime-ethers **317** with alkynyl sulfones **329** under $Fe(acac)_3$ photoredox conditions.



Scheme 129 Decarboxylative alkynylation of glyoxylic acid acetal **26** with alkynyl bromides **330** under 4CzIPN (**25**) photocatalysis.

A reacts with the terminal acetylene to form the corresponding acetylide **B**, which is photoexcited to intermediate **C**. This photosensitive Cu(I) acetylide **C** undergoes a SET process with the NHPI ester to afford, after decarboxylation, alkyl radical **D** and Cu(II)-acetylide **E**. Ligand exchange of **E** with $Cu(acac)_2(NEt_3)$ gives the copper complex **F**. Final addition of radical **D** to **F** provides the Cu(III) intermediate **G**, which after reductive elimination furnishes acetylene **327** and **H**. For photoexcitation of copper acetylide the use of a conjugate aromatic terminal alkyne is required to work in the visible light energy range. Secondly, the ligand NEt_3 promotes the electron transfer from the copper acetylide to NHPI ester. Finally, the acac ligand intervenes in the generation of bi-copper complexes, which inhibits the homo-coupling of the terminal alkyne.

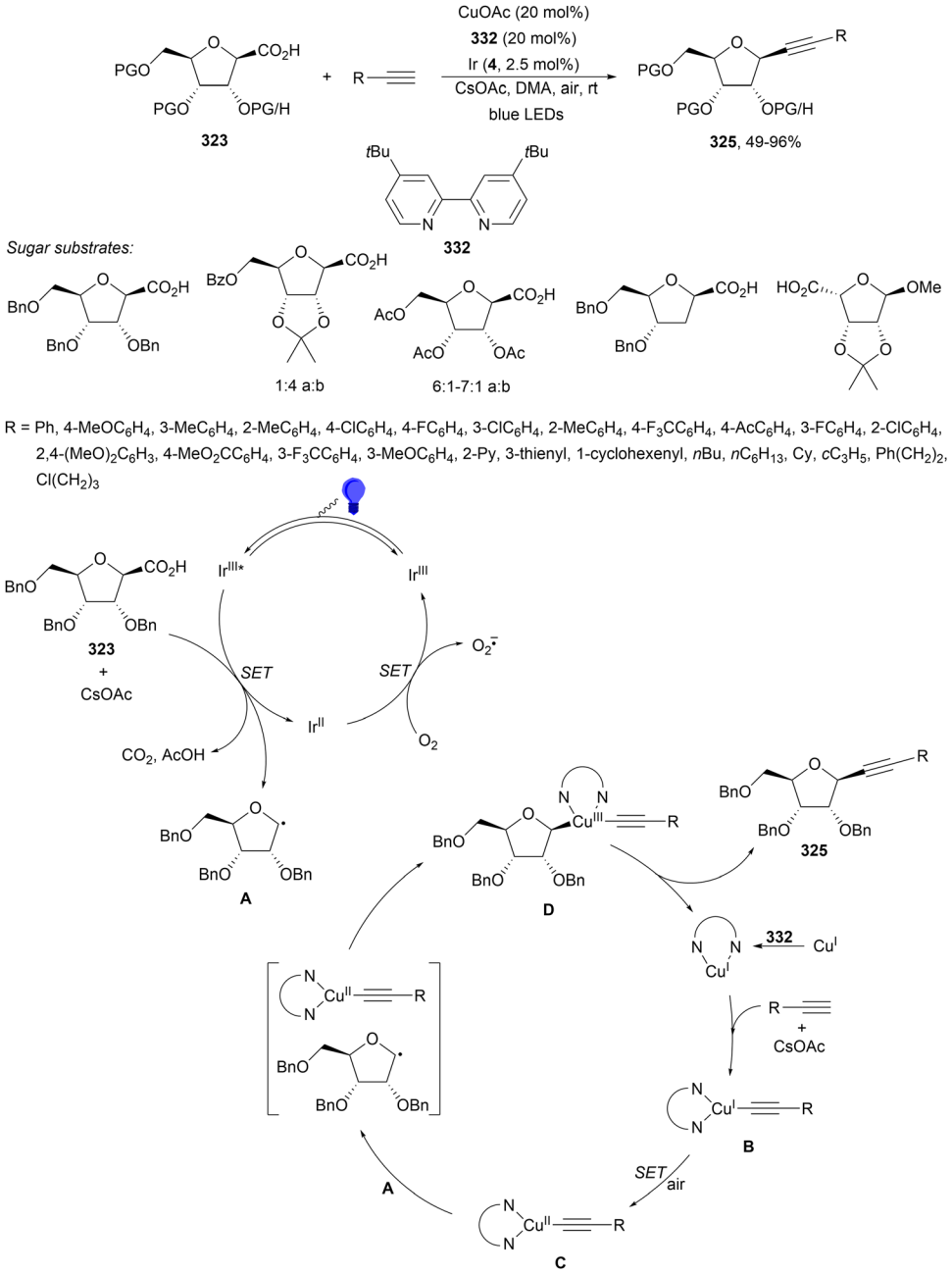
Enantioconvergent[140] decarboxylative alkynylation of NHPI esters with terminal alkynes has been described by Liu and co-workers.[246] *N*-Hydroxy-2,3-naphthalimide **337** derived from carboxylic acids bearing at the α-position a stereocenter reacted with aliphatic and aromatic terminal alkynes using Cu(I) as a PC, chiral phosphine **338** as a ligand, and Cs_2CO_3 as a base in trifluoromethylbenzene at room temperature under blue LED irradiation. The corresponding enantioenriched alkynes **339** were obtained in up to 81% yield and up to 99% ee (Scheme 135). A wide range of NHPI esters **337** and terminal alkynes were employed, and a one-pot synthesis and gram-scale preparation were successfully performed. These NHPI esters **337** quenched the excited copper acetylide **A** very efficiently enabling Glaser coupling.

Decarboxylative alkynylation of aliphatic carboxylic acids or their NHPI esters under visible-light photoredox conditions is an excellent protocol for the formation of $C(sp^3)$–$C(sp)$ bonds using mild reaction conditions. Hypervalent iodine reagents, alkynyl sulfones and terminal alkynes have been employed for the synthesis of internal alkynes. Peptides can be alkynylated at the C-terminus and glycosylic acids at the anomeric carbon atom with high diastereoselectivity. All these alkynylation reactions can be carried out using mainly 4CzIPN as an organocatalyst. However, copper-catalyzed processes are more effective with terminal alkynes and have been applied to the enantioconvergent decarboxylative alkynylation of NHPI esters using an amino phosphine as a chiral catalyst.

2.10. Acylation reactions

$C(sp^3)$–$C(sp^2)$ bond formation using acyl radicals allowed the synthesis of ketones and carbamoyl radicals giving amides by decarboxylation of α-keto acids and oxamic acids, respectively. Acyl radicals reacted with alkenes and imines by addition reactions and can be arylated, allylated and alkynylated. Zhu and co-workers[247] developed a visible-light-mediated decarboxylative acylation of styrenes **2** with α-keto acids **15** using Ir complex **4** as a PC (Scheme 136). The corresponding α,β-unsaturated phenones **18** were obtained with good yields in the presence of Selectfluor and NaOAc as a base in a 1 : 1 mixture of $MeCN/H_2O$ at room temperature. In the proposed mechanism, photoexcited Ir(III) oxidized the α-keto acid by a SET process to an acyl radical **A** after decarboxylation. This radical **A** adds to styrene to deliver the benzylic radical **B**. Subsequently, Selectfluor reacts with **B** to provide a β-fluoro ketone and the radical **C**, which oxidizes Ir(II) by a SET procedure to give Ir(III). The α-fluoro ketone eliminates HF in the presence of base to provide the final α,β-unsaturated ketone **18**. Tunge and co-workers[63] employed cobaloxime **16** and [Mes-Acr-Ph]BF_4 **17** as dual catalysis (see Scheme 6).

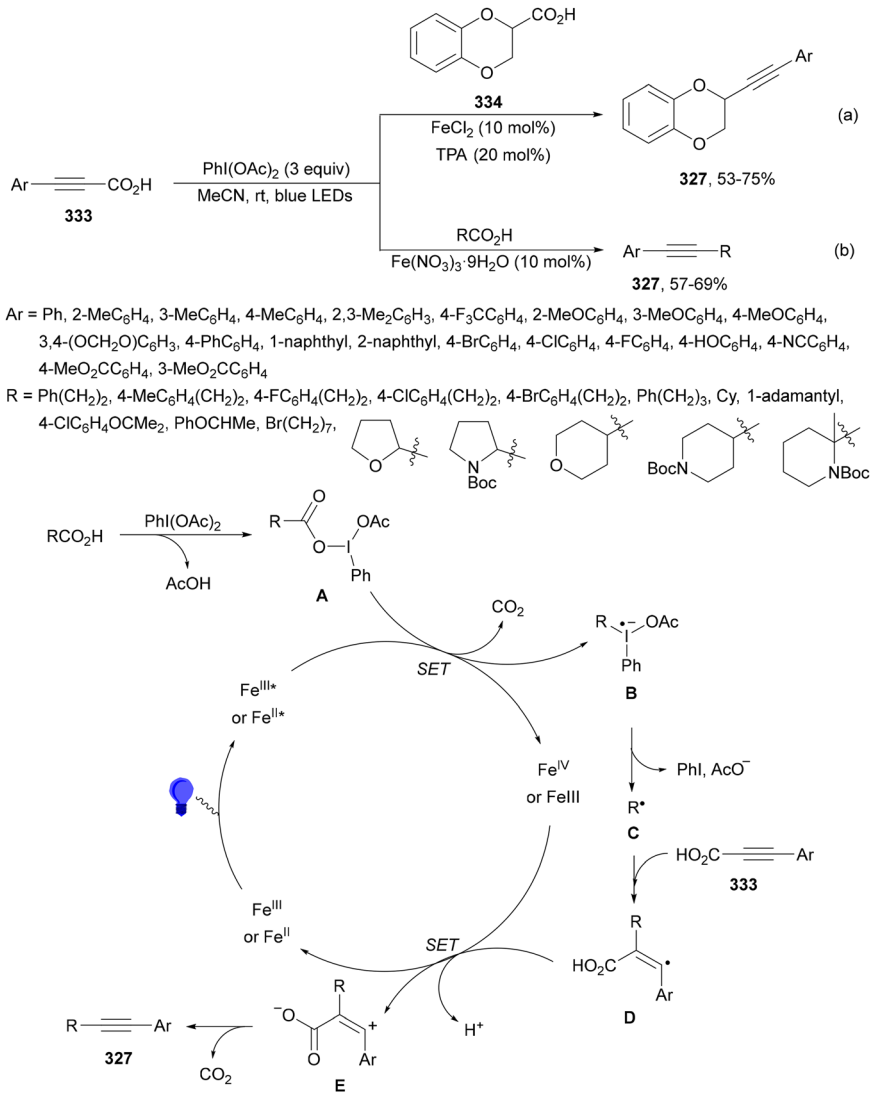
Alkylation of *N*-acyl saccharins **340** by photoredox decarboxylation of NHPI esters **69** under visible-light has been reported by Opatz and co-workers.[248] In the presence of Hantzsch ester



Scheme 130 Decarboxylative alkynylation of furanosyl carboxylic acids **323** with terminal alkynes under Ir/Cu dual photocatalysis.

(HE) as a photoreductant to promote radical generation and to participate in the Ni-catalyzed cycle to restore the reaction species, the corresponding ketones were formed in moderate to good yields (Scheme 137). Aroyl and alkanoyl moieties were alkylated with primary, secondary, benzylic, α-oxy and α-amino radicals. According to computational (COSNAR method) and spectroscopic studies, a catalytic cycle was proposed. The Ni(II) complex is reduced by HE to generate Ni(0) species, which undergoes oxidative addition to the *N*-acyl saccharin **340** to lead to intermediate **A**. This intermediate trapps radical **B** from the NHPI ester **69** to give the Ni(II) intermediate **C**, which after reductive elimination provides the ketone and the Ni(II) species **D**. Final reduction of **D** by photoexcited HE closes the catalytic cycle.

Glycosyl esters **37** have been acylated with carboxylic acids to the corresponding *C*-acyl furanosides using 4CzIPN (**25**) and $NiCl_2$·DME with 2,2′-bis-2-oxazoline **341** as the ligand in the presence of diethyl dicarbonate (DEDC) in dioxane under blue LED irradiation. Diao and co-workers[249] employed a large number of furanoses, pyranoses and carboxylic acids and obtained acylated furanosides **342** with, in general, good yields including a thymidine analogue, and diplobifuranylone B and

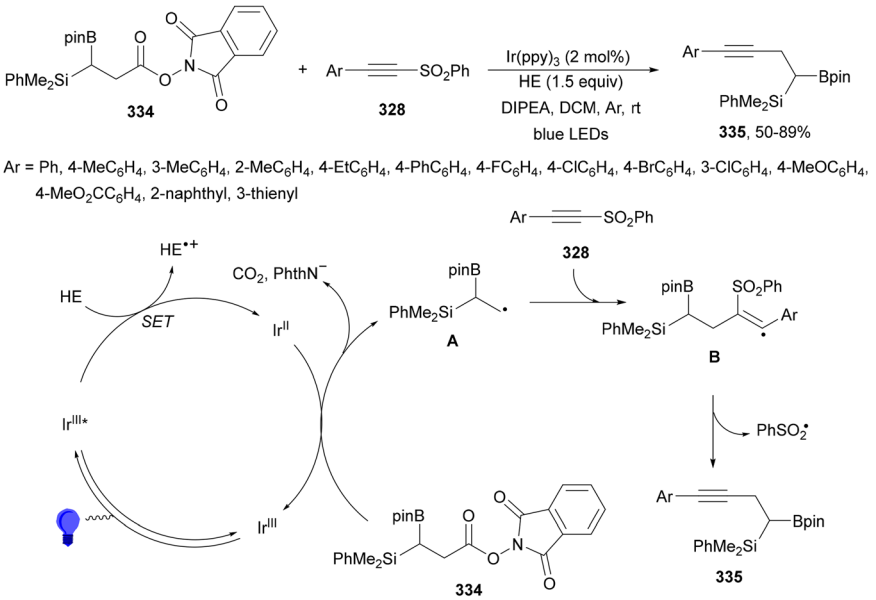


Scheme 131 Double decarboxylative alkynylation of alkyl carboxylic acids with alkynoic acids **333** under iron photocatalysis (a, b).

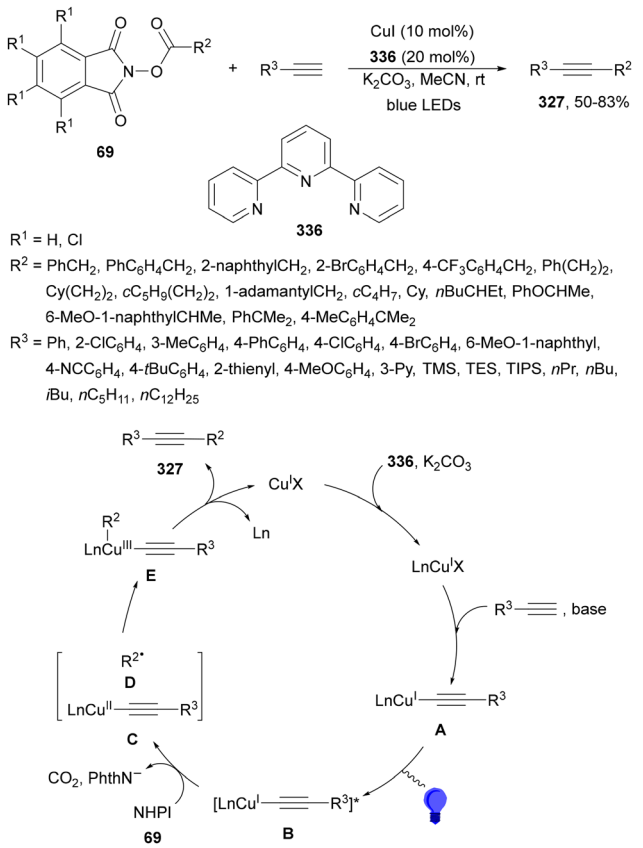
the modification of (+)-sclareolide (Scheme 138). In the proposed mechanism, the dihydropyridine (DHP) esters undergo anomeric homolysis under photoexcited PC **25** through CO_2 and HE-derived pyridine evolution to form a glycosyl radical **A**, which reacts with the Ni(II) intermediate **B** to form the Ni(III) complex **C**. Subsequent reductive elimination gives the product and Ni(I)Br, which is reduced by $PC^{\bullet -}$ to Ni(0). Reaction of diethyl dicarbonate with the acid provides the mixed anhydride **D**, which reacts with Ni(0) to regenerate **B** and CO_2.

Molander and co-workers[250] performed the synthesis of *C*-acyl glycosides **342** using furanosyl and pyranosyl acids as acylating agents and NHPI esters **69** as sources of alkyl radicals. This Ni-mediated reaction took place through an electron donor–acceptor (EDA) complex between HE and NHPI ester[170] (see Scheme 75). In the presence of HE and dimethyl dicarbonate (DMDC) using complex Ni(dtbpy)Br_2 (**210**) as a catalyst, this photoredox acylation provided products **342** with moderate to good yields (Scheme 139). In the proposed mechanism, HE and NHPI ester forms a molecular aggregate **A**, which after irradiation at 390 nm triggers SET to give $HE^{+\bullet}$ and radical $R^{\bullet}$. DMDC activates the saccharide acid affording *in situ* a carbonic anhydride **B**. The alkyl radical can follow two pathways based on computational studies, initial oxidative addition of a Ni(0) species to **B**, forming the Ni(II) intermediate **C**, which undergoes radical addition to afford the Ni(III) complex **D**. Subsequent reductive elimination from **D** gives the product and the Ni(I) complex **F**, and the Ni(0) catalyst is regenerated from photoexcited HE. The other possible mechanistic pathway starts with the reaction of the alkyl radical and Ni(0) affording the Ni(I) intermediate **E**, which undergoes oxidative addition of anhydride **B** to give the Ni(III) species **D**.

The reductive decarboxylative acyl cross-coupling between 2-pyridyl esters **343** and NHPI esters **69** has been carried out by Qi, Yuan and co-workers[251] using 4CzIPN (**25**) and $NiBr_2$·glyme with **344** as a ligand under dual photocatalytic conditions to provide ketones (Scheme 140). A broad range of primary,



Scheme 132 Decarboxylative alkynylation of *gem*-borylsilyl NHP esters **334** with alkynyl sulfones **328** under $Ir(ppy)_3$ photocatalysis.

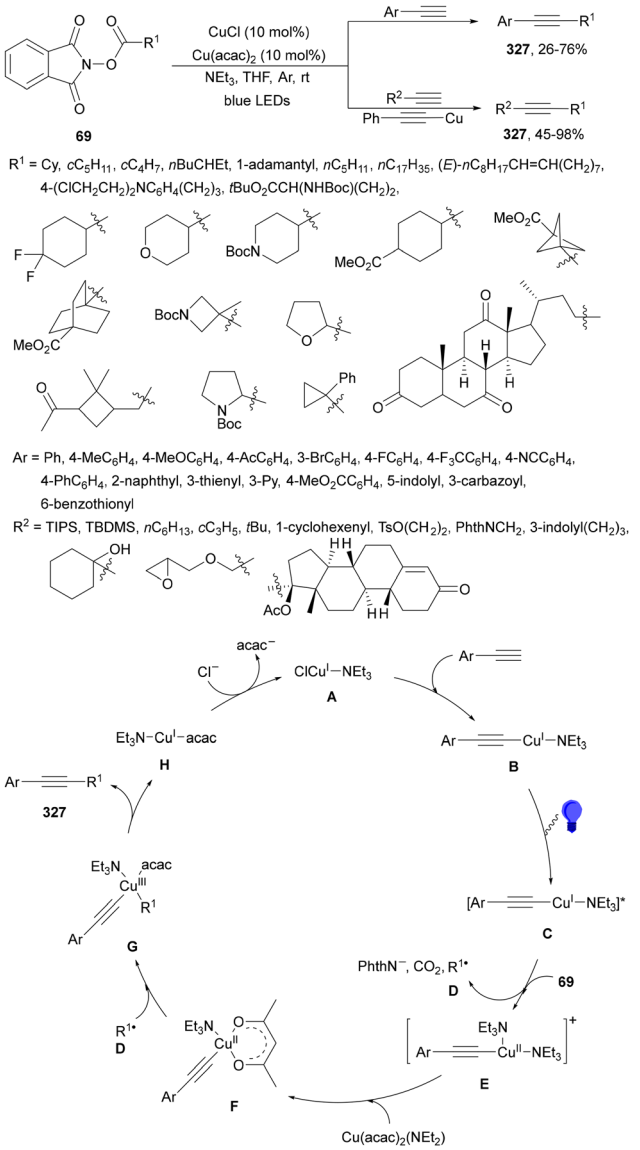


Scheme 133 Decarboxylative alkynylation of NHPI esters **69** with terminal alkynes under Cu(I) photocatalysis.

secondary and tertiary alkyl NHPI esters **69** as radical precursors and 2-pyridyl esters **343** as acylating components were employed. The presence of HE was crucial to form the photoactive electron donor–acceptor (EDA) complex between NHPI ester and HE[170] (see Schemes 75 and 139), which by irradiation evolves to give the corresponding radical, CO_2 and phthalimide anion. This radical enters the Ni-catalytic cycle Ni(0)/Ni(I)/Ni(III) to give after final reductive elimination of the Ni(III) intermediate, the ketone.

A related procedure has been recently reported using *S*-2-pyridyl thioesters **345** instead of 2-pyridyl esters **343**. Guo, Wu and co-workers[252] performed the alkylation of *S*-2-pyridyl (SPy) aryl thioesters **345** with alkyl NHPI esters **69** in the presence of HE, $NiCl_2$·DME, and ligand **344** as a catalyst to furnish alkyl aryl ketones with good yields (Scheme 141). In the proposed mechanism, HE is excited by a blue LED irradiation and promotes the formation of the alkyl radical **A** from the NHPI ester. This radical **A** reacts with Ni(0) to form the Ni(I) intermediate **B**, which undergoes oxidative addition to SPy to give the Ni(III) intermediate **C**. Alternatively, Ni(0) gives oxidative addition to SPy followed by radical recombination with **A**. Reductive elimination of **C** regenerates Ni(I) intermediate **D** and the product. The oxidized $HE^{+\bullet}$ undergoes deprotonation to form a PyH derivative from HE as a by-product.

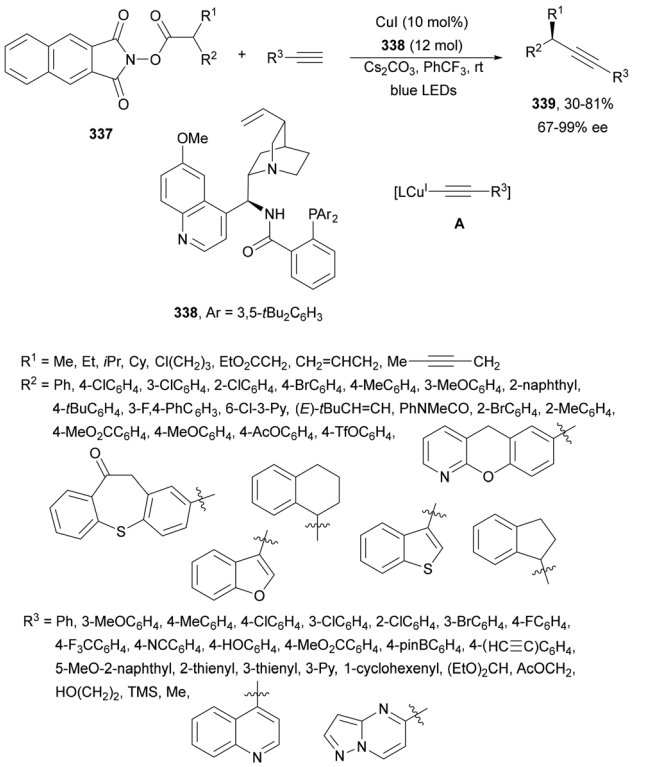
Acylation of aryl halides with α-keto acids **15** was initially described by MacMillan[253] and Fu[254] groups under photocatalytic decarboxylation conditions to provide the corresponding phenones. These $C(sp^2)$–$C(sp^2)$ cross-coupling reactions were carried out using Ir/Ni[253] and Ir/Pd[254] photoredox dual catalysis. The organic dye 2-chlorothioxanthen-9-one (ClTXO, **346**) has been used instead of an Ir PC by Li and co-workers.[255] This process was effective for the acylation of aryl bromides with aryl and some alkyl α-keto acids using $NiCl_2$·glyme and the ligand dtbbpy as a catalyst in aqueous DMF to give diaryl ketones with good yields under visible light (Scheme 142a). These reaction conditions in the absence of Ni have been employed for the hydroacylation of electron-deficient alkenes, such as acrylates



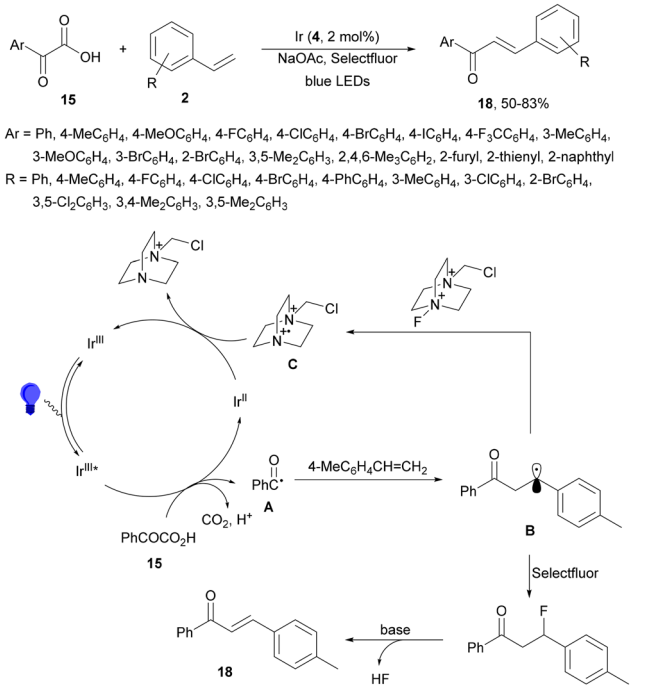
Scheme 134 Decarboxylative alkynylation of NHPI esters **69** with terminal alkynes under Cu(I) photocatalysis.

and α,β-unsaturated ketones to furnish the corresponding 1,4-dicarbonyl compounds (Scheme 142b).

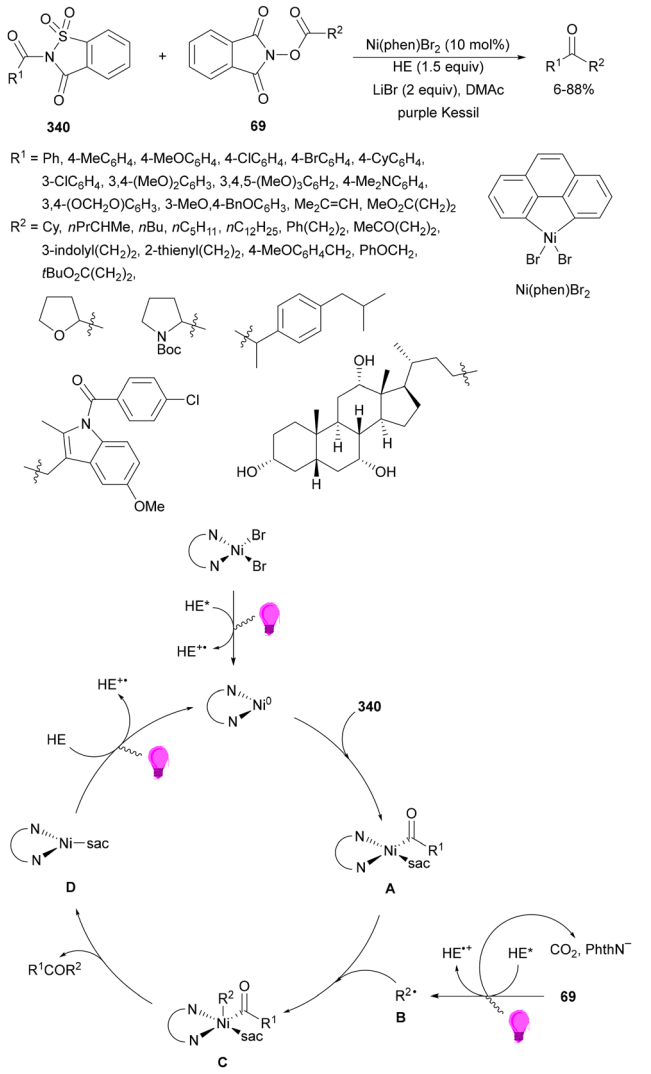
Oxalates derived from alcohols were used by Zhang and MacMillan[256] for the cross-coupling of aryl halides with alkyl radicals. More recently, Xia and co-workers[257] employed potassium oxalates **347** for the alkoxycarbonylation of aryl and alkenyl bromides with Ir complex **4** as a PC and $NiBr_2(PCy_3)_2$ and dtbbpy as a catalyst under blue LED irradiation. This method gave the corresponding esters with good yields using 1,4-dioxane as solvent at room temperature (Scheme 143). Some synthetic applications allowed the synthesis of probenecid, mefenamic and adapalene, which were prepared with good yields. According to mechanistic studies a plausible mechanism was proposed, starting with the generation of an alkoxycarbonyl radical **A** by reduction of the hemioxalate *via* SET in



Scheme 135 Enantioconvergent decarboxylative alkynylation of NHPI esters **337** under CuI/**338** photocatalysis.



Scheme 136 Decarboxylative acylation of styrenes **2** with α-keta acids **15** under Ir photocatalysis.



Scheme 137 Decarboxylative acylation of NHPI esters **69** with *N*-acyl saccharins **340** under HE and Ni(phen)Br_2 photocatalysis.

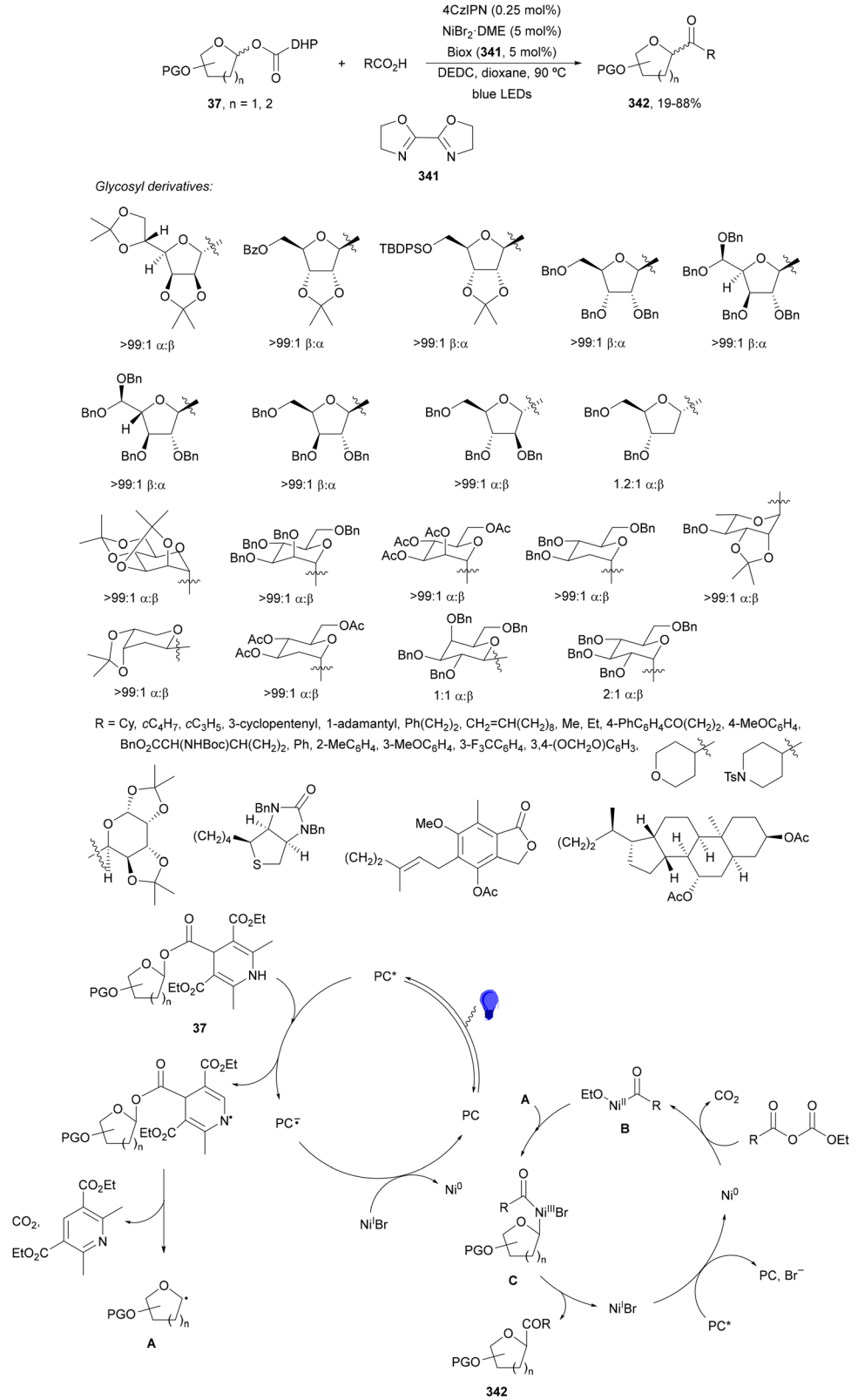
the Ir catalyzed cycle. This radical **A** (path b) is captured by the LnNi(0) species to give the (alkoxycarbonyl)Ni(I) species **B**. Subsequent oxidative addition of organic bromide to **B** generates the Ni(III) intermediate **C**, which by reductive elimination furnish the ester product and the Ni(I) complex **D**. Final reduction of **D** by Ir(II) regenerates Ni(0) species. An alternative possible pathway a proceeds by oxidative addition of the organic halide to Ni(0) species to give Ni(II) species **E**, which was trapped by the alkoxycarbonyl radical to provide the same Ni(III) species **C**. However, the stoichiometric coupling experiment may not support this pathway.

Photoredox decarboxylation of α-keto acids **15** in the presence of 4CzIPN (**25**) as a PC and cobaloxime **348** as a catalyst has been employed by Zhong and co-workers[258] for the allylation reactions with methacrylates to furnish allylic ketones **349** (Scheme 144). These allylated compounds **349** were formed by dehydrogenation promoted by the cobaloxime $Co(dmgBF_2)_2(H_2O)_2$ (**348**) as a catalyst. Products **349** were mainly formed using 2,6-lutidine as a base with good yields, whereas in the presence of *t*BuOK as a base the corresponding saturated 1,4-dicarbonyl compounds **350** were obtained. In the proposed mechanism, the excited 4CzIPN is reductively quenched by the anion of the keto acid leading to a benzoyl radical **A** with CO_2 extrusion and the reductive species $4CzIPN^{-\bullet}$. Benzoyl addition of **A** to ethyl methacrylate generates radical **B**, which is captured by Co(II) to form **C**, an intermediate Co(III). The cleavage of the Co–C bond and subsequent β-H elimination gives the allylic ketone **349** and Co(III)–H. This hydride reacts with ethyl methacrylate to generate Co(III) and a reductive by-product. Subsequent SET from $4CzIPN^{\bullet-}$ to Co(III) regenerates the photoredox catalytic cycle and the cobaloxime catalytic cycle. Co(III)–H can also react with a proton to form H_2 but only 23% of H_2 was detected.

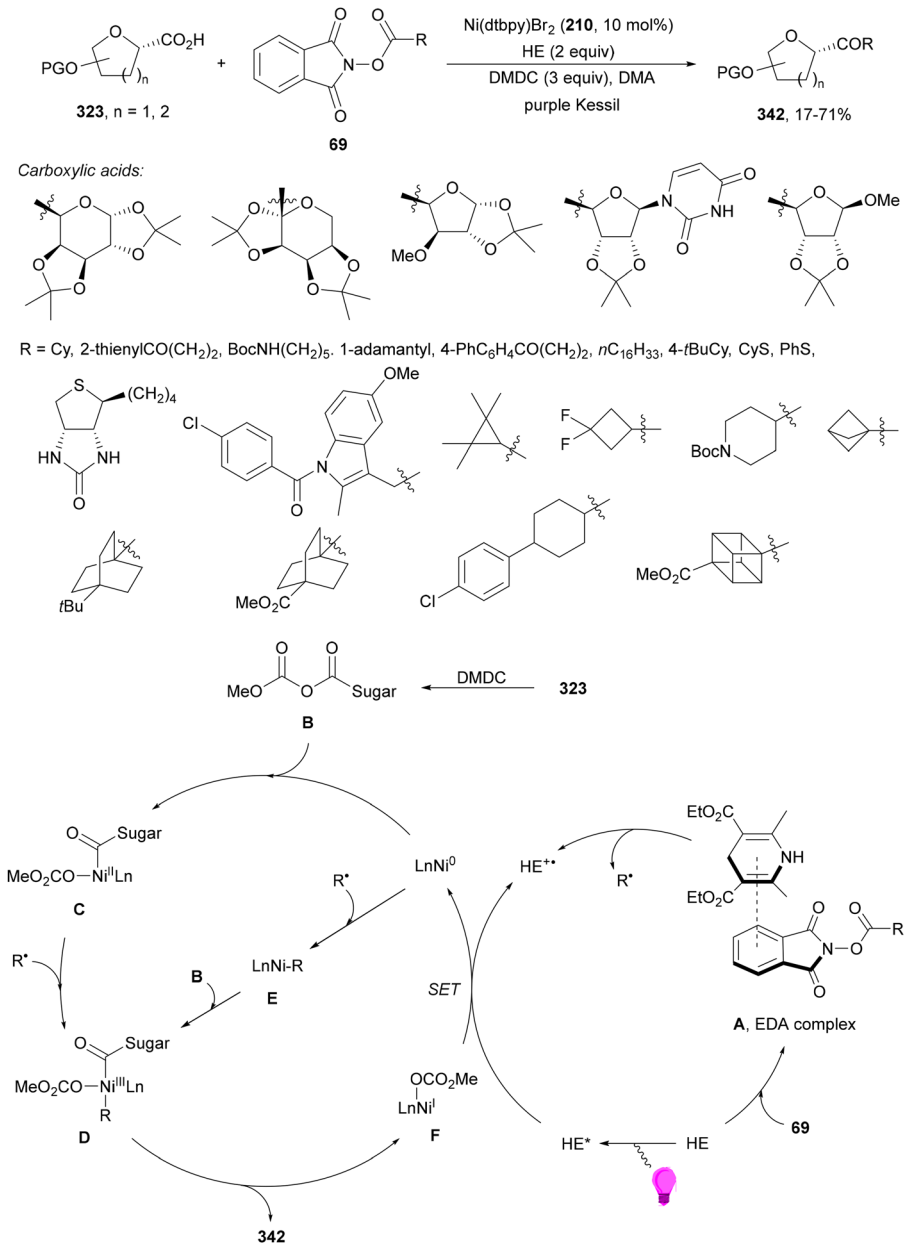
Decarboxylative acylation of Morita–Baylis–Hillman carbonates **351** with α-keto acids **15** has been carried out with $Ru(bpz)_3(PF_6)_2$ (**352**) as a PC under blue LED irradiation.[259] Different aromatic α-keto acids were employed as acylating agents, whereas aliphatic ones failed. The corresponding α,β-unsaturated esters **353** were obtained with moderate yields. In some cases, carboxylation products **354** were formed by oxidation of radical **A** with Ru^{2+*} to give the corresponding cation, which reacted with water to give the carboxylic acid that adds to **351** in a Michael-type process (Scheme 145). The formation of the acyl radical **A** after oxidation of the α-keto acid by Ru^{2+*} and decarboxylation has been postulated. Subsequent addition to **351** generates radical **B**, which is reduced by Ru^{+} to give anion **C**. Final elimination of $BocO^{-}$ as CO_2 and $tBuO^{-}$ provides product **352**.

Recently, Xie, Loh and co-workers[260] employed MBHAs **286** as allylating reagents for decarboxylative coupling with α-keto acids **15** using triphenylphosphine and Mes-$Acr^{+}Ph(BF_4)$ **17** as catalysts under blue LED irradiation (Scheme 146). When oxamic acids ($R^1 = NR_2'$) were used as acylating agents the corresponding amides **353** were formed in 42–96% yield. Products **353** were obtained with moderate to high yields and, in general, with >98 : 2 *E*/*Z* diastereoselectivity. In the plausible mechanism two possible pathways were proposed. Initial oxidation by PC* *via* SET of α-keto acid **15** gives radical **A** and CO_2. In path a, MBHA reacts with PPh_3 to give the phosphonium salt **B**, which after SET with $PC^{\bullet-}$ leads to allylic radical **C**. Subsequently, radical–radical coupling of **A** and **C** gives the product. In path b, radical **A** adds to MBHA to afford radical **D**, which accepts an electron from $PC^{\bullet-}$ to form anion **E**. Final elimination of acetate yields the product. MBHAs bearing α-D-galactopyranose, L-(−)-menthol and cholesterol were successfully employed.

$C(sp^2)$–C(sp) bond formation by decarboxylative alkynylation of α-keto acids to provide ynones[261] was described independently by Chen and co-workers[262] and by Li, Wang and co-workers[263] in 2015. Hypervalent iodine(III) reagents and $Ru(bpy)_3(PF_6)_2$ as a PC under blue LED irradiation were used by the first group to give the corresponding ynones with good yields. Oxamic acids were also employed for the synthesis of ynamides. The second Chinese group[263] performed the synthesis of enones by alkynylation of α-keto acids with



Scheme 138 Decarboxylative acylation of glycosyl esters **37** with carboxylic acids under 4CzIPN (**25**) and $NiBr_2$ photocatalysis.

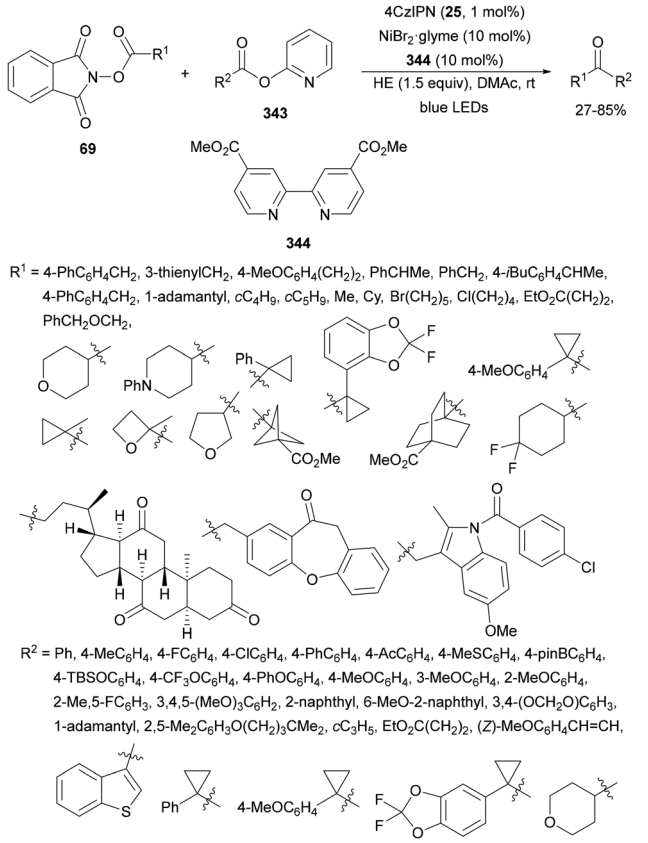


Scheme 139 Decarboxylative acylation of NHPI esters **69** with glycosyl acids **323** under HE and Ni complex **210** photocatalysis.

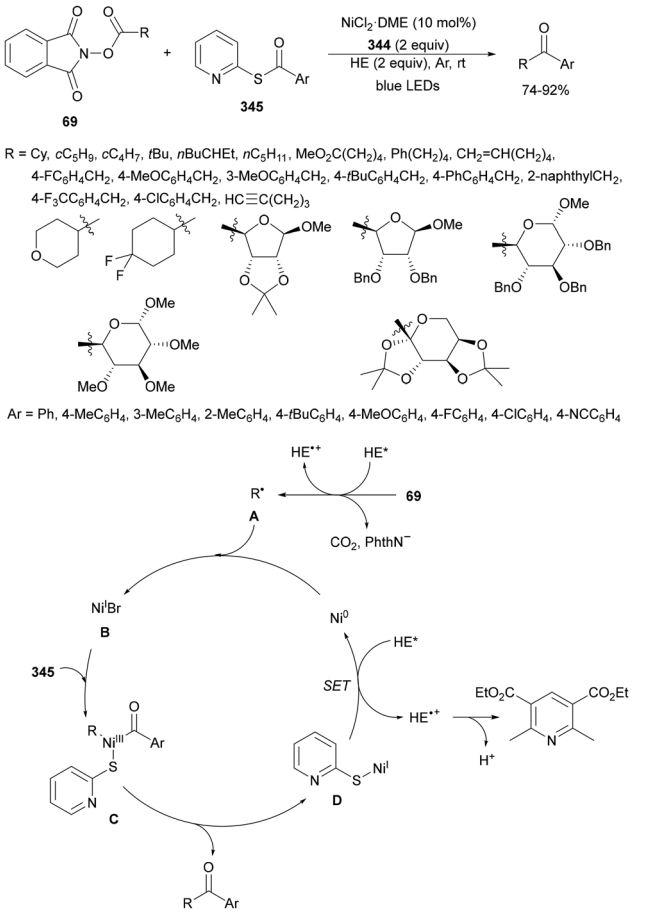
bromoacetylenes **330** photocatalyzed by hypervalent iodine(III) reagent BI–OH.

Oxamic acids **15** ($R^1 = R_2N$) generate, by single-electron oxidation, the corresponding carbamoyl radicals after decarboxylation and have been applied to the synthesis of amides.[264,265] Decarboxylative arylation allows the synthesis of benzamides under photoredox conditions. Jiang, Yu and co-workers[266] employed 4-cyanopyridines **63** for the arylation of oxamic acids **15** ($R^1 = R_2N$) with 4CzIPN (**25**) as a PC and Cs_2CO_3 as a base in DMSO at room temperature under purple LED irradiation to furnish isonicotinamides **355** with good yields (Scheme 147). In the proposed catalytic cycle, the carbamoyl radical **A** adds to radical **B** to form intermediate **C**, which after decyanation yields product **355**.

Decarboxylative arylation of oxamic acids with aryl bromides has been independently reported by Song[267] and Sparr[268] groups. In the first case, 4CzIPN (**25**) and $NiBr_2$·glyme and 4,4′-dimethoxy-2,2′-bipyridine (**185**) as ligands were used as catalysts to give aromatic and heteroaromatic amides **356** with 35–94% yields (Scheme 148a).[267] In the second protocol, they employed 4CzIPN (**25**) and $NiCl_2$·glyme and dtbbpy as ligands and catalysts providing amides **356** with very modest to good yields (17–87%) (Scheme 148b).[268] In both methods, two catalytic cycles have been proposed, the photoredox cycle, which generates a carbamoyl radical, and the Ni catalytic cycle starting from Ni(0) to give a Ni(III) intermediate, which by reductive elimination furnishes the product.

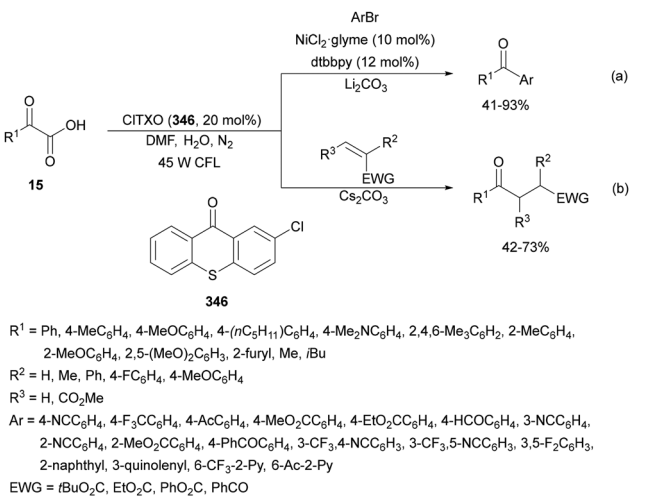


Scheme 140 Decarboxylative acylation of NHPI esters **69** with 2-pyridyl esters **343** under 4CzIPN (**25**)/$NiBr_2$ photocatalysis.



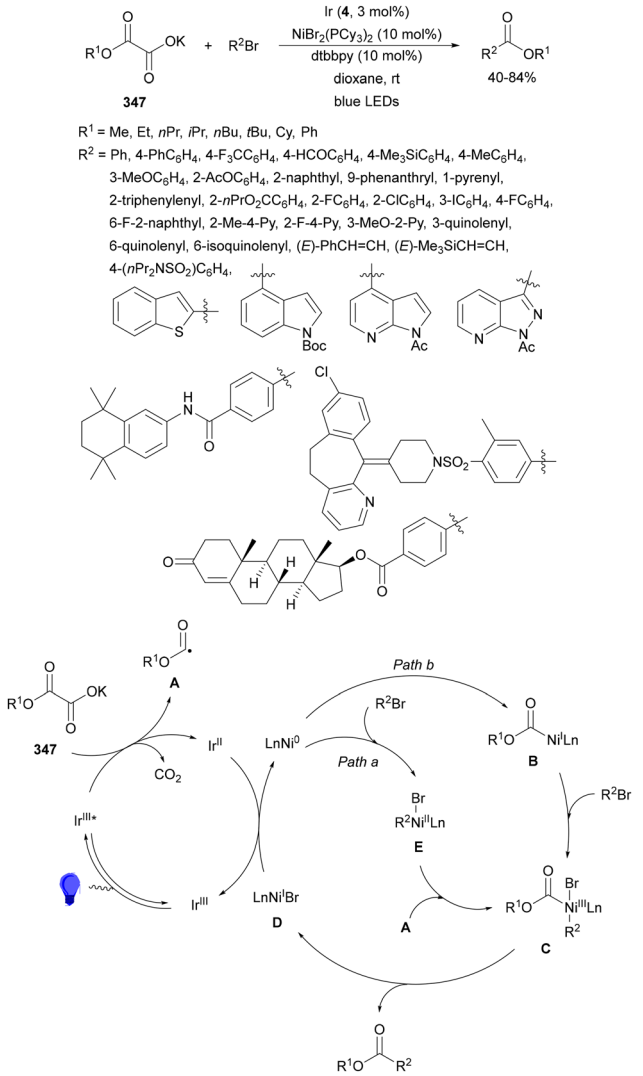
Scheme 141 Decarboxylative acylation of alkyl NHPI esters **69** with *S*-2-pyridyl thioesters **345** under HE and $NiCl_2$ photocatalysis.

Recently, Landais and co-workers[269] reported decarboxylative addition of oxamic acids to imines **108** in the presence of ferrocene acting both as a PC under visible-light and as a Lewis acid. This process took place in the presence of 2-picolinic acid, which likely provides mixed Cp_2Fe-picolinate complexes, and $KBrO_3$ as an oxidant to generate the catalytically active species Fe(III)Ln in DCE at room temperature. A broad range of α-amino acid derived amides **357** were obtained in good yields (Scheme 149a). A 3-component strategy using oxamic acids, aromatic aldehydes and anilines afforded amides **357** in moderate to good yields (28–73%) (Scheme 149b). According to control experiments it was proposed that oxamic acid reacts with catalyst Fe(III)Ln to give the iron carboxylate **A**. Photoexcitation of **A** by a LMCT[54,55] process gives carboxy radical **B** and Fe(II)Ln. Decarboxylation of **B** forms the carbamoyl radical **C**, which adds to imine **D** activated by a Brønsted (TFA, picolinic acid, or oxamic acid) or a Lewis acid [BF_3 or Fe(III)Ln] to provide the radical cation **E**. Reduction of **E** by Fe(II)Ln (path a) and subsequent protonation give product **357** and regenerate the catalyst. The presence of $KBrO_3$ is needed to reoxidize Fe(II)Ln into Fe(III)Ln in order to maintain sufficient Fe(III) in the catalytic cycle (path b).



Scheme 142 Decarboxylative acylation of aryl bromides (a) and electrophilic olefins (b) with α-keto acids **15** under CITXO (**346**) photocatalysis.

As acylating agents, α-keto acids, *N*-acylsaccharins, carboxylic acids and 2-pyridyl esters have been alkylated with styrenes and NHPI esters to provide the corresponding ketones by photoredox decarboxylation. The presence of Hantzsch ester as a photoreductant and for the formation of an electron donor–acceptor (EDA) complex with NHPI esters generates alkyl



Scheme 143 Decarboxylative acylation of organic bromides with potassium oxalates **347** under Ir/Ni photocatalysis.

radicals, whereas Ni complexes form alkyl radicals. In these cases, the corresponding ketones are formed by a $C(sp^3)$–$C(sp^2)$ cross-coupling. Arylation of α-keto acids with aryl bromides needs a Ni complex as a catalyst to achieve the $C(sp^2)$–$C(sp^2)$ bond formation. Allylation reactions of α-keto acids with methacrylates and NBH esters give the corresponding unsaturated 1,4-dicarbonyl compounds. Oxamic acids generate by a SET process the corresponding carbamoyl radicals after decarboxylation and are arylated with 4-cyanopyridines or aryl bromides giving benzamides. Addition to imines provides α-amino carboxamides using ferrocene as a PC by a LMCT process.

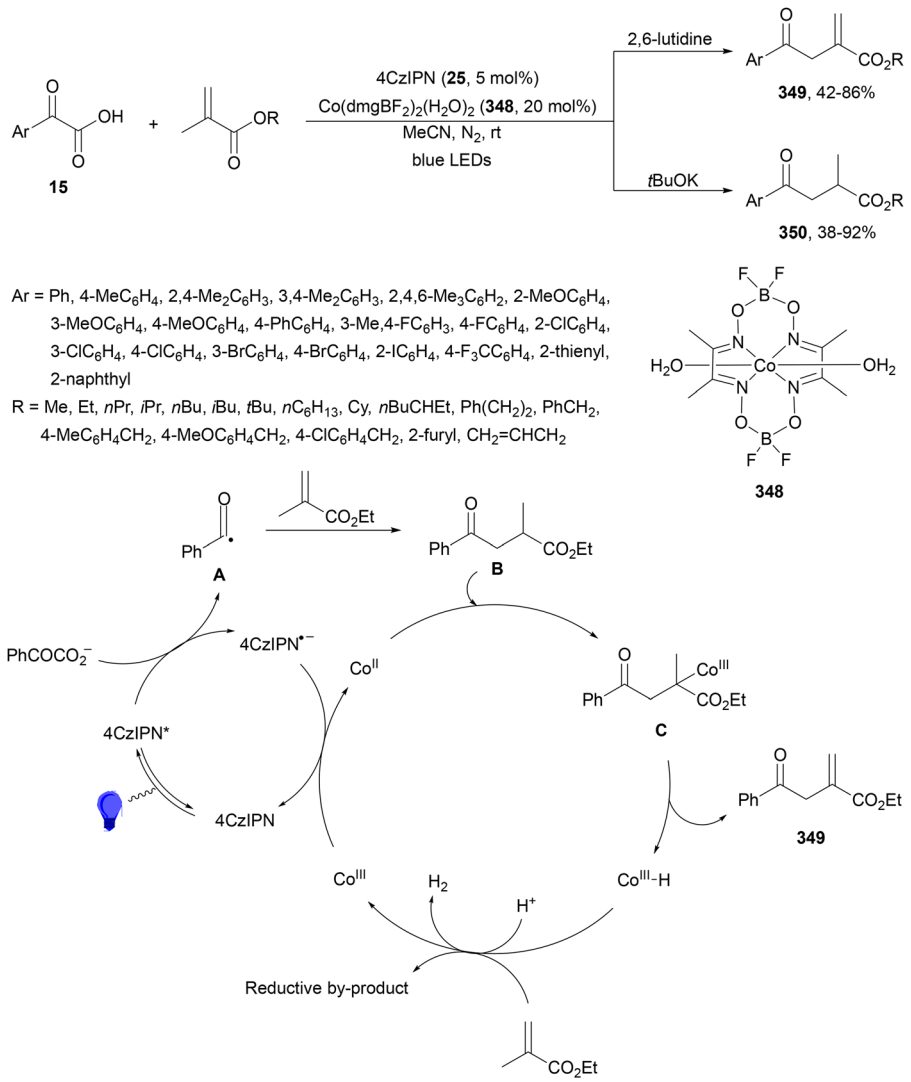
2.11. Cyanation reactions

Direct cyanation of carboxylic acids and derivatives by decarboxylative photoredox catalysis is a very efficient approach. Waser and co-workers[270] reported in 2017 a room temperature cyanation of carboxylic acids using cyanobenziodoxolones (CBX)[224,225] as cyanation reagents. Asymmetric cyanation of carboxylic acids has been carried out using a photoelectrochemical method by Song, Xu and co-workers[271] with cerium/copper relay catalysis and trimethylsilyl cyanide with a chiral bisoxazoline ligand. A similar enantioconvergent[140] cyanation was described by Fu and co-workers[272] and by Zhang and co-workers.[273]

Enantioconvergent decarboxylative cyanation was initially described with NHPI esters **69** and TMSCN by Lin, Liu and co-workers[274] employing $Ir(ppy)_3$ as a PC and CuBr with bisoxazoline **246** as a catalyst under blue LED irradiation. A broad range of enantioenriched alkyl nitriles were obtained both with good yields and enantiomeric excesses (Scheme 150). Theoretical mechanistic studies of this cyanation method was performed by Guan and co-workers[275] suggesting a radical mechanism merging oxidative quenching Ir(III)–Ir(III)*–Ir(IV)–Ir(III) and Cu(III)–Cu(I) catalytic cycles. Photoexcited Ir(ppy)* is oxidatively quenched by NHPI ester **69** to give after decarboxylation radical **A**. Meanwhile, LCuCN **B** can reduce Ir(IV) to provide Ir(III) and the Cu(II) complex **C**. Then, complex **C** and TMSCN undergo cyanide exchange to give dicyanide complex **D**, which reacts with radical **A** providing the Cu(III) intermediate **E**. Finally, the *enantio*-determining C–CN reductive elimination of **E** occurs with an energy barrier difference of 2.1 kcal mol^{-1} to deliver the nitrile and regenerates the copper catalyst **B**. This energy barrier difference corresponds to a 94% ee in favor of the *R*-enantiomer in agreement with the observed 84% ee. The most favorable TS is consistent with the observed enantioselectivity and the intramolecular π–π interaction stabilizes this R-type TS.

Photoredox and copper catalysis have been employed for the cyanoalkylation of alkenes,[276] 1,3-dienes[277] and 1,3-enynes[278] with NHPI esters **69** and TMSCN. Enantioselective cyanoalkylation of styrenes with alkyl NHPI esters **69** has been carried out by Han and co-workers[276] using $Ir(ppy)_3$ as a PC and CuBr/chiral box **358** as a catalyst to furnish nitriles **359** with good yields and enantioselectivities (Scheme 151). This procedure took place in a three-component reaction in NMP/PhCl at room temperature under blue LED irradiation. Radical **A**, generated from NHPI esters in the photoredox catalytic cycle, adds to styrene to give benzylic radical **B**, which reacts with the Cu(II) complex to form a Cu(III) intermediate **C** after reaction with TMSCN. Subsequently, complex **C** undergoes reductive elimination to give product **359** and regenerates the Cu(I) catalyst.

Xiao and co-workers[277] described the enantioselective decarboxylative carbocyanation of 1,3-dienes by using NHPI esters **69** and trimethylsilyl cyanide. In the presence of perylene as an organic PC and $Cu(MeCN)_4BF_4$ with **246** as a chiral ligand in anhydrous DCE at 29 °C, the corresponding chiral allyl cyanides **360** were obtained in good yields and high enantioselectivities (Scheme 152a). In the proposed mechanism, radical **A** generated from NHPI ester adds to (*E*)-1-phenyl-1,3-butadiene to give allyl radical **B**, which reacts with LCu(II)CN to provide the chiral allyl Cu(III) species **C**. Subsequently, intermediate **C** undergoes reductive elimination to furnish product **360** and the Cu(I) catalyst. Using these reaction conditions, 1,3-enynes reacted



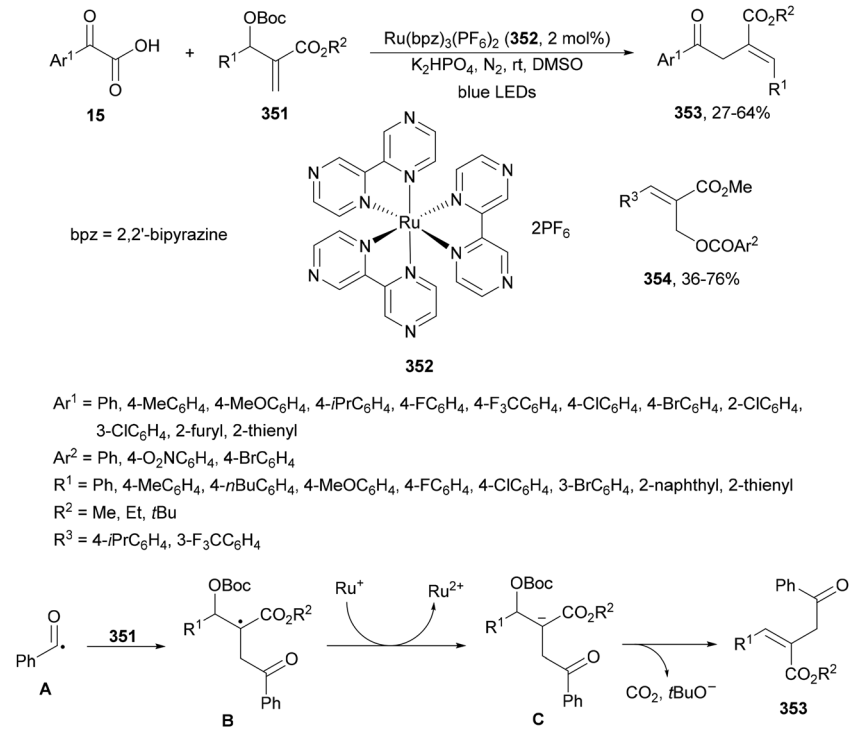
Scheme 144 Decarboxylative acylation of methacrylates with α-keto acids **15** under 4CzIPN (**25**) and cobaloxime **348** photocatalysis.

with NHPI acetate and TMSCN to provide propargyl cyanides **361** in up to 65% yield and up to 87% ee (Scheme 152b).

In the case of disubstituted 1,3-enynes **362**, decarboxylative 1,4-carbocyanation took place with $Ir(ppy)_3$ and $Cu(MeCN)_4PF_6$ photoredox dual catalysis using NHPI esters **69** and TMSCN to provide tetrasubstituted allenes **363** (Scheme 153). Lu and co-workers[278] performed this protocol in DMA and a N_2 atmosphere at room temperature under blue LED irradiation giving the corresponding allenes **363** with, in general, good yields. In the proposed mechanism, radical **A** from NHPI ester generated in the Ir catalytic cycle, adds to 1,3-enyne to form a propargyl radical **B** and its resonance form the allene radical **B′**. Subsequently, this radical reacts with LCu(II) species and TMSCN to provide the Cu(III) species **C**, which suffers reductive elimination forming the allene **363**.

Allenenitriles **365** have been prepared from propargylic oxalates **364** employing a photoredox and copper dual catalysis by Zhang and co-workers.[279] In the presence of $Ir(ppy)_3$ **89** as a PC, CuBr and 4,4′-di-*tert*-butyl-2,2′-bipyridine (dtbbpy) as a ligand, propargylic oxalates **364** reacted with TMSCN in MeCN at room temperature under blue LED irradiation to give exclusively allenenitriles **365** with, in general, good yields (Scheme 154). Experimental and theoretical studies suggested that this process occurred *via* a visible light-induced redox-neutral reductive quenching radical mechanism instead of the well-established oxidative quenching mechanism. In the photoredox catalytic cycle, photoexcited Ir(III) is quenched by an LCu(I)CN catalyst to generate LCu(II)CN and $Ir(III)^-$ species. Oxalate **364** can be reduced by $Ir(III)^-$ to form anionic radical intermediate **A** *via* one electron reduction. This intermediate releases the oxalate anion to form propargylic radical **B** and its resonance structure the allenyl radical **B′**, which binds to $LCu(II)(CN)_2$ followed by reductive elimination to deliver allenenitrile **365**.

Decarboxylative cyanation reactions performed with carboxylic acids use cyanobenziodoxolones and recently by photoelectrochemical methods. Generally, NHPI esters react with



Scheme 145 Decarboxylative acylation of MBH carbonates **351** with α-keto acids **15** under Ru^{2+} photocatalysis.

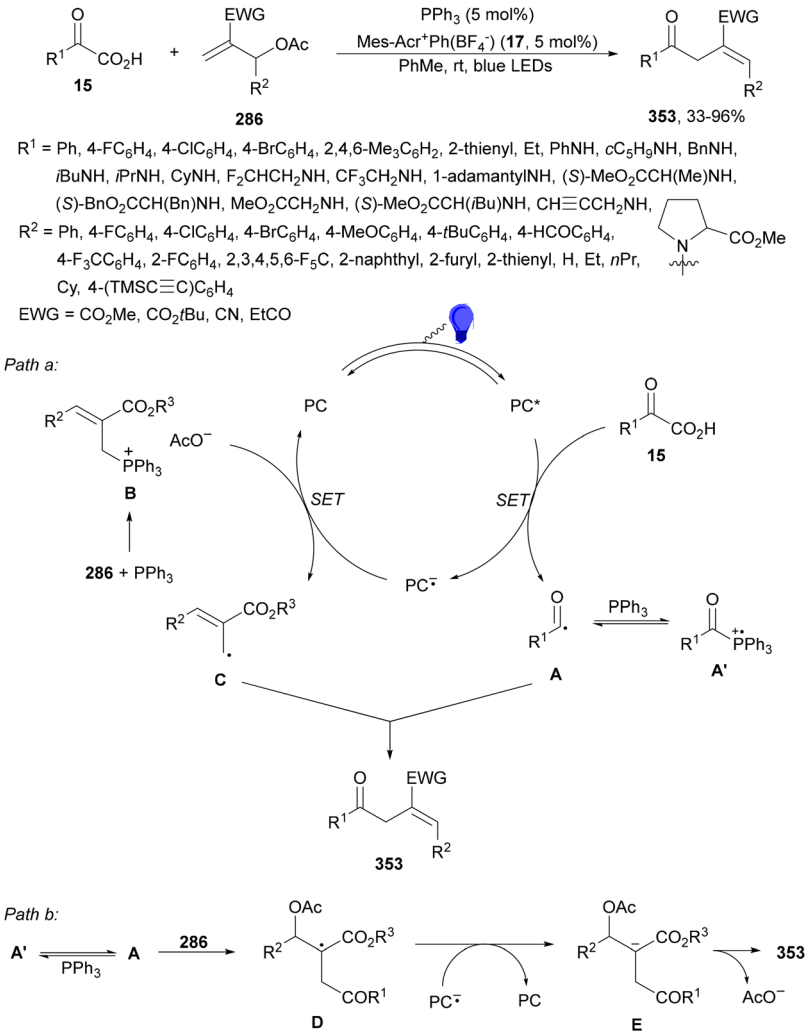
trimethylsilyl cyanide under Ir/Cu dual catalysis and in the presence of chiral ligands such as bixoxazolines to give enantioenriched nitriles. Cyanoalkylation of styrenes, 1,3-dienes and 1,3-enynes can be carried out through three-component reactions with NHPI esters and TMSCN under PC and Cu dual catalysis. In the case of propargylic oxalates, the reaction with TMSCN provides allene nitriles.

2.12. C–H functionalization reactions

Photoredox decarboxylative Minisci reactions have been used mainly for the alkylation, acylation and arylation of aromatic and heterocyclic compounds by C–H functionalization.[280,281] These reactions involve addition of carbon-centered radicals to C═C and C═N bonds followed by hydrogen atom loss under mild reaction conditions using metal and organic-based photoredox catalytic systems or just under visible-light irradiation.

2.12.1. Alkylation reactions. The classical Minisci reaction conditions for the alkylation of heteroarenes with carboxylic acids promoted by visible-light requires harsh conditions and forms byproducts limiting its scope.[282] Glorius and co-workers[283] in 2017 reported the visible-light mediated C–H alkylation of heteroarenes using both cyclic and acyclic primary, secondary and tertiary carboxylic acids as well as amino and fatty acids. Different heteroarenes such as quinolines, isoquinolines, pyridines, phthalazine, 6-chloroimidazo[1,2-*b*]pyridazine, benzimidazole, benzothiazole, quinazoline and phenanthridine, in the presence of Ir complex **4** as a PC and ammonium persulfate as an oxidant, were alkylated generally at the α-position of the nitrogen atom under blue LED irradiation (Scheme 155). It has been proposed that the excited Ir(III)*–PC reduces the persulfate anion to afford Ir(IV), as well as the sulfate dianion and the sulfate radical anion. The alkyl radical **A** is formed by hydrogen-atom transfer (HAT) between the acid and the sulfate radical-anion. Addition of **A** to an electron-deficient heteroarene such as lepidine gives radical **B**, which through a SET process regenerates the Ir(III)–PC and the product. Alternatively, the persulfate anion can act as a chain carrier oxidizing **B** to give the product.

Minisci alkylation of N-heteroarenes with aliphatic carboxylic acids has been performed using hypervalent iodine-promoted decarboxylation.[284,285] Genovino, Frenette and co-workers[284] employed bis(trifluoroacetoxy)iodo benzene (PIFA) and MesAcrMe ClO_4 (**301**) as a PC in MeCN at room temperature under blue LED irradiation to provide alkylated heteroarenes (Scheme 156a). 4-Substituted quinolines, benzothiazole, benzimidazole, 2,6-dichloropurine, 2,6-diphenylpyridine, 4-*tert*-butylpyridine, phthalazines, 4-phenylpyrimidine, 2,3,5-trimethylpyrazine and drugs such as voriconoazole, varenicline and quinine were alkylated with 17–94% yields. Independently, Li, Chen and co-workers[285] described this type of Minisci alkylation using acetoxybenziodoxole (BI-OAc) and $Ru(bpy)_2Cl_2$ as a PC in HFIP at 30 °C under CFL irradiation (Scheme 156b). In this case, 4-chlorosubstituted quinolines, isoquinolines, pyrazine, pyridines, 3,6-dichloropyridazine, benzothiazole, benzimidazole, a *O*-Ac protected purine nucleoside derivative and bioactive molecules such as quinoxylen and fasudil were alkylated at the 2-position of the nitrogen atom with 38–97% yields. In the first case,[284] experimental and theoretical calculations (DFT) supported an initial chain reaction, with the carboxylate ion oxidized only in part by

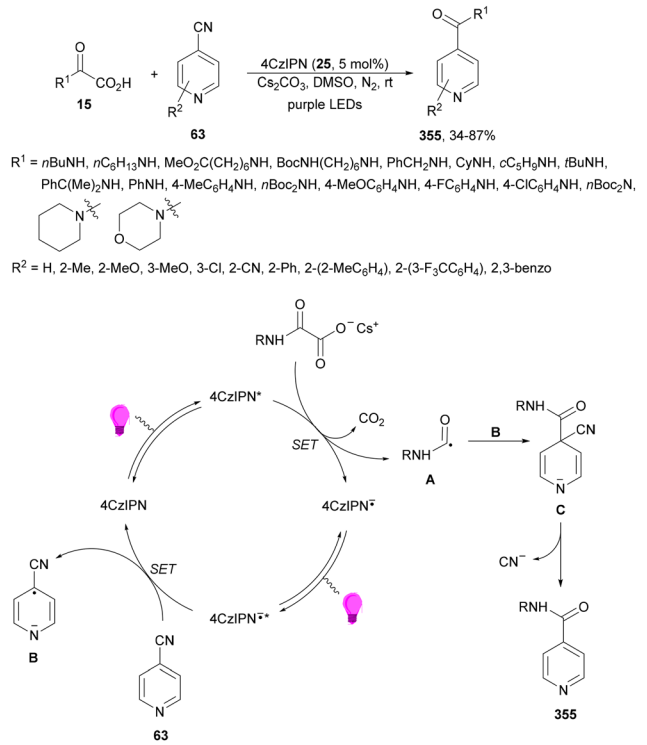


Scheme 146 Decarboxylative acylation of MBHAs **286** with α-keto acids **15** under PPh_3 and Mes-Acr$^+$Ph(BF_4^-) **17** photocatalysis.

MesAcrMe^{+}* to give reduced MesAcrMe*, which transfers one electron to PhI(TFA)$_2$ to initiate the catalytic cycle. The [PhI(O$_2$CR)$_2$]$^{-\bullet}$ generates the radical **A** and CO_2. Subsequently, radical **A** adds to protonated lepidine to give radical cation **B**, which reacts with the carboxylate ion (RCO_2^- or TFA^-) providing radical **C**. Finally, **C** reacts with PIFA to give the alkylated product and regenerates [PhI(O$_2$CR)$_2$]$^{-\bullet}$. In the second case,[285] a possible mechanism would be that the carboxylic acid reacts with BI-OAc *in situ* to provide the iodonium ester **D**. This ester **D** is reduced by Ru(II)* by a SET to form radical **E** and 2-iodobenzoate. Decarboxylation of **E**, addition to protonated pyridine, SET oxidation by Ru(III) and deprotonation affords the product and regenerates the PC Ru(II).

Yang, Zhang and co-workers[286] described a hypervalent iodine-promoted decarboxylation with PIFA in the absence of a PC under blue LED irradiation. The coupling of aliphatic carboxylic acids was carried out with 4-methylquinoline, 4,7-dichloroquinoline, 4-chloro and 4-bromoquinoline, 3-methylquinoline, 3,4-diphenylisoquinoline, 3-chloroisoquinoline, 4-*tert*-butyl and 4-cyanopyridine, quinazoline, 4,6-dimethylpyrimidine, 5-bromopyrimidine, 2-chloroquinoxaline, phthalazine, benzothiazole and phenanthridine to provide alkylated heterocycles with 30–96% yields.

Another general method for decarboxylative alkylation of heterocycles with carboxylic acids was reported by Jin and co-workers[287] *via* iron photocatalysis by an intramolecular charge transfer pathway of iron carboxylate complexes (LMCT).[54,55] In the presence of $FeSO_4{\cdot}7H_2O$ (5 mol%), picolinic acid (10 mol%) and 2 equivalents of $NaBrO_3$ or $NaClO_3$ as oxidants in aqueous DMSO at room temperature under blue LED irradiation, a broad range of heteroarenes were alkylated with 30–97% yields. Several 4-substituted quinolines 3 and 4-substituted isoquinolines, phenanthridine, quinazolines, phthalazines, quinoxalines, pyridines, pyrimidines, pyridazines, pyrazines, benzothiophenes, benzothiazoles, benzimidazoles and purine derivatives were satisfactorily alkylated at the vicinal carbon atom of the heteroatom. Recently, Li and co-workers[288] described this Minisci reaction using palladium-loaded gallium



Scheme 147 Decarboxylative carbamoylation of 4-cyanopyridines **63** with oxamic acids under 4CzIPN (**25**) photocatalysis.

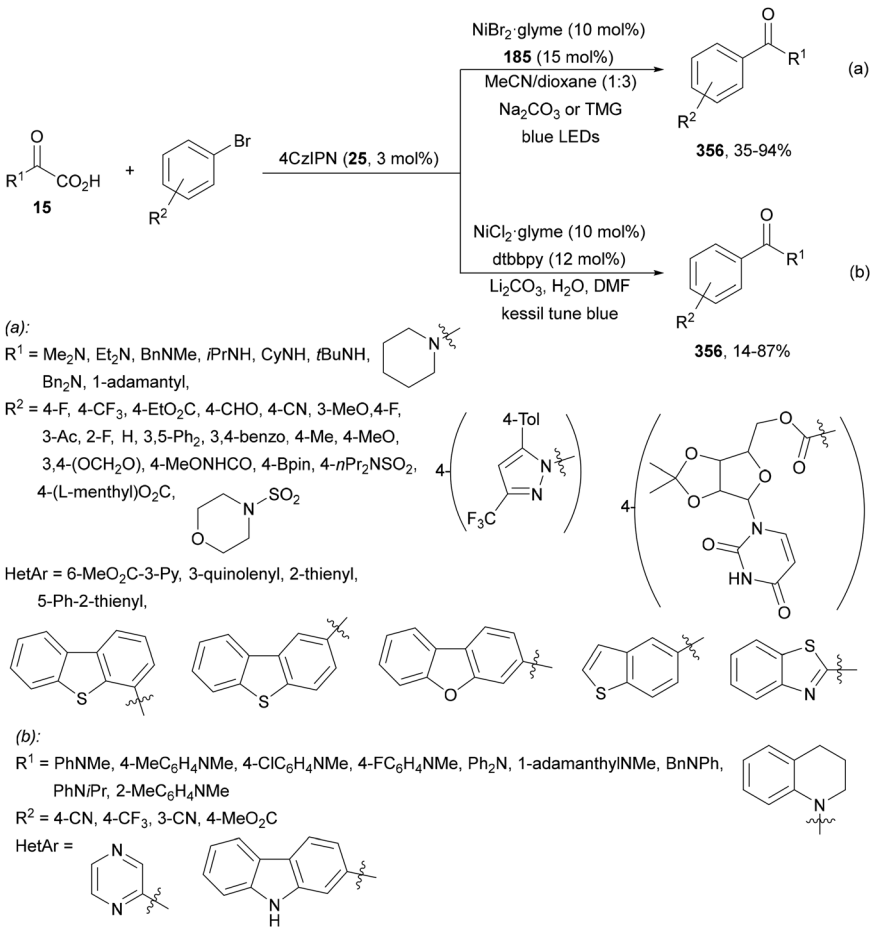
nitride (3 mol%) as a heterogeneous PC working in MeCN, at room temperature under Xe light irradiation. In this case, 4-methylquinoline and 2-substituted quinolines were alkylated at the 2- and 4-position, respectively with 33–95% yields. Other heterocycles such as 1-methylquinoxaline and benzoquinoline were mono- and dialkylated, respectively.

Shen, Zhang and co-workers[289] reported a general alkylation of heteroarenes in the presence of TBHP (2 equivalents) and dimethyl carbonate (DMC) as solvent at room temperature under 395 nm LED irradiation. This green and efficient methodology was applied to the alkylation of quinoxalinones, phenanthridine, isoquinoline, quinazoline, quinoxaline, phthalazine, benzoxazinone, and azauracil to provide the corresponding products in 17–84% yields. Other substrates such as quinolines, pyridines, benzothiazoles, theophylline and purine failed. Primary, secondary and tertiary aliphatic carboxylic acids as well as *N*-protected α-, β-, γ- and δ-AAs gave the corresponding aminoalkylated quinoxalinones with 50–64% yields. In the proposed mechanism, the *t*-BuO$^{\bullet}$ radical is formed by irradiation of TBHP in the presence of light, which starts the radical mechanism of this transformation.

Decarboxylative alkylation of heteroarenes with carboxylic acids without the requirement of stoichiometric amounts of oxidants was reported by Li and co-workers.[290] In the presence of Ir complex **4** as a PC and Co(dmgH)$_2$PyCl (**16**) as a H_2 release catalyst, *n*-Bu_4NOAc as a base in EtOAc at room temperature under blue LEDs irradiation, the corresponding alkylated heterocycles were obtained in 37–94% yields (Scheme 157). Benzothiazoles, 4,5-dimethylthiazole, benzoxazoles, oxazoles, benzimidazoles, *N*-Boc-imidazole, benzofuran, benzothiophenes, 3-substituted thiophenes, quinazolin-4(3*H*)-one, phenanthridine and quinazoline were alkylated with secondary and tertiary carboxylic acids and with α-AAs. In the proposed reaction pathway, the Ir catalytic cycle generates the corresponding radical by decarboxylation of the carboxylic radical and forms Ir(II). This Ir(II) transfers one electron to Co(III) and produces Co(II) species, which is further reduced to Co(I) by accepting one electron. This Co(I) is transformed into Co(III)–H and reacts with another proton to release H_2 and closes the cobalt cycle (path a). In path b, Co(III)–H is reduced to Co(II)–H, which after protonation forms H_2. Alternatively, Ir(III)* is oxidatively quenched by Co(III) *via* SET to form Ir(IV) and Co(II). Subsequently, Ir(IV) abstracts one electron from RCO_2^- to give radical $RCO_2^{\bullet}$ and regenerates Ir(III) to close the catalytic cycle. Then, $RCO_2^{\bullet}$ and Co(II) follow the similar process as described in path a to afford the product with H_2 release.

A general method for the aminoalkylation of a wide range of heterocycles has been described by Liu, Sun and co-workers.[291] *N*-Protected α-AAs reacted with these heterocycles in the presence of 4CzIPN as a PC and Cs_2CO_3 as a base in DMA at room temperature under blue LED irradiation to furnish the corresponding products (Scheme 158). Quinoxalines, 3,6-dichloropiridazine, 2-methyl-3-acetylpyrazine, quinazoline, 2-methoxycarbonylquinoline, benzothiazole and coumarin provided the aminoalkylated derivatives with in general good yields (37–85%). In the proposed mechanism, the deprotonated α-AA was oxidized by 4CzIPN* to deliver the α-aminoalkyl radical **A**, which adds to 1-methylquinoxalin-2(1*H*)-one to form radical intermediate **B**. Subsequent 1,2-H migration in radical **B** produces radical **C**. Meanwhile, $^1O_2$ was generated through energy transfer from 4CzIPN* to $^3O_2$ followed by the reduction of 4CzIPN to produce $O_2^{-\bullet}$. Finally, $O_2^{-\bullet}$ abstracts a hydrogen atom from radical **C** to give the alkylated quinoxaline.

Decarboxylative trifluoromethylation of aromatic and heteroaromatic compounds with trifluoroacetic acid under photoredox conditions was described in 2017 by Su, Li and co-workers.[292] In the presence of Rh-modified anatase TiO_2 nanoparticles as a PC and $Na_2S_2O_8$ (10–40 mol%) as an external oxidant at room temperature in trifluoroacetic acid under 365 nm ultraviolet irradiation, the corresponding trifluoromethylated products were obtained in 34–75% yields. Qing and co-workers[293] reported a general method for the trifluoromethylation of arenes and heteroarenes using $C_6F_5I(O_2CCF_3)_2$ (FPIFA) (2.5 equivalents), $Ru(bpy)_3(PF_6)_2$ as a PC in MeCN at 35 °C under blue LED irradiation (Scheme 159a). A wide range of aromatic compounds and heterocycles such as furans, thiophenes, pyridines, pyrimidines, pyrazines and thiazoles were trifluoromethylated with moderate to good yields with excellent regioselectivity at the electron-rich position. Recently, simple and general decarboxylation of trifluoroacetates has been described by Juliá-Hernández and co-workers,[294] for the trifluoromethylation of arenes and heterocyclic compounds. Using $Fe(OTf)_2$ as a PC, 4,4′-dimethoxy-2,2′-bipyridine (**185**) as a ligand, $K_2S_2O_8$ as an external oxidant in MeCN at room temperature under 405 nm irradiation afforded the corresponding products (Scheme 159b). Electron-rich arenes



Scheme 148 Decarboxylative carbamoylation of aryl bromides with oxamic acids **15** under 4CzIPN (**25**) (a) and Ni photocatalysis (b).

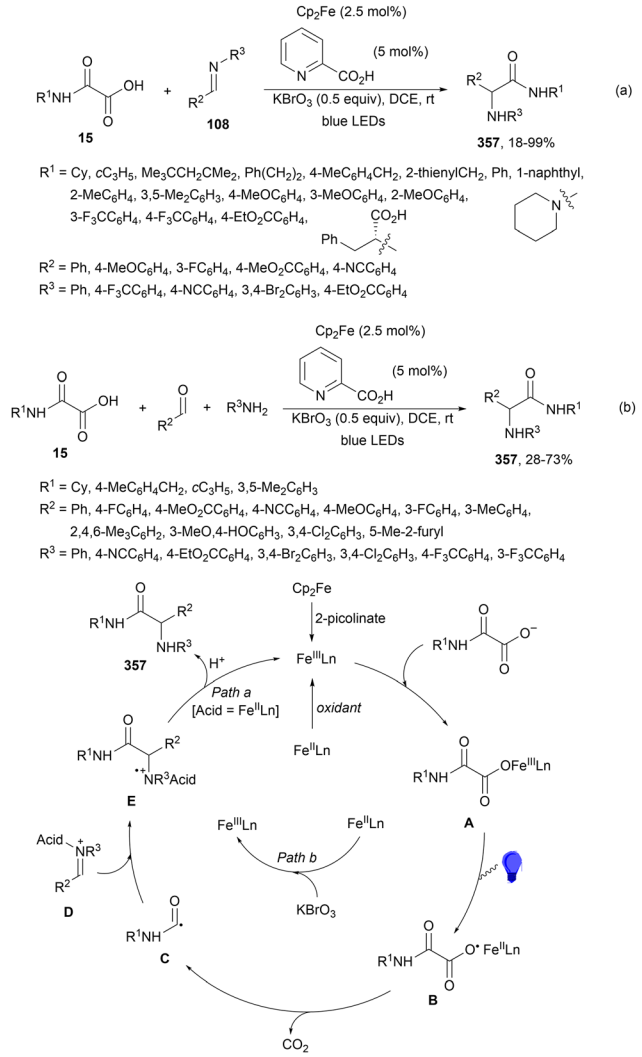
and substituted pyrroles, thiophenes, pyrimidine, *N*-methylpyridone, coumarin, indoles and ferrocene were functionalized with modest to good yields. Natural products and drug-like molecules such as caffeine, theophylline, pentoxifylline, uracil, trifluridine, griseofulvin, metaxalone, visnagin, indomethacin and melatonin were also trifluoromethylated with 18–67% yields. This method involves LMCT photocatalysis[54,55] by intermediacy of $Fe^{III}O$-$COCF_3$, which after irradiation provides a trifluoroacetate radical. Subsequent decarboxylation affords the trifluoromethyl radical.

Iron-mediated decarboxylative alkylation of arenes and heteroarenes with carboxylic acids represents a general strategy for C–C bond formation. Yoon and co-workers[295] employed $FeCl_3$ and NaOAc as a base in DCM at room temperature under blue LED irradiation. Alkylated arenes and heterocycles such as substituted indole, benzothiophene, furan, benzofuran, pyrrole and pyridine were isolated with moderate to good yields (Scheme 160). It has been postulated that alkyl chlorides are formed as intermediates by reaction of the alkyl radical with $FeCl_3$. In addition, $FeCl_3$ can act as Lewis acid to facilitate the Friedel–Crafts alkylation of the arenes or heteroarenes.

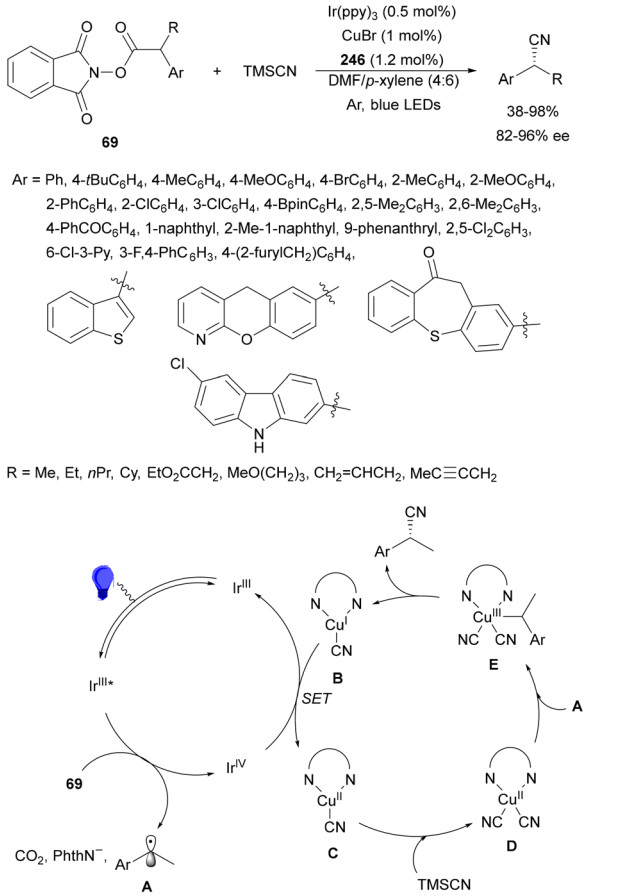
Specific alkylation of quinoxaline-2-(1*H*)-ones with aliphatic carboxylic acids in aqueous conditions was reported by Qin, Li and co-workers.[296] In this case, Ir complex **4**, $K_2S_2O_8$ as an oxidant, Li_2CO_3 as a base, in DMSO/H_2O (1 : 1) at room temperature under blue LED irradiation were efficient reaction conditions to give the corresponding products in 30–93% yields (Scheme 161). Drug molecule and natural product derived aliphatic acids were also employed such as indomethacin and dehydrochlolic acid. An aldose-reductase inhibitor precursor was prepared by reaction of *N*-(ethoxycarbonyl)methyl quinoxaline with 4-bromophenylacetic acid. The biological activity of several alkylated quinoxalinones as antifungal agents against *Magnaporthe grisea* GD08-T19 has been studied.

Roy and co-workers[297] performed a decarboxylative alkylation of quinoxaline-2(1*H*)-ones by a photoinduced ligand to metal charge transfer (LMCT)[54,55] using $CeCl_3$ and *t*-BuOK as a base in MeCN at room temperature under blue LED irradiation. A broad range of primary, secondary and tertiary carboxylic acids were employed to provide alkylated quinoxalinones in 36–92% yields.

Decarboxylative C–H adamantylation of azoles, such as benzothiazoles, benzoxazoles, benzimidazoles and caffeine derivatives, was carried out with $[MesAcrMe]ClO_4$ (**301**) as an organic PC and $Co(dmgH)(dmgH_2)Cl_2$ as a H_2 release catalyst, K_2HPO_4 as a base, in aqueous DCM at 25–30 °C under blue LED irradiation.[298] The resulting adamantly azoles were obtained with 40–83% yields.



Scheme 149 Decarboxylative carbamoylation of imines **108** with oxamic acids **15** under ferrocene photocatalysis (a, b).



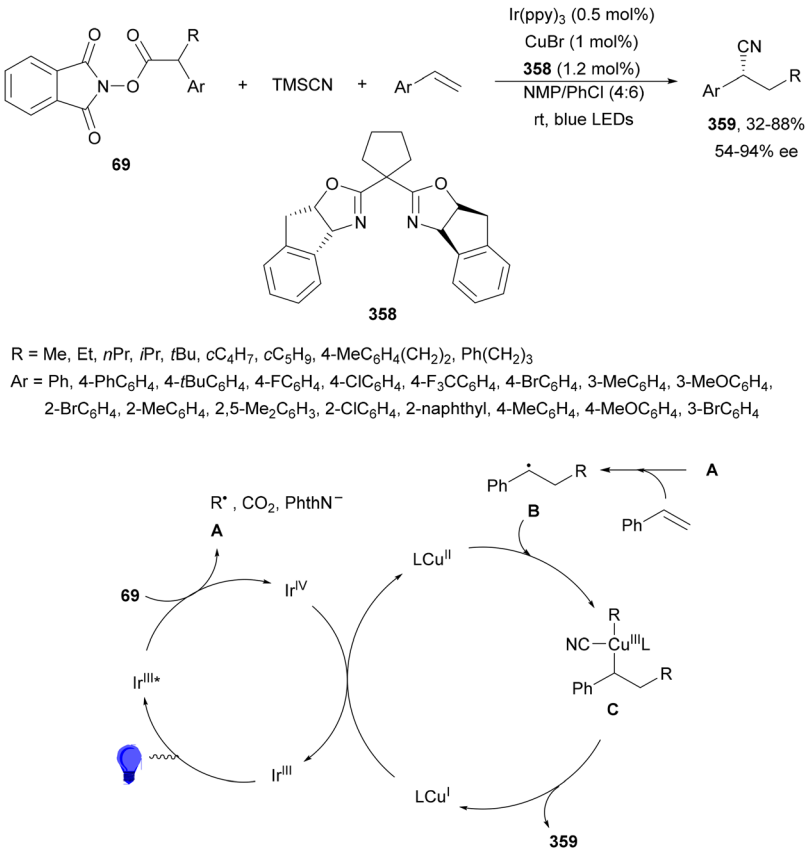
Scheme 150 Enantioconvergent decarboxylative cyanation of NHPI esters **69** with TMSCN under Ir/Cu photocatalysis.

Imidazo[1,2*a*]pyridines **366**[299] have been alkylated with *N*-arylglycines under photocatalyst-free conditions. Zhu, Le and co-workers[300] reported the aminoalkylation of these imidazopyridines in toluene at room temperature under blue LED irradiation to afford the corresponding products **367** with good yields (Scheme 162). The reaction has to be performed in air involving a radical process. Oxidation of *N*-aryl glycine with $^1O_2$, generated under visible light from molecular oxygen, generates an aminyl radical cation **A** and a superoxide radical anion ($O_2^{-\bullet}$). Further protonation of **A** gives the α-amino radical **B** after decarboxylation induced by $O_2^{-\bullet}$. Subsequent oxidation of **B** by $HO_2^\bullet$ leads to the imine intermediate **C**, which undergoes electrophilic addition with the imidazopyridine to produce product **367**.

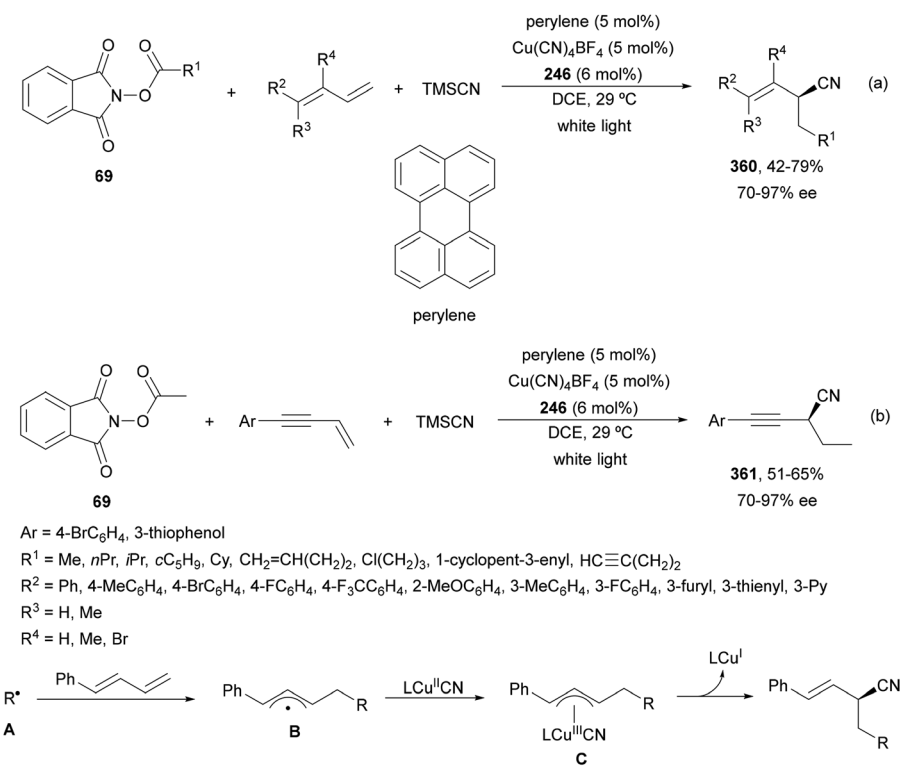
The aminoalkylation of imidazopyridines **366** and benzo[*d*]-imidazo[2,1-*b*]thiazole has been reported by Chen, Yu and co-workers[301] using 5 mol% of recyclable perovskite ($CsPbBr_3$) as a heterogeneous PC. This process was carried out in DCE under 25 W white LED irradiation under aerobic conditions with 44–94% yields and was applied for the gram-scale preparation of product **367** ($R^1 = R^2 = H$; $R^3 = Ph$).

Photocatalytic decarboxylative alkylation of pyridines at the four position has been achieved using *N*-amidopyridinium salts **368**. Hong and co-workers[302] performed the regioselective synthesis of 4-substituted pyridines **369** in the presence of (tBu$_2$MesAcrPh)BF_4 **287** as a PC and K_2HPO_4 as a base in toluene at room temperature under N_2 and blue LED irradiation (Scheme 163). A wide range of pyridines **369** were obtained using primary, secondary and tertiary aliphatic carboxylic acids including α-AAs with good yields. Based on experimental observations, a plausible mechanism was proposed involving the formation of the carboxylic radical MesAcr$^+$*. After decarboxylation radical **A** is formed, which adds at the 4-position of the *N*-amidopyridinium salt to give **B**. Intermediate **B** undergoes deprotection and homolytic cleavage to furnish the product **369** and amidyl radical **C** by a SET process and regenerate the PC and give anion **C**.

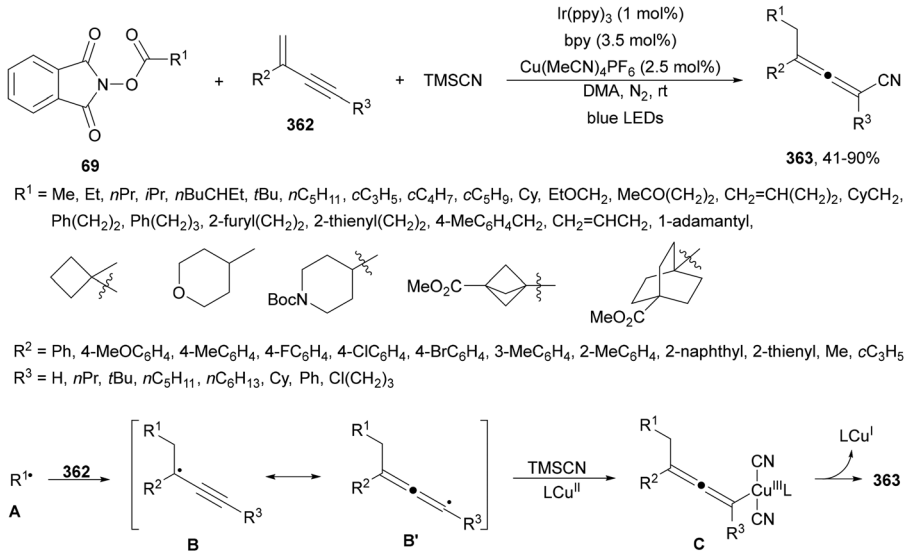
In 2017, as in the case of decarboxylative C–H alkylation of heteroarenes with carboxylic acids reported by Glorius,[283] Shang, Fu and co-workers[303] reported the same reaction with NHPI esters **69**. An Ir-photoredox catalyst **4** in the presence of TFA or In(OTf)$_3$ in DMA at room temperature under blue LED



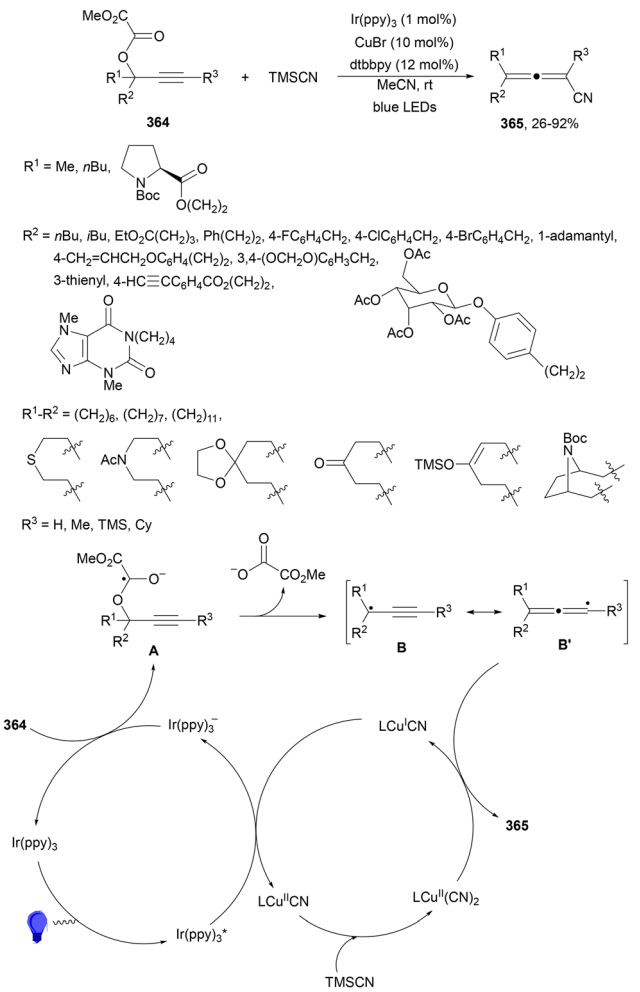
Scheme 151 Decarboxylative enantioselective cyanoalkylation of styrenes with NHPI esters **69** and TMSCN under $Ir(ppy)_3$/CuBr/**358** photocatalysis.



Scheme 152 Decarboxylative enantioselective carbocyanation of 1,3-dienes (a) and 1,3-enynes (b) with NHPI esters and TMSCN under perylene/Cu(I) photocatalysis.



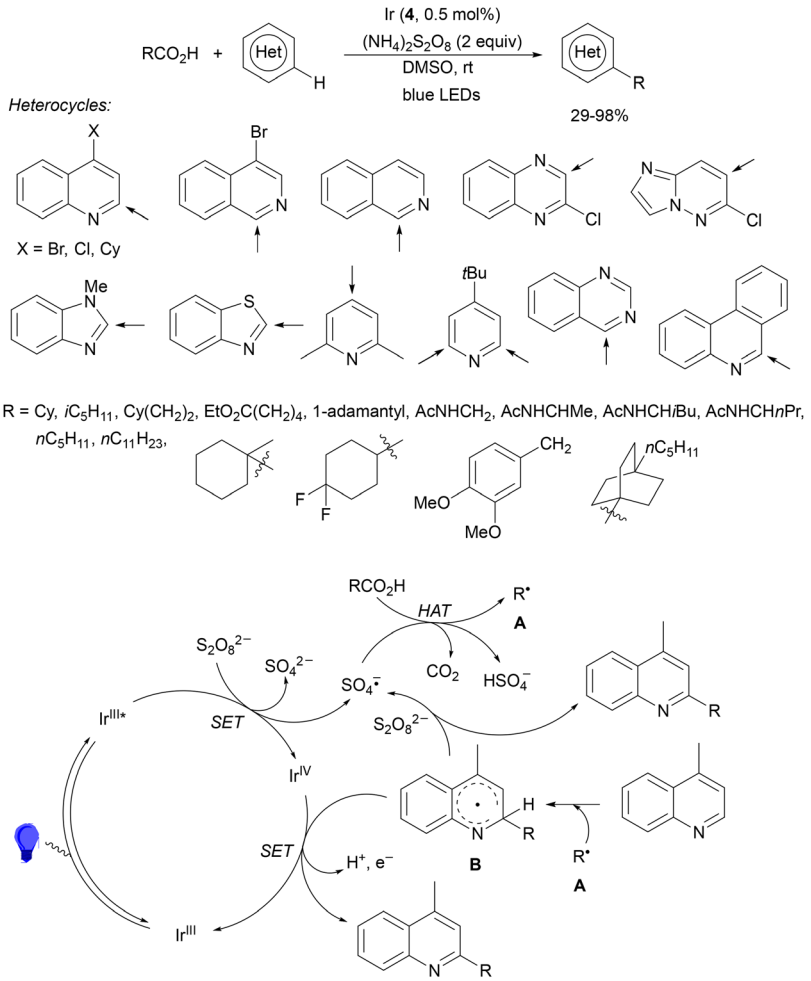
Scheme 153 Decarboxylative 1,4-carbocyanation of 1,3-enynes **362** with NHPI esters **69** and TMSCN under $Ir(ppy)_3$/$Cu(MeCN)_4PF_6$ dual photocatalysis.



Scheme 154 Decarboxylative cyanation of propargylic oxalates **364** with TMSCN under Ir/Cu photocatalysis.

irradiation enabled a general alkylation of a broad range of N-heteroarenes (Scheme 164). Quinolines, quinoxaline, phthalazine, isoquinoline, pyridine, pyrimidine, pyrazine, bipyridine, phenanthroline, and purine reacted with primary, secondary and tertiary alkyl NHPI esters **69** in the presence of an excess of TFA to provide the corresponding alkylated products at the most electrophilic position in 45–92% yields. When 10% of Lewis acid was used for sensitive substrates to Brønsted acids, the resulting products were obtained in 32–94% yields. In the proposed mechanism, the alkyl radical from the NHPI ester adds to protonated heteroarene, *e.g.* lepidine, to give a radical cation **A**, which is oxidized by Ir(III)* to regenerate Ir(II) and the alkylated heterocycle.

Several enantioselective Minisci-type addition reactions of α-aminoalkyl radicals to heteroarenes have been described.[304–306,308–311] Phipps and co-workers[304] employed pyridines and quinolines as heteroarenes and α-AA derived NHPI esters **143** in the presence of Ir complex **4** as a PC and (*R*)-TRIP (**370**) or (*R*)-TCYP (**371**) as CPAs under blue LED irradiation to give the corresponding aminoalkylated products **372** in up to 98% yield and up to 97% ee (Scheme 165). In the proposed mechanism, upon formation of the α-aminoalkyl radical **A** from NHPI ester **143** under photocatalysis, addition to pyridine takes place to give by participation of the CPA, intermediates **B** and **C**. Intermediate **C** forms radical **D** and liberates the CPA. Subsequent oxidation of **D** and deprotonation gives product **372** and regenerates Ir(II). Further studies by a predictive mathematical model through evaluation of catalyst/substrate training sets and parameter acquisition platform suggested that other heteroarenes should be amenable for the same enantioselective Minisci reaction.[305] Specific predictions through multivariate linear regression (MLR) analysis for pyrimidines and pyrazines were in agreement with experimental results. Under the same reaction conditions several pyrimidines and pyrazines were



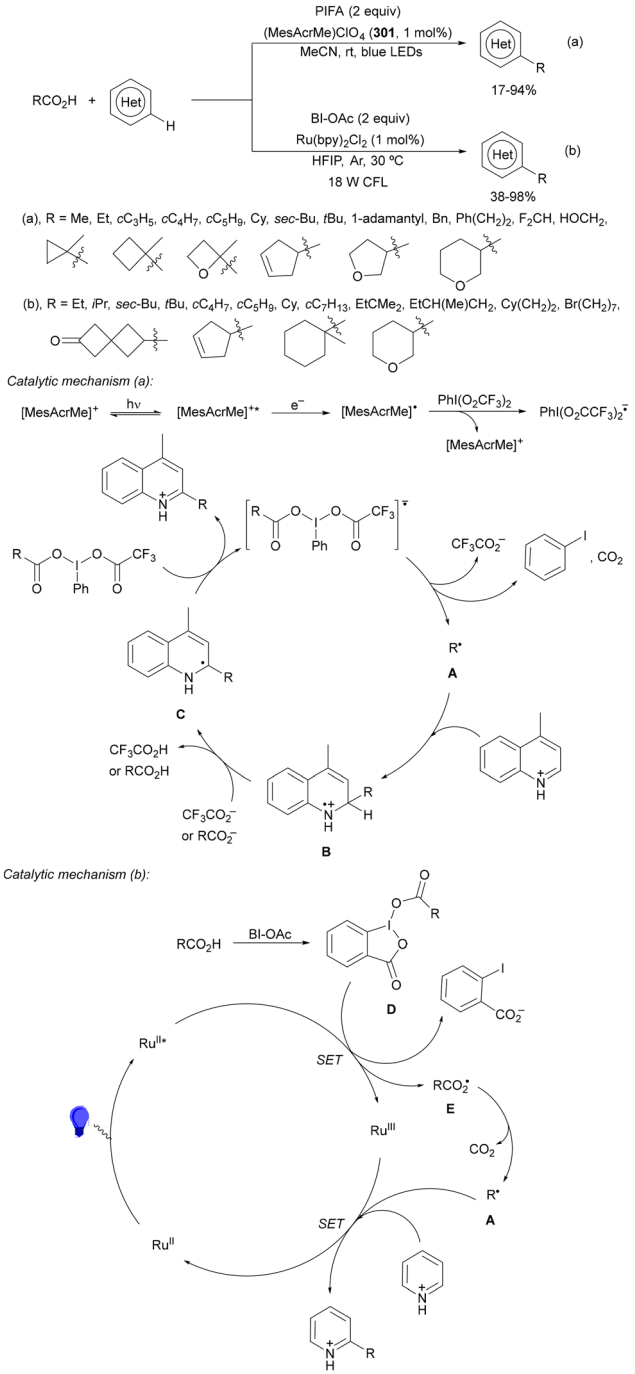
Scheme 155 Decarboxylative alkylation of heteroarenes with carboxylic acids under Ir (**4**)/$(NH_4)_2S_2O_8$ photocatalysis.

alkylated with *N*-aryl AAs derived NHPI esters to furnish aminomethylated products in 23–93% yields.

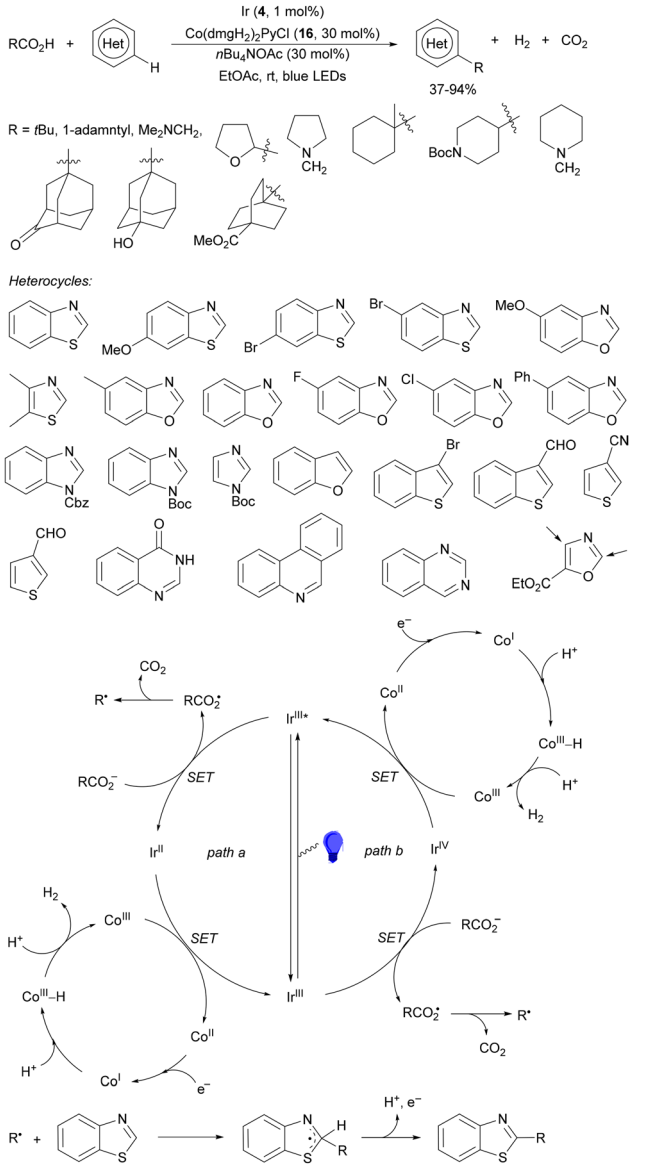
Computational (DFT calculations) and experimental investigations were performed to elucidate the origin of selectivity in collaboration with Ermanis and Goodman.[306] The Curtin–Hammett principle was in operation: a fast and reversible radical addition followed by a slower irreversible enantioselective deprotonation, which determined the enantioselectivity of this Minisci-type reaction. In Scheme 166 is depicted the proposed reaction mechanism: firstly, the α-aminoalkyl radical **A** generated by reduction of NHPI ester interacts with the quinolinium-TRIP complex **B** to give complex **C**. Addition to quinolinium *via* one of the four possible diastereomeric **C**-TS gives intermediate **D**. Deprotonation by the carbonyl oxygen of the *N*-acetyl group assisted by the phosphate through **D**-TS provides intermediate **E**. Deprotonation of **E** by another quinoline molecule regenerates **B** and forms radical **F**, which by a SET process undergoes oxidation giving the product **372** after proton loss. Chain processes[303,307] and direct HAT processes[308] have been proposed also for the Minisci reactions involving photoredox catalysis.

Jiang and co-workers[309] reported a similar decarboxylative enantioselective alkylation of isoquinolines with α-AA-derived NHPI esters **143** in the presence of DPZ **92** as an organic PC and SPINOL-CPA **373** to provide 1-isoquinoline-substituted chiral secondary amines **374** in high yields with good to excellent enantioselectivities (Scheme 167). This Minisci-type asymmetric reaction was carried out in the presence of 4 Å MS, in DME at −10 °C under blue LED irradiation.

Wang and co-workers[310] reported a similar enantioselective Minisci reaction by decarboxylative photoredox of α-AA-derived NHPI esters **143** and β-carbolines **375** (Scheme 168). In the presence of Ir complex **4** and SPINOL-CPA **376** in THF at −40 °C under blue LED irradiation, enantioenriched products **377** alkylated at the 1-position were obtained in up to 87% yield and up to 97% ee. This method was applied to the total synthesis of marine alkaloids eudistomin X, (+)-eudistomidin B and (+)-eudistomidin I. In the chiral Brønsted acid cycle, the α-aminoalkyl radical **A**, generated from **143** through the Ir photoredox cycle, interacts with β-carboline by the bifunctional phosphoric acid catalyst affording intermediate **B**, which after radical addition gives radical cation species **C**. Intermediate **C** undergoes an internal proton abstraction promoted by the carbonyl oxygen of the *N*-acetyl group providing intermediate **D**. Deprotonation of **D** by an external β-carboline forms the



Scheme 156 Decarboxylative alkylation of heteroarenes with carboxylic acids using hypervalent iodine reagents and [MesAcrMe]ClO_4 (**301**) (a) or $Ru(bpy)_2Cl_2$ (b) photocatalysis.

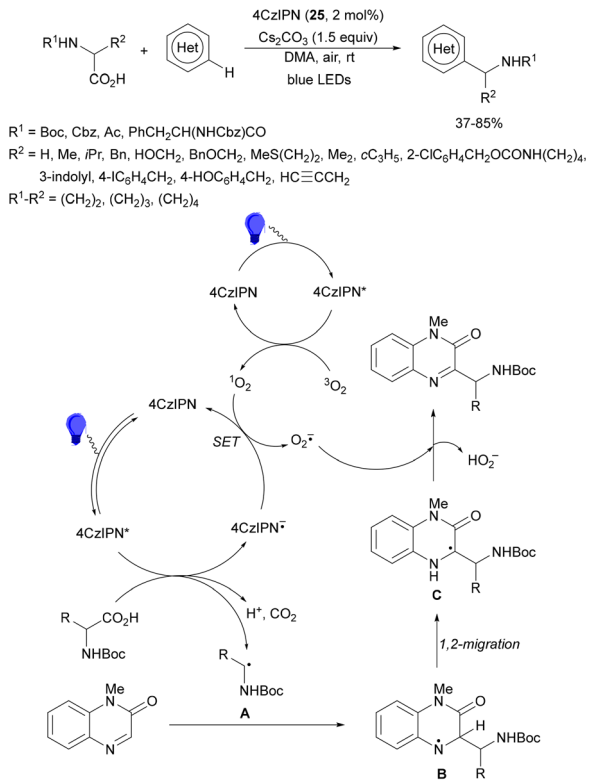


Scheme 157 Decarboxylative alkylation of heterocycles with carboxylic acids under Ir/Co photocatalysis.

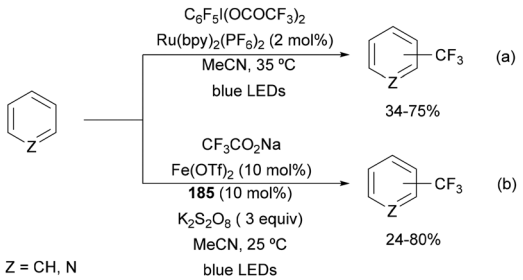
radical intermediate **E**, which is oxidized by Ir(III)* to give product **376.** This deprotonation is an irreversible and enantio-determining step in this transformation.[306]

Synthesis of oxalyl chiral heterocyclic molecules has been achieved by asymmetric Minisci reaction of 5-arylpyrimidines and α-AA-derived NHPI esters **143.**[311] In the presence of 4CzIPN as a PC and CPAs such as (*R*)-**379** and (*R*)-**380** in dioxane at 15 °C under blue LED irradiation, pyrimidines **378** were transformed into products **381** in up to 82% yield, >19:1 dr and >99% ee (Scheme 169). This desymmetrization process[312,313] was also carried out on a gram-scale and also under sunlight irradiation. Radical **A** undergoes chiral phosphoric acid-catalyzed regio- and enantioselective addition to the pyrimidine unit to provide phosphoric acid-coordinated radical cation **B** through the depicted TS.

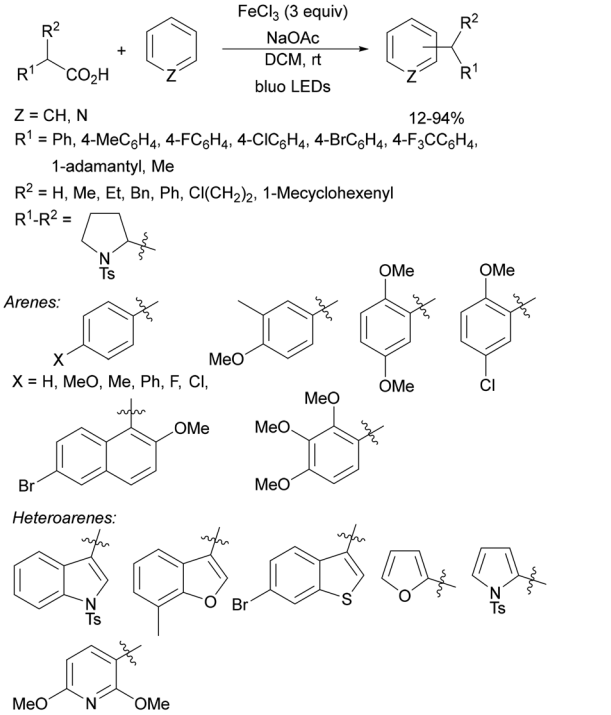
A general method for decarboxylative alkylation of N-heteroarenes with AAs and peptides derived NHPI esters **143** was reported in 2017 by Fu and co-workers.[314] As in the case of aliphatic carboxylic acids (Scheme 164),[303] Ir complex **4** (2 mol%) in the presence of BINOL derived phosphoric acid (10 mol%) as a Brønsted acid was employed under blue light irradiation with different heterocycles such as quinoline, quinoxaline, phthalazine, isoquinoline, quinazoline, pyrimidine, phenanthridine,



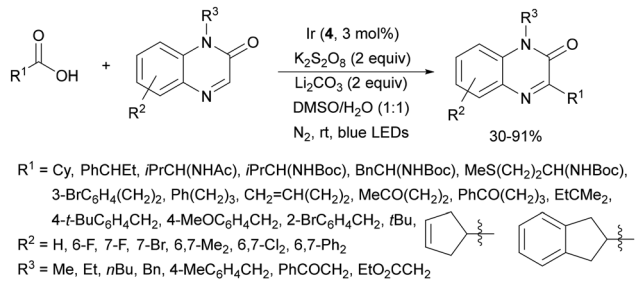
Scheme 158 Decarboxylative alkylation of heteroarenes with α-AAs under 4CzIPN (**25**) photocatalysis.



Scheme 159 Decarboxylative trifluoromethylation of arenes and heterocyclic compounds under Ru (a) or Fe (b) photocatalysis.

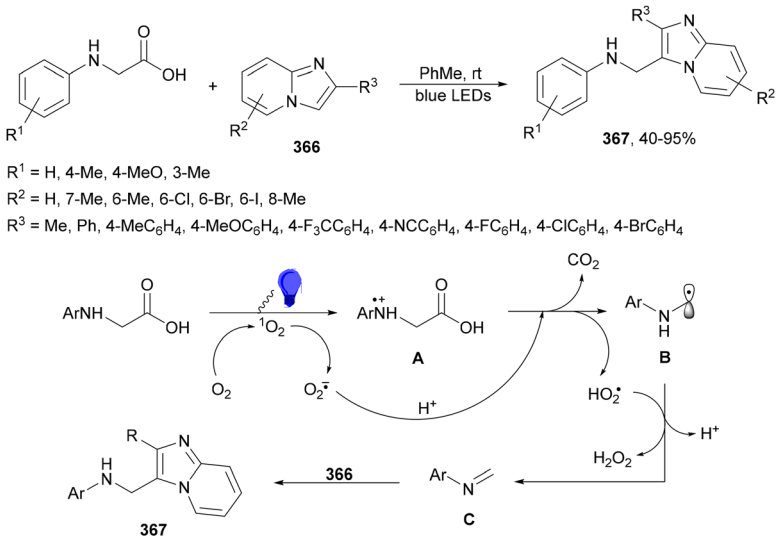


Scheme 160 Decarboxylative alkylation of arenes and heteroarenes with carboxylic acids under $FeCl_3$ photocatalysis.

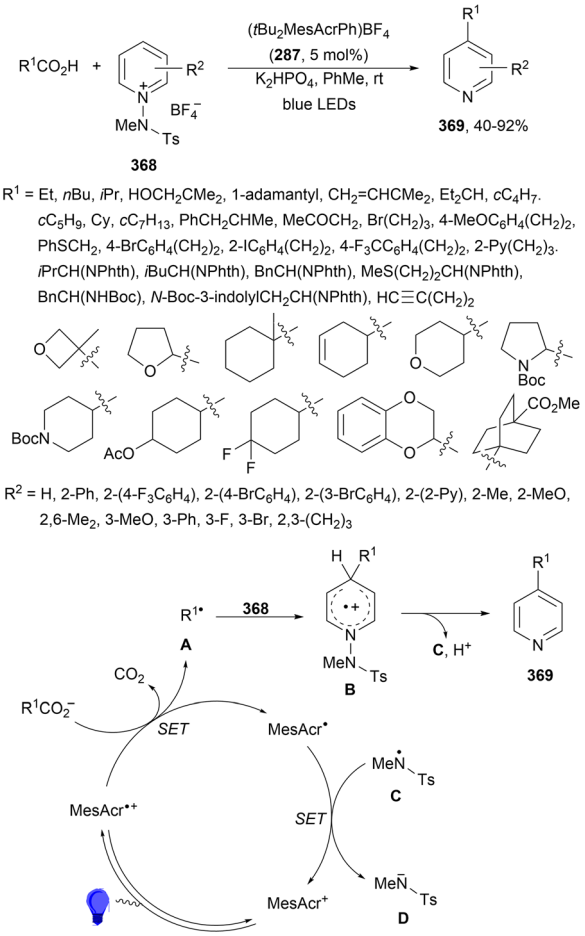


Scheme 161 Decarboxylative alkylation of quinoxaline-2(1*H*)-ones with carboxylic acids under Ir and $K_2S_2O_8$ photocatalysis.

phenanthroline and purine. The corresponding aminoalkylated products were obtained with 24–95% yields and this process was also applied to the functionalization of drugs such as fasudil hydrochloride, caffeine and famciclovir. Another general method for the alkylation with aliphatic carboxylic acids derived NHPI esters **69** of heterocyclic compounds was described by Opatz and co-workers.[307] In this case, $Ru(bpy)_3Cl_2$ (1 mol%) was used as a PC and *p*-TsOH as a Brønsted acid in DMF at room temperature under blue LED irradiation. Heterocyclic compounds such as isoquinoline, benzothiazole, pyrazine and quinoline gave the corresponding products, which were obtained with 16% to quantitative yields. Mechanistic investigations revealed a radical chain mechanism, which in some cases can proceed even if no PC is added. Under organocatalyzed (4CzIPN, **25**) visible-light photoredox conditions, *via* the intermediacy of the *in situ* generated NHPI esters, in the presence of TFA or CSA as Brønsted acids, Sherwood and co-workers[315] performed the alkylation with aliphatic acids and protected AAs and hydroxy acids of quinoline, pyridine, isoquinoline, quinaldine, phthalazine, quinoxaline, quinazolinone, azaindole, benzimidazole, benzothiazole and caffeine to provide the resulting products in general with modest yields (5–76%). Other bioactive compounds such as nebularine and peracetylated nebularine, adenosine, camptothecin, vemuraferib and imatinib were alkylated providing derivatives to establish SAR. Copper-catalyzed decarboxylative alkylation of isoquinolines, quinolines, pyridine, pyrimidine, quinazoline, phthalazine, phenanthridine and pyridazine derivatives has been accomplished by Wang and co-workers.[316] They



Scheme 162 Decarboxylative aminoalkylation of imidazo[1,2*a*]pyridines (**366**) with *N*-arylglycines under visible light irradiation.



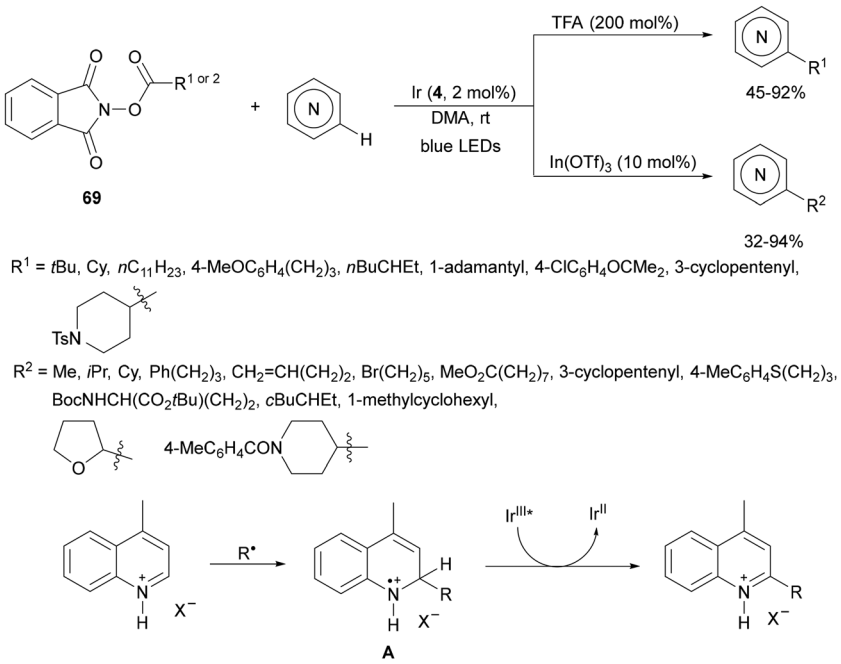
Scheme 163 Decarboxylative alkylation of *N*-amidopiridinium salts **368** with carboxylic acids under MesAcr$^+$ **287** photocatalysis.

employed $Cu(MeCN)_4PF_6$ (10 mol%), 2,9-dimethyl-1,10-phenanthroline (dmp, 15 mol%) and Xantphos (15 mol%) as ligands, $Zn(OTf)_2$ (10 mol%) as a Lewis acid in DMA at room temperature under blue LED irradiation providing products with in general good yields (18–99%). [Cu(dmp)(Xantphos)]BF_4, which was formed *in situ*, was the PC.

A general method for the decarboxylative alkylation of electron-rich heteroarenes with NHPI esters **69** was reported by Deng, Tang and co-workers.[317] In the presence of $Ir(ppy)_3$ (0.5 mol%) as a PC in DMSO at room temperature under white LED irradiation, furans, benzofurans and thiophenes were alkylated at the 2-position with in general moderate yields (21–84%).

Decarboxylative alkylation of quinoxalin-2(1*H*)-ones with NHPI esters has been carried out by Jin and co-workers[318] with Eosin Y-Na_2 (**139**, 1 mol%) as a PC and TFA in DMSO under white LED irradiation. These milder reaction conditions, compared to those described with carboxylic acids (Scheme 161),[296,297] gave the corresponding 3-alkylated products in higher yields (63–99%). Independently, Li and coworkers[319] performed the same alkylation using $Ir(ppy)_3$ (2 mol%) and TFA in DMSO under white LED irradiation providing 3-alkylated quinoxaline-2(1*H*)-ones also with in general very good yields (30–95%). More recently, Yatham and co-workers[320] described the same photoinduced decarboxylative alkylation just with K_2CO_3 as a base in DMF at room temperature under 395–400 nm irradiation to furnish the corresponding 3-alkylated quinoxaline-2(1*H*)-ones with 40–91% yields. These simple reaction conditions were implemented using medicinally important carboxylic acid derived NHPI esters, for instance, fenofibric acid, gemfibrozil, loxoprofen and levulinic acid.

Papaioannou, Fray and co-workers[321] carried out regioselective photoredox amido methylation of 4-chloro-3-fluoropyridine (**382**) with α-AA derived NHPI esters **143**. In this case, 4CzIPN (**25**) was employed as a PC and DMA as solvent at 36 °C by irradiation using a Kessil H150 blue grow light (400–520 nm). The resulting trisubstituted pyridines **383** were obtained with 39–74% yield and 87 : 13–97 : 3 isomeric ratios (Scheme 170). The best results were obtained with *N*-Boc protected esters **143**, which were scaled-up to 77 mmol.



Scheme 164 Decarboxylative alkylation of N-heterocycles with NHPI esters **69** under Ir/acid photocatalysis.

8-Acylaminoquinoline (**384**) has been alkylated regioselectively at the 2-position with aliphatic primary and tertiary carboxylic acid derived NHPI esters **69** in the presence of $Ir(ppy)_3$ as a PC and TFA in DMSO under white LED irradiation.[322] The resulting 2-alkylated quinolines **385** were isolated in good yields using *N*-acylated derivatives, whereas 9-aminoquinoline failed (Scheme 171). When secondary alkyl NHPI esters were employed, dialkylated quinolines **386** were obtained with good yields.

The 2*H*-indazole unit is present in many drugs and bioactive molecules and also in materials science. Jiang, Yu and co-workers[323] developed a photoredox decarboxylative alkylation of 2-aryl-2*H*-indazoles **387** with alkyl NHPI esters **69** in the presence of 4CzIPN (**25**) as a PC and DABCO as a base in dimethyl carbonate (DMC) at 35 °C under N_2 and blue LED irradiation (Scheme 172). The resulting 3-alkylated indazoles **388** were obtained under these mild and green reaction conditions with good yields. This protocol was applied to the late-stage modification of drug molecules such as elaidic acid, levulinic acid and gemfibrozil.

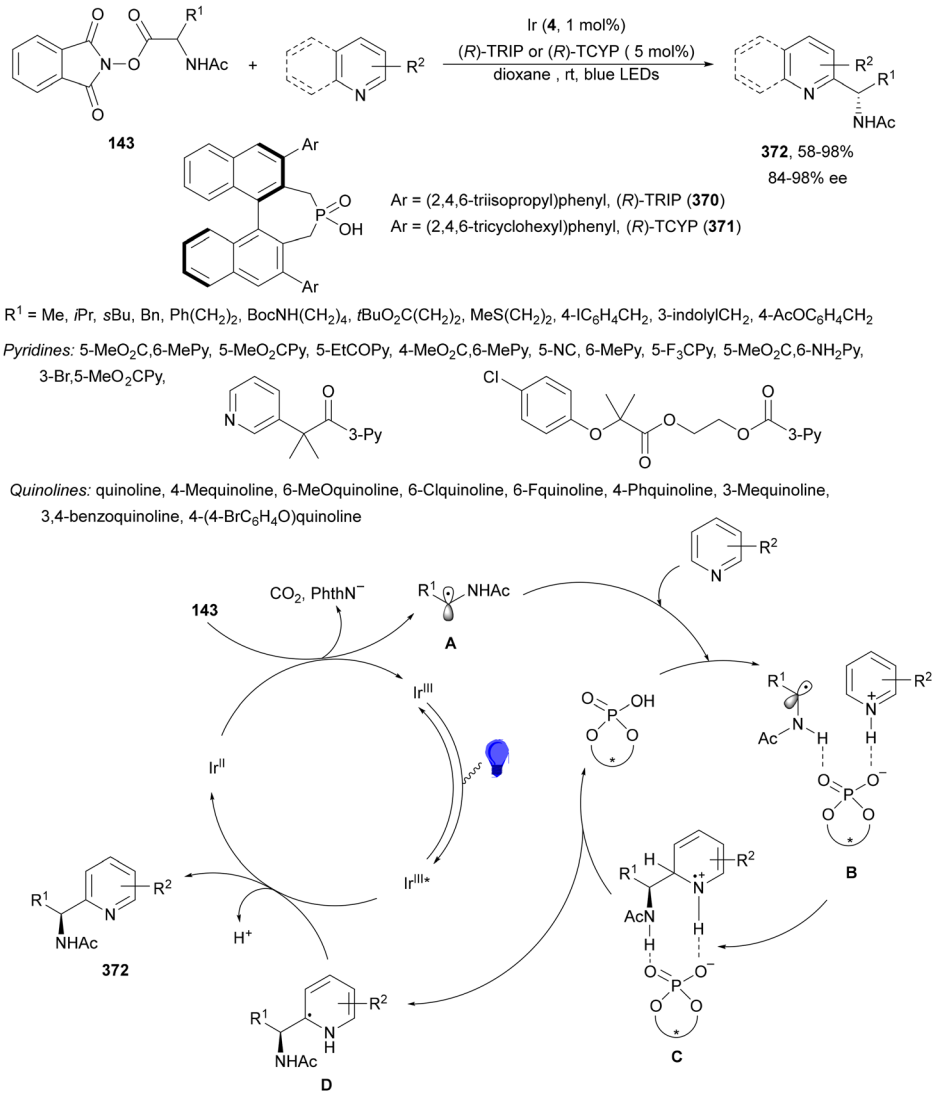
The same group[324] recently reported the regioselective alkylation of 2,1,3-benzothiazoles **389** under the above described reaction conditions. In this case, the alkylation took place in *N*,*N*-dimethylacetamide (DMAc) at the four position of the heterocycles affording products **390** with moderate to good yields (Scheme 173). The reaction of compound **389a** (R^2 = H) with the cyclohexyl derived NHPI ester was carried out on a gram scale to give product **390a** (R^1 = Cy; R^2 = H) in 60% yield. NHPI esters derived from biologically active molecules such as gemfibrozil, elaidic acid and dehydrochlolic acid were also employed.

Decarboxylative alkylation of imidazo[1,2*a*]pyridines **366** was also carried out with alkyl NHPI esters **69**[325] instead of carboxylic acids as it was previously described[300] (Scheme 162). In this case, Eosin Y was used as an organic PC in the presence of TfOH at room temperature in DMSO under blue LED irradiation to afford products **367** alkylated at the five position with 38–86% yields.

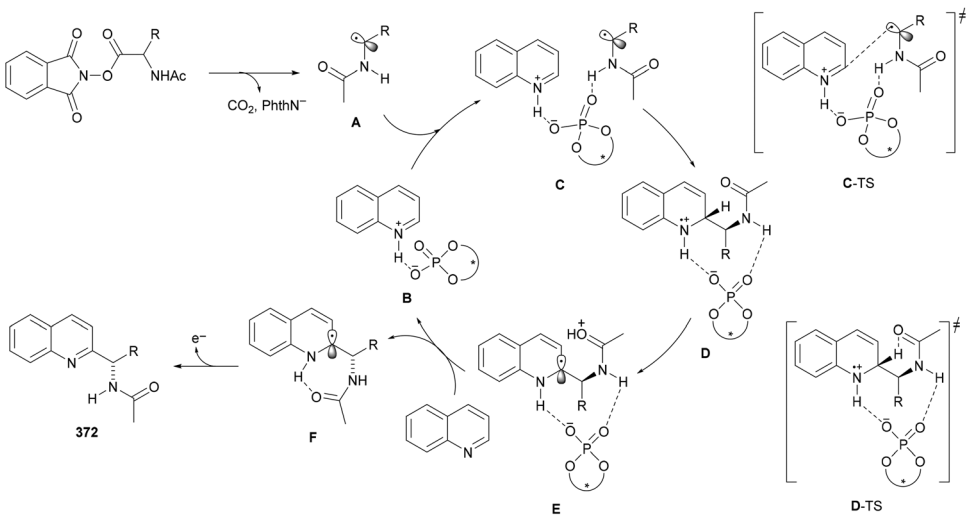
Sun, Zhou and co-workers[326] reported a C-2 alkylation of quinoline **391** and pyridine *N*-oxides **392** with alkyl NHPI esters **69** in the presence of Eosin Y as a PC and Cs_2CO_3 as a base in DMF at room temperature under blue LED irradiation. Products **393** and **394** were obtained in moderate to good yields (Scheme 174). Quinoxaline and quinazoline *N*-oxides were also alkylated at the 2-position with 51 and 26% yields, respectively. Glycosyl-based NHPI ester as well as dehydroabietic acid and quinine derived esters were employed for the alkylation of lepidine *N*-oxide at the two position.

C–H alkylation of azauracils **395** has been carried out by Murarka and co-workers[327] using alkyl NHPI esters **69** in the presence of NaI/PPh_3 and TMEDA as a base in MeCN at room temperature under blue LED irradiation (Scheme 175). This alkylation took place to give products **396** with very good yields and was also carried out with other heterocycles such as cinnolinone, quinoxalinone and pyrazinone. In the proposed mechanism, the reaction begins by the formation of a charge-transfer complex (CTC) assembly **A** based on cation–π and electronic interactions. Upon irradiation, a SET process from an iodine anion to NHPI ester leads to the generation of alkyl radical **B** and iodide radical **C**, after CO_2 elimination. Subsequent addition of **B** to the 6-position of azauracil gives radical **D**, which after oxidation by **C** forms intermediate **E**. Finally, TMEDA or $PhthN^-$ deprotonates **E** to provide the product.

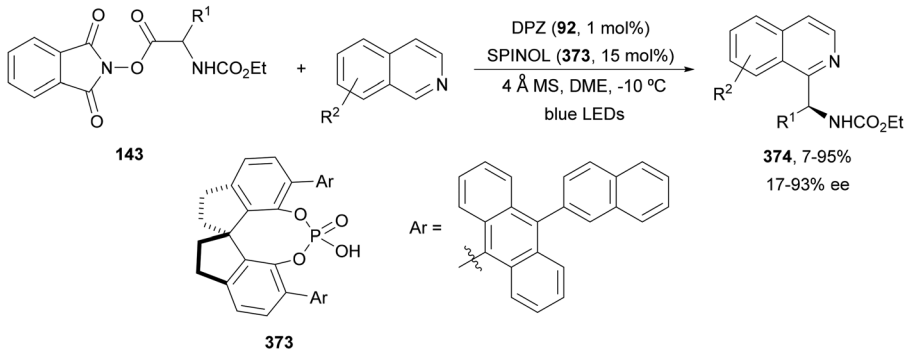
Non-aromatic heterocycles such as coumarins **397** have been alkylated by carboxylic acid decarboxylation[291] and also by



Scheme 165 Decarboxylative asymmetric alkylation of quinolines and pyridines with α-AAs derived NHPI esters **143** under Ir/CPAs **370** and **371** photocatalysis.



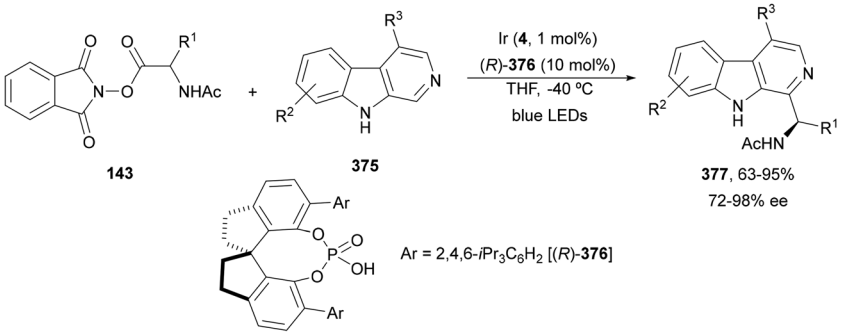
Scheme 166 Mechanism for CPA-catalyzed Minisci reaction of NHPI esters with quinoline.



R^1 = Me, *i*Pr, *i*Bu, Ph, Bn, 4-$FC_6H_4CH_2$, 3-$FC_6H_4CH_2$, 2-$FC_6H_4CH_2$, 4-$ClC_6H_4CH_2$, 3-$ClC_6H_4CH_2$, 4-$BrC_6H_4CH_2$, 3-$BrC_6H_4CH_2$, 2-$BrC_6H_4CH_2$, 4-$MeC_6H_4CH_2$, 3-$MeC_6H_4CH_2$, 2-$MeC_6H_4CH_2$, 4-*i*$PrC_6H_4CH_2$, 4-$MeOC_6H_4CH_2$, 3-indolylCH_2

R^2 = H, 6-Cl, 6-Br, 6-MeO, 7-OMe

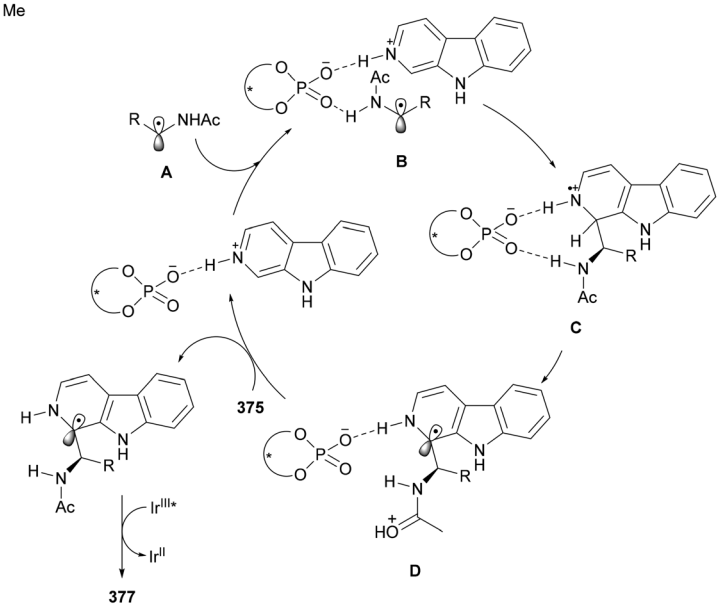
Scheme 167 Decarboxylative asymmetric alkylation of isoquinolines with α-AA derived NHPI esters **143** under DPZ (**92**)/SPINOL-CPA **373** photocatalysis.



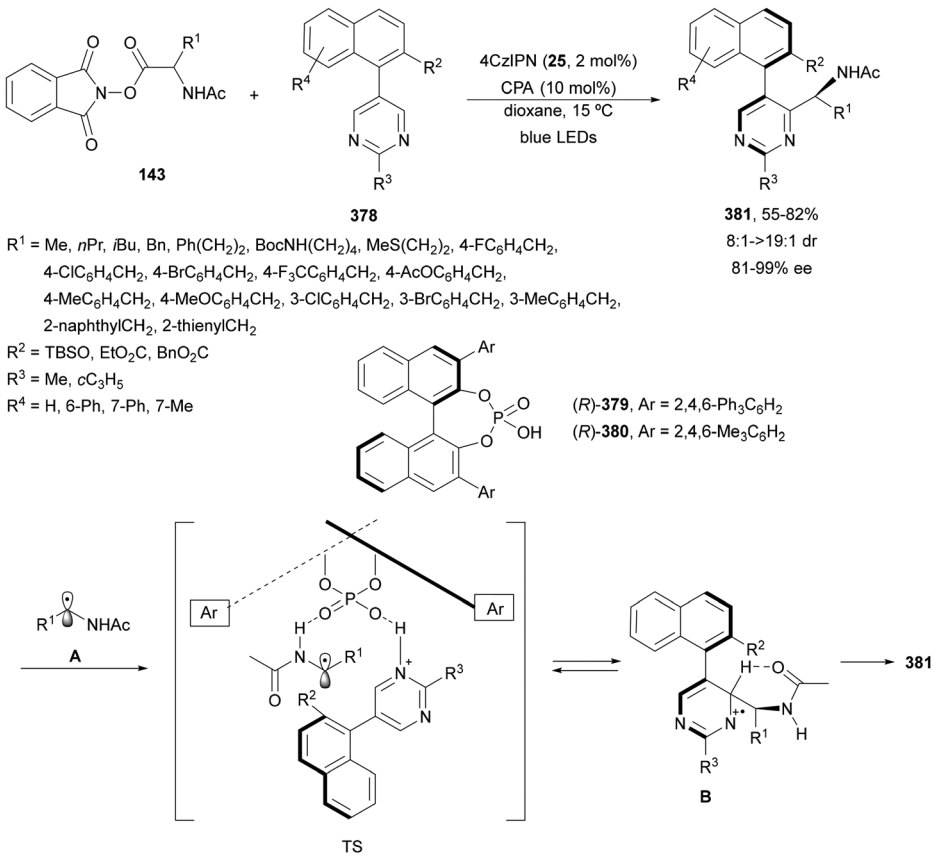
R^1 = Me, Et, *n*Pr, *n*Bu, Bn, *n*C_6H_{13}, *i*Bu, $CyCH_2$, $Ph(CH_2)_2$, CH_2=$CHCH_2$, $MeS(CH_2)_2$, $BnSCH_2$, $EtO_2C(CH_2)_2$, 4-$BrC_6H_4CH_2$, 4-$FC_6H_4CH_2$, 4-$ClC_6H_4CH_2$, 4-$MeC_6H_4CH_2$, 4-$PhC_6H_4CH_2$, 4-$MeOC_6H_4CH_2$, 4-$BnOC_6H_4CH_2$, 4-*t*$BuOC_6H_4CH_2$, 4-$AcOC_6H_4CH_2$, 4-$NCC_6H_4CH_2$, 1-naphthylCH_2, 2-naphthylCH_2, HC≡CCH_2

R^2 = H, 6-Ph, 6-Me, 8-Me, 5-Me, 6-MeO, 6-HO, 6-Br, 7-Br, 6-Cl, 6-F

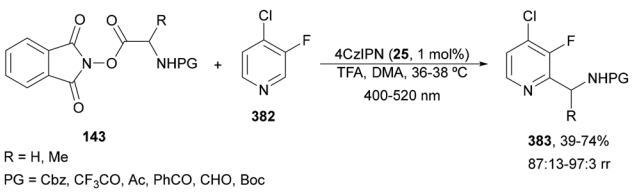
R^3 = H, Me



Scheme 168 Decarboxylative asymmetric alkylation of β-carbolines **375** with α-AA derived NHPI esters **143** under Ir/SPINOL-CPA **376** photocatalysis.

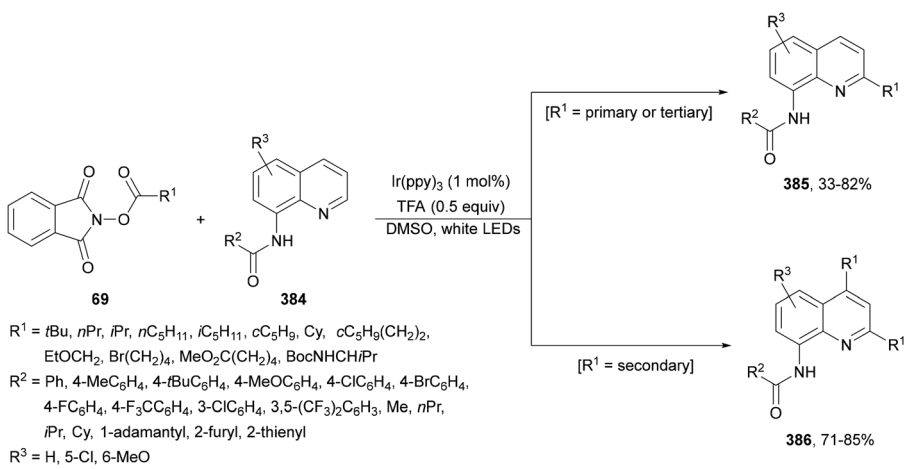


Scheme 169 Decarboxylative asymmetric alkylation of 5-arylpyrimidines **378** with α-AA-derived NHPI esters **143** under 4CzIPN/CPA **370**, **379** or **380** photocatalysis.

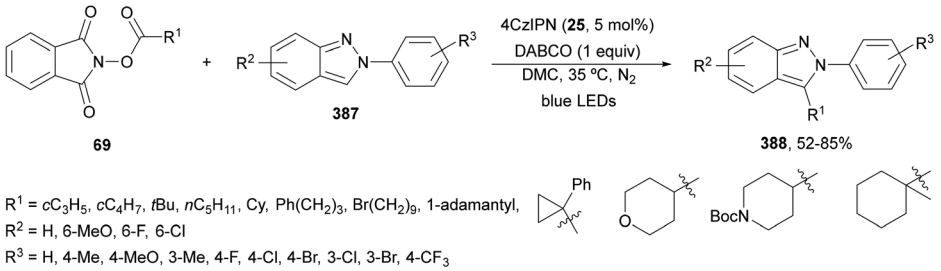


Scheme 170 Decarboxylative alkylation of 4-chloro-3-fluoropyridine (**382**) with α-AA derived NHPI esters (**143**) under 4CzIPN photocatalysis.

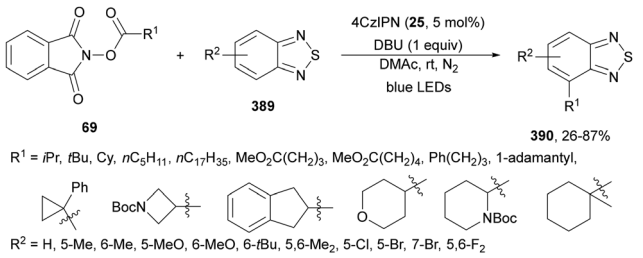
means of alkyl NHPI esters.[328] This alkylation took place regioselectively at the 3-position using $Ir(ppy)_3$ as a PC and TFA as a Brønsted acid in DMSO at room temperature under N_2 and blue LED irradiation (Scheme 176). Products **398** were obtained with 30–92% yields and it was proposed that the alkyl radical **A**, generated from NHPI ester **69**, adds to coumarin to give radical **B**, which was further oxidized by Ir(IV) to carbocation **C**. Final deprotonation by trifluoroacetate gives product **398**. Independently,



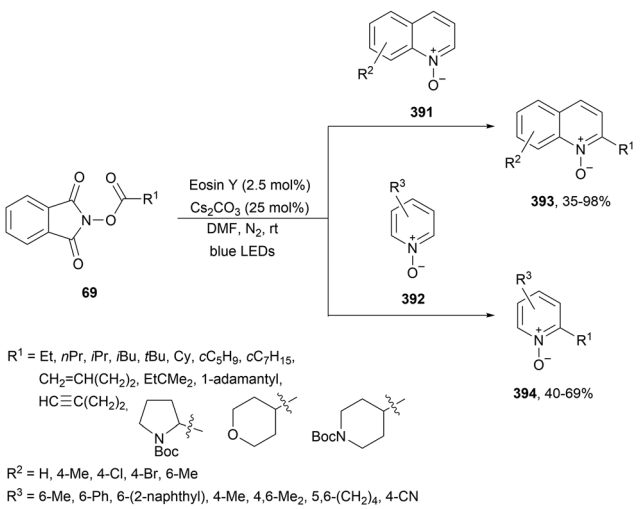
Scheme 171 Decarboxylative mono- and di-alkylation of 8-acylaminoquinoline (**384**) with aliphatic NHPI esters **69** under $Ir(ppy)_3$ photocatalysis.



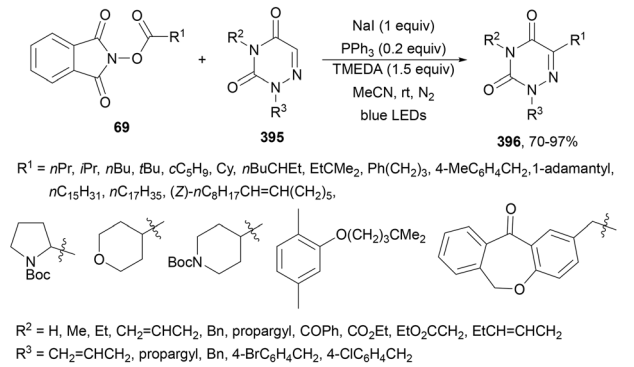
Scheme 172 Decarboxylative alkylation of 2-aryl-2*H*-indazoles **387** with alkyl NHPI esters **69** under 4CzIPN (**25**) photocatalysis.

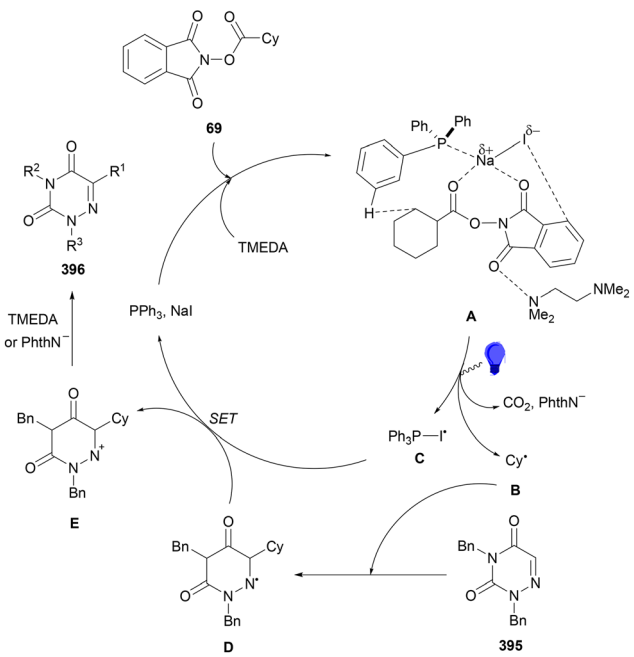


Scheme 173 Decarboxylative C-4 alkylation of 2,1,3-benzothiadiazoles **389** with alkyl NHPI esters **69** under 4CzIPN photocatalysis.



Scheme 174 Decarboxylative C-2 alkylation of heterocyclic *N*-oxides with alkyl NHPI esters **69** under Eosin Y photocatalysis.



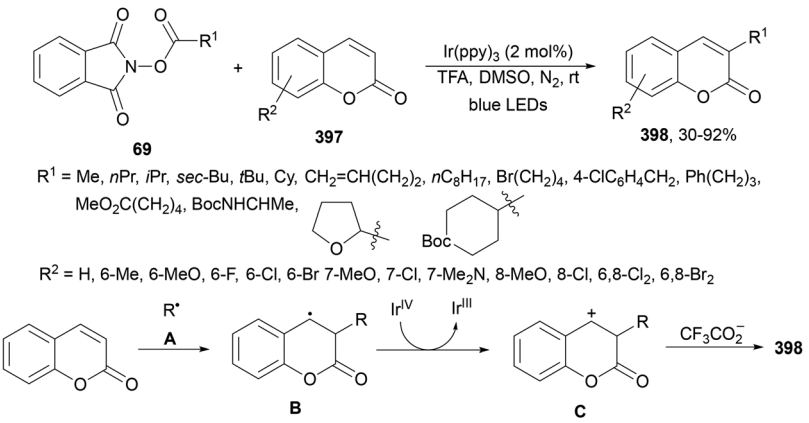


Scheme 175 Decarboxylative C-6 alkylation of azaurazils **395** with alkyl NHPI esters under PPh_3/NaI photocatalysis.

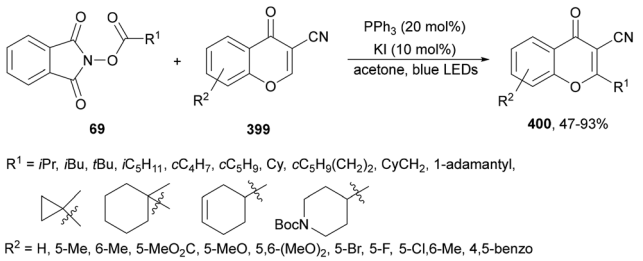
Dong, Zhou and co-workers[329] reported this alkylation using $Ru(bpy)_2Cl_2{\cdot}6H_2O$ (0.2 mol%) as a PC and DABCO as a base in DMAc at room temperature under sunlight or blue LED irradiation to give products **398** in 40–81% yields. Other heterocyclic compounds such as quinolinones or quinoxalinones were alkylated in 60–73% yields.

Albrecht and co-workers[330] employed catalytic amounts of PPh_3/KI for the decarboxylative alkylation of 3-cyanochromones **399** with alkyl NHPI esters **69** in acetone as solvent and under blue LED irradiation to give 2-alkylated derivatives **400** (Scheme 177). This process took place by a CTC assembly as depicted in Scheme 175.

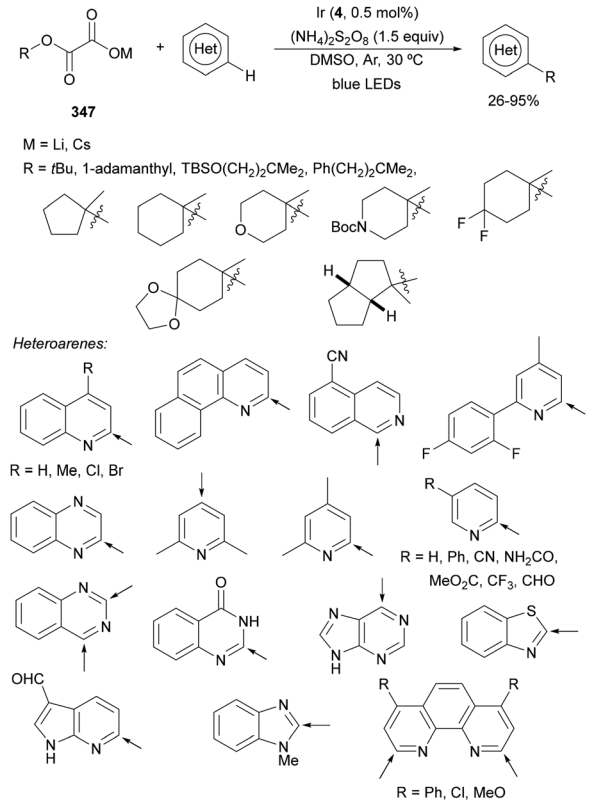
Other esters have been used as sources of alkyl radicals instead of NHPI esters. In 2015, Overman and MacMillan groups[60] reported that *tert*-alkyl oxalate salts, such as **347**, can generate tertiary radicals for 1,4-addition to electrophilic alkenes. In 2019, Overman and co-workers[331] incorporated tertiary alkyl substituents into a variety of heterocyclic substrates by means of *tert*-alkyl oxalate salts **347**. They employed Ir complex **4** as a PC



Scheme 176 Decarboxylative C-3 alkylation of coumarins **397** with alkyl NHPI esters (**69**) under $Ir(ppy)_3$ photocatalysis.



Scheme 177 Decarboxylative C-2 alkylation of 3-cyanochromones **399** with alkyl NHPI esters **69** under PPh_3/KI photocatalysis.



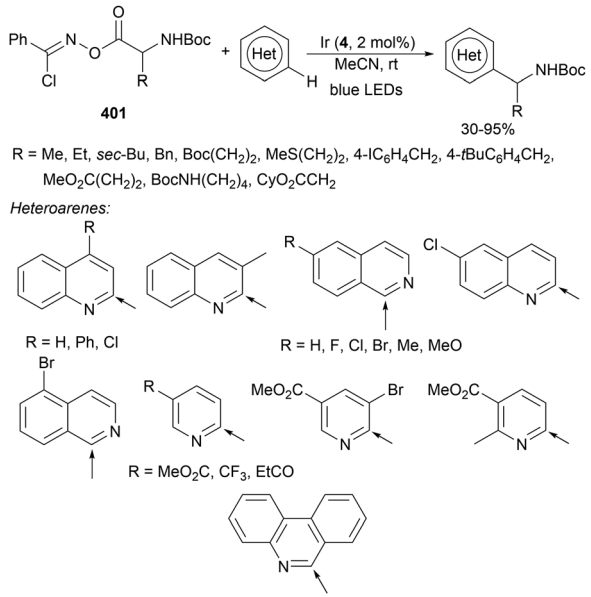
Scheme 178 Decarboxylative alkylation of heteroarenes with *tert*-alkyl oxalate salts **347** under photocatalysis.

and $(NH_4)_2S_2O_8$ as an external oxidant and one equivalent of HCl for this alkylation (Scheme 178). Heteroarenes such as quinolines, pyridines, quinoxaline, quinazolin-4(3*H*)-one, 7-azaindole, phenanthroline, benzothiazole and 1-methylbenzimidazole were alkylated with moderate yields. This method was also applied to biologically relevant heteroarenes such as purine riboside, quinine, the rho-kinase inhibitor and vasodilator fasudil.

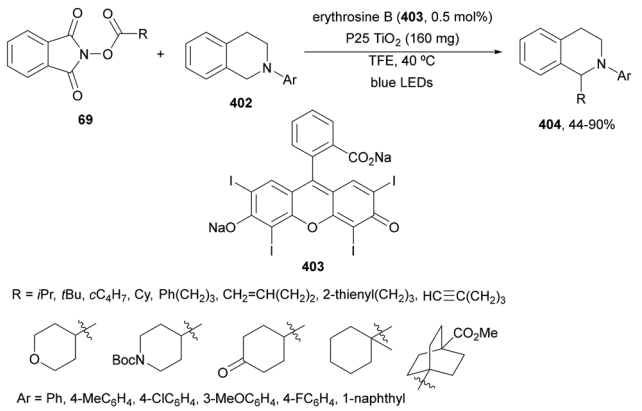
Decarboxylative alkylation of heteroarenes has been carried out with *N*-hydroxybenzimidoyl chloride (NHBC) esters **401** as RAEs for the coupling of α-aminoalkyl radicals.[332] This type of RAE was previously employed for the photoinduced hydrofluoroalkylation of unactivated alkenes.[333] In the presence of Ir complex **4** and in the absence of external oxidant, in MeCN at room temperature under blue LED irradiation, the corresponding α-aminoalkylated products were obtained with good yields (Scheme 179). Quinolines, isoquinolines, pyridines and phenanthridine were α-aminoalkylated with a broad variety of *N*-Boc α-AAs. This protocol has been applied to the functionalization of thymopentin, a pentapeptide with potential biomedical applications. NHBC esters **401** generate, by photoexcited Ir(III), the corresponding α-amino radicals, chloride, CO_2 and benzonitrile.

Alkylation of aliphatic C–H bonds with NHPI esters was described by Ren and Cong[334] using *N*-aryl tetrahydroisoquinolines **402.** In this decarboxylative alkylation, erythrosine B (**403**) and P25-type TiO_2 were used as visible light PC in 2,2,2-trifluoroethanol (TFE) at 40 °C (Scheme 180). The corresponding 1-substituted tetrahydroisoquinolines **404** were isolated with in general good yields employing primary, secondary and tertiary alkyl NHPI esters **69.**

C(sp^3)–H alkylation of *N*-aryl glycines with NHPI esters **69** for preparing α-alkylated unnatural α-AAs has been carried out under copper-catalyzed decarboxylative conditions.[335] Working with 10 mol% of $Cu(MeCN)_4PF_6$, 15% of dmp or Xantphos as ligands, DABCO as a base in DMF under blue LEDs irradiation, different glycine derivatives were alkylated with very good yields (Scheme 181a). This process was also applied for the modification of peptides which were regioselectively alkylated at the α-position of the glycine unit with good yields and low diastereoselectivity



Scheme 179 Decarboxylative α-aminoalkylation of N-heteroarenes with *N*-hydroxy benzimidoyl chloride esters **401** under Ir photocatalysis.



Scheme 180 Decarboxylative alkylation of *N*-aryl tetrahydroisoquinolines **402** with alkyl NHPI esters **69** under erythrosine B (**403**) sensitized TiO_2 photocatalysis.

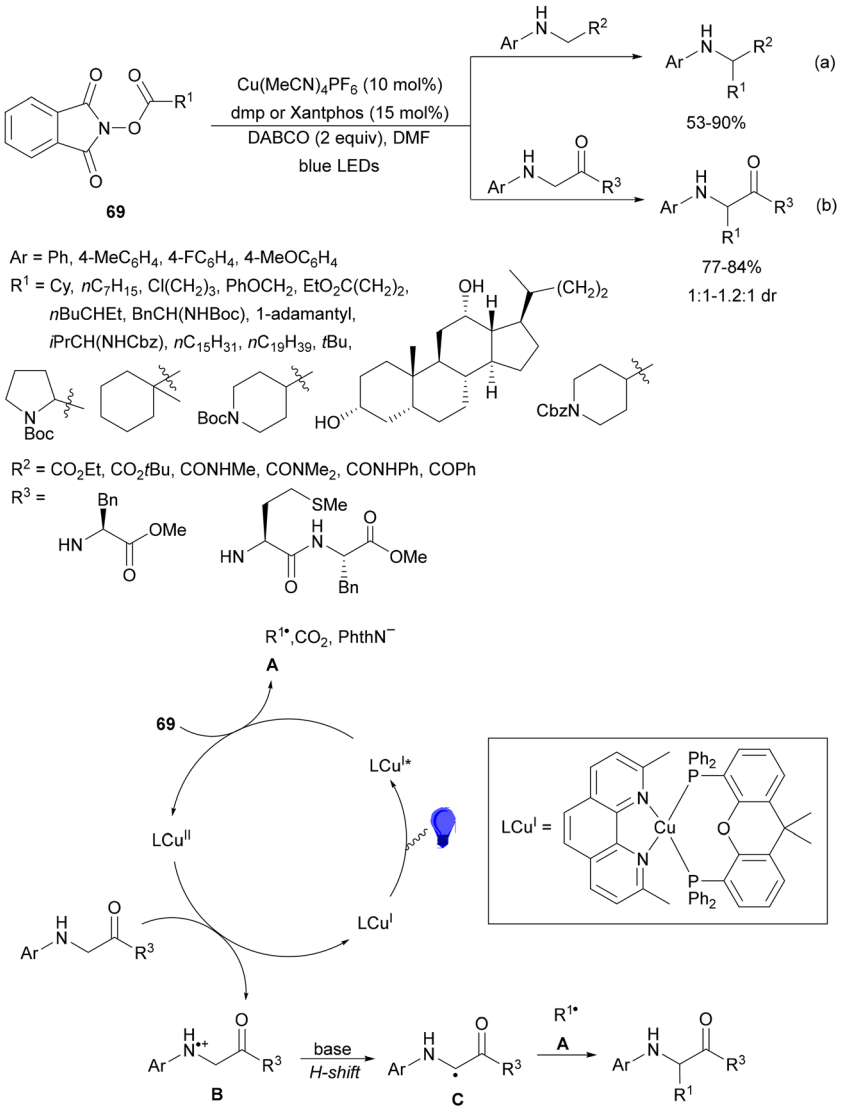
(Scheme 181b). In the proposed mechanism, the LCu(I) complex is excited to LCu(I)*, which undergoes a SET with alkyl NHPI ester **69** followed by generation of the alkyl radical **A** and LCu(II). The glycine derivative is oxidized by LCu(II) generating a radical cation **B** and regenerating the catalyst. Intermediate **B** is deprotonated by the base or $PhthN^-$ and after a 1,2-H shift process the stable α-carbon radical **C** is formed. Finally, radical–radical coupling of **C** and **A** gives the product.

Glycosylation with α-AAs to construct *C*-glycopeptides has been achieved by visible-light copper-catalyzed cross-coupling by Liang and co-workers.[336] This asymmetric $C(sp^3)$–$C(sp^3)$–H reaction was carried out between glycosyl NHPI esters **405** and *N*-(8-quinolyl)glycine esters **406** using $Cu(OTf)_2$ and (*S*)-XylBINAP (**407**) as a chiral ligand and DABCO as a base in DMF under blue LED irradiation (Scheme 182). Resulting *C*-glycosides **408** were obtained with moderate to good yields and excellent diastereoselectivity. Different α-AAs as well as dipeptides formed by condensation of glycine with Val, Phe, Ala and Met, and tripeptides such as Gly–Phe–Phe–OMe, Gly–Met–Phe–OMe and Gly–Phe–Val–OMe were also employed. Protected ribose and pyranoses including galactose, mannose and glucose derived NHPI esters proceeded in excellent dr and good yields. The proposed mechanism starts with the Cu(I)-AA complex **A**, which after irradiation *via* a SET process reacts with **405** to give the glycosyl-Cu(III) species **B** *via* glycosyl radical formation. Intramolecular LMCT[54,55] of **B** forms a radical intermediate **C**, which by a 1,2-H shift produces species **D**. Subsequent intramolecular recombination of alkyl radical promotes the formation of the chiral Cu(III) **E**, which evolves to give product **408** through a reductive elimination step and regenerates the catalyst.

MacMillan and co-workers[337] performed the $C(sp^3)$–$C(sp^3)$–H cross-coupling of bicyclo[1.1.1]pentane (BCP, **157**) with N-heterocycles and other nucleophiles and alkyl carboxylic acids *via* iodonium dicarboxylates **236**. The three-component reaction was carried out under $Cu(acac)_2$ and bathophenanthroline (BPhen) catalysis using $Ir(ppy)_3$ as a PC and BTMG as a base in dioxane under blue LED irradiation to provide diverse functionalized bicyclopentanes **409** with good yields (Scheme 183). In the proposed mechanism, photoexcited Ir(III)* reduces iodonium dicarboxylate **236** to generate radical **A** upon CO_2 extrusion. Subsequent radical addition to BCP (**157**) generates radical **B**, which reacts with complex **C** to give the Cu(III) intermediate **D**. After subsequent reductive elimination, product **409** is formed and the Cu(I) complex **E** regenerated. Finally, reaction of **E** with the nucleophile provides the Cu(I) species **F**, which after oxidation by Ir(IV) forms the PC. These products are valuable pharmaceutical bioisosteres of benzene.

Decarboxylative alkylation of arenes and heteroarenes can be carried out directly with carboxylic acids or with activated esters such as NHPI. In the first case, different photoredox catalysts such as Ir complexes used $S_2O_8^{2-}$ as an external oxidant, whereas organocatalysts were used in the presence of acids or bases. Metal salts as Fe and Ce worked *via* photoinduced LMCT. In the case of NHPI esters derived from α-AAs, asymmetric α-aminoalkylation of heterocycles can be performed in the presence of chiral phosphoric acids under Ir or organophotocatalysis. Reaction conditions for NHPI esters are, in general, milder than with carboxylic acids either with Ir, Ru or organic PCs or with Cu complexes. Alternatively, PPh_3 and metal iodides have been employed by formation of a charge-transfer complex for azauracils and 3-cyanochromones. Alkylation of $C(sp^3)$–H bonds especially of glycine derivatives has been carried out with copper salts by LMCT processes.

2.12.2. Acylation reactions. Minisci C–H acylation of heteroarenes can be achieved with α-keto acids as sources of acyl radicals under visible light irradiation conditions. A general process involves the same reaction conditions previously described for alkylation reaction of heteroarenes with carboxylic acids,[286] using $PhI(O_2CCF_3)_2$ (PIFA) in the absence of a PC just under blue LED irradiation in MeCN. This decarboxylative acylation was carried out with quinoline, isoquinoline,



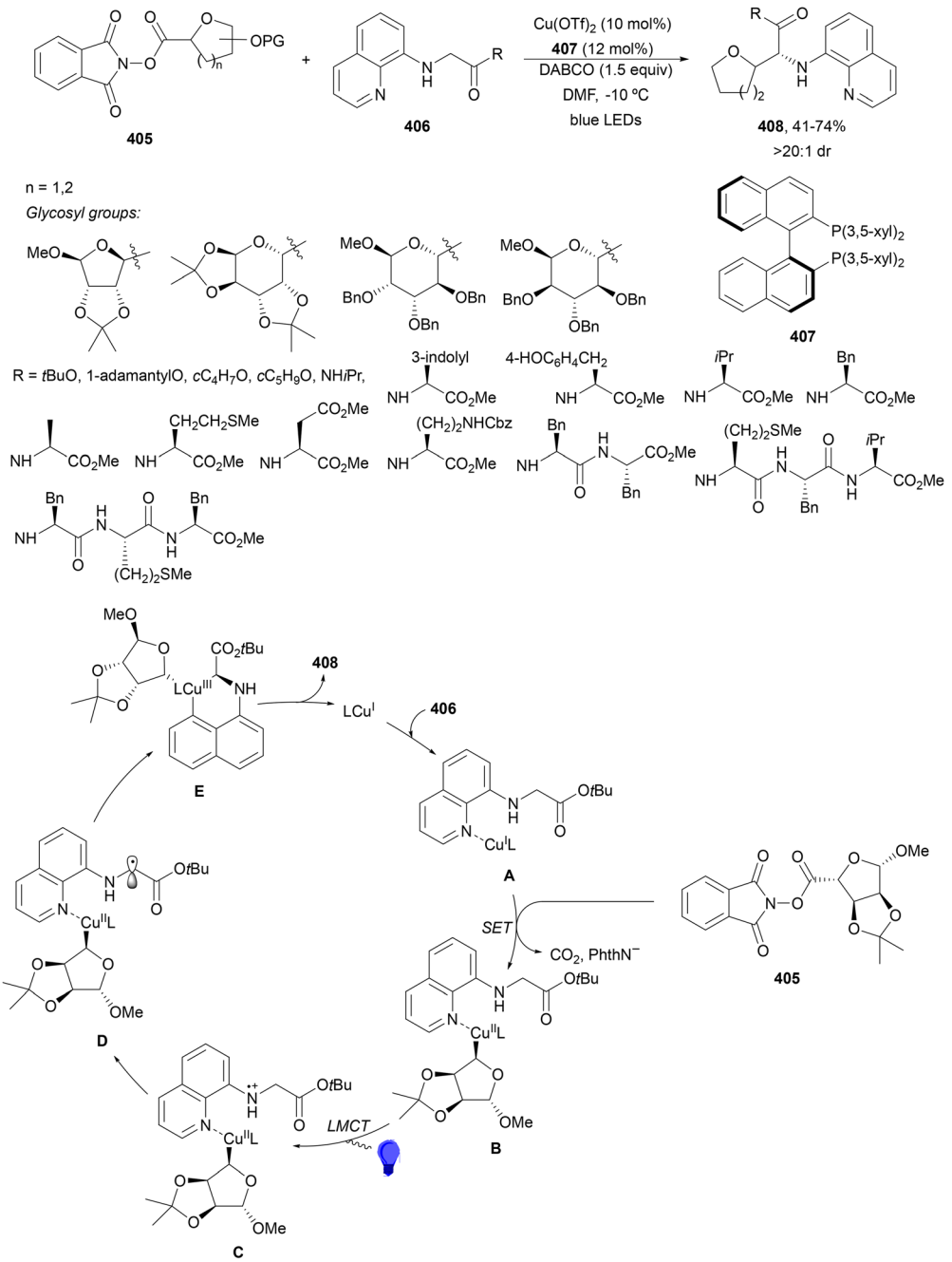
Scheme 181 Decarboxylative C(sp^3)–H alkylation of glycines (a) and peptides (b) with NHPI esters **69** under Cu(I) photocatalysis.

phenanthridine and benzo[*d*]thiazole, which were acylated in 43–80% yields.

Wencel-Delord and co-workers[338] performed a general photo-induced acylation of N-heterocycles in the absence of a PC. In the presence of $K_2S_2O_8$ as external oxidant in a 1 : 2 mixture of MeCN/H_2O at room temperature, different N-heterocycles including 2- and 4-methylquinolines, isoquinolines, pyridines, pyrimidines, acridine, quinoxaline, quinazoline, phthalazine, 1,10-phenanthroline, benzothiazole and caffeine were acylated with 23–86% yields (Scheme 184). According to mechanistic studies, three different pathways were proposed: (a) direct generation of the acyl radical; (b) generation of the EDA complex **A** absorbing the visible light and thus enhancing photodecarboxylation; and (c) generation of the EDA complex **B** promoting homolytic cleavage of $S_2O_8^{2-}$ to produce $SO_4^{-\bullet}$ triggering decarboxylation of the α-keto acid and generation of the acyl radical.

In the case of electron-deficient N-heterocyclic compounds, the presence of Ir complex as a PC is crucial for the acylation with α-keto acids. Manna and Prabhu[339] employed 2 mol% of Ir complex **52** and 2 equivalents of $Na_2S_2O_8$ as an external oxidant in a 1 : 1 mixture of MeCN/H_2O at room temperature under CFL irradiation for the acylation of isoquinolines, quinolines, pyridines and quinoxaline (Scheme 185). In the proposed mechanism, the acyl radical **A** is generated through hydrogen atom transfer (HAT) between the α-keto acid and the sulfate radical anion followed by decarboxylation. Addition of **A** to isoquinoline gives the radical cation **B**, which after deprotonation affords the α-amino radical **C**. Subsequent reduction by Ir(IV) forms the product and regenerates the PC.

Decarboxylative formylation of heterocycles has been achieved with 2,2-diethoxyacetic acid **26** without a PC, just with $(NH_4)_2S_2O_8$ as an external oxidant. Yang, Xia and co-workers[340] performed the formylation of isoquinolines, quinolines, quinoxaline,

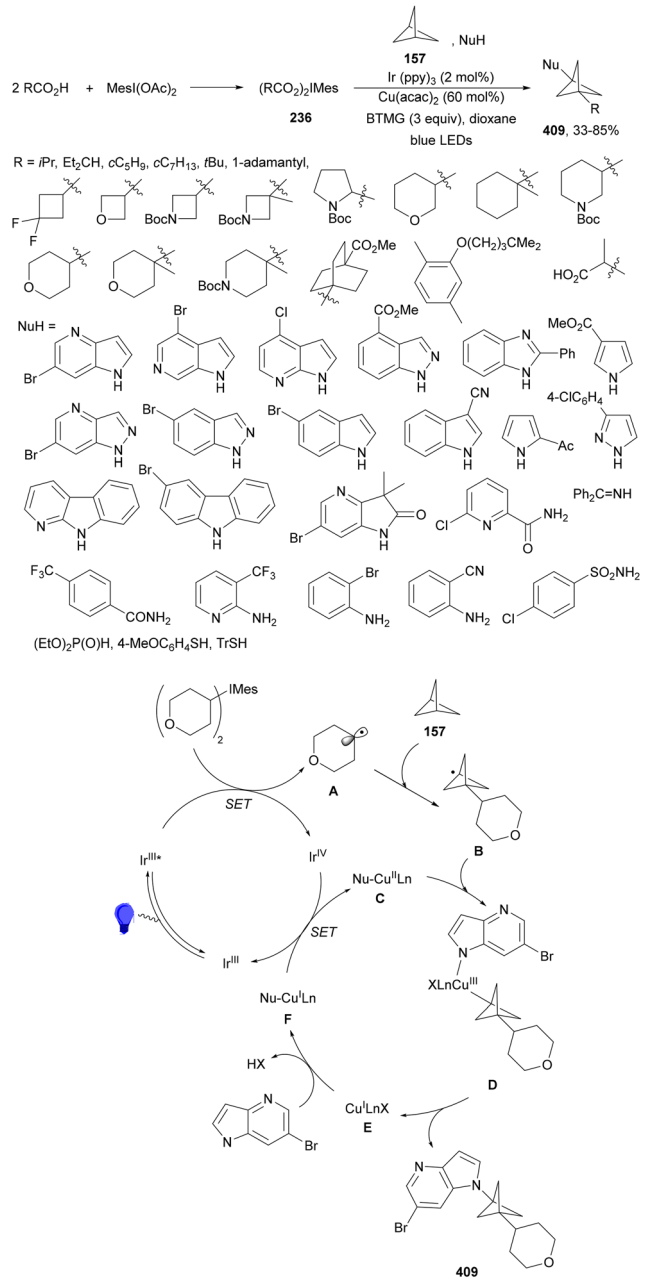


Scheme 182 Decarboxylative asymmetric C(sp^3)–H alkylation of *N*-quinolineglycine **406** with glycosyl NHPI esters **405** under Cu photocatalysis.

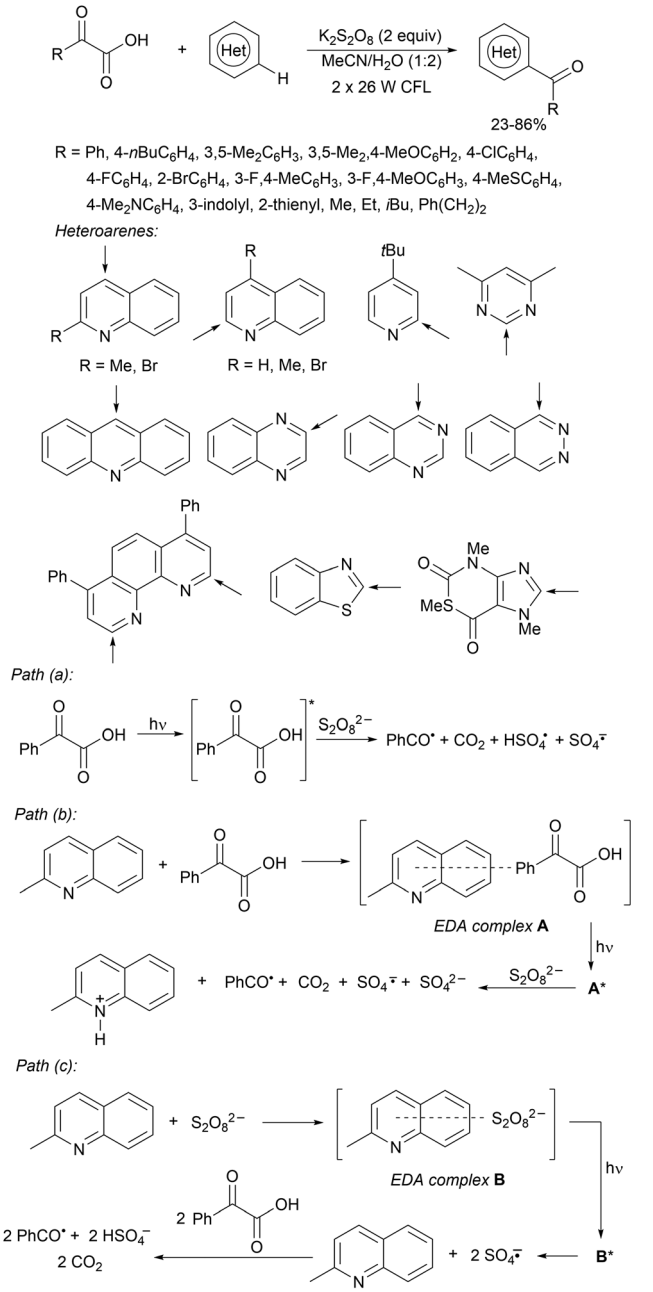
phenanthridine, benzimidazole, benzothiazole and caffeine using 2 equivalents of $(NH_4)_2S_2O_8$ and Cs_2CO_3 as a base in N_2 under blue LED irradiation followed by hydrolysis with 3 M HCl (Scheme 186a). However, when α-keto acids were used, the presence of 0.2 mol% of Ir complex **4** as a PC was needed, as well as 0.2 mol% of $(NH_4)_2S_2O_8$ (Scheme 186b).

In the case of acylation of quinoxalin-2(1*H*)-ones with α-keto acids, Yue, Wei and co-workers[341] used Acridine Red (**410**) as a PC in DCE and air as an oxidant under blue LED irradiation (Scheme 187). These mild reaction conditions with favorable functional group tolerance afforded 3-acylquinoxalin-2(1*H*)-ones with good yields. In the proposed mechanism, acridine is photoexcited in the presence of visible-light irradiation and interacts with the α-keto acid to produce the acyl radical **A**, after decarboxylation, and the hydroperoxyl radical. Addition of **A** to quinoxaline-2(1*H*)-one produces radical **B**, which undergoes a 1,2-H shift to radical **C**. Further oxidation of **C** by $HO_2^{\bullet}$ provides cation intermediate **D**, which after deprotonation gives the product.

Acylation of quinoxaline-2(1*H*)-ones has been carried out with 2,2-diethoxyalkylcarboxylic acids **411** in the presence of



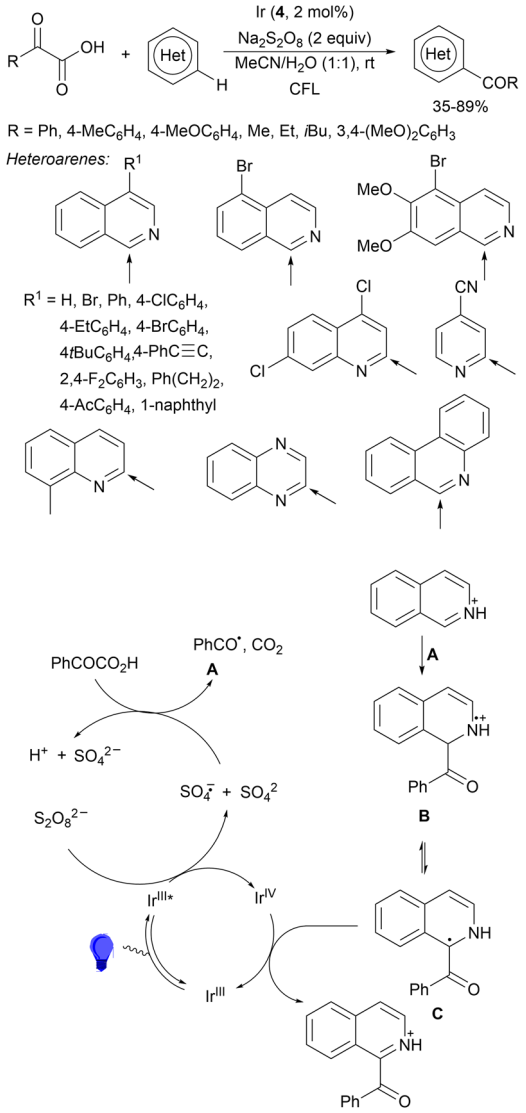
Scheme 183 Decarboxylative alkylation of bicyclo[1.1.1]pentane **157** and heteroatom nucleophiles under Ir/Cu photocatalysis.



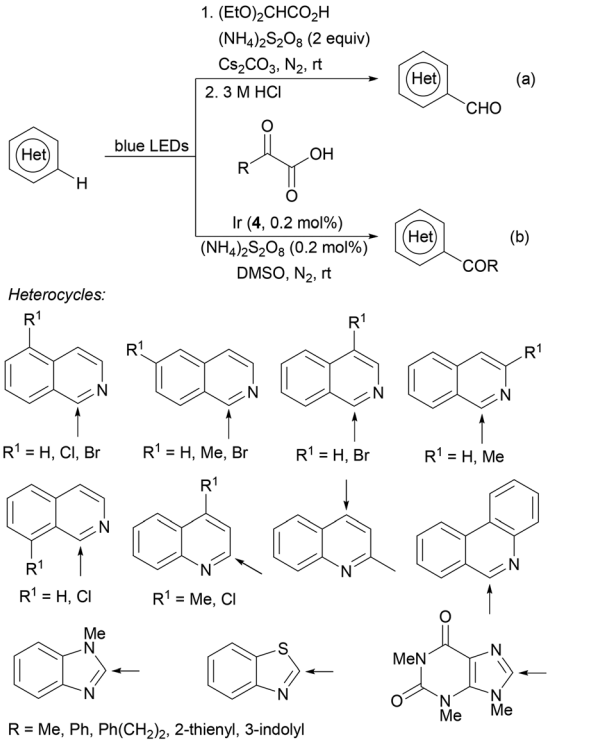
Scheme 184 Decarboxylative acylation of N-heteroarenes with α-keto acids in the presence of $K_2S_2O_8$ under photocatalysis.

4CzIPN (**25**) as a PC and Cs_2CO_3 as a base in DMF at 35 °C under air and green LED irradiation.[342] The corresponding 3-substituted quinoxaline-2(1*H*)-ones were isolated as diethyl acetals **412** in good yields (Scheme 188). The quinoxaline-2(1*H*)-ones carrying drug molecules including dehydrocholic acid (choleretics), indomethacin (a nonsteroidal anti-inflammatory drug) and a levulinic acid derivative were acetylated with moderate yields. In the proposed mechanism, 4CzIPN* was reductively quenched by quinoxaline-2(1*H*)-one to give $4CzIPN^{-\bullet}$ and the radical cation **A**. On the other hand, the glyoxylic acid acetal Cs salt is oxidized by **A** to generate the acetal radical **B**. Meanwhile, $4CzIPN^{-\bullet}$ is oxidized by O_2 in the air to generate 4CzIPN and the photoredox cycle. Radical **B** attacks the 3-position of quinoxaline-2(1*H*)-one to afford radical **C**, which after 1,2-H shift forms radical **D**. Subsequently radical **D** is oxidized by a SET process by 4CzIPN* generating cation **E**. Final deprotonation of **E** gives the product. In addition, radical **C** could be deprotonated by Cs_2CO_3 to form radical anion **F**, which by a SET process with 4CzIPN* affords product **412**.

Recently, Sing and co-workers[343] reported the regioselective decarboxylative acylation of *N*-methyl-3-arylquinoxalin-2(1*H*)-ones **413** with α-keto acids at the aryl substituent *via* dual palladium-photoredox catalysis. In the presence of $Pd(OAc)_2$,



Scheme 185 Decarboxylative acylation of N-heterocycles with α-keto acids under Ir **52** photocatalysis.



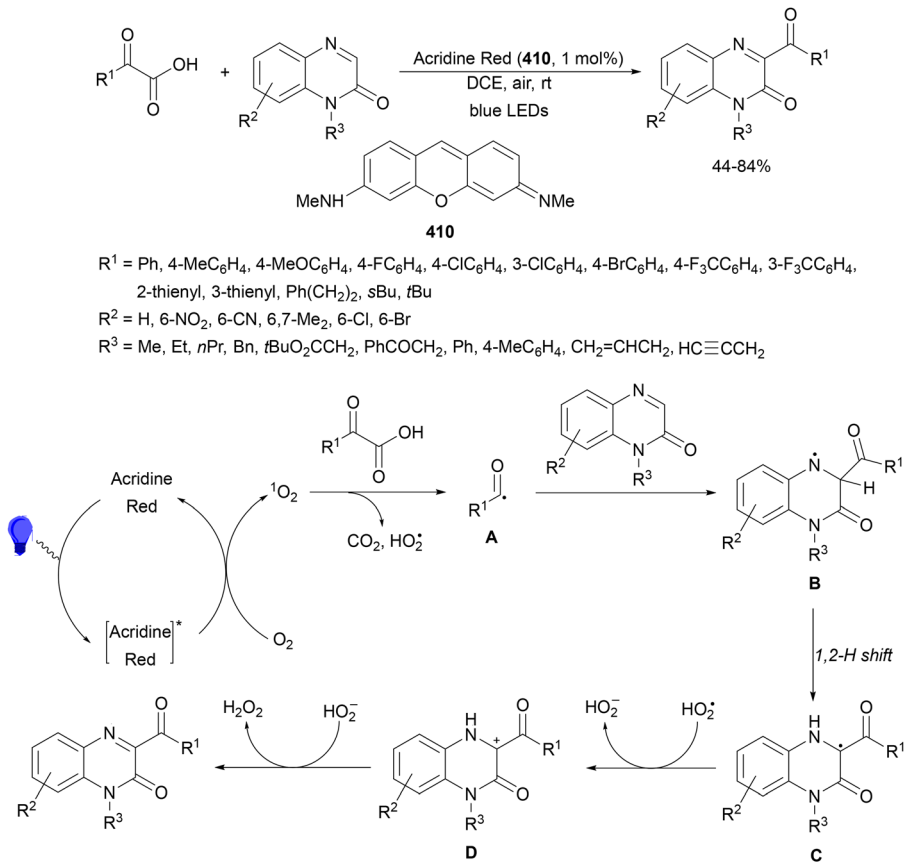
Scheme 186 Decarboxylative formylation (a) and acylation (b) of N-heteroarenes with 2,2-diethoxyacetic acid and α-keto acids, respectively, under photocatalysis.

tert-butyl peroxybenzoate (TBPB) as an oxidant in air, fluorescein dye as a PC, in EtOH at room temperature under blue LED irradiation, the corresponding acylated products **414** were obtained with good yields (Scheme 189). On the basis of control experiments a plausible mechanism starts with the photoexcitation of fluorescein dye (FI) to give FI*. Meanwhile, cyclopalladation of **413** gives palladacycle **B**, which reacts with acyl radical **A** to give the Pd(III) intermediate **C**. Then, intermediate **C** can undergo a SET process to form the Pd(IV) intermediate **D** with simultaneous reduction of FI* to $FI^{-\bullet}$. This radical anion $FI^{-\bullet}$ closes the photocatalytic cycle by generating *t*BuO$^\bullet$ and benzoate. The radical *t*BuO$^\bullet$ reacts with α-keto acid to create the acyl radical **A** after decarboxylation. Intermediate **D** gives after reductive elimination the product and Pd(II).

Decarboxylative acylation of 2*H*-indazoles **387** with α-keto acids has been carried out with visible-light in the absence of PC and oxidants.[344] The reaction took place in a 3 : 1 mixture of MeCN and HFIP as solvents under 420–425 nm irradiation at room temperature to furnish 3-acylated products **415** in moderate to good yields (Scheme 190). It has been proposed that the 2*H*-indazole absorbs visible-light transitioning to an excited state, which by energy transfer to the α-keto acid facilitates the homolysis to form an acyl radical after decarboxylation.

Decarboxylative hydroxyalkylation of quinolines with α-keto acids has been described by Ji and co-workers.[345] In the presence of Ir complex **4** as a PC, $Zn(OTf)_2$ and TfOH as Lewis and Brønsted acids, respectively, in aqueous MeOH under N_2 and blue LED irradiation, hydroxyalkylated products **416** are obtained with, in general, good yields (Scheme 191). 2-Substituted quinolines gave 4-hydroxyalkylated derivatives **416a**, whereas 4-substituted quinolines provided the corresponding 2-hydroxyalkylated ones **416b**. 6-Bromoisoquinoline reacted at the 1-position with benzoylformic acid and 2-methylpyridine reacted at the 6-position to give the corresponding product in 60 and 25% yield, respectively. In the plausible reaction mechanism, the acyl radical **A** from the α-keto acid is formed by the oxidized PC Ir(IV). Addition of **A** to protonated quinoline gives radical cation **B**, which after protonation leads to the α-amino radical **C**. This radical **C** undergoes a spin center shift (SCS) process to afford the α-oxy radical **D**. The subsequent SET process of **D** with Ir(III)* followed by protonation provides the product.

Carbamoylation of heteroarenes with oxamic acids **15** was carried out by Landais and co-workers[346] in the presence of 4CzIPN (**25**) as a PC and acetoxybenziodoxole (BI-OAc) as an external oxidant in DCM at room temperature under blue LED



Scheme 187 Decarboxylative acylation of quinoxaline-2(1*H*)-ones with α-keto acids under Acridine Red (**410**) photocatalysis.

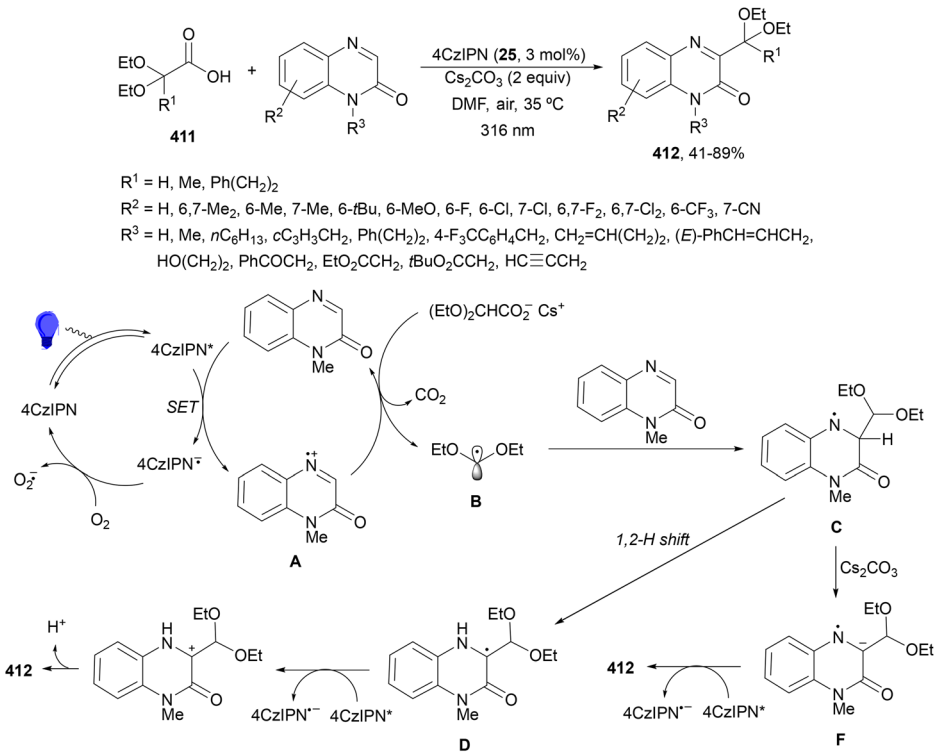
irradiation (Scheme 192). Quinolines, isoquinolines, pyridines, phenanthridine, quinoxaline, benzothiazole and benzimidazole gave the corresponding carboxamides with moderate to good yields. In the tentative mechanism, oxamic acid reacts with BI-OAc to form the hypoiodite species **A**, which after reaction with 4CzIPN* gives a radical anion **B**. Cleavage of the O–I bond in **B** leads to the amidocarbonyl radical **C**, CO_2 and *o*-iodobenzoic acid. Radical addition of **C** to quinoline forms intermediate **D**, which after oxidation with $4CzIPN^{+\bullet}$ generates cationic species **E** and after deprotonation the product.

Jouffroy and Kong at Merck[347] employed oxamic acids or potassium oxamates for the C–H carbamoylation of heterocycles. In the presence of acridinium tetrafluoroborate **287** as a PC, $K_2S_2O_8$ as an external oxidant, and TFA in aqueous DMSO at 30 °C under blue LED irradiation, heterocyclic carboxamides were obtained with good yields (Scheme 193). Quinolines, isoquinolines, pyridines, pyrimidines, quinoxaline, phthalazine and caffeine performed well in the reaction. In this case, it was proposed that the PC* oxidizes the oxamate salt to the carbamoyl radical **A** after decarboxylation. Radical addition of **A** to protonated quinoline provides radical cation **B**. Simultaneously $PC^{\bullet-}$ could be oxidized by persulfate to the sulfate dianion and the sulfate radical anion regenerating the PC. This radical anion $SO_4^{-\bullet}$ oxidizes **B** through HAT to yield the product after deprotonation.

Decarboxylative acylation reactions of heterocyclic compounds with α-keto acids have been carried out in the presence of oxidants such as PIFA, persulfates or air and Ir or organic photocatalysts. The corresponding acylated heterocycles were obtained with good yields and only in the case of quinolines hydroxyalkylation products were formed. General methods for carbamoylation reactions employed organic photocatalysts and external oxidants such as BI-OAc or $K_2S_2O_8$ to give the corresponding heteroaromatic carboxamides.

2.12.3. Arylation reactions. Decarboxylative arylation of C(sp^2)–H bonds was described by Glorius and co-workers[348] in 2017. Starting from benzoic acids and using Ir complex **4** as a PC and Cs_2CO_3 as a base at 55 °C in the presence of diethyl bromo-α-methyl malonate as a brominating agent, instead of toxic bromine, under blue LED irradiation, these benzoic acids reacted with benzene, 1,4-disubstituted arenes and pyridines to give the corresponding biaryls with moderate to good yields (Scheme 194). Experimental and theoretical results suggested that the benzoate anion is oxidized by Ir(III)* to give the carboxy radical **A**. Bromination of **A** furnishes hypobromite **B**, which by reduction with Ir(II) gives radical anion **C**. Subsequent C–C and O–Br concerted cleavage yields CO_2, the bromide anion and the aryl radical **D**. This aryl radical **D** is trapped by an arene or a heteroarene to give the cyclohexadienyl radical **E**, which after rearomatization affords the biaryl product.

Direct arylation of quinoxalin-2(1*H*)-ones has been achieved with acyl peroxides under visible light.[349] In the absence of PCs and additives these heterocycles reacted with different dibenzoyl



Scheme 188 Decarboxylative acetalation of quinoxaline-2(1*H*)-ones with 2,2-diethoxyalkyl carboxylic acids **411** under 4CzIPN photocatalysis.

peroxides (BPO) in acetone, under air at room temperature to give 3-arylquinoxalin-2(1*H*)-ones with good yields (Scheme 195). Arylation of 2*H*-benzo[*b*]oxazin-2-one took place with 53% yield. In the proposed mechanism, BPO generates, after decarboxylation, the phenyl radical **A**, which adds to quinoxalinone to give a N-centered radical **B**. Final abstraction of the hydrogen atom by a $PhCO_2^{\bullet}$ generates the 3-phenylquinoxalin-2(1*H*)-one.

Independently, He and co-workers[350] reported the same arylation of quinoxaline-2(1*H*)-ones with aryl peroxides under visible-light irradiation working in AcOEt instead of acetone. The corresponding 3-arylated quinoxalin-2(1*H*)-ones were obtained with 63–82% yields.

A general method for decarboxylative arylation of arenes and pyridines involves diethyl bromo-α-methylmalonate as a brominating agent forming the corresponding hypobromite in the presence of Ir as a PC. Acyl and aryl peroxides have been employed for the arylation of quinoxaline-2*H*-ones only under visible-light irradiation.

2.13. Cyclization reactions

This subject has been recently reviewed[351–353] and therefore it will be not considered in this survey.

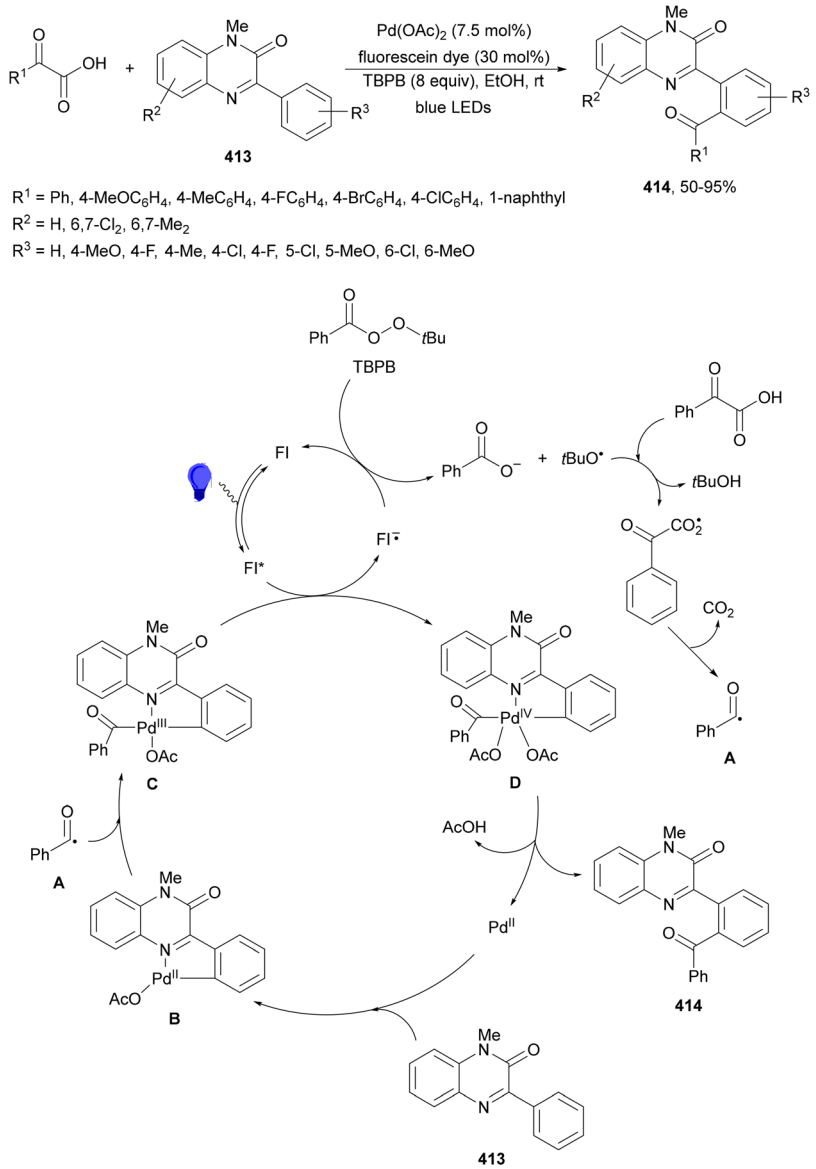
3. Carbon-heteroatom bond forming reactions

In this section photodecarboxylative heterofunctionalization of carboxylic acids and derivatives will be considered including C–Hal, C–O, C–S, C–N, C–P, C–B and C–Si bond formation. Recent reviews until 2021[354–356] cover partially this topic, and thus new achievements made in the last four years will be considered.

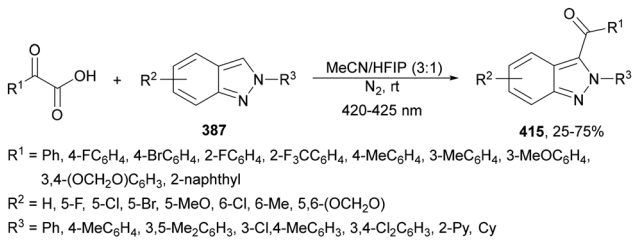
3.1. Carbon–halogen bond forming reactions

Decarboxylative halogenations have been achieved by photochemical methods. Organofluorine compounds are very important in medicinal chemistry and ^{18}F-labeled molecules act as contrast agents for positron emission tomography (PET). Ir complex,[357] [Mes-AcrMe]ClO_4 (**301**)[358] and carbonitride[359] have been employed as PCs in the presence of Selectfluor for decarboxylative fluorination of aliphatic carboxylic acids. In the case of NHPI esters **69**, triethylamine trihydrofluoride ($Et_3N{\cdot}3HF$) or $K^{18}F$ under Ir photocatalysis has been employed.[360]

In recent studies, carboxylic acids have been transformed into organofluorides *via* ligand-to-metal charge transfer (LMCT).[54,55] Ritter and co-workers[361] performed decarboxylative fluorination of benzoic acids in the presence of TBAF·(tBuOH)$_4$ complex as a fluoride source, $Cu(OTf)_2$ and $Cu(MeCN)_4BF_4$ as PCs in MeCN at 35 °C under purple LED irradiation (Scheme 196). Electron-neutral and rich benzoic acids and some heterocyclic compounds reacted smoothly to give the corresponding aryl fluorides with good yields. In the proposed mechanism, photoactive copper(II) benzoate **A** generates by photoinduced LMCT carboxy radical **B** and Cu(I), which by homolysis releases CO_2 and forms the aryl radical **C**. This radical **C** is captured by Cu(II) salts to afford the arylCu(II) fluoride **D**, which is oxidized to ArCu(III)F (**E**). Final reductive elimination gives the aryl fluoride.



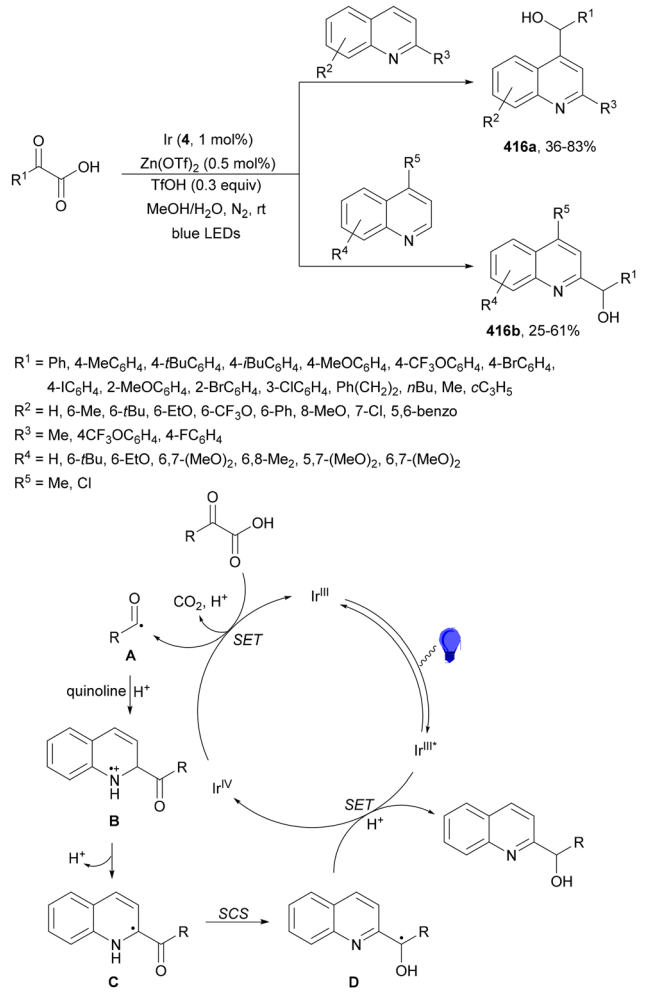
Scheme 189 Decarboxylative acylation of *N*-methyl-3-arylquinoxalin-2(1*H*)-ones **413** with α-keto acids under $Pd(OAc)_2$/fluorescein dye photocatalysis.



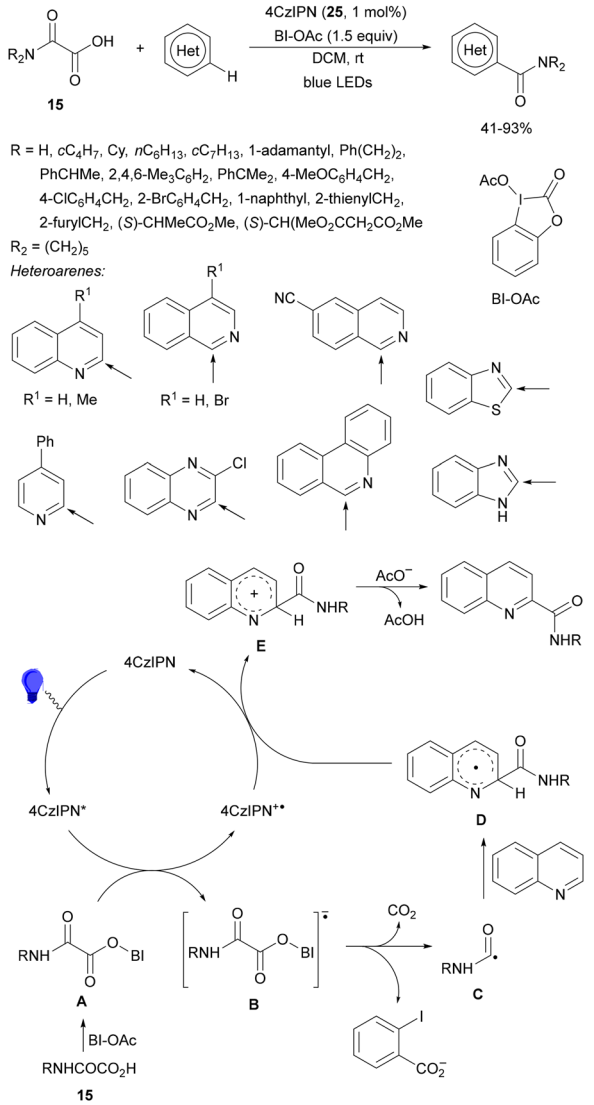
Scheme 190 Decarboxylative acylation of 2*H*-indazoles **387** with α-keto acids under visible light photocatalysis.

MacMillan and co-workers[362,363] performed a general approach to obtain aryl halides by decarboxylative halogenation of (heteroaryl)carboxylic acids *via* a LMCT[54,55] mechanism. In this case, $Cu(MeCN)_4BF_4$ (20 mol%) was used as a PC and 1-fluoro-2,4,6-trimethylpyridinium tetrafluoroborate (NFTPT, **417**) or dicumyl peroxide as an external oxidant in MeCN under 365 nm LED irradiation. When 1,3-dibromo-5,5-dimethylhydantoin (DBDMH, **418**) or CCl_3Br was used, the corresponding brominated products were obtained in 41–85% yields (Scheme 197). In the presence of $ZnCl_2$ heteroaryl chlorides were obtained with 41–>99% yield and with *N*-iodosuccinimide (NIS) heteroaryl iodides were formed with 56–89% yields. Fluorodecarboxylation reaction was carried out with 2 equivalents of NFTPT (**417**) as a source of fluoride and in some cases CsF was added with 3 equivalents of $Cu(MeCN)_4BF_4$ to give the corresponding fluorides in 41–81% yields.

Decarboxylative fluorination of aliphatic carboxylic acids has been achieved with $Fe(OAc)_2$ as a PC by a LMCT[54,55] mechanism.[364] In the presence of bipyridine ligand **185**, 2,6-lutidine as



Scheme 191 Decarboxylative hydroxyalkylation of heteroarenes with α-keto acids under Ir photocatalysis.

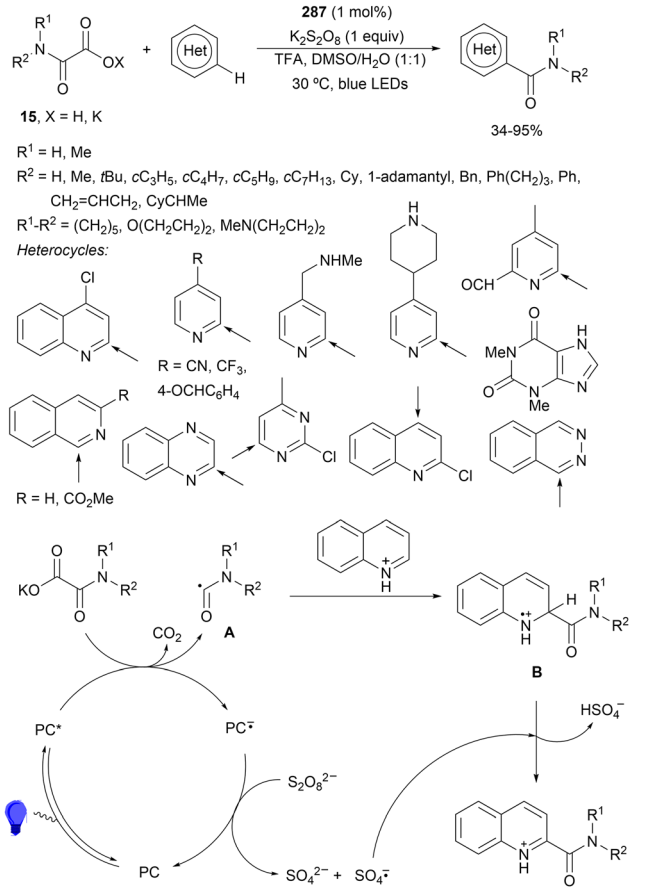


Scheme 192 Decarboxylative carbamoylation of heteroarenes with oxamic acids **15** under 4CzIPN (**25**) and BI-OAc photocatalysis.

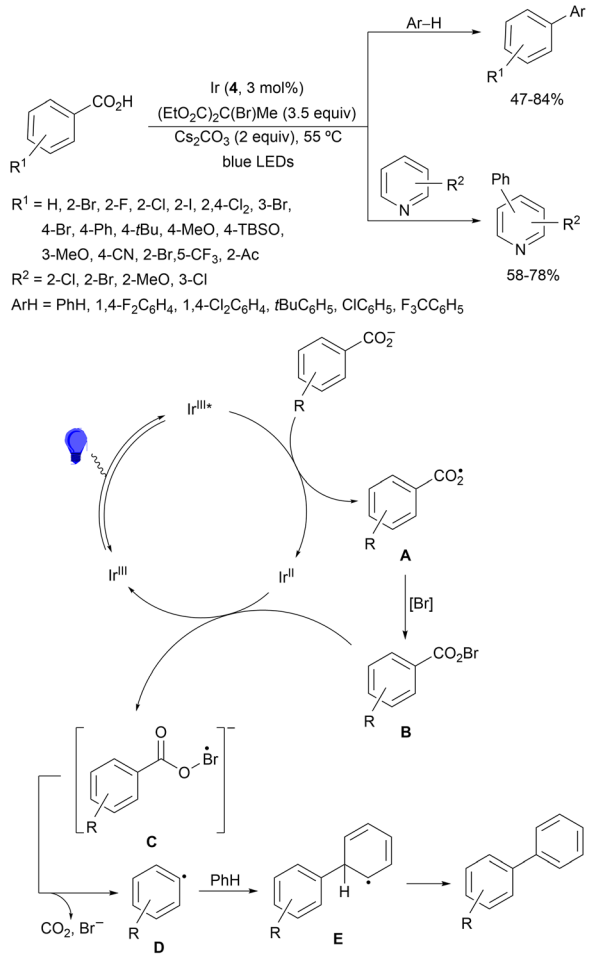
a base and Selectfluor in aqueous MeCN at room temperature under N_2 and blue LED irradiation, the corresponding alkyl fluorides were isolated in up to 92% yield (Scheme 198). In the proposed mechanism, firstly the iron(III) carboxylate **A** is formed by oxidation with Selectfluor. This complex **A** undergoes photoexcitation *via* LMCT to produce the iron(II) species **B** and the carboxy radical **C**. Upon decarboxylation of **C** an alkyl radical **D** is formed, which is fluorinated by Selectfluor to afford the product. The iron(II) species **B** was oxidized by Selectfluor or its radical cation to give the Fe(III) species **E**. Coordination of **E** with another alkyl carboxylic acid in the presence of base generates **A**.

Iron salts have been recently used also by Hu and co-workers[365] as PCs for decarboxylative chlorination, bromination and iodination of aliphatic carboxylic acids. Under similar reaction conditions to that for fluorination using 2,4,6-collidine as a base and MeCN under N_2 and NCS, *N*-bromosaccharine and NIS as source of halogens (Scheme 199), primary, secondary and tertiary carboxylic acids were transformed into alkyl chlorides, bromides and iodides with 27–94% yields.

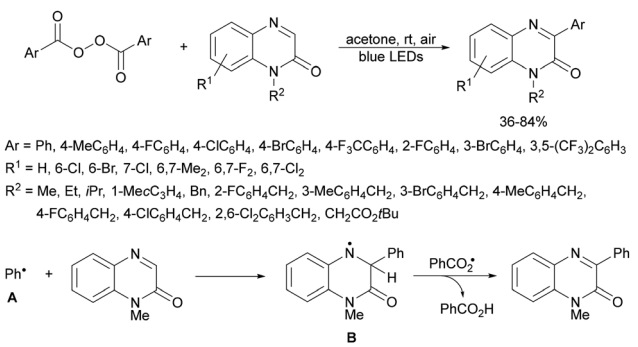
A general protocol for the photohalodecarboxylation of aliphatic carboxylic acids by a LMCT[54,55] mechanism with $CeCl_3$ has been described by Sun, Jin and co-workers.[366] Primary, secondary and tertiary carboxylic acids were transformed into the corresponding chloro-, bromo- and iodoalkanes using *t*BuONa as a base, H_2O as solvent at room temperature under air and blue LED irradiation (Scheme 200). As halogenating reagents, trichloroisocyanuric acid (TCCA), NBS and NIS, respectively, were employed. Based on experimental studies, a proposed mechanism is depicted in Scheme 200. Initially, *t*BuONa ($O_2^{-\bullet}$ or HO_2^-) abstracts a proton from the acid and the resulting carboxylate ion reacts with Ce(III) to produce complex **A** followed by oxidation with O_2 (or $HO_2^\bullet$) to generate the Ce(IV) species **B**. This species **B** undergoes a phototriggered LMCT process releasing the alkyl radical **C**, after decarboxylation, and Ce(III). Subsequent halogen atom transfer from the *N*-haloamide produces the product.



Scheme 193 Decarboxylative carbamoylation of heteroarenes with oxamic acids **15** or oxamates under acridinium tetrafluoroborate **287** photocatalysis.



Scheme 194 Decarboxylative arylation of arenes and heteroarenes with benzoic acids under Ir photocatalysis.



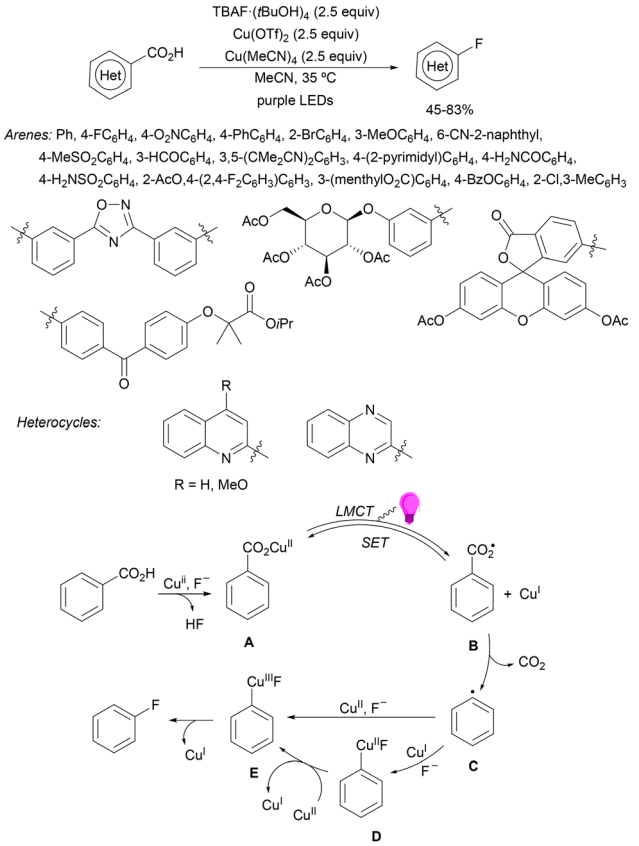
Scheme 195 Decarboxylative arylation of quinoxalin-2(1*H*)-ones with aryl peroxides under visible-light irradiation.

Photoinduced LMCT decarboxylative bromination of aromatic carboxylic acids has been carried out by Xia and co-workers,[200] using 2 equivalents of $Cu(OTf)_2$. This process took place in the presence of Li_2CO_3 as a base, in MeCN at room temperature under N_2 and 390 nm LED irradiation to give the corresponding aryl bromides in 63–75% yields.

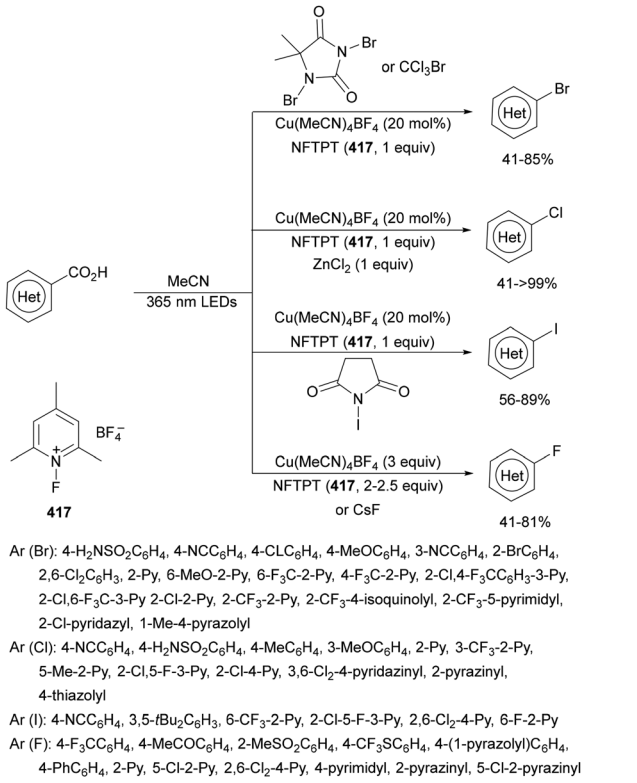
A covalent organic framework (COF)-based PC has been employed for the decarboxylative fluorination of aliphatic carboxylic acids by Banerjee, Maj and co-workers.[367] This anthraquinone-based COF PC TpACl exhibits high durability and can be reused multiple times without significant activity loss (>80% after eight cycles). This fluorination was carried out with Selectfluor in the presence of 2,6-lutidine as a base in aqueous MeCN (1 : 1) at 40 °C under N_2 and purple LED irradiation to give alkyl fluorides with 39–96% yields. Gram-scale fluorination of ketoprofen was performed under batch and flow reaction conditions.

Enantiopure fluoropiperidine **420** has been prepared by decarboxylative fluorination of carboxylic acid **419** using photoredox conditions.[368] Starting acid **419** was prepared on a >400 g scale by biocatalytic desymmetrization[369] of *N*-Cbz diethyl 3,5-piperidinedicarboxylate using the *Candida antartica* lipase A Novocar ADC with 94.3% ee. Subsequent decarboxylative fluorination of **419** with Ir complex **4** as a PC in the presence of Selectfluor under blue LED irradiation using flow conditions gave diastereoselectively product **420** in 52% yield and 99.3% ee, after chiral SFC purification (Scheme 201).

Molander and co-workers[370] reported a metal-free decarboxylative chlorination of aliphatic carboxylic acids by their activation with (diacetoxyiodo)benzene (PIDA). This process



Scheme 196 Decarboxylative fluorination of aromatic and heteroaromatic carboxylic acids with TBAF·(*t*BuOH)$_4$ under Cu photocatalysis.



Scheme 197 Decarboxylative halogenation of aromatic and heteroaromatic carboxylic acids in the presence of NFTPT (**417**) under Cu photocatalysis.

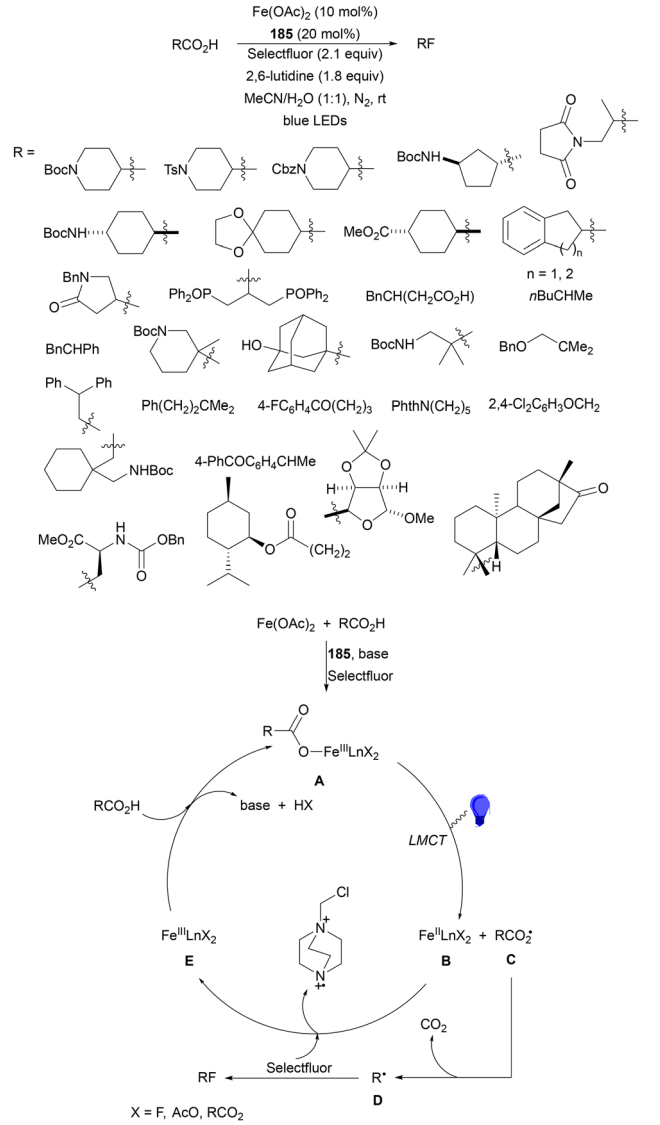
used 1,2-dichloroethane (DCE) as a halogen source, with the halogen-atom transfer (XAT) being the key step. In this case, 4CzIPN (**25**) was used as an organophotocatalyst and DCE also as solvent at room temperature under Ar and blue LED irradiation (Scheme 202). Primary, secondary and tertiary carboxylic acids were transformed into alkyl chlorides in modest to good yields. In the proposed mechanism photoexcited 4CzIPN* reacts with (diacetoxyiodo) complex **A**, generated *in situ*, to give by a SET process the carboxy radical **B**. Decarboxylation of **B** affords the alkyl radical **C**. This radical reacts with DCE *via* a XAT to form the alkyl chloride and the chlorinated radical **D**. This radical evolves to give ethyl chloride or 1,4-dichlorobutane. Radical **D** can give ethylene and, by a SET process, the anion chloride, which abstracts a hydrogen atom to give HCl and the carboxylate ion.

Cheng[371] and Shang[372] groups described independently decarboxylative iodination under visible-light of aliphatic NHPI esters **69** with NHC/NaI for secondary alkyl iodides and PPh_3/LiI for primary alkyl iodides, respectively. Noble and Aggarwal[373] reported chlorination and bromination of primary, secondary and tertiary aliphatic NHPI esters **69** using LiCl and LiBr as halogen sources (Scheme 203). Chlorination reactions were carried out in the presence of Ir complex **4**, $CuCl_2$ and 2,9-dimethyl-1,10-phenanthroline (dmp) as a ligand in MeCN at 30 °C under N_2 and blue LED irradiation to provide alkyl chlorides with 33–92% yields, whereas for bromination reactions 4CzIPN was used as a PC giving alkyl bromides with modest to good yields (26–94%). In the proposed mechanism for chlorodecarboxylation reactions the NHPI ester is reduced by Ir(II) to form the alkyl radical **A**, CO_2 and $PhthN^-$. This radical **A** reacts with $CuCl_2$ and LiCl to give the alkyl chloride and CuCl *via* reductive elimination of an alkylCu(III)X_2 species or through an outer-sphere pathway involving atom transfer. In the case of bromodecarboxylation reactions, 4CzIPN* oxidizes Br^- to $Br^\bullet$. Subsequently, the alkyl radical is formed by reduction of NHPI ester with 4CzIPN$^-$·Trapping of radical **A** could occur by radical–radical coupling of **A** with $Br^\bullet$. Alternatively, $Br^\bullet$ can be stabilized by Br^- generating dibromide radical $Br_2^{-\bullet}$, which generates the alkyl bromide. A third possible pathway involves dimerization of two $Br^\bullet$ to form Br_2, which is unlikely because substrates with C=C bonds are not affected.

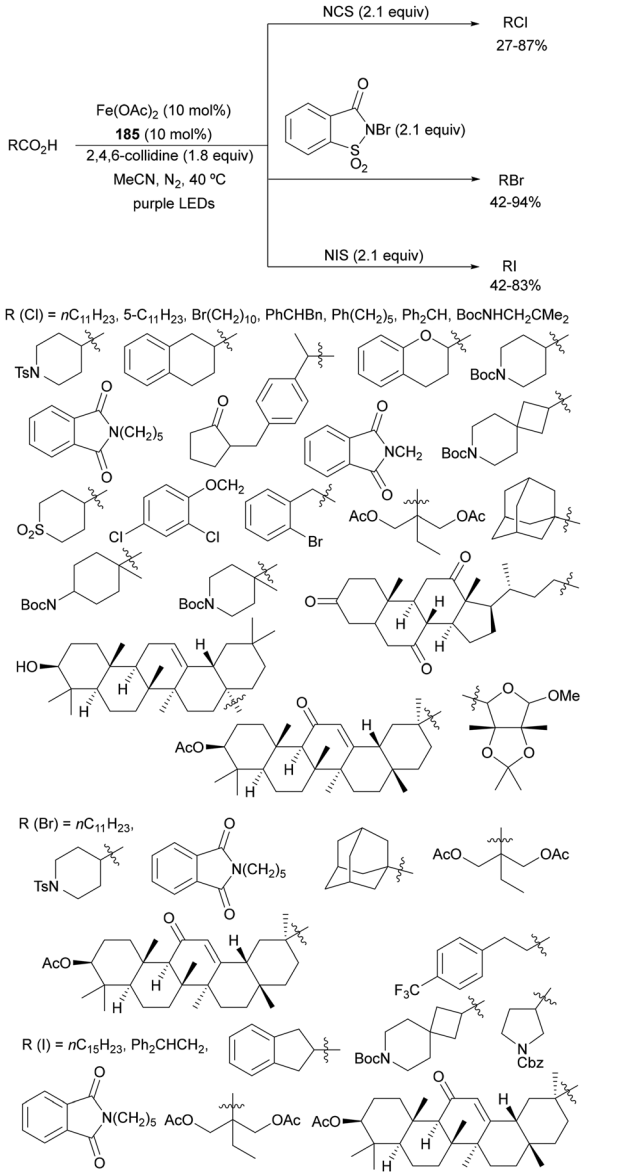
A general method for decarboxylative halogenation of aliphatic, aromatic and heteroaromatic carboxylic acids is based on a metal photocatalyzed LMCT mechanism.

3.2. Carbon–oxygen bond-forming reactions

Decarboxylative oxygenation, etherification and acyloxylation of carboxylic acids or photoactive esters under photoredox conditions will be considered. The corresponding products can be further converted into hydroxylated compounds. If oxamic acids were used, the corresponding urethanes were obtained.



Scheme 198 Decarboxylative fluorination of aliphatic carboxylic acids with Selectfluor under Fe photocatalysis.

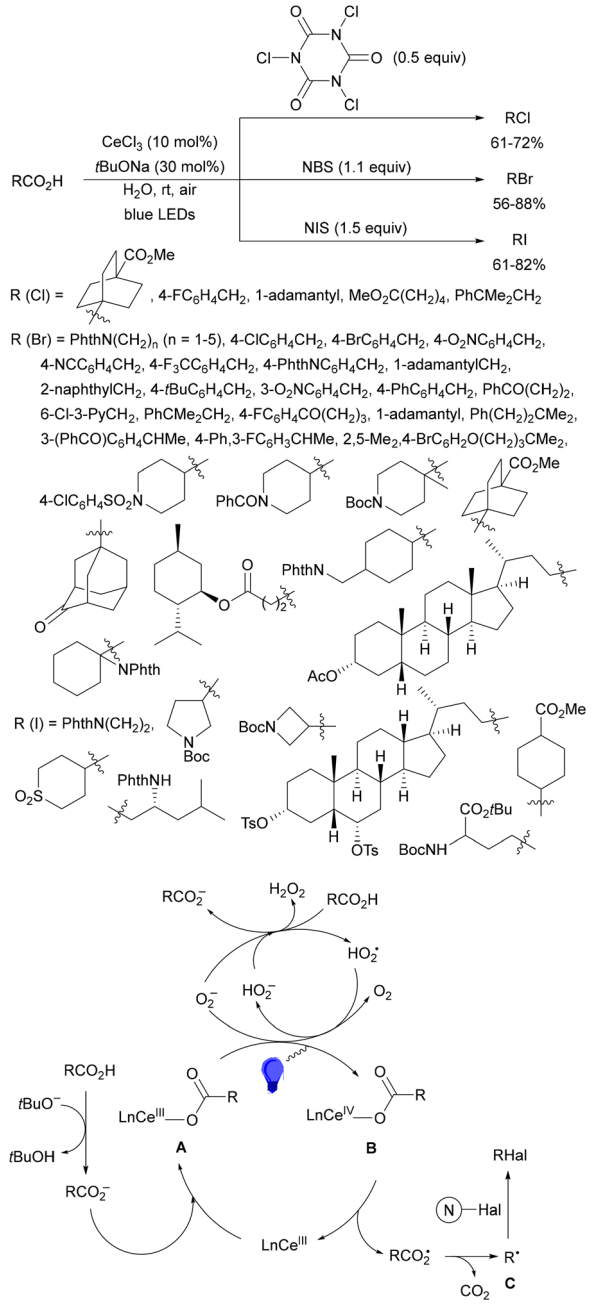


Scheme 199 Decarboxylative chlorination, bromination and iodination of carboxylic acids with *N*-haloamides under Fe photocatalysis.

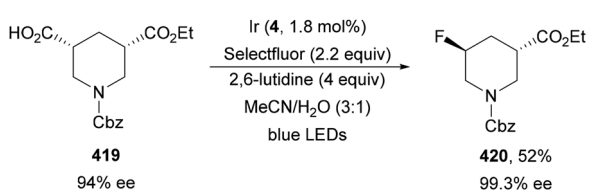
3.2.1. Oxygenation. Decarboxylative oxygenation of aliphatic carboxylic acids under (Mes-Acr-Me)ClO_4 **301** photocatalysis was carried out in 2016 by Lu and co-workers[374] using oxygen, to give the corresponding ketones. Alternatively, Ru,[375] Ir[376,377] and Ce[378] photocatalysis has been employed for this decarboxylative oxygenation to give ketones. Arylacetic acids have been transformed into aldehydes or ketones using 4CzIPN (**25**) as a PC.[379]

Huang, Xiao and co-workers[380] employed more recently a non-heme manganese **421** as a PC for decarboxylative oxygenation of carboxylic acids with oxygen in MeCN at 45 °C under blue LED irradiation (Scheme 204). Primary and secondary aliphatic carboxylic acids including pharmaceutical compounds were transformed into aldehydes and ketones, respectively, with modest to good yields. A range of amino acids and a dipeptide were oxidized selectively to amide products in 48–67% yields. Based on experimental studies, a plausible mechanism was proposed starting from the formation of intermediate **A** by reaction of the catalyst and phenylacetic acid. This complex **A** is oxidized by O_2 under blue LED irradiation to give species **B**. The superoxide radical attacks intramolecularly the benzylic carbon releasing CO_2 and forming the Mn(II)–peroxide **C**. Subsequent decomposition of **C** produces benzaldehyde and a Mn(II)–OH species **D**, which reacts with phenylacetic acid regenerating **A**.

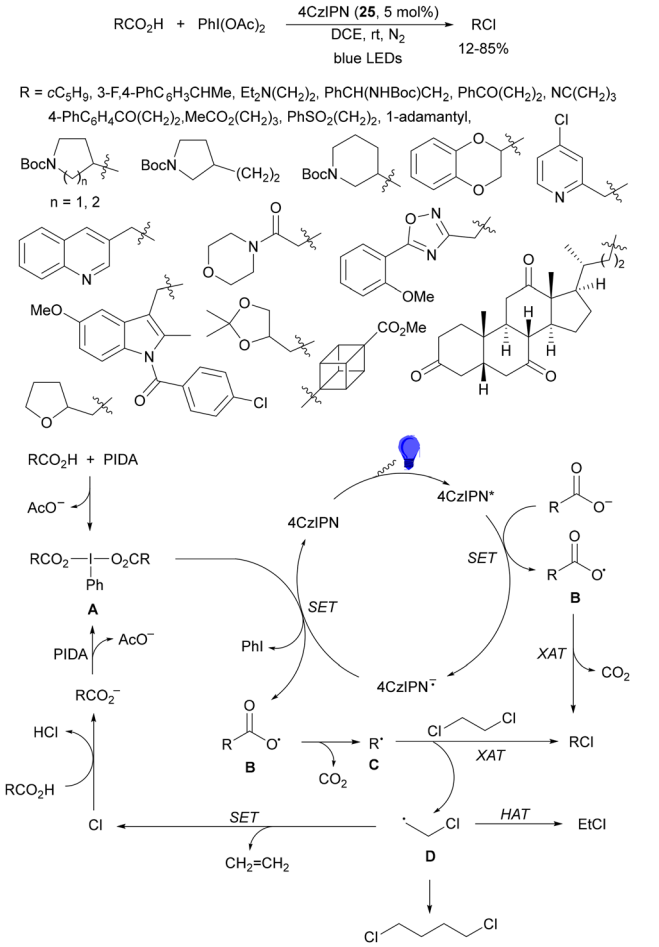
Chemodivergent[381] decarboxylative oxygenation of carboxylic acids using $CeCl_3$ as a PC and O_2 as the oxidant was further reported by Huang, Xiao and co-workers.[382] By changing the base employed, this process gave hydroperoxides **422** with NaOAc or carbonyl compounds with 2,6-lutidine (Scheme 205).



Scheme 200 Decarboxylative halogenation of aliphatic carboxylic acids under $CeCl_3$ photocatalysis.



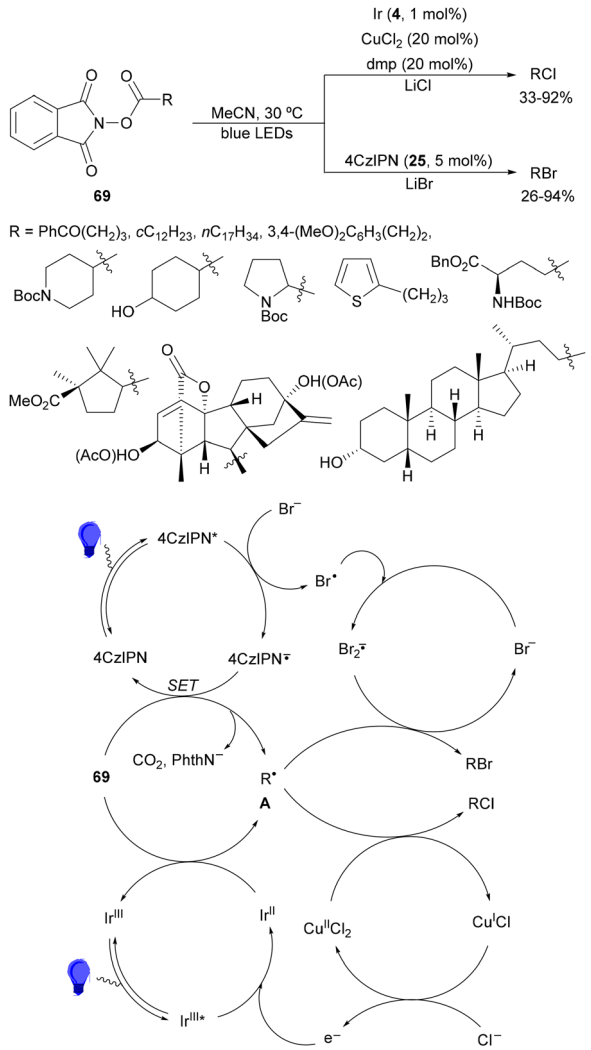
Scheme 201 Decarboxylative fluorination of carboxylic acid **419** with Selectfluor under Ir photocatalysis.



Scheme 202 Decarboxylative chlorination of aliphatic carboxylic acids mediated by XAT under 4CzIPN (**25**) photocatalysis.

The proposed simplified mechanism suggests that Ce(III) reacts with a carboxylic acid forming complex **A**, which is oxidized by O_2 to afford a Ce(IV) superoxide species **B**, under blue LED irradiation. This species **B** undergoes decarboxylation to form the Ce(III) peroxide species **C**, which reacts with another molecule of acid to afford the alkyl hydroperoxide **422**, stable in the presence of NaOAc. However, this hydroperoxide is transformed into the corresponding carbonyl compound in the presence of 2,6-lutidine as a base under blue LED irradiation.

Iron-catalyzed photoinduced oxygenative decarboxylation has been independently reported by Guo and Xia[383] and Guérinot[384] groups *via* LMCT[54,55] processes. In the first case, a decarboxylative ring-opening of cyclic tertiary carboxylic acids **423** gave 1,*n*-dicarbonyl compounds **424** through homolytic C–C bond cleavage (Scheme 206). By employing $Fe(acac)_3$, DABCO as a base in MeCN at 35 °C under air and 390 nm LED irradiation this protocol was also applied to acyclic primary, secondary and tertiary carboxylic acids to obtain the corresponding aldehydes and ketones with 49–99% yields. In the proposed reaction mechanism for cyclic carboxylic acids, the coordination to iron gives the carboxylate-iron complex **A.** Photoexcitation of **A** gives the reduced Fe(II) complex and the aryloxy radical **B.** Subsequent



Scheme 203 Decarboxylative chlorination and bromination of alkyl NHPI esters **69** with LiCl and LIBr respectively under photocatalysis.

decarboxylation of **B** gives the tertiary radical **C**, whereas *via* a SET process between dioxygen and Fe(acac)$_2$ the Fe(III) catalyst is regenerated. Intermediate **C** would be trapped by oxygen to give the peroxyl radical **D**. This species **D** undergoes an intramolecular HAT to give the β-carbon radical **E**, which releases the dioxetane **F** with the aid of the superoxide radical anion. Dioxetane **F** undergoes thermal cleavage yielding the dicarbonyl product.

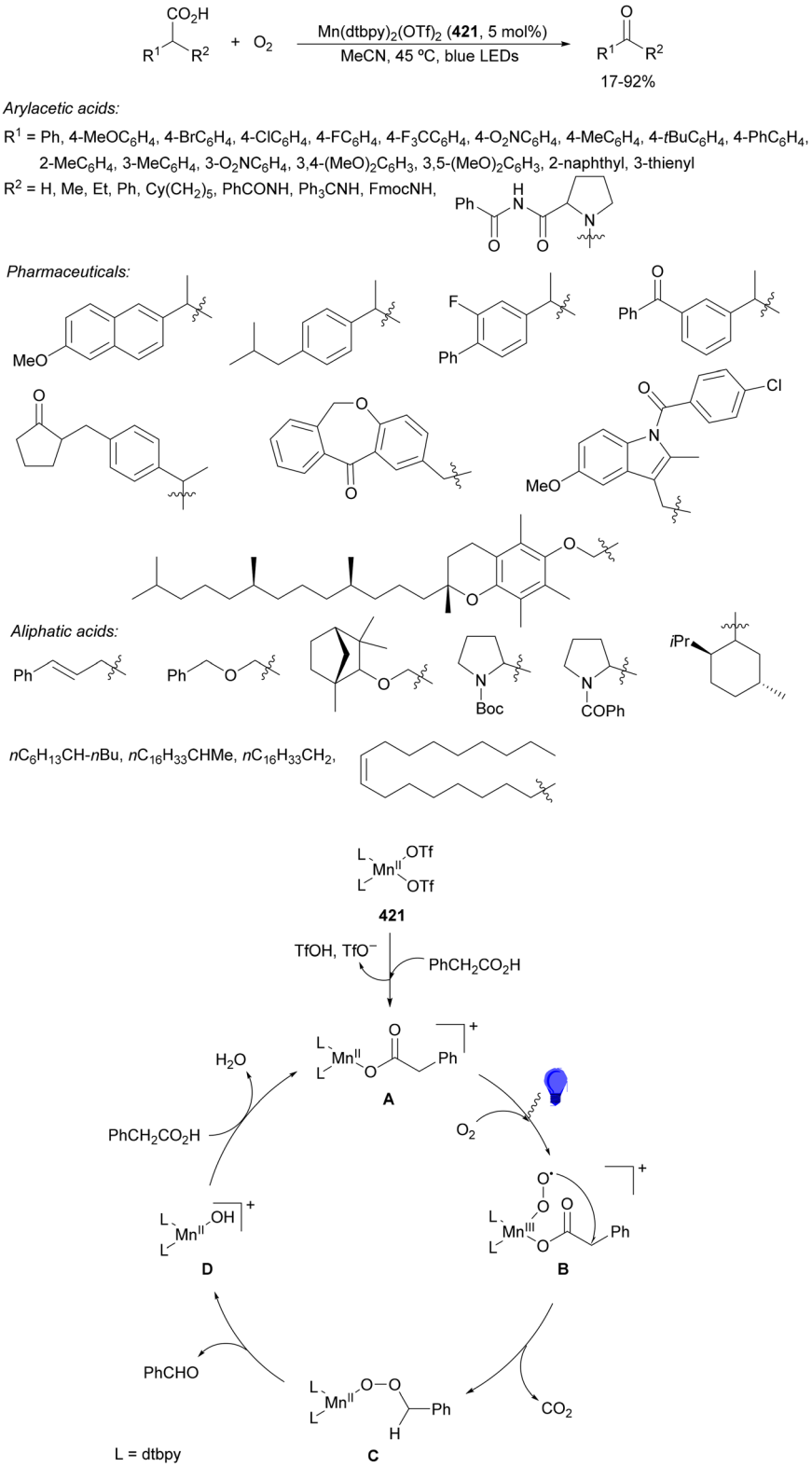
In the case of Guérinot and co-workers,[384] Fe(NH$_4$)$_2$(SO$_4$)$_2$·6H$_2$O (5 mol%) as a PC and di-(2-picolyl)amine (10 mol%) as a ligand in MeCN at room temperature under air and blue LED irradiation were used for decarboxylative oxygenation. Arylacetic acid was transformed into aromatic aldehydes in 80–94% yields and α-AAs into amides in 77–80% yields. Recently, an iron-catalyzed decarboxylative oxygenation of a broad range of aliphatic carboxylic acids has been performed using TEMPO as an oxidant.[385] In the presence of Fe(OTf)$_3$ as a PC and *N*,*N*-bis(pyridyn-2-ylmethyl)ethane-1,2-diamine (**425**) as a ligand, in MeCN at room temperature under air and blue LED irradiation, the corresponding TEMPO adducts **426** were obtained in 53–99% yields (Scheme 207). This protocol was employed for the late-stage functionalization of ibuprofen derivatives in 78–99% yields as well as the sweetener Neotame, cholic acid and the plant hormone indole-3-butyric acid in 24–56% yields. These TEMPO derived products **426** were further transformed into ketones, by treatment with MCPBA, and into ether derivatives. Different kinetic, electrochemical, EPR, UV/vis, HRMS and DFT studies revealed the possible mechanism depicted in Scheme 207. Complex **A** undergoes ligand substitution with the carboxylate ion to form the Fe(III) intermediate **B**. Photoexcitation of **B** induces LMCT[54,55] to give **C**, which after decarboxylation generates the alkyl radical **D**. Reaction of this radical **D** with TEMPO forms the product **426** and the complex **E**, which is oxidized by a SET process regenerating the catalyst. The same group[386] recently reported the same process using FeBr$_3$ (2.5 mol%) as a PC to give the corresponding arylacetic acid TEMPO adducts **426** with high yields (70–99%). The reaction between phenylacetic acid and TEMPO was scaled up to 5 mmol with 76% yield. Other primary, secondary and tertiary aliphatic carboxylic acids were transformed into TEMPO adducts **426** in modest to high yields (16–92%).

Wang and co-workers[387] have performed a high yield decarboxylative oxygenation of 2-phenylpropionic acid to acetophenone using (Mes-Acr-Me)ClO$_4$ **301** as a PC in oxygen-liquid flow. This process was carried out in a photomicroreactor in continuous gas-liquid flow and represents an efficient, green and mild industrial production of ketones from carboxylic acids.

3.2.2. Etherification. Decarboxylative etherification of carboxylic acids has been described by Waser and co-workers[388] by coupling of small peptides with alcohols to give *N*,*O*-acetals **427** (Scheme 208). In the presence of 1.5 equivalents of hypervalent acetoxybenziodoxolone (BI-OAc) as an oxidant, Ru(bpy)$_3$Cl$_2$ as a PC in MeCN at room temperature under blue LED irradiation, different dipeptides were transformed into *N*,*O*-acetals **427** in moderate to good yields.

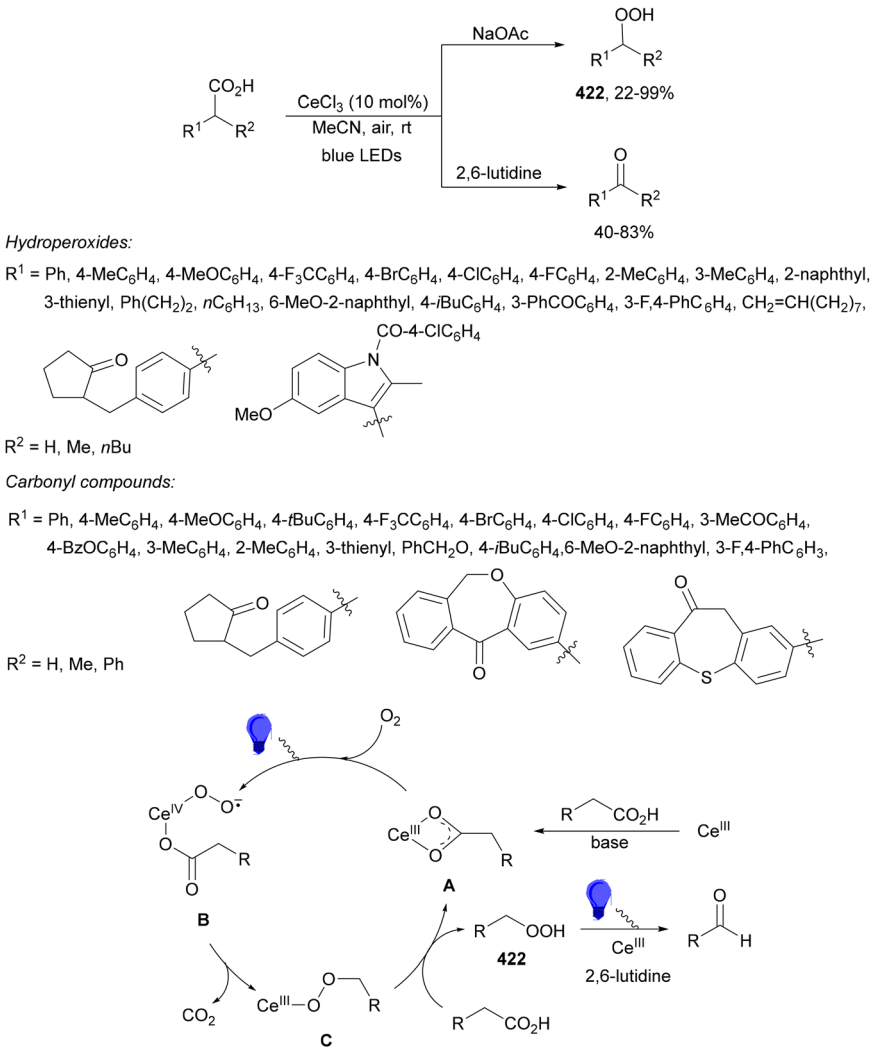
Terret and coworkers[389] reported a similar etherification of carboxylic acids in the presence of hypervalent iodine reagent **428** and Ru(dtbbpy)$_3$(PF$_6$)$_2$ **429** as a PC in a 2 : 1 mixture of DCE/HFIP at room temperature under N$_2$ and blue LED irradiation (Scheme 209). The corresponding dialkyl ethers **430** were isolated with good yields by intermediacy of transient carbocations from carboxylic acid substrates. In the proposed mechanism, the carboxylic acid is activated by the iodine(III) oxidant **428** to form the iodocarboxylate species **A** with loss of AcOH. Photoexcited Ru(II)* species reduces **A** *via* a SET process to generate the radical **B** after formation of CO$_2$ and the aryl iodide **C**. The highly oxidizing Ru(III) species would oxidize radical **B** to carbocation **D** and regenerate Ru(II). Finally, carbocation **D** reacts with an alcohol to form the C–O bond.

Under similar reaction conditions previously described for the iron-mediated decarboxylative alkylation of arenes with carboxylic acids (Scheme 160),[295] FeCl$_3$ or Fe(OTf)$_3$ (3 equiv.) and K$_2$HPO$_4$ as a base in DCM at room temperature under air and blue LED irradiation were employed for the etherification of arylacetic acids with alcohols, which took place with 42–97% yields.



Scheme 204 Decarboxylative oxygenation of carboxylic acids with oxygen under Mn **421** photocatalysis.

Etherification of NHPI esters under decarboxylation was described in 2018 by Hu and co-workers[390] in the presence of a dual Ir complex **52** (1 mol%) and $Cu(OTf)_2 \cdot C_6H_6$ (10 mol%). Aliphatic carboxylic acid derived NHPI esters **69** and phenols gave the corresponding ethers in 49–94% yields. Tertiary benzylic and α-heteroatom aliphatic carboxylic acid derived

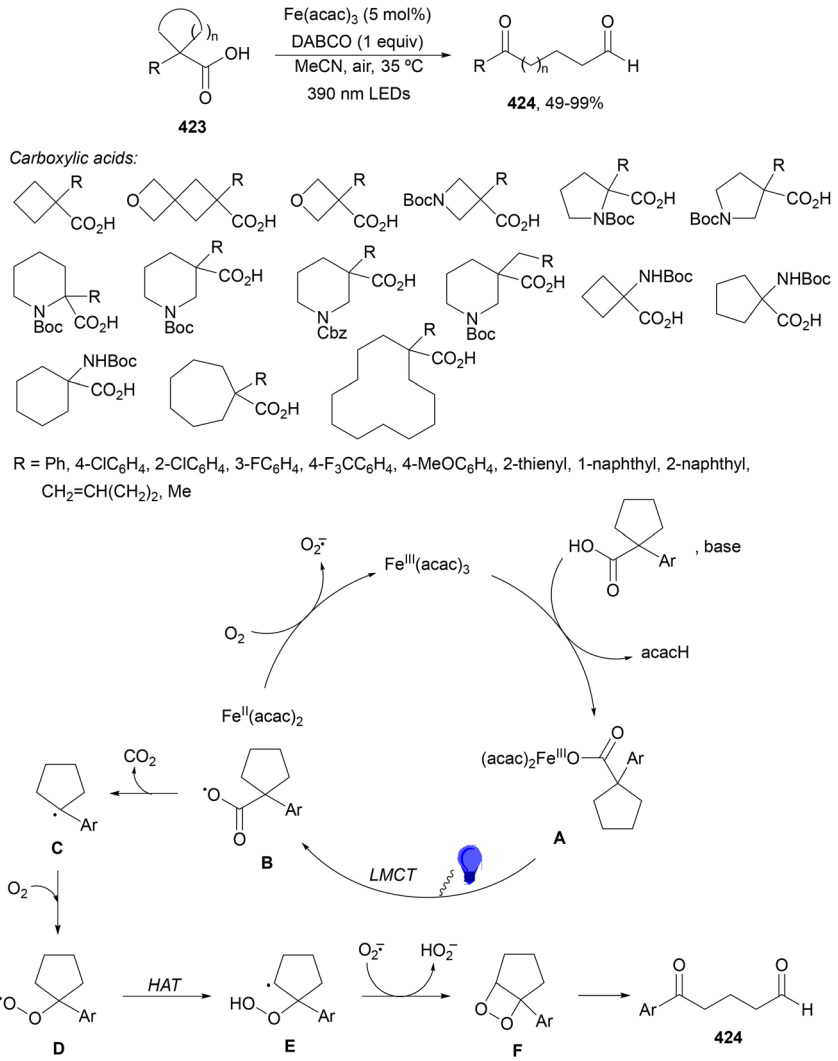


Scheme 205 Decarboxylative oxygenation of carboxylic acids under $CeCl_3$ photocatalysis.

NHPI esters have been etherified with aliphatic alcohols in 25–96% yields using phenothiazine (10 mol%) as a PC and $LiBF_4$ (10 mol%) in MeCN at room temperature under blue LED irradiation.[391] Decarboxylative hydroxylation was also carried out in the presence of water. Li, Guan and co-workers[392] employed PPh_3/NaI as a photoredox catalyst, and [Cu(BPhen)]Br as a catalyst and BTMG as a base in dioxane at room temperature under blue LED irradiation for the reaction of alkyl NHPI esters with phenols (Scheme 210). The corresponding aryl alkyl ethers **430** were obtained with high yields (≥90%). Theoretical and experimental studies support the formation of the ester–NaI–PPh_3 acceptor–donor complex, which is converted to a triplet excited species and after irradiation a subsequent decarboxylation generates the alkyl radical. In the Cu(I)–Cu(II)–Cu(I) catalytic cycle, the radical is captured, which by SET, base-mediated proton transfer and reductive elimination affords the C–O cross-coupling product.

3.2.3. Acyloxylation. Decarboxylative acetoxylation of aliphatic carboxylic acids under photoredox conditions was reported by Tunge and co-workers[393] in 2019. The reaction was carried out in the presence of acridinium (Mes-2,7-Me_2-Acr-Ph)BF_4 as a PC and $Cu(OAc)_2$ as an oxidant and as an acetoxylating agent to give the corresponding acetates with 25–98% yields. More recently, Murakami, Itami and co-workers[394,395] reported decarboxylative acyloxylation mainly of arylacetic acids with hypervalent iodine reagents **432** using $Ru(bpy)_3(PF_6)_2$ as a PC under LED irradiation (Scheme 211). The resulting benzyl carboxylates **433** were obtained with moderate yields *via* a radical-polar crossover under mild reaction conditions. In the proposed mechanism, arylacetic acid reacts with IBB **431** to afford intermediate **A** (**432**). Subsequent SET between **A** and photoactivated Ru(II) gives after decarboxylation the benzyl radical **B**, 2-iodobenzoate **C** and Ru(III). Oxidation of radical **B** by Ru(III) forms the benzyl cation **D**, which reacts with 2-iodobenzoate **C** to provide the product.

Acyloxylation of benzoic acids has been reported by Ritter and co-workers[396] *via* photoinduced LMCT[54,55] radical decarboxylation. In the presence of 1.5 equivalents of CuTC and 2.5

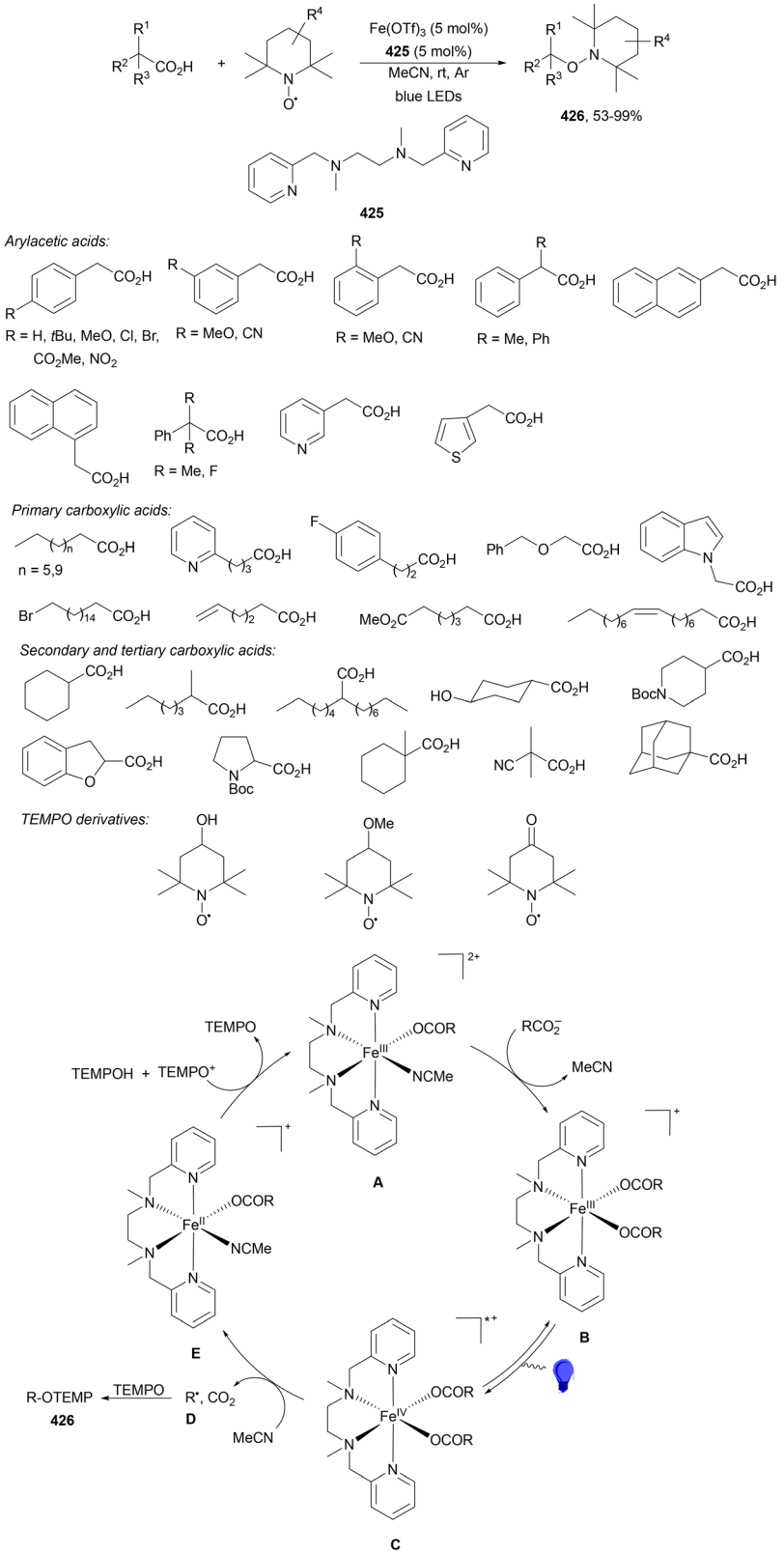


Scheme 206 Decarboxylative ring-opening oxygenation of cyclic carboxylic acids **423** under $Fe(acac)_3$ photocatalysis.

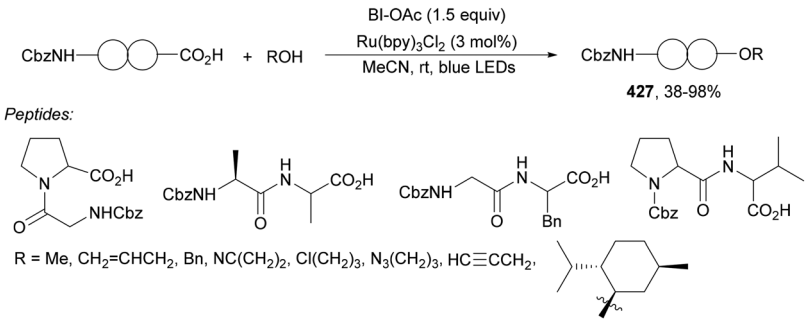
equivalents of $Cu(OTf)_2$ at 35 °C under purple LED irradiation, a broad range of benzoates were converted into esters **434**, which by hydrolysis with LiOH provided the corresponding phenols (Scheme 212). This two-step procedure is a practical decarboxylative hydroxylation of benzoic acids under mild reaction conditions. The proposed mechanism starts with the formation of Cu(II) carboxylate **A**, which after irradiation gives the carboxy radical **B**. Subsequent decarboxylation provides the aryl radical **C** captured by copper. While the LMCT from Cu(II)TC gives $TC^{\bullet}$, which by BET or HAT forms TC^{-}. Intermediate **D** results by reaction of aryl radical **C** with Cu(II)TC with subsequent oxidation by Cu(II) to give the arylcopper(III)TC **D**. Final reductive elimination of **D** yields an ester and Cu(I).

Mandal, Das and co-workers[397] recently reported a photoinduced decarboxylative C–O bond functionalization of isatoic anhydride **345** with phenols to give 2-aminobenzoates **436** (Scheme 213). This process took place in the presence of 0.2 equivalents of KI and TBHP as an oxidant in MeCN at room temperature under blue LED irradiation to furnish products **436** with good yields.

Oxidative decarboxylation of oxamic acids **15** has been described by Landais' group.[398–400] In the presence of 4CzIPN (**25**) as a PC and BI-OAc, a hypervalent iodine reagent, as an oxidant in DCE at room temperature under blue LED irradiation, oxamic acids reacted with alcohols to give the corresponding urethanes **437** with 30–90% yields (Scheme 214a).[398] A plausible mechanism has been proposed involving the formation of isocyanates **162** as intermediates. Initially, intermediate **A**, resulting by reaction of oxamic acid with BI-OAc, is reduced by PC* to give the radical anion **B**. Subsequent decarboxylation of **B** gives the amidocarbonyl radical **C** and 2-iodobenzoic acid. Radical **C** would be oxidized by the $PC^{+\bullet}$ to form the isocyanate **162**, which by addition of alcohol generates the urethane. This transformation was further carried out using $Os(bptpy)_2(PF_6)_2$ **438** as a PC under near-infrared (660 nm) irradiation to give the resulting urethanes in 40–87% yields.[399] In addition, in a third alternative for the preparation of urethanes **437**, ferrocene was used as a PC, 2-picolinic acid as a ligand and $KBrO_3$ as an oxidant in DCE at room temperature under blue LED irradiation (Scheme 214b).[400] In this case,



Scheme 207 Decarboxylative oxygenation of aliphatic carboxylic acids with TEMPO under $Fe(OTf)_3$ photocatalysis.



Scheme 208 Decarboxylative etherification of peptides with BI-OAc as an oxidant under $Ru(bpy)_3Cl_2$ photocatalysis.

Fe(pinacolate) or FeCp-pinacolate complexes give upon oxidation with potassium bromate the catalytically active species Fe(III)Ln. This complex reacts with oxamic acid to provide a Fe(III) carboxylate complex **D**, which after irradiation a LMCT[54,55] process gives the carboxy radical **E**. Subsequent decarboxylation forms the amidocarbonyl radical **C**, which undergoes further oxidation by Fe(III)Ln to give isocyanate **162** and by reaction with the alcohol urethane **437**. These processes avoid the isolation of carcinogenic isocyanates.

In summary, decarboxylative oxygenation of carboxylic acids to carbonyl compounds can be carried out using Mn, Ce or Fe salts as PCs in the presence of oxygen. In the case of α-AAs, the corresponding amides are prepared. Etherification of carboxylic acids with alcohols required Ru or Fe complexes as PCs and hypervalent iodine reagents as oxidants. Acyloxylation of carboxylic acids has been carried out with Ru complexes as PCs and hypervalent iodine reagents. Benzoic acids have been transformed into phenols by reaction with Cu complexes. In the case of oxamic acids, 4CzIPN and BI-OAc or Cp_2Fe and $KBrO_3$ were converted into urethanes by intermediacy of *in situ* generated isocyanates.

3.3. Carbon–sulfur bond-forming reactions

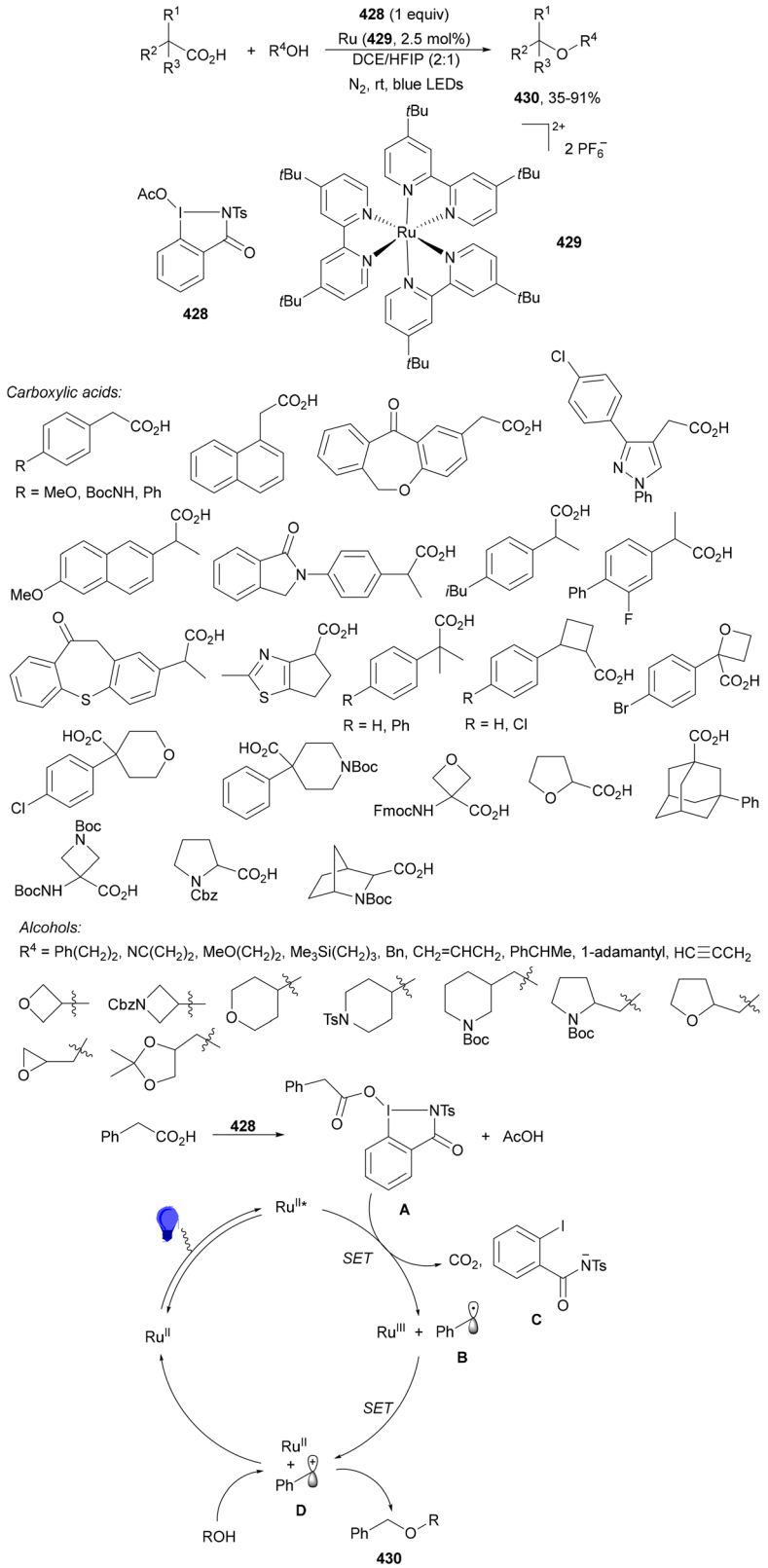
Decarboxylation of carboxylic acids or their active esters has been employed under photoredox conditions for thiolation, thioetherification, thioesterification, sulfilimination, sulfinylation and sulfonylation reactions.

3.3.1. Thiolation. Direct access to thiols from carboxylic acids and a thionocarbonate reagent **439** has been recently described by Dilman and co-workers.[401] This photocatalytic thiolation was performed with acridine **125** as a PC in DCM at room temperature under air and purple (400 W) LED irradiation. Progressive addition of acridine **125** with a syringe pump improved the formation of thionocarbonates **440**, which after work-up with aqueous K_2CO_3 gave free thiols (Scheme 215). Primary, secondary and tertiary aliphatic carboxylic acids and *N*-protected AAs gave the corresponding thiocarbonates **440** in 35–87% yields and thiols in 29–85% yields. Late-stage functionalization of drugs such as gemfibrozil and clofibrate was performed, as well as valproic acid, picamilon and the herbicide 2,4-D were also transformed into thionocarbamates. Unfortunately, ibuprofen and other benzylic acids cannot be thiolated. The prepared thionocarbonates **440** can also be converted into sulfonyl chlorides by treatment with chlorine and acetic acid. In addition, thiocarbonates can be alkylated with alkyl halides and transformed into sulfonyl fluorides by treatment with Selectfluor. Experimental and theoretical studies supported the proposed mechanism: photoexcited acridine **125*** reacts with a carboxylic acid *via* a proton-coupled electron transfer (PCET) followed by decarboxylation to form the alkyl radical **A**. This radical **A** attacks the C═S bond of **439** with subsequent N–O bond cleavage to form the phthalimide radical, which regenerates the acridine PC through consecutive electron and proton transfer steps.

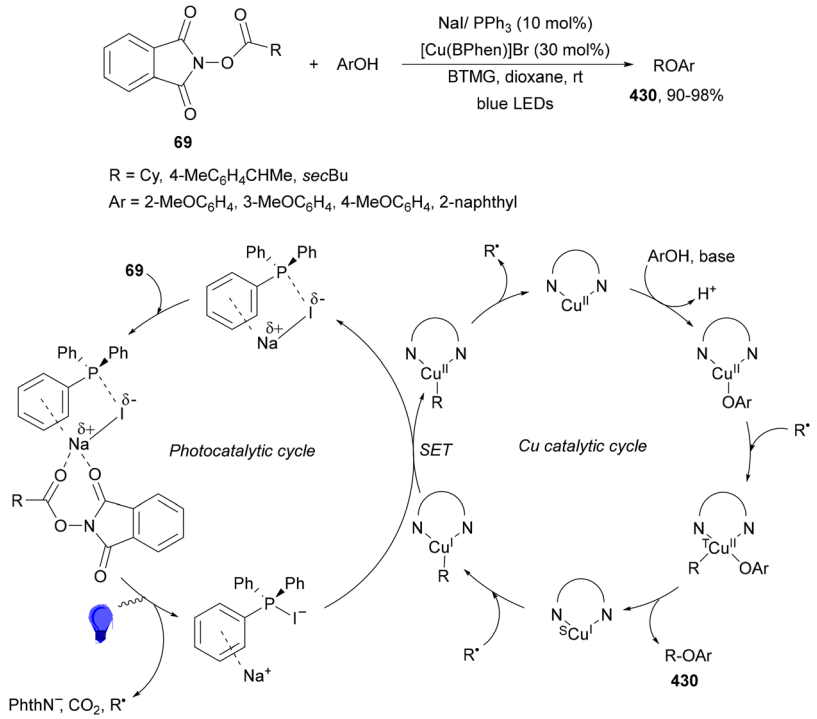
Larionov and co-workers[402] performed acridine **441** photocatalysis for the direct access to thiols from carboxylic acids and elemental sulfur. This economical thiolation took place in MeCN at 100 °C under 400 nm LED irradiation followed by transformation of the oligosulfide intermediates into thiols by means of phenylsilane in 45–71% yields (Scheme 216a). Alternatively, disulfide derivatives **442** can be obtained by *in situ* treatment with diphenyl disulfide in 42–75% yields (Scheme 216b). A wide range of carboxylic acids and medicinally relevant acids as well as natural products have been employed.

Thiolation of alkyl NHPI esters **69** has been previously described by Liao and co-workers[403] using 4-methoxybenzothioamide (**443**) as a sulfur donor, Eosin Y-Na_2 (**139**) as an organophotocatalyst, and DIPEA as a base in MeCN under Ar and blue LED irradiation (Scheme 217). A wide range of primary, secondary and tertiary alkyl NHPI esters gave the corresponding thiols in 10–81% yields. Volatile thiols were isolated as disulfides **442** by *in situ* trapping with diphenyl disulfide in 24–80% yields. As a plausible mechanism, excited PC* is quenched by DIPEA or by thioamide **443** affording $PC^{-\bullet}$. Subsequent SET from $PC^{-\bullet}$ to NHPI esters forms the radical anion **A** and regenerates the PC. This intermediate **A** undergoes fragmentation to give CO_2, $PhthN^-$ and radical **B**. Addition of **B** to **443** generates intermediate **C**, which can be oxidized to imine **D** by a SET from PC*. Imine **D** gives after ArCN elimination the corresponding thiol.

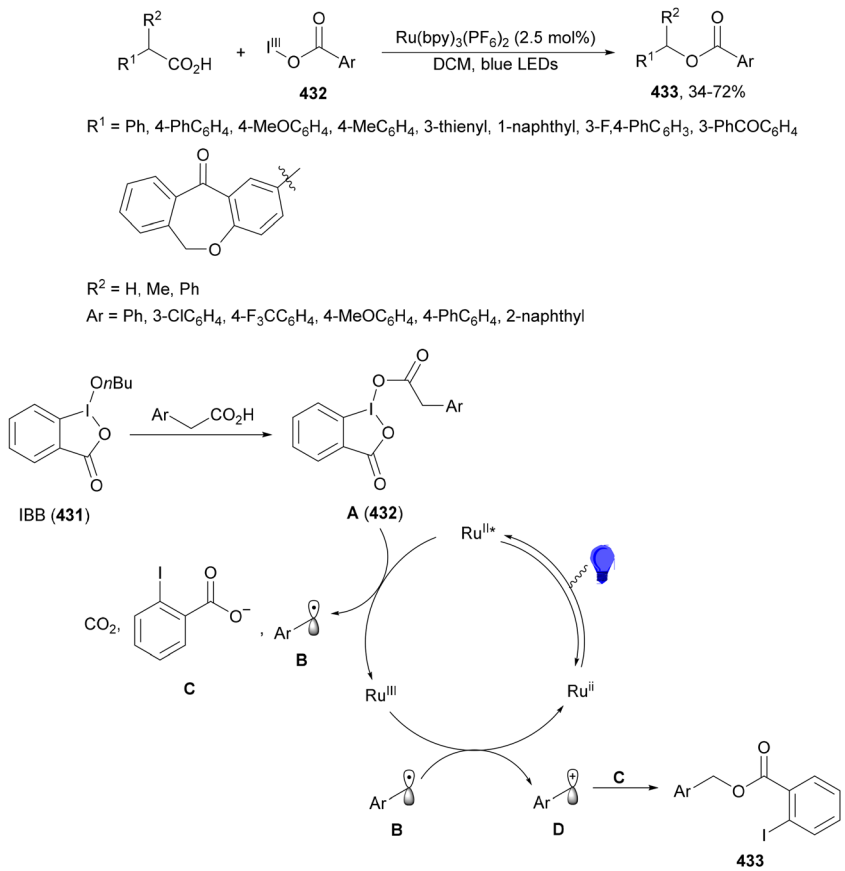
3.3.2. Thioetherification. Thioetherification of carboxylic acids was reported in 2016 by Glorius and co-workers[404] using Ir complexes as PCs and CsOBz as a base in fluorobenzene under blue LED irradiation. Di- and trifluoromethyl thiolation



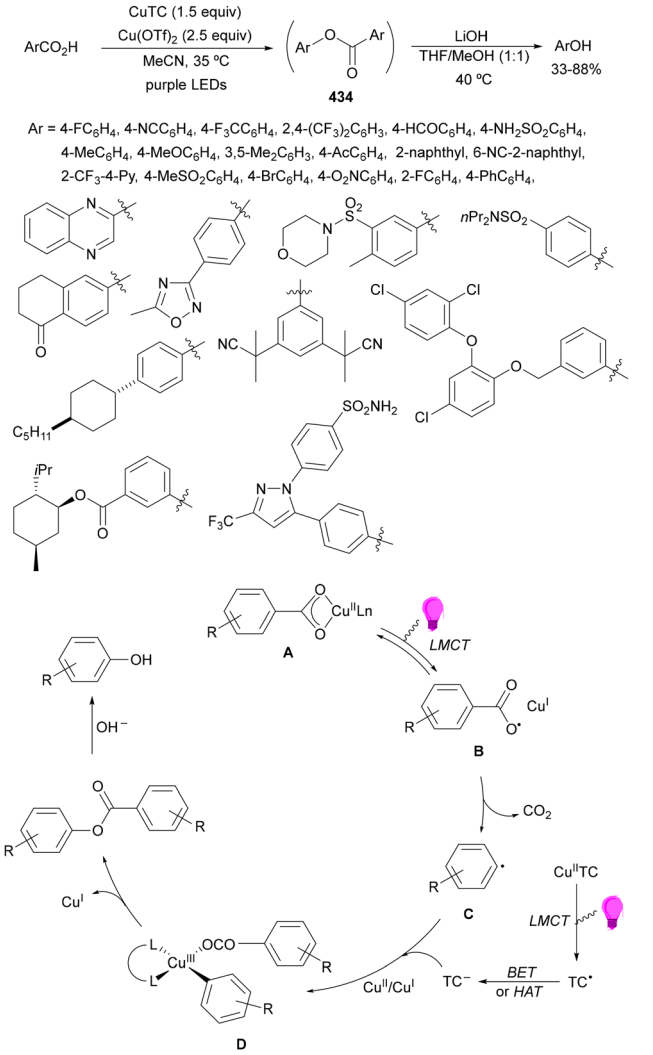
Scheme 209 Decarboxylative etherification of carboxylic acids with alcohols and **428** as an oxidant under Ru **429** photocatalysis.



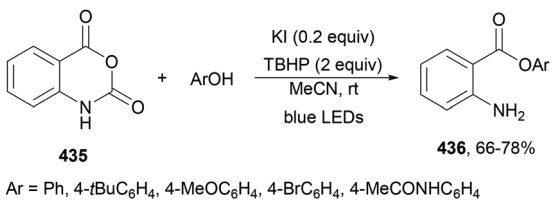
Scheme 210 Decarboxylative etherification of alkyl NHPI esters **69** with phenols under Cu(I) and NaI/PPh_3 photocatalysis.



Scheme 211 Decarboxylative acyloxylation of carboxylic acids with hypervalent iodine reagents **432** under Ru(II) photocatalysis.



Scheme 212 Decarboxylative acyloxylation/hydroxylation of benzoic acids under CuTC/Cu(OTf)$_2$ photocatalysis.



Scheme 213 Decarboxylative C–O bond formation of isatoic anhydride (**435**) and phenols under KI photocatalysis.

reactions were carried out with PhthNSCF$_2$H and PhthNSCF$_3$, respectively, with 68–88% and 49–94% yields, respectively. Wang, Xu and co-workers[405] described the decarboxylative sulfenylation of α-AAs with *N*-arylsulfenyl succinimides in the presence of Ir complex **4** as a PC and Ni(acac)$_2$/dtbpy as a catalyst, and K$_2$HPO$_4$ as a base in dioxane at room temperature under blue LED irradiation to obtain the corresponding products in 26–97% yields.

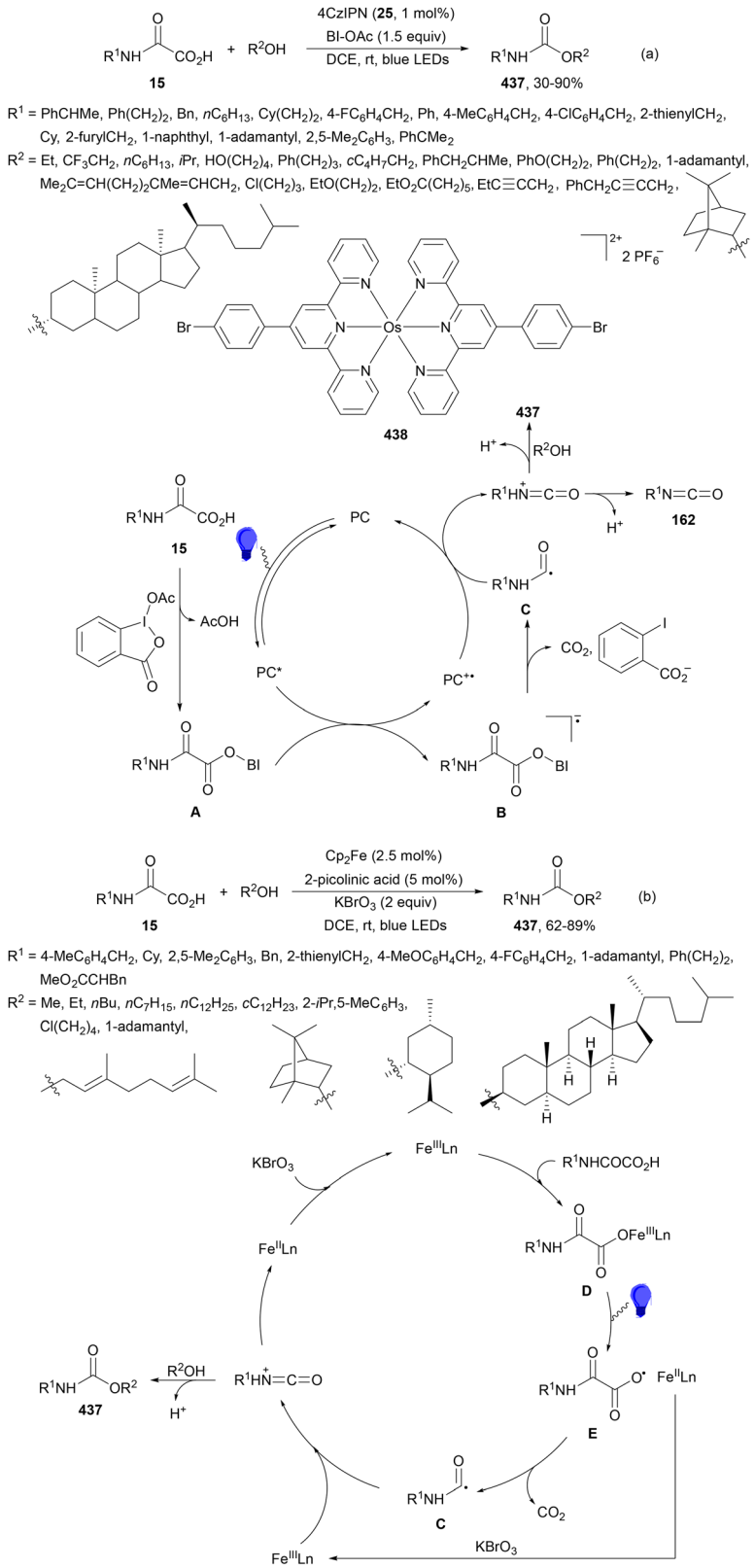
A more recent thioetherification procedure involved trisulfide dioxides **444** as disulfuration agents of carboxylic acids. Wu and Pratt[406] performed this process with [Mes-Acr-Ph]BF$_4$ **287** as a PC and CsF as a base in EtOAc at room temperature under N$_2$ and blue LED irradiation to give disulfides **442** with good yields (Scheme 218). A range of primary, secondary and tertiary carboxylic acids including α-AAs were efficiently converted into the corresponding disulfides **442**. These trisulfide-1-dioxides **444** undergo homolytic substitution with the alkyl radical generated from the carboxylic acid at the PhSO$_2$–S bond to give the phenylsulfonyl radical and the product.

Guo, Xia and co-workers[407] employed thiosulfonates **445** as thioetherification reagents for the iron-catalyzed LMCT[54,55] chemodivergent[381] process of aliphatic and heteroaromatic carboxylic acids into thioethers **446** or sulfoxides **447**. In the presence of 10 mol% of Fe(NO$_3$)$_3$·9H$_2$O and K$_2$CO$_3$ as a base in MeCN at 35 °C under N$_2$ and LED (390 nm) irradiation, the corresponding thioethers **446** were obtained with 32–94% yields (Scheme 219a). Furthermore, it was found that in the presence of air a decarboxylative sulfinylation of heteroaromatic carboxylic acids occurred giving sulfoxides **447** with modest yields (Scheme 219b). Diverse drug active molecules, natural products and α-AAs were modified at the late-stage to obtain the corresponding thioethers with 39–63% yields. In the plausible pathway proposal for decarboxylative thiolation reaction, firstly the base deprotonates the carboxylic acid and forms a carboxylate-iron(III) intermediate **A**. Subsequent photoinduced LMCT gives Fe(NO$_3$)$_2$ and the carboxy radical **B**, which after decarboxylation generates radical R$^\bullet$ (**C**). This radical **C** attacks the thiosulfonate **445** to form the thioether **446** and a sulfonyl radical **D**. Radical **D** converts Fe(II) into Fe(III) regenerating the catalyst. Wei, Hu and co-workers[210] employed also Fe(NO$_3$)$_3$ and bis[(2-pyridyl)methyl]amine (**298**) as a ligand for the thiolation reaction of carboxylic acids with thiosulfonates **445** to give thioethers **446** in 50–89% yields.

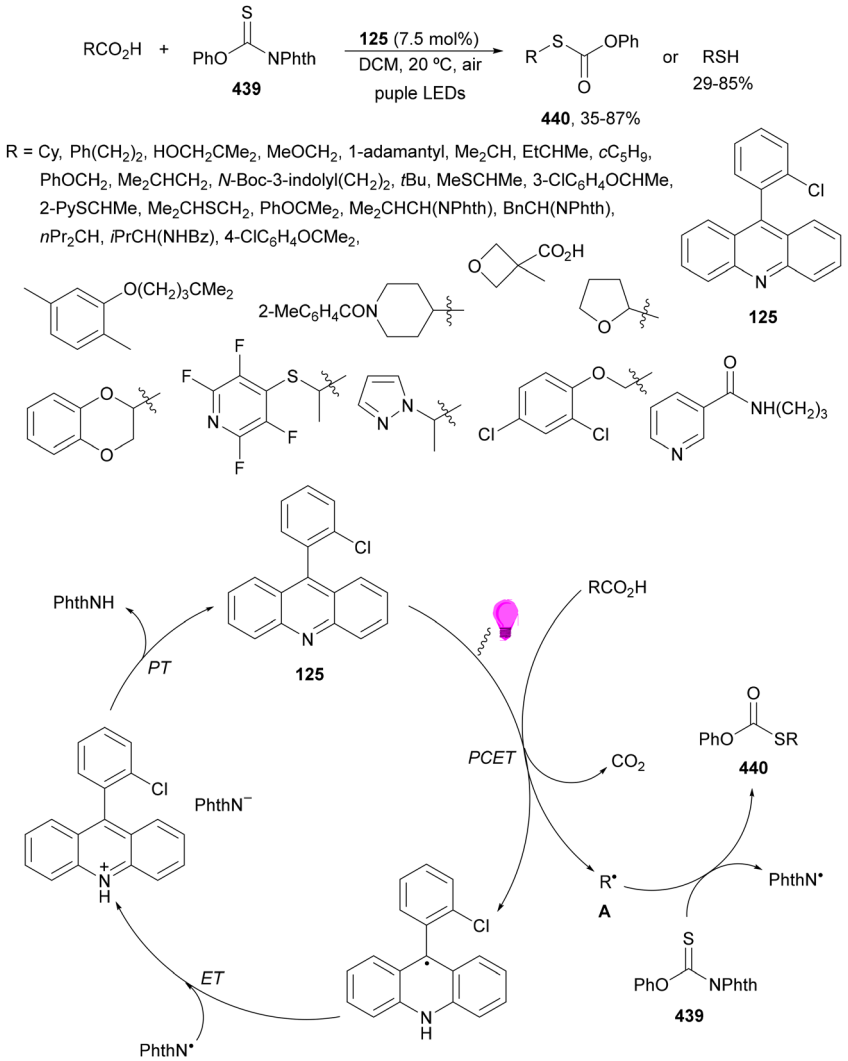
A similar decarboxylative thiolation of aromatic carboxylic acids with thiosulfonates **445** has been recently performed by Xia and co-workers.[200] In this case, Cu(OTf)$_2$ (2 equivalents) was used for the LMCT process and Li$_2$CO$_3$ as a base in MeCN at 35 °C under N$_2$ and 390 nm LED irradiation to obtain thioethers **446** with 43–73% yields.

Dilman and co-workers[408] reported that a perfluorinated disulfide **448** can be employed for the thiolation of carboxylic acids. In the presence of acridine **449** as a PC for PCET catalysis, sodium perborate as a reoxidant of the forming thiol in aqueous DCM at room temperature under 400 nm LED irradiation resulted in sulfides **450** in moderate to good yields (Scheme 220). A wide range of primary, secondary and tertiary aliphatic carboxylic acids were employed as well as α-AAs and drugs such as ketoprofen, naproxen, indomethacin, ibuprofen and gemfibrozil. As natural products, pinonic and ursodeoxycholic acids also delivered the corresponding sulfides in good yields.

Yoon and co-workers[295] employed FeCl$_3$-mediated decarboxylative photoredox conditions for C–H activation of arenes and heteroarenes (Scheme 160). By photochemical decarboxylation



Scheme 214 Decarboxylative oxidation of oxamic acids under 4CzIPN (**25**) (a) or Cp_2Fe (b) photocatalysis.



Scheme 215 Decarboxylative thiolation of carboxylic acids with thiocarbonate **439** under acridine **125** photocatalysis.

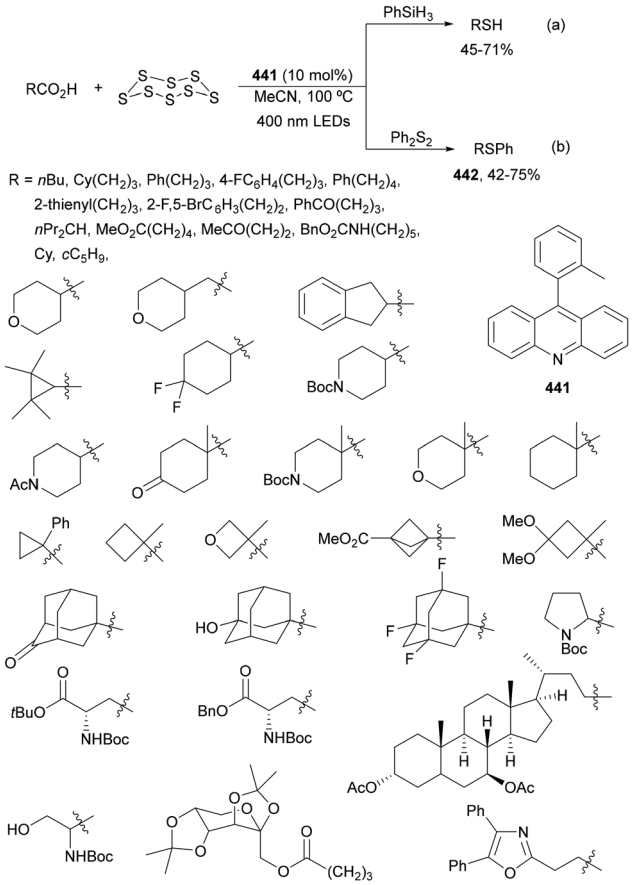
followed by radical-polar crossover, diverse C–O, C–N and C–S bonds can be formed. In the case of thioetherification reactions, phenylacetic acid, as the only example, was allowed to react with cyclohexanethiol to give the corresponding sulfide in 53% yield.

Recently, He and Dydio[409] reported thianthrenation of aryl and heteroaryl carboxylic acids by photoinduced LMCT[54,55] mediated by Cu(II) salts. The reaction of carboxylic acids with thianthrenes **451** in the presence of $Cu(OTf)_2$ and $Cu(MeCN)_4OTf$ with NaF as a base in MeCN under purple LED irradiation provided thianthrenium salts **452** in modest to good yields (Scheme 221). These salts **452** were further transformed into ^{13}C-labeled carboxylic acids by reaction with $^{13}CO_2$ and $ZnCl_2$ in boronates, sulfonamides, phosphate esters and by Negishi-type coupling to alkyl derivatives.

The use of NHPI esters in thioetherification reactions was described in 2016 by Fu and co-workers[410] using thiophenols and Cs_2CO_3 as a base under 40 W CFL irradiation to give alkyl aryl sulfides in 44–94% yields. Zheng and co-workers[411] described a Ru-photoredox catalysis for the thioetherification of NHPI esters with alkyl and aryl disulfides under blue LED irradiation to give the corresponding sulfides in 24–98% yields. Wang and co-workers[412] used thiosulfonates and 4-$TolSO_2SR$ as a thiolating reagent, giving sulfides in the presence of 4CzIPN as a PC under LED irradiation with 43–91% yields.[412]

Oxime esters derived from benzophenone $RCO_2N{=}CPh_2$ were employed by Glorius and co-workers[413] for trifluoromethylthiolation with Ir complex **4** as a PC under blue LED irradiation. Later, Wu and Pratt[414] prepared unsymmetrical disulfides by reaction of benzophenone oxime esters with tetrasulfides with Ir complex **4** as a PC under blue LED irradiation.

Recently, Noble, Aggarwal and co-workers[373] reported a decarboxylative thiocyanation of NHPI esters **69** with potassium thiocyanate under blue LED irradiation. In the presence of Ir complex **4** as a PC, CuSCN, 2,9-dimethyl-1,10-phenanthroline (dmp) as a ligand in acetone at 30 °C, the corresponding alkyl thiocyanates **453** were obtained in 44–79% yields accompanied by small amounts of isothiocyanates (Scheme 222). The proposed



Scheme 216 Decarboxylative thiolation of carboxylic acids with elemental sulfur under acridine **441** photocatalysis (a, b).

mechanism was similar to the one depicted in Scheme 203 for the chlorination of NHPI esters **69**.

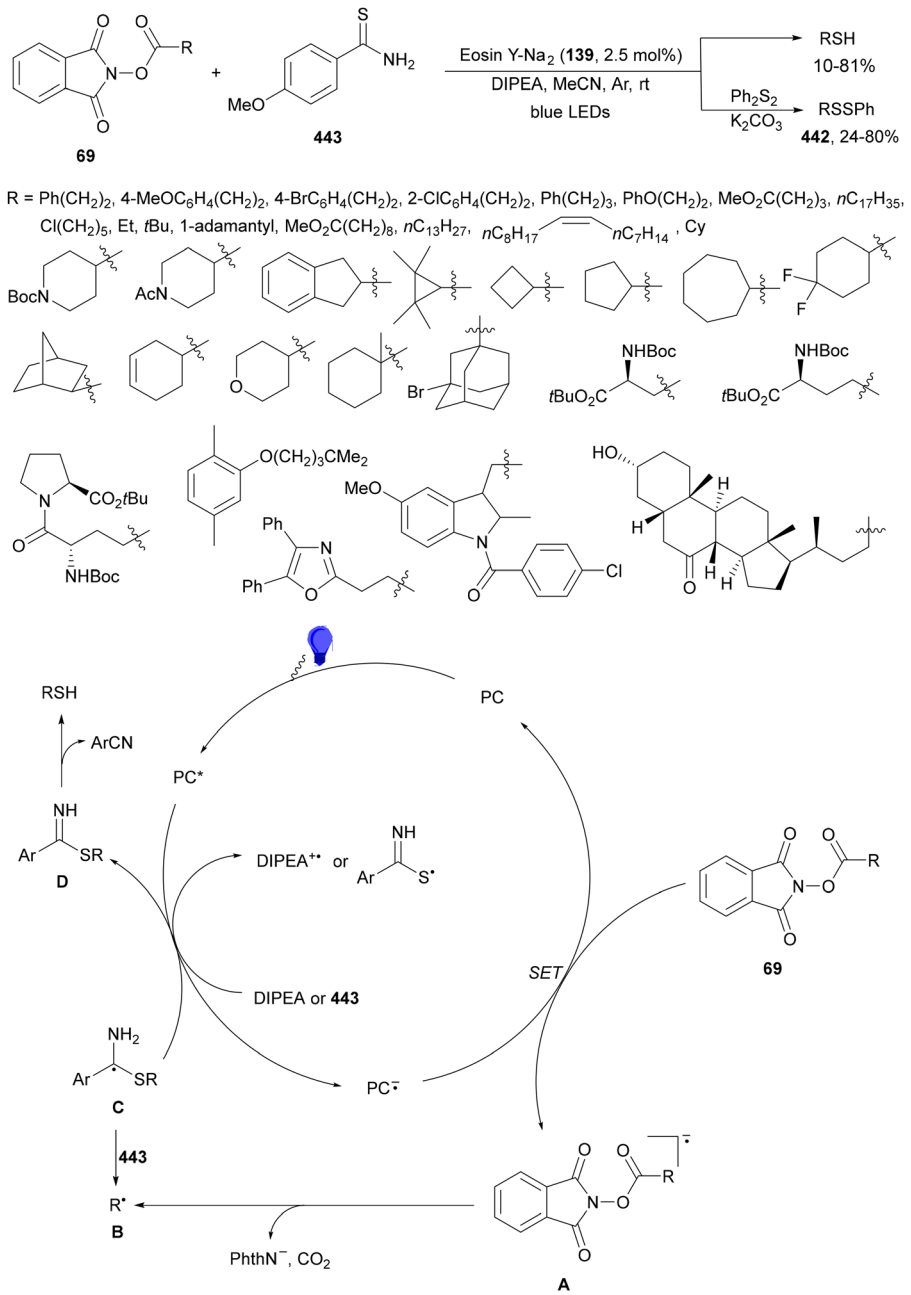
3.3.3. Thioesterification. Thioesterification of carboxylic acids was carried out in 2020 by Alexanian and co-workers[415] using *N*-xanthyl amides to provide ethyl xanthates in 41–99% yields. This transformation was carried out in trifluoromethylbenzene at room temperature under blue LED irradiation. Starting from NHPI esters **69**, Liao and co-workers[416] performed a thioesterification with thiobenzoic acid in the presence of $Ru(bpy)_2Cl_2$ (mol%), CuBr (20 mol%), PPh_3 (20 mol%), and Et_3N as a base in MeCN at room temperature under blue LED irradiation. The corresponding thiobenzoates RSCOPh were obtained with 17–89% yields.

Prieto and co-workers[417] employed benzophenone oxime esters **454** and xanthate dimer **455** for the synthesis of xanthates with moderate to good yields (Scheme 223). This xanthylation process was carried out in the presence of thioxanthone (TX) and EtOH as a solvent at room temperature under purple LED (390 nm) irradiation. Primary, secondary and tertiary esters **454** including gibberellic acid, gemfibrozil and enoxolone were converted into the corresponding thioxanthates. Mechanistic investigations revealed that only xanthate dimer **455** is involved giving the xanthyl radical **A**, which reacts with iminyl radical **B** to give intermediate **C**. Subsequent β-scission of **C** by reacting with $R^{\bullet}$ gives product **456**.

3.3.4. Sulfilimination. Decarboxylative sulfilimination of alkyl NHPI esters **69** with sulfenamides **457** has been recently reported by Wang and co-workers.[418] This process was achieved *via* a combination of photoredox with Ir complex **52**, CuCl and DIPEA as a base in DCE at room temperature under Ar and blue LED irradiation (Scheme 224). The resulting sulfilimines **458**, aza-variants of sulfoxides, derived from aliphatic carboxylic acids were isolated in moderate to good yields (31–96%). A late-stage modification of natural products and drug molecules such as baclofen, L-glutamic acid, isoxepac, gemfibrozil, pentanoic acid, mycophenolic acid, gabapentin, linoleic acid, chlorambucil and dehydrocholic acid was also carried out with 41–84% yields. On the basis of experimental studies, it was proposed that PC* oxidizes the Cu(I)-DIPEA complex **A** to give Cu(II) complex **B**. Ir(II) species reduces NHPI ester generating Ir(III) and the alkyl radical, after extrusion of CO_2 and $PhthN^-$. Transmetalation of sulfenamide **457** with **B** produces Cu(II)-sulfenamide complex **C** and $DIPEAH^+$, which reacts with $PhthN^-$ to give PhthNH and DIPEA. Complex **C** captures the radical R^1 to form the Cu(III) complex **D**, which after reductive elimination gives product **458** and the Cu(I) salt.

3.3.5. Sulfinylation. Direct decarboxylative sulfinylation of aliphatic carboxylic acids to sulfoxides has been achieved by Larionov and co-workers[419] using sodium sulfinates and acridine **123** as an organic PC (Scheme 225). Based on a reaction chemical space mapping, they developed a Python-based analytical tool termed Prospective analysis of the reaction space (PARSE) providing insights into molecular structures of reaction products. This sulfinylation can be carried out in the presence of *p*-bromobenzoyl chloride (PBC), which mediated the formation of an intermediate sulfinyl sulfone **460** through mixed anhydride RSO_2COAr **461** (Scheme 225b). The sulfinylation reaction took place in DCM under 400 nm LED irradiation to give sulfoxides **459** with 50–81% yields (Scheme 225a). Functionalization of natural products and drugs was evaluated with azelaic acid, *cis*-epoxyoleic acid, gemfibrozil, sulfinpyrazone, glutamic acid, santonic acid, D-fructose, ursodeoxychlolic acid and gibberellic acid. Experimental and computational studies indicate that decarboxylation of the acid takes place by irradiation of intermediate **A** to give the corresponding alkyl radical $R^{1\bullet}$. This radical couples with the *in situ* formed sulfinyl sulfone **460** to form the product and the sulfonyl radical **B**. The PC is regenerated by hydrogen atom transfer (HAT) between sulfonyl **B** and acridinyl **C** radicals. Recently,[420] a decarboxylative sulfinylation has been carried out starting from NHPI esters **69** and sodium sulfinates in the presence of 4CzIPN (2 mol%) as a PC and $Cu(OTf)_2$ (20 mol%) in MeCN at 55 °C under blue led irradiation to give the corresponding sulfoxides **459** with 29–61 yields.

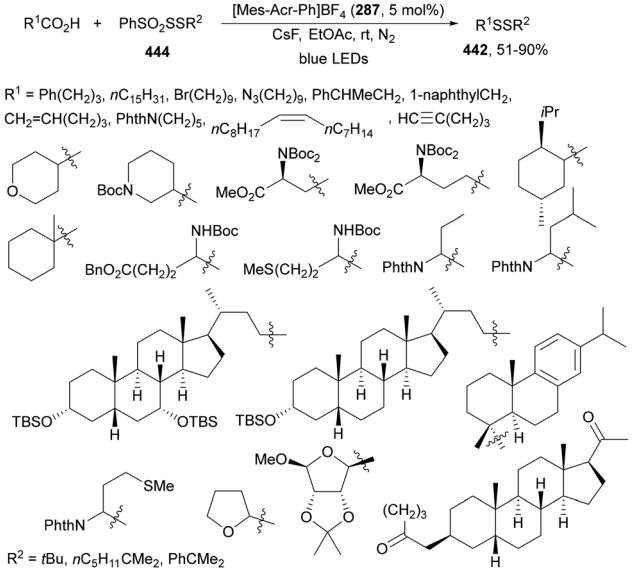
3.3.6. Sulfinamidation. Independently Willis[421,422] and Larionov[423] groups developed the direct conversion of carboxylic acids to sulfinamides under photocatalytic decarboxylation. Initial studies by Willis and co-workers[421] employed alkyl carboxylic acids and *N*-trityl sulfinylamine reagent TrNSO (**462**) and acridine **123** as a PC in DCM at room temperature under 395–405 nm LED irradiation to provide sulfinamides **463** with



Scheme 217 Decarboxylative thiolation of alkyl NHPI esters with 4-methoxybenzothioamide (**433**) under Eosin Y-Na_2 (**139**) photocatalysis.

good yields (Scheme 226a). Later, this process was slightly modified for the preparation of *N*-alkyl sulfinimides **463** (Scheme 226b).[422] The reaction of carboxylic acids with TrNSO (**462**) in the presence of aliphatic primary amines and acridine **123** as a PC under 405 nm LED irradiation furnished the corresponding sulfinimides with good yields. This process was improved by allowing the reagents to reach equilibrium (during 30 minutes at 40–60 °C) prior to irradiation. It was also possible to employ ammonia in MeOH and 4-tolylamine and 4-anisidine to give the corresponding sulfinamides in moderate yields (30–44%). The reaction proceeds by a PCET mechanism by formation of alkyl radical **A**, which adds to TrNSO to give radical **B**.

In the case of Larionov and co-workers,[423] acridine **125** was used as a PC and $Cu(MeCN)_4BF_4$ as a catalyst with dtbpy as a ligand in a 2 : 1 mixture of DCM and MeCN under 400 nm LED irradiation (Scheme 227a). Primary, secondary and tertiary aliphatic carboxylic acids and *N*-aryl or heteroaryl sulfinylamines **462** gave sulfinamides **463** with very good yields. Primary sulfinamides **464** were prepared using silyl sulfinylamines followed by treatment with TBAF (Scheme 227b). Active pharmaceutical ingredients (APIs) and natural products such as gemfibrozil, mycophenolic acid, *N*-Boc-proline and aspartic acid derivative, oxaprozin, isoxepac, erucic acid, linoleic acid, 10,12-pentacosadinoico acid, *cis*-pinonic acid, oleanolic acid,



Scheme 218 Decarboxylative thioetherification of aliphatic carboxylic acids with trisulfide dioxides **444** under [Mes-Acr-Ph]BF_4 **287** photocatalysis.

glycyrrhetinic acid and unprotected chenodeoxycholic acid were transformed into the corresponding sulfinamides in 51–99% yields. In the case of gemfibroxil, the reaction with *N*-phenyl sulfinylamine was carried out on a gram-scale with 96% yield. Based on experimental and computational data the proposed catalytic cycle starts with the formation of intermediate **A** between acridine **125** and the acid. Photoinduced proton-coupled electron transfer (PCET) of **A** forms, after decarboxylation, the alkyl radical **B**, which reacts with the sulfinylamine **462** to give the amino sulfinyl radical **C**. This radical **C** is stabilized by the Cu(I) catalyst to form complex **D**. Subsequent PCET with acridinyl radical **E** releases the product **463** and the Cu(I) catalyst.

3.3.7. Sulfonylation. Decarboxylative sulfonylation of carboxylic acids or NHPI esters **69** can be directed to the synthesis of sulfones, alkyl sulfinates, sulfonyl halides, sulfonamides and sulfonimidamides. In 2020, Li and co-workers[424] reported the synthesis of sulfones by reaction of NHPI esters **69** with sodium sulfinates using 4CzIPN (2 mol%) and $Cu(OTf)_2$ (20 mol%) as catalysts under blue LED irradiation with 23–98% yields.

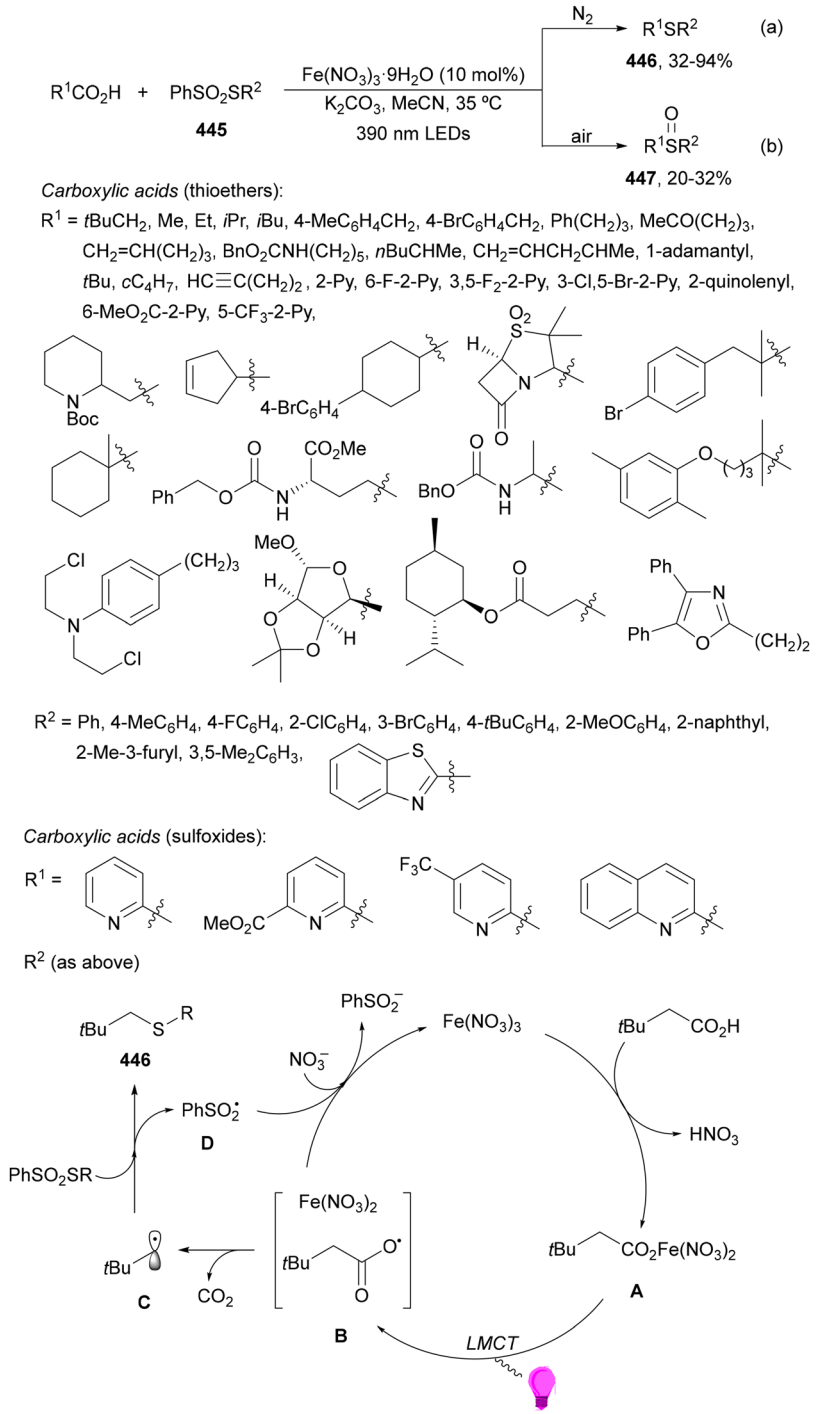
More recently, Larionov and co-workers[425] reported a three-component reaction for the synthesis of sulfones **466** using carboxylic acids, 1,4-diazabicyclo[2.2.2]octane bis(sulfur dioxide) (DABSO, **465**) or sodium metabisulfite and alkyl or heteroaryl halides or electrophilic alkenes with acridine **125** as a PC under LED irradiation (400 nm) (Scheme 228a). A wide range of sulfones **466–468** have been prepared including those derived from natural products and drugs in 52–95% yields. This decarboxylative sulfonylation was applied to the preparation of sodium sulfinates **469** after a simple basic work-up in 54–96% yields (Scheme 228b). Moreover, sulfonyl chlorides **470** and fluorides **471** can be prepared under the same reaction conditions by addition of NCS followed by an aqueous solution of KHF_2 and NFSI, respectively (Scheme 228c and d). Mechanistic studies showed that the photocatalytic decarboxylation takes place in the excited state of the acridine-carboxylic acid complex *via* a PCET process (see Scheme 207).

The same group[426] developed a dual acridine/copper photocatalytic system for the tricomponent decarboxylative sulfonylation of carboxylic acids to sulfones. Acridine **472** and CuOTf/diamine **473** were used as catalysts for the synthesis of alkyl aryl or heteroaryl sulfones **467** with good yields in the presence of $K_2S_2O_5$ or DABSO as a stable sulfur dioxide donor and Cs_2CO_3 or DABCO as a base, in MeCN at 100 °C under purple LED (400 nm) irradiation (Scheme 229). This method was applied to primary, secondary and tertiary carboxylic acids (see Scheme 228) as well as natural products and drugs such as gemfibrozil, oxaprozin, mycophenolic acid, Boc–Glu–OMe, a biotin derivative, D-fructose, ursodeoxycholic acid, cholic acid, deoxycholic acid, chenodeoxycholic acid, picamilon, bedaquiline, empagliflozin, canagliflozin and lapatinib in 43–92% yields.

Zeng and co-workers[427] reported recently a similar three-component reaction between aliphatic carboxylic acids, DABSO (**465**) and alkyl halides using $TBAFeCl_4$ as a PC, Et_3N as a base in DCM at room temperature under Ar and 390 LED irradiation (Scheme 230). The corresponding dialkyl sulfones **466** were obtained in modest to good yields. In the proposed mechanism, a SET between the carboxylate ion and Fe(III) generates Fe(II) and $RCO_2^{\bullet}$. A subsequent decarboxylation of **A** forms the alkyl radical **B**, which reacts with DABSO (**465**) to give $RSO_2^{\bullet}$ species **C**. This radical **C** regenerates Fe(III) and furnishes the sulfinate anion **D**. The final reaction of **D** with allyl bromide produces the sulfone.

Vinyl sulfones have been prepared by decarboxylative sulfonylation of cinnamic acids. In 2016, Cai and co-workers[428] described this sulfonylation using sulfonyl hydrazides in the presence of oxygen as an oxidant and Eosin Y (**139**) as a PC in aqueous DMF under visible light to afford styryl sulfones in 35–92% yields. Later, arylsulfonate phenol esters **473** have been used for the decarboxylative sulfonylation of cinnamic acids only under visible-light in the absence of PC and oxidant (Scheme 231).[429] The corresponding styryl aryl sulfones **295** were obtained stereoselectively with good yields in the presence of Cs_2CO_3 as a base at room temperature in DMA under blue LED irradiation. As a plausible mechanism, the initial formation of an electron donor–acceptor complex **A** between aryl sulfonate phenol ester **473** and DMA with the assistance of Cs_2CO_3 is postulated. After irradiation, the excited complex A* undergoes a SET process to deliver radical anion **B** and the carbon-centered radical **C**. Fragmentation of **B** forms the sulfonyl radical **D**, which adds to cinnamic acid to give the benzyl radical **E**. SET of **E** by A* affords **F** and regenerates radical anion **B**. Finally, decarboxylation of **F** produces the sulfone **295**.

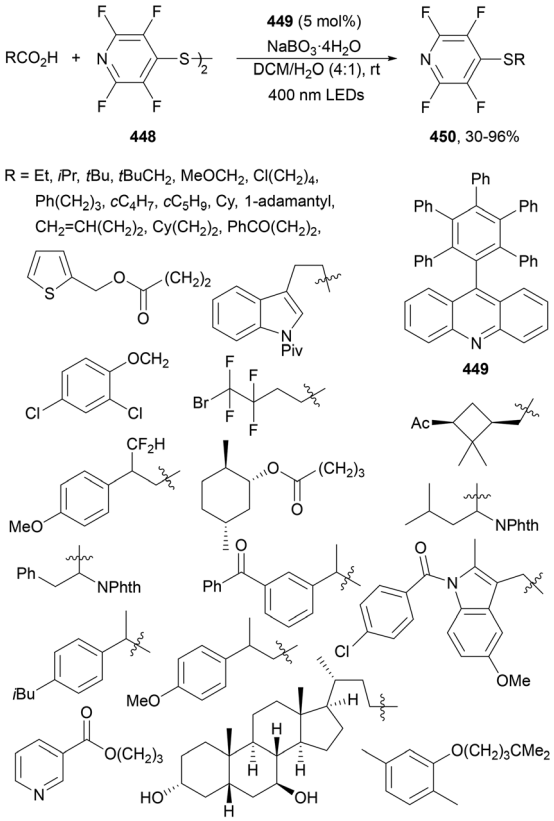
Recently, Sing and co-workers[430] employed sulfonylazides **474**, tosylmethyl isocyamide **475** (TosMIC) and β-keto sulfones **476** as sulfonating agents of cinnamic acids in the presence of rhodamine B (**477**) or Eosin Y (**139**) as a PC, TBHP as an oxidant and Cs_2CO_3 as a base. In the case of sulfonylazides **474**, rhodamine B (**477**) was used as a PC and DMSO as solvent to give styryl aryl sulfones **295** in 42–87% yields (Scheme 232a).



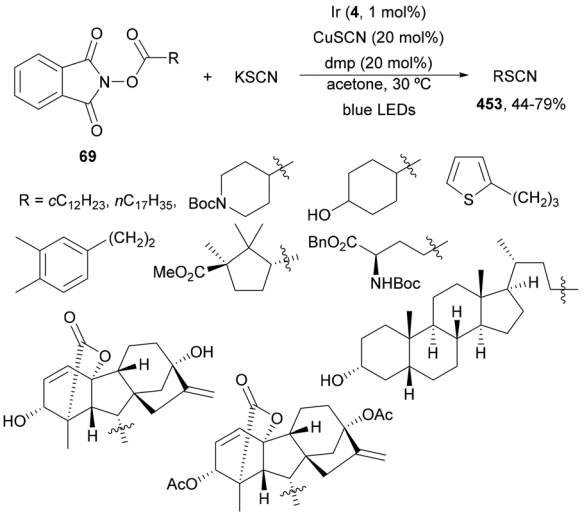
Scheme 219 Decarboxylative thioetherification of aliphatic and heteroaromatic carboxylic acids with thiosulfonates **445** under $Fe(NO_3)_3$ photocatalysis (a, b).

Propane-2-sulfonylazide gave styryl isopropyl sulfone in 72% yield. When tosylmethyl isocyanide **475** was employed in DMF as solvent and Eosin Y (**139**) as a PC, the corresponding styryl 4-tolyl sulfones **295** were obtained with 67–97% yields (Scheme 232b). In addition, under the same reaction conditions, β-keto sulfones **476** afforded styryl sulfones **295** in 69–89 yields (Scheme 232c). In the proposed mechanism, an aryl sulfonyl radical is formed in the three cases, which undergoes conjugate addition to the cinnamic acid as shown in Scheme 231.

Fluorosulfonylation of primary and secondary aliphatic carboxylic acids by decarboxylative photoredox reaction was described by Larionov and co-workers[425] using acridine **125** as a PC and DABSO (**465**) (see Scheme 228). Lu, Weng and co-workers[431] performed a copper-catalyzed decarboxylative fluorosulfonylation



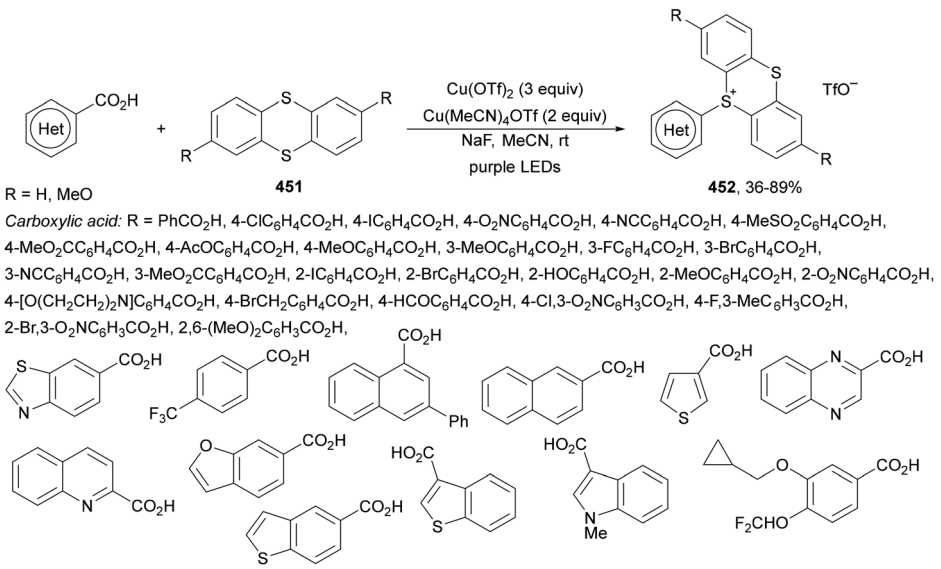
Scheme 220 Decarboxylative thioetherification of aliphatic carboxylic acids with perfluorinated disulfide **448** under acridine **449** photocatalysis.



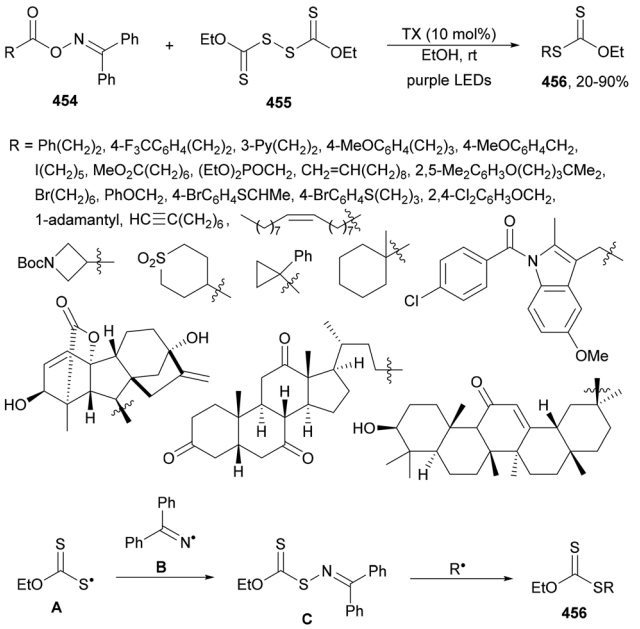
Scheme 222 Decarboxylative thiocyanation of alkyl NHPI esters **69** with KSCN under Ir complex **4** photocatalysis.

of primary, secondary and tertiary aliphatic carboxylic acids by two methods with different *N*-centered HAT reagents. Firstly, Cu powder, sodium metabisulfite and *N*-fluorobenzene sulfonimide (NFSI) at room temperature gave sulfonyl fluorides (**471**) derived from 3-arylpropionic acid in 5–65% yields. In the second method, 9-mesitylacridine (**123**) as the HAT reagent and PC, DABSO (**465**) and Selectfluor, Cu powder, 5,5′-dimethyl-2,2′-bipyridine (**478**) as a ligand in DCM at room temperature under 400 nm LED irradiation were employed giving sulfonyl fluorides **471** in 35–66% yields (Scheme 233). In the proposed mechanism, the acridine catalyst activates the carboxylic acid after irradiation to give a carboxy radical **A**, which after decarboxylation forms the alkyl radical **B**. After trapping of radical **B** by SO_2, the alkylsulfonyl radical **C** is formed. The Cu(II) complex undergoes SET with Selectfluor to generate a Cu(II) complex and radical **D**. The last step is a fluorine atom transfer (FAT) process to yield the product and regenerate the Cu(I) complex.

The same group[432] reported the decarboxylative fluorosulfonylation of aldoxime esters **479** with DABSO (**465**) and NFSI in



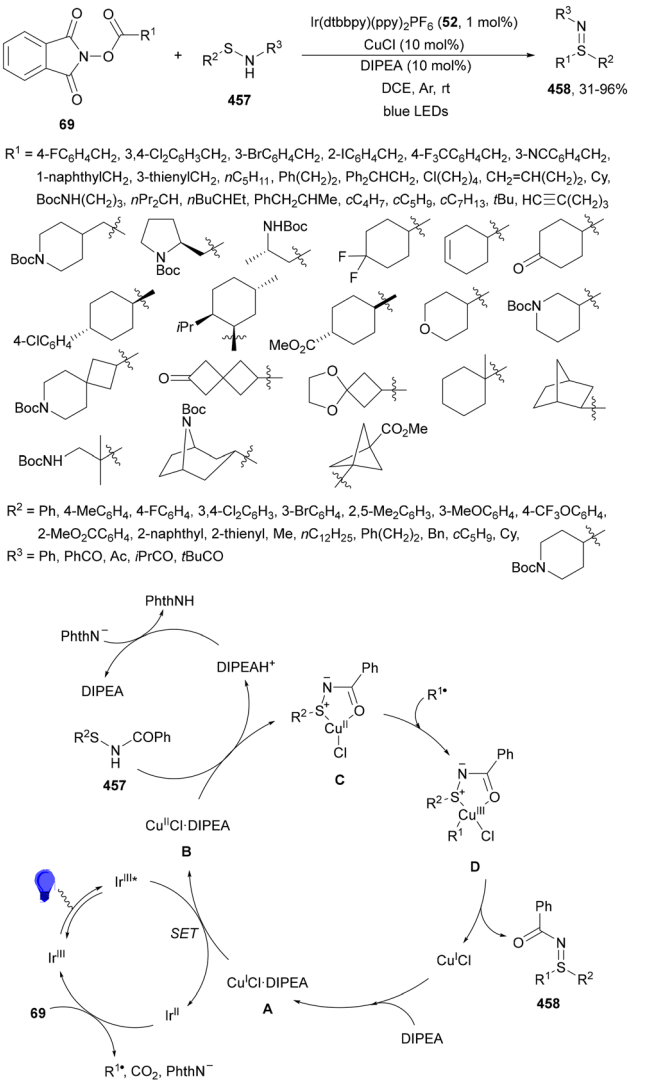
Scheme 221 Decarboxylative thianthrenation of aromatic and heteroaromatic carboxylic acids with thianthrenes **451** under Cu(II) photocatalysis.



Scheme 223 Decarboxylative xanthylation of benzophenone oxime esters **454** with xanthate dimer **455** under thioxanthone photocatalysis.

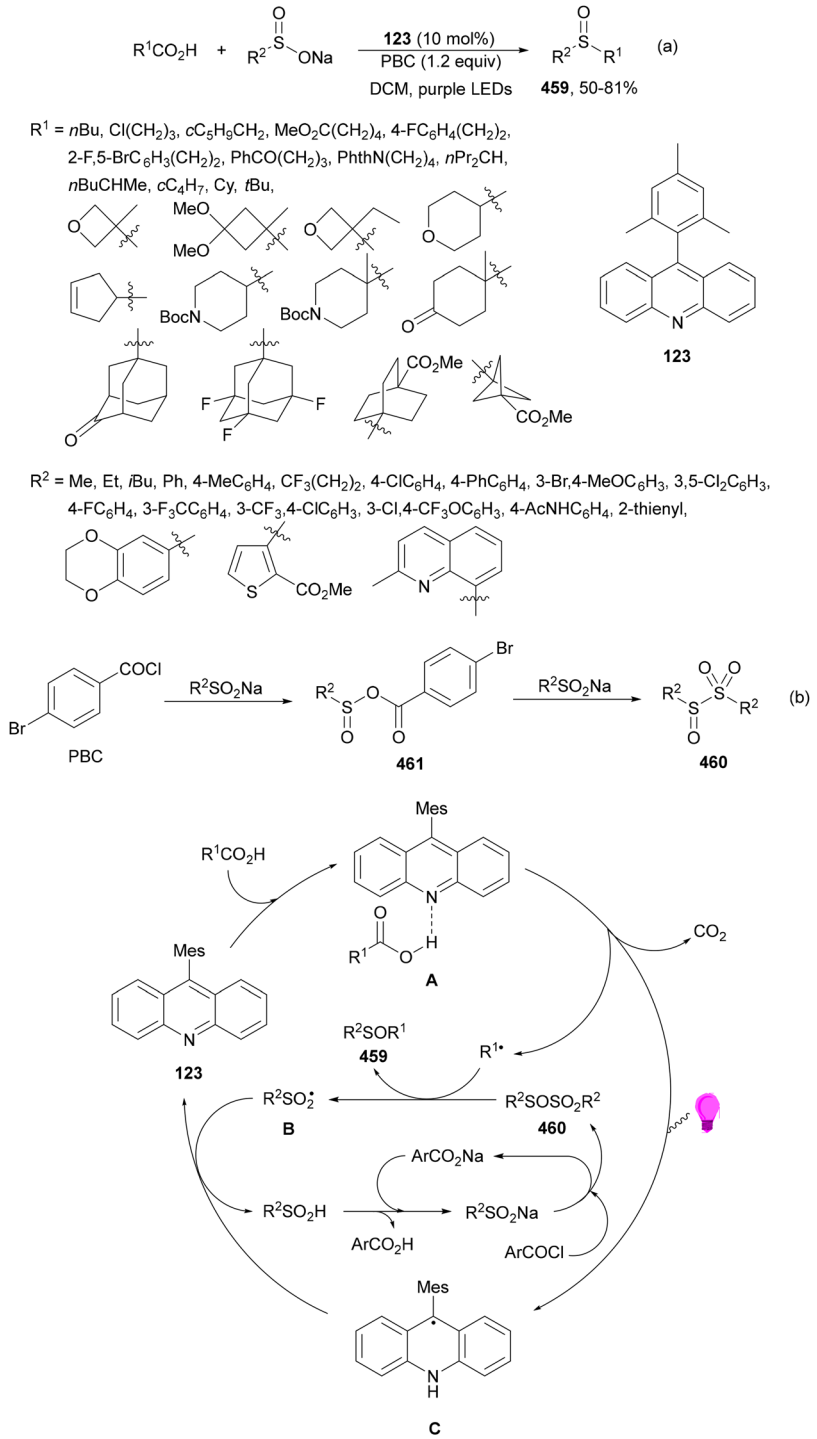
the presence of Ir complex **4** as a PC, K_3PO_4 as a base in a 2 : 1 MeCN/DCM mixture at room temperature under blue LED irradiation (Scheme 234). Primary and secondary alkyl esters were transformed into sulfonyl fluorides **471** with good yields. In the proposed mechanism, photoexcited PC* sensitizes the oxime esters **479** to the excited state **A** through a triple-triplet energy-transfer process. Subsequent homolysis of the N–O bond affords the iminyl radical **B** and the alkyl radical **C** by releasing CO_2. Radical **C** is trapped by SO_2 to deliver the alkylsulfonyl radical **D**, which is captured by NFSI through the FAT process to give the sulfonyl fluoride **471**.

Copper LMCT[54,55] has been employed by MacMillan and co-workers[433] for the synthesis of sulfonyl fluorides **471** and chlorides **470** from aromatic and heteroaromatic carboxylic acids. Decarboxylative fluorosulfonylation was carried out using $Cu(MeCN)_4BF_4$ (50 mol%), Selectfluor, a solution of SO_2 in MeCN under high intensity source of 365 nm LED irradiation to provide the corresponding sulfonyl fluorides **471** in 48–82% yields (Scheme 235a). This method was applied to late stage modification of drugs such as ataluren, lumacaftor and celebrex in 41–62% yields. In the case of sulfonyl chlorides **470**, apart from $Cu(MeCN)_4BF_4$ (20 mol%) and SO_2, 1-fluor-2,4,6-trimethylpyridinium tetrafluoroborate (NFTPT) as an oxidant and 1,3-dichloro-5,5-dimethylhydantoin (DCDMH) as a chlorine atom source were used (Scheme 235b). The resulting sulfonyl chlorides **470** were transformed into sulfonamides by adding morpholine and DIPEA to the crude reaction mixture after irradiation and removal of unreacted SO_2. The addition of $LiBF_4$ was beneficial to avoid the formation of the sulfonyl fluoride byproduct. The corresponding amine was then added and MeCN or THF was used as solvent providing sulfonamides **479** with 45–64% overall yields.



Scheme 224 Decarboxylative sulfilimination of alkyl NHPI esters **69** with sulfenamides **457** under Ir complex **52** and CuCl photocatalysis.

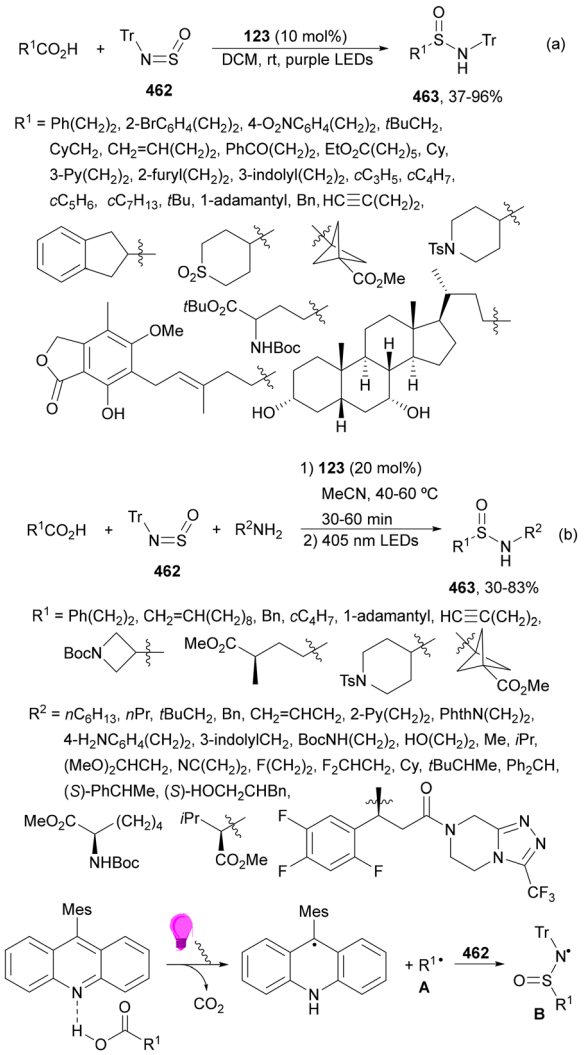
Larionov and co-workers[434] reported a direct amidosulfonylation of aliphatic carboxylic acids by *in situ* generation of sulfinic acids using acridine and Cu dual photocatalysis. In the presence of acridine **123**, DABSO (**465**), CuF_2 and *O*-benzylhydroxylamine as a ligand for aliphatic amines in DCM under 400 nm LED irradiation, the corresponding sulfonamides **479** were isolated in 50–92% yields (Scheme 236a). When aromatic or heteroaromatic amines were used, CuOTf, acridine **125**, DABSO (**465**) and *tert*-butyl perbenzoate as oxidants gave sulfonamides **479** in 51–91% yields (Scheme 236b). Sulfonyl azides **474** were prepared using copper 2-thiophene carboxylate (CuTC) and acridine **123** as catalysts in the presence of DABSO as a SO_2 source, $tBuO_2Bz$ as an oxidant and NaN_3 in a 3 : 1 mixture of $PhCF_3$/MeCN under 400 nm LED irradiation (Scheme 236c). Sulfonamides derived from chenodeoxycholic acid, aleuritic acid, gibberellic acid and carbohydrate derivatives as well as pinonic acid have been produced in 52–89% yields.



Scheme 225 Decarboxylative sulfinylation of aliphatic carboxylic acids with sodium sulfinates and PBC under acridine **123** photocatalysis.

Willis and co-workers[421] employed sulfinylamine TrNSO (**462**) for the synthesis of sulfinamides **463** (Scheme 226). When *N*-*t*-butoxysulfinamide (tBuONSO, **480**) was used as a sulfinamidation reagent, intermediate sulfinamides **481** were formed. Subsequent *in situ* transformation by hydrolysis with NaOH in IPA or an amine in toluene under MW irradiation at 90 °C, sulfonamides **479** or sulfonimidamides **482**, respectively, were isolated (Scheme 237a or b).

Aminosulfonylation of aromatic and heteroaromatic carboxyl oxime esters **454** under visible-light induced decarboxylation has been recently reported by Zhang, Yang and co-workers.[435] Working with Ir complex **4** as a PC, in the presence of DABSO (**465**) and NH_4Cl in MeCN under Ar and blue LED irradiation, the corresponding *N*-sulfonyl ketimines **483** were formed. These products were transformed into sulfonamides **479** by deprotection with 4 M HCl in dioxane at room temperature (Scheme 238).



Scheme 226 Decarboxylative sulfinamidation of alkyl carboxylic acids with TrNSO (**462**) under acridine **123** photocatalysis.

This procedure was applied to the large-stage modification of drugs and natural products such as acipimox, dehydrochlolic acid, fusaric acid, a picolinafen intermediate and a PHA-543613 (selective α7-nAChR) intermediate, sorafenib and flazasulfuron.

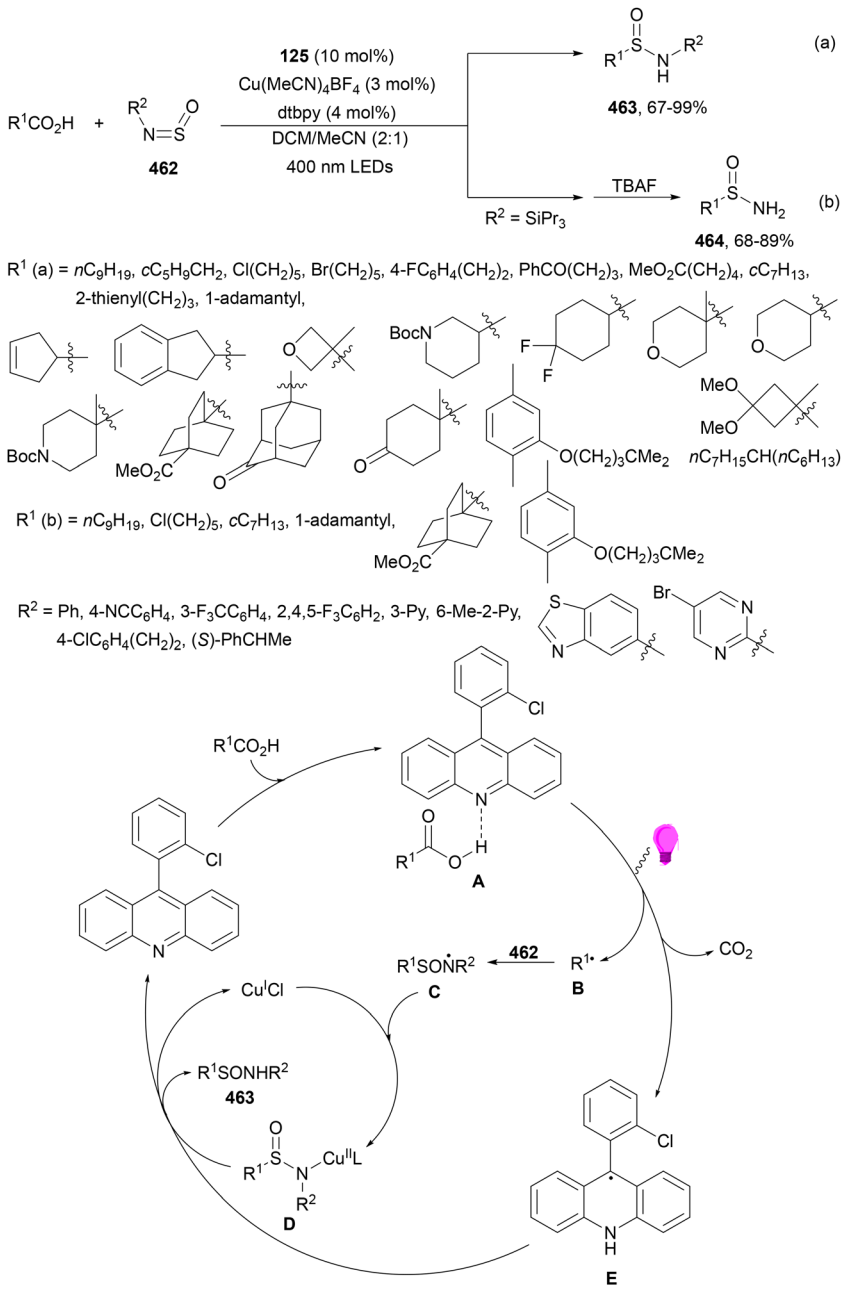
Chen, Wu and co-workers[436] performed a similar aminosulfonylation of aliphatic and aromatic carboxylic oxime esters **454** derived from benzophenone using 4,4-dimethoxybenzophenone as a PC. When the reaction was carried out in MeCN at 40–50 °C under N_2 and 390 nm Kessil lamp irradiation, the corresponding *N*-sulfonyl ketimines **483** were isolated in 28–77% yields (Scheme 239a), whereas in the presence of NH_4Cl resulted in sulfonamides **479** in 46–95% yields (Scheme 239b). Both procedures were applied to natural products and drugs such as stearic acid, α-tocopheryl succinate and dehydrochlolic acid.

As a summary of Section 3.3, acridine-photocatalyzed thiolations have been employed for alkyl carboxylic acids using thionocarbonates or a more economical elemental sulfur. In the case of alkyl NHPI esters, Eosin Y-$Na_2$was used as a PC and 4-methoxybenxylamide as a sulfur source. Recent thioetherification of aliphatic carboxylic acids has been performed with trisulfide dioxides, thionosulfonates and a perfluorinated disulfide. The most sustainable method used $Fe(NO_3)_2$ as a LMCT catalyst not only for aliphatic but also for heteroaromatic carboxylic acids for the thioetherification with thiosulfonates. Aliphatic NHPI esters have been recently transformed into thiocyanates under Ir photocatalysis. Xanthylation photodecarboxylative processes have been used for thioesterification of carboxylic acids and benzophenone oxime esters. Sulfilimination of alkyl NHPI esters have been recently described under Ir and Cu dual photocatalysis using sulfenamides. Direct sulfinylation of aliphatic carboxylic acids has been achieved with sodium sulfinates and *p*-bromobenzoyl chloride, which generates *in situ* the sulfinyl sulfone. Acridine-photocatalyzed reaction provides the corresponding sulfoxides. Sulfinamidation of aliphatic carboxylic acids can be performed using sulfinylamine reagents RNSO and acridine as photocatalysts. Sulfonation of aliphatic carboxylic acids to give sulfones employed DABSO as a source of SO_2 and acridines or $TBAFeCl_4$ as PCs. In the case of vinyl sulfones decarboxylative sulfonylation of cinnamic acids used aryl sulfonate phenol ethers without a PC. When arylsulfonyl azides, TosMIC or β-keto sulfones were used as sulfonylating reagents, vinyl aryl sulfones can also be prepared with rhodamine or Eosin Y as PCs. Fluorosulfonylation of aliphatic carboxylic acids has been carried out with DABSO and *N*-fluorobenzene sulfonamide using acridine as a PC or with Selectfluor with acridine and copper. Amidosulfonylation of carboxylic acids employed DABSO, Cu salts and acridines as PCs. *N*-*t*-Butoxy sulfinamide can also be used in the presence of amines.

3.4. Carbon–nitrogen bond-forming reactions

Decarboxylative C–N bond formation has been achieved by amination of aliphatic carboxylic acids and NHPI esters with aliphatic, aromatic and heteroaromatic amines. Amidation has been reported with sulfonamides, sulfoximines ureas and isocyanates, and by amination of α-keto acids. Other reactions used azides, nitro compounds, nitrites, diaziridines and azodicarboxylates delivering C–N and C=N bonds.

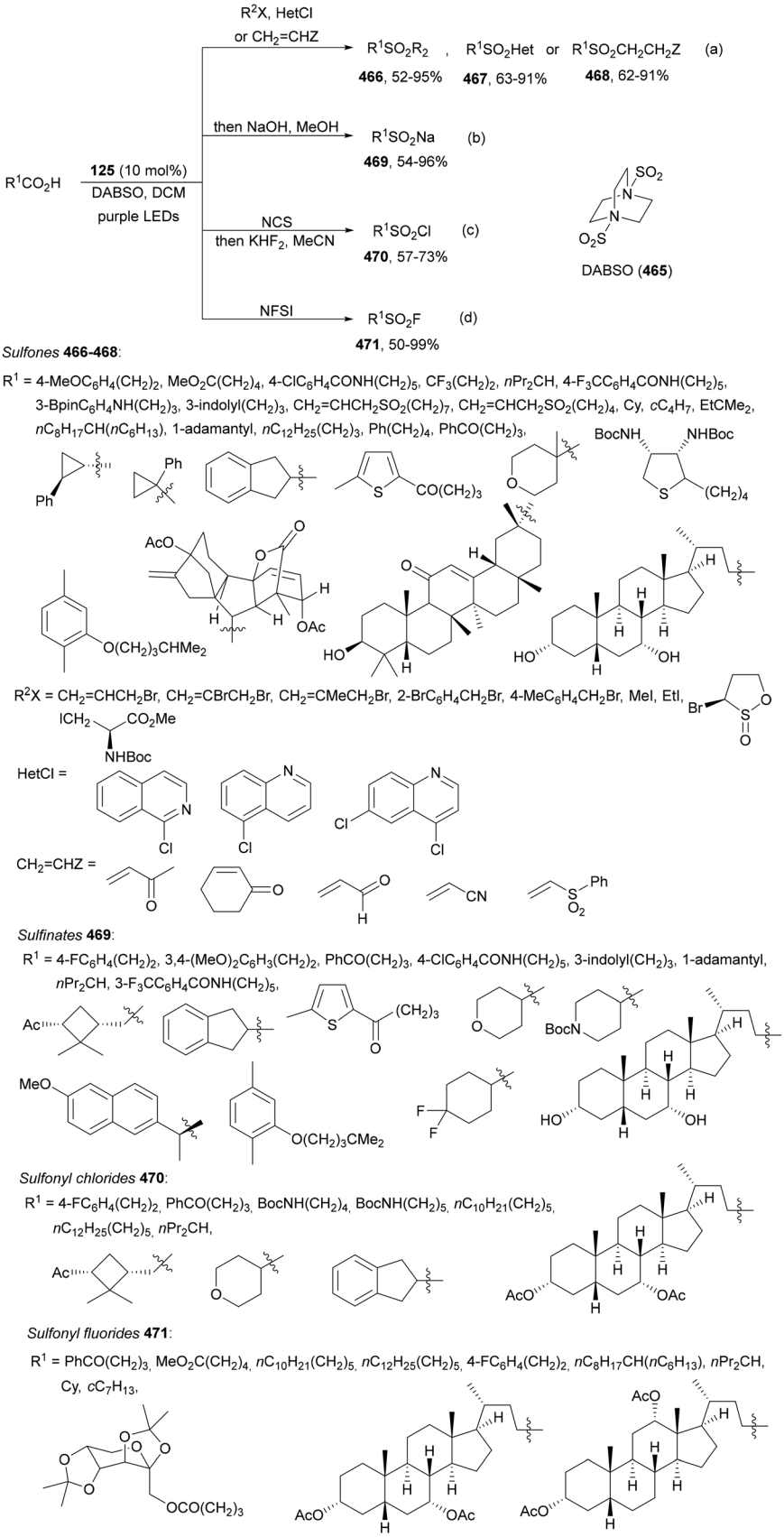
3.4.1. Amination. Amination of aliphatic carboxylic acids was described in 2018 by MacMillan and co-workers[437] using Ir complex **244** and BphenCuTC under dual photocatalysis. This procedure needed the preformed activation of carboxylic acids with $MesI(OAc)_2$ forming the corresponding iodine(III) carboxylates. They employed nitrogen heterocycles including indazoles, azaindoles, indoles, pyrazoles, pyrroles, imidazoles, triazoles, benzimidazoles, benzotriazoles, purines and carbazoles. In addition, other nucleophiles such as anilines, sulfonamides, amides, phthalimides and cyclic carbamates were also used. In 2020, Larionov and co-workers[438] described the direct *N*-alkylation with similar nitrogenated compounds using acridines **123** and **125**, and $Cu(hfac)_2$ under dual photocatalysis in the presence of di-*tert*-butyl peroxide (DTBP) as an oxidant. They proposed the already mentioned proton-coupled electron transfer (PCET) process based on experimental and theoretical studies.



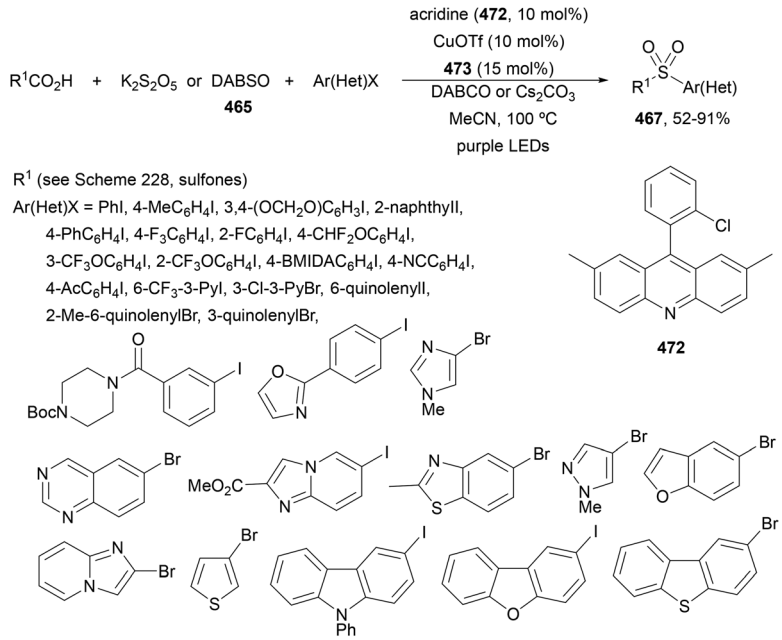
Scheme 227 Decarboxylative sulfinamidation of alkyl carboxylic acids with RNSO (**462**) under acridine **125** and $Cu(MeCN)_4PF_4$ photocatalysis.

The direct decarboxylative *N*-alkylation of aliphatic carboxylic acids under $Ru(dtbbpy)_3(PF_6)_2$ (**429**) photocatalysis in the presence of hypervalent iodine reagent **428** was described by Terrett and co-workers.[439] Similar reaction conditions were previously applied to etherification of carboxylic acids (Scheme 209).[389] A wide range of azoles were alkylated with primary, secondary and tertiary aliphatic carboxylic acids in DCE/HFIP (2 : 1) at room temperature under visible-light irradiation to give products **484** with good yields (Scheme 240).

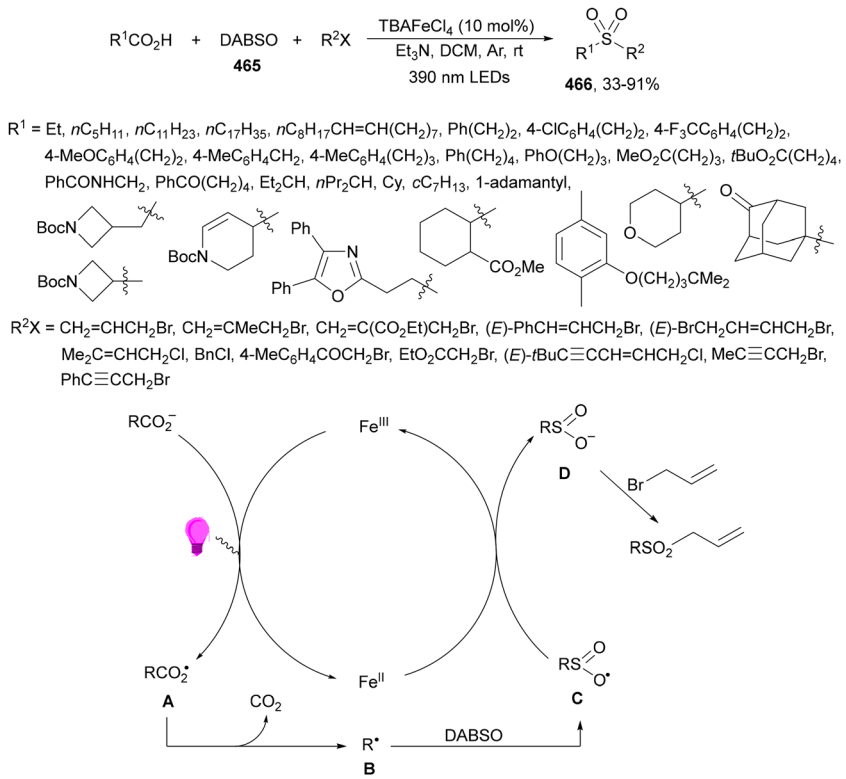
Photoinduced iron/copper dual catalysis was applied to C–C bond formation by decarboxylative Giese reaction of carboxylic acids and electron-deficient alkenes (Scheme 2).[53] These reaction conditions were applied to form C–N bonds by amination of carboxylic acids. In the presence of $Fe(OAc)_2$ and $Cu(acac)_2$ with DTBP as an oxidant, DBU as a base in EtOAc at room temperature under N_2 and purple LED irradiation, the corresponding amines were obtained in moderate to very good yields (Scheme 241). Aromatic amines were alkylated by decarboxylation of primary, secondary and tertiary aliphatic carboxylic acids. In the proposed mechanism, in the iron catalytic cycle, Fe(II) is oxidized to Fe(III) in the presence of DTBP and DBU. Then, the LMCT process under 390 nm irradiation generates $R^1CO_2^\bullet$ (**A**) and subsequently $R^{1\bullet}$ after decarboxylation. In the Cu catalytic cycle, the amine and Cu(II) forms intermediate **B** after deprotonation with DBU. This species **B** is trapped by radical $R^{1\bullet}$ to form an alkyl Cu(III) species **C**, which after reductive



Scheme 228 Decarboxylative sulfonylation of aliphatic carboxylic acids with DABSO (**465**) under acridine **125** photocatalysis.



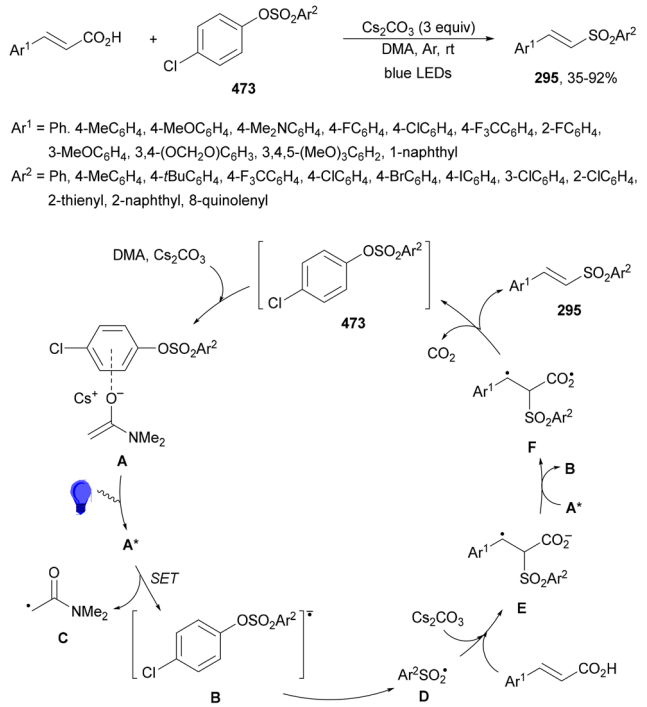
Scheme 229 Decarboxylative sulfonylation of aliphatic carboxylic acids with DABSO (**465**) under acridine **472** and CuOTf dual photocatalysis.



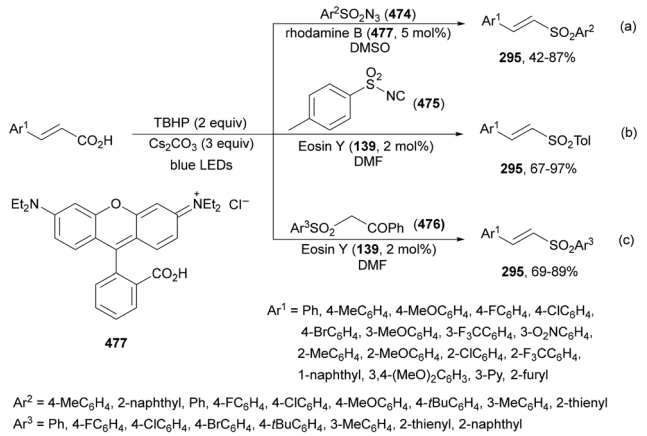
Scheme 230 Decarboxylative sulfonylation of aliphatic carboxylic acids with DABSO under $TBAFeCl_4$ photocatalysis.

elimination formed the product and Cu(I). In the last step, Cu(I) is oxidized by DTBP to Cu(II).

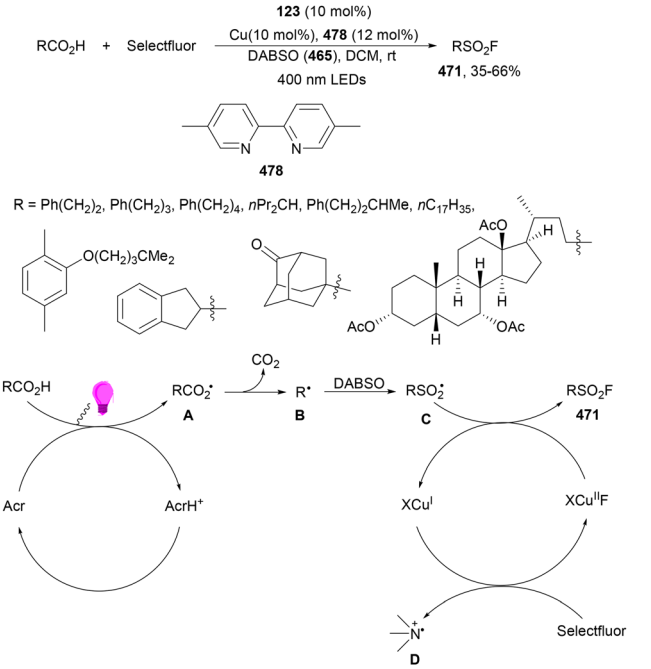
Yoon and co-workers[295] employed 3 equivalents of $FeCl_3$ for the amination of flurbiprofen with aliphatic and aromatic amines. In this case, the amine should be added once to the reaction mixture and irradiated with 427 nm blue LEDs in order to avoid binding of the amine with $FeCl_3$. This salt acted as a PC through the LMCT process and also as a terminal oxidant. Working in the presence of Na_3PO_4 as a base in MeCN at room temperature, the corresponding amines, including imidazole, were obtained in 59–94% yields (Scheme 242).



Scheme 231 Decarboxylative sulfonylation of cinnamic acids with aryl sulfonate phenol esters **473** under photocatalysis.



Scheme 232 Decarboxylative sulfonylation of cinnamic acids with sulfonylazides **474**, tosyl metyl isocyanide **475** and β-keto sulfones **476** under rhodamine B (**477**) or Eosin Y (**139**) photocatalysis.



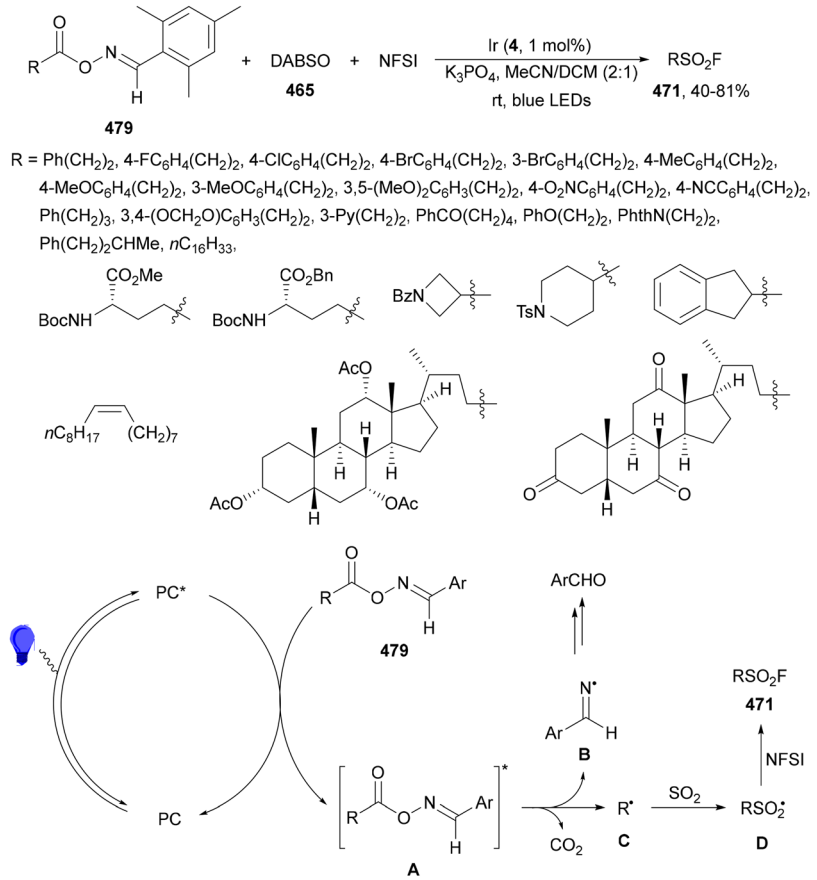
Scheme 233 Decarboxylative fluorosulfonylation of aliphatic carboxylic acids with selectfluor and copper under photocatalysis.

Decarboxylative amination of alkyl NHPI esters **69** was described in 2018 by Hu and co-workers[440] using $Ru(bpy)_3(PF_6)_2$ (10 mol%) and CuBr (20 mol%) as catalysts under blue LED irradiation. Alkyl NHPI esters and primary anilines gave the corresponding products in 28–96% yields. When benzophenone-derived imines were employed as nucleophiles and Ir complex **4** and $Cu(MeCN)_4PF_6$ as catalysts even hindered alkyl NHPI esters were iminated with 36–99% yields.[441] This process can also be carried out under metal-free conditions using 4CzIPN (**25**) as a PC.[442]

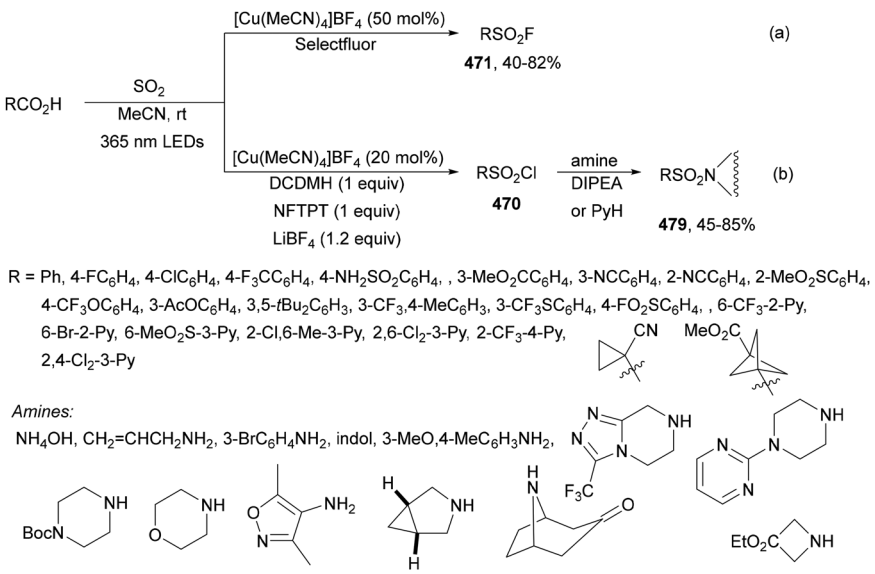
Li, Guan and co-workers[392] described not only etherification reactions with NHPI esters **69** (see Scheme 210), but also amination with indoles, indazoles and azaindoles using NaI-PPh_3 and CuBr as a dual metallaphotoredox catalytic system (Scheme 243). The resulting alkylated heterocyclic amines were obtained with excellent yields working with BTMG as a base, in dioxane at room temperature under blue LED irradiation. Mechanistic proposal is depicted in Scheme 210 for the etherification process.

Decarboxylative *N*-alkylation of azoles with NHPI esters **69** has been carried out with *N*-phenylbenzo[*b*]phenothiazine (PTH, **484**)[443] as an organophotoredox catalyst. Ohmiya and co-workers[444] performed this amination in the presence of the pyridinium salt of 2,4,6-collidine (**485**) in DCE under blue LED irradiation to give the corresponding *N*-alkylated azoles in moderate to good yields (Scheme 244). The proposed mechanism for this radical-polar crossover starts with the formation of a charge-transfer complex **A** between the phenothiazine (PTH) and the NHPI ester. Irradiation induces SET from PTH to ester affording radical cation species from PTH **B** and the radical anion of NHPI ester **C**. In the presence of collidine/HBF_4, **C** generates an alkyl radical **D** after CO_2, $PhthN^-$ and collidine release. Combination of **B** and **D** through SET affords alkylsulfonium intermediate **E**, which reacts with azole to give the product and regenerate **485** and PTH **484**.

Glycosyl NHPI esters **405** have been used by Yang, Li and co-workers[445] for the synthesis of nucleoside analogues under Ir/Cu photoredox conditions. This reaction was performed with $Ir(ppy)_3$ complex **89** and $Cu(MeCN)_4PF_6$ as a catalyst and Et_3N as a base at room temperature in MeCN under blue LED irradiation. Different nucleobase derivatives were used as nucleophiles to provide the corresponding nucleoside analogues in 40–74%

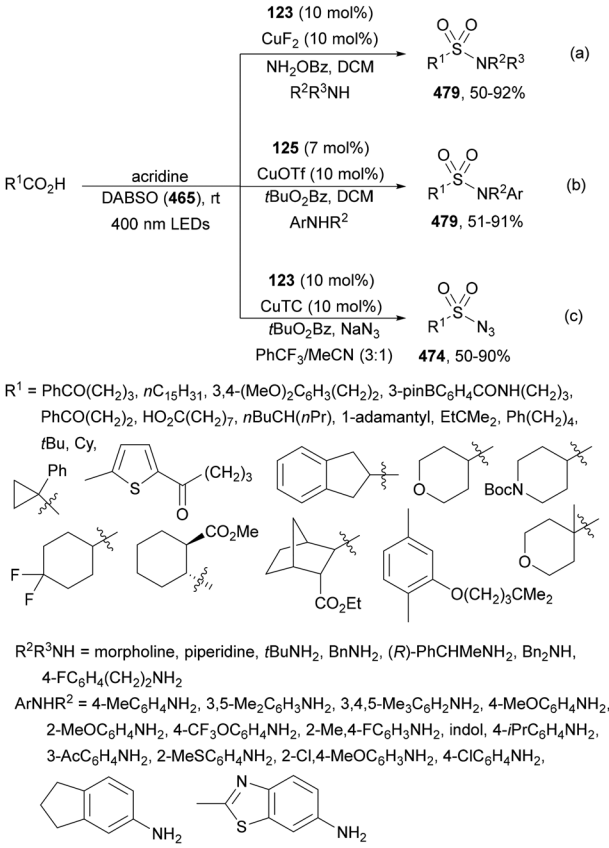


Scheme 234 Decarboxylative fluorosulfonylation of aldoxime esters **479** with DABSO (**465**) and NFSI under Ir **4** photocatalysis.

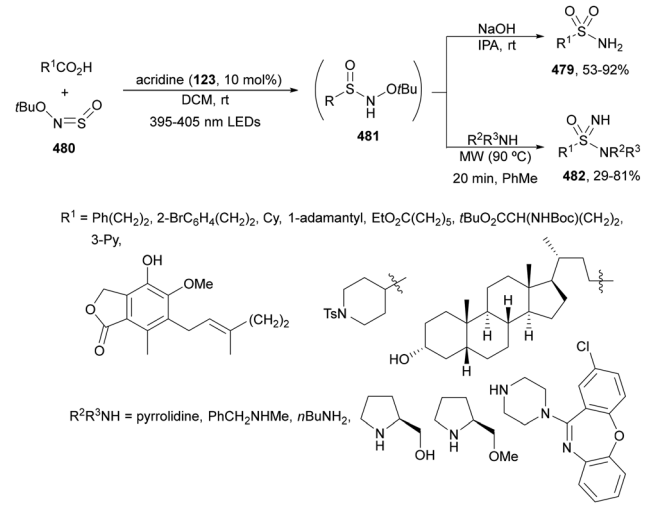


Scheme 235 Decarboxylative fluoro- and chlorosulfonylation of aromatic and heteroaromatic carboxylic acids under Cu LCTM photocatalysis.

yields (Scheme 245). This method was applied to the total synthesis of the acid-labile oxetanocin A, a natural product isolated from *Bacillus megaterium*, which exhibits inhibitory activity against a wide range of viruses including HIV and HBV.[446] Bristol-Myers-Squibb developed the broad-spectrum antiviral agent lobucavir based on oxetanocin A structure.



Scheme 236 Decarboxylative amido- and azidosulfonylation of aliphatic carboxylic acids using DABSO (**465**) under dual acridine/Cu photocatalysis.



Scheme 237 Decarboxylative sulfinamidation of aliphatic carboxylic acids with *t*BuONSO (**480**) under acridine photocatalysis followed by hydrolysis or aminolysis.

3.4.2. Amidation. This decarboxylative C–N bond formation can be achieved not only with carboxamides, ureas and carbamates, but also with sulfonamides, sulfoximines, and isocyanates. In the case of α-keto acids, cinnamic acids and oxamic acids, amines were used as nucleophiles.

In the case of carboxylic acids, Terrett and co-workers[439] applied similar reaction conditions already described for azoles (Scheme 240), for ureas, carbamates and sulfonamides. 6-MeO-2-naphthyl-1-ethanecarboxylic acid reacted with these nucleophiles in the presence of iodine(III) reagent **428** as an oxidant of the benzylic radical intermediate to a carbocation by Ru **429** as **a** PC (Scheme 209). The resulting products were obtained with modest to good yields and in the case of Cbz-carbamate the subsequent hydrogenation step gives the primary amine in 45% yield after two steps (Scheme 246).

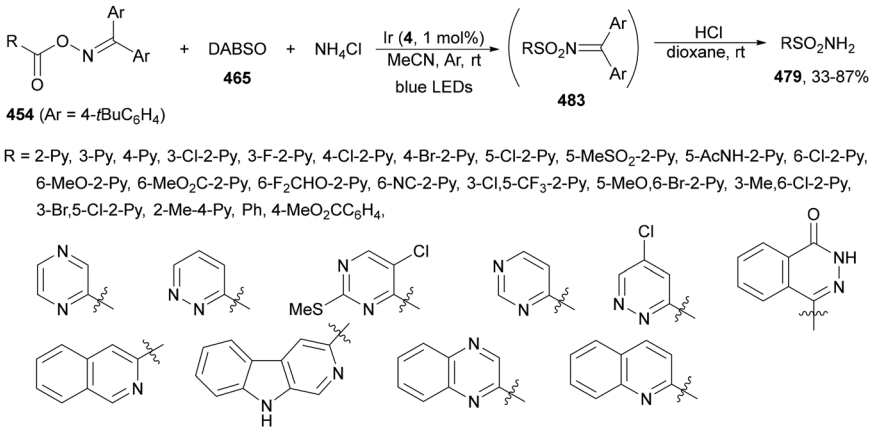
Yoon and co-workers[447] reported decarboxylative cross-coupling of carboxylic acids with sulfonamides, carboxamides and carbamates under copper-mediated visible-light irradiation (Scheme 247). Aliphatic secondary and tertiary carboxylic acids were amidated in the presence of 2.5 equivalents of $Cu(OTf)_2$, Na_3PO_4 as a base in MeCN at room temperature under blue LED irradiation to afford the corresponding products with, in general, very good yields. In this reaction a LMCT process[54,55] is operating, with Cu(II) carboxylate species being the chromophore.

Decarboxylative sulfonamidation of carboxylic acids was described by the same group[295] using 3 equivalents of $FeCl_3$ as in the case of amination reactions (see Scheme 242). In this case, different aliphatic carboxylic acids and sulfonamides were allowed to react under blue LED irradiation to give the corresponding *N*-alkylated sulfonamides with modest to high yields (Scheme 248).

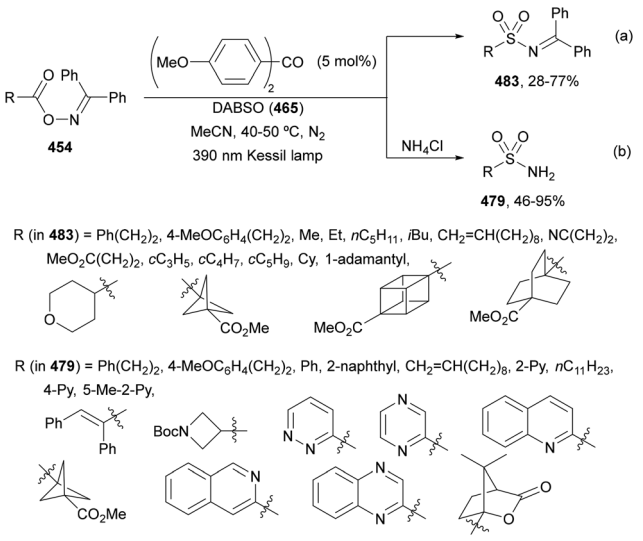
Sulfoximination of benzoic acids has been achieved by a photoinduced LMCT[54,55] process by Ritter and co-workers.[448] *N*-Arylated sulfoximines **488** were prepared by decarboxylative arylation of sulfoximines **487** with lithium benzoates in the presence of 2.5 equivalents of $Cu(OTf)_2$, LiOMe as a base, DTBP as an oxidant in MeCN at 35 °C under purple LED irradiation (Scheme 249). Enantiopure sulfoximines gave the corresponding *N*-arylated products **488a** and **488b** without racemization. In the proposed mechanism, photoinduced LMCT of copper carboxylates **A** gives aryl carboxy radical intermediates **B**, which after decarboxylation affords aryl radicals **C**. Subsequent capture of **C** by copper generates the arylcopper(III) intermediate **D**. Final reductive elimination of **D** provides products **488** and Cu(I), which can be oxidized by DTBP regenerating Cu(II).

Decarboxylative amidation of α-keto acids with primary aliphatic and aromatic amines was performed by Lan, Lei and co-workers[449] in 2014 under $Ru(phen)_3Cl_2$ visible-light photocatalysis. The same amidation was further carried out in the absence of PC by Xu and co-workers[450] under an O_2 atmosphere.

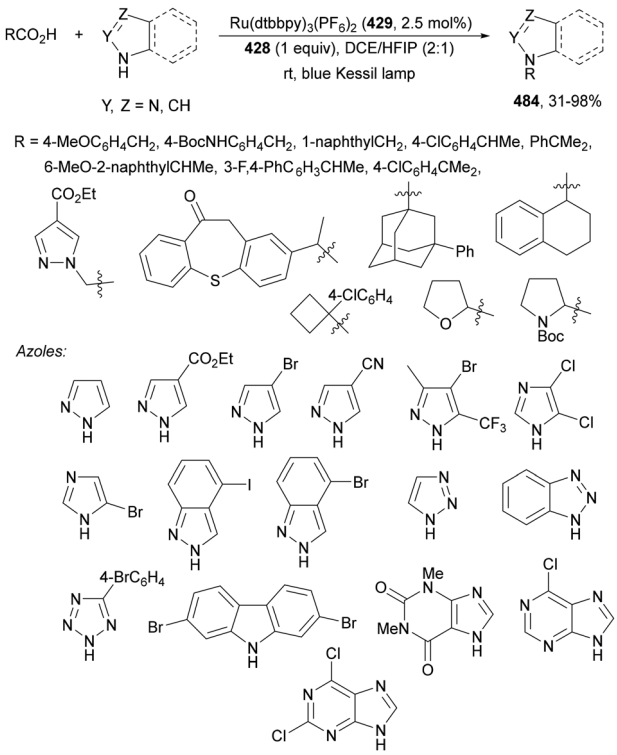
Landais and co-workers[398] reported the synthesis of ureas by decarboxylation of oxamic acids **15** in the presence of aliphatic primary amines. This amidation procedure was carried out with 4CzIPN (**25**) as a PC and BI-OAc as an oxidant in DCE at room temperature under blue LED irradiation followed by adding Et_3N as a base and the amine in the same reaction media (Scheme 250). In the first step, decarboxylation takes place to give the carbamoyl radical, which by oxidation generates intermediate isocyanate **162** (see Scheme 214). In the second step,



Scheme 238 Decarboxylative aminosulfonation of aromatic and heteroaromatic oxime esters **454** with DABSO (**465**) and NH_4Cl under Ir **4** photocatalysis.



Scheme 239 Decarboxylative aminosulfonylation of aliphatic and aromatic carboxylic oxime esters **454** with DABSO (**465**) under $(4\text{-}MeOC_6H_4)_2CO$ photocatalysis.

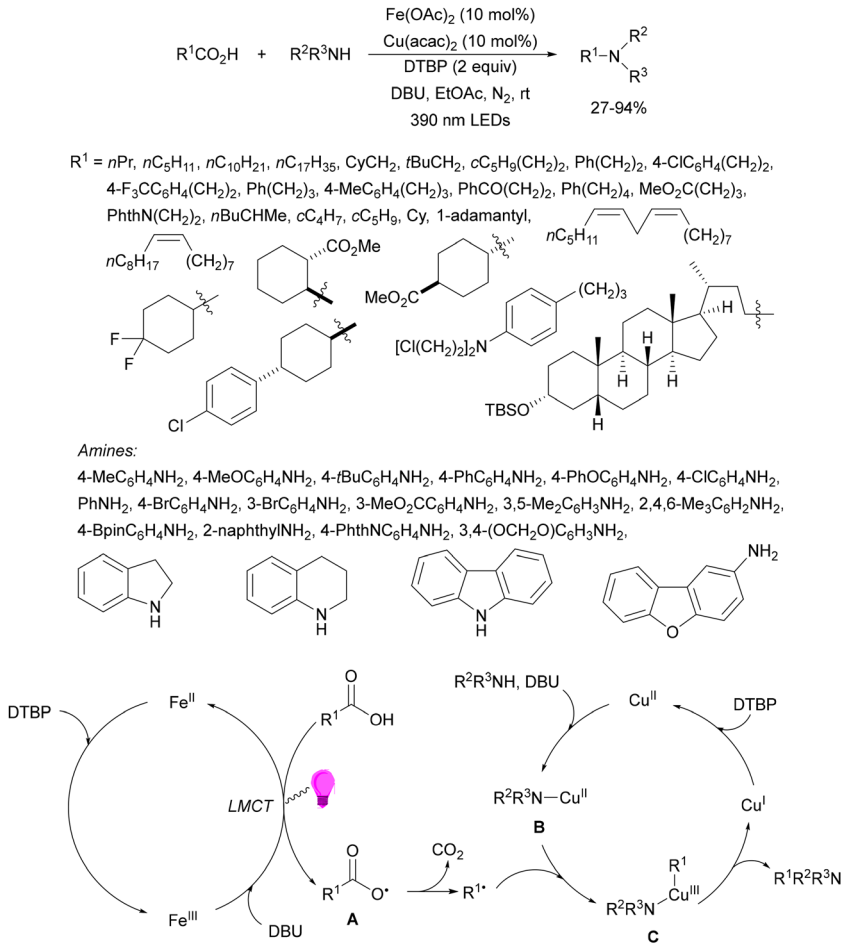


Scheme 240 Decarboxylative amination of aliphatic carboxylic acids with azoles under Ru **429** photocatalysis.

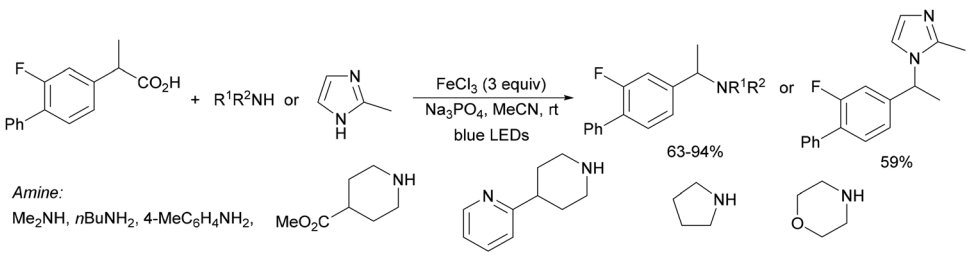
the amine was added and reacted with isocyanate to give the corresponding urea.

Decarboxylation of carboxylic acids under iron photocatalysis *via* a photoinduced LMCT[54,55] mechanism allowed the formation of alkyl radicals[210] (Schemes 110 and 127). When phenyl isocyanate **162** was employed as a radical acceptor, the corresponding amides were obtained in 43–97% yields (Scheme 251). In this case, the reaction was performed in the absence of ligand **298**.

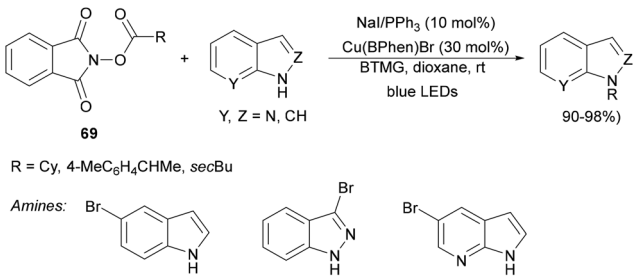
Midya, Ghosh and co-workers[451] recently reported an oxidative decarboxylative cross-coupling of α,β-unsaturated acids with aromatic amines under Ir/Pd dual photocatalysis. This α-ketoamidation took place with Ir complex **4** as a PC, $Pd(TFA)_2$ as a catalyst, K_2HPO_4 as a base in aqueous DMSO in open air at room temperature under 465 nm LED irradiation affording α-keto amides **489** with good yields (Scheme 252). In the photocatalytic cycle, Ir(III)* is reduced by a SET with cinnamic acid to generate a radical cationic species **A** and Ir(II). SET from Ir(II) to molecular oxygen promoted superoxide radical anion $O_2^{-\bullet}$ generation and regenerated an Ir(III) PC. Addition of water to species **A** in the presence of K_2HPO_4 forms the benzyl alcohol intermediate **B**. Oxidation of **B** by $O_2^{-\bullet}$ gives the β-keto radical species **C**, which by oxidative addition to Pd catalyst **D** forms the Pd(III) intermediate **E**. Subsequent SET of **D** by $O_2^{-\bullet}$ provides Pd(IV) intermediate **F** and peroxide O_2^{2-}. Reductive elimination of species **F** gives intermediate **G** with



Scheme 241 Decarboxylative amination of aliphatic carboxylic acids with amines and azoles under Fe and Cu photocatalysis.



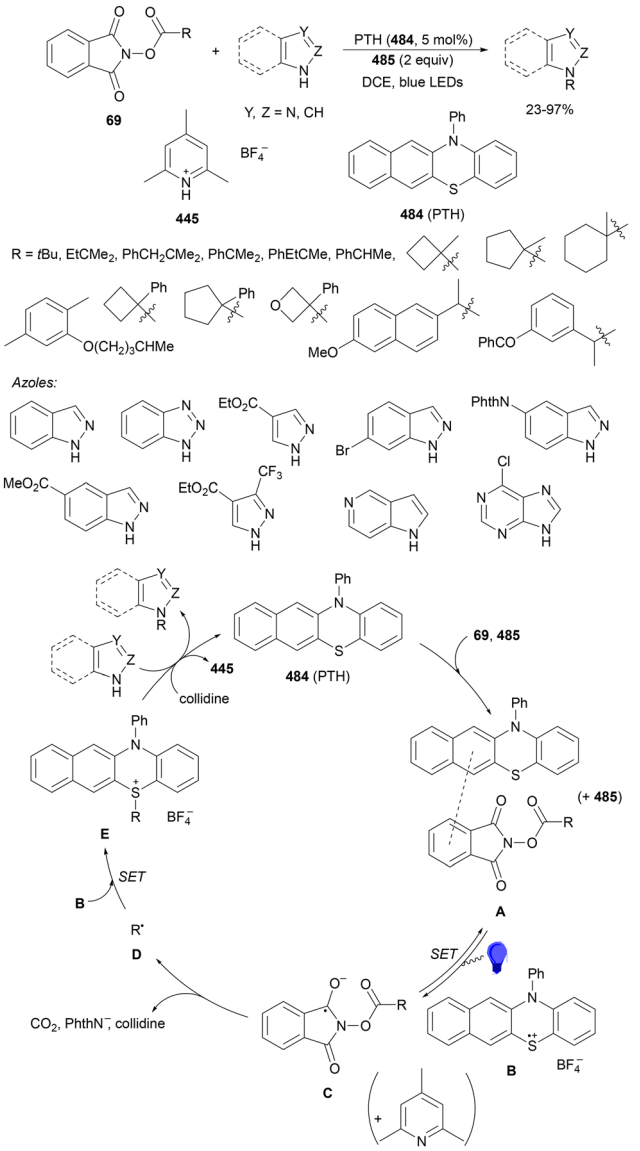
Scheme 242 Decarboxylative amination of flurbiprofen with amines in the presence of $FeCl_3$ photocatalysis.



Scheme 243 Decarboxylative amination of alkyl NHPI esters **69** with heterocyclic amines under NaI-PPh_3/CuBr photocatalysis.

autogeneration of precatalyst $Pd(TFA)_2$. Intermediate **G** undergoes decarboxylative protonation giving **H**, which by oxidation with O_2 forms imine **I** and $O_2^{-\bullet}$ addition gives **J**. Kornblum de la Mare rearrangement of **J** forms the keto amide **489**. This mechanism was supported through intermediate trapping and isotope labeling experiments.

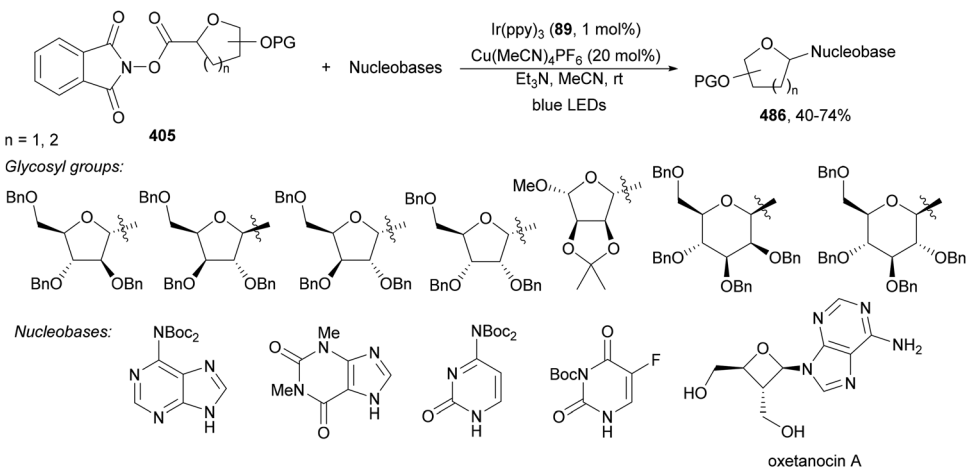
3.4.3. Other nitrogen nucleophiles. Photodecarboxylative azidation of cyclic AAs and tertiary alkyl carboxylic acids was described in 2019 by Leonori and co-workers[452] with 2,4,6-triisopropylphenylsulfonyl azide (**474**) in the presence of rhodamine 6G or Mes–Acr–Me ClO_4 (**301**) as a PC to provide the



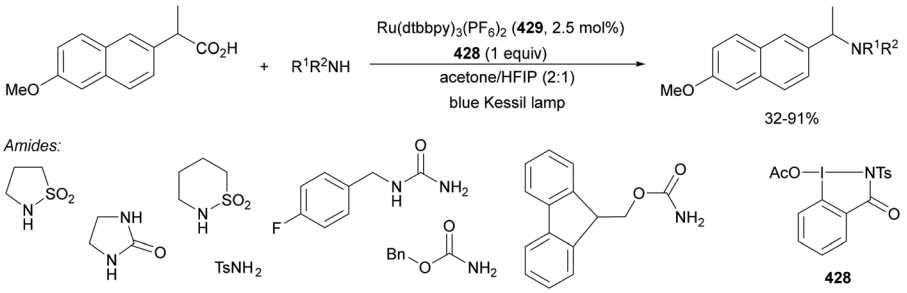
Scheme 244 Decarboxylative amination of NHPI esters **69** with azoles under PTH **484** and **485** photocatalysis.

corresponding azides in 46–90% yields. Recently, West and co-workers[453] performed the decarboxylative azidation of primary, secondary and tertiary aliphatic carboxylic acids with azidotrimethylsilane, Na_2CO_3 as a base in MeCN at room temperature under $Fe(NO_3)_3{\cdot}9H_2O$ LMCT photocatalysis (Scheme 253). The resulting azides were obtained in modest to good yields including late-stage azidation of *N*-Boc-Pro, ibuprofen, flurbiprofen, loxoprofen, naproxen, gemfibrozil, zaltoprofen and indomethacin. In the proposed conventional mechanism, after LMCT process generating the corresponding alkyl radical, it reacts with the iron-azide species by a radical-ligand-transfer (RLT) to deliver the products. Both releases Fe(II) species, from both steps, could be oxidized to Fe(III) by nitrogen oxide species from the nitrate counterion.

Decarboxylative amination with nitroarenes has been developed by Xie and co-workers.[454,455] Working with arylacetic acid and nitroarenes in the presence of 4CzIPN (**25**) as a PC and FeI_2/tetraphenylporphirin (TPP) as a catalyst, $(EtO)_3SiH$ as a reductant, and 2,6-lutidine as a base in MeCN at 65 °C under blue LED irradiation, the corresponding aromatic tertiary amines **490** were obtained with good yields (Scheme 254a).[454] In this case, the carboxylic acid and the nitroarene were used in a 3 : 1 molar ratio. Moreover, when two different arylacetic acids and a nitroarene were employed in a 3 : 3 : 2 molar ratio a three-component reaction provided non-symmetrical aromatic tertiary amines **491** with moderate yields (Scheme 254b).[454] However, when α-alkyl arylacetic acids were used, under similar reaction conditions, secondary aromatic amines **492** (Scheme 254c) were obtained. In the proposed mechanism, the alkyl radical **A** can be produced *via* either SET between the carboxylate ion and (4CzIPN)* or direct LMCT pathway. The reduction of nitroarenes with Fe(II) and $(EtO)_3SiH$ leads to nitrosoarene intermediate **B**, which reacts with radical **A** to form the Fe(III) complex **C**. Subsequently, intermediate **C** undergoes ligand exchange with the carboxylic acid to give **D** and **E**. Intermediate **E** is further reduced by Fe(II) and $(EtO)_3SiH$ to give the secondary aromatic amine **492**.[454]



Scheme 245 Decarboxylative amination of glycosyl NHPI esters **405** with nucleobases under Ir/Cu photocatalysis.

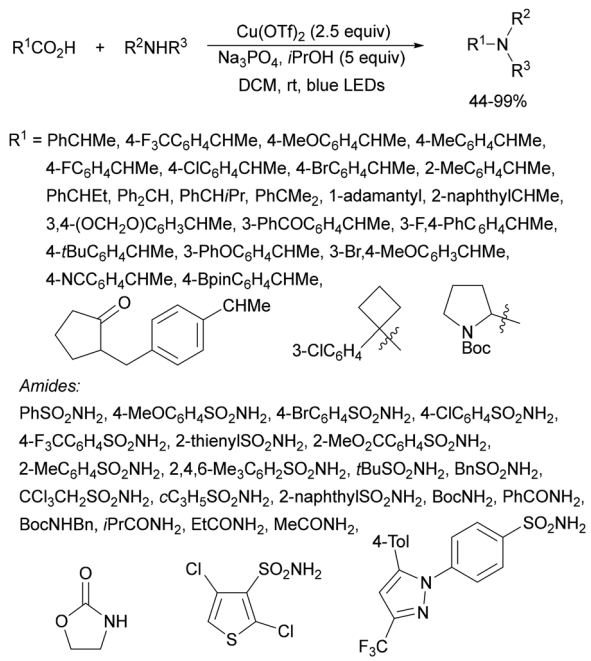


Scheme 246 Decarboxylative amidation of carboxylic acids with sulfonamides, ureas and carbamates in the presence of iodine reagent **428** under Ru **429** photocatalysis.

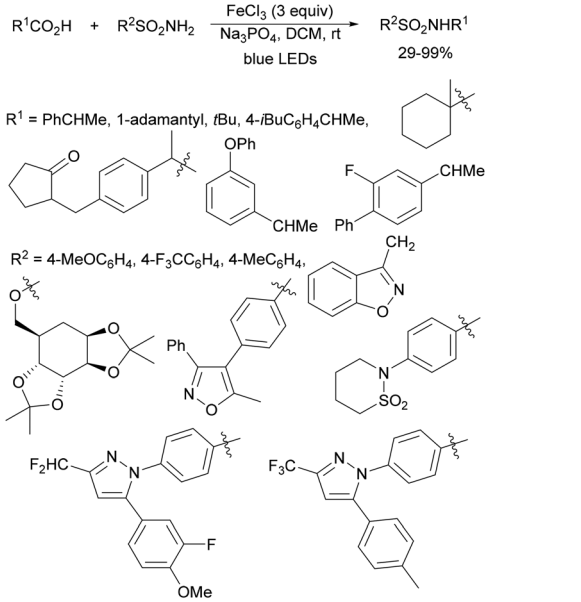
Xu and co-workers[456] reported an iron-catalyzed decarboxylative C–N coupling of alkyl carboxylic acids with sodium nitrite. In the presence of $Fe(NO_3)_3{\cdot}9H_2O$, AcOH (2 equivalents) in aqueous THF at room temperature under N_2 and 400 nm LED irradiation the corresponding oximes were obtained with very good yields (Scheme 255). This simple and efficient procedure seems to take place by initial ligand exchange of $Fe(NO_3)_2$ with $NaNO_2$ to give complex **A**, which forms complex **B** by reaction with the carboxylic acid. Photoexcitation of **B** involves a LMCT process to afford complex **C** and the carboxy radical **D**. Fe(II)NO_2 (**C**) leads to after irradiation Fe(II)NO^+ (**F**) in equilibrium with Fe(III)–NO (**G**). Subsequent NO releases from **G** and regenerates Fe(III)NO_3 (**A**). The alkyl radical **E** reacts with NO producing the nitroso compound **H**, which tautomerizes to the oxime product.

Diazirine **493** has been employed for the decarboxylative amination of alkyl NHPI esters **69** by Liao and co-workers.[457] A chemodivergent[381] transformation was achieved depending on the reaction conditions. Thus, working with Eosin Y-Na_2 (**139**), DIPEA as a base in *t*BuOH under Ar at room temperature and green LED irradiation, imines **494** were isolated in 31–86% yields (Scheme 256a). When DIPEA was replaced by Hantzsch ester (HE) and DME was used as solvent under blue LED irradiation, diaziridines **495** were formed in 36–92% yields (Scheme 256b). These experimental results were explained by the plausible mechanism depicted in Scheme 256. Eosin Y-Na_2 (**139**) is photoexcited to PC* and then is reductively quenched by DIPEA or HE through SET processes affording $PC^{-\bullet}$. This $PC^{\bullet-}$ reduces NHPI ester **69** to **A** by SET followed by N–O scission and CO_2 release to give the alkyl radical **B**. Addition of **B** to **493** gives intermediate **C**, which dimerizes to form tetraazo intermediate **D**. Subsequently, **D** undergoes N_2 extrusion to produce two molecules of imine **494**. On the other hand, intermediate **C** abstracts a hydrogen from $HE^{+\bullet}$ to give diaziridine **495**.

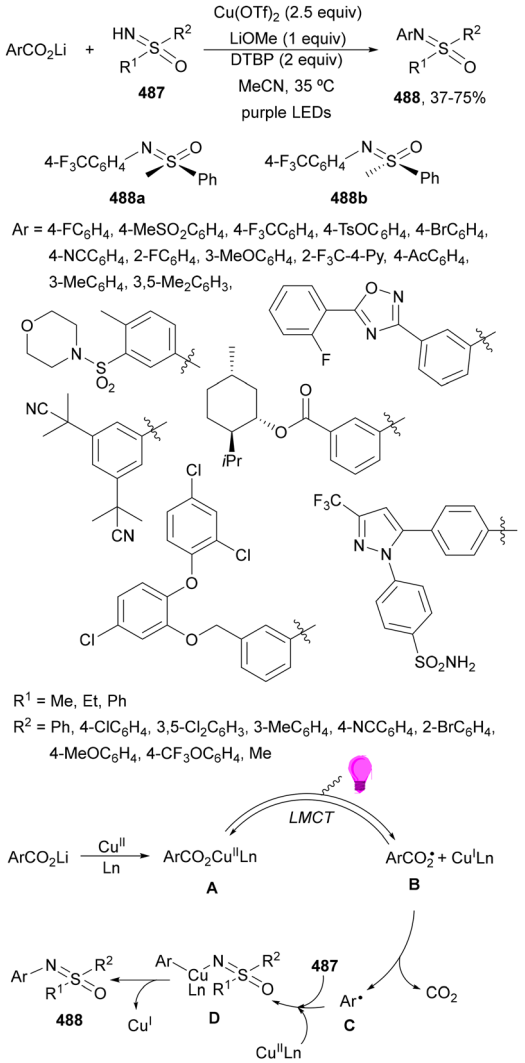
Photoredox decarboxylative hydrazination has been carried out by addition of alkyl radicals of aliphatic carboxylic acids to azodicarboxylates.[458–462] Wang and co-workers[463] have reported



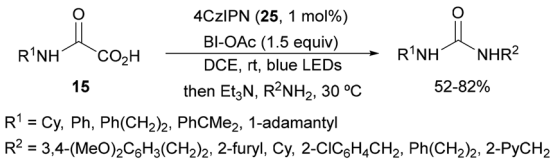
Scheme 247 Decarboxylative amidation of aliphatic carboxylic acids with sulfonamides, carboxamides and carbamates under $Cu(OTf)_2$ photocatalysis.



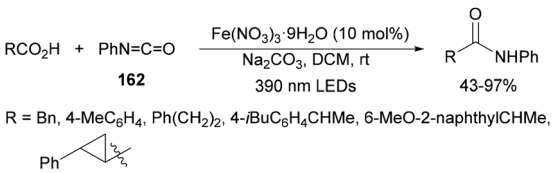
Scheme 248 Decarboxylative sulfonamidation of aliphatic carboxylic acids under $FeCl_3$ photocatalysis.



Scheme 249 Decarboxylative sulfoximination of lithium benzoates with sulfoximines **487** under $Cu(OTf)_2$ photocatalysis.



Scheme 250 Decarboxylative amidation of oxamic acids **15** with primary aliphatic amines under 4CzIPN (**25**) and BI-OAc photocatalysis.



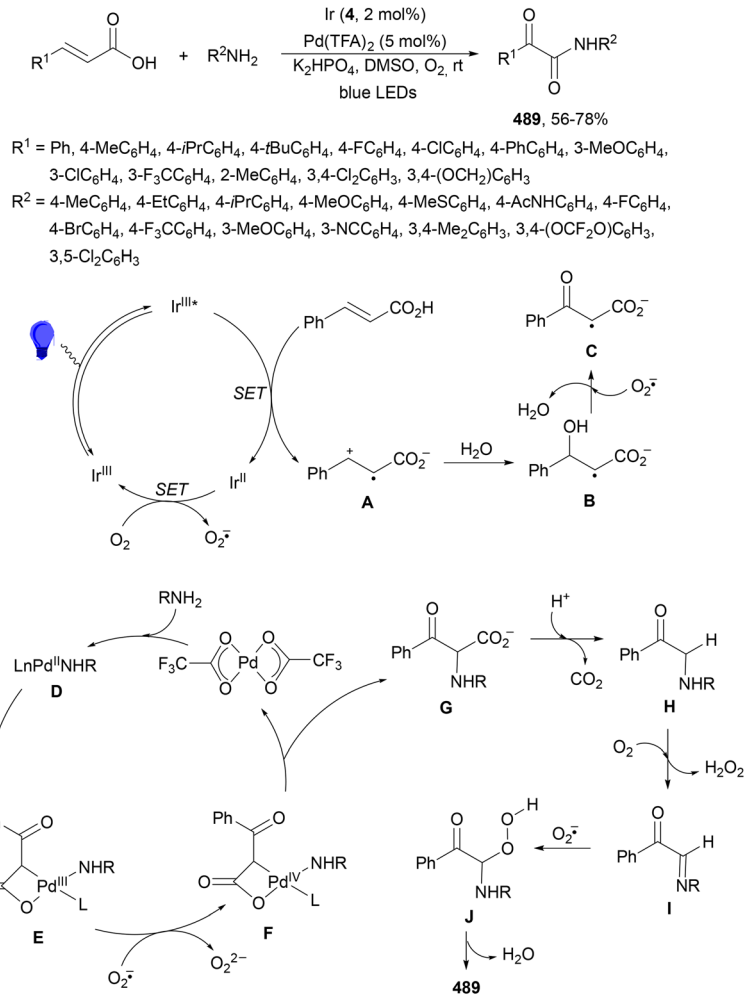
Scheme 251 Decarboxylative amidation of aliphatic carboxylic acids with phenyl isocyanate **162** under $Fe(NO_3)_3$ photocatalysis.

the addition of *N*-aryl glycines to symmetrical azobenzenes using methylene blue (MB, **496**) as a PC in MeCN at room temperature under air and blue LED irradiation providing 1,2,4-triaryl-1,2,4-triazolidines **497** with modest to very good yields (Scheme 257). In the case of unsymmetrical azobenzenes, the corresponding thiazolidines **498** were obtained in good yields under the same reaction conditions (Scheme 257b). The proposed mechanism for this decarboxylative addition/cyclization process starts by photoexcitation of MB^+ to MB^{+*}, which promotes the oxidative decarboxylation of *N*-phenyl glycine to produce the aminomethyl radical **A** and $MB^{\bullet}$. Then, addition of **A** to azobenzene gives radical **B**, which couples with another radical **A** to form intermediate **C**. Subsequent protonation of **C** gives intermediate **D**, which after releasing an aniline molecule forms iminium cation **E**. Intramolecular cyclization of **E** and deprotonation provides product **497**. In the case of $MB^{\bullet}$, after oxidation by O_2 is back to MB^+ generating superoxide radical $O_2^{-\bullet}$. This $O_2^{\bullet-}$ combines with a proton to give the hydroxyperoxyl radical ($HOO^{\bullet}$), which abstracts a proton from *N*-phenyl glycine to form H_2O_2. Alternatively, oxidation of *N*-phenyl glycine by photoexcited azobenzene, generated by energy transfer between azobenzene and MB^{+*}, cannot be ruled out.

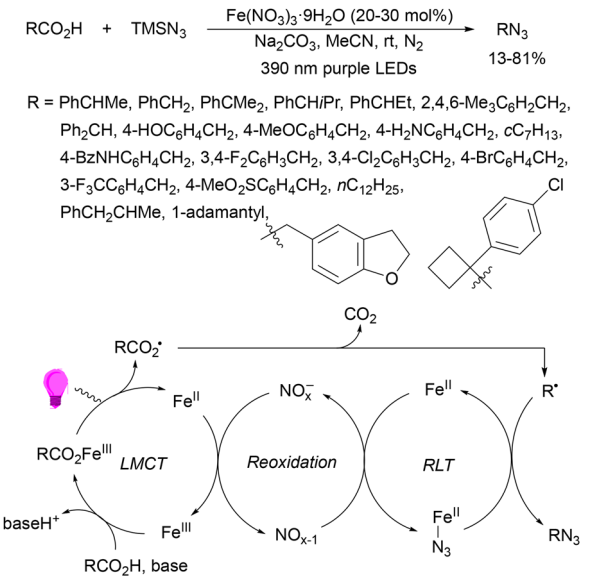
Recent progress in decarboxylative amination reactions of aliphatic carboxylic acids used $Fe(OAc)_2/Cu(acac)_2$ and DTBP as an oxidant with aromatic and heteroaromatic amines. Aliphatic amines are used by $FeCl_3$-mediated decarboxylation of arylacetic acids. In the case of NHPI esters, amination with heteroaromatic amines can be carried out under NaI-PPh_3 and CuBr photocatalysis. A benzophenothiazine (PHT) can also be used as an organophotoredox catalyst with a broad range of azoles. Glycosyl NHPI esters react with nucleobases under dual Ir/Cu photocatalysis. Decarboxylative amidation of aliphatic carboxylic acids has been performed by LMCT processes mediated by $Cu(OTf)_2$ or $FeCl_3$ and sulfonamides, ureas, carbamates and sulfoximines. Recent amination of oxamic acids with amines to the corresponding ureas is carried out under 4CzIPN and BI-OAc photocatalysis. Aliphatic carboxylic acids can be transformed into carboxamides using phenyl isocyanate under $FeCl_3$ photocatalysis. Amidation of cinnamic acids with aromatic amines under Ir/Pd dual photocatalysis provides α-keto amides. Other nucleophiles such as trimethylsilyl azide and nitroarenes have transformed aliphatic acids into azides and arylamines, respectively, under Fe photocatalysis. In the case of sodium nitrite, the corresponding oximes are prepared also under Fe(III) nitrate LMCT photocatalysis. *N*-Aryl glycines react with azodicarboxylates under methylene blue photocatalysis forming triazolidines. Diaziridine derived from trifluoroacetophenone has been employed as a nucleophile with aliphatic NHPI esters under an Eosin Y-Na_2 organophotoredox catalyst to give either imines in the presence of DIPEA or *N*-alkyl diaziridines in the presence of Hantzsch ester.

3.5. Carbon-phosphorous bond-forming reactions

Decarboxylative C–P bond formation has been carried out with different phosphorous compounds such as chlorophosphines,



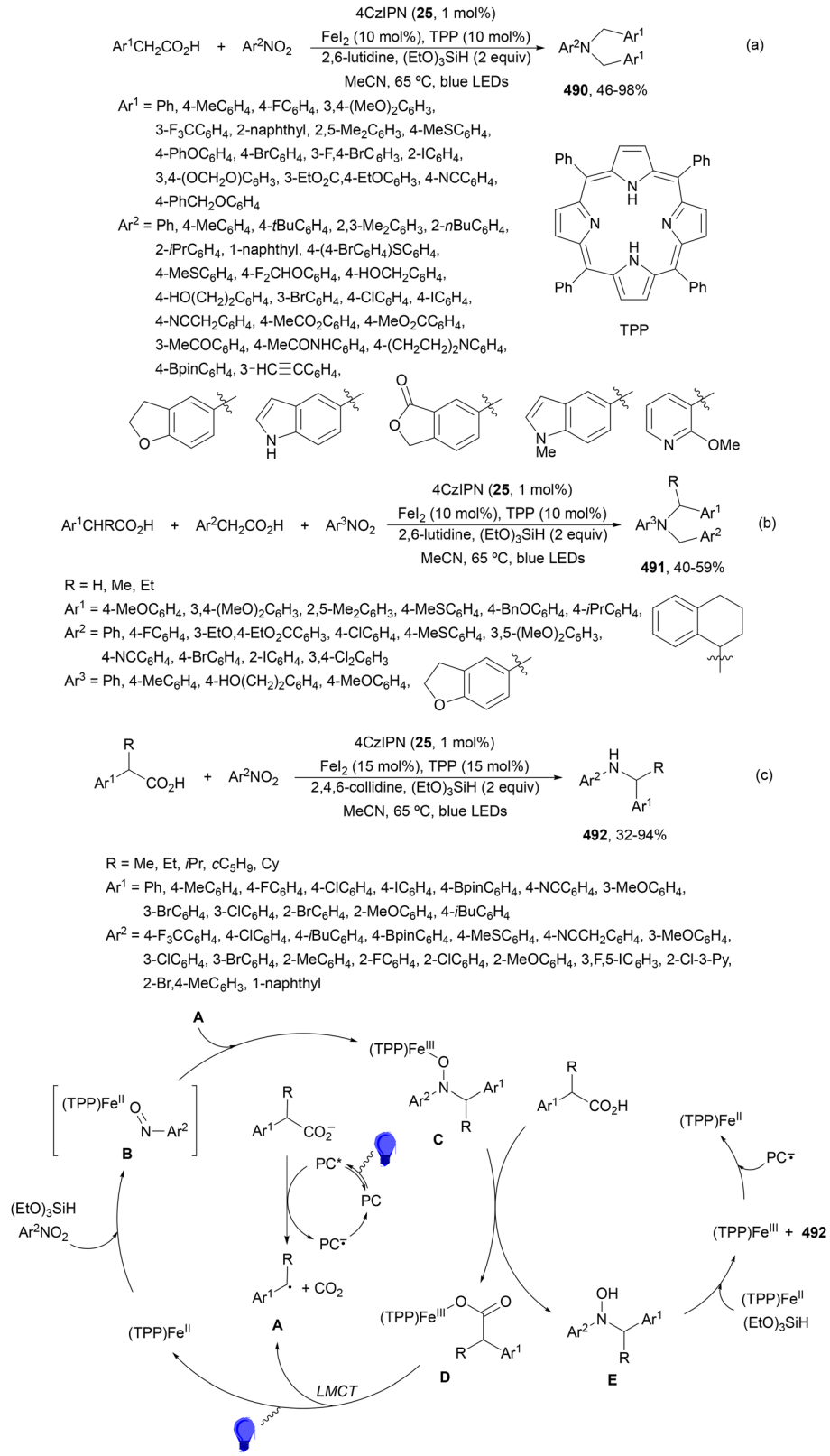
Scheme 252 Decarboxylative α-keto amidation of α,β-unsaturated acids with aromatic amines under Ir/Pd photocatalysis.



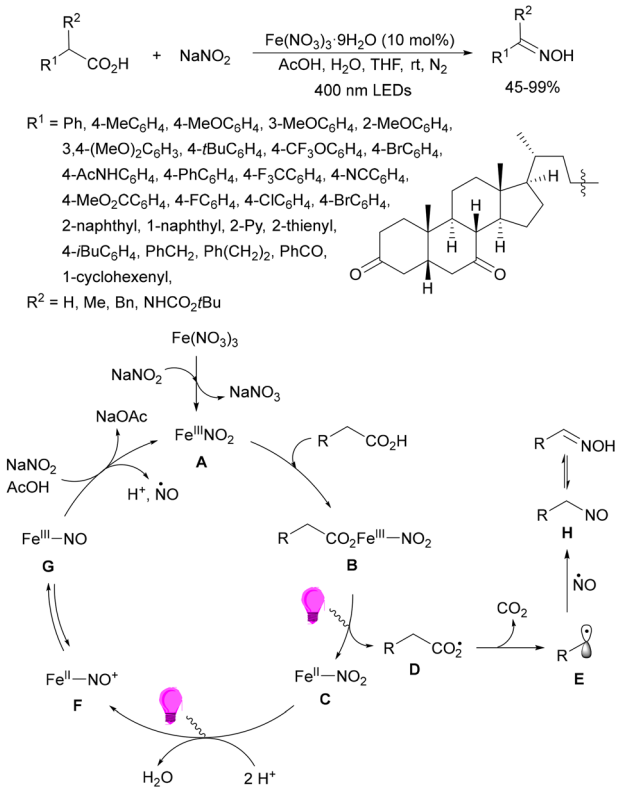
Scheme 253 Decarboxylative azidation of aliphatic carboxylic acids with $TMSN_3$ under $Fe(NO_3)_3$ photocatalysis.

phosphites, phosphine oxides, phosphonites and white phosphorus mainly with NHPI esters **69**.

Larionov and co-workers[464] reported in 2019 the coupling of NHPI esters **69** with chlorophosphines using Ir complex **260** as PC under 400 nm LED irradiation to give phosphines. Aggarwal and co-workers[465] reported the decarboxylative phosphonylation of *N*-protected α-amino acid derived NHPI esters **143** with trimethyl phosphite to provide α-amino phosphonates **499** with modest to high yields (Scheme 258). This procedure took place with 4CzIPN (**25**) as a PC, trifluoroacetic acid in MeCN at room temperature under blue LEDs irradiation and was also applied to dipeptides Gly-Pro, acetyl captopril and fosinopril. In the proposed mechanism, the protonated NHPI ester by TFA undergoes SET to provide after decarboxylation the α-aminoalkyl radical **A**. Subsequent oxidation of **A** by $PC^{+\bullet}$ by a polar crossover process gives rise to *N*-acyliminium ion **B** and regenerates the PC. Cation **B** reacts with trimethyl phosphite leading to phosphonium ion **C**, which undergoes Arbuzov-type demethylation promoted by trifluoroacetate to provide the α-amino phosphonate **499**.



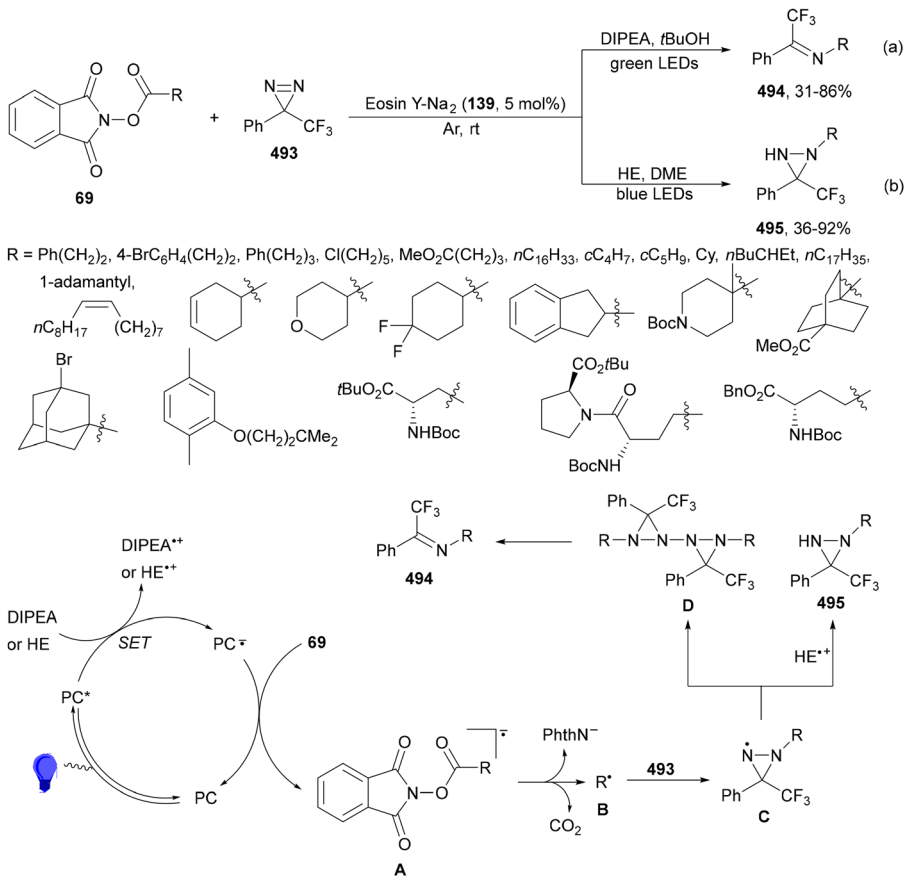
Scheme 254 Decarboxylative amination of carboxylic acids with nitroarenes under 4CzIPN/FeI_2 photocatalysis.



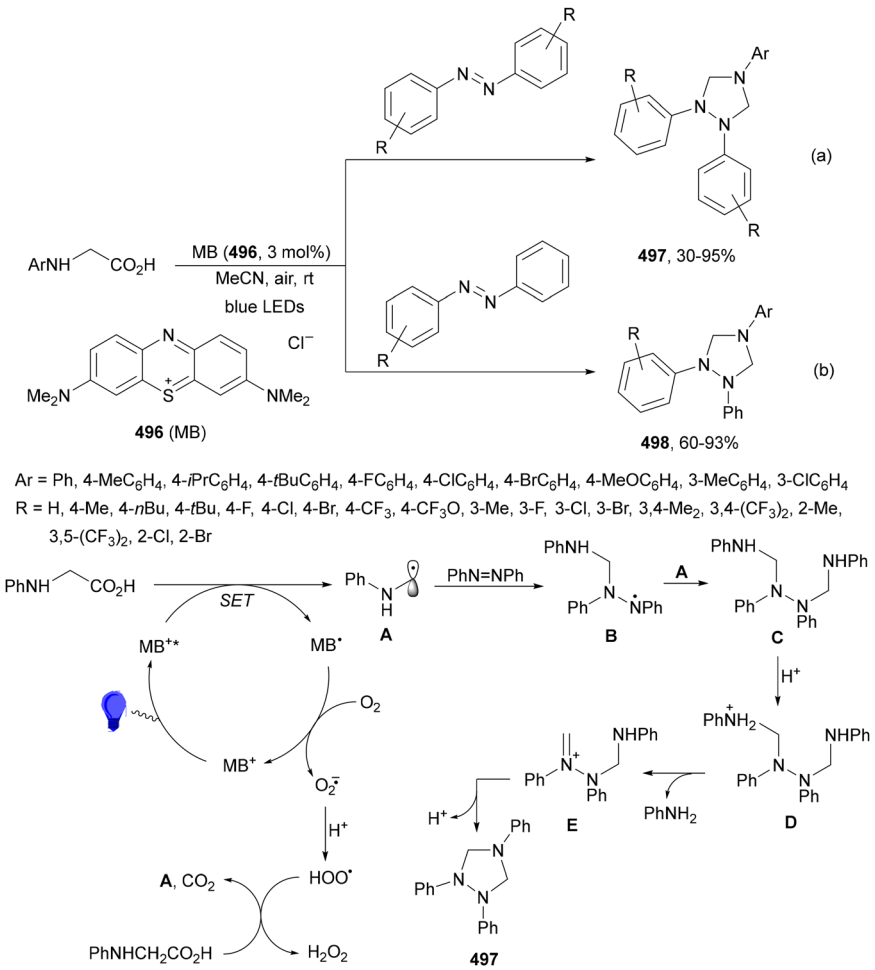
Scheme 255 Decarboxylative nitrosation of aliphatic carboxylic acids with $NaNO_2$ under $Fe(NO_3)_3$ LMCT photocatalysis.

Decarboxylative phosphonylation of alkyl NHPI esters **69** with benzhydryl-catechol-phosphite (Beca P, **500**) was performed by Aggarwal and co-workers.[466] This phosphite reagent **500** enables a more efficient phosphonylation than common trialkyl phosphites. In this case, Ir complex **4** was used as a PC in the presence of 4 equivalents of MeOH in MeCN at 30 °C under blue LED irradiation to give phosphonates **501** with good yields for primary and secondary alkyl NHPI esters (Scheme 259). This procedure was applied to the large-stage functionalization of several natural products and drugs. In addition, MeOH can be replaced by other alcohols to provide phosphonates **501** with ethyl, isopropyl, and benzyl groups. The proposed mechanism starts with SET reduction of NHPI ester by Ir(III)* to form after decarboxylation the alkyl radical **A**. Beca P **500** reacts with radical **A** to form phosphonate radical **B**, which after β-scission gives intermediate **C** and benzhydryl radical **D**. Intermediate **C** reacts with MeOH to give the product. Radical **D** can be oxidized to cation **E** by the oxidized state of the catalyst, and after trapping by MeOH provides by-products PhthNH and Ph_2CHOMe.

Phosphonylation of alkyl NHPI esters **69** with trialkyl phosphites was also achieved using 1 mol% of 1,2,3,5-tetrakis-(diphenylamino)-4,6-dicyanobenzene (4DPAIPN, **502**) as a PC, $Cu(OAc)_2$, lithium benzoate as a base in chlorobenzene at room temperature under blue LEDs irradiation (Scheme 260).[467] The corresponding primary and secondary alkylphosphonates **503** were isolated with good yields. In the proposed mechanism, the



Scheme 256 Decarboxylative divergent amination of NHPI esters with diazirine **493** under Eosin Y-Na_2 (**139**) photocatalysis.

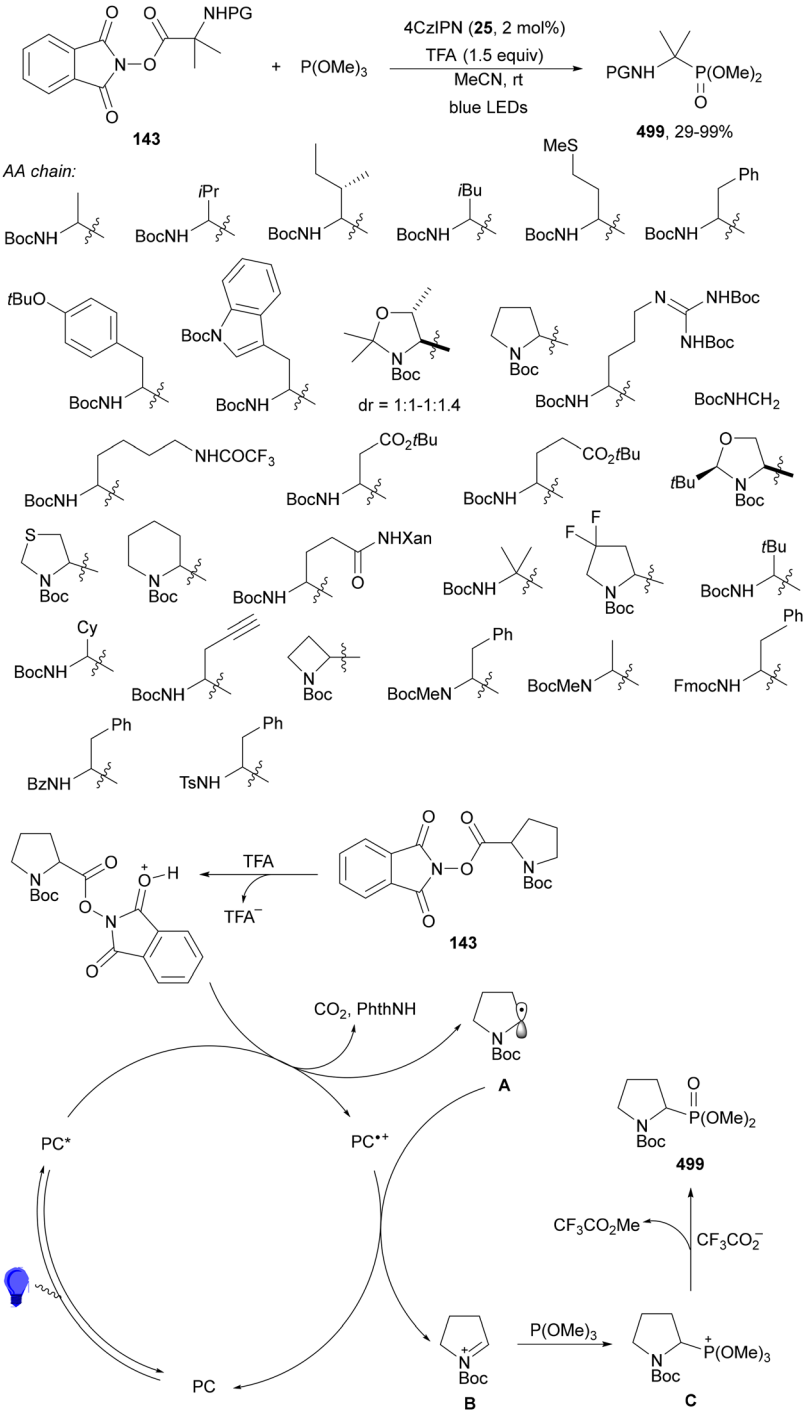


Scheme 257 Decarboxylative hydrazination of *N*-aryl glycines with azobenzenes under methylene blue (**496**) photocatalysis.

photoexcited **502*** is oxidatively quenched by NHPI ester to give **502**$^{+\bullet}$ and NHPI ester radical anion, which after decarboxylation gives PhthN$^-$ and radical **A**. Complex **B** is formed by reaction of Cu(I) with P(OEt)$_3$, which by SET from radical cation **502**$^{+\bullet}$ forms the Cu(II) complex **C** and regenerates the PC **502**. Complex **C** reacts with radical **A** providing the phosphonium intermediate **D**, which is de-ethylated by nucleophilic attack of benzoate (Arbuzov type) to furnish the product **503** regenerating the Cu(I) catalyst.

Photoinduced decarboxylative phophinylation of aliphatic NHPI esters **69** with dialkylaryl or alkyl phosphonites **504** has been reported by the same Chinese group.[468] Working with 4CzIPN (**25**) as a PC in DMA at room temperature under blue LED irradiation resulted in phosphinates **505** with, in general, very good yields (Scheme 261). This method was applied to the synthesis of bioactive phosphinic acids such as kynureninase inhibitor and glutamine synthetase inhibitor phosphinothricin. A plausible mechanism was proposed involving the generation of radical **A**, which reacts with dimethyl phenyl phosphonite to give the phosphoranyl radical **B**. A subsequent SET process of radical **B** with (4CzIPN)$^{+\bullet}$ forms the phosphonium cation **C** and the ground state of 4CzIPN. Arbuzov demethylation of **C** with PhthN$^-$ gives the product PhthNMe.

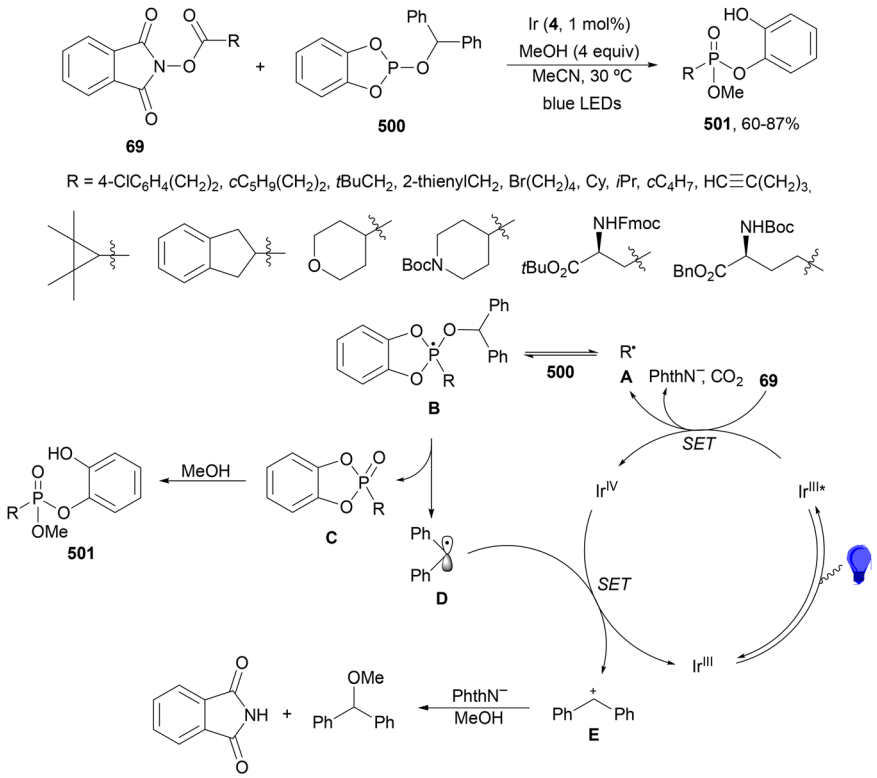
White phosphorus has been alkylated with alkyl NHPI esters **69** in the presence of HE and NaI in DMF/toluene at room temperature under Ar and visible-light irradiation without PC.[469] Dialkyl phosphines were isolated as dialkyl phosphine oxides (DAPOs) in air with high yields (52–82%) for primary alkyl groups (Scheme 262a). However, secondary alkyl NHPI esters gave lower yields (12–84%) and tertiary ones failed. Several scale-up experiments afforded the corresponding products in good yields. When the amount of NHPI ester was increased from 3.5 to 8.0 equivalents, in the presence of air, the corresponding trialkyl phosphines (TAPOs) were obtained with yields ranging from 47 to 87% (Scheme 262b). In the proposed mechanism, an EDA complex between NHPI ester, an iodide anion and HE is formed (see Scheme 92), which after photoexcitation resulted in an alkyl radical. This radical reacts with P_4 yielding an unstable phosphorus-centered radical **A**, which absorbs a H atom from HE$^{+\bullet}$ to give species **B**. Subsequent alkylation provides the primary phosphine (RPH_2) **C**. Finally, the alkyl radical abstracts a H atom to form the hydro



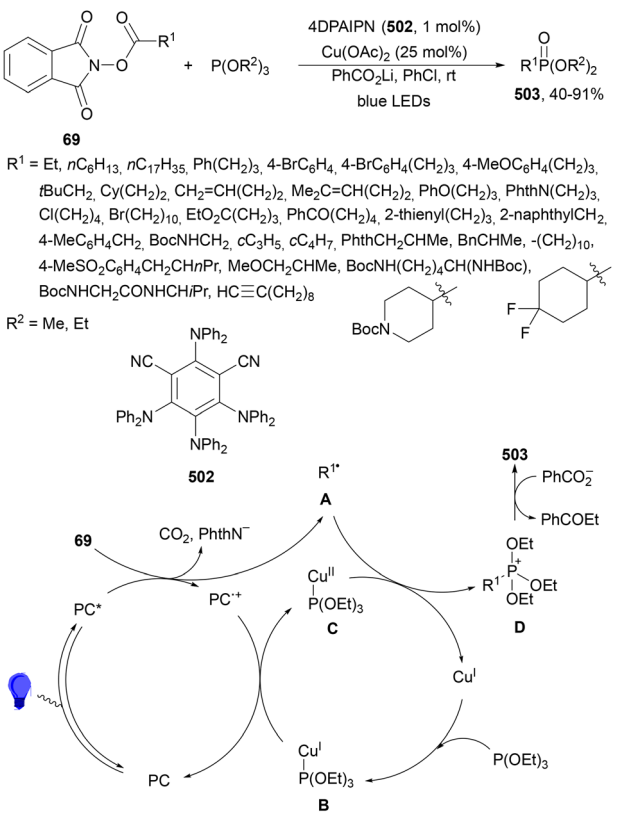
Scheme 258 Decarboxylative phosphonylation of α-AA-derived NHPI esters **143** with trimethyl phosphite under 4CzIPN (**25**) photocatalysis.

phosphonyl radical **D**. A radical coupling between **D** and R$^{\bullet}$ yields the secondary phosphine **E**, which after oxidation forms product DAPO.

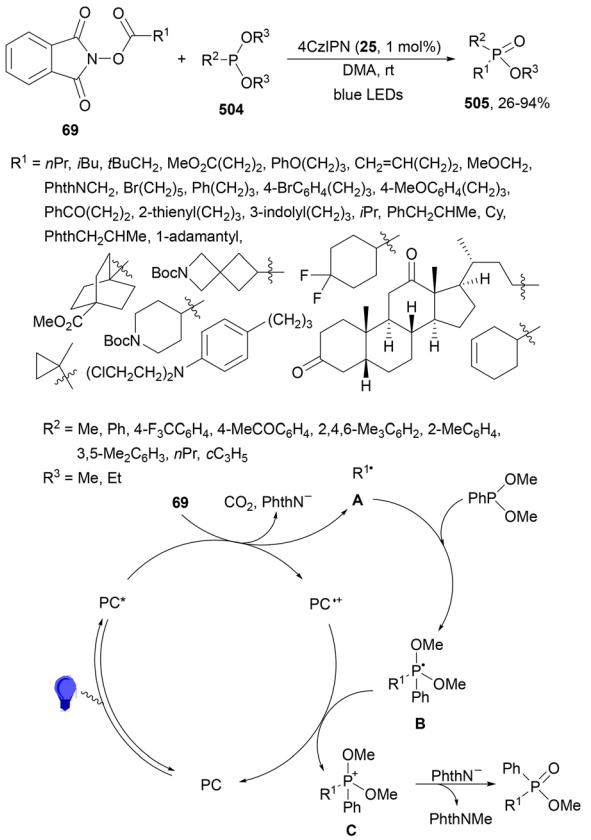
Direct decarboxylative/dehydrogenative coupling of α-fluoro-α,β-unsaturated carboxylic acids **506** with diaryl phosphine oxides **507** was described by Lu, Zhou and co-workers.[470] Working with $Ru(bpy)_3Cl_2$ as a PC, *tert*-butyl peroxybenzoate (TBPB) as an oxidant, DABCO as a base in MeCN at room temperature and blue LED irradiation, monofluoroalkenyl phosphine oxides **508** were obtained in 46–80% yields and 30 : 1 *E*/*Z* diastereoselectivity (Scheme 263a). This procedure was also applied to the late-stage modification of an estrone derivative and a vitamin E derivative. In the case of alkoxy phosphine oxides **509** the reaction was sluggish giving the corresponding phosphonates **510** with modest yields and lower *E*/*Z* diastereoselectivity owing to the low stability of the alkoxy



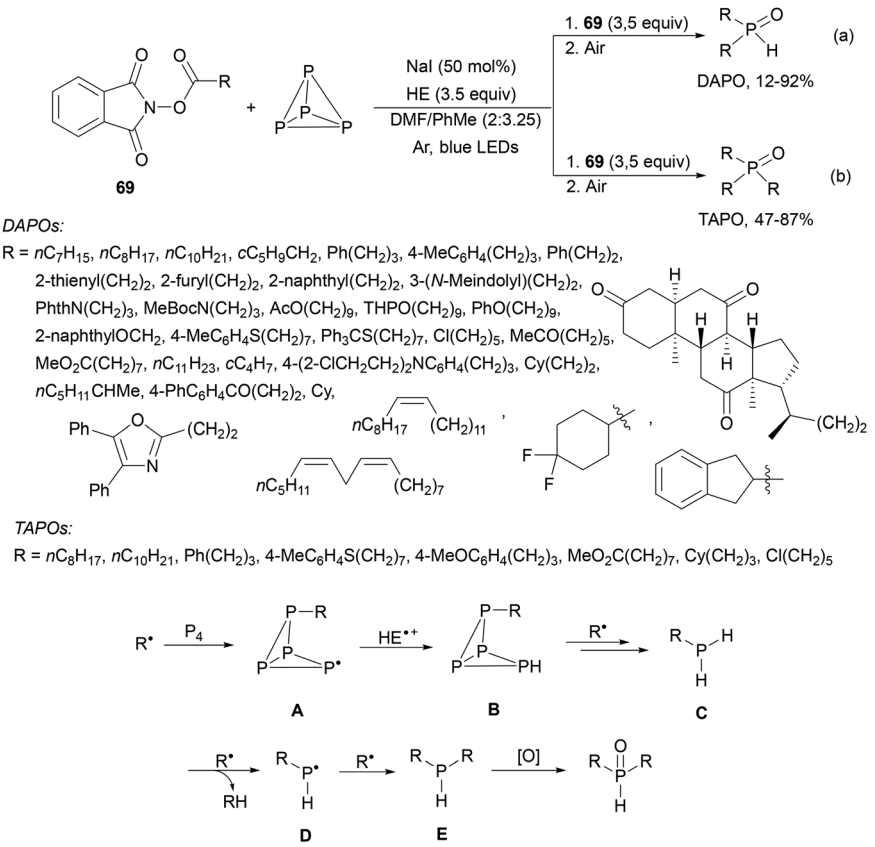
Scheme 259 Decarboxylative phosphonylation of NHPI esters **69** with Beca P (**500**) under Ir complex **4** photocatalysis.



Scheme 260 Decarboxylative phosphonylation of alkyl NHPI esters **69** with trialkyl phosphites under 4DPAIPN (**502**) and $Cu(OAc)_2$ photocatalysis.



Scheme 261 Decarboxylative phosphinylation of aliphatic NHPI esters **69** with phosphonates **504** under 4CzIPN (**25**) photocatalysis.



Scheme 262 Decarboxylative phosphorylation of alkyl NHPI esters **69** with P_4 under NaI/HE photocatalysis.

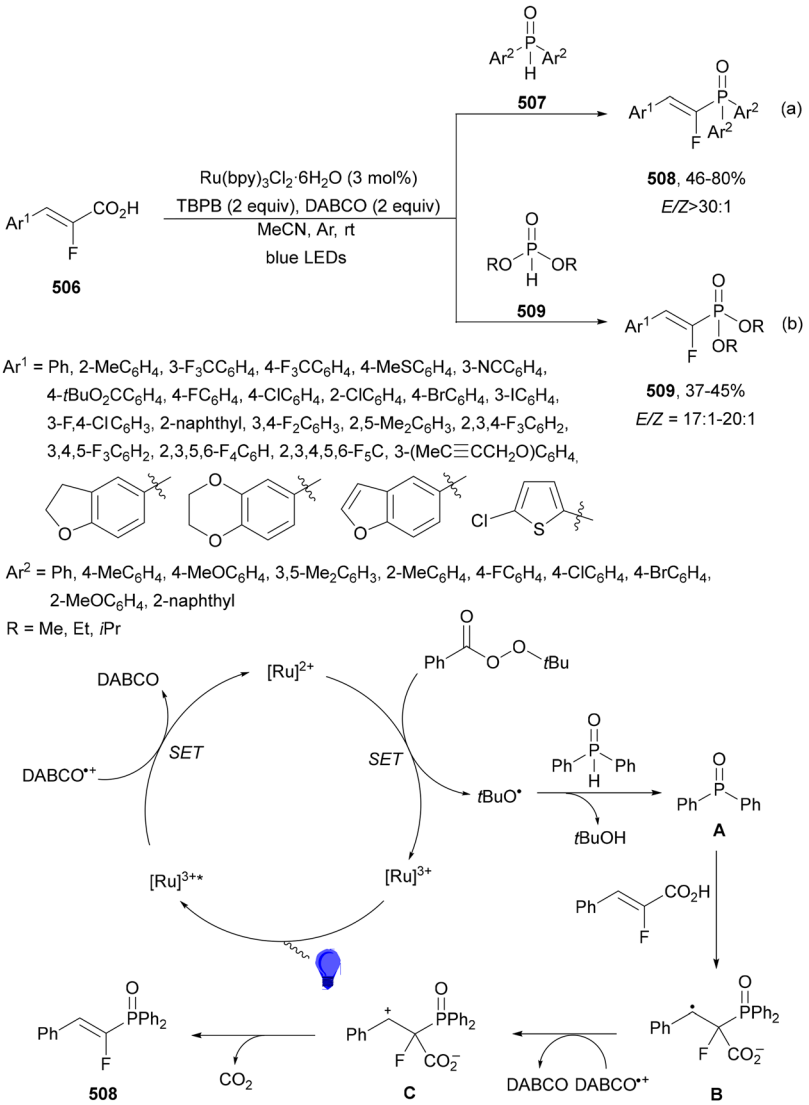
substituted phosphinoyl radical compared to the diaryl substituted phosphinoyl radical (Scheme 263b). In the proposed mechanism, photoexcited $[Ru^{3+}]^*$ oxidizes DABCO to form $DABCO^{+\bullet}$ and $[Ru]^{2+}$ *via* a SET. Then, $[Ru]^{2+}$ was oxidized by TBPB regenerating $[Ru]^{3+}$ and tBuO$^\bullet$, which is captured by **507** to give the diphenyl phosphinoyl radical **A**. Subsequent addition of **A** to α-fluoro cinnamic acid forms the β-radical carboxylate intermediate **B**. This radical **B** releases an electron to $DABCO^{+\bullet}$ to form intermediate **C**. Final decarboxylation of **C** gives product **508**.

Phosphorus derivatives such as phosphonates and phosphinates are accessible by photoredox decarboxylative C–P bond forming reactions working with NHPI esters under LED irradiation. Phosphites react with NHPI esters using an Ir complex as a PC or 4CzIPN or 4DPSIPN as organic photoredox catalysts to provide phosphonates. In the case of using phosphonites as nucleophiles with 4CzIPN as a PC and $Cu(OAc)_2$ as a catalyst resulted phosphinates. Dialkyl and trialkyl phosphine oxides are accessible by reaction of NHPI esters with phosphorus under blue LED irradiation. Diaryl phosphine oxides react with α-fluoro-α,β-unsaturated carboxylic acids using Ru(III) and DTPB as an oxidant to give monofluoroalkenyl phosphine oxides.

3.6. Carbon–boron bond-forming reactions

Decarboxylative borylation reactions were reported in 2017 by Aggarwal[471] and Li[472] groups using alkyl NHPI esters **69** and B_2cat_2 under blue LED irradiation,[471] whereas in the second case B_2pin_2 or $B_2(OH)_6/KHF_2$ with an Ir complex as PC under 45 W CFL irradiation, were employed. Aryl NHPI esters were borylated with B_2pin_2 under blue LED irradiation in the absence of a PC by Glorius and co-workers.[473] In 2020, Wang and co-workers[474] employed *N*-hydroxybenzimidoyl chloride (NHBC) esters **401** for the borylation with B_2cat_2 or bis(dimethylpentanediol)diboron (B_2dmpd_2) for aliphatic or aromatic carboxylic acid derivatives, respectively, using an Ir complex as a PC under blue LED irradiation.

Recent developments in decarboxylative borylation of aliphatic NHPI esters under visible-light conditions (developed by the Aggarwal group[471]) were carried out by Masson and co-workers.[475] Borylation of NHPI esters **69** containing α- or β-heteroatoms, including α- and β-amino acids, was carried out with B_2cat_2 in DMA followed by *in situ* transamination with 1,8-diaminonaphthalene ($DANH_2$) to provide stable α- and β-substituted boronamides **510** in moderate to excellent yields (Scheme 264). Carboxy group-containing drugs such as baclofen and isoxepac were transformed into the corresponding DAN-boronates **510**. In the mechanism proposed by Aggarwal and co-workers,[471] under photochemical conditions, NHPI ester, B_2cat_2 and DMA form complex **A**, which after irradiation cleaves the B–B bond to deliver a DMA-stabilized boryl radical **C** and *O*-boryl-NPhth ester radical **B**. This radical **B** gives, after decarboxylation and release of *O*-borylphthalimide, an alkyl radical **D**. Reaction of **D** with DMA-coordinated B_2cat_2 **E** yields

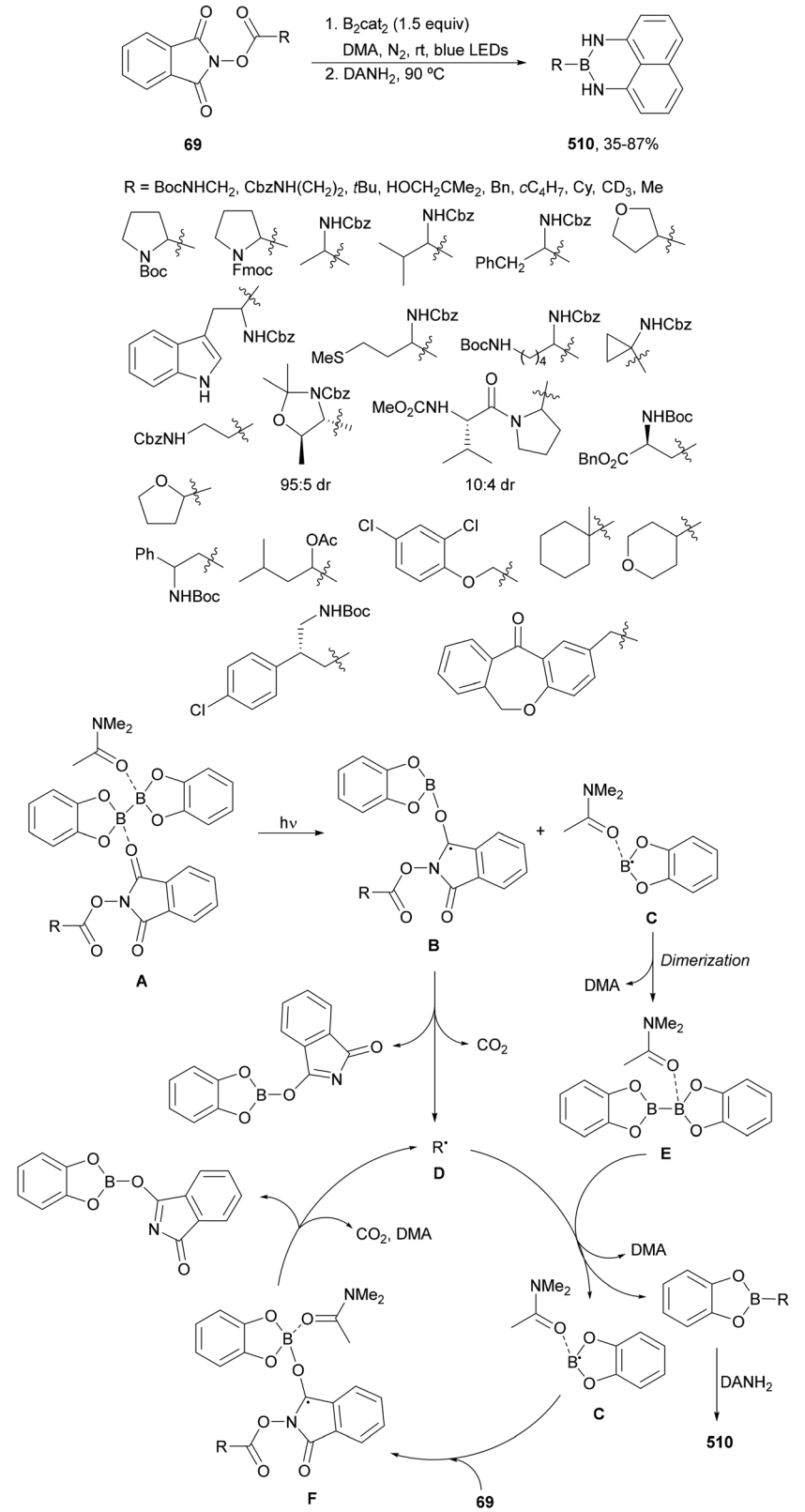


Scheme 263 Decarboxylative coupling of α-fluoro-α,β-unsaturated carboxylic acids **506** with diaryl phosphine oxides **507** and dialkoxy phosphine oxides **509** under Ru photocatalysis.

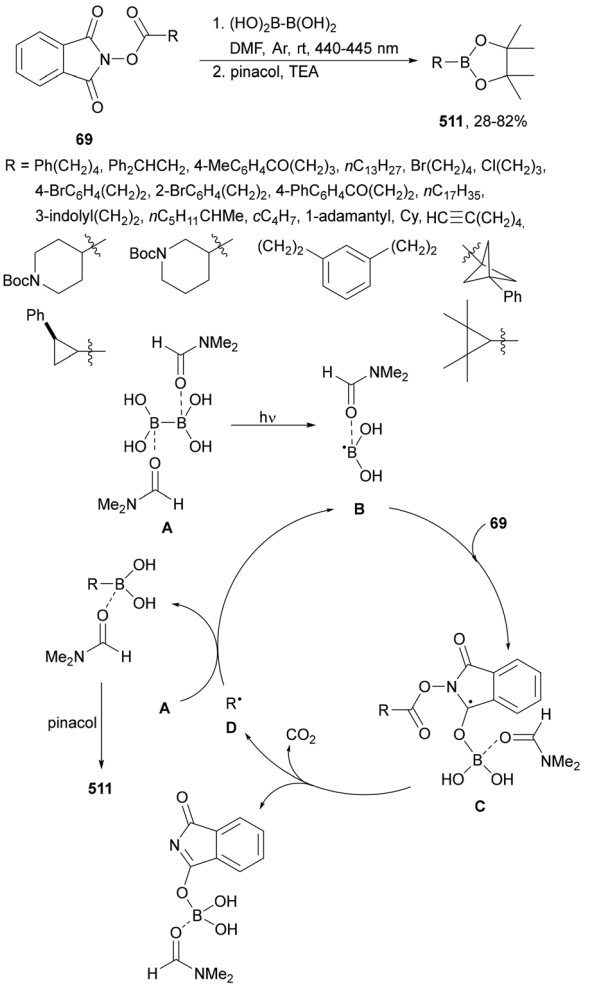
an alkylboronate ester and DMA-stabilized boryl radical **C**. Subsequently, NHPI ester reacts with **C** to give radical **F**, which regenerates radical **D**.

Recently, Tolnai, Novák and co-workers[476] employed hypoboric acid for the borylation of alkyl NHPI esters **69** under Ar and visible-light irradiation in DMF at room temperature. After *in situ* addition of 1.5 equivalents of pinacol the corresponding boronic esters **511** were isolated with good yields (Scheme 265). This borylation did not proceed under dark conditions even at 110 °C. In the proposed mechanism, complex **A** between hypoboric acid and DMF can be formed, which by irradiation generates the boron radical **B**. This radical **B** reacts with NHPI ester to form radical **C**. Subsequent decarboxylation of **C** generates an alkyl radical **D**, which reacts with complex **A** to give the alkylboronic acid and radical **B**.

Direct decarboxylative borylation of (hetero)aryl acids was reported in 2022 by MacMillan and coworkers[477] by copper LMCT photocatalysis. This borylation was performed using B_2pin_2 in the presence of $Cu(MeCN)_4BF_4$, NFSI as an oxidant, NaF and $LiClO_4$ as MeCN-soluble ion sources to generate the activated lithium fluoroborate in an integrated photoreactor with a 365 nm LED module. The corresponding borylated arene products **512** were isolated with good yields under these mild reaction conditions (Scheme 266). In addition, this borylation was combined with a Suzuki–Miyaura reaction and also with a double decarboxylative coupling of two (hetero)aryl acids under parallel Cu-LMCT bromination and borylation procedures. A plausible mechanism for the borylation process involves the formation of the Cu(I) carboxylate, which after oxidation gives complex **A**. Under near-UV irradiation this complex **A** undergoes LMCT from the carboxylate ion to the Cu(II) center to produce Cu(I) and an aryloxy radical **B**. Subsequent decarboxylation of **B** gives aryl radical **C**, which reacts with an activated



Scheme 264 Decarboxylative borylation of NHPI esters **69** with B_2cat_2 under visible light photocatalysis followed by amination with $DANH_2$.

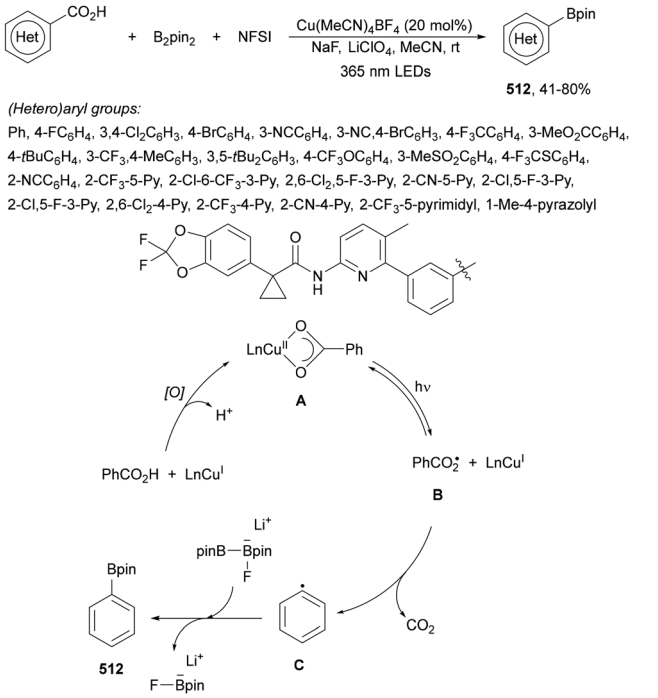


Scheme 265 Decarboxylative borylation of alkyl NHPI esters **69** with hypoboric acid under 440–445 nm light followed by esterification with pinacol.

metal boronate, generated *in situ* from B_2pin_2 and metal salt additives, to deliver the arylboronic ester **512**.

Liu and co-workers[478] reported the borylation of aromatic acids with B_2pin_2 using Ir complex (**324**) as a PC, $Co(dmgH)_2PyCl$ (**16**) as an oxidant, and TMG as a base, to activate the carboxylic acid in *t*BuOAc under air and blue LED irradiation (Scheme 267). The resulting aryl boronates **512** were isolated in moderate to good yields and this procedure was also applied to bioactive molecules. In the proposed mechanism, TMG forms a complex **A** with the acid and Ir(III) was photoexcited to Ir(III)*, which after oxidative quenching with Co(III) gives Ir(IV). Then, complex **A** is oxidized to complex **B** and Ir(III) is regenerated. Decarboxylation of **B** gives the aryl radical **C** and $TMGH^+$. Borylation of radical **C** takes place by complex **D**, formed by reaction of B_2pin_2 and TMG.

Decarboxylative borylation has been performed with alkyl NHPI esters in the absence of photocatalyst either with B_2cat_2 or hypoboric acid followed by esterification with pinacol. (Hetero)-aryl acids have been transformed into (hetero)arylboronates with Cu LMCT photocatalysis and NFSI as an oxidant or with Ir as a PC and a cobalamin as an oxidant.



Scheme 266 Decarboxylative borylation of (hetero)aryl acids with B_2pin_2 under Cu-LMCT photocatalysis.

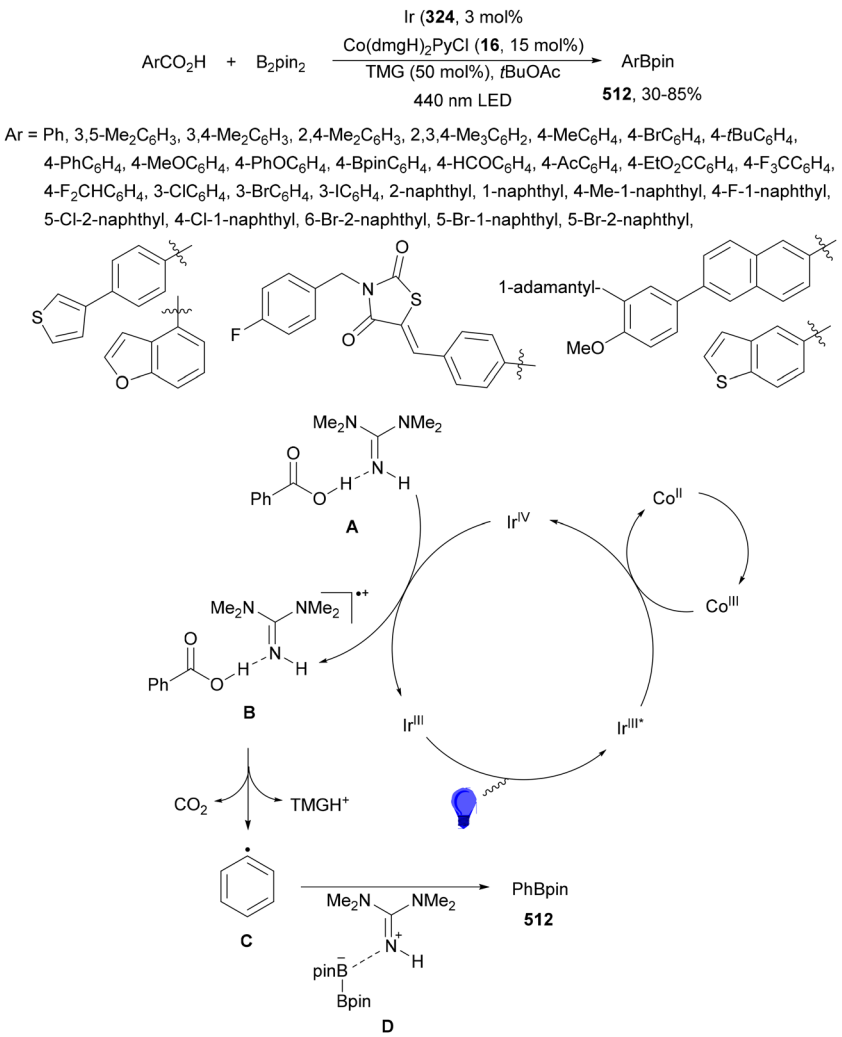
3.7. Carbon–silicon bond-forming reactions

The first decarboxylative silylation of silacarboxylic acids **513** was described in 2020 by Uchiyama and co-workers[479] under 4CzIPN (**25**) photocatalysis. Silicon-based radicals were trapped by alkenes to give the hydrosilycated products in good yields. More recently Jin, Ren and co-workers[480] performed this silylation reaction in the presence of α-trifluoromethylaryl alkenes **514**, which underwent a photoredox defluorinative silylation to furnish silylated *gem*-difluoroalkenes **515** in moderate to good yields (Scheme 268). This defluorinative silylation was carried out on a 2 molar scale to give **515a** ($R^1 = R^2 = Me$; $R^3 = Ph$) in 74% yield. A plausible mechanism was proposed starting by oxidative decarboxylation of silacarboxylate by PC* to give radical **A**. Subsequent radical addition of **A** to trifluoroalkene **514** provides a benzyl radical **B**, which undergoes a SET forming benzyl anion **C**. After a defluorination process of **C** product **515** is obtained.

Lu, Zhou and co-workers[470] reported a decarboxylative coupling of α-fluoro-α,β-unsaturated carboxylic acids **506** with diaryl and dialkyl phosphine oxides **507** and **509** (Scheme 263). When this photoinduced decarboxylation was carried out with triethylsilane instead of **507**, in the presence of $Ru(bpy)_3Cl_2$ and TBPB as an oxidant in DMSO under Ar and blue LED irradiation monofluoroalkenyl silanes **516** were obtained in good yields and excellent diastereoselectivity (Scheme 269).

4. Hydro- and deuterodecarboxylation

Photomediated decarboxylative protonation or deuteration of carboxylic acids and derivatives is a mild procedure for the C–H[481] and C–D[482] bond formation. In 2014, Wallentin and



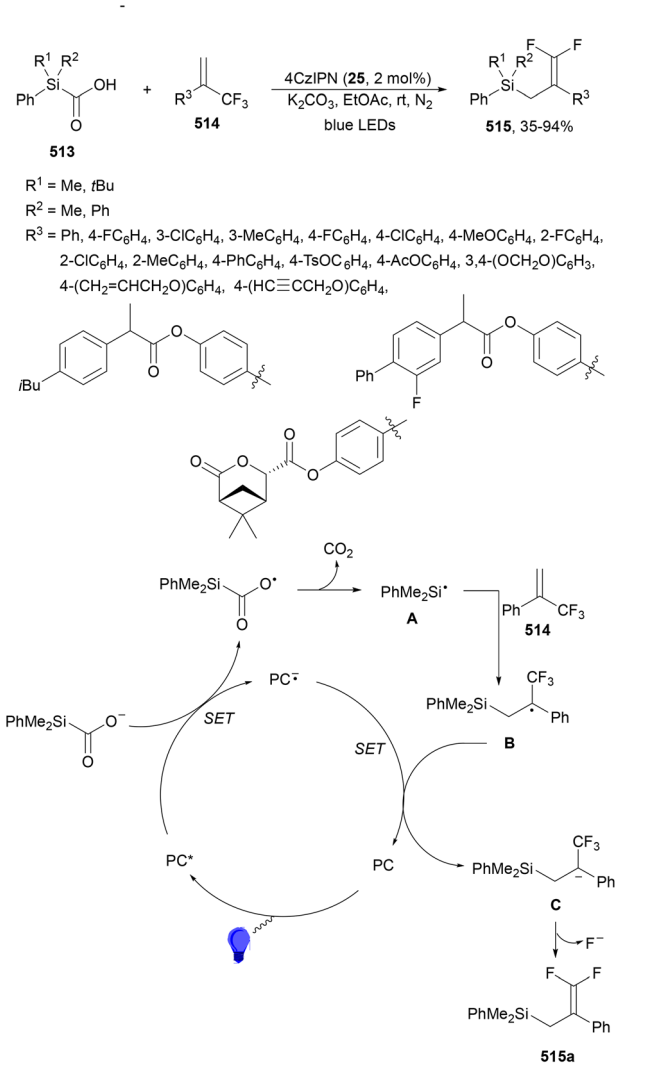
Scheme 267 Decarboxylative borylation of aromatic carboxylic acids with B_2pin_2 under Ir/Co photocatalysis.

co-workers[483] employed an acridinium (Mes-Acr-Me)BF_4 (1 mol%) as a strong oxidizing PC and phenyl disulfide (10 mol%) as a source of a hydrogen donor for the protonation of α-AAs and α-hydroxy acids. Nicewicz and co-workers[484] reported a similar hydrodecarboxylation of aliphatic carboxylic acids using (Mes-Acr-Ph)BF_4 (**17**) as a PC.

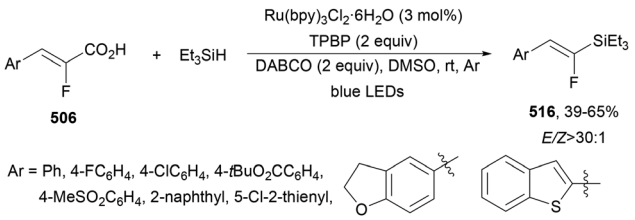
More recent applications of decarboxylative protonation or deuteration have been described using mainly acridinium salts for aliphatic carboxylic acids and Cu or Fe LMCT processes also for aromatic acids. Li, Zhu and co-workers[485] reported a deuterodecarboxylation procedure from aliphatic carboxylic acids including erdosteine, ambrisentan, gemfibrozil and oleanic acid. They employed (Mes-Acr-Me)ClO_4 (**301**) as a PC and 2,4,6-triisopropylbenzenethiol as a HAT catalyst, 2,4,6-collidine as a base in a 4 : 1 mixture of DCM/D_2O for benzylic and α-heteroatom substituted carboxylic acids under LED irradiation in moderate to good yields and good D-incorporation (up to 99%). Alternatively, CsOH and Ir complex **4** (1 mol%) as a PC have also been employed (Scheme 270). A scalable process was carried out using a recirculation reaction with a peristaltic pump up to a 50 mmol scale. The proposed mechanism starts with the generation of an alkyl radical **A** after oxidation of the carboxylate ion by PC*. Then, deuterated thiol acts as a HAT catalyst and transfer D to radical **A** generating a thiyl radical **B**, which can accept an electron from the $PC^{-\bullet}$ and regenerate the PC.

Fatty acids underwent decarboxylative protonation and deuteration using (Mes-1,3,6,8-tetramethoxy-Acr-3″,5″-dimethoxy-Ph)BF_4 (**517**) as a PC, (4-methylphenyl) disulfide as a HAT catalyst in EtOAc and in EtOAc/D_2O (4 : 1), respectively.[486] In this case, *n*-Bu_4NOAc (TBAA) was employed as a base at 35–40 °C under Ar and blue LED irradiation to give the corresponding alkanes and deuterated alkanes with good yields. This procedure was scaled-up to the gram-scale (Scheme 271).

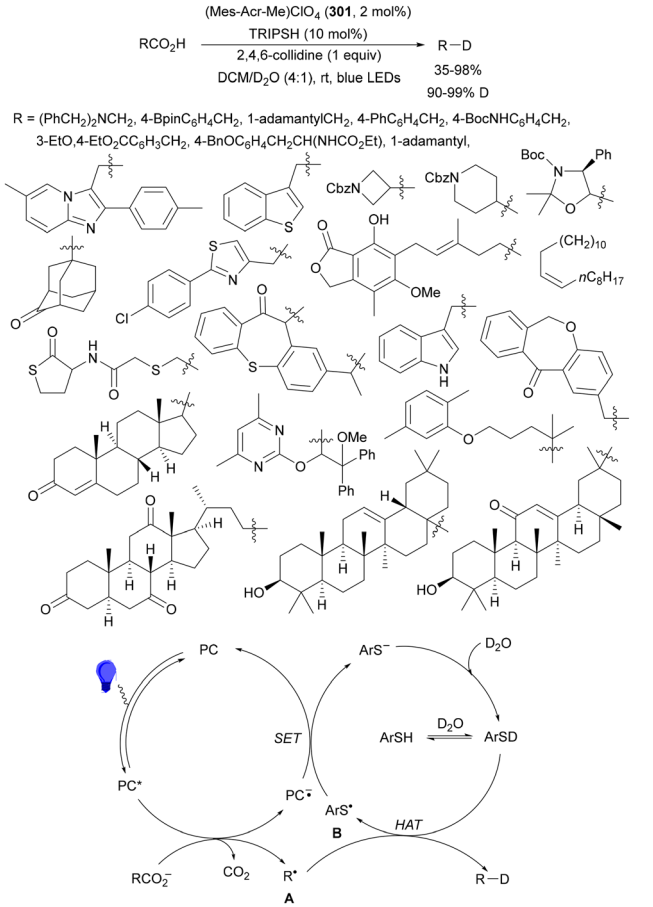
Cavalcanti and co-workers[487] described the hydrodecarboxylation of fatty acids using 10 mol% of acridine **125** as a PC, benzenethiol (20 mol%) as a HAT catalyst at room temperature in aqueous DCM under N_2 and LED irradiation. The fatty acids were converted into hydrocarbons in excellent yields (95–99%). This protocol was applied to a mixture of fatty acids obtained



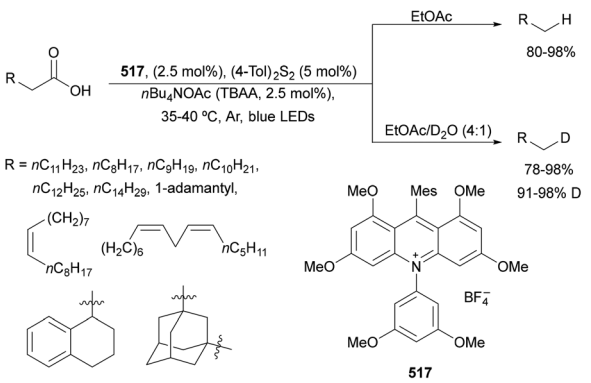
Scheme 268 Decarboxylative defluorinative silylation of α-trifluoromethyl alkenes **514** with silacarboxylic acids **513** under 4CzIPN (**25**) photocatalysis.



Scheme 269 Decarboxylative coupling of α-fluoro-α,β-unsaturated acids **506** with Et_3SiH under Ru photocatalysis.



Scheme 270 Deuterodecarboxylation of aliphatic carboxylic acids under (Mes-Acr-Me)ClO_4 (**301**) photocatalysis.

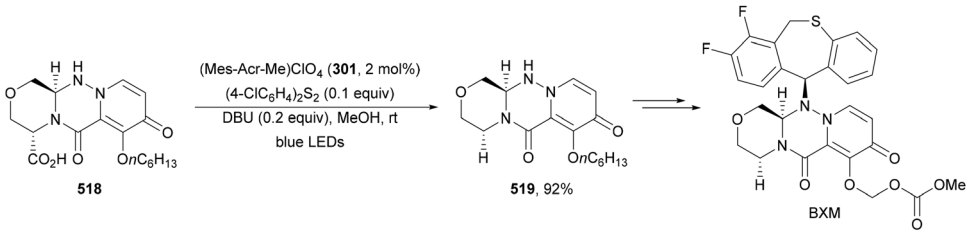


Scheme 271 Proto- and deuterodecarboxylation of fatty acids under acridinium salt **517** photocatalysis.

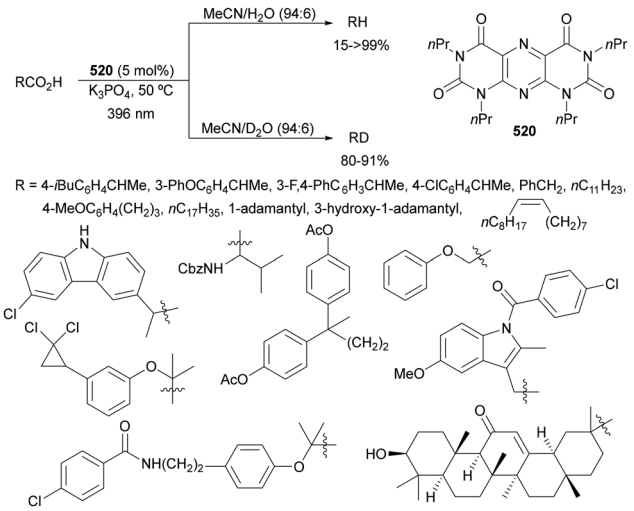
from the hydrolysis of Licuri oil affording a mixture of C9–C17 hydrocarbons in quantitative yield and has potential application to produce drop-in biofuels.

Perfluorinated disulfide **448**, previously described by Dilman and co-workers[408] for decarboxylative thiolation of aliphatic carboxylic acids (Scheme 220) providing effective hydrodecarboxylation of gemfibroxil and ursodeoxycholic acid. In this case, 5 mol% of mesylacridine **123** as a PC, sodium perborate as oxidant in aqueous DCM at room temperature under blue LEDs irradiation furnished the corresponding products in 72 and 92%, respectively.

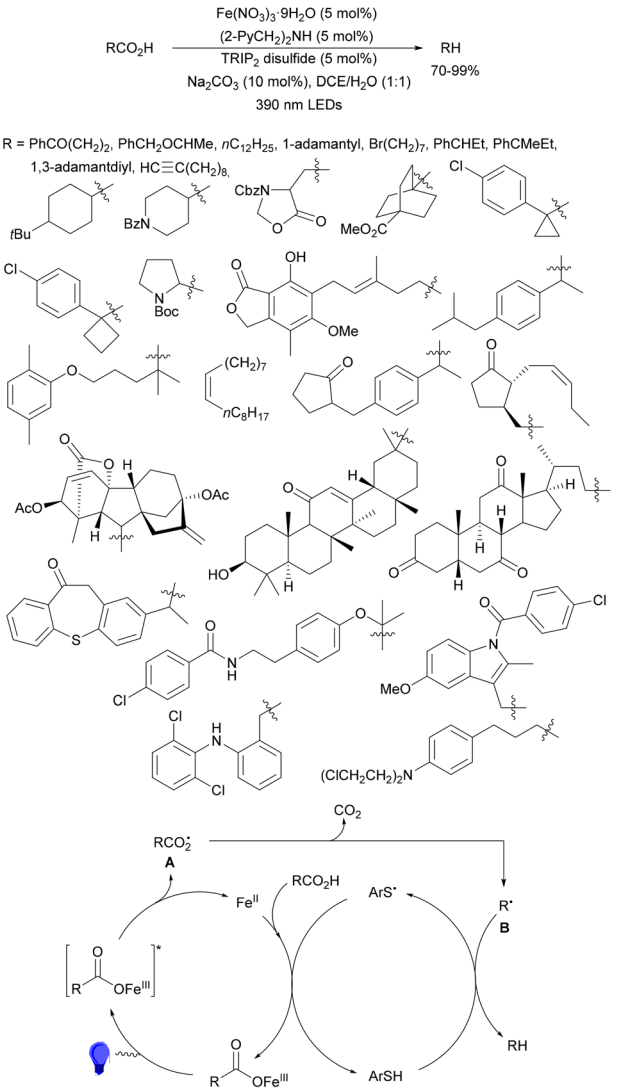
Okamoto and co-workers[488] have recently described the stereoselective synthesis of baloxavir marboxil (BXM), an



Scheme 272 Hydrodecarboxylation of compound **518** under acridinium salt **301** photocatalysis.



Scheme 273 Hydro- and deuterodecarboxylation of aliphatic carboxylic acids under pyrimidopteridine **520** photocatalysis.

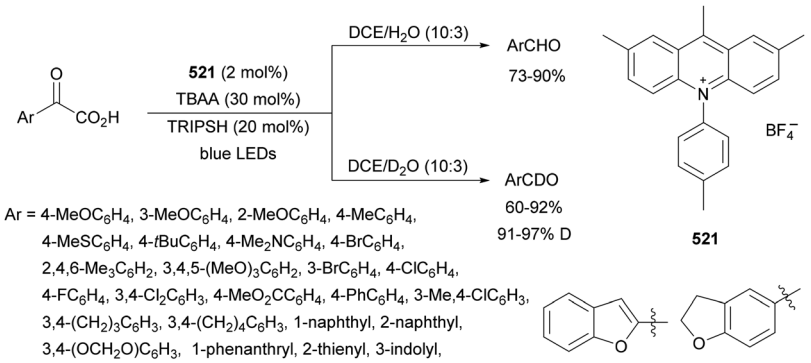


Scheme 274 Protodecarboxylation of aliphatic carboxylic acids under Fe/thiol photocatalysis.

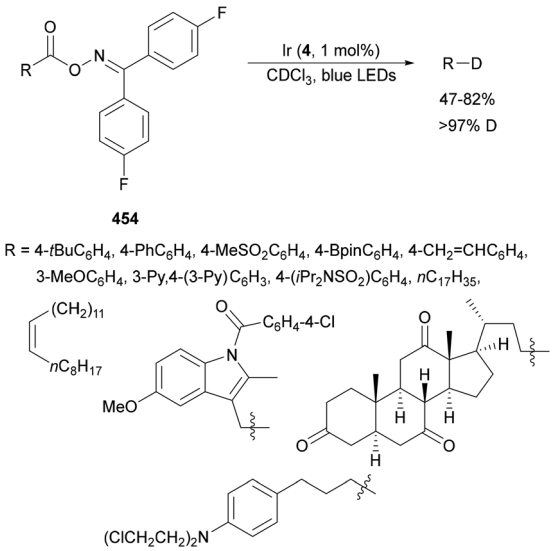
inhibitor of cap-dependent endonuclease used for treating influenza infections. The synthesis of the triazinone core **519** was carried out under mild reaction conditions by photoredox hydrodecarboxylation of compound **518.** In this step, (Mes-Acr-Me)ClO_4 (**301**) was used as a PC, $(4\text{-}ClC_6H_4)_2S_2$ as a HAT catalyst, DBU as a base in MeOH at room temperature under blue LED irradiation to give compound **519** in 92% yield (Scheme 272).

Pospech and co-workers[489] performed hydro- and deutero-decarboxylation of carboxylic acids using an organic pyrimidopteridine **520** as a photoredox catalyst. Primary, secondary and tertiary aliphatic biologically active carboxylic acids were treated with **520**, K_3PO_4 as a base in MeCN/H_2O or MeCN/D_2O at 50 °C under 396 nm irradiation to provide the corresponding products in modest to high yields (Scheme 273).

A cooperative iron/thiol catalyst has been employed for decarboxylative protonation of aliphatic carboxylic acids. Lu and West[490] employed $Fe(NO_3)_3{\cdot}9H_2O$, di(2-pinacol)amine as a ligand and TRIP disulfide as a catalyst, and Na_2CO_3 as a base in DCE/H_2O (1 : 1) under 390 LED irradiation. A broad range of carboxylic acids including natural products and drugs were efficiently transformed into decarboxylated products in excellent yields (Scheme 274). A couple of examples were treated with DCE/D_2O to give deuterated products with 95 and 98% deuterium incorporation. These processes took place *via* a photoinduced LMCT mechanism by initial formation of Fe(III) carboxylate, which after irradiation gives a carboxy radical **A** and a Fe(III) species. After decarboxylation of **A** an alkyl radical **B** is formed, which can be reduced by HAT from the thiol co-catalyst to produce the product.



Scheme 275 Hydro- and deuterodecarboxylation of α-keto acids **15** under acridinium salt **521** photocatalysis.



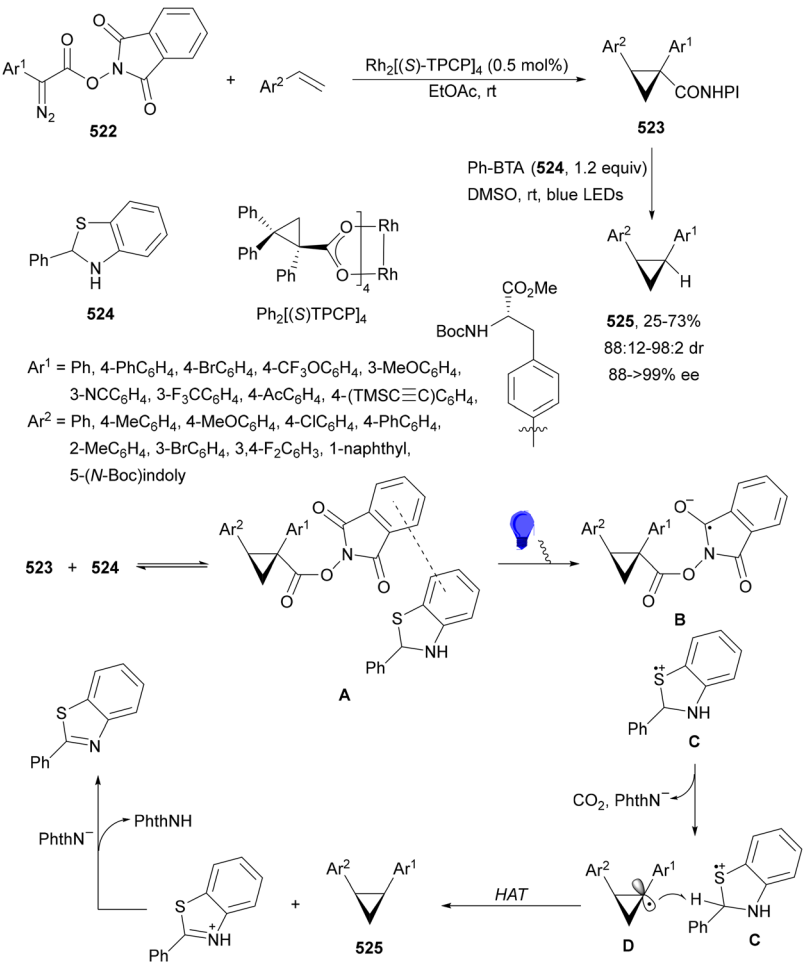
Scheme 276 Decarboxylative deuteration of 4-fluorobenzophenone oxime aromatic and aliphatic esters (**454**) under Ir complex **4** photocatalysis.

In the case of α-keto acids **15**, Hu and Li[491] described their hydro- and deuterodecarboxylation using an acridinium salt **521** as a PC and TRIPSH as co-catalyst, TBAA as a base in DCE/H_2O and DCE/D_2O (10 : 3), respectively, under blue LED irradiation. These processes led to the formation of aldehydes and deuterated aldehydes, respectively (Scheme 275). In this case, carbonyl radicals are formed after decarboxylation of the α-keto acid, which reacts by HAT with TRIPSH or TRIPSD to give the products.

Photoredox hydrodecarboxylation of carboxylic acids has been carried out also under heterogeneous conditions, Bayzar and Hosseini-Sarvari[492] employed Au@ZnO core-shell nanoparticles (NPs) as semiconductor photocatalyst for aliphatic and aromatic carboxylic acids protodecarboxylation. Working with 4 mg (1.89 wt% Au) per 1 mmol of carboxylic acid and K_2CO_3 as a base in $CHCl_3$ at room temperature under Ar and blue LED irradiation, the corresponding products were isolated in 51–96% yields. These NPs exhibited excellent reusability without appreciable decrease of activity after 5 runs. Wang and co-workers[493] reported a photocatalytic decarboxylation of fatty acids to long-chain alkanes in high yields (>90%) using Pt/TiO_2 as a PC under a H_2 atmosphere and 365 nm LED irradiation. Hu and García groups[494] performed a photocatalytic hydrodecarboxylation of octanoic acid by Ni NPs deposited on TiO_2 previously treated with $NaBH_4$ using UV/vis light irradiation with a 300 W lamp. The photocatalytic performance was maintained for six consecutive runs. A metal-free heterogeneous semiconductor was developed by Wang and co-workers[495] for visible light photocatalytic hydro- and deuterodecarboxylation of aliphatic and aromatic carboxylic acids. Ceramic boron carbon nitrides (BCN, 30 mg per 0.2 mmol of acid) in MeOH or CD_3OD at 40 °C under Ar and 420 nm LED irradiation furnished the corresponding products in 25–93% yields and 86–99% deuterium incorporation. Recycling tests show a slight decrease on activity after 5 recycles. Recently, Gao and co-workers[496] described protodecarboxylation of fatty acids over α-Fe_2O_3 under visible light-induced self-heating.

Enzymatic decarboxylation of carboxylic acids to alkanes has been reported by Hollmann and co-workers.[497,498] By using a photodecarboxylase from *Chlorella variabilis* NC64A (*Cv*FAP),[499] fatty acids[497] and short-chain aliphatic carboxylic acids[498] were transformed into the corresponding alkanes working in DMSO at 30 °C under blue LED irradiation with modest turnover numbers. Wu and co-workers[500] developed a divergent protein engineering of WT-*Cv*FAP as more efficient photodecarboxylase for decarboxylative deuteration of fatty acids, working in 20% DMSO or MeCN and D_2O under blue LED irradiation with high yields and excellent D incorporation. Recently, a triple mutant *Cv*FAP (Y466T/P460A/G4621) has shown excellent performance in biobased ethylbenzene production from β-phenylpropionic acid derived from phenylalanine in 82% conversion.[501]

Redox active esters (RAEs) derived from 4-fluorobenzophenone oximes **454** were employed by Glorius and co-workers[502] as substrates for decarboxylative deuteration in the presence of Ir complex **4** as a PC in $CDCl_3$ under blue LED irradiation. Aliphatic and aromatic carboxylic acid derivatives **454** were deuterated in good yields and >97% deuterium incorporation (Scheme 276).



Scheme 277 Stereoselective hydrodecarboxylation of *cis*-cyclopropanes **523** under benzothiazine **524** photocatalysis.

Constantini and Mendoza[503] synthesized *cis*-cyclopropanes **525** by decarboxylation of NHPI esters **523** in the presence of benzothiazoline **524** in DMSO at room temperature under blue LED irradiation (Scheme 277). These NHPI esters **523** were prepared by enantioselective cyclopropanation[504,505] of styrenes with diazo compounds **522** under $Rh_2[(S)\text{-TPCP})]_4$ catalysis and then subjected to decarboxylation. This stereoselective decarboxylation was explained by a stereoretentive HAT. NHPI esters **523** and benzothiazoline **524** associate in solution to form the EDA complex **A**, which undergoes a photoinduced electron transfer (PET) in the excited state to form the radical ion par between **B** and **C**. Subsequent fragmentation and decarboxylation gives the cyclopropyl radical **D**, which abstracts a hydrogen atom from the benzyl C–H bond of the benzothiazoline radical cation **C**. *cis*-Cyclopropane product **525** is kinetically preferred.

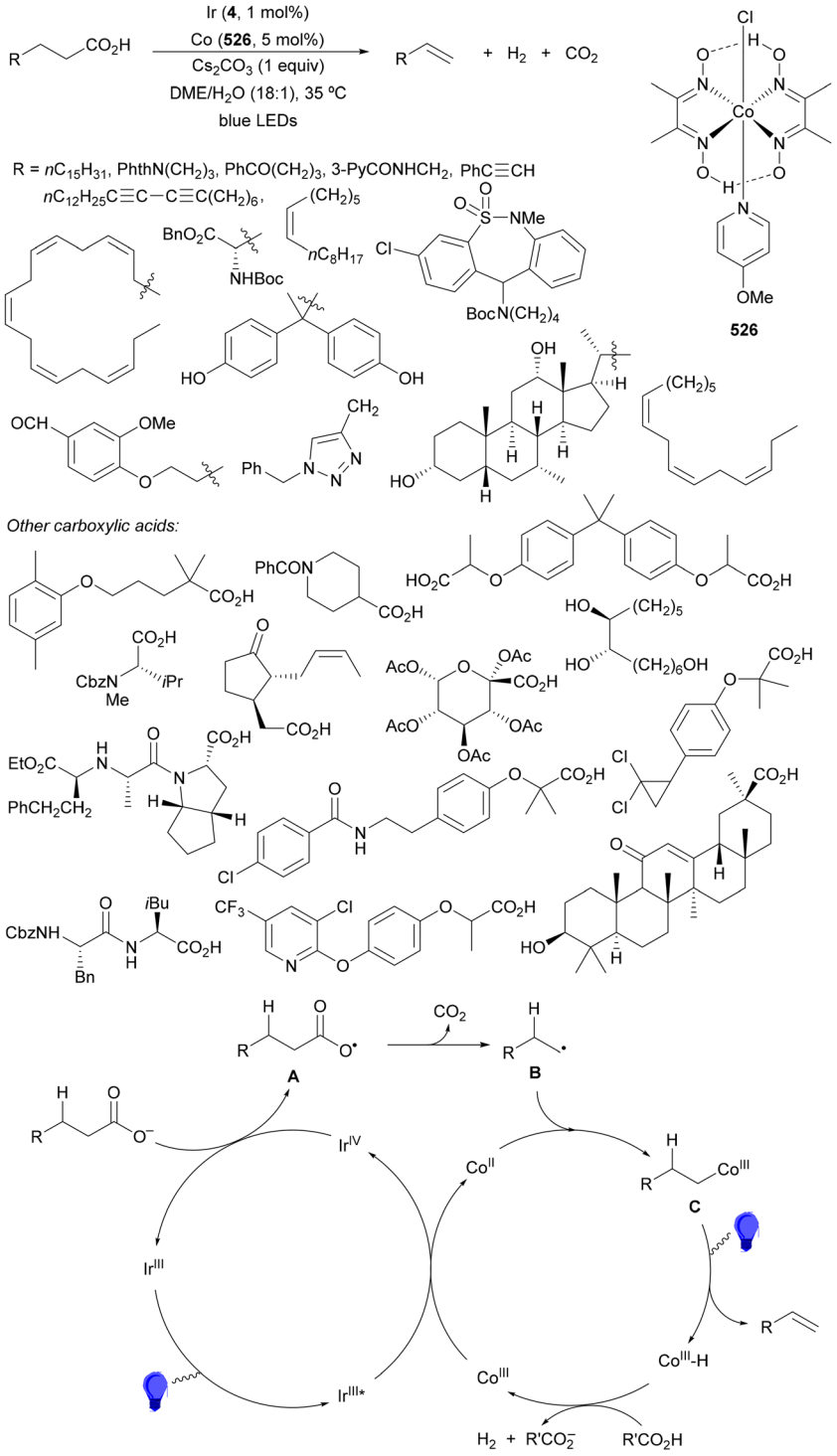
Carboxylic acids can be subjected to photoinduced decarboxylative protonation under homogeneous, heterogeneous and enzymatic conditions. For aliphatic carboxylic acids acridinium salts are the most appropriate PC in combination with thiols as HAT. In the case of α-keto acids aldehydes and deuteroaldehydes are obtained by hydro- and deuterodecarboxylation, respectively. For heterogeneous conditions Au@ZnO NPs and ceramic boron carbon nitrides are the best catalysts for aliphatic and aromatic carboxylic acids. Enzymatic processes are based on *Cv*FAP photodecarboxylase for aliphatic acids. Redox active esters derived from benzophenone oximes and aliphatic or aromatic acids have been deuterated under Ir complex as a PC. I the case of NHPI esters derived from cyclopropane carboxylic acids, the decarboxylation takes place under blue LED irradiation and a benzothiazoline as a HAT reagent to give diastereoselectively *cis*-1,2-diarylcyclopropanes.

5. Decarboxylative eliminations

In this section photoredox retro-hydrocarboxylation of aliphatic carboxylic acids and their NHPI esters to afford alkenes pioneered by Kochi[506] will be considered. Ring-opening of cyclic tertiary carboxylic acids by photoredox C–C bond cleavage will be included as well.

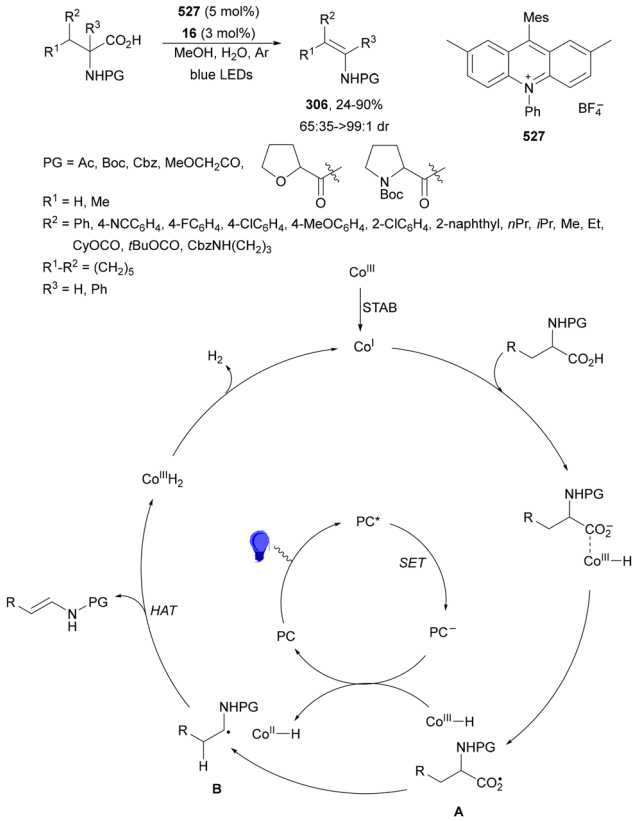
5.1. Retro-hydrocarboxylation

Ritter and co-workers[507] reported a decarboxyolefination of primary, secondary and tertiary aliphatic carboxylic acids by a



Scheme 278 Decarboxylative olefination of aliphatic carboxylic acids under dual Ir/Co photocatalysis.

cooperative interplay between a cobaloxime complex Co(dmgH)$_2$-(4-MeO-Py)Cl (**526**), as a proton reduction catalyst, and a Ir complex **4** as a photoredox catalyst. The resulting alkenes were obtained in good yields using Cs_2CO_3 as a base in DME/H_2O (18 : 1) at 35 °C under blue LED irradiation (Scheme 278). A broad range of carboxylic acids including jasmonic acid, picamilon, aleuritic acid, quinic acid, ciprofibrate, benzafibrate, tianeptine, haloxyfop, ramipril, Cbz–Phe–Leu, 18β-glycyrrhetinic acid and cholic acid were transformed into the corresponding alkenes. In the proposed mechanism, the carboxylate ion is oxidized by Ir(IV) to give radical **A**, which after decarboxylation generates an alkyl centered radical **B**. In the dehydrogenative



Scheme 279 Decarboxylative olefination of α-AAs under dual acridinium salt **16** and Co **527** photocatalysis.

catalytic cycle, Co(III)-hydride can release H_2 by protonation forming Co(III). This is reduced to Co(II) by Ir(III)*. This Co(II) complex accepts radical **B** providing complex **C**. Upon photolysis, homolytic cleavage of the Co–C bond followed by β-hydrogen abstraction by Co(II) produces the olefin and the Co(III)-hydride complex, which after protonation by the carboxylic acid regenerates the Co(III) catalyst.

The former catalytic strategy was simultaneously reported by Cartwright and Tunge[508,509] for the decarboxylative elimination of *N*-acyl AAs to enamides **306**. They used (Mes-2,7-Me_2-Acr-Ph)BF_4 (**527**) as a PC and cobaloxime Co(dmgH)$_2$ClPy (**16**) as a catalyst in aqueous MeOH under Ar and blue LED irradiation (Scheme 279). In this case, Co(III) was previously reduced to Co(I) by sodium triacetoxyborohydride (STAB) and Na_2CO_3 in refluxing methanol. Enamides **306** were obtained with good yields and moderate to good diastereoselectivities. This decarboxylative elimination would take place by protonation of the Co(I) complex by an α-AAs to give the Co(III)–H species and the α-AA carboxy radical **A**. Photooxidation of **A** followed by decarboxylation gives radical **B**. The reduced PC^- can reduce Co(III) to Co(II), which is a HAT acceptor of the β-C–H bond of the radical **B** to produce the product and Co(III)H_2, which after H_2 evolution regenerates the Co(I) catalyst. These reaction conditions were also applied to a variety of aliphatic carboxylic acids.[510]

Larionov and co-workers[511] reported a cooperative dehydrodecarboxylation of numerous aliphatic carboxylic acids including biomass and bioderived chemicals using acridine **123** and cobaloxime **16** as catalysts. The corresponding alkenes were obtained with, in general, very good yields working in DCM/MeCN (2 : 1) at room temperature under 400 nm LEDs irradiation (Scheme 280a). These reaction conditions are compatible with an enzymatic process LACo (lipase–acridine–cobaloxime) for conversion of triglycerides to long-chain alkenes. Amano lipase PS from *Burkholderia cepacia* was used in the cooperative chemoenzymatic LACo process in DCM/MeCN at pH 7 buffer solution of stearin **528** (glyceryl tristearate) to give alkene **529** in 74% yield (Scheme 280b). This LACo process was extended to other triglycerides, for instance glycerol tripalmitate (palmitin, 83% yield) and also to sunflower, canola, corn and soybean oils.

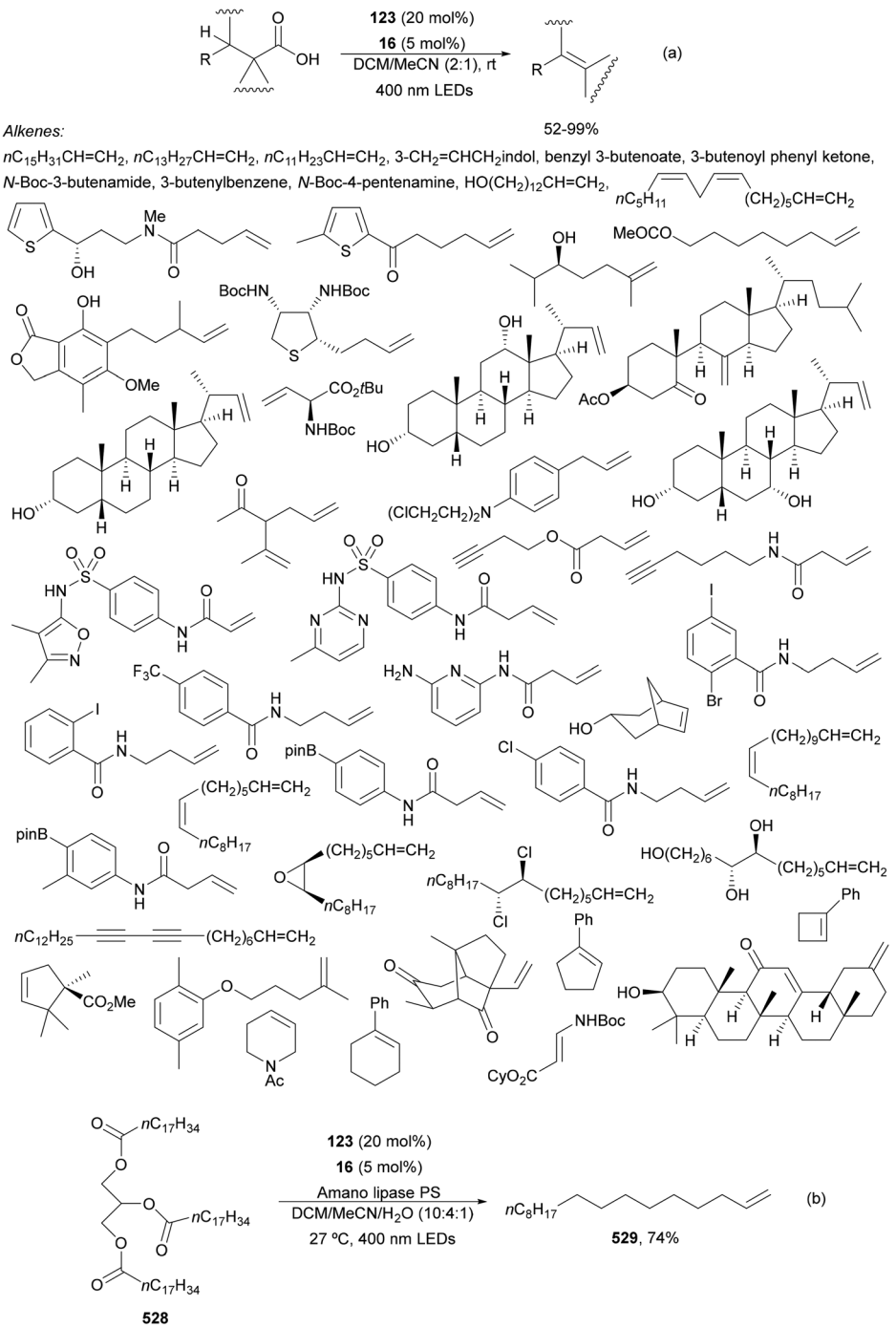
Hydrophobic two-dimensional lead and tin halide perovskites, prepared by intercalating 1-hexadecylammonium (HDA) cation between the inorganic layers, have been employed as PCs in the decarboxylative dehydrogenation of indoline acids to indoles.[512] As a conceptual demonstration $(HDA)_2PbI_4$ or $(HDA)_2SnI_4$ were employed as photoredox catalysts (1 mol%) in DCM under white LEDs irradiation in the presence of oxygen. The lead catalyst gave the best results, with 20–84% yields for indole and 5-bromo- and 5-chloroindole.

Photoinduced decarboxylative elimination of AAs or acyclic tertiary carboxylic acids has been achieved using $Fe(OAc)_2$ and $Cu(acac)_2$ as PCs, DTBP as an oxidant, DBU as a base in EtOAc at room temperature under 390 nm LED irradiation (Scheme 281).[53] This LMCT process has been applied to Giese reaction (Scheme 2) and amination reactions (Scheme 241). In the case of AAs, the efficient N–atom might stabilize the copper intermediate and promote the β-elimination instead of C–N bond reductive elimination to give enamines **306**. When the nitrogen is protected by an acetyl group a *Z*/*E* mixture of products was obtained. However, when a Boc group was used as a protecting group to form styryl derivatives only *Z*-products were obtained, what is an alternative to Tunge's work.[508,509]

Seidel, Sumerlin and co-workers[513] performed the degradation of polyacrylates by photoredox dehydrodecarboxylation followed by one-pot ozonolysis. Under Tunge's reaction conditions[508] (Scheme 279) carboxylic acids were converted into internal alkenes and oxidatively cleaved.

Decarboxylative olefination of NHPI esters **69** was reported by Glorius and co-workers[514] in 2018. Using a dihydrophenazine **530** as an organophotocatalyst and Cu(II) 2-ethylhexanoate as a catalyst in toluene at room temperature under Ar and 400 LED irradiation, the corresponding alkenes were obtained in general with good yields (Scheme 282). The mechanistic proposal started with a SET process by a photoexcited PC of the NHPI esters to give an alkyl radical **A** after CO_2 and $PhthN^-$ extrusion. This radical **A** is trapped by the Cu(II) catalyst leading to an alkylCu(/III) species **B**, which gives rise to an olefin and the Cu(I) intermediate **C** *via* an oxidative elimination process. This dual catalytic cycle is closed by SET between $PC^{+\bullet}$ and the Cu(I) species **C**.

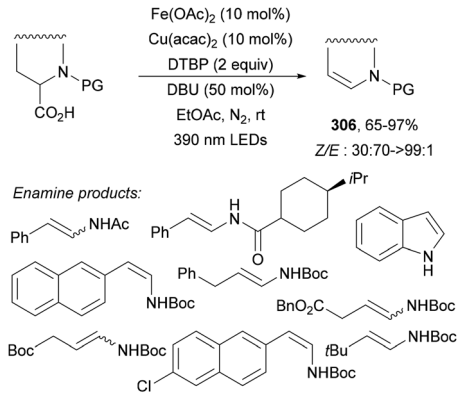
Palladium-catalyzed decarboxylative alkenylation of NHPI esters **69** has been achieved by a dual ligand system under blue LED irradiation.[515] Working with $PdCl_2$ as a metal source,



Scheme 280 Decarboxylative olefination of aliphatic carboxylic acids under acridine **123** and cobaloxime **16** photocatalysis.

Xantphos and Cy-Johnphos as ligands, 2,4,6-collidine as a base in DMA at room temperature under Ar, aliphatic alkenes, styrenes, enol ethers, enamides and peptide enamides were obtained in good yields and moderate to good diastereoselectivity (Scheme 283). This process was applied to a three-step synthesis of cytotoxic chondriamide A and C in 68% overall yield. Based on mechanistic studies, it was proposed that Pd(0) complex **A** coordinated with both Xantphos and Cy-Johnphos transfers one electron to NHPI ester inducing decarboxylation to form an alkyl radical and a Pd(I) intermediate (**B**). This intermediate **B** can dissociate one weakly coordinate phosphine ligand under irradiation to allow alkyl binding to undergo β-H elimination. The dissociate monodentate phosphine rebinds the Pd(0) catalyst after releasing the olefin.

An alternative method for the synthesis of olefins from NHPI esters **69** is based on an electron donor-acceptor (EDA) complex.[516] Using NaI (2 equivalents) in acetone under blue LED irradiation, alkyl NHPI esters were transformed into the

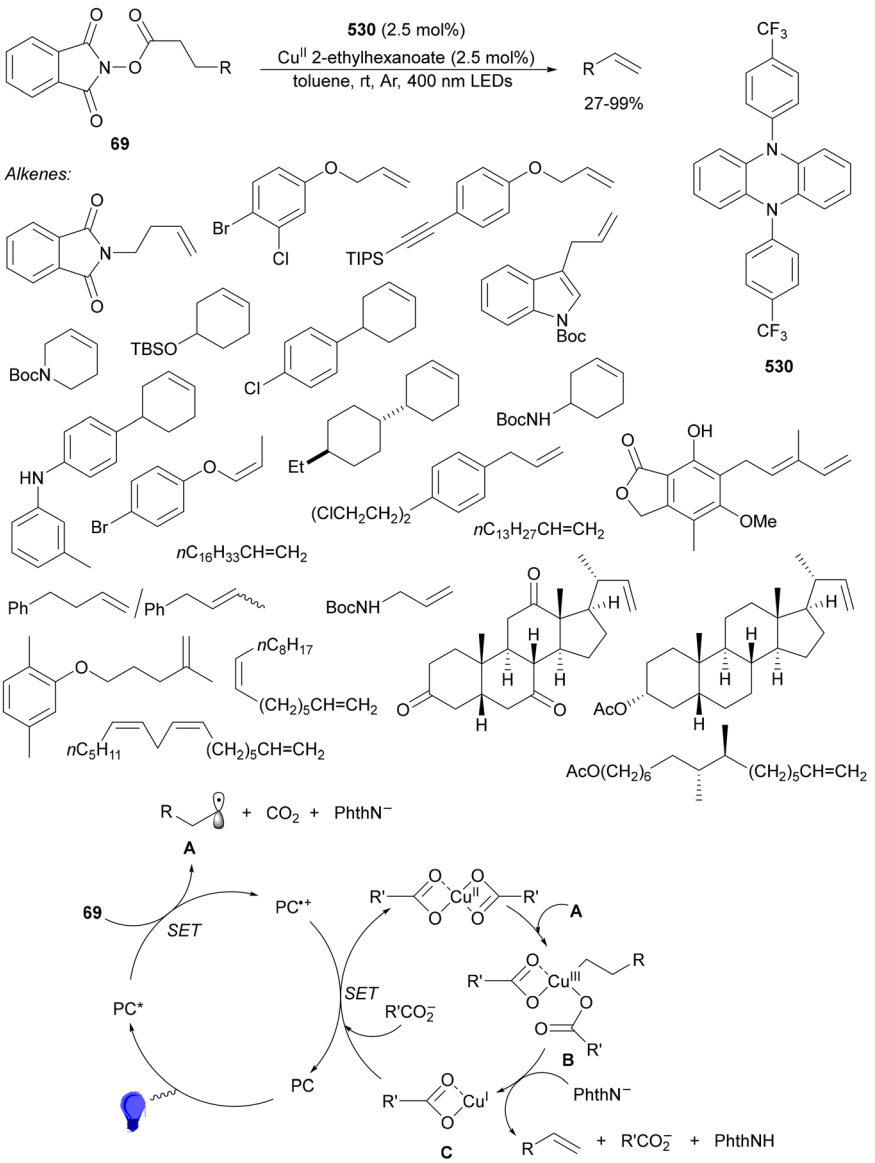


Scheme 281 Decarboxylative elimination of α-AAs under Fe/Cu LCMT photocatalysis.

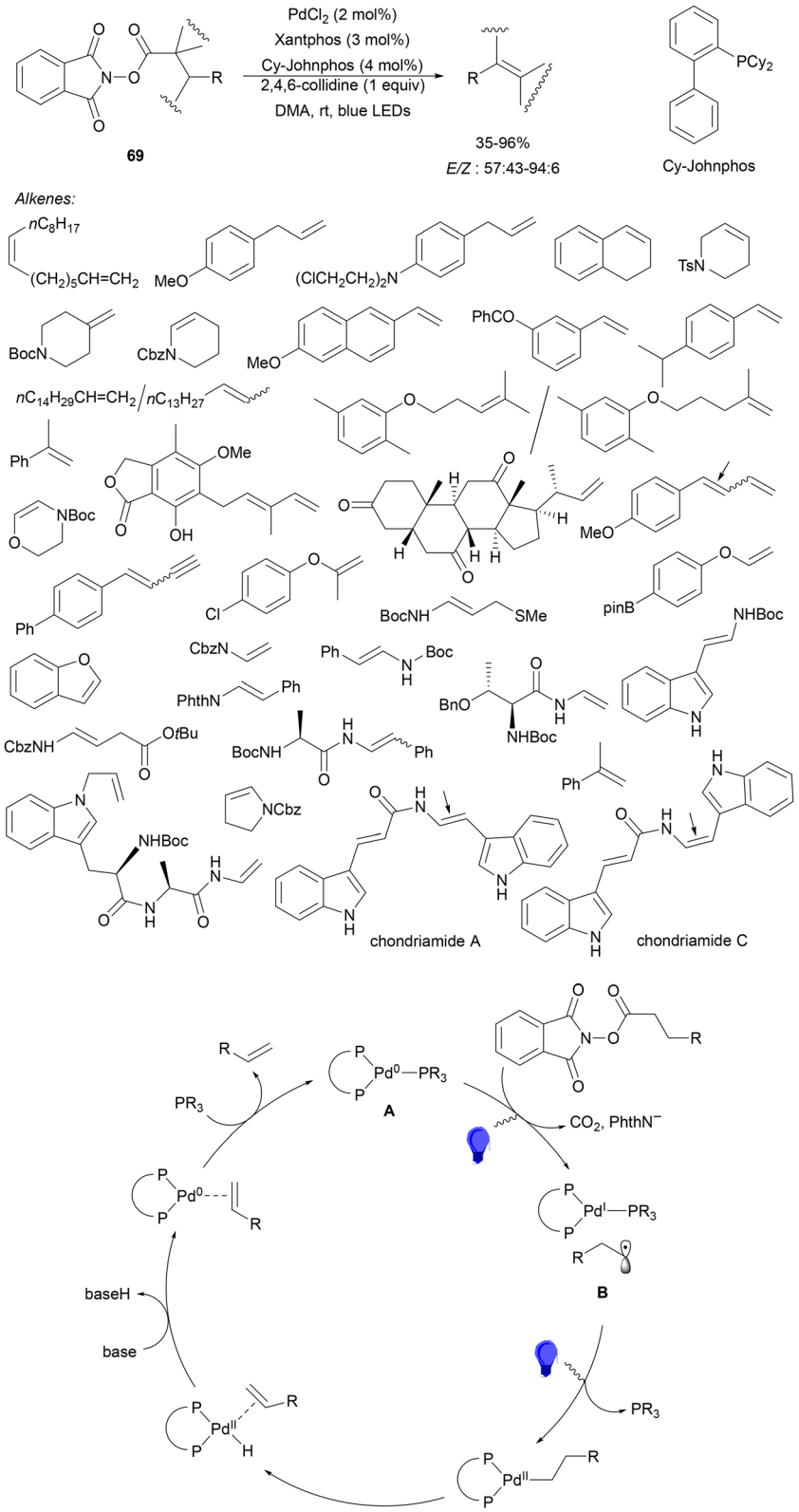
corresponding alkenes with very good yields (Scheme 284). This process probably takes place by formation of the EDA complex **A** between the NHPI ester and NaI, which after irradiation provides carbon centered radical **B** and iodine radical **C**. Subsequently, the iodine radical abstracts a hydrogen atom from radical **B** to form the olefin.

5.2. Decarboxylative C–C bond cleavage

Homolytic C–C bond cleavage of carbo- and heterocyclic carboxylic acids has been achieved by photoinduced ligand-to-metal charge transfer (LMCT, see Scheme 200).[383] This process was carried out with $Fe(acac)_3$ as a catalyst and DABCO as a base in MeCN at 35 °C under air and 390 nm LED irradiation to give 1,*n*-dicarbonyl compounds **531** with very good yields (Scheme 285a). In the proposed mechanism, the carboxylate–iron(III) complex **A** is formed, which after photoexcitation forms

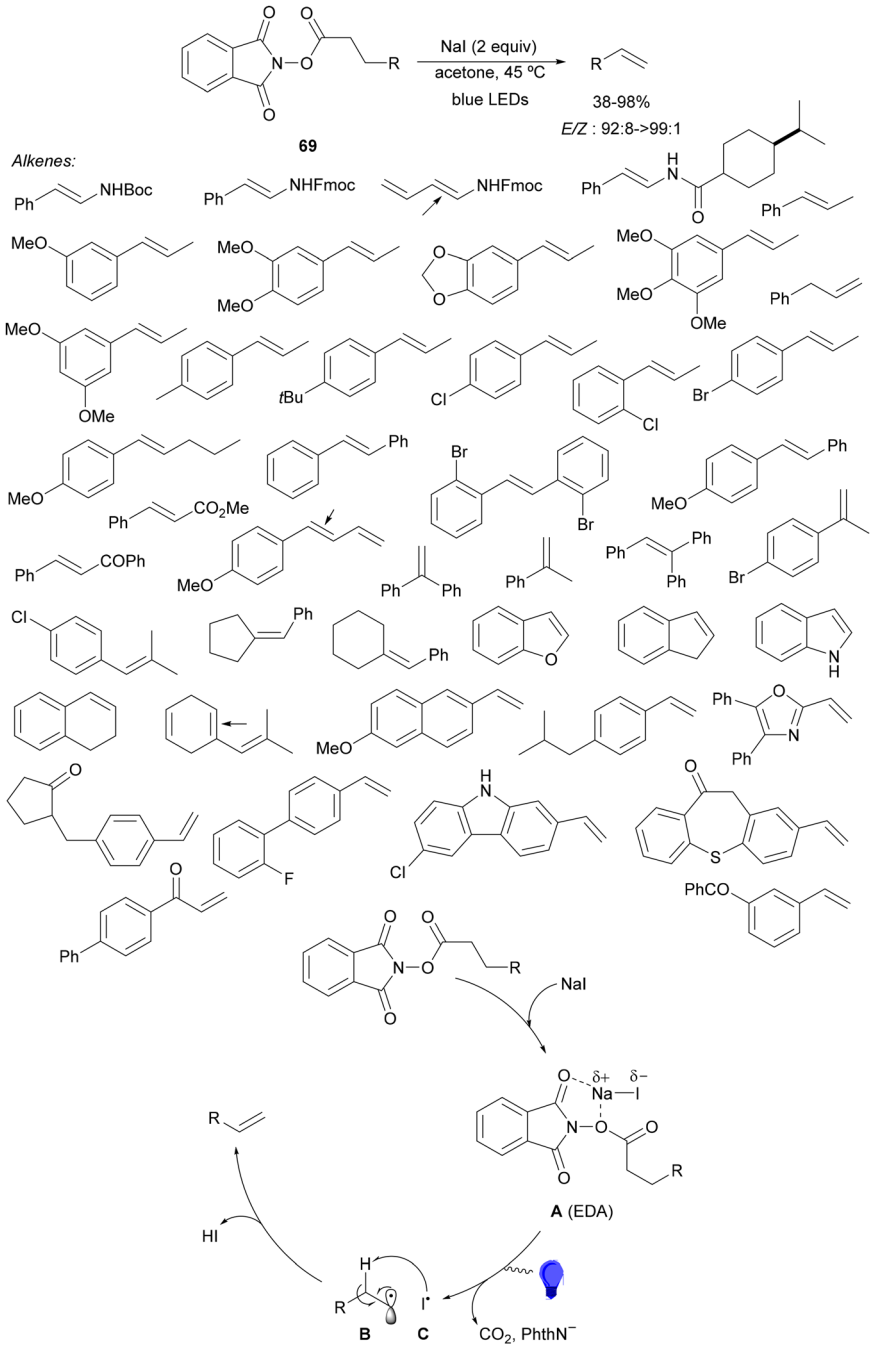


Scheme 282 Decarboxylative elimination of alkyl NHPI esters **69** under dihydrophenazine **530** and Cu(II) 2-ethylhexanoate photocatalysis.



Scheme 283 Decarboxylative olefination of alkyl NHPI esters **69** under Pd and synergistical ligands photocatalysis.

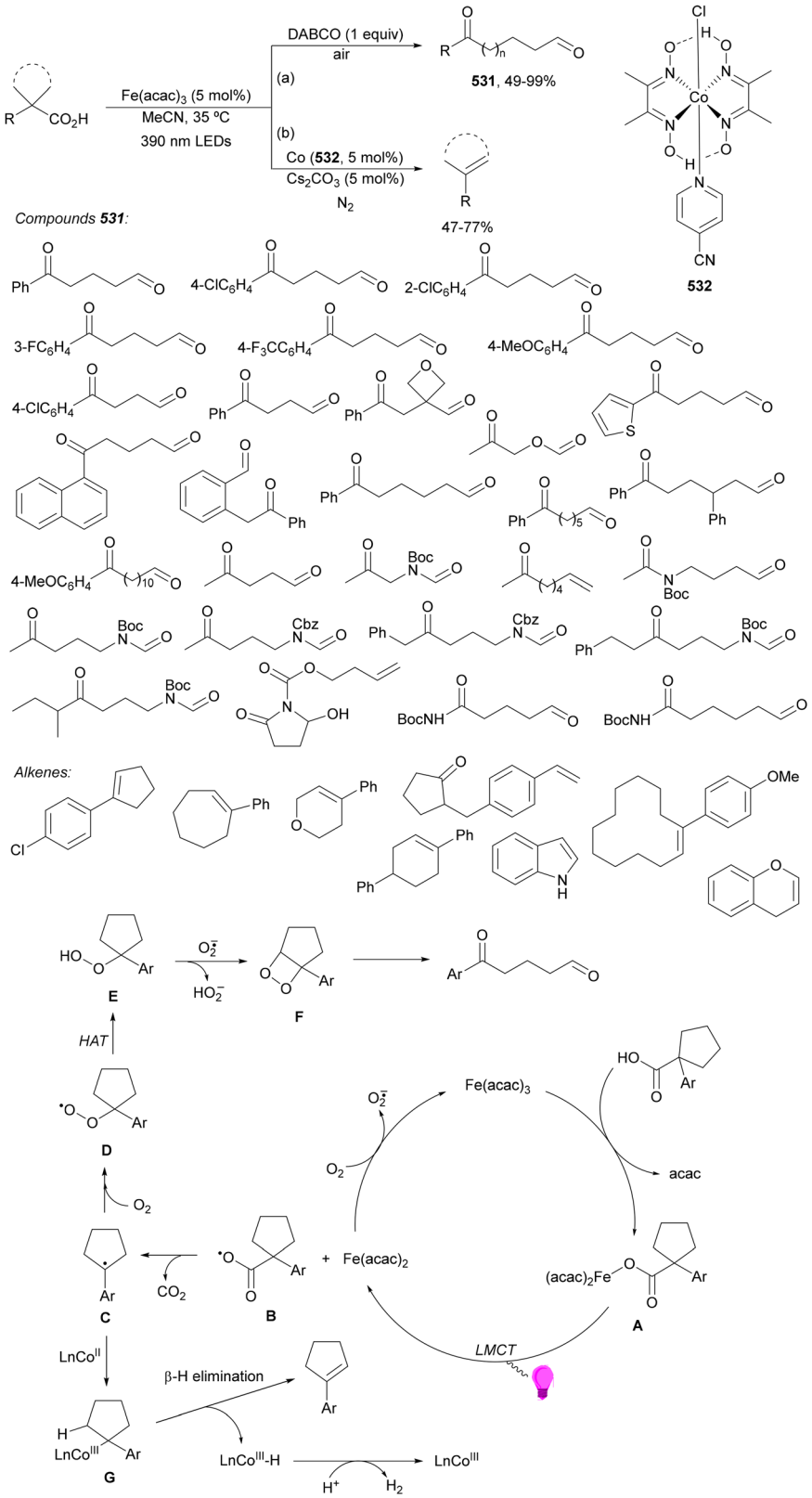
by LMCT the reduced Fe(II) complex and the carboxy radical **B**. Subsequent decarboxylation of **B** releases the carbon centered radical **C**. A SET process between dioxygen and Fe(II) regenerates the Fe(III) catalyst. Intermediate **C** can be trapped by oxygen to provide the peroxyl radical **D**, which by an intramolecular HAT gives intermediate **E**. Intermediate **E** reacts with the superoxide



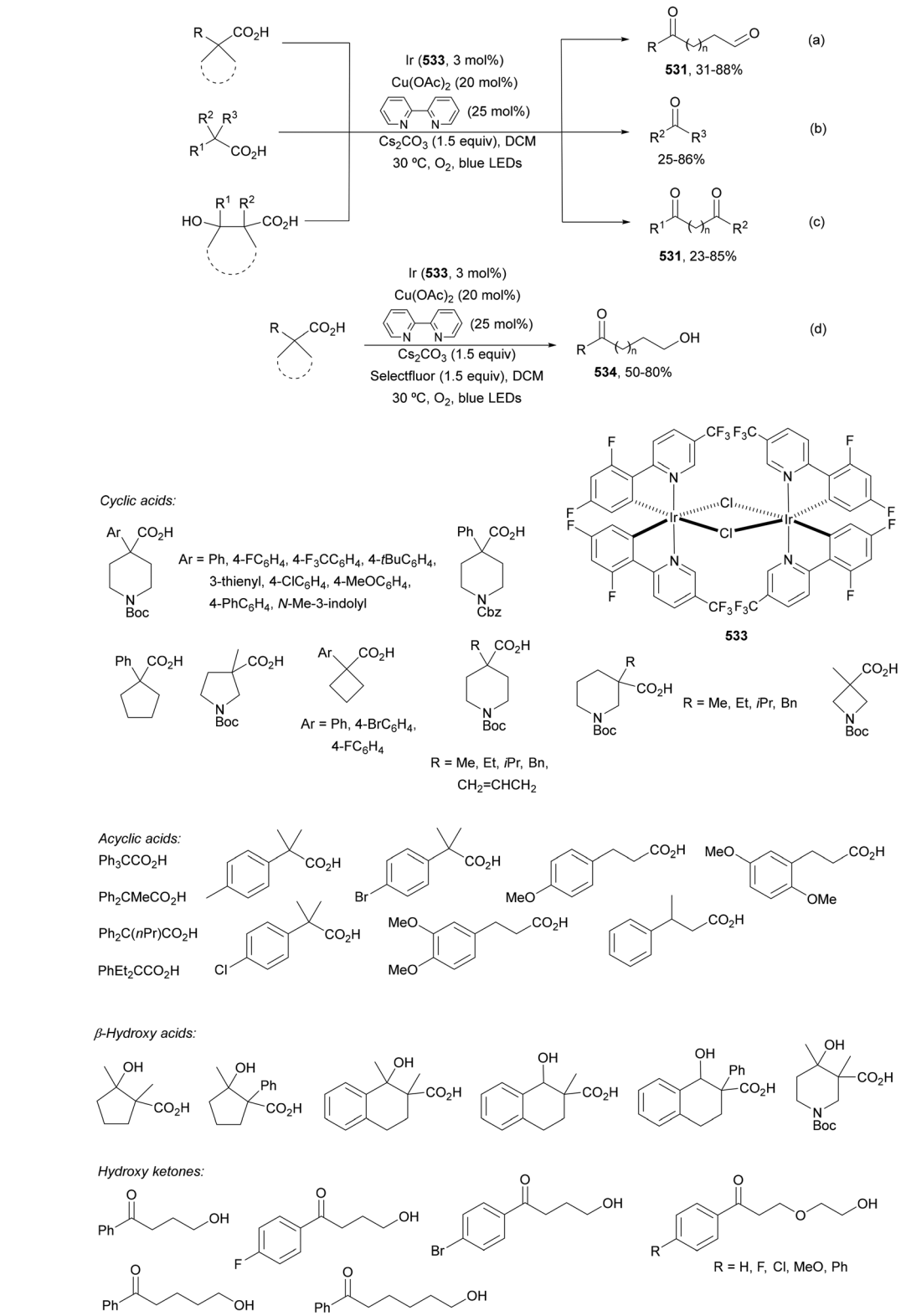
Scheme 284 Decarboxylative olefination of NHPI esters under NaI photocatalysis.

radical anion to form dioxetane **F**, which undergoes cleavage to yield the dicarbonyl product. When this Fe-catalyzed process was carried out in the presence of cobaloxime **532** and Cs_2CO_3 as a base a decarboxylative elimination process took place giving the corresponding alkenes with good yields (Scheme 285b). As a plausible mechanism, it was proposed that radical **C** reacts with Co(II) species to form the complex **G**, which after a β-H elimination step furnishes the alkene and the Co(III)–H species. This hydride reacts with a proton to form hydrogen and the Co(III) species serves to convert Fe(II) to Fe(III) to close the iron catalytic cycle.

Sun and co-workers[517] reported simultaneously the C–C bond cleavage not only of cyclic carboxylic acids but also of α-trisubstituted carboxylic acids. In this case, $[dF(CF_3)(ppy)_2\text{-}Ir\text{-}\mu Cl]_2$ complex **533** was used as a PC, $Cu(OAc)_2$ and 2,2′-bipyridine as a ligand, and Cs_2CO_3 as a base at 30 °C under air and blue LED irradiation provided 1,*n*-dicarbonyl compounds **531** and ketones for cyclic acids (Scheme 286a and b). Under these reaction conditions, cyclic β-hydroxy carboxylic acids were also transformed into 1,*n*-dicarbonyl compounds **531** (Scheme 286c). In addition, cyclic carboxylic acids were transformed into *n*-hydroxy ketones **534** when Selectfluor was



Scheme 285 Decarboxylative ring-opening of cyclic carboxylic acids under $Fe(acac)_3$ LMCT photocatalysis and decarboxylative elimination under Fe/Co photocatalysis.



Scheme 286 Decarboxylative C–C bond cleavage of carboxylic acids under Ir **533** and $Cu(OAc)_2$ photocatalysis.

added to the reaction mixture (Scheme 286d). All these transformations took place with, in general, good yields and were applied to the synthesis of drugs such as primaperone, melperone and haloperidol and the natural product sertraline. The proposed mechanism is similar to the one proposed by Xia's group.[383] In this case, Cu-catalysis promotes a last additional oxidative transformation by a second C–C bond cleavage.

Photoredox decarboxylative olefination of carboxylic acids can be carried out under Ir, acridinium salts and acridine as PCs and cobaloximes as proton reduction catalysis to give the corresponding alkenes. In the case of α-AAs, $Fe(OAc)_2$ and $Cu(acac)_2$ as dual catalysts and DTBP as an oxidant the corresponding enamides were obtained with moderate to high diastereoselectivity. NHPI esters have been transformed into alkenes using a dihydrophenazine as a PC and a Cu carboxylate under a LMCT process. Palladium-catalyzed processes need two type of ligands, a bidentate and a monodentate ones, allowing a broad scope of decarboxylative alkenylation. A simpler method is based on the formation of an EDA complex of the NHPI ester with NaI giving *E*-alkenes with very good diastereoselectivity. Decarboxylative C–C cleavage of cyclic carboxylic acids under $Fe(acac)_3$ photocatalysis and oxygen can be used for the synthesis of 1,*n*-dicarbonyl compounds under LMCT conditions. This process, in the presence of cobaloxime, allows the decarboxylative elimination. In the presence of Ir and $Cu(OAc)_2$, cyclic carboxylic acids and β-hydroxy acids were transformed into 1,*n*-dicarbonyl compounds.

6. Conclusions

Carbon–carbon bond-forming reactions by decarboxylative photocatalysis of carboxylic acids or active esters can be carried out by addition reactions to electron-deficient alkenes, hydroalkylation of alkenes and of alkynes and by addition to carbon heteroatom multiple bonds. $C(sp^2)$–$C(Csp^3)$ cross-coupling reactions are performed by arylation of carboxylic acid or active ester derived radicals with aryl halides. Alkylation reactions are appropriate for $C(sp^3)$–$C(sp^3)$ carbon–carbon bond-formation between alkyl, allyl and benzyl electrophiles and aliphatic carboxylic acids. For vinylation reactions, alkenyl halides and sulfones give the corresponding alkenes. A second strategy is a decarboxylative Heck-type reaction of aliphatic acids or their active esters with alkenes, and the third one employs cinnamic acids and active esters for this type of $C(sp^2)$–$C(sp^3)$ bond-forming reaction. Photoredox-mediated decarboxylative alkynylation of aliphatic carboxylic acids can be carried out using hypervalent iodine reagents. Acylation reactions of aryl halides are mainly performed with α-keto acids, oxalates and oxamic acids. Decarboxylative cyanations are carried out between TMSCN and active esters. For C–H functionalization reactions, decarboxylative alkylation, acylation and arylation procedures, mainly for heterocyclic compounds, can be performed.

The third section involves carbon–heteroatom bond-forming reactions by photoredox-mediated decarboxylation of carboxylic acids or their active esters. Aromatic, heteroaromatic and aliphatic acids have been halogenated mainly under metallocatalysis under different halogen sources. In the case of C–O bond-forming reactions, carboxylic acid oxygenation affords carboxy compounds. Decarboxylative etherification of carboxylic acids with alcohols resulted in the presence of hypervalent iodine reagents as well as acyloxylation. For C–S bond-forming reactions, thiolation, thioetherification, thioesterification, sulfilimination, sulfinylation and sulfonylation processes are possible for aliphatic carboxylic acids and their active esters. The corresponding thiols, thioethers, thioesters, sulfilimines, sulfinimides, sulfones, sulfinates, sulfonyl halides, sulfonamides and sulfonyl ketimines can be prepared. Decarboxylative C–N bond forming reactions involve mainly amination and amidation reactions and also azidation and hydrazination processes. In the case of C–P bond-forming reactions, chlorophosphines, phosphites, phosphine oxides and phosphonites are appropriate reagents mainly for active esters. White phosphorus can be employed for aliphatic carboxylic acids. Aliphatic and aromatic carboxylic acids and their active esters are transformed into boronates. For C–Si bond-formation, silacarboxylic acids transfer silyl radicals as well as trialkyl silanes.

Hydro- and deuterodecarboxylation reactions are considered in Section 4 for aliphatic carboxylic acids in the presence of thiols as HAT agents and water of deuterium oxide. In the case of α-keto acids, aldehydes or deuterated ones can be prepared. Heterogeneous conditions can be used for aliphatic and aromatic carboxylic acids. Enzymatic processes based on photodecarboxylase allow protodecarboxylation of aliphatic carboxylic acids.

In Section 5, decarboxylative elimination reactions such as retro-hydrodecarboxylation and decarboxylative C–C bond cleavage are described. In the first case, terminal alkenes and enamides can be prepared from aliphatic carboxylic acids and their active esters. This methodology has been applied to biomass and a broad range of bioactive molecules. Homolytic C–C bond cleavage of cyclic carboxylic acids and cyclic γ-hydroxy acids gives 1,*n*-dicarbonyl compounds.

Conflicts of interest

There are no conflicts to declare.

Abbreviations

AA	α-Amino acid
AAA	Asymmetric allylic alkylation
Ac	Acetyl
acac	Acetylacetonate
Acr	Acridine
Adm	Adamantyl
Admnsilane	Adamantylaminosupersilane
AFDC	3-Aminofluorene-2,4-dicarbonitrile
alk	Alkyl
amyl	Pentyl
API	Active pharmaceutical ingredient
AQ	Anthraquinone
Ar	Argon, aryl
BBI	*n*-Butoxybenziodoxole
BCN	Boron carbon nitrides
Beca P	Benzydryl-catechol-phosphite
BCP	Bicyclo[1.1.1]pentane
BET	Back electron transfer
BINAP	2,2′-Bis(diphenylphosphino)-1,1′-binaphthyl

BI-OAc	Acetoxybenziodoxole
BI-OH	Hydroxybenziodoxole
Biox	2,2′-Bis-2-oxazoline
Bn	Benzyl
Boc	*tert*-Butyloxycarbonyl
BP	Biphenyl
Bphen	Bathophenantroline, 4.7-diphenyl-1,10-phenantroline
Bpin	Pinacolate boron
BPO	Dibenzoyl peroxide
bptpy	2,6-Di(2-pyridyl)-3-(4-bromophenyl)pyridine
bpy	2,2′-Bipyridine
bpz	2,2′-Bipyrazine
BrettPhos	Dicyclohexyl-[2′,4′,6′-triisopropyl-3,6-dimethoxy-(1,1′-biphenyl)-2-yl]phosphine
BTMG	Barton base, 2-*tert*-butyl-1,1,3,3-tetramethyl-guanidine
BXM	Baloxavir marboxil
Bz	Benzoyl
C3G	Cyanidin-3-*O*-glucoside
CBX	Cyanobenziodoxolone
Cbz	Benzyloxycarbonyl
CDCB	Carbazolyldicyanobenzene
CFL	Compact fluorescent lamp
Chembead	Chemical-coated glass bead
10Ci-C_3H_4	Heterocatalyst from melamine and glyoxal
ClTXO	2-Chlorothioxanthem-9-one
CMA	9-Cyano-10-methoxycarbonylanthracene
CN	Cyano, carbon nitride
COF	Covalent organic framework
collidine	Trimethylpyridine
COSNAR	Carbonyl substitution nitrogen atom replacement
Cp	Cyclopentadienyl
CPA	Chiral phosphonium acid
CPME	Cyclopentyl methyl ether
CSA	Camphor sulfonic acid
CTC	Charge transfer complex
Cy	Cyclohexyl
4CzIPN	1,2,3,5-Tetrakis(carbazole-9-yl)-4,6-dicyanobenzene
DABCO	1,4-Diazabicyclo[2.2.2]octane
DABSO	1,4-Dithiabicyclo[2.2.2]octane bis(sulfur dioxide)
$DANNH_2$	1,8-Diaminonaphthalene
DAPO	Dialkyl phosphine oxide
dba	Dibenzylideneacetone
DBC	Dibenzo[*g*,*p*]chrysene
DBDMH	1,3-Dibromo-5,6-dimethylhydantoin
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DCA	9,10-Dicyanoanthracene, dicyanoarene
DCB	Dicyanobenzene
DCC	*N*,*N*′-Dicyclohexylcarbodiimide
DCE	1,2-Dichloroethylene
DCM	Dichloromethane
DCN	1,4-Dicyanonaphthalene
DEDC	*N*,*N*-Diethylthiocarbamate
DEL	DNA-encoded library
dF	Difluor
dFMeppy	2-(2,4-Difluorophenyl)-5-methylpyridine
DFT	Density functional theory
DGR	Decarboxylative Giese reactions
DHP	1,4-Dihydropyridine, 3,4-dihydropyran
DIC	Diisopropyl carbodiimide
DIPEA	Diisopropyl ethyl amine
DMA	*N*,*N*-Dimethylacetamide
DMAc	*N*,*N*-Dimethylacetamide
DMAP	4-Dimethylaminopyridine
DMC	Dimethyl carbonate
DMDC	Dimethyl dicarbonate
DME	Dimethoxyethane
dMebpy	4.4′-Dimethyl-2,2′-bipyridine
DMF	Dimethyl formamide
$dmgBF_2$	Difluoroboryl dimethylglyoxymate
$dmgH_2$	Dimethylglyoxime
dmp	2,9-Dimethyl-1,10-phenanthroline
DMP	Dimethoxyphenyl
DMPU	1,3-Dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidone
DMSO	Dimethyl sulfoxide
DNA	Deoxyribonucleic acid
4DPAIPN	1,2,3,5-Tetrakis(diphenylamino)-4,6-dicyanobenzene
DPZ	2,3-Dicyano-5,6-di[2′-(5′-methoxythienyl)]pyrazine
dr	Diastereomers ratio
dtbbpy	4,4′-Di-*tert*-butyl-2,2'dipyridyl
DTBP	Di-*tert*-butyl peroxide
EA	Electron acceptor
EBX	Ethylbenziodoxolone
ED	Electron donor
EDA	Electron donor-acceptor
ee	Enantiomeric excess
EPR	Electron paramagnetic resonance
equiv.	Equivalent(s)
ET	Energy transfer
EWG	Electron withdrawing group
$EYNa_2$	Disodium EosinY
FAP	Fatty acid photodecarboxylase
FAT	Fluorine atom transfer
FI	Fluorescein dye
FL	Flavin
Fmoc	9-Fluorenylmethyloxycarbonyl
FPIFA	Bis(trifluoroacetoxy)iodo pentafluorobenzene
GABA	γ-Amino butyric acid
gCN	Graphite carbon nitride
GSK	Glycogen synthase kinase
HAT	Hydrogen atom transfer
HBV	Hepatitis B viruses
HDA	Hexadecylammonium cation
HE	Hantzsch ester
Het	Heterocycle, heterocyclic
HFIP	Hexafluoroisopropanol
HIV	Human immunodeficiency viruses
HOMO	Highest occupied molecular orbital
HP	2,6-Dimethyl-3,5-di-(ethoxycarbonyl)pyridine

HRMS	High resolution mass spectroscopy
THE	High-throughput experimentation
IgA	Inmunoglobulin A
IPA	Isopropanol
Johnphos	(2-Biphenyl)di-*tert*-butylphosphine
kDa	Kilodalton
KHMDS	Potassium hexamethyldisilazide
L (Ln)	Ligand(s)
LACo	Lipase-acridine-cobaloxime
LED	Light-emitting diode
Leu	Leucine
LG	Leaving group
LMCT	Ligand to metal change transfer
LNPO23	Iptacopan, 4-{(2*S*,4*S*)-4-ethoxy-1-[(5-methoxy-7-methyl-1*H*-indol-4-yl)methyl]piperidin-2-yl}-benzoic acid
LUMO	Lowest unoccupied molecular orbital
lutidine	Dimethylpyridine
MB	Methylene blue
MBH	Morita–Baylis–Hilman
MBHA	Morita–Baylis–Hilman acetate
MCPBA	*meta*-Chloroperbenzoic acid
Mes	Mesityl, 2,4,6-trimethylphenyl
MIC	Methylisocyanide
MLR	Multivariate linear regression
M_n	Number-average molecular weight
Ms	Methanesulfonyl
MS	Molecular sieves
MW	Microwave irradiation
M_x/M_n	Polydispersity
NBS	*N*-Bromosuccinimide
NFSI	*N*-Fluorobenzene sulfonimide
NFTPT	1-Fluoro-1,3,5-trimethylpyridinum tetrafluoroborate
NHBC	*N*-Hydroxybenzimidoyl chloride
NHC	N-Heterocyclic carbenes
NHPI	*N*-(Acyloxy)phthalimide
NIS	*N*-Iodosuccinimide
NMP	*N*-Methylpyrrolidone
NMR	Nuclear magnetic resonance
NP	Nanoparticle(s)
Nu, NuH	Nucleophile
OEP	Octaethylporphirin
P25	Commercial photocatalyst
PARSE	Prospective analysis of the reaction space
PBC	*para*-Bromobenzoyl chloride
PC	Photocatalyst
PCET	Proton coupled electron transfer
Pent	Pentyl
PET	Photoinduced electron transfer, positron emission tomography
PG	Protecting group
PHA	Polyhydroxy acid
Phe	Phenylalanine
Phen	Phenanthrene
PHT	Benzophenothiazine
PhthN	Phthalimido
PIDA	Phenyliodine(III) diacetate
PIFA	Bis(trifluoroacetoxy)iodo benzene
pinB	Pinacolateboryl
PMB	*para*-Methoxybenzyl
PMP	*para*-Methoxyphenyl
PNH	Paroxysmal nocturnal hemoglobinuria
PP	Polypeptide
PPTNO	Pyrimidopteridine *N*-oxide
ppy	2-Phenylpiridine
Pro	Proline
PTH	*N*-Phenylbenzo[*b*]phenothiazine
PVAc	Polyvinyl acetate
Py	Pyridyl
PyCam	Pyridine carboxamide
rac	Racemic
RAE	Redox active ester
RAFT	Reversible addition-fragmentation chair-transfer
RFTA	Riboflavin tetraacetate
RLT	Radical-ligand transfer
rr	Regiosomers ratio
RS	Rose Bengal
rt	Room temperature
Sac	Saccharine
SAR	Structure–activity relationship
Selectfluor	Chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis(tetrafluoroborate)
SET	Single-electron transfer
SPINOL	3,3-Diaryl-1,1′-spiroblindane-7,7′-diol
Spy	S-2-Pyridyl
STAB	Sodium triacetoxyborohydride
TAPO	Trialkyl phosphine oxide
TBA	Tetra-*n*-butylammonium
TBAA	Tetra-*n*-butylammonium acetate
TBAC	Tetra-*n*-butylammonium chloride
TBADT	Tetra-*n*-butylammonium decatungstate
TBAF	Tetra-*n*-butylammonium fluoride
TBAI	Tetra-*n*-butylammonium iodide
TBDP	Tetra-*n*-butylphosphonium bromide
TBDPS	*tert*-Butyldiphenylsilyl
TBHP	*tert*-Butyl hydroperoxide
TBPB	*tert*-Butyl peroxybenzoate
TBS	*tert*-Butyldimethylsilyl
TCCA9	Trichloroisocynamic acid
TCNHPI	*N*-Hydroxytetrachlorophthalimide
TCYP	3,3′-Bis(2,4,6-tricyclohexylphenyl)-1,1′-bi-2-naphthol cyclic monophosphate
TEA	Triethylamine
TEBACl	Benzyltriethylammonium chloride
TEMPO	2,2,6,6-Tetramethylpiperidinyloxy
TES	Triethylsilyl
Tf	Triflic, trifluoromethylsulfonyl
TFA	Trifluoroacetic acid, trifluoroacetate
TFE	2,2,2-Trifluoroethanol
TIPS	Triisopropylsilyl
TMEDA	Tetramethylethylenediamime

TMG	1,1,3,3-Tetramethylguanidine
TMHD	Bis-(2,2,6,6)-tetramethyl-3,5-heptanedioate
TMP	3,4,7,8-Tetramethyl-1,10-phenanthroline
TMS	Trimethylsilyl
Tol	4-Methylphenyl
Tp	1,3,5-Trifromylphloroglucinol
Tp*	Tri-(2,5-dimethyl-1-pyrazolyl)borohydride
TPA	Tris-(2-pyridylmethyl)amine
TPP	Tetraphenylporphirine
Tr	Trityl, triphenylmethyl
TRIP	3,3′-Bis(2,4,6-triisopropylphenyl)-1,1′-binaphthyl-2,2′-diyl hydrogenphosphate
Ts	Tosyl, 4-methylphenylsulfonyl
TS	Transition state
TX	Thioxanthone
UV	Ultraviolet
Vis	Visible light
W	Watt, decatungstate
Xantphos	(9,9-Dimethyl-9*H*-xanthene-4,5-diyl)bis(diphenylphosphine)
XAT	Halogen atom transfer
XylBINAP	2,2′-Bis[di(3,5-xylyl)phosphino]-1,1′-binaphthyl

Data availability

No primary research results, software or code have been included and no new data were generated or analysed as part of this review.

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