Topics in Heterocyclic Chemistry 54
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Free-Radical Synthesis and Functionalization of Heterocycles

Springer

54
Topics in Heterocyclic Chemistry

Aims and Scope

The series Topics in Heterocyclic Chemistry presents critical reviews on present and future trends in the research of heterocyclic compounds. Overall the scope is to cover topics dealing with all areas within heterocyclic chemistry, both experimental and theoretical, of interest to the general heterocyclic chemistry community.

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Yannick Landais
Editor

Free-Radical Synthesis and Functionalization of Heterocycles

With contributions by

A. P. Antonchick · S. Chiba · S. Crespi · F. Dénès · M. Fagnoni · A. Gansäuer · S. Hildebrandt · J. Joseph · S. Kamijo · J. Lei · D. Li · J. Y. Mo · M. Rueda-Becerril · G. M. Sammis · C. Tejo · Q. Zhu

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Preface

After being considered as curiosities at the beginning of the last century, radicals have emerged as particularly useful intermediates for organic transformations. Radical organic chemistry thus enjoyed a rapid growth in the 1980s, principally due to the availability of a large amount of kinetic and thermodynamic data allowing rationalized organic transformations. While for a long time tin reagents remained essential to generate radical species, a wealth of "tin-free" methods have since appeared to overcome toxicity issues associated with the use of tin reagents. Recently UV-photochemical activation, also used for a long time to generate radical species, has undergone a renaissance with the rise of visible-light photoredox catalysis, certainly a hot topic in the field. Radical chemistry has thus rapidly become an indispensable tool, particularly in total synthesis, offering access to increasingly complex structures through cascade processes, most often avoiding the deleterious use of protecting groups. Complex heterocycles, including alkaloids or oxacycle natural products, are now accessible through multiple radical cyclizations. Small promising heterocyclic "lead" compounds in drug discovery, particularly relevant for pharmaceutical and agrochemical industries, may now be prepared in a limited number of synthetic steps based on radical processes.

This volume has thus been compiled to best describe the profound evolution of the field of radical chemistry in recent years and the impact on the synthesis of heterocycles. The various chapters deal with the functionalization of existing heterocyclic skeletons, but also the formation of heterocycles through cyclization of C-, O-, N-, P-, Si-centered radical species onto unsaturated moieties (alkenes, arenes, isonitriles, etc.). Particular attention has been paid to the mode of generation of these radical species. As mentioned above, the use of photosensitive catalysts to initiate radical processes is becoming prominent. A quick search for the term "photocatalysis" in a chemical database provided 46,000 occurrences for the period between 1970 and 2007 and 125,500 for the 2007–2017 decade, illustrating the recent blooming of "light activation" in radical chemistry. Following this trend, a chapter is dedicated to the photo-induced functionalization of inert C–H bonds with ensuing applications to the synthesis of heterocyclic skeletons. Oxidative and reductive electron transfers using catalytic amounts of metals and the subsequent

heterocycle formation through radical intermediates have also been highlighted. Finally, the last chapter is dedicated to the total synthesis of complex natural heterocycles, based on cascade radical processes, illustrating the mastery now acquired by organic chemists in the field of radical chemistry and the power of this tool in synthetic strategies.

Throughout the volume, relevant examples have been provided to delineate the scope and limitation of the discussed radical processes. Fundamental concepts and principles that govern radical transformations are discussed and mechanisms are often provided to offer a clear rationalization of the processes.

I am particularly grateful to all contributors, experts in the field, for agreeing to share their knowledge and take stock of the most recent and modern aspects of radical chemistry and its use in heterocycles formation. Their deep insights into radical processes and their enthusiasm to provide the readers the most recent illustration of the development of radical chemistry are acknowledged and will hopefully serve as a source of inspiration.

I hope that this volume will help the practitioners in their daily research and will convince those reluctant to use radical reactions that these processes may solve some of their synthetic problems.

Bordeaux, France Yannick Landais
January 2018

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Photocatalyzed Formation of Heterocycles

Stefano Crespi and Maurizio Fagnoni

Abstract Among the several approaches available for the formation of heterocycles, in the last years photocatalysis has become a unique tool. This peculiar strategy relies on the photocatalyzed formation of ground-state high-energy intermediates (e.g., radicals or radical ions) that furnishes the desired compounds upon a cyclization step, mostly involving an unsaturated or an aromatic moiety. The photocatalyzed approach is especially well suited for the formation of five- and six-membered rings containing oxygen and nitrogen, as detailed in the following.

Keywords Electron transfer • Photocatalysis • Radical ions • Radicals • Visible light

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1 Introduction

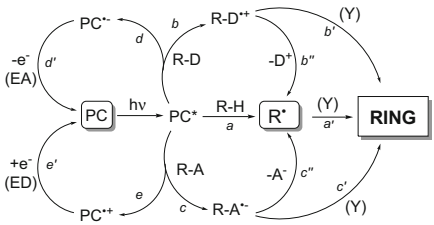
As apparent from this book, the synthesis of heteroaromatic derivatives is of crucial importance due to their biological activities and to their typical molecular scaffolds, ubiquitous in materials science, life science, and pharmaceuticals [1–6]. The preparation of these compounds is mainly based on two strategies, namely, the functionalization of a preexisting ring or the construction of a new ring, and radicals are often used for these purposes. In this respect, photochemistry is a valid and eco-sustainable tool for the smooth generation of reactive intermediates (e.g., radicals or radical ions) [7, 8]. In the last years, photocatalyzed processes have gained a primary role in the clean preparation of valuable compounds [9–15]. This is mainly due to the ability of the photocatalyst to act as a good oxidant (or reductant) in the excited state, being able to promote the so-called photoredox catalysis [9–15]. The photocatalysts may belong to different classes, including aromatic ketones, cyanoarenes, dyes, or other organic compounds as well as metal complexes [9–15]. Redox potentials of representative photocatalysts (PCs) used in the photocatalyzed synthesis of heterocycles are gathered in Table 1. As apparent from the table, the excited state of the PCs may oxidize (up to 2.32 V vs. SCE) or reduce (up to −1.76 V vs. SCE) the desired organic compounds, forming the corresponding radical ion or a radical (if the reagent is charged).

Alternatively, a PC may be able to perform hydrogen atom transfer (HAT) reactions by homolytic cleavage of a C–H bond in organic molecules and the resulting radical then involved in a cyclization process [18]. Sparse reviews may be found dealing with the photocatalyzed construction of rings containing a heteroatom [17, 19–25].

Table 1 Redox potentials (in V vs. SCE) of selected photocatalysts (PCs)

Photocatalyst (PC)[a]	E_{red} (PC/PC$^{\bullet-}$)	E_{ox} (PC$^{\bullet+}$/PC)	E^*_{red} (PC*/PC)	E^*_{ox} (PC$^{\bullet+}$/PC*)	Ref.
Rose Bengal	−0.78	1.09	0.99	−0.68	[11]
Acr^+Mes	−0.43		2.32		[11]
Eosin Y	−1.14	0.72	1.18	−1.60	[11]
TPT^+	−0.35		2.30		[15]
DCA	−0.89		1.97		[11]
DCN	−1.28		2.19		[16]
Benzophenone	−1.68		1.55		[11]
Phenanthrene	−2.49	1.83	1.10	−1.76	[11]
$Ru(bpy)_3^{2+}$	−1.33	1.29	0.84	−0.86	[17]
$Ru(bpz)_3^{2+}$	−0.80	1.86	1.45	−0.26	[17]
$Ru(phen)_3^{2+}$	−1.36	1.26	0.82	−0.87	[17]
fac-$Ir(ppy)_3$	−2.19	0.77	0.31	−1.73	[17]
$Ir(ppy)_2(dtbbpy)^+$	−1.51	1.21	0.66	−0.96	[17]

[a]*Acr^+Mes* 9-mesityl-10-methylacridinium cation, *TPT^+* 2,4,6-triphenylpyrylium cation, *DCA* 9,10-dicyanoanthracene, *DCN* 1,4-dicyanonaphthalene



Scheme 1 Typical mechanistic pathways for the photocatalyzed formation of a heterocycle

PC = Photocatalyst; ED = Electron Donor; EA = Electron Acceptor

The aim of this review is to gather representative examples of those photocatalyzed reactions that lead to the generation of radicals or radical ions, which will then be used for the construction of a ring. The simple functionalization of heterocycles/heteroaromatics will not be treated here. The rings are usually formed by the intramolecular radical/radical ion addition onto an unsaturated core (either a double bond, a triple bond, or an aromatic) or an intramolecular closure following the first radical addition step. Scheme 1 roughly gives an idea of the typical processes involved.

The excited PC (PC*) should be able to abstract a hydrogen from an organic compound (R–H, path a), and the resulting radical may react with a suitable reagent (Y) and form a ring (path a′). However, despite the great potential of the method, this is a rare occurrence. The alternative is an oxidative pathway that involves an electron abstraction from an organic molecule (R–D) to form the corresponding radical cation (path b), and the ring could be formed either by reaction with Y (path b′) or via fragmentation to give a radical and the concomitant release of an electrofugal group D^+ (path b″). A corresponding reductive pathway generates a radical anion (path c) and the ring again by reaction with a reagent Y (path c′) or by the elimination of an anion A^- (path c″).

In order to regenerate the PC, either an electron acceptor (EA, path d′) or an electron donor (ED, path e′) is required, unless an intermediate formed in the reaction may serve to this aim. In other cases, $PC^{\bullet-}$ or $PC^{\bullet+}$ may function as effective photoactive species in the generation of radicals/radical ions.

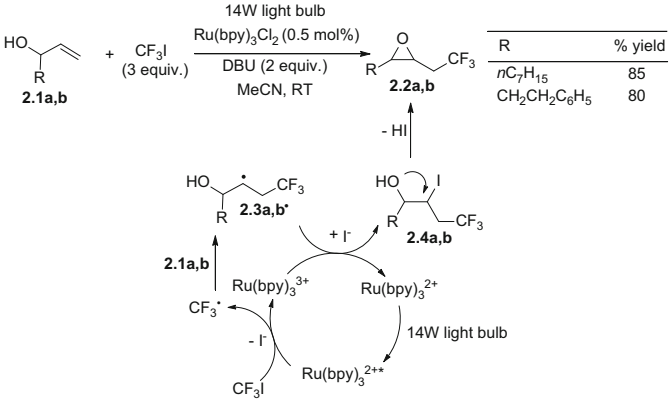
The reductive pathway is the preferred one since several radicals may be formed including CF_3, C_nF_{2n+1}, and alkyl, malonyl, imidoyl, aryl, α-oxy, or α-keto radicals. The oxidative pathway is usually preferred for the formation of α-amino radicals.

2 Three- and Four-Membered Ring

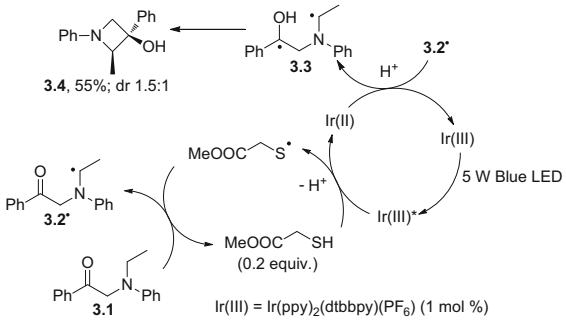
The construction of a three-membered ring under photocatalyzed conditions is quite uncommon. Epoxides were formed starting from the corresponding alkenes where *t*-BuOOH (or O_2) functioned as oxygen source. Recent examples include the Ru (III)-photocatalyzed reaction of styrenes with aromatic aldehydes for the synthesis of α,β-epoxy ketones [26] and the epoxidation of cyclic olefins by using titanium

dioxide–cobalt–ascorbic acid nanohybrid as the photocatalyst [27]. In the latter case, the epoxides could be prepared in up to quantitative yield, and, noteworthy, the catalytic system could be reused at least five times. A more versatile approach is shown in Scheme 2 since both CF_3-containing epoxides and aziridines were prepared starting from allyl alcohols and allylamines, respectively [28]. The CF_3 radical, generated by the Ru(III)-photocatalyzed reduction of CF_3I, added to the double bond of the allyl alcohols **2.1a**,**b**, and further oxidation, followed by iodide addition, allowed the formation of iodo alcohols **2.4a**,**b**, which upon intramolecular cyclization gave the desired epoxides **2.2a**,**b** in a very good yield (Scheme 2).

To our knowledge, photocatalyzed formation of four-membered rings is quite rare. An example is depicted in Scheme 3. The strategy is based on the photocatalyzed formation of a ketyl and a α-amino radical in one catalytic cycle and on their intramolecular radical-radical coupling. The photogenerated thiyl radical (from methyl thioglycolate) was first able to form α-amino radical **3.2**$^{\bullet}$ by a HAT reaction. Then, **3.2**$^{\bullet}$ was subjected to a proton-coupled electron transfer to form biradical **3.3**, which upon cyclization gave 2-methyl-1,3-diphenylazetidin-3-ol **3.4** in a modest yield. The reaction was performed in DMF and required K_2HPO_4 (0.2 equiv.) to occur [29].



Scheme 2 Formation of epoxides through photocatalyzed trifluoromethylation of allylic alcohols



Scheme 3 Photocatalyzed synthesis of azetidin-3-ol derivatives

3 Five-Membered Ring

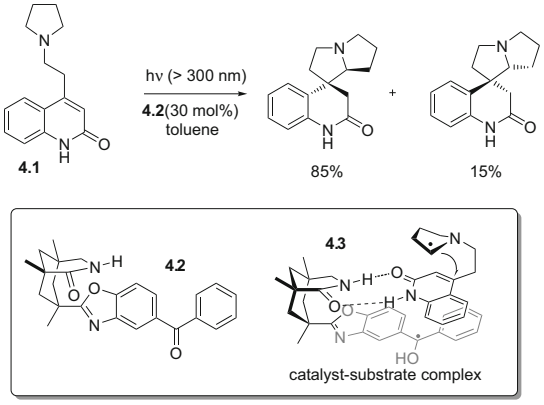
The importance of the five-membered ring motif containing a heteroatom led to the development of a plethora of different photocatalytic protocols to obtain whether aromatic or nonaromatic derivatives.

3.1 Nitrogen-Containing Heterocycles

3.1.1 Nonaromatic

The pyrrolidine motif is extremely appealing for synthetic chemists and biochemists due to its ubiquity in various natural and nonnatural compounds, being the main core of a wide number of organocatalysts and building blocks in organic synthesis. A seminal work was the enantioselective synthesis of nitrogen-based five-membered rings via a photoinduced electron transfer reaction (Scheme 4) [30]. The reaction is driven by an electron-accepting chiral organocatalyst **4.2**, which is able to bind the substrate through hydrogen bonding. The PET (photoinduced electron transfer) reaction between the carbonyl moiety of the organocatalyst and the pyrrolidine ring in **4.1** (see formula **4.3**) allowed to obtain the product in a significant enantiomeric excess.

However, the vast majority of the reports now present in the recent literature apply photoredox catalysis to build up the pyrrolidine ring making use of several strategies. Photocatalysis involving dimeric gold complexes [31] was applied to cleave carbon-halogen bonds starting from vinyl halides bearing a nitrogen on the tethered chain [32]. The carbon radical thus formed cyclized on the double bond, eventually leading to the desired heterocyclic structure. The key radical intermediate in the last transformation can also be obtained starting from a radical addition

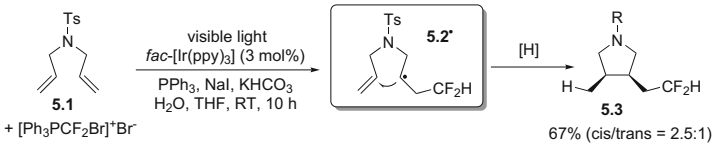


Scheme 4 Enantioselective synthesis of nitrogen-based five-membered rings

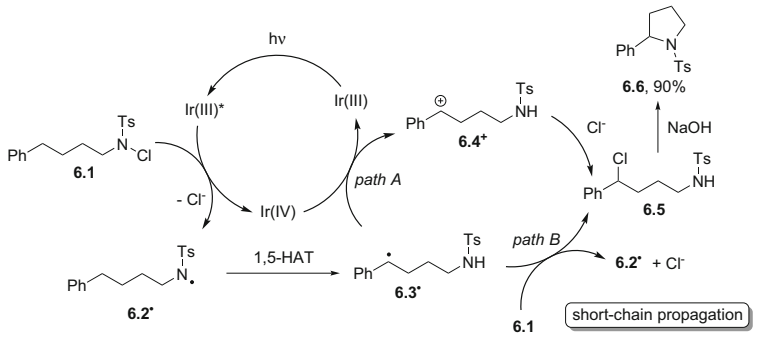
onto a diallyl-substituted amine **5.1**, forming radical **5.2**$^{\bullet}$. This strategy was widely applied by using fluorinated radicals and pyrrolidines **5.3** incorporating hydrodifluoromethyl (Scheme 5) [33], trifluoromethyl [34], or perfluoropropyl [35] groups which were thus synthesized.

An alternative route involving a related carbon–carbon bond formation is offered by the visible light-driven asymmetric intramolecular ketyl/α-amine radical coupling, via proton-coupled electron transfer (PCET), without an extra sacrificial electron donor [29]. The irradiation of variously substituted keto-amines with visible light in the presence of $Ir(ppy)_2(dtbbpy)PF_6$, K_2HPO_4, and methyl thioglycolate in DMF led to the formation of pyrrolidines in high yields (up to 93%) with good diasteroselectivity (from 1.4:1 to 20:1 in favor of the cis configuration) [29].

In order to obtain the pyrrolidine core, C–N bond-forming reactions were likewise useful. An interesting example is testified by the C−H amination/amidation protocol that involves the formation of nitrogen-centered amidyl radical **6.2**$^{\bullet}$ from *N*-chloro tosylamide **6.1** under visible-light irradiation (Scheme 6) [36]. This transformation lays its foundations on the Hofmann−Löffler−Freytag (HLF) reaction, discovered in the late nineteenth century [37], and starts with the photocatalyzed cleavage of the N–Cl bond. In the proposed mechanism, the excited Ir(III) photocatalyst is oxidatively quenched by **6.1**, with generation of an Ir(IV) species and a nitrogen-centered radical **6.2**$^{\bullet}$, respectively. The latter undergoes an intramolecular 1,5-hydrogen atom transfer (1,5-HAT), forming the benzyl radical **6.3**$^{\bullet}$, that is easily oxidized into carbocation **6.4**$^{+}$ by Ir(IV) with regeneration of Ir(III) (path A, Scheme 6). Cation **6.4**$^{+}$ is trapped by the chloride ion to give the chlorinated product **6.5** that, under basic conditions, can easily cyclize to the desired pyrrolidine **6.6** in high yield. The authors,



Scheme 5 Ir(III)-photocatalyzed preparation of pyrrolidines



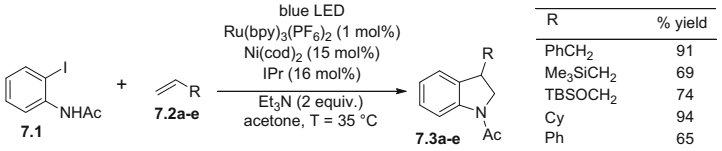
Scheme 6 Synthesis of a pyrrolidine core via intramolecular 1,5-hydrogen atom transfer reaction

however, did not exclude the presence of a short-chain propagation mechanism (path B, Scheme 6).

Another reaction based on a scheme that clearly resembles the Hofmann–Löffler–Freytag reaction involved a catalytic photoredox hydroamination of olefins [38]. In the specific example, an aminium radical cation is formed after selective oxidation of a phenylamine with an acridinium photocatalyst. Its intramolecular attack onto an alkene followed by a single-electron transfer and a proton transfer step led to the five-membered heterocycle [38].

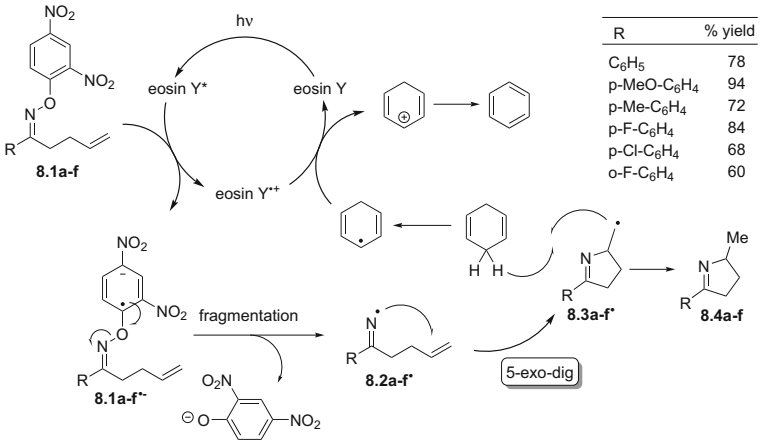
As for the synthesis of indolines, the majority of the methods described requires several steps [39]. A nice entry that circumvents this drawback makes use of a dual nickel/photoredox catalysis [40], allowing a highly regioselective access to 3-substituted indolines **7.3a–e** (Scheme 7). The reaction made use of a broad selection of both styrenyl and aliphatic olefins **7.2a–e** as starting materials. On the other hand, better results were obtained with a 2-iodoacetanilide **7.1** substituted in 4- or 5-position as the coupling reagent and by raising the temperature to 35°C.

Even though pyrroline is present in a huge variety of natural compounds [41], examples regarding photocatalytic synthetic methodologies to access this core are fairly limited in number. A recent report was based on an eosin-Y catalyzed reaction of functionalized *O*-aryl oximes (Scheme 8) [42]. These compounds serve as bench stable nitrogen-centered radical precursors that could deliver iminyl



R	% yield
$PhCH_2$	91
Me_3SiCH_2	69
$TBSOCH_2$	74
Cy	94
Ph	65

Scheme 7 Synthesis of indolines by dual nickel/photoredox catalysis



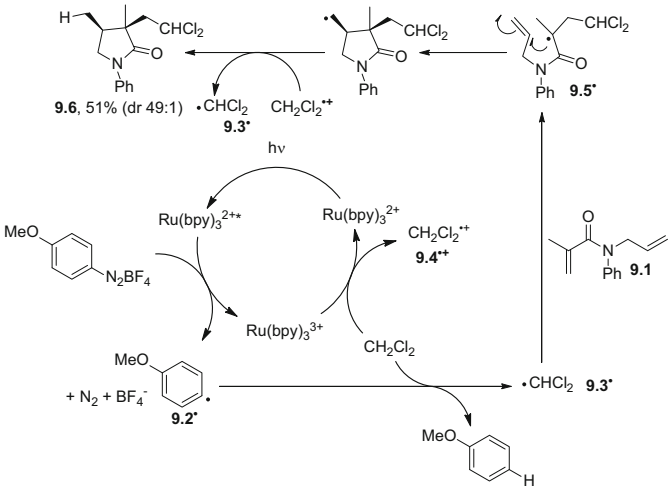
R	% yield
C_6H_5	78
p-MeO-C_6H_4	94
p-Me-C_6H_4	72
p-F-C_6H_4	84
p-Cl-C_6H_4	68
o-F-C_6H_4	60

Scheme 8 Photocatalyzed construction of the pyrroline ring from *O*-aryl oximes

radicals by means of photoredox activation under mild conditions [43]. In order to tune the imine reduction potentials, electron poor aryls were incorporated in hydroxylamines **8.1a–f**. The excited photocatalyst reduces **8.1a–f** to give radical anion **8.1a–f**$^{\bullet-}$. This unstable species easily fragments, due to the low N–O bond dissociation energy [44], to give the desired nitrogen-centered radicals **8.2a–f**$^{\bullet}$. The facile 5-exo-trig ring closure leads to the primary radicals **8.3a–f**$^{\bullet}$ that is reduced by cyclohexadiene, used as sacrificial donor, to form pyrrolines **8.4a–f**. More interestingly, the authors speculated that a simple tertiary amine could interact with the aryl moiety of **8.1a–f** [42], forming a donor-acceptor complex that could absorb visible light [45–47]. These considerations paved the way for the development of an unprecedented Et_3N-visible-light-mediated iminohydroxylation cyclization, where the aryl unit sequentially acts as a sensitizer, electron acceptor, and oxidant [42]. A variation of this methodology was later described having recourse to *O*-acyl oximes [48].

N-Methyl pyrrolidone is one of the main pharmaceutical co-solvents and can be used as an excipient in drugs, and the presence of the pyrrolidone scaffold in natural products is largely documented. A strategy to access pyrrolidone derivatives consists in building the ring via a C–C bond formation.

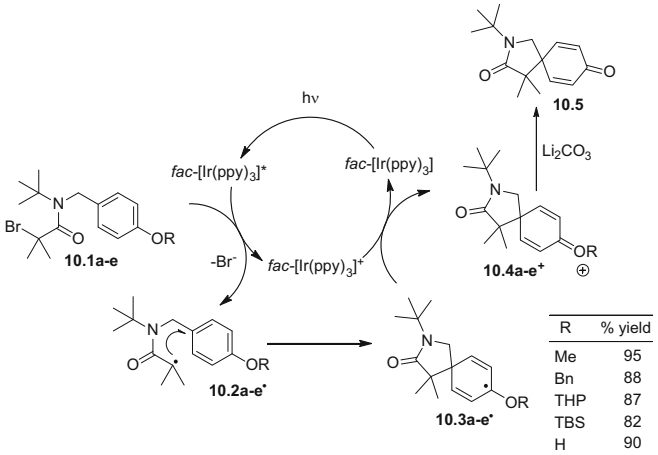
A first approach is conceptually similar to the one presented in Scheme 5, where an allyl-substituted acrylamide **9.1** is used instead of the amine **5.1** (Scheme 9) [49]. Initially, the 4-$MeOC_6H_4N_2BF_4$ salt is converted into the 4-methoxyphenyl radical **9.2**$^{\bullet}$ by visible light $Ru(bpy)_3Cl_2$-photocatalyzed reduction [50]. The catalyst is regenerated by oxidation of dichloromethane, forming radical cation **9.4**$^{\bullet+}$. The faith of **9.2**$^{\bullet}$ in dichloromethane is to abstract hydrogen from the medium, leading to anisole, while generating radical **9.3**$^{\bullet}$. Attack of **9.3**$^{\bullet}$ onto **9.1** followed by the 5-exo-trig cyclization of the thus obtained radical **9.5**$^{\bullet}$ led to pyrrolidone **9.6** (51% yield).



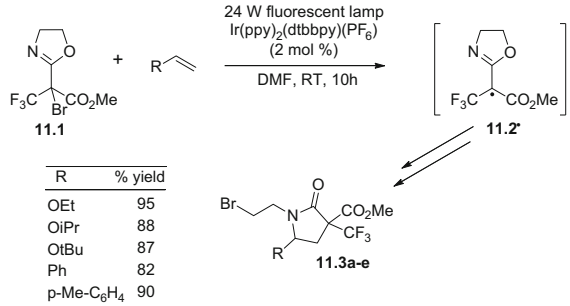
Scheme 9 Ru(II)-mediated decomposition of diazonium salts for the synthesis of pyrrolidones

A similar approach made use of rhodamine B as the PC for the cleavage of the C–I bond in *i*-C_3F_7I to generate a carbon-centered radical that added to an allyl acrylamide [51]. Another ingenious example of C–C bond cyclization to obtain pyrrolidone cores is testified by the highly regioselective dearomative cyclization of α-bromo-*N*-benzyl-alkylamides **10.1a–e** (Scheme 10) [52]. A single-electron transfer between the excited *fac*-[Ir(ppy)$_3$]* and bromoamides **10.1a–e** generated the electrophilic radicals **10.2a–e**$^{\bullet}$, after bromide loss. Cyclization of **10.2a–e**$^{\bullet}$ onto the aromatic ring led to the dearomatized intermediate **10.3a–e**$^{\bullet}$ that upon oxidation into the corresponding cation **10.4a–e**$^{+}$ and deprotonation afforded the 2-azaspiro [4.5]decane **10.5**, a molecule extremely appealing for its intrinsic complexity [53, 54] and for the potential biological and pharmaceutical applicability due to its spiro core. The final yield of **10.5** was quite independent of the substituent R used.

Visible-light-induced photoredox catalysis was employed to construct a trifluoromethylated quaternary carbon center onto pyrrolidone cores, starting from the tertiary bromide **11.1** (Scheme 11) [55]. Alkyl and aryl groups present



Scheme 10 Synthesis of spiro heterocycles via a dearomatization strategy



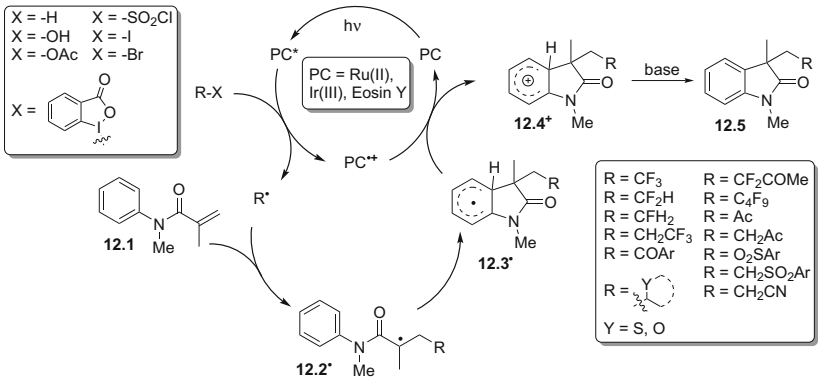
Scheme 11 Photocatalyzed synthesis of pyrrolidones from dihydrooxazoles

on the oxazolyl ring or on the olefin were tolerated, apart from electron-poor heteroaromatics on the vinyl moiety. The reaction proved to be effective in forming products **11.3a–e** and could be carried out in the air.

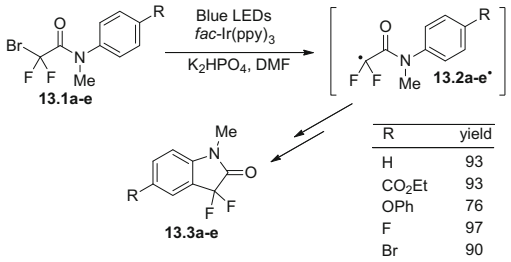
An interesting alternative for obtaining fluorinated quaternary carbons in the α-position of the carboxyl group in pyrrolidones is offered by a cascade photoredox/iodide catalytic system that enables the alkenes to attack the radical formed from bromodifluoroacetamides [56]. A variation of the protocol presented in Scheme 11 was efficiently exploited to generate 5-methylenepyrrolidines, versatile building blocks for complex molecular synthesis [57, 58]. The key intermediate proposed in this report is the amidyl radical [59] that can also be obtained via photoredox PCET activation [60], promoting a carboamination ring-closure reaction that leads to pyrrolidones.

The discovery of isatin in the early nineteenth century was the milestone that started a systematic study on the reactivity and synthesis of indole-containing structures [61]. Among all the isatin derivatives, oxindoles stand out as a special case due to the increased bioavailability of pharmaceuticals containing this moiety [62, 63].

One of the most popular approaches to oxindoles is depicted in Scheme 12, where *N*-aryl acrylamide derivatives **12.1** are functionalized and cyclized via photoredox catalysis. The general mechanistic scheme involves the reduction of a species R–X via single-electron transfer from the excited catalyst (Scheme 12). The labile R–X bond is mesolytically cleaved forming the radical that attacks **12.1**, generating the electrophilic radicals **12.2**$^{\bullet}$. Ring closure generates species **12.3**$^{\bullet}$ that are oxidized to **12.4**$^{+}$. Proton loss affords products **12.5**. The nature of R and X groups can be varied to afford a different series of functionalized oxindoles. Trifluoromethylation (R=CF_3) can be achieved using either Togni's reagent (X=3,3-dimethyl-1,2-benziodoxole; $Ru(phen)_3Cl_2$ is used as the PC) [64] or CF_3SO_2Cl (X=SO_2Cl; *fac*-$Ir(ppy)_3$ as the PC) [65]. Difluoroethyl (R=$-CHF_2$), monofluoromethyl (R=$-CH_2F$), nonafluorobutyl (R=$-C_4F_9$), trifluoroethyl



Scheme 12 Photocatalyzed synthesis of variously substituted oxindoles, starting from *N*-aryl acrylamides



Scheme 13 Ir(III)-photocatalyzed construction of the oxindole core

(R=CH_2CF_3), and R=−CF_2COMe substituents can be introduced using the corresponding sulfonyl chloride derivative (X=−SO_2Cl) [65]. Trifluoroethylated compounds could be achieved also via iridium photocatalysis, after the cleavage of the C–I bond in trifluoroethyl iodide (X=I) [66].

Carboxylic acids [67] and aryl anhydrides [68] in combination with *fac*-Ir(ppy)$_3$ photocatalyst are efficient acyl radical precursors (R–X=Ac-OH or Ac-OAc, Scheme 12) that can be trapped by *N*-aryl acrylamides **12.1**, promoting simple tandem radical acylation/cyclization to obtain acyloxindoles. On the other hand, the radical that reacts with **12.1** can be generated by eosin Y disodium salt photocatalysis, starting from sulfinic acids (R–X=$ArSO_2$-H), to obtain sulfonated oxindoles [69]. Most notably, the authors underlined that direct conversion of sulfonates to sulfones was rarely achieved in synthetic chemistry [70]. Furthermore, (arylsulfonyl)methylation of **12.1** (R=−CH_2SO_2Ar; X=Br) was achieved by using Ir(ppy)$_3$ as photocatalyst [71]. Selective C(sp^3)–H (X=H) bond cleavage of hydrogens in α-position with respect to a heteroatom (in ethers or thioethers) was obtained by eosin Y catalysis, allowing the tandem functionalization/cyclization of the arylacrylamides **12.1** [72]. In a similar manner, the α-hydrogen in acetonitrile is activated by a Ru-based photocatalyst (R–X=$NCCH_2$-H) [73].

The oxindole core was also synthesized via an intramolecular C–H difluoroacetamidation of easily available tertiary aryl bromodifluoroacetamides **13.1a–e** by using *fac*-Ir(ppy)$_3$ as the photocatalyst and a 3 W blue LED as the light source. Differently substituted difluoroxindoles **13.3a–e** were prepared after homolytic cleavage of the C–Br bond, affording intermediates **13.2a–e**$^{\bullet}$ (Scheme 13) [74].

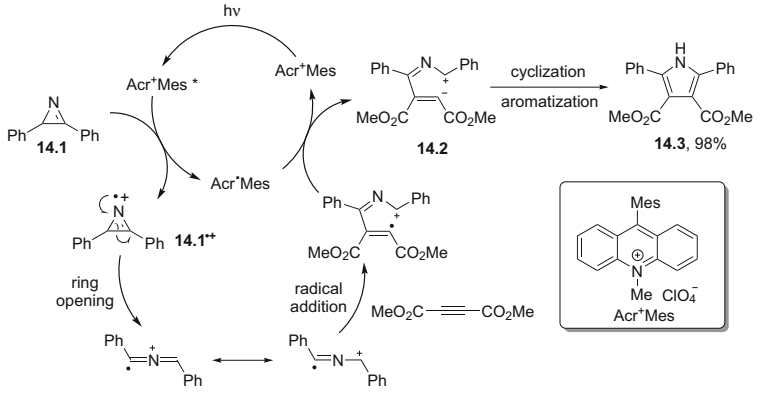
The same reaction was carried out intermolecularly starting from anilines and $BrCF_2CO_2Et$, leading to **13.3a–e** via an amidation reaction [75]. Other strategies involve an intramolecular 1,5-H transfer reaction of the aryl radicals generated from unactivated aryl iodides bearing an acrylamide [76] or by a SET (single-electron transfer) facilitated by a sulfur ylide in α-position to the acrylamide [77].

3.1.2 Aromatic

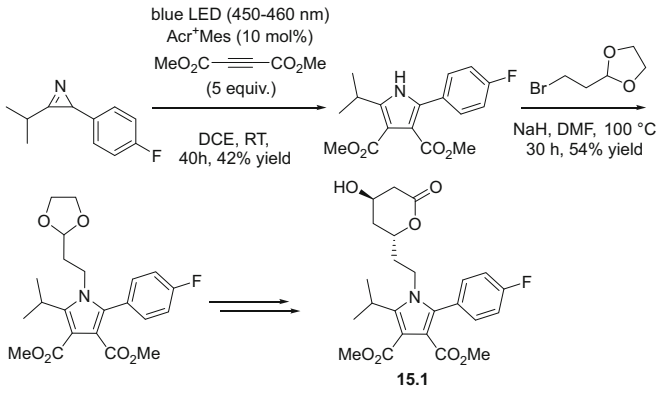
The importance of pyrroles and polysubstituted pyrroles is reflected by the vast number of literature reports on their synthesis [78–81]. One photocatalytic strategy consists in a formal [3 + 2] cycloaddition of 2*H*-azirines with alkynes in the

presence of an acridinium ion-based photocatalyst under visible-light irradiation [82]. The reaction relies on the SET oxidation of the azirine **14.1** into the corresponding radical cation (**14.1**$^{\bullet+}$). Such an odd-electron species is unstable and opens, forming a distonic radical cation that can be easily trapped by dimethyl but-2-yne-dioate. Further reduction mediated by the catalyst leads to a zwitterion (**14.2**) that cyclizes and aromatizes to give the pyrrole **14.3** in a high yield (Scheme 14).

Excellent yields of pyrroles were obtained both with electron-withdrawing and electron-donating groups and decent yields with other functional groups, such as naphthyl, furyl, vinyl, and alkyl groups. To further widen the scope and applicability of this photocatalytic formal [3 + 2] cycloaddition, the authors performed a formal synthesis of **15.1** (an inhibitor of HMG-CoA reductase, Scheme 15) [82]. The fully substituted pyrrole core was obtained in two steps in moderate yields. This work can be seen as an evolution of the first studies conducted by Mattay et al. using UV light and DCN or DCA as photocatalysts (Table 1) [83, 84].



Scheme 14 Photoorganocatalyzed ring opening of 2*H*-azirines for pyrrole synthesis

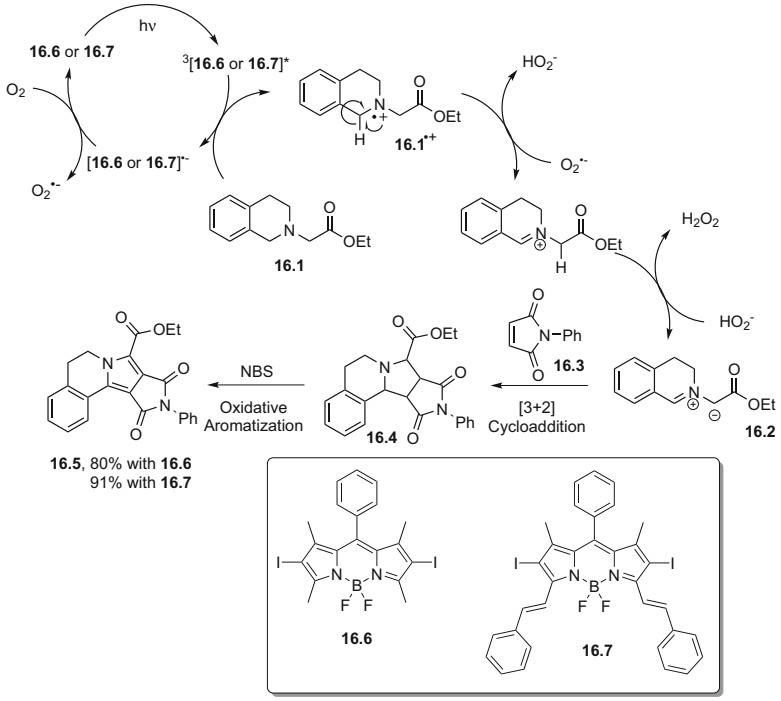


Scheme 15 Photocatalyzed preparation of an inhibitor of HMG-CoA reductase

An alternative formal [3 + 2] cyclization that affords the pyrrole core is the oxidation/[3 + 2] cycloaddition/aromatization tandem reaction on tetrahydroisoquinoline derivatives catalyzed by iodo-Bodipy-based triplet photosensitizers **16.6** and **16.7** (Scheme 16) [85]. The reaction proceeds through a single-electron transfer from the tertiary amine **16.1** to the triplet state of the Bodipy catalyst. Hydrogen abstraction by the superoxide anion (generated by the reduction of oxygen) and deprotonation by HO_2^- of the resulting cation $\mathbf{16.1}^{\bullet+}$ gave access to zwitterion **16.2.** This formal 1,3-dipole undergoes a [3 + 2]-cyclization with a suitable dipolarophile such as **16.3**. The cyclized product **16.4** is oxidized into the pyrrolic compound **16.5** with NBS directly in situ.

A similar approach was developed by using Rose Bengal as photocatalyst [86] or in a flow system with Ru catalyst and *t*-BuOOH as the oxidant, to afford fused β-carbolines [87]. A different route to the pyrrolic core involved the irradiation ($\lambda = 450$ nm) of a mixture of enamines and α-bromoketones, with $Ir(ppy)_3$ as the photocatalyst [88]. The α-bromoketones are converted into alkyl radicals via single-electron transfer, and these intermediates react with the double bond of enamines to form the core that undergoes the Hantzsch cyclization reaction, ultimately leading to the pyrrole.

A multitude of photocatalytical methods have been developed to construct the indole scaffold due to its importance as a key structural motif. As an example, a



Scheme 16 Iodo-Bodipy-based triplet photosensitized synthesis of pyrrole core

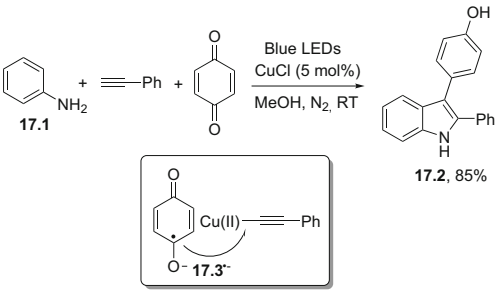
visible-light-induced copper-catalyzed process for C–H annulation of arylamines **17.1** with terminal alkynes and benzoquinone was reported for the formation of indoles **17.2** (Scheme 17) [89]. The mechanism proceeds with the formation of a Cu(I) adduct with the terminal alkyne. This species can be excited by means of visible light, with a consequent single-electron transfer to the quinone, forming the radical anion **17.3**$^{\bullet-}$ that will eventually react with an activated alkyne. The reaction yields are quite high, and this route is considered a sustainable and atom economical approach to construct indoles from easily accessible starting materials.

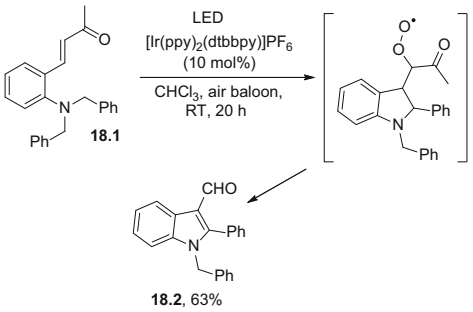
A similar approach involving the coupling of anilines with alkynes was developed by means of gold catalysis coupled with visible-light irradiation [90]. In this case, the gold complex that is formed thermally upon the attack of the aniline onto the alkyne is excited by irradiation with a household compact bulb, leading to a SET with oxygen that forms a radical cation cyclizing to give the indole moiety. The intramolecular version of the previous reaction can be accomplished starting from intramolecular oxidative cyclization of o-alkynylated *N*,*N*-dialkylamines promoted by iridium photocatalysis under oxygen atmosphere [91]. A slight variation of the strategy consists in the intramolecular radical cyclization of *N*-[2-(alkynyl)phenyl] trifluoroacetimidoyl chlorides using $Ru(phen)_3Cl_2$ as a catalyst [92]. The reaction is characterized by a sequential C–C and C–O bond formation to yield 2-trifluoromethyl indoles.

Starting from substituted dibenzylaniline **18.1**, a photocatalyzed Michael addition/aromatization/C–C bond cleavage cascade reaction, under oxygenated conditions, afforded indole-3-carboxaldehyde **18.2** in 63% yield (Scheme 18) [93]. An α-amino radical addition onto the enone moiety was invoked as the key step that in the absence of oxygen led to the corresponding tetrahydroquinoline. When oxygen was present, it added to the adduct radical, affording the desired **18.2** after an oxidative aromatization.

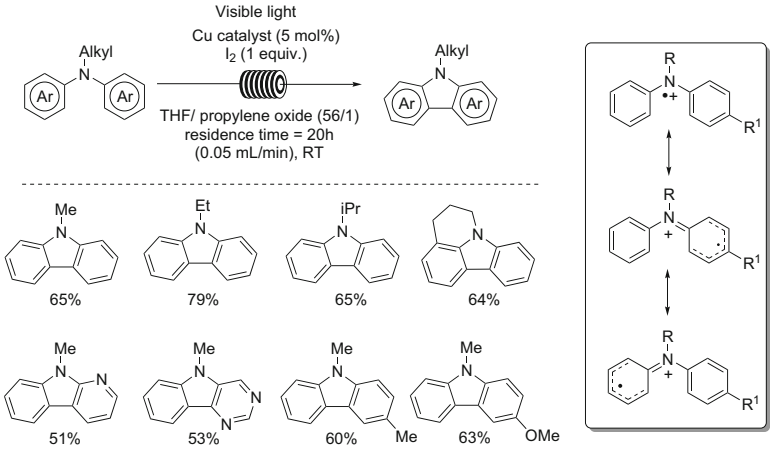
Similarly, indole can be synthesized by C–H activation of aromatic enamines. Contrary to the previous example, the olefinic moiety is linked to the nitrogen and will form a C–C bond by means of dual Pd/Ir catalysis [94]. Alternatively, *N*-aryl enamines can be transformed into indoles under oxidant-free conditions and visible-light irradiation of an iridium(III) photosensitizer and cobaloxime catalyst, along with molecular hydrogen evolution [95].

Scheme 17 Three-component photocatalyzed synthesis of indoles





Scheme 18 Photocatalyzed oxidative route to indole-3-carboxaldehydes



Scheme 19 Visible light photocatalysis applied to the flow synthesis of carbazoles

The indole molecule can be synthesized exploiting a visible light-induced photocatalytic dehydrogenation/6π-cyclization/oxidation cascade that converts 1-(nitromethyl)-2-aryl-1,2,3,4-tetrahydroisoquinolines into 12-nitroindolo[2,1-*a*] isoquinoline, using 1,5-diaminoanthraquinone as the photocatalyst [96]. Photocatalyzed C-halogen mesolysis was used to start the intramolecular cyclization of substituted arylamines into indole [97, 98], as well as the use of Brønsted acid co-catalysis coupled with $Ir(ppy)_2(dtbbpy)PF_6$ [99].

Sparse examples are known for the synthesis of carbazoles. An intriguing entry is the visible light-mediated cyclization of diaryl or triaryl amines, in the presence of a Ru or Cu catalyst (Scheme 19) [100]. Most interestingly, the reaction was optimized under flow conditions. The best catalyst was generated in situ by mixing $[Cu(MeCN)]BF_4$, Xantphos, and 2,9-dimethyl-1,10-phenanthroline (dmp). The key intermediate is the radical cation of the amine, generated by the action of the catalyst, that cyclizes spontaneously. A sacrificial oxidant such as I_2 is mandatory to close the catalytic cycle.

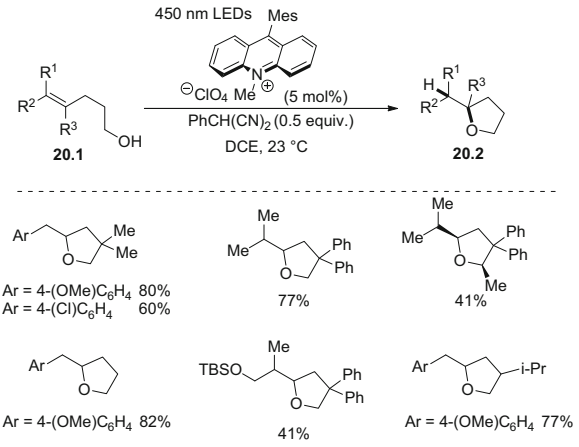
An alternative approach to the C–C bond formation is the C–N bond formation through an intramolecular C−H bond amination of *N*-substituted 2-amidobiaryls [101]. The approach makes use of a dual catalytic system employing $Pd(OAc)_2$ and $[Ir(dFppy)_2phen]PF_6$, the latter used for the first time in synthesis.

3.2 Oxygen-Containing Heterocycles

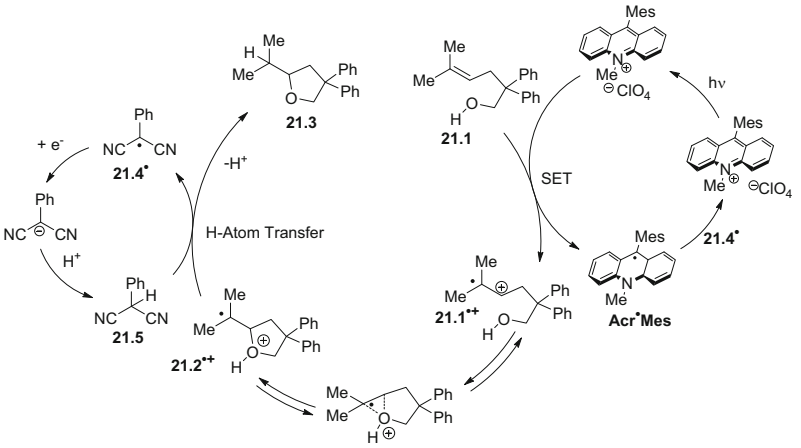
3.2.1 Nonaromatics

Tetrahydrofuran rings are commonly found in a plethora of natural compounds possessing biological or medicinal features, including a number of marine macrolides, annonaceous acetogenins, and polyether antibiotics. Consequently, the relevance of this core structure in a vast number of naturally occurring products has led to devise different (photo)catalytic approaches for their synthesis. A first example is the intramolecular anti-Markovnikov hydroetherification of alkenols that leads to the formation of five-membered ring heterocycles [102]. In this seminal work, Acr^+Mes (E^*_{red} = + 2.06 V vs. SCE) [103] was used to oxidize alkenols **20.1** having oxidation potentials <+2.0 V (Scheme 20). The use of 2-phenylmalononitrile as H-atom donor furnished anti-Markovnikov adducts in high yields with marked regioselectivity, with no trace of the undesired Markovnikov product.

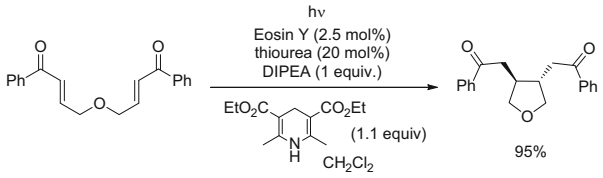
The mechanistic hypothesis is outlined in Scheme 21 and proposes that, following H-atom transfer from **21.5**, the resulting radical **21.4**$^\bullet$ could serve as an oxidant for radical $Acr^\bullet$-Mes, regenerating the ground-state photocatalyst Acr^+-Mes. Following this redox event, proton transfer would regenerate the H-atom donor **21.5** furnishing the desired product **21.3**.



Scheme 20 Photocatalyzed anti-Markovnikov hydroetherification of alkenols for the synthesis of the tetrahydrofuran ring



Scheme 21 Mechanism of the anti-Markovnikov hydroetherification of alkenols

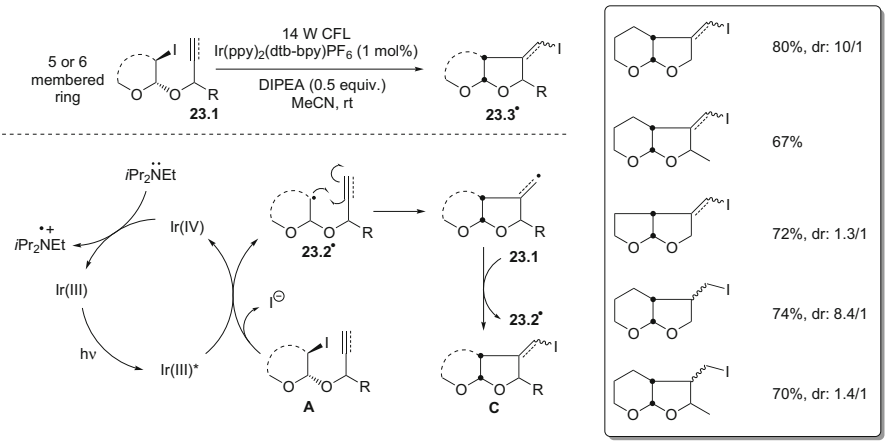


Scheme 22 Tetrahydrofuran synthesis starting from bisenones

The key intermediate of this methodology is the radical cation **21.1**$^{\bullet+}$. Consequently, the same group employed such a peculiar catalytic strategy to synthesize highly substituted tetrahydrofurans from allylic alcohols and alkenes by a polar radical crossover cycloaddition (PRCC) sequence [104].

Conversely, the chemistry of radical anions was employed to synthesize the tetrahydrofuran core starting from a SET reaction of a bisenone (Scheme 22) [105]. Eosin Y served as the organic photoredox catalyst to access a ketyl radical anion, in combination with thiourea used as Lewis acid activator of the carbonyl compound, to lead the reaction toward a reductive cyclization, instead of a redox neutral [2 + 2] cycloaddition [106, 107]. The umpolung of the α,β-unsaturated derivative drives the radical cyclization, with high yields and diasteroselectivity. Hantzsch ester and DIPEA as reductive quenchers were found to be crucial in closing the catalytic cycle.

Recently, photocatalysis was employed to construct the tetrahydrofuran ring in a series of compounds possessing the biologically interesting oxabicyclic framework, via a photoredox atom transfer Ueno-Stork reaction (Scheme 23) [108]. 2-Iodoethyl allyl/propargyl ethers linked to a tetrahydropyran or tetrahydrofuran ring **23.1** were irradiated with a compact fluorescent lamp (CFL) in the presence of an iridium catalyst, leading to substituted oxabicyclic frameworks, with the retention of the halogen functionality.

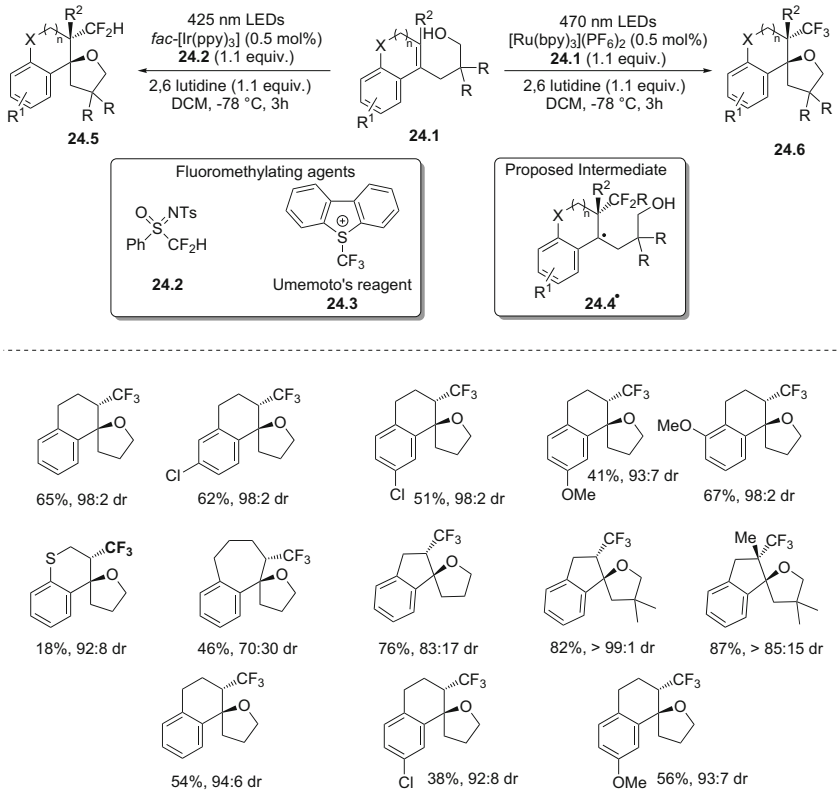


Scheme 23 2-Iodoethyl allyl/propargyl ethers as precursors of tetrahydrofurans

The proposed mechanism is illustrated in Scheme 23. α-Haloacetal **23.1** ($E_{red} = -0.55$ V vs. SCE) is reduced by the excited Ir(III)* catalyst ($E_{red} = -0.88$ V vs. SCE) to form radical **23.2**$^{\bullet}$. A subsequent 5-exo intramolecular radical addition to the unsaturated bond follows. The final product **23.3** is obtained either via a chain propagation reaction or via a radical/ionic crossover path. Such an approach is particularly appealing due to the intrinsic atom economy of the reaction. The C–X bond formed in the product results to be useful for further chemical transformations [109]. Noteworthy, this atom transfer radical addition/cyclization (ATRA/ATRC) is performed under mild conditions, while these transformations often employ stoichiometric toxic organotin compounds, pyrophoric alkylborane/O_2 combinations, or explosive peroxides [108].

Another convenient strategy to promote the cyclization of alkenols consists in the radical attack on the olefinic moiety and subsequent SET oxidation of the newly formed radical, to generate a cationic intermediate. Such a species is prone to react with the nucleophilic alcohol to form a tetrahydrofuran core. This scheme was employed to successfully access a small variety of spiroethers containing CF_3 and CF_2H groups from cycloalkenylalkanols **24.1** via fluoromethylative spiroetherification (Scheme 24) in a highly diasteroselective fashion [110]. The fluoromethylating agents (**24.2** or the Umemoto's reagent **24.3**) are reduced by the excited photocatalyst, generating the radicals that react with the olefin, forming intermediate **24.4**$^{\bullet}$. Noteworthy, the subsequent nucleophilic attack of the dangling alcohol proceeds in an anti-fashion, presumably because the ring formation is favored on the opposite side of the electronegative fluoromethyl group, leading to the predominant formation of the anti-fluoromethylated spiroethers **24.5** or **24.6** [111–113], the yield and selectivity of the reaction being increased when working at a low temperature.

This mechanistic scheme is extremely valuable because it allows the double functionalization of alkenols through radical addition, followed by intramolecular

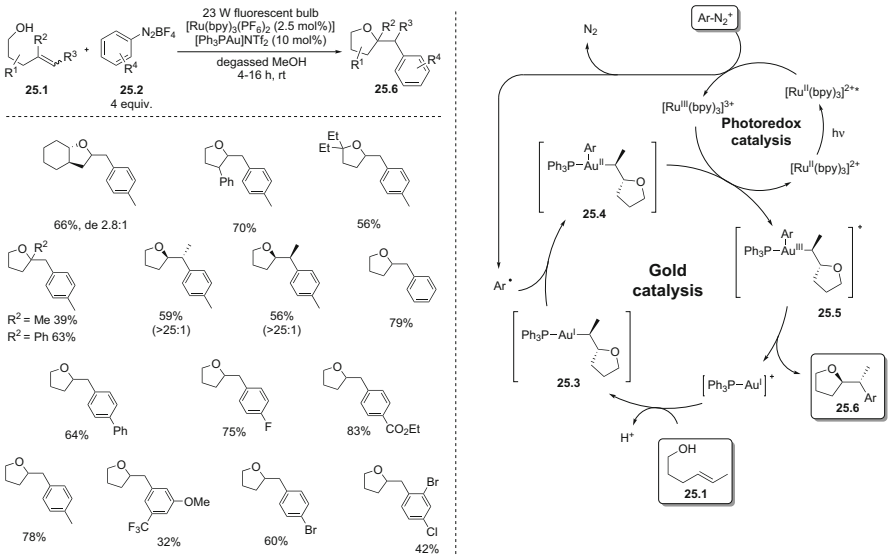


Scheme 24 Photocatalyzed fluoromethylative spiroetherification of alkenols

etherification. Indeed, styrene derivatives bearing an alcoholic group were cyclized to tetrahydrofurans, using α-bromoesters as alternative radical source maintaining the anti-diasteroselectivity of the cyclization [114].

In a similar fashion, a radical cation is generated after SET oxidation of different phenylsulfanyl substituted aromatic alkanols [115]. The phenylsulfanyl substituent acts as a leaving group, and, after selective homolytic cleavage of the C–S bond, a cation intermediate is eventually formed. The oxidative cleavage of the sulfide ($E_{ox} = +0.72$ V vs. SCE) [115] can be easily accomplished using excited $Ru(bpy)_3^{2+}$ as an oxidant (E^*_{red} (PC*/PC) = + 0.84 V vs. SCE) [116, 117]. The catalyst is then restored to its original oxidation state by the oxygen present in solution. The cation triggers the cyclization of the alcoholic moiety that leads to the heterocycle.

A very elegant way to promote the cyclization of alkenols was accomplished by the development of a dual gold and photoredox catalytic system, applicable to the intramolecular oxyarylation of alkenes with aryldiazonium salts (Scheme 25) [118]. The oxyarylation process proceeded readily with a range of substituted 4-penten-1-ol derivatives **25.1** and was successful with a variety of aryldiazonium salts **25.2**. The first step of the reaction consists in the interaction between the

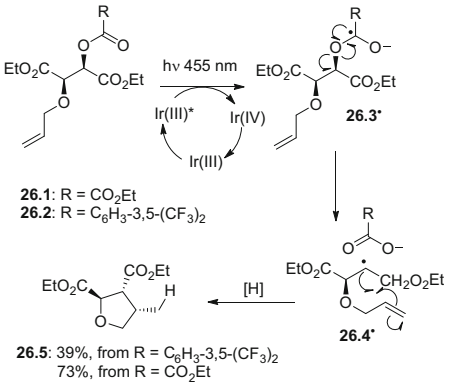


Scheme 25 Dual catalytic approach for the intramolecular oxyarylation of alkenes

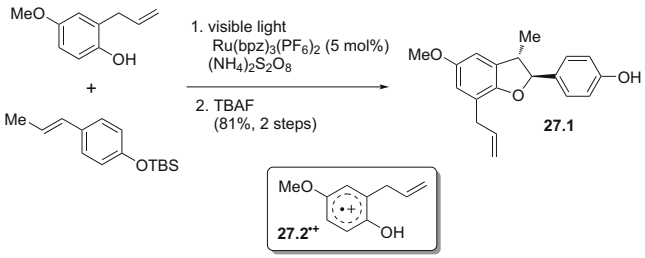
cationic Au(I) with the alkenol **25.1** to afford the alkyl-gold(I) intermediate **25.3** in an anti-selective fashion. The diazonium salts **25.2** are decomposed by means of photoredox catalysis to afford an aryl radical that could react with **25.3** [50, 119, 120]. The unstable Au(II) intermediate **25.4** thus generated donates an electron to Ru(III), affording the restored photocatalyst and the highly electrophilic Au(III) species **25.5**. Reductive elimination delivers the product **25.6** and regenerates the Au(I) catalyst [121].

All of the aforementioned routes for the formation of the tetrahydrofuran core involve the formation of a C–O bond in the cyclization step, starting from appropriately substituted alcohols. In contrast, a recent approach reported the tetrahydrofuran formation through C–C bond-forming reactions starting from monoallylated 1,2-diols (Scheme 26) [122]. In this study, the cyclization is triggered by a photoredox-catalyzed radical deoxygenation of ethyl oxalates **26.1** [123, 124] or 3,5-bis(trifluoromethyl)benzoates **26.2** [125] mediated by Ir(III) catalyst. The reaction was conducted either by employing **26.1** in combination with sacrificial electron donors or **26.2**, without sacrificial amines. The first approach allowed for a very short reaction times and was crucial to achieving challenging substrates, while the second protocol represents a lower-priced valid alternative, even though oxalates were sometimes found to decompose or hydrolyze. The mechanism for both deoxygenation protocols involves the carbon–oxygen bond mesolysis in the radical anion **26.3**$^{\bullet}$ to generate radical **26.4**$^{\bullet}$ that forms the tetrahydrofuran core (**26.5**) via a 5-exo-trig fashion cyclization.

The 2,3-dihydrobenzofuran scaffold is present in a vast number of bioactive compounds. Photoredox catalysis was successfully applied to develop an efficient



Scheme 26 Ir(III)-photocatalyzed deoxygenation of substituted 1,2-diols for the synthesis of tetrahydrofurans



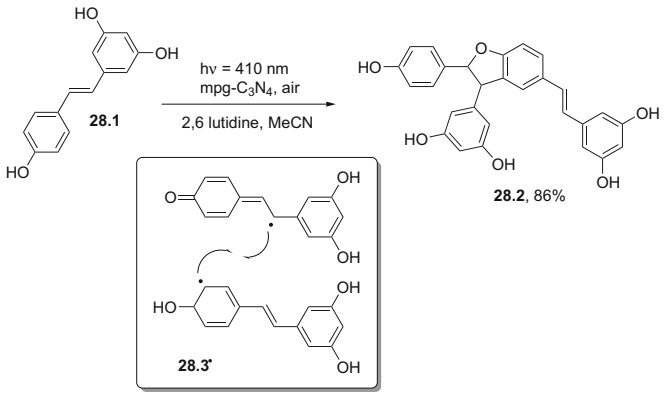
Scheme 27 Dihydrobenzofurans from a photocatalyzed [3 + 2] cycloaddition reaction

oxidation of phenols by $Ru(bpz)_3(PF_6)_2$ that yields dihydrobenzofurans via a [3 + 2] cycloaddition (Scheme 27) [126]. This allowed synthesizing product **27.1**, a member of the neolignan family, isolated from *Piper aequale*, in a two-step procedure, along with other benzofuranoid compounds. Radical cation **27.2**$^{\bullet+}$ was suggested as the intermediate of the reaction.

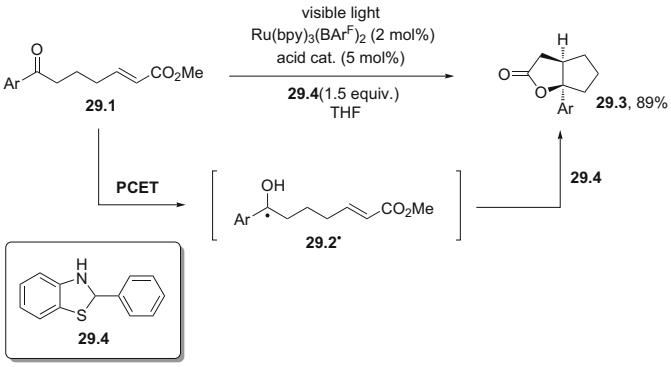
On the other hand, the natural compound resveratrol **28.1**, a molecule extensively used in drug development [127], was successfully dimerized to δ-viniferin **28.2** [128–130] by photoredox catalysis (Scheme 28) [131]. Mesoporous graphitic carbon nitride coupled with molecular oxygen as the ideal oxidant acts as a bioinspired catalyst to synthesize complex structures bearing a dihydrobenzofuran core, by coupling of the radicals **28.3**$^{\bullet}$.

Dihydrobenzofurans can also be achieved via fluorescein photoredox-mediated alkoxycabonylation of ortho-allyl-substituted benzenediazonium salts [132].

Various publications have been devoted to the synthesis and functionalization of valuable γ-lactones [133], generally by reaction of alkenes with either nucleophiles or radicals [134, 135]. However, in these protocols, stoichiometric oxidants and/or harsh conditions are necessary to promote the transformation. Photoredox catalysis offers a valuable and milder alternative, and two approaches are normally followed



Scheme 28 Metal-free photocatalyzed synthesis of δ-viniferin



Scheme 29 Preparation of γ-butyrolactones through the combined use of a photoredox and a Brønsted acid catalyst

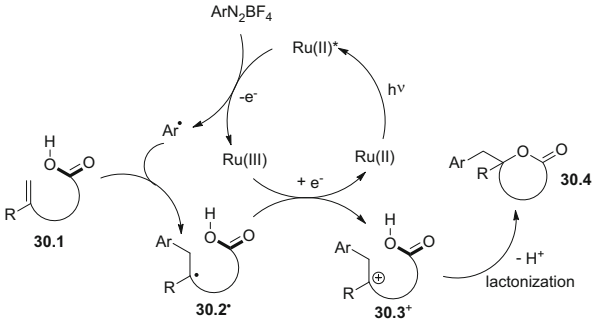
in the reaction planning: either an intra- or an intermolecular strategy. In the former case, an interesting example is the one involving the cyclization of aryl ketone **29.1** [136] through a proton-coupled electron transfer (PCET) mechanism (Scheme 29) [137–139]. In this work, a "concerted PCET" is invoked thus implying the simultaneous transfer of electrons and protons from independent donors to a single acceptor [136]. In particular, the joint action of a photoredox and a Brønsted acid catalyst allows the formation of a long-lived ketyl intermediate **29.2**• [140, 141]. The cyclization of the aforementioned radical gives γ-butyrolactone **29.3**, after hydrogen atom transfer (HAT) from 2-phenylbenzothiazoline (**29.4**). The HAT transfer process rate appeared to be crucial in the distereoselectivity of the reaction.

An elegant alternative route to γ-butyrolactones consists in the arylation–lactonization sequence involving aryldiazonium salts and olefinic carboxylic acids under irradiation with visible light [142]. Noteworthy, this specific strategy gives access to a library of diversely functionalized lactones with a γ-quaternary

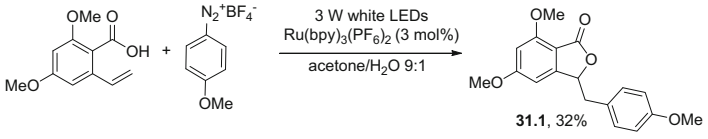
carbon, representing a mild way to synthesize sterically hindered γ,γ-disubstituted butyrolactones. The mechanism proposed is initiated by the electron uptake from the excited state of the photocatalyst $Ru(bpy)_3(PF_6)_2$, by aryldiazonium salts ArN_2BF_4 (Scheme 30) [142]. The in situ generated aryl radicals add regioselectively to the alkene **30.1**, generating a tertiary carbon radical intermediate **30.2**$^{\bullet}$. The photocatalyst is regenerated after oxidation of **30.2**$^{\bullet}$ to **30.3**$^{+}$ that eventually cyclizes to lactone **30.4**.

This protocol was efficiently extended to the preparation of phthalides [isobenzofuran-1(3H)-ones]. As an example, product **31.1**, otherwise isolated from the Australian liverwort *Frullania falciloba*, was synthesized in a one-pot reaction (Scheme 31) [142].

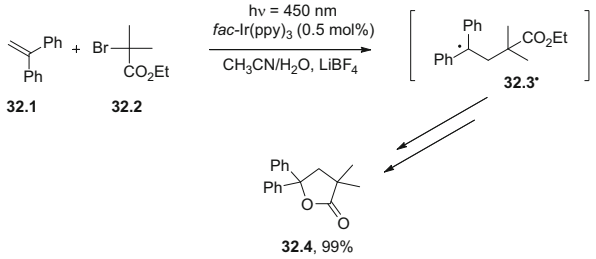
Another photocatalytic intermolecular γ-lactone synthesis is the reaction of styrene **32.1** with α-bromoester **32.2**, in the absence of any external oxidants leading to radical intermediate **32.3**$^{\bullet}$ (Scheme 32) [143]. The product **32.4** has



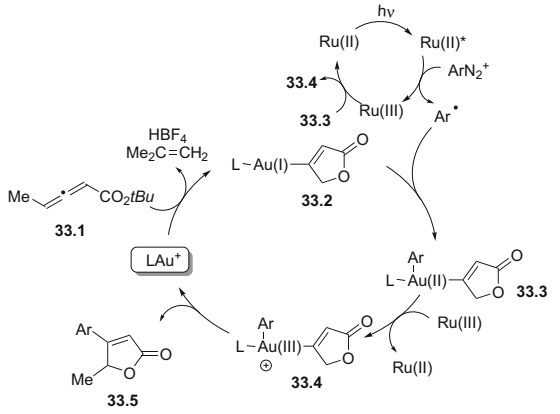
Scheme 30 Photocatalyzed preparation of sterically hindered γ,γ-disubstituted butyrolactones



Scheme 31 Ru(II)-photocatalyzed synthesis of a naturally occurring compound having the γ-lactone core



Scheme 32 Photocatalyzed synthesis of γ-lactone by the reaction of styrenes with α-bromoesters



Ar	% yield
C_6H_5	92
p-NO_2-C_6H_4	75
p-Me-C_6H_4	93
p-F-C_6H_4	79
p-Cl-C_6H_4	81
p-CO_2Me-C_6H_4	82

Scheme 33 Unsaturated lactones from a dual Ru(II)/Au(I) catalytic approach

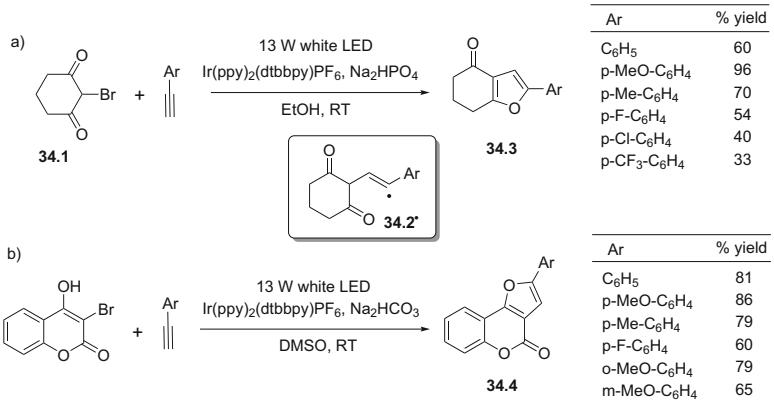
been efficiently obtained via the hydroxylalkylation of aromatic alkenes followed by a transesterification step. This photocatalytic protocol shows good regioselectivity and substrate compatibility with a broad range of carbonyl alkyl bromides and substituted styrenes.

Another intermolecular strategy involves the photocatalytic synthesis of substituted α-benzyloxyamino-γ-butyrolactones starting from oxime acids and alkenes [144]. The proposed mechanism suggests a polar radical crossover cycloaddition (PRCC) [145] between a substituted *O*-benzyloxime acid and oxidizable alkenes, making use of an acridinium catalyst and substoichiometric amounts of a redox-active co-catalyst.

The efficient conversion of *tert*-butyl allenoate to γ-crotonolactone was accomplished by the cross-coupling with arenediazonium salts, forming a novel C(sp^2)–C(sp^2) bond [146]. The Au(I)-Au(III) gold cycle is triggered by photoredox catalysis (Scheme 33) [10, 147]. In particular, the reaction starts with the interaction between **33.1** and the cationic gold complex to form the cyclic intermediate **33.2**. The aryl radical generated photocatalytically combines with the Au(I) intermediate and forms Au(II) species **33.3** that is further oxidized by Ru(III). Reductive elimination from **33.4** gives rise to the product **33.5** and restores the gold catalyst. The authors investigated the apparent quantum yield of the reaction, proving that when the Au complex is generated from Ph_3PAuCl and AgOTf, a radical chain mechanism contributed to some extent.

3.2.2 Aromatics

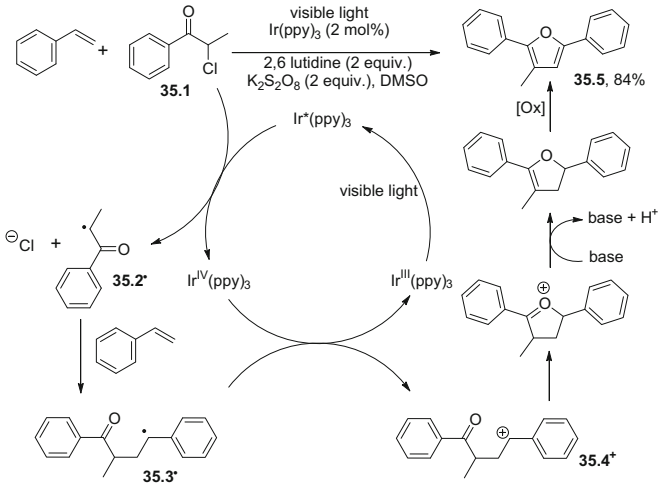
Different photoredox approaches were developed for the synthesis of five-membered furans due to their importance in many fields. An interesting example is depicted in Scheme 34a, involving a photoredox-neutral coupling between alkynes and 2-bromo-1,3-dicarbonyls **34.1**, proceeding through radical intermediate



Ar	% yield
C_6H_5	60
p-MeO-C_6H_4	96
p-Me-C_6H_4	70
p-F-C_6H_4	54
p-Cl-C_6H_4	40
p-CF_3-C_6H_4	33

Ar	% yield
C_6H_5	81
p-MeO-C_6H_4	86
p-Me-C_6H_4	79
p-F-C_6H_4	60
o-MeO-C_6H_4	79
m-MeO-C_6H_4	65

Scheme 34 Ir(III)-photocatalyzed routes to substituted furans



Scheme 35 Preparation of substituted furans from styrenes

34.2• [148]. Yields of **34.3** were found to be dependent on the electronic nature of the substituents on the aryl group and on the alkyne, and the best results were obtained with electron-rich substituents. Following this seminal work, the same group extended the scope of this transformation to the synthesis of furocoumarins **34.4** (Scheme 34b), a class of furan-fused coumarin derivatives [149]. The interest that drove researchers toward these particular compounds is due to their challenging synthesis and the variety of their biological applications. The main drawback of the method is the formation of naphthols in place of polysubstituted furans when the reaction is applied to α-bromo-aryl ketones.

This limitation was, however, overcome employing α-chloroaryl ketones that enabled the preparation of a wide array of polysubstituted furans (Scheme 35)

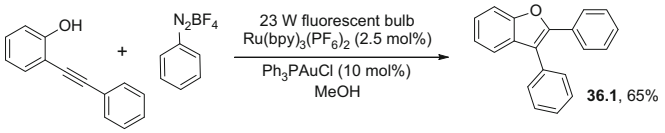
[150]. The excited photocatalyst reduces **35.1** via a SET reaction. The subsequent mesolytic cleavage of the C–Cl bond liberates the electron-deficient α-keto radical **35.2**$^{\bullet}$ that is prone to react with styrene. The resulting benzyl radical **35.3**$^{\bullet}$ is oxidized by Ir(IV) leading to carbocation **35.4**$^{+}$, which after an intramolecular cyclization followed by a deprotonation, is further oxidized by $K_2S_2O_8$ into the desired product **35.5**.

Benzofurans like **36.1** can be easily accessed by reaction between aryldiazonium salts and o-alkynylphenols via dual photoredox/gold catalysis (Scheme 36) [151]. Even though the yields of the reactions are good to excellent, the regioselective outcome of the cyclization is strongly dependent on the electron demanding nature of the substituents on the aryl groups.

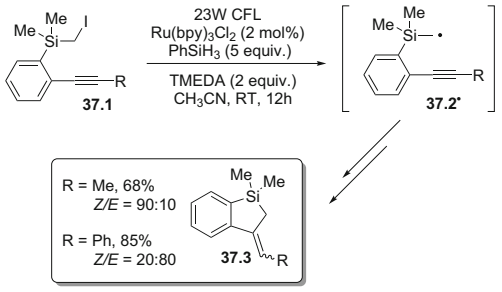
3.3 Other Atoms in the Heterocycles

A single example of the photoredox-catalyzed synthesis of silicon-containing five-membered heterocycle with the intermediacy of radicals is known (Scheme 37) [152]. Silacycles (important compounds as electroluminescent materials, for instance) [153, 154] were then easily formed from aryl alkyne **37.1**. The reaction proceeds through the homolytic cleavage of the C–I bond in **37.1** via photoredox catalysis.

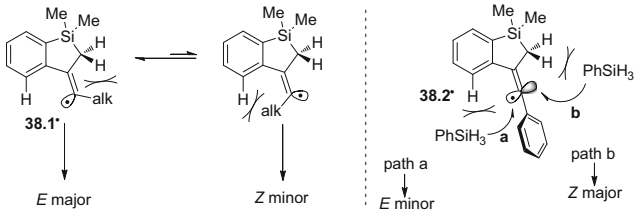
The α-Si radical **37.2**$^{\bullet}$ thus generated, cyclizes in a 5-exo-dig fashion, with a quite high diasteroselectivity of final product **37.3** (Scheme 37). In particular, with alkyl substituents, the diasteroselectivity favors the *Z* diastereomer, while with aryl substituents, the *E* one is preferred. Probably, the steric demand of the radical



Scheme 36 Dual photoredox/gold catalytic approach to benzofurans



Scheme 37 Photocatalyzed preparation of silacycles



Scheme 38 Synthesis of silacycles: selectivity in the radical cyclization

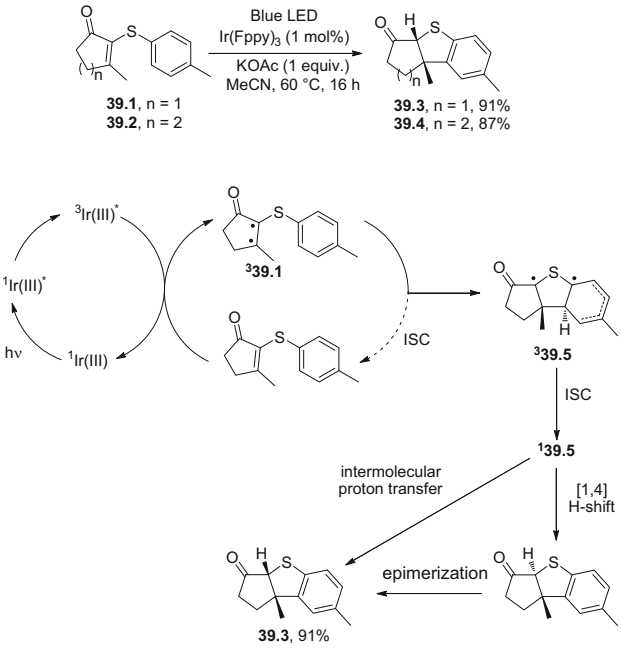
intermediate **38.1**• and **38.2**• leads to different stereochemical outcomes. The stability of the *E* and *Z* conformers of **38.1**• slightly favors the configuration that will give rise to product *E* (Scheme 38). On the other hand, such an explanation cannot be given for intermediate **38.2**• that is characterized by a planar sp^2 geometry. The selectivity can be obtained by the reduction of radical **38.2**• following the less hindered path **b** that will eventually form the *Z* product.

Photocatalytic procedures devoted to the construction of sulfur-containing five-membered rings are extremely rare. A typical example of the synthesis of a benzothiophene is represented by the reaction of a o-methylthio-benzenediazonium salt with phenylacetylene, using eosin Y as a photoredox catalyst by irradiating at 530 nm in DMSO [155]. A more recent discovery focuses on the photo-mediated 6π cyclization as a valuable method to form fused heterocyclic systems. The irradiation of cyclic 2-arylthioketones with blue LED light in the presence of an Ir(III) complex leads to efficient arylations by triplet energy transfer (Scheme 39). The reaction proceeds via conrotatory ring closure in the triplet excited state ^{3}**39.1** to form ^{3}**39.5** that eventually intersystem crosses to its singlet ^{1}**39.5**. A suprafacial 1,4-hydrogen shift and a final epimerization lead to the desired heterocycle **39.3** in high yield. The same product can be obtained following an intermolecular proton transfer directly forming **39.3** from ^{1}**39.5** [156].

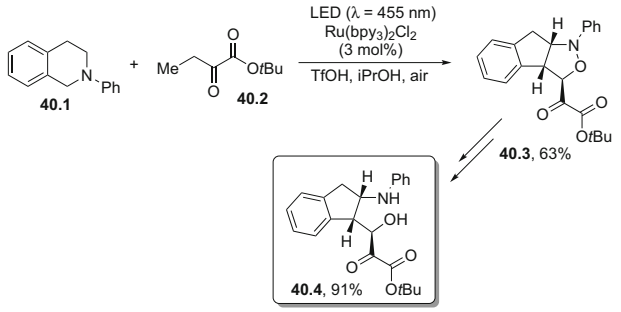
3.4 More than One Heteroatom in the Ring

3.4.1 Two Heteroatoms in the Ring

Syntheses of 1,2-heterosubstituted five-membered rings are sparsely reported in the recent literature. The synthesis of the isoxazolidine skeleton was achieved through a C–H activation-retro-aza-Michael-oxidation-[3 + 2] cycloaddition tandem sequence [157], applying a biomimetic route using amine **40.1**, commonly found in alkaloid derivatives. The reaction in the presence of α-ketoester **40.2** was optimized to give tricyclic product **40.3** in 63% yield, by using $Ru(bpy_3)_2Cl_2$ as the PC and irradiating the solution at room temperature with a strip of royal blue LEDs. The present route is an advancement with respect to the former way based on the [3 + 2] cycloadditions of nitrones with alkenes. To stress the importance of this



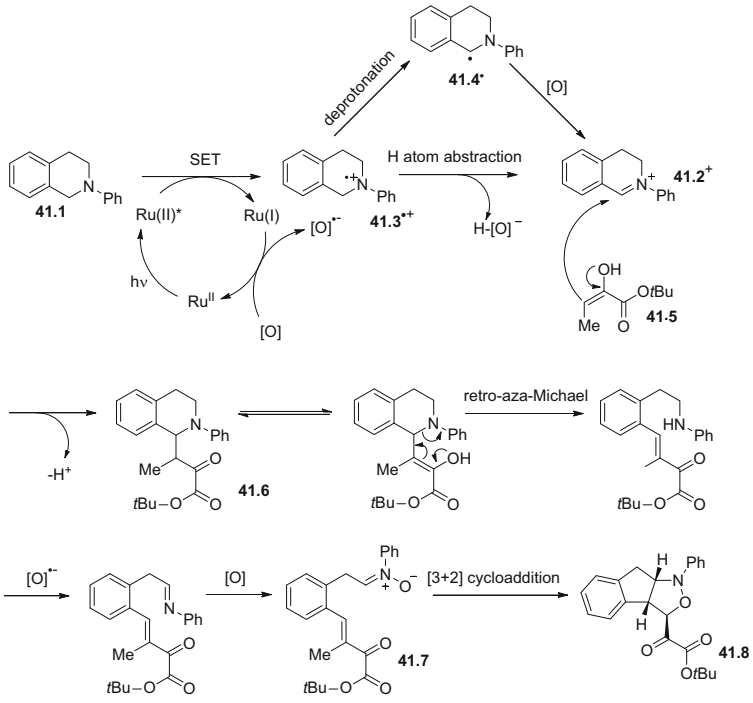
Scheme 39 Photocatalyzed preparation of sulfur-containing five-membered rings



Scheme 40 Isoxazolidines from Ru(II)-photocatalyzed reaction of α-ketoesters and tetrahydroisoquinolines

1,2-disubstituted heterocyclic ring as a precursor of more complex motifs, the authors performed the synthesis of the α,β-dihydro-δ-amino acid **40.4** from **40.3**, as a single diastereomer in 91% overall yield (Scheme 40) [157].

The proposed mechanism follows a biomimetic cascade reaction, initiated by the single-electron transfer of the excited ruthenium catalyst, which oxidizes the tertiary amine **41.1** (Scheme 41). The thus formed Ru(I) species is able to reduce dioxygen to its radical anion [158]. The iminium ion $\mathbf{41.2}^{+}$ can be formed from $\mathbf{41.3}^{\bullet+}$ competitively by H-atom abstraction or by deprotonation to give $\mathbf{41.4}^{\bullet}$, followed



Scheme 41 Synthesis of isoxazolidines: mechanistic proposal

by oxidation. Then, trapping of **41.2**$^+$ by **41.5** (the enol form of **40.2** efficiently formed by TfOH catalysis) results in product **41.6**. Compound **41.7** was obtained by a retro-aza-Michael reaction and a series of oxidations mediated by the superoxide radical anion. A [3 + 2] cycloaddition produces the desired bicyclic isoxazolidine **41.8**. Interestingly, an intermolecular variation of this approach was developed applying a photoredox-catalyzed oxidative [3 + 2] cycloaddition by using ethyl 2-(hydroxy(phenyl)amino)acetate and ethoxyethene as dipolarophile in the presence of 1 mol% of [Ir(ppy)$_2$bpy]-PF$_6$ as photoredox catalyst [159].

A library of differently substituted 4,5-dihydropyrazoles was synthesized starting from β,γ-unsaturated tosylhydrazones, through the intermediacy of *N*-centered hydrazonyl radicals generated by means of [Ru(bpy$_3$)$_2$]Cl$_2$ catalysis, under blue LEDs irradiation [160]. This strategy provides an efficient access to intramolecular alkene hydroamination and oxyamination. To further enlarge the scope of the reaction, the authors performed the removal of the tosyl group under basic conditions, leading to an NH substituted pyrazole in high yield (91%).

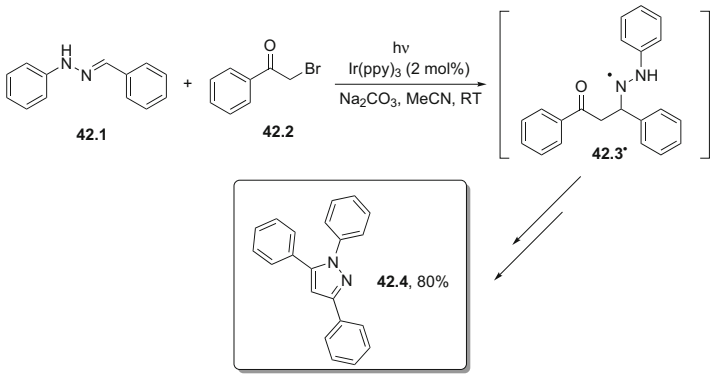
A convenient way to synthesize 1,2-dioxolanes was developed as a variation of the photocatalytic oxidation of styrenes [161]. The authors apply a [3 + 2] photooxygenation of disubstituted aryl cyclopropanes, considered as carbon homologous of styrenes [162]. The aerobic oxidation mediated by Ru(bpz$_3$)$^{2+}$ allowed to

synthesize a library of five-membered heterocycles in high yield with a marked diastereoselectivity for the syn product. A more complex synthesis of indazolo [2,3-a]quinoline derivatives from 2-(2-nitrophenyl)-1,2,3,4-tetrahydroquinolines via visible light photoredox catalysis was also reported [163]. The key step in the synthesis was the ruthenium-catalyzed intramolecular formation of the N–N bond of the indazole ring. A total of 18 examples were given with the isolated yields ranging from 66 to 96%. The precursors for the photochemical step are synthesized following a three-component Povarov reaction [164].

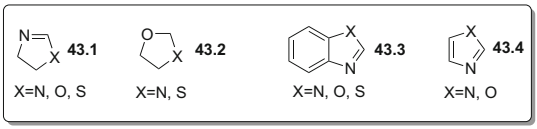
Another approach to forming a five-membered ring containing an N–N bond is the tandem reaction of hydrazone **42.1** with α-bromoketone **42.2** for the preparation of 1,3,5-trisubstituted pyrazole **42.4** (Scheme 42) [165]. The reaction proceeds via the $Ir(ppy)_3$-photocatalyzed homolytic cleavage of the C–Br bond. The carbon-centered radical thus formed adds onto the hydrazone C=N double bond, affording **42.3**$^{\bullet}$, which will eventually cyclize thermally after oxidation. The reaction has been demonstrated to be general for a wide range of functional groups. A similar approach was used for the formal [4 + 1] annulation of hydrazones with 2-bromo-1,3-dicarbonyl compounds [166].

In addition, the photocatalytic oxidation of oximes to nitrile oxides, via the intermediacy of an α-amino radical, allowed for the [3 + 2] cyclization of this dipole with alkenes and alkynes to afford isoxazolines and isoxazoles [167].

Various photocatalytic approaches were developed to easily give access to different 1,3-heterosubstituted five-membered heterocycles. Numerous examples of both nonaromatic and aromatic compounds (**43.1**–**43.4**) can be prepared following different conceptual approaches (Scheme 43).



Scheme 42 Photocatalyzed preparation of 1,3,5-trisubstituted pyrazoles



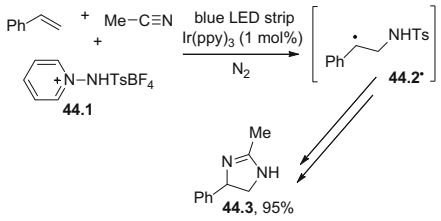
Scheme 43 1,3-Heterosubstituted five-membered heterocycles accessible by photocatalytic means

Imidazolines (general formula **43.1**, X=N) are smoothly synthesized via a formal [3 + 2] annulation mediated by iridium catalysis [168]. The reaction is driven by the photocatalyzed reductive cleavage of **44.1** that forms pyridine and an *N*-centered radical that can be easily trapped by styrene (Scheme 44). The intermediate **44.2**$^{\bullet}$ obtained can be oxidized to restore the catalyst in its original form and to generate a cation that can be trapped by a modest nucleophile such as acetonitrile, used as the solvent. The ensuing ring closure led to product **44.3** in 95% yield.

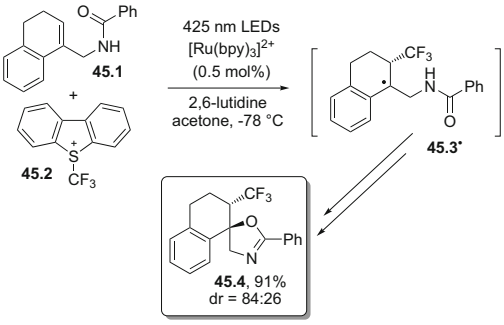
Interestingly, changing the solvent to acetone may lead to oxazolidines. A slight variation in the protocol, viz., using $Ir(ppy)_2(dtbbpy)PF_6$ as the catalyst, allows obtaining the corresponding 2,2-dimethyl oxazolidine in 88% yield [168].

Another way to synthesize imidazolines is the trifluoromethylative spirocyclization of alkenes bearing an amide pendant such as **45.1** in the presence of Umemoto's reagent **45.2** [169] and a Ru photocatalyst (Scheme 45) [170]. The key intermediate is the benzyl radical **45.3**$^{\bullet}$ derived from the attack of the photocatalytically generated CF_3 radical onto the alkene **45.1**. Oxidation of **45.3**$^{\bullet}$ to the corresponding benzyl cation allowed for the ring closure and the formation of the spiro compound **45.4**. In order to achieve a high diastereomeric ratio, the reactions are conducted at −78°C. The presence of a base such as 2,6-lutidine was found to be mandatory to obtain good reaction yields.

A photocatalytic method to construct 2-oxazolines and 2-thiazolines (formula **43.1**, X = O, S) from the corresponding allylic amides and thioamides was reported.



Scheme 44 Photocatalyzed synthesis of substituted imidazolines



Scheme 45 Synthesis of imidazolines via trifluoromethylative spirocyclization of alkenes

9-Mesityl-*N*-methyl acridinium tetrafluoroborate and phenyl disulfide were used to catalyze a redox-neutral intramolecular hydrofunctionalization showing a marked anti-Markovnikov regioselectivity [171]. The excited acridinium salt oxidized the allylic moiety promoting the cyclization.

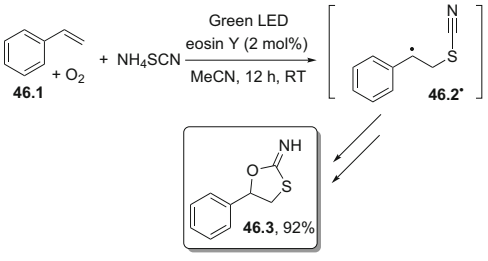
Oxathiolane synthesis (formula **43.2**, X = S) was achieved by photocatalytic functionalization of alkenes with NH_4SCN under aerobic conditions [172]. The novelty of the photocatalytic approach consists in the synthesis of an interesting class of compounds [173] without using lachrymatory agents such as phenacyl bromides and avoiding a multistep approach [174]. The mechanism involves the addition of the oxidized SCN radical onto the alkene **46.1** with the formation of the benzyl radical **46.2**$^{\bullet}$. The subsequent oxidation by oxygen and further cyclization leads to the product **46.3** in 92% yield (Scheme 46).

In a similar fashion, the same authors propose the synthesis of oxathiolane-2-thiones, substituting the thiocyanate anion with CS_2 [175].

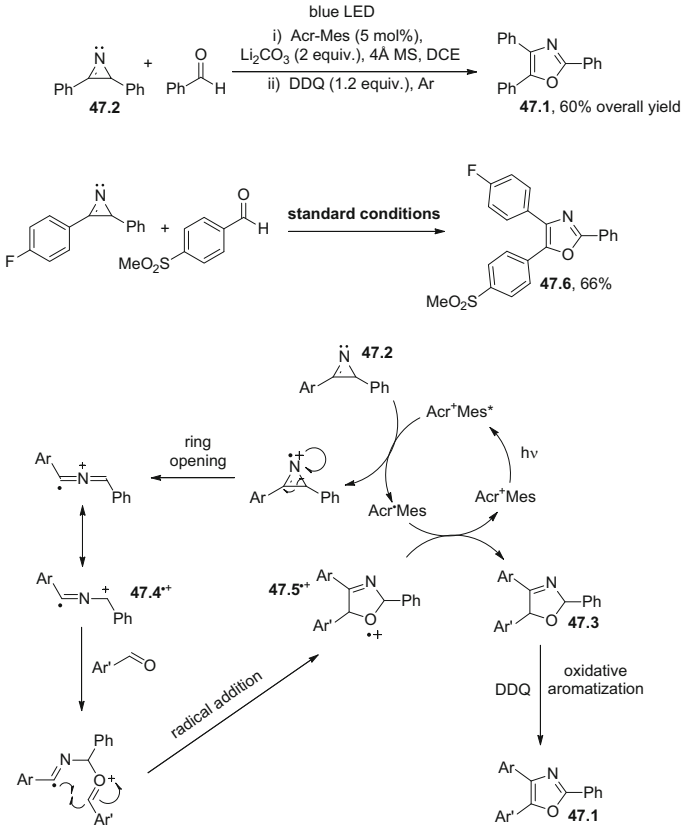
The synthesis of oxazoles **47.1** was accomplished starting from 2*H*-azirine **47.2**, with the intermediacy of the dihydrooxazole **47.3** (Scheme 47) [176]. The acridinium salt $Acr^{+}Mes$ in its excited state easily oxidizes the aziridine **47.2**, causing a ring opening to the distonic radical cation (**47.4**$^{\bullet+}$), which is then attacked by the oxygen of the benzaldehyde thus forming upon ring closure the radical cation **47.5**$^{\bullet+}$. The latter species is reduced to restore the catalyst in its original form, with the concomitant formation of **47.3**. Compound **47.1** was then prepared by a subsequent, one-pot oxidation with DDQ as the oxidant. In order to broaden the scope of the reaction, the authors accomplished the synthesis of a cyclooxygenase-2 inhibitor (**47.6**) using the aforementioned photocatalytic scheme [176].

A similar route to prepare oxazoles starting from the extremely reactive 2*H*-azirine moiety [177] made use of the three-component cyclization of 2*H*-azirines, alkynyl bromides, and molecular oxygen (an acridinium salt as PC) [178]. The use of azirines was inspired by the seminal work of Mattay et al. that made use of DCN as organic photocatalyst for the ring opening of the azirines to afford *N*-substituted imidazoles, after reaction with acetonitrile used as the solvent [83].

The imidazole moiety can also be obtained by a visible-light-induced photocatalytic aerobic oxidation/[3 + 2] cycloaddition/aromatization cascade between secondary amines and isocyanides. The reaction is catalyzed by an Ir complex and proceeds by the photocatalytic oxidation of the amine into the corresponding imine. A [3 + 2] cycloaddition took place between the imine with the isocyanide ultimately



Scheme 46 Eosin Y-photocatalyzed synthesis of 5-aryl-2-imino-1,3-oxathiolanes

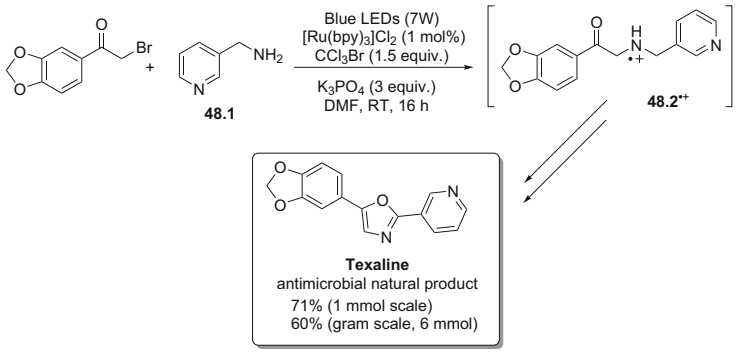


Scheme 47 Synthesis of oxazoles via ring opening of 2*H*-azirines

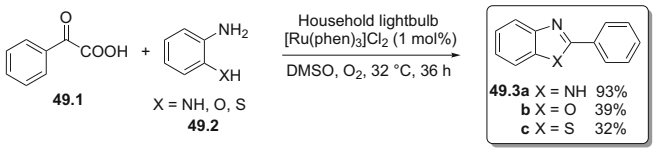
providing the imidazole core. This strategy allows to synthesize diversely substituted imidazoles in good yields and provide an access to the more complex imidazo[1,5-*a*]quinoxalin-4 (5H)-one structure [179].

As for the above, the oxidation of a primary amine (**48.1**) into its radical cation **48.2**$^{\bullet+}$ is the key step for the synthesis of the oxazole ring in a photocatalytic strategy based on Ru catalysis (Scheme 48) [180]. The secondary amine was made in situ by reaction of a primary benzylamine and an α-bromoketone. The validity of the method is underlined by the facile synthesis in a high yield of texaline, a natural product showing antibiotic properties, in high yield both in the sub-gram and in the gram scale.

A general method to synthesize products belonging to the compounds of general formula **43.3** is represented by the ruthenium-catalyzed decarboxylation/oxidative amidation of α-keto acids under an oxygen atmosphere. The combination of the photoinduced electron transfer mediated by the metal catalyst and the oxidative conditions allowed the decarboxylation of the acid **49.1** to afford an acyl radical that easily coupled with aniline **49.2** (Scheme 49). The outcome of the reaction



Scheme 48 Photocatalyzed preparation of the antimicrobial texaline



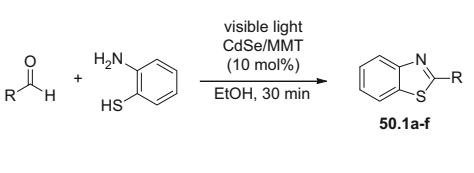
Scheme 49 Photocatalyzed approach for the synthesis of benzimidazole, benzoxazole, and benzothiazole

depends on the X substituent on **49.2**. Thus, benzimidazole, benzoxazole, and benzothiazole **49.3a–c** were synthesized when the ortho positions of the anilines bore NH_2, OH, and SH groups, respectively [181]. The yields of the reaction depended on the substituent X, with benzimidazoles formed in a higher yield.

Another one-pot synthesis of benzoxazoles, benzimidazoles, and benzothiazoles is reported to occur between benzylamines and **49.2** under aerobic oxidative conditions (carbon nitride as PC) [182]. In this case, the catalyst with the concurrence of the superoxide anion oxidizes the benzylamine to imine. This umpolung promotes the addition – elimination of **49.2** to give another imine that eventually cyclizes.

A common strategy to build compounds **43.3** consists in the reaction of an aldehyde with a substituted aniline under photocatalytic conditions. CdSe nanoparticles (NPs) dispersed in a montmorillonite (MMT) clay matrix are able to catalyze under visible-light irradiation the synthesis of a broad scope of 2-substituted benzothiazoles **50.1a–f** (Scheme 50) [183].

The same reaction can also be catalyzed via CdS nanospheres [184] and by 3,6-di(pyridin-2-yl)-1,2,4,5-tetrazine (pytz) used as organic photocatalyst [185]. In the latter case, benzoimidazoles can be likewise easily accessed. All of these examples presumably proceed via the thermal formation of the imine and the photocatalytic stepwise generation of a radical centered on the sulfur (or on the free nitrogen for benzoimidazoles) and in the α-position with respect to the imine nitrogen [183]. Benzothiazoles can be efficiently synthesized via a dual catalytic



R	% yield
C_6H_5	93
p-MeO-C_6H_4	95
p-Me-C_6H_4	93
p-F-C_6H_4	91
p-Cl-C_6H_4	92
m-NO_2-C_6H_4	96

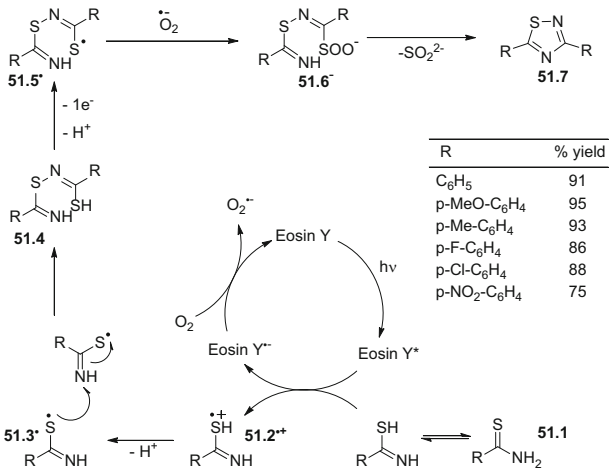
Scheme 50 CdSe nanoparticle-photocatalyzed synthesis of 2-substituted benzothiazoles

approach combining a Ru-mediated photoredox and an oxidative cobalt catalytic cycle. A broad series of thiobenzanilides were cyclized into the corresponding benzothiazoles in excellent yields [186].

3.4.2 Three Heteroatoms in the Ring

Only a few examples of photocatalytic synthesis of five-membered rings containing three heterocycles are present in the recent literature. A particular case is the visible-light-driven aerobic oxidative conversion of primary thioamides into 1,2,4-thiadiazoles [187]. The reaction was optimized in DMF using eosin Y as photocatalyst and an 18 W fluorescent lamp as the light source. The reaction was conducted at room temperature under aerated conditions. The thiolic form of the thioamide **51.1** is oxidized by eosin Y excited triplet species (EY*). The subsequent formation of the radical cation $\mathbf{51.2}^{\bullet+}$ and the loss of a proton form the neutral radical $\mathbf{51.3}^{\bullet}$ that is prone to dimerize to generate intermediate **51.4** (Scheme 51). The sulfide **51.4** follows the same photocatalytic pathway than **51.1** and generates the stable radical $\mathbf{51.5}^{\bullet}$, upon eosin Y-mediated electron transfer and subsequent proton loss. Radical $\mathbf{51.5}^{\bullet}$ can be reduced to $\mathbf{51.6}^{-}$ by the superoxide radical anion, formed after the reductive quenching of dioxygen present in solution by the reduced form of eosin Y. Anion $\mathbf{51.6}^{-}$ can lose the SO_2^{2-} group and forms **51.7** via a cyclodesulfurization reaction. The reaction gives a high yield of valuable products, due to the presence of the thiadiazole core in various biological and pharmaceutical applications.

An interesting variation of the click chemistry reaction is represented by the azide–alkyne cycloaddition reaction for the synthesis of 1,4-disubstituted 1,2,3-triazoles, via the catalysis of graphitic carbon nitride supported copper nanoparticles (Cu–gCN) [188]. Interestingly, the experiments were conducted with different light sources, finding in the UV-light-irradiated MeOH solution (without the addition of a base) the perfect catalytic conditions. Several azides and alkynes were studied, allowing to isolate differently substituted products with a yield between 83 and 94% if a UV irradiation was employed.



R	% yield
C_6H_5	91
p-MeO-C_6H_4	95
p-Me-C_6H_4	93
p-F-C_6H_4	86
p-Cl-C_6H_4	88
p-NO_2-C_6H_4	75

Scheme 51 Preparation of the thiadiazole core via a cyclodesulfurization reaction

4 Six-Membered Ring

4.1 Nitrogen-Containing Heterocycles

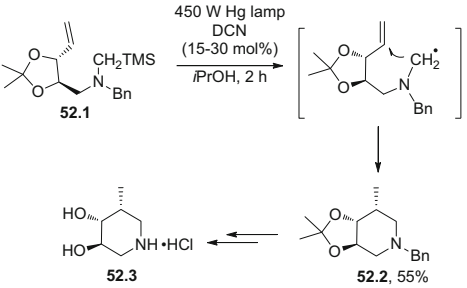
Photocatalysis is a very powerful tool for the preparation of six-membered nitrogen-containing heterocycles/heteroaromatics. In the majority of cases, the ring was formed during an intramolecular reaction of a photogenerated radical. Both non-heteroaromatics and heteroaromatics (e.g., pyridines, quinolines, phenanthridines) were accessed as detailed in the following.

4.1.1 Non-heteroaromatics

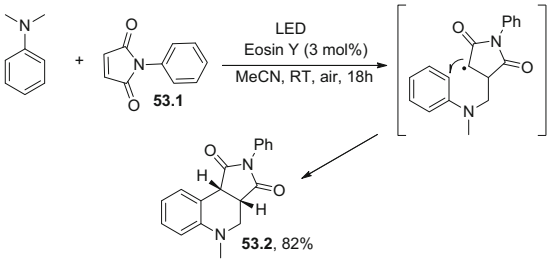
The main approach made use of a cyclization step involving α-amino radicals obtained from α-silylamines or *N*,*N*-dimethylanilines. In the first case, functionalized piperidines having biological activity were readily prepared. An example is depicted in Scheme 52, where silylamine **52.1** was easily converted into piperidine **52.2** in only 2 h irradiation, in the presence of 1,4-dicyanonaphthalene (DCN) as the photocatalyst [189]. The α-trimethylsilylmethylamine **52.1** was readily oxidized into the corresponding radical cation that upon TMS^+ loss yielded an α-amino radical prone to cyclize onto the tethered double bond functionality. Azasugar **52.2** was then isolated in 55% yield and used for the preparation of 5′-deoxy-5-*epi*-isofagomine (**52.3**) [189].

The same approach was likewise applied to the synthesis of other azasugars (showing high inhibitory potencies toward β-glycosidases) belonging to the isofagomine [189], decahydroisoquinoline [190], and 1-*N*-iminosugar families [191].

Scheme 52 DCN-photocatalyzed formation of a ring as a key step for the synthesis of 5′-deoxy-5-*epi*-isofagomine



Scheme 53 Eosin Y-mediated synthesis of tetrahydroquinolines



Interestingly, the carboxylate group may be used in place of the TMS group for the photocatalyzed generation of α-amino radicals. Thus, *N*-phenyl glycine was readily reacted with maleimide via a decarboxylative annulation to yield the skeleton of various natural product-like compounds. Costless fluorescein (2 mol%) was adopted here as the PC that allowed the use of sunlight to promote the reaction [192].

An interesting variation is the formation of α-amino radicals directly from tertiary amines. The typical case is that of *N*,*N*-dimethylaniline. This compound is very easily oxidized (E_{ox} = ca. 1 V vs. SCE) so that a variety of photocatalysts may be used for this purpose. The nucleophilic α-amino radical formed by deprotonation of the resulting radical cation is able to add to a variety of electron-poor olefins. Scheme 53 illustrates an example where *N*,*N*-dimethylaniline was added to maleimide **53.1** and the resulting radical cyclize onto the aromatic ring to form tetrahydroquinoline **53.2**. Such aerobic oxidative cyclization was carried out under visible-light irradiation under metal-free conditions making use of eosin Y [193] or chlorophyll as the PC [194]. As an alternative, bis(1,10-phenanthroline)-copper (I) photocatalyst $[Cu(dap)_2]Cl$ was used for the same reaction and involved again an aerobic oxidative quenching helped by the presence of an excess of trifluoroacetic acid (TFA) [195].

Related reactions have been carried out on cyclic chiral Michael acceptors such as 5-menthyloxy-2,5-dihydrofuran-2-ones forming tetrahydroquinoline derivatives with a decent degree of stereoselectivity [196–198]. In the latter case, aromatic ketones (e.g., Michler's ketone) were used as the PC.

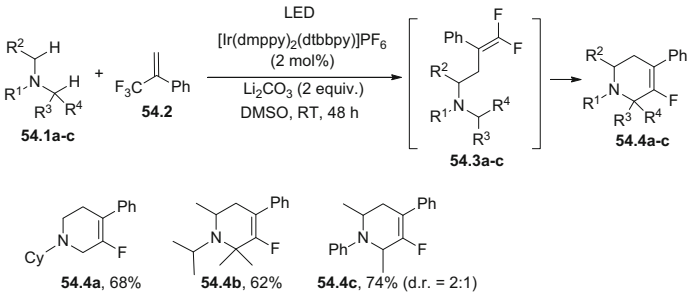
Tertiary amines (**54.1a–c**) were likewise photoadded under visible-light irradiation to α-trifluoromethyl alkenes, and a [3 + 3] annulation resulted to give

fluorinated tetrahydropyridines **54.4a–c** (Scheme 54) [199]. The reaction is peculiar since it involved an initial addition of the α-amino radical onto **54.2**. A further intramolecular addition of a photogenerated α-amino radical onto the difluoroalkene intermediates (**54.3a–c**) gave compounds **54.4a–c** in a good yield upon double C–F bond cleavage [199].

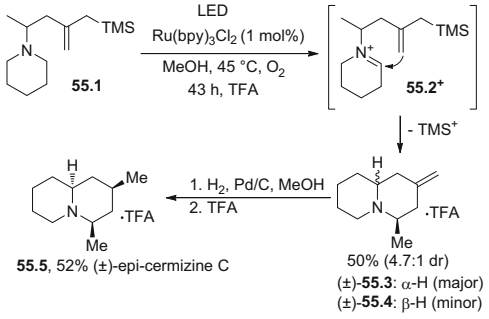
The facile oxidation of tertiary amines was the key step in the preparation of epi-cermizine C (**55.5**, a quinolizidine alkaloid, Scheme 55). The α-amino radical intermediate here was further oxidized to the corresponding iminium ion **55.2**$^+$, which readily cyclized onto the allylsilane moiety present in compound **55.1**. The reaction showed a modest degree of selectivity (±)-**55.3**:(±)-**55.4** 4.7:1 dr that was, however, higher with respect to the same reaction carried out under stoichiometric thermal Polonovski–Potier conditions [200].

Similarly, a visible-light-photocatalyzed annulation occurring in tetrahydroisoquinoline **56.1** was used as the key step for the synthesis of (±)-tetrabenazine **56.2** (Scheme 56). This was an interesting case where the solvent has a crucial role in the cyclization outcome since aqueous acetonitrile gave better results with respect to neat MeOH, in which a mixed ketal was formed instead [201].

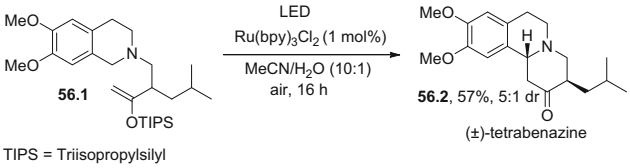
Acrylamide derivatives are another class of interesting precursors for the construction of six-membered rings. A typical case is depicted in Scheme 57, where an



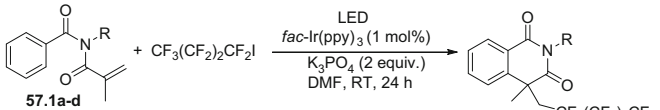
Scheme 54 Photocatalyzed [3 + 3] annulation for the formation of fluorinated tetrahydropyridines



Scheme 55 Photocatalyzed synthesis of epi-cermizine C



Scheme 56 Ru(II)-photocatalyzed preparation of (±)-tetrabenazine



R	% yield
*n*Bu	80
*i*Pr	75
Bn	78
Ph	traces

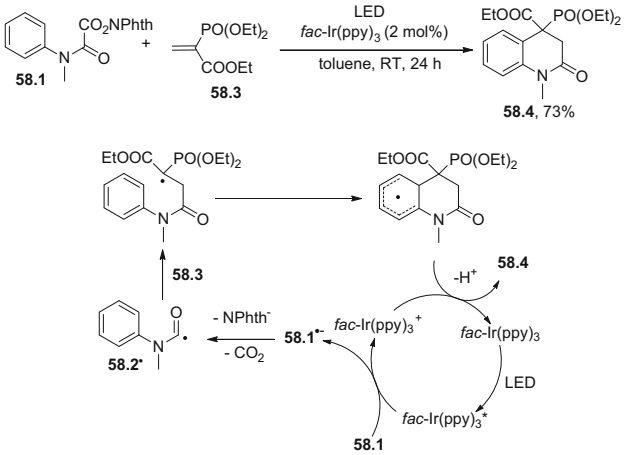
Scheme 57 Formation of isoquinoline-1,3-diones via carboperfluoroalkylation of *N*-alkyl-*N*-methacryloyl benzamides

initial carboperfluoroalkylation of the C=C double bond in *N*-alkyl-*N*-methacryloyl benzamides **57.1a–d** further led to isoquinoline-1,3-diones **57.2a–d** by a radical addition onto the aromatic ring [202]. Compounds **57.1a–d** were suitable as starting material for the Ru(II)-based photocatalyzed syntheses of other isoquinoline-1,3-diones via CF_3 [203] or $ArSO_2$ [204] radical addition onto the acrylamide moiety. A particular case is that of cinnamides that were aryldifluoroacetylated to give quinolone-2-ones [205].

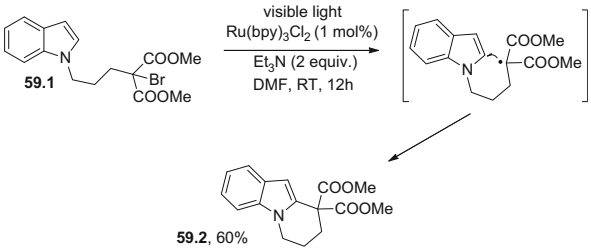
The synthesis of functionalized 3,4-dihydroquinolin-2-ones was carried out starting from phthalimides (e.g., **58.1**). The phthalimide moiety (NPhth) was introduced here to make the starting oxamide easy to reduce by the excited photocatalyst (fac-Ir(ppy)$_3$). Loss of the NPhth$^-$ anion allowed the generation of a carbamoyl radical **58.2**$^\bullet$, which upon addition onto an electron-poor olefin **58.3** and subsequent cyclization gave the functionalized heterocycle (**58.4**) in good yield (Scheme 58) [206].

An unexpected way to prepare isoquinolones is the photocatalyzed regioselective denitrogenative insertion of terminal alkynes into 1,2,3-benzotriazinones. The initial reduction of the latter compounds induced a dinitrogen loss, and the alkyne reacted with the resulting distonic radical anion and cyclization ensued [207].

A six-membered ring may be constructed starting from a preformed indole skeleton. As an example, the malonyl radical obtained under photocatalytic conditions starting from *N*-substituted indole **59.1** easily cyclized, and tricyclic derivative **59.2** was smoothly prepared (Scheme 59) [208]. The Ru(II)-based catalyst may be replaced by a dimeric Au(I) photocatalyst allowing the reactions even for indoles bearing an unactivated bromoalkane tether on the indole nitrogen [209]. A related



Scheme 58 Synthesis of functionalized 3,4-dihydroquinolin-2-ones



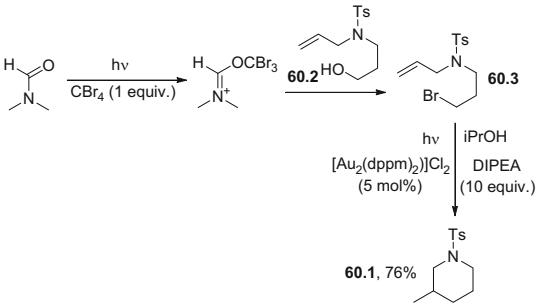
Scheme 59 A convenient route for the synthesis of tricyclic tetrahydropyridoindoles

process made use of an intermolecular rather than an intramolecular reaction, due to the photocatalyzed generation of a 3-indolyl radical that upon addition to a Michael acceptor and cyclization onto the indole ring gave the corresponding tricyclic tetrahydropyridoindoles [210].

In other cases, the reaction led to a dearomatization of the indole ring. In fact, the Ir(III)-photocatalyzed reaction between *N*-(2-iodoethyl)indoles and several alkenes yielded tri- and tetracyclic benzindolizidines. An excess of tertiary amines (e.g., DIPEA, 6 equiv.) in the role of electron and hydrogen atom donor was mandatory here [211]. A related dearomatization took place during the aerobic oxyamidation of 3-benzylindoles, thus giving access to tetrahydro-5H-indolo[2,3-b]quinolinols, a potential bioactive derivative having the indoline core [212].

The last example deals with the preparation of the piperidine **60.1** (Scheme 60) [213]. The first step is a photoinduced bromination of alcohol **60.2** by irradiation of CBr_4 in DMF. Then, the Au(I)-photocatalyzed reduction of **60.3** formed a carbon-centered radical that upon cyclization onto the alkene tether gave **60.1** in 76% yield [213].

Scheme 60 Construction of the piperidine scaffold via Au(I)-photocatalyzed reduction of alkyl bromides



4.1.2 Pyridines

Sparse examples were found for the construction of the pyridine ring. One dated example dealt with the inefficient synthesis of diphenylpyridine by tetracyanoanthracene (TCA) or pyrylium salt-photocatalyzed reactions of phenylacetylene with the solvent acetonitrile [214]. The reaction was repeated with some success by using a chlorinated pyrylium salt (T(*p*-Cl)PPT) as the photocatalyst. In such a way, 2,3,6-trisubstituted pyridines (e.g., **61.1**) were smoothly formed starting from aromatic acetylenes **61.2** [215]. The mechanism of this highly regioselective [2 + 2 + 2] cyclization is shown in Scheme 61.

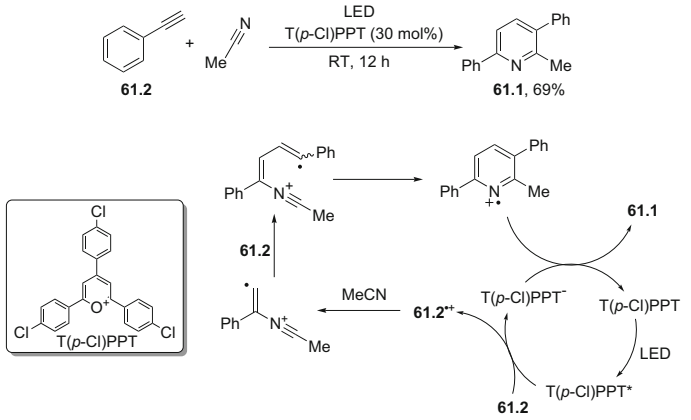
A more efficient approach is described in Scheme 62 for the preparation of ortho-trifluoromethylated pyridines **62.1a–d**, starting from isocyanides **62.2a–d** and Umemoto's reagent **62.3** [216]. The strategy was based on the CF_3 radical addition onto the isocyanide moiety, followed by cyclization. This was found particularly efficient when R was an aromatic substituent.

Other approaches were based on the photocatalytic oxidation of primary amines. Thus, 2,4,6-triarylpyridines were obtained by the eosin Y-photocatalyzed reactions between acetophenones and benzyl amines (as nitrogen donors) [217]. A photoinduced aerobic C–N bond activation in 1,3-diamines was useful for the synthesis of 2-arylpyridines, where acetophenones were again the reaction partners [218].

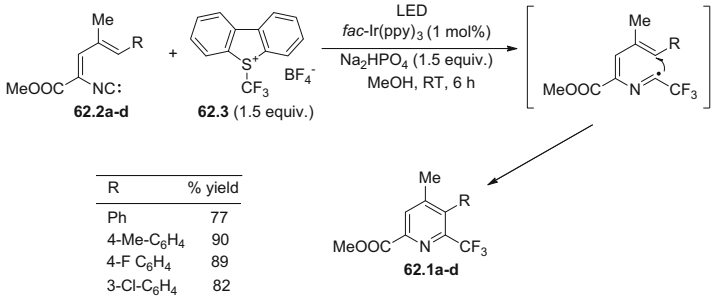
4.1.3 Quinolines

The quinoline scaffold is one of the preferred structures accessible by photocatalyzed reactions. An example is the Ru(II)-photocatalyzed visible-light-induced reaction between trifluoroacetimidoyl chloride **63.1** and phenyl acetylenes. The reaction was made possible by the photocatalyzed formation of an imidoyl radical by cleavage of a $C(sp^2)$–Cl bond under mild and eco-sustainable conditions (Scheme 63) [219].

α-Carbonylbenzyl bromides were used as a source of electrophilic radicals that upon addition onto vinyl azides generated an iminyl radical and polysubstituted quinolines from them via a C–C and C–N bond formation sequence [220].

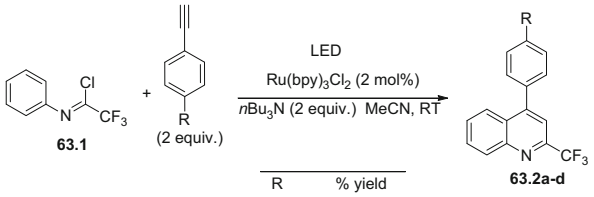


Scheme 61 Photoorganocatalyzed preparation of substituted pyridines via pyrylium salts



R	% yield
Ph	77
4-Me-C_6H_4	90
4-F C_6H_4	89
3-Cl-C_6H_4	82

Scheme 62 Synthesis of trifluoromethylated pyridines starting from isocyanides



R	% yield
H	83
Me	80
OMe	75
COMe	76

Scheme 63 Photocatalyzed synthesis of quinolines via cleavage of a $C(sp^2)$–Cl bond

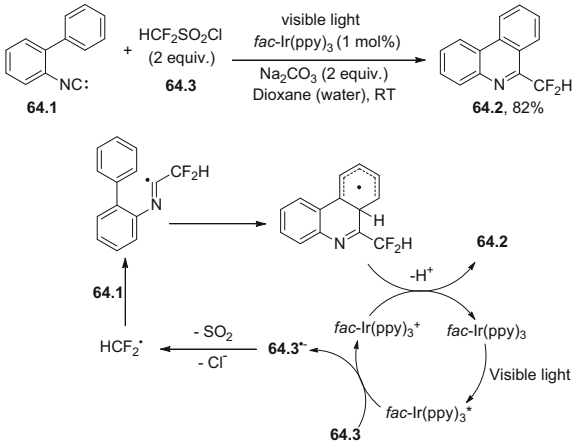
Isonitriles are important starting materials where the nitrogen atom of these compounds is incorporated into the quinoline or isoquinoline rings. As an example, an Ir(III)-based photocatalyst was used to generate either CF_3 radical [221] or aryl radicals (form aryldiazonium salts) [222] to give substituted isoquinolines upon addition onto vinyl isocyanides.

4.1.4 Phenanthridines

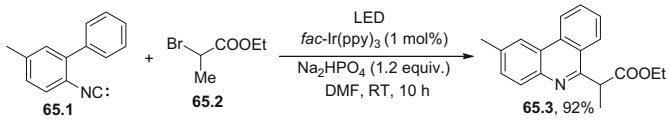
The best way to access phenanthridines is the radical addition onto a biphenyl isocyanide followed by radical cyclization. The addition/cyclization/oxidation sequence involved in such approach is exemplified by the reaction reported in Scheme 64. Thus, a difluoromethyl (or a difluoroalkyl) radical was obtained under photocatalytic conditions, and addition onto isonitrile **64.1** led to 6-(difluoromethyl)- or 6-(1,1-difluoroalkyl)phenanthridines **64.2** in a good yield [223]. Following the same strategy, 6-difluoromethylenephosphonated [224] or trifluoromethylated [225] phenanthridines were easily prepared.

Similarly, 2-isocyanobiphenyls were used as starting materials for the preparation of 6-aryl substituted phenanthridines in the reaction with arylsulfonyl chlorides [226] or 6-difluoromethylenephosphonated phenanthridines. Scheme 65 illustrates another example dealing with the use of aryl isonitriles. A visible-light-absorbing PC such as an Ir(III)-based complex formed an α-carboxyl radical from bromoester **65.2**. Addition of the resulting radical onto isonitrile **65.1** gave access to the imidoyl radical, which upon a cyclization/oxidation/deprotonation sequence yielded phenanthridine **65.3** in a very good yield (92%) [227].

Several variants of this approach are known, relying on a radical addition onto 2-isocyanobiphenyls. The method is very versatile since aryl, acyl, and alkyl radicals are generated from hydrazine hydrochlorides and eosin B is used as the PC [228].

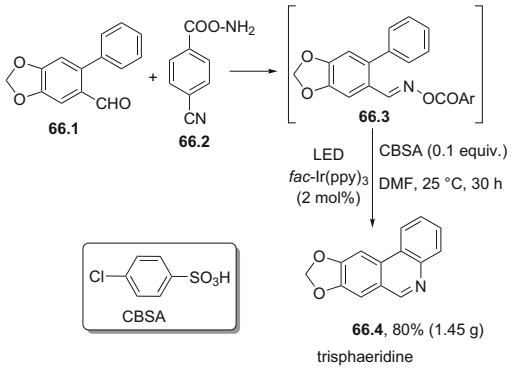


Scheme 64 Biphenyl isocyanides as starting materials for the synthesis of the phenanthridine core



Scheme 65 Ir(III)-photocatalyzed preparation of phenanthridines from biphenyl isocyanides

Scheme 66 Preparation of the alkaloid trisphaedrine



The preparation of the alkaloid trisphaedrine **66.4** was easily carried out in a one-pot fashion, starting from the biphenyl aldehyde **66.1** in a gram scale. The first step is the in situ formation of *O*-acyl oxime **66.3** from *O*-(4-cyanobenzoyl)-hydroxylamine **66.2**. Then, a reduction of **66.3** led to an iminyl radical that finally afforded phenanthridine **66.4** (Scheme 66) [229]. The presence of Brønsted acids (e.g., *p*-Cl-benzenesulfonic acid, CBSA) was shown to improve the overall yield.

Iminyl radicals were also generated by the reaction of trifluoromethyl radicals with vinyl azides that underwent intramolecular homolytic aromatic substitution to give 6-(fluoro)alkylated phenanthridine derivatives [43].

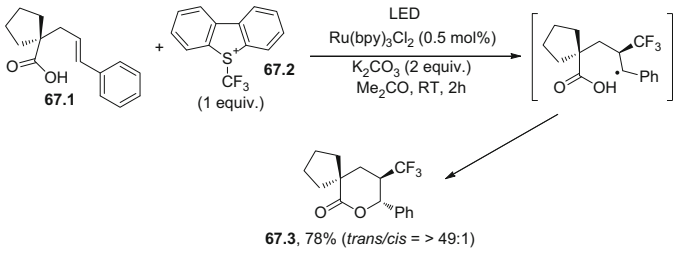
4.2 Oxygen- and Sulfur-Containing Heterocycles

4.2.1 Lactones and Coumarins

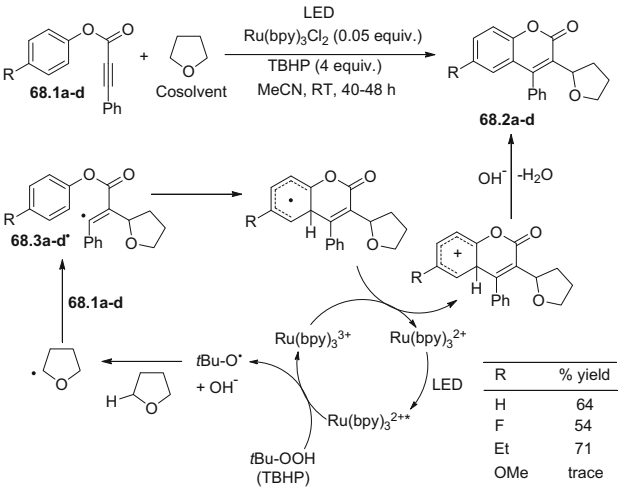
A cyclization step was usually adopted for the preparation of lactones and coumarins. An approach consists in the carbolactonization of alkenoic acids as illustrated in Scheme 67. The CF_3 radical (from the photocatalyzed reduction of **67.2**) added to the C–C double bond in **67.1**. The resulting benzyl radical was then oxidized into the corresponding cation, and cyclization of the nucleophilic COOH group led to the spiro compound **67.3** in very good yield and high diastereoselectivity [230].

The oxygen-containing six-membered ring in isochromanones and isochromenones was formed by aryl radical (having a COOH as a ring substituent) addition onto styrenes. These aryl radicals were formed by Ru(II)-photocatalyzed reduction of differently substituted anthranilic acids [231].

In other instances, the ester group was still present in the starting substrate, and the cyclization took place after the radical addition. As an example, Scheme 68 shows a typical preparation of coumarin derivatives following this approach. Thus, the radical addition of the α-oxy radical (generated from THF) onto phenyl 3-arylpropiolates **68.1a–d** led to the resulting vinyl radical **68.3a–d**$^{\bullet}$, which



Scheme 67 Photocatalyzed carbolactonization of alkenoic acids



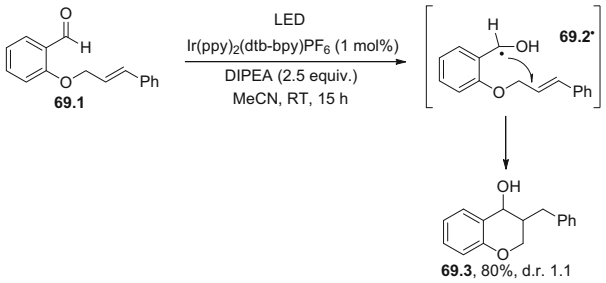
Scheme 68 Ru(II) photocatalyzed preparation of coumarin derivatives

cyclized onto the aromatic ring affording the desired heterocycle. The generation of radicals here was promoted by the photocatalyzed reduction of the peroxide TBHP, which liberated a very reactive *t*BuO radical. The yields of coumarins **68.2a–d**, however, largely depended on the nature of the substituents present on the aromatic ring (Scheme 68) [232]. A related approach was used for the preparation of coumarins under metal-free conditions (eosin Y as the photocatalyst) by radical addition of sulfinic acids onto propiolates **68.1a–d** [70].

4.2.2 Chroman Derivatives

Chroman derivatives may be accessed in different ways. Thus, benzaldehyde **69.1** was smoothly converted into chromanol **69.3** in a very good yield upon irradiation in the presence of an Ir(III) photocatalyst and an excess of a base (Scheme 69) [233]. The latter facilitates the photocatalyzed PCET reaction to give radical **69.2**• and then **69.3** after cyclization onto the double bond.

Scheme 69 Iridium-mediated synthesis of chroman derivatives



The core of chromane derivatives was likewise synthesized by eosin Y photoorganocatalyzed cyclization of phenols substituted with a polyene unit (e.g., 2-geranylphenol). The formation of a radical cation species at the end-alkene moiety promoted a stereoselective radical cascade cyclization to form hexahydro-1*H*-xanthenes in variable yields [234]. The main drawback of the reaction was the use of expensive hexafluoroisopropanol (HFIP) as the reaction medium. Chromones were obtained by a radical-triggered tandem cyclization of *o*-hydroxyaryl enaminones. In this case, photogenerated fluorinated radicals added to the double bond of the enaminone moiety, promoting a radical cascade and the formation of a C–O bond with the concomitant elimination of a secondary amine [235].

4.2.3 Other Oxygen Heterocycles

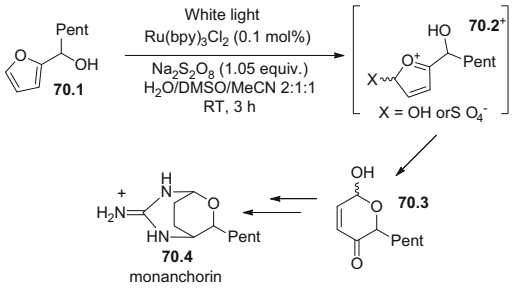
Again, a cyclization step is involved in the synthesis of β-tetrahydropyrans by bromoetherification of alkenols [236]. The excited Ru(II) photocatalyst was responsible for the visible-light generation of Br_2 from CBr_4 (via CBr_3 radical). Addition of bromine to an aromatic pentenol induced a cyclization to form the desired tetrahydropyran.

An interesting photocatalyzed ring enlargement/dearomatization mimicking the Achmatowicz rearrangement was involved in the synthesis of 2*H*-pyran-3(6*H*)-one **70.3** from **70.1**. The photocatalyzed degradation of persulfate anion induced the formation of oxocarbenium **70.2**$^+$, which upon detachment of X furnished **70.3**. Noteworthy, the latter compound was used as an intermediate for the preparation of monanchorin **70.4**, a bicyclic alkaloid (Scheme 70) [237].

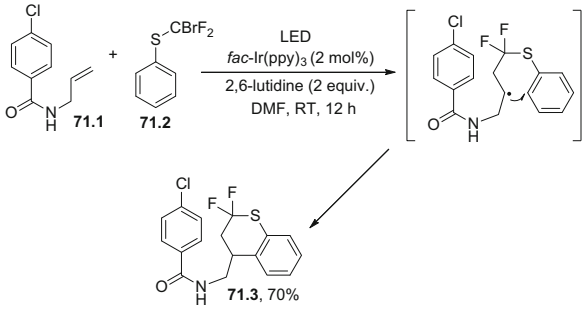
4.2.4 Sulfur Heterocycles

One example is worth to be mentioned here and is related to a phenylthiodifluoromethylation of amide **71.1** with reagent **71.2** (Scheme 71) [238]. An arylthiofluoroalkyl radical was first generated and upon addition to C=C and cyclization afforded **71.3** in 70% yield. The method is likewise useful for the direct introduction of the $PhSCF_2$ group onto electron-rich heteroaromatics.

Scheme 70 Preparation of the bicyclic alkaloid monanchorin



Scheme 71 Formation of a sulfur-containing six-membered heterocycle



4.3 More than One Heteroatom in the Ring

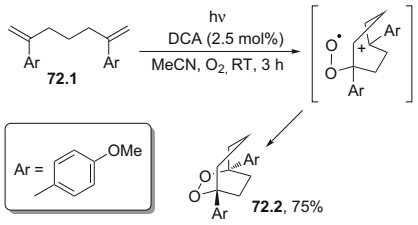
4.3.1 Two Heteroatoms in the Ring

One of the green approaches to build a heterocycle containing two oxygen atoms is the addition of dioxygen to a radical cation generated photocatalytically. One seminal work in this field is exemplified by the reaction in Scheme 72. The DCA-photocatalyzed oxidation of the 2,6-diaryl-1,6-heptadiene (**72.1**) under oxygenated conditions led to the incorporation of O_2, the ensuing cyclization affording the dioxabicyclo[3.2.2]nonane **72.2** in 75% isolated yield [239]. The reaction was likewise effective when applied to 3,6-bis(*p*-methoxyphenyl)-2,6-octadiene or 2,6-diarylhepta-1,6-dienes to form the corresponding 1,2-dioxanes [240] or 1,2-dioxepanes [241].

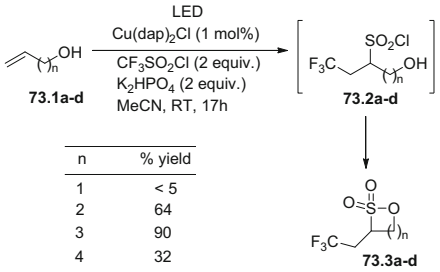
More recently, hexa-1,5-dienes were used as substrates to form endoperoxides by pyrylium salt-photocatalyzed oxidation [242]. In all cases, the resulting endoperoxides are key compounds since this moiety is found in several naturally occurring compounds. A related process was applied to anthracene by using Acr^+-Mes as the photocatalyst, an interesting route for the preparation of epidioxyanthracenes [243].

A photocatalytic cyclization was used for the preparation of sultones (Scheme 73) [244]. The main advantage of the reaction is that the Cu(I)-photocatalyzed reaction between alkenols **73.1a–d** and CF_3SO_2Cl led to the complete incorporation of the latter (compounds **73.2a–d**) and formed sultones **73.3a–d**, upon intramolecular

Scheme 72 Synthesis of dioxabicyclo[3.2.2]nonanes via DCA-photocatalyzed oxidation of the 2,6-diaryl-1,6-heptadienes



Scheme 73 Cu(I)-photocatalyzed preparation of sultones



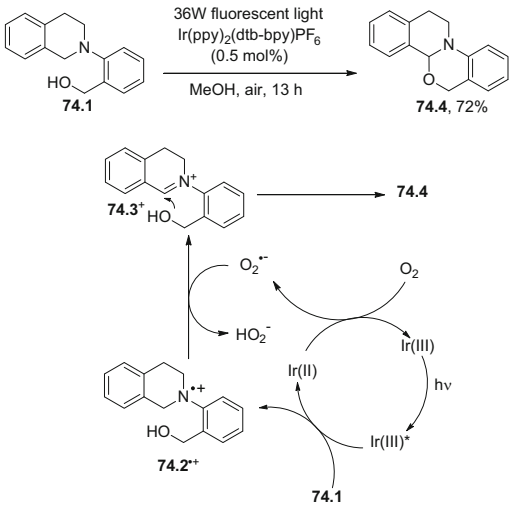
n	% yield
1	< 5
2	64
3	90
4	32

nucleophilic substitution [244]. Yields were however strictly dependent on the size of the ring formed, being poor for the four-membered ring but excellent for a six membered-ring (Scheme 73).

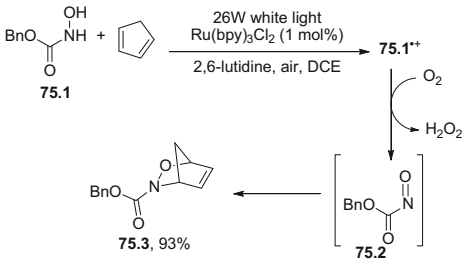
Different strategies were considered to incorporate both an O and an N atom in a six-membered ring. The isoquino[2,1-*a*][3,1]oxazine structure was accessed by an intramolecular C–O bond formation in benzyl alcohol **74.1** under aerated conditions (Scheme 74). The initial formation of $\mathbf{74.2}^{\bullet+}$ promoted by the excited Ir(III) complex was followed by a deprotonation induced by the photogenerated $O_2^{\bullet-}$. The resulting iminium ion $\mathbf{74.3}^{+}$ then underwent a nucleophilic addition of the OH group to afford **74.4** in 72% yield [245].

Alternatively, hydroxymethyl aniline derivatives were subjected to a photocatalyzed reaction with CBr_4 under basic conditions (2,6-lutidine) in a flask, open to the air, under sunlight irradiation. Following this strategy, a cyclic carbamate was formed, and several benzo[*d*][1,3]oxazin-2(4*H*)-one were prepared, even under flow conditions, showing some promise for an industrial application [246]. An oxidative carbonylation of enamides was found useful for the synthesis of 1,3-oxazin-6-ones by combining palladium and Ru(II) photoredox catalysis. The reaction started with the palladium-catalyzed incorporation of CO in enamides. The role of the photocatalyst was to oxidize Pd(0) into the Pd(II) species, the actual catalytic species [247]. A Ru(II)-based catalyst was also found sufficient to promote an oxytrifluoromethylation of *N*-allylamides under blue LED irradiation. As a result, trifluoromethylated benzoxazines were formed in up to 98% yield [248]. Another approach consists in the photocatalyzed formation of a reactive species (Scheme 75). In this case, a nitrosocarbonyl (**75.2**) was generated with both temporal and spatial control by oxidation of *N*-substituted hydroxylamine **75.1** and used in a hetero Diels–Alder (HDA) reaction to give azabicyclo[2.2.1]hept-5-ene **75.3** [249].

Scheme 74 Preparation of heterocycles via C–O bond formation



Scheme 75 Azabicyclo [2.2.1]hept-5-enes via photogenerated nitrosocarbonyls

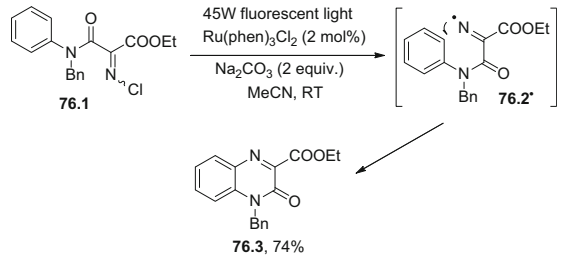


Sparse are the examples where a six-membered ring containing two nitrogen atoms were formed. A typical example was the synthesis of quinoxalin-2(1*H*)-one **76.3** (Scheme 76). In this case, the photocatalyzed reduction of chloroiminoacetate **76.1** formed an iminyl radical (structure **76.2**$^{\bullet}$), the cyclization of which formed the heterocyclic derivative **76.3** in 74% yield [250]. The reaction was catalyzed by a Ru (II) complex and required an inexpensive base such as Na_2CO_3.

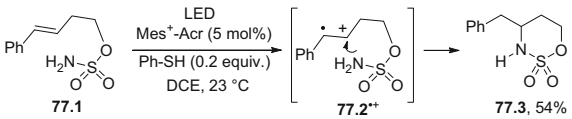
An iminyl radical was likewise involved in the construction of the quinoxaline skeleton. An Ir(III) photocatalyst helped here in the generation of alkyl radicals, which upon cyclization onto a phenyl isocyanide, followed by cyclization onto a pyrrole (or other heteroaromatic rings), led to highly substituted quinoxalines [251]. 2-Perfluoroalkyl-3-iodoquinoxalines were prepared in an analogous way by a double radical isocyanide insertion starting from 1,2-diisocyanobenzenes [252].

4.3.2 Three Heteroatoms in the Ring

Only one example belonging to this category is worth mentioning (Scheme 77). Thus, irradiation of sulfamate **77.1** in the presence of Mes^+-Acr as the photocatalyst



Scheme 76 Photocatalyzed synthesis of quinoxalin-2(1*H*)-ones



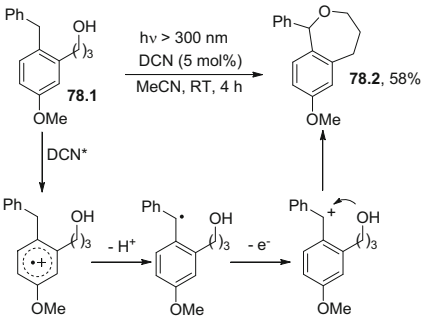
Scheme 77 Photocatalyzed construction of a six-membered heterocycle containing three heteroatoms

caused the oxidation of the double bond to give the corresponding radical cation **77.2**$^{\bullet+}$. The amino group was found nucleophilic enough to perform a clean 6-exo cyclization to afford 1,2,3-oxathiazinane 2,2-dioxide **77.3** in a modest yield [253]. A substoichiometric amount of thiophenol was required as H-atom donor.

5 Larger than Six-Membered Ring

The photocatalyzed formation of rings larger than six is quite unusual since the required cyclization is not favorable and only a couple of examples will be reported here. An interesting example deals with the direct benzylic C–H activation in compound **78.1** (Scheme 78). The oxidation of this anisole derivative caused a deprotonation from the benzylic site and a further oxidation allowed to the generation of a carbocation. An intramolecular cycloetherification finally led to tetrahydrobenzo[c]oxepine **78.2** in 58% yield [254].

The cyclization of an OH group onto an electrophilic site was likewise used for the synthesis of oxepanes starting from alkenols in the presence of $PhCH(CN)_2$ as H-atom donor. The excited photocatalyst (an acridinium salt) oxidized the olefin moiety, and the intramolecular nucleophilic addition of the OH group onto the resulting radical cation was the key step of this anti-Markovnikov hydroetherification [102]. A smooth way (albeit inefficient) to construct oxygen-containing macrocycles made use of a homocoupling of C-centered radicals arising from a bis-phenylacetic acid under titanium dioxide photoredox catalysis. However, the reaction was not clean, and only a modest amount (not exceeding 13%) of dioxadibenzenacyclododecaphanes was obtained [255].



Scheme 78 Oxepine derivatives from a photocatalyzed intramolecular cycloetherification

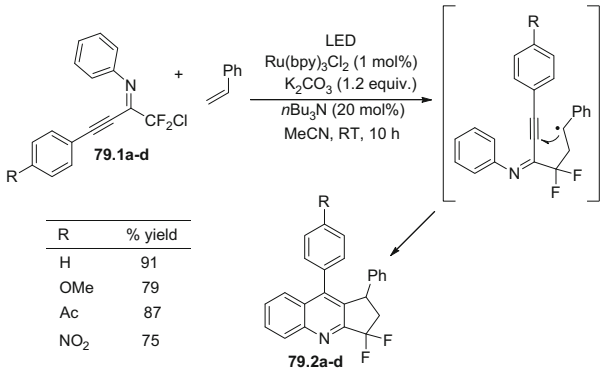
6 Two or More Rings

The situation here is more diverse since in a single step more than one ring is formed where at least one contains a heteroatom. Oxygen- or nitrogen-containing heterocycles were usually prepared. A representative example of nitrogen-containing heterocycles is the preparation of gem-difluorinated fused quinolines (**79.2a–d**) starting from imines **79.1a–d** (Scheme 79). The Ru(II)-based catalyst was reduced by a purposely added amine (nBu$_3$N), and the resulting Ru(I) was able to reduce **79.1a–d**, which upon chloride anion loss gave a difluoromethyl radical. Addition onto a styrene initiated a radical cascade that ultimately led to **79.2a–d** [256]. The overall yield was quite good, whatever the substituent present on the phenylacetylene moiety.

A related synergistic domino bicyclization was applied to the preparation of cyclopenta[*c*]quinolines and benzo[*j*]phenanthridines by diethyl malonate radical addition onto a 1,7-enyne containing an acrylamide moiety. The reaction was photocatalyzed by an Ir(III) complex [257]. The same starting materials were reacted under similar photocatalyzed conditions with acyl chlorides to form fused pyran derivatives [258]. Two nitrogen-containing rings were formed in one step by the Ir(III)-photocatalyzed reaction of *N*-(2-iodobenzyl)-*N*-acylcyanamides. An aryl radical was first generated by iodine loss, which then added to the nitrile group. The thus formed iminyl radical again cyclized onto another aromatic ring, and the corresponding tetracyclic pyrroloquinazolines were isolated in yields up to 88% [259].

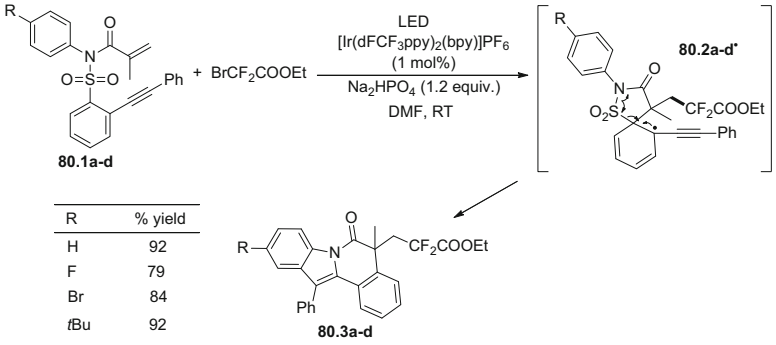
One recent example in the construction of complex structures is illustrated in Scheme 80. The reaction was applied to 1,8-enynes **80.1a–d** that underwent a difluoroalkylation/cyclization cascade process to give tetracyclic derivatives **80.3a–d**. The latter derivatives were formed by an initial addition of the CF_2COOEt radical onto the acrylamide moiety in **80.1a–d**, followed by a cyclization, generating radicals **80.2a–d**$^{\bullet}$ that underwent SO_2 loss and cyclization of the resulting N-centered radical onto the triple bond [260].

Scheme 81 depicts an example of the synthesis of fused *N*-arylindolines starting from diarylamines **81.1a–d**. The initial photocatalytic oxidation of the nitrogen gave the corresponding radical cation that upon cyclization onto the tethered olefin



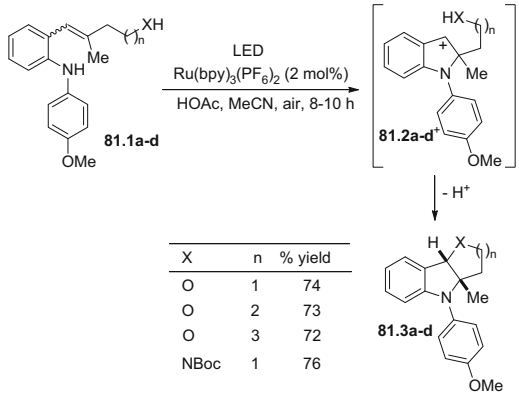
R	% yield
H	91
OMe	79
Ac	87
NO_2	75

Scheme 79 Photocatalyzed formation of two rings



R	% yield
H	92
F	79
Br	84
*t*Bu	92

Scheme 80 Photocatalyzed difluoroalkylation/cyclization cascade for the synthesis of tetracyclic derivatives



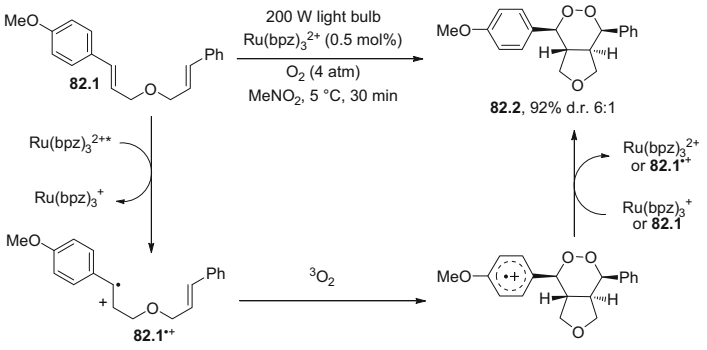
X	n	% yield
O	1	74
O	2	73
O	3	72
NBoc	1	76

Scheme 81 Diarylamines as precursors of fused *N*-arylindolines

moiety gave cations **81.2a–d**$^{+}$, which underwent an intramolecular nucleophilic addition to yield **81.3a–d** [261]. The versatility of the method is witnessed by the fact that five to seven oxygen-containing membered rings along with a nitrogen-containing membered ring were formed in roughly the same yield.

Another interesting reaction is the synthesis of quinoline-fused lactones starting from cinnamyl 2-(*p*-tolylamino)acetates. The reaction was initiated by a Ru(II) photocatalytic aerobic oxidation of the starting cinnamate, followed by a Povarov cyclization induced by the presence of a Lewis acid ($BF_3{\cdot}Et_2O$ 5 mol%) [262]. Moreover, the addition of CF_3 radical onto isonitrile-substituted methylenecyclopropanes induced a tandem reaction responsible for the direct formation of two six-membered rings, thus forming substituted 6-(trifluoromethyl)-7,8-dihydrobenzo[k]phenanthridines [263]. The last intriguing example of nitrogen-containing heterocycles involved the synthesis of 1,3-diazabicyclo[3.1.0]hexanes by visible light-driven photocascade catalysis. The PC here (a Ru(II) complex) has the double role to sensitize the formation of azirine (from α-azidochalcones) and at the same time to form an azomethine ylide from *N,N*-dimethylanilines. Coupling of the azirine with the azomethine ylide gave the desired heterocycles by making one C−C and two C−N new bonds in continuous flow system [264].

A representative example of oxygen-containing heterocycles is depicted in Scheme 82 for the preparation of endoperoxides. A bis(styrene) **82.1** was oxidized into the corresponding radical cation **82.1**$^{\bullet+}$, which upon oxygen addition and further reduction yielded oxygenated heterocycle **82.2** in a very good yield but with a modest dr [265]. The thus formed 1,2-dioxolanes were easily elaborated and converted into γ-hydroxyketones and 1,4-diols since they showed promising cancer cell growth inhibition.



Scheme 82 Photocatalyzed synthesis of endoperoxides

7 Conclusion

This book chapter provides an up-to-date review of the multifaceted photoredox catalytic approaches for the generation of radicals that lead to heterocyclic scaffolds. Albeit the formation of three- or four-membered rings is quite rare, several strategies to build five- and six-membered rings are reported here. However, the number and variety of examples clearly underline the maturity of photoredox catalysis in accomplishing the task of generating highly energetic intermediates under mild conditions, affording novel and, wherever possible, simpler ways to construct heterocycles.

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C–H Activation via Radical Processes Using Photo-Excited Ketones

Shin Kamijo

Abstract This chapter covered recent advancements in nonreactive C(sp^3)–H bond functionalization using photo-excited aryl ketones. The C–H bond cleaving ability of photo-excited ketones plays an important role in these reactions. Transformations targeting nonreactive C–H bonds can dramatically simplify synthetic sequences and improve synthetic efficiency as described in this chapter.

Keywords C(sp^3)–H bond functionalization · Free radicals · Heterocycles · Insertion · Photoreaction · Substitution

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1 Introduction

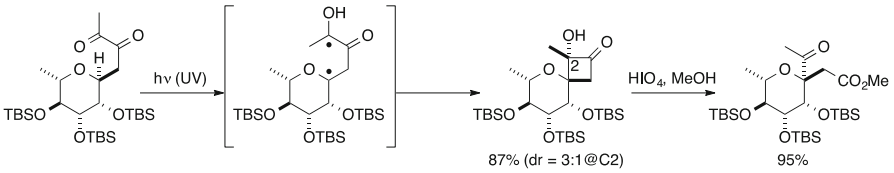
Direct transformations of C–H bonds have attracted attention because they avoid the need for prior functional group manipulations in syntheses of pre-activated precursors and therefore greatly streamline synthetic sequences [1–3]. Among such reactions, functionalization of C(sp^3)–H bonds in the carbon framework of organic substances is particularly advantageous for the construction of structurally complex molecules, which generally contain a high ratio of sp^3-hybridized carbon centers. Established synthetic protocols allow functionalization only at acidic C(sp^3)–H bonds activated by polarization with an adjacent electron-withdrawing group. Those acidic C–H bonds can be converted under ionic conditions, deprotonation with a base to generate a reactive nucleophilic species and subsequent reaction with an electrophile, but such reactive bonds are limited as a component of the carbon framework. The most ubiquitous component should be nonacidic C(sp^3)–H bonds in general, although such C–H bonds are considered inert because of their low reactivity under ionic conditions. Accordingly, functionalization at nonacidic C–H bonds remains challenging, due mainly to the lack of general strategies for activating those nonreactive C–H bonds, despite their potential for simplifying synthetic sequences and improving synthetic efficiency. The key for converting nonreactive C–H bonds can be found in examples of photoreactions such as pinacol syntheses [4, 5], the Norrish-Yang reaction [6], remote C–H functionalization [7], and photoaffinity labeling [8]. All of these transformations proceed through cleavage of nonreactive C(sp^3)–H bonds effected by in situ generated, highly reactive photo-excited ketones. This chapter presents recent advancements in radical processes for functionalization at nonreactive C(sp^3)–H bonds through the use of photo-excited aryl ketones.

2 Substitutive Introduction of Carbon Units

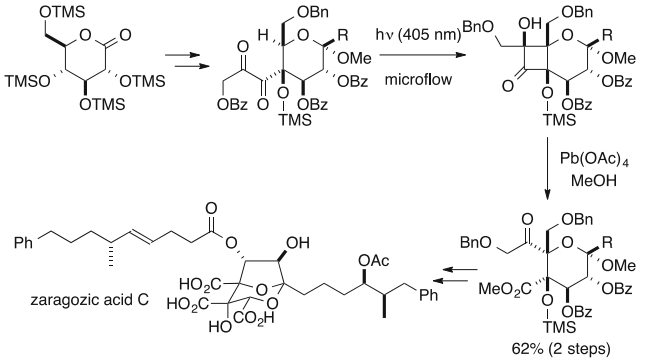
2.1 Acylation

The functionalization of nonreactive C–H bonds was investigated by applying the Norrish-Yang photocyclization for the derivatization of cyclic compounds. Suárez and coworkers examined the photocyclization of 1-glycosyl-2,3-butadione derivatives and obtained spirocyclic monosaccharide derivatives (Scheme 1) [9, 10]. The reaction proceeded through hydrogen atom abstraction promoted by the photo-excited 1,2-diketone, followed by diastereoselective C–C bond formation between the two radical carbon centers. Oxidation of the derived α-hydroxycyclobutanones induced ring-opening to generate the acyl group, establishing the two-step acylation protocol of cyclic ethers.

The two-step intramolecular acylation protocol for cyclic carbon skeletons was applied to the synthesis of zaragozic acid C by Inoue and coworkers (Scheme 2) [11, 12]. The target molecule, zaragozic acid C, has a dioxabicyclo[3.2.1]octane core



Scheme 1 Two-step acylation of cyclic ethers via Norrish-Yang photocyclization

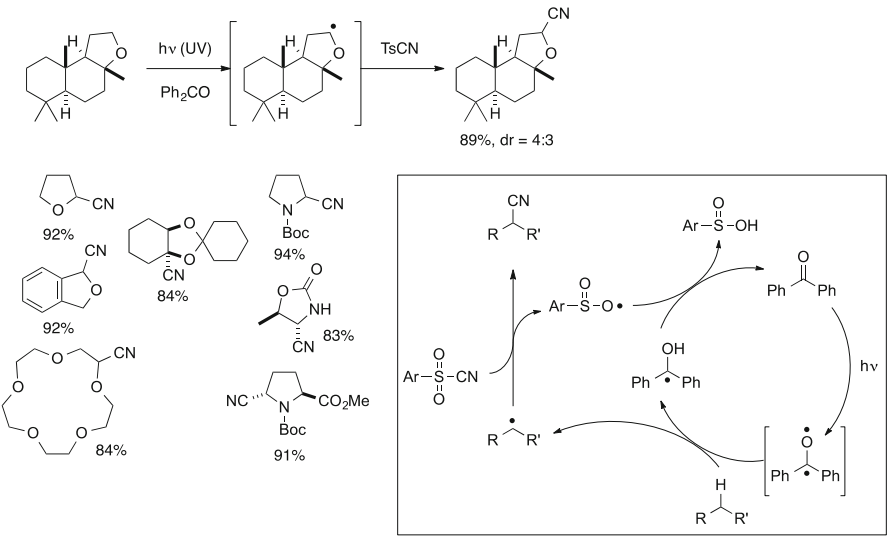


Scheme 2 Synthesis of zaragozic acid C

with six continuous stereogenic carbon centers and multiple oxygen-containing functionalities such as hydroxy groups and carboxylic acids. The greater reactivity of the electron-rich C–H bond adjacent to the electron-donating oxygen functionality allowed the starting 1,2-diketone to be precisely designed to obtain the expected regioselectivity. Conditions for the cyclobutane formation were optimized using microflow techniques with a careful selection of irradiation wavelength. A LED lamp at 405 nm was optimal, whereas that of a UV-LED lamp at 365 nm was reported to give a complex mixture of products.

2.2 Cyanation

The high reactivity of photo-excited aryl ketones promotes C–H bond cleavage in an intermolecular manner as well. Among ketones, benzophenone (Ph_2CO) is a well-known photo-mediator and was selected for photochemically induced transformation of C–H bonds to C–CN bonds using p-tosyl cyanide (p-TsCN) as a cyanogen source (Scheme 3) [13]. Despite an excess amount of starting material (8 equiv) that was necessary to obtain the expected nitrile products in high yield, a wide range of compounds, including ethers, alcohols, amine derivatives, alkanes, and alkylated benzenes, have been used as starting substances. The proposed reaction mechanism involves hydrogen atom abstraction by photo-excited Ph_2CO, acting in a manner



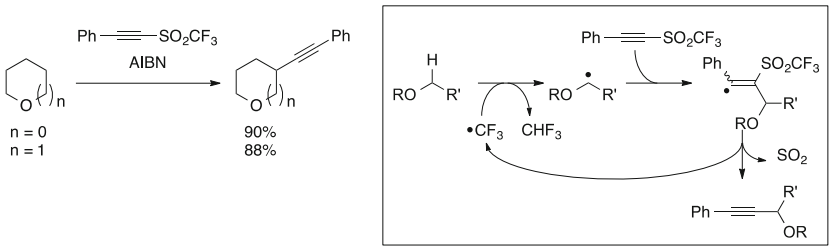
Scheme 3 Cyanation of heterocyclic compounds

similar to that of an electron-deficient oxyl radical, leading to the generation of a carbon radical intermediate. The derived radical was readily trapped with p-TsCN to furnish the cyanated products. Ring-opening of 1-cyclopropylethanol and subsequent CN trapping provided the corresponding acyclic nitrile compound, which supports the radical mechanism. Further optimization revealed that some nitrogen-containing compounds, such as Boc-protected pyrrolidine and piperidine, were cyanated even when they were the limiting reagent (1 equiv) [14]. Moreover, in some cases, cyanation could be realized with a catalytic amount of Ph_2CO (20 mol %), although a longer reaction time was required.

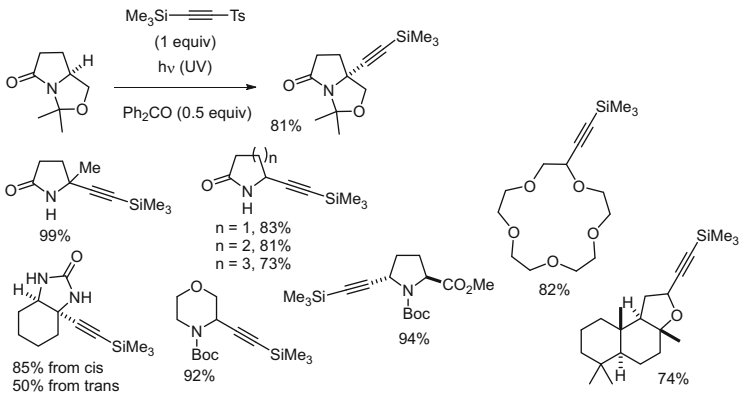
2.3 *Alkynylation*

Pioneering work on the substitutive introduction of alkynyl functionality at the non-reactive C–H bonds has been reported by Fuchs and coworkers (Scheme 4) [15–17]. Trifluoromethanesulfonyl phenylacetylene was employed as an alkynylating agent, and the reaction was conducted under heating conditions in the presence of AIBN or under UV irradiation. Simple compounds, such as ethers, thioethers, and alkanes, were suitable starting substances. This reaction is proposed to proceed through C–H bond cleavage effected by in situ generated trifluoromethyl radical species.

Substitutive introduction of a two-carbon alkynyl functional unit was achieved using 1-tosyl-2-(trimethyl)silylacetylene as an alkynylating agent (Scheme 5) [18]. A variety of starting substances, such as nitrogen-containing compounds, cyclic ethers, alcohols, and alkanes, could be transformed in a single step utilizing photo-excited



Scheme 4 Alkynylation of cyclic ethers

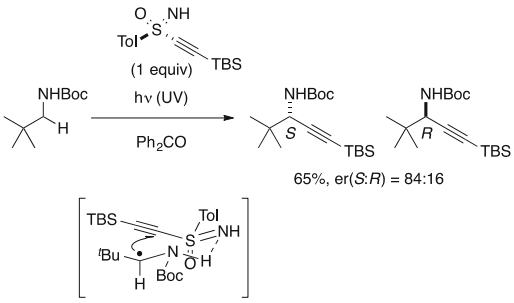


Scheme 5 Alkynylation of heterocyclic compounds

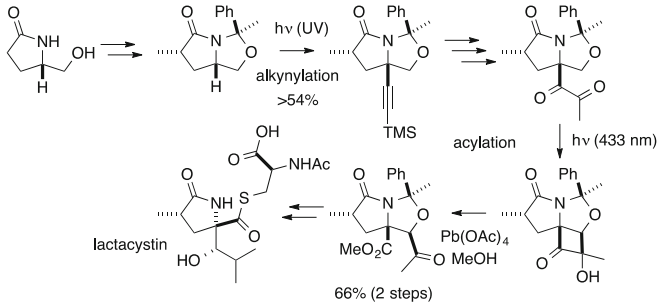
Ph_2CO as a C–H bond cleaving agent. In addition, the reaction could be conducted with a starting material that was a limiting agent (1 equiv) for alkynylation at methine C–H bonds. Further optimization revealed that the methine functionalization proceeded using substoichiometric amount of Ph_2CO (0.5 equiv). Reaction starting from either the cis- or trans-diaminocyclohexane derivative furnished the same cis-fused bicyclic alkynylated product, supporting the generation of a common carbon radical intermediate during the reaction course.

Enantioselective alkynylation of C–H bonds was investigated by Inoue's group using sulfoximine as a traceless chiral auxiliary (Scheme 6) [19]. The reaction was conducted in the presence of Ph_2CO under photoirradiation, and nitrogen-containing substances such as carbamates and amides were converted successfully to the corresponding propargyl amines in chemo- and enantioselective fashion. The strong hydrogen-bond capability between the basic S=NH and protic NHBoc moieties was proposed to be responsible for the enantioselective outcome.

Inoue and coworkers completed the total synthesis of (+)-lactacystin through the use of two different substitutive C–H functionalization reactions: intermolecular alkynylation and intramolecular acylation (Scheme 7) [20]. The first key transformation was the introduction of an alkynyl group to the (*S*)-pyroglutaminol derivative. The alkynyl unit then was oxidized to derive a 1,2-diketone, which acted as the starting material for the



Scheme 6 Enantioselective alkynylation of amine derivatives



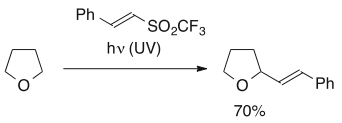
Scheme 7 Synthesis of lactacystin

second key reaction. Under irradiation from a blue LED lamp at 433 nm, the diketone was transformed smoothly to a cis-fused cyclobutanone in a chemo- and stereoselective manner, followed by oxidation to open the cyclobutane ring and introduce an acyl group next to the ether moiety. The total synthesis of (+)-lactacystin elegantly demonstrated the power of direct C–H functionalization for assembly of multiply functionalized structures.

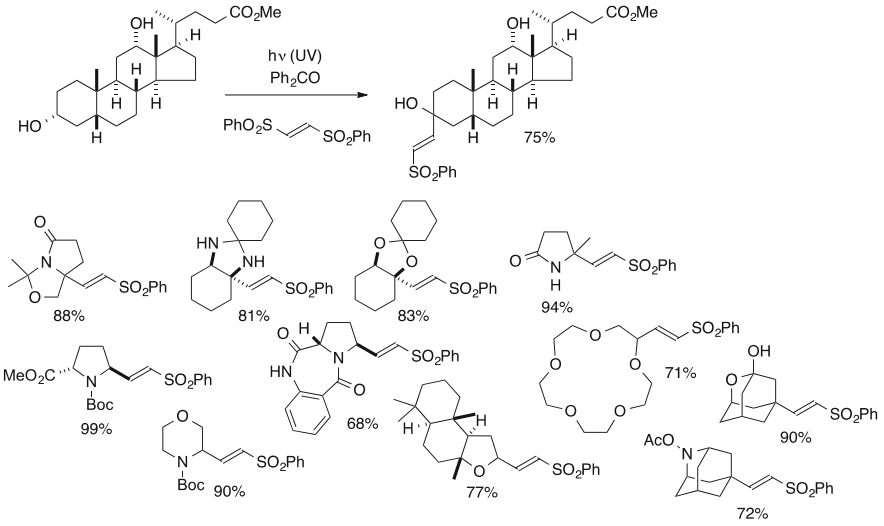
2.4 Vinylation

Fuchs and coworkers achieved vinylation at nonreactive C–H bonds of tetrahydrofuran and cyclohexane using a trifluoromethanesulfonylated olefin as the vinylating agent (Scheme 8) [21, 22]. Reaction was initiated by heating in the presence of AIBN or by UV-light irradiation. For the present reaction, the C–H bond cleaving ability of the trifluoromethyl radical species generated in situ from the starting vinylating agent was key.

Based on the C–H bond cleaving ability of photo-excited Ph_2CO, vinylation of a wide range of substances, including amine derivatives, ethers, alcohols, and alkanes, was investigated (Scheme 9) [23]. A typical reaction used an excess amount of the



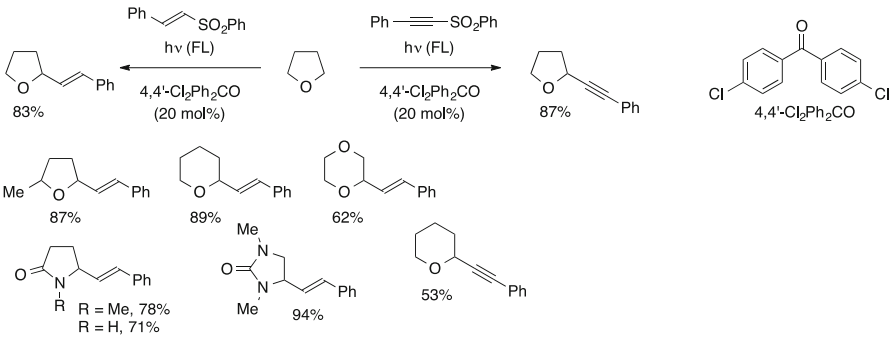
Scheme 8 Vinylation of cyclic ethers



Scheme 9 Vinylation of heterocyclic compounds

starting material (5–10 equiv), with 1,2-bis(phenylsulfonyl)ethylene (1 equiv) as the vinylating agent in the presence of a stoichiometric amount of Ph_2CO (1 equiv). For some vinylation reactions at the methine C–H bonds, the starting material could be a limiting reagent (1 equiv), with a slight excess of the vinylating agent (1.2 equiv), although longer reaction times were required and lower yields were observed in general. Cyclopropane ring-opening during the reaction verified the involvement of a radical intermediate, and the kinetic isotope effect observed for the vinylation of deuterated cyclohexane implied that the C–H bond cleavage was the rate-determining step in this transformation.

One disadvantage of the photoinduced vinylation and alkynylation of C–H bonds is the requirement of a stoichiometric amount of Ph_2CO to promote smooth formation of the corresponding products. Guin and coworkers designed a catalytic reaction for these C–H functionalization reactions when starting materials were also used as a solvent (Scheme 10) [24]. Reaction involved 20 mol% of 4,4′-dichlorobenzophenone (4,4′-Cl_2Ph_2CO) as a C–H bond cleaving agent instead of Ph_2CO and irradiation with a fluorescent lamp. Conditions for the present reaction allowed the catalytic substitutive transformation of C–H bonds; however, the need for a large excess of reagents limits applicable starting materials.



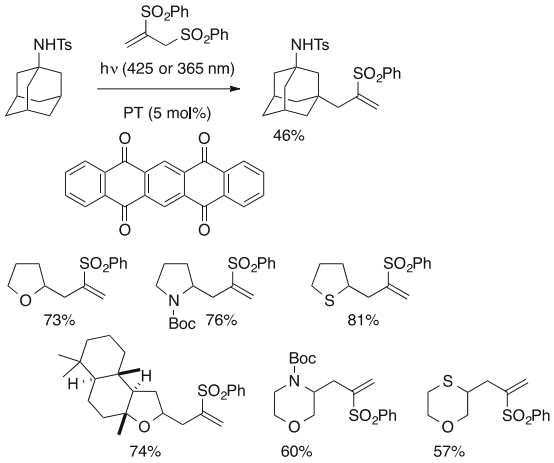
Scheme 10 Catalytic vinylation and alkynylation of heterocyclic compounds

2.5 *Allylation*

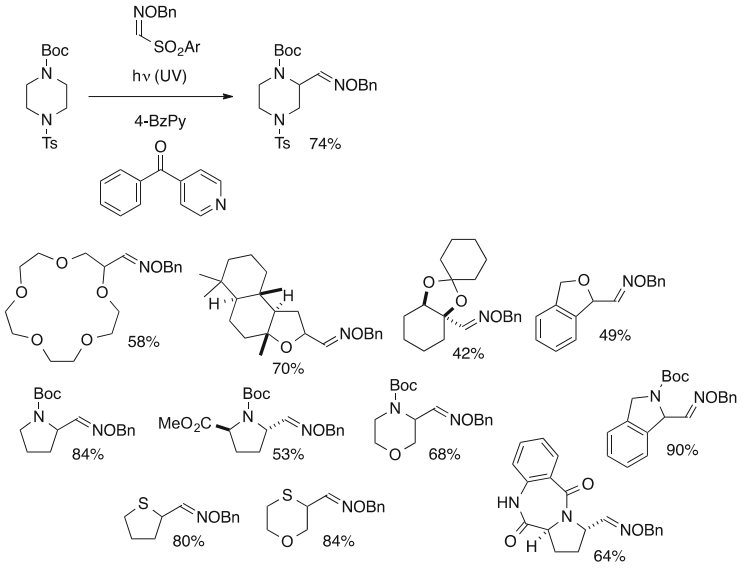
Further investigation of the photo-excited aryl ketone-mediated intermolecular substitutive functionalization of C–H bonds enabled catalytic installation of a three-carbon allyl functional unit to a range of substances including alkanes, ethers, alcohols, and amine derivatives (Scheme 11) [25]. The allylsulfone acted as the allylating agent, and the reaction was catalyzed, not only by Ph_2CO but also by 5,7,12,14-pentacenetetrone (PT), under UV-light irradiation at 365 nm. Moreover, the π-extended aryl ketone, PT, could catalyze the allylation under visible light irradiation at 425 nm. The kinetic isotope effect observed for the allylation of deuterated cyclohexane implied that C–H bond cleavage was the rate-determining step. In addition, in situ generated cyclooctyl radical was trapped successfully by tetramethylpiperidine *N*-oxyl radical (TEMPO), suggesting the involvement of a radical mechanism.

2.6 *Introduction of Aldoxime Functionality*

Next, photoinduced introduction of aldoxime functionality as a masked formyl group was accomplished by designing the sulfonyl oxime as the aldoxime source (Scheme 12) [26]. The aldoxime functionality was selected instead of a formyl group because introduction of formyl functionality was not practical under such radical conditions; cleavage of the formyl $C(sp^2)$–H bond was expected to occur preferentially over nonreactive $C(sp^3)$–H bonds due to the lower bonding energy of the formyl $C(sp^2)$–H bond. Screening of aryl ketones clarified that electron-deficient 4-benzoylpyridine (4-BzPy) gave a higher product yield than did Ph_2CO. The applicability of the starting material was broad, including oxygen-, nitrogen-, and sulfur-containing cyclic compounds as well as alkanes. In addition, reactivity of C–H bonds adjacent to the nitrogen atom could be regulated by the protecting group;



Scheme 11 Allylation of heterocyclic compounds



Scheme 12 Introduction of aldoxime functionality to heterocyclic compounds

the Boc group allowed and the Ts group inhibited C–H functionalization of the piperazine derivative.

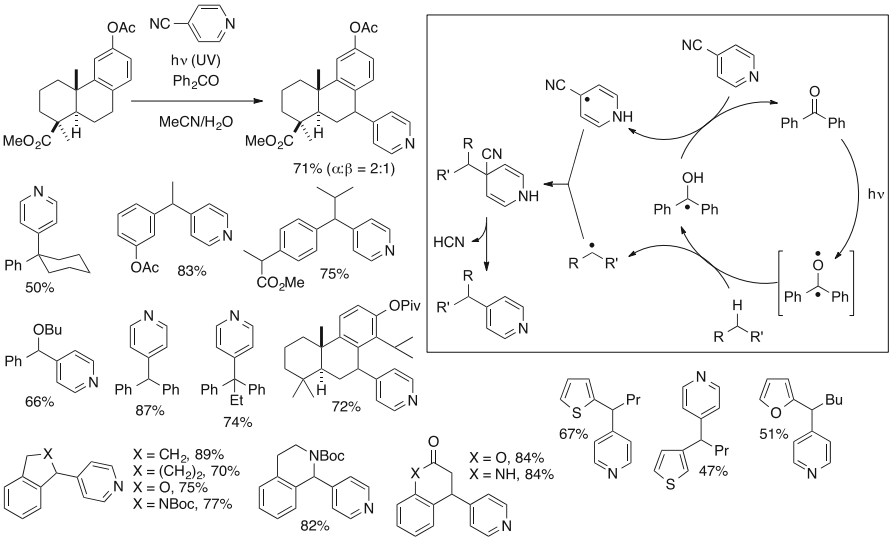
2.7 Heteroarylation

2.7.1 Pyridination

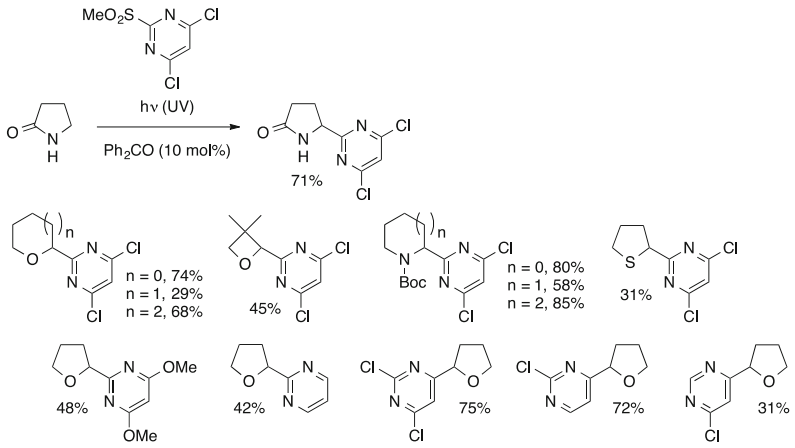
Under similar reaction conditions using photo-excited Ph_2CO, a pyridine ring was introduced chemoselectively to benzylic C–H bonds (Scheme 13) [27]. Treatment of alkylbenzenes with 4-cyanopyridine in the presence of a substoichiometric amount of Ph_2CO (0.5 equiv) in aqueous CH_3CN under photoirradiation promoted substitution at the 4-position of pyridine to afford diarylated products. In addition to alkylbenzenes containing a functional group, benzene-fused tricyclic compounds and alkylated heteroaromatics could also be used as starting materials. Some allylic C–H bonds and aliphatic C–H bonds were also pyridinated. The proposed reaction pathway involves generation of stabilized benzyl radical species by hydrogen atom abstraction with photo-excited Ph_2CO and subsequent proton-coupled electron transfer between an in situ generated ketyl radical and 4-cyanopyridine. Facile radical coupling and re-aromatization, along with elimination of HCN, afforded the coupling product.

2.7.2 Pyrimidination

The synthesis of alkylated pyrimidines utilizing photo-excited Ph_2CO was achieved via coupling between saturated heterocycles and sulfonylpyrimidines (Scheme 14) [28]. The present transformation allowed direct substitutive introduction of pyrimidine rings at nonreactive C–H bonds proximal to heteroatoms, including oxygen,



Scheme 13 Pyridination at benzylic C–H bonds

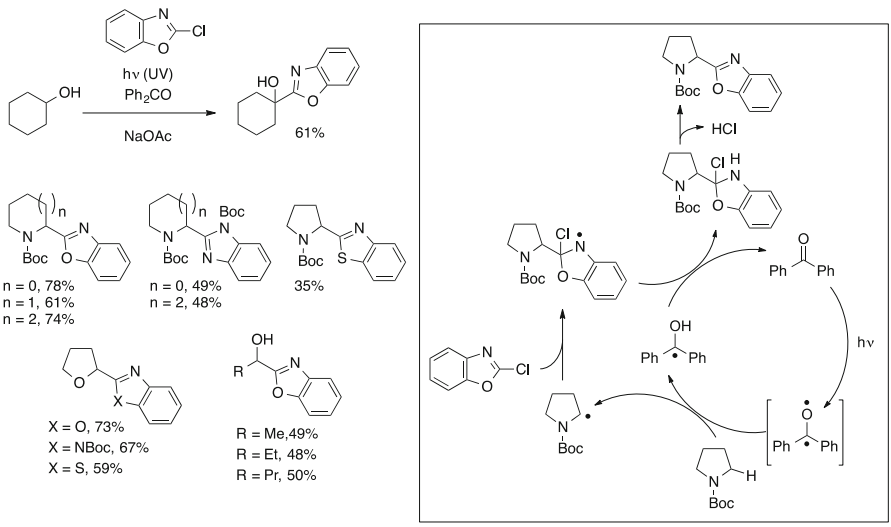


Scheme 14 Pyrimidination of heterocyclic compounds

nitrogen, and sulfur, under neutral reaction conditions at ambient temperature. Catalytic coupling (10 mol% Ph_2CO) was successful for highly electron-deficient dichlorinated sulfonylpyrimidines. When more electron-rich dimethoxy-substituted sulfonylpyrimidines and nonsubstituted sulfonylpyrimidines were employed, a stoichiometric amount of Ph_2CO and the use of the starting material as solvent were required to obtain a high yield of the coupling products.

2.7.3 Introduction of Benzazole Unit

The Ph_2CO-mediated photoinduced coupling reaction was extended to the one-step introduction of benzazoles, such as benzoxazoles, benzimidazoles, and benzothiazoles, to aliphatic carbamates, alcohols, and ethers (Scheme 15) [29]. An excess amount of starting material was treated with 2-chlorobenzazole (1 equiv) in the presence of Ph_2CO (1 equiv) and NaOAc (2.5 equiv) in aqueous CH_3CN under UV irradiation (368 nm). In the proposed mechanism, reaction was initiated by hydrogen atom abstraction with photo-excited Ph_2CO from the starting material. The derived carbon radical intermediate is added to the chlorinated carbon center of 2-chlorobenzazole. After hydrogen atom transfer between the derived aminyl radical and ketyl radical, expulsion of HCl completed re-aromatization to furnish the coupling adduct. Coupling could be conducted with a catalytic amount of Ph_2CO (25 mol%) when Boc-azepane, ethanol, or THF were used as starting materials.



Scheme 15 Introduction of benzazole unit to heterocyclic compounds

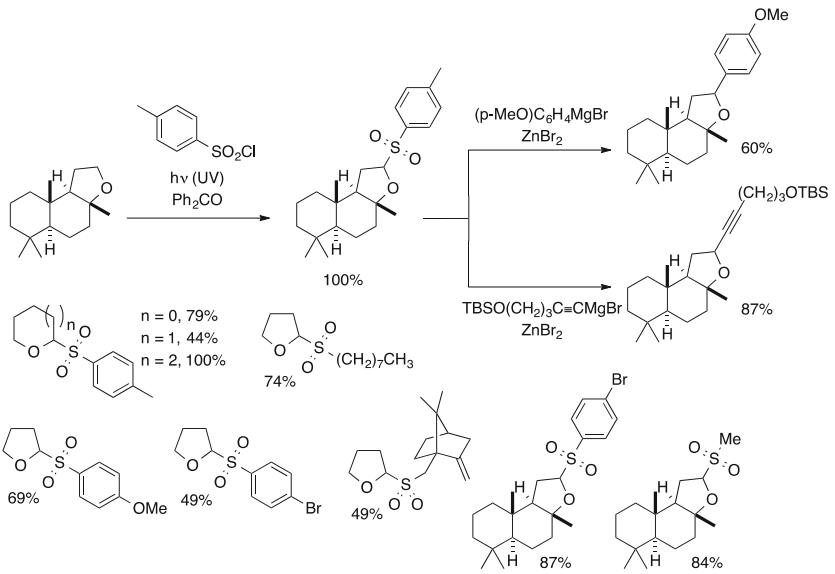
3 Substitutive Introduction of Heteroatom Units

3.1 Sulfonylation

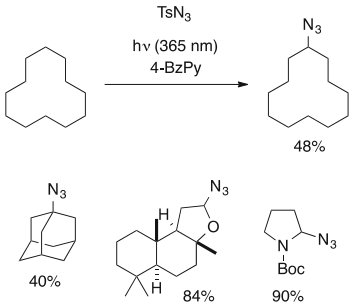
Substitutive introduction of heteroatom units at nonreactive C–H bonds has taken advantage of the highly reactive nature of photo-excited aryl ketones as a key feature. The first example involved sulfonylation of cyclic ethers in the presence of a stoichiometric amount of Ph_2CO under UV irradiation (Scheme 16) [30]. In this reaction, sulfonyl chloride acted as an efficient precursor of the sulfonyl unit. The five- to seven-membered cyclic ethers were transformed successfully, and chemoselective sulfonylation of the ethereal C–H bond was clearly observed, even when ambroxide was used as the starting material. Further transformations of the tosylated ambroxide provided the arylated and alkynylated ambroxides. Thus, a two-step protocol involving arylation and alkynylation at ethereal C–H bonds was developed via direct ether sulfonylation.

3.2 Azidation

Photoinduced synthesis of aliphatic azides was achieved in a single step starting from the parent cyclic alkanes, as well as from tetrahydrofuran and pyrrolidine derivatives (Scheme 17) [31]. The reaction proceeded via direct azidation of C–H bonds in the presence of 4-benzoylpyridine (4-BzPy) under photoirradiation using tosyl azide (TsN_3) as the azide source. Despite the potential photolability of azide



Scheme 16 Sulfonylation of heterocyclic compounds

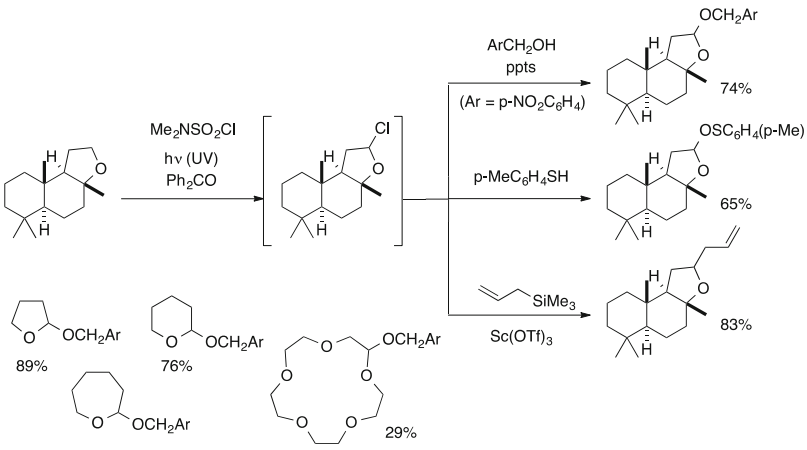


Scheme 17 Azidation of cyclic compounds

compounds, the current azidation provided the corresponding mono-azide adducts in a chemoselective manner.

3.3 Halogenation

With careful screening of potential chlorinating agents, photochemical chlorination of ethereal C–H bonds was achieved. The derived α-chlorinated ethers were somewhat unstable, so nucleophilic substitution was combined with the two-step protocol for ether derivatization (Scheme 18) [32]. In the presence of a stoichiometric amount of



Scheme 18 Two-step ether derivatization via chlorination of ethereal C–H bonds

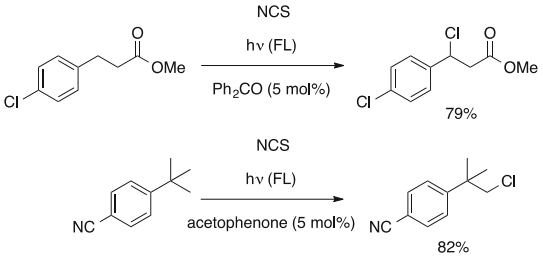
Ph_2CO, ethers were chlorinated with *N*,*N*-dimethylsulfamoyl chloride (Me_2NSO_2Cl) under photoirradiation. Carbon tetrachloride (CCl_4) also acted as a chlorinating agent, although Me_2NSO_2Cl was superior for this purpose. The derived α-chlorinated ether then was reacted with nucleophiles without isolation. This resulted in introduction of oxygen and sulfur functionalities as well as an allyl unit at the ethereal carbon center. This one-step ether chlorination provides rapid access to acetals, *O*,*S*-acetals, and allylated ethers from simple ethereal compounds.

Photochemical catalytic chlorination of C–H bonds was achieved by Chen and coworkers employing aryl ketones (5 mol%) and *N*-chlorosuccinimide (NCS) as a chlorinating agent (Scheme 19) [33]. Benzophenone (Ph_2CO) was optimal for chlorination at benzylic C–H bonds, while acetophenone was a better catalyst for less reactive C–H bonds of aliphatic carbon chains.

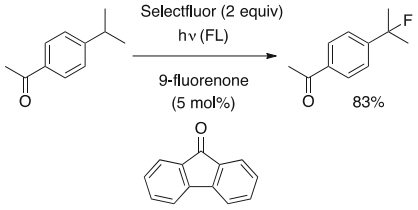
Chen and coworkers reported photoinduced catalytic fluorination at benzylic C–H bonds. They controlled mono-fluorination and di-fluorination by the choice of the aryl ketone used as a catalyst [34]. Mono-fluorination was achieved by treatment with Selectfluor in the presence of 9-fluorenone (Scheme 20), and di-fluorination was realized using Selectfluor II in the presence of xanthone (Scheme 21). Kappe and coworkers improved photoinduced benzylic mono-fluorination by using a flow system [35]. Use of the flow system promoted greater catalytic activity of xanthone, and the higher yields of mono-fluorinated products were obtained in shorter reaction times.

Lectka and coworkers applied similar reaction conditions with a photo-excited aryl ketone to achieve the benzylic fluorination of peptides (Scheme 22) [36]. Screening of potential photosensitizers revealed that 5-dibenzosuberenone was optimal for the present peptide fluorination. The benzylic C–H bond of the phenylalanine moiety was chemoselectively reacted with Selectfluor as a fluorinating agent under visible light irradiation.

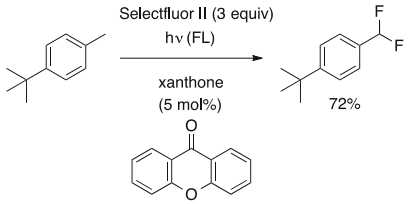
Scheme 19 Chlorination of benzylic and aliphatic C–H bonds



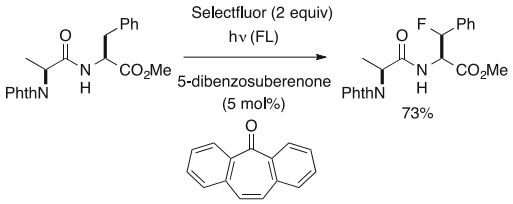
Scheme 20 Mono-fluorination of benzylic C–H bonds



Scheme 21 Di-fluorination of benzylic C–H bonds



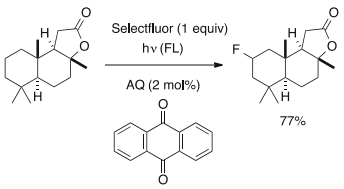
Scheme 22 Benzylic fluorination of peptides



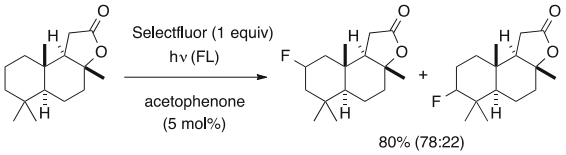
Tan and coworkers reported photoinduced fluorination of aliphatic C–H bonds using anthraquinone (AQ) as a catalyst (Scheme 23) [37]. A variety of functional groups, such as esters, carboxylic acids, carbonyl groups, amides, and mesyloxy, bromo, and cyano groups, were compatible.

Chen and coworkers achieved photoinduced catalytic fluorination of C–H bonds of alkanes under conditions modified from their benzylic fluorination reaction (Scheme 24) [38]. Intensive screening of aryl ketones revealed that acetophenone was the optimal catalyst and that mono-fluorination of alkanes could be realized using Selectfluor. Not only simple cycloalkanes but also carboxylic acids, ketones, ester, and protected amino acids could be used as suitable starting materials. For compounds with multiple reactive C–H bonds, the formation of the regioisomeric mixtures of fluorinated products was observed.

Scheme 23 Fluorination of aliphatic C–H bonds



Scheme 24 Fluorination of aliphatic C–H bonds



4 Insertive Introduction of Carbon Units

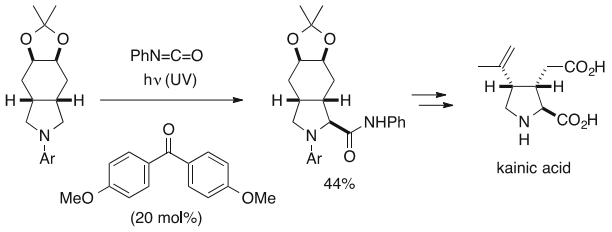
4.1 Carbamoylation

Exploration of appropriate radical trapping agents, for substitutive as well as insertive functionalization at nonreactive C–H bonds, was achieved by taking advantage of the highly reactive nature of photo-excited aryl ketones. Yoshimitsu and coworkers developed a photoinduced carbamoylation of a pyrrolidine derivative using phenyl isocyanate as a precursor of the carbamoyl functionality in the presence of 4,4′-dimethoxybenzophenone (20 mol%) as a catalyst (Scheme 25) [39]. The carbamate functionality was introduced in a single step in a chemo- and stereoselective manner at the carbon center adjacent to nitrogen atom. A precisely planned transformation of the derived tricyclic compound accomplished the total synthesis of kainic acid.

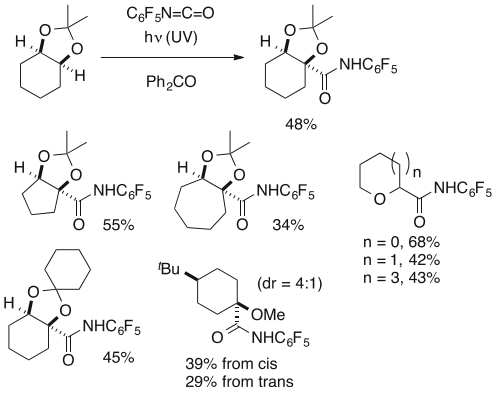
Under closely related reaction conditions, utilizing photo-excited Ph_2CO, the carbamoylation of ethereal C–H bonds was accomplished using electrophilic pentafluorophenyl isocyanate (Scheme 26) [40]. The reaction was chemoselective at the geminal carbon center to the oxygen functionality, despite the steric hindrance, providing a new tetrasubstituted carbon center. The configurational change that occurred during the reaction strongly supported the formation of a common radical intermediate after hydrogen atom abstraction with photo-excited Ph_2CO.

4.2 Alkylation

The Giese reaction involves the addition of free radicals to electron-deficient olefins to form carbon-carbon bonds [41, 42]. A standard method involves the generation of free radical species by treatment of alkyl halides with stannyl radical, which is conveniently derived from tributyltin hydride and 2,2′-azodiisobutyronitrile (AIBN) under heating. In



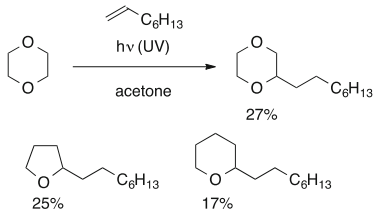
Scheme 25 Carbamoylation of nitrogen-containing cyclic compound



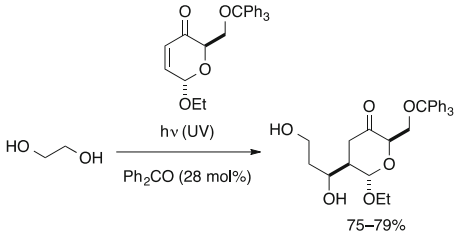
Scheme 26 Carbamoylation of oxygen-containing cyclic compounds

addition, examples of olefin insertion into nonreactive C–H bonds have also been reported; these transformations were promoted in the presence of ketones under photoirradiation. During the early stage of investigation, photoinduced alkylations were performed using ethereal starting materials, such as tetrahydrofuran, tetrahydropyran, and 1,4-dioxane with 1-octene as the olefin (Scheme 27) [43, 44]. The reactions were conducted in ether as the solvent, and the alkylations were promoted by photo-excited acetone. Photoinduced alkylation was then successfully applied to polyoxygenated functionalized enones having a pyranose core in alcohol solvent (Scheme 28) [45, 46]. Electron-deficient vinylsulfones were suitable olefinic substances for the alkylation of ethers and alcohols (Scheme 29) [47–49]. In this case of the reaction using isopropanol, the alkylation could be realized with a catalytic amount of Ph_2CO (20 mol%) without serious problems, although an amount of alcohol suitable for use as a solvent was required. Diastereoselective alkylation was achieved using chiral vinylsulfoxide as the olefinic substance (Scheme 30) [50]. Application of microflow techniques to the alkylation between furanones and alcohols utilizing 4,4′-dimethoxybenzophenone catalyst dramatically shortened reaction time [51]. The alkylations employing amines as starting materials occurred chemoselectively at the C–H bond adjacent to the nitrogen atom (Scheme 31) [52, 53].

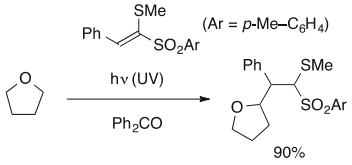
Scheme 27 Alkylation of cyclic ethers with hexene



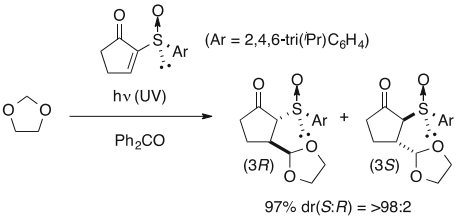
Scheme 28 Alkylation of polyoxygenated cyclic ethers



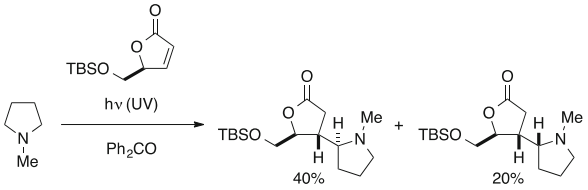
Scheme 29 Alkylation of cyclic ethers with vinylsulfones



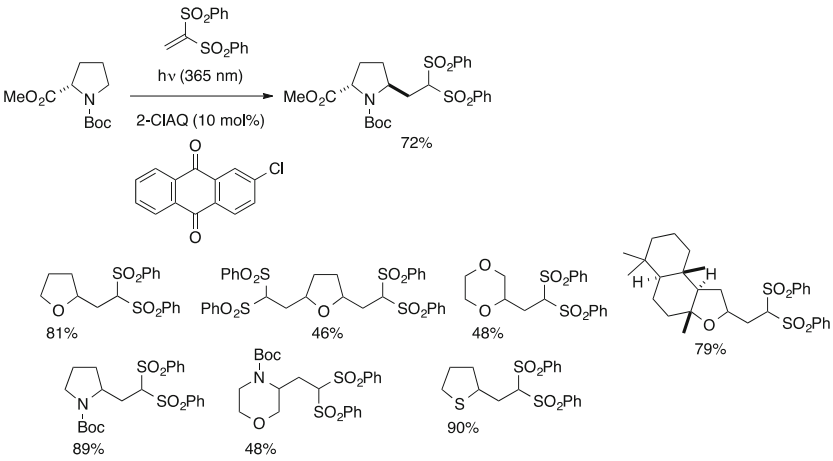
Scheme 30 Diastereoselective alkylation of dioxolane



Scheme 31 Alkylation of pyrrolidine derivatives



The scope of applicable starting materials for photoinduced alkylation was expanded by using 1,1-bis(phenylsulfonyl)ethylene as the olefinic substrate (Scheme 32) [54]. Various



Scheme 32 Catalytic alkylation of heterocyclic compounds

starting materials, including alkanes, functionalized adamantanes, ethers, carbamates, thioether, and alcohols, were alkylated in the presence of a catalytic amount of 2-chloroanthraquinone (2-ClAQ, 10 mol%) as a C–H bond cleaving agent. In addition, the reaction also occurred at the allylic and benzylic C–H bonds. Similar yields and diastereoselectivity of the alkylated adducts were obtained for both cis- and trans-substituted 4-(*t*-butyl)cyclohexanols, which suggested the involvement of the same carbon radical intermediate. The present protocol allowed carbon chain extension stemming from nonreactive C–H bonds and introduction of an active methine site that acted as a versatile synthetic handle for further transformations.

5 Conclusions

This chapter covered recent advancements in nonreactive C–H bond functionalization using photo-excited aryl ketones. The C–H bond cleaving ability of photo-excited ketones plays an important role in these reactions. Transformations targeting nonreactive C–H bonds can dramatically simplify synthetic sequences and improve synthetic efficiency as demonstrated by the total synthesis of structurally complex molecules described in this chapter. Further investigations to improve chemoselectivity that is not dependent on the bonding energy of C–H bonds in starting materials, to develop methods resulting in high stereoselectivity, and to expand the synthesis to other functional groups are underway to investigate the inherent potential of C–H bond functionalization.

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Free Radicals in Heterocycle Functionalization

Jomy Joseph and Andrey P. Antonchick

Abstract Functionalization of heterocycles through free radical intermediates has been widely employed in a diverse array of synthetic transformations. This chapter focuses on the recent developments in the light-assisted as well as traditional free radical generation methodology and the subsequent utilization in functionalization of various heterocycles.

Keywords Alkylation · Arylation · Cross-dehydrogenative coupling · Free radicals · Heterocycles · Minisci reaction · Photocatalysis

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1 Introduction

Functionalized heterocycles are present in many biologically active molecules. Therefore, any effort that scientific community makes to expand the methodology for the synthesis of such molecules is justified. Various strategies are routinely employed for heterocyclic synthesis and functionalization. As the topic is broad, this discussion is solely concentrated on heterocyclic functionalization through radical intermediates. Radical heterocyclic functionalization by means of light (photocatalysis), metals, peroxides, persulfates, and hypervalent iodine compounds have dramatically advanced in the recent years.

Photocatalysis opens diverse pathways to realize previously challenging transformations [1, 2]. This is possible through the capacity of long living excited states of suitable photoactive organic molecules or metal complexes to interact with different chemical entities through electron transfer. The general scheme is shown below (Fig. 1).

There are two modes in which a potent free radical could be generated by means of photocatalysis. In one mode, the excited state of the photocatalyst promotes an oxidative/reductive quenching with one of the intended coupling partners to its radical ions (cation or anion) through single-electron transfer (SET), which eventually leads to the corresponding radical formation (Fig. 1A). When the interaction of a photocatalyst with either of the intended coupling partners, e.g., due to mismatching of the optimum electrochemical potential, does not lead to a productive radical formation, the free radical generation is still possible through the intermediacy of a suitable mediator (second type) that can interact with the photocatalyst and catalyze the electron transfer (Fig. 1B).

Traditional ways of functionalization mostly use the innate reactivity of heterocycles. Such innate reactivity of heterocycles, in general, can be propelled by suitable nucleophilic (Minisci type reactions) [3–5] or electrophilic radicals that are formed through the abovementioned strategies (ionic processes are also possible but are not discussed here). Therefore, this chapter is entirely focused on the recent but important developments of heterocyclic functionalization through radical intermediates for the formation of new carbon–carbon and carbon–heteroatom bonds. A new branch which combines polar intermediates and free radicals also found remarkable success in the recent years [6].

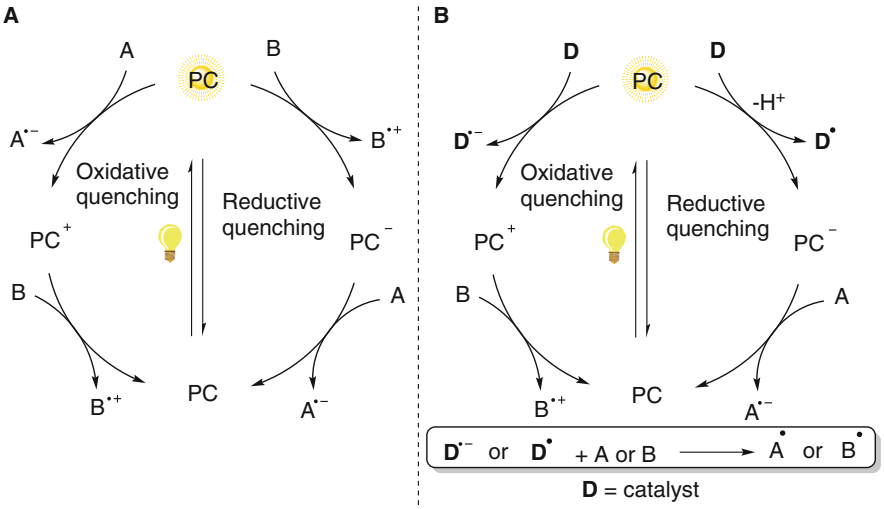


Fig. 1 Redox pathways of photocatalysis (PC = photocatalyst): Radical formation through direct (**A**) and indirect (**B**) interactions with photocatalyst

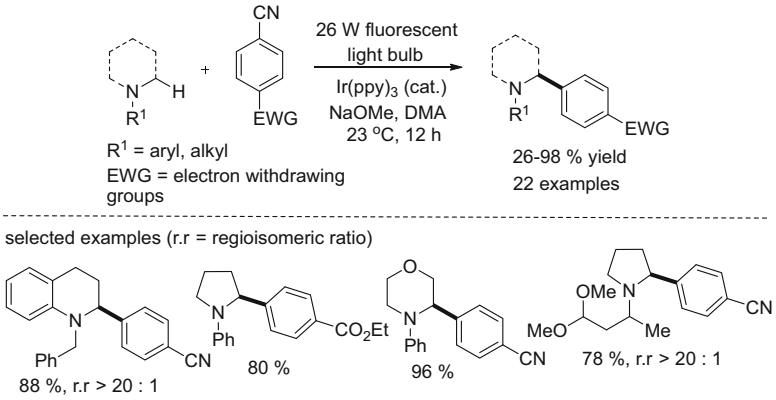
2 Functionalization of Saturated Heterocycles

2.1 Functionalization of Saturated Heterocycles Through C-H Bond Transformation

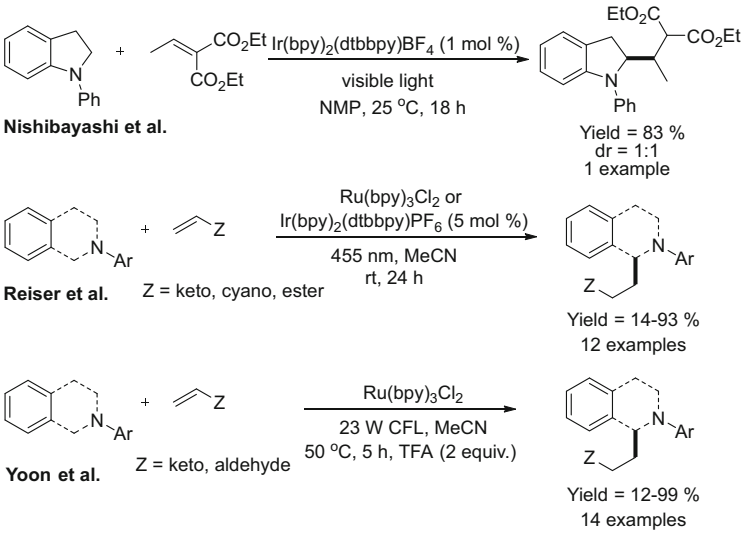
The development of photocatalysis contributed to the progress of saturated heterocycle functionalization. By making use of an accelerated serendipity driven approach, MacMillan and coworkers reported a coupling reaction between trisubstituted amines and cyanoarenes under photoredox catalysis using $Ir(ppy)_3^{3+}$ as photocatalyst [7]. The benzylamine products were formed under mild conditions (Scheme 1). Various cyclic amines like pyrrolidine, piperidine, morpholine, *N*-(Boc)piperazine, and azepane rings provided excellent yields of benzyl amines. As aryl counterparts, benzonitriles substituted with esters, amides, phosphonate esters, and electron-deficient tetrazoles were found to be suitable substrates. Synthetic utility of the process was also showcased by the direct derivatization of a pharmaceutical agent.

Subsequently, Nishibayashi's, Reiser's, and Yoon's research groups independently showed that α-amino alkyl radicals generated through photoredox catalysis could be trapped by electron deficient alkenes through conjugative addition (Scheme 2) [8–10].

All these aforementioned reactions were proposed to proceed through either oxidative or reductive quenching of the photocatalyst with one of the coupling partners and resulted in the formation of the key α-amino radical **C** as depicted below. These α-amino radicals were further engaged in radical-radical coupling with the second coupling partner and formed the corresponding products (Fig. 2).



Scheme 1 Photocatalytic functionalization of saturated heterocycles



Scheme 2 Photocatalytic alkylation of amines

In a further report, α-oxyradical was generated using photocatalyst ($Ir(ppy)_2(dtbbpy)PF_6$) through the thiyl radical (generated from **D**), coupled with Schiff bases and formed the corresponding β-amino ethers (Scheme 3) [11].

Molander's group reported the cooperative association of polar intermediates and free radicals for saturated heterocycle functionalization. The authors developed a Ni/Ir cooperatively catalyzed process for the arylation of various oxygen, nitrogen and sulfur containing heterocycles with electron deficient aryl bromides (Scheme 4) [12]. The process started with an oxidative addition of aryl halide onto a nickel complex to the corresponding Ar-Ni(II)-Br complex. A light energy

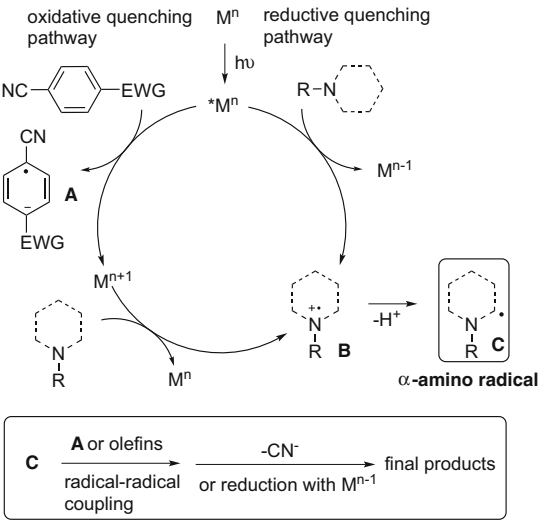
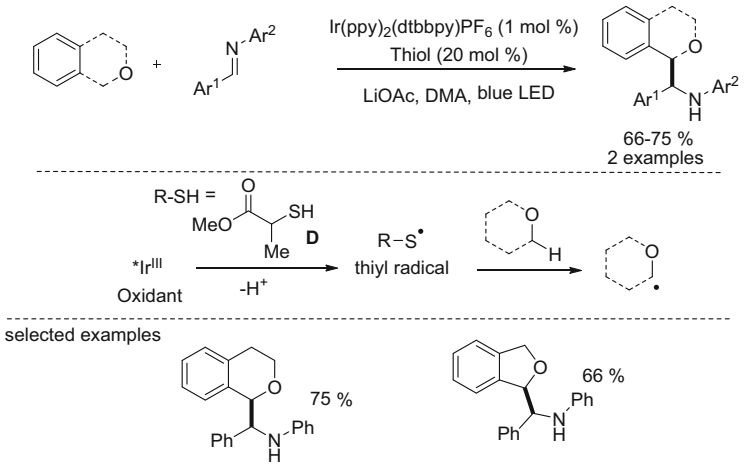
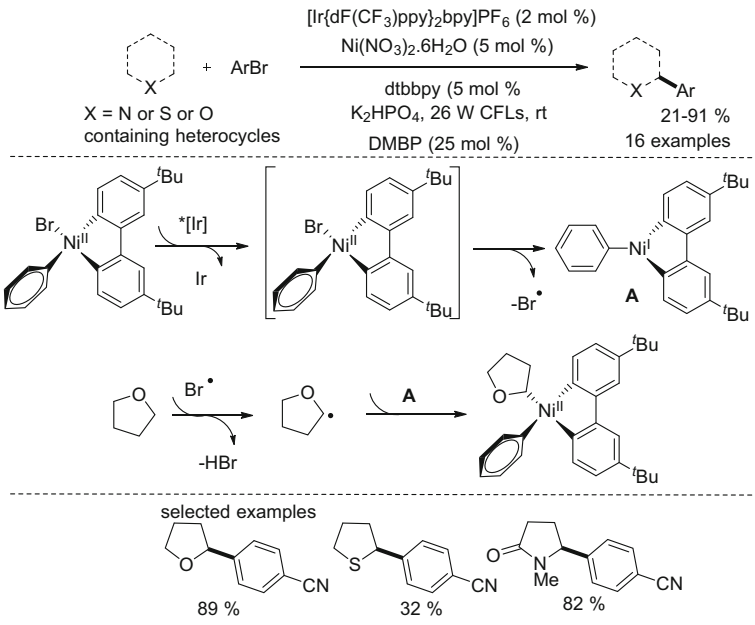


Fig. 2 Photocatalytic α-amino radical formation



Scheme 3 Photocatalytic functionalization via α-oxyradicals

driven dissociation mechanism mediated by Ir photocatalyst dissociated Ar-Ni(II)-Br complexes to the corresponding bromine radical. This bromine radical could be utilized for α-hydrogen atom abstraction of aliphatic heterocycles and formed the corresponding α-heteroatom free radical. This radical recombined with Ni (I) complex and was further engaged in reductive elimination to the intended product.

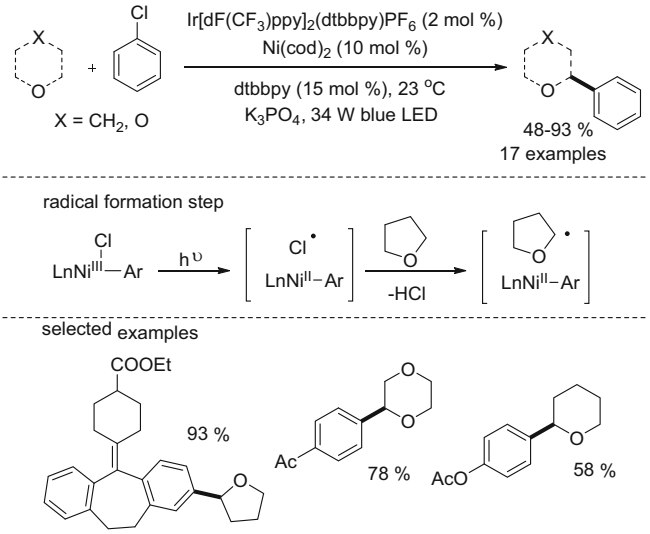


Scheme 4 Cross-coupling reaction between saturated heterocycles and aryl bromides

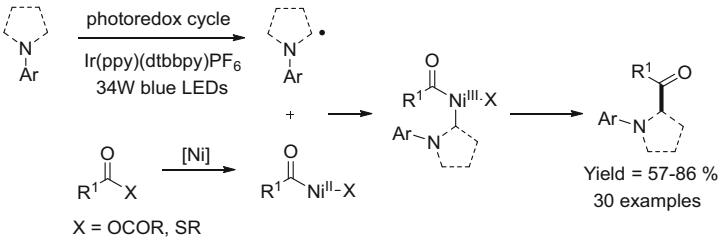
In a similar mechanistic approach, Doyle's group showed that the α-oxy alkyl radicals of aliphatic ethers (linear and cyclic) could be generated by means of chlorine radical, which is formed through photocatalysis. The resulting α-oxyalkyl radicals could intercept polar nickel intermediates and thus be used to functionalize oxygen containing heterocycles (Scheme 5) [13]. Homolytic fragmentation of the Ni(III)-Cl complex through photon absorption was responsible for the Cl radical formation. This chlorine radical abstracted the hydrogen in α-position to oxygen and formed an α-oxy radical which recombined to the Ni(II) complex.

A direct acylation of nitrogen containing heterocycles was further reported using photoredox [$Ir(ppy)_2(dtbbpy)PF_6$] and nickel catalysis [$Ni(cod)_2$] [14]. In this process, an α-amino radical was formed through a photoredox cycle intercepted by a Ni(II)-acyl complex, which generated the corresponding Ni(III) complex. A subsequent reductive elimination formed the desired product. Various anhydrides or thioesters were found to be acylating reagents of choice (Scheme 6).

Though the Ir-Ni photocatalysis finds more applications, corresponding radical-based palladium-catalyzed cross-coupling processes are rare. One such example was provided by Xuan et al. where the authors succeeded in the development of an α-allylation of amines with various allylic compounds, combining visible light iridium photocatalysis and palladium catalysis (Scheme 7). The proposed mechanism involved the generation of α-amino and allyl radicals through iridium single electron transfer (SET) cycles. The method was also successfully applied for the synthesis of an intermediate of an 8-oxoptotoberberine derivative [15].



Scheme 5 Cross-coupling reaction between saturated heterocycles and aryl chlorides

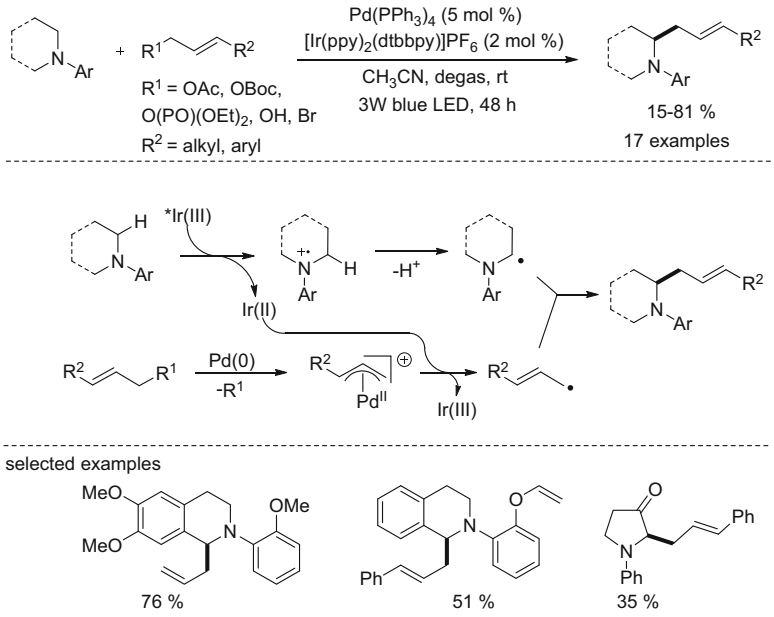


Scheme 6 Direct acylation of nitrogen heterocycles

MacMillan et al. achieved a free radical interception of polar intermediates through a novel triple catalytic system. In this mode, three catalytic cycles, i.e., an organocatalytic cycle, a Ni-based catalytic cycle and a photocatalytic cycle were synergistically operated. Proposed mechanistic cycles are depicted below (Fig. 3). Electron deficient aryl(hetero) halides (Cl or Br) were coupled with nitrogen heterocycles through this pathway (Scheme 8) [16].

2.2 *Functionalization of Saturated Heterocycles Through C-Z (Z = COOH, BF_3K, Halides) Bond Transformation*

MacMillan's group developed a method where α-heteroatom substituted carboxylic acids were used to generate α-amino/α-oxy radicals under Ir(II)-Ir(III) or Ir(III)-Ir (IV) photoredox conditions. Oxidative single electron transfer from the suitable Ir



Scheme 7 Allylation of saturated heterocycles with cooperative Ir-Pd catalysis

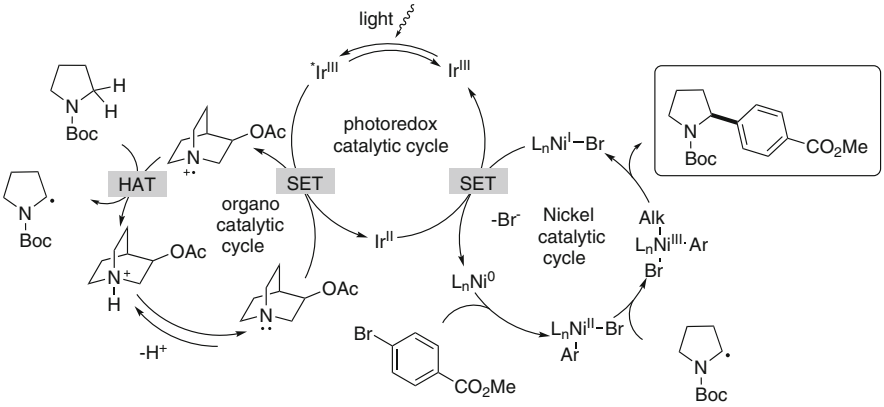
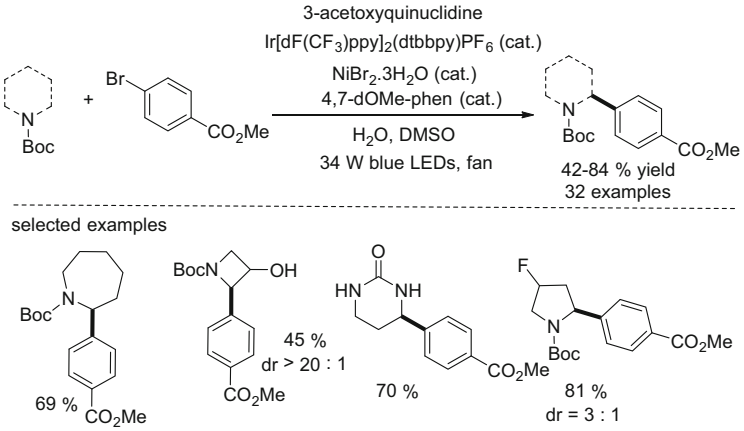


Fig. 3 Mechanism of arylation of saturated heterocycles through a triple catalytic system

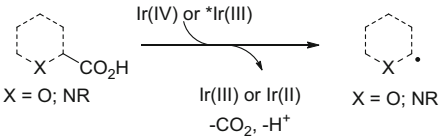
catalyst towards the carboxylic acid was responsible for the radical generation (Scheme 9).

The readily formed radicals were thereby used for arylation [17], alkylation [18] or alkenylation. On the other hand, when vinyl sulfones were used as coupling partner, the corresponding allylic amines were readily formed (Scheme 10) [19].

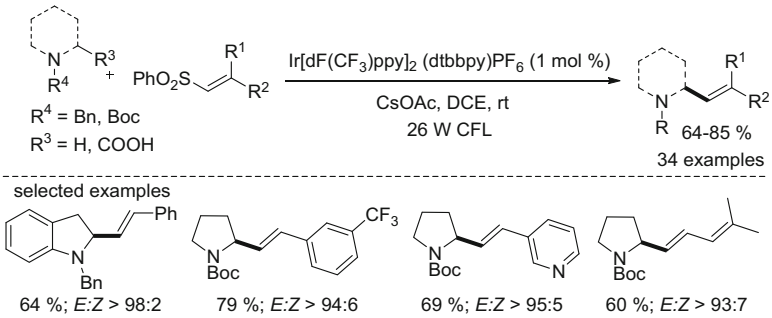
A photocatalytic method of direct interception of radical intermediates towards polar metal complexes was reported by MacMillan and coworkers. This process



Scheme 8 Arylation of saturated heterocycles through a triple catalytic system

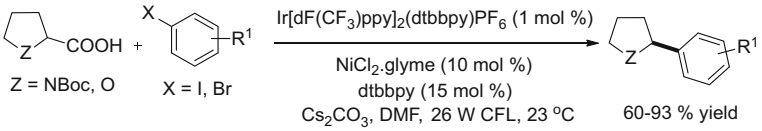


Scheme 9 α-Amino and α-oxy radical formation from corresponding carboxylic acids



Scheme 10 Alkenylation of heterocycles

was developed for the cross-coupling reaction between *N*-substituted α-amino acids and aryl halides (I or Br) with catalytic amounts of $NiCl_2$.glyme and Ir(III) photocatalyst [Ir{dF(CF_3)ppy}(dtbbpy)PF_6]. The benzylamine product was formed in excellent yield under mild conditions [20]. Tetrahydrofuran-2-carboxylic acid was arylated using the same protocol (Scheme 11).



Scheme 11 Arylation of saturated heterocycles through Ir-Ni cooperative catalysis

Based on the mechanistic proposal, Ni(II) intermediate, which was formed by the oxidative addition of Ni(0) to aryl halide, was intercepted by α-amino radical **A** (formed by SET from excited state *Ir(III) catalyst to amino acid, followed by CO_2 and proton expulsion) formed a new nickel(III) complex **B**. A reductive elimination of Ni(III) to Ni(I) caused the formation of a new C-aryl bond. Ni (I) was reduced to Ni(0) by a SET process with Ir(II) reductant (Fig. 4).

In a following report, this new type of cooperative Ir/Ni catalysis was utilized for the cross-coupling between α-oxocarboxylic acids and alkenyl halides to afford the corresponding alkenylated oxygen heterocycles [21]. 2-Trifluoroboratochromanones were found to be a potent source of α-oxy radicals under photoredox conditions. Such chromanones were arylated with aryl bromides using a 4CzIPN/$NiCl_2$·dme dual catalytic system to give the corresponding flavanones [22]. 4CzIPN was the active photoredox catalyst in this process (Scheme 12).

Photoassisted alkyl radical formation was also proposed to proceed through the intermediacy of bromine radicals. By this mode, MacMillan et al. showed that saturated heterocyclic bromides could be cross-coupled with aryl bromides (Scheme 13) [23].

3 Functionalization of Maleimides

Maleimides are also an important class of heterocycles and were engaged in a variety of free radical reactions. Manna and Antonchick developed a novel copper-catalyzed stereoselective cyclopropanation of maleimides with acetophenone derivatives. In this process, α-carbonyl alkyl radical could be generated from acetophenones under Cu(I)/Cu(II)-peroxide-mediated conditions (Scheme 14) [24].

The proposed mechanism involved, initially, Cu(II)-catalyzed hydrogen abstraction of methyl ketones to α-carbonyl alkyl free radical **A**. This radical added to maleimide's olefinic bond and formed the free radical **B** which underwent SET with Cu(II) to intermediate **C** [Cu(III)] which upon enolate-directed elimination of ^{t}BuOH led to the cyclic intermediate **D**. The intermediate further rearranged to a four-membered transition state followed by reductive elimination of Cu(III) to Cu (I) which formed the corresponding cyclopropane **E** (Fig. 5).

A free radical-mediated cyclization between maleimide and alkyl anilines was reported with Eosin Y as a photocatalyst [25]. Energized Eosin Y promoted SET with amines to the corresponding α-amino radicals, which were efficiently trapped by maleimides through a radical cascade. As a result, six-membered tetrahydroisoquinoline

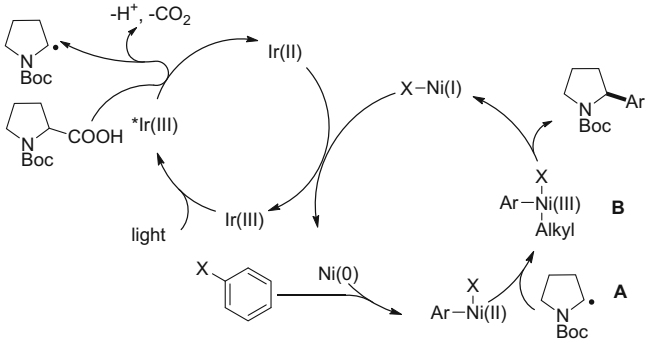
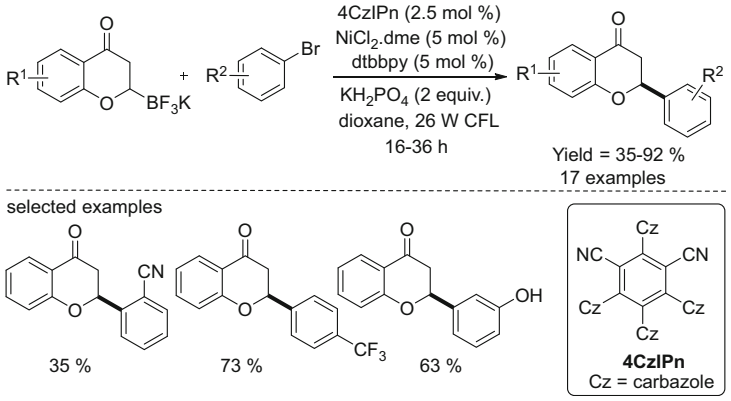
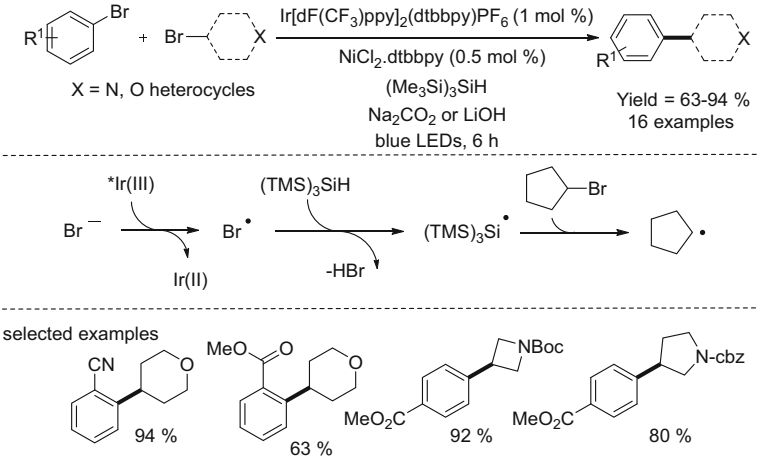


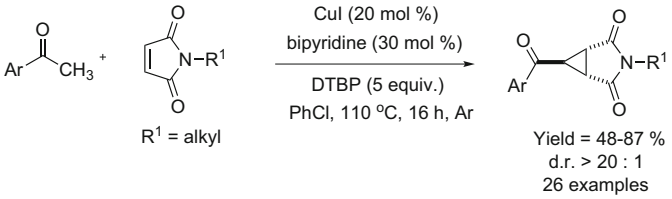
Fig. 4 Mechanism of heterocyclic functionalization through photo-Ni cooperative catalysis



Scheme 12 Trifluoroborates in free radical coupling



Scheme 13 Cross-coupling process between aliphatic bromoheterocycles and arylbromides



Scheme 14 Cyclopropanation of maleimides with acetophenones

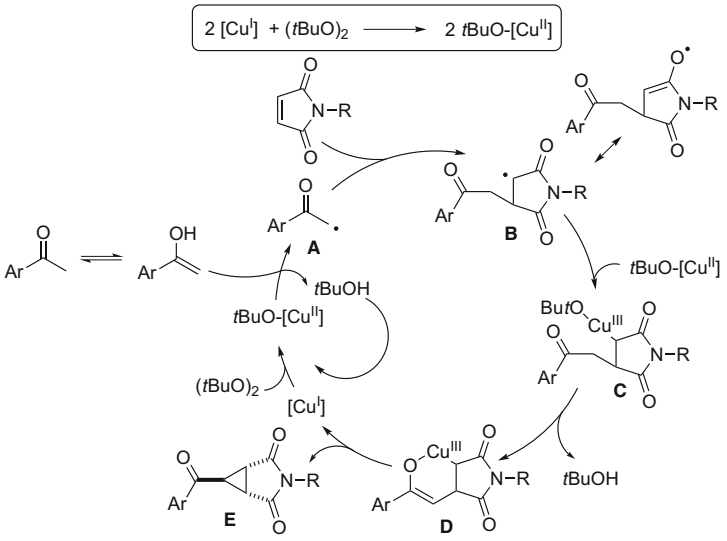
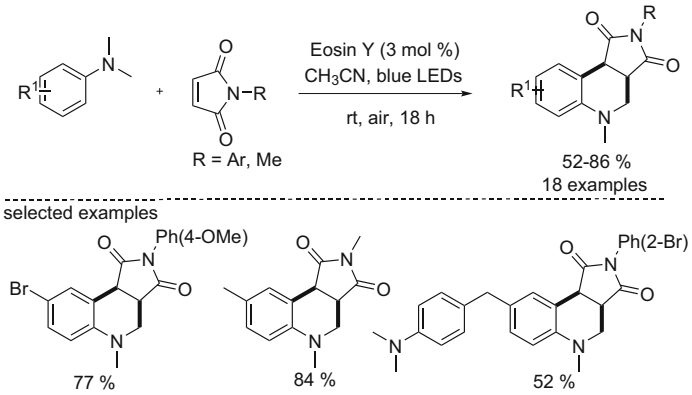


Fig. 5 Mechanism of copper-catalyzed cyclopropanation of maleimides

rings were formed. Amines containing both electron deficient and electron rich substituents were equally reactive under the developed conditions (Scheme 15).

The triplet excited state of Eosin Y (Eosin Y*) oxidized amines to the α-amino radicals **A** through an initial SET, followed by proton abstraction. This radical **A** was captured by maleimide, further moved through a radical cascade to the corresponding cyclized intermediate **C**. Intermediate **C** underwent hydrogen atom transfer and the corresponding tetrahydroisoquinoline was formed. Catalytic cycle was completed by a reaction of reductant Eosin Y radical anion with molecular oxygen (Fig. 6).

Recently, two new photocatalytic systems, one based on chlorophyll/O_2 [26] and another one based on *N*-hydroxyphthalimide (NHPI) [27] were developed for the same transformation. Antonchick's group developed a metal-free method of cyclization between maleimides and tertiary alkyl anilines. The α-aminoalkyl radicals as



Scheme 15 Organic photocatalytic tetrahydroisoquinoline synthesis

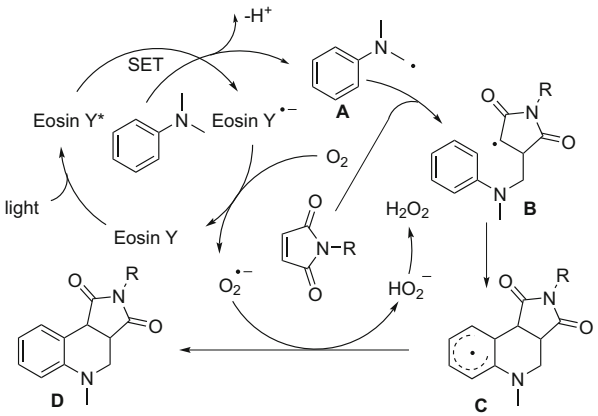
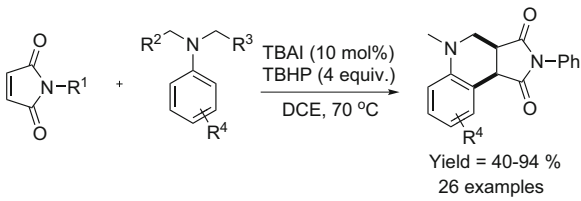


Fig. 6 Mechanism of Eosin Y photocatalytic tetrahydroisoquinoline synthesis

reaction intermediates were formed under a TBAI (tetrabutylammonium iodide)/TBHP (*tert*-butylhydroperoxide) system without formation of the corresponding iminium ions. A broad range of tricyclic tetrahydroquinoline products were smoothly formed under the developed reaction conditions with good yields (Scheme 16) [28]. A plausible mechanism was proposed. Initially, *tert*-butoxyl and *tert*-butylperoxyl radicals were formed by a reaction between *tert*-butylperoxide and an iodide ion. A SET from *N*,*N*-dimethylaniline to *tert*-butoxyl or *tert*-butylperoxyl radicals followed by deprotonation formed the α-aminoalkyl radical. This nucleophilic radical added onto the maleimide followed by cyclization, oxidation, and deprotonation, forming the desired product. Yadav and coworkers also developed a method of cyclization of *N*-methylanilines with maleimides using $K_2S_2O_8$ as a cheap radical initiator [29].

Scheme 16 Metal-free cyclization of maleimides with alkyl anilines



4 Functionalization of Unsaturated Heterocycles

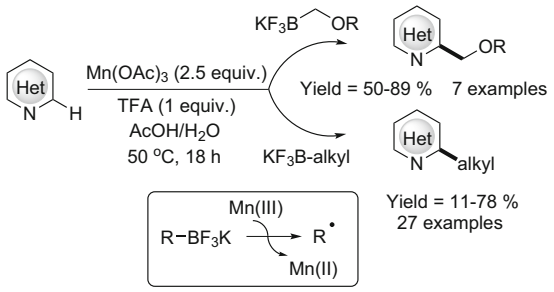
Unsaturated heteroaromatic functionalization largely deals with the cases when radicals are added to heteroaromatic bases (Minisci type reactions). The topic was extensively covered by Duncton where a comprehensive picture related to common heterocyclic structures and free radical precursors and various biological applications was provided [30]. Another promising area in free radical-mediated unsaturated heterocyclic functionalization is based on recently explored cross-coupling strategies as already discussed in saturated heterocyclic cases. In the following section, reports related to both processes are presented.

4.1 Organoboranes as Alkyl/Aryl Radical Sources

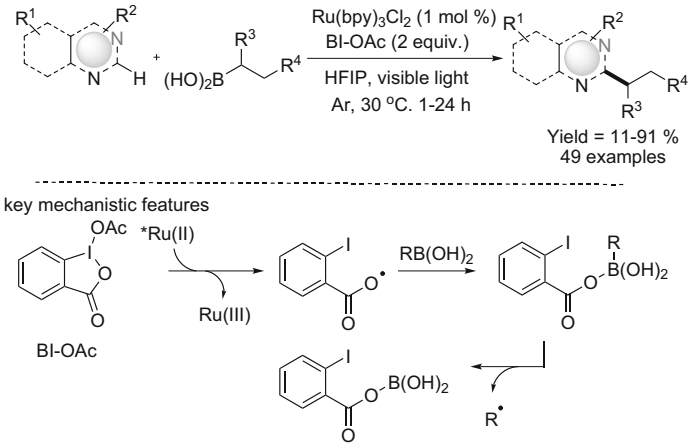
Organoboranes are useful radical precursors for C–C bond forming reactions. Molander et al. reported that potassium alkyl- and alkoxymethyltrifluoroborates could be nucleophilic radical precursors for the alkylation of *N*-heteroarenes. Mn $(OAc)_3$ was found to be effective for the generation of alkyl radicals from organoboranes. This protocol represented an efficient way for the introduction of unique alkyl substituents (e.g., cyclobutyl and alkoxymethyl groups) into diverse *N*-heteroarenes (including quinolones, isoquinolines, benzopyrimidines, benzimidazoles, and benzothiazoles) (Scheme 17) [31, 32].

Chen's group employed alkylboronic acids as radical precursors for C-H alkylation of *N*-heteroarenes via a photoredox strategy. A broad range of primary and secondary alkyl groups were efficiently incorporated into various *N*-heteroarenes using $[Ru(bpy)_3]Cl_2$ as photocatalyst and acetoxybenziodoxole (BI-OAc) as oxidant under mild conditions (Scheme 18) [33]. This reaction exhibited excellent substrate scope and functional group tolerance, and offered a broadly applicable method for late-stage functionalization of drug molecules. In the alkylation, the active species Bl-2 initiated with the SET from photo-excited Ru(II)* to Bl-OAc was crucial for the formation of alkyl radical from alkylboronic acid.

An important advancement in the Minisci type reaction was reported from Baran's laboratory, where was successfully generated nucleophilic aryl radicals from aryl boronic acids under standard Minisci conditions. The reaction conditions were mild and operationally simple. A mixture of regioisomers was observed in



Scheme 17 Alkylation and alkoxymethylation of heterocycles



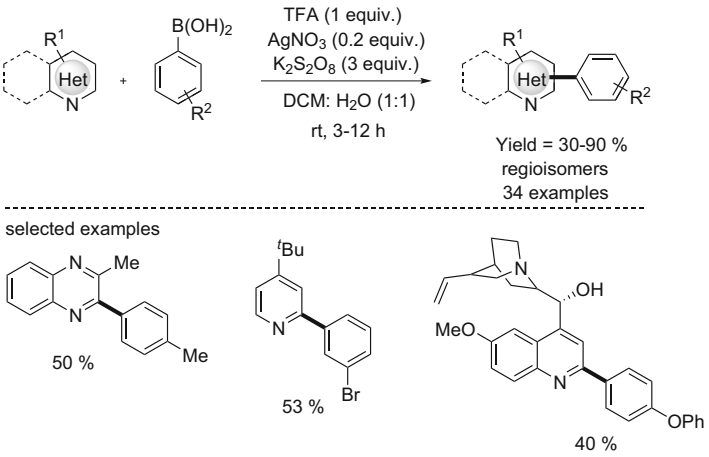
Scheme 18 Boronic acids as alkyl radical source

most cases in which the reaction was mainly selective at the C2 and C4 positions (Scheme 19) [34].

A mechanistic explanation showed that in the presence of Ag(I) salt, persulfate anion disproportionated into sulfate dianion and sulfate radical anion (**A**). The reaction between these radical anions and boronic acid generated aryl radical (**B**), which further reacted with protonated heterocycles and furnished a radical cation. This radical cation then reoxidized by Ag(II), providing the product and regenerating the Ag(I) catalyst (Fig. 7).

Maity and coworkers extended the use of aryl boronic acid as a source of aryl radical for their C3 arylation of 2-pyridones under iron catalysis. Mechanistically, the process was similar to Baran's work. Electron rich arenes were more compatible with this procedure though the yields in almost all cases were moderate to low (Scheme 20) [35].

The ferric (II) sulfide/$K_2S_2O_8$ combination was also reported to generate sulfate radical anion ($SO_4^{\bullet -}$) which was capable of producing aryl radicals from arylboronic



Scheme 19 Arylation of nitrogen heterocycles

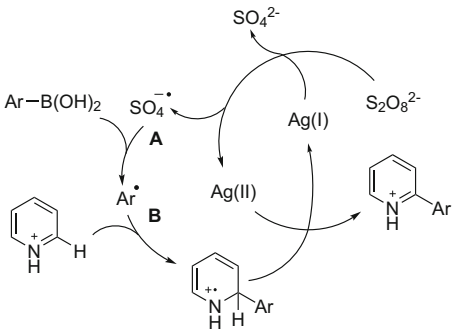
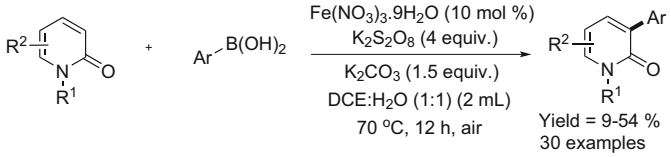


Fig. 7 Mechanism of aryl radical generation from arylboronic acids

acids. A variety of heterocycles like pyridines, pyrimidines, pyrazine, quinolone, quinoxaline, and pyridazine were prone to arylation under these conditions [36]. On the other hand, pyrrole, imidazole, indole, benzoxazole, quinine, and caffeine were unreactive. Except for the cases in which formation of regioisomers was not possible, a mixture of various regioisomers was observed. A metal-free arylation of electron deficient heterocycles with $K_2S_2O_8$ at elevated temperatures was also reported [37].

4.2 Functionalization with Fluorine-Containing Radicals

The fluorinated alkyl groups play a privileged role in the medicinal chemistry because its incorporation into small molecules often enhances biological activities like cellular membrane permeability, promotion of electrostatic interactions with



Scheme 20 Arylation of 2-pyridones with boronic acids

targets, and increase of robustness towards oxidative drug metabolism. Therefore, the introduction of such groups gained tremendous attention. Both photocatalytic and traditional ways of fluoroalkyl radical formation and its subsequent consumption with suitable heterocycles were developed.

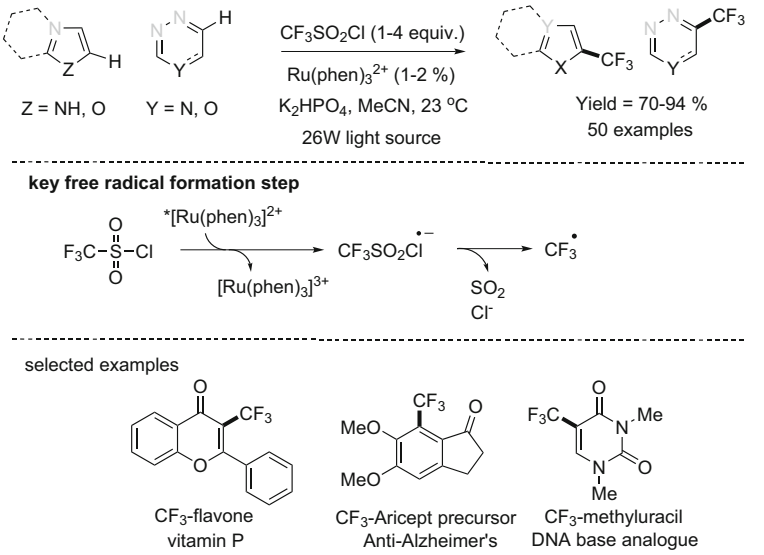
A facile trifluoromethylation of various arenes and heteroarenes was reported by MacMillan et al. The reaction relied on the capacity of excited $*Ru(phen)3^{2+}$ photocatalyst to generate CF_3 radical from CF_3SO_2Cl. A set of pyrazine, pyrimidine, pyridine, and pyrone heterocycles were perfluoromethylated in a highly regioselective manner (Scheme 21). The method was also effectively utilized to functionalize biologically active molecules [38].

Stephenson and coworkers extended the trifluoromethylation protocols by using trifluoroacetic anhydride as CF_3 radical source in presence of pyridine *N*-oxide under photoredox catalysis. The reaction was susceptible with a range of vinyl, aryl, and heteroaryl substrates (Scheme 22). The CF_3 radical generation from trifluoroacetic anhydride was assumed to proceed through a decarboxylation pathway. The difficulties of such decarboxylation processes were overcome by appending a sacrificial redox auxiliary, pyridine *N*-oxide. This combination was supposed to shift the requisite electrochemical potential in favor of CF_3 radical formation by the use of a photocatalyst. $Ru(bpy)_3Cl_2$ was found to be the optimum catalyst for this purpose [39, 40].

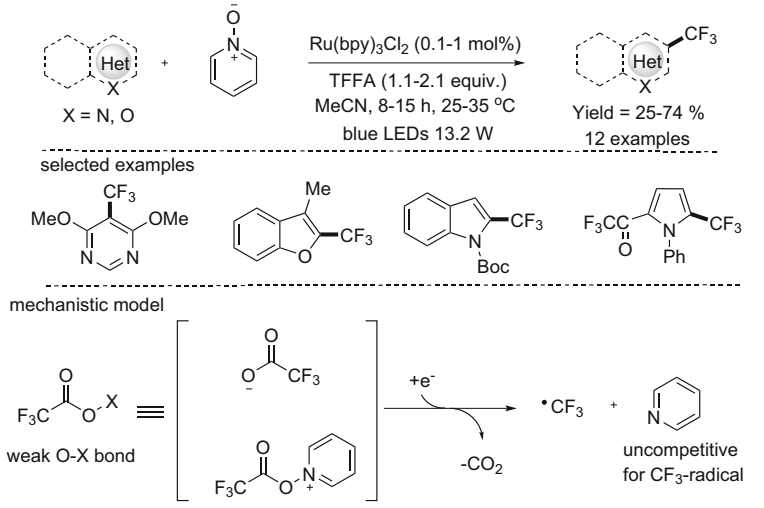
A photocatalytic Smiles rearrangement was reported by Stephenson and coworkers to introduce the difluoroethanol group into aryl or heteroaryl cores. In this process aryl/heteroaryl sulfonates tailed with a difluorobromo group underwent rearrangement in the presence of photocatalyst $Ru(bpy)_3{\cdot}6H_2O$ to yield the corresponding difluorosubstituted scaffolds. In summary, the sulfonyl group was replaced through ipso attack. Amine salt was used to function as an electron source. The method was also applied in the synthesis of a key intermediate of the antidepression and/or anti-obesity drug ORL-1 (opioid receptor-like 1) (Scheme 23) [41].

A novel method for visible-light photoredox-catalyzed difluoromethylation of electron-rich *N*-, *O*-, and *S*-containing heteroarenes under mild reaction conditions was developed by Wang's group. Mechanistic investigation indicated that the net C−H difluoromethylation proceeded through an electrophilic radical-type pathway (Scheme 24) [42].

A metal-free radical trifluoromethylation of indoles, pyrroles, and thiophenes was reported by Scaiano and coworkers (Scheme 25). In this metal-free method, methylene blue was used as an organic photocatalyst under mild conditions [43].

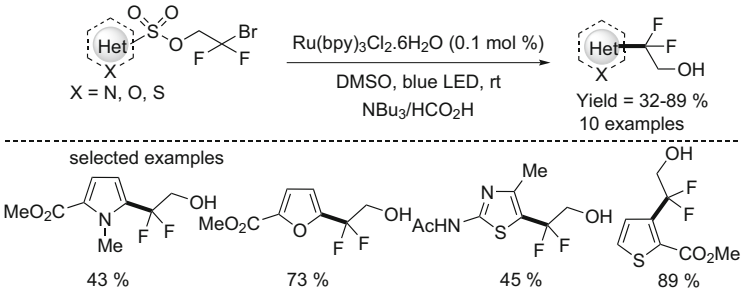


Scheme 21 Photocatalytic perfluoromethylation of heterocycles

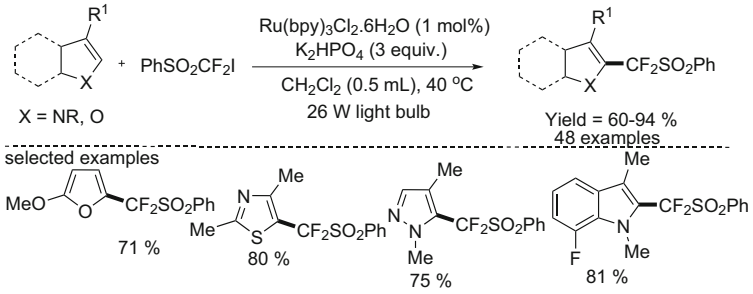


Scheme 22 *N*-oxide-mediated perfluorination of heterocycles with trifluoroacetic anhydride

The conventional ways of fluorinated heteroaromatics syntheses also flourished these days through the effort of primarily Baran and coworkers. An operationally simple trifluoromethylation of heteroaromatic systems that is scalable and proceeds at ambient temperature was developed. Among various trifluoromethyl sources tested, Langlois



Scheme 23 Difluoroethanolation of aromatic heterocycles through photocatalytic Smiles rearrangement

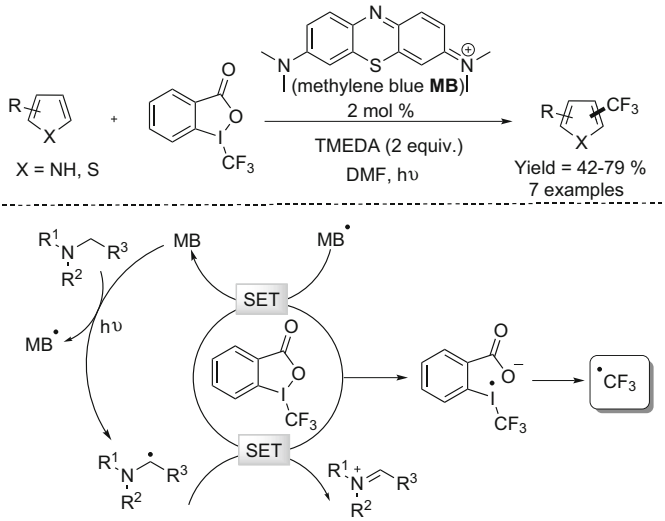


Scheme 24 Difluoromethylation of heteroarenes with difluoroiodomethylbenzene sulfonate

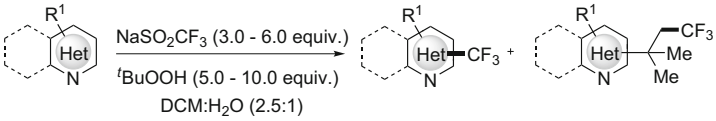
reagent (sodium trifluoromethanesulfinate, CF_3SO_2Na, benchtop stable), which generated an electrophilic trifluoromethyl radical with TBHP, was found to be broadly effective on a variety of electron-deficient and -rich heteroaromatic systems. Along with its user-friendly conditions, the key advantages of the protocol included direct usability on unprotected molecules, functional group compatibility (keto, cyano, halo, amino, ester, and amide groups are compatible), and predictable positional selectivity (Scheme 26) [44].

A mechanistic explanation of the process was given as following. CF_3SO_2• was generated from *tert*-butoxy radical, presumably generated from metals trace or another initiator and $CF_3SO_2^-$. This transient intermediate released SO_2 and CF_3 radical, through α-scission. The formed CF_3 radical was trapped with heteroarenes thereby the corresponding heteroaryl radical formation occurred. This was followed by a reoxidation to the corresponding products (Fig. 8). Undesired by-products also observed through the consumption of CF_3• radical by other two competing pathways. In one pathway, abstraction of hydrogen atom produced CF_3H. In the second pathway, CF_3• radical was consumed by isobutene, which was supposed to be formed through a reaction between *tert*-butylhydroperoxide and molecular oxygen.

Following this initial development, the same group came up with a new set of zinc sulfinate salts for the effective installation of fluorinated alkyl groups and alkyl groups,



Scheme 25 Trifluoromethylation of indoles, pyrroles, and thiophenes



Scheme 26 Trifluoromethylation of heterocycles with Langlois reagent

including zinc trifluoromethanesulfinate (TFMS), zinc difluoromethanesulfinate (DFMS), zinc trifluoroethanesulfinate (TFES), zinc monofluoromethanesulfinate (MFMS), zinc isopropylsulfinate (IPS), zinc triethyleneglycolsulfinate (TEGS), and zinc bis(phenylsulfonylmethanesulfinate) (PSMS) (Scheme 27). Through these easily accessible zinc salts which were capable of releasing alkyl free radicals by the reaction with peroxides, a variety of heterocycles including xanthines, pyridines, quinoxalines, pyrimidines, pyridazines, and pyrroles were functionalized into their fluoro-alkylated and alkylated counterparts [45–47].

Recently, Li and coworkers developed a simple trifluoromethylation protocol of various heterocycles using sodium triflinate ($NaSO_2CF_3$) as trifluoromethyl source. In this process, photo-excited acetone or diacetyl acted as radical initiators to generate CF_3 radical from sodium triflinate [48].

Beller and coworkers developed a $Pd(OAc)_2$/$BuPAd_2$-catalyzed trifluoromethylation of heteroarenes and arenes using CF_3Br as CF_3 radical source. This new method was suitable for trifluoromethylation of different heterocycles like indoles, pyrroles, thiophene, and bioactive molecules including melatonin, caffeine, pentoxifylline, and theophylline (Scheme 28). Regioselectivity was observed at the 2-position to the nitrogen atom. Based on experimental observations, a CF_3 radical formation by the

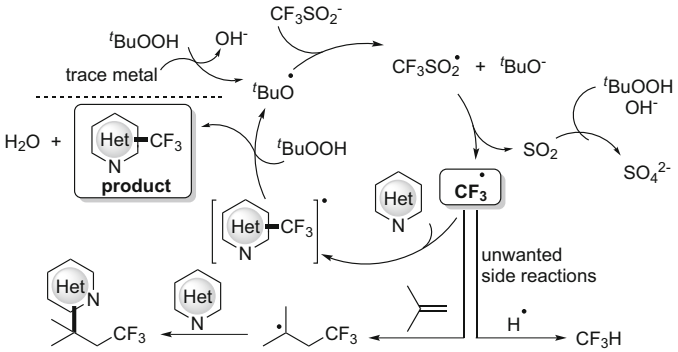
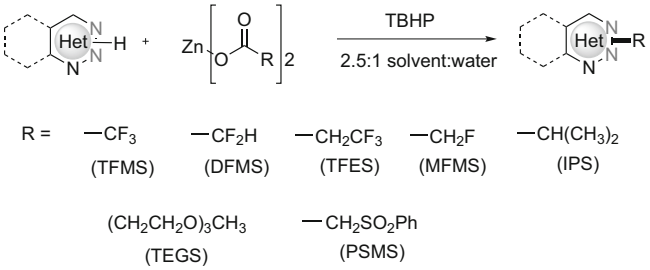


Fig. 8 Mechanism of peroxide-mediated trifluoromethyl radical formation



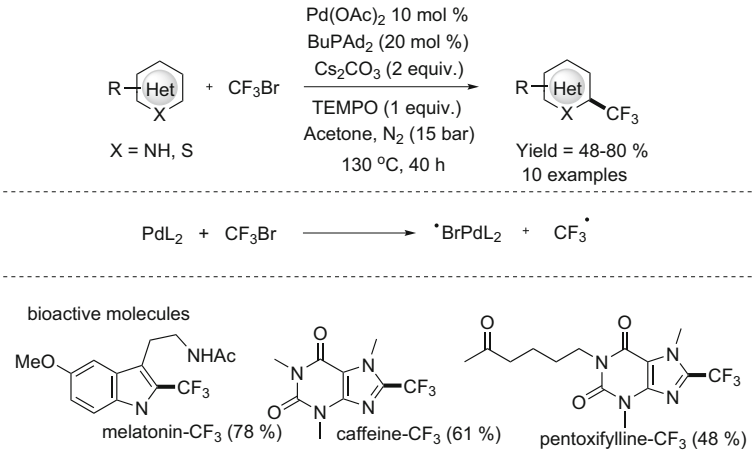
Scheme 27 Different zinc fluoroalkylsulfinate salts for the fluoroalkylation of heterocycles

reaction between PdL_2 and CF_3Br was proposed which reacted with arenes and formed the corresponding products [49].

A unique way for CF_3 radical generation and its trapping with heterocycles was reported by Fensterbank et al. In this method, a well-defined Cu(II) complex **A** [Cu^{2+} (L^{SQ})2; SQ = iminosemiquinone] converted electrophilic CF_3^+ species (Togni's reagent) into CF_3 radical by reduction. This redox communication was mediated by a redox-active ligand through a SET process (ligand-centered oxidation), the redox state of copper being unchanged and the electronic transfer occurring only on the ligand (Fig. 9). Pyrrole, indoles, and furans were trifluoromethylated under this new, mild protocol (Scheme 29) [50].

Togni and coworkers developed a perfluoroalkylation strategy of ketene silyl acetals by using perfluoroalkyl substituted hypervalent iodine reagents (Scheme 30).

$TMSNTf_2$ was employed as a catalyst, which was responsible for the activation of hypervalent iodine reagent for the generation of the CF_3 radical (Fig. 10). The generated radical was trapped by the heterocyclic compounds [51, 52].



Scheme 28 Palladium-catalyzed trifluoromethylation of heterocycles

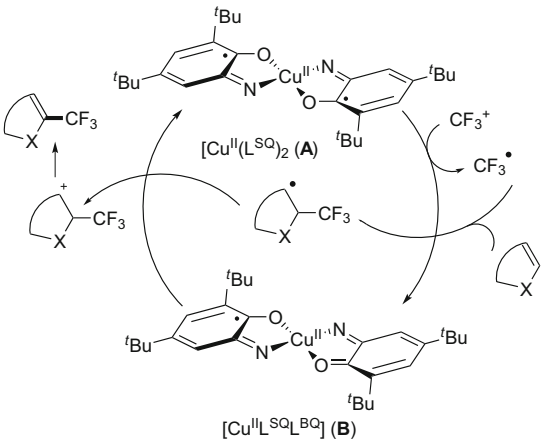
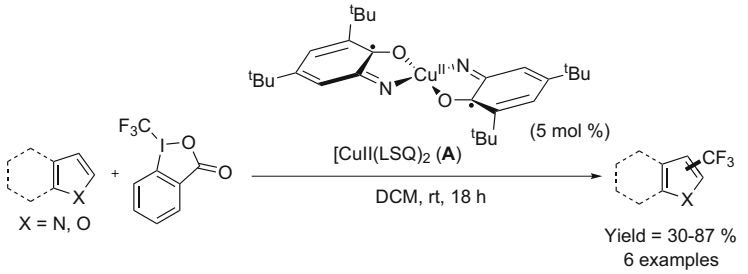
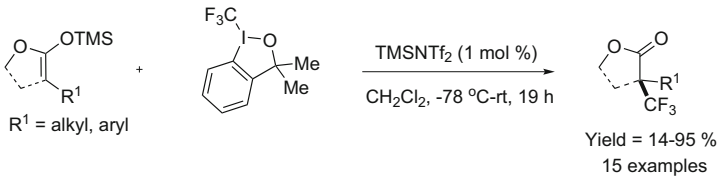


Fig. 9 Mechanism of copper-catalyzed trifluoromethylation of heterocycles



Scheme 29 Copper-catalyzed trifluoromethylation of heterocycles



Scheme 30 Trifluoromethylation of ketene silyl acetals

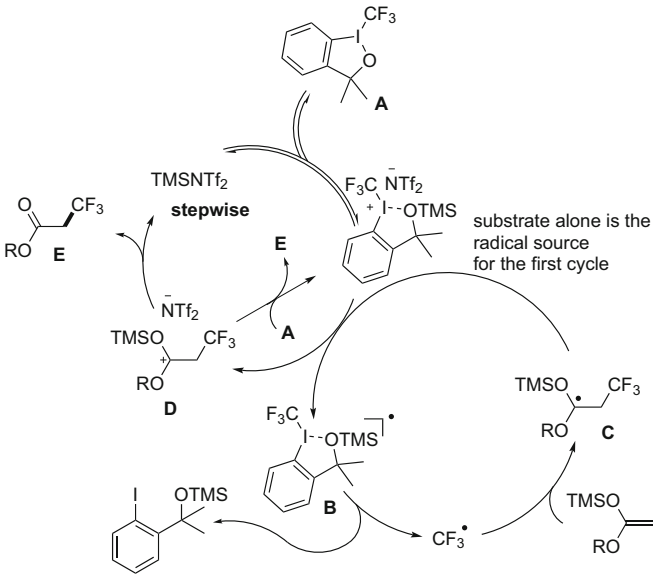


Fig. 10 Mechanism of perfluoroalkylation with hypervalent iodine

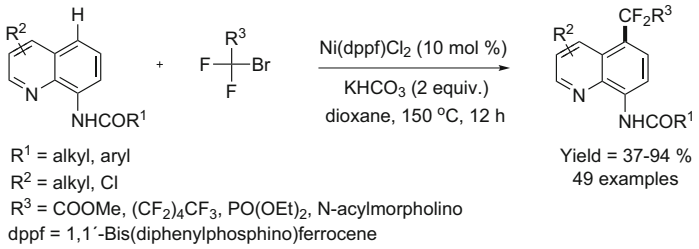
Later, the authors developed a similar system in which lactam-derived ketene silyl amides were converted to perfluoromethylated lactams. Various fluoro-containing radicals were efficiently produced and utilized under the developed conditions [53].

The C5 position of 8-aminoquinoline was difluoroalkylated with various difluorobromides under nickel(II)-catalyzed conditions (Scheme 31) [54].

The effective difluoroalkyl radical generation was postulated by a reaction between Ni(II) complex and difluorobromides through a single electron transfer-guided dissociation (Fig. 11).

4.3 Hydrocarbons and Cyanides as Alkyl Radical Sources

A photoactive Ir-thiol cooperative redox catalysis is efficient to produce allyl radicals from olefins equipped with allylic hydrogens. The corresponding radicals could be trapped by electron deficient sites of various heterocycles. Pyridines and



Scheme 31 Difluoroalkylation of nitrogen heterocycles

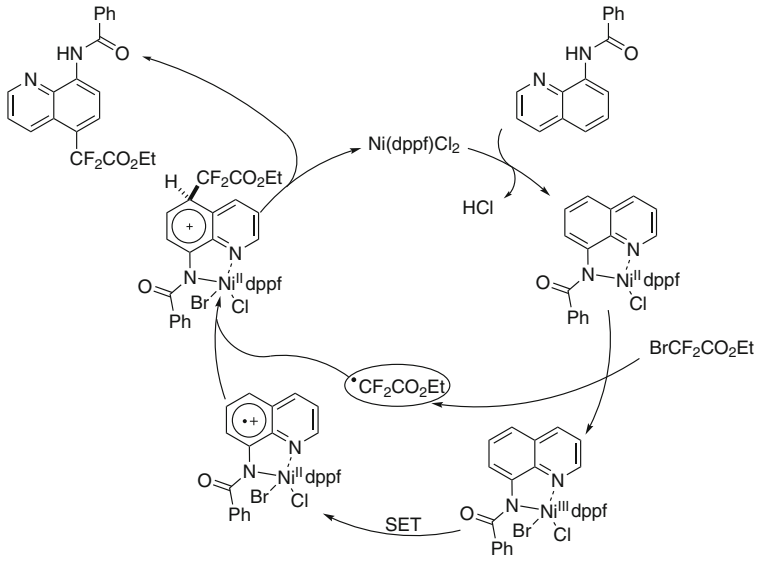
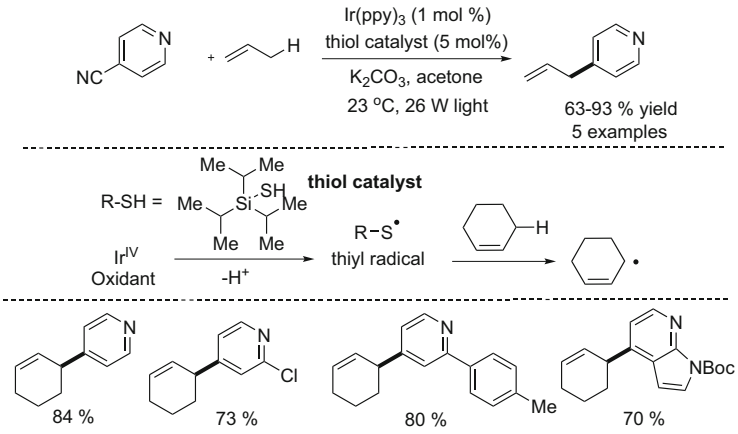


Fig. 11 Mechanism of nickel-catalyzed difluoroalkylation

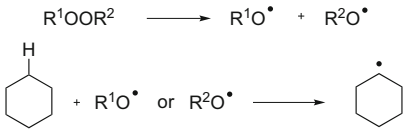
indole were allylated through this pathway. Triisopropylsilanethiol was found to be the optimum thiol catalyst (Scheme 32) [55].

Similarly to thiols, peroxides can generate free radicals from aliphatic hydrocarbons through the following general mechanism (Scheme 33). These free radicals could be trapped with various heterocycles. A radical cross-coupling of substituted indoles with cycloalkanes was reported by Yi's group using di-*tert*-butyl peroxide (DTBP) as the oxidant. In this process, various substituted indoles were alkylated (pentane, hexane, heptane, octane, dodecane) with moderate to good regioselectivity. C4, C2 and C7-cycloalkylated products were obtained with differently substituted indoles, in which predominant alkylation occurred at the C4 position. When C4 position was blocked, C2-cycloalkylation occurred preferentially (Scheme 34) [56].

A similar DTBP-mediated metal-free indole cycloalkylation strategy was also reported by Kwong et al. under oxidative conditions. In their case, C3 or C2-alkylated



Scheme 32 Allylation of aromatic heteroarenes



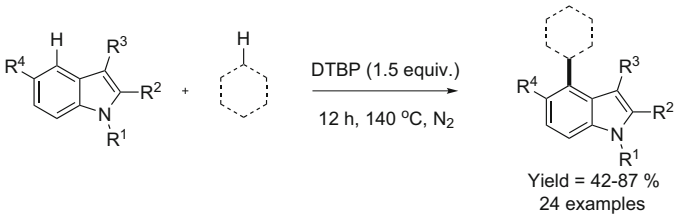
Scheme 33 General mechanism of free radical formation from peroxides

indole derivatives were obtained [57]. An iron(III)-catalyzed C-3 alkylation of flavones has been reported by Patel et al. using a *tert*-butyl peroxybenzoate (TBPB)-$K_2S_2O_8$ oxidant combination (Scheme 35). Different flavones containing both electron-withdrawing as well as electron-donating substituents were functionalized at C3 with various cycloalkanes. Yields were good to moderate in most cases. Mechanistic investigations showed the formation (by the reaction of cycloalkanes with peroxide) and the addition of cycloalkyl radical to flavones and regeneration of the double bond to the desired compounds [58].

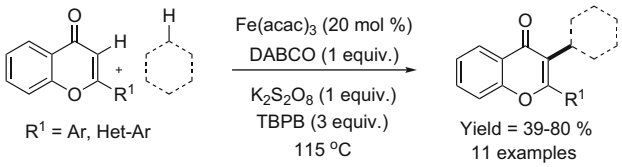
A variety of chromones were alkylated with a range of alkanes (cyclic and acyclic) via alkyl free radicals. The process was mediated by the oxidant DTBP (di-*tert*-butylperoxide). Chromones with different electronic environments afforded their anticipated 2-alkylchromanones in moderate to good yields (50–83%). (Scheme 36) [59].

Alkylation of C3-substituted coumarins with control over C3 or C4 positions was achieved. C3-alkylation was promoted with the Fe(III)/DTBP (di-*tert*-butylperoxide) system. On the other hand, C4 alkylation was achieved by metal-free conditions in which DTBP was used as oxidant in presence of acetic acid. In the case of C4 alkylation, C3 peroxidation also occurred (Scheme 37) [60].

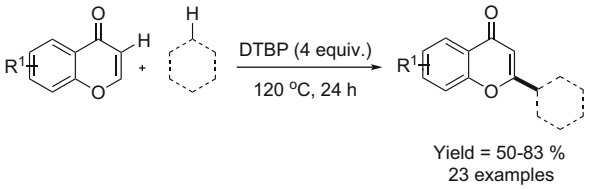
Metal-free radical C-H alkylation of purine nucleosides with cycloalkanes was reported with DTBP (di-*tert*-butylperoxide) at elevated temperatures. By proper control of reaction time and DTBP loading, C6-monocycloalkylated or C6, C8-dicycloalkylated



Scheme 34 DTBP-mediated alkylation of indoles



Scheme 35 Iron-catalyzed alkylation of chromones

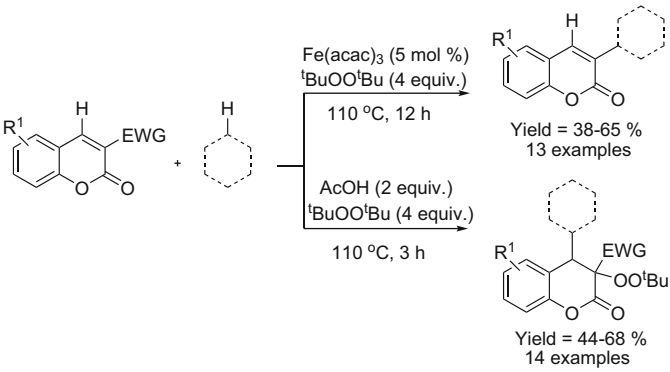


Scheme 36 Metal-free conjugate addition of alkanes with chromones

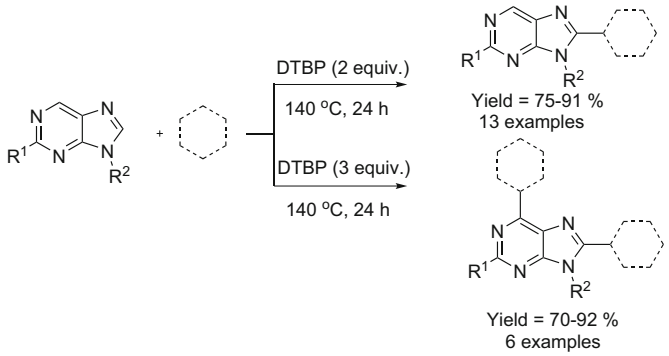
purine nucleosides could be selectively obtained (Scheme 38). C5-cyclohexylation of uracil and related nucleosides could also be achieved with high regioselectivity by this protocol [61].

Guo and coworkers also reported a C8 selective cycloalkylation of purines with oxidant DTBP (di-*tert*-butylperoxide) under metal-free conditions. However, under CuI/DTBP catalytic conditions, *N*-alkylation of *N*6 via C–N bond formation occurred (Scheme 39) [62]. A cycloalkyl radical was believed to be responsible for C8 alkylation while the cycloalkyl carbocation was involved in C–N bond formation. This cycloalkyl carbocation was generated from cycloalkyl radical via CuI-mediated oxidation. Various purines, benzothiazole, purine nucleosides, and benzoxazole reacted smoothly, giving good yield of products.

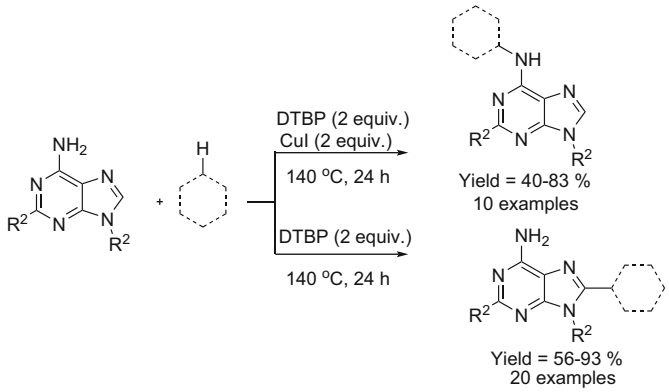
An efficient oxidative cross-coupling of heteroarenes with simple unfunctionalized alkanes was reported by Antonchick et al. The corresponding alkyl radical was formed through the combined activity of PIFA [$PhI(OCOCF_3)_2$]/NaN_3. Various nitrogen containing heterocycles and (thio)chromones were alkylated through this novel method (Scheme 40) [63, 64].



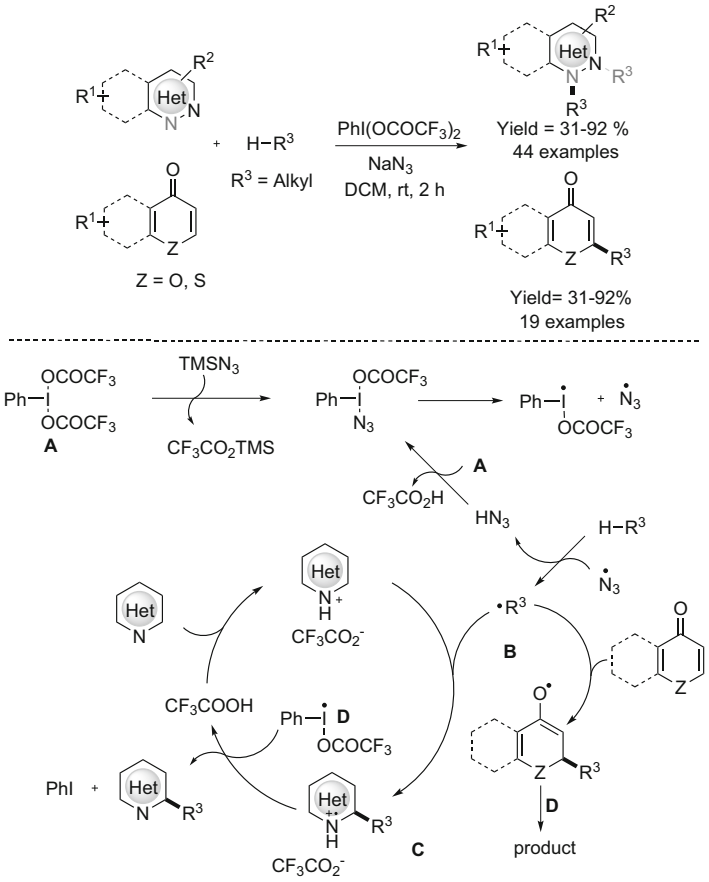
Scheme 37 Peroxide-mediated alkylation of coumarins



Scheme 38 Peroxide-mediated alkylation of purines



Scheme 39 DTBP-mediated alkylation of purines

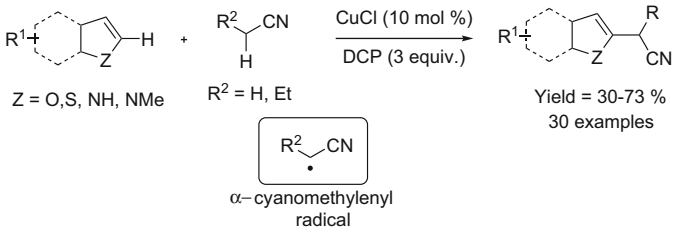


Scheme 40 Alkylation of nitrogen heterocycles and chromones

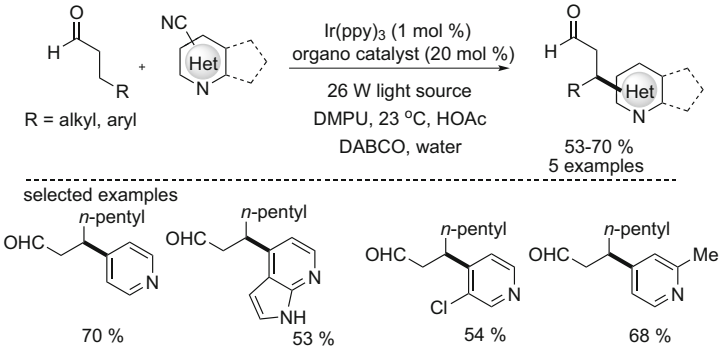
Nitriles also could be a source of alkyl free radicals under metal-catalyzed conditions. In a CuCl/DCP (dicumyl peroxide)-mediated process, various furans, thiophenes, indoles, and pyrroles were C2-cyanoalkylated with alkyl cyanides (Scheme 41) [65]. Mechanistically, the reaction between Cu(I) and DCP (dicumyl peroxide) produced Cu(II), acetophenone, *t*-BuO$^-$ anion, and a methyl radical. Subsequently, hydrogen atom transfer from nitrile to the methyl radical generated CH_4 and α-cyanomethylenyl radical, which added to the heterocycle leading to the final product.

4.4 Carbonyls, Ethers, and Amines as Alkyl Radical Sources

A photocatalytic β-arylation of carbonyls with cyano-substituted aryls or heteroaryls was developed by MacMillan and coworkers (Scheme 42) [66].



Scheme 41 Copper-catalyzed cyanoalkylation of heterocycles



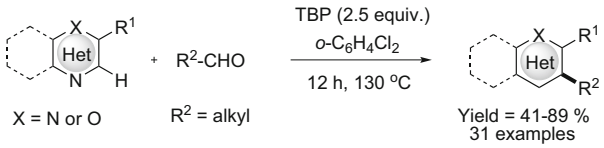
Scheme 42 β-Arylation of carbonyls

Aliphatic aldehydes could provide an alkyl radical for alkylation of electron-deficient heterocycles. By treatment with *tert*-butyl peroxybenzoate (TBP), aliphatic aldehydes underwent a decarbonylation process to generate an alkyl radical in the absence of metal catalyst. This alkyl radical was trapped with various electron-deficient heteroarenes to produce alkylated *N*-heteroarenes at 130°C for 12 h (Scheme 43) [67].

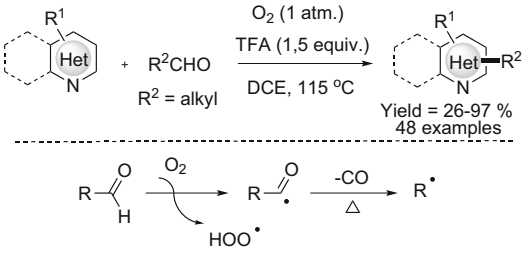
Molecular oxygen-trifluoroacetic acid combination was found to be effective for the generation of alkyl radicals from aliphatic aldehydes through decarbonylation. The proposed reaction mechanism showed that the auto-oxidation of aldehyde with molecular oxygen produced acyl radical, which then delivered the corresponding alkyl radical for alkylation of *N*-heteroarenes under heating conditions (Scheme 44) [68].

The α-oxy radical, generated from benzyl ethers through thiol-mediated photoredox catalysis was shown to couple with electron deficient aryl cyanides to form the corresponding benzylated arenes (Scheme 45) [69].

Sodium persulfate was also shown to be susceptible to SET with excited photocatalyst *Ir(III) and formed the corresponding radical anion. This sulfate radical anion abstracted α-protons from ethers and formed the corresponding



Scheme 43 Aliphatic aldehydes as alkyl radical sources



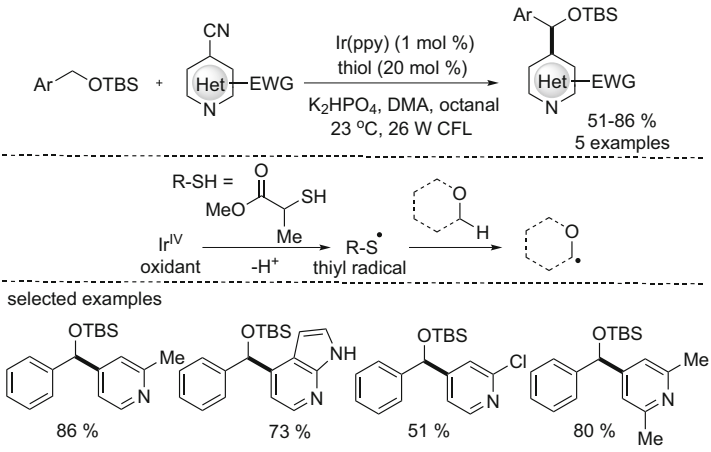
Scheme 44 Alkylation of heterocycles with aldehydes as alkyl sources

α-oxy-radical. Various heterocycles like pyridines, isoquinolines, and pyrimidines were etherified using this procedure (Scheme 46) [70].

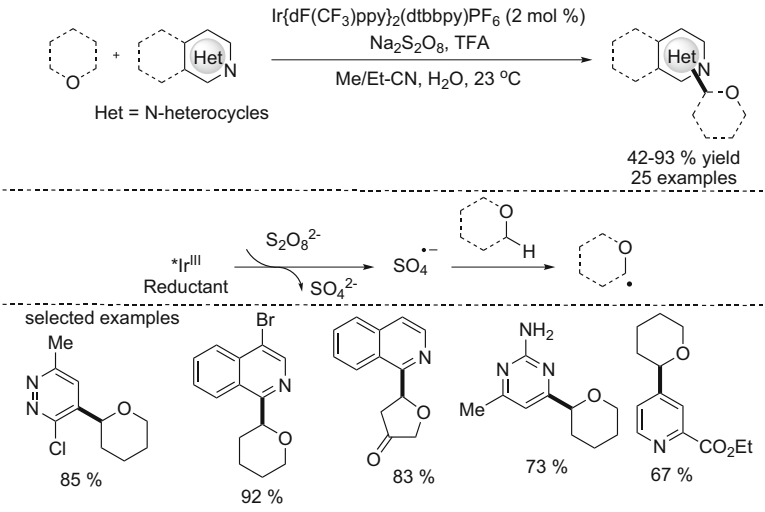
Cyclic or acyclic ethers could be used to generate α-alkoxy radicals by means of persulfate under metal free conditions. This radical was also coupled with a variety of electron-deficient heteroarenes such as isoquinolone, quinoline, pyridine, pyrazines, and pyrimidines and generated the corresponding α-oxyalkyl containing heteroarenes in moderate to excellent yields. Along with monosubstituted products, disubstitution also occurred in some cases [71]. A combination of $Cu(OTf)_2$/$K_2S_2O_8$ system was successful in alkylating benzo and non-benzo fused azoles with cyclic ethers (Scheme 47) [72].

Wang and coworkers showed that TBHP (*tert*-butylhydroperoxide) as oxidant is sufficient for the direct C2-alkylation of azoles with alcohols or ethers. Azoles such as benzothiazoles, benzoxazoles, and benzimidazoles were suitable for this alkylation. Primary and secondary alcohols were compatible in this process (Scheme 48) [73].

Watson and coworkers showed that pyridinium salts could be used as source of alkyl radicals through C–N bond homolytic cleavage [74]. They proposed, this was realized through a SET from a Ni(II) source onto pyridinium salts to the corresponding radical cation, which propelled homolytic fragmentation of the C–N bond (Fig. 12). Pyridines and indoles could be alkylated through this way (Scheme 49). In a report by MacMillan and coworkers, chloroheteroarenes were shown to be possible coupling partners for the α-arylation of a variety of cyclic and acyclic amines [75].



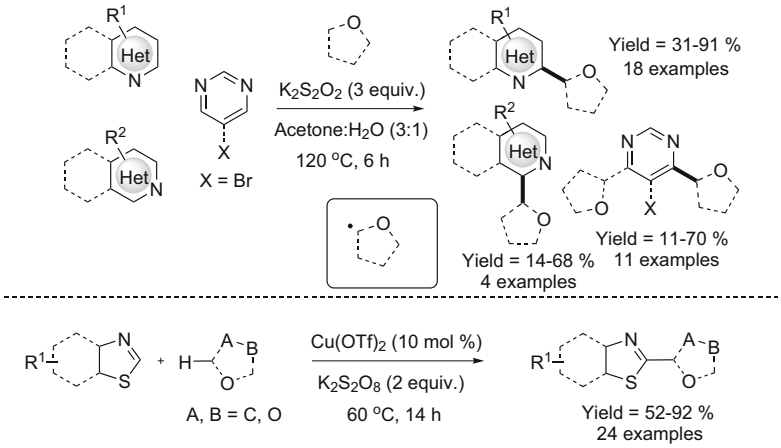
Scheme 45 Benzylated heteroarene synthesis



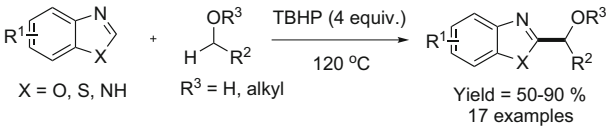
Scheme 46 Etherification of heterocycles

4.5 Alcohols and Alkyl Halides as Alkyl Radical Sources

Very recently, methanol as well as diverse alcohols could be treated as source of alkyl radicals under photocatalytic conditions as well. A variety of *N*-heteroarenes such as isoquinolines, quinolines, phthalazines, phenanthridines, and pyridines underwent easy methylation at the electron deficient position of the heterocycles (Scheme 50) [76].



Scheme 47 Cyclic ethers as alkyl radical sources



Scheme 48 Direct C-2 alkylation of azoles with alcohols or ethers

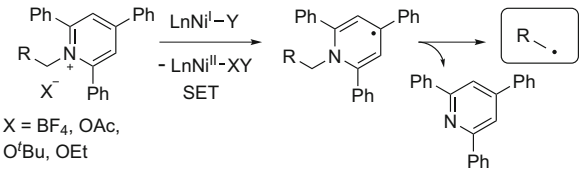
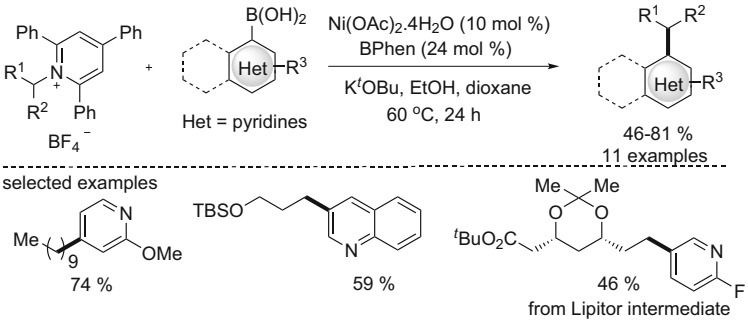


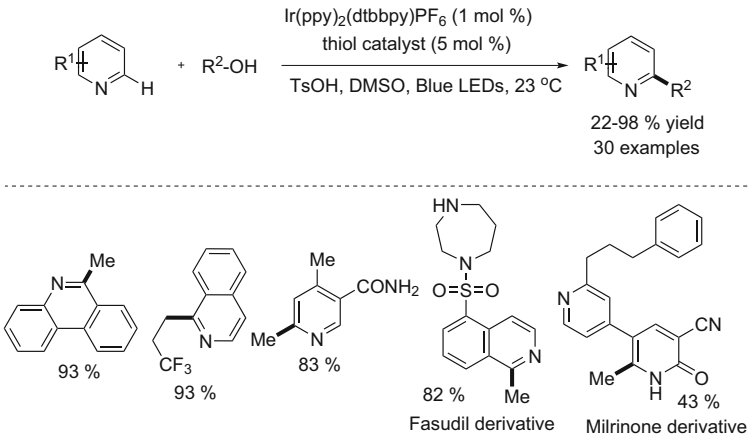
Fig. 12 Nickel-catalyzed alkyl radical generation from pyridinium salts

An elaborated mechanistic picture is provided below for the alkylation of heterocycles using alcohols (Fig. 13).

Mechanistic description started with single electron transfer from $*Ir(ppy)_2(dtbbpy)^+$ (**A**) to heterocyclic substrate. This led to the formation of $Ir(ppy)_2(dtbbpy)^{2+}$ (**B**). **B** was engaged in single electron transfer with thiol to form the thiyl radical **C**. The key step involved the α-hydrogen abstraction from alcohol by the thiyl radical to form α-oxy radical **D**. This nucleophilic α-oxy radical was trapped by a heterocycle through a Minisci type pathway and formed aminyl radical cation **E**. A subsequent deprotonation from **E** led to the formation of α-amino radical **F**. **F** suffered a spin-center shift (SCS)



Scheme 49 Cross-coupling of boronic acid with alkyl free radicals



Scheme 50 Methylation of aromatic heterocycles

that eliminated a water molecule and formed the benzylic radical **G**. A second single electron transfer between **A** and **G** along with protonation led to the desired alkylation product.

Lectka et al. found that, in the presence of manganese (IV) dioxide and TFA, a ring-opening of cyclopropanols occurred for direct alkylation of heteroarenes to afford a variety of ketone-containing alkylated heteroarenes in moderate to good yields with broad functional group tolerance. The proposed reaction mechanism showed that two different oxidation states of manganese (III and IV) might play a role in the cyclopropanol C–C bond cleavage and rearomatization steps (Scheme 51) [77].

Tertiary cycloalkanols could also be a source of free radicals under persulfate-mediated, silver-catalyzed conditions. The resulting free radicals could be trapped by quinoline or benzothiazole to afford the corresponding 2-substituted derivatives (Scheme 52) [78].

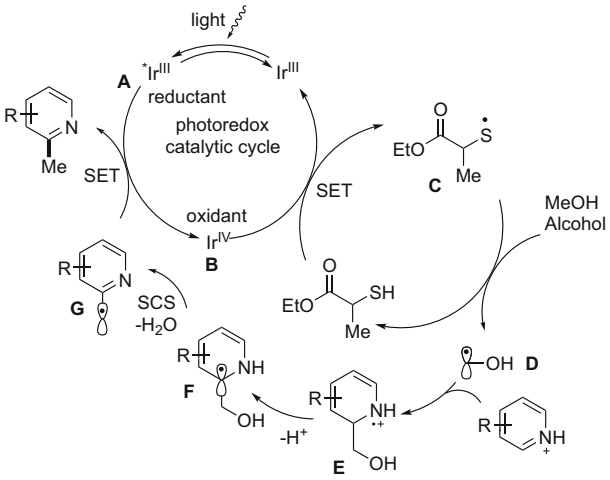
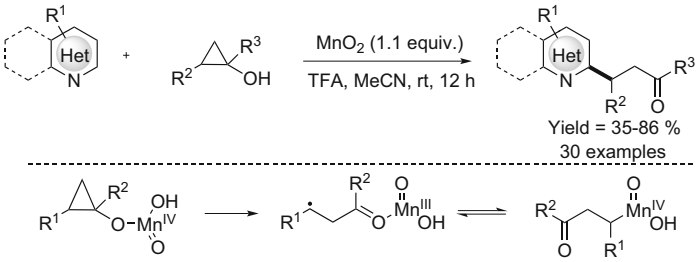


Fig. 13 Mechanism of photocatalytic methylation of heteroaromatics

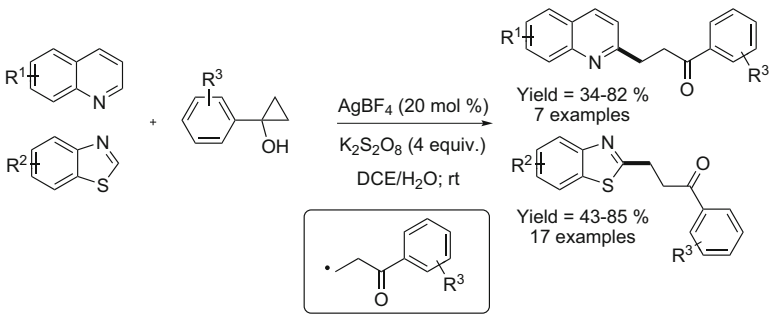
Hydroxyalkyl groups can also be attached to heteroarenes through a radical oxidative C-H alkylation process. Neubert et al. developed a hydroxyalkylation of 3,6 dichloropyridazines with diverse alkyl alcohols in the presence of TBHP (tert-butylhydroperoxide) and $TiCl_3$ (Scheme 53). The key free radical formation step was also shown [79].

A free radical-mediated palladium-catalyzed Minisci reaction of *N*-heterocycles with simple alcohols was reported by Li and coworkers [80]. An interesting, highly selective cross-coupling reaction between aryl halides with alkyl halides under Ni(II) catalysis was developed by Weix and coworkers. In this process, aryl (or heteroaryl) halides were effectively coupled with alkyl iodides or bromides in the presence of catalytic amounts of Ni(II) complex, bipyridyl ligand and stoichiometric Zn or Mn powder. The corresponding C(sp2)-C(sp3) bond was formed selectively (Scheme 54) [81–83].

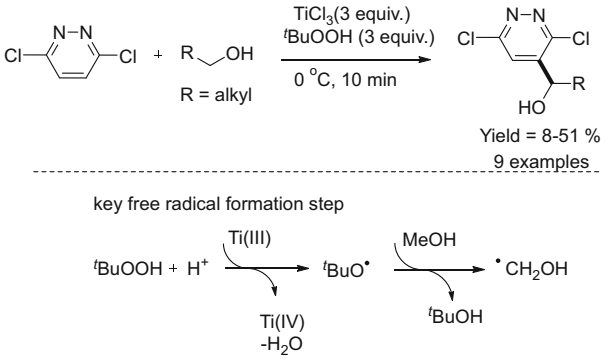
The mechanistic studies revealed that the cross selectivity arose through a catalytic cycle where both polar and free radical intermediates effectively combined to form the new C–C bond. The transformation of Ni(I)I–Ni(II)I_2, assisted with alkyl iodide (halogen abstraction mechanism), generated the key alkyl radical (Fig. 14). The observed selectivity was justified by two factors: (a) The relative rate of oxidative addition of LnNi(0) towards halides was in the order Ar-X > alkyl-X, and (b) The relative rate of halogen abstraction of LnNi(I) towards halides was in the order alk-X > Ar-X. Later, they found that 2-chloropyridines were more viable substrates for the cross-coupling with alkyl halides in the presence of bathophenanthroline ligand [84].



Scheme 51 Manganese dioxide-mediated alkylation of heterocycles with cyclopropanol as alkyl free radical source



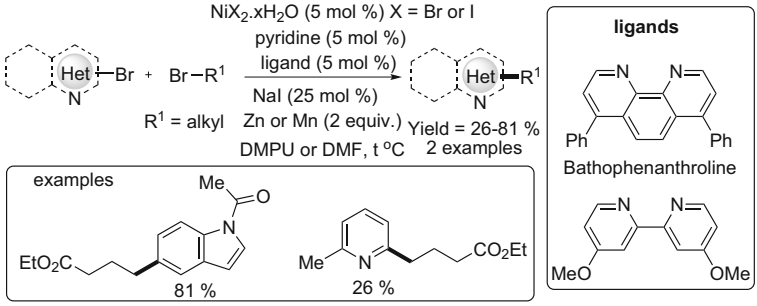
Scheme 52 Tertiary cycloalkanols as a source of alkyl radicals



Scheme 53 Titanium-catalyzed hydroxyalkylation of heterocycles

4.6 Acids and Acid Derivatives as Alkyl Radical Sources

DiRocco and coauthors applied alkylation strategies through visible-light photoredox catalysis on pharmaceutically important leads and drug candidates. In this promising



Scheme 54 Nickel-catalyzed cross-coupling between alkyl bromide and aryl(heteroaryl) bromide

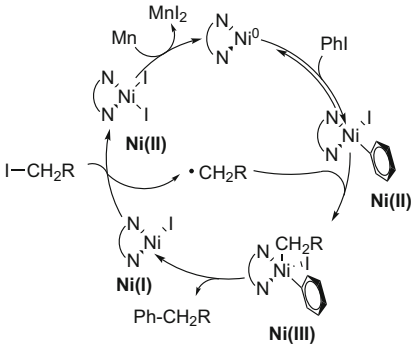


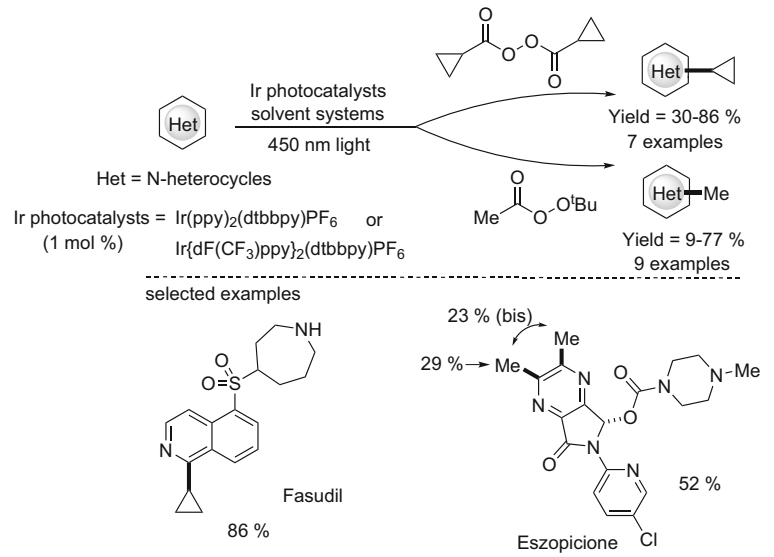
Fig. 14 Mechanism of nickel-catalyzed cross-coupling between alkyl halide and aryl(heteroaryl) halide

study, organic acylperoxides were used as source of alkyl radicals under photocatalyzed conditions. Diverse mono- or dialkylated drugs were prepared under mild reaction conditions [85] (Scheme 55).

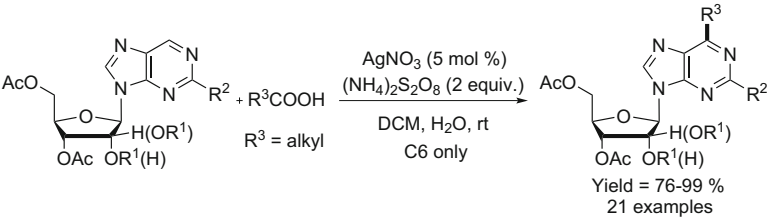
Aliphatic acids could be efficient alkyl radical precursors in Minisci reactions. Guo et al. reported a C6 selective alkylation of purine nucleosides at room temperature (Scheme 56). The process was catalyzed by $AgNO_3$ in the presence of ammonium persulfate as oxidant. Various purine nucleosides (such as ribosyl, deoxyribosyl, and arabinosyl purine nucleosides) and aliphatic acids (including primary, secondary, and tertiary aliphatic carboxylic acids) were compatible with the developed conditions [86].

Employing similar conditions, Estrada et al. showed that electron-deficient pyrimidines could also be alkylated with carboxylic acids (Scheme 57) [87].

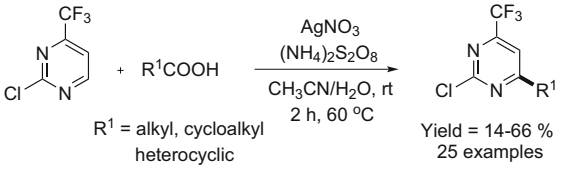
A room temperature, silver-catalyzed decarboxylative alkylation of heterocycles was also reported to functionalize benzothiazoles, thiazoles, and benzoxazoles at the C-2 position. Potassium persulfate was used as the superstoichiometric oxidant in this protocol (Scheme 58) [88]. The decarboxylative free radical formation and its utilization are depicted below (Fig. 15).



Scheme 55 Organic acylperoxides as alkyl radical sources

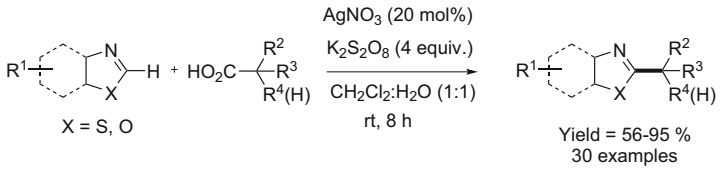


Scheme 56 Alkylation of purine nucleosides with alkyl carboxylic acids as alkyl source



Scheme 57 Alkylation of pyrimidines with alkyl carboxylic acids as alkyl source

In a silver(I)-catalyzed process, a variety of protonated *N*-heteroarenes were alkylated with natural and unnatural amino acids. Various pyridines, pyrimidines, pyrazines, and pyridazines were predominantly monoalkylated with different amino acid sources. An excess of ammonium persulfate was used as the oxidant. According



Scheme 58 Silver-catalyzed C-2 alkylation of azoles using alkyl carboxylic acids

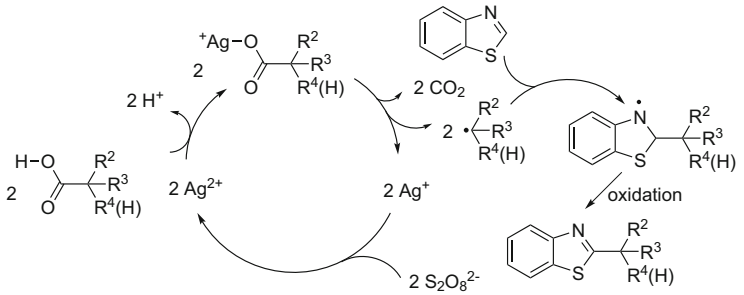


Fig. 15 Mechanism silver-catalyzed C-2 alkylation of azoles using alkyl carboxylic acids

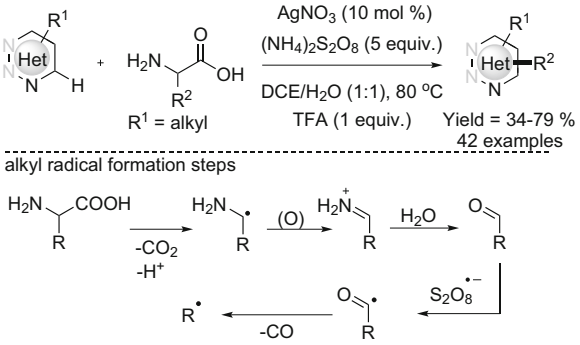
to mechanism below, the amino acids underwent an oxidative decarboxylation to form aminoalkyl radicals. Subsequent oxidation and hydrolysis produced the corresponding alkyl aldehydes. A decarbonylation of aldehyde afforded alkyl radicals for the next alkylation (Scheme 59) [89].

4.7 Arylation and Acylation Through Aryl and Acyl Radicals

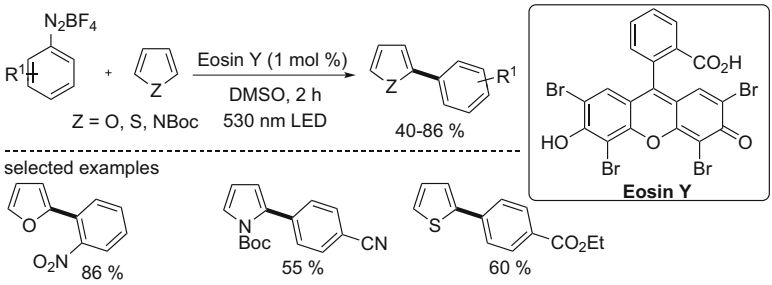
The common sources of aryl radicals, which are used to functionalize heteroaromatics, either originate from aryl diazonium salts, diaryliodonium salts, aryl sulfonyl chlorides, or aryl halides (iodide, bromides, chloride). In the following section, the use of various photocatalytic processes towards heterocyclic functionalization, is discussed.

An interesting arylation of furans, pyrroles(N-Boc) and thiophenes with aryl diazonium salts was developed by König and coworkers [90]. The transformation was catalyzed by Eosin Y photocatalyst under mild conditions. In general, aryl diazonium salts substituted with electron withdrawing groups gave higher yields compared to their electron donating counterparts (Scheme 60).

The reaction proceeded through the involvement of an aryl radical, formed through single electron transfer from excited state Eosin Y to aryl diazonium salts. This electron transfer endorsed self-fragmentation of aryl diazonium salt in such a way, that an aryl radical and N_2 were formed. A subsequent radical trap with heterocycle, a reductive quenching of the photocatalyst with the heterocycle-aryl free radical adducts and a final deprotonation were responsible for the arylated heterocycle formation (Fig. 16).



Scheme 59 Silver-catalyzed alkylation of heterocycles with amino acids as alkyl source



Scheme 60 Eosin Y-catalyzed arylation of furans, pyrroles, and thiophenes

Heterogeneous TiO_2-visible light combination was also used to generate aryl radicals from aryl diazonium salts. Such aryl radicals were used to functionalize various furans, thiophenes, and pyridines [91]. In two independent reports, various *N*-heteroarenes were arylated with aryldiazonium salts in the presence of ruthenium photocatalyst, $[Ru(bpy)_3]Cl_2{\cdot}6H_2O$. Pyridines, xanthenes, thiazoles, pyrazines, and pyridazines were compatible with these new arylation conditions. The mechanism of the process was similar to the previously discussed case of eosin with the only difference being that excited state of ruthenium promotes the diazonium salt dissociation [92–93].

Suitably tuned porphyrins can act as photocatalysts and can generate aryl radicals from aryldiazonium tetrafluoroborate salts. Gryco and coworkers developed an arylation of various heterocycles by means of photocatalyst tetraphenylporphyrin (H_2TPP). Various heterocycles such as furans, benzofurans, thiophenes, indoles, and coumarins were susceptible to this free radical process and formed the corresponding arylation products (Scheme 61). On the other hand, arylation of pyrroles was found to be challenging under the given conditions [94].

In another report, in situ generated aryl diazonium salts from aryl amines and *t*-BuONO were employed as aryl radical sources under photocatalytic conditions.

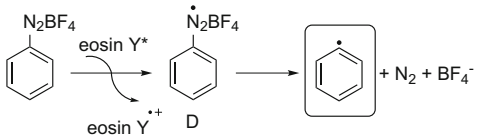
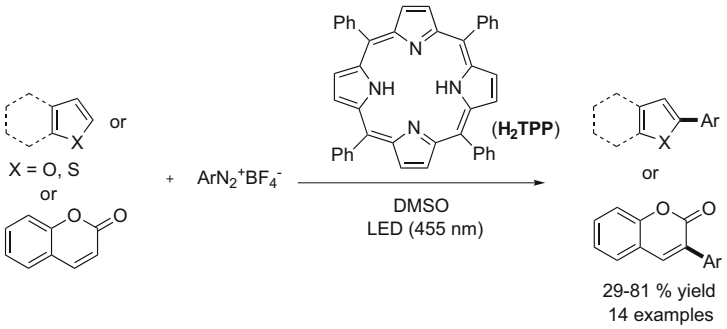


Fig. 16 Eosin Y-catalyzed aryl radical formation



Scheme 61 Arylation of heterocycles with porphyrin as a photocatalyst

Various heterocyclic diazonium salts containing pyridines, thiazole, and quinoline moieties were coupled with furans, thiophenes, and *N*-substituted pyrroles by using this method [95].

Xiao and Chatani's research groups independently reported that diaryliodonium salts could be an alternative source for aryl radicals under photocatalytic conditions (Fig. 19) which could be used for the functionalization of numerous heterocycles [96, 97]. In another interesting report, Natarajan and coworkers revealed that aryl sulfonyl chloride could be a potent source for aryl radicals (Fig. 17). In this case, various substituted pyrroles, furans, and thiophenes were arylated as well [98].

Wang and coworkers showed that triazenes could be used as sources of aryl free radicals under Ag(I)/$S_2O_8^{2-}$-mediated conditions. The aryl radicals thus generated were used to functionalize various heterocycles like pyridine, quinoline, isoquinoline, pyrimidine, pyridazine, pyrazine, phthalazine, quinoxaline, and their substituted derivatives (Scheme 62) [99]. Regioisomeric products were generally observed in the cases of substrates where a clear regioselectivity preference was not attainable.

Aryl radical generation from aryl halides, especially bromides and chlorides, is a challenging process due to the high energy barrier associated with the corresponding homolytic cleavage. König and coworkers devised a solution to this problem through a double photo-excitation strategy of the organic dye PDI [*N*,*N*-bis(2,6-diisopropyl) perylene-3,4,9,10-bis(dicarboximide)], thereby acquiring sufficient energy to perform a charge transfer to the aryl halide (Fig. 18). Triethylamine was used as sacrificial oxidant. This novel pathway resulted in the formation of an aryl radical which was trapped with various substituted pyrroles. Various aryl iodides, bromides

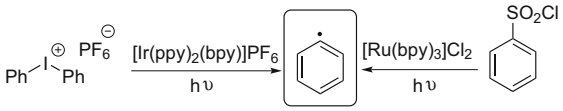
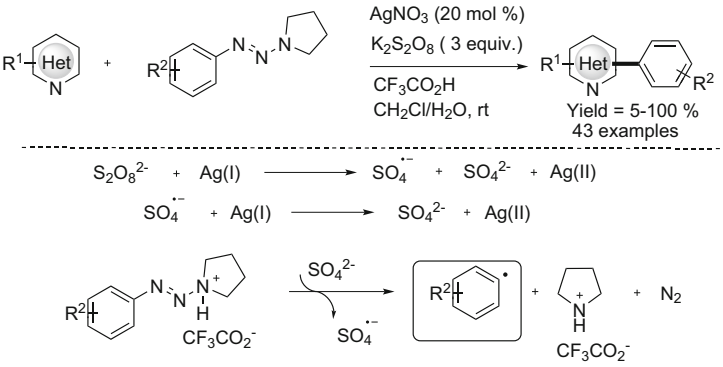


Fig. 17 Aryl radical formation from diaryliodonium salts or aryl sulfonyl chlorides



Scheme 62 Aryl triazenes as aryl radical for heterocyclic functionalization

and chlorides were smoothly converted into the corresponding aryl radical through this process (Scheme 63) [100].

In a further report, they developed a sequential activation of polyhalogenated aryl halides with different light sources [101]. Heteroaryl radicals could be generated from heteroaryl bromides under photocatalytic conditions. Weaver's group achieved a reductive alkylation of 2-bromoazoles with an Ir photocatalyst where the key heteroaryl radical was formed through an oxidative quenching of heteroaryl bromide with excited iridium photocatalyst (Scheme 64) [102].

When compared to alkylation or arylation, photocatalytic acylations through acyl radicals are rare. MacMillan's group employed photoredox catalytic conditions to generate the acyl radical from α-oxocarboxylic acids to realize decarboxylative acylation with different aryl and alkyl iodides/bromides [103]. Here, the target ketone could be seen as a result of the cross-coupling between newly generated acyl radical and organic halides by cooperative photoredox and nickel-catalytic cycles (Scheme 65).

A similar transformation was also achieved by Fu et al. using palladium instead of nickel catalyst under otherwise identical conditions. In this case, the desired decarboxylated coupling product could also be achieved from monoamide oxalates, which gave different amides (Scheme 66) [104].

Indoles (free and *N*-substituted) could be easily acylated with α-oxocarboxylic acids to 3-acyl indoles using organo-photoredox catalysis. Rose Bengal was found to be the most efficient organo-photocatalyst when 3W green LEDs were used as light source in ethanol medium under air (Scheme 67). Mechanistically, an acyl radical formation was postulated by a reaction between singlet oxygen ($^1O_2$) and

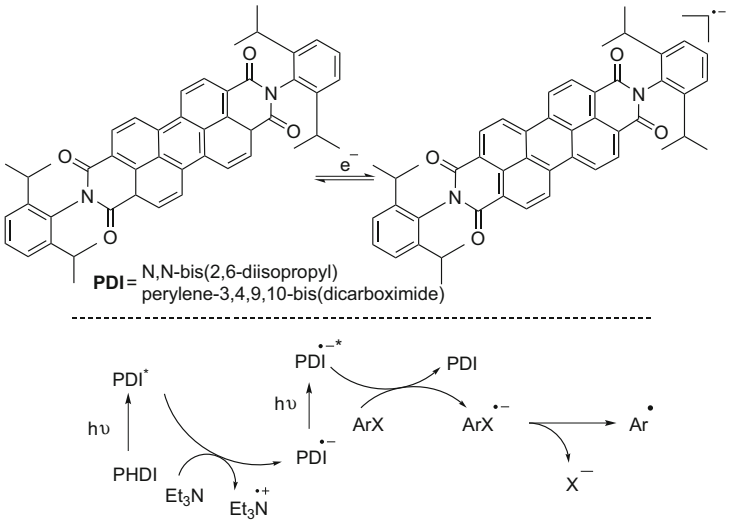
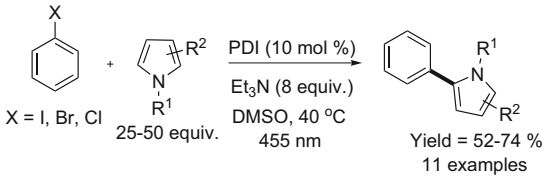
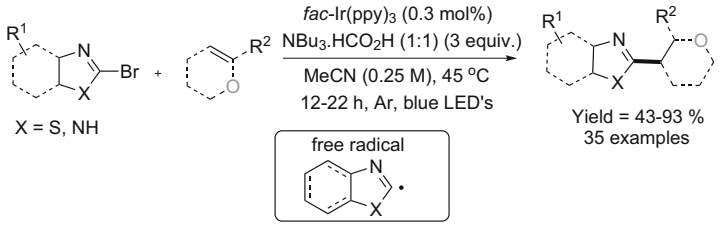


Fig. 18 Electron transfer to PDI to generate the corresponding radical anion

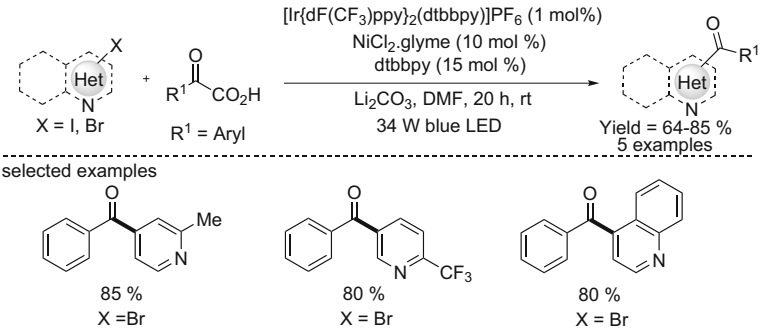


Scheme 63 Organo-photocatalyzed cross-coupling of heterocycles with aryl halides

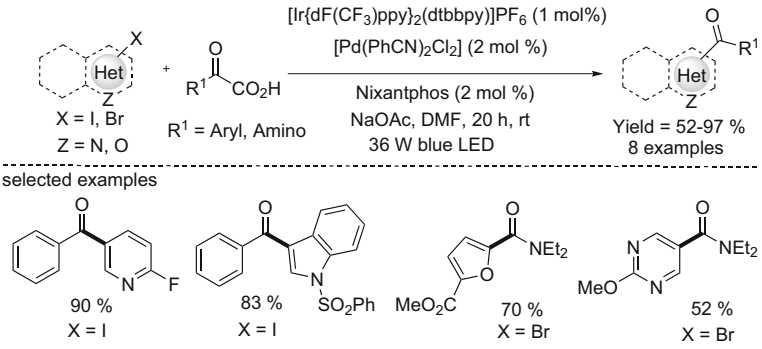


Scheme 64 Cross-coupling of heterocyclic bromides with olefins

α-oxocarboxylic acids through decarboxylation of the latter. On the other hand, singlet oxygen was formed by the reaction between exited state Rose Bengal (*RB) with molecular oxygen. A variety of indoles containing both electron donating and withdrawing groups were acylated using this protocol [105].



Scheme 65 Ni-Photocatalytic cross-coupling of heterocyclic halides with α-oxocarboxylic acids

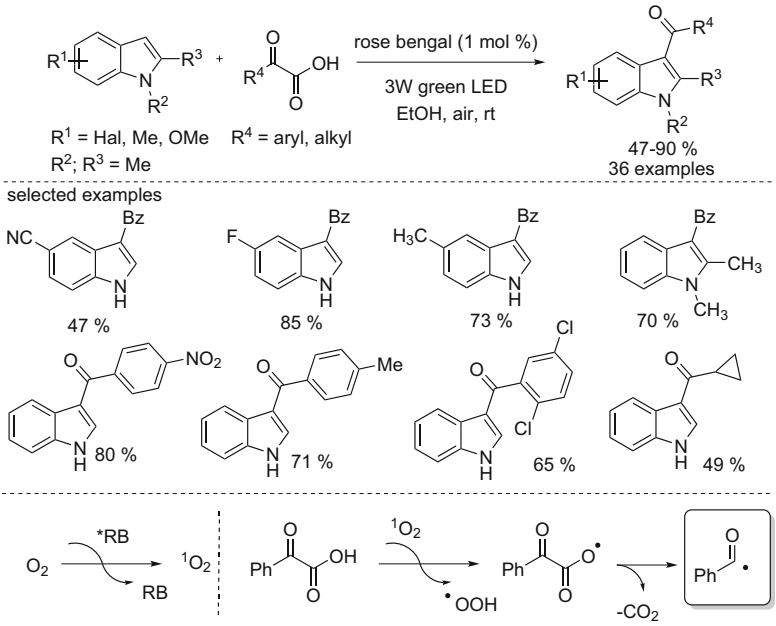


Scheme 66 Pd-Photocatalytic cross-coupling between heterocyclic halides and α-oxocarboxylic acids

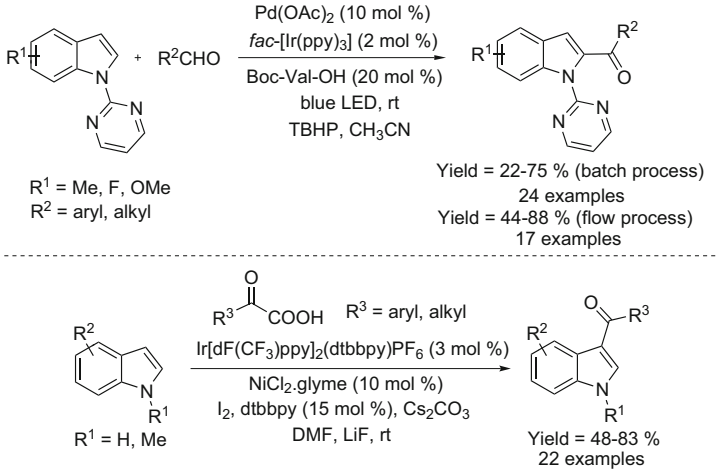
C2 as well as C3 acylation of indoles was achieved through dual photoredox/transition metal catalysis. Van der Eycken et al. showed that *N*-pyrimidylindoles could be acylated at the C2 position with various aromatic and aliphatic aldehydes at room temperature. $Pd(OAc)_2$ and *fac*-$Ir(ppy)_3$ were employed as the corresponding metal and photocatalyst in a batch process or micro flow process (Scheme 68) [106]. Free and *N*-alkyl indoles were acylated at the C3 position with α-oxo acids under visible light induced Ir/Ni co-catalytic conditions (Scheme 68) [107].

In a similar way, acylation of phenanthridines was also achieved by thermolytic and photolytic methods. The thermolytic method was mediated by substoichiometric amounts of TBAB (tetrabutylammonium bromide, 30 mol%) and $K_2S_2O_8$ as oxidant, whereas in the photocatalytic method, $K_2S_2O_8$/TBAB was replaced by $(NH_4)_2S_2O_8$ and *fac*-$Ir(ppy)_3$ was used under visible light irradiation. This intermolecular acylation reaction provided an easy access to 6-acylated phenanthridine derivatives (Scheme 69) [108].

Antonchick et al. developed an efficient acylation of nitrogen heterocycles with aldehydes under PIFA/$TMSN_3$-mediated conditions. Along with the functionalization of various heterocycles like isoquinoline, quinoxaline, pyridine, benzothiazole, and

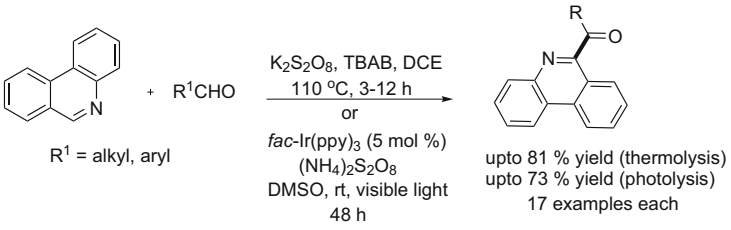


Scheme 67 Rose Bengal-catalyzed cross-coupling of indoles with α-oxocarboxylic acids

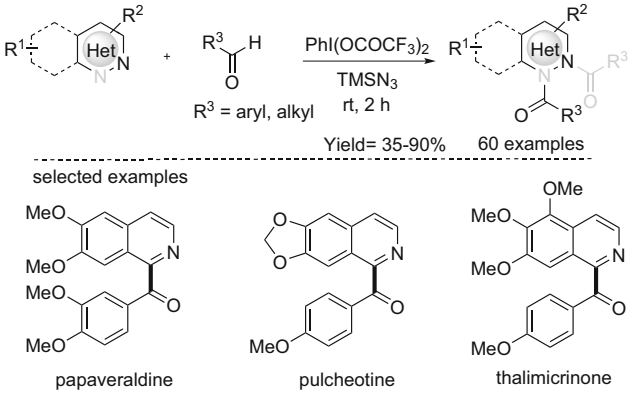


Scheme 68 Ni/Pd-Ir synergistic catalysis for the cross-coupling of indoles with aldehydes and α-oxocarboxylic acids

caffeine, the method was also employed for the synthesis of a collection of natural products (Scheme 70) [109].



Scheme 69 Acylation of phenanthridines using persulfate or Ir photocatalysis



Scheme 70 Hypervalent iodine-mediated acylation of *N*-heterocycles

The key nucleophilic acyl radical was generated from aldehyde by the acyl hydrogen abstraction with N_3 radical. The latter on the other hand was formed through a homolytic cleavage of $PhI(N_3)_2$, which was formed by the double exchange of trifluoracetyl groups in **A** by azide ions. Nucleophilic acyl radical **B** targeted the electrophilic position of the protonated heterocycle. Rearomatization of **C** provided the desired product (Fig. 19).

Following this study, new reports were published for the same transformation using different stoichiometric systems like TBAB/$K_2S_2O_8$ [110], NCS/TBHP [111], or TBHP/TFA [112]. In all these systems, the acyl radical was proposed to be the key intermediate.

Patel and coworkers employed a substituted methyl arene/TBHP combination as acyl radical source. $AlCl_3$ was used as the catalyst. The developed process is suitable for functionalizing a variety of isoquinolines, quinolines, and quinoxalines [113]. Instead of $AlCl_3$, MnO_2 could also be used as an efficient catalyst in the case of isoquinoline functionalization (Scheme 71) [114].

A decarboxylative acylation of pyridine *N*-oxides was reported with various α-oxocarboxylic acids as free radical source. The process was catalyzed by silver nitrate under $K_2S_2O_8$-mediated conditions. Silver salt of carboxylic acids underwent

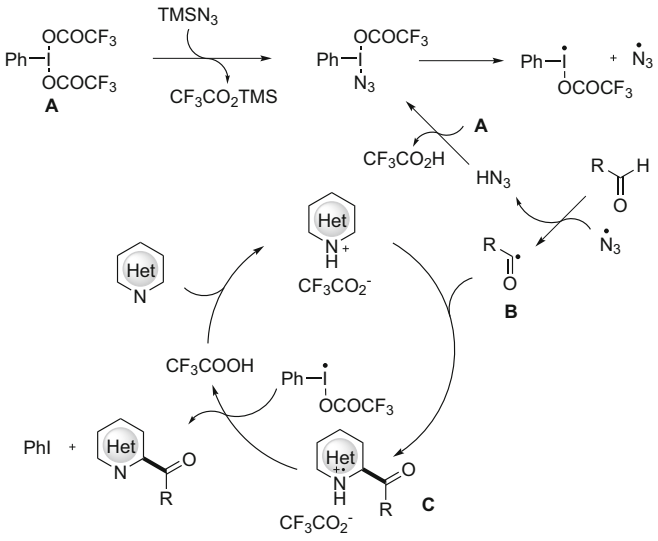


Fig. 19 Hypervalent iodine-mediated acylation of *N*-heterocycles

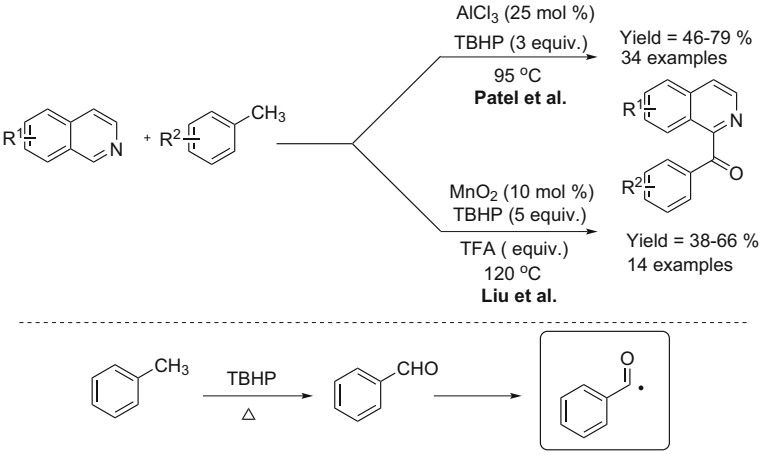
decarboxylation in the presence of sulfate radical anion, thereby forming an acyl radical which further promoted acylation (Scheme 72) [115].

3- or 4-Aryl pyridines suitably substituted with α-acyl carboxylic acid underwent sulfate radical anion ($SO_4^{\bullet -}$)-mediated decarboxylation and formed acyl radicals. This acyl radical was trapped by the pyridine fragment resulting in the formation of azafluorinones (Scheme 73) [116]. A mixture of regioisomers was formed depending on the substrate structure.

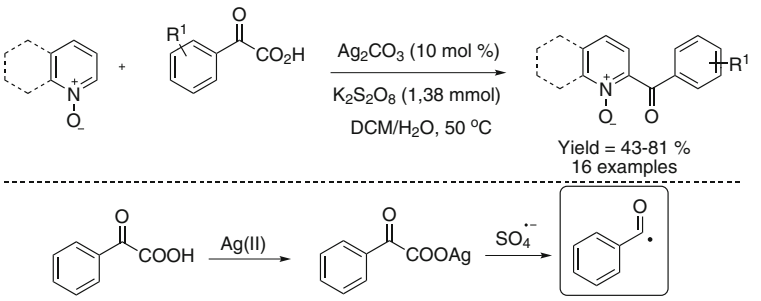
4.8 Heterocyclic Functionalization Through Metal Hydride–Hydrogen Atom Transfer Process

Olefins can be the radical source for unsaturated heterocyclic functionalization through Minisci type reactions or cross-coupling. In this process, the radical generation is achieved through metal hydride–hydrogen atom transfer (MH-HAT).

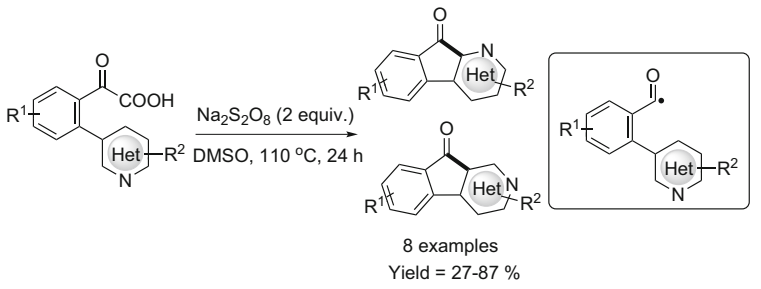
An iron-catalyzed C–C bond formation, which could also functionalize heterocycles, was devised by Baran's Group. In this operationally simple system, through the intermediacy of either $Fe(acac)_3$ or $Fe(dibm)_3$ and $PhSiH_3$, two different olefinic bonds were coupled under air or moisture compatible conditions (Scheme 74). The free radical donor component could also be accommodated with various heterocycles, which is a notable advantage of the protocol. Common acceptors include carbonyl or sulfonyl attached olefins (Scheme 74, Eq. 1) [117]. Under slightly modified conditions, various heterocycles were employed as suitable acceptors and simple olefins as donors (Scheme 74, Eq. 2) [118].



Scheme 71 Use of toluene as an acyl radical source

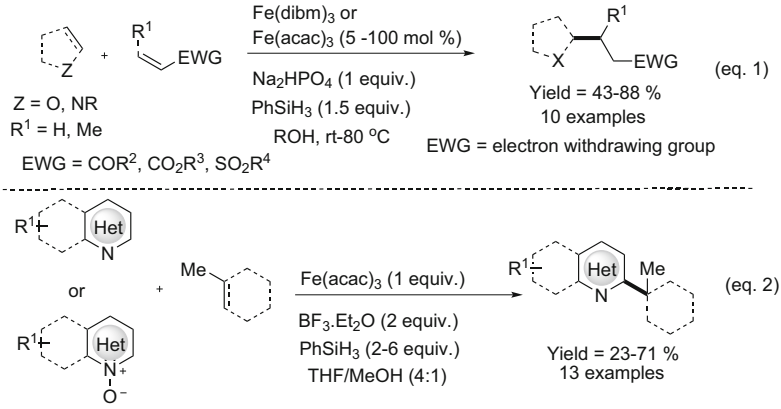


Scheme 72 Decarboxylative acylation of *N*-oxides



Scheme 73 Intramolecular acylation of heterocycles

The mechanism involves a metal-hydride HAT process (MH-HAT) to the olefin to form the carbon centered radical. This radical was trapped with olefin acceptor to



Scheme 74 Alkylation of heterocycles through cobalt-mediated hydrogen atom transfer

form the free radical intermediate. The radical was reduced with iron catalyst followed by proton abstraction to reach the end product (Fig. 20).

Shenvi et al. devised a method for the facile synthesis of 8-aryl/heteroaryl menthol starting from isopulegol through a radical arylation process. The process was based on the ability of Mn-H, which is formed from $Mn(dpm)_3$ and $PhSiH_3$, to proceed with a hydrogen atom transfer (HAT) to terminal alkene, thereby forming a carbon-centered radical which was prone to ipso attack with heteroaryl sulfonyl group to form a heteroaryl radical. This radical further underwent Smiles rearrangement and reduction to form the target compound (Scheme 75) [119].

Herzon and coworkers showed that carbon centered free radicals derived from unfunctionalized alkenes through cobalt-mediated HAT could be coupled with various *N*-methoxy heterocyclic salts. These salts include *N*-methoxypyridinium, *N*-methoxypyridiazinium, *N*-methoxyquinolinium, and *N*-methoxyisoquinolinium derivatives. The resulting alkylated heterocycles were formed in good yields. Et_3SiH and $Co(acac)_2$ were used as corresponding hydride source and catalyst. Site selectivity in case of pyridinium derivatives (C2/C4) was influenced by the nature of the radical intermediates. Selective C2 alkylation was observed with secondary radicals. With tertiary radicals, predominant C4 alkylation was observed (Scheme 76) [120, 121].

Shenvi and coworkers reported a branch selective (Markovnikov) olefin hydroarylation that combined MH-HAT with a nickel catalytic cycle. Terminal alkenes reacted with various aryl(hetero aryl) iodides in the presence of a dual catalytic system based on Ni(II) and Co(II) (Scheme 77) [122].

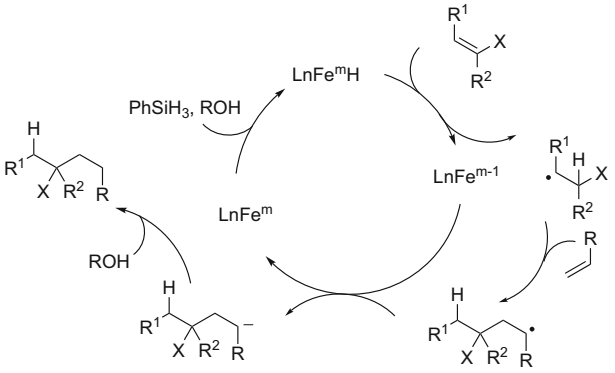
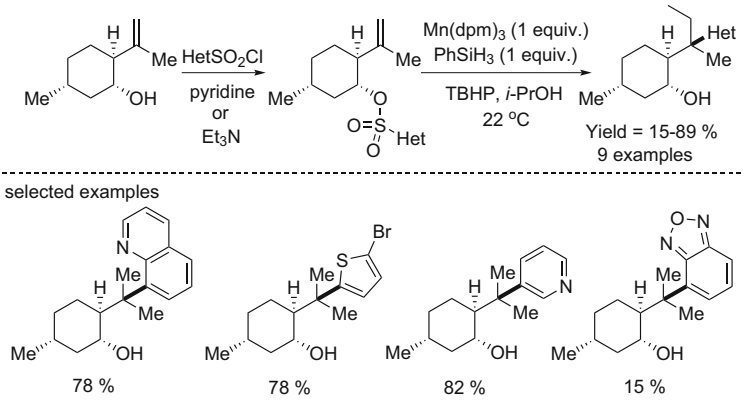


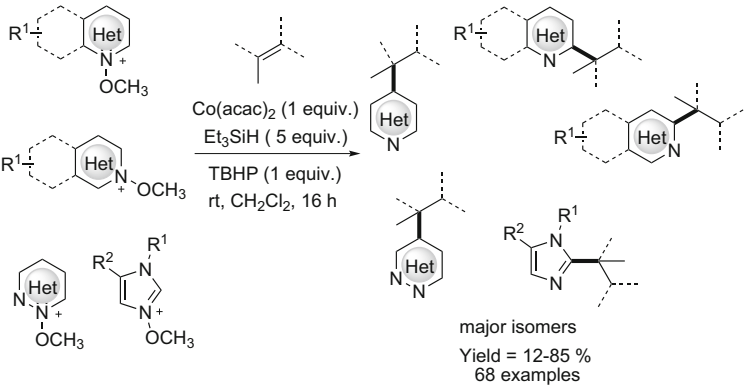
Fig. 20 Mechanism of alkylation of heterocycles through iron-mediated hydrogen atom transfer mechanism



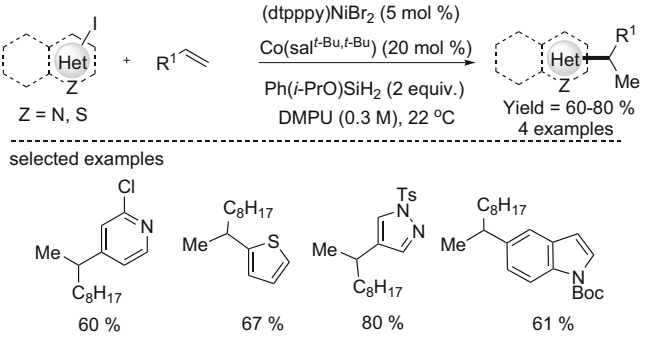
Scheme 75 Alkylation of heterocycles through manganese-mediated hydrogen atom transfer mechanism

4.9 Carbon–Heteroatom Bond Formations

Along with carbon–carbon bond forming reactions, radical-mediated carbon–heteroatom bond formation was also well studied. A unique amidation of heterocycles was developed by Baran et al. by employing the new amide source *N*-succinimidyl perester (NSP) as a source of nitrogen centered radical. The reaction was operated in presence of catalytic amounts of Cp_2Fe. A variety of heterocycles, i.e., pyridines, pyrroles, pyrimidines, thiophenes, thiazoles, pyrazines, and purines, were functionalized through this new method. The regioselectivity pattern observed is similar to aromatic electrophilic substitution in which electron-richer positions are preferred (Scheme 78) [123].



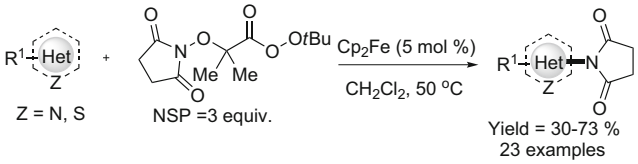
Scheme 76 *N*-Methoxy heterocyclic salts as acceptors for MH-HAT



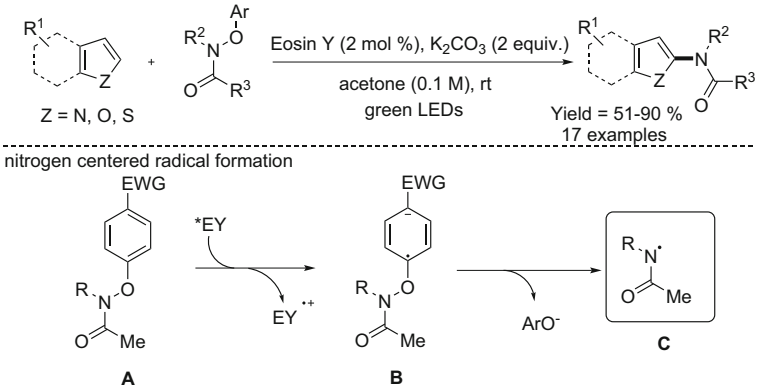
Scheme 77 Alkylation of heterocycles through a coupled Co-mediated MH-HAT/Ni-catalyzed cross-coupling

A transition metal-free photocatalytic amidation of heterocycles was achieved by a reaction between aryloxy amide and various heterocycles through free radical intermediates. Organic dye eosin Y was used as a photoredox catalyst (Scheme 79). Different heterocycles like indoles, azaindoles, pyrroles, furan, and thiazoles were amidated using aryloxy amide. Amidyl-free radical as the amide source was generated through a SET process between the eosin Y excited state (*EY) as a reductant and aryloxy amide, thereby forming a radical anion **B** and concomitant release of aryloxide anion [124].

A method for the introduction of trifluoromethylthio groups into coumarin-3-carboxylic acids was developed by Hoover and coworkers. Silver salt of trifluoromethylthiolate was used as the source of the trifluorothiolate group. This methodology utilized existing carboxylic acid functionalities for the direct conversion into CF_3S groups and resulted in a broad scope of 3-trifluoromethylthiolated coumarins, including analogues of natural products, in moderate to excellent yields. The



Scheme 78 Iron-catalyzed amination of heterocycles

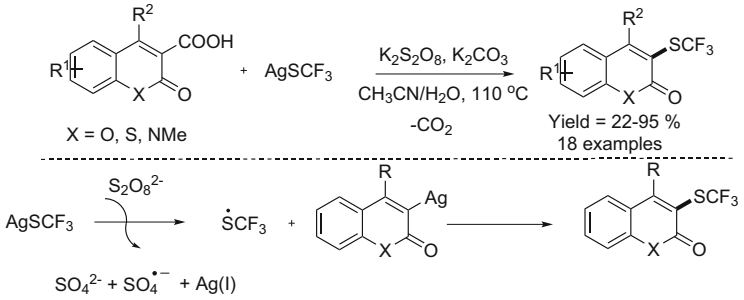


Scheme 79 Organo-photocatalytic amidation of N, O, S-heterocycles

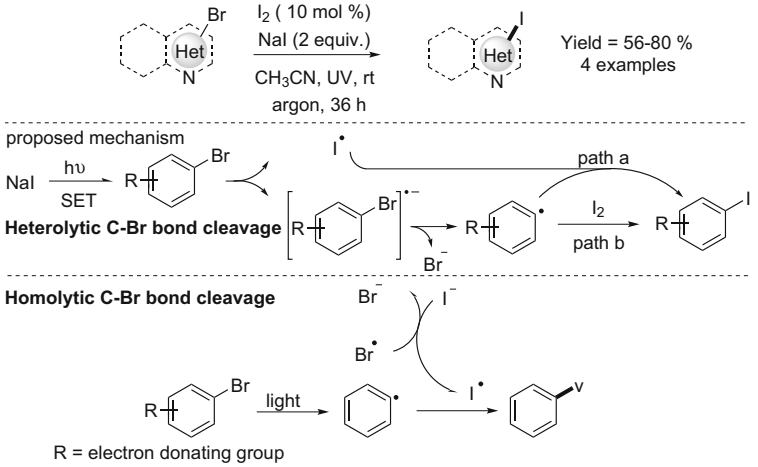
authors proposed a persulfate-mediated formation of CF_3S radical from $AgSCF_3$ and its subsequent reaction with coumarin-3-carboxylic acids (Scheme 80) [125].

Li's group introduced photo-induced halogen exchange for the iodination of aryl/heteroaryl bromides (aromatic Finkelstein reaction) with sodium iodide by means of UV-light irradiation. Molecular iodine was used as catalyst in this process. Heterocycles like indole, pyrimidine, quinolone and isoquinolines were smoothly iodinated under mild conditions (Scheme 81). Mechanistic explanation was provided based on an iodide and UV light-mediated heterolytic or homolytic C–Br bond cleavage of aryl bromide [126, 127]. The resulting aryl radical combines with iodine radical forms the final product.

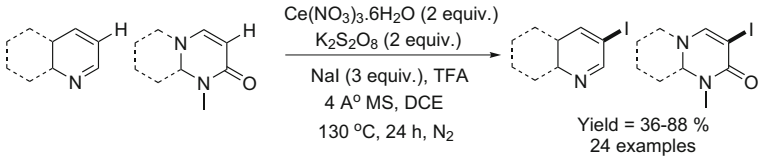
A regioselective iodination of heterocycles was realized by means of a $K_2S_2O_8$/NaI/$Ce(NO_3)_3{\cdot}6H_2O$ system. Quinolines, quinolones, pyridines, and pyridines proceeded with C3 or C5 iodination depending on the substituent attached to the heterocyclic ring (Scheme 82). The reaction was proposed to proceed through the intermediary of an iodine radical along with a sulfate radical anion, which was formed by a reaction of $K_2S_2O_8$ with NaI at higher temperature. Ce(III) was used for a single electron transfer with sulfate radical anion to yield the corresponding sulfate dianion [128].



Scheme 80 Trifluoromethylthiolation of coumarin-3-carboxylic acids



Scheme 81 Photoinduced iodination of heteroaryl bromides



Scheme 82 Persulfate-mediated iodination of nitrogen heterocycles

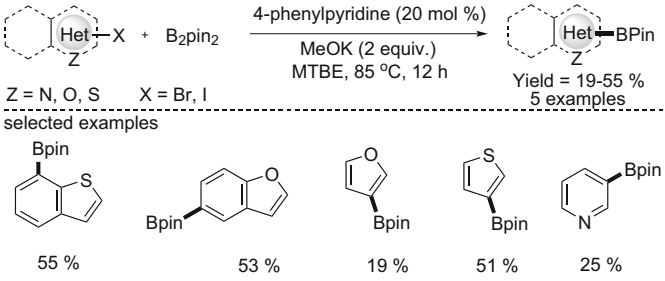
Nitrogen heterocycles were also regioselectively iodinated using molecular iodine and TBHP through free radical intermediates. Iodination was effective at the C-3 position [129].

$Mn(OAc)_3$-mediated radical phosphonylation/phosphinylation of heterocycles through intermediary of phosphonyl radical [$(RO)_2PO•$] or phosphinoyl radicals [$R_2PO•$], is a well-studied process [130, 131]. Benzothiazoles and thiazoles

were also phosphinylated with diphenylphosphine oxide under ball-milling conditions [132].

Recently, a novel, base-assisted, pyridine-catalyzed, metal-free cross-coupling reaction between aryl(hetero) or alkenyl halides (I or Br) and bis(pinacolato) diboron [B_2pin_2] was developed by Jiao and coworkers (Scheme 83). Various heterocycles like pyridines, furans and thiophenes were borylated through this new pathway albeit with moderate yield under mild conditions. Potassium methoxide and 4-phenylpyridine were found to be the optimum base and catalyst in this process [133].

Mechanistic explanation of the protocol was given on the basis of free radical involvement. The key features involved methoxide ion addition to B_2pin_2 to an -ate complex **A**, which further led to the complex **B** by the reaction with pyridine. Complex **B** underwent a homolytic cleavage, thereby yielding pyridine stabilized boryl radical **C** and methoxyboronate radical anion **D**. The required aryl radical **E** was formed through a SET process with aryl halide and complex **D**. Aryl radical **E** was then trapped with complex **C** and formed the corresponding C–B bond (Fig. 21).



Scheme 83 Borylation of heterocycles

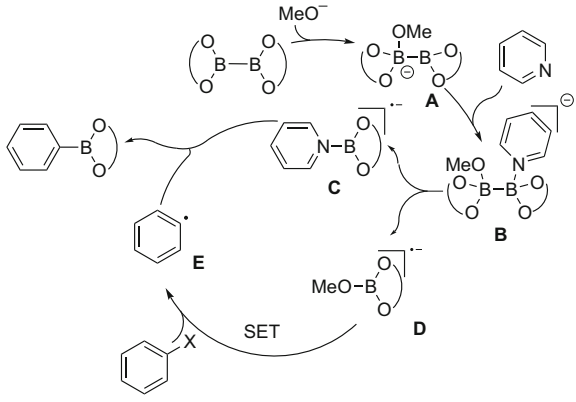


Fig. 21 Mechanism of borylation of heterocycles

5 Conclusions

The purpose of this review is to report recent developments in the field of heterocyclic functionalization through radical intermediates. A variety of alkyl, aryl, acyl, and heteroatom-centered radical sources and their subsequent incorporation on various heterocycles are reviewed. In a broad sense, Minisci-type reactions and polar-free radical cooperative catalysis were more explored in heterocyclic functionalization in the recent years. The radical sources have been extended to carboxylic acids, alcohols, alkyl and aryl halides, aldehydes, organoboranes, and other sources. In addition, photoredox strategy presents promising alternatives for C-H functionalization of various heterocycles with high efficiency and mild conditions. The current trend shows significant expansion of the field, where investigations are taking place for quick installation of various functional groups onto heterocyclic drugs. It is expected that these attempts will lead to an exponential progress in the drug development area.

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Heteroatom-Centred Radicals for the Synthesis of Heterocyclic Compounds

Fabrice Dénès

Abstract An overview of the synthetic methods allowing the preparation of heterocyclic structures based upon the use of heteroatom-centred radicals (R–X•) is presented here. The discussion will be limited to specific examples for which the heteroatom (X = SiR_2, GeR_2, SnR_2, PR, NR, O, S, SO_2, Se) is included in the heterocyclic structure itself during the cyclisation process leading to its formation. These include the cyclisation of heteroatom-centred radicals onto unsaturated partners such as alkenes, alkynes, arenes, ketones or nitriles and the formation of the heterocycle via a sequence involving remote functionalisation reactions leading to halogenated intermediates, followed by ionic cyclisation (e.g. Hofmann–Löffler–Freytag reaction), as well as cascade reactions terminating with an intramolecular homolytic substitution (S_Hi) at the heteroatom in the final step.

Keywords Alkoxy radicals · Germyl radicals · Heteroatom-centred radicals · Intramolecular homolytic substitution (S_Hi) · Intramolecular hydrogen atom transfer (1,n-HAT) · Nitrogen-centred radicals · Phosphorus-centred radicals · Radical cyclisation · Selenyl radicals · Silyl radicals · Sulphonyl radicals · Thiol–ene · Thiol–yne · Thiyl radicals

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1 Introduction

Five- and six-membered ring saturated heterocycles are key fragments that can be found in numerous compounds of natural sources, presenting potent biological activities. Tetrahydrofurans (THFs) and tetrahydropyrans (THPs) are recurrent motifs present in the skeleton of very complex compounds such as those depicted in Fig. 1. The complexity of these structures is highlighted by the presence of substituents at the different possible positions of the ring and by the relative configuration of the stereogenic centres. The aza-, thio- and seleno-analogues of THFs and THPs represent other important classes of compounds. For instance, the piperidine ring is present in many biologically active compounds (natural products and therapeutic agents), including iminosugars. The thiosugar analogues have been less studied. However, these carbohydrate analogues, where one or more oxygen atoms are substituted with sulphur, both in furanoside and pyranoside structures,

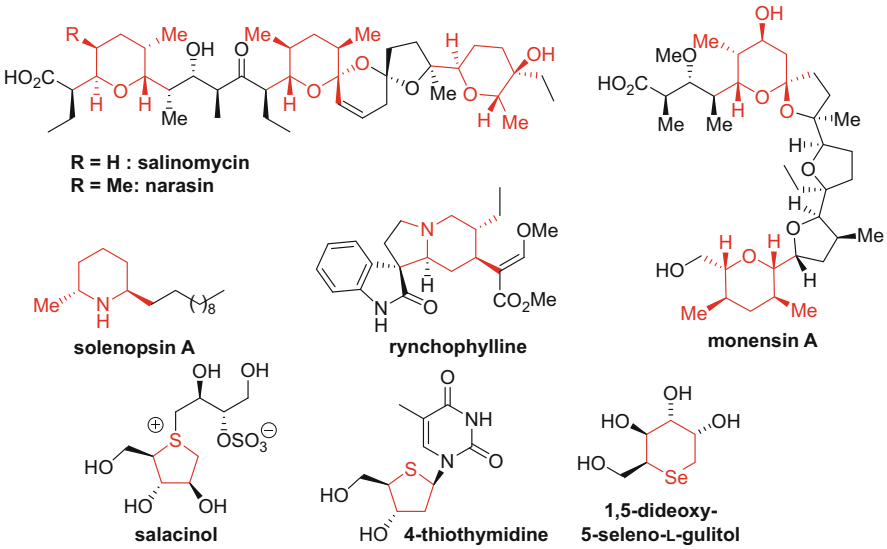


Fig. 1 Examples of biologically relevant saturated heterocycles

present unique conformational and electronic properties conferred by the presence of the sulphur atom. These compounds demonstrated potent biological activity as antiviral, antidiabetic and anticancer compounds. Organoselenium compounds can act as scavenger and inhibitors of reactive oxygen species (ROS), and as a result they present interesting antioxidant and anti-inflammatory activities (see, for instance, the 1,5-dideoxy-5-seleno-L-gulitol depicted in Fig. 1).

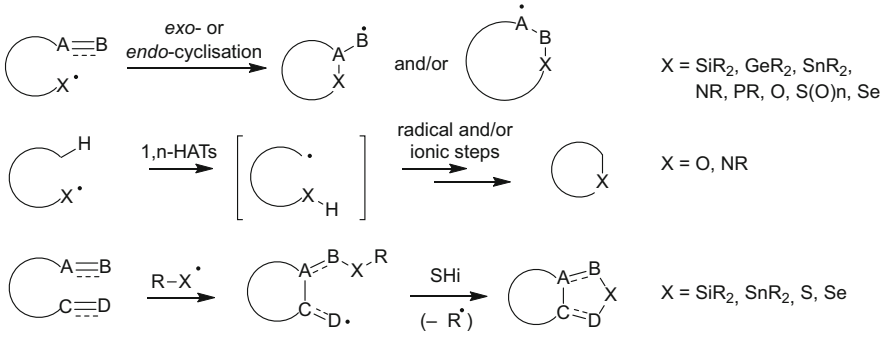
Several efficient synthetic methods have been reported for the preparation of heterocyclic compounds. Radical chemistry allows the formation of cyclic structures via the cyclisation of a radical species onto an unsaturated partner (e.g. alkene, alkyne, arene). The following chapter is focused on the generation and reactivity of heteroatom-centred radicals in the context of their cyclisation onto unsaturated acceptors (Scheme 1). The scope of this review has expanded to include cascade reactions initiated by the addition of a heteroatom-centred radical and eventually completed by the formation of the heterocycle via intramolecular homolytic substitution (S_Hi) at the heteroatom, as well as intramolecular hydrogen atom transfers (HAT) in heteroatom-centred radicals, which deliver heterocyclic structures after ionic cyclisation.

2 Group 14 (Silicon-, Germanium- and Tin-Centred Radicals)

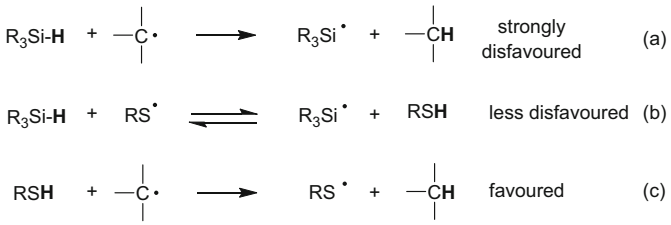
2.1 Formation of Heterocycles Involving Silyl Radicals

2.1.1 Generation of Silyl Radicals

The addition of organosilanes across C=C bonds has been achieved upon thermal or photochemical initiation [1], with peroxides, γ-irradiation or under polarity reversal catalysis conditions [2]. Silyl radicals can be generated by hydrogen atom abstraction from the Si–H bond. The latter is relatively strong in simple trialkylsilanes compared to the Sn–H or to the $(Me_3Si)_3Si$–H bonds [3–5]. The strength of the silicon–hydrogen bond strongly limits the use of trialkylsilanes as reducing agents



Scheme 1 Scope of the review

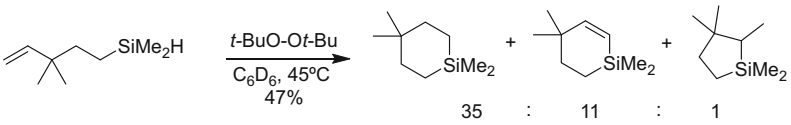


Scheme 2 Polarity reversal catalysis applied to the generation of silyl radicals

for carbon-centred radicals (Scheme 2, Eq. a) [6–10], but, as shown by Roberts and co-workers, this unfavourable step can be replaced by two more efficient steps, namely, the hydrogen atom abstraction by a thiyl radical (Scheme 2, Eq. b) and the reduction of a carbon-centred radical by the corresponding thiol (Scheme 2, Eq. c). Despite being slower than the reverse reaction [11], the hydrogen atom abstraction from organosilanes by thiyl radicals is particularly useful to generate silyl radicals, with rate constants in the range $k_{SH} = 10^4$–10^5 M^{-1} s^{-1} at 60°C (Scheme 2) [11]. The hydrogen atom abstraction from organosilanes by thiyl radicals benefits from favourable polar effects between the electrophilic thiyl radical and the nucleophilic silyl radical [12, 13], but low triplet repulsion between the two unpaired electrons on the heavy atoms has also been put forward to account for the small energy of activation [14]. Silyl radicals add rapidly onto unsaturated systems, including alkenes, displacing the equilibrium (Scheme 2, Eq. b) by leading to a new radical that is reduced by the thiol, thus making the overall process very efficient.

2.1.2 Intramolecular Hydrosilylation Reactions

The absolute rate constants for the intermolecular addition of Et_3Si• onto alkenes have been measured in the range 10^5–10^9 M^{-1} s^{-1} at 27°C [10, 15]. In contrast with the related addition of stannyl radicals to olefins, the addition process with silyl radicals is essentially irreversible, even at high temperature (140°C) [16]. Intramolecular additions have been achieved by treating alkenyldimethylsilanes with *tert*-butyl peroxide either upon photolysis or thermal initiation [17, 18]. Interestingly, pent-4-enylsilyl radical derivatives undergo highly selective 6-*endo*-trig cyclisation process (Scheme 3), in stark contrast with the related hex-5-enyl radicals [18, 19]. The high preference for the 6-*endo*-trig cyclisation mode can be attributed to the longer C–Si bond compared to the C–C bond, which forces the attack at the terminal position of the olefin due to stereoelectronic factors in the transition state. It was found that *tert*-butoxyl radical abstracts the hydrogen atom from the Si–H bond at a rate comparable to that of abstraction from the C–H bond at the allylic position. Therefore, the best results under these reaction conditions were obtained with substrates lacking allylic C–H bonds, such as the example depicted in Scheme 3 [18]. The rate constants for the cyclisation were estimated to lie in the range 10^7–10^9 s^{-1} at room temperature, and more accurate values could not be measured by the



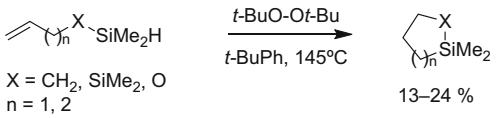
Scheme 3 *Endo*-cyclisation of silyl radicals

kinetic electron spin resonance method as the silyl radical could not be detected, even at very low temperature, suggesting a rapid cyclisation process [18].

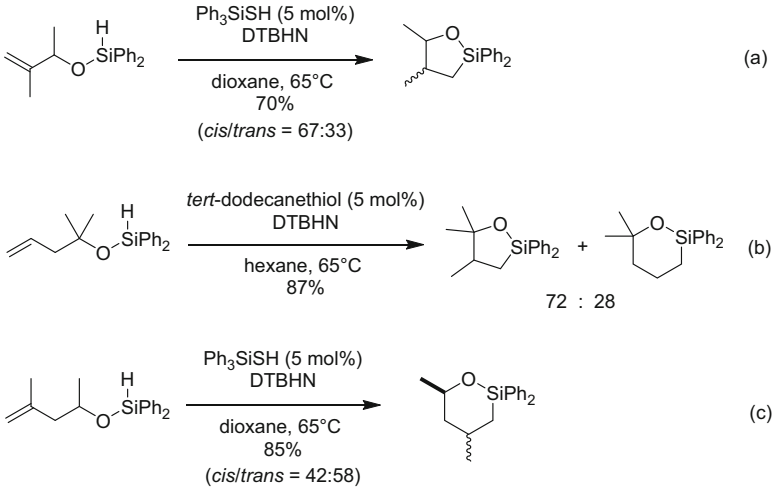
Surprisingly, the preference for the *endo*-cyclisation mode still applies for (3-butenyl)dimethylsilane and allyl-1,1,2,2-tetramethyldisilane, which both cyclise in a 5-*endo*-trig cyclisation mode, and for 4-(tetramethyldisilanyl)-1-butene and 4-(dimethylsiloxy)-1-butene, which both undergo 6-*endo*-trig cyclisation at 145°C in *tert*-butylbenzene in the presence of di-*tert*-butyl peroxide (Scheme 4) [19]. Based on calculations carried at the (UHF) MINDO/3 level of theory, the reversal of the regioselectivity, compared to that observed for more classical systems [20, 21], was attributed to an enthalpy factor caused by electronic effects [22].

Intermolecular hydrosilylation of alkenes with trialkylsilanes has been achieved at 60°C in the presence of sub-stoichiometric amounts of a thiol as the catalyst and di-*tert*-butylhyponitrite (DTBHN) as a radical initiator [23]. The addition of the silyl radical to the C=C bond must compete with the reversible addition of the thiyl radical. Arylsilanes proved to be amongst the most efficient, the adducts being obtained in good to high yields with only a slight excess of silane [24]. Intramolecular additions have been achieved under similar reaction conditions. For instance, alkenyloxysilanes derived from allylic and homoallylic alcohols undergo 5-*endo*-trig (Scheme 5, Eq. a) [25] and 5-*exo*-trig (or 6-*endo*-trig) cyclisation (Scheme 5, Eq. b–c), respectively, depending on the substitution pattern [26]. Rate constants have been estimated by EPR spectroscopy to be $\geq 10^6\ s^{-1}$ (60°C) for the cyclisation [26]. Seven-membered rings could also be prepared via a 7-*endo* cyclisation process [26]. Hydrogen atom abstraction at the allylic position of alkenyloxysilanes derived from allylic alcohols by the thiyl radical can compete with the desired hydrogen abstraction at the Si–H bond. In this context, silanethiols such as triphenylsilanethiol (Ph_3SiSH) or tri-*iso*-propylsilanethiol (*i*-Pr_3SiSH) were shown to give better results than *tert*-dodecanethiol.

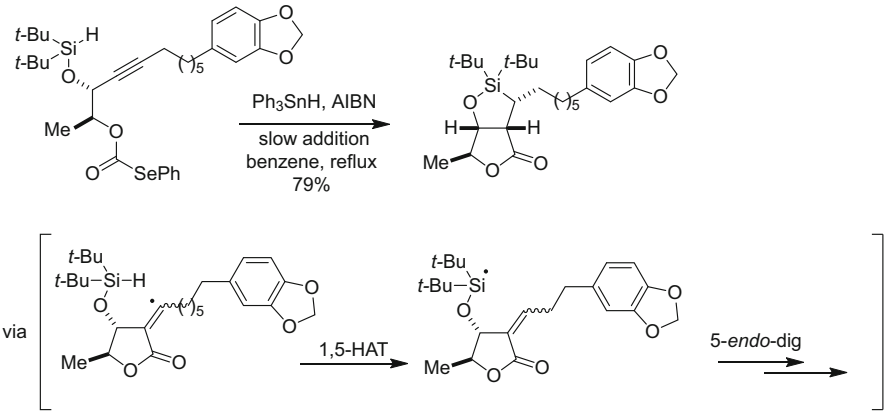
As previously mentioned, alkyl radicals are usually not reactive enough to abstract the hydrogen atom from the relatively strong Si–H bond in trialkylsilanes. By contrast, alkenyl radicals have been found to be capable of abstracting hydrogen atoms from alkoxysilanes, in an intramolecular manner. Clive and co-workers successfully used this approach for the preparation of polycyclic systems (Scheme 6) [27–31]. Interestingly, the use of xanthates, bromo- or seleno-precursors to achieve the initial 5-*exo*-dig radical cyclisation proved to be crucial as the silyl radicals obtained from the corresponding iodo-derivatives did not undergo 5-*endo*-trig cyclisation, but instead underwent halogen atom abstraction to give the iodosilane derivatives [32, 33]. In this case the iodosilanes were obtained with complete control of the configuration of the C=C bond.



Scheme 4 Regioselective 5- and 6-*endo*-cyclisation with silyl radicals



Scheme 5 Intramolecular hydrosilylation with silyl ethers under polarity reversal catalysis conditions



Scheme 6 Clive's approach to bicyclic lactones based upon 1,5-hydrogen atom transfer (HAT) at the silicon atom

The regioselectivity of the addition of silyl radicals onto other unsaturated systems, such as the C=N bond of imines, was also studied by computational methods [34–36].

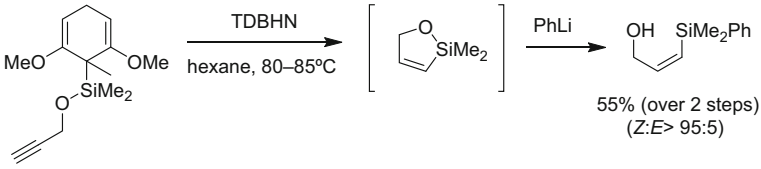
Studer developed an alternative method for the generation of silyl radicals based upon the use of cyclohexadienyl derivatives. This methodology was applied to intramolecular processes using allylic and propargylic silyl ethers. Owing to the instability of the cyclic vinylsilanes resulting from the cyclisation process, the heterocyclic compounds were converted in situ into more stable allylic alcohols by treatment with phenyllithium (Scheme 7) [37].

In this reaction the cyclohexadiene moiety plays the role of a hydrogen atom donor. The resulting cyclohexadienyl radical rearomatizes to give the corresponding arene and a silyl radical. The *endo* mode of cyclisation was demonstrated by running the intermolecular addition of the silyl radical onto a protected silyl ether, which delivered the vinylsilane as a mixture of stereoisomers [37]. Computational studies showed that multicomponent orbital interactions could explain unexpected regioselectivity in the cyclisation of silyl radicals [34].

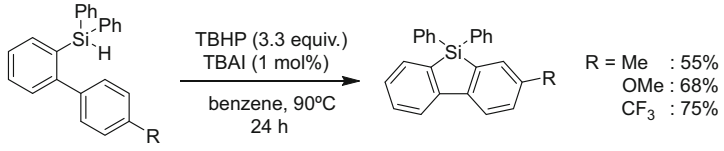
2.1.3 Aromatic Substitution with Silyl Radicals

Studer reported an efficient, metal-free route to 9-silafluorenes based upon the cyclisation of silyl radicals and observed that the presence of electron-withdrawing groups, as well as electron-releasing substituents on the aromatic group, is tolerated (Scheme 8) [38].

The formation of the silyl radical is achieved by hydrogen atom abstraction by an oxygen-centred radical. The latter is produced by reduction of *tert*-butylhydroperoxide (TBHP), a cheap oxidant used in excess. Amongst the different initiators tested, tetrabutylammonium iodide (TBAI) proved to give the best results. Hydrogen atom abstraction from the Si–H bond by the electrophilic *tert*-butoxyl



Scheme 7 Rare example of 5-*endo*-dig cyclisation involving silyl radicals

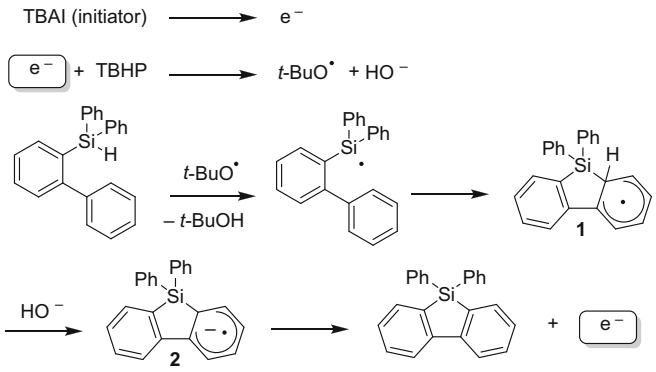


Scheme 8 Studer's approach to 9-silafluorenes

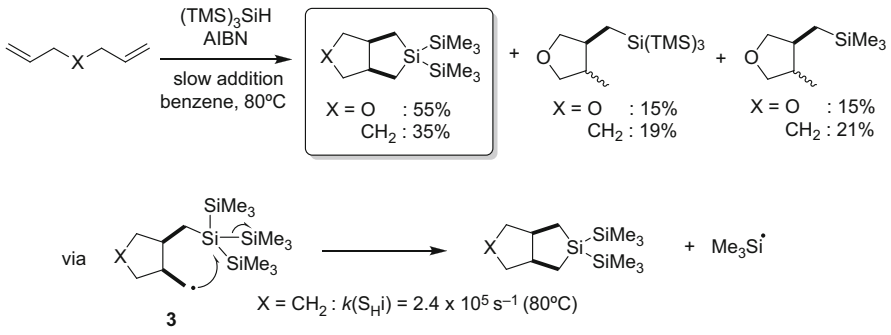
radical generates a silyl radical, which undergoes cyclisation onto the aromatic group to give radical **1**. Deprotonation of the acidic proton of **1** by the hydroxide anion leads to radical anion **2**, which acts then as an electron donor. In this process, the electron can be considered as a catalyst (Scheme 9).

2.1.4 Homolytic Substitution at Silicon

Another approach to silacarbocycles or sila-heterocycles relies on the intramolecular homolytic substitution (S_Hi) at the silicon atom. Cascade reactions involving the intermolecular addition of the tris(trimethylsilyl)silyl radical onto 1,6-dienes [39–42] and 1,6-enynes [40, 41], followed by 5-*exo*-trig cyclisation and subsequent S_Hi reaction at silicon, have been reported. Under diluted conditions, the aforementioned S_Hi process at silicon competes favourably with the intermolecular hydrogen atom abstraction from the silane. A high rate constant of 2.4×10^5 s^{-1} (80°C) was determined by Chatgilialoglu and Giese for the cyclisation of **3** (Scheme 10) [39],



Scheme 9 Mechanism of the preparation of 9-silafluorene under Studer's conditions



Scheme 10 Silyl radical-mediated cyclisation of 1,6-dienes, followed by S_Hi at the silicon atom

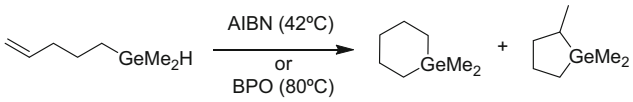
indicating that such intramolecular pathways leading to the cleavage of a Si–Si bond are relatively fast, in agreement with calculations made by Matsubara and Schiesser [43]. Efficient S_Hi processes at the silicon atom involving carbon-centred radicals generated from B-alkylcatecholboranes have also been reported [44].

2.2 Cyclisation of Germyl Radicals

Radical reactions based upon the use of germyl radicals [17] have been studied since the 1960s, but, despite their synthetic potential, research in this field has yet to gain traction. Tri-*n*-butylgermane Bu_3GeH has been used to achieve dehalogenation reactions. The homolytic substitution reaction at halogen and chalcogen atoms tends to be faster with the tri-*n*-butylgermyl radical than with the corresponding stannyl radical, with absolute rate constants being about one order of magnitude higher for reactions with sulphides and selenides [45]. Tri-*n*-butylgermane, however, is less reactive than nBu_3SnH in the hydrogen abstraction steps by alkyl radicals, and this can be advantageous when attempting cyclisation or cascade reactions [46–48]. Like tri-*n*-butylstannyl radical, germyl radicals are nucleophilic. As a result, one of the limitations to the use of tri-*n*-butylgermane is the high reactivity of germyl radical towards unsaturated systems, in combination with the fact that the addition of a germyl radical onto a C=C bond is an irreversible process at room temperature [16]. This precludes tri-*n*-butylgermane from being used at this temperature for reactions in which homolytic substitution does not compete favourably with the intermolecular addition process. However, in contrast with silyl radicals, the reversibility of the addition of germyl radicals has been observed at higher temperatures.

The cyclisation of alkenyldimethylgermyl radicals has been briefly mentioned in the literature. Mochida and Asami reported in the early 1980s the first examples of intramolecular addition of germyl radicals [49]. Germane derivatives underwent cyclisation in low to good yields, predominantly or exclusively in an *endo* mode. This process allows for the synthesis of germanium containing heterocycles, such as germacyclopentane, germacyclohexane, germacycloheptane and germacyclooctane derivatives (Scheme 11).

Although numerous reports on the preparation of germanium-containing heterocycles have appeared in the literature, and despite the mild reaction conditions, the use of free radicals to form these cyclic skeletons is still underexploited compared to



Scheme 11 Highly regioselective 6-*endo*-trig cyclisation of germyl radicals

other approaches such as the transition metal-catalysed C–H activations [50] or reaction of bimetallic species with dialkyldichlorogermane [51].

2.3 Tin-Centred Radicals

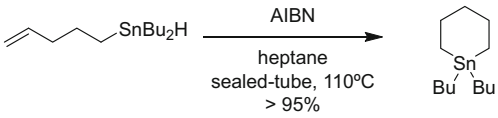
2.3.1 Cyclisation of Tin-Centred Radicals

Despite being widespread in the intermolecular approach, the reversible olefin hydrostannation process [52] has only been rarely used to access stannacycloalkanes. In the late 1980s, Issleib reported examples of intramolecular hydrostannation initiated by thermal decomposition of AIBN in refluxing benzene. Under these reaction conditions, the process was low-yielding, and 1-stanna-bicycloalkanes were obtained only as side products, together with polymeric compounds [53]. Later, Jousseaume and co-workers showed that an excellent yield could be obtained for the preparation of stannacyclohexane when a solution of 4-pentenyldibutyltin in heptane was heated at 110°C in a sealed tube, in the presence of AIBN (Scheme 12) [54]. The exclusive formation of the six-membered ring via a 6-*endo* mode can be explained by the larger radius of tin and the longer C–Sn bond compared to the C–C bond and/or by the reversibility of the addition process. However, the reaction proved to be quite limited in scope as precursors with shorter or longer alkenyl chains led to the corresponding cyclic stannacycloalkanes in only low yields.

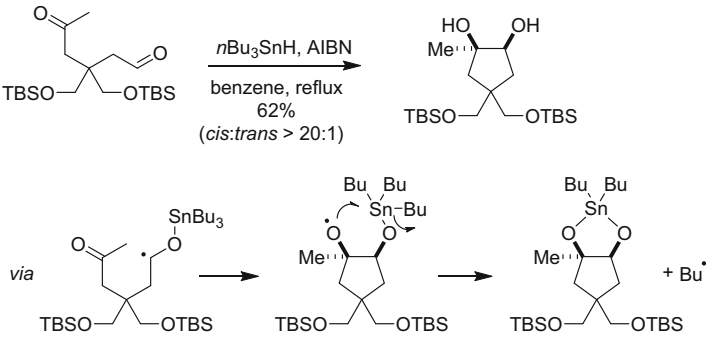
2.3.2 Homolytic Substitution at the Tin Atom

Examples of intramolecular homolytic substitution (S_Hi) at the tin atom are exceedingly rare. Fu reported the preparation of 1,3,2-dioxastannolanes (precursors of vicinal diols) via a radical pinacol coupling reaction mediated by nBu$_3$SnH in the presence of AIBN or under irradiation with UV light. A mechanistic rational involving the homolytic substitution at the tin atom, with concomitant release of a butyl radical, was postulated to account for the formation of the observed 1,2-diols (Scheme 13) [55].

The more stable stannolanes have been obtained from the corresponding 1,6-enynes. Kamimura and co-workers reported that the addition of the



Scheme 12 Highly regioselective 6-*endo*-trig cyclisation of a stannyl radical



Scheme 13 Preparation of 1,3,2-dioxastannolanes via S_Hi at the tin atom

tributylstannyl radical onto *N*-propargylated aza-Morita–Baylis–Hillman adducts led to bicyclic stannolanes in high yields (Scheme 14) [56, 57]. S_Hi at the tin atom in cascade reactions involving 1,6-dienes and tributylstannyl radical have also been observed [42].

3 Group 15 (N- and P-Centred Radicals)

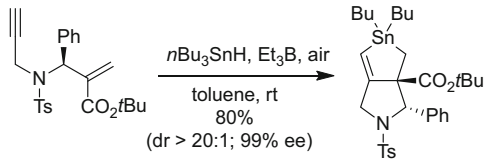
3.1 Nitrogen-Centred Radicals

Nitrogen-centred radicals [58] can add onto unsaturated systems [59] or abstract a hydrogen atom from electron-rich C–H bonds. The reactivity will be discussed here in the context of the formation of heterocyclic structures. The formation of cyclic imines, quinoxalines and related systems can be realised through the cyclisation of iminyl radicals, while pyrrolidinones and related lactams can be obtained via the intervention of amidyl radicals [60].

The methods used for the generation of nitrogen-centred radicals, such as aminyl, hydrazonyl, iminyl and amidyl radicals, together with their reactivity and application in organic synthesis, have been collected in a comprehensive review in 2008 [61], as well as more recently in several more specific reviews [60, 62, 63]. The discussion will be limited here to a brief overview of the existing methods, with an emphasis on the more recent developments in the burgeoning field of photoredox catalysis.

3.1.1 Aminyl and Hydrazonyl Radicals: Cyclisation onto Unsaturated C–Y Bonds (Y = C, N, O)

Aminyl radicals can be generated by addition of a radical species onto the carbon atom of a carbon–nitrogen double bond, by reduction of azides with nBu$_3$SnH or by



Scheme 14 Kamimura's approach to bicyclic stannolanes via S_Hi at the tin atom

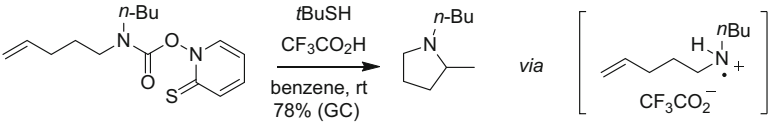
homolytic cleavage of a relatively weak nitrogen–heteroatom bond [60–63]. Neutral aminyl radicals can also be produced by oxidation of the corresponding lithium amides [64]. Along the same line, more electrophilic aminium radical cations can be obtained directly from the parent amines under very mild oxidative conditions [65], which also allows for the generation of the related hydrazonyl radicals.

The intramolecular addition of aminyl radicals onto unsaturated C=C bonds allows for a rapid access to heterocyclic structures [66]. Neutral aminyl radicals are weakly nucleophilic, and thus they are not prone to undergo rapid addition onto electron-rich olefins [59, 67, 68]. A rate constant of 1×10^4 s^{-1} (50°C) has been determined for the 5-*exo*-trig cyclisation of the neutral *N*-butyl-4-pentenaminyl radical [68], while the corresponding *N*-butyl-4-pentenaminium radical cation cyclises about a hundred times faster (k_c = ca. 1×10^6 s^{-1}) [69]. Accordingly, the aminyl radical generated from *N*-hydroxypyridine-2-thione carbamate depicted in Scheme 15 failed to cyclise onto the C=C bond in the presence of a good hydrogen atom donor such as *tert*-butanethiol, while the corresponding aminium radical cation (formed in the presence of trifluoroacetic acid) underwent 5-*exo*-trig cyclisation smoothly, giving the pyrrolidine derivative in good yield (Scheme 15) [70]. Perhydroindoles and pyrrolizidines have also been prepared using this approach [70]. The 5-*exo*-trig cyclisation can be facilitated by the presence of a phenyl substituent at the alkenyl side chain, which results in a dramatic increase in the cyclisation rate [67, 68, 71]. Similar radical cyclisation processes proved to proceed smoothly in CH_2Cl_2 or THF, even at −78°C, provided that the reactions are performed in the presence of a Lewis acid such as $LiBF_4$, $MgBr_2$ or BF_3, in order to make the nitrogen-centred radical more electrophilic [71].

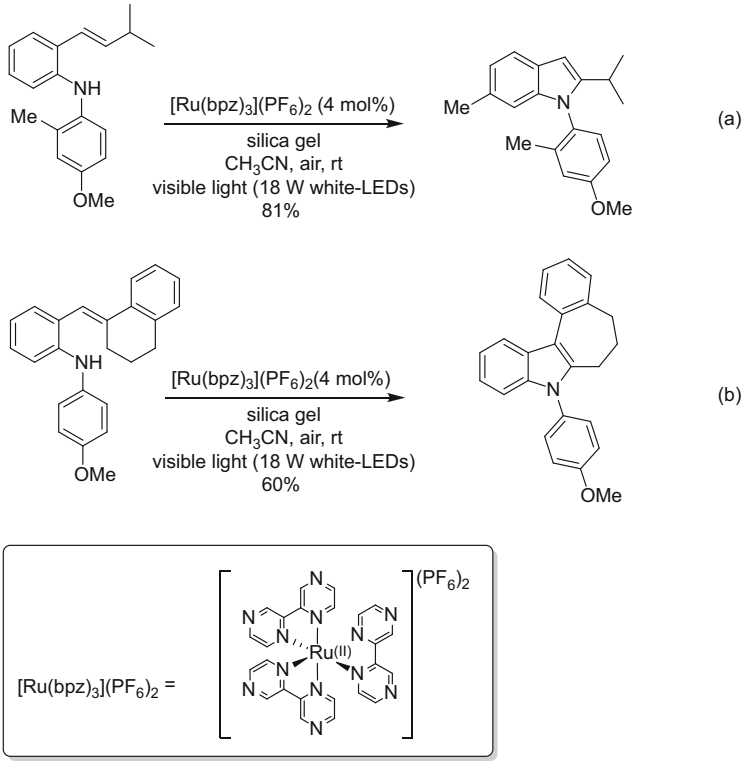
The same type of aminium radical cations can be obtained in the absence of a proton source by one electron oxidation of secondary amines under visible light photoredox catalysis conditions. Indeed, it is well known that tertiary amines can be used as sacrificial donors in reactions carried out in the presence of a photocatalyst. Depending on their structures, the resulting aminium radical cations can follow different pathways. The most common are the formation of iminium ions by hydrogen atom abstraction, the conversion into the α-amino radical by deprotonation and the fragmentation that releases a carbon-centred radical. In the presence of a C=C bond, aminium radical cations can also undergo classical radical addition processes. Zheng and co-worker showed that polysubstituted indoles can be easily obtained from styryl anilines upon irradiation in the presence of catalytic amounts of tris(2,2′-bipyrazine)ruthenium(II) bis(hexafluorophosphate) ($[Ru(bpz)_3](PF_6)_2$) in

an open-air reaction vessel. Following a 5-*endo*-trig cyclisation process, aromatisation occurs either via direct deprotonation (Scheme 16, Eq. a) or via a sequence involving a 1,2-carbon shift followed by deprotonation (Scheme 16, Eq. b) [72].

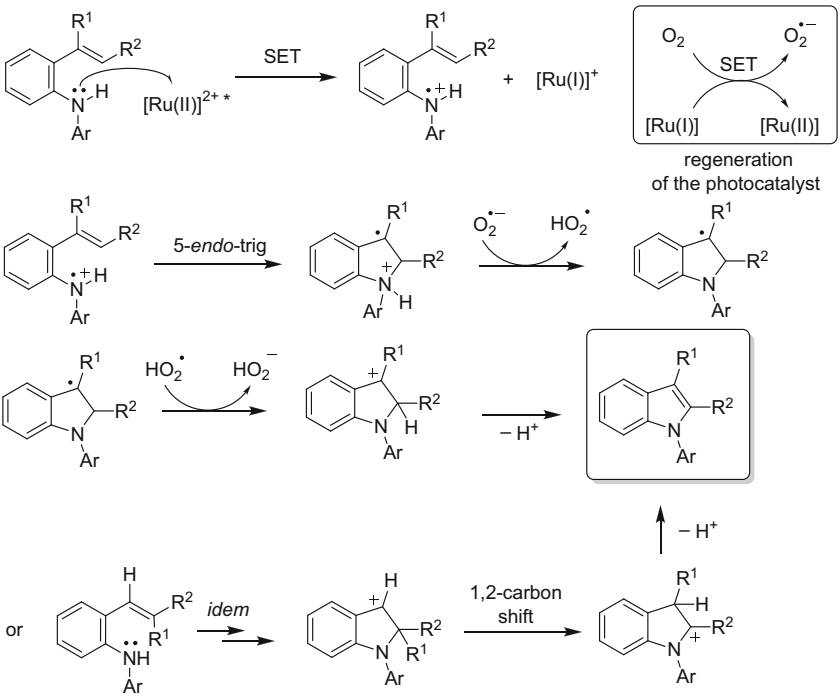
Under these very mild reaction conditions, the secondary amine is converted into the corresponding aminium radical cation, which undergoes 5-*endo*-trig cyclisation. The resulting benzylic radical is then oxidised to give a benzylic carbocation, which eventually delivered the aromatised product via direct deprotonation or sequential 1,2-carbon shift and deprotonation (Scheme 17). The synthesis of indoles via a related cascade reaction involving 4-*exo*-trig cyclisation of aminyl radicals generated



Scheme 15 Preparation of pyrrolidines via the cyclisation of aminium radical cations



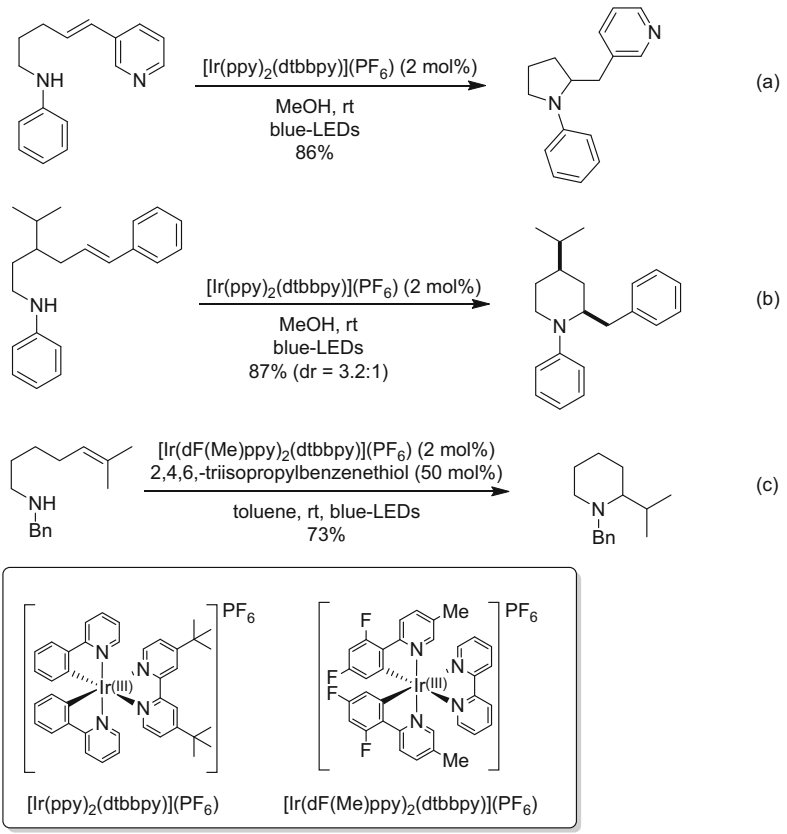
Scheme 16 Synthesis of polysubstituted indoles under photoredox catalysis conditions



Scheme 17 Proposed reaction mechanism for the preparation of indoles under Zheng's photoredox catalysis conditions

under oxidative conditions onto an aromatic group, followed by rearrangement, has also been reported [73].

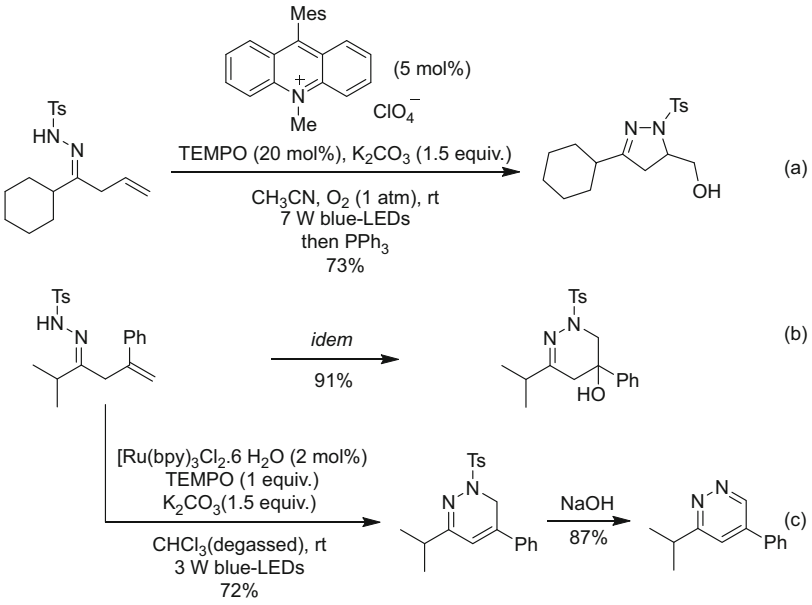
Similarly, Knowles and co-workers showed that *N*-aryl-5-aryl-4-pentenylamines and *N*-aryl-6-aryl-5-hexenylamines can be converted into the corresponding pyrrolidines and piperidines, respectively, in high yields in the presence of an iridium(III) photocatalyst (Scheme 18, Eqs. a, b) [74]. In this case, the use of a strongly reducing species (the photocatalyst in its reduced iridium(II) state) allows for the regeneration of the iridium(III) photocatalyst by SET to the benzylic radical, which is then converted into the corresponding benzylic carbanion. The latter is trapped with the proton released in the process to give the final product. Interestingly, these very mild reaction conditions allowed for the challenging 6-*exo*-trig cyclisation to outcompete the hydrogen atom abstraction from the allylic position. The scope of the reaction has been extended to include non-aromatic amines, offering a more general route to diversely substituted pyrrolidines (via 5-*exo*-trig cyclisation) and piperidines (via either 6-*endo* or 6-*exo*-trig cyclisation processes) [65]. In this case, a thiol is used as a hydrogen atom donor to trap the carbon-centred radical resulting from the cyclisation process, and the photocatalyst is regenerated by SET to the thiyl radical (Scheme 18, Eq. c).



Scheme 18 Preparation of pyrrolidines under Knowles' photoredox catalysis conditions

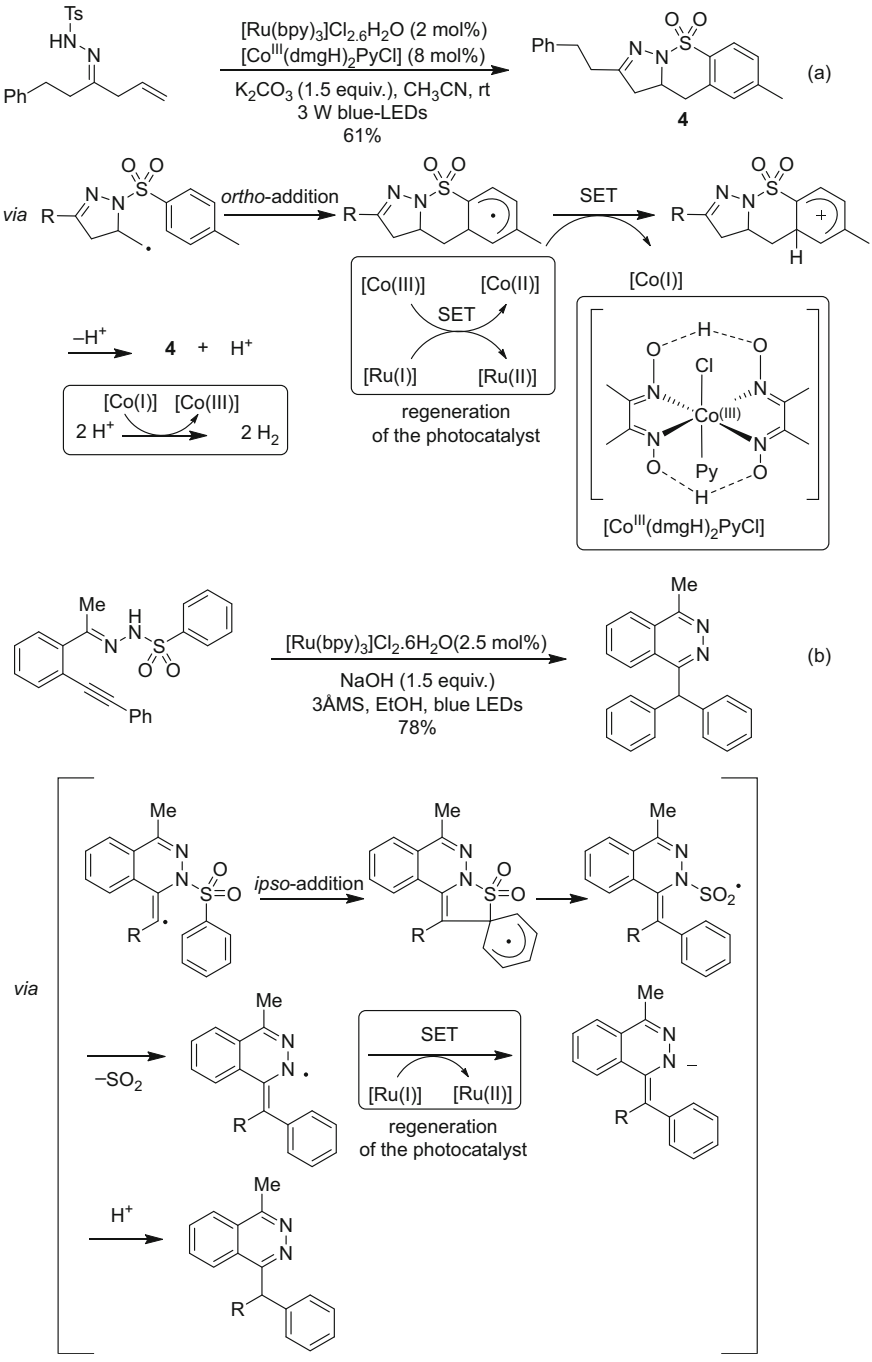
Chen, Xiao and co-workers reported the extension of this process to hydrazones as precursors for the radical cyclisation [75–78]. The hydrazonyl radical is generated by an oxidative process in the presence of a photocatalyst (such as an iridium (III) or ruthenium(II) complex or 9-mesityl-10-methylacridinium perchlorate) in a very similar manner as for the generation of aminium radical cations. Intramolecular addition onto a C=C bond, either in a 5-*exo*-trig or 6-*endo*-trig manner, leads to a carbon-centred radical, which can then be trapped by a hydrogen atom donor [75], engages in intermolecular carbon–carbon bond-forming reactions [78], reacts with TEMPO to give the oxyamination products (Scheme 19, Eqs. a, b) [76] or alternatively undergoes oxidation into the corresponding carbocation to ultimately give dehydrogenated products such as 1,6-dihydropyridazines (Scheme 19, Eq. c). The latter can then easily be transformed into the corresponding diazinium salts [77].

In the absence of stoichiometric oxidant or external radical trap, the outcome for carbon-centred radicals can be slightly different. The fate of the carbon-centred radical resulting from the cyclisation process strongly depends upon both the structure of the hydrazone precursor and the reaction conditions. For instance,



Scheme 19 Generation of hydrazonyl radicals and regioselectivity of their cyclisation under photoredox catalysis conditions

Chen, Xiao and co-workers showed that the trapping of the radical could be achieved in an intramolecular manner by addition onto the aromatic substituent (*N*-tosyl group). By using a dual catalytic system composed of sub-stoichiometric amounts of $[Ru(bpy)_3]Cl_2{\cdot}6H_2O$ and chloro(pyridine)*bis*(dimethylglyoximato)cobalt(III) ($[Co(III)(dmgH)_2PyCl]$) complexes, dihydropyrazole-fused benzosultams **4** can be obtained (Scheme 20, Eq. a) [79]. In this catalytic system, deprotonation of the starting hydrazone followed by SET to the photoexcited [Ru(II)]* species gives the hydrazonyl radical and the reduced form of the photocatalyst. Following 5-*exo*-trig cyclisation, the resulting carbon-centred radical is then trapped by intramolecular addition at the *ortho* position of the aromatic group. The resulting radical is proposed to be oxidised by the cobalt(II) species resulting from a former SET between the [Co (III)] and the [Ru(I)] species, which allows for the regeneration of the photocatalyst. Aromatisation of the carbocation formed in this oxidation process gives the final dihydropyrazole-fused benzosultams **4**. The reduced [Co(I)] species is suggested to be reoxidised into its [Co(III)] form by two SET processes, which generate H_2 from the protons liberated during the rearomatisation step. This mechanistic rational is supported by the detection of H_2 by gas chromatography (Scheme 20, Eq. a). Trapping of the carbon-centred radical resulting from the cyclisation of a hydrazonyl radical by *ipso*-substitution at the *N*-arenesulphonyl group has been observed in related systems. Brachet, Belmont and co-workers showed that alkenyl radicals resulting from the related 6-*exo*-dig cyclisation process undergo a Smiles rearrangement. Following this radical cascade, phthalizine derivatives were obtained



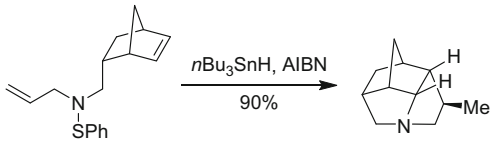
Scheme 20 Preparation of dihydropyrazole-fused benzosultams (Eq. a) and phthalizine derivatives (Eq. b) in the presence of photocatalysts

in moderate to high yields (Scheme 20, Eq. b) [80]. One-pot processes that include the formation of the hydrazone precursors from the ketone in situ have also been reported [80].

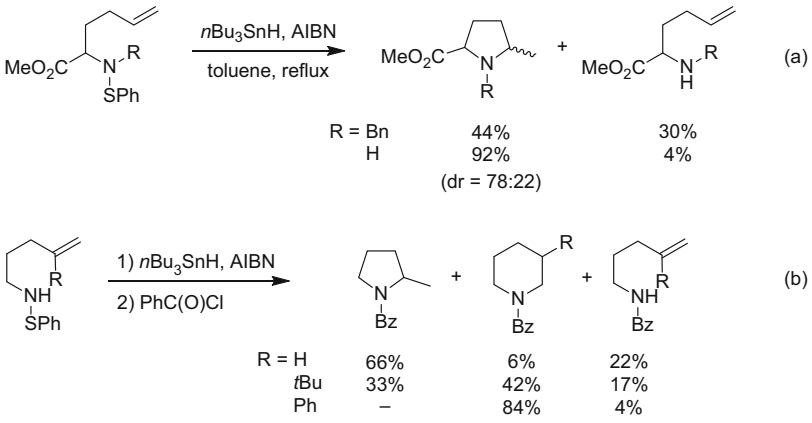
Although kinetically unfavourable and despite the fact that the reaction has been shown to be reversible [64, 70, 81, 82], the cyclisation of neutral aminyl radicals has nevertheless been successfully used for the preparation of cyclic products. Bowman developed an easy access to pyrrolizidine and indolizidines based upon the use of sulfenamides (Scheme 21) [83–86].

The presence of an electron-withdrawing group close to the nitrogen atom renders the aminyl radical more electrophilic, thus making the cyclisation more efficient [87]. Bowman also showed that aminyl radicals derived from primary amines are more electrophilic than the corresponding *N*,*N*-dialkylaminyl radicals (Scheme 22, Eq. a) [87]. These observations have been confirmed more recently by Li and co-workers who studied the cyclisation of primary aminyl radicals using both experimental and computational approaches [88]. Depending on both the steric and electronic nature of the substituent at the internal position of the alkenyl moiety, the regioselectivity can be driven towards either the 5-*exo* or the 6-*endo* modes (Scheme 22, Eq. b) [88].

The presence of a substituent at the terminal position of the alkene capable of stabilising the carbon-centred radical obtained after the cyclisation process results in



Scheme 21 Tin-mediated cyclisation of neutral aminyl radicals obtained from sulfenamides

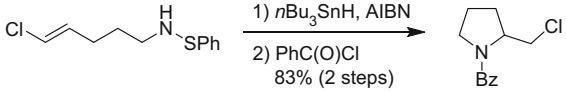


Scheme 22 Substituent effects in the cyclisation of neutral aminyl radicals

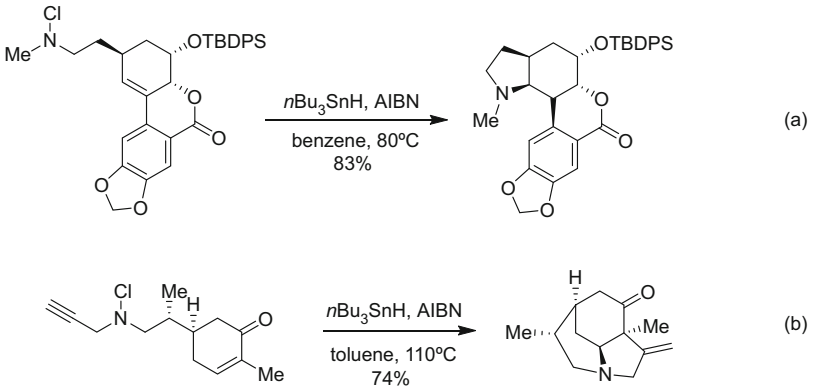
a significant increase both in the yields and regioselectivity. For instance, a complete regioselectivity in favour of the *exo*-cyclisation products was observed in the cyclisation onto vinyl chlorides (Scheme 23) [88] or silyl enol ether moieties [89–91].

Chloroamines can be easily prepared by reaction of the free amine with *N*-chlorosuccinimide (NCS). The cyclisation onto alkenes and arenes can be carried out in acidic media in the presence of a reducing metal salts such as Fe(II) [92], Cu (II) or Ti(III) [93–95]. Under these conditions, cyclised products resulting from the chlorine atom transfer are obtained (see Scheme 25). Neutral aminyl radicals can be generated upon heating in the presence of nBu$_3$SnH and AIBN, giving access to pyrrolidines in good to high yields. Cascade reactions have been designed to prepare polycyclic structures such as pyrrolizidines [96] or aza-triquinanes [94]. The efficiency of the 5-*exo*-trig radical cyclisation process with neutral aminyl radical is illustrated by the preparation of an advanced intermediate for the synthesis of C11b-epi-(+)-clividine (Scheme 24, Eq. a) [97]. The analogous 6-*exo*-trig cyclisation is somewhat more difficult to achieve due to competitive hydrogen atom abstraction from the allylic position [87]. Nevertheless, efficient 6-*exo*-trig cyclisation processes have been successfully achieved in some rigid systems, as shown by Stockdill and co-workers who developed a rapid access to the heterocyclic core of calyciphylline A and daphnicyclin A (Scheme 24, Eq. b) [98]. In this case the presence of a carbonyl group conjugated with the C=C bond proved crucial in order to ensure good yield for the cyclisation, as the corresponding allylic alcohol failed to give the cyclised compound. Interestingly, the authors showed that the reaction could also be achieved in the absence of nBu$_3$SnH [99].

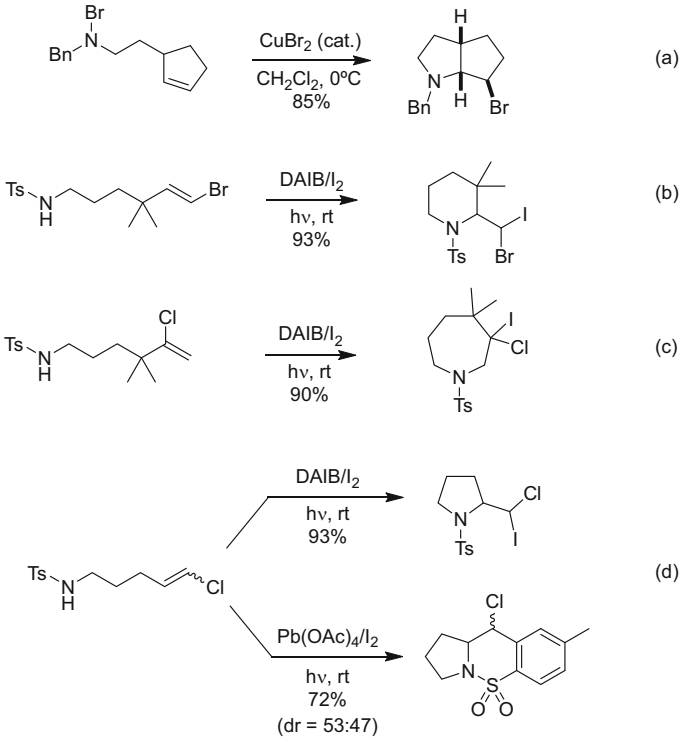
As previously mentioned, unsaturated haloamines (X = Cl, Br, I) also undergo cyclisation under mild, tin-free conditions (sometimes at temperatures as low as −78°C) upon irradiation or in the presence of a catalyst such as $CuBr_2$. Under these reaction conditions, the atom transfer cyclisation products are obtained in high yields (Scheme 25, Eq. a) [100]. Iodoamines are too unstable to be isolated, and they need to be prepared in situ by treatment of the parent amine with a mixture of $Pb(OAc)_4$ or (diacetoxyiodo)benzene (DAIB) and iodine. Li and co-workers showed that the regioselectivity of the cyclisation process can be controlled by the presence of a halogen atom at the C=C bond, giving access to *gem*-dihalogenated derivatives in high yields (Scheme 25, Eqs. b, c) [101]. Interestingly, the course of the reaction can be modified by using $Pb(OAc)_4/I_2$ in refluxing 1,2-dichloroethane. In this case, cyclisation of the carbon-centred radical intermediate onto the aromatic ring of the tosyl protecting group occurs, giving access to tricyclic structures (Scheme 25,



Scheme 23 Regioselective 5-*exo*-trig cyclisation of neutral aminyl radicals onto chloroalkenes



Scheme 24 Cascade reactions applied to the synthesis of C11b-epi-(+)-clividine (Eq. a) and approach to the core of calyciphylline A (Eq. b)



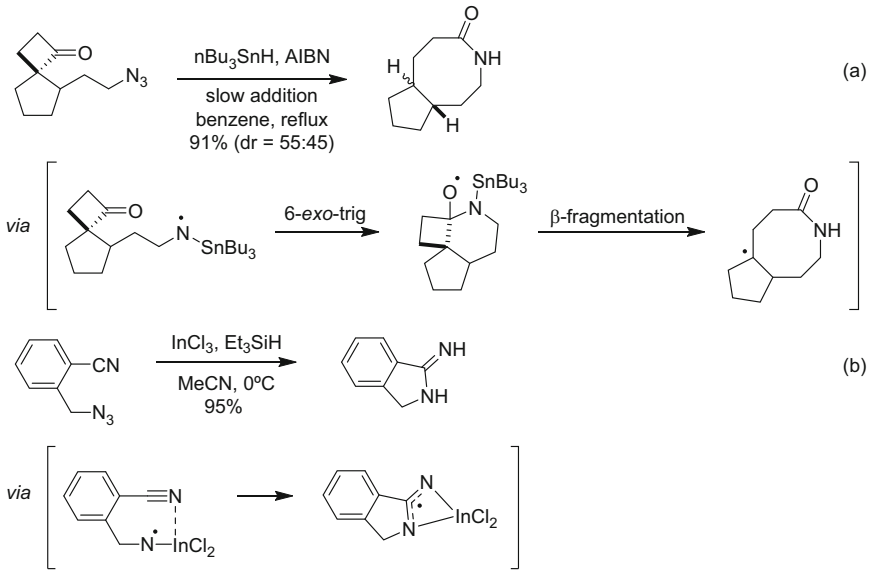
Scheme 25 Regioselectivity of the cyclisation of haloamines under radical conditions

Eq. d) [101]. Related radical cascades with anilines under oxidative conditions have also been reported [102, 103].

As mentioned in the introduction, aminyl radicals can be obtained by reduction of organic azides with nBu$_3$SnH. The addition of aminyl radicals onto aldehydes and ketones leads to very reactive oxygen-centred radical intermediates. Although this process is thermodynamically unfavourable, the subsequent rapid β-fragmentation via the cleavage of the carbon–carbon bond results in the formation of a more stable carbon-centred radical as well as in a resonance stabilised amide group. Kim and co-workers applied this strategy to cycloalkanones, offering an access to medium-sized ring lactams via a ring expansion process (Scheme 26, Eq. a) [104, 105]. Slow addition technique is required to prevent the early reduction of the oxygen-centred radical prior to fragmentation. As expected, the fragmentation process is particularly efficient with small-sized ring cycloalkanones such as cyclobutanone derivatives, for which the initial ring strain is important. Both 5-*exo*-trig and 6-*exo*-trig cyclisation take place efficiently [105]. Under similar reaction conditions, aminyl radicals generated from azides also add onto nitriles to give iminyl radical intermediates (Scheme 26, Eq. b) [106, 107].

3.1.2 Iminyl Radicals

Iminyl radicals (and related species) can be obtained from a variety of precursors, such as sulfenimines, *N*-chloroimines, *N*-benzotriazolimines, oxime ethers and carbonyl oxime derivatives [108]. Alternatively, they can also be generated by addition of a radical species onto nitriles. The discussion that follows is limited to a brief



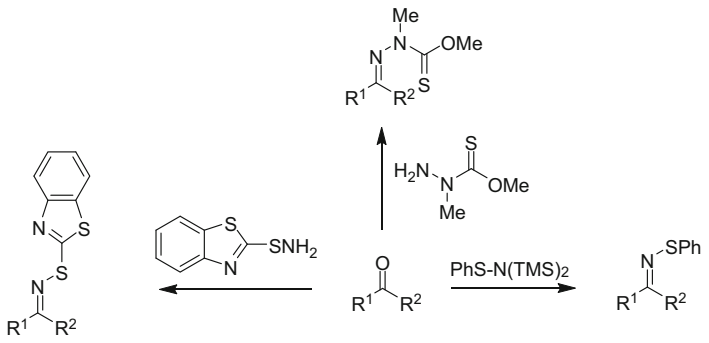
Scheme 26 Kim's ring expansion approach to medium-sized ring lactams from ketoazides (Eq. a) and Bencivenni and Nanni's approach to pyrrolidin-2-imines (Eq. b)

overview of the chemistry of iminyl radicals applied to the preparation of heterocyclic structures, from the early development to the most recent advances [59, 61, 63, 109–112].

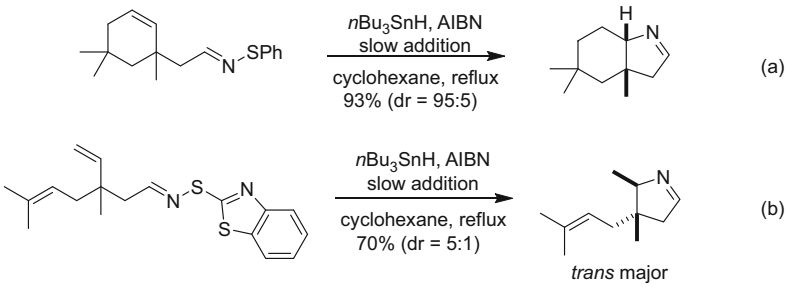
Depending on the structure of the radical precursors, iminyl radicals can be generated in the presence of nBu$_3$SnH or under tin-free conditions, such as thermal or photochemical initiation (irradiation with UV light or visible light), initiation under oxidative conditions or in the presence of a transition metal. Irrespective of the method chosen for their formation, iminyl radicals can undergo either hydrogen atom abstraction, fragmentation to give nitriles or cyclisation onto unsaturated system (alkenes, alkynes and arenes), typically in a 5-*exo* or 6-*endo* modes. Examples of 5-*endo* and 6-*exo* cyclisation processes have also been reported. The cyclisation of iminyl radicals onto C=C bonds is relatively slow, with rate constants about 1×10^4 s^{-1} (27°C) for a typical 5-*exo*-trig cyclisation onto terminal alkene [110, 113], but the rate of cyclisation can be significantly enhanced by the use of *gem*-diphenyl-substituted alkenes [114].

S-Phenylsulfenylimines and carbazones are prepared by condensation of ketones and aldehydes with *N*,*N*-*bis*(trimethylsilyl)phenylsulfenamide and thiosemicarbazide, respectively (Scheme 27) [115]. 2-Benzothiazolyl-sulfenylimines are prepared by condensation of the carbonyl derivatives with 2-benzothiazolyl-sulfenamide, a crystalline solid obtained from 2-mercaptobenzothiazole, ammonia and sodium hypochlorite [116].

These precursors lead to iminyl radicals upon heating in the presence of nBu$_3$SnH and AIBN. Unsaturated precursors undergo cyclisation to give the corresponding cyclic imines in good yields, provided that the concentration of tin hydride is maintained sufficiently low in order for the cyclisation to compete favourably with the hydrogen atom abstraction from chain carrier reagent. Zard and co-workers showed that monocyclic 1-pyrroline derivatives as well as fused- and spiro-bicyclic pyrrolines could be efficiently prepared with this methodology (Scheme 28). The carbon-centred radical resulting from the cyclisation process can be trapped in an intermolecular manner by addition onto electron-poor alkenes [109].



Scheme 27 Some sources of iminyl radicals

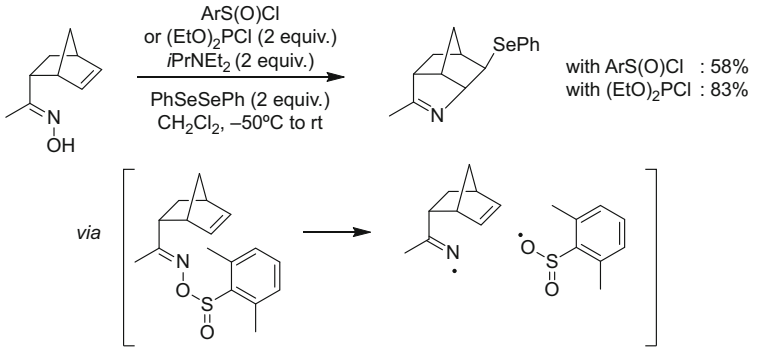


Scheme 28 Zard's cyclisation reaction to access pyrrolines from sulfenylimines

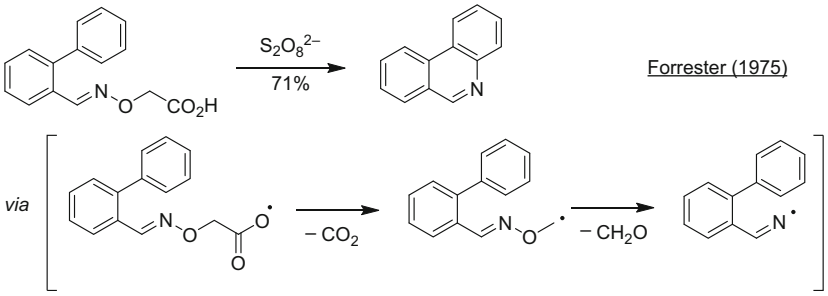
Inspired by the seminal work of Hudson who showed that unstable *O*-sulfinylated oximes spontaneously rearrange into the corresponding *N*-sulfonylimines via a radical mechanism [117], Weinreb and co-workers developed an elegant cyclisation based upon the generation of iminyl radicals from simple oximes in situ [118–120]. Upon treatment with 2,6-dimethylbenzenesulfinyl chloride in the presence of Hünig's base, aldoximes and ketoximes are converted at low temperature into the unstable sulfinate esters, which undergo N–O bond cleavage upon warming to room temperature. The iminyl radical intermediate either recombine with the sulphonyl radical to give the *N*-sulfonylimines, as observed by Hudson, or undergo cyclisation onto a C=C bond. The resulting carbon-centred radical can be trapped with various radical traps such as TEMPO, PhSeSePh, PhSSPh and 1,4-cyclohexadiene (CHD) (Scheme 29). Amongst the various sulfinyl chlorides tested, the best results were obtained with the bulky 2,6-dimethylbenzenesulfinyl chloride, which allows to slow down the radical recombination process leading to *N*-sulfonylimines. Diethyl chlorophosphite also promotes the transformation of oximes into iminyl radicals, and, in most cases, the yields were found to be even slightly higher than those with sulfinyl chlorides [120]. The reaction, however, is limited to reasonably rapid 5-*exo*-trig cyclisation processes, and attempts to extend this methodology to the preparation of six-membered rings were unsuccessful. Interestingly, the same strategy allows for the preparation of amidyl radicals from simple hydroxamic acids [120].

In the 1970s Forrester and co-workers showed that oximinoacetic acid derivatives lead to iminyl radicals in the presence of persulfate. The initial carboxyl radical undergoes fragmentation with loss of CO_2 to give an oximinomethyl radical, which in turn fragments to give formaldehyde and an iminyl radical. The latter can undergo cyclisation onto an adjacent aromatic group to produce phenanthridine derivatives (Scheme 30) [121].

Following the seminal work of Forrester, Zard [122, 123] and very recently Studer [124] and Leonori [125, 126] reported successive improvements of this reaction (Scheme 31, Eqs. a–c). The reaction conditions developed independently by the groups of Studer and Leonori are extremely mild, and they offer the possibility to achieve cascade reactions. For instance, Leonori showed that the carbon-centred radical resulting from the cyclisation of the iminyl radical intermediate can



Scheme 29 Weinreb's strategy using oximes as convenient sources of iminyl radicals

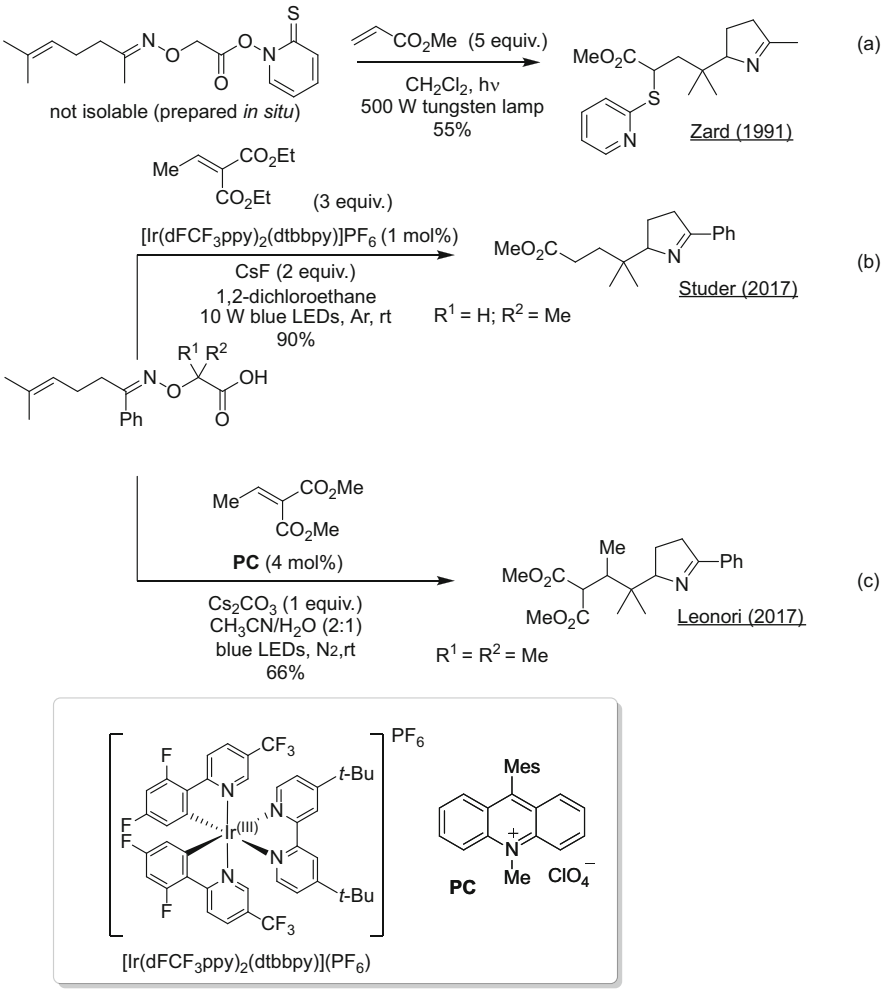


Scheme 30 Forrester's seminal work for generation of iminyl radicals from oximinoacetic acid derivatives

be trapped efficiently with a large variety of reagents, allowing the introduction of a plethora of substituents in the final compound. These include halides and chalcogenides, nitrogen-containing functional groups (azide and hydrazine), alkenes and alkynes [125].

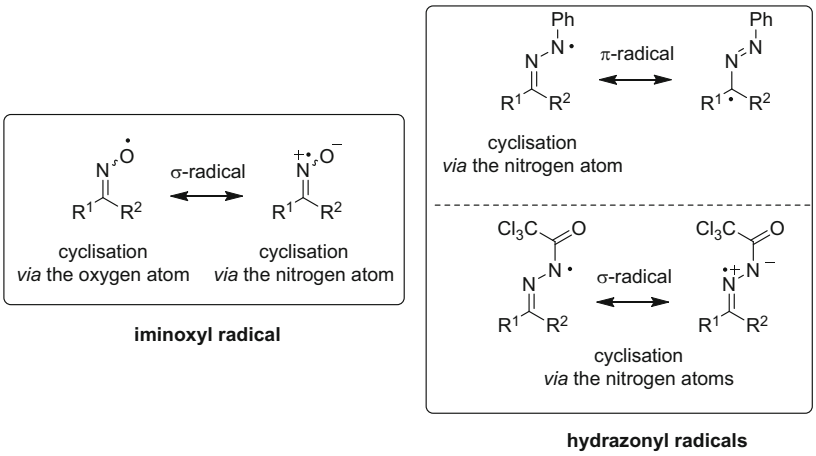
The reactivity of hydrazonyl radicals has already been discussed in the context of the formation of heterocycles such as phthalizines or 1,6-dihydropyridazines (vide infra). However, the picture is not as simple as it seems at first glance. Both iminoxyl radicals and hydrazonyl radicals have been found to undergo cyclisation via one resonance structure or the other, depending on the position of the C=C bond and, in the case of hydrazonyl radicals, on the substituent on the nitrogen atom (Scheme 32) [127].

Depending on the position of the C=C bond, 5-*exo*-trig cyclisation of iminoxyl radicals can take place either at the oxygen or at nitrogen atom. In the case of hydrazonyl radical, Han and co-workers showed that the "classical" reactivity via the phenyl-substituted nitrogen atom in *N*-phenyl-substituted hydrazones can be reversed by replacing the *N*-phenyl group with a trichloroacetyl group [127]. The presence of the trichloroacetyl protecting group switches the structure of the *N*-phenyl-substituted hydrazonyl radical from a π-radical to a σ-radical, which is then able to react in a similar manner as the iminoxyl radical, via one of the two

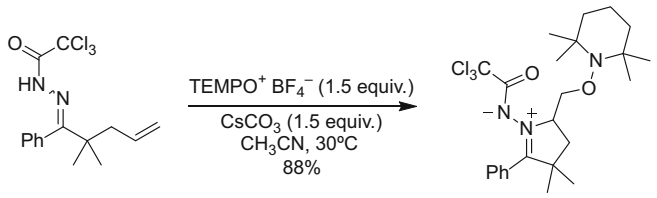


Scheme 31 Evolution of the reaction conditions to generate iminyl radicals from oximinoacetic acid derivatives

heteroatoms. The nitrogen-centred radical is generated in acetonitrile from *N*-trichloroacetyl hydrazones by oxidation of the corresponding anion by $TEMPO^+$ BF_4^-. This oxidation process releases TEMPO, which is able to trap the carbon-centred radical resulting from the 5-*exo*-trig cyclisation. Under these reaction conditions, *N*-trichloroacetyl hydrazonyl radicals lead to azomethine imines in good to high yields (Scheme 33).



Scheme 32 Resonance structures of iminoxyl and hydrazonyl radicals



Scheme 33 Unusual cyclisation of hydrazonyl radicals: influence of the protecting group on the nitrogen atom

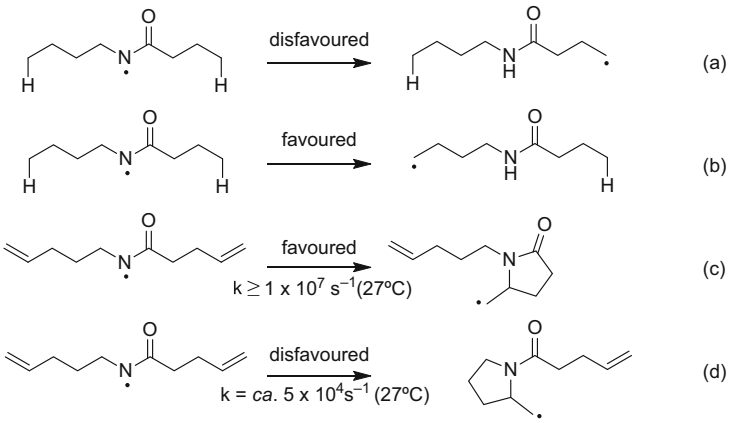
3.1.3 Amidyl Radicals

Amidyl radicals can be generated from a variety of precursors containing a weak N–X (X = halogen), N–O, N–S or N–N bond. These include *N*-haloamides, pyridinethione oxycarbonyl (PTOC) imidate esters, *N*-acyl PTOC carbamates, *O*-acyloximes, *N*-(phenylthio)amides, *N*-(*O*-ethyl thiocarbonylsulfanyl)amides, *N*-nitrosoamides, thiosemicarbazone derivatives, *N*-aminopyridinium salts and *N*-acyltriazenes. Alternative routes based upon single-electron transfer processes were explored during the early development of chemistry of amidyl radicals. For instance, *N*-lithio-*N*-methylphenylacetamide could be oxidised into the corresponding amidyl radical in THF in the presence of tetracyanoethylene [128]. This opened the way to the development of efficient methods, such as electro-oxidative methods [129–131], and the application of proton-coupled electron transfer [132–136], which both offer new entries to this type of radical species from simple amides.

Depending upon the nature of the precursors, mediation with tin-centred radicals is sometimes required. This is the case, for instance, for the *N*-(phenylthio)amide, *O*-

acyloxime and thiosemicarbazone derivatives. Fortunately, small modifications allow for the development of alternative tin-free conditions. For instance, *N*-(phenylthio)amides can be advantageously replaced with *N*-(*O*-ethyl thiocarbonylsulfanyl)amides, which lead to amidyl radicals upon heating in the presence of dilauroyl peroxide (DLP).

Early studies by electron paramagnetic resonance (EPR) spectroscopy supported a π-electronic ground state for most amidyl radicals [137–139]. The amidyl radical can be regarded as an electrophilic nitrogen-centred radical, and this representation is actually more accurate than a delocalised 1-oxo-3-azaallyl radical. The electrophilic amidyl radical can abstract a hydrogen atom from various sources (e.g. nBu$_3$SnH, RS–H or unactivated C–H bonds) or add onto an unsaturated partner. As amidyl radicals are electrophilic, the hydrogen atom abstraction from unactivated C–H bonds can easily compete with an intermolecular radical addition process [140]. Hydrogen atom abstraction from unactivated, electron-rich C–H bonds, either in an intramolecular [141] or intermolecular manner [134, 142], have been developed to achieve selective functionalisation. The kinetics of amidyl radical reactions have been established by electron paramagnetic resonance (EPR) [143] and laser flash photolysis (LFP) [144]. In the intramolecular hydrogen atom abstraction, it was found that abstraction from the alkyl chain is favoured over the abstraction from the acyl chain (Scheme 34, Eqs. a, b) [143]. This selectivity was explained by stereoelectronic factors, the attack at the C–H bond on the alkyl chain taking place in a nearly collinear approach, thus allowing for a maximum orbital overlap in the transition state. On the contrary, the cyclisation of an amidyl radical is faster on the acyl chain than on the alkyl chain (Scheme 34, Eqs. c, d). When the hydrogen atom abstraction is in competition with an intramolecular addition, the latter is usually faster [145]. Accordingly, the cyclisation of amidyl radicals suitably substituted allows for an efficient preparation of γ-lactams and related compounds.



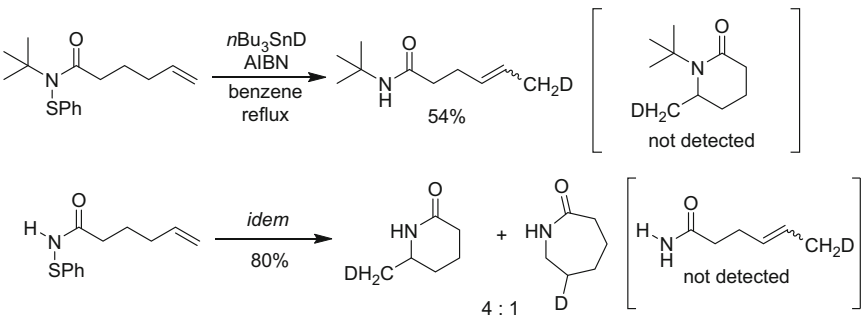
Scheme 34 Selectivity in the intramolecular hydrogen atom abstraction (iHAT) and 5-*exo*-trig cyclisation with amidyl radicals (rate constants from Ref. [143])

The stereoselectivity of these 5-*exo*-trig cyclisation processes has been studied with substrates presenting a substituent at the allylic position (for cyclisation at the acyl chain) [146] or at the alpha position of the nitrogen atom (for cyclisation at the alkyl chain) [147]. With the former, the levels of stereoselectivity observed proved to be surprisingly lower than those observed for the cyclisation of the corresponding hex-5-enyl radicals.

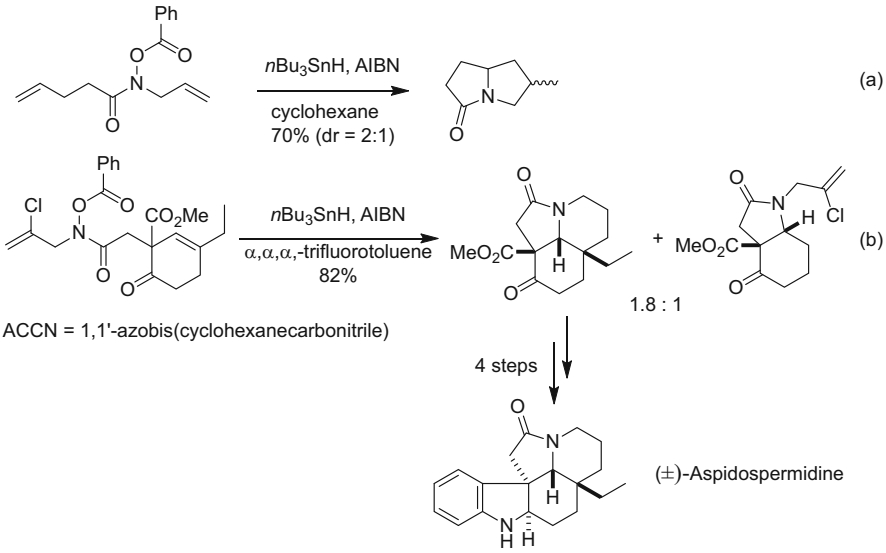
The formation of δ-lactams via a 6-*exo*-trig cyclisation is usually inefficient as the hydrogen atom abstraction from the allylic C–H bond is a rapid process (a rate constant about 5×10^6 s^{-1} (27°C) has been measured by electron paramagnetic spectroscopy for *N*-ethyl-4-pentene carboxamidyl radical) [143]. It is worthy of note that the activation energy for the 6-*exo*-trig cyclisation proved to depend dramatically upon the bulkiness of the substituent on the nitrogen atom. For instance, the 6-*exo*-trig cyclisation could be observed in the case of the *N*-methyl-4-pentene carboxamidyl radical, while only hydrogen atom abstraction at the allylic position took place with the *N*-ethyl analogue [143]. Theoretical calculations performed at the B3LYP/6-31G* level indicated a correlation between the size of the *N*-substituent and the activation energies for the 6-*exo*-cyclisation, while the activation energies for the 1,5-hydrogen atom abstraction seemed to be less dependent of the size of the *N*-substituent (Scheme 35) [148].

The Zard group has extensively investigated the cyclisation of amidyl radicals and their use in the total synthesis of alkaloids. Cascade reactions allowed for a rapid access to important classes of compounds such as indolizidines via a sequence involving two consecutive 5-*exo*-trig cyclisation steps (Scheme 36, Eq. a) [149, 150]. The preparation of indolizidines is somewhat more difficult, but the regioselectivity of the second radical cyclisation can be elegantly reversed by using an internal chloroalkene side chain (Scheme 36, Eq. b) [151–153]. The same strategy allowed the preparation of the *Stemona* skeleton via a 5-*exo*-trig/7-*endo*-trig radical cascade [153].

Thiosemicarbazone derivatives obtained by reaction between an acyl chloride and HNMe-NMeC-S(SMe) [154–156] can be cleaved with carbon-centred radicals,



Scheme 35 Influence of steric effects on the cyclisation of amidyl radicals



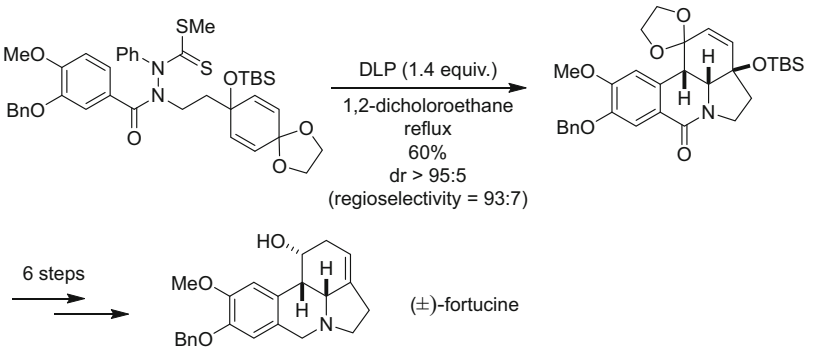
Scheme 36 Preparation of indolizidines (Eq. a) and Zard's total synthesis of (±)-aspidospermidine (Eq. b) [152]

thus allowing the use of DLP to promote the reaction (Scheme 37). *N*-Allylsulfonimides have also been used as precursors for amidyl radicals [157]. In this case, the reaction requires the use of sub-stoichiometric amounts of DLP and the presence of a xanthate. The reaction is carried out at elevated temperature in order to facilitate the loss of SO_2 in the *N*-amidosulfonyl radical intermediate. However, the SO_2 extrusion is not always competing favourably with the cyclisation of the sulphonyl radical and, accordingly, products resulting from the cyclisation of the *N*-amidosulfonyl radical intermediate have also been observed (see below).

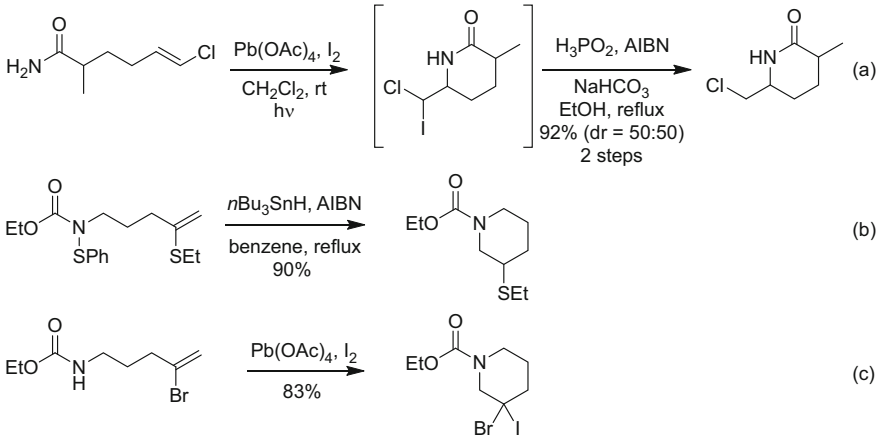
As previously mentioned, the formation of six-membered rings such as piperidines and δ-lactams via the radical cyclisation of amidyl radicals is difficult to achieve due to the propensity of these radical species to abstract a hydrogen atom at the allylic position. Strategies to overcome this limitation rely either on the acceleration of the 6-*exo*-trig cyclisation (Scheme 38, Eq. a) [158] or the use of internal alkenes favouring the 6-*endo*-trig over the 5-*exo*-trig cyclisation process (Scheme 38, Eqs. b, c) [159, 160].

The use of amidyl radical for the preparation of β-lactams has also been explored. These strained four-membered rings could be obtained in good yields from *O*-benzoyl hydroxamic acid precursors presenting an aromatic group at the alkenyl side chain in order to block (or at least slow down) the reverse reaction thanks to the formation of a stabilised benzylic radical after the 4-*exo*-trig cyclisation process [161, 162].

Very recently, visible light photocatalysis emerged as a powerful tool for the generation of amidyl radicals [60]. Leonori and co-workers showed that aryloxy



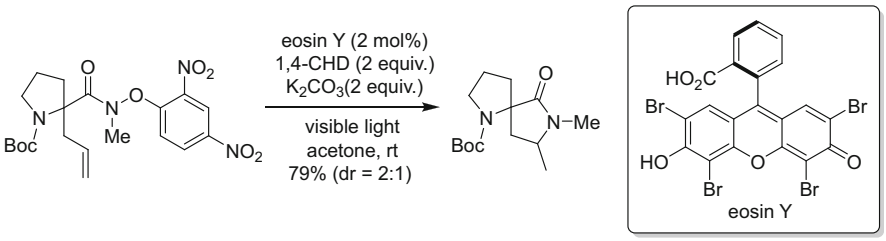
Scheme 37 Zard's total synthesis of (±)-fortucine [154]



Scheme 38 Strategies to avoid undesired 1,5-HAT and access piperidine derivatives

amides are suitable precursors for the formation of amidyl radicals. Upon irradiation with green light, and in the presence of an organophotocatalyst (eosin Y) and 1,4-cyclohexadiene (1,4-CHD), which plays the role of a hydrogen atom donor, γ-lactams and cyclic carbamates could be obtained in good to high yields (Scheme 39) [163]. Interestingly, the analogous 5-*exo*-dig cyclisation leading to 5-methylenepyrrolidinones proved to be effective even in the absence of the organophotocatalyst [164].

The postulated mechanism involves SET from the excited state of eosin Y (EY*) to the aryloxy amide. The amidyl radical resulting from the cleavage of the N–O bond undergoes 5-*exo*-trig cyclisation, and the newly formed carbon-centred radical abstracts a hydrogen atom from the allylic position of 1,4-CHD. The bis-allylic radical is then easily oxidised into the corresponding carbocation by EY^+, thus regenerating the photocatalyst. The aromatisation of the bis-allylic carbocation



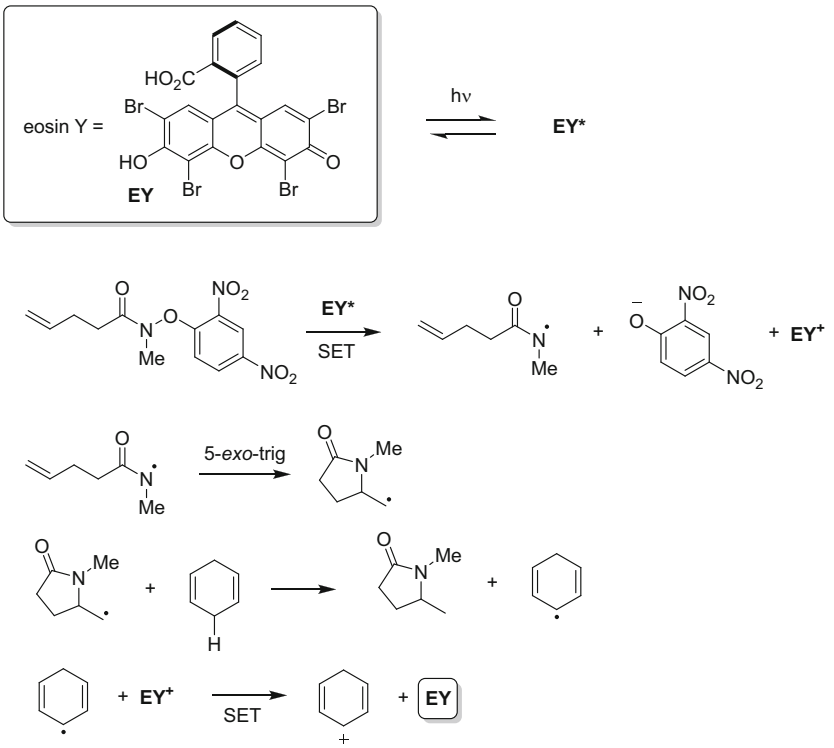
Scheme 39 Leonori's approach for the generation and cyclisation of amidyl radicals from aryloxy amides in the presence of an organophotocatalyst

gives benzene and a proton, which is trapped by the mild base used in this process (Scheme 40).

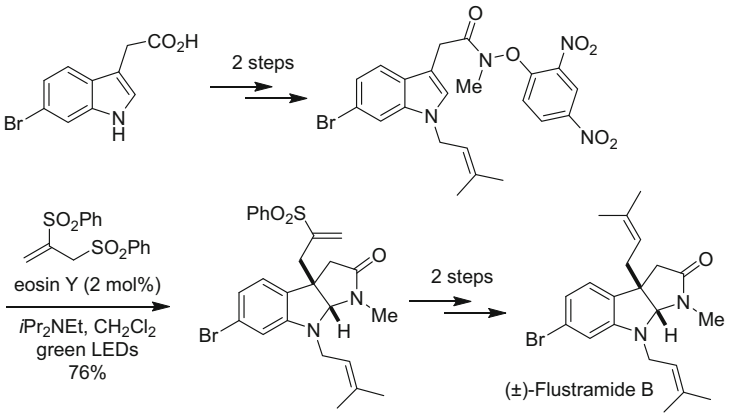
Radical cascades allowing for the carbon-centred radical resulting for the cyclisation process to engage in carbon–carbon bond forming reactions have also been developed. Wang and co-workers applied the aforementioned strategy to indole derivatives and showed that the benzylic radical resulting from an initial 5-*endo*-trig cyclisation could be trapped by addition onto an electron-poor alkene (typically an allylsulfone), giving access to pyrroloindolines in good to high yields (Scheme 41) [165]. Under these reaction conditions, the organophotocatalyst is regenerated from its oxidised form thanks to the use of a tertiary amine, which plays the role of a sacrificial electron donor. The trapping of the radical resulting from the cyclisation process with TEMPO has also been reported [165].

The cleavage of the weak N–O bond can also be promoted by the use of transition metal photocatalyst. Xu, Lu and co-workers developed an intramolecular oxyamination reaction based upon the cyclisation of amidyl radicals generated by SET mediated by an iridinium(III) complex upon visible light irradiation, followed by the formation of a bicyclic aziridine intermediate. Surprisingly, the spontaneous ring opening of the *anti*-aziridine under the reaction conditions proved to depend dramatically on the nature of the sacrificial donor used. The stereoselectivity could be controlled and reversed (dr up to >20:1) by simply changing the base from Et_3N to Ph_3N, giving access to *anti* or *syn*-1,2-amino alcohol derivatives in good to high yields (Scheme 42) [166].

The Knowles group recently reported the generation of amidyl radicals and related species from simple amides under very mild reaction conditions [134–136]. Concerted proton-coupled electron transfer (PCET) [167–170] allows for the formation of the nitrogen-centred radical by cleavage of the relatively strong N–H bond (BDE for *N*-aryl amides = ca. 100 kcal mol^{-1}). The reaction is carried out upon visible light irradiation in the presence of an iridium(III) complex as the photoredox catalyst and sub-stoichiometric amounts of a phosphate base. Following radical cyclisation of the amidyl radical, the resulting carbon-centred radical can either be trapped by hydrogen atom abstraction from an arene thiol (Scheme 43, Eq. a) [133] or by addition onto an unsaturated radical trap such as an alkene (Scheme 43, Eq. b) [132]. Proton-coupled electron transfers applied to the

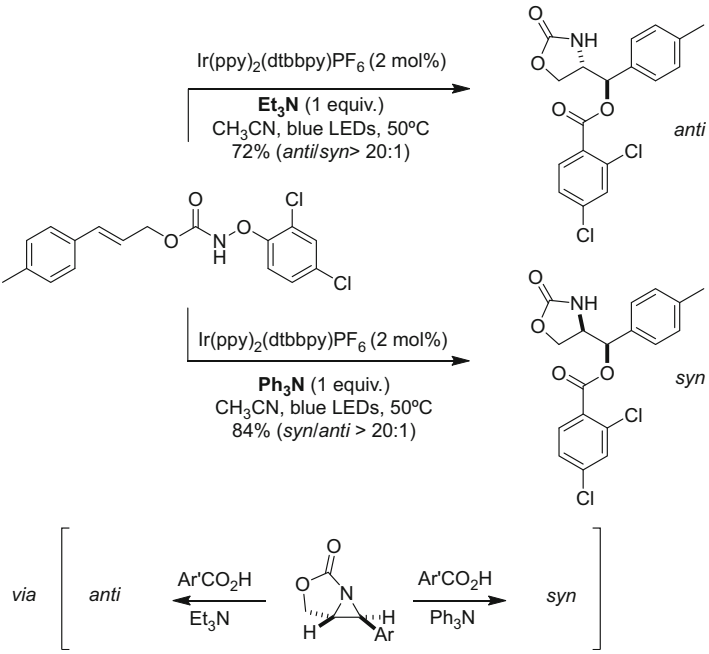


Scheme 40 Postulated reaction mechanism for the generation of amidyl radicals from aryloxy amides



Scheme 41 Wang's total synthesis of (±)-flustramide B

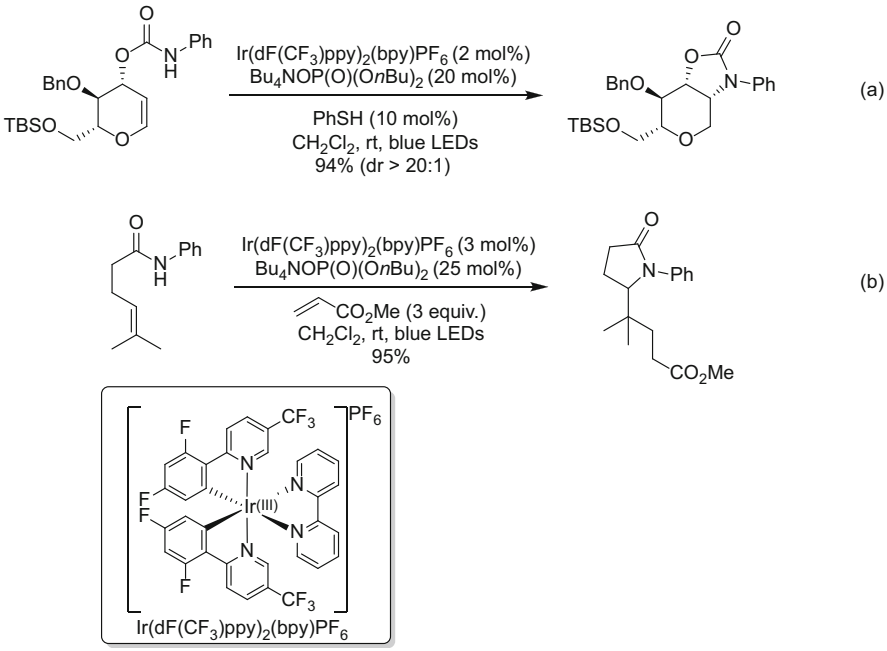
generation of amidyl radicals have also been reported with other catalytic systems such as the combination of a titanocene(III) complex and TEMPO [135] or the use of



Scheme 42 Stereodivergent oxyamination of alkenes

copper(II) complexes [171, 172]. Related processes involving the use of *o*-iodoxybenzoic acid (IBX) as an oxidising agent [173] or the use of electrochemical methods [129–131, 174] for the generation of amidyl radicals have also been reported.

The mechanisms of these transformations both follow the same initial reaction pathway. Upon irradiation with visible light, the cationic iridium(III) photocatalyst generates its excited form: $[Ir(III)]^{+}*$. Concerted proton-coupled electron transfer involving the excited photocatalyst $[Ir(III)]^{+}*$, the amide precursor and the base, leads to the reduced form of the photocatalyst (a neutral iridium(II) complex), the amidyl radical and the dialkyl phosphate (Scheme 44). The cyclisation of the amidyl radical intermediate leads to a carbon-centred radical, which abstracts a hydrogen atom from the arene thiol to give the cyclised product and a thiyl radical. In this case, the cationic iridium(III) photocatalyst is presumably regenerated by SET to the thiyl radical to give the corresponding thiolate ion, which deprotonates the dialkyl phosphate to regenerate the phosphate base and the thiol. Alternatively, in the presence of an electron-poor alkene, intermolecular radical addition can take place, leading to a stabilised carbon-centred radical, which is reduced into the corresponding enolate by electron transfer from the reduced iridium(II) complex. Protonation of the enolate by the dialkyl phosphate gives the functionalised product and regenerates the phosphate base. If the cyclisation is carried out in the presence of thiophenol (BDE = ca. 79 kcal mol^{-1}), the chemoselectivity favours the formation

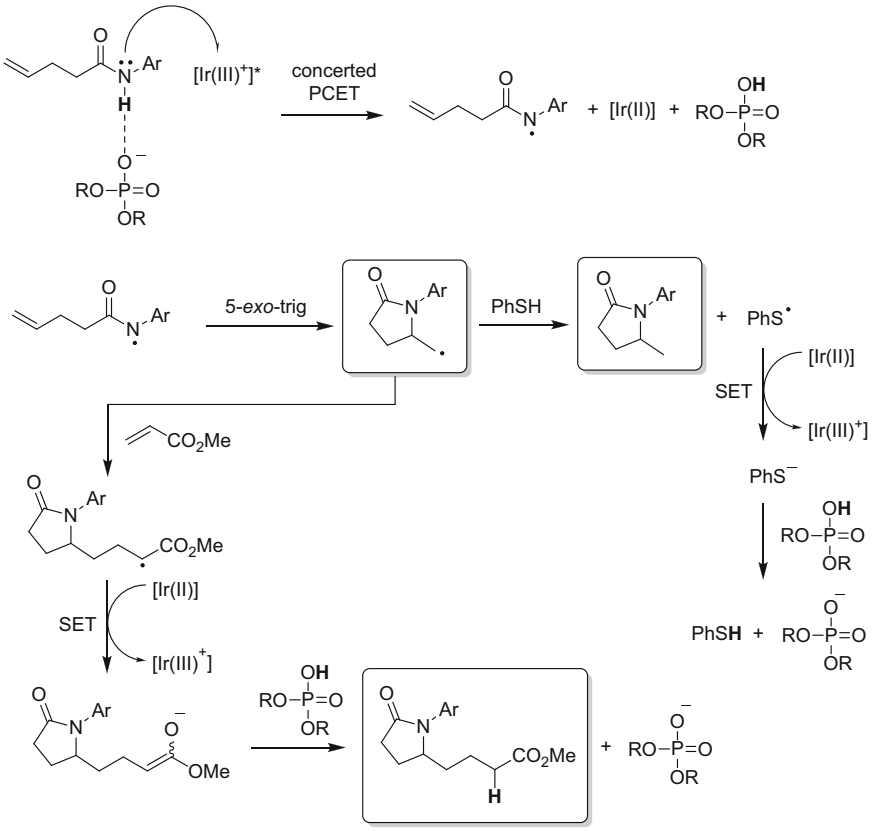


Scheme 43 Knowles' approach to amidyl radicals using proton-coupled electron transfer conditions

of the amidyl radical from the amide (BDE = ca. 99 kcal mol^{-1}) in the PCET process, instead of the formation of a thiyl radical, which is explained by a more favourable amide–phosphate hydrogen bond being formed instead of a thiol–phosphate hydrogen bond.

3.1.4 C–H Bond Activation: The Hofmann–Löffler–Freytag (HLF) Reaction

Nitrogen-centred radicals are prone to abstract hydrogen atoms from C–H bonds. This long-known process (the first examples were reported in 1883 by Hofmann) [175] is extremely powerful and can be regarded as a way to achieve remote C–H activations [176, 177]. *N*-Haloamines were found to provide electrophilic aminium radical cations upon heating or irradiation in strongly acidic media. In the absence of a C=C bond, intramolecular hydrogen atom transfer (HAT) occurs, leading to a carbon-centred radical, which is usually halogenated under the reaction conditions (either by recombination with a halogen radical or by halogen atom transfer). Treatment with a base liberates the free amine, which cyclises to give the heterocyclic structure (Scheme 45). Most of the time, and in the absence of conformational constraints, 1,5-HAT via a six-membered ring transition state is favoured over the

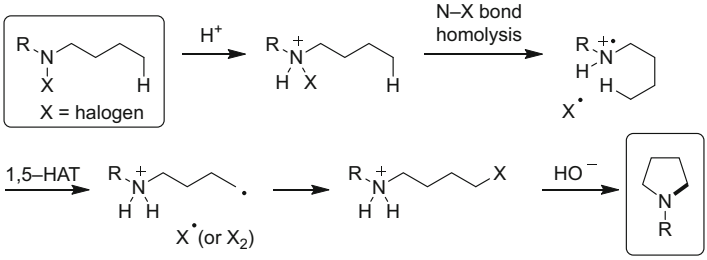


Scheme 44 Mechanism for the proton-coupled electron transfer applied to the generation of amidyl radicals

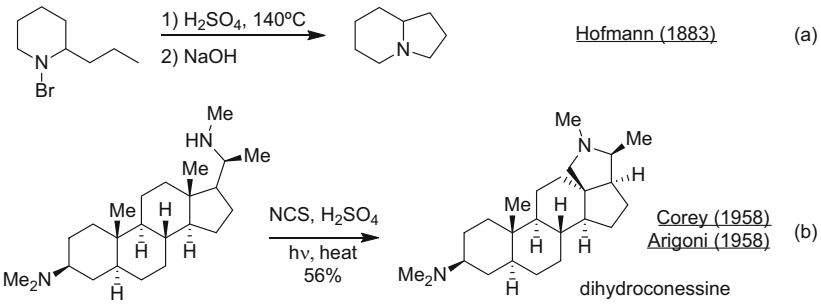
other possible translocation processes, leading in this case to pyrrolidines after ionic cyclisation.

Since its early developments (Scheme 46, Eq. a), this reaction, known as the Hofmann–Löffler–Freytag (HLF) reaction [175, 178–180], has found numerous applications in organic synthesis. Corey's [181] and Arigoni's [182] syntheses of dihydroconessine, a pentacyclic aminosteroid containing a pyrrolidine moiety, illustrate the efficiency of this strategy to achieve C–H bond activations that would be difficult to realise by other approaches (Scheme 46, Eq. b). More recently, milder reaction conditions have been developed for the HLF reaction with chloroamines. The irradiation with UV light has been advantageously replaced with visible light by using white LEDs in conjunction with sub-stoichiometric amounts of a photocatalyst (such as $Ir(ppy)_2(dtbbpy)PF_6$) [183].

The major limitation of the original HLF reaction is the utilisation of strongly acidic conditions necessary for the generation of electrophilic aminium radical cations. The proton on the nitrogen atom can be advantageously replaced by an

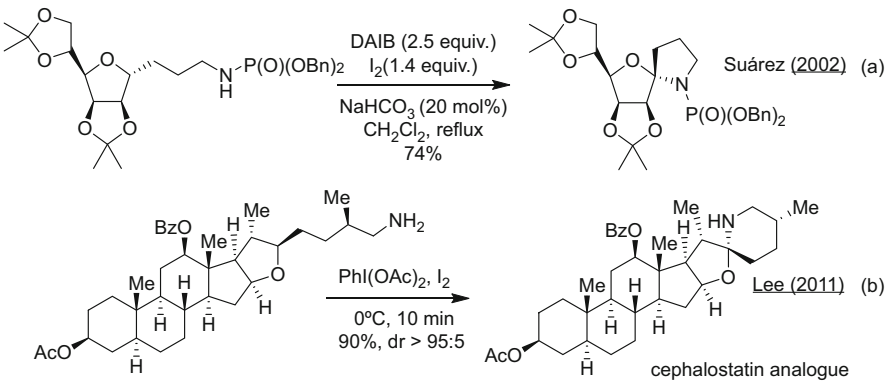


Scheme 45 General reaction mechanism of the Hofmann–Löffler–Freytag reaction



Scheme 46 The Hofmann–Löffler–Freytag reaction applied to the formation of pyrrolidine derivatives

electron-withdrawing group, thus allowing the reaction to be carried out in the absence of a proton source. Suárez and co-workers have extensively studied this reaction, and they showed that precursors such as *N*-nitroamines [184], *N*-phosphoramidates (Scheme 47, Eq. a) [185–188] or *N*-sulfonamidates are suitable precursors for HLF reactions under non-acidic conditions [189]. Corey showed that trifluoroacetamides are also good precursors for HLF reactions [190]. Computational chemistry allows one to predict the feasibility of the hydrogen atom transfer step in HLF reactions. Parameters such as the nature of the precursor and the compatibility with the solvent used for the transformation can be taken into account. Recently, using different computational methods, including the very accurate G3(MP2)-RAD method [191], Zipse provided a rational for HLF reactions based upon the radical stabilisation energies (RSEs) of aminium radical cations and neutral nitrogen-centred radicals [192]. In the second case, the influence of the nature of the *N*-protecting group (Boc, Ts, $C(O)CF_3$, etc.) on the stability of the radical species could be appreciated. The oxazaspiroketal moiety of the cephalostatin analogue depicted in Scheme 47 (Eq. b) [193, 194] was assembled via a highly regioselective 1,6-HAT, which was achieved under very mild, neutral reaction conditions using the synergistic pairing of iodobenzene diacetate (DAIB) and iodine developed by Suárez and co-workers (see below). This last example represents a rare case of HLF reaction, for

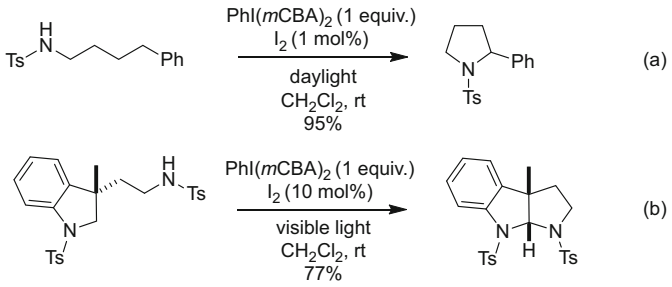


Scheme 47 Suárez' conditions to achieve HLF reactions (Eqs. a, b) and Lee's synthesis of oxazaspiroketals (Eq. c)

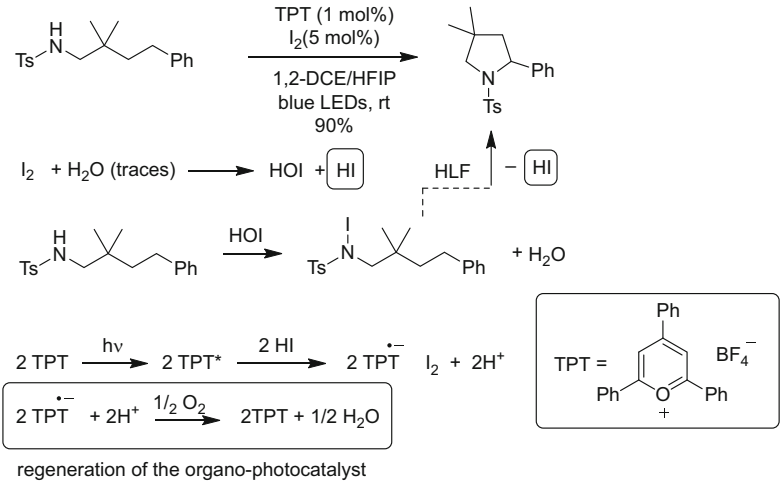
which the reactive nitrogen-centred radical intermediate is generated from a free primary amine, which are known to be poor substrates for HLF reactions, without the need for an external proton source or an electron-withdrawing protecting group on the nitrogen atom. The regioselectivity can be explained by the stability of the α-alkoxy radical resulting from the translocation process. As this reaction was carried out in the absence of a base, it is likely that under these reaction conditions, the iodhydric acid produced during the ionic cyclisation serves to facilitate the formation of an aminium radical cation intermediate.

Muñiz showed that the amount of iodine can be lowered down to 1 mol%, provided that DIAB is replaced by another iodine(III) reagent: PhI(*m*CBA)$_2$ (*m*CBA = 3-chlorobenzoate). Under these optimised reaction conditions, the preparation of *N*-tosyl pyrrolidines could be achieved in CH_2Cl_2 at room temperature upon exposure to Spanish daylight (Scheme 48, Eqs. a, b) [195]. In reactions using iodine(III) reagents, Nagib and co-workers have generated iodine in situ from sodium iodide in order to increase the chemoselectivity of the oxidising system [196].

The system was improved even further by the use of an organic photoredox catalyst (2,4,6-tris(4-methoxyphenyl)pyrylium tetrafluoroborate (TPT)) [197] in place of the iodine(III) species to generate the *N*-iodo-*N*-tosylamine in situ (Scheme 49) [198]. The reaction is conducted in a 1,2-diclohoroethane/hexafluoropropan-2-ol mixture at room temperature, upon irradiation with blue LEDs. In agreement with the observations that, firstly, traces of water are required to initiate the reaction and secondly that hypoiodite was detected in the reaction medium, the authors proposed the following reaction mechanism: iodine reacts with traces of water to produce hypoiodite, which reacts with the *N*-tosylamine to give the unstable *N*-iodination precursor. Homolytic cleavage of the N–I bond followed by the classical HLF reaction delivers the pyrrolidine and iodhydric acid. The latter is oxidised into iodine by the photoexcited form of TPT: TPT*. The organic photocatalyst is finally regenerated from its reduced form by oxidation with molecular oxygen (Scheme 49).



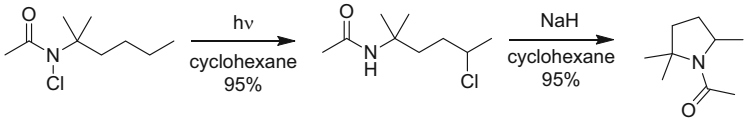
Scheme 48 Muñiz' conditions for HLF reactions with sub-stoichiometric amounts of iodine



Scheme 49 HLF reaction with sub-stoichiometric amounts of iodine under photoredox catalysis conditions

As mentioned previously, amidyl radicals are also capable of abstracting hydrogen atom from C–H bonds, either in an intramolecular (see Scheme 34) [141] or intermolecular manner [142]. When amidyl radicals are generated from *N*-haloamides, a radical chain reaction mechanism can take place, leading preferentially to the chlorination of one position of the alkyl chain. For instance, *N*-chloro-*N*-(1,1-dimethylpentyl)acetamide can be converted in excellent yield into *N*-(1,1-dimethyl-4-chloropentyl)acetamide, which undergoes cyclisation in the presence of sodium hydride to give the corresponding γ-lactam (Scheme 50) [199]. As mentioned previously, trifluoroacetamides are also good precursors for HLF reactions under neutral conditions [190].

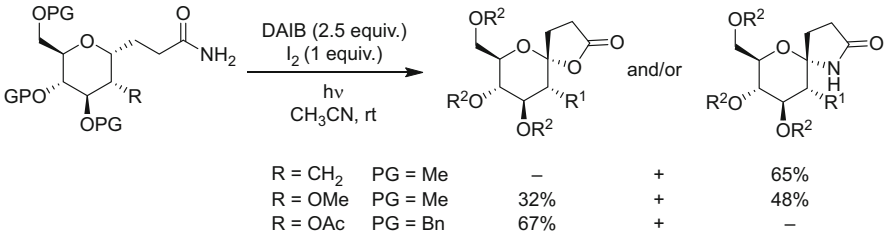
With primary amides, the ionic cyclisation can take place either via the oxygen atom, leading in this case to lactones [200, 201], or via the nitrogen atom to give lactams [202]. The regioselectivity of the nucleophilic attack was attributed to the



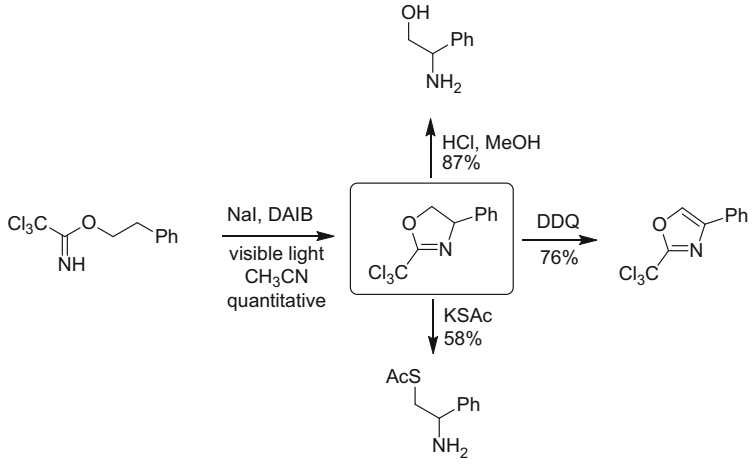
Scheme 50 HLF reactions with haloamides

nature of the carbocation obtained by oxidation of the carbon-centred radical generated in the hydrogen atom transfer step. In many cases, the reaction was found to be highly selective, leading exclusively either to lactones or to lactams, but this rule does not always apply and the situation can be more complex, especially in the sugar series [186, 203]. Suárez and co-workers applied their conditions to sugar derivatives [203]. They studied the trapping of the oxocarbenium ion intermediates and showed that the C-5 substituent plays a role in the outcome of the ionic cyclisation. The presence of OMe group at the C-5 position of the sugar leads to a mixture of spirolactams and spirolactones, both in the mannose and glucose series (Scheme 51). On the contrary, the presence of a more electron-withdrawing group (OAc) at C-5 allowed for a regioselective *O*-cyclisation, while the absence of substituent at C-5 gives exclusively the spirolactam via *N*-cyclisation. Again, the changes in the regioselectivity in the nucleophilic attack were attributed to the electronic nature of the oxocarbenium ion intermediates. The latter were proposed to be harder acids in the HSAB theory with an adjacent OAc group than are oxocarbenium ions substituted at the alpha position by an OMe group. In the absence of a substituent at C-5, the softer oxocarbenium ions would then be trapped regioselectively via *N*-cyclisation.

HLF-type reactions involving iminyl radicals have been far less studied than their parent aminyl and amidyl radicals. However, this field has witnessed a regain of interest very recently with the works from the Leonori [126] and Nagib [204] laboratories. Following the seminal work of Forrester [205, 206], Leonori and co-workers studied 1,5-HATs in iminyl radicals generated from oximinoacetic acid derivatives. The iminyl radicals were generated under mild, non-acidic reaction conditions, in the presence of Fukuzumi's acridinium salt as an organophotocatalyst. As in Forrester's studies, no product resulting from the cyclisation via the imine moiety was observed for the reactions carried out in the presence of a radical trap. Instead, the carbon-centred radical resulting from the translocation process was trapped to give the products of remote functionalisation [126]. Nagib and co-workers showed that cyclisation takes place when imidate radicals are produced under mild conditions [204], using the NaI/DAIB oxidising system developed by the same group for classical HLF reactions [196]. Optimum results were obtained with trichloroacetimidates, which were converted into oxazolines in high yields. The latter can be oxidised with DDQ to give oxazole derivatives, opened with a variety of nucleophiles to give functionalised amines, or hydrolysed under acidic conditions to deliver 1,2-amino alcohols with high levels of regio- and stereoselectivity (Scheme 52).



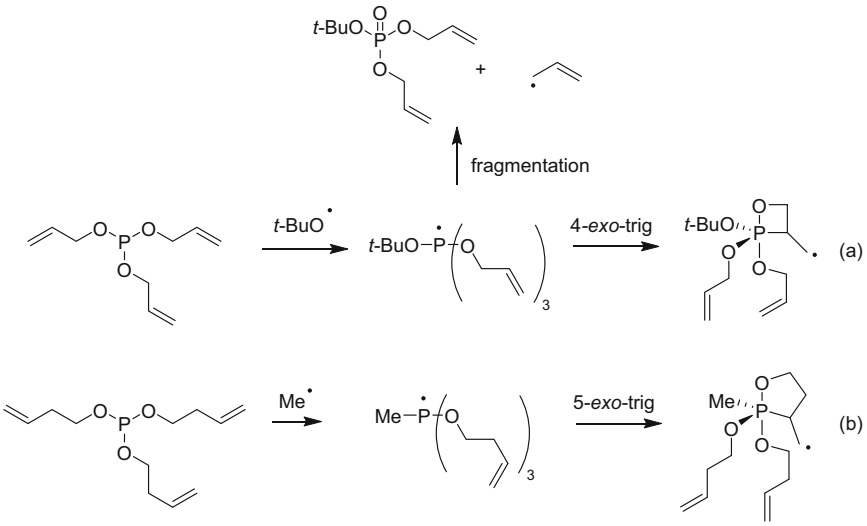
Scheme 51 *N*- versus *O*-ionic cyclisation in HLF reactions with amidyl radicals



Scheme 52 HLF-type reaction with imidate radicals

3.2 Phosphorus-Centred Radicals

The intermolecular radical addition of phosphorus-centred radicals onto alkenes and alkynes is well documented [207, 208], but the intramolecular counterpart to produce phosphorus-containing cyclic systems seems to have been overlooked. The first reports can be dated back to the mid-1970s with the seminal work of Davies who studied the cyclisation of unsaturated alkoxyphosphoranyl radicals by electron spin resonance spectroscopy at low temperature (typically −120°C) [209, 210]. The phosphoranyl radicals were generated from the corresponding 2- or 3-alkenoxyphosphites by reaction with alkoxy or methyl radicals. The cyclisation process delivered oxaphosphetans (Scheme 53, Eq. a) or oxaphospholans (Scheme 53, Eq. b), respectively, via *exo*-cyclisation modes. The structures were confirmed by the large phosphorus hyperfine splitting in the electron spin resonance spectra, in

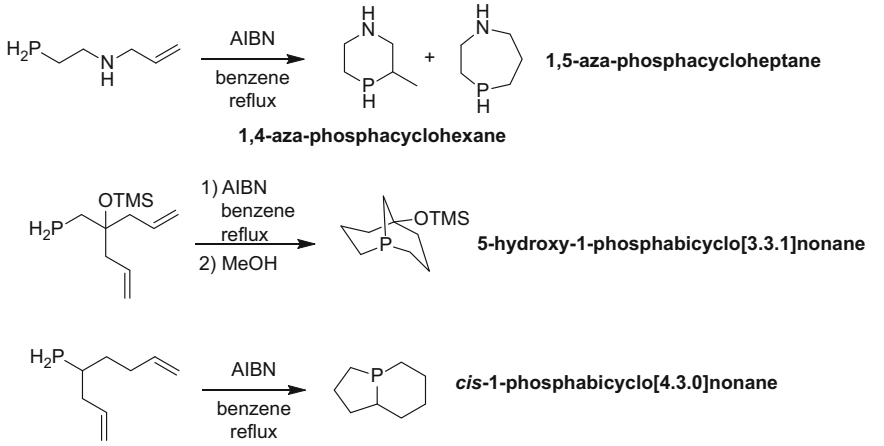


Scheme 53 Access to oxaphosphetans and oxaphospholans via the cyclisation of phosphoranyl radicals

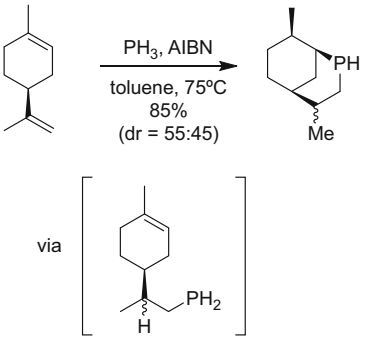
agreement with β-phosphorus-substituted alkyl radical structures. In some cases, the cyclisation is in competition with β-fragmentation, especially when the process can lead to a stabilised radical such as the allyl radical (Scheme 53, Eq. a). Under similar reaction conditions, neither the tri-pent-4-enylphosphite nor the diethyl hex-5-enylphosphite led to a cyclised compounds (six- or seven-membered rings) that could be observed by electron spin resonance [210].

The cyclisation of phosphorus-centred radicals derived from phosphines was later studied by Krech, Issleib and co-workers [211–214]. They showed that (poly) unsaturated compounds containing a phosphine moiety could undergo radical cyclisation in the presence of AIBN in refluxing benzene, giving access to interesting phosphorus-based heterocyclic structures such as *cis*-1-phosphabicyclo [4.3.0]nonane, 1,5-aza-phosphacycloheptane, 1,4-aza-phosphacyclohexane and 1,5-aza-phosphabicyclo[3.2.1]octane (Scheme 54) [215]. The reversibility of the radical addition [216] may account for the regioselectivity observed for these cyclisation reactions.

Cascade reactions involving the introduction of the phosphine moiety via an intermolecular radical addition was described more recently. For instance, the addition of PH_3 onto (*S*)-(−)-limonene in the presence of AIBN was found to lead to 4,8-dimethyl-2-phosphabicyclo[3.3.1]nonane in high yield (Scheme 55) [217].



Scheme 54 Cyclisation of phosphorus-centred radicals derived from phosphines



Scheme 55 Cascade reaction with PH_3 as a source of phosphorus-centred radical

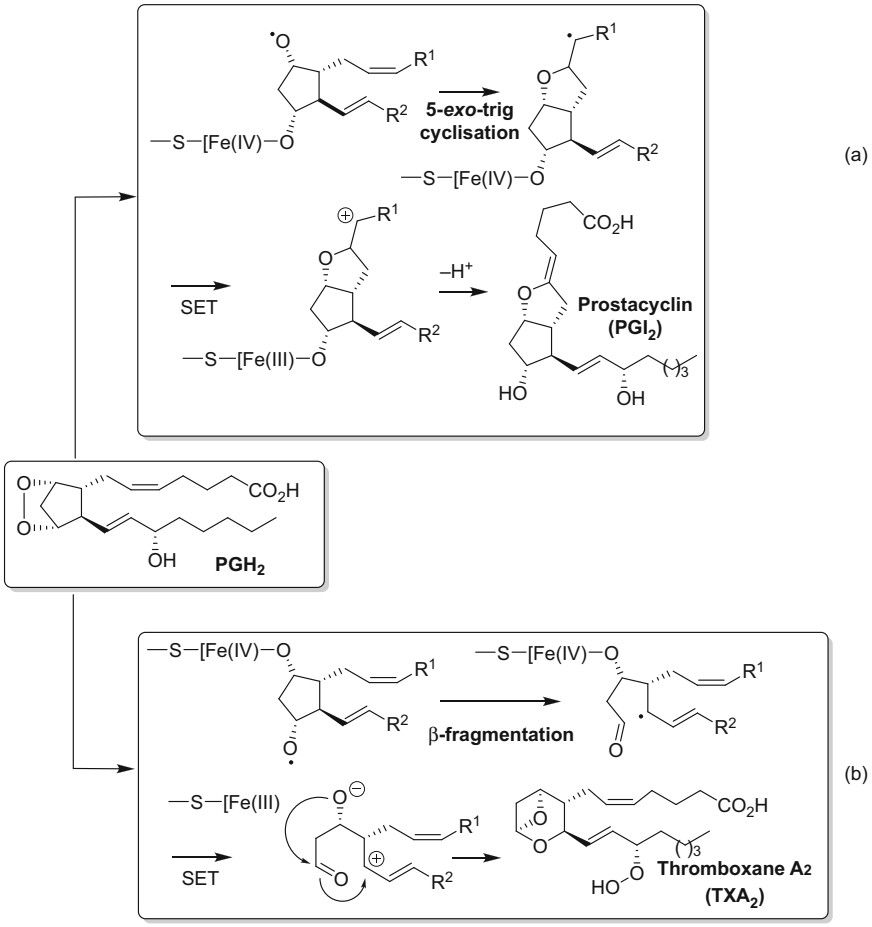
4 Group 16 (O-, S- and Se-Centred Radicals)

4.1 Oxygen-Centred Radicals (Alkoxy and Peroxy Radicals)

4.1.1 Generation and Reactivity of Alkoxy and Peroxy Radicals

Alkoxy and peroxy radicals are key reactive species in many biological processes, including the biosynthesis of important classes of molecules such as prostaglandins and phytoprostanes. Electron transfers involving the Fe(III) heme–thiolate binding site of PGI synthase have been postulated to account for the reductive cleavage of the endoperoxide moiety in prostaglandin H_2 (PGH_2) and the subsequent

rearrangement into PGI_2. This process involves the 5-*exo*-trig cyclisation of the alkoxy radical resulting from the cleavage of the endoperoxide moiety in PGH_2 (Scheme 56, Eq. a) [218] The formation of thromboxane A_2 (TXA_2) follows a similar pathway, except that in this case, the regioselectivity of the O–O bond cleavage is reversed and the alkoxy radical intermediate does not cyclise but undergoes instead fragmentation (C–C bond cleavage) to give a stabilised carbon-centred radical (Scheme 56, Eq. b). The latter is then oxidised into the corresponding carbocation, which is trapped in an intramolecular manner by the iron-alkoxide nucleophile. It is worthy of note that prostaglandin H_2 (PGH_2) itself results from a radical cascade initiated by cyclooxygenase and involving the radical cyclisation of a peroxy radical (see below). Besides their role in the biosynthesis of important classes of compounds, these reactive oxygen species are also responsible for degradation



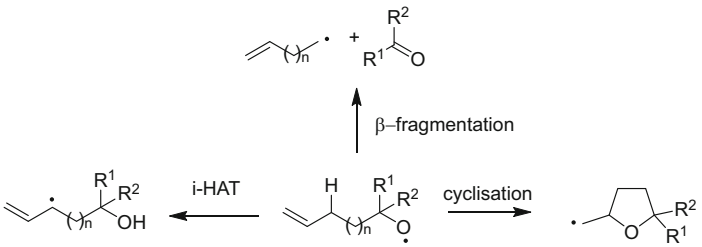
Scheme 56 Some biosynthetic pathways from PGH_2 involving the 5-*exo*-trig cyclisation of alkoxy radicals (Eq. a) and the β-fragmentation process (Eq. b)

processes, such as DNA damages or lipid peroxidation. These involve the initial hydrogen atom abstraction from unactivated C–H bonds, a process made possible by the electrophilic character of oxygen-centred radicals.

These biological processes illustrate very well the different types of reactivity that can be observed with alkoxy radicals. Those are summarised in Scheme 57. Alkoxy radicals are electrophilic radical species, which undergo cyclisation onto electron-rich alkenes with high rate constants (Scheme 57) [219, 220]. However, the efficiency of the reaction is hampered by the high reactivity of the alkoxy radicals. As previously mentioned, the latter can also evolve through hydrogen atom abstraction at C–H bonds (Scheme 57) [221] or by β-fragmentation (Scheme 57) [222]. For these reasons, the scope of the radical cyclisation has been mainly limited, until very recently, to the formation of tetrahydrofurans [223, 224].

For synthetic purposes, a variety of precursors can be employed for the generation of alkoxy radicals. These include, amongst others, precursors having a relatively weak O–X bond, where X = $Pb(OAc)_3$, N=O, halides, OR, SAr as well as thiohydroxamates and related compounds. For instance, alkyl benzenesulfenates are easily prepared in good yields by reaction of the corresponding alcohols with benzenesulfenyl chloride in the presence of triethylamine. Beckwith reported that alkoxy radicals can be generated by reaction of alkyl benzenesulfenates with nBu$_3$SnH in the presence of a radical initiator [220]. Due to the strength of the O–H bond (BDE = 435 kJ mol^{-1}), simple alcohols are usually not suitable for the direct generation of oxygen-centred radicals, albeit some (very) rare examples involving intramolecular hydrogen atom abstraction (HAT) have been reported [225]. The utilisation of cobalt(II) complexes (see below) was found to promote the cyclisation onto alkenes, leading eventually to carbon-centred radicals [226–228]. However, in this case, and despite the formation of a radical species in the cyclised intermediate, the cyclisation step itself does not involve an alkoxy radical.

In summary, alkoxy radicals undergo characteristic reactions such as fragmentation and addition, but the more typical feature of these radicals in terms of reactivity is their propensity to undergo intramolecular hydrogen atom abstraction [220, 229, 230].



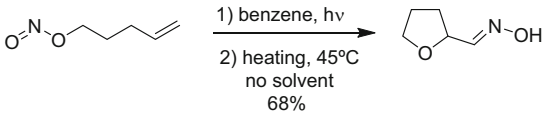
Scheme 57 Reactivity of alkoxy radicals

4.1.2 Preparation of Tetrahydrofurans and Related Heterocycles by Radical Cyclisation

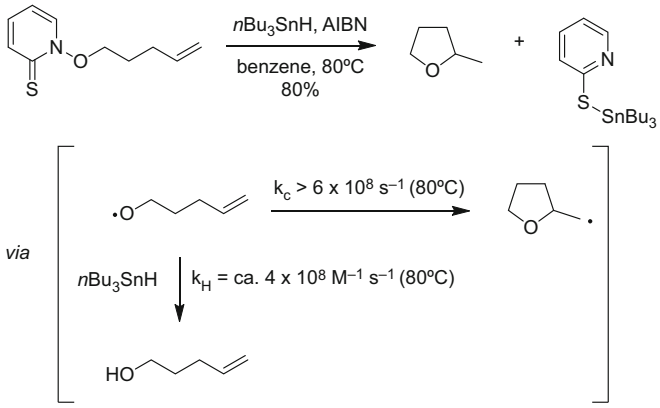
The cyclisation of 4-pentenoxyl radical and related species was first reported in the late 1960s [231]. It was found that the photolysis of 4-pentenol nitrite ester promoted the 5-*exo*-trig cyclisation, leading to a mixture of oxime and nitroso dimer. The latter could be converted into the oxime upon extended heating without solvent (Scheme 58) [232].

Beckwith showed that *N*-alkoxypyridinethiones, easily prepared from alkyl halides and 2-mercaptopyridine-*N*-oxide, were suitable precursors for the generation of alkoxy radicals. *N*-Alkoxypyridinethiones were found to react cleanly with nBu$_3$SnH in the presence of AIBN, allowing kinetic studies to be performed [219]. A rate constant $k_c \geq 6 \times 10^8$ s^{-1} (80°C) was determined for the 5-*exo*-trig cyclisation of the *N*-alkoxypyridinethione derived from pent-4-en-1-ol (Scheme 59) [219]. Similar results were obtained from the corresponding sulfenate [220].

O-Alkyl thiohydroxamates also proved to be suitable precursors for the generation of oxygen-centred radicals. The selective cleavage of the nitrogen–oxygen bond can be achieved in the presence of nBu$_3$SnH [229], possibly under microwave irradiation [233], or a thiol [234] which adds rapidly onto the C=S bond, thus generating a radical species that fragments easily to give the alkoxy radical. The possible contamination with sulphur-containing heterocyclic side products could be avoided by loading the precursors onto solid support as illustrated by the radical

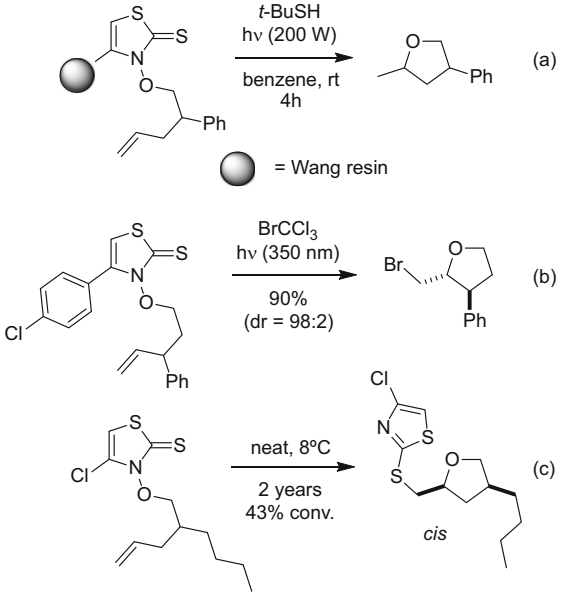


Scheme 58 Moore's cyclisation of 4-pentenoxyl radicals generated from nitrite esters



Scheme 59 *N*-Alkoxypyridinethiones as sources of alkoxy radicals

cyclisation of *N*-alkoxythiazole-2(3*H*)-thiones upon irradiation in the presence of *tert*-butanethiol (Scheme 60, Eq. a) [234]. The photolysis of *N*-alkoxythiazole-2 (3*H*)-thiones derived from 4-pentenols in the presence of bromotrichloromethane gave access to functionalised tetrahydrofurans (Scheme 60, Eq. b) [233, 235–238]. The regioselectivity complements nicely the corresponding ionic bromocyclisation reactions [239]. The corresponding iodination was also reported in the presence of diethyl 2-iodo-methylmalonate or perfluoroalkyl iodides [240]. In the absence of light, all these precursors proved relatively stable when stored under refrigeration. However, the Hartung's group showed that samples stored at low temperature for two years slowly rearranged into tetrahydrofurans presenting a thiazole moiety (Scheme 60, Eq. c) [241]. Interestingly, in the absence of a C=C bond on the alkoxy side chain, 1,5-hydrogen atom transfer can take place. The resulting carbon-centred radicals can then react with $BrCCl_3$ to give the corresponding brominated products. The latter also provide access to tetrahydrofurans after intramolecular nucleophilic displacement of the bromine atom [237]. More examples of this type of translocation process will be discussed in the next section. The extension of this chemistry to the preparation of another important class of

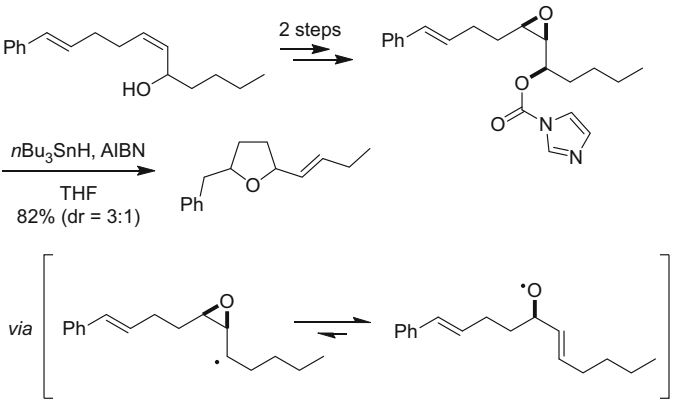


Scheme 60 *N*-Alkoxythiazole-2(3*H*)-thiones as precursors for the preparation of tetrahydrofurans

oxygen-containing heterocycles, namely, tetrahydropyrans, was reported from *N*-alkoxythiazole-2(3*H*)-thiones derived from 4-pentenols suitably substituted in order to force the cyclisation to follow a 6-*endo* mode [226, 242–244].

By taking advantage of the ring strain in oxiranylmethyl radicals, which undergo rapid fragmentation, allyloxyl radicals can be efficiently obtained. Following the pioneering work of Motherwell and Barton who observed cyclisation of allylic alkoxy radicals as a side reaction in their attempts to prepare (−)-*cis*-carveol [245], Murphy's group developed efficient cascade reactions to access tetrahydrofurans [246, 247]. These cascade reactions have been studied by EPR spectroscopy [248]. Radical deoxygenation in the presence of nBu$_3$SnH and AIBN followed by ring opening of the epoxide led to alkoxy radicals that cyclised efficiently onto an alkenyl side chain, giving tetrahydrofurans in high yields, but with only moderate levels of diastereoselectivity (Scheme 61) [247]. The preparation of tetrahydropyrans using this strategy proved more diastereoselective but was hampered by the propensity of alkoxy radicals to abstract hydrogen atom from the allylic position [246].

Irrespective of the method chosen for the generation of the alkoxy radical, the formation of tetrahydropyrans based upon a radical 6-*exo*-trig cyclisation is particularly challenging due to the competition with intramolecular hydrogen atom abstractions. The activation of remote C–H bonds is particularly efficient when the newly formed radical is highly stabilised compared to the alkoxy radicals, and because entropic factors tend to favour 1,5-HAT, the allylic C–H bonds in hexenyloxy radicals are particularly reactive. In order to overcome this problem, the Sammis group developed an elegant strategy based upon the use of electron-rich silyl enol ether acceptors in order to accelerate the radical cyclisation of the electrophilic alkoxy radical [223, 224]. This approach allows for the 6-*exo*-trig cyclisation to compete favourably with the two other possible side reactions, namely, the hydrogen atom abstraction and the β-fragmentation. This strategy was applied to the preparation of interesting hydroxylated tetrahydrofurans (via 5-*exo*-trig

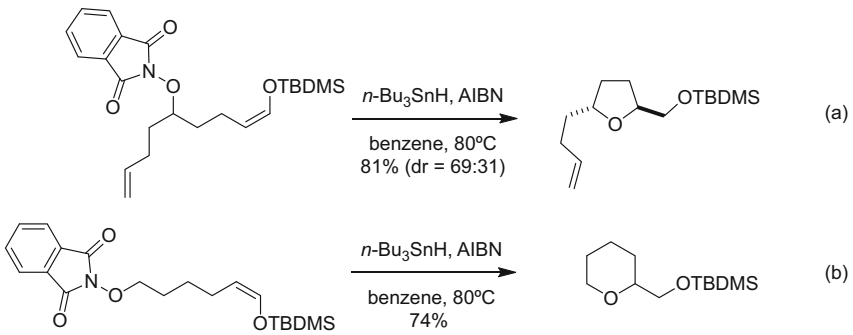


Scheme 61 Generation of alkoxy radicals via the ring opening of epoxides

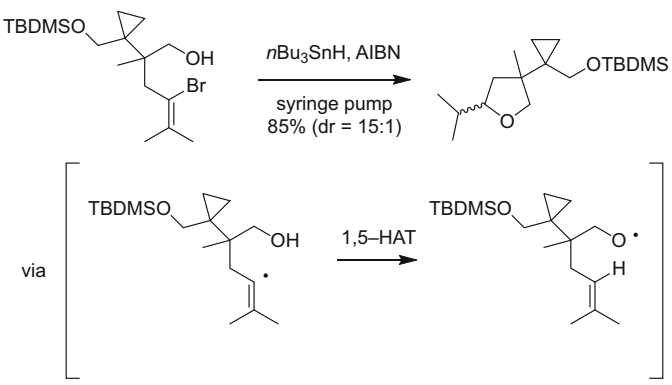
cyclisation), sometimes with excellent chemoselectivity when two C=C bonds are present (Scheme 62, Eq. a), and also to the preparation of tetrahydropyrans (Scheme 62, Eq. b).

Because of the high BDE of the O–H bond, most radical reactions can be carried out in protic solvents (e.g. *t*-BuOH) without protection of the free hydroxyl groups of the precursor. However, the BDEs of sp^2 C–H bonds are in the same range as the O–H bond, and this property was used for the generation of alkoxy radicals via 1,5-HAT in alkenyl radicals. The newly formed alkoxy radical is then ideally located to undergo 5-*exo*-trig cyclisation [249], giving tetrahydrofuran derivatives (Scheme 63). The presence of a *gem*-disubstitution within the chain between the two reactive centres proved crucial in order to ensure high yields [225].

Simple alkenols undergo cyclisation in the presence of cobalt(II) complexes under oxidative conditions [250–254]. The proposed mechanism, however, does not involve the formation of an alkoxy radical but instead the oxidation of the alkene into a radical cation in the presence of Co(II)/O_2. Ionic cyclisation leads then to a



Scheme 62 Sammis' approach to tetrahydrofurans and tetrahydropyrans via a radical cyclisation onto silyl enol ethers



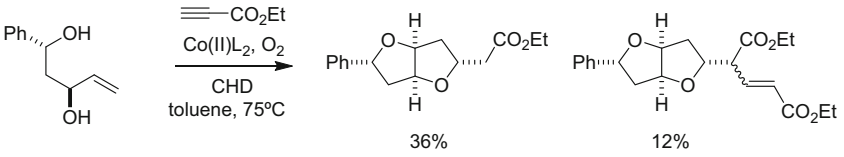
Scheme 63 Rare example of 1,5-HAT leading to an alkoxy radical

carbon-centred radical, whose formation is supported by trapping experiments with 1,4-cyclohexadiene as a source of hydrogen atom, as well as electron-deficient alkenes (Scheme 64) [227, 228].

4.1.3 Preparation of THFs and Related Heterocycles by Remote C–H Activation

Alkoxy radicals are very reactive electrophilic species, prone to undergo hydrogen atom transfers. When carried out in an intramolecular fashion, these can become powerful tools for organic chemists to achieve site-selective C–H activation reactions. Several comprehensive reviews have appeared on this topic [179, 180, 255–262]. Čeković and co-workers investigated in details the addition, to activated olefins, of δ-carbon-centred radicals generated through 1,5-HAT in alkoxy radical intermediates [263–267]. The following discussion will briefly highlight the synthetic potential of such C–H functionalisation for the preparation of oxygen-containing heterocycles, including tetrahydrofurans, tetrahydropyrans and related δ-lactones.

As mentioned previously, alkoxy radicals are electrophilic, and this property makes them extremely reactive in remote functionalisation of electron-rich C–H bonds. A rate constant in the range 3.4–8.8 $\times$ 10^5 M^{-1} s^{-1} (20°C) was determined for the intermolecular hydrogen atom abstraction from cyclopentane by the *tert*-butoxy radical [268, 269]. Although not exclusive [270], 1,5-HAT is by far the most commonly observed mode of radical translocation, irrespective of the nature of radical species involved. Alkoxy radicals can be formed by photolysis of nitrites (Barton's reaction) [221, 271, 272]. Upon irradiation in benzene, the transposition of an oxygen-centred radical gives a carbon-centred radical, which eventually leads to a C-nitroso derivative. When the reaction is conducted in the presence of iodine or $BrCCl_3$, the carbon-centred radical intermediate can be trapped by the source of halogen to give the corresponding iodo- or bromo-derivatives [273, 274]. Under these reaction conditions, tetrahydrofurans have sometimes been observed, but only as minor products [273]. δ-Chloro-alcohols can be prepared in high yields from hypochlorite derivatives by photolysis at 0°C [275]. The δ-chloro-alcohols undergo cyclisation into tetrahydrofurans in high yields upon treatment with a base. Upon



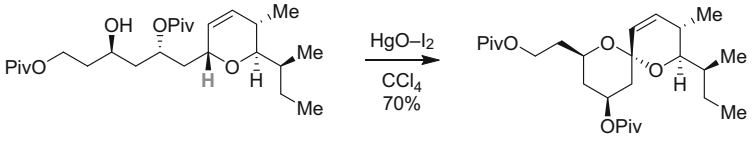
CHD = 1,4-cyclohexadiene
L = bis-[1,1,1-trifluoro-2-(oxo-κO)-4-phenylbut-3-en-4-olato-κO]

Scheme 64 Cyclisation of alkenols in the presence of cobalt(II) complexes under oxidative conditions

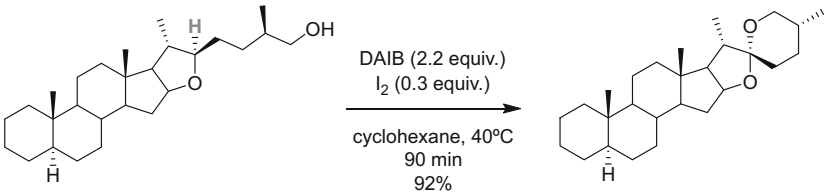
photolysis, the corresponding hypoiodites are directly converted into tetrahydrofurans. Hypoiodites are too unstable to be stored and must be prepared in situ from the free alcohols by reaction with an oxidant (e.g. lead tetraacetate, mercury oxide, silver oxide, iodosobenzene diacetate or diphenylhydroxyselenium acetate) in the presence of iodine. When the hydrogen atom abstraction takes place in the alpha position of an alkoxy group, the resulting carbon-centred radical is either rapidly oxidised into oxonium ion under the reaction conditions, or it evolves by intermolecular hydrogen atom abstraction to give the corresponding enol ether. Whatever the nature of the postulated intermediate, spontaneous cyclisation occurs with the free alcohol to give the corresponding cyclic acetals. In the following example, Danishefsky and co-workers used a highly regioselective 1,6-HAT to access the spirocyclic system of avermectin A_{1a} (Scheme 65) [276]. The high stabilisation energy for the formation of the carbon-centred, allylic, α-alkoxy radical accounts for the complete regioselectivity in favour of the 1,6-HAT [277–279] over the entropically favoured 1,5-HAT.

The Suárez group showed that some of the side reactions commonly observed with the lead tetraacetate–iodine couple, such as the formation of lactol and/or α-iodo-tetrahydrofurans, can be usually suppressed by the use of iodosobenzene diacetate (DAIB)–iodine to mediate the reaction [278]. Under these mild reaction conditions, tetrahydrofurans and tetrahydropyrans could be obtained in high yields from the corresponding linear alcohols (Scheme 66). Deuterium labelling experiments, with complete retention of the deuterium atoms at the 5-position, support a direct 1,6-HAT process to account for the formation of six-membered ring spiroketals. The alternative mechanism involving a 1,5-HAT followed by elimination to give the enol ether and H–I, and then acid-catalysed ionic addition of the free alcohol, could then be excluded in this case [277].

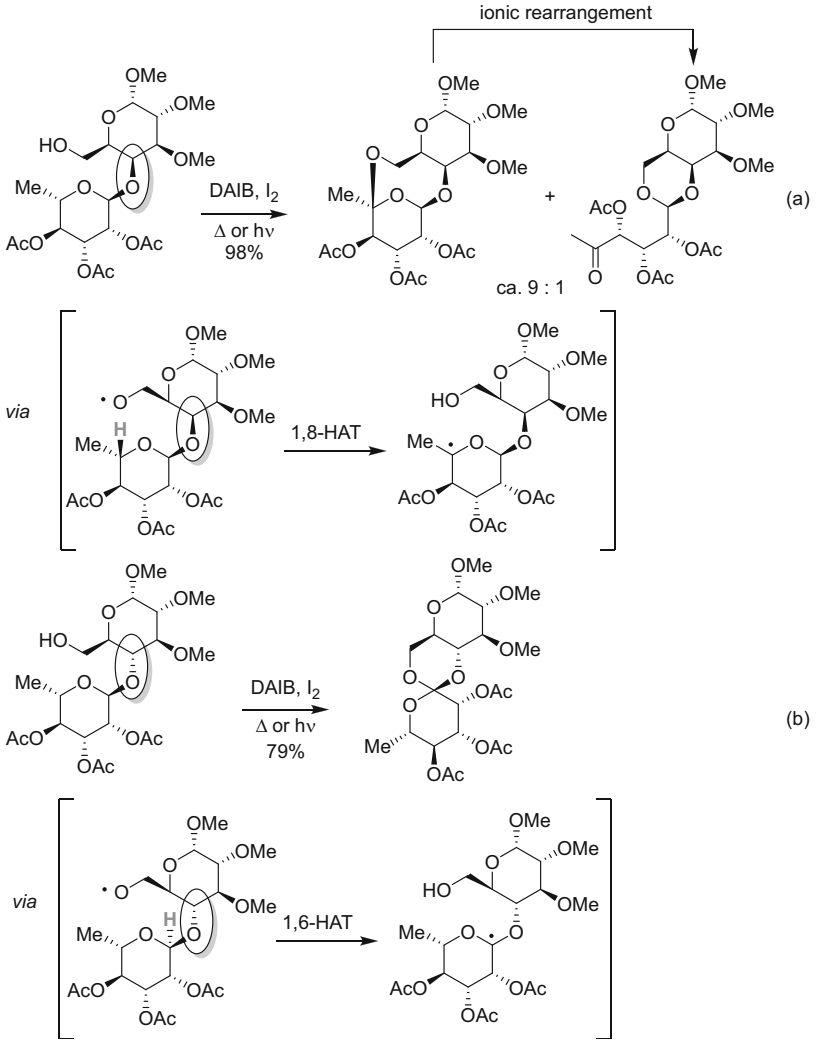
Highly regioselective intramolecular 1,6- and 1,8-hydrogen atom abstractions have been observed between glucopyranose moieties in disaccharides [280, 281]. The Suárez group demonstrated that the inversion of one single stereogenic centre could reverse completely the regioselectivity of the hydrogen atom abstraction. As previously, under oxidative conditions (DAIB, I_2), the carbon-centred radical resulting from the translocation process is presumably oxidised into the corresponding carbocation. Ionic cyclisation of the free hydroxyl onto the oxonium ion led either to 1,3,5-trioxocane system or to spirocyclic systems, depending on the regioselectivity of the hydrogen atom abstraction by the alkoxy radical intermediate (Scheme 67). Similar translocation reactions have been found to



Scheme 65 Danishefsky's approach to the spirocyclic system of avermectin A_{1a}



Scheme 66 Suárez' conditions for highly regioselective intramolecular hydrogen atom abstraction



Scheme 67 Regioselective 1,6- versus 1,8-HATs in carbohydrates

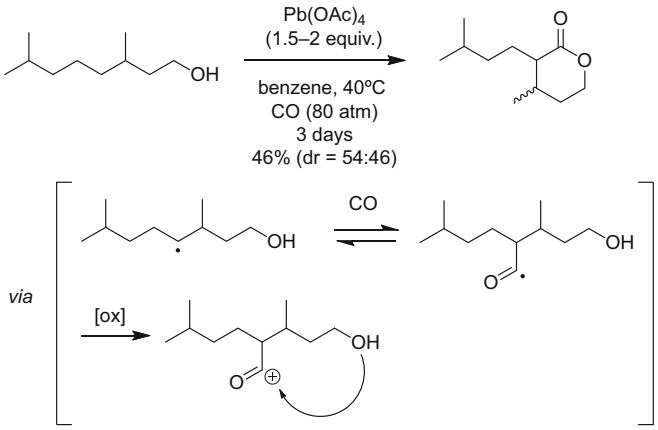
take place in disaccharides containing furanose units [282], as well as in more complex cyclodextrins, where these intramolecular 1,8-HATs allowed for highly selective modifications [283, 284].

The carbon-centred radical generated during the 1,5-HAT process can be trapped by CO to give the corresponding acyl radical. Ryu and co-workers showed that linear alcohols could be converted into δ-lactones in moderate to good yields in the presence of $Pb(OAc)_4$, under diluted conditions (benzene, 0.02 M) and under a high pressure of CO (105 atm). The temperature (40°C) proved to be crucial as the formation of tetrahydrofurans was found to be a competing reaction at higher temperatures. Under the optimised reaction conditions, regioselective 1,5-HATs occurred at the most activated positions (Scheme 68) [285].

4.1.4 Cyclisation of Peroxy Radicals to Give Endoperoxides

Biosynthesis of Prostaglandins

In nature, cyclic endoperoxides are formed when polyunsaturated lipids undergo peroxidation [286–290]. Arachidonic acid possesses three C=C bonds and bis-allylic positions and is thus a very good substrate for the formation of carbon-centred radicals via hydrogen atom abstraction at the allylic positions. The reaction with molecular oxygen results in the formation of a peroxy radical that can either fragment, abstract a hydrogen atom or cyclise to give a variety of isoprostane endoperoxides. As the formation of isoprostanes does not require the involvement of an enzyme, the compounds are synthesised as racemic mixtures. On the contrary, the enzymatic formation of prostaglandin H_2 (PGH_2) endoperoxide [288, 291] from arachidonic acid involves "classical" radical reactions, whose stereochemistry is controlled by the enzyme cyclooxygenase (COX). The radical cascades for the



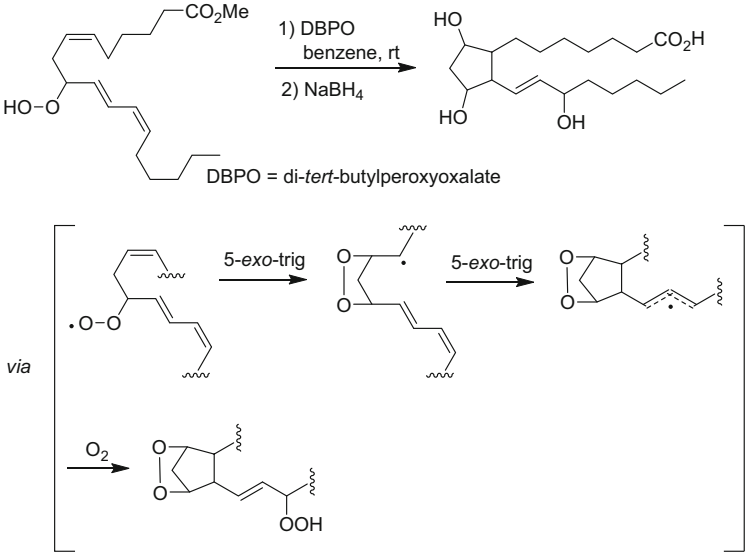
Scheme 68 Ryu's conditions for the preparation of lactones via a 1,5-HAT/carbonylation sequence

production of both PGH_2 and isoprostanes involve the 5-*exo*-trig cyclisation of a peroxy radical [292]. Besides the fact that prostaglandins are optically active and isoprostanes are not, one of the key differences between prostaglandins and most of isoprostanes is the *cis* relative configuration of the side chains on the latter. Porter postulated that a second route, independent of COX, could also lead to bioactive prostaglandins in vivo from isoprostanes. Indeed, prostaglandins such as PGD_2 and PGE_2 could be obtained by a simple epimerisation mechanism from the corresponding isoprostanes. Such a route is potentially of significant importance as this process would not be inhibited by any COX inhibitors, including aspirin [293].

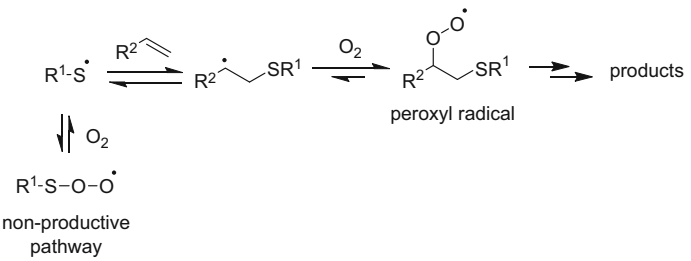
In the mid-1970s Porter developed a simple method to generate peroxy radicals from the corresponding hydroperoxides and studied their radical cyclisation under an atmosphere of molecular oxygen [294]. The methodology was applied to hydroperoxides derived from polyunsaturated fatty acids in order to support the mechanistic proposals for the biosynthesis of prostaglandins, which was believed to involve the cyclisation of a peroxy radical (Scheme 69) [295].

Oxidation with Molecular Oxygen: TOCO Process

Thiyl radicals form thiylperoxy radicals by reaction with molecular oxygen. The reaction occurs at diffusion-controlled rates, but because the reverse process is also a very fast process, cascade reactions involving thiyl radicals, alkenes (or alkynes) and molecular oxygen can be realised (Scheme 70).



Scheme 69 Porter's biomimetic synthesis of biologically relevant endoperoxides

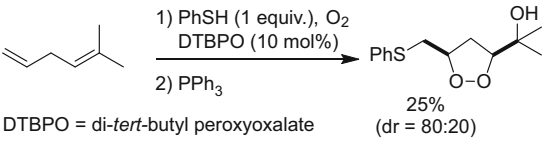


Scheme 70 General reaction mechanism of the thiol-olefin co-oxidation (TOCO) process

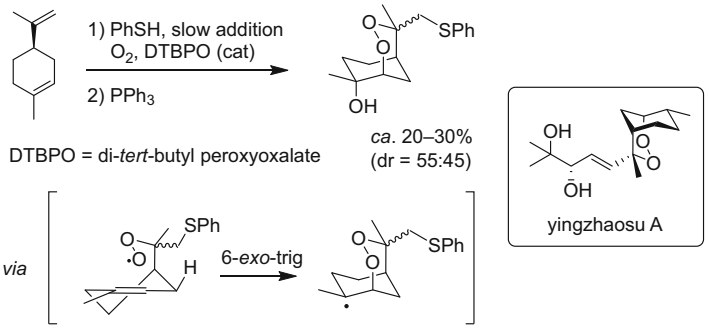
Since the pioneering work of Kharasch in the early 1950s [296], the thiol-olefin co-oxidation (TOCO) process has been extensively studied. The peroxy radical obtained by reaction between the carbon-centred radical resulting from the thiyl radical addition and molecular oxygen can abstract a hydrogen atom to give hydroperoxide. When the TOCO process is carried out onto polyunsaturated systems, the peroxy radical intermediate can engage in intramolecular addition reaction to give an endoperoxide. The TOCO process was tested onto 1,3-dienes [297], 1,4-dienes [298], 1,5-dienes [299, 300], 1,3,6-trienes [20, 301, 302], as well as conjugated enynes [303, 304]. For the formation of endoperoxides to be successful, it is crucial that intramolecular addition of the peroxy radical onto the alkenyl side chain competes favourably with hydrogen atom abstraction from the thiol [286, 299, 300, 305, 306]. Using this approach 1,2-dioxolanes were prepared in moderate yields from 1,4-dienes (Scheme 71) [298] and 1,3,6-trienes [301, 302].

The preference for the formation of *cis*-3,5-disubstituted 1,2-dioxolanes is in agreement with the Beckwith–Houk transition state model for 5-*exo*-trig cyclisations [20, 21, 307]. Six-membered ring endoperoxides were obtained from 1,5-dienes, as illustrated by Bachi's total synthesis of antimalarial agent yingzhaosu A (Scheme 72) and its C_{14} epimer [308]. A series of active analogues presenting promising activities for the treatment of malaria have also been prepared from limonene [309–315]. The formation of six-membered ring endoperoxides is extremely challenging, the 6-*exo*-cyclisation process involving the reactive oxygen-centred radical being in competition not only with hydrogen atom abstraction from the thiol but also 1,5-HAT from the allylic position. The yields of these endoperoxides remain relatively low (ca. 20–30%, calculated on the diene) [313], but still synthetically useful thanks to the low cost and accessibility of the reactants (thiophenol, limonene and oxygen).

Feldman applied the TOCO process to vinylcyclopropanes. In this variant, the carbon-centred radical resulting from the initial addition of the thiyl radical is a cyclopropylmethyl radical. The latter fragments rapidly to give a new carbon-centred radical that reacts with molecular oxygen. The resulting peroxy radical is now ideally located to undergo 5-*exo*-trig cyclisation onto the allylsulphide moiety to give, after β-fragmentation, 1,2-dioxolane and a thiyl radical that propagates the chain [316–319].



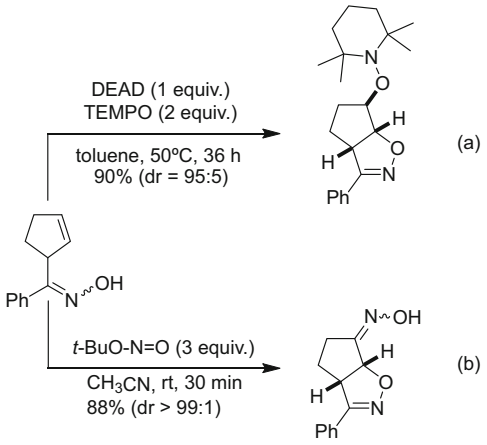
Scheme 71 Thiol-olefin co-oxidation (TOCO) process applied to the preparation of endoperoxides



Scheme 72 Bachi's total synthesis of antimalarial agent yingzhaosu A

4.1.5 Cyclisation of Oxime Radicals and Related Species

More recently, the chemistry of oxygen-centred radicals has witnessed a renewed interest with the use of alternative sources for these species. Amongst them, oximes are particularly attractive, owing to their weak O–H bond (BDE about 80 kcal mol^{-1}) [320]. Although oxime radicals were long known [321, 322], their cyclisation onto alkenes has been studied only very recently. Han, Yu and co-workers showed that 4,5-dihydroisoxazolines could be efficiently prepared from simple β,-γ-unsaturated ketoximes. The 5-*exo*-trig radical cyclisation process via the oxygen atom can be achieved in the presence of a cobalt(II) catalyst, together with cyclohexa-1,4-diene as a hydrogen atom donor [323]. Dioxygenation takes place when the reaction is carried out in the presence of TEMPO, which serves as both a radical initiator and a radical trap for the carbon-centred radical species resulting from the cyclisation process (Scheme 73, Eq. a) [323, 324]. In this process, TEMPO abstracts the hydrogen atom from the O–H bond of the ketoxime to generate the oxime radical. The authors observed a significant increase in the yields by using TEMPO in conjunction with diethyl azodicarboxylate (DEAD). It is worthy of note that, under the same reaction conditions, the analogous γ,δ-unsaturated ketoximes underwent 5-*exo*-trig cyclisation via the nitrogen atom [324]. This sequence was modified to allow for the introduction of a new oxime moiety in the

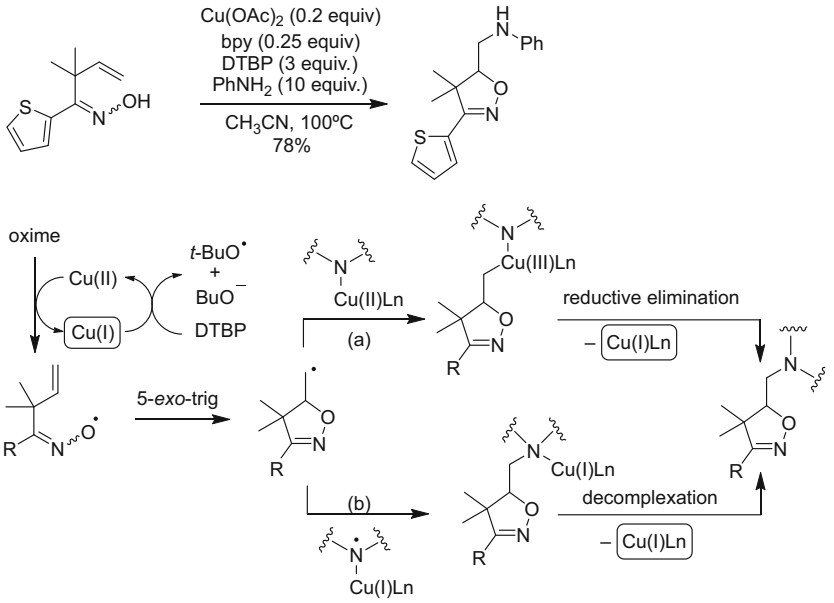


Scheme 73 Cyclisation of oxime radicals and subsequent trapping with TEMPO (Eq. a) or *tert*-butyl nitrite (Eq. b)

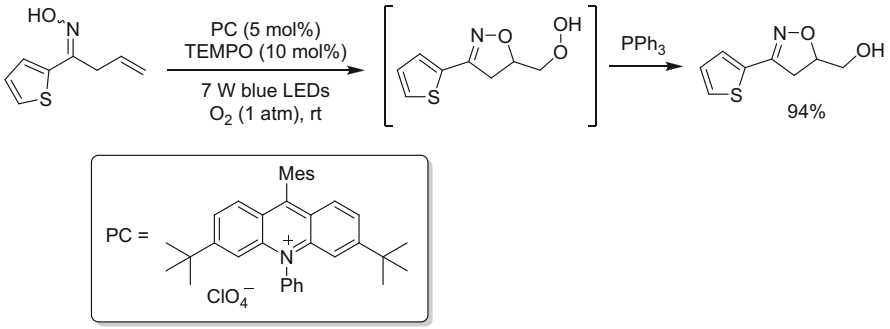
cyclised compound. The use of *tert*-butyl nitrite (TBN) as a radical trap in place of TEMPO led to functionalised 4,5-dihydroisoxazolines in moderate to good yields (Scheme 73, Eq. b) [325].

Related oxiamination of ketoximes has also been achieved by carrying out the reaction in the presence of a primary (or secondary) amine, di-*tert*-butyl peroxide (DTBP), and sub-stoichiometric amounts of $Cu(OAc)_2$ (Scheme 74) [326]. The peroxide can be advantageously replaced by oxygen by simply carrying out the reaction under an air atmosphere. The proposed reaction mechanism involves the formation of the iminoxyl radical by SET to the Cu(II) species, followed by 5-*exo*-trig cyclisation. Depending on the length of the alkenyl side chain, radical cyclisation can occur either via the oxygen or via the nitrogen atom. The carbon-centred radical resulting from the cyclisation process reacts then with an amine Cu (II) complex (pathway a) or, alternatively, with an aminyl radical Cu(I) complex (pathway b). Both routes lead ultimately to the oxiamination product, a nitrogen-containing 4,5-dihydroisoxazole.

The radical cyclisation of ketoxime radicals was also performed under visible light-induced photocatalysis conditions. Chen reported that the cyclisation of β,-γ-unsaturated ketoximes could be achieved in acetonitrile upon irradiation with 7 W blue LEDs (450–460 nm), in the presence of 9-mesityl-10-methylacridinium perchlorate (5 mol%) as a photocatalyst. The resulting hydroperoxides were reduced in situ into the corresponding alcohols by treatment with triphenylphosphine. In this reaction, TEMPO serves as a single-electron transfer co-catalyst (Scheme 75) [76].



Scheme 74 Han and Yu's conditions for the intramolecular oxiamination of alkenes



Scheme 75 Chen's conditions for the cyclisation of β,γ-unsaturated ketoximes

4.2 Sulphur-Centred Radicals

4.2.1 Thiyl Radicals

The reactivity of thiyl radicals has been studied and discussed in details in several comprehensive reviews [327–333]. Specific aspects of this chemistry such as the intramolecular thiol–ene coupling reaction [334], the thiol–yne version [335–338] and the reversibility of the addition have already been discussed [339]. Only specific

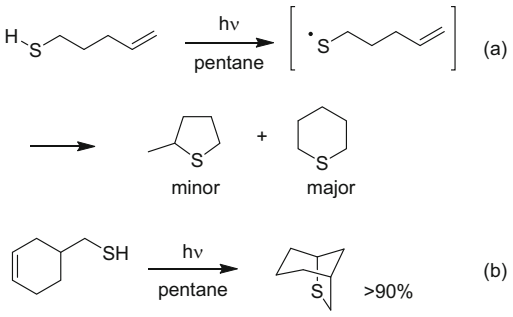
data relevant to the preparation of sulphur-containing heterocycles will be discussed here.

Thiyl radicals can be generated from the corresponding thiols or disulphides [333]. Alkanethiols and arenethiols transfer hydrogen atoms to alkyl radicals with high rate constants [$k_H = 2.8 \times 10^7$ M^{-1} s^{-1} (at 25°C) for the reaction of an alkanethiol with a primary alkyl radical] [340]. Accordingly, almost any classical radical initiator will allow for the generation of thiyl radical under thermochemical initiation. The S–S bond in disulphides is much weaker than any S–H bonds, and this is then easier to cleave photochemically [341].

To understand the regioselectivity of intramolecular thiol–ene reaction, it is necessary to have in mind some aspects of the kinetics for the intermolecular process. The addition of thiyl radicals onto unsaturated system is, in most cases, a fast and reversible process [342]. The kinetics for the intermolecular addition of a thiyl radical to an alkyne does not differ largely from the addition onto alkenes [343]. On the contrary, the reverse reaction that releases the thiyl radical is rather slow from the adducts obtained by addition onto alkynes, while it is a rapid process in the case of the thiol–ene reaction [339]. Therefore, differences in terms of regioselectivity can be expected in the intramolecular versions of the thiol–ene and thiol–yne reactions.

Cyclisation of Thiyl Radicals

The intramolecular addition of thiyl radicals to alkenes leads to sulphur-containing heterocycles. Due to the reversibility of the addition of thiyl radicals onto alkenes, the thermodynamically favoured six-membered rings can be formed preferentially over the corresponding five-membered rings. Surzur and co-workers extensively studied the cyclisation of alkenyl mercaptans. They showed that the 6-*endo*-trig cyclisation was usually favoured for this type of cyclisation (Scheme 76, Eq. a) [344–350]. They attributed the formation of a mixture of compounds resulting from 5-*exo*-trig and 6-*endo*-trig cyclisation processes to the reversibility of the radical addition. Accordingly, both the temperature and the dilution proved to impact the



Scheme 76 Surzur's seminal work on the cyclisation of thiyl radicals

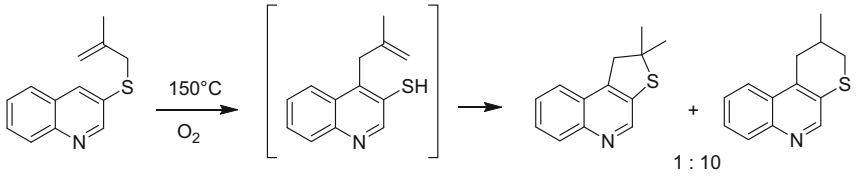
product distribution [344–346]. In some specific cases, highly regioselective processes have also been observed, as it is the case for the formation of thia-6-bicyclo [3.2.1]octane (Scheme 76, Eq. b) [351]. Under the reaction conditions used by the authors, most allylic amines could be cyclised without the hydrogen abstraction from the allylic position competing with the cyclisation process [352, 353]. These intramolecular hydrogen atom transfers were nevertheless observed in several cases, as, for instance, during the cyclisation of *N*-allyl-2-aminothiols under chemical or photochemical initiation [352–357].

In some specific cases, the radical cyclisation proved to complement nicely alternative ionic processes in terms of regioselectivity. For instance, the radical cyclisation of methallyl-3-quinolyl sulphide carried out in the presence of a radical initiator, such as oxygen or benzoyl peroxide, or, alternatively, promoted upon UV light irradiation, gave the 6-*endo*-trig cyclisation product selectively (Scheme 77) [358, 359], in stark contrast with the related acid-catalysed version [360, 361].

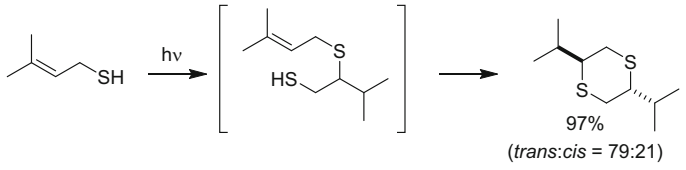
The intramolecular thiol–ene reaction was applied to suitably substituted disulphides for the preparation of penicillin derivatives, and it was observed that the regioselectivity could be controlled by the dilution conditions [362–365].

1,4-Dithianes have been obtained upon irradiation by dimerisation of prenyl mercaptan followed by a 6-*exo*-trig cyclisation process (Scheme 78) [366].

Following these pioneering works, the intramolecular thiol–ene strategy to access tetrahydrothiopyrans has been overlooked for about 20 years. It is only recently that more elaborate precursors have been tested in this reaction. The Scanlan's group reported an elegant approach for the preparation of thiosugar derivatives based upon this strategy [367]. The precursors were easily prepared from *per*-benzylated sugars. The radical cyclisation took place under mild conditions (DMF at room temperature), upon UV light irradiation in the presence of a radical initiator (2,2-dimethoxy-2-phenylacetophenone, DPAP) and a photosensitiser (4-methoxy-acetophenone,



Scheme 77 Regioselective 6-*endo*-trig cyclisation of methallyl-3-quinolyl sulphide

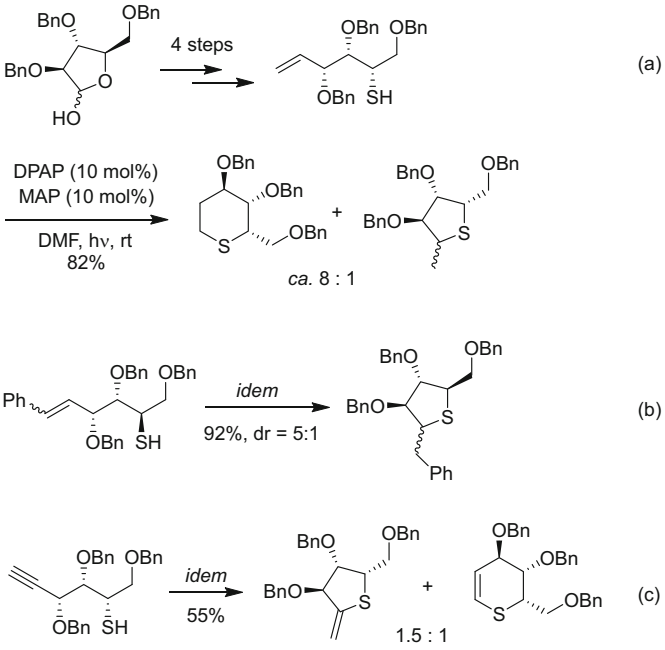


Scheme 78 Preparation of 1,4-dithianes by dimerisation of allyl mercaptans

4-MAP). As previously observed, the *endo*-cyclisation products were obtained preferentially from simple terminal alkenes (Scheme 79, Eq. a), but the regioselectivity could be fully reversed by using a more substituted alkene or a styrene derivative. In this case, this strategy gave access to thiofuranoside derivatives in excellent yields and good to excellent levels of stereoselectivity (dr up to >13:1) (Scheme 79, Eq. b) [368]. The first examples of intramolecular thiol–yne reaction were also reported by the same group [369]. In this case, careful handling of the thiol precursors proved crucial in order to prevent ionic cyclisation leading to 5-*exo*-thioglycals. The regioselectivity of the radical reaction was found to depend upon the relative configuration in the precursors (Scheme 79, Eq. c). The intramolecular thiol–ene reaction was also applied to preparation of large-membered rings, such as cyclic peptides [370].

Radical Cascades Involving Cyclisation onto the Unsaturated Partner Introduced with the Heteroatom-Centred Radical

The cascade reactions described here are limited to examples involving an initial intermolecular thiol–ene or thiol–yne step. They are followed by the intramolecular trapping of the resulting carbon-centred radical by subsequent addition onto the substituent introduced with the thiol or, alternatively, by intramolecular homolytic



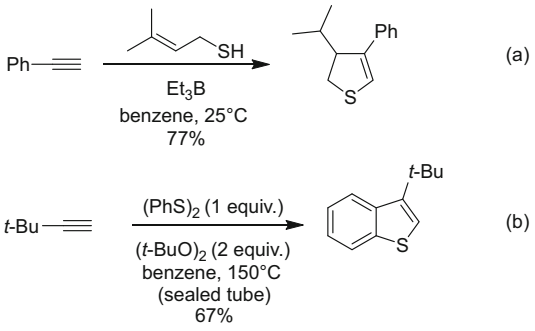
Scheme 79 Scanlan's approach to thiosugar derivatives

substitution (S_Hi) at the sulphur atom. Some of them initially appeared as side reactions, but became efficient routes to specific classes of heterocycles after careful optimisation.

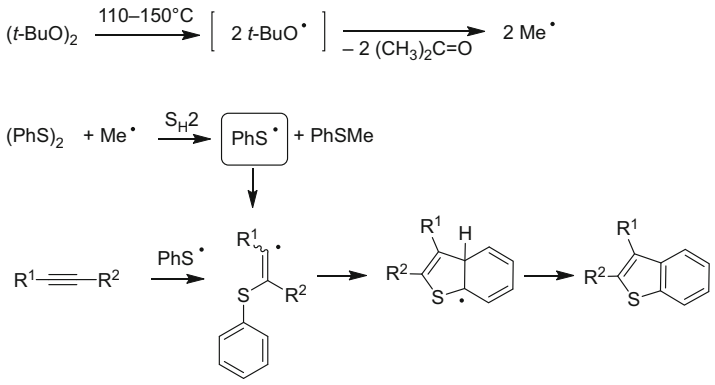
As mentioned before (see Scheme 78), allyl mercaptans tend to dimerise to give 1,4-dithianes. However, in the presence of a terminal alkyne, the course of the reaction changes dramatically. Oshima and co-workers showed that dihydrothiophene derivatives could be obtained via an Et_3B-promoted annulation reaction involving a 5-*exo*-trig cyclisation (Scheme 80, Eq. a) [371]. Not only allyl mercaptans but also other unsaturated thiols, such as arene thiols and the corresponding disulphides, can take part in such annulation processes. The process leads to substituted benzo[*b*]thiophene derivatives via the cyclisation of the alkenyl radical intermediate onto the aromatic ring of the thiol and subsequent aromatisation (Scheme 80, Eq. b) [372–375].

The efficiency of the initiation with di-*tert*-butyl peroxide was explained by the fragmentation of the *tert*-butoxyl radical at high temperature to give acetone and a methyl radical. The latter undergoes homolytic substitution at the sulphur atom in diaryl disulphides to give the corresponding thioether and the arenethiyl radical, which adds to the terminal position of the alkyne. The resulting alkenyl radical cyclises onto the aromatic group, and aromatisation leads to the observed product (Scheme 81).

This type of cyclisation onto the aromatic (or heteroaromatic) substituent of thiols also explains skeletal rearrangements observed in the addition of unsaturated thiols to alkynes [374, 376–379]. Depending on the substitution, the cyclisation of the alkenyl radical onto the aromatic substituent could occur either at the *ipso* or *ortho* position, with the *ipso* position being favoured because it leads to a resonance-stabilised radical intermediate. Not only C=C bonds but also unsaturated carbon–heteroatom bonds proved to be efficient radical traps for the radical resulting from the initial radical addition. Nanni and co-workers described cascade reactions involving the addition of alkane- and arenethiyl radicals presenting a cyano group at the β-position onto aromatic isonitriles [380, 381]. The cyclisation of the α-thioimidoyl radicals generated by addition of the thiyl radical bearing a cyano group at the β-position onto aromatic isonitriles must be faster than other competing intramolecular (the β-fragmentation leading to isothiocyanates) and intermolecular



Scheme 80 Oshima's approach to dihydrothiophene (Eq. a) and Montevecchi's synthesis of benzo[*b*]thiophenes (Eq. b)



Scheme 81 Mechanism of the formation of benzo[*b*]thiophenes from diaryl disulphides

(e.g. the hydrogen atom abstraction) reactions. For these reasons, disulphides (i.e. aromatic disulphides) usually gave better results than the corresponding thiols. Arenethiyls lead to α-thioimidoyl radicals that are less prone to undergo the C–S bond fragmentation. Their photolysis in the presence of aromatic isonitriles delivered polycyclic heterocycles in moderate to high yields (Scheme 82) [380, 381].

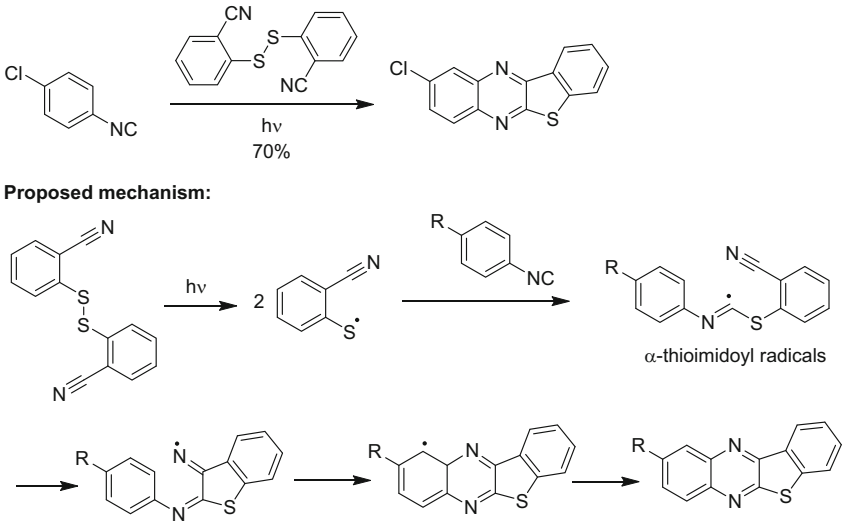
Homolytic Substitution at the Sulphur Atom

The formation of sulphur-containing heterocycles can be achieved by homolytic substitution at the sulphur atom. Only examples in which the sulphur atom was introduced by initial addition of a thiyl radical will be described here.

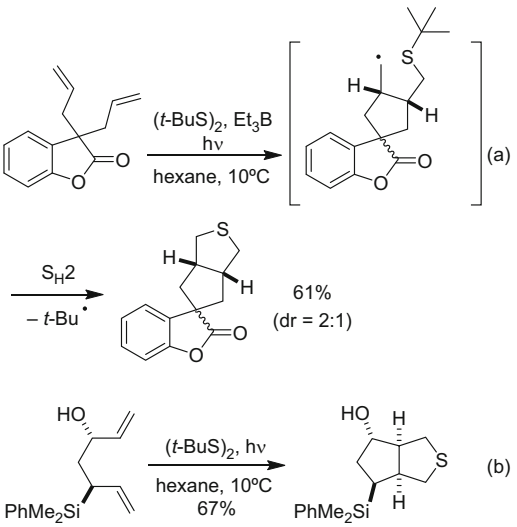
The addition of thiyl radicals to 1,6-dienes leads to cyclopentane derivatives via a 5-*exo*-trig cyclisation process. If the radical cyclisation is *cis*-selective, as expected for a 5-*exo*-trig cyclisation of this type [21, 307], then the carbon-centred radical resulting from the cyclisation is in a suitable position to undergo intramolecular homolytic substitution (S_Hi) at the sulphur atom [382], delivering thiabicyclo[3.3.0] derivatives. For instance, thiabicyclo[3.3.0] skeletons were prepared in good yields from simple 1,6-dienes (Scheme 83, Eq. a) [383], as well as 1,6-dienes presenting an allylsilane moiety (Scheme 83, Eq. b) [384]. This type of homolytic substitution is possible only if the C-centred radical released during the process is reasonably stabilised [383, 384]. Accordingly, the use of dialkyl disulphides leading to stabilised carbon-centred radicals should facilitate the ultimate cyclisation. This trend, however, is not always followed [385].

Similarly, 1,6-diynes proved to be suitable partners in such radical cascades, leading eventually to thieno[3,4,*c*]pyrroles. For instance, *N*,*N*-bis-(2-propynyl) benzenesulfonamide could be converted into 5-(phenylsulfonyl)-5,6-dihydro-4*H*-thieno[3,4,*c*]pyrrole in the presence of thioacetic acid and AIBN (Scheme 84, Eq. a) [386]. Dihydrothiophenes have also been prepared following this strategy by using this time 1,6-enynes, in the presence of either thiols under thermal initiation

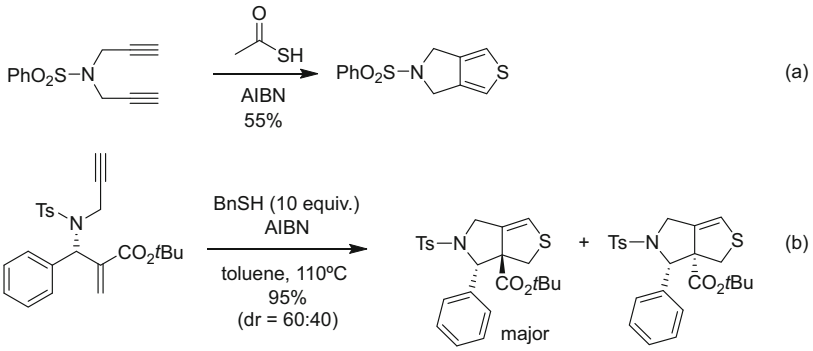
(Scheme 84, Eq. b) or dimethyl disulphides upon irradiation (hν > 340 nm) at room temperature [385].



Scheme 82 Cascade reactions involving arenethiyl radicals



Scheme 83 Harrowven (Eq. a) and Landais' approach (Eq. b) to thiabicyclo[3.3.0] derivatives



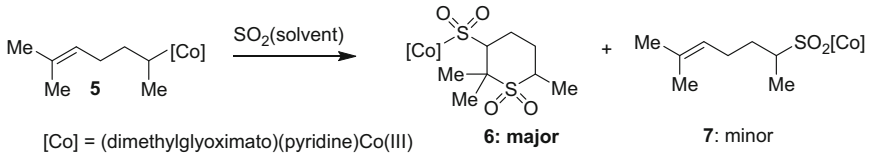
Scheme 84 Padwa's approach to thieno[3,4,*c*]pyrroles (Eq. a) and Kamimura's synthesis of dihydrothiophenes (Eq. b) based upon S_Hi at the sulphur atom

4.2.2 Sulphonyl Radicals

A variety of precursors have been used to generate alkane- and arenesulphonyl radicals. Despite the numerous methods existing for their production, very few examples of intramolecular additions of sulphonyl radicals onto alkenes or alkynes have appeared in the scientific literature. This is in stark contrast with the intermolecular approach, which is well documented under atom transfer radical addition (ATRA) conditions. Intramolecular additions of an alkanesulphonyl radical should be favoured over the competitive SO_2 extrusion leading to carbon-centred radicals [387–390].

Alkylcobaloximes have been used as a source of carbon-centred radicals under photochemical initiation to give persistent cobalt complexes [391, 392]. In the 1970s, Johnson and co-workers showed that the insertion of sulphur dioxide used as solvent into some organocobaloximes took place via a free-radical mechanism involving sulphonyl radicals as reactive intermediates [393]. The initial photolysis of the carbon–cobalt bond in organocobaloxime **5** leads to a carbon-centred radical, which can be trapped by SO_2. The resulting sulphonyl radical can then recombine to give the insertion product. The presence of a carbon–carbon double bond can change the course of the reaction, and the cyclisation of the sulphonyl radical, preferentially in a 6-*endo* mode, was observed. When SO_2 is used as a solvent, the carbon-centred radical resulting from the cyclisation process could be trapped to give a new sulphonyl radical, which ultimately recombines with the persistent cobalt(II) complex to give cyclic organocobaloxime **6** containing two SO_2 moieties (Scheme 85) [394]. The reversibility of the radical addition of sulphonyl radicals to alkenes was postulated to account for the formation of the thermodynamically favoured 6-*endo*-trig cyclisation products.

Upon photolysis of the carbon–cobalt bond in the presence of trichloromethanesulfonyl chloride, sulphonyl radicals can be generated and trapped to give sulphonyl halides in high yields, presumably via a non-chain radical mechanism [395]. Different hypotheses have been proposed to explain the formation of the



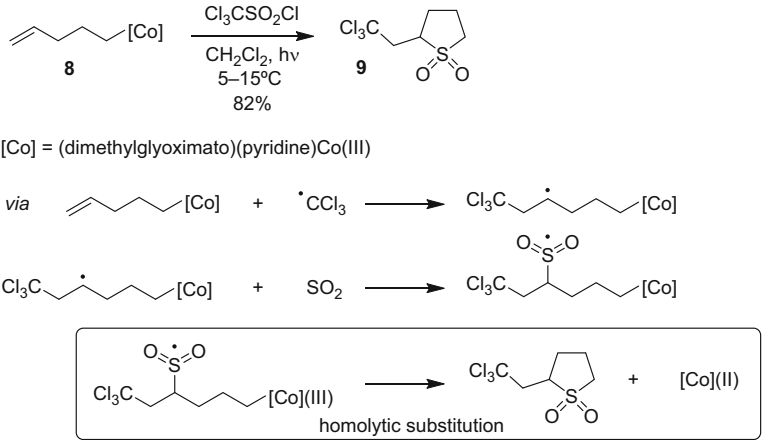
Scheme 85 Cyclisation of organocobaloximes using SO_2 as a solvent

carbon–sulphur bond, including a homolytic substitution at sulfone, but this possibility seems unlikely in the light of more recent studies [396, 397]. The course of the reaction with unsaturated substrates is dramatically different. For instance, the photolysis of pent-4-enylbis(dimethylglyoximato)(pyridine)cobalt(III) **8** under irradiation by a tungsten lamp and in the presence of trichloromethanesulfonyl chloride gave trichloromethanesulfolane **9** as the major product (82% yield) (Scheme 86) [394, 398]. In this case the preferential formation of the five-membered ring over the six-membered ring was explained by the initial addition of a trichloromethyl radical to the terminal position of the alkene, followed by trapping of the resulting carbon-centred radical by SO_2 (generated by loss of SO_2 from the trichloromethyl sulphonyl radicals). It was suggested that the sulphonyl radical could then undergo a homolytic substitution at the alpha-carbon of the carbon–cobalt bond to form the five-membered ring and a cobaloxime(II) complex, which could then propagate the chain by reacting with trichloromethanesulfonyl chloride [398]. However, alternative mechanisms cannot be excluded.

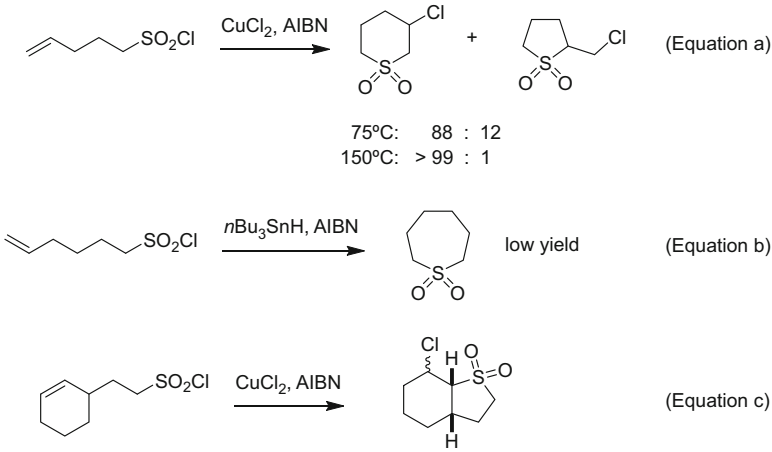
The radical cyclisation of unsaturated sulphonyl chlorides was examined by Walton and Culshaw. The cyclisation of pent-4-enesulfonyl chloride in the presence of $Cu(II)Cl_2$/AIBN or $Ru(II)Cl_2(PPh_3)_3$ at high temperature (150–170°C) led to 3-chlorotetrahydrothiopyran-1,1-dioxide as the major compound (Scheme 87, Eq. a). The low yields of isolated products are probably due to the competing loss of SO_2 that can easily occur at such high temperatures [388, 399]. At lower temperature (75°C), the 5-*exo*-trig cyclisation product could be observed as the minor regioisomer in the Cu(II)-catalysed reaction. Larger rings could be prepared by this approach, as illustrated by the nBu$_3$SnH-mediated 7-*endo*-trig cyclisation of hex-5-enesulfonyl chloride leading to thiepane-1,1-dioxide (Scheme 87, Eq. b) [388, 399]. The mechanism of the Cu(II)-catalysed radical cyclisation of unsaturated sulphonyl chlorides involves a chlorine atom transfer from $CuCl_2$ to the carbon-centred radical resulting from the cyclisation step. The Cu(I)Cl thus generated can propagate the chain by abstracting the chlorine atom from another molecule of sulphonyl chloride. *Exo*-cyclisation modes have been observed for rigid substrates that do not allow for the *endo*-cyclisation to proceed (Scheme 87, Eq. c) [388, 399].

More recently, much higher yields were obtained for the cyclisation products by applying this methodology to non-volatile compounds presenting the spongiane skeleton (Scheme 88) [400].

During their studies on the use of *N*-allylsulfonimides as precursors for amidyl radicals, Zard and Moutrille observed the radical cyclisation of the *N*-amidosulfonyl radical intermediate (Scheme 89) [157]. The nature of the substituent on the nitrogen



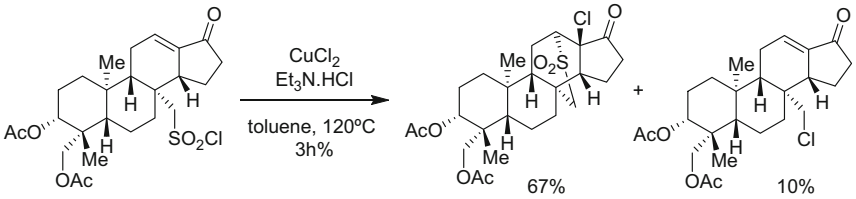
Scheme 86 Photolysis of pent-4-enylbis(dimethylglyoximato)(pyridine)cobalt(III) in the presence of trichloromethanesulfonyl chloride



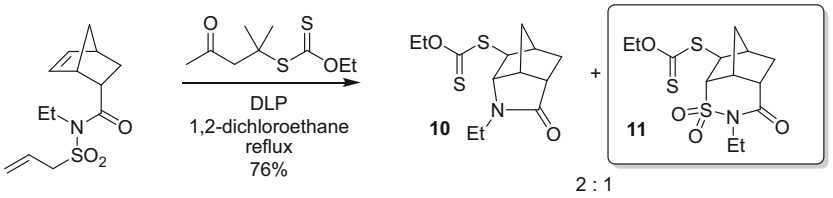
Scheme 87 Radical cyclisation of unsaturated sulphonyl chlorides

atom proved crucial as it influences the loss of SO_2. For instance, the presence of a phenyl group accelerates the SO_2 extrusion sufficiently to avoid the formation of the product resulting from the cyclisation of the *N*-amidosulfonyl radical intermediate, leading exclusively to the γ-lactam. This effect is in agreement with the enthalpies of formation of amidyl radicals [401].

In this case, the carbon-centred radical generated by homolytic cleavage of DLP upon heating adds at the sulphur atom of the C=S bond to give a new radical species that undergoes fragmentation. Under these non-reducing conditions, the newly formed carbon-centred radical can add efficiently onto the C=C of the allyl sulfone



Scheme 88 Radical cyclisation of unsaturated sulphonyl chlorides applied to the spongiane skeleton



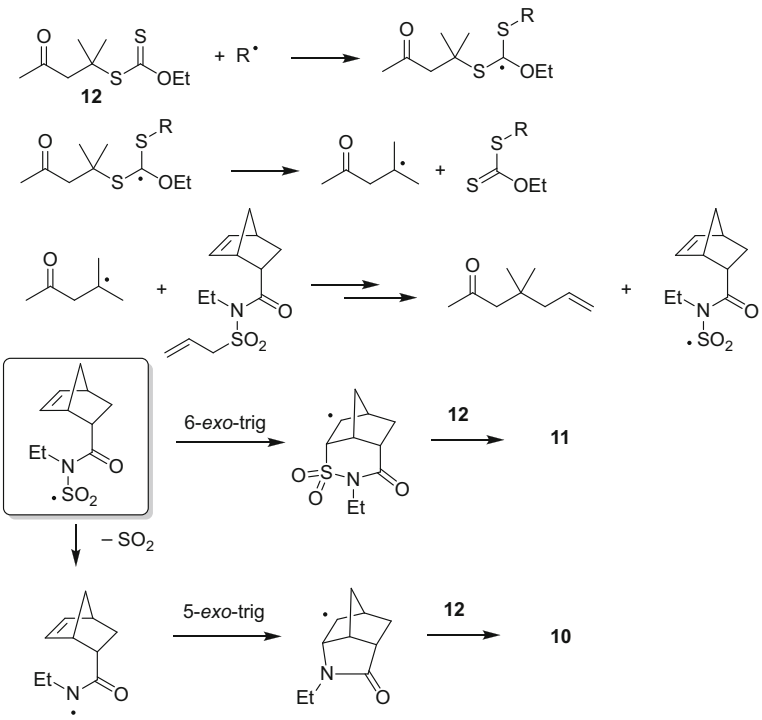
Scheme 89 Zard's cyclisation of a *N*-amidosulfonyl radical

moiety. The addition–fragmentation sequence releases a sulphonyl radical, which can either undergo 6-*exo*-trig cyclisation or, alternatively, evolve by SO_2 extrusion to give the corresponding amidyl radical, which undergoes 5-*exo*-trig cyclisation. The propagation of the radical chain is achieved by the trapping of the carbon-centred radical resulting from the 5-*exo*-trig cyclisation processes by the xanthate (Scheme 90).

4.3 Selenyl Radicals

Despite their renowned acute toxicity (organoselenium compounds are cumulative poison), several natural or synthetic compounds containing a selenium atom in their structure were found to have interesting biological properties [402, 403]. Despite the current interest in organoselenium compounds [404, 405], very few methods, if any, have been reported to access these types of valuable cyclic compounds via the cyclisation of selenyl radical species.

The addition of areneselenyl radicals to unsaturated systems is well established [406]. However, the reverse reaction is a very fast process, which competes with most intermolecular trapping, making the process non-productive in most cases. When another unimolecular process competes with the β-fragmentation, then the addition process can be clearly demonstrated. The addition of diphenyl diselenide to 1,6-enynes derivatives under photochemical initiation was found to give the



Scheme 90 Mechanism of the cyclisation of *N*-amidosulfonyl radical

corresponding cyclised adducts, indicating that the trapping of the alkenyl radical resulting from the initial attack could be faster than the reverse addition or the trapping by $(PhSe)_2$ [407]. Selenyl radicals can be trapped by nBu$_3$SnH to give the corresponding selenol derivatives [408]. The latter are extremely good hydrogen atom donors. A rate constant of $k_{SeH} = 1.2 \times 10^9$ M^{-1} s^{-1} (25°C) was determined for reaction of PhSeH with primary alkyl radicals [409], about one order of magnitude higher than those of nBu$_3$SnH or PhSH. The use of such a good hydrogen atom donor proved useful to prevent fragmentation reactions, such as the ring opening of strained radical species [410, 411]. It is therefore somewhat surprising that the cyclisation of unsaturated RSeH derivatives does not seem to have attracted more attention.

4.3.1 Selenium-Centred Radicals

Examples of cyclisation involving a selenyl radical and giving a heterocyclic structure in which the selenium atom is incorporated within the ring are, at best, very rare. Few reports on the preparation of such heterocycles describe the

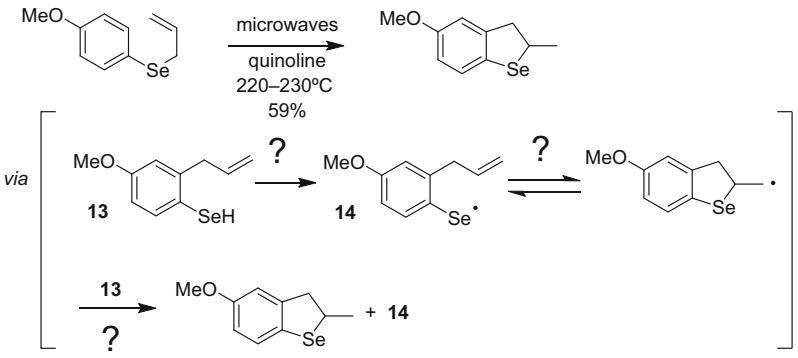
preparation and the cyclisation of a selenol (RSeH) derivative, but no evidence has been provided to support a radical mechanism.

Selenols having a C=C bond located at a suitable position for a radical cyclisation can be easily prepared from allyl phenyl selenides via a seleno-Claisen rearrangement [412]. The preparation of 2,3-dihydrobenzo[b]selenophene-5-ol, a potential antioxidant, was achieved via a sequence involving a seleno-Claisen rearrangement, followed by the cyclisation of the resulting selenol derivative (Scheme 91) [413]. Although no mechanistic rational was proposed by the authors, the formation of the product could be explained by a radical mechanism involving a 5-*exo*-trig cyclisation, followed by the rapid trapping of the resulting carbon-centred radical by hydrogen atom abstraction from a Se–H bond. However, at such high temperatures, an alternative ionic mechanism cannot be excluded.

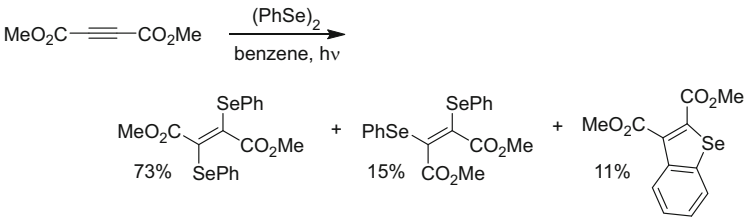
4.3.2 Addition–Cyclisation Cascade

Here again, very few examples of addition–cyclisation cascades have been reported. During the course of their work on the intermolecular addition of selenyl radicals onto electron-deficient alkynes, Back and Krishna reported that the formation of benzoselenophene was observed in the reaction between diphenyl diselenide and dimethyl acetylenedicarboxylate [414]. Besides the expected intermolecular trapping by diphenyl diselenide leading to 1,2-addition products, the alkenyl radical resulting from the addition of the phenylselenyl radical onto the alkyne undergoes cyclisation onto the aromatic ring. Following aromatisation, the benzoselenophene was isolated in 11% yield (Scheme 92) [414].

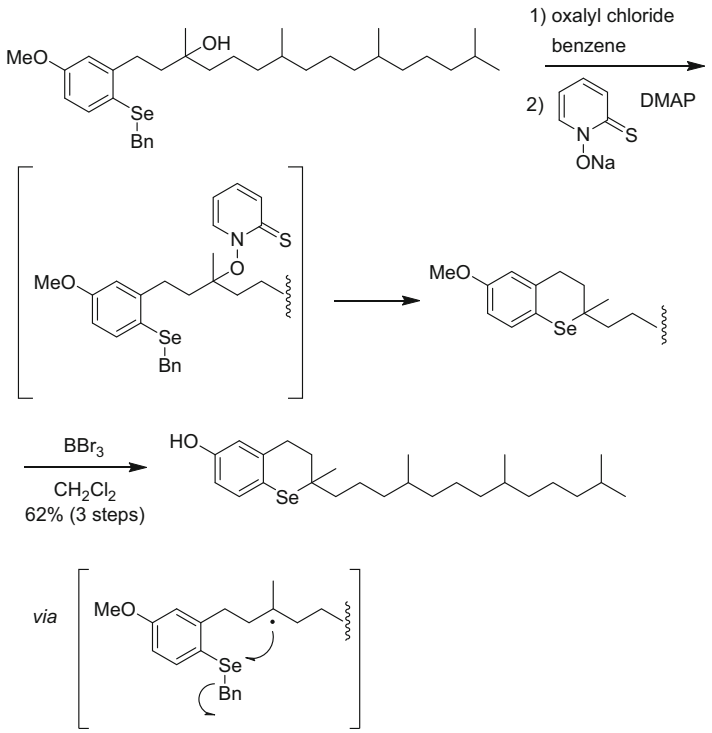
Currently, the most efficient radical approach to benzoselenophene derivatives and other types of Se-heterocycles relies on the cyclisation via intramolecular homolytic substitution (S_Hi) at the selenium atom (Scheme 93) [382, 415–426].



Scheme 91 Hypothetical mechanism for the formation of 2,3-dihydrobenzo[b] selenophene-5-ol derivatives from allyl aryl selenides



Scheme 92 Formation of a benzoselenophene derivative by condensation between an alkyne and a phenylselenyl radical



Scheme 93 Schiesser and Engman's synthesis of a selenium-containing vitamin E analogue via S_Hi at the selenium atom

5 Conclusion

Heteroatom-centred radicals have found numerous applications in the preparation of heterocyclic structures. Since the early developments of radical chemistry, heteroatom-centred radicals proved to undergo cyclisation onto unsaturated partners. Depending upon the nature of the radical species, these cyclisation processes were found to be, for some of them, reversible under certain conditions. Five-*exo*-trig

cyclisation processes are usually favoured over the 6-*endo* processes, but fundamental studies showed that this trend is dramatically influenced by the nature of the heteroatom involved in the radical cyclisation process. Highly reactive alkoxy and nitrogen-centred radicals also allow remote functionalisation via hydrogen atom abstraction from nonactivated positions, giving access to heterocyclic structures after ionic cyclisation. These hydrogen atom transfers (and more specifically 1,5-HAT at allylic positions) were found to compete with 6-*exo* cyclisation processes, making the formation of six-membered rings sometimes very challenging via a cyclisation strategy. Some heavy atoms, such as silicon and tin, or chalcogenides such as sulphur and selenium can also react via intramolecular homolytic substitution, offering an alternative to the formation of the heterocycles by direct cyclisation. In the last years, the burgeoning field of the photoredox catalysis allowed the chemistry of heteroatom-centred radicals to be revisited. Alternative methods have been developed to circumvent the problems posed by the lack of truly satisfying methods for the preparation of some of these radical species. For instance, more than a hundred years after the discovery of the Hofmann–Löffler–Freytag reaction, this reaction is still a topic of constant interest, as are other processes derived from it. In this context, the quest for innovative, optimised reaction conditions to solve chemoselectivity and regioselectivity issues of this powerful transformation is still very contemporary. Very mild reaction conditions have been developed to achieve complex transformations from simple precursors, and there is no doubt that the chemistry of some heteroatoms that have been partially overlooked until now will witness a second phase of their development in the near future.

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Metal-Mediated Oxidative Radical Processes for the Synthesis of Heterocycles

Ciputra Tejo and Shunsuke Chiba

Abstract This chapter describes recent development on synthesis of heterocycles via metal-mediated oxidative radical reactions. Oxidative radical processes enabling difunctionalization of carbon-carbon unsaturated bonds (alkenes or alkynes) or functionalization of carbon-hydrogen bonds for heterocycle synthesis will be discussed. The mechanistic insight of each transformation will also be addressed.

Keywords Cascade reactions • C-H functionalization • Difunctionalization of alkene • Heterocycles • Metals • Oxidation • Radicals • Single-electron transfer

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1 Introduction

Heterocyclic motifs are found in myriad of biologically active natural products and pharmaceutical compounds [1–4] as well as material-based application [5, 6]. There is therefore a high demand for efficient production of heterocycles of needs and interests [7–9]. Oxidative molecular transformations that incorporate heteroatom units into carbon-based organic scaffolds are one of the most frequently used methods to construct heterocyclic skeletons with enhancement of the molecular complexity. In this context, various radical species have been utilized under metal-mediated/catalyzed oxidative reaction conditions for the development of new methodologies to convert readily accessible substrates into highly oxidized targeted heterocycles. This chapter will cover the recent selected reports (mainly published in the last decade) on metal-mediated oxidative carbon-heteroatom bond formation for the construction of heterocycles via a free-radical mechanism.

2 Heterocycle Synthesis via Oxidative Difunctionalization of Alkenes or Alkynes

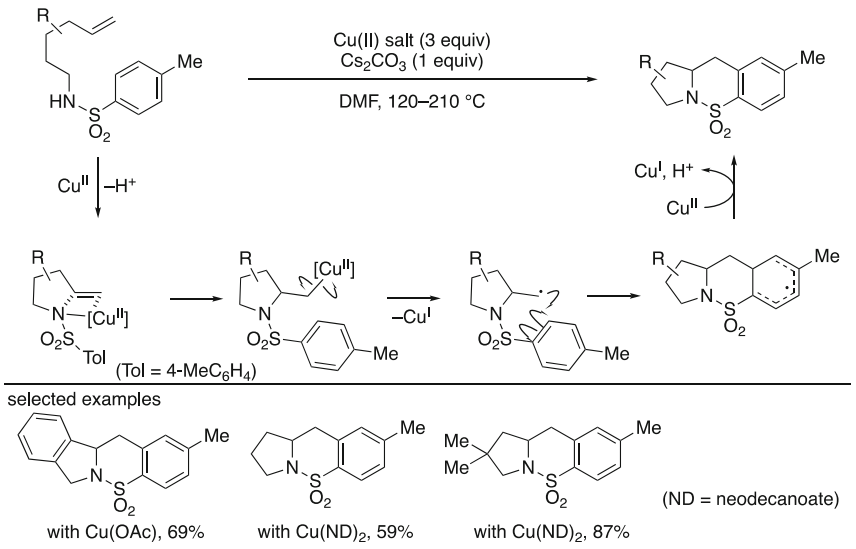
The construction of heterocycles triggered by cyclization or annulation onto alkenes or alkynes provides a variety of reaction patterns in terms of the functionality installed onto the heterocyclic scaffolds. The use of radical species or radical intermediates under metal-mediated/catalyzed oxidative reaction conditions enables facile oxidative difunctionalization of alkenes or alkynes.

2.1 Carboamination

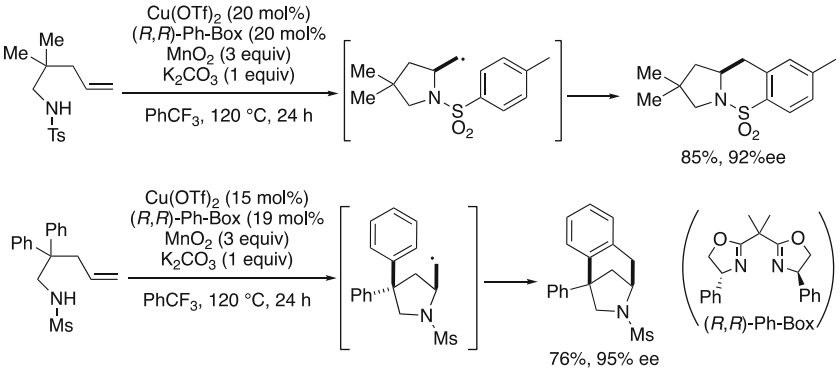
Chemler's group reported a Cu(II)-mediated intramolecular carboamination of *N*-alkenyl-*N*-arylsulfonamides for the synthesis of bicyclo[4.3.0]sultams (Scheme 1) [10]. Elucidation of the reaction mechanism revealed that the process is initiated by a concerted *syn* aminocupration of alkenes to provide organocopper(II) intermediates, which undergo homolysis of the C-Cu(II) bond to form the C-centered radicals [11]. Subsequent radical cyclization onto the aromatic ring followed by oxidation/re-aromatization affords bicyclo[4.3.0]sultams.

The catalytic asymmetric variant of this transformation was realized by using a combination of $Cu(OTf)_2$ and (*R*,*R*)-BOX ligand with MnO_2 as the terminal oxidant (Scheme 2) [12]. Interestingly, the reaction of *N*-mesyl-4-pentenylamines bearing the C2 geminal diphenyl moiety gave 6-azabicyclo[3.2.1]octanes [13, 14].

Matsunaga and Kanai reported the use of *N*-fluorobenzenesulfonylimide (NFSI) in the Cu(I)-catalyzed carboamination of unactivated alkenes, leading to the synthesis of sultam derivatives (Scheme 3) [15]. The process is initiated by a single-electron



Scheme 1 Cu(II)-catalyzed synthesis of bicyclo[4.3.0]sultams

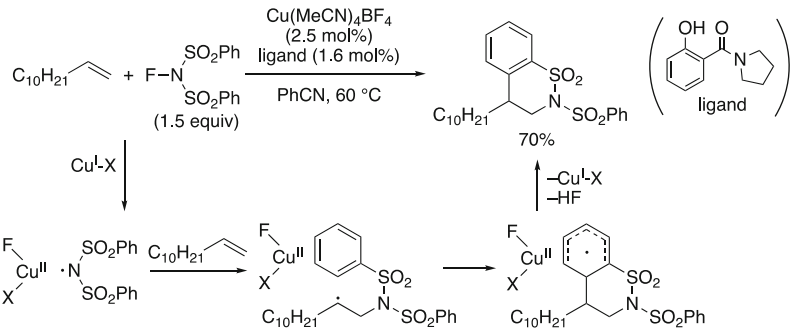


Scheme 2 Cu(II)-catalyzed enantioselective carboamination

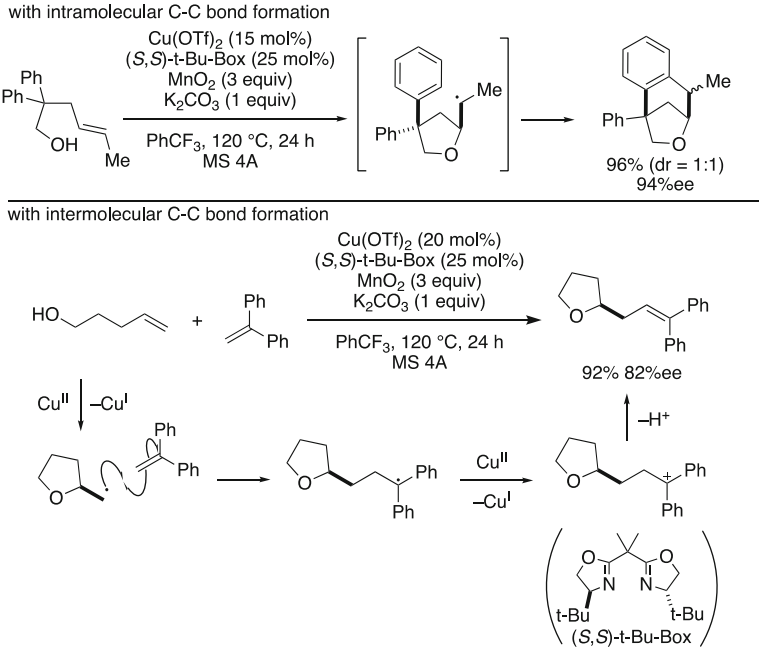
reduction of NFSI by the Cu(I) catalyst, generating a Cu(II)-bound sulfonylimide radical, which subsequently adds onto alkenes in an *anti*-Markovnikov fashion to provide C-centered radicals. The ensuing intramolecular radical cyclization onto the phenylsulfonyl moiety delivers sultams.

2.2 Carbooxygenation

Chemler's group successfully extended the Cu(II)-catalyzed MnO_2-mediated carboamination strategy to the corresponding carbooxygenation of alkenyl alcohols



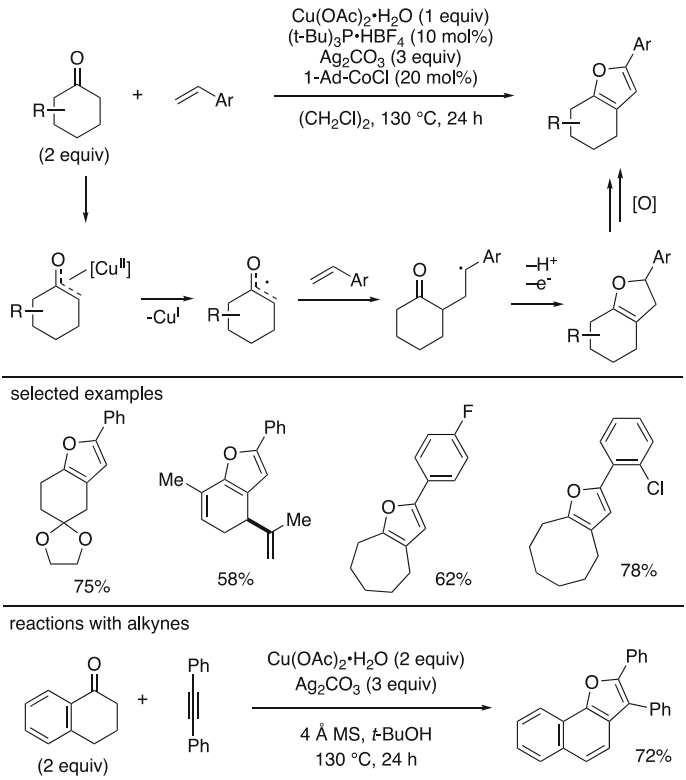
Scheme 3 Cu(I)-catalyzed carboamination with NSFI



Scheme 4 Cu(II)-catalyzed carbooxygenation of alkenes for the construction of furans

[16]. For example, the reaction of 4-pentenyl alcohol having a C2-geminal diphenyl moiety was transformed into 6-oxabicyclo[3.2.1]octanes through oxycupration of alkenes, followed by intramolecular radical C-C bond formation (Scheme 4). Moreover, the resulting C-centered radicals formed via oxycupration and ensuing C-Cu bond homolysis can be trapped by external aryl alkenes [17].

Recently, Maiti's group reported a $Cu(OAc)_2$-mediated intermolecular annulation between simple ketones and alkenes for the synthesis of furan derivatives (Scheme 5) [18]. The process is initiated by an oxidative generation of α-keto

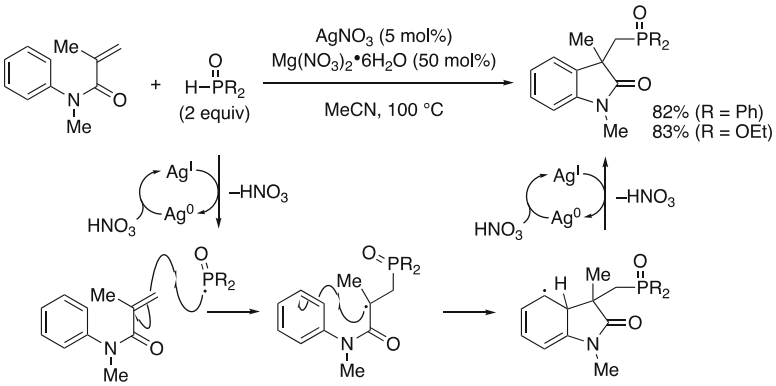


Scheme 5 Cu(II)-mediated carbooxygenation of alkenes and alkynes through annulation with ketones

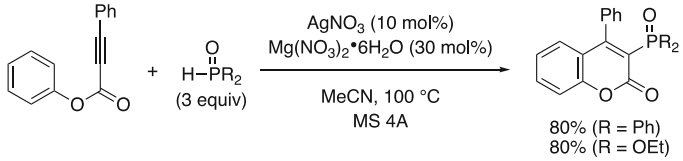
radicals, which subsequently add onto alkenes to generate the first C-C bond. The resulting C-centered radicals are oxidatively coupled intramolecularly with the carbonyl oxygen to form dihydrofurans, which are further aromatized under the reaction conditions. This method can also be applied to the annulation of ketones with alkynes.

2.3 Carbophosphination

Synthesis of oxindoles bearing a phosphine oxide moiety was realized by Yang's group through Ag-catalyzed carbophosphination of acrylamides with secondary phosphine oxides (Scheme 6) [19]. Single-electron oxidation of phosphine oxides by $AgNO_3$ generates P-centered radicals, which add onto acrylamides to form α-amido radicals. Subsequent radical cyclization with the aryl moiety, followed by oxidation/re-aromatization, delivers oxindoles. The catalytic cycle is supposed



Scheme 6 Ag-catalyzed radical carbophosphination of alkenes



Scheme 7 Ag-catalyzed radical carbophosphination of alkynes

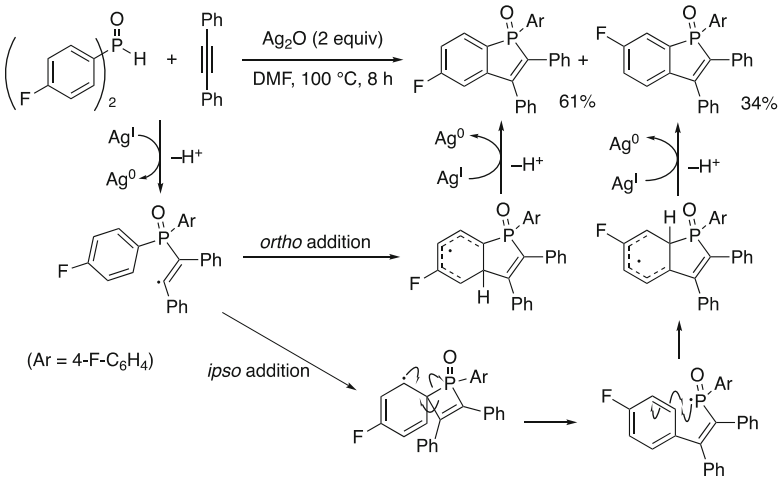
to be maintained by regeneration of $AgNO_3$ by oxidation of Ag(0) with HNO_3, $Mg(NO_3)_2$ supplying sufficient amount of nitrate ion in the reaction mixture.

Huang and Wu applied the Yang's reaction conditions to elaborate 3-phosphorated coumarins from phenyl alkynoates through radical carbophosphination of alkynes (Scheme 7) [20].

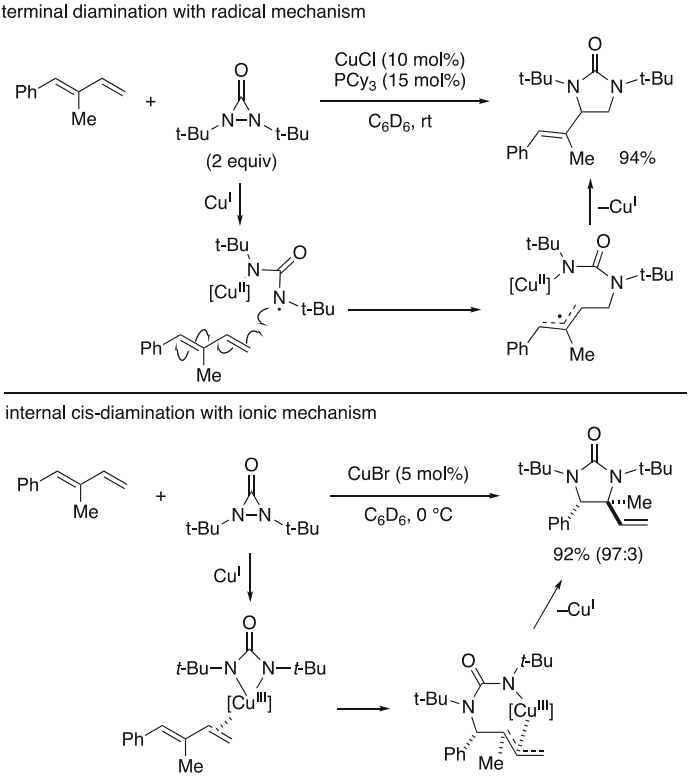
Duan's group developed an Ag(I)-mediated carbophosphination of alkynes with diarylphosphine oxides for the synthesis of benzo[*b*]phospholes (Scheme 8) [21]. The reaction started with the oxidative generation of P-centered radicals and their addition onto alkynes to form vinylic radicals. The ensuing radical cyclization onto the aryl moiety occurred through two different pathways, either on *ortho*- or *ipso*-carbons, leading to two different benzo[*b*]phosphole products after oxidative re-aromatization. The ratio of *ortho*- and *ipso*-cyclization products varied depending on the nature of the substituents on the aryl moiety.

2.4 Diamination

Shi's group disclosed intermolecular diamination of conjugated dienes with diaziridinone, catalyzed by the CuCl-phosphine system for the synthesis of cyclic ureas (Scheme 9) [22, 23]. Single-electron reduction of the diaziridinone by the CuCl-phosphine complex gave the Cu(II)-N radical species, which undergoes



Scheme 8 Ag-mediated carbophosphination of alkynes through annulation with diarylphosphine oxides

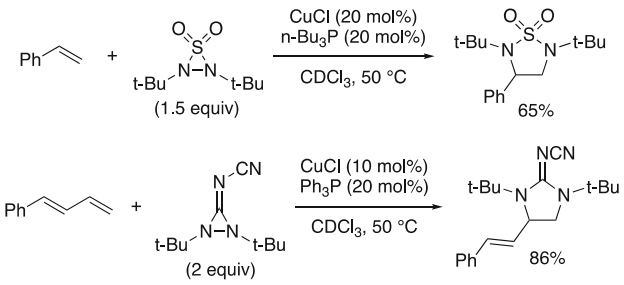


Scheme 9 Cu-catalyzed oxidative diamination of conjugated dienes with diaziridinone

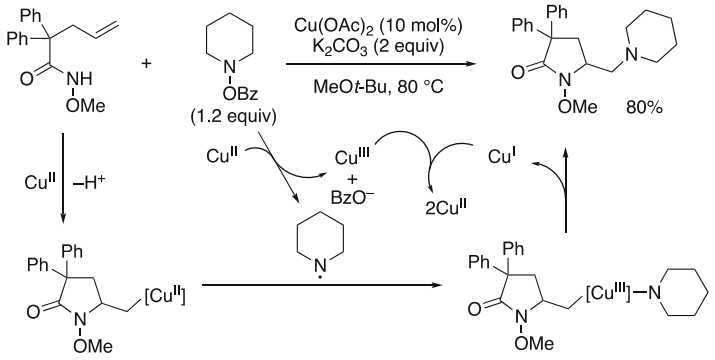
radical addition onto the sterically less hindered terminal carbon of conjugated dienes to construct the first C-N bond with generation of allylic radicals. The second C-N bond formation takes place by subsequent radical recombination of the allylic radicals with the Cu(II)-amide moiety to furnish cyclic urea products with regeneration of the Cu(I)-catalyst. It is worth of note that the reactions of conjugated dienes with diaziridinone using CuBr as the catalyst induce *cis*-diamination of internal alkenes through the four-membered Cu(III)-metallacycle, undergoing ionic migratory insertion, followed by C-N reductive elimination. This radical diamination method was extended to diamination of 1,1-disubstituted alkenes [24]. Asymmetric variants were developed using the Cu(I)-chiral phosphine/phosphate catalytic systems [25, 26].

Cu-catalyzed radical diamination of conjugate alkenes is also enabled by using *N*,*N*-di-*t*-butylthiadiaziridine 1,1-dioxide and *N*,*N*-di-*t*-butyl-3-(cyanimino)-diaziridine under the CuCl-phosphine catalysis systems [27, 28] (Scheme 10).

Wang's group developed a Cu-catalyzed synthesis of *N*-methoxylactams from alkenyl *N*-methoxyamides and *O*-benzoylhydroxylamines through diamination of alkenes (Scheme 11) [29]. In this process, *O*-benzoylhydroxylamines serve as the external nitrogen source and the stoichiometric oxidant to maintain the catalytic turnover. It was proposed that the Cu(II) species play two roles: one is to initiate



Scheme 10 Cu-catalyzed diamination of conjugated alkenes



Scheme 11 Cu(II)-catalyzed diamination of alkenylamides with hydroxylamines

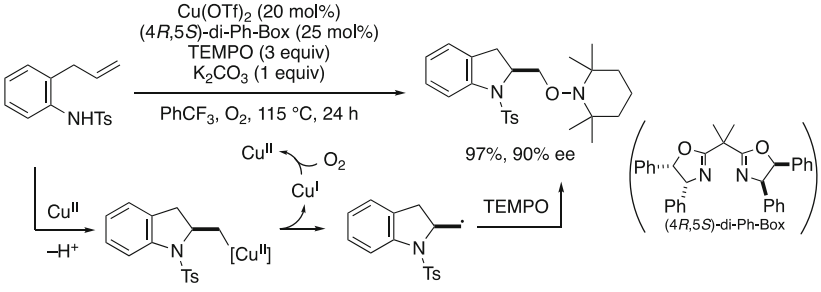
aminocupration of alkenyl *N*-methoxyamides to give organocopper intermediates; another is to reduce *O*-benzoylhydroxylamines to generate aminyl radicals and Cu(III) species. Subsequent radical recombination between the organocopper intermediates and aminyl radicals, followed by C-N reductive elimination, completes the diamination along with formation of Cu(I) species. Comproportionation of the resulting Cu(I) and Cu(III) species generates the active Cu(II) species.

2.5 *Aminooxygenation*

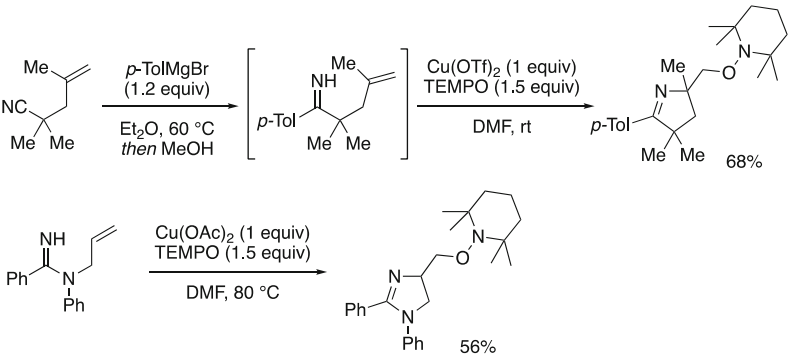
Chemler's group reported the Cu-catalyzed asymmetric synthesis of indolines from *o*-allyl-*N*-Ts-anilines and TEMPO through aminooxygenation of alkenes. Similarly with these authors' earlier studies, the reaction was initiated by aminocupration of alkenes. Subsequent homolysis of the C-Cu bond generates C-radicals, which are trapped by TEMPO to give the aminooxygenation products [30]. In this reaction, the Cu(I) species is reoxidized to the Cu(II) by molecular oxygen to maintain the catalytic turnover (Scheme 12).

Similarly, Chiba's group reported a synthesis of 2-(oxymethyl)dihydropyrroles by Cu(II)-mediated aminooxygenation of alkenyl *N*-H imines (generated from alkenyl carbonitriles and Grignard reagents) with TEMPO (Scheme 13) [31]. The method was extended to the use of *N*-allylamidines for synthesis of 2-(oxymethyl) dihydroimidazoles.

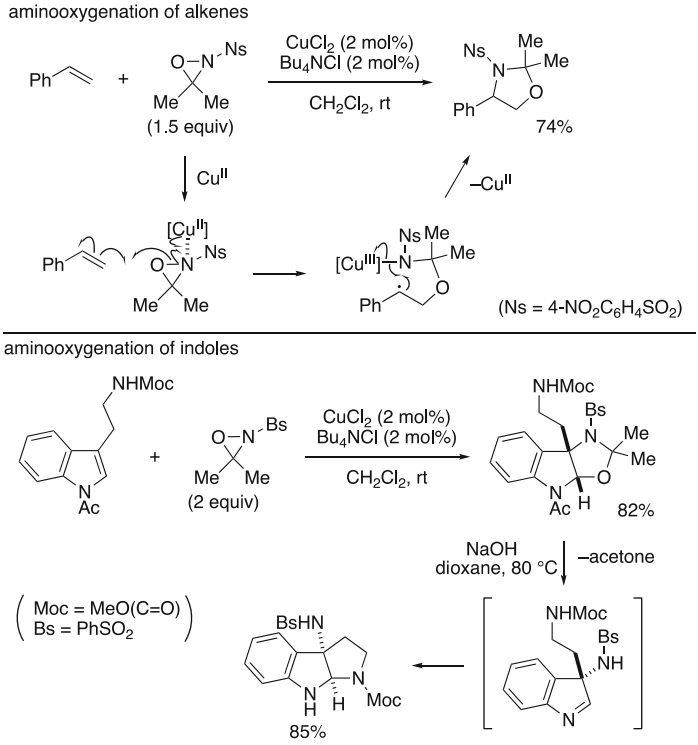
Yoon's group developed $CuCl_2$-catalyzed aminooxygenation of alkenes with *N*-sulfonyloxaziridine. The transient Cu(II)-oxaziridine complex undergoes radical C-O bond formation with alkenes to give C-centered radicals bearing the Cu(III)-sulfonamide moiety. Subsequent C-N bond formation with radical recombination provides oxazolidines with regeneration of the Cu(II) species (Scheme 14) [32–35]. This method is capable of converting indoles through aminooxygenation of the C2 and C3 positions. The resulting aminooxygenation products derived from *N*-acyltryptamines can be further transformed into the 3-aminopyrroloindoline derivatives through treatment with NaOH (Scheme 14) [36].



Scheme 12 Cu(II)-catalyzed aminooxygenation of *o*-allyl-*N*-Ts-anilines with TEMPO

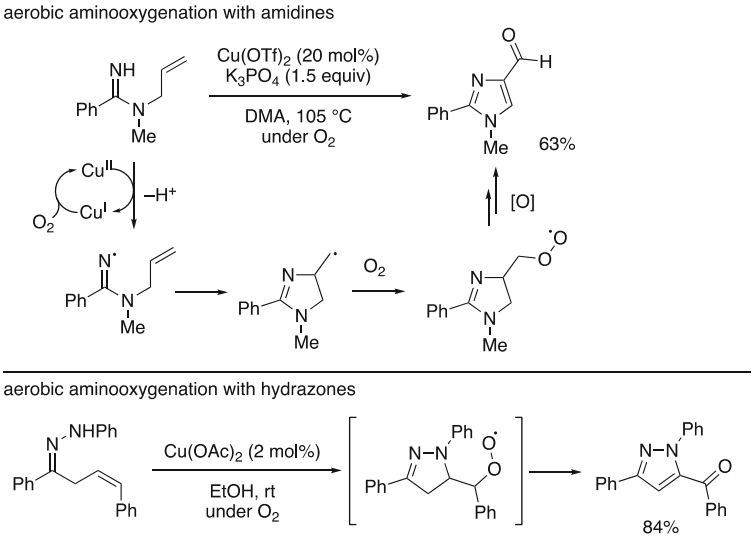


Scheme 13 Cu(II)-mediated aminooxygenation of alkenes with TEMPO



Scheme 14 Cu(II)-catalyzed aminooxygenation of alkenes and indoles with oxaziridines

Zhang and Zhu disclosed Cu(II)-catalyzed aerobic construction of formylimidazole scaffolds through aminooxygenation of *N*-allylamidines (Scheme 15) [37]. Single-electron oxidation of the amidine moiety by the Cu(II) species generates amidinyl radicals that cyclize with the pendant alkene to form the C-N bond with generation of C-centered radicals. Subsequent oxygenation of the C-radicals with molecular oxygen



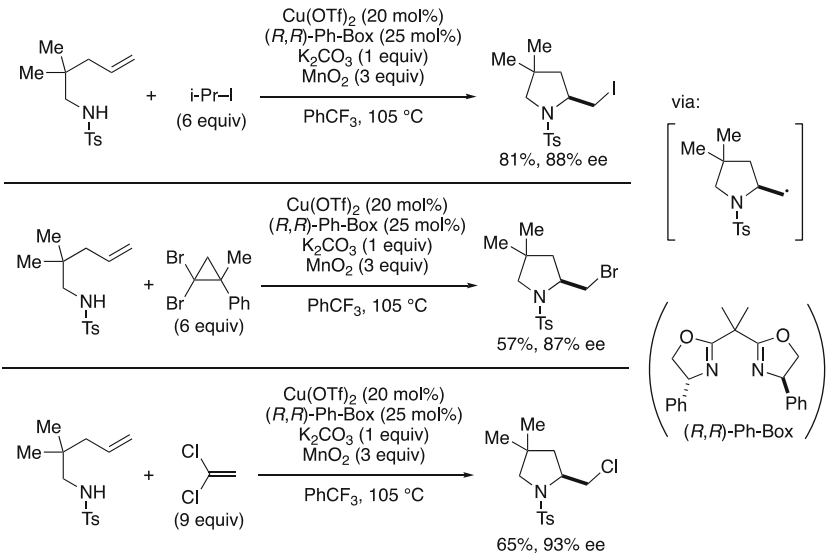
Scheme 15 Cu-catalyzed aerobic aminooxygenation with amidines or hydrazones

forms peroxy radicals. Further fragmentation of the peroxy moiety and oxidative aromatization of the dihydroimidazole part provide the final products. Similarly, Sodeoka's group recently adopted alkenylhydrazones for Cu-catalyzed aerobic aminooxygenation for the synthesis of pyrazoles [38].

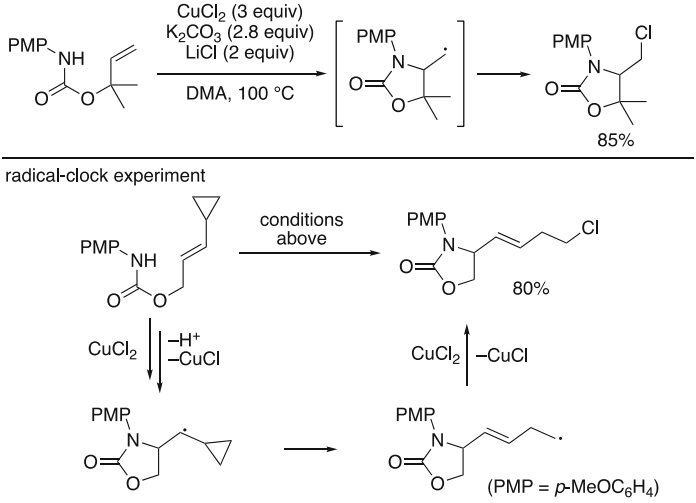
2.6 Haloamination

Chemler's group developed Cu(II)-catalyzed MnO_2-mediated enantioselective iodoamination of *N*-pentenylsulfonamides with 2-iodopropane as the iodine source for the synthesis of 2-(iodomethyl)pyrrolidines (Scheme 16) [39]. The transient C-centered radicals formed through aminocupration of alkenes and subsequent C-Cu bond homolysis finally capture the iodine atom from 2-iodopropane to afford the desired iodopyrrolidine. This system also allows for use of (2,2-dibromo-1-methylcyclopropyl)benzene and 1,1-dichloroethylene, enabling bromoamination and chloroamination, respectively.

Xu's group reported $CuCl_2$-mediated synthesis of 4-(chloromethyl)oxazolidin-2-ones through chloroamination of *O*-allylcarbamates (Scheme 17) [40]. The radical- clock experiment suggests that C-centered radical intermediates are involved, undergoing radical chlorination with $CuCl_2$. The initial aminocupration of alkenes/C-Cu bond homolysis takes place to form the C-radical intermediates. The method is amenable to chloroamination of *N*-allylureas, alkenylamides, and *N*-Ts-pentenylamine as well as to *O*-propargyl and *O*-allenylcarbamates (Scheme 18).



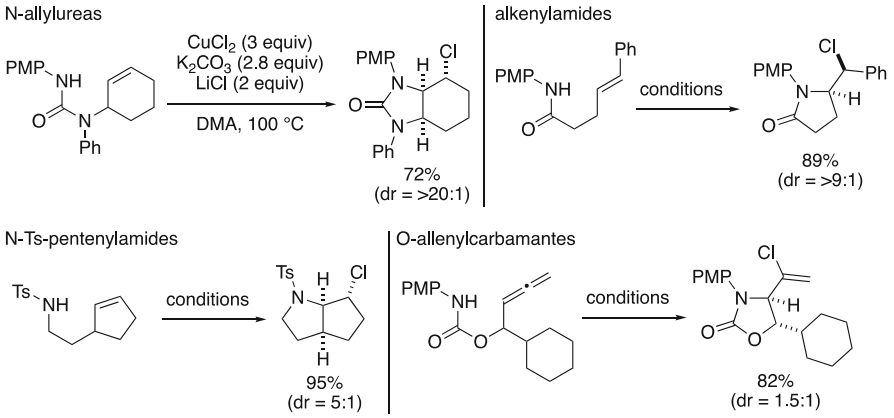
Scheme 16 Cu-catalyzed haloamination of alkenes



Scheme 17 Cu-mediated chloroamination of *O*-allylcarbamates

3 Heterocycle Synthesis via C-H Bond Oxidation

Intramolecular oxidative functionalization of a carbon-hydrogen (C-H) bond to form a new carbon-heteroatom bond offers an atom- and step-economical way to construct a heterocyclic scaffold. This section will highlight recent development on



Scheme 18 Cu-mediated chloroamination with ureas and amides as well as allenes

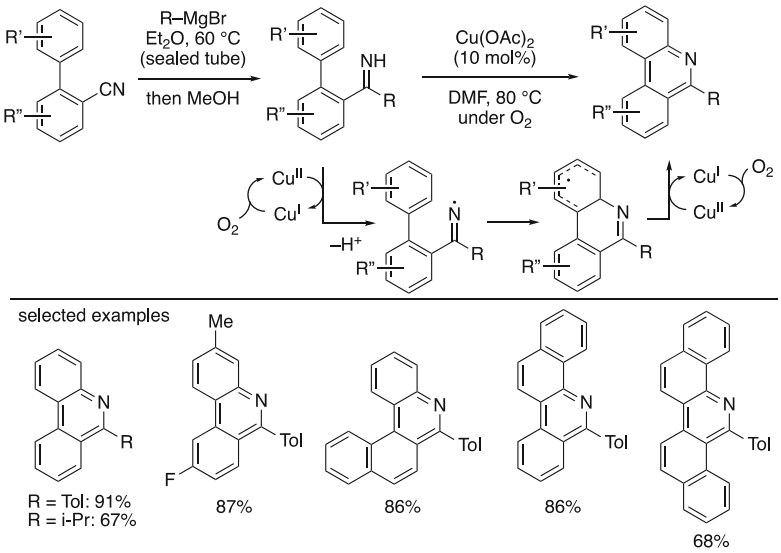
heterocycle synthesis through C-H oxidation using metal-mediated oxidative radical reactions.

3.1 C-H Amination

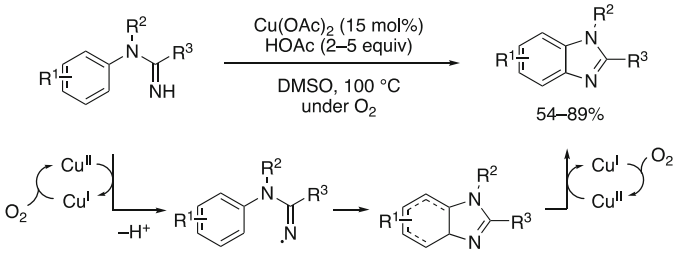
There is an increasing use of iminyl radicals that can be generated by single-electron oxidation of *N*-H imines and their derivatives for construction of nitrogen heterocycles [41]. In 2010, Chiba's group disclosed a one-pot synthesis of phenanthridines via Cu-catalyzed aerobic C-H amination of biaryl-*N*-H-imines, which can be generated in situ from 2-biarylcarbonitriles and Grignard reagents (Scheme 19) [42]. Single-electron oxidation of *N*-H imines by the Cu(II) species generates iminyl radicals, the addition of which onto the benzene ring followed by oxidative aromatization furnishes phenanthridines [43]. The catalytic turnover is maintained by reoxidation of Cu(I) to Cu(II) by molecular oxygen. This method allowed for efficient construction of aza-polynuclear aromatic hydrocarbons (aza-PAHs) such as aza-chrysene and aza-picene.

Buchwald's group disclosed Cu(II)-catalyzed aerobic oxidation of *N*-arylbenzyl-amidines that provides 2-arylbenzimidazoles through C-H amination (Scheme 20) [44]. As one of the possible reaction pathways, it is proposed that oxidative generation of amidinyl radicals and their cyclization onto the aromatic ring followed by oxidative aromatization furnish 2-arylbenzimidazoles, while other pathways involving organometallic intermediates or nitrene species are not ruled out.

Chiba's group in turn demonstrated the use of amidinyl radicals derived from *N*-alkylamidines under $Cu(OAc)_2$-catalyzed $PhI(OAc)_2$-mediated reaction conditions for synthesis of dihydroimidazoles via aliphatic C-H amination. Single-electron



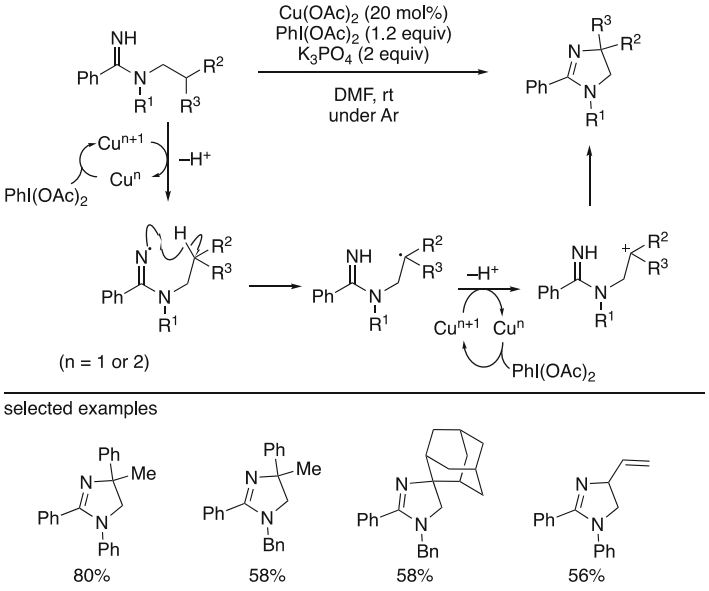
Scheme 19 Cu-catalyzed aerobic C-H amination of biaryl-*N*-H-imines for synthesis of phenanthridines and their derivatives



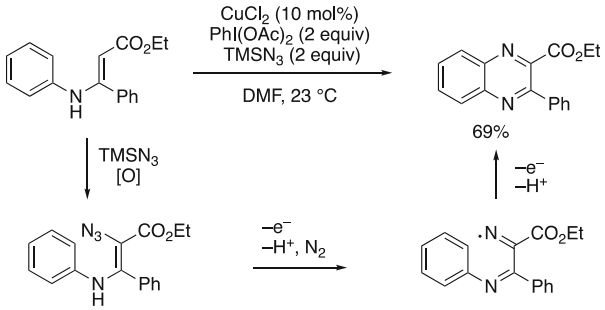
Scheme 20 Cu-catalyzed aerobic C-H amination of *N*-arylamidines

oxidation of *N*-alkylamidines generates amidinyl radicals, which undergo 1,5-H radical shift to form C-centered radicals. Subsequent C-N bond formation via oxidation of alkyl radicals into carbocations furnished dihydroimidazole products (Scheme 21) [45]. Another possibility for the C-N bond formation is radical recombination with the Cu species followed by C-N reductive elimination.

Yu's group reported synthesis of quinazoline derivatives from *N*-aryl enamine carboxylates and $TMSN_3$ in the presence of a catalytic amount of $CuCl_2$ and PhI $(OAc)_2$ (Scheme 22) [46]. The oxidative azidation of the enamine moiety first takes place to form vinylazides, the ensuing single-electron oxidation of the latter affording iminyl radicals with elimination of dinitrogen. Radical C-N bond formation followed by oxidative re-aromatization delivers the quinazoline derivatives. The role of $CuCl_2$ is likely to facilitate the electron-transfer processes. The overall process offers formal double C-H amination of alkenyl and aromatic C-H bonds.

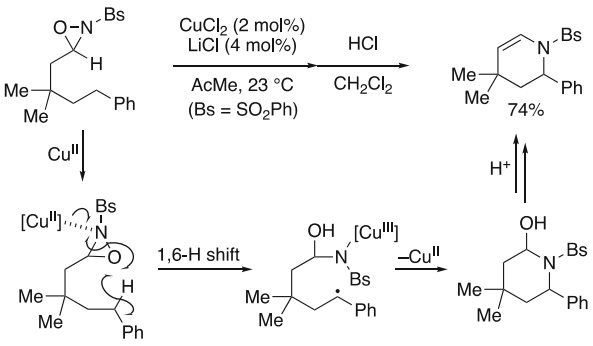


Scheme 21 Cu-catalyzed I(III)-mediated C-H amination of *N*-alkylamidines



Scheme 22 Cu-catalyzed I(III)-mediated amination of double C(sp^2)-H bonds of *N*-phenylenamine carboxylates

Yoon reported the synthesis of cyclic enamides from alkyl-tethered *N*-sulfonyloxaziridines under the $CuCl_2$-LiCl catalytic system (Scheme 23) [47]. The process is initiated by a 1,6-H radical shift onto the putative Cu(II)-oxaziridine complex to form C-centered radicals bearing the Cu(III)-amide moiety, which undergo radical recombination to give cyclic hemiaminals. Subsequent treatment with an acid promotes dehydration to afford cyclic enamides.



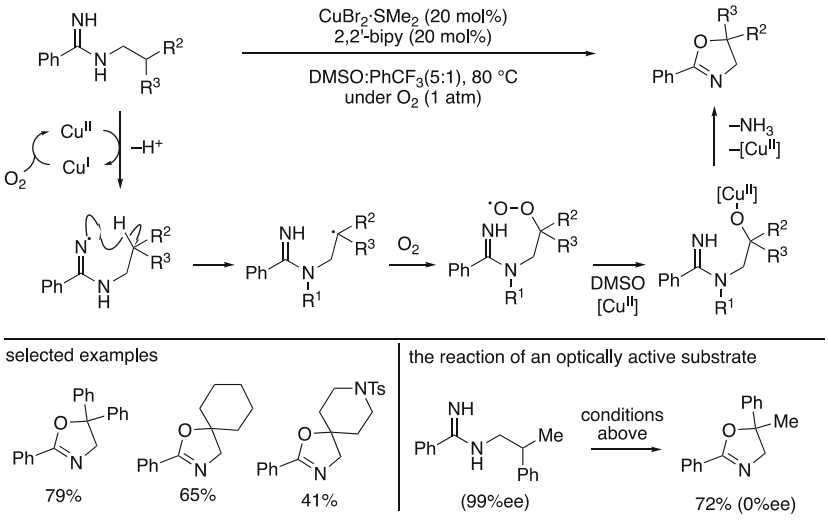
Scheme 23 Cu(II)-catalyzed C-H amination with *N*-sulfonyloxaziridines

3.2 C-H Oxygenation

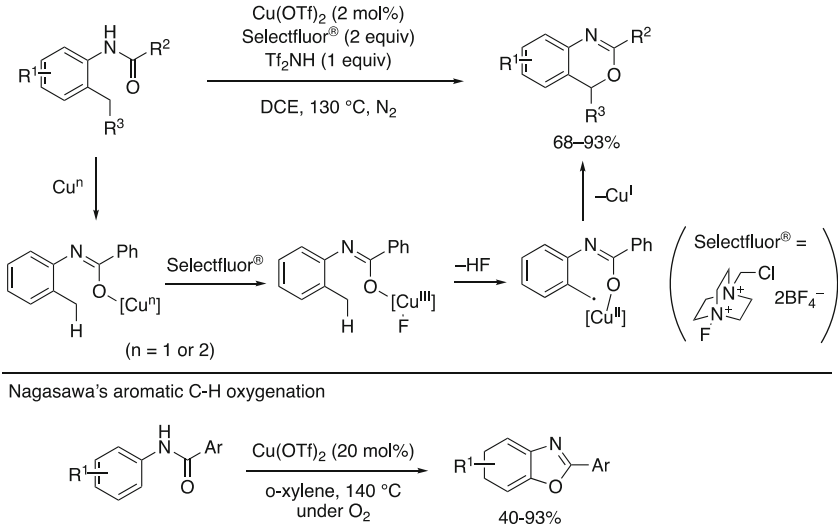
Chiba's group demonstrated that when *N*-alkylamidines are treated under Cu-catalyzed aerobic reaction conditions, the process delivered dihydroxazoles through aliphatic C-H oxygenation. In this case, the resulting C-centered radicals are captured by molecular oxygen to form peroxy radicals, which are reduced into alkoxy copper species, by the assist of DMSO. Final intramolecular condensation furnishes dihydroxazoles with elimination of ammonia (Scheme 24) [48]. The reaction of an optically active substrate resulted in racemization, which proves the presence of the C-centered radical species in the present process.

In 2012, Zhang's group reported a Cu-catalyzed oxidative intramolecular benzylic C-H oxygenation of *N*-arylamides in the presence of 1-chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis(tetrafluoroborate) (Selectfluor®) for synthesis of 4*H*-3,1-benzoxazines (Scheme 25) [49]. The process is initiated by the oxidation of initially formed amide-Cu(II) enolates by Selectfluor® to generate higher valent Cu(III) species that undergo H-radical abstraction from the benzylic position with elimination of HF. The resulting benzylic radicals subsequently form the C-O bond probably through radical recombination, followed by C-O reductive elimination to afford 4*H*-3,1-benzoxazines. This approach is complementary to the Cu-catalyzed aerobic conversion of *N*-arylamides into benzoxazoles through aromatic C-H oxygenation reported by Nagasawa's group [50].

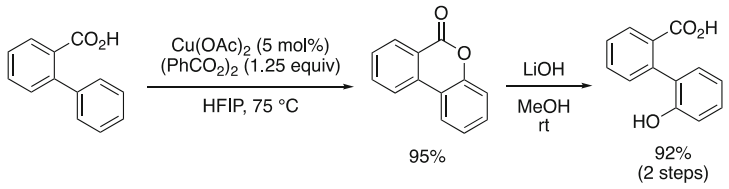
Martin's group developed a Cu-catalyzed oxidative synthesis of benzolactones from 2-arylbenzoic acids in the presence of benzoyl peroxide as the stoichiometric oxidant (Scheme 26) [51]. A series of mechanistic studies indicated the involvement of aryl radical species for the C-O bond formation, while concerted metalation-deprotonation process is not ruled out. Subsequent saponification of lactones provides hydroxylated arenes. The overall process thus offers remote aromatic C-H hydroxylation of 2-arylbenzoic acids.



Scheme 24 Cu-catalyzed aerobic aliphatic C-H oxygenation with amidines



Scheme 25 Cu-catalyzed oxidative aliphatic C-H oxygenation for synthesis of 4*H*-3,1-benzoxazines

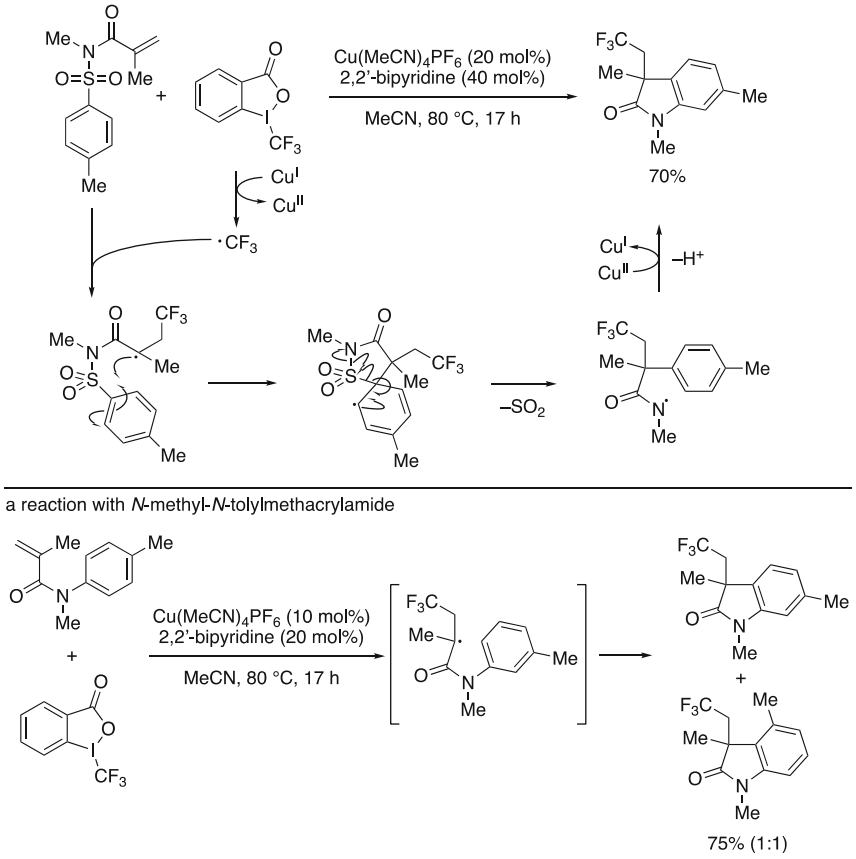


Scheme 26 Cu-catalyzed aromatic C-H oxygenation of 2-arylbenzoic acids

4 Heterocycle Synthesis via Oxidative Radical Cascades

Cascade processes enable facile construction of complex structures from readily available starting materials [52–57]. This section highlights recent development of metal-mediated oxidative radical cascade reactions, which include multi-steps of bond-forming/breaking processes, in the construction of heterocycles.

Nevado's group reported Cu-catalyzed radical cascade triggered by radical trifluoromethylation of *N*-arylsulfonylmethacrylamides (Scheme 27) [58]. This process is initiated by a single-electron reduction of the Togni reagent to deliver the CF_3 radical, which adds onto the methacrylamide moiety to give α-amido radicals. Subsequently, 1,4-aryl migration/desulfonylation is induced to give amidyl radicals that add onto the migrated tolyl group to form oxindoles as a single regioisomer. It is noteworthy that radical trifluoromethylation-cyclization cascade from *N*-methyl-*N*-tolylmethacrylamide affords an inseparable mixture of regioisomers of oxindoles through radical cyclization of the resulting α-amido radicals [59].

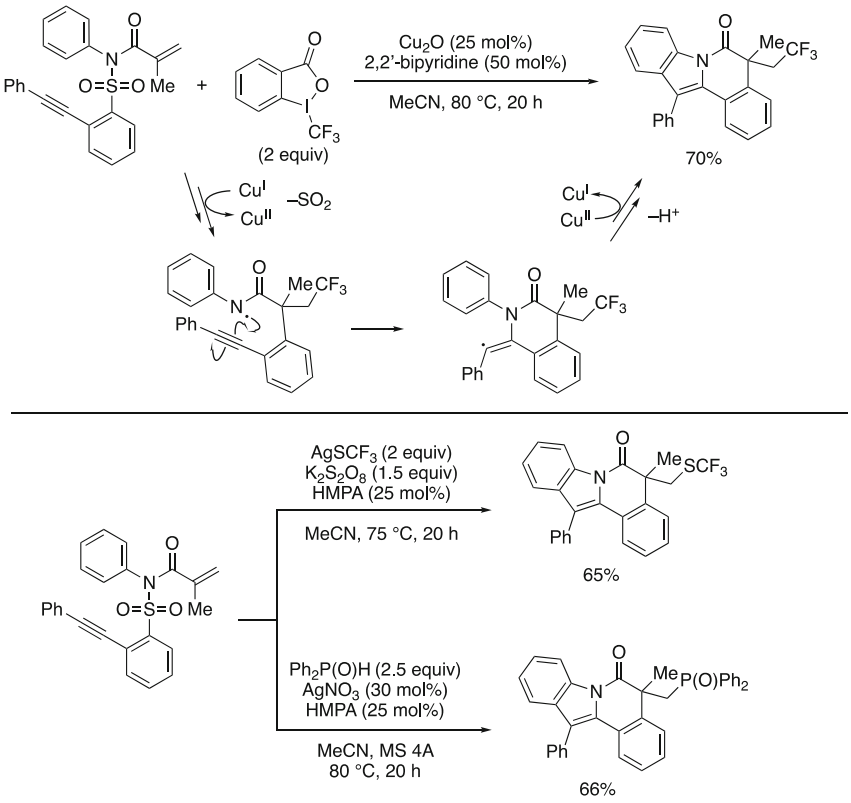


Scheme 27 Cu-catalyzed radical cascade from *N*-arylmethacrylamides and Togni reagent in the synthesis of oxindoles

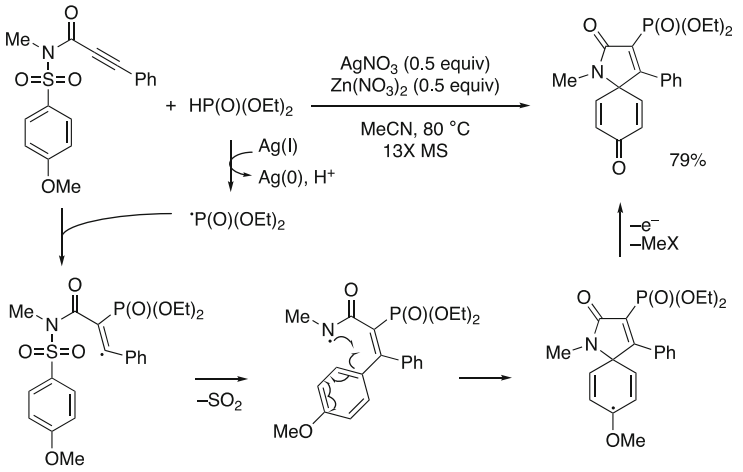
Nevado's group demonstrated further the use of 2-alkynylarylsulfonyl group to trap the *N*-amidyl radical generated through 1,4-migration/desulfonylation sequence and illustrated this cascade with the construction of indolo[2,1-*a*]isoquinoline-6(5*H*)-ones (Scheme 28) [60]. Other radical sources such as trifluoromethylthio and phosphonyl radicals were also employed under Ag-mediated oxidative reaction conditions.

Liang's group developed the desulfonylative radical cascade reaction of *N*-((4-methoxyphenyl)sulfonyl)-3-phenylpropiolamides with diethyl phosphite in the presence of $AgNO_3$ (Scheme 29) [61]. Interestingly, the resulting *N*-amidyl radical undergoes oxidative spirocyclization onto the methoxyphenyl moiety to give azaspirocyclohexadienone scaffolds.

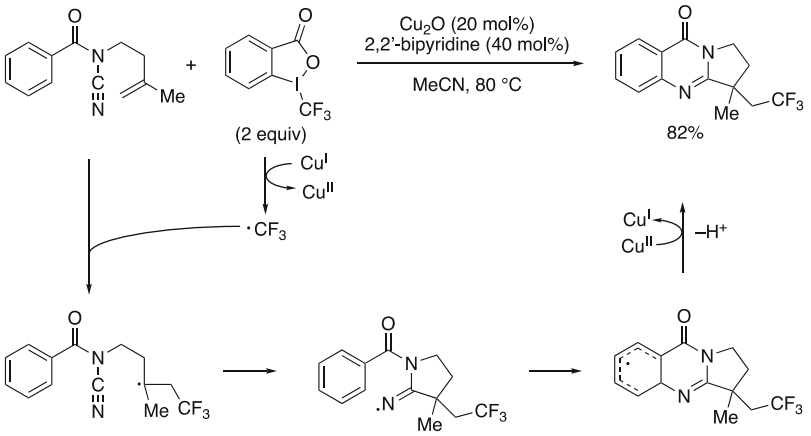
Cui's group reported an oxidative radical cascade to construct quinazolinone scaffolds from *N*-alkenyl-*N*-cyanobenzamides and the Togni reagent in the presence of Cu_2O as the catalyst (Scheme 30) [62]. Upon addition of the trifluoromethyl radical onto the alkene moiety, the resulting C-centered radical adds onto the cyano group to give an aminidyl radical, which in turn undergoes radical cyclization onto the benzoyl moiety to form the quinazolinone skeleton.



Scheme 28 Construction of indolo[2,1-*a*]isoquinoline-6(5*H*)-ones through radical cascade involving *N*-arylmethacrylamides



Scheme 29 Ag-mediated oxidative radical cascade for construction of azaspirocyclohexadienones



Scheme 30 Cu-catalyzed oxidative radical cascade of alkenylcyanamides for the synthesis of quinazolinones

5 Summary and Outlook

Metal-mediated oxidative radical cyclization/annulation has recently emerged as a robust strategy for the synthesis of various heterocycles. In such processes, copper salts are mainly utilized to generate the radical species, owing to their superior reactivity to induce the SET process to generate radical species. Employment of such first-row transition metals is advantageous from the viewpoint of sustainability as these base metals are ubiquitous in nature and lower in cost and toxicity [63].

Choice of stoichiometric oxidants, which often serve as to trigger bond-forming processes, is also important to design efficient synthesis of targeted heterocycles [64]. Thus, it is our strong belief that the leveraging of metal-mediated oxidative radical processes to exploit new routes for the synthesis of heterocycles of medicinal and material interests continues to flourish and thus enhance our synthetic capability.

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Reductive Electron Transfer in the Synthesis of Heterocycles

Andreas Gansäuer and Sven Hildebrandt

Abstract This review summarizes the concepts involved in reductive electron transfer to organic substrates and subsequent heterocycle formation via radical intermediates. Furthermore, representative examples of existing methodologies are discussed that elucidate the scope and applicability of reductive electron transfer in heterocycle synthesis from simple five- and six-membered ring formation to complex structural motifs. The discussion mainly focuses on low-valent metal complexes as well as selected examples of organic ground-state reductants.

Keywords Catalysis · Electron transfer · Heterocycle · Radical · Reduction

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1 Introduction: Reductive Electron Transfer and Its Implications for Substrate Scope and Catalysis

1.1 Scope and Structure of This Review

Reductive electron transfer as part of synthetic transformations has become a versatile tool in organic chemistry. Based on comprehensive studies on the reactivity and selectivity of carbon-centered radical intermediates during the last 40 years, many processes were developed that involve single electron transfer from metal reductants or organic reductants to organic substrates to induce radical formation. Only recently, with the development of photoredox- and 3D-transition metal-catalyzed radical reactions, the power of radical processes that do not follow radical chain mechanisms could be fully demonstrated [1–4].

This review focuses on reductive electron transfer in the synthesis of heterocycles via radical intermediates. Due to the vast number of reports on heterocycle synthesis via radical intermediates, the scope of this review is limited to the strict definition of reductive electron transfer. Processes such as hydrogen atom transfer, radical chain reactions involving Sn and Ge, atom transfer/Kharasch reactions, and photoredox catalysis are covered by other parts of this book or are summarized in existing review articles [4]. Furthermore, syntheses based on classical concepts of heterocycle synthesis via ionic intermediates such as substitution, elimination, or condensation are not part of this review.

Section 1 of this artilce will dissect the individual steps of heterocycle syntheses by reductive electron transfer and aims to conceptualize the underlying reactivity principles in four subsections (Fig. 1). In Sect. 1.2, reductive electron transfer resulting in radical formation will be discussed with respect to mechanisms and reactant properties. Section 1.3 will cover the radical translocation processes that

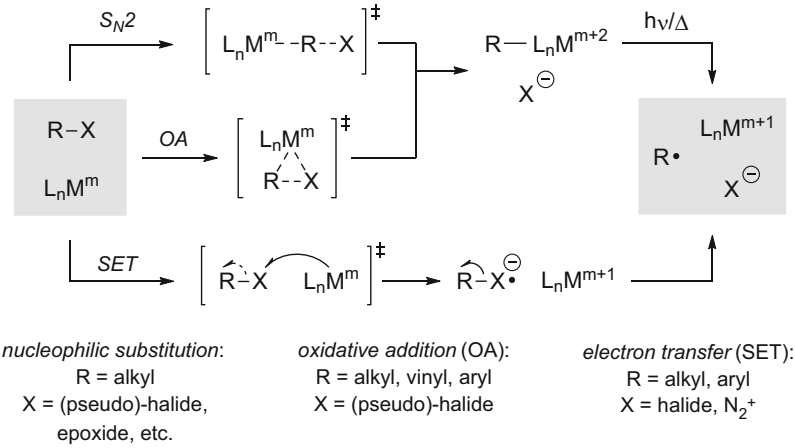


Fig. 1 Reaction pathways for reductive electron transfer of metal complexes to organic halides

lead to heterocycle formation or functionalization by cyclization and addition of radical intermediates. Section 1.4 discusses mechanisms for product liberation and catalyst regeneration.

On the basis of the mechanistic discussion in Sects. 1 and 2 of this article, it summarizes reaction conditions for the synthesis of individual classes of saturated five- and six-membered heterocycles (Sect. 2.1) and heteropolycycles (Sect. 2.2) via reductive electron transfer. The section covers addition of alkyl radicals to unsaturated functionalities to obtain tetrahydrofurans, tetrahydropyrans, pyrrolidines, piperidines, γ- and δ-lactones, and lactams (selected).

Section 2.3 describes the synthesis of unsaturated heterocycles via cyclization of aryl radicals to obtain benzofurans, dihydrobenzofuran, dihydrochromenes, indolines, tetrahydroquinolines, dihydroquinolinones, and oxindoles.

1.2 Reductive Electron Transfer

Several distinct pathways of radical generation by reductive electron transfer have been described so far. For most metal complexes described throughout this section, the mechanism of radical generation could be assigned to one of the following.

Radical generation from organic halides can occur in three different pathways. Alkyl halides as well as many other typical carbon electrophiles can undergo nucleophilic substitution at low-valent metal centers (L_nM^m) to form an organometallic species R-L_nM^{m+2} (Fig. 1). Stereochemical probes have revealed inversion of configuration at the carbon center; thus an S_N2 mechanism is assumed. This type of reactivity is mainly displayed by Co(I) complexes such as vitamin B_{12} or cobalt-salen complexes (Table 1). The intermediate R-L_nM^{m+2} can also be accessed from

Table 1 Representative examples of metal complexes inducing reductive electron transfer

	S_N2	OA	SET	iSET
Sm			$Sm(II)I_2$	$Sm(II)I_2$
Ti			$Cp_2Ti(III)R_2^-$, $Ti(III)Cl_3$	$Cp_2Ti(III)Cl$
Zr			$Cp_2Zr(II)$(olefin), $Cp_2Zr(III)Cl$	
V			$Cp_2V(IV)Cl_2$	
Cr			$CpCr(II)[(XylNCMe)_2CH]$, $Cr(II)(en)_2^{2+}$	
Mn			$Mn(II)R_3^-$	
Fe			$[Li(tmeda)]_2[Fe(-II)(C_2H_4)_4]$, $[Ph_4Fe(0)][Li(OEt_2)]_4$, $Fe(II)Br_2[Mg(acac)_2]THF_2$	Fe(I)(salen)
Co	Cobalamin(I), Co(I)(salen)	Co(I)(NHC)	$[Co(0)Ph_2(dppe)](MgBr)_2$, Co(I)(salen), Co(I)(oxim)	
Ni			Ni(I)(salen), Ni(I)(cyclam), Ni(I)(terpy)R	
Pd		$Pd(0)(PPh_3)_4$, Pd(0)(dppp)	$Pd(0)(PPh_3)_4$, Pd(0)(dppp)	
Cu			$Cu(I)(dtbpy)_2^+$, $Cu(I)(PPh_3)(L_n)$	

aryl electrophiles via concerted oxidative addition. Depending on the BDE of the R-M bond, thermal or photochemical homolytic cleavage can occur to obtain the carbon-centered radical and L_nM^{m+1}.

Low-valent metal complexes that do not possess unsaturated coordination sites can transfer electrons onto organic halides and other leaving groups via an outer sphere mechanism. Following the electron transfer, either concerted or stepwise dissociation to the radical and the halide anion occurs. Many 3D-metal ate complexes induce radical formation by this type of mechanism in conjunction with organometallic reagents as terminal reductants.

Apart from the reduction of organic halides that do not exhibit substantial donor ligand properties, oxygen- and nitrogen-containing functional groups coordinate to the low-valent metal center prior to electron transfer (Fig. 2). Subsequently, ketyl and alkyl radicals are formed from carbonyl groups or strained ring systems such as epoxides or aziridines via intramolecular electron transfer (iSET). The required Lewis acidity is displayed by higher-valent metal complexes such as $Sm(II)I_2$, $Cp_2Ti(III)Cl$, and Fe(I)(salen) complexes that preferably react via iSET.

The in situ generation of low-valent metal species capable of inducing reductive electron transfer is mostly, especially in catalytic applications, achieved by in situ reduction of a precatalyst with higher oxidation state. Suitable reductants are Zn or Mn (Ti(IV)/(III), V(V)/(IV), Cr(III)/(II), Fe(II)/(I), Co(II)/(I), Ni(II)/(I)), as well as $NaBH_4$ in certain cases. Even lower oxidation states are synthesized in situ by consumption of Grignard or organozinc reagents under reductive homo-coupling (Fe(II)/(0)/(-II), Co(II)/(0), Ni(II)/(0), and Pd(II)/(0)). The detection of homo-coupling by-products in the reaction mixture therefore indicates precatalyst reduction by this mechanism. Apart from this mode of reduction, some catalytic systems have been reported where homo-coupling of Grignard reagents was not observed and thus higher oxidation states prevail ($Fe(II)Br_2$(tmeda)) [5]. References for the catalyst systems mentioned in Table 1 will be given in Sect. 2.

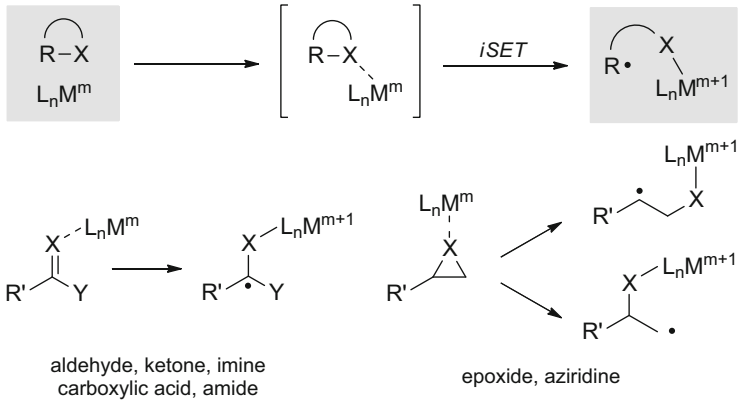


Fig. 2 SET after coordination at C-X double bonds and strained heterocycles

Organic ground-state reductants such as TTF (tetrathiafulvalene) and TDAE-type reagents (tetrakis(dimethylamino)ethylene) provide an alternative to metal-based systems by inducing single electron transfer to organic halides and diazonium salts. Furthermore, organic reductants have been employed as terminal reductants in metal-catalyzed reactions [6, 7].

1.3 Selectivity of Radical Cyclizations and Additions in the Synthesis of Saturated Heterocycles

Cyclization of radical intermediates is central to heterocycle synthesis via reductive electron transfer. The observed product distribution for most reactions presented throughout the next sections arises from highly selective 5-*exo* cyclizations. The cyclization of 5-hexenyl radicals is governed by electronic effects that lead to a 50-fold acceleration of 5-*exo* cyclization over 6-*endo* (Fig. 3). The orbital overlap in the 5-*exo* cyclization transition state occurs in an angle close to 107° comparable to the Bürgi-Dunitz angle known from ionic reactions [8, 9]. The 6-*endo* reaction is much slower due to a decreased angle in the transition state. Independent of the nature of the radical (alkyl, vinyl, aryl, ketyl), the unsaturated radical acceptor (alkene, allene, alkyne), or heteroatom substitution, 5-*exo* products are formed.

The stereochemical outcome of the reaction of, e.g., secondary alkyl radicals is governed by equatorial conformations of substituents in the transition state. 1-methyl-5-hexenyl radical cyclization therefore leads to the cis-pentane structure. Four substituents show induction of trans-selectivity, again arising from equatorial positioning in the transition state. The formation of bicyclic systems proceeds by same-side attack of the radical onto the alkene that leads to an all-cis product.

The reaction of 6-hexenyl radicals is slower than its analog while also preferably forming the *exo* product. The reaction proceeds much faster when electron withdrawing groups such as aryl or carbonyl groups are attached to the alkene. The adjustment of alkene electrophilicity is referred to as polarity matching.

The addition of radicals to arenes followed by rearomatization or reduction of the resulting σ-complex radical leads to the formation or functionalization of unsaturated heterocycles. To achieve efficient radical addition onto arenes, the abovementioned polarity matching is again of importance. The inherent nucleophilicity of heteroarenes increases from structures such as oxazole to pyridine to quinoline to pyrrole (Fig. 4). Radical addition to nucleophilic arenes is fastest for electrophilic radicals such as trifluoromethyl or enoyl radicals. Less nucleophilic arenes react fast with aryl and alkyl radicals. Even within a single heteroaromatic scaffold, there may exist different reaction sites for different radicals. 3-alkyl-6-methoxyquinolines react with electrophilic radicals at the 2-position, whereas nucleophilic radicals attack the 7-position selectively.

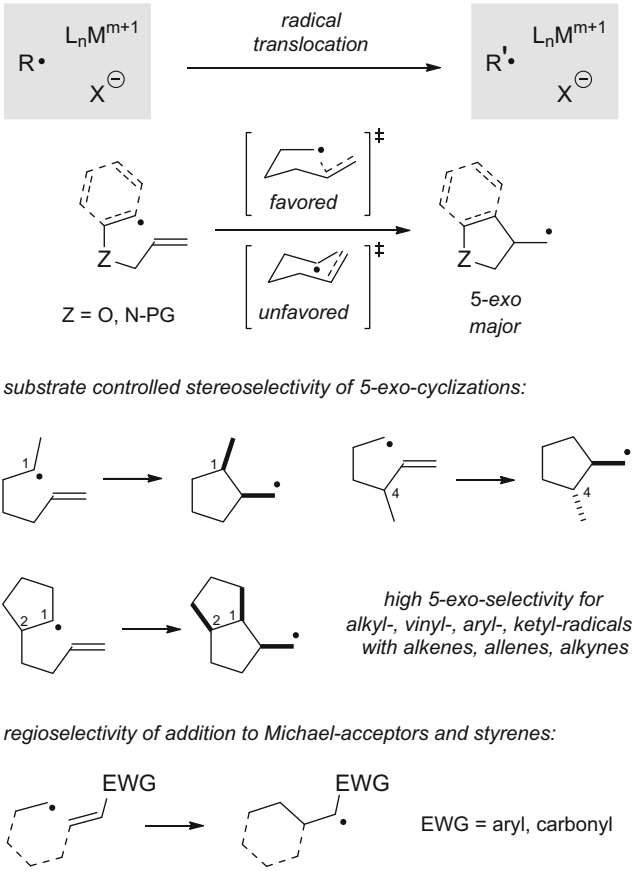


Fig. 3 Radical addition to unsaturated functionalities resulting in 5-*exo* product formation

1.4 Product Liberation and Catalyst Turnover

The last steps of the individual stages of heterocycle synthesis via reductive electron transfer are product liberation and catalyst turnover. First and foremost, the translocated radical R' in the form of an alkyl, vinyl, or radical arene σ-complex needs to be saturated to obtain the desired product. Simple saturation of alkyl or vinyl radicals to R'-H can be achieved by hydrogen atom transfer (HAT) from the solvent or a hydrogen atom donor such as 1,4-cyclohexadiene (Fig. 5). The intramolecular reaction of radical R' with the bound catalyst L_nM^{m+1} can lead to homolytic substitution (S_Hi) of the M-X bond. This results in product liberation and reduction of the catalyst to L_nM^m. An example for this type of product formation is shown in Fig. 6. The tertiary radical undergoes homolytic substitution at the Ti(IV)-O bond to form the bicyclic tetrahydrofuran product and the reduced catalyst $Cp_2Ti(III)Cl$ [10–13].

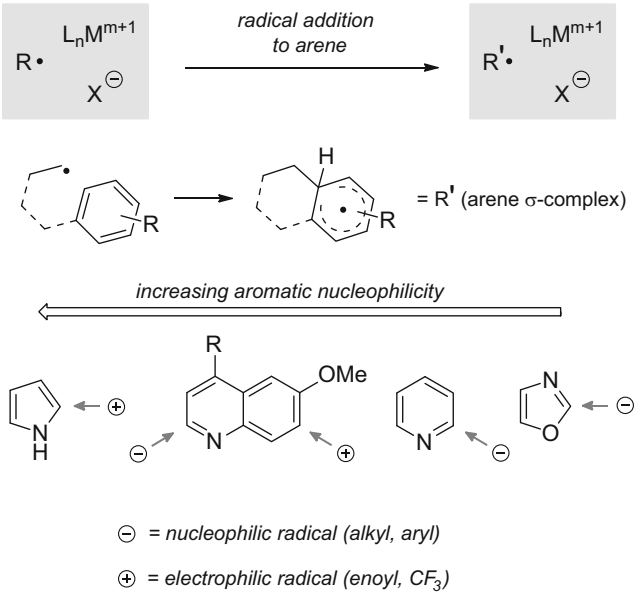


Fig. 4 Polarity matching and selectivity in the addition of radicals to (hetero-)arenes

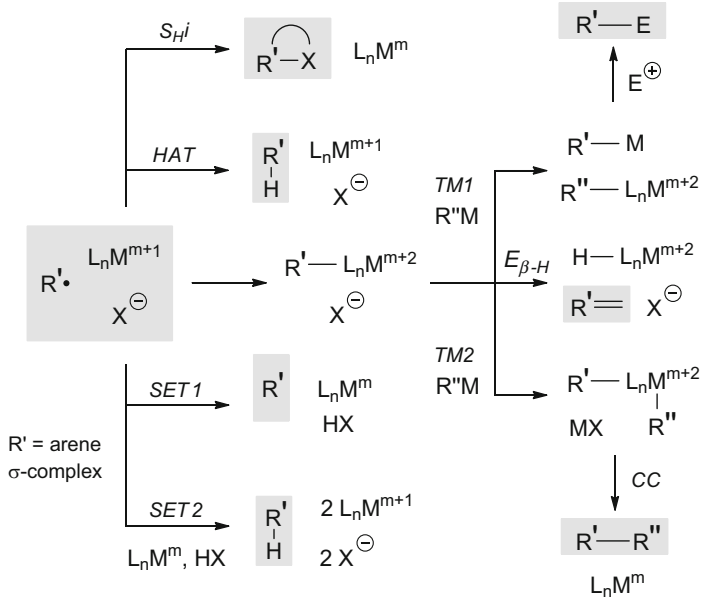


Fig. 5 Reaction pathways for radical follow-up reactions and product liberation

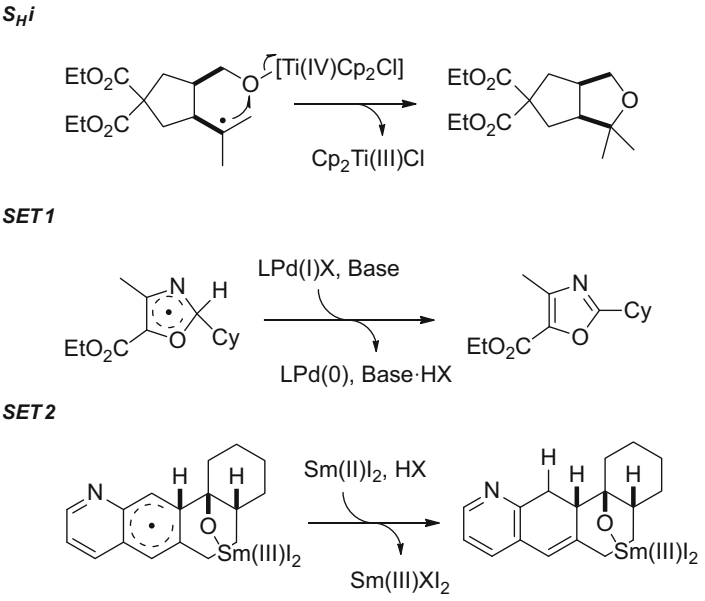


Fig. 6 Examples for S_Hi and SET processes that lead to product liberation

In cases where R' represents a radical arene σ-complex, two reaction pathways are possible. Oxidation of the delocalized radical by L_nM^{m+1} (SET1) leads to a cationic σ-complex that rearomatizes under proton loss to R' and L_nM^m. Reduction of the radical arene σ-complex (SET2) under consumption of another equivalent of reductant L_nM^m on the other hand leads to an anionic σ-complex that can be protonated to yield dihydrobenzenes R'-H. Examples for this type of reactivity are shown in Fig. 6. During the Pd-catalyzed alkylation of oxazoles, SET1 from the radical σ-complex to Pd(I) occurs to obtain the functionalized oxazole and the Pd(0) catalyst [14]. Sm(II) complexes can be used to reduce radical σ-complexes initially generated by Sm(II)-mediated ketyl radical cyclization. The presence of the weak acid tert-Butanol furnishes the dihydroquinoline structure after protonation of the anionic σ-complex [15].

The most common reaction pathways of radical intermediates involve recombination of R' and L_nM^{m+1} to R'-L_nM^{m+2} (Fig. 7). This organometallic intermediate can undergo multiple follow-up reactions, highly dependent on the nature of the metal and the ligands bound to the metal [16]. In the presence of other organometallic species that serve as terminal reductants, transmetallation can occur in two ways. The first pathway (TM1) leads to transmetallation at the alkyl R' to form the species R'-M. This intermediate can be functionalized by virtually any electrophile (E) in a separate step. An example is shown in the Pd-catalyzed zincation and pyrrolidine formation in Fig. 7 [17–19]. The Pd(II)-R' intermediate undergoes transmetallation with diethylzinc to R'-Zn(II) and Pd(0) after reductive elimination of butane. The addition of deuterated acetic acid leads to the protonation of R'-Zn (II) and incorporation of deuterium in the product.

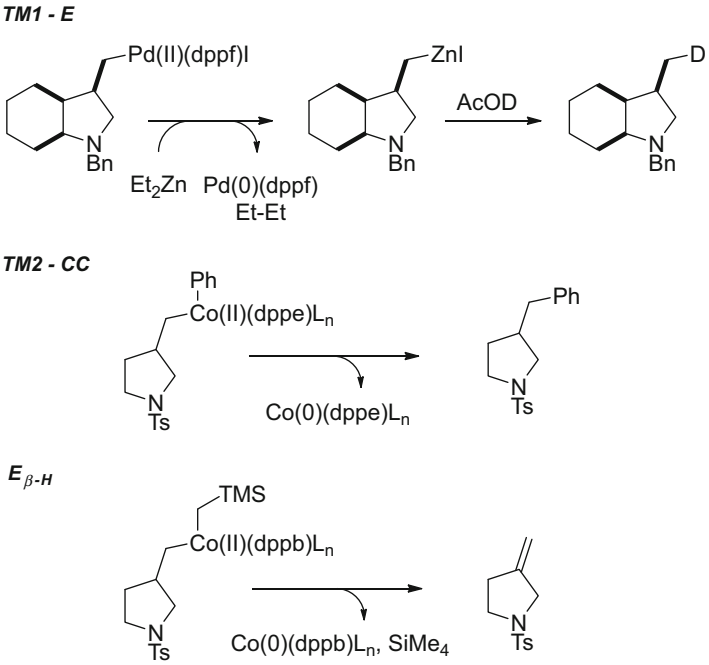


Fig. 7 Transmetallation and elimination processes as possible pathways for product liberation. *dppf* 1,1′-bis(diphenylphosphino)ferrocene, *dppe* 1,2-bis(diphenylphosphino)ethane, *dppb* 1,4-bis (diphenylphosphino)butane

The Co(II)(dppe)$(Ph)_n$ complex of an analogous pyrrolidine intermediate R', on the other hand, reacts by reductive elimination and thereby cross-coupling of a phenyl ligand [20]. Therefore transmetallation of the terminal reductant occurs at the cobalt center (TM2) which subsequently undergoes cross-coupling, though the individual order of transmetallation events may alter with each catalyst system.

The third pathway for the reaction of R'-L_nM^{m+2} intermediates is β-hydride elimination ($E_{β\text{-}H}$). In the example shown in Fig. 7, the terminal reductant Me_3SiCH_2MgCl does not undergo cross-coupling at the Co(II) center. Instead, β-hydride elimination and subsequent reductive elimination to Co(0) and Me_4Si takes place to furnish the unsaturated pyrrolidine [21]. For tertiary radicals, $E_{β\text{-}H}$ after recombination might become unlikely, and hydrogen atom abstraction might take place instead [22]. During the next sections, references to the mechanisms discussed will be given if no other mechanistic description is provided.

2 Reductive Electron Transfer in the Synthesis of Saturated and Unsaturated Heterocycles

2.1 Synthesis of Five- and Six-Membered Saturated Oxa- and Azacycles

2.1.1 Halo-Alkene Cyclization

The most common model substrates for reductive cyclization via radical intermediates are 2-halo-acetals known from Ueno-Stork cyclization [23–25]. The facile access to these substrates from, e.g., dihydrofuranes and allylic alcohols has led to a large number of literature reports on their cyclization mediated or catalyzed by low-valent metal complexes as well as organic reductants. Mostly iodo- and bromo-acetals are employed, while the iodo-compounds are most easily reduced. The examples presented herein have been and can be transferred to the synthesis of related heterocycles on the basis of the underlying 5-*exo* cyclization and stereoselectivity. Furthermore, it has already been shown in the first reports that acetal cyclization products can be converted into the respective lactones by oxidation.

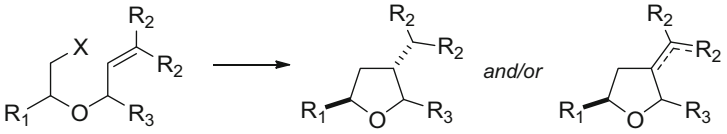
The reductive cyclization of an acyclic allylic iodoacetal is catalyzed by $Cp_2Ti(III)Cl$ generated from $Cp_2Ti(IV)Cl_2$ and Mn powder (Table 2, entry 1). The C-I bond is cleaved by formation of $Cp_2Ti(IV)ICl$, followed by 5-*exo* radical cyclization. The formation of the saturated product presumably proceeds via reduction of the product radical into the corresponding anion or the organomanganese complex which is protonated upon workup. The product is obtained in 70% yield and low diastereomeric ratio.

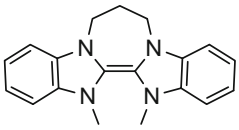
A Cr-mediated procedure has been reported employing the Cr-bis-ethylenediamine complex derived from $Cr_2(OAc)_4$ (Table 2, entry 2). The electron-rich Cr(II) complex unlike $Cr_2(OAc)_4$ itself induces SET to the C-Br bond and subsequent 5-*exo* cyclization. The cyclized radical intermediate is intercepted by another equivalent of Cr(II) and hydrolyzed upon workup. Furthermore, resulting Cr(III) species can be regenerated electrochemically or with $LiAlH_4$ in situ to achieve catalytic reaction conditions. The product is obtained in 75% yield and high diastereomeric ratio.

Electron-rich ate complexes of Mn, Fe, and Co generated from M^{2+} precursors and organolithium or Grignard reagents also induce radical generation at C-I and C-Br bonds. The unsaturated product is obtained throughout after $E_{\beta\text{-}H}$ (Table 2, entries 3–5). Although a formal $E_{\beta\text{-}H}$ reaction pathway involves the intermediacy of an M-C bond, these bonds might not form easily with tertiary radicals. Therefore hydrogen atom abstraction pathways need to be considered to explain the observed product distribution [22]. For primary radicals cross-coupling may occur depending on the metal complex and the terminal reductant (see section below).

Co(I) species generated from Co(salen) or Co(oxime) complexes by metal or electrochemical reduction react via S_N2 and Co(III)-C bond homolysis to induce radical formation and 5-*exo* cyclization. Without additives $E_{\beta\text{-}H}$ leads to alkene product formation, while in the presence of visible light and a hydrogen atom donor (e.g., thiol), the saturated product is obtained (Table 2, entries 6 and 7).

Table 2 Reaction conditions for halo-alkene cyclization via reductive electron transfer to yield tetrahydrofurans



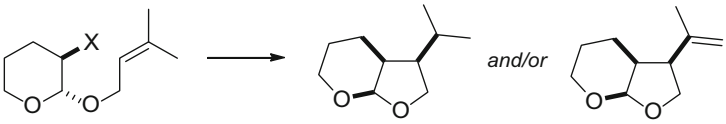
	X =	R =	Conditions	Yield	Ref
1	I	R_1 = OBu	10 mol% Cp_2TiCl_2, Mn, TMSCl, THF	70% (60:40 dr)	[26]
2	Br	R_1 = OBu	$Cr_2(OAc)_4(H_2O)_2$, en, THF/H_2O	75% (86:14 dr)	[27]
3	I	R_1 = OBu, R_2 = Me	Bu_3MnLi, THF	82% (alkene)	[28, 29]
4	Br	R_1 = OBu, R_2 = Me	5 mol% $FeCl_2$, PhMgBr, THF	77% (alkene)	[30]
5	I	R_1 = OBu, R_3 = pentyl	10 mol% $CoCl_2$(dppp), Me_3SiCH_2MgBr, THF	68% (alkene)	[21]
6	Br	R_1 = OBu, R_2 = Me	20 mol% CoI_2(oxime), Zn, hν, DMF	99% (alkene)	[31]
7	Br	R_1 = OBu, R_2 = Me	5 mol% CoI_2(oxime), −1.6 V, TBAP, $C_{12}H_{25}SH$, hν, MeCN	96%	[31]
8	I	R_1 = *p*-OMe-Ph	10 mol% Cp_2TiCl_2, Mn, TMSCl, THF	83% (80:20 dr)	[26]
9	I	R_1 = *p*-OMe-Ph	10 mol% Cp_2VCl_2, Mn, TMSCl, THF	62% (80:20 dr)	[26]
10	I	R_1 = *p*-OMe-Ph	 , THF, PhMe	83%	[32]

R = H unless noted otherwise. *en* ethylenediamine, *dppp* 1,3-bis(diphenylphosphino)propane

Benzylic allylic alcohols instead of acetals provide cyclization products with higher diastereomeric ratios. Furthermore it has been shown that $Cp_2V(IV)Cl_2$ can be as effective as $Cp_2Ti(IV)Cl_2$ in this type of cyclization (Table 2, entries 8 and 9). Also a bis(benzimidazole)carbene organic ground-state reductant furnishes the product in high yield via radical intermediates (Table 2, entry 10).

Other widely used substrates are halo-acetals derived from dihydropyrans or dihydrofurans and serve as a comparable model system. Low-valent Zr(III) and Zr (II) complexes have been shown to generate radicals from iodoalkanes. $Cp_2Zr(H)Cl$ serves a dual role in this reaction (Table 3, entry 1). Upon reaction with Et_3B and oxygen, $Cp_2Zr(III)Cl$ is obtained that homolytically cleaves the C-I bond. The cyclized radical is saturated via hydrogen atom transfer from $Cp_2Zr(H)Cl$ that in turn generates $Cp_2Zr(III)Cl$ that carries on the reaction. The saturated product is obtained in 89% yield and low diastereomeric ratio.

Table 3 Reaction conditions for halo-alkene cyclization via reductive electron transfer to yield bicyclic tetrahydrofurans



	X =	Conditions	Yield	Ref
1	Br	$Cp_2Zr(H)Cl$, Et_3B, O_2, THF	89% (67:33 dr)	[33]
2	Br	Cp_2Zr-(butene), THF	48% (67:33 dr)	[34]
3	Br	2 mol% $CpCr[(XylNCMe)_2CH]$, Mn, γ-terpinene, THF	85% (65:35 dr)	[35]
4	I	5 mol% $[Li(tmeda)]_2[Fe(C_2H_4)_4]$, PhMgBr, THF	77% (alkene)	[36]
5	I	10 mol% $Pd(PPh_3)_4$, CO, PMP, PhH	62% (alkene)	[37]

PMP 1,2,2,6,6-pentamethylpiperidine, *tmeda* tetramethylethylene-diamine

$Cp_2Zr(II)$ in the form of an olefin complex also cleaves C-I bonds leading to an overall carbo-zirconation sequence where the saturated product is obtained in moderate yield after protonation and workup (Table 3, entry 2).

The electron-rich Cr(II) complex $CpCr[(XylNCMe)_2CH]$ has been used to form the saturated bicyclic product in the presence of Mn powder and the hydrogen atom donor γ-terpinene (Table 3, entry 3). High yield was obtained with a catalyst loading as low as 2 mol%.

The Fe(-II) complex $[Li(tmeda)]_2[Fe(C_2H_4)_4]$ is a model system for active catalysts that form from the reaction of $FeCl_2$ and organometallic reagents. Therefore it catalyzes the reaction to the unsaturated alkene product with PhMgBr as terminal reductant in good yield (Table 3, entry 4).

The complex $Pd(PPh_3)_4$ known from cross-coupling applications generates radical intermediates from alkyl iodides and leads to a Heck-type product formation after $E_{\beta\text{-}H}$ (Table 3, entry 5). Applications of Pd complexes in radical reactions have been the subject of a recent review [38].

An always efficient way to access alkene cyclization products is the reaction of propargylic acetals [30, 39]. The highly reactive vinyl radical intermediates are most often saturated by hydrogen atom transfer from the solvent.

Most reaction conditions could be applied not only to the synthesis of tetrahydrofurans but also to pyrrolidines and piperidines (Fig. 8a, b). The Pd-catalyzed Heck-type transformations proceeded in the presence of tosyl-protected amines to furnish the alkene cyclization products. Radical cyclization occurs at a trisubstituted alkene to the 5-*exo* product [37], while a 1-substituted styrene derivative leads to a 6-*endo* cyclization that is governed by steric repulsion of the phenyl substituent in a 5-*exo* transition state and the stabilizing effect of the resulting benzylic radical [40].

Even tetrasubstituted alkenes can be employed, as shown by Pattenden en route to the natural product forskolin (Fig. 8c) [41]. The electrochemical generation of vitamin B_{12} in Co(I) oxidation state led to S_N2, followed by 5-*exo* cyclization and reduction of the radical after workup. The 5-*exo* cyclization results in the expected

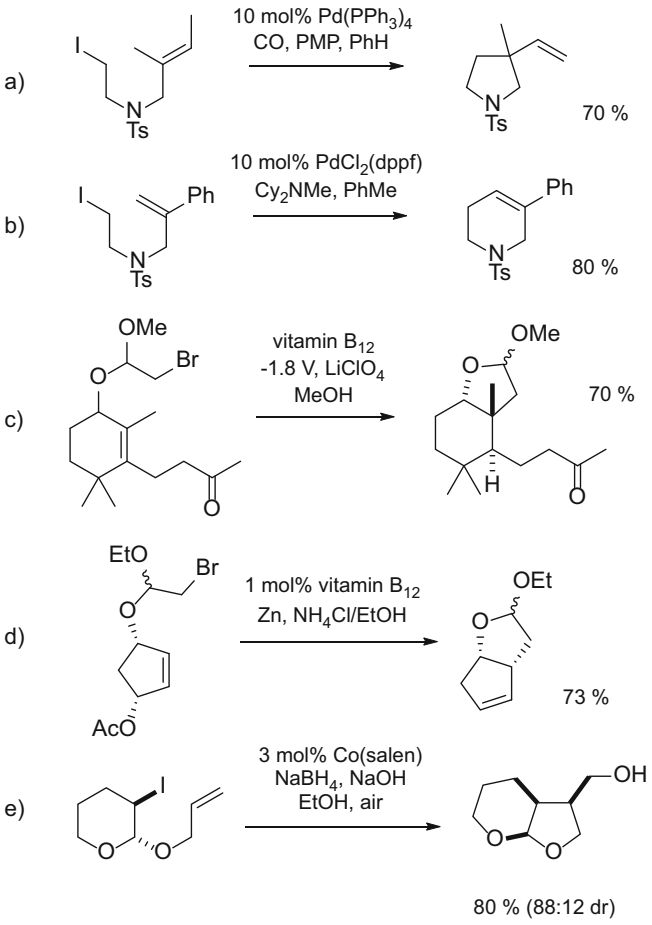


Fig. 8 Further examples of halo-alkene cyclizations. *PMP* 1,2,2,6,6-pentamethylpiperidine

formation of the *cis*-fused bicyclic system. Radical reduction proceeds with almost complete diastereoselectivity (>90:<10) to the product shown.

An experiment with catalytic amounts of vitamin B_{12} and a comparable substrate showed that generation of a 2-acetyl radical is followed by elimination to obtain the unsaturated product in good yield (Fig. 8d) [42]. The product has been used in the synthesis of prostaglandins.

Finally, oxidative cleavage of Co(III)-C bonds has been applied to the oxy-functionalization of 5-*exo* products resulting from reductive radical generation of Co(I)(salen) complexes (Fig. 8e) [43]. The resulting alcohol has been obtained in high yield and diastereomeric ratio by conducting the reaction under air.

2.1.2 Halo-Alkene Cyclization Followed by Cross-Coupling

The incorporation of organometallic species serving as terminal reductants into the product is highly dependent on the substrate. For most 5-*exo*-derived tertiary radicals, cross-coupling does not occur; instead $E_{\beta\text{-H}}$ leads to the unsaturated product. The reaction to primary heterocyclic radicals can be followed by cross-coupling of the radical with catalyst-bound aryl or alkyl groups under reductive elimination and catalyst regeneration. Reactions that proceed via addition of the heterocyclic radical to multiple bonds are not referred to as cross-coupling in this section.

Cobalt-complexes have been employed mostly in cross-coupling of Grignard reagents [44]. Low-valent bisphosphine-cobalt complexes formed from aryl Grignard reagents promote radical generation, as terminal reductants get incorporated into the product after reductive elimination (Fig. 9a) [45]. Also allyl and benzyl Grignard reagents undergo cross-coupling in the presence of a similar co-catalyst (Fig. 9b) [46, 47]. The coupling of alkynyl Grignard reagents has not been effective at low catalyst loadings [48] before N-heterocyclic carbene ligands were employed (Fig. 9c) [49]. Furthermore the use of cyclohexyldiamine ligands

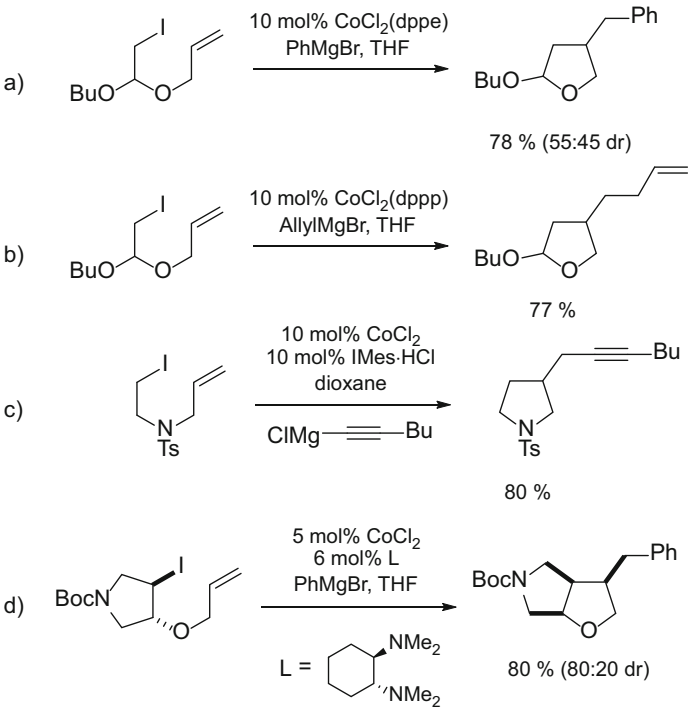


Fig. 9 Cobalt-catalyzed cross-coupling of Grignard reagents and heterocyclic radicals. *IMes* 1,3-bis(2,4,6-trimethylphenyl)-imidazolium, *dppe* 1,2-bis(diphenylphosphino)ethane, *dppp* 1,3-bis(diphenylphosphino)propane

has been shown to promote Fe- and Co-catalyzed cross-coupling of aryl Grignard reagents with primary and secondary radicals (Fig. 9d) [50].

The use of $[Li(tmeda)]_2[Fe(C_2H_4)_4]$ during the formation of primary heterocyclic radicals leads to cross-coupling of the terminal aryl Grignard reagent in high yield and diastereoselectivity (Fig. 10a) [51].

Cross-coupling of less nucleophilic organometallic reagents has been achieved through Ni catalysis. Formal oxidative addition of alkyl-X bonds at nickel complexes proceeds via radical intermediates and subsequent recombination with the nickel center. Thus, a Ni-bipyridine catalyst system has been shown to effectively catalyze the Stille-type 5-*exo* cyclization and cross-coupling of aryltrichlorotin compounds (Fig. 10b) [52]. Even better results were obtained with aminoalcohols as ligands and arylboronic acids as nucleophiles [53]. Both methods use a strong base to facilitate transmetallation to the Ni center. Cross-coupling of alkylzinc reagents that exhibit a better functional group tolerance than Grignard reagents has been achieved with a pyridine-bisoxazoline (PyBox) ligand (Fig. 10c) [54]. The

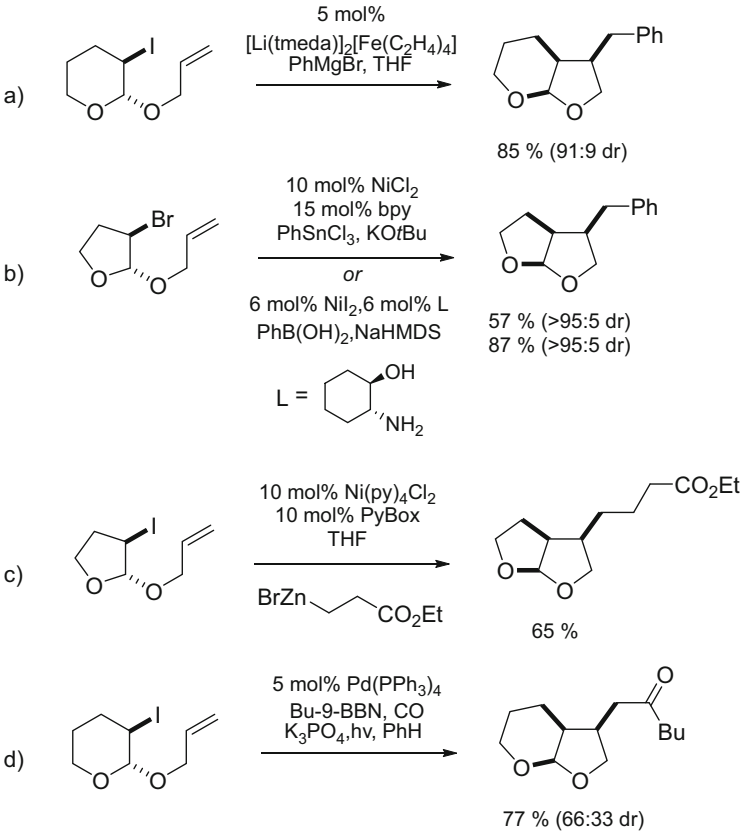


Fig. 10 Iron-, nickel-, and palladium-catalyzed cross-couplings of organometallics with heterocyclic radicals. *bpy* 2,2′-bipyridine

oxidation state of the active catalyst species in this Ni-catalyzed radical reaction has been described as a square-planar Ni(II) complex with an anionic ligand rather than a Ni(I) complex. This might also apply for the other systems described.

The previously described tendency of $Pd(PPh_3)_4$ to induce radical formation at alkyl iodides has been applied to carbonylation and cross-coupling (Fig. 10d) [55]. The heterocyclic radical intermediate undergoes recombination with the Pd (I) complex to obtain an alkyl-Pd(II) species that, unlike the follow-up chemistry for tertiary radicals, is stable toward CO insertion and cross-coupling with butyl-9-BBN borane to yield the ketone product.

Furthermore, Cu(I)-catalyzed cyclization/silylation has been achieved with silicon pro-nucleophiles [56].

2.1.3 Ketyl Cyclization

Apart from carbon-halogen bonds, carbonyl groups are excellent radical precursors as well. The most prominent system for the generation of ketyl radicals is SmI_2 [57, 58]. The cyclization of ketyl radicals can be employed to construct complex heterocyclic scaffolds from acyclic precursors (Fig. 11). Boc-protected pyrrolidines can be accessed from ketones and aldehydes that undergo cyclization to many unsaturated functionalities. The cyclization onto a Michael acceptor mediated by SmI_2 and HMPA as additive has been shown to be highly diastereoselective (Fig. 11a) [59]. Allenes also react in a 5-*exo* manner with aldehyde-derived ketyl radicals to afford *anti*-homoallylic pyrrolidines (Fig. 11b) [60]. Six-membered ring cyclizations can be highly effective when Michael acceptors are employed (Fig. 11c). This highly diastereoselective transformation has been used in the synthesis of polyether natural products [61–65].

In the absence of an aldehyde or ketone, the SmI_2-HMPA reagent can undergo iSET at α,β-unsaturated esters and subsequent vinylogous cyclization onto an alkyne (Fig. 11d) [66]. The resulting bromo-alkene product is formed stereoselectively and can be used in cross-coupling reactions. Ketyl radical cyclization onto alkynes has also been used to construct medium-sized macrocyclic ring systems [67].

2.1.4 Epoxide Cyclization

The formation of radicals from epoxides has been first described by Nugent and RajanBabu [68–71]. After coordination of $Cp_2Ti(III)Cl$ to an epoxide, kinetically controlled homolytic cleavage (iSET) occurs to provide secondary radicals from terminal epoxides or tertiary radicals from 1,1-di- and trisubstituted epoxides [2].

Subsequent 5-*exo* cyclization into a tertiary radical can lead to catalyst liberation by S_Hi (Fig. 12a) [11–13]. The cis-fused products are obtained in good yield and high diastereomeric ratio using catalytic amounts of Cp_2TiCl_2 and the additives Mn and collidinium chloride.

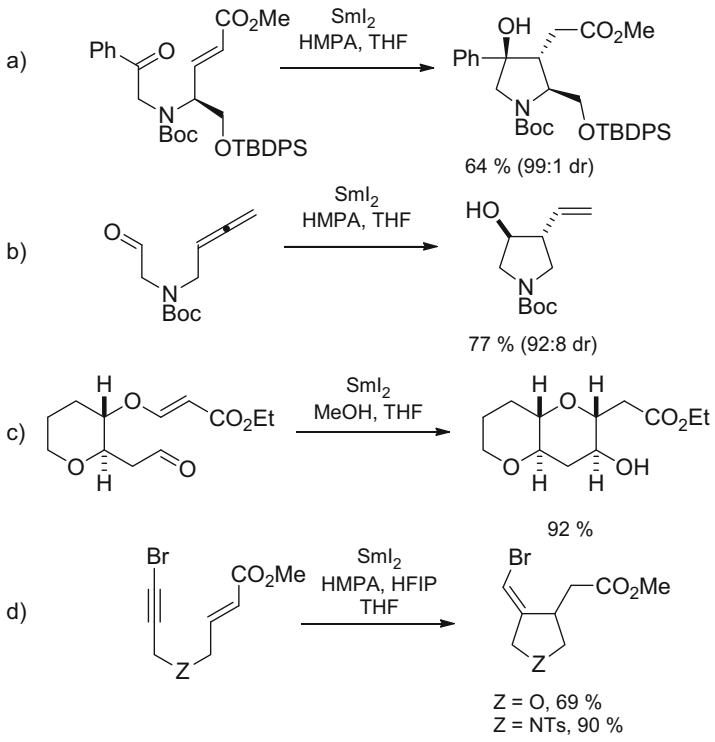


Fig. 11 Sm(II)-mediated heterocycle synthesis via ketyl radicals. *HMPA* hexamethylphosphoramide, *HFIP* hexafluoroisopropanol

Epoxide-alkyne cyclization can be terminated by addition of the resulting vinyl radical intermediate to an acrylate acceptor (Fig. 12b) [10]. The tetrasubstituted alkene is accessed with high selectivity under consumption of stoichiometric amounts of reductant and proton source collidinium chloride. Regular alkyne cyclization can be terminated by hydrogen atom transfer from Ir-H bonds that originate from oxidative addition of hydrogen to Vaska's complex to give rise to pyrrolidines (Fig. 12c) [72].

Sharpless epoxidation-derived enantiopure epoxides show selective epoxide opening to furnish 1,2-diol radicals [73–75] that have been used in the diastereoselective synthesis of pyrrolidines (Fig. 12d) [76]. The resulting enoyl radical is reduced by another equivalent of $Cp_2Ti(III)Cl$ and protonated upon workup.

The synthesis of tetrahydrofurans from epoxides and alkenes is highly atom-economical and has been expanded by reports on Fe-catalyzed reaction of styrenes and styrene oxides (Fig. 13) [77–79]. The in situ reduced Fe(I)(salen) complex opens styrene oxides selectively into the benzylic radical that adds to the styrene to furnish another benzylic radical (Fig. 13a). S_Hi reaction again liberates the product and ideally the catalyst in oxidation state +I. However, stoichiometric amounts of

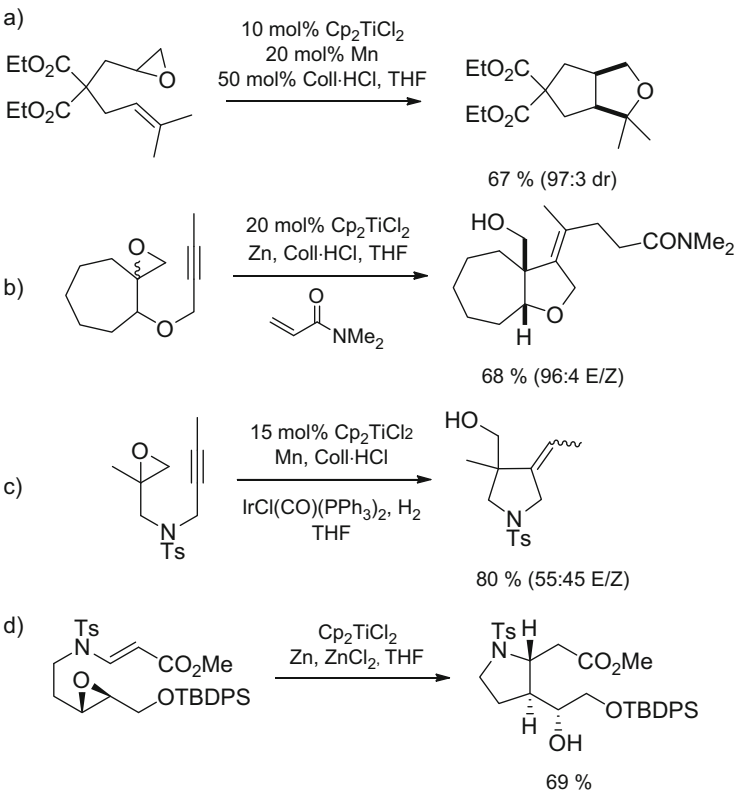


Fig. 12 Examples of titanocene(III)-epoxide cyclizations. *Coll* 2,4,6-trimethylpyridine

reductant are used to obtain the products in high yield. The reaction of styrene oxide and maleimides proved to be fully diastereoselective for the cis-fused product (Fig. 13b).

2.2 *Functionalization of Five- and Six- Membered Oxa- and Azacycles in the Synthesis of Polycyclic Heterocycles*

The synthesis of polycyclic heterocycles via radical intermediates in its entirety is beyond the scope of this section. Nonetheless, most recent and elegant examples utilizing samarium and titanium chemistry will be highlighted in this section.

The selectivity of SmI_2 for functional groups has been exploited in recent syntheses to construct complex heterocyclic scaffolds. Substrate conformation can lead to full control of diastereoselectivity of radical cyclizations. The Sm-mediated ketyl

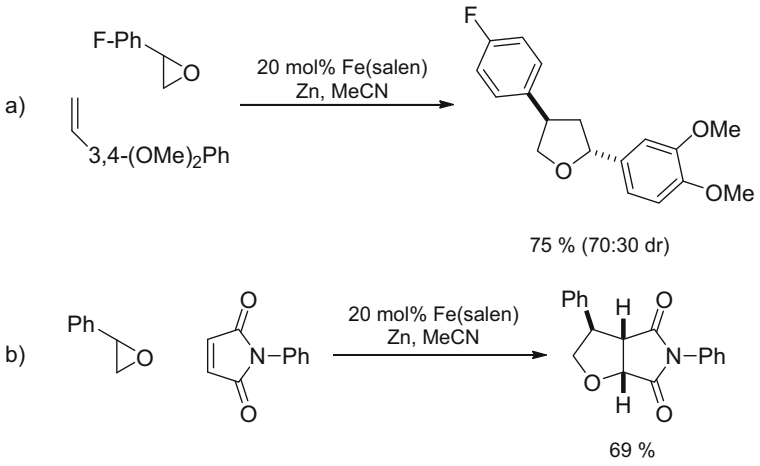


Fig. 13 Examples of iron(I)-catalyzed tetrahydrofuran synthesis

radical cyclization of a protected sugar-derived ketone onto a propargylic alcohol therefore leads in high yield and selectivity to the bicyclic core scaffold of Miharamycins (Fig. 14a) [80].

The selectivity of SmI_2 toward different aldehyde groups within the same molecule has been exploited in the synthesis of maoecrystal Z [81]. Ketyl radical formation proceeds at the less hindered aldehyde which undergoes addition to the Michael acceptor (Fig. 14b). The resulting enoyl radical is reduced by another equivalent of SmI_2 to obtain a Sm-enolate. Subsequent aldol reaction of the Sm-enolate leads to the tetracyclic core of maoecrystal as a single diastereomer. Notably, the present terminal alkene does not react fast enough in a 5-*exo* manner compared to the Michael acceptor.

The rational design of cyclization substrates has been demonstrated by Procter in the functionalization of barbiturates (Fig. 14c) [82]. One of the amide-carbonyls is reduced by SmI_2-H_2O and reacts in a same-side attack 5-*exo* cyclization with the terminal olefin. The resulting primary radical undergoes subsequent 6-*exo* cyclization with the styrene acceptor. The stereochemistry of the last cyclization is governed by steric repulsion of the styrenyl residue with the barbiturate core leading to a 1,4-cis configuration.

Titanocene(III) chemistry has evolved into a viable catalytic substitute for SmI_2 in many applications. The reductive umpolung of quinolones and chromones allows the selective β-functionalization of these heterocyclic scaffolds with Michael acceptors via vinylogous ketyl radicals (Fig. 15a) [83]. In a second step under the same reaction conditions, ketyl radical addition to a Ti(III)-activated nitrile leads to the formation of a bicyclic benzazozine in high yield as a single diastereomer (Fig. 15b).

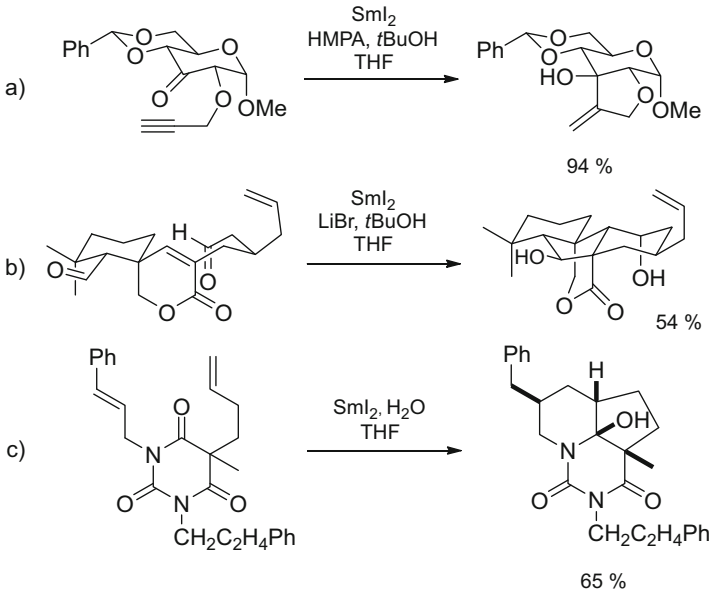


Fig. 14 Examples of Sm(II)-mediated functionalization of heterocyclic systems

A comparable carbonyl umpolung reaction has been applied to the synthesis of bicyclic amines (Fig. 15c) [84]. In situ iminium formation followed by titanocene (III)-catalyzed umpolung and radical addition to methyl acrylate leads to a 1-azadecalin structure in high yield and diastereoselectivity.

Furthermore, hemiaminals were engaged in titanocene(III)-catalyzed umpolung reactions (Fig. 15d) [85]. In situ conversion of the hemiaminal substrate to the chlorolactam by reaction with TMSCl is followed by radical generation via chloride abstraction by $Cp_2Ti(III)Cl$. A seven-membered ring cyclization onto the α,β-unsaturated γ-lactone leads to the formation of a cis-fused tricyclic structure.

2.3 Synthesis of Unsaturated Oxa- and Azacycles

2.3.1 Halo-Alkene Cyclization

The inherently stronger aryl-halogen bond compared to alkyl-halogens precludes some reagent systems from efficient radical generation and subsequent cyclization. However, many reactions are viable for alkyl-halogens as well as aryl-halogens. The strong reductants formed from M^{2+}-salts and organometallic reagents such as the Mn-ate complex Bu_3MnLi or Fe(0) and Co(0) complexes are capable of SET to aryl-halogen bonds (Table 4, entries 4–7). The product of these reactions is dependent on the substitution pattern of the resulting radical. While tertiary radicals

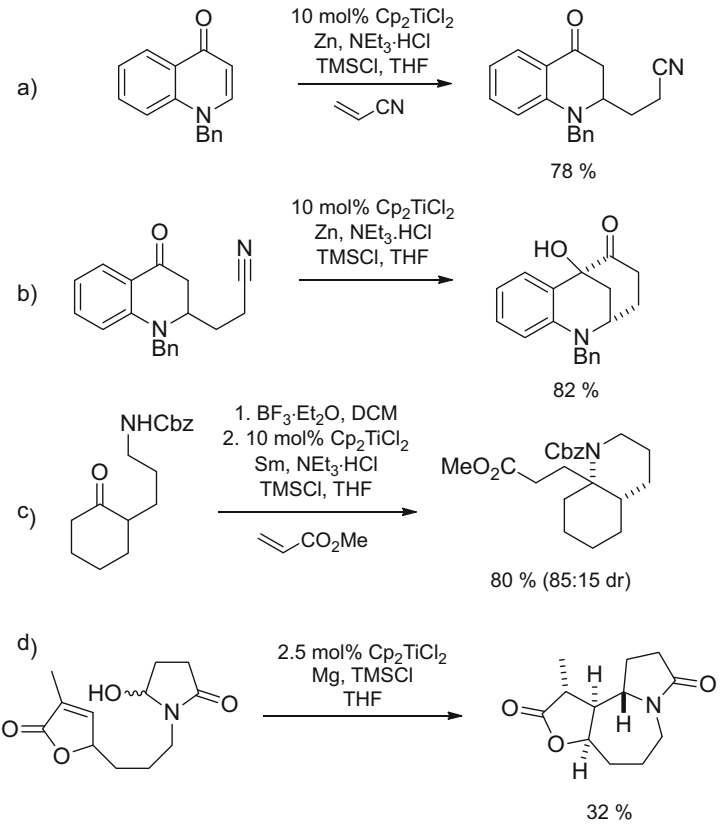


Fig. 15 Examples of titanocene(III)-catalyzed functionalizations of heterocycles

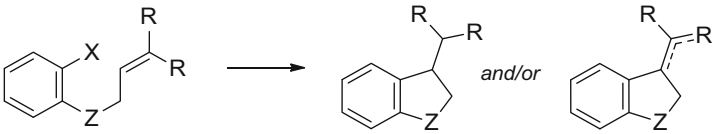
ultimately undergo $E_{\beta\text{-H}}$, primary radicals remain metallated and result in the saturated product after workup (Table 4, entry 6). Indolines as well as dihydrobenzofurans can be accessed from the substituted anilines and phenols.

The Schwartz reagent in combination with Et_3B and air leads to radical formation, cyclization, and hydrogen atom transfer as in the case of aliphatic iodides (Table 4, entry 3). Also, titanocene-catalyzed carbo-magnesation of related substrates leads to heterocyclic Grignard reagents that can be trapped by a variety of electrophiles [91, 92].

Interestingly, electrochemically reduced Co(I)(salen) complexes are not only capable of S_N2 at aliphatic halides but also capable of SET at aromatic iodides. Electrolysis of allyl-2-iodophenol in the presence of catalytic amounts of the Co(I)(salen) precursor $CoBr(PPh_3)$(salen) leads to the formation of 3-methyl-2,3-dihydrobenzofuran in moderate yield (Table 4, entry 8).

SmI_2 in combination with redox-modulating additives is capable of inducing SET at aryl iodides and bromides to obtain dihydrobenzofurans or indolines (Table 4, entries 1 and 2). The use of an excess Sm(II) leads to reduction of the

Table 4 Reaction conditions for halo-alkene cyclizations of aromatic halides



	X =	Z =	R =	Conditions	Yield	Ref
1	I	O	H	SmI_2, H_2O, NEt_3, THF	99%	[86]
2	Br	N-prenyl	Me	SmI_2, HMPA, *t*BuOH, THF	75%	[87]
3	I	N-prenyl	Me	$Cp_2Zr(H)Cl$, Et_3B, O_2, THF	68%	[33]
4	I	N-prenyl	Me	Bu_3MnLi, THF	92% (alkene)	[29]
5	I	N-prenyl	Me	5 mol% $FeCl_2$, PhMgBr, THF	98% (alkene)	[30]
6	I	O	H	$CoCl_2$, MeMgI, THF	54%	[88]
7	I	N-prenyl	Me	10 mol% $CoCl_2$(dppp), Me_3SiCH_2MgBr, THF	88% (alkene)	[21]
8	I	O	H	12 mol% $CoBr(PPh_3)$(salen), $LiClO_4$, MeOH, pyridine, −1.8 V	45%	[89, 90]

5-*exo* radical and subsequent protonation of the Sm(III)-alkyl intermediate from the additives. The extension of SmI_2 cyclization to alkynes can have different product distributions depending on the additives. The reaction of a propargyl bromoaniline with SmI_2 and HMPA and isopropanol as additives leads to the reduction of the resulting vinyl radical and subsequent double-bond migration to obtain 3-methylindole (Fig. 16a) [87]. The acetyl group gets removed under the reaction conditions.

In contrast, triethylamine and water as additives increase the reduction potential of SmI_2 so that the exocyclic alkene formed from 5-*exo* cyclization gets reduced to 3-methyl-2,3-dihydrobenzofuran (Fig. 16b) [86].

Organic ground-state reductants have been successfully employed in cyclizations via radical intermediates [93]. The role of the simple organic reductant KO*t*Bu in conjunction with heterocyclic ligands has been clarified only recently [94]. A combination of phenanthroline-type ligands and KO*t*Bu leads to the formation of anionic homo-coupling products of phenanthroline that are powerful reductants. Thereby radical formation occurs with aryl iodides to obtain, e.g., benzofurans in good yield after double-bond migration (Fig. 16c) [95].

The more elaborate tetrathiafulvalene has been used in catalytic radical-polar-crossover applications (Fig. 16d) [96]. The organic reductant induces radical formation at diazonium salts, and the resulting radical cation is able to recombine with the 5-*exo* cyclization product. The catalyst is liberated by trace amounts of water from the solvent to obtain the secondary alcohol product in good yield.

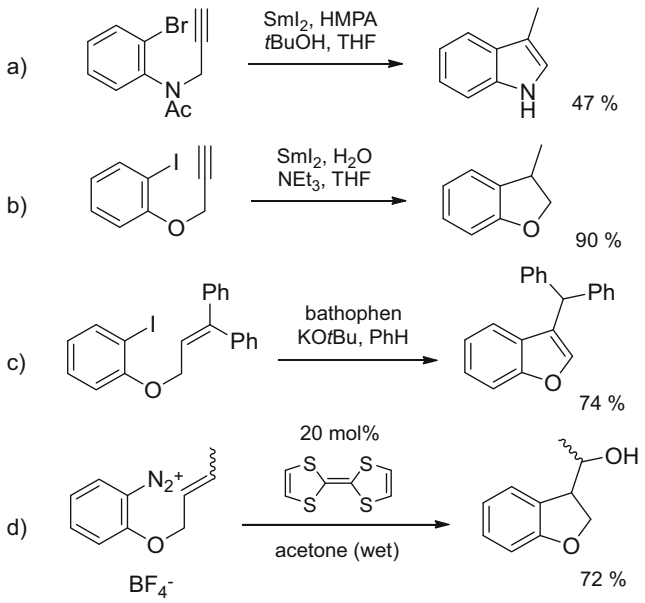


Fig. 16 Examples of halo-alkyne cyclizations and cyclizations mediated by organic reductants. *bathophen* bathophenanthroline

2.3.2 Cyclization onto Aromatic Systems

The outcome of cyclization of an aryl radical onto an arene can again be altered by the choice of the reagent system. SmI_2-induced radical formation at 2-iodoanilines leads to a spirocyclic radical σ-complex. Depending on the substitution pattern and on the rate of reduction of the spirocyclic radical σ-complex, 1,2-rearrangement occurs followed by reduction into the anion. For the SmI_2/HMPA/*i*PrOH reagent system, the spirocyclic dihydroxyindole product is obtained in 89% yield (Fig. 17a) [97]. Without an alcohol additive and with a different methyl substitution, the rearranged dihydroquinoline is obtained in moderate yield (Fig. 17b) [98].

Less reducing organic reductant systems are still capable of inducing SET at similar 2-iodoanilines, although no second reduction either of the spirocyclic radical σ-complex or the quinolonyl radical occurs. Instead, rearomatization follows rearrangement to the 2-quinolone scaffold (Fig. 17c) [99].

Not only aryl radical cyclizations give rise to unsaturated heterocycles but also alkyl radical addition to arenes. Since this topic will be covered in another chapter of this book, selected examples are presented herein.

Pd-catalyzed radical formation has been exploited for tandem addition/cyclization sequences to obtain indolinones (Fig. 18a) [100–102]. In the present example, a cyclohexyl radical is generated from a low-valent Pd(dppf) species that adds to an acrylate. The resulting enoyl radical attacks the arene and forms a radical σ-complex. This intermediate is oxidized by the pending Pd-catalyst and rearomatizes under proton loss.

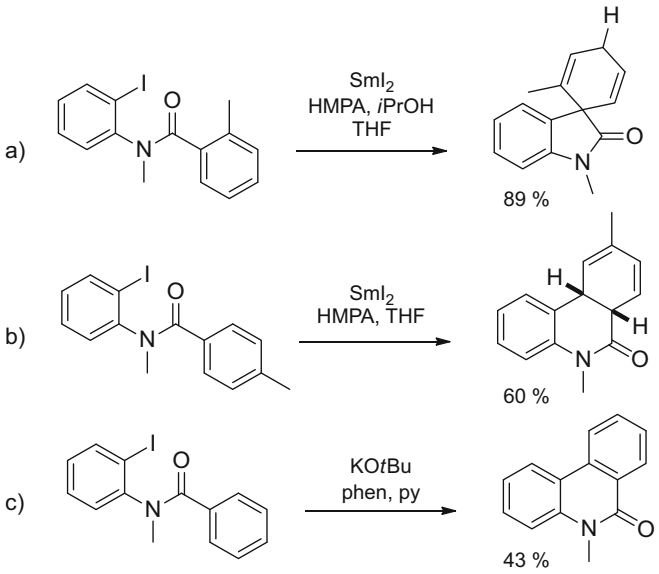


Fig. 17 Different outcomes in cyclizations of benzoate anilides depending on the reaction conditions. *phen* phenanthroline

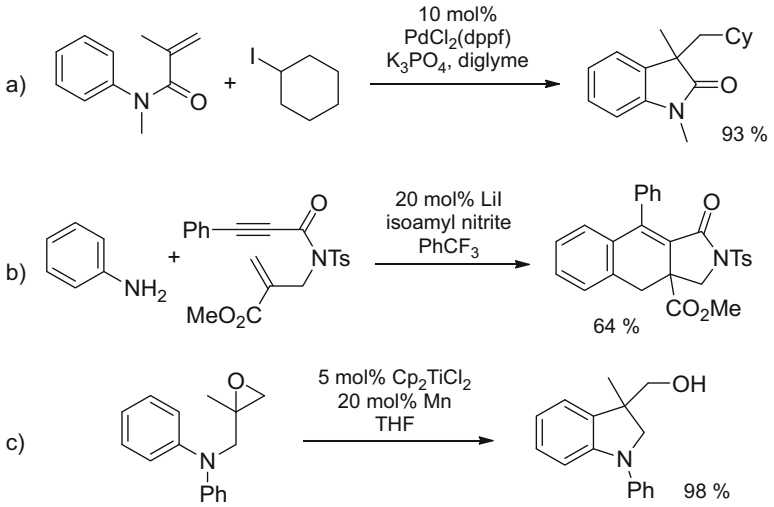


Fig. 18 Cyclizations of alkyl radicals to furnish indoline-type heterocycles

A cascade cyclization sequence has recently been reported for the rapid construction of polycyclic lactams (Fig. 18b) [103]. In situ diazonium salt formation is followed by SET from iodide to obtain a phenyl radical. The phenyl radical adds to the Michael acceptor and the enoyl radical in turn undergoes 5-*exo* cyclization to

the alkene furnishing a vinyl radical. The vinyl radical adds to the arene, and the radical σ-complex is oxidized by pending iodine produced during the reduction of the diazonium salt. This iodide-catalyzed cyclization is high yielding for a variety of lactams and lactones.

Finally, homolytic epoxide ring opening has been applied to the functionalization of anilines and pyrroles via an atom-economical reaction pathway (Fig. 18c) [104–111]. Indolines were obtained using catalytic amounts of Cp_2TiCl_2 as well as reductant and other additives in excellent yield via the formation of an alkyl radical, in addition to the arene and intramolecular electron transfer to the catalyst.

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Synthesis of Nitrogen-Containing Heterocycles via Imidoyl or Iminyl Radical Intermediates

Jian Lei, Dengke Li, and Qiang Zhu

Abstract Synthesis of nitrogen-containing heterocycles with isocyanides, isothiocyanates, nitriles, imines, oxime derivatives, and other related compounds has been deeply investigated in organic synthesis. This chapter mainly focuses on summarizing radical cyclization reactions of these C-N unsaturated precursors to afford *N*-heterocycles in the past decade as well as some earlier feature examples. In most cases, imidoyl or iminyl radicals are involved in cyclizing onto unsaturated systems or heteroatoms to generate *N*-heterocycles, such as phenanthridines, (iso) quinolines, pyridines, indoles, and pyrroles. A few examples via other types of radical intermediates starting from isothiocyanates, isocyanates, and analogous structures are also included.

Keywords Cyclization reactions · Homolytic substitution · Imidoyl radicals · Iminyl radicals · Nitrogen heterocycles · Radical reactions

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1 Introduction

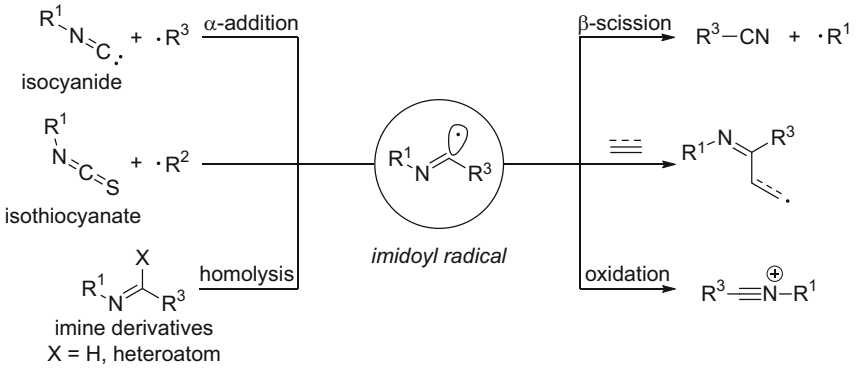
Structures containing carbon-nitrogen unsaturated bonds, including double and triple bonds, are widely distributed, showing diverse reactivity in organic synthesis.

Substrates containing C-N unsaturated bonds are also extensively applied in radical reactions. In this chapter, radical cyclization reactions involving isocyanides, isothiocyanates, nitriles, imines, oxime derivatives, and other related compounds to afford *N*-heterocycles are summarized. In most of the processes, imidoyl and iminyl radical intermediates are formed, generated from the corresponding C- and N-centered radicals. The review is organized around functional groups that generate these two types of radicals.

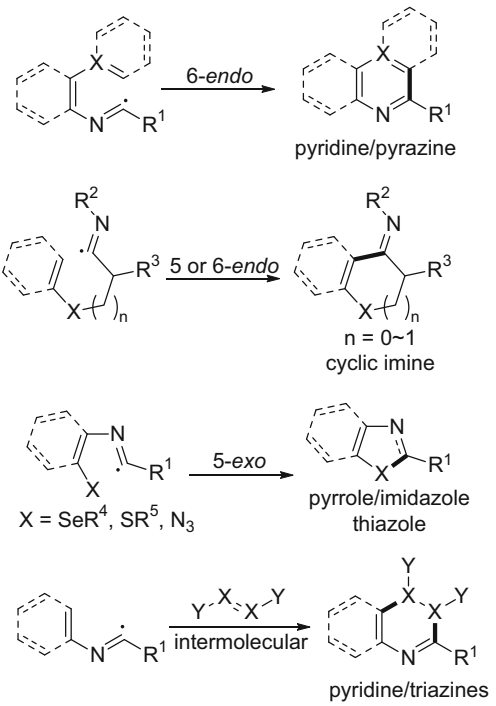
Imidoyl radical was first described over 50 years ago, and a comprehensive review covering its history, generation, structure, and reactivity was presented by Nanni in 2007 [1]. General structure of imidoyl radical can be described as a carbon radical with a single electron occupying the σ-orbital of the imidoyl group [2]. The most common way to give an imidoyl radical is α-addition of carbon-, tin-, sulfur-, phosphine-, oxygen-, and tellurium-centered radicals onto isocyanide. Radical addition to isothiocyanates also generates the corresponding sulfur-containing imidoyl radical, although limited examples were available in the literature. Homolysis of imines and their derivatives is also an efficient way to give related imidoyl radicals. The unique structure of imidoyl radical leads to three special reactivities, such as α-scission to go back to isocyanide [3] or β-scission to generate nitrile and another radical [4], which is used in cyanation or deamination [5]; oxidation of imidoyl radicals to nitriliums followed by nucleophilic attack to provide amide derivatives is also reported (Scheme 1) [6, 7].

Most importantly, like other radicals, imidoyl radicals can be trapped by alkenes, alkynes, or arenes, to generate a variety of *N*-heterocycles when processes take place intramolecularly. This process is probably the most useful transformation of imidoyl radicals, and thus it has been deeply investigated during the past decade. The products are normally 5-membered or 6-membered heterocycles including pyridines, pyrroles, pyrazine, and imidazoles (Scheme 2).

The study of iminyl radicals through EPR spectroscopy traces back to 50 years ago, [8] figuring that the single electron occupies a 2p orbital that lies orthogonal to the π-orbitals of the C-N double bond [9, 10]. The practical generation pathways of iminyl radicals include addition of carbon or nitrogen radicals to nitriles; thermal or photo-homolysis of N-X bonds in oxime derivatives, in which X may refer to O, S, N, Cl, and H; and decomposition of organic azides to release nitrogen and iminyl

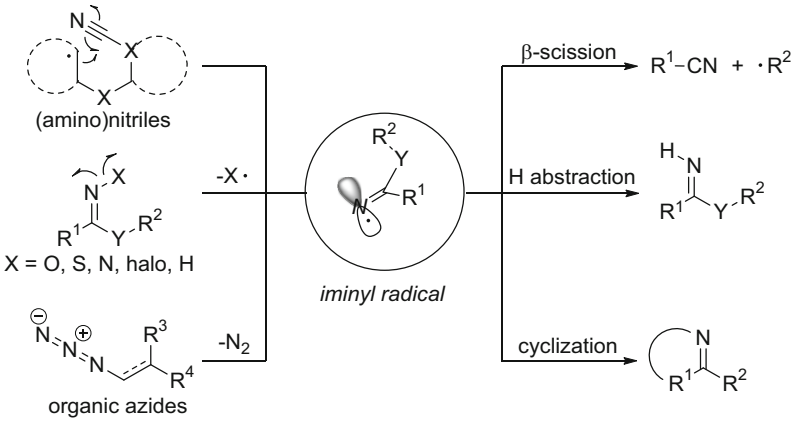


Scheme 1 Generation and conversion of imidoyl radicals

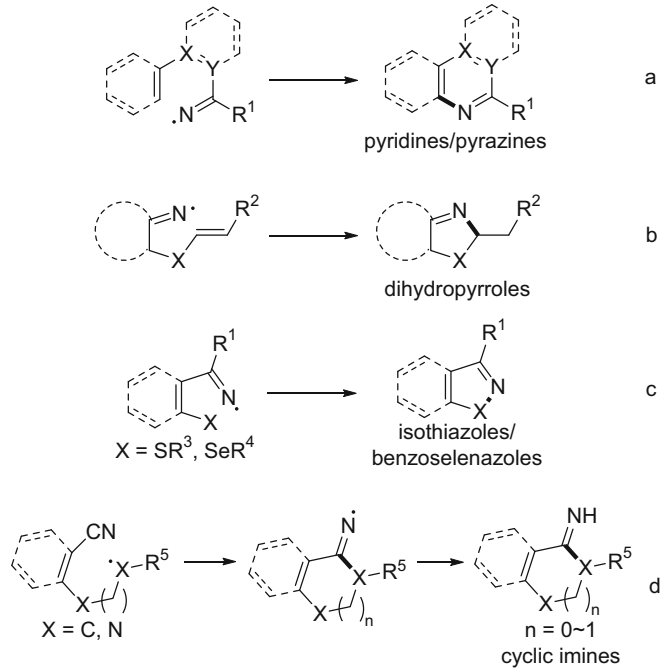


Scheme 2 Scaffolds of cyclization products of imidoyl radicals

radicals (Scheme 3). However, organic azides are not covered in this chapter for their special structure and reactivity [11, 12]. Like imidoyl radicals, the major fate of iminyl radicals is trapping by intramolecular functional groups to give nitrogen heterocycles including pyridines/pyrazines, dihydropyrroles, isothiazoles, etc. (Scheme 4). Other pathways to iminyl radical include β-scission into nitriles and alkyl radicals [13] and hydrogen abstraction to form imines and subsequent



Scheme 3 Generation and transformation of iminyl radicals



Scheme 4 Basic scaffolds of annulation products of iminyl radicals

hydrolysis into ketones. Recently, Walton and Castle reported several reviews on synthesis utilizing iminyl radicals [14–16].

Cyclization of imidoyl/iminyl radicals can result into the following two types of products: one in which both C and N atoms in the C=N bond are present into the ring (route a, b, c, Scheme 4) and the other in which only the carbon in C=N participates to the ring construction, the N atom in the heterocycle coming from

other functionalities (route d, Scheme 4). In the following parts, radical cyclization has been organized around the nature of the substrate functional groups.

2 Cyclization via Imidoyl Radicals

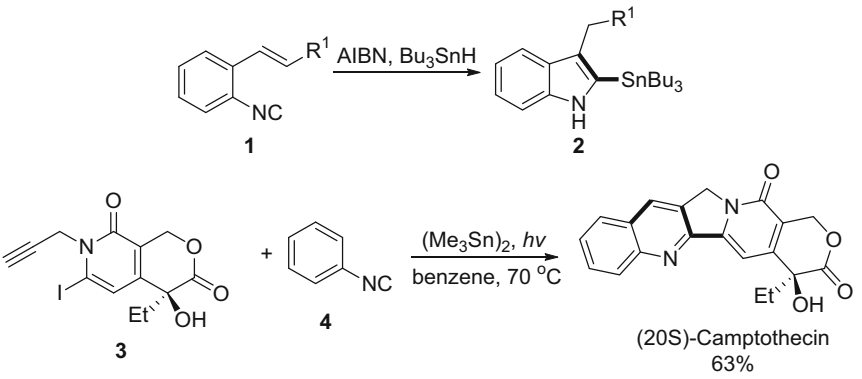
2.1 Starting from Isocyanides

Isocyanide which is isoelectronic to carbon monoxide is well-known for its versatility in bond formation. The resonance structures of isocyanide can be described as in Eq. (1). The two resonance forms are responsible for its amphiphilic reactivity [17–20], its reactivity in radical-mediated [21], and in transition metal-catalyzed insertion [22–24].

(1)

The terminal divalent carbon of isocyanide can form an imidoyl radical by accepting a radical species, forming simultaneously a σ-bond and a radical on the geminal carbon. Subsequent intramolecular addition of the resulting imidoyl radical onto unsaturated bonds or heteroatoms forms nitrogen heterocycles after radical termination. Thus, the whole cyclization process consists in the formation of two chemical bonds from the isocyanide carbon.

Cyclization of imidoyl radical to synthesize nitrogen heterocycles has been reported for decades. A seminal application of this strategy was developed by Curran for the synthesis of camptothecin and its derivatives [25–27]. Another early example was demonstrated in indole alkaloids synthesis, also known as Fukuyama indole synthesis [28–31]. These reactions could be performed under mild conditions with high bond forming efficiency, thus providing efficient alternatives for *N*-heterocycle construction. However, toxic tin reagents were inevitably used in these processes (Scheme 5).



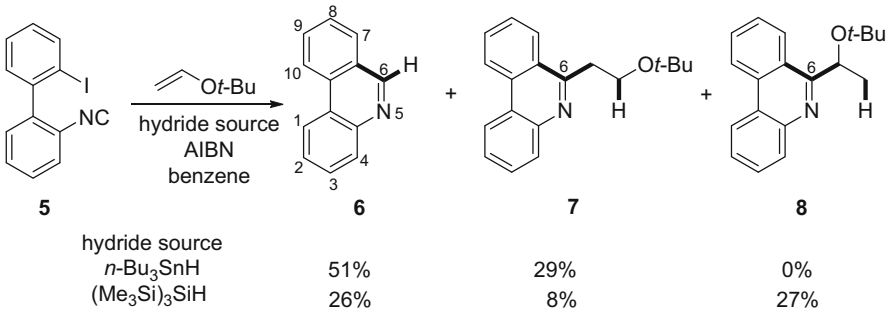
Scheme 5 Fukuyama's indole synthesis and Curran's approach to camptothecin

In recent years, significant development has been made in this area owing to the application of new free radical generation protocol and diversified functionalized isocyanides. Reviews on the synthesis of nitrogen heterocycles via imidoyl radical intermediates generated from isocyanides were reported by Studer, Xu, and Zhu group [32–34].

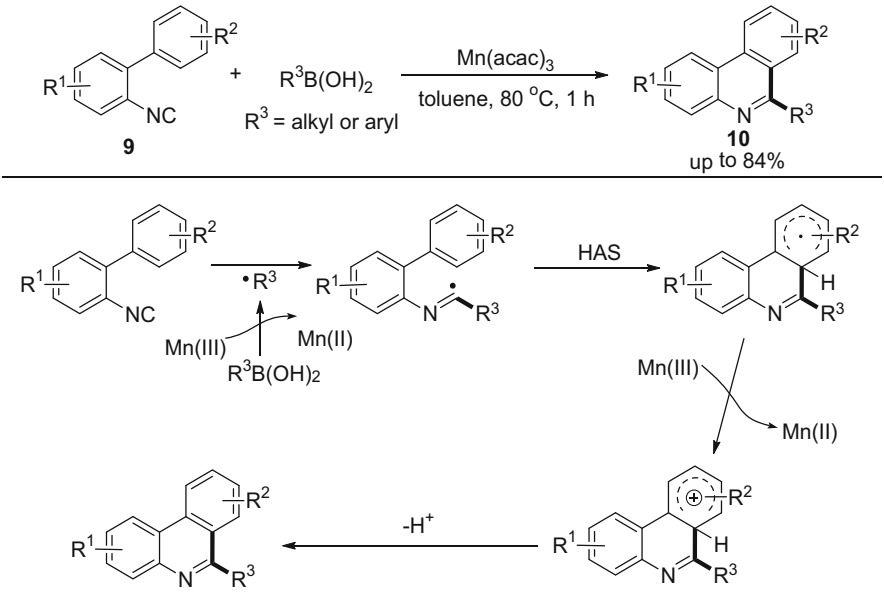
The phenanthridine core is widely distributed in natural and synthetic compounds exhibiting various biological activities [35, 36]. In 1995, Nanni reported the synthesis of 6-cyanopropyl-substituted phenanthridines with 2-isocyanobiphenyl with the aid of AIBN via an imidoyl radical intermediate [37]. Beyond cyanopropyl radical generated from AIBN, phenyl and tristrimethylsilylsilyl radicals may also be incorporated at C6 in phenanthridines. In 2000, Smith described another high-yield approach to 6-alkyl phenanthridines, starting from 2′-iodo-2-isocyanobiphenyls in the presence of *n*-Bu_3SnH/AIBN (Scheme 6) [38]. Interestingly, in the presence of excess vinyl *t*-butyl ether, addition of phenanthridine C6 radical to vinyl *t*-butyl ether affords C6-alkylated products.

In 2012, Chatani reported a novel imidoyl radical cyclization reaction starting from 2-isocyanobiphenyls and boronic acids promoted by $Mn(acac)_3$ to afford the C6-aryl- or alkyl-substituted phenanthridines in good yields (Scheme 7) [39]. Mechanistic studies revealed that over two equivalents of manganese were necessary, since $Mn(acac)_3$ acted as a single-electron oxidant for both radical generation from boronic acids and oxidation of the cyclohexadienyl radical into the corresponding cation. Moreover, the reaction was shut off by addition of TEMPO, suggesting that radical intermediates were involved in the reaction. The mechanism they proposed was well accepted, and similar mechanisms were reported in most of the following studies using other radical species.

Zhu reported an alternative method for the synthesis of 6-arylphenanthridines using aryl radicals generated in situ from inexpensive and readily available anilines and *t*-BuONO [40]. Both radical clock and radical inhibition experiments revealed that aryl radical intermediates were involved. It is known that imidoyl radicals are prone to oxidation into nitriliums. Therefore, a competitive reaction pathway was proposed, including an intramolecular homolytic aromatic substitution (HAS) or a SET oxidation to nitrilium followed by an electrophilic aromatic substitution.



Scheme 6 Phenanthridine synthesis with 2′-iodo-2-isocyanobiphenyls



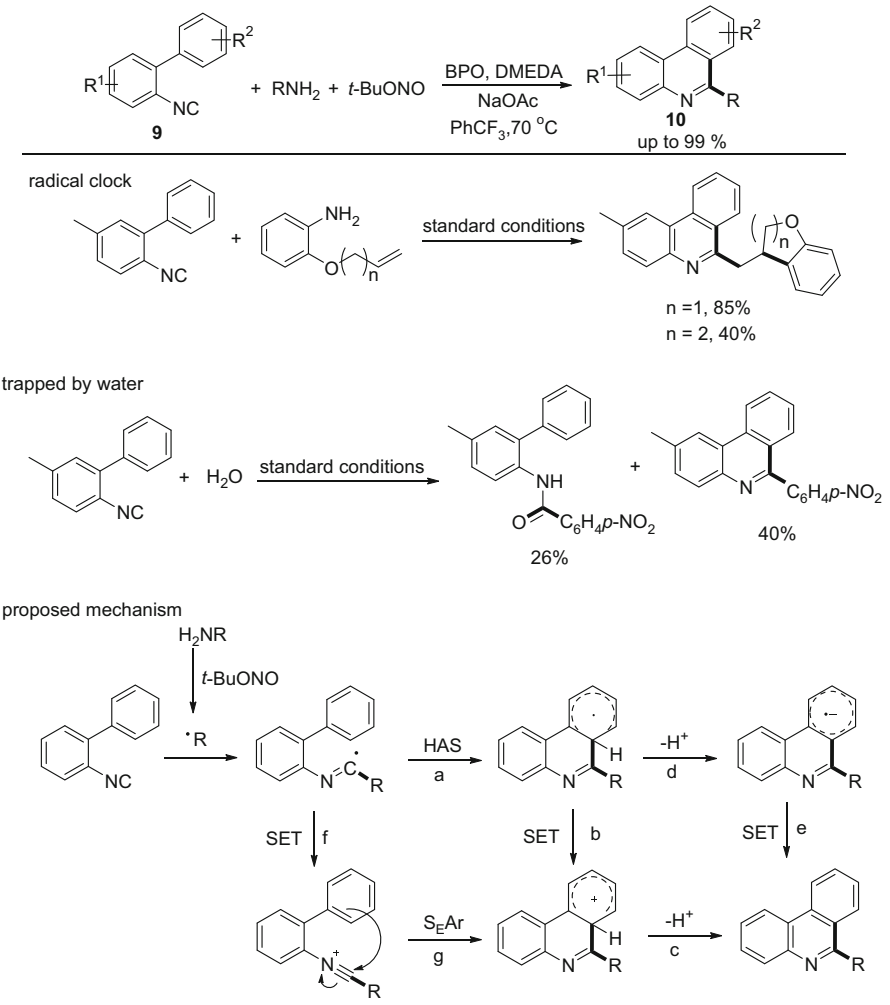
Scheme 7 Synthesis of 6-aryl/alkylphenanthridines from organoborons and $Mn(acac)_3$

When water was added into the reaction medium, the related amide product derived from addition of water to the nitrilium intermediate was isolated in low yield (vide infra). The Hammett curve with unsymmetrical 2,6-diaryl phenylisocyanides suggested that both pathways involving S_EAr of nitrilium cation and HAS of imidoyl radical were likely involved in the annulation step (f vs. a, Scheme 8). The importance of phenanthridine scaffold has prompted the incorporation of various radicals including CF_3, aryl, alkyl, $C_xH_yF_z$, acyl, phosphine, and silyl radicals to synthesize various C6-substituted phenanthridines [32–34].

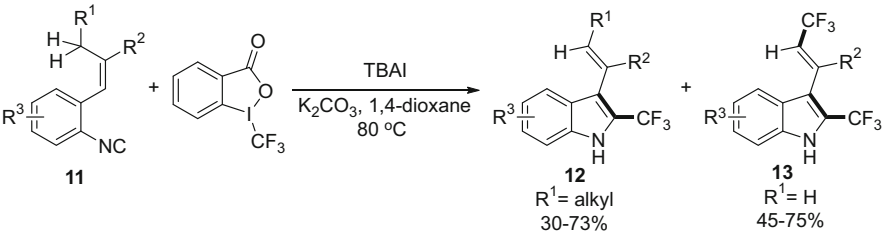
Beyond phenanthridines, other heterocycles can also be synthesized with this method by modifying isocyanide structure. For example, Studer reported radical trifluoromethylation/cyclization of 2-vinyl-substituted arylisocyanide **11** with hypervalent iodine-CF_3 reagent (Togni's reagent) and TBAI as an initiator to afford 2-trifluoromethylated indoles **12** via 5-*exo-trig* cyclization (Scheme 9) [41, 42]. When R^1 is a hydrogen, the 3-alkenyl product was trifluoromethylated further with excess Togni's reagent to provide **13**.

When 2-alkynyl arylisocyanide was used as radical acceptor, 2-substituted quinolines were synthesized. Ogawa described the synthesis of 2,4-bis-chalcogenated quinolines via visible-light-induced chalcogenation of isocyanides in modest to good yield (Scheme 10) [43]. Besides the mechanism involving an imidoyl radical-mediated cyclization, an alternative approach through addition of a phenyltellurium radical to alkyne, followed by capture of the resulting vinyl radical with isocyanide, was proposed. The 2-quinolinyl radical was then quenched by dichalcogenides to give the final product **15**.

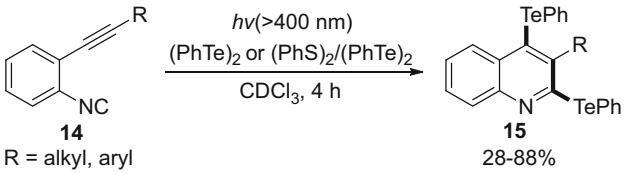
When vinyl isocyanide was used as substrate, isoquinoline or pyridine derivatives could be obtained. In 2014, Yu reported visible-light-promoted cyclization of



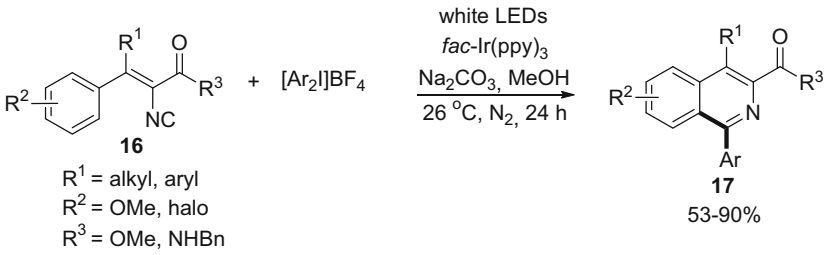
Scheme 8 Synthesis of 6-arylphenanthridines from anilines and *t*-BuONO



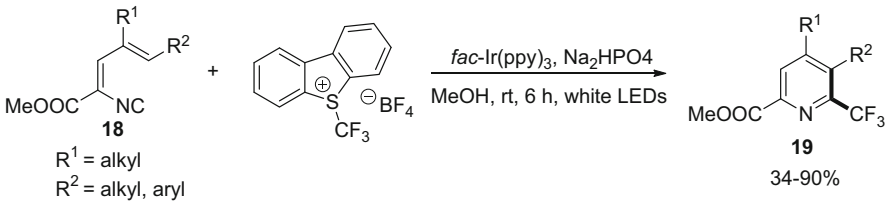
Scheme 9 Synthesis of 2-trifluoromethylated indoles with 2-vinyl arylisocyanides



Scheme 10 Reaction of O-ethynylarylisocyanides with dichalcogenides



Scheme 11 Synthesis of isoquinolines using isocyanide and diaryliodonium salt

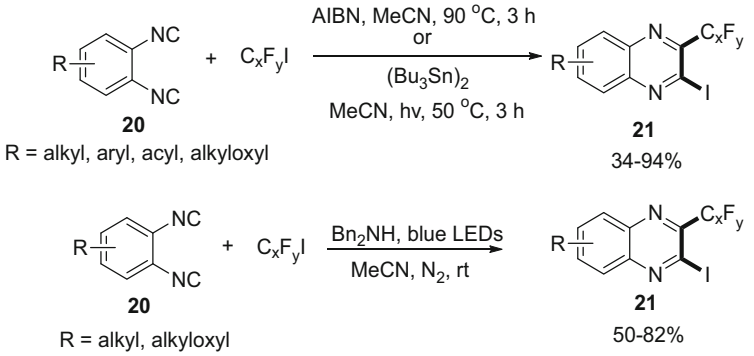


Scheme 12 Reaction of vinyl isocyanides and Umemoto's reagent to synthesize polysubstituted pyridines

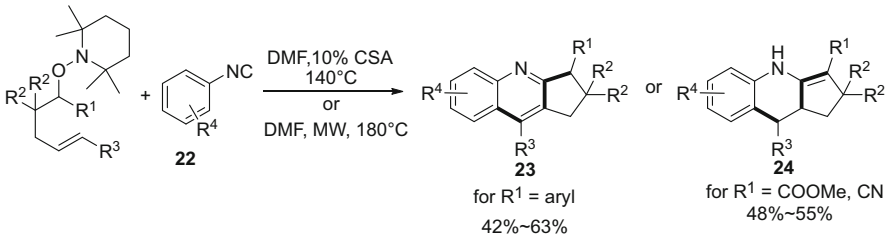
vinyl isocyanides with diaryliodonium salts to afford isoquinolines **17** (Scheme 11) [44]. Later on, they used 1,3-dienyl isocyanides to synthesize 2-(fluoro)alkylated pyridine derivatives **19** in the presence of Umemoto's reagent under visible-light conditions (Scheme 12) [45].

Recently, Studer and Yu independently explored reactions of *ortho*-diisocyanoarenes as radical acceptors with (perfluoro)alkyl iodides to provide (perfluoro)alkyl-substituted iodoquinoxalines **21** [46, 47]. The former used traditional AIBN or Bu_3SnH/*hv* to initiate the reaction; the latter applied amines as halo-bond acceptor to promote the generation of fluoro-bearing radicals under visible-light irradiation. Following double addition of perfluoroalkyl radicals to isocyanide, an atom transfer radical addition (ATRA) took place to furnish 2-iodo-3-(perfluoro)alkyl quinoxalines in modest to excellent yields (Scheme 13).

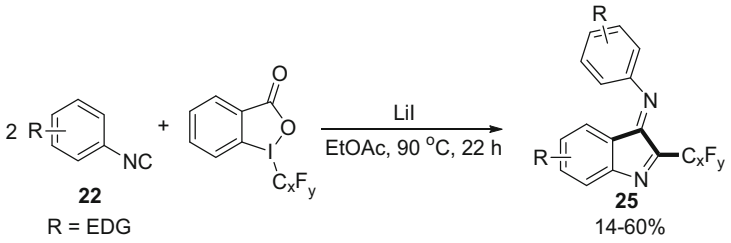
The unsaturated functionality to trap the imidoyl radical intermediate may also be introduced in situ. Pioneering work in this context was reported by Curran and coworkers during their studies on the synthesis of camptothecin and analogous alkaloids [25–27]. Later development on this protocol was developed by Studer



Scheme 13 Synthesis of iodinated (perfluoro)alkyl quinoxalines using *ortho*-diisocyanoarenes



Scheme 14 Quinoline synthesis with arylisocyanide and alkoxyamines



Scheme 15 Synthesis of indole-3-imines via a three-component reaction involving isocyanides

[48, 49]. In their approach, thermal homolysis of vinyl-substituted alkoxyamines generated alkyl radicals, which added intermolecularly to isocyanides. Sequential 5-*exo-trig* cyclization of imidoyl radical, HAS process of the alkyl radical intermediate, and rearomatization led to quinolines **23** or dihydroquinolines **24**, depending on the nature of R^1 substituent (Scheme 14).

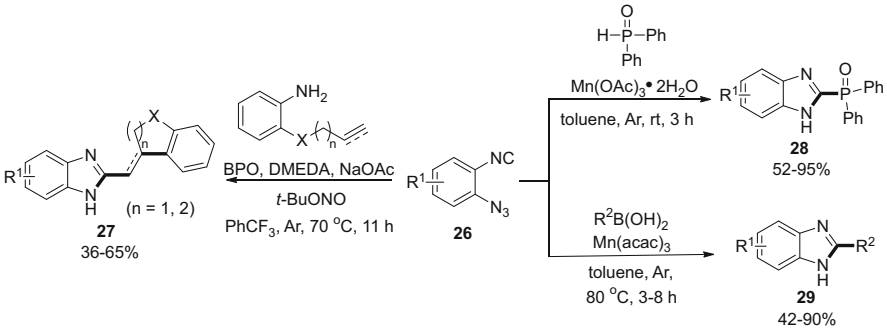
Studer and coworkers developed a multicomponent reaction in which they observed a double addition of (perfluoro)alkyl radical to arylisocyanide, yielding 2-substituted indole-3-imines **25** in low to modest yields (Scheme 15) [50].

In most cases, intramolecular imidoyl radical cyclization forms a C-C σ-bond. However, heteroatoms, like sulfur (see Sects. 2.2 and 2.3) and nitrogen, can also trap imidoyl radicals. Very recently, Zhu's group reported the first intramolecular

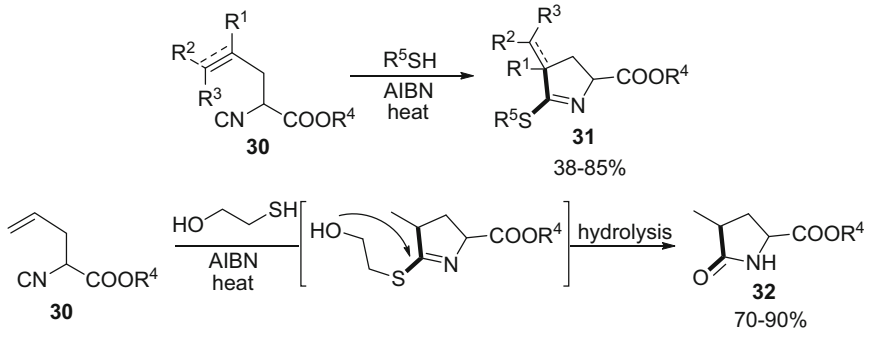
nitrogen trap for imidoyl radicals to synthesize 2-substituted benzoimidazoles starting from 1-azido-2-isocyanoarenes **26** (Scheme 16) [51, 52]. Phosphinoyl, aryl, and alkyl radicals were added to the isocyanide carbon, which was followed by a denitrogenative imidoyl radical cyclization affording the desired products. Tandem reactions to achieve synthesis of complex heterocycle-linked benzoimidazole derivatives were also realized.

Preparation of aliphatic heterocycles from isocyanide is less common in literature. Bachi reported the synthesis of pyrrolines from amino acid-derived isocyanides with suitable alkenyl or alkynyl substitution [53]. Sulfur-centered radical initiated the cyclization, delivering 2-thiopyrrolines or pyroglutamates when using 2-mercaptoethanol (Scheme 17).

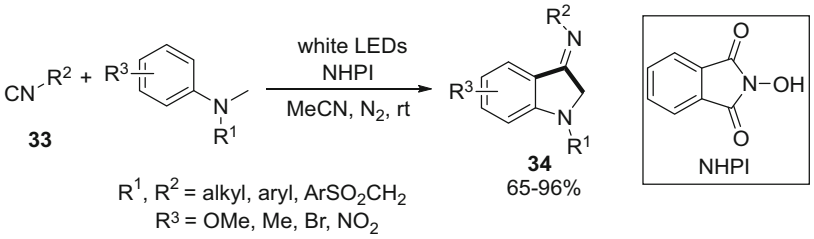
Very recently, Yadav reported radical cyclization reaction of *N*-methylanilines with isocyanides to synthesize 3-iminodihydroindoles **34** with the help of *N*-hydroxyphthalimide (NHPI) under visible-light conditions [54]. *N*-methylanilines reacted with *N*-hydroxyphthalimide radical by SET to form a radical cation. Then, *N*-methyl radical was formed after proton transfer, followed by addition to isocyanide, imidoyl radical cyclization, and aromatization to give the final 3-iminodihydroindoles (Scheme 18).



Scheme 16 Synthesis of benzoimidazoles from 1-azido-2-isocynoarenes



Scheme 17 Cyclization of amino acid-derived isocyanides to access 2-thiopyrrolines



Scheme 18 Cyclization of *N*-methylanilines with isocyanides to genesis of 3-iminodihydroindoles

2.2 Starting from Isothiocyanates

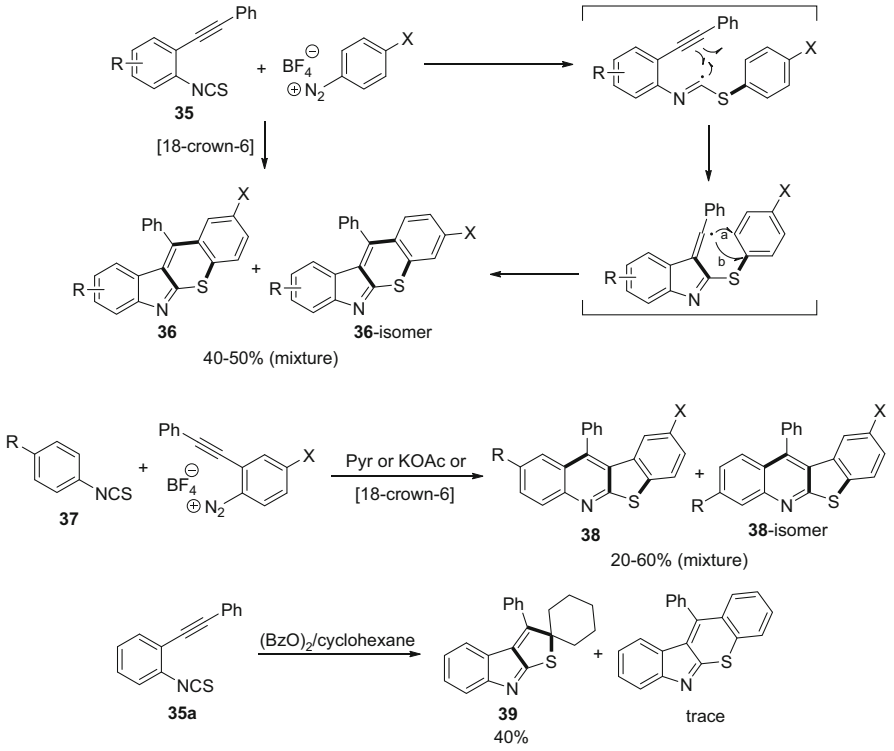
Isothiocyanates are heterocumulenes which are widely used in cycloaddition and nucleophilic addition reactions [55]. They can react with radicals as well. However, both sulfur and carbon atoms in isothiocyanates are ready to accept radicals, leading to the corresponding thioimidoyl and sulfur radicals, respectively (see part 4, Miscellaneous). This section focuses on reactions involving thioimidoyl radical intermediates. Thioimidoyl radical can also be obtained by reaction of an isocyanide with a thiyl radical (RS) [53, 56]. Cascade cyclizations of thioimidoyl radical provide an efficient way to construct complex heterocycles, although competing β-scission to produce thiocyanates may also take place [1].

In 2003, Nanni and Zanardi reported a cascade radical addition/cyclization of 2-alkynylisothiocyanates **35** with aryl diazonium salts as radical precursors (Scheme 19) [56]. A mixture of tetracyclic nitrogen heterocycles, arising from nonselective 6-*endo*- and 5-*exo*-cyclization of the vinyl radical intermediate, was obtained. Reaction of alkynyl aryl diazonium with arylisothiocyanates **37** gave similar results [57]. Cyclohexyl radical generated from cyclohexane/dibenzoyl peroxide was also used in the reaction with **35a**, delivering a unique spiro skeleton **39** via a 1,5-*H* migration. The formation of the thioimidoyl radical was confirmed by reacting isocyanide with an alkylthiol under standard radical conditions (Scheme 19) [58].

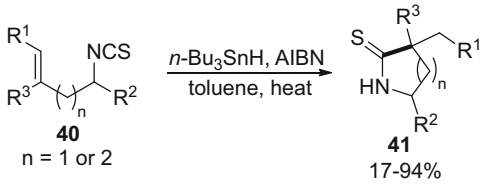
Bachi used alk-3-enyl- and alk-4-enylisothiocyanates **40** with tri-*n*-butyltin hydride and AIBN to produce tinthioimidoyl radicals, which were trapped intramolecularly by alkenes to give γ- and δ-thiolactams **41** (Scheme 20) [59]. Thomas and coworkers exploited an intramolecular addition of thioimidoyl radicals onto sulfur with cleavage of the C-S bond to provide thiazolines using methyl 6*β*-isothiocyanatopenicillanate **42** in the presence of *n*-Bu_3SnH and AIBN. Subsequent cleavage of the tin-sulfur bond was realized by treatment with TBAF (Scheme 21) [60].

2.3 Starting from Imine Derivatives

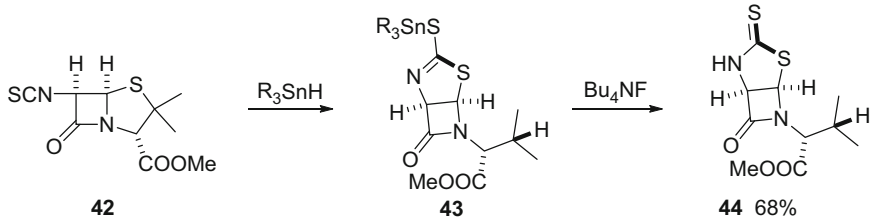
Imidoyl radicals generated by homolysis of imines or their derivatives could also be applied to heterocycle synthesis, which was reviewed by Nanni in 2007 [1].



Scheme 19 Cascade radical cyclization of alkynyl-substituted aryl isothiocyanates

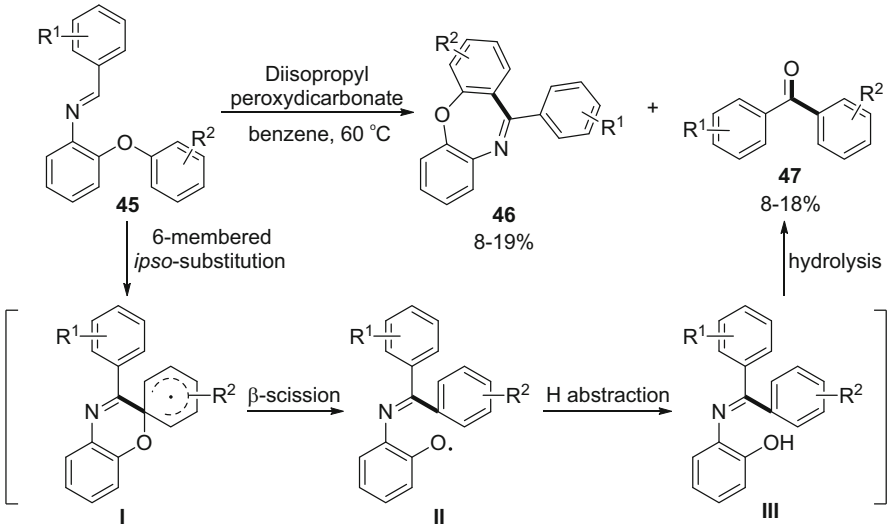


Scheme 20 Synthesis of thiolactams with isothiocyanates

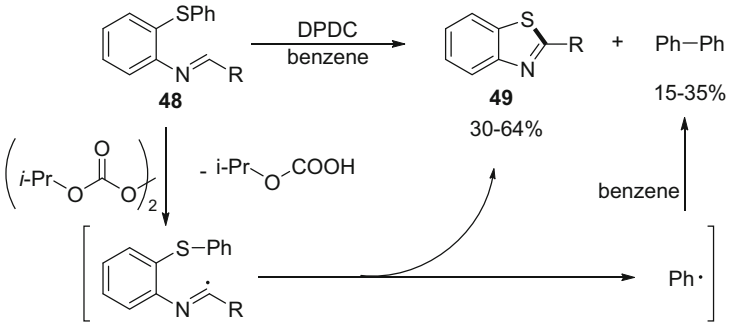


Scheme 21 Tinthioimidoyl radical-induced sulfur-carbon cleavage

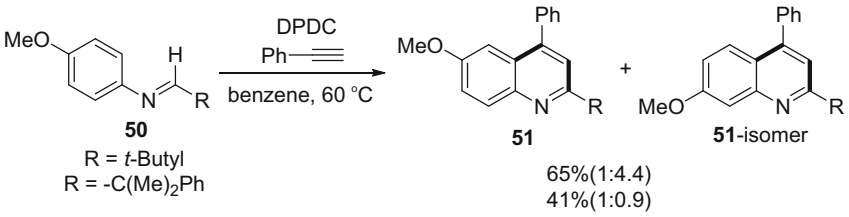
Interestingly, no larger than 6-membered ring construction was realized from isocyanide-derived imidoyl radicals. However, a work by Nanni demonstrated that imidoyl radical generated by hydrogen abstraction in *N*-arylidene-2-phenoxyanilines **45** allowed the formation of 7-membered oxazepine **46**, albeit in very low yield (Scheme 22) [61, 62]. Benzophenones were isolated as by-products, resulting from intermediate **I** and consequent hydrolysis. Leardini reported a novel synthesis of benzothiazoles by reaction of 2-phenylthioarylimines **48** with diisopropyl peroxydicarbonate (DPDC), which resulted in the capture of imidoyl radicals by sulfur with phenyl radical as a leaving group (Scheme 23) [63]. In another example reported by Nanni, arylimine reacted with phenylacetylene to afford polysubstituted quinoline **51** in modest yield. However, along with the desired quinoline product, a regioisomer was also isolated, resulting from a



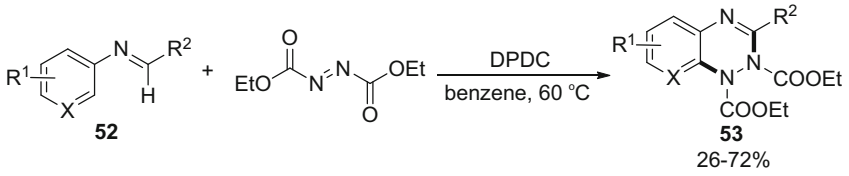
Scheme 22 Synthesis of 7-membered ring starting from imines



Scheme 23 Synthesis of benzothiazoles from imines via a radical pathway



Scheme 24 Intermolecular trapping of imidoyl radical with alkynes to approach polysubstituted quinoline



Scheme 25 Intermolecular capture of imidoyl radical with DEAD to provide 1,2,4-triazines

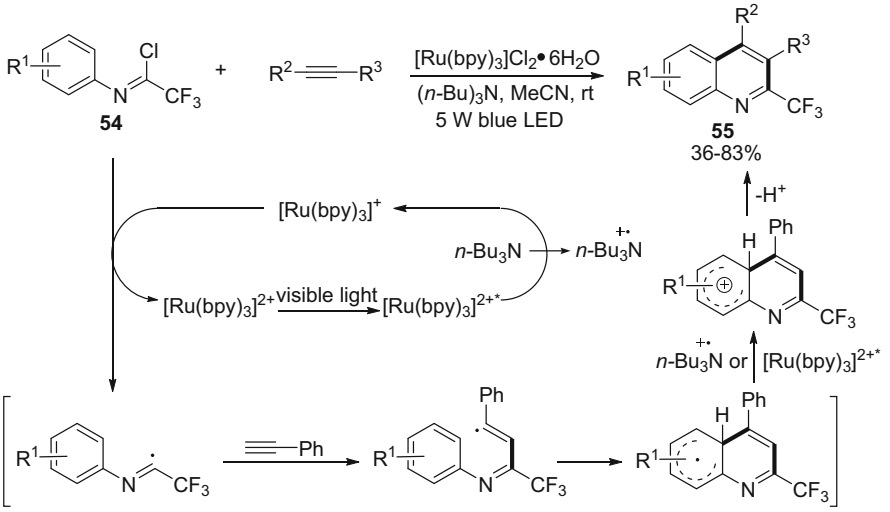
5-membered *ipso*-cyclization of a vinyl radical intermediate (Scheme 24) [3]. Besides carbon unsaturated system, diethyl azodicarboxylate (DEAD) could act as an intermolecular imidoyl radical trap to give 1,2,4-triazine derivatives **53** (Scheme 25) [64].

However, little progress has been made on this topic in the past 10 years. In 2013, Zhou reported a photoinduced intermolecular alkyne addition and cyclization of trifluoroacetimidoyl chlorides to form 2-trifluoromethylquinolines such as **55** at ambient temperature (Scheme 26) [65]. The reaction was initiated by photoactivation of $[Ru(bpy)_3]^{2+}$ to $[Ru(bpy)_3]^{2+}*$, followed by SET from $(n\text{-}Bu)_3N$ to $[Ru(bpy)_3]^{2+}*$. The resulting $[Ru(bpy)_3]^{+}$ was oxidized by the imidoyl chloride affording the imidoyl radical. The latter then underwent sequential intermolecular addition to alkynes, followed by an intramolecular homolytic aromatic substitution (HAS) to provide a cyclohexadienyl radical intermediate. Then, another SET led to the cyclohexadienyl cation intermediate. Finally, elimination of a proton and aromatization provided the quinoline products. Later, Zhou and Fu independently reported light-induced intramolecular versions to synthesize trifluoromethyl-substituted 3-acylindoles **57** and phenanthridines **59** (Scheme 27) [66, 67].

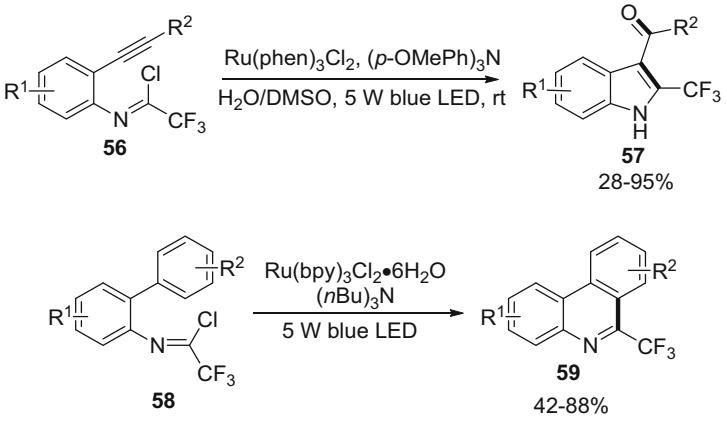
3 Cyclization via Iminyl Radicals

3.1 Starting from Nitriles

Nitriles can also act as free radical acceptors, generating iminyl radicals after addition of a radical species on the carbon center. Two modes of cyclization have



Scheme 26 Visible-light-promoted imidoyl radical addition and cyclization to provide quinolines



Scheme 27 Synthesis of 2-trifluoromethyl indoles and 6-trifluoromethyl phenanthridines with imidoyl chloride

been documented to construct heterocycles via iminyl radical intermediates. One is the intramolecular addition of heteroatom-centered radicals onto the nitrile followed by H-abstraction; the other is a cyclization of the iminyl radical onto an unsaturated system. In some cases, side reaction such as β-scission may occur depending on the nature of the substituents [68].

To illustrate the first type of cyclization, Spagnolo and Leardini reported a reaction of azidoalkyl malononitrile in the presence of *n*-Bu_3SnH and AIBN. Stannylaminyl radical was initially formed from tin radical and azide, followed

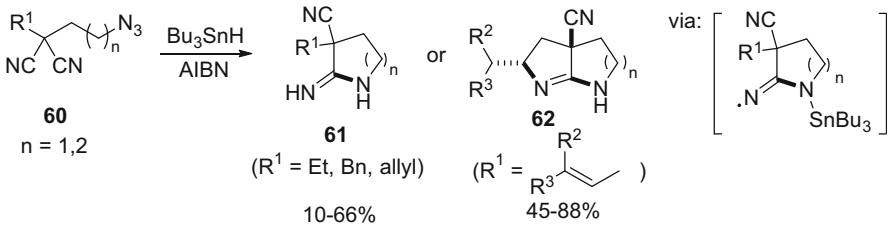
by 5- or 6-*exo*-cyclization onto one of the cyano groups to give aminoiminyl radicals. H-abstraction gave the cyclic amidines **61** [69]. The iminyl radicals could also be trapped by an internal alkene functionality, delivering bicyclic amidines **62** (Scheme 28).

For the second type of cyclization, Curran reported that vinyl radical could undergo tandem radical cyclization to give quinolines in good yields. The reaction was initiated by a tin radical, which was formed from hexamethylditin through photo-irradiation (Scheme 29) [70].

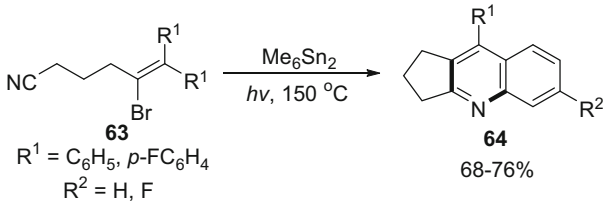
By elegant design, cascade iminyl and imidoyl radical formation have been utilized in the construction of complex heterocyclic systems. Nanni pioneered the area in 1998 with the reaction of cyano-substituted alkyl iodide **65** and arylisocyanide in the presence of hexamethylditin and sunlamp irradiation, which afforded cyclopentaquinoxalines **66** (Scheme 30) [71]. In this study, cyano-substituted thiols and disulfides were also examined as substrates to give thienoquinoxalines **68** and **70** in modest yields under thermal or photochemical conditions.

In 2014, Yu reported visible-light-promoted cascade reaction of arylisocyanides and bromo-substituted alkylnitriles to prepare quinoxalines **72** under mild conditions in 43–88% yields (Scheme 31) [72]. Homolysis of the C-Br bond generated alkyl radicals with the help of a photocatalyst and light, which then added onto the isocyanide.

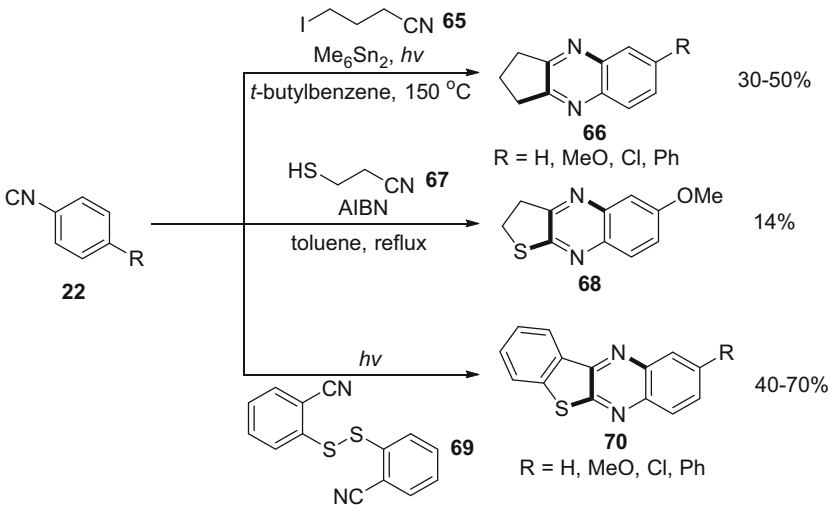
Nanni and coworkers reported another example of imidoyl and iminyl radical cyclization cascades starting from 2-cyanoaryl diazonium salts **73** and arylisothiocyanates **37**. The reaction proceeded through an intermolecular thioimidoyl radical formation, then a 5-*exo*-dig cyclization on the cyano group, followed by an *ortho*- or *ipso*-aryl cyclization of the resulting iminyl radical intermediate.



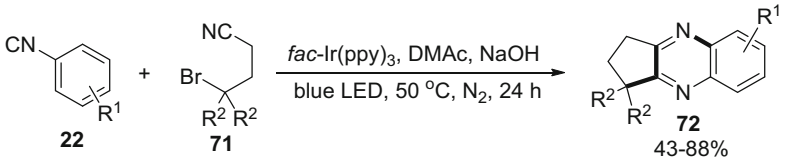
Scheme 28 Reductive cyclization of azide onto substituted nitriles mediated by tin hydride



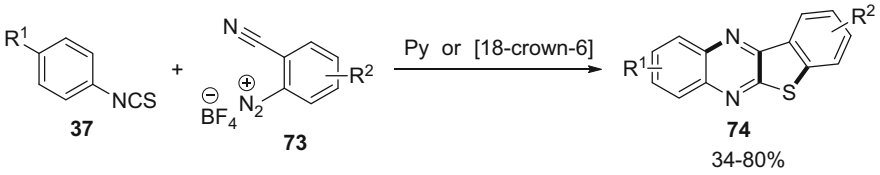
Scheme 29 Synthesis of quinolines from alkenylnitriles bearing a vinyl bromide moiety



Scheme 30 Cascade radical process of arylisocyanides and functionalized nitriles



Scheme 31 Visible-light-mediated cascade reactions of arylisocyanides and bromo-substituted alkylnitriles



Scheme 32 Radical cascades starting from arylisothiocyanates and 2-cyanoaryl diazonium salts

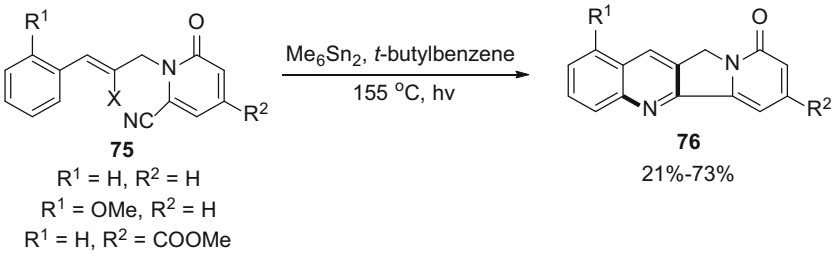
After rearrangement (in case of the *ipso*-aryl cyclization), SET oxidation, and deprotonation-aromatization, a tetracyclic fused scaffold **74** was formed in one step (Scheme 32) [73].

3.2 *Starting from Cyano-Amides*

Cyano-amides in this review refer to structures in which the cyano group is located one or more carbons away from nitrogen or the cyano group is directly attached to the nitrogen amide. Guanidines and quinazolinone-type alkaloids were approached efficiently with the latter strategy, which was pioneered by Lacôte, Malacria, Fensterbank, and coworkers [74, 75].

Bowman reported an alternative approach to Curran's synthesis of camptothecin. 2-Cyanopyridinone derivatives **75** were exposed to hexamethylditin and *t*-butylbenzene under UV irradiation at 150°C to give tetracyclic alkaloids **76** in low to good yields (Scheme 33) [76, 77].

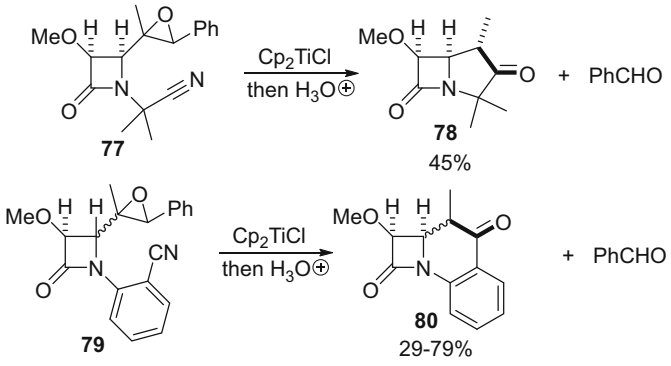
A Ti(III)-assisted reductive cyclization of β-lactams containing epoxide and nitrile functionalities as in **77** and **79** was reported by Grande and coworkers [78]. The reaction was regio- and diastereoselective via 5-*exo* or 6-*exo* processes, affording carbapenem and benzocarbacephem scaffolds. Reductive ring opening of the epoxide with Cp_2TiCl generated alkyl radicals, which cyclized onto the cyano group. Reduction of the iminyl radical intermediate and hydrolysis gave the corresponding cyclic ketones **78** and **80** (Scheme 34). Later, these authors extended the protocol to 1,5- and 1,6-epoxynitriles [79].



75
R^1 = H, R^2 = H
R^1 = OMe, R^2 = H
R^1 = H, R^2 = COOMe

76
21%-73%

Scheme 33 Synthesis of tetracyclic and pentacyclic alkaloids via iminyl radicals



77

78
45%

79

80
29-79%

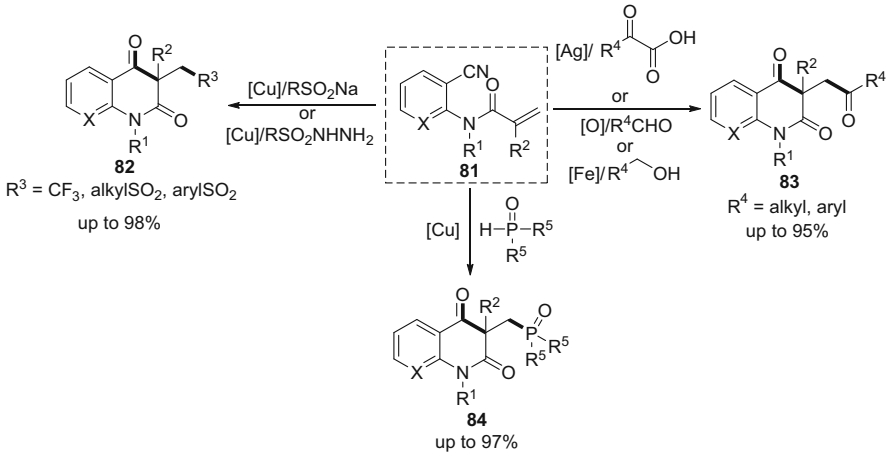
Scheme 34 Reductive cyclization of epoxynitriles with Ti(III) species

Cascade radical addition to alkenes and cyclization onto nitriles were applied to the construction of quinoline-2,4(1*H*,3*H*)-diones [80–84]. With this protocol, aldehydes [80], phenylglyoxylic acids [80], sodium trifluoromethanesulfonate [81], sulfinic acid salts [81], diphenylphosphine oxide [82], sulfonylhydrazides [83], and alcohols [84] acted as radical precursors under oxidative conditions (Scheme 35).

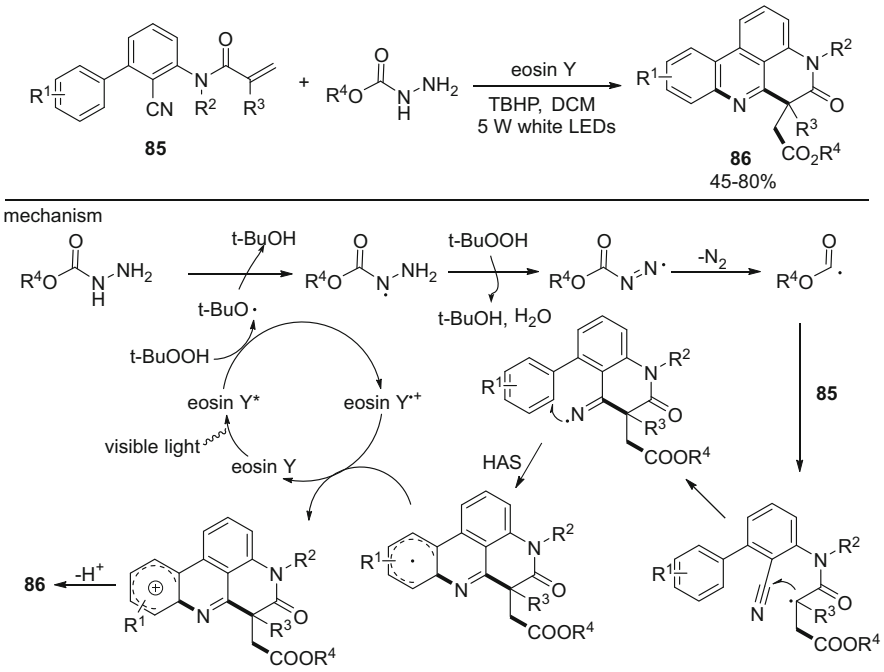
In this context, Sun developed a novel and efficient visible-light-induced cascade reaction for the preparation of ester-functionalized pyrido[4,3,2-*gh*] phenanthridine derivatives **86** under metal-free conditions (Scheme 36) [85]. The reaction was initiated by an intermolecular radical addition to *N*-arylacrylamide derivatives using alkylcarbazates as the ester source, followed by the cyclization of the resulting iminyl radical onto the cyano group. The desired products were obtained in moderate to good yields with broad substrate scope.

Fensterbank et al. designed a series of *N*-acylcyanamide for the synthesis of natural and biologically active quinazolinone derivatives [86, 87]. They tested alkyl phenylselenates as alkyl radical precursors to prepare quinazolinones **88** under slow addition of Bu_3SnH and AIBN in refluxing benzene [88]. Iodoaryl-substituted *N*-acylcyanamides **89** were designed to approach alkaloids of the luotonin A family in modest yield [89, 90]. Interestingly, during their study using vinyl iodide **91** in cascade annulation reactions, the same authors found an unprecedented substituent migration from the *ortho*-position of aryl groups to the alkenyl moiety [91]. The migration could be finely controlled with a selection of solvent. Finally, azide-substituted *N*-acylcyanamide was also used in cascade reactions to generate guanidines **94** in modest to good yields (Scheme 37) [92].

Hu reported a SmI_2-promoted cascade cyclization with imine-substituted cyanamides or cyanamines **95** to provide polycyclic nitrogen heterocycles **96** (Scheme 38) [93]. Aryl radical generated by single-electron reduction of SmI_2 initiated the radical addition, which was followed by the cyclization through the resulting aminoiminyl radical intermediate.



Scheme 35 Radical cascades of O-cyanoarylacrylamides

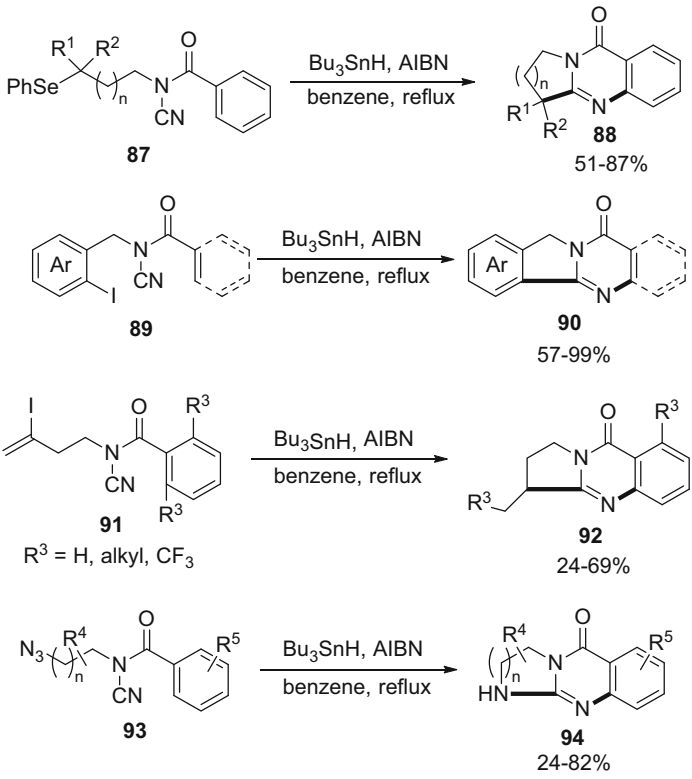


Scheme 36 Visible-light-induced cascade reaction of *N*-(2-cyano-[1,1-biphenyl]-3-yl)-*N*-arylacrylamides

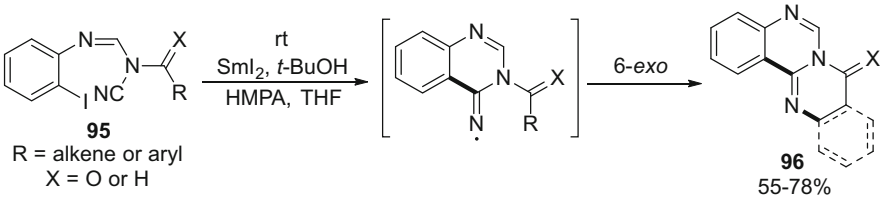
Recently, Cui reported a phosphorylation/cyclization cascade of *N*-acylcyanamide **97** bearing an alkenyl moiety to access dihydroisoquinolinones **98** or quinazolinones **99** [94]. Reaction of diphenylphosphine oxide with $AgNO_3$ provided the phosphoryl radical. Subsequent radical addition of the latter to the alkene fragments generated alkyl radicals, which were trapped by the aryl group or the cyano group, depending on the proximity between alkyl radical and the cyano group, depending on the proximity between alkyl radical and the cyano group (Scheme 39).

3.3 Starting from Oxime and Derivatives

Oxime and its derivatives, like hydrazones and sulfenimines, contain relative weak N-X (X refers to O, S, N, halo, etc.) bonds which can be cleaved homolytically into iminyl radicals and X-centered radicals under thermal conditions, transition metal catalysis, UV irradiation, or photoredox catalysis. Many oxime derivatives are easily available, nontoxic, and bench stable, making them versatile precursors of iminyl radicals for heterocycle synthesis [95]. Recently, Walton and Castle independently reviewed this chemistry [14–16].

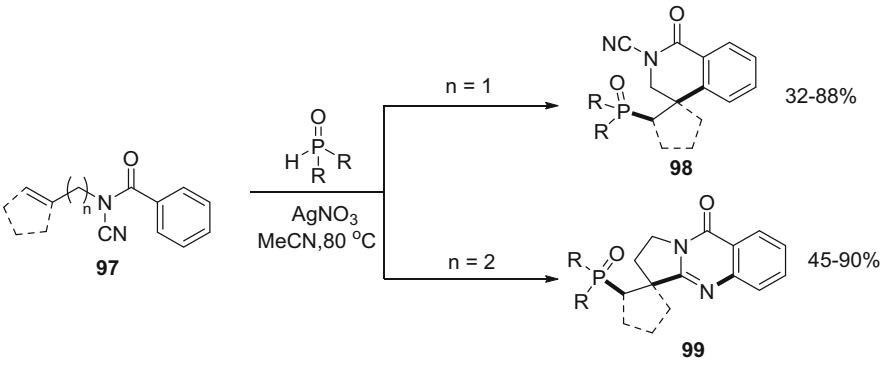


Scheme 37 Radical cyclization of *N*-acylcyanamide to access quinazolinones

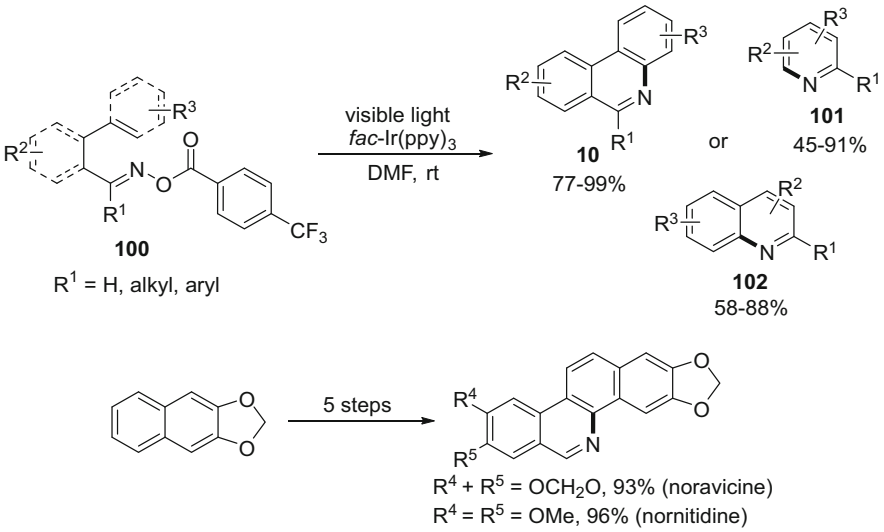


Scheme 38 Radical cascades of imine-substituted cyanamide to generate heterocycles

Yu and Zhang reported visible-light-promoted cyclization of acyl oximes to access 6-membered azaheterocycles [96]. They carefully screened acyl substituents in acyl oximes to find that *p*-trifluoromethylbenzoate oxime substrate is highly active with *fac*-Ir(ppy)$_3$ (ppy = 2-phenylpyridine) as photocatalyst at room temperature. The active photocatalyst reduced acyl oxime into iminyl radicals, which were then engaged into cyclization processes. With this methodology, phenanthridines **10**, pyridines **101**, and quinolines **102** were prepared in good to excellent yields. Moreover, this protocol was used as a key step in a five-step total synthesis of biologically active alkaloids noravicine and nornitidine (Scheme 40).



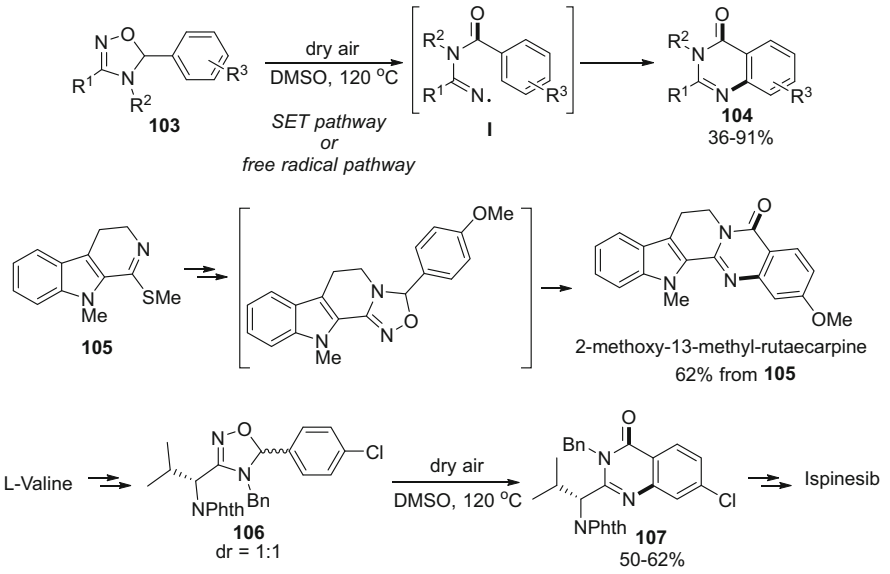
Scheme 39 Phosphorylation/cyclization cascade of *N*-cyanamide alkenes to provide heterocycles



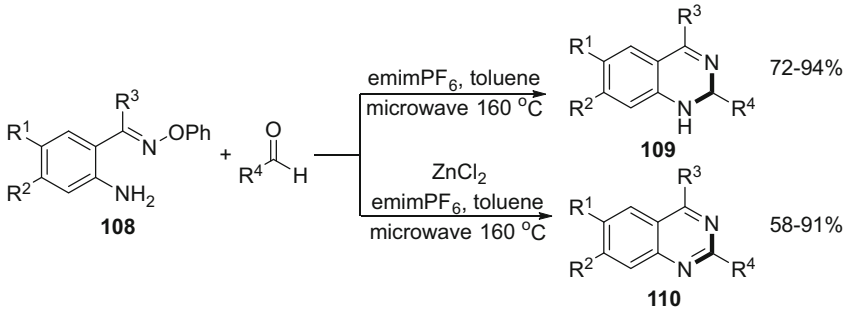
Scheme 40 Visible-light-promoted iminyl radical formation from acyl oximes for the elaboration of pyridines, quinolines, and phenanthridines

Chiba and coworkers designed an oxidative skeletal rearrangement of 5-aryl-4,5-di- hydro-1,2,4-oxadiazoles **103** into quinazolinones **104** in DMSO at 120°C [97]. The proposed mechanism involved thermolysis of dihydro-1,2,4-oxadiazoles to generate iminyl radicals **I**, which gave heterocyclic products after HAS and SET process. To demonstrate the utility of this protocol, they synthesized an indoloquinazoline alkaloid and a key precursor of ispinesib, a potent, specific, and reversible inhibitor of kinesin spindle protein (Scheme 41).

Walton discovered that 2-(aminoaryl)alkanone O-phenyl oximes **108** and carbonyl compounds could provide dihydroquinazolines **109** under microwave conditions in ionic liquid emimPF_6 [98, 99]. Possible mechanism involved the imine



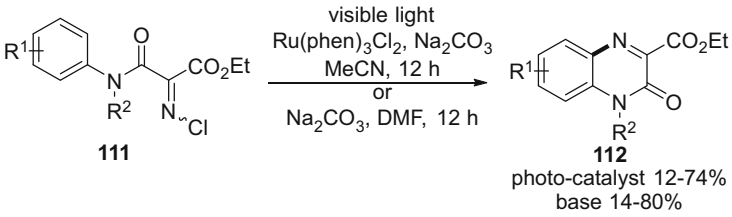
Scheme 41 Synthesis of quinazolinones via oxidative radical rearrangement



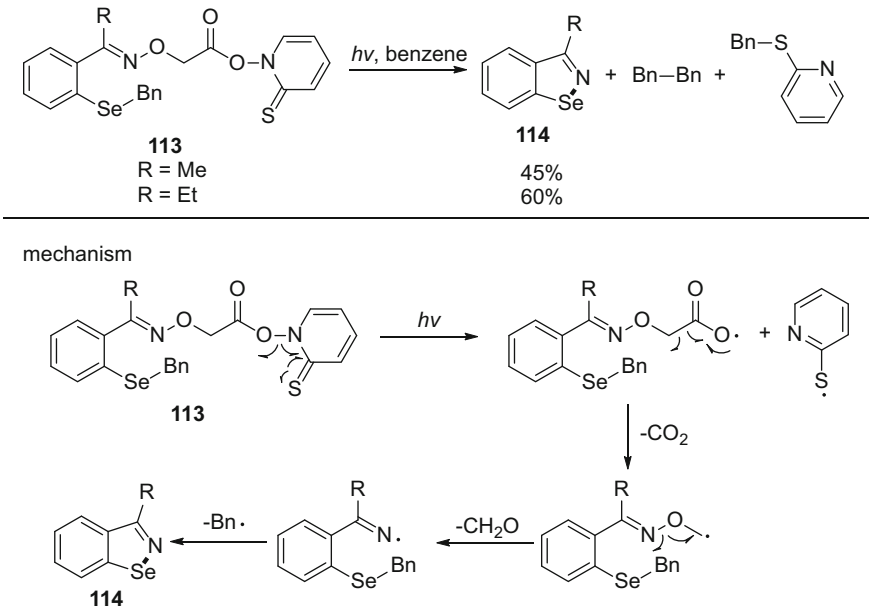
Scheme 42 Synthesis of dihydroquinazolines or quinazolines with O-phenyl imines

formation and thermolysis of the N-O bond of the oxime into an iminyl radical. Toluene acted as a hydrogen donor to trap the aminyl radical. In the presence of $ZnCl_2$, aromatic quinazolines **110** were formed instead of dihydroquinazolines (Scheme 42).

In 2015, Yu and coworkers developed two efficient photochemical protocols for the generation of iminyl radicals from easily available 2-(*N*-arylcarbamoyl)-2-chloroiminoacetates **111** via N-Cl cleavage (Scheme 43) [100]. $Ru(phen)_3Cl_2$ acted as a photoredox catalyst under visible-light irradiation to induce N-Cl bond cleavage by a single-electron transfer pathway. Interestingly, when the reaction was performed in DMF in the presence of Na_2CO_3, only visible light was required to initiate the reaction without a photocatalyst. The methodology provided a practical approach to quinoxalin-2(1*H*)-ones **112** via iminyl radical intermediates.



Scheme 43 Photoinduced iminyl radical cyclization via N-Cl bond cleavage



Scheme 44 Synthesis of benzoselenazoles with O-carboxymethyl oxime derivatives

Besides carbon unsaturated systems, benzylthio- and selenoethers were also suitable traps for iminyl radicals [101]. Schiesser and coworker realized cyclization of benzylseleno-substituted thiohydroxamic esters **113** to produce l,2-benzoselenazoles **114** in modest yield [102]. Upon irradiation, oxime **113** decomposed, through release of a 2-pyridinethiyl radical, followed by decarboxylation and elimination of formaldehyde, into an iminyl radical, which reacted at selenium (homolytic substitution) affording benzoselenazoles. A benzyl radical was also formed which dimerized (Scheme 44).

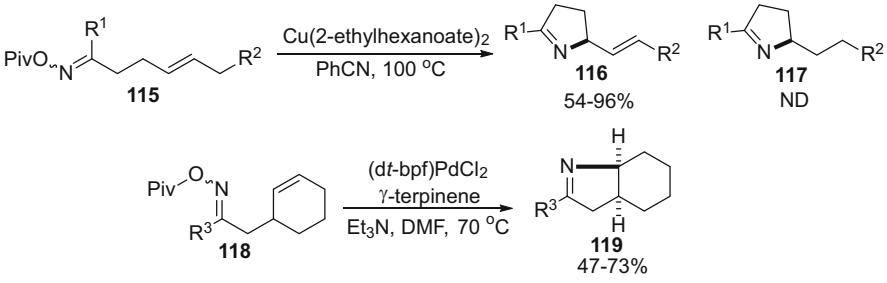
For aliphatic heterocycle synthesis, Bower reported copper-catalyzed radical cyclization of alkenyl oxime esters **115**, which provides alkene-substituted dihydropyrroles **116** in high yields [103]. No corresponding alkyl-substituted by-product **117** was found. Later, they investigated the Pd-catalyzed cyclization of alkene-substituted oxime esters **118** [104]. Interestingly, the reaction mechanism was

ligand-dependent. Electron-deficient phosphine ligands like $P[3,5\text{-}(CF_3)_2C_6H_3]_3$ led to aza-Heck products, while electron rich ligands such as 1,1′-bis(di-*tert*-butylphosphino)ferrocene (dt-bpf) resulted in **119** through iminyl radical intermediates (Scheme 45).

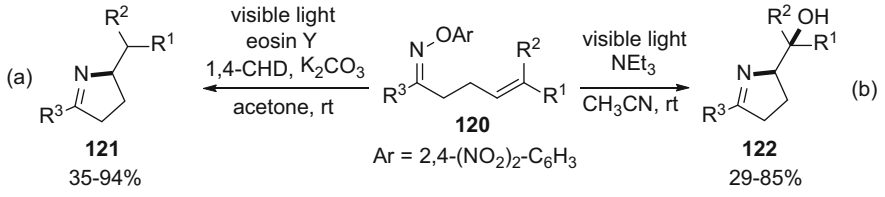
Leonori developed iminyl radical-mediated cyclizations of unactivated olefins under visible-light irradiation (Scheme 46) [105]. When organic dye eosin Y was used as a photocatalyst in the presence of 1,4-cyclohexadiene (CHD) as a hydrogen donor and K_2CO_3, dihydropyrroles **121** were obtained in good yields (route a, Scheme 46). Interestingly, when the reaction was irradiated in the absence of a photocatalyst, a complementary iminohydroxylation process occurred to deliver alcohol **122** (route b, Scheme 46). The oxygen atom in the alcohol products **122** was believed to originate from one of the nitro groups of the leaving phenoxy moiety.

Later, to extend the scope of the valuable imine motif, Leonori reported decarboxylation of oxyacid **123** with methyl acridinium perchlorate **124** under visible-light conditions, generating an iminyl radical, which cyclized in a 5-exo-mode (Scheme 47) [106]. The resulting radical then reacted intermolecularly with various radical acceptors, including *N*-chlorosuccinimide (NCS), *N*-iodosuccinimide (NIS), *N*-fluorobenzenesulfonimide (NFSI), but also TsN_3, DEAD, or ethynylbenziodoxolones and vinylbenziodoxolones, as carbon sources.

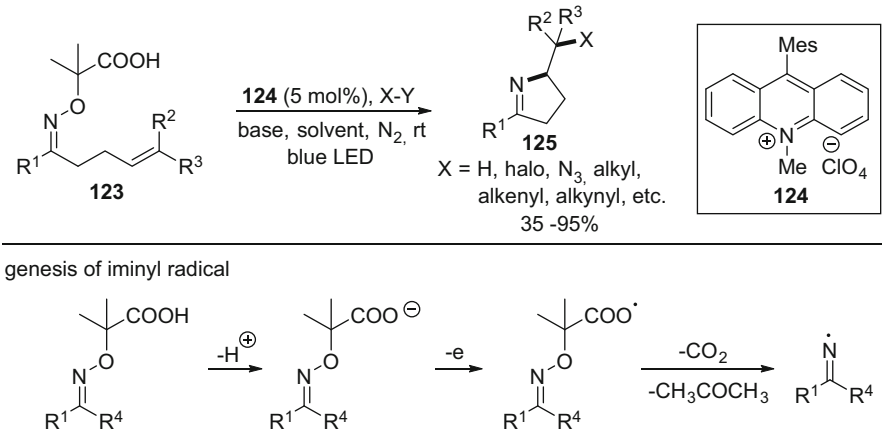
Independently, Studer developed a related decarboxylation of α-iminooxy propionic acids **126** to form iminyl radicals using photoredox catalyst **127** (Scheme 48) [107]. Through this initiation process, they achieved the carboimination of alkenes. The sequence of iminyl radical generation, 5-exo-trig



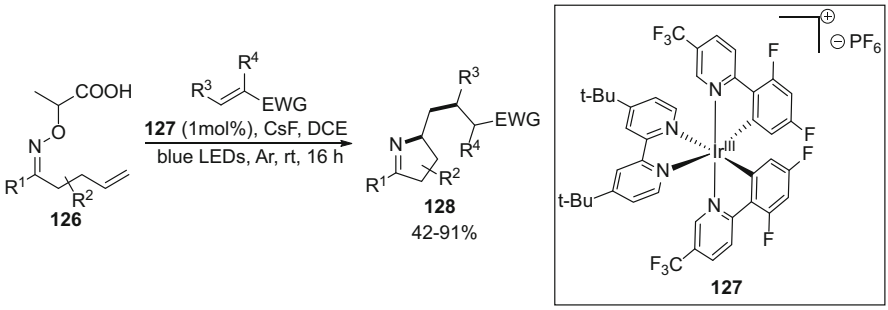
Scheme 45 Copper- or palladium-catalyzed cyclization via iminyl radicals



Scheme 46 Visible-light-mediated hydroimination and iminohydroxylation cyclizations of iminyl radicals



Scheme 47 Imino-functionalizations of alkenes under photoredox conditions

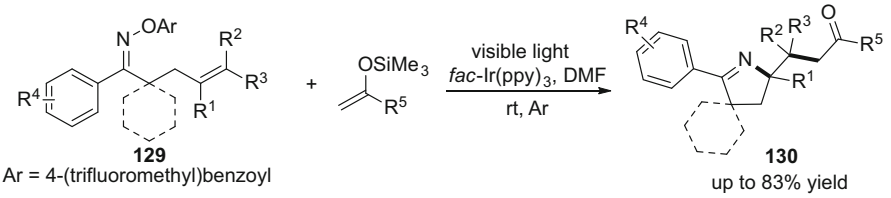


Scheme 48 Genesis of iminyl radicals by oxidation of α-imino-oxy acids

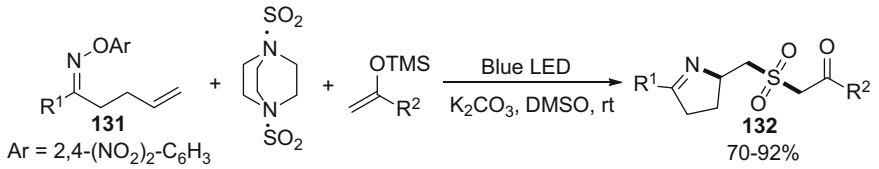
cyclization, intermolecular conjugate addition to a Michael acceptor, completed with a SET reduction process, was shown to provide various pyrrole derivatives **128**.

When iminyl radical undergoes cascade cyclization and functionalization instead of hydrogen abstraction, densely substituted pyrroline derivatives **130** are expected. Loh applied silyl enol ethers as coupling partners to trap the alkyl radical intermediate generated from iminyl radical cyclization, which eventually gave alkyl ketone-substituted pyrrolines (Scheme 49) [108].

Wu reported a novel *N*-radical-initiated cyclization, followed by sulfonylation and alkene addition under visible-light irradiation and catalyst-free conditions (Scheme 50) [109]. A range of sulfonyl compounds **132** could be easily produced through the cascade radical process involving sulfur dioxide insertion using 1,4-diazabicyclo[2.2.2]octane disulfate (DABCO·$(SO_2)_2$ or DABSO) as surrogate of gaseous sulfur dioxide.



Scheme 49 Visible-light-induced cascade cyclization and functionalization of iminyl radicals



Scheme 50 Photoinduced *N*-radical-mediated cyclization through insertion of sulfur dioxide

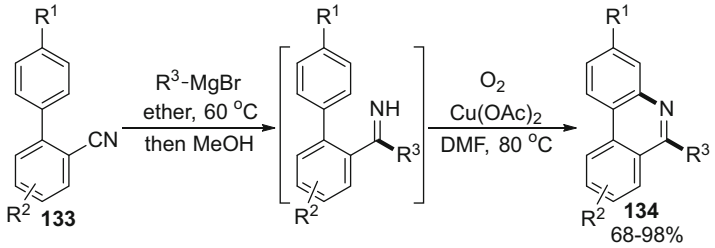
3.4 Starting from N-H Ketimines or Amidines

Single-electron oxidation of N-H ketimines or amidines could also generate iminyl radical in an environmentally benign manner. Chiba and coworkers reported a series of transformations involving iminyl radicals generated from imines under copper-catalyzed aerobic conditions [110]. They used biaryl-2-carbonitriles **133** and Grignard reagents to generate imines in situ. Cu-iminyl radical was formed after aerobic oxidation, and subsequent cyclization delivered phenanthridine derivatives **134** (Scheme 51) [111]. Based on a similar protocol, azaspirocyclohexadienone **136** synthesis was also achieved efficiently from the corresponding arylnitriles (Scheme 52) [112].

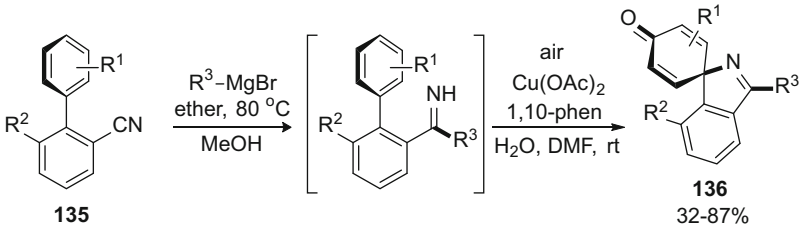
Very recently, Nagib reported an unprecedented β-C−H amination of imidates **137** using a NaI/PhI(OAc)$_2$ system to generate β-amino alcohols (Scheme 53) [113]. The process includes the oxidation of a trichloroacetimidate or a benzimidate into an imidate radical, which is followed by a 1,5-hydrogen atom transfer (HAT), generating regioselectively a carbon radical. The latter is then trapped by an iodine radical, nucleophilic substitution eventually forming oxazoline **138**. A simple hydrolysis finally leads to the related β-amino analogs.

Yu used stable α-imino-*N*-arylamides **141** as precursors of iminyl radical [114]. In this reaction, TBHP/TBAI promoted iminyl radical formation through single-electron oxidation of the imino moiety. Subsequent intramolecular 5-*exo*-mode cyclization onto the aryl group gave azaspirocyclohexadienyl radical intermediates, which were trapped by oxygen to form azaspirocyclohexadienones **142**. In the absence of oxygen, quinoxalin-2-ones were detected as by-products (Scheme 54).

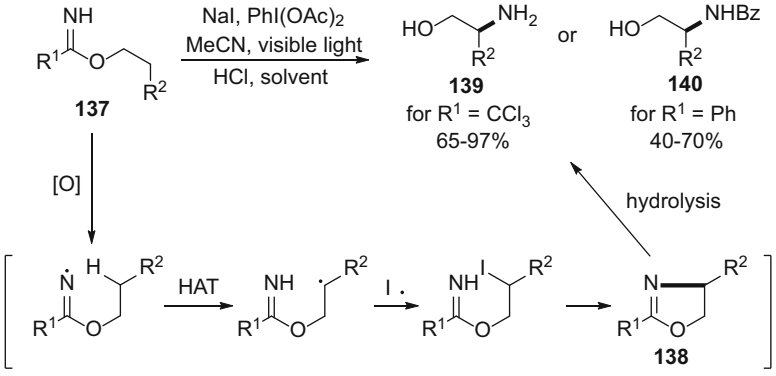
Electron-rich amidines are relatively stable and easy to handle. Oxidation of N-H bond of amidines generates amidinyl radicals, which can be used in nitrogen heterocycle synthesis as well. Very recently, Xu reported the anodic cleavage of



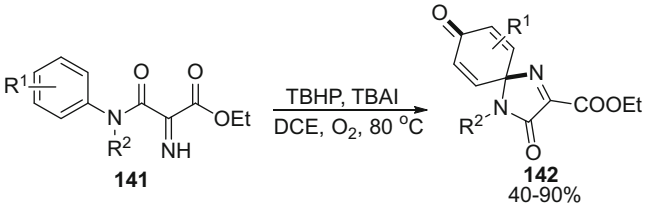
Scheme 51 Cu-iminyl radical cyclization to phenanthridine via Cu/O_2 oxidation of imines



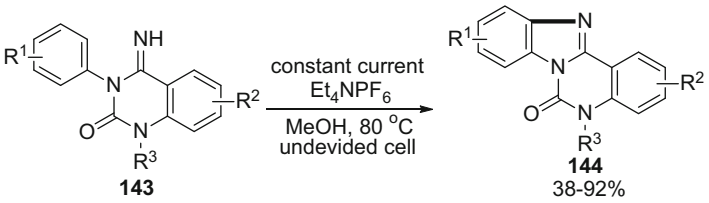
Scheme 52 Cu/O_2 oxidation of imines to provide azaspirocyclohexadienones



Scheme 53 β-C−H amination of imidates under oxidative conditions



Scheme 54 Oxidation of imine with TBHP/TBAI to approach azaspirocyclohexadienones



Scheme 55 Anodic cleavage of N-H bonds of amidines to access tetracyclic benzimidazoles

N-H bonds of amidines **143** to provide aminoiminyl radicals, which were captured by (hetero)arenes to afford tetracyclic benzimidazoles **144** (Scheme 55) [115].

4 Miscellaneous

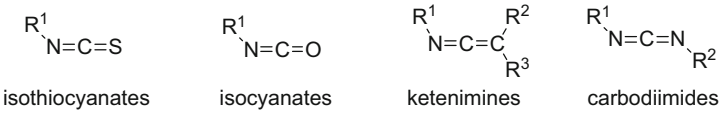
Both sulfur and carbon atoms in isothiocyanates can accept radical attack, generating the corresponding imidoyl radical and sulfur radical, respectively. Some related structures like isocyanates, ketenimines, and carbodiimides exhibit similar reactivity (Scheme 56). In this section, only scattered examples are given using these heterocumulenes in radical cyclization (Scheme 57).

Yadav reported a copper-catalyzed synthesis of 2-alkylbenzoxa(thia)azoles from arylisocyanates/isothiocyanates and simple alkanes [116]. The protocol utilized di-*tert*-butyl peroxide (DTBP) as a radical initiator to generate the alkyl radical, which adds onto the NCX moiety at the central carbon. Sequential C-C and C-X (X=O, S) bond formation was followed by aromatization to afford expected **146** (Scheme 58).

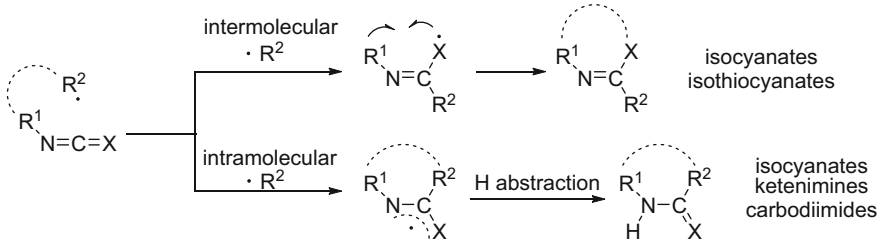
Zhu et al. described the reaction between aryl isothiocyanates and formamides under metal-free conditions, which led to the synthesis of 2-aminobenzothiazoles **147** (Scheme 59) [117]. Mechanistic studies suggest that the reaction is initiated by decarbonylative aminyl radical formation in the presence of *n*-Bu_4NI and TBHP, followed by aminyl radical addition to isothiocyanates and cyclization via sulfur-centered radical intermediates.

Lei also developed a mild method for the synthesis of 2-aminobenzothiazoles **148** from isothiocyanates and commercially available amines via an intramolecular dehydrogenative C-S bond formation. Catalyst- and external oxidant-free electrolytic conditions were demonstrated to be efficient in this cross-coupling reaction (Scheme 60) [118].

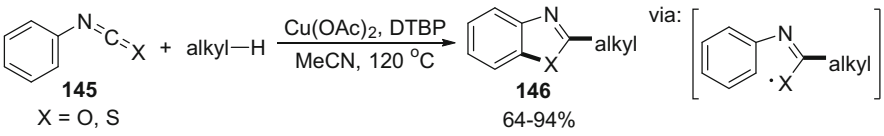
Walton reported that radical cyclization of 2-(2-isocyanatophenyl)ethyl bromide **149** led to 2,3-dihydroindole-1-carbaldehyde **150** and 3,4-dihydro-1*H*-quinolin-2-one **151**, respectively, in 16% and 44% yield [119]. In this case, the 6-*endo*-mode for the cyclization of the alkyl radical was preferable over the 5-*exo*-cyclization onto the isocyanate. DFT calculations of reaction enthalpies and rate constants were performed to rationalize the selectivity (Scheme 61).



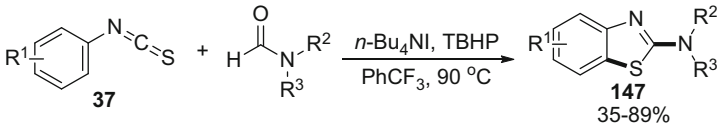
Scheme 56 Structure of isothiocyanates, isocyanates, ketenimines, and carbodiimides



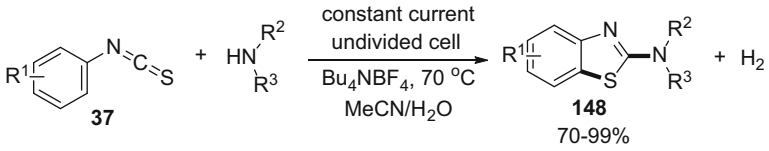
Scheme 57 Reaction mode of isothiocyanates, isocyanates, ketenimines, and carbodiimides



Scheme 58 Construction of 2-alkylbenzo-1,3-azoles from iso(thio)cyanates and alkanes

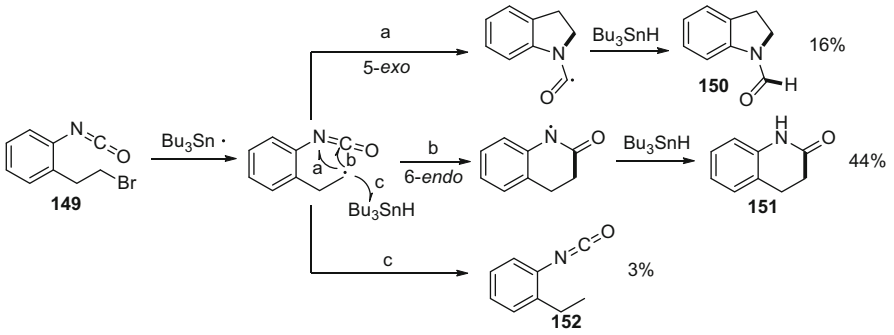


Scheme 59 Synthesis of 2-aminobenzothiazoles from isothiocyanates and formamides

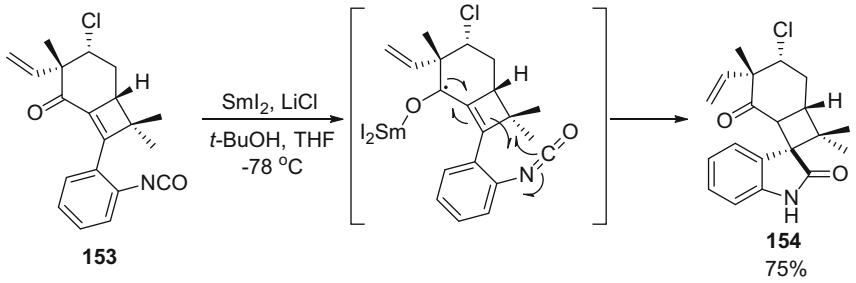


Scheme 60 Synthesis of 2-aminobenzothiazoles from isothiocyanates and amines under undivided electrolytic conditions

Another isocyanate that participated in radical cyclization reaction was reported by Wood and coworkers during their studies on the synthesis of welwitindolinone A [120–122]. The key step involved a SmI_2-mediated reductive cyclization of a precursor bearing an isocyanate, to build up the spiro-oxindole core structure **154** in good yield. The reaction was highly regio- and diastereoselective (Scheme 62).



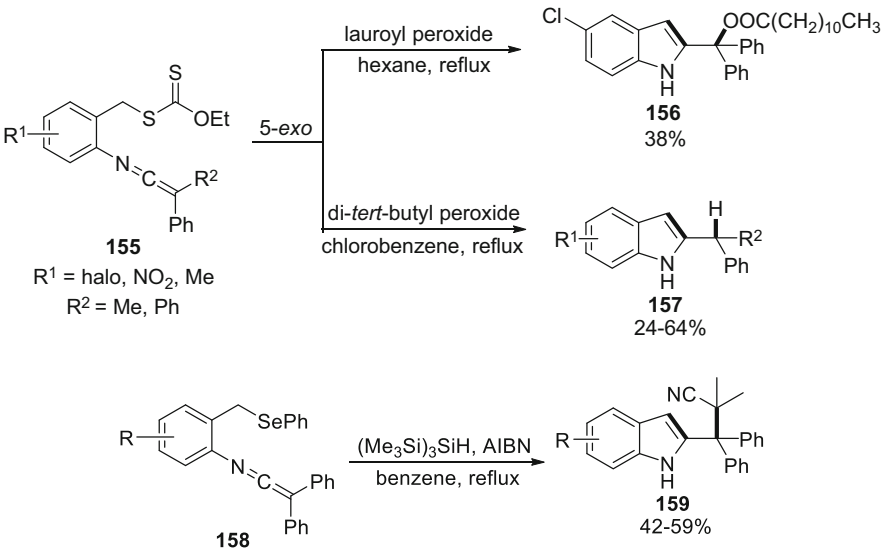
Scheme 61 Isocyanates as radical acceptors in cyclization



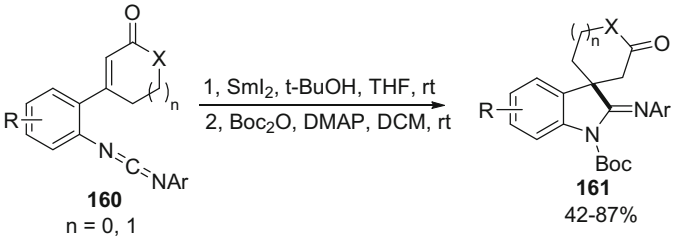
Scheme 62 SmI_2-promoted reductive cyclization of isocyanate

Ketenimines and carbodiimides were also reported to be potent radical acceptors in radical annulation reactions [123]. Vidal reported an intramolecular addition of benzylic radical to ketenimines, leading to 2-alkylindoles **156**, **157**, and **159** in low to modest yields [124, 125]. The fate of the triarylmethyl-type radical intermediate was determined by the nature of the radical initiator. A lauroyloxy fragment was thus incorporated into the product when lauroyl peroxide was used, while H-abstraction product was obtained when di-*tert*-butyl peroxide in chlorobenzene was applied. Later, they reported a similar reaction of ketenimines with a pending phenyl selenide in the presence of a silane and AIBN to afford indole derivatives with the 1-cyano-1-methylethyl group from AIBN being trapped (Scheme 63) [126].

Takemoto reported a SmI_2-mediated reductive cyclization of carbodiimides bearing an α,β-unsaturated carbonyl moiety to give spiro-2-iminoindolines **161** [127]. The proposed mechanism included a one-electron reduction of the unsaturated carbon group into a radical anion, a subsequent addition to the carbodiimide moiety, further reduction by SmI_2 to an amidinate, and finally hydrolysis by *t*-BuOH to afford the iminoindoline (Scheme 64). They also used the strategy to construct the core structure of perophoramidine [128].



Scheme 63 Construction of 2-substituted indole core with ketenimines



Scheme 64 Reductive cyclization of carbodiimides to approach spiro-2-iminoindolines

5 Conclusion

This chapter described various radical cyclizations of isocyanides, isothiocyanates, nitriles, and other C-N unsaturated bond systems. A variety of 5- and 6-membered nitrogen-containing heterocycles were prepared via imidoyl or iminyl radical intermediates. In general, multiple chemical bonds are formed in these processes, and the reaction conditions are mild, representing an environmentally benign approach for heterocycle synthesis. With the rapid growth especially in the area of photoinduced radical processes, more practical heterocycle synthesis is expected in not too distant a future, which should meet with the strong requirements for application in medicinal chemistry and material science.

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Radical Cascades in the Total Synthesis of Complex Naturally Occurring Heterocycles

Montserrat Rueda-Becerril, Jia Yi Mo, and Glenn M. Sammis

Abstract Radical cascades reactions have been extensively used in organic synthesis for the rapid construction of molecular complexity, and have shown to be particularly effective in the assembly of polycyclic cores. Through careful substrate design, their application has extended from carbocyclic to heterocyclic frameworks. In this chapter, we describe radical cascade processes that generate oxygen- and nitrogen-containing polycyclic structures in the context of total synthesis. The radical cascades either directly form the heterocycle or incorporate/modify preexisting heterocycles to further elaborate the target's core. Total syntheses where the radical cascade had no impact on the formation or modification of the heterocyclic moiety are not included in this review.

Keywords Azacycles · Cascade · Domino · Heterocycles · Natural products · Oxacycles · Radical · Total synthesis

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1 Introduction

Radical reactions have been utilized in the total syntheses of natural products for decades [1–3]. The diverse modes of reactivity for radicals, such as addition, fragmentation, and atom-transfer, allow for the construction of complex molecular architectures, including both carbocycles [4] and heterocyles [5–8]. Furthermore, the typically neutral and mild reaction conditions required for radical formation and the compatibility of a variety of functional groups with radical processes facilitate their application at any stage of a total synthesis [9].

Radicals possess an intrinsic tendency to propagate, which makes them excellent candidates to participate in cascade, or domino, reactions for the syntheses of polycyclic molecular architectures. Not only have cascade reactions involving cationic, anionic, carbene, and pericyclic reactions [10–13] been extensively utilized in total synthesis [14–16], but radical processes have also been demonstrated to be a powerful approach for the rapid assembly of complex molecular structures [17].

While the initial reports of cascade radical reactions in the syntheses of natural products have largely focused on the construction of carbocyclic frameworks [18–21], the prevalence of oxygen- and nitrogen-containing heterocycles in naturally occurring molecules has motivated the incorporation of radical transformations that address the construction of oxacycles and azacycles in cascade processes applied to total synthesis. The present review will specifically focus on radical cascades processes leading to naturally occurring oxygen- and nitrogen-containing heterocycles.

2 Oxygen-Containing Heterocycles

Oxacycles are common motifs in polyketides, terpenes, alkaloids, and other classes of natural products. They can occur as single cyclic units, macrocyclic structures, or as part of intricate fused polycyclic cores (Fig. 1). Radical reactions have been developed to address synthetic challenges for all three classes of oxacycles [1, 22].

Radical cascades have found exclusive application in the formation of naturally occurring polycyclic molecules [16]. There are two strategies that have been utilized in radical cascades for the incorporation of oxacycles: (a) direct formation of the oxygen-containing cycle as part of a radical cyclization cascade and, (b) incorporation of a preformed oxacycle into the polycyclic framework (Fig. 2). Examples of these two approaches will be described separately in this section.

2.1 Oxacycle-Forming Radical Cascades

Radical cyclization reactions are among the fastest processes in organic chemistry [23]. For instance, 5-*exo* cyclizations of carbon radicals have been reported to have

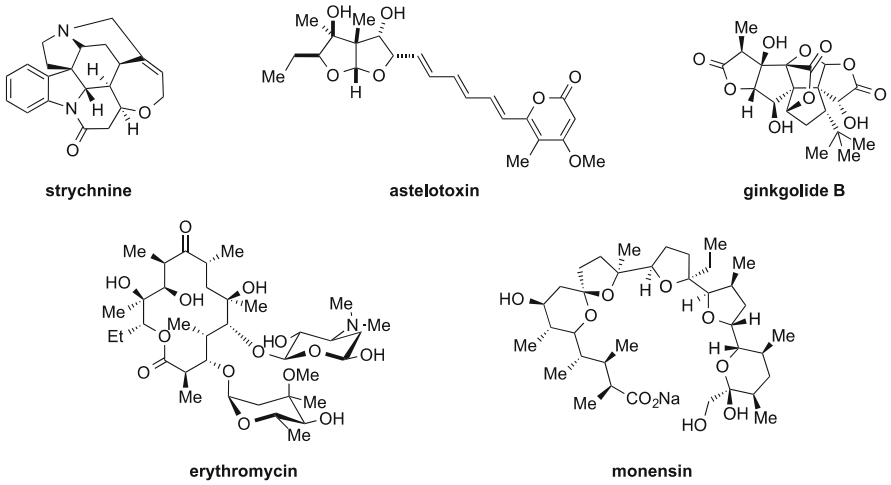


Fig. 1 Selected oxacycle-containing natural products

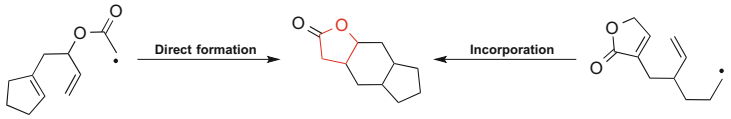


Fig. 2 Representative examples of different modes of oxacycle-formation and incorporation in radical cascades

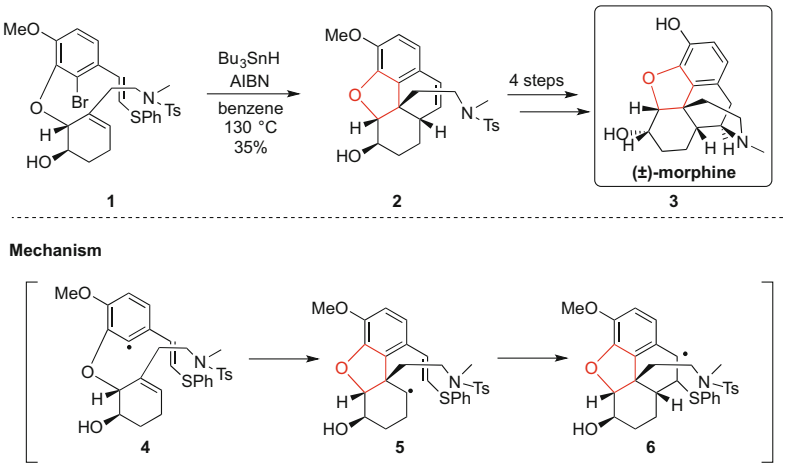
rates in the order of 10^5 s^{-1} [24, 25]. This characteristic, along with their kinetically determined reactivity, can be strategically used to control the possible reaction pathways of the radicals formed in each step and thus achieve elegant syntheses of polycyclic molecules.

Although strategies to form oxacycles using oxygen-centered radicals have been developed [26–28], studied [29], and utilized in synthesis [30], these methodologies are yet to be used as part of radical cascades in the total synthesis of secondary metabolites.

In this section, we highlight the use of domino radical reactions in the formation of oxacycles, such as cyclic ethers, acetals, and lactones, contained in naturally occurring compounds, through carbon-radical reactions.

2.1.1 Cyclic Ether Formation

In 1992, Parker and coworkers reported a convergent synthesis of (±)-morphine **3** [31]. The key step involved a cascade radical cyclization to form morphine's central oxygen-containing tetracyclic core (Scheme 1). The cascade was initiated

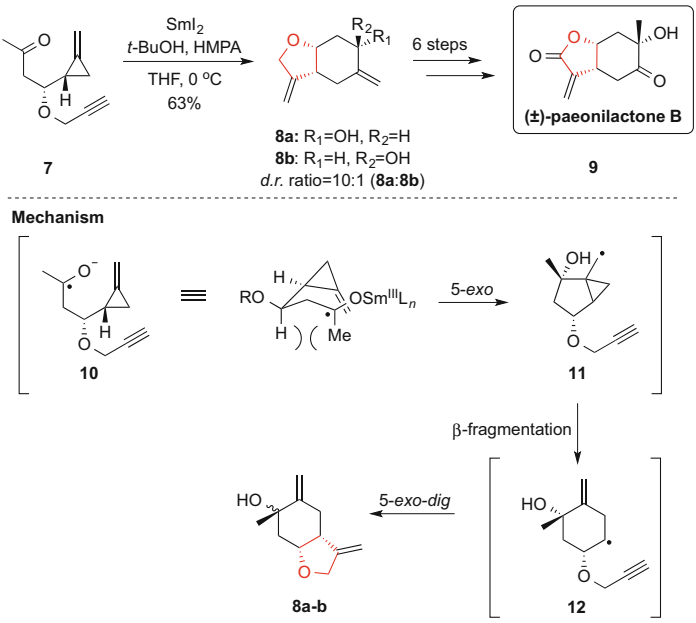


Scheme 1 Parker's synthesis of (±)-morphine

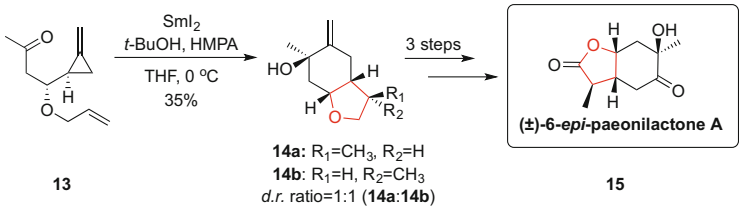
by subjecting racemic bromoaryl ether **1** to tributyltin hydride and 2,2′-azobisisobutyronitrile (AIBN), which resulted in the generation of radical **4**. The sp^2 carbon radical then underwent tandem 5-*exo* cyclization followed by a 6-*endo* cyclization. β-Fragmentation of SPh radical **6** afforded tetracyclic styrene **2** in a 35% yield for the cascade. The tetracyclic styrene **2** was then converted to (±)-morphine in four steps. In 2006, the same group reported an asymmetric version using enantiomerically enriched bromoaryl ether **1** [32].

Another example of radical cascades in the formation of cyclic ethers was reported in 1998 by Kilburn and coworkers for the synthesis of (±)-paeonilactone B (Scheme 2, **9**). The central *cis*-fused bicyclic core was synthesized in a highly diastereoselective manner, through a SmI_2-mediated radical cyclization cascade of methylenecyclopropane derivative **10** [33]. Treatment of propargyl ether **7** with SmI_2 afforded ketal radical **10**, which then underwent a 5-*exo* cyclization onto a methylenecyclopropane moiety to produce radical **11**. In the initial cyclization step, both prop-2-ynyl ether substituent and the bulky O-$Sm^{III}L_n$ adopted pseudo-equatorial positions to minimize steric repulsion, resulting in the desired configuration of the tertiary alcohol. A subsequent cyclopropyl ring opening generated radical intermediate **12**, which underwent a 5-*exo-dig* cyclization to give the *cis*-fused bicyclic methylenecyclohexane **8a-b** in 63% yield for the cascade as a 10:1 mixture of diasteromers. This key intermediate **8a** could be converted to (±)-paeonilactone B **9** in 6 additional synthetic steps.

Three years later, Kilburn and coworkers reported a similar cascade approach for the synthesis of (±)-6-*epi*-paeonilactone A (Scheme 3, **15**) using allyl ether **13** as the radical precursor for the tandem radical cyclization [34]. The resulting cascade resulted in the formation of a pair of diastereomers **14a** and **14b** in 1:1 ratio with 35% overall yield. The diastereoisomeric mixture of alcohols **14a** and **14b** was converted into (±)-6-*epi*-paeonilactone A in three synthetic steps.



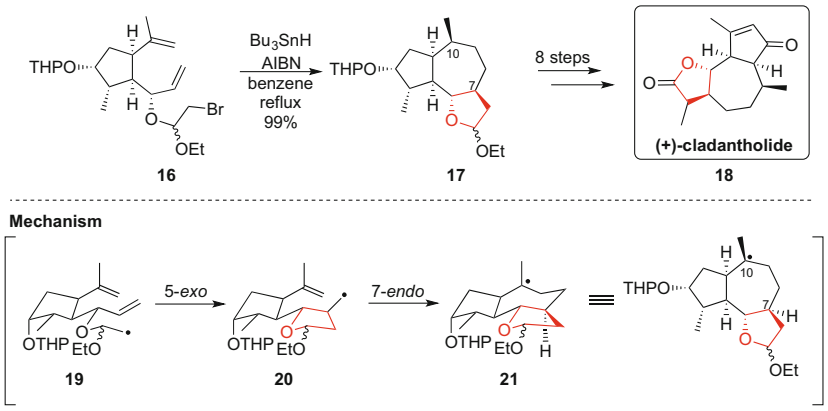
Scheme 2 Kilburn's synthesis of (±)-paeonilactone B



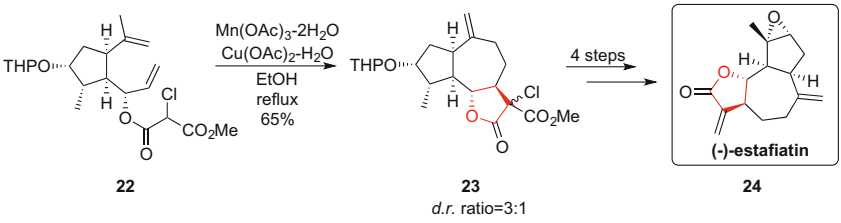
Scheme 3 Kilburn's synthesis of (±)-6-*epi*-paeonilactone A

2.1.2 Cyclic Acetal and Lactone Formation

One of the early applications for the use of radical cascades for the formation of cyclic acetals and lactones in total synthesis was reported by Lee and coworkers in 1997 for the stereoselective total syntheses of (+)-cladantholide **18** and (−)-estafiatin **24** [35]. A similar radical cascade strategy was utilized to synthesize two of the three central rings in both natural products. In the synthesis of (+)-cladantholide (Scheme 4, **18**), bromoacetal **16** was treated with tributyltin hydride and AIBN to afford the cis-fused hydroazulenic acetal **17** in 99% yield. The cascade begins with the formation of alkyl radical **19**, which then undergoes a diastereoselective 5-*exo* cyclization followed by a 7-*endo* cyclization to afford **21**. The ensuing tertiary radical was quenched by tributyltin hydride from the less steric α-face to give the correct configuration at C-10. Hydroazulenic acetal **17** was then converted to (+)-cladantholide **18** in 8 synthetic steps [35].



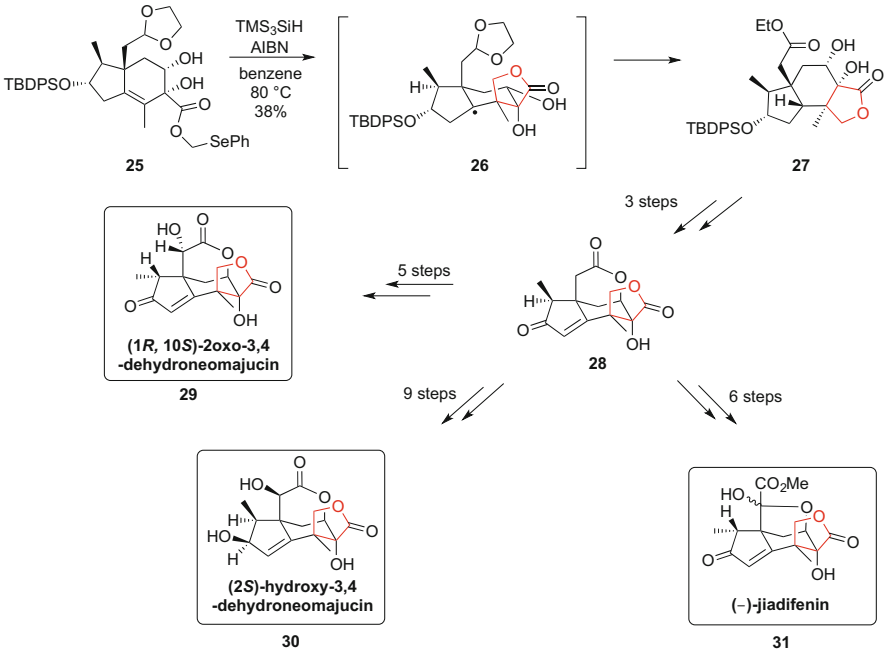
Scheme 4 Lee's synthesis of (+)-cladantholide



Scheme 5 Lee's synthesis of (−)-estafiatin

For the synthesis of (−)-estafiatin (Scheme 5, **24**) [35], Lee and coworkers subjected chloromalonate **22** to manganese(III) acetate and copper(II) acetate to afford the *cis*-fused tricyclic chlorolactone **23** in a 3:1 diastereomeric ratio and 65% yield. The tricyclic chlorolactone **23** was then converted to (−)-estafiatin **24** in 4 synthetic steps.

In 2016, Micalizio and coworkers successfully synthesized the neurotrophic *seco*-prezizaane sesquiterpenes from a common intermediate using an intramolecular radical cascade reaction to synthesize the lactone and the quaternary stereocenter (Scheme 6, **29–31**) [36]. The cascade begins with the formation a carbon-centered radical from selenophenyl methyl ester **25.** The radical then undergoes a stereoselective 5-*exo* cyclization to form radical **26**. A subsequent abstraction of the acetal hydrogen followed by fragmentation forms **27** as the major product. A minor product was also formed in this cascade, which was formed from a 5-*exo* cyclization followed by quenching with TMS_3SiH. Both the major and minor cyclized products were converted to the intermediate tetracyclic bis-lactone **28** in 3 and 4 steps, respectively. The key intermediate **28** was then converted into different *seco*-prezizaane sesquiterpene derivatives: (1*R*,10*S*)-2-oxo-3,4-dehydroneomajucin **29**, (2*S*)-hydroxy-3,4-dehydroneomajucin **30**, and (−)-jiadifenin **31**.

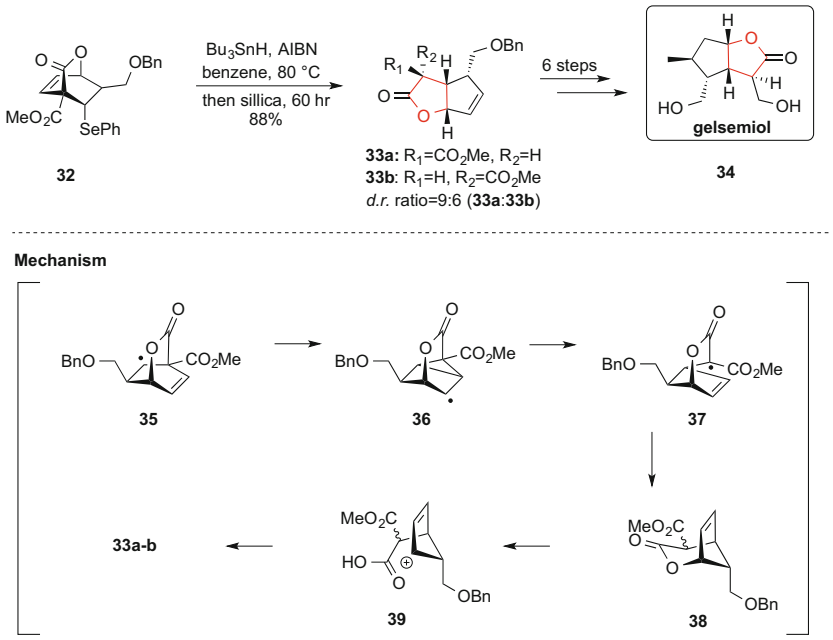


Scheme 6 Synthesis of (1*R*,10*S*)-2-oxo-3,4-dehydroneomajucin, (2*S*)-hydroxy-3,4-dehydroneomajucin, and (−)-jiadifenin

Cascade radical skeletal rearrangements have been utilized in the construction of fused lactones for over two decades. Renaud and coworkers explored the use of bicyclic rearrangements to synthesize the prostaglandin core in 1993 [37] and a related rearrangement was later developed by Markó in 2000 [38]. In 2013, Gademann and coworkers used a modified version of the Markó radical cascade/skeletal rearrangement [38] in the first enantioselective total synthesis of gelsemiol (Scheme 7, **34**) [39]. Treatment of **32** with Bu_3SnH and AIBN generates radical **35**, which then undergoes a 3-*exo* cyclization to form cyclopropylmethyl radical **36**. Subsequent ring fragmentation produces the more stable radical intermediate **37**, which is quenched with Bu_3SnH to form **38**. A subsequent rearrangement forms the desired bicyclic compound, **33a-b** in 88% yield. This could then be converted into gelsemiol **34** in 6 synthetic steps with an overall yield of 14%.

2.1.3 Endoperoxide Formation

In 2014, Lee and coworkers reported a biomimetic synthesis of (±)-yezo'otogirin C **42** via a cascade radical cyclization to form key endoperoxide intermediate **41** (Scheme 8), which was used to synthesize the key tetrahydrofuran moiety in the natural product [40]. The endoperoxide was formed through the treatment of

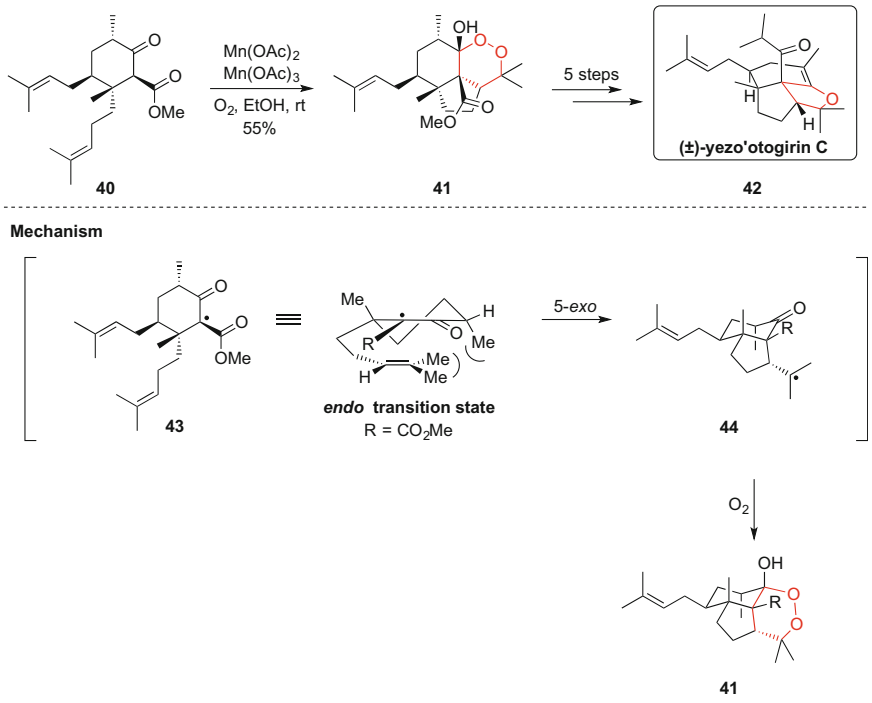


Scheme 7 Gademann's synthesis of gelsemiol

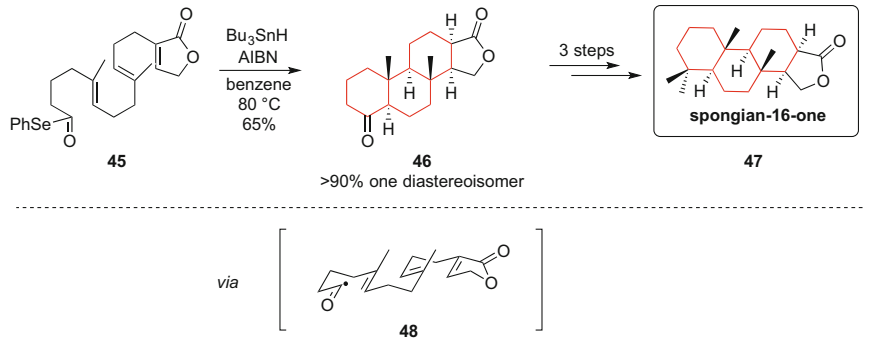
β-ketoester **40** with Mn(II) acetate and Mn(III) acetate in the presence of oxygen. The cascade began through generation of alkyl radical **43**, which then cyclized through a 5-*exo* mode to generate **44**. The reaction proceeds through the more favorable *endo* transition state to set the correct configuration in intermediate **44**. This tertiary carbon radical then reacted with oxygen to form the endoperoxide **41** in 55% yield. The peroxy-bridged compound **41** was converted into (±)-yezo'otogirin C **42** in 5 synthetic steps with 23% overall yield.

2.2 *Incorporating Preformed Oxacycles*

Radical cascade reactions are not only a useful method for the synthesis of heterocycles in natural product synthesis, but they can also be utilized to incorporate preformed heterocycles into polycyclic molecules. In 1998, Pattenden and coworkers reported the synthesis of (±)-spongian-16-one **47** via serial 6-*endo-trig* radical cyclizations from polyene acyl radical precursors (Scheme 9, **45** [41]). The radical cascade was initiated with the treatment of dienebutenolide selenoate **45** with Bu_3SnH and AIBN to generate acyl radical **48**. This radical then underwent three consecutive 6-*endo-trig* radical cyclization to afford the tetracyclic keto-lactone **46** in 65% yield. This advanced intermediate was converted to (±)-spongian-16-one **47** in 3 steps.

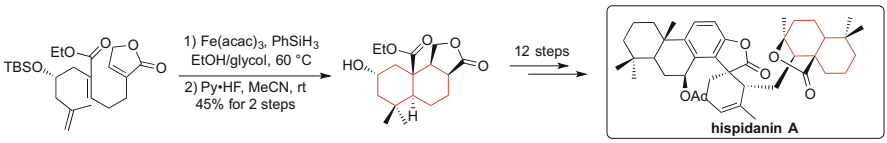


Scheme 8 Lee's synthesis of (±)-yezo'otogirin C



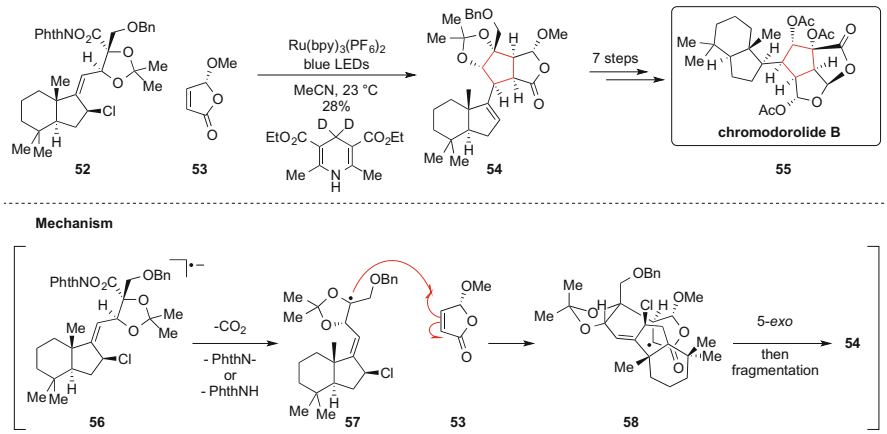
Scheme 9 Pattenden's synthesis of (±)-spongian-16-one

Liu and coworkers explored the use of a diastereoselective, cascade 6-*endo-trig* radical cyclization approach in the synthesis of hispidanin A **51** (Scheme 10) [42]. While ester substituted acyl radical intermediates have been reported to produce the undesired *cis*-decalin tricyclic compound as the major product [43], Liu and coworkers found that the Fe-catalyzed radical conditions developed by Boger and coworkers [44–46], and later modified by Baran and coworkers [47],



[45]

Scheme 10 Liu's synthesis of hispidanin A



Scheme 11 Overman's synthesis of (−)-chromodorolide B

preferentially formed *trans*-decalin tricyclic compound **50** in 45% yield over 2 steps. Tricyclic compound **50** was then converted to the hispidanin A **51** in 12 steps. The proposed reaction mechanism involves a radical hydrogen atom transfer to the olefin from an Fe(III) hydride, which is generated in situ through the reaction of the silane with the iron complex [47].

The incorporation of a preformed hydrindanone derivative into a natural product intermediate was effectively demonstrated by Overman and coworkers in their bimolecular radical addition/cyclization/fragmentation (ACF) cascade toward the asymmetric total synthesis of (−)-chromodorolide B **55** (Scheme 11) [48]. The cascade was effected via radical decarboxylation of bicyclic intermediate **52** to form radical **57** under photoredox catalytic condition with a ruthenium catalyst and visible light [49, 50]. The generation of the radical is a result of a photoredox process that starts with the irradiation of $Ru(bpy)_3^{2+}$ to generate an excited state – $Ru(bpy)_3^{2+*}$ – that after a reductive quench by d2-Hantzsch ester generates $Ru(bpy)_3^{+}$, which is a strong reductant. Single electron transfer (SET) to bicyclic intermediate **52** generates radical anion **56** that upon loss of carbon dioxide and phthalamide effectively generates carbon radical **57** [51–54]. Radical **57** then adds to (*R*)-4-methoxybutenolide **53** to form α-acyloxy-radical intermediate **58**, which then undergoes an intramolecular 5-*exo* cyclization, followed by β-fragmentation of

the adjacent C–Cl to generate **54** with the desired configuration in 28% yield. Tricyclic intermediate **54** was then converted to (−)-chromodorolide B **55** in 7 steps.

3 Nitrogen Containing Heterocycles

Alkaloids constitute a large class of secondary metabolites that contain at least one nitrogen atom in their structure, typically incorporated in azacycles (Fig. 3). Their complex structures as well as biological properties have made them common targets of organic synthesis [55].

Cascade radical reactions have been found to be valuable methods in the construction of synthetically challenging and/or structurally complex polycyclic alkaloids [14–16, 56]. Similar to the construction of oxacycle-containing natural products, the elaboration of nitrogen-containing frameworks in natural products through tandem radical cascades can be accomplished either by forming the azacycles in the cascade process, or modifying a preexisting azacycle. The two cases will be discussed separately in this section, which compiles the use of tandem radical reactions in the total synthesis of nitrogen-containing natural products.

3.1 Azacycle-Forming Radical Cascades

The construction of azacycles is an important synthetic challenge that has been extensively explored [57, 58]. While the majority of methods for the synthesis of azacycles rely on ionic intermediates, radical mediated methodologies have also

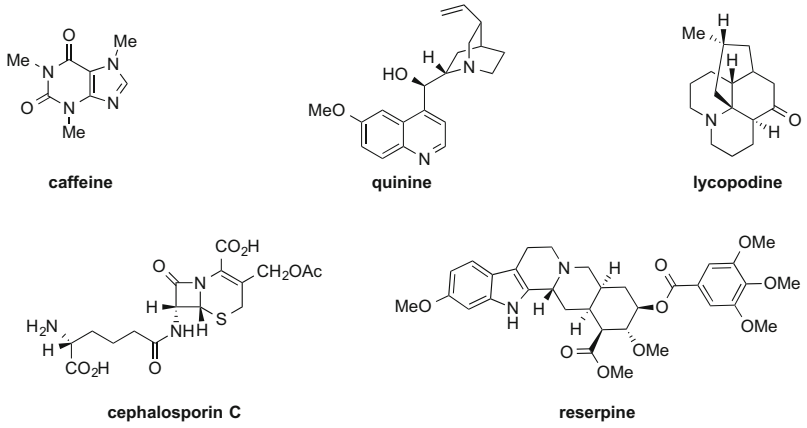


Fig. 3 Selected azacycle-containing naturally occurring products

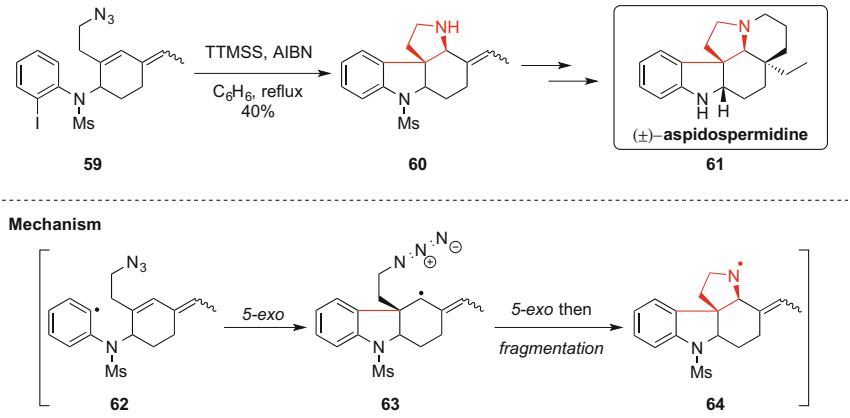
been developed using both carbon- and nitrogen-centered radicals as intermediates [59, 60].

In this section, we highlight the use of cascade radical reactions in the formation of azacycles, such as pyrrolidines, pyrimidine, indolizidines, and indolizidones contained in naturally occurring compounds, through both carbon- and nitrogen-centered radical reactions.

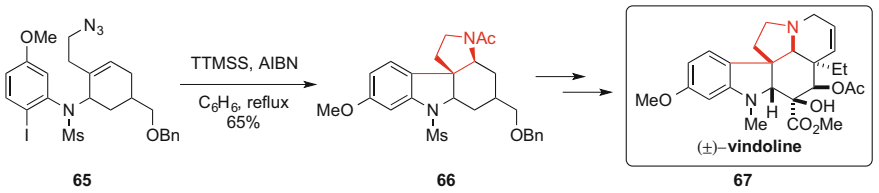
3.1.1 Pyrrolidine Formation

In 2000, Murphy and coworkers reported a total synthesis of pyrrolidine-containing (±)-aspidospermidine **61** (Scheme 12) using a cascade radical cyclization starting from iodoaryl azides [61]. In the key step, iodoaryl azide **59** is treated with tris(trimethylsilyl)silane (TTMSS) and AIBN in refluxing benzene to generate tetracyclic amine **60**. The reaction conditions lead to the generation of aryl radical **62**, which undergoes a 5-*exo* intramolecular cyclization to form alkyl radical **63**. A subsequent 5-*exo* cyclization onto the azide followed by extrusion of nitrogen gas and quenching of the nitrogen-centered radical **64** yields **60** in 40% yield. Two ensuing synthetic transformations intercept a late synthetic intermediate of the groups' prior total synthesis of (±)-aspidospermidine (**61**) [62].

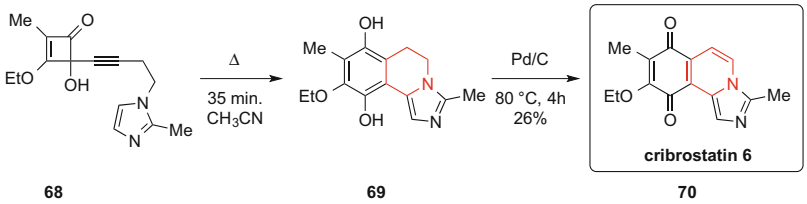
Iodoaryl azides were again utilized in 2001 by Murphy and coworkers in the formal synthesis of (±)-vindoline **67** (Scheme 13), one of the fragment of the anticancer agent vinblastine [63]. Aryl iodide **65** was subjected to TTMSS and AIBN in refluxing benzene to afford pyrrolidine **66** in 35% yield. Seven more synthetic steps provide access to an advanced intermediate of a total synthesis previously reported by Büchi [64].

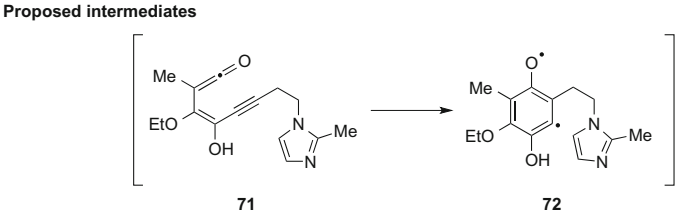


Scheme 12 Murphy's key tandem radical cyclization step of the formal total synthesis of (±)-a aspidospermidine



Scheme 13 Murphy's tandem radical cyclization of iodoaryl azides in the formal synthesis of (±)-vindoline





Scheme 14 Knueppel and Martin's total synthesis of cribrostatin 6

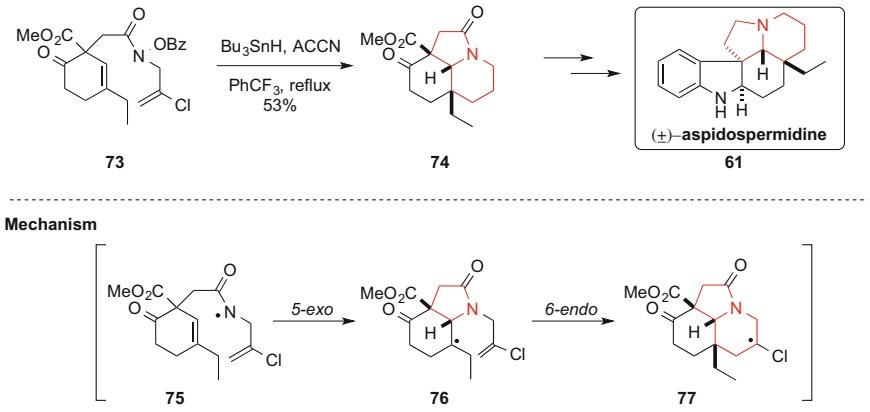
3.1.2 Pyrimidine Formation

Pyrimidine ring systems have also been synthesized utilizing cascade radical cyclization reactions in total synthesis. In 2009, Knueppel and Martin reported the total synthesis of cribrostatin 6 (**70**) (Scheme 14) [65], a tricyclic alkaloid isolated from the blue marine sponge *Cribrochalina* that exhibited potent antimicrobial activity against antibiotic-resistant Gram-positive bacteria and pathogenic fungi [66]. Their radical cascade approach reduced the number of steps from 15 [67, 68] to only 4. The key synthetic step started with squarate derivative **68**, which was heated to reflux in acetonitrile to effectively generate hydroquinone **69**. The detection of the hydroquinone derivative as a byproduct of the reaction is consistent with the proposed formation of biradical intermediate **72**. A subsequent in situ oxidation with air in the presence of Pd/C yielded cribrostatin 6 in 26% yield over two steps.

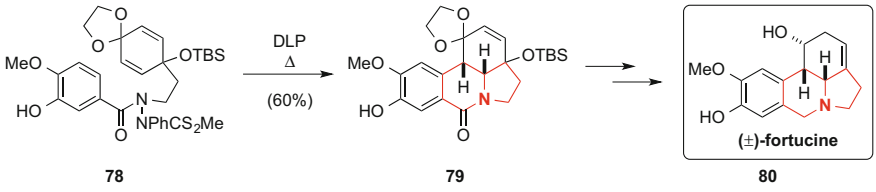
3.1.3 Indolizidine Formation

In 2008, Zard and coworkers reported the total synthesis of (±)-aspidospermidine **61** utilizing a radical cascade as the key step (Scheme 15) [69]. Unlike the synthesis reported by Murphy (discussed in Sect. 3.1.1) where the tandem radical reaction generates the pyrrolidine ring, Zard's radical cascade strategy generates the bicyclic indolizidine core (Scheme 15). Treatment of benzoate ester **73** with tributyltin hydride and 1,1′-azobis-cyclohexanecarbonitril (ACCN) generated indolizidone **74** in 53% yield. The amidyl radical 75, formed through an initial N-O bond cleavage, undergoes a 5-*exo* cyclization, followed by a 6-*endo* cyclization to afford radical **71**. The chlorine substituent effectively biases the system towards the 6-*endo* cyclization in the second step. The chlorine was removed in situ by the excess of tributyltin hydride. Lactam **74** was effectively transformed into the natural product **61** in 4 additional steps.

(±)-Fortucine (**80**), a lycorine alkaloid containing indolizidine isolated from the Amaryllidaceae family, was also targeted by Zard in the same year. The formation of the indolizidine core of (±)-fortucine was accomplished through the strategic use of an amidyl radical cascade (Scheme 16) [70, 71]. The initial amidyl radical was generated through the homolytic cleavage of a N–N bond, by heating a solution of



Scheme 15 Zard's amidyl initiated radical cascade key step in the total synthesis of (±)-aspidospermidine

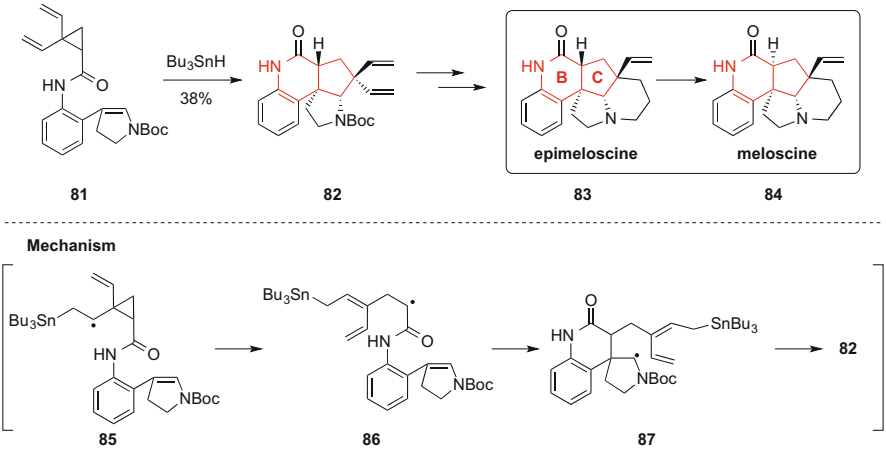


Scheme 16 Zard's total synthesis of (±)-fortucine via an amidyl radical cascade

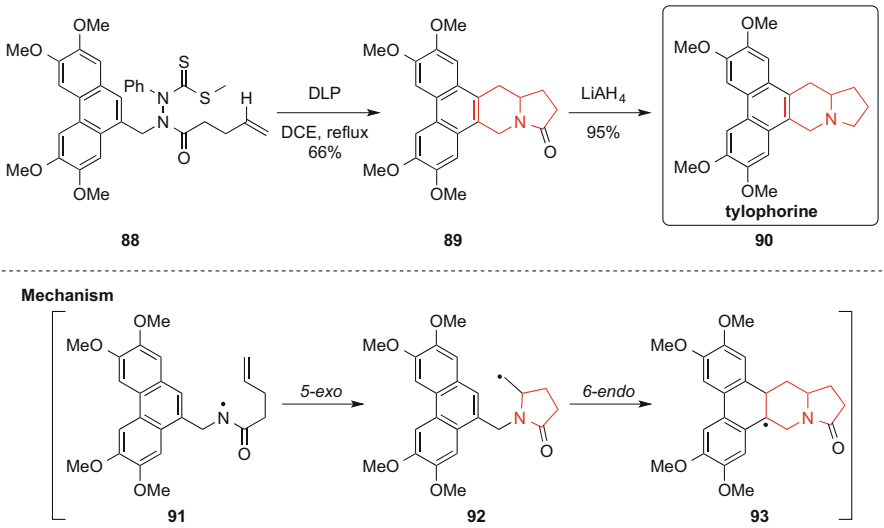
precursor **78** with dilauroyl peroxide (DLP), which then underwent a 5-*exo* cyclization followed by a *6-endo* cyclization to stereo- and regioselectively generate **79** in 60% yield. Intermediate **79** was then converted to (±)-fortucine in 12 steps and 9% overall yield.

Another radical cascade to form an indolizidine core was reported by Curran and Zhang in 2011, in their total synthesis of (±)-epimeloscine (**83**) and (±)-meloscine (**84**) (Scheme 17) [72]. The radical strategy used by Curran leads to a shorter synthesis as compared to previous reports [73–77]. The cascade converted **81** to tetracyclic compound **82** in 38% yield. Initial addition of tributyltin radical to one of the terminal double bonds of amide **81** generates radical **85**, which undergoes a cyclopropyl ring opening to generate secondary radical **86**. Two consecutive cyclizations and fragmentation of Bu_3Sn• yielded **82**. Further synthetic manipulations enabled the synthesis of (±)-epimeloscine (**83**) with an overall yield of ~6% over 10 steps in the longest linear sequence. Epimerization of **83** readily produces (±)-meloscine (**84**).

Amidyl radicals were utilized by Wang and coworkers to initiate a cascade process in the total synthesis of tylophorine **90** (Scheme 18) [78]. Radical precursor **88** was reacted with DLP in refluxing 1,2-dichloroethane (DCE) to afford indolizidine **89** in 66% yield, via a 5-*exo* followed by 6-*endo* cyclization cascade. A subsequent lithium aluminum hydride reduction generates alkaloid tylophorine **90** in 95% yield. Modifications on the substituents attached to the phenanthrene moiety provide access to tylophorine analogues, including antofine, deoxyperfularine, and hypoestestatin 1.



Scheme 17 Curran's total synthesis of (±)-epimeloscine and (±)-meloscine



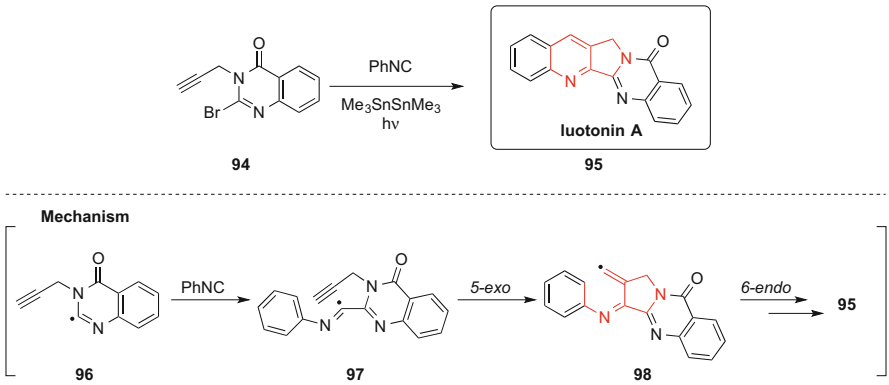
Scheme 18 Wang's amidyl radical cascade synthesis of tylophorine, a general strategy towards phenanthroindolizidine alkaloids

3.1.4 Other Azacycle Formation

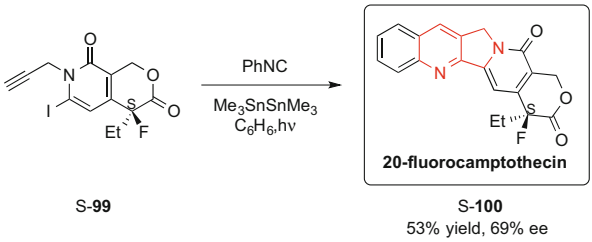
In 2005, Curran and coworkers reported a four-step total synthesis of luotonin A (**95**) through a cascade radical annulation as the key step (Scheme 19) [79]. Photoirradiation of radical precursor **94** with a sunlamp in the presence of phenylisonitrile and hexamethyldistannane afforded luotonin A in 47% yield. Previous studies by the same research group [80, 81] suggest that the reaction mechanism proceeds via an initial intermolecular addition of radical **96** (generated through abstraction of the Br atom in **94** by the Me_3Sn radical) to phenylisonitrile to generate vinyl radical **97**. A 5-*exo* followed by a 6-*endo* cyclization sequence effectively constructs the pentacyclic core of luotonin A (**95**).

The same radical annulation cascade strategy was later applied to the synthesis of 20-fluorocamptothecin (**100**), also by the Curran group (Scheme 20) [82]. Precursor (*S*)-**99** was treated with phenylisonitrile, hexamethyldistannane, and light to provide (*S*)-**100** in 53% yield and 69% ee. The radical annulation reaction conditions did not affect the configuration of the stereocenter present in the starting material.

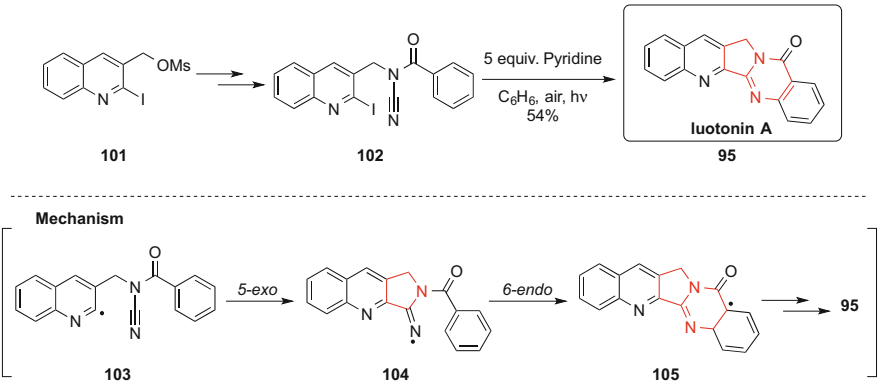
Three years after Curran's report, Malacria and coworkers presented their own approach to the total synthesis of luotonin A (**95**) based on radical addition onto cyanamides (Scheme 21) [83] that also utilized a tandem radical mediated process to construct the pentacyclic core. However, Malacria's strategy circumvents the use of tin-containing reagents by successfully initiating the reaction through the use of an aryl iodide and UV-light. The mechanism starts with the formation of aryl radical **103**, which then undergoes a *5-exo* cyclization onto the cyanamide to



Scheme 19 Curran's total synthesis of luotonin A

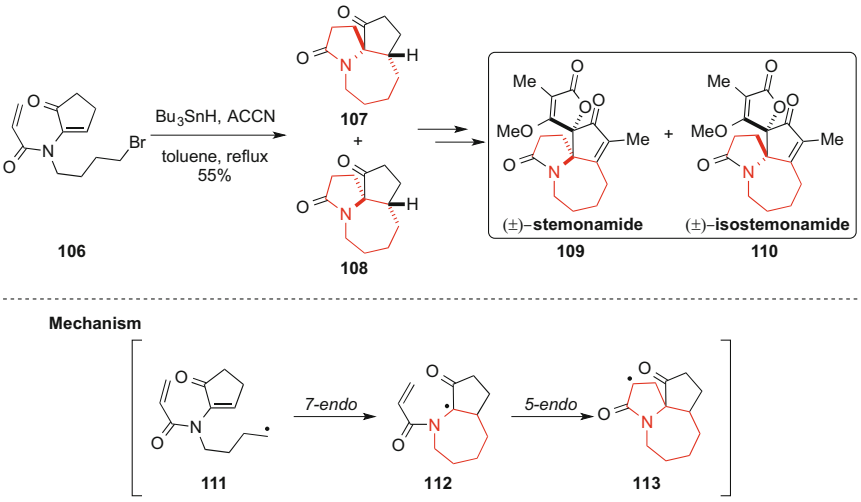


Scheme 20 Curran's total synthesis of 20-fluorocamphotecin



Scheme 21 Malacria's total synthesis of luotonin A

generate amide-iminyl radical **104**. The authors acknowledge that there are multiple possible reaction pathways to explain the formation of luotonin A from **104**. The most direct pathway is depicted in Scheme 21.

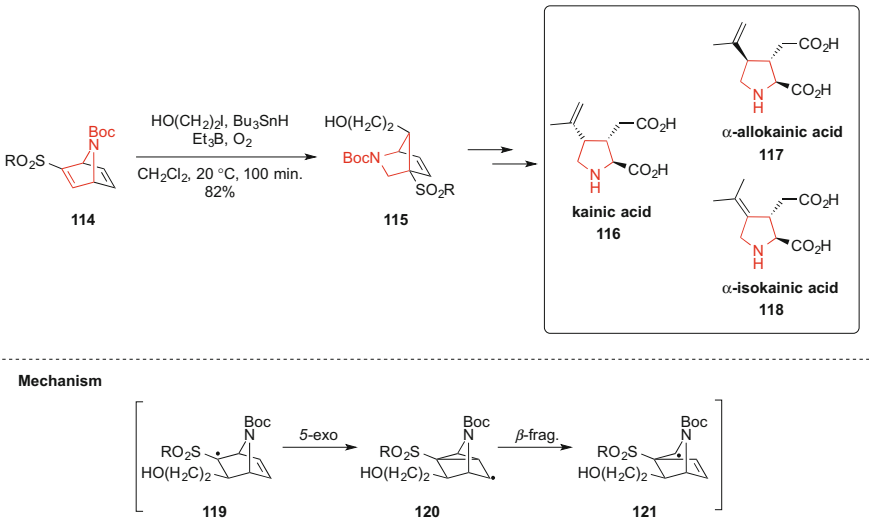


Scheme 22 Ishibashi's total synthesis of (±)-stemonamide and (±)-isostemonamide

In 2008, Ishibashi and coworkers reported the total syntheses of (±)-stemonamide (**109**) and (±)-isostemonamide (**110**) (Scheme 22) [84]. Both alkaloids have an intricate tetracyclic structural core with two contiguous spirocyclic quaternary centers. Ishibashi's strategy effectively constructs three core cycles through a radical cascade key step (Scheme 22). Treatment of radical precursor **106** with tributyltin hydride and ACCN in refluxing toluene generates primary radical **111**, which undergoes a *7-endo* followed by *5-endo* cyclization sequence to afford a 1:1 mixture of amides **107** and **108** in 55% yield. These tricyclic intermediates were used to access both (±)-stemonamine and (±)-isostemonamine [85].

3.2 Modification of Preformed Azacycles

Radical cascades have been used not only to generate but also to modify heterocycles in total synthesis strategies. Examples of syntheses relying on tandem radical reactions to modify already existing nitrogen-containing heterocycles were reported by Hodgson and coworkers in 2005. The authors used a tandem radical addition-homoallylic rearrangement as the key step in the construction of α-kainic acid (**116**) [86], (±)-α-isokainic acid (**118**), and (±)-α-dehydroallokainic acid (**117**) (Scheme 23) [87]. The key step begins with the generation of an alkyl radical from 2-iodoethanol, followed by addition to 7-azabicyclo[2.2.1]heptadiene (**114**), yielding tertiary radical **119**. A 5-*exo* cyclization followed by a β-fragmentation step generates the more stable radical **121**. Radical quenching generates 2-azabicyclo [2.2.1]hept-5-ene **115** in 82% yield. Further synthetic manipulations enabled access to α-kainic acid **116** and its congeners (±)-α-isokainic acid (**118**) and (±)-α-dehydroallokainic acid (**117**).



Scheme 23 Hodgson's synthesis of kainoid amino acids

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