Applications of Halogen-Atom Transfer (XAT) for the Generation of Carbon Radicals in Synthetic Photochemistry and Photocatalysis

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ABSTRACT: The halogen-atom transfer (XAT) is one of the most important and applied processes for the generation of carbon radicals in synthetic chemistry. In this review, we summarise and highlight the most important aspects associated with XAT and the impact it has had on photochemistry and photocatalysis. The organisation of the material starts with the analysis of the most important mechanistic aspects and then follows a subdivision based on the nature of the reagents used in the halogen abstraction. This review aims to provide a general overview of the fundamental concepts and main agents involved in XAT processes with the objective of offering a tool to understand and facilitate the development of new synthetic radical strategies.

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1. INTRODUCTION

The direct conversion of an organic halide into the corresponding carbon-radical represents a versatile and programmable way to access a reactive synthetic intermediate to then engage in subsequent chemical transformations. The development of reactions like the Giese addition of alkyl halides to acrylate acceptors,[1] the Ueno-Stork cyclization of β-halo-acetals,[2,3] as well as landmark applications of radical reactivity in total synthesis like Stork's synthesis of prostaglandin $F_{2\alpha}$,[4] Curran's approach to hirsutene,[5] and Hart's preparation of pleurotin,[6] have played a fundamental role in shaping the development of synthetic radical chemistry.[7]

Generating C-radicals from the corresponding halides can be achieved by three distinct mechanistic pathways (Scheme 1):

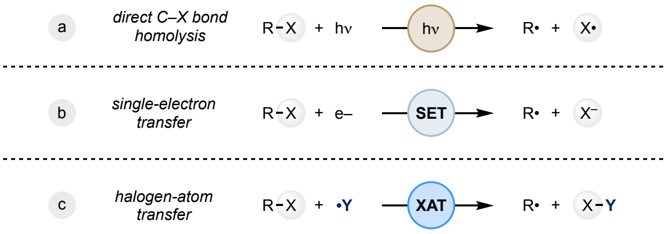
(a) Homolytic C–halogen (C–X) bond cleavage. Approaches based on direct C–X bond homolysis depend on the specific absorbance of the organic halide ($\lambda < 320$ nm for R–I, $\lambda < 280$ nm for R–Br)[8,9] and usually require high-energy light. These methods have found limited synthetic application in comparison to SET- and XAT-based approaches, mainly due to the requirement for specialised equipment and low functional group compatibility.[10]

(b) Single-electron transfer (SET) reduction followed by fragmentation. SET-based activation requires reduction of the organic halide, which can lead to the immediate rupture of the C–halogen bond (e.g. alkyl iodides and bromides and aryl iodides) or to the formation of a discrete radical anion from which a mesolytic cleavage takes place (e.g. aryl bromides and chlorides).[11] Approaches based on SET generally require the utilization of strong reductants, either in the ground or the excited state, unless electron-withdrawing groups (either by resonance or inductive effects) are present to increase the reduction potential of the halide and aid electron transfer.

(c) Halogen-atom transfer (XAT). XAT-based activation involves the direct homolytic abstraction of the halogen atom by an appropriate "abstractor" radical like, for example, the archetypical tin/silicon species.[12] Under this scenario, matching redox potentials are not relevant anymore and the reactivity is mostly controlled by the respective bond-dissociation energies (BDEs) and the polarizability of the C–halogen bond. Since most XAT agents display strong chemoselectivity and react with organic

halides in the presence of many functional groups, this approach represents a particularly powerful tool for the elaboration of densely functionalised molecules.

Scheme 1. Mechanistic Approaches to C-Radical Generation from Organic Halides.

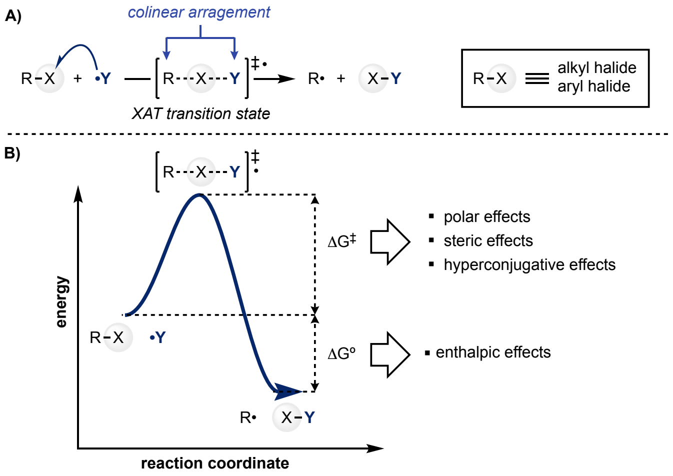


In the last 20 years, photochemistry has become a powerful and highly adopted tool in organic synthesis.[13-15] In particular, the ability of low-energy visible light photocatalysis to generate radical species under mild conditions has led to an increase in the use of radical chemistry to tackle synthetic problems and also provided new avenues for further exploitations (e.g. dual catalysis with metals).[16] The aim of this Review is to present key examples for the utilization of halogen-atom transfer in photochemistry and photo(redox)catalysis. The discussion will start with the analysis of the key mechanistic aspects associated with XAT reactivity, which will be followed by state-of-the-art examples and synthetic applications.

2. MECHANISTIC ASPECTS OF XAT REACTIVITY

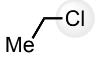
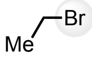
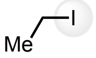
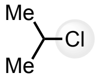
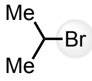
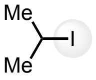
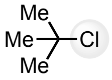
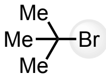
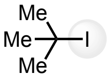
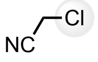
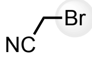
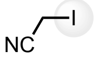
XAT belongs to the class of "atom transfer" reactions, which are one of the fundamental types of "elementary processes" in radical chemistry.[17] As in the majority of these bimolecular transformations (S_H2), XAT is characterized by a simple reaction profile with a transition state (TS) displaying a colinear arrangement of attacking (Y) and leaving (R) groups with several factors controlling and modulating its outcome (Scheme 2A).[18,19] In general, the thermodynamic aspects of the process (ΔG^o) are controlled by enthalpic effects while the kinetics ($\Delta G^‡$) result from the interplay of predominantly polar but also steric and hyperconjugative effects (Scheme 2B).[20]

Scheme 2. (A) XAT Mechanism. (B) XAT Energy Profile.



Enthalpic effects. Like all types of radical abstractions, enthalpic effects dictate the overall energetic feasibility (ΔG°) of XAT reactions. In order for these processes to be exergonic, the Y–halogen bond needs to be stronger than the C–halogen bond in the starting materials (i.e. $\mathrm{BDE}_{X\text{–}Y} > \mathrm{BDE}_{R\text{–}X}$). This can be easily assessed by looking at literature or computed bond dissociation energies (BDEs).[21] Table 1 contains some key BDEs for common organic halides as well as the most employed XAT reagents. It is clear from these values how the halogen abstracting ability of tin and silicon species is greatly facilitated by the stronger nature of Sn/Si–X bonds with respect to both sp^3 and sp^2 C–X bonds.

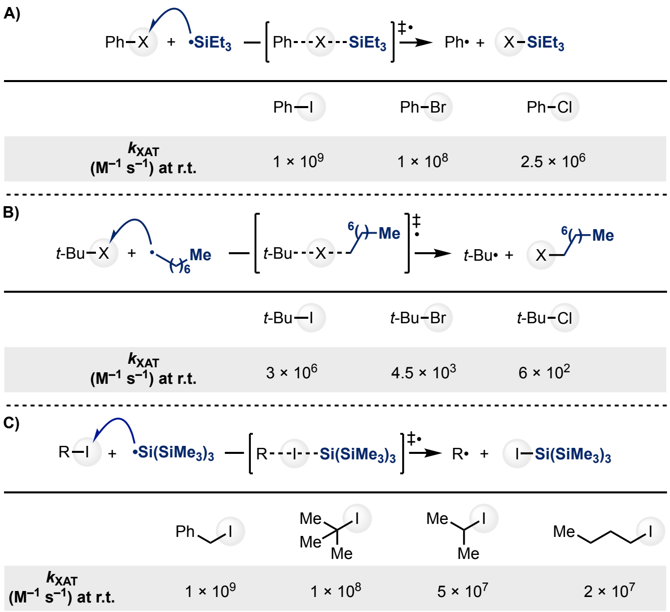
Table 1. BDEs of organic halides[21]

Bond	BDE (kcal mol^{-1})	Bond	BDE (kcal mol^{-1})	Bond	BDE (kcal mol^{-1})
Me–Cl	83.7	Me–Br	70.3	Me–I	57.1
	84.2		70.0		55.8
	84.6		71.5		56.1
	84.1		70.0		54.3
	66.4		56.8		44.7
Cl_3C–Cl	70.9	Cl_3C–Br	52.3	Cl_3C–I	40.1
Ph–Cl	96.5	Ph–Br	80.4	Ph–I	65.0
Me_3Sn–Cl	101.6	Me_3Sn–Br	91.3	Me_3Sn–I	76.5
Me_3Si–Cl	117.0	Me_3Si–Br	101.4	Me_3Si–I	82.1

According to the Bell-Evans-Polanyi principle,[22] when polar or other effects do not significantly perturb the halogen abstraction step, a linear correlation is predicted between the logarithm of the XAT rate constants and the heat effect. This means that the relative rates for halogen abstractions follow the strength of the C–halogen bonds with the general trend being iodides > bromides > chlorides (Scheme 3A and B).[23-25] The correlation between the rate of XAT and C–X BDEs is also consistent with these abstractions having early TSs (Hammond postulate).[26]

The stability of the ensuing C-radical is also important in facilitating XAT and this results in the general trend benzylic > tertiary > secondary > primary > phenyl (Scheme 3C).[24,25,27]

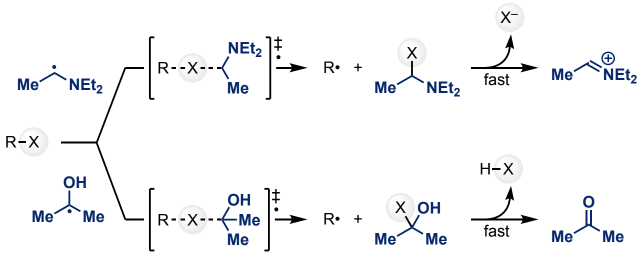
Scheme 3.[a] XAT Rate Constants Depending on: (A) Nature of the Halide on Aryl Derivatives; (B) Nature of the Halide on Alkyl Derivatives and (C) Alkyl Halide Substitution Pattern.



[a] The rate constants for XAT (k_{XAT}) have been approximated to the near integral number.

It is important to note that favourable enthalpic effects are not essential to drive halogen abstractions. In the case of systems where the product's Y–halogen bond has a similar (or even slightly weaker) strength than the substrate's C–halogen bond (i.e. $BDE_{X-Y} \leq BDE_{R-X}$), the abstraction can occur if there is a subsequent fast and irreversible reaction taking place. This scenario is generally occurring when using nucleophilic α-*N*-[28] and α-*O*-radicals[20] as XAT reagents, whereby the corresponding α-halo-amines/alcohols undergo fast fragmentation to more stable iminium/carbonyl species (Scheme 4). This fast reaction can be effectively considered as the overall thermodynamic driving force for the abstraction process.

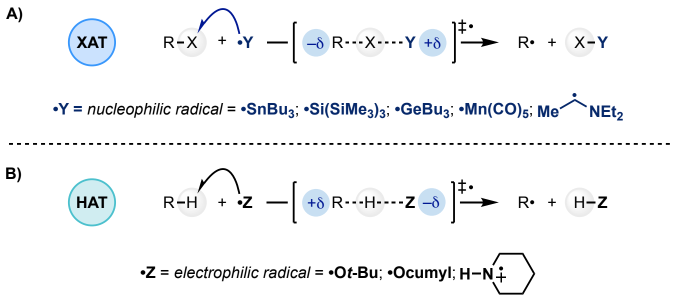
Scheme 4. Mechanism of XAT using α-Aminoalkyl and α-Hydroxyalkyl Radicals.



Polar effects. Polar effects pervade all aspects associated with reactivity and selectivity in radical reactions.[29] While the interplay of these effects is frequently used to rationalize the outcome of hydrogen-atom transfer (HAT) processes,[30] they also have a profound impact on XAT reactivity. Indeed, it is the stabilizing charge-transfer character operating at the TS level that usually provides crucial kinetic acceleration to halogen abstractions.

Mechanistic studies using Hammett plot analysis on XAT reactions of aryl and benzylic halides with Ph•, Bu_3Sn• and Et_3Si• have demonstrated that these processes build a partial negative charge on the carbon from which the halide is abstracted while a partial positive charge is accumulated on the halogen-abstracting atom (Y). This means that nucleophilic radicals maximize charge transfer in the TS which facilitates the abstraction (Scheme 5A).[31-34] Based on this analysis, it is interesting to note that *polar effects operating in XAT reactions are therefore opposed to the ones orchestrating HAT processes* where strongly electrophilic radicals (e.g. *t*-BuO•) are usually employed (Scheme 5B).[31,32] In these cases, a strong preference for the abstraction of hydridic H-atoms is observed where their bound C-atoms can effectively stabilize an incoming positive charge accumulation. Overall, the opposite polarity in charge separation in the transition state of XAT vs HAT reactions is due to the difference in electronegativity of halogen vs H atoms and the polarizability of the corresponding C–X vs C–H bonds.[35]

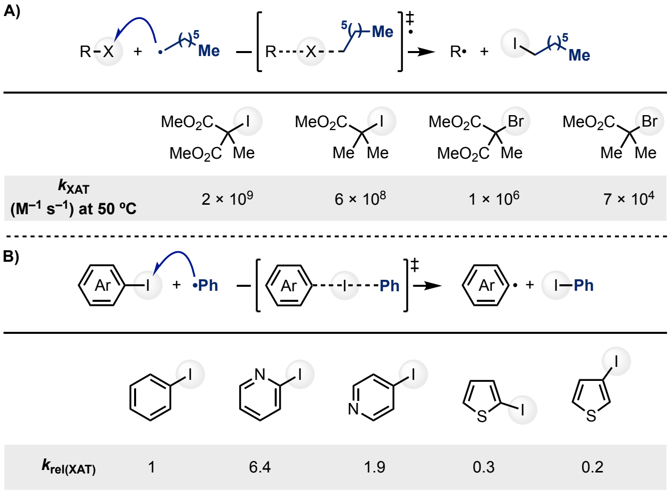
Scheme 5. Differences in Charge Separation Occurring in the Transition State of: (A) XAT Reactions and (B) HAT Reactions.



The requirement for nucleophilic radicals in XAT chemistry demonstrates how polar and enthalpic effects operate synergistically in the case of tin and silicon reagents due to the excellent ability of their corresponding radicals to stabilize the development of a positive charge in the TS.[36] The increased reactivity of Si-radicals over Sn-radicals is generally rationalized on the basis of both their stronger Si–X bonds (see Table 1) and higher ability to promote charge separation.[31,34,37]

The electronic properties of the halogen atom donor (R) are also important for the modulation of XAT reactivity. As an example, kinetic studies on the reaction between the heptyl radical and several α-halo-esters and diesters demonstrated how the rate for both iodine and bromine abstraction increased with the increased ability of the ester groups to stabilize a partial negative charge in the TS (i.e. going from α-halopropanoates to the corresponding methyl propanoates) (Scheme 6A).[25,38,39] Additional evidence has been provided by Danen's pioneering work on XAT reactions promoted by Ph•. As shown in Scheme 6B, abstraction from aryl iodides is accelerated in the case of 2- and 4-iodo-pyridines but is retarded in the case of 2- and 3-iodothiophenes. In the pyridines, the N-atom removes electron density from the aromatic ring which aids XAT, while an opposite effect is exerted by the S lone pairs in the thiophenes which retards the process.[31,34,37]

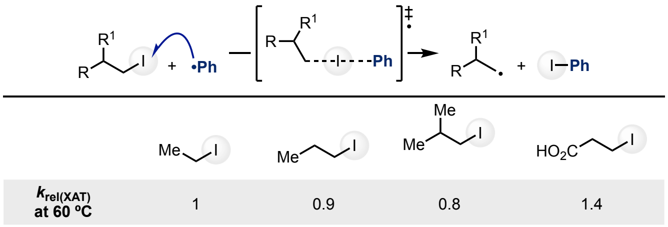
Scheme 6. XAT Rate Constants Depending on: (A) Alkyl Halide Substitution Pattern and (B) Aryl Halide Substitution Pattern.[a]



[a] The rate constants for XAT (k_{XAT}) have been approximated to the near integral number.

Inductive effects can also influence XAT reactivity as demonstrated in the iodine abstraction from primary alkyl derivatives by Ph• (Scheme 7).[32] In these cases, the introduction of electron-donating Me groups on the β-carbon of the iodide decreases the rate of XAT by destabilizing negative charge accumulation on the I-bound carbon in the TS. In contrast, an electron-withdrawing carboxylic acid group provides stabilization and accelerates the process. While these effects were quantified by competition experiments, it is important to note that the differences in reactivity are small and therefore they might not translate into observable reactivity changes under synthetic settings.

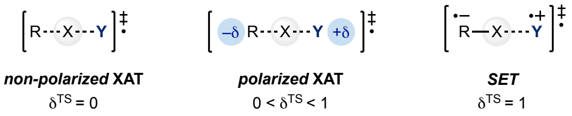
Scheme 7. [a] **Modulation of XAT by Inductive and Steric Effects.**



[a] The rate constants for XAT (k_{XAT}) have been approximated to the near integral number.

Since XAT reactivity is accelerated when nucleophilic radicals abstract halogen atoms from electron-poor alkyl/aryl halides, a fundamental question is at which point radical generation follows XAT over SET. In general, experimental and/or computed redox potentials for both the substrate and the abstracting radical can be used to determine the thermodynamic viability of direct SET. However, it is important to remember that the true nature of very polarized processes most probably lies between the XAT and SET mechanism.[40] In these cases, XAT can be approached as an inner-sphere SET especially since factors influencing the rate of SET will have the same impact on XAT. The determination of the "charge-transfer character"[41] ($0 < \delta^{TS} < 1$) in the TS can be particularly useful as processes characterized by δ^{TS} approaching 1 are likely to take place via SET (Scheme 8).

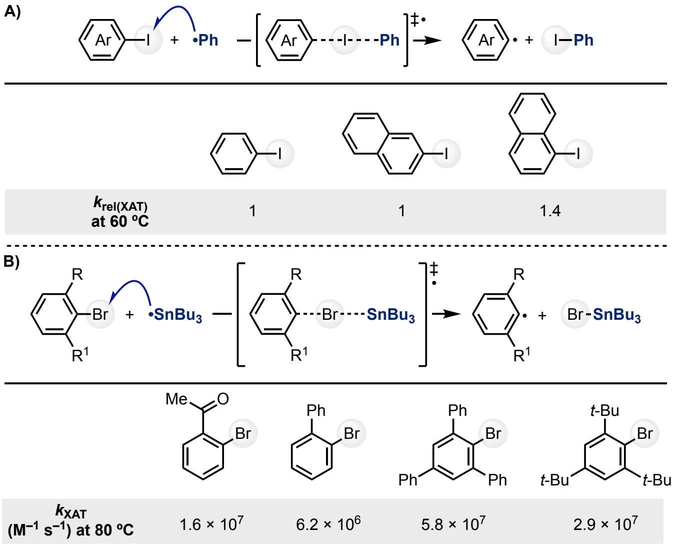
Scheme 8. XAT vs SET.



Other effects. As XAT reactions are generally highly exothermic they are characterized by early TSs with a limited degree of Y–halogen bond formation (i.e. the X----Y bond in the TS is long). This means that the interplay of other effects generally provides a small impact on the reaction profile and they are normally observed on narrow classes of substrates with specific substitution patterns.[36]

Steric effects have been observed in XAT reactions and were employed to rationalize the increased rate for abstraction on *ortho*-substituted aryl halides by both aryl and alkyl radicals.[39] As an example, while Ph–I and 1- and 2-I-naphthalenes are electronically very similar, there is a noticeable acceleration for XAT with Ph• in the case of 1-I-naphthalene which was explained on the basis of a favourable release of steric strain upon iodine abstraction (Scheme 9A).[38] A similar trend in reactivity was determined in the reaction between aryl bromides and Bu_3Sn• where highly hindered derivatives also displayed increased reactivity despite being more electron-rich (Scheme 9B).[42]

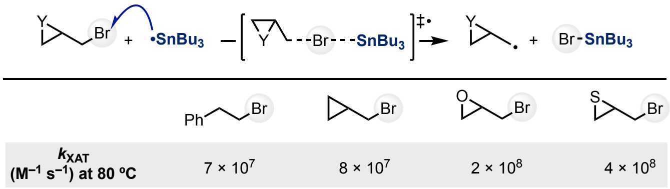
Scheme 9.[a] XAT Rate Constants Depending on: (A) Nature of the Aryl Iodide and (B) *ortho* Substitution Pattern of Aryl Bromides.



[a] The rate constants for XAT (k_{XAT}) have been approximated to the near integral number.

Hyperconjugative assistance was observed in XAT between α-cyclopropyl-, α-oxirane-and α-thiirane alkyl bromides and $Bu_3Sn•$. These substrates display slight acceleration when compared to the XAT of standard primary alkyl bromides and this effect was explained on the basis of a synchronous C–C/O/S bond β-scission of the neighbouring 3-membered ring substituent (Scheme 10).[43]

Scheme 10.[a] Modulation of XAT Rate Constants due to Hyperconjugative Effects

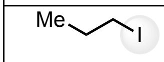
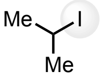
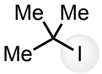
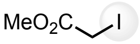
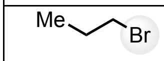
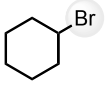
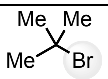
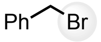
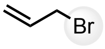
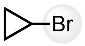
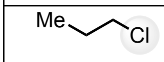
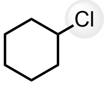
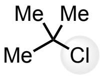
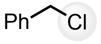
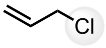


[a] The rate constants for XAT (k_{XAT}) have been approximated to the near integral number.

Scheme 10.

Rate Constants. The development of synthetic strategies based on XAT processes has been largely impacted by understanding the factors which govern this radical reactivity.[44] Fundamental work from Ingold,[45-47] Danen,[31,32,38,39,48], Lorand,[49] Scaiano,[50] Lusztyk,[23] Newcomb,[24] Curran,[25,36] Chatgilialoglu,[51,52] Giese,[53] Crich[42] and Galli[26] has provided extensive knowledge in this respect and many absolute rate constants have been determined. While a detailed discussion of these mechanistic experiments is beyond the scope of the review, a summary of the rate constants for commonly used XAT reagents and alkyl/aryl halides is presented in Table 2.

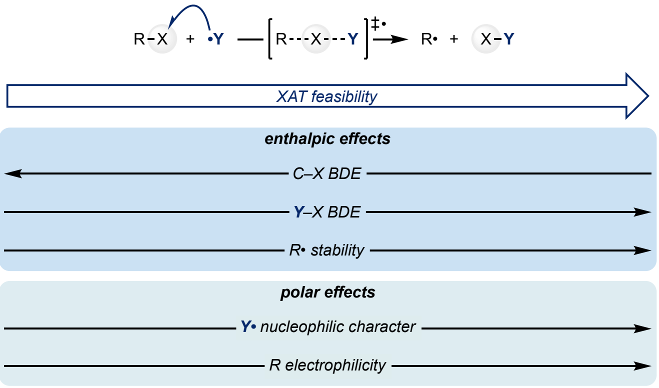
Table 2.[a] **Experimental Rate Constants for XAT Reactions (all rates are in $M^{-1}\ s^{-1}$)**

Substrate	$Bu_3Sn\bullet$	$Et_3Si\bullet$	$(Me_3Si)_3Si\bullet$		
Me–I	4×10^9	8×10^9			
		4×10^9			3×10^5
		1×10^{10}	4×10^9	4×10^8	9×10^5
					3×10^6
					1×10^7
Ph–I		1×10^9			
	3×10^7	5×10^8	2×10^7	$< 10^5$	1×10^3
	2×10^7			$< 10^5$	1×10^3
	1×10^8	1×10^9	2×10^7	$< 10^5$	5×10^3
	1×10^9	2×10^9	$> 10^9$		
		1×10^9			
		3×10^8			
Ph–Br		1×10^8			
Br_3C–Br				3×10^9	
		3×10^5			
	2×10^3				
	1×10^4	3×10^6	5×10^5		6×10^2
	1×10^6	2×10^7	5×10^6		
		2×10^6			
Ph–Cl	1×10^4	2×10^7			
Cl_3C–Cl		5×10^9	4×10^8	2×10^8	

[a] The rate constants for XAT (k_{XAT}) have been approximated to the near integral number.

Summary of Mechanistic Aspects on XAT reactivity. Scheme 11 summarizes the most important effects participating in controlling the outcome of XAT reactions. *Enthalpic effects:* XAT exothermicity increases the more (a) the C–halogen bond is weak; (b) the resulting Y–halogen bond is strong and (c) the R• is a stable radical. *Polar effects:* XAT is kinetically accelerated the more (a) Y• is a nucleophilic radical and (b) R–X is electron-poor.

Scheme 11. Key Aspects Affecting XAT Reactivity.



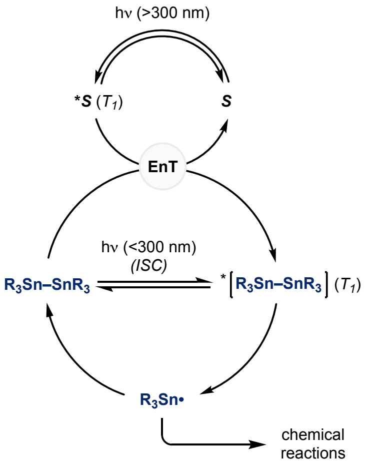
3. APPLICATIONS OF XAT REACTIVITY IN SYNTHETIC PHOTOCATALYSIS

3.1. Heteroatom-Based XAT Reagents

3.1.1. Tin Radicals

The use of organotin reagents for the conversion of alkyl/aryl halides into the corresponding radicals has had a fundamental impact on synthetic radical chemistry since its introduction by Menapace in 1963.[54,55] The vast majority of tin radical chemistry is performed using trialkyl/triaryl tin hydrides through the thermal decomposition of AIBN (azo(bis)isobutyronitrile) as the initiation mechanism.[56,57] Photochemical activation has mostly been applied to engage ditin reagents as they undergo efficient Sn–Sn σ-bond homolysis.[58] Upon irradiation with a suitable wavelength (usually high-energy light – e.g. Ph_6Sn_2: $\lambda_{\max} = 276$ nm), these species populate a long-lived triplet excited state[58,59] from which Sn–Sn bond cleavage takes place (Scheme 12). The resulting tin radicals can either recombine or engage in secondary photochemical reactions like XAT with organic halides. The use of longer wavelength light is also possible if an appropriate photosensitizer (*S*) (e.g. acetophenone derivatives) is present to trigger Dexter energy transfer (EnT) (triplet sensitization)[60] or S_H2 reactions (e.g. acetone).[61]

Scheme 12. Pathways for the Photochemical Generation of Tin Radicals from Ditin Species.

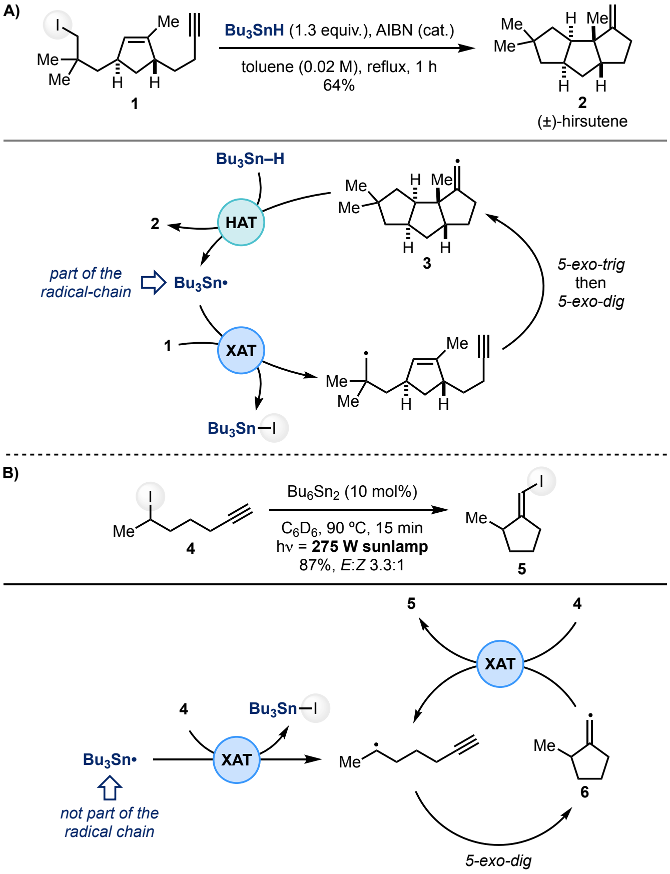


The utilization of ditin compounds in synthetic chemistry has proved advantageous as they do not contain a weak Sn–H bond (e.g. Sn–H BDE for Bu_3SnH is 78 kcal mol^{-1})[21] and therefore minimise unwanted radical hydrogenation reactions which are a common drawback of tin/silicon hydride chemistry. This has facilitated the development of cascade processes based on radical generation followed by intra- as well as intermolecular processes[62] and free radical polymerization (FRP).[63]

Application in Radical Cyclizations. The ditin compounds $(Me_3Sn)_2$ and $(Bu_3Sn)_2$ have been extensively applied to achieve cyclization of alkyl halides as they avoid direct radical reduction.[64] The possibility of straying away from HAT as a product-forming step has been fundamental for the development of cyclization-halogenation processes, which are commonly referred to as atom-transfer radical cyclisation reactions, ATRCs.

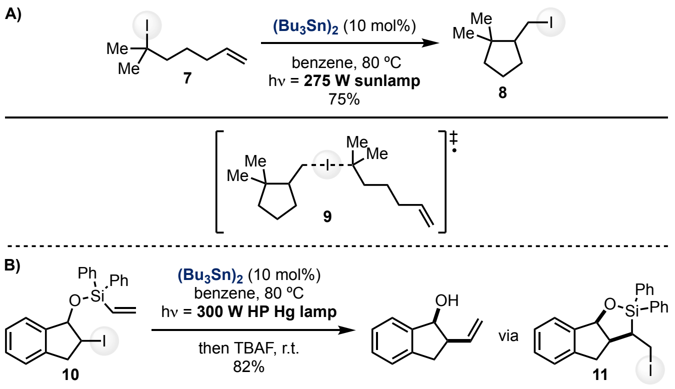
A powerful example showcasing the utility of these processes is the total synthesis of (±)-hirsutene by Curran, where a Bu_3SnH-mediated XAT → *5-exo-trig* → *5-exo-dig* cascade was used to convert iodide **1** into **2** (Scheme 13A).[5,65] This synthesis exemplifies a class of radical processes that are terminated by a HAT step between a vinyl radical (e.g. **3**) and the tin hydride, which is a mechanistic requirement to regenerate the chain carrier $Bu_3Sn\bullet$. Following the pioneering work of Brace,[66] Curran later demonstrated that by using $(Bu_3Sn)_2$ under photochemical conditions (275 W sunlamp) the I-atom present in the starting material **4** could be incorporated into the product of the XAT → *5-exo-dig* cascade leading to **5** (Scheme 13B).[64] This development was one of the first examples of ATRC processes and represented a breakthrough in the field as it validated XAT between two organic fragments (i.e. $R–I + R^1\bullet \rightarrow R\bullet + R^1–I$) as the terminal chemical step delivering the product in similar cascade reactions. An additional mechanistic difference to classical radical cyclization-reduction processes is that $Bu_3Sn\bullet$ initiates the process but is not involved in the radical chain propagation, which is therefore sustained by halogen-transfer between two carbon-based species.[67] Hence, the intermediacy of a vinyl radical (e.g **6**) is crucial for the success of this approach as it makes the chain-carrying XAT step fast and irreversible. Indeed, kinetic studies demonstrated that iodine abstraction between vinyl radicals and alkyl iodides approaches the diffusion control limit ($k_{XAT} \geq 10^9$ M^{-1} s^{-1} at 80 °C),[68] and can therefore outcompete any unwanted HAT process (e.g. from the solvent).

Scheme 13. (A) Tin-Mediated Thermal Reductive Cascade Radical Cyclisations in Curran's Total Synthesis of Hirsutene (B) Photochemical Atom Transfer Radical Cyclisation of Hexynyl Iodides.



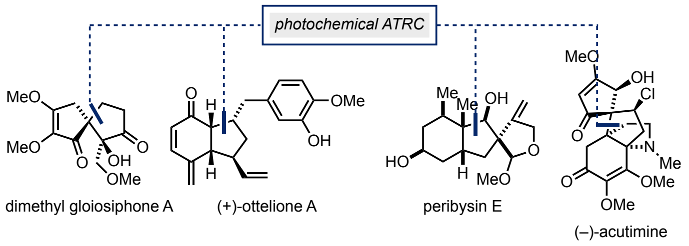
The behaviour of 5-iodohexene derivatives (e.g. **7**) is dramatically different to the one of 5-iodo-hexynes (e.g. **4**, Scheme 13B) as in the former case the chain-carrying XAT involves I-transfer between two alkyl fragments. These types of abstractions are significantly slower ($k_{XAT} \sim 10^5$ M^{-1} s^{-1} at 60 ºC), potentially reversible and therefore there is a requirement for the radical generated upon cyclization to be less stable than the starting one.[69] This is exemplified by the efficient conversion of **7** into **8** where the I-atom is transferred from a tertiary alkyl iodide to a less stable primary radical (via TS **9**) (Scheme 14A). These processes are sluggish using Bu_3SnH under thermal conditions but become synthetically useful when 10 mol% $(Bu_3Sn)_2$ is used under sunlamp irradiation as these conditions minimise the facile reduction of **7** (HAT from Bu_3SnH) that would outcompete a slower XAT.[64] A similar reactivity was also observed with diphenylvinylsilyl protected α-iodo-alcohols **10** that gave, upon treatment with TBAF, products of overall α-vinylation via the diphenyl-1,2-oxasilolane intermediates **11** (Scheme 14B).[70]

Scheme 14. (A) Tin-Mediated ATRC of Hexenyl Iodides (B) Application of ATRC to Ethynylation of α-Iodosilylethers.



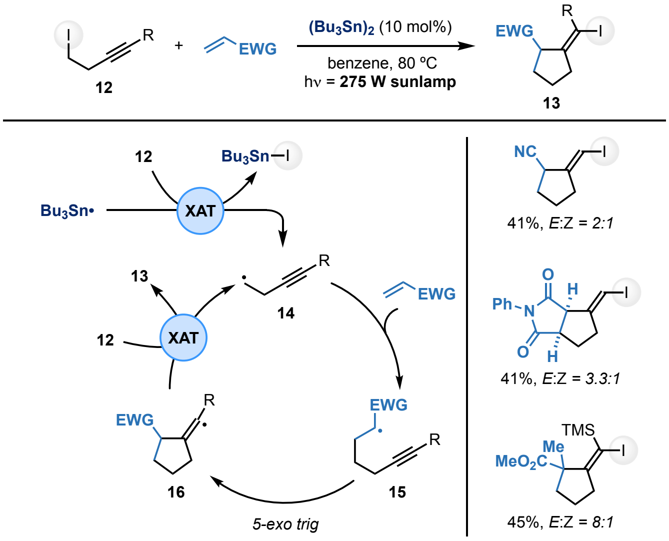
The versatility of ATRC reactivity via the photochemical activation of ditin reagents has been frequently applied in total synthesis. A detailed discussion of these synthetic efforts is beyond the scope of this review so the key targets and their corresponding bond disconnections based on ATRC are illustrated in Scheme 15.[71-76] It is worth noting that in each case, the ATRC was followed by the reduction of the iodide product with Bu_3SnH, as this two-step procedure gives higher yields than attempting a one-step cyclisation-reduction with Bu_3SnH, because of the formation of large amounts of direct reduction products in the latter case.

Scheme 15. Examples of Natural Products Prepared Using Photochemical Tin-Mediated ATRC Reactions.



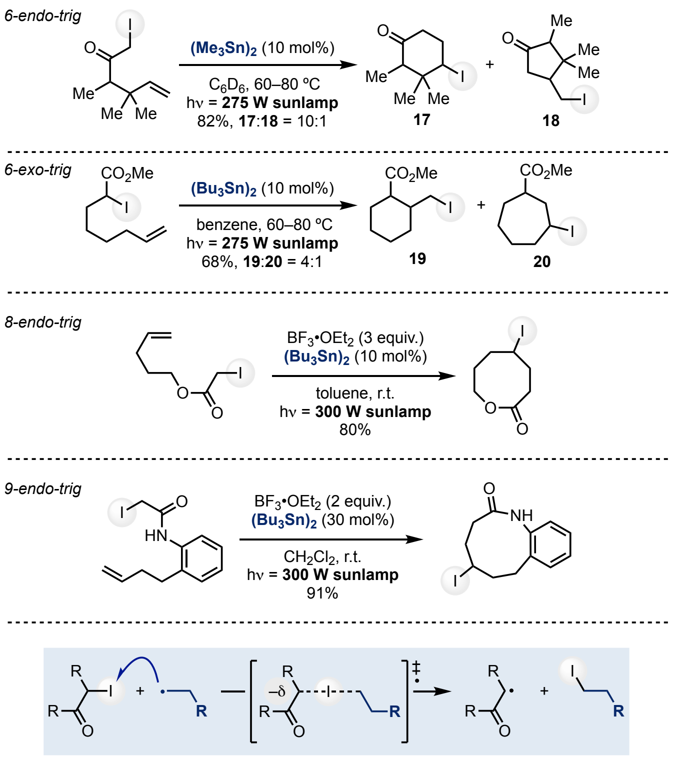
The absence of a HAT termination channel in XAT-based photochemical reactions using $(Bu_3Sn)_2$ enabled Curran to develop multicomponent processes between butynyl iodides **12** and several Giese acceptors to give functionalised (methylene)cyclopentanes **13** (Scheme 16).[77] These processes are initiated by XAT from $Bu_3Sn•$, and the ensuing primary homopropargylic radical **14** undergoes Giese addition to the electron-deficient olefin (**14** → **15**) followed by ATRC-type reactivity (**15** → **16** → **13**). There are two aspects relevant to this process: (i) the radical resulting from the Giese addition (**15**) is moderately electrophilic (α-EWG) and therefore it does not display appropriate philicity to undergo XAT with **12**. This effectively suppresses unwanted α-EWG iodination. (ii) The activated nature of the vinyl radical **16** towards XAT minimises competing HAT or Giese reactions, which could lead to reduction or oligomerization respectively. Overall, this strategy provides a solution to obtain products of formal [3+2] cycloaddition in good-to-moderate yields as a mixture of *5-exo-dig* (major – in various *E*:*Z* ratio depending on the acceptor) and *6-endo-dig* (minor) products.

Scheme 16. Tin-Mediated Cascade Giese/ATRC Reaction for the Synthesis of Vinyl Iodides.



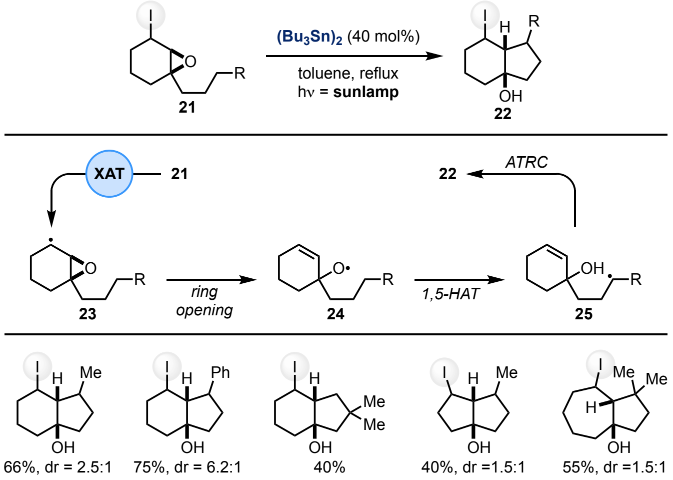
During fundamental studies on *5-exo-trig* ATRC reactions, Curran assessed both thermal and photolytic activation modes concluding that "*the photolytic initiation method with ditin was so rapid and effective relative to the other methods that it was adopted as the standard procedure*".[78] It is also worth noting that, although tin hydrides can be employed to achieve radical cyclisations, high dilution conditions (0.02 M) are usually required to avoid premature termination via HAT, while ditin compounds can be used in concentrated media (0.3 M) which makes them more practical. This has been pivotal to successfully extend ATRC chemistry to cyclisation reactions that are slower than the *5-exo-trig/dig*[79-84] like *6-endo-trig*,[85] *6-exo-trig*, *7-endo-trig*,[78,86] *7-exo-trig*, *8-endo-trig*[87,88] and *9-endo-trig*[89] (Scheme 17). These processes usually exploit the reactivity of α-halocarbonyls as starting materials for three main reasons: (i) they are excellent halogen-atom donors due to their synergistic weak sp^3 C–X bond and their ability to stabilise an incoming negative character in the XAT TS; (ii) the carbonyl group provides a conformational bias towards the cyclization and (iii) they are readily available/accessible. Overall, the development of these processes has had a major impact not only in radical chemistry but in synthesis as a whole given the difficulties in the assembly of large cyclic systems. While the key mechanistic features around XAT reactivity are analogous to the example we have presented before, a discussion of the aspects controlling these radical cyclisations is beyond the aim of this review and the reader is referred to excellent resources in the literature.[90,91]

Scheme 17. Photochemical Tin-Mediated Atom Transfer Radical Cyclisations of Alkyl Iodides.



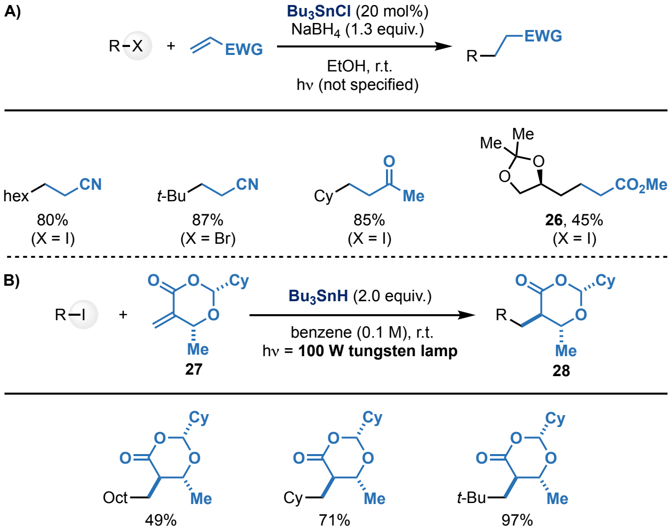
α-Iodo-epoxides **21** have been shown to be precursors to bicyclic cyclopentanols **22** through a photochemical, ditin mediated ATRC cascade reaction (Scheme 18).[92] While the ATRC reactivity is identical to the one illustrated above, these class of substrates do not contain an olefin and the I-atom seems not to move during the process. Here, the initial tin radical-mediated XAT on **21** was used to generate an α-epoxy-radical **22** that underwent fast ring-opening to **23**. This step revealed the olefin for radical cyclization and also provided an electrophilic *O*-radical that transposed via 1,5-HAT onto the tethered alkyl chain. The resulting carbon radical **24** cyclized as part of the ATRC process delivering [5,5]-, [6,5]- and [7,5]-fused bicyclic iodides in moderate to good yields.

Scheme 18. Tin-Mediated Photochemical Rearrangement of α-Iodo-epoxides.



Intermolecular C–C bond formation. One of the first applications of photochemistry to explore the reactivity of tin radicals in synthetic chemistry has been introduced by Corey in 1975 for the dehalogenation of alkyl halides (see Section 3.1.4, Scheme 63).[93] As we will discuss below, a sub-stoichiometric amount of Bu_3SnH was used with an excess of $NaBH_4$ used to regenerate the hydride. This "catalytic in tin" approach has also been applied to achieve intermolecular alkylation of alkyl iodides with Giese acceptors (Scheme 19A).[1,94] Primary and secondary alkyl iodides and tertiary alkyl bromides were successfully engaged in this reactivity, which was also used to access **26** as part of the total synthesis of (–)-malyngolide.[95,96] Utilization of *cis*-substituted methylidenedioxane acceptor **27** enabled the diastereoselective preparation of *anti*-β-hydroxyester derivatives **28** (Scheme 19B).[97]

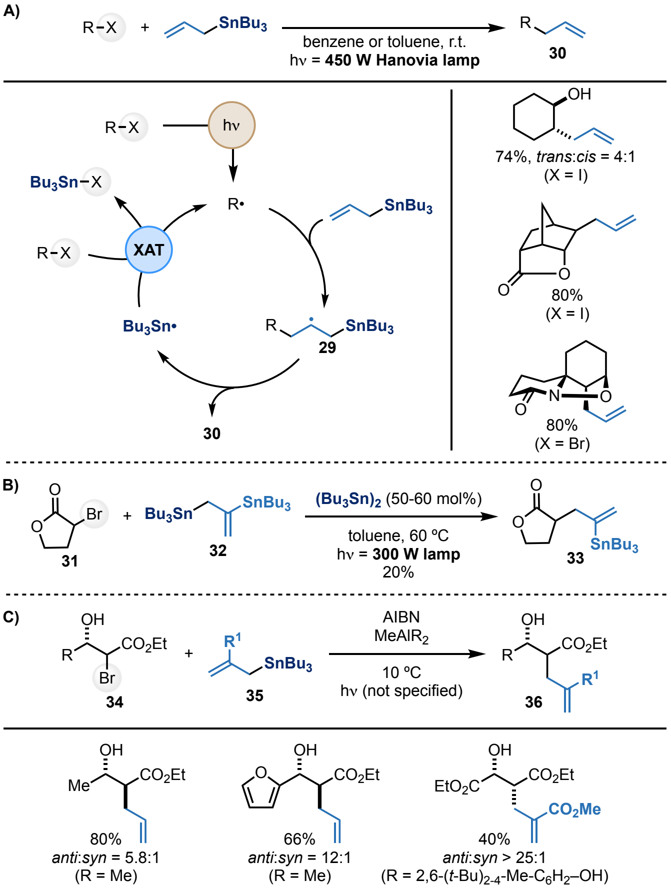
Scheme 19. (A) "Catalytic in Tin" Photochemical Giese Reaction of Alkyl Halides (B) Diastereoselective Photochemical Giese Reaction of Alkyl Iodides.



Allyltributylstannane is a useful reagent for the allylation of alkyl halides under UV light irradiation (450W Hanovia lamp equipped with a Pyrex filter) as demonstrated by Keck (Scheme 20A).[98] In these examples, photochemical C–halogen bond homolysis was used as the initiation to generate the corresponding alkyl radical (R•) and start a radical-chain propagation based on the formation of **29** and its following β-scission. This step generated the allylated product **30**, along with the chain carrier Bu_3Sn•. This method showcased the high chemoselectivity offered by XAT chemistry, as free alcohol, lactone, epoxide and polycyclic *N*-oxylactam were allylated in good yields. Alkyl iodides and bromides as well as activated alkyl chlorides were also successfully engaged using this protocol.

This chemistry has also been extended to the use of a distannylated reagent **32** that, under irradiation in the presence of $(Bu_3Sn)_2$, provided the Bu_3Sn-substituted allyl derivatives **33** from activated α-bromo-carbonyls **31** (Scheme 20B).[99] α-Bromo-β-hydroxyesters **34** have also been used in related settings to access valuable α-allyl-β-hydroxyesters **36** with high diastereoselectivty depending on the substitution pattern of the allyl-tin reagent **35** (Scheme 20C).[100] In these examples, irradiation in the presence of AIBN and a Lewis acid was used to generate the β-aluminium hydroxide radicals for chain allylation with the tin reagent. This strategy was also extended to iodohydrins.[101]

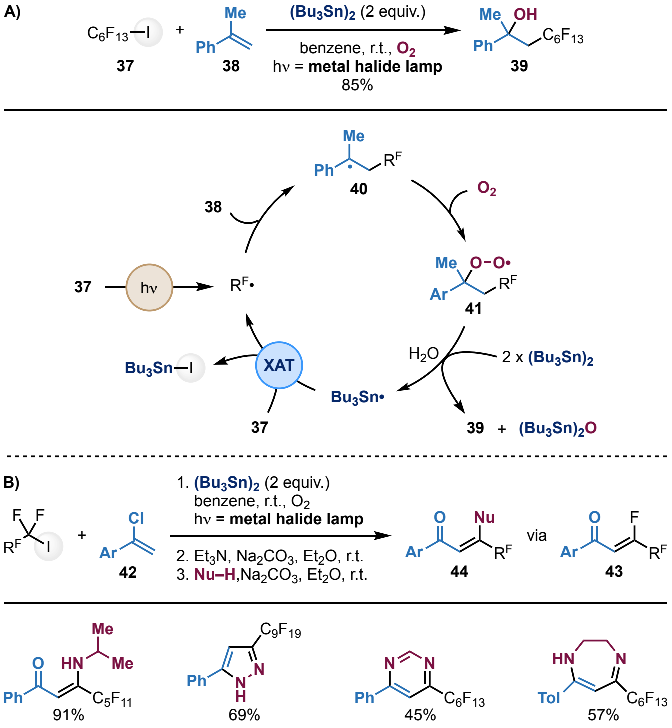
Scheme 20. (A) Allylation of Alkyl Halides with Allyltributylstannane (B) Tin-Mediated synthesis of Tributyl(vinyl)stannane (C) Diastereoselective Allylation of α-Hydroxyesters.



Perfluoroalkyl iodides are an activated class of halides for both photochemical sp^3 C–I bond homolysis and XAT by Bu$_3$Sn•. Furthermore, the high electrophilicity of the resulting perfluoroalkyl radical makes them powerful reagents for atom transfer radical addition (ATRA) reactivity with olefins.[102-104] Yoshida and Iyoda demonstrated that ATRA can be avoided if these species (e.g **37**) are reacted with styrenes (e.g. **38**) in the presence of (Bu$_3$Sn)$_2$ and oxygen under high-energy light irradiation (Scheme 21A).[105,106] These photochemical conditions enable olefin perfluoro-hydroxylation in generally good yield (e.g. **39**). The mechanism is based on a radical-chain propagation where the perfluoroalkyl radical (R^F•) adds onto the styrene to deliver a stabilised benzylic radical **40** which is sluggish at XAT reactions but can be readily oxidised to the peroxide radical **41**. The reaction of **41** with (Bu$_3$Sn)$_2$ was proposed to generate the chain-carrying Bu$_3$Sn• and the product **39**. Bu$_3$SnH was also assessed under similar conditions but resulted in the direct reduction of **37**, which again underscores the benefit that ditin reagents offer when HAT processes need to be avoided.

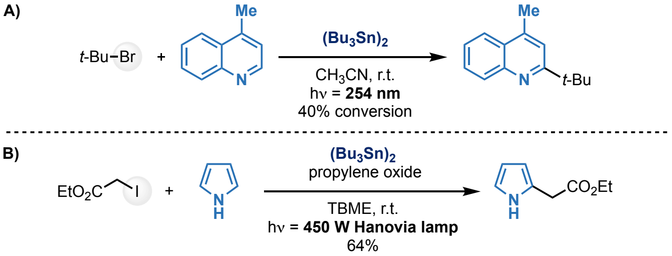
Under the same mechanistic framework, the use of α-chlorostyrenes acceptors **42**, followed by basic treatment, was then shown to deliver β-fluoro-enones **43** that can easily be diversified upon nucleophilic addition to provide different acyclic and aromatic derivatives **44** (Scheme 21B).[107,108]

Scheme 21. (A) Tin-Mediated Perfluoroalkylhydroxylation of Styrene Derivatives (B) Tin-Mediated Reaction of α-Chlorostyrene with Perfluoroalkyl Iodides.



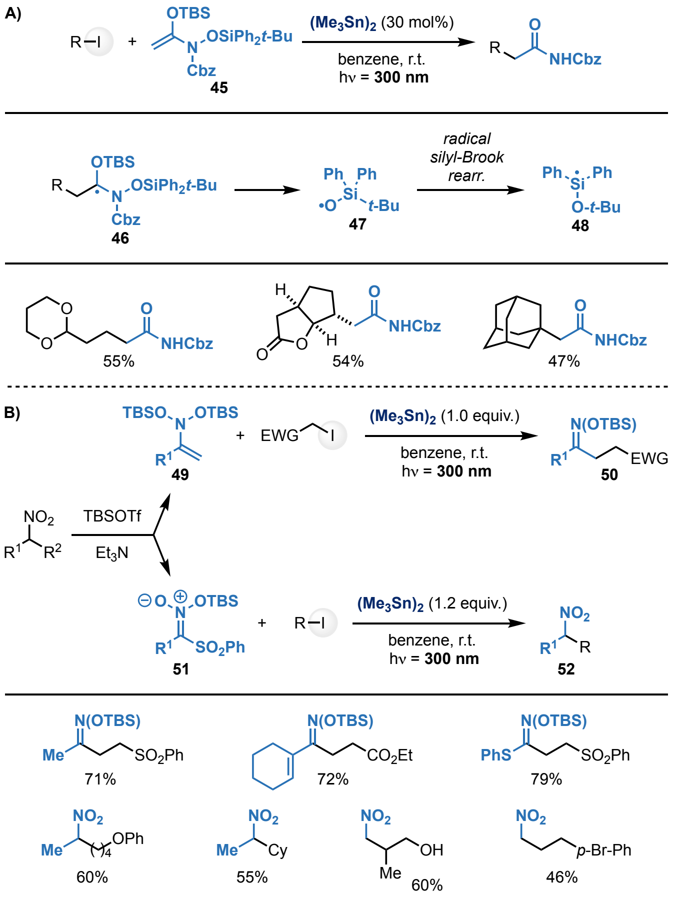
The use of tin radical chemistry for the addition of organic halides to aromatic acceptors under photochemical conditions has been significantly less established compared to other methods based on other XAT reagents (see below) or SET activation.[109-113] So far, this reactivity has been demonstrated using $(Bu_3Sn)_2$ and high-energy light irradiation on lepidine by Minisci (Scheme 22A)[114] and pyrrole by Byers (Scheme 22B)[115] in moderate and good yield respectively. The reaction with electron-rich pyrrole required the use of an electrophilic α-ester radical and propylene oxide as the additive to trap HI in order to prevent the accumulation of I_2, which is a known chain suppressant.[116]

Scheme 22. (A) Photochemical Minisci Reaction of *tert*-Butyl Bromide with Lepidine (B) Photochemical Tin-Mediated Alkylation of Pyrrole.



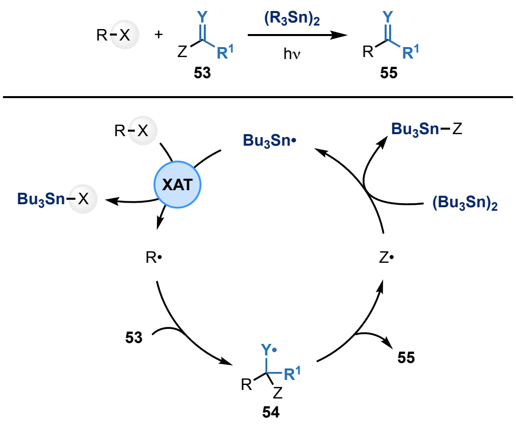
A more synthetically successful application of tin radical-mediated XAT in photochemistry has been the addition of alkyl halides to activated π-acceptors using $(Me_3Sn)_2$ under high-energy light irradiation (Scheme 23). Ketene *N*,*O*-acetals **45** have been employed as radical acceptors to achieve the formal α-alkylation of amides which can be challenging via enolate chemistry especially with tertiary electrophiles (Scheme 23A).[117] In this case the exact mechanistic pathway followed by the process is difficult to ascertain due to the likely generation of the silicon radical $Ph_2(O\textit{t}\text{-}Bu)Si•$ (**48**) upon addition of the alkyl radical to **45**, followed by N–O bond fragmentation and radical silyl-Brook rearrangement (**46** → **47** → **48**), which can act as XAT agent along $Me_3Sn•$.[118] Primary, secondary and tertiary alkyl iodides were suitable substrates under these photochemical conditions while α-EWG alkyl bromides required thermal activation (80°C, AIBN). Nitroalkanes proved to be versatile starting materials upon enolization (TBSOTf, Et_3N) depending on their substitution pattern (Scheme 23B). α-Me derivatives underwent efficient conversion into bis(silyloxy)enamines **49** which were used as acceptors for the synthesis of oxime ethers **50**.[119] In this case, the electron-rich nature of **49** meant that electron-poor alkyl iodides (e.g. α-iodo-carbonyls) were required. The oxime ethers were obtained as a mixture of *E* and *Z* isomers and could be hydrolysed to the corresponding ketones under acidic conditions. In the case of α-SO_2Ph derivatives, OTBS-nitronates **51** were formed and reacted with nucleophilic radicals, to give, upon β-fission and acidic work-up, products **52** of overall α-NO_2 alkylation.[120] Primary, secondary, tertiary (not shown here) and benzyl iodides reacted smoothly.

Scheme 23. (A) Tin-Mediated Alkylation of Ketenes *N*,*O*-acetals (B) Tin-Mediated Reactions of Alkyl Iodides with Nitroalkanes Derivatives.



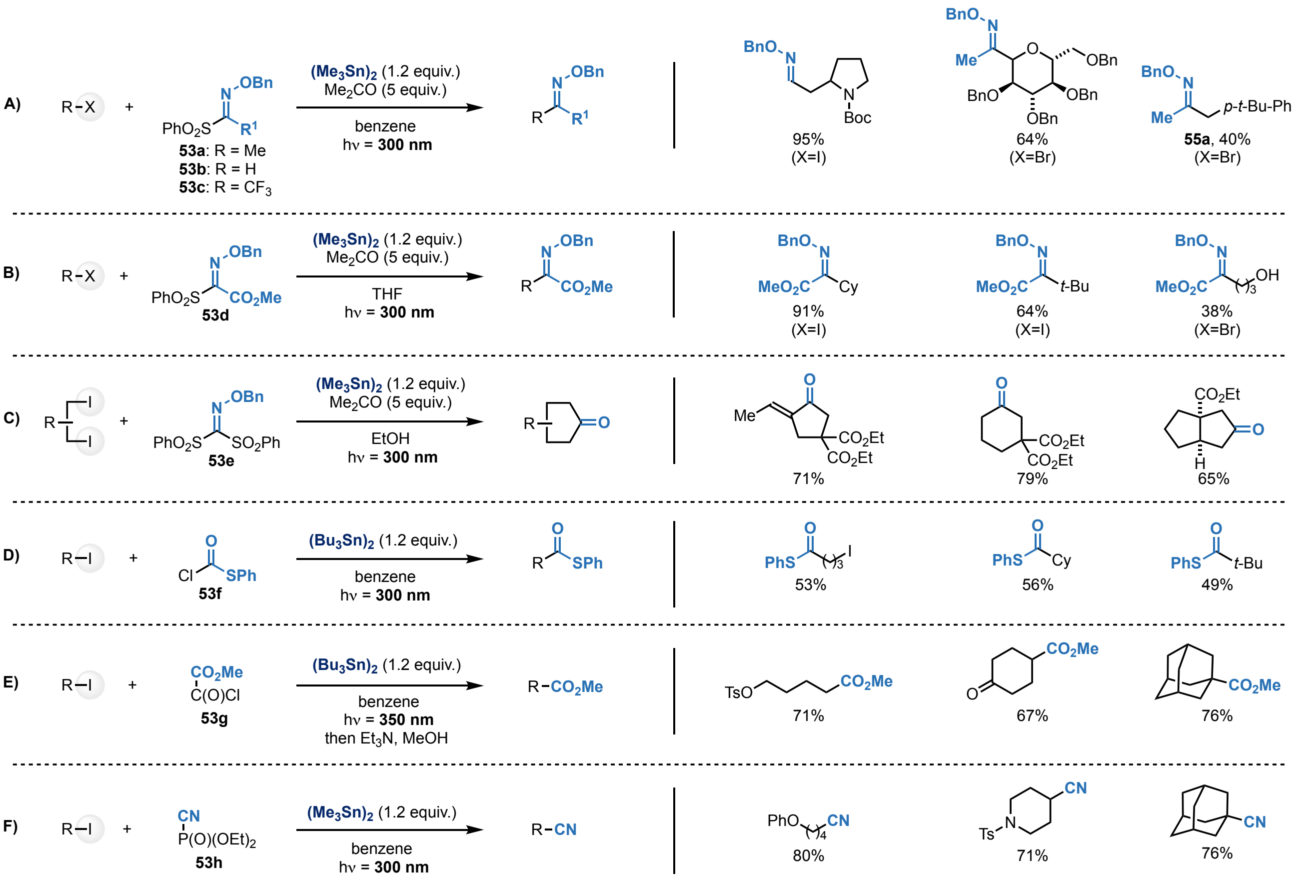
Other activated carbonyl acceptors have been successfully employed in related photochemical strategies. In general, all these reactions require similar conditions involving ditin reagents: high-energy light irradiation and carbonyl/imine acceptors **53** containing a good leaving group (Z) (Scheme 24). These derivatives ensure fast addition using nucleophilic radicals and the resulting heteroatom-radical **54** (Y is an *O*- or more generally *N*-based group) intermediate undergoes a β-scission extruding Z• which re-generates the carbonyl/imine functionality in the product **55**. The nature of the Z group is crucial for radical fragmentation and also to ensure chain propagation. Indeed, these species are generally good atom/group transfer agents (e.g. PhO_2S•) and can react with the ditin species to generate the required tin radical for following XAT.

Scheme 24. Mechanism of XAT-Mediated Carbonylation of Alkyl Halides.



For simplicity, the details of these reactions are illustrated in Scheme 25 and discussed below, while examples demonstrating application in cascade and intramolecular processes are presented in Scheme 26–28.

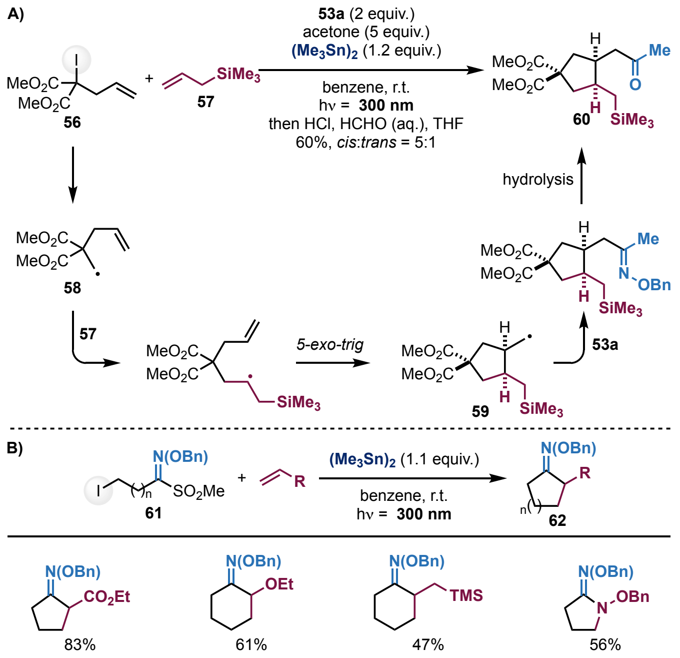
Scheme 25. Tin-Mediated Reactions of Alkyl Halides with (A) Phenylsulfonyl oxime ethers (B) Phenylsulfonyl Methoxycarbonyl Oxime Ethers (C) Bis-Sulfonyl Oxime Ethers (D) S-Phenyl Thiochloroformate (E) Methyl Oxalyl Chloride (F) Diethyl Cyanophosphonates.



Phenylsulfonyl oxime ethers **53a–c** are highly activated carbonyl species, which can undergo radical addition/fragmentation sequence. Radicals generated by XAT on alkyl iodides and bromides using Me_3Sn• (generated by EnT using acetone as the triplet sensitizer), were reacted with these radical acceptors to yield the corresponding alkylated *O*-benzyl oximes ethers (Scheme 25A).[121] The reaction was amenable to primary, secondary and tertiary alkyl iodides and bromides. Substrates leading to stabilized radicals (i.e. benzylic radical, leading to **55a**) can be challenging to engage in radical addition reactions but delivered the corresponding products, albeit in lower yields, owing to the excellent leaving group ability of the SO_2Ph group.[122] The use of trifluoromethyl phenylsulfonyl oxime ether **53c** was successfully used to obtain α-trifluoromethyloxime ethers, which were further diversified into highly sought-after α-CF_3-amines or trifluomethylketones (Scheme 24A).[123]

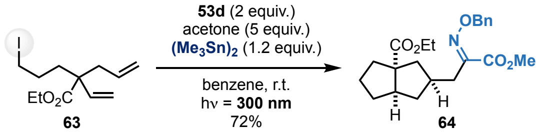
This methodology was later extended to cascade reactions involving XAT → cyclisation → carbonylation sequences, as well as the 3-component processes using homo-allylic iodide **56**, **53a** and allyltrimethylsilylane **57** (Scheme 26A).[121] In this case upon Me_3Sn• mediated XAT, the electrophilic malonyl radical **58** underwent a polarity matched addition to the electron-rich olefin **57**. This step was followed by a fast *5-exo-trig* cyclization and the resulting nucleophilic primary radical **59** was trapped by **53a**. This sequence of steps yielded an oxime ether, which was hydrolyzed to ketone **60**. Furthermore, formal [3+2] or [4+2] cycloadditions between sulfonyloxime-containing short-chain alkyl iodides **61** and various electron-rich olefins (e.g. enol ethers and enamides) were developed to access cyclic products **62** (Scheme 26B).[124-126]

Scheme 26. (A) Photosensitized Three-Components Reactions of α-Iodomalonates (B) Cascade Addition across Olefins/Cyclisation/Carbonylation Reaction for the Synthesis of Cyclic Benzyl Oximes



Shortly after, Kim reported a similar strategy for the synthesis of α-ketoesters through addition onto phenylsulfonyl methoxycarbonyl oxime ether **53d** (Scheme 25B).[127,128] Consistently with their previous developments, primary, secondary and tertiary alkyl iodides, including allylic and benzylic iodides, were successfully converted into the corresponding α-ketoesters under similar photochemical conditions. Alkyl bromides were also suitable substrates albeit in lower yield. The methodology was extended to the di-olefin containing iodide **63**, which underwent an efficient radical cascade involving two sequential *5-exo-trig* cyclizations resulting in the bicycle **64** in good yield and as a single diastereomer (Scheme 27).[127]

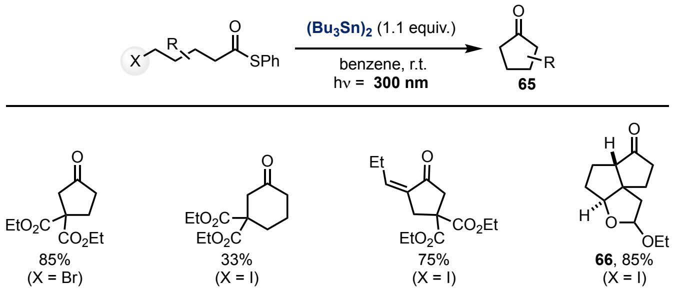
Scheme 27. Tin-Mediated Cascade Reaction of Di-olefin Containing Alkyl Iodide for the Assembly of 5,5-Fused Bicyclic Benzyl Oximes



When the bis-sulfonyl oxime ether **53e** was used, symmetrical and unsymmetrical ketones were obtained after hydrolysis (Scheme 25C).[129] Primary and secondary alkyl iodides and bromides, aryl iodides, as well as iodomethane were successfully engaged in this reactivity. 5- As well as 6-membered ring cyclic ketones were obtained when substrates bearing two iodine atoms were employed. In line with previous examples, cascade reactions of di-iodo-alkanes with a pendant allyl unit delivered bicyclic ketones.

In the quest for novel and structurally simpler reagents for radical carbonylation, the same authors also developed an alternative strategy utilizing S-phenyl thiochloroformate **53f** as CO surrogate (Scheme 25D).[130] During the screening of potential carbonyl donors, it was found that the reaction yield correlated with the LUMO level of the donor, with **53f** being the best partner. Exposure to conditions similar to the one used for the oxime reagents **53a**–**e**, enabled the reaction of alkyl iodides to furnish the corresponding S-phenyl thioates. This reactivity has also been translated to intramolecular settings thus providing a fast entry into a range of 5- and 6-membered cyclic ketones **65** in high yield (Scheme 28).[131] In addition, tandem *5-exo-trig*/carbonylation allows for the rapid assembly of complex tricyclic systems (e.g. **66**) in high yields.

Scheme 28. Tin-Mediated Radical Cyclisation of Halide-Containing S-Phenyl Thioesters.



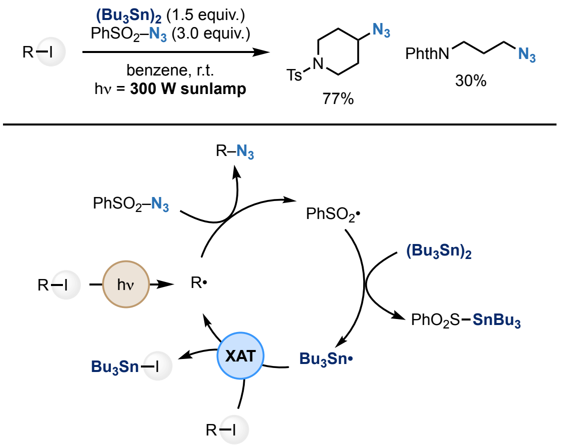
Methyl oxalyl chloride **53g** was identified as a powerful radical trap for XAT-mediated carboxymethylation of alkyl iodides (Scheme 25E). In these examples, the ester functionality in the products was formed through radical addition across the acyl chloride (major pathway) or the methyl ester (minor pathway) functionality of **53g** (followed by treatment with Et_3N in MeOH to give methyl ester products). Using 350 nm light in the presence of a stoichiometric amount of $(Me_3Sn)_2$, primary, secondary and tertiary alkyl iodides were converted into the corresponding methyl esters in good yields.[132]

Alkyl iodides can also be converted into nitriles using a similar strategy utilising diethylphosphoryl cyanide **53h** as the radical acceptor (Scheme 25F).[133] In this case, the addition of the C-radicals onto the CN group gives an iminyl radical that upon β-fragmentation across the weak C–P bond generates the nitrile product. In spite of the putative ability of the phosphoryl radicals to act as XAT reagents and activate directly the alkyl iodides,[134] a large excess of Me_6Sn_2 was used in this procedure. Primary, secondary and tertiary alkyl iodides were all efficiently functionalised but the methodology was not found compatible for the utilisation of stabilised benzylic or electrophilic α-SO_2 radicals. This cyanation method was also demonstrated in cascade settings on iodides with tethered olefins after *5-exo-trig* cyclization.

Carbon-Heteroatom Bond Formations. The ability of ditin reagent-based photochemical strategies to avoid premature HAT reduction of the generated C-radical has also facilitated the development of radical strategies for C-heteroatom bond formation.

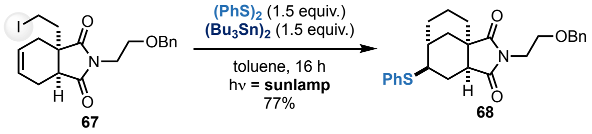
Sulfonyl azides are powerful group-transfer reagents for C–N bond assembly as identified by Renaud[135,136] who developed thermal and photochemical protocols using primary and secondary alkyl iodides.[137,138] While conditions using $(Bu_3Sn)_2$ under irradiation (300W sunlamp) led to a useful amount of products (Scheme 29), improved yields were generally obtained under thermal conditions. The authors proposed that photochemical homolysis of the sp^3 C–I bond provided the C-radical for subsequent group transfer azidation. The resulting sulfonyl radical was proposed to generate the chain carrying Bu_3Sn• via addition/fragmentation sequence with $(Bu_3Sn)_2$.[138]

Scheme 29. Tin-Mediated Radical Azidation of Alkyl Iodides.



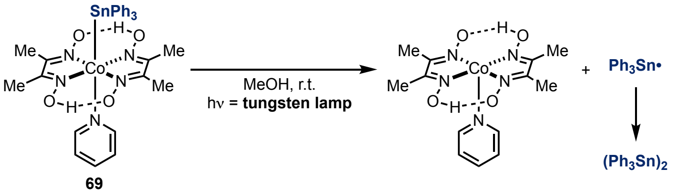
Photoinitiated tin-mediated halogen-atom transfer was exploited for the assembly of C–S bonds in the total synthesis of concavine (Scheme 30).[139] The alkyl iodide **67** was by XAT from Bn_3Sn•, and the resulting radical underwent *5-exo-trig* cyclization followed by reaction with PhSSPh to generate the corresponding phenylsulfide **68** that was further derivatised into the natural product.

Scheme 30. Radical *6-exo-trig* Cyclisation/C–S Bond Formation.



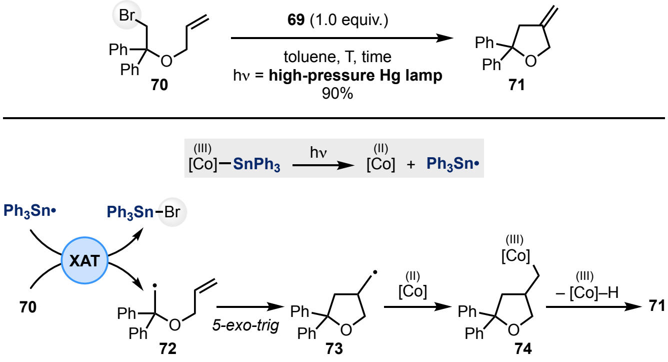
Radical Olefinations. The photochemical generation of tin radicals for application in XAT reactivity is not restricted to tin hydrides and ditin reagents and it has also been exploited using [Co]–SnR_3 systems. This line of work has been pioneered by Schrauzer and Kratel who prepared the cobaloxime Ph_3Sn–$Co(dmgH)_2Py$ (dmg = dimethylglyoxymato) **69** and investigated its photolysis in MeOH.[140] This species, upon irradiation, undergoes Co–Sn bond homolysis to give a stable Co(II) species and Ph_3Sn• that readily dimerized to $(Ph_3Sn)_2$ (Scheme 31).

Scheme 31. Photochemical Reactivity of Cobaloximes with a $SnPh_3$ Ligand.



Cobaloximes have been intensively studied as model systems for vitamin B12.[141] In particular, alkyl radicals have been demonstrated to trap [Co(II)] species at diffusion-controlled rates thus leading to alkyl–[Co(III)] complexes that undergo facile β-hydride-type elimination reactions.[142,143] This reactivity profile has been used to achieve cyclization–elimination of *O*-allyl-tethered alkyl bromides **70** to give methylenetetrahydrofurans **71** (Scheme 32).[144] The process started with the photochemical generation of Ph_3Sn• by Co–Sn bond homolysis which enables the formation of a tin radical for XAT reaction with **70**. Fast *5-exo-trig* cyclization of **72**, gave the primary exocyclic radical **73** that was trapped by the [Co(II)] species. This step generated the alkyl–[Co(III)] intermediate **74** from which dehydrogenation took place. While this reactivity required stoichiometric amounts of **69**, a catalytic approach was more recently developed by Carreira using low-intensity blue LEDs as the light source. This approach has been generally applied on alkyl iodides and used to achieve intramolecular Heck-type reactions,[145] intermolecular olefinations with styrene acceptors as well as electron-poor alkyl iodides and bromides[146,147] and was further showcased in the total synthesis of (+)-daphmanidin E.[148] In these cases, however, XAT is used only to initiate a redox [Co(I)/(II)/(III)] catalytic cycle and the alkyl halide is converted into the corresponding alkyl–[Co(III)] intermediate by S_N2 reaction with a nucleophilic [Co(I)] species.[149]

Scheme 32. Cyclisation/Desaturation of Alkyl Bromides with Ph_3Sn–$Co(dmgH)_2Py$.



Other Tin Reagents. Although versatile and powerful, standard tin reagents suffer from common drawbacks mostly associated with reaction work-up and purification as well as their final waste disposal.[12] Several reagents have been developed to circumvent these issues like water-soluble di-tin reagents, which can be removed by liquid-liquid extraction,[150] or polymer-supported reagents, that can be filtered at the end of the reaction.[151,152] In all cases, the supported tin reagents can be recovered from the reaction mixture and recycled by reduction.

3.1.2. Silicon Radicals

Despite being powerful and versatile XAT mediators, organotin species suffer from severe drawbacks associated to their toxicity and difficulty of disposal. This has driven a quest for alternative reagents for homolytic activation of C–halogen bonds as discussed by Walton in 1998 in the topical review entitled "*Flight from the Tyranny of Tin*".[12] Over the last three decades silicon reagents have been established as potent XAT mediators displaying a reactivity profile frequently superior to the one of tin radicals, a better safety profile, and simplified work-up procedures.[153-155] The power of this class of species in XAT chemistry can be aptly realised by considering the impact that $(Me_3Si)_3Si–H$ (abbreviated to TTMSS or referred to as "supersilane")[52,155] has had in the development of synthetic radical chemistry where it is still one of the most commonly used radical promoters despite its relatively high price.

Mechanistically it is important to note that the superior XAT reactivity typical of silicon radicals does not always translate into superior synthetic versatility. As an example, trialkyl silanes (e.g. Et_3SiH) are poor reductants in radical chemistry because, despite their corresponding silicon radicals (e.g. Et_3Si•) being the most powerful XAT promoters, their Si–H bonds are too strong to sustain radical-chain propagation (see Table 3).[21]

Table 3. BDEs of Various Si–H Bonds.[21]

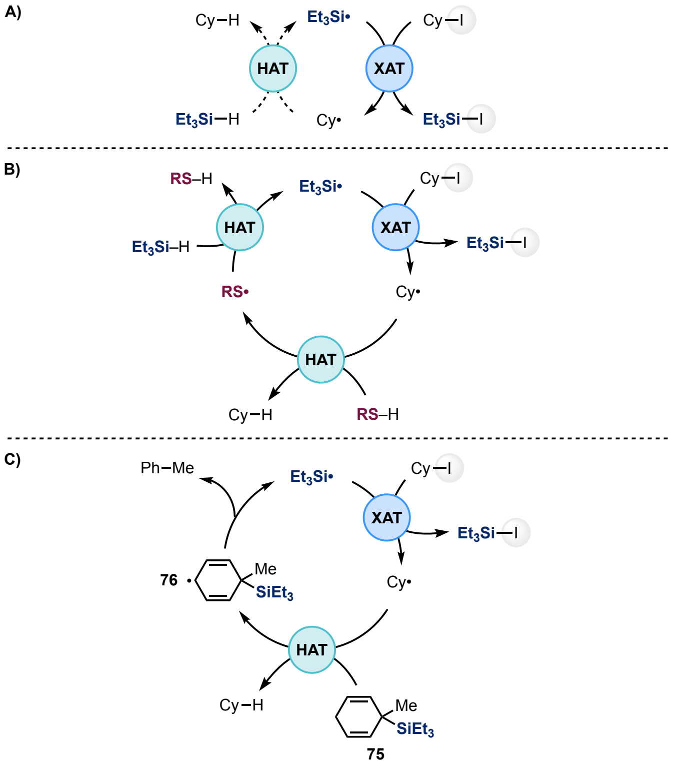
Silane	Si–H BDE (kcal mol^{-1})	Silane	Si–H BDE (kcal mol^{-1})
$H_3Si–H$	91.7	$Me_3Si–H$	94.7
$Et_3Si–H$	94.6	$(Me_3Si)_3Si–H$	83.7
$(Me_3S)_3Si–H$	87.0	$Bu_3Sn–H$	78.0

This can be exemplified by considering the reductive de-iodination of Cy–I with Et_3SiH (Scheme 33A). This reactivity would require a chain propagation based on XAT between Et_3Si• and Cy–I, followed by HAT between Cy• and Et_3SiH. While the XAT step is very favourable (matching enthalpic and polar effects) the sequent HAT process is difficult and effectively thwarts reactivity.

This fundamental challenge in silicon radical reactivity has been generally addressed by modifying the Si-substitution pattern. In particular, the replacement of alkyl groups (e.g. Et) at the Si with Me_3Si groups has been demonstrated to progressively lower the corresponding Si–H BDE by ~4 kcal mol^{-1}, and this has led to the identification and the extensive synthetic application of TTMSS (see Table 3). Alternatively, the use of thiols as polar reversal catalysts[156] or bespoke Me_3Si-substituted cyclohexadienyl reagents have provided powerful solutions to the employment of silicon radicals in chain-processes.[12,157] In the first case, the slow HAT process between the Cy• and $Et_3Si–H$ is replaced by a polarity matched and very fast HAT from a thiol. This generates an electrophilic thiyl radical that is efficient at undergoing HAT with the hydridic Si–H bond, thus regenerating the chain carrying Si-radical (Scheme 33B). In the second approach, cyclohexadienyl reagents like **75** have been demonstrated effectively sustain silicon radical-based chain propagations (Scheme 33C). In this case, the activated cyclohexadienyl C4 position enables HAT from Cy• which generates the cyclohexadienyl radical **76**. This species undergoes a thermodynamically favourable aromatisation via fast fragmentation across the C–Si bond, thus generating Et_3Si• and enabling radical propagation.

These two alternative strategies for silicon radical generation and reactivity have so far found application mostly under thermal conditions.

Scheme 33. Strategies for the Use of $Et_3Si^•$ in Halogen Atom Transfer

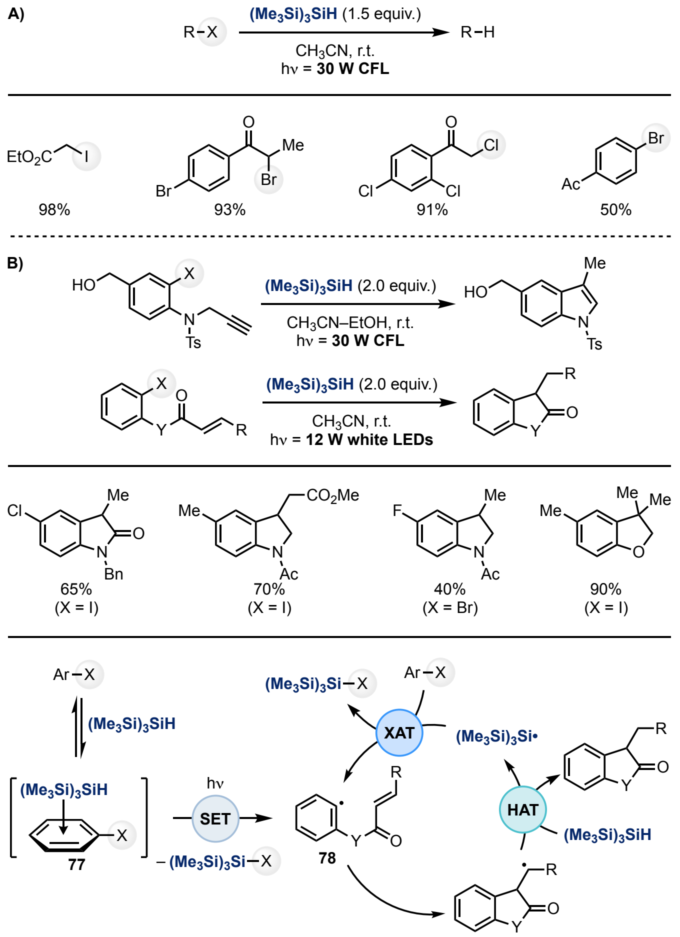


Just like in the case of tin radicals, the utilization of silicon radicals in XAT protocols has been mostly done using TTMSS under thermal decomposition of AIBN as the initiation mechanism. Photochemical methodologies have nevertheless found relevant application since the initial reports of Haszeldine and Young in 1960.[158] The discussion of these methods has been organised into three distinct group, direct photolysis first and then photoredox and metallaphotoredox catalysis respectively.

Direct Photolysis. Despite their close structural similarity to tin species, silanes and disilanes display quite different photochemical behaviour and they do not absorb in the near UV (e.g. the absorption of Me_6Si_2 ceases after 240 nm).[159,160] This has somewhat limited silicon radical generation to photochemical methods based on far-UV light,[158,161-165] γ-rays[166-168] and Hg-photosensitisation which have narrow synthetic applications.[169,170] Structural modifications of disilanes have been attempted to achieve photolysis with near-UV light but these approaches are so far mostly restricted to tetrakis(trisalkyl)silanes, $(R_3Si)_4Si$, and hexakis(trisalkylsilane)disilanes, $[(R_3Si)_3Si]_2$.[171,172] For example, when the decasilane $[(Me_3Si)_3Si(SiMe_2)]_2$ was irradiated with a low-pressure 450 W Hg-lamp in the presence of CCl_4, the XAT product, $(Me_3Si)_3Si(SiMe_2)Cl$ was obtained as the main product.[173]

One of the first synthetic applications where direct irradiation was used in XAT chemistry using TTMSS was reported by Jørgensen for the dehalogenation of α-halo-carbonyls and aryl iodides and bromides using a 30 W compact fluorescence light (CFL) bulb (Scheme 34A).[174] The mechanism of photoinitiation with the CFL lamp is still uncertain, but the authors proposed that the phosphorous coating of the light source could emit just enough UV-A light to photolyze a small fraction of TTMSS.[175] This would serve as initiating mechanism for the radical-chain dehalogenation process. Building on this precedent, Paixão used TTMSS and CFL irradiation to generate aryl radicals from the corresponding iodides or bromides as part of a cyclisation protocol leading to indoles, indolines, oxindoles and dihydrobenzofuran derivatives (Scheme 34B).[176,177] In these examples however, the generation of $(Me_3Si)_3Si$• was rationalised on the basis of the formation of an electron donor-acceptor (EDA) complex **77** between TTMSS and the aryl halide, which upon irradiation at the charge-transfer band led to a SET event. This step would generate the key aryl radical **78** which initiated a chain propagation process ($\Phi > 28$).

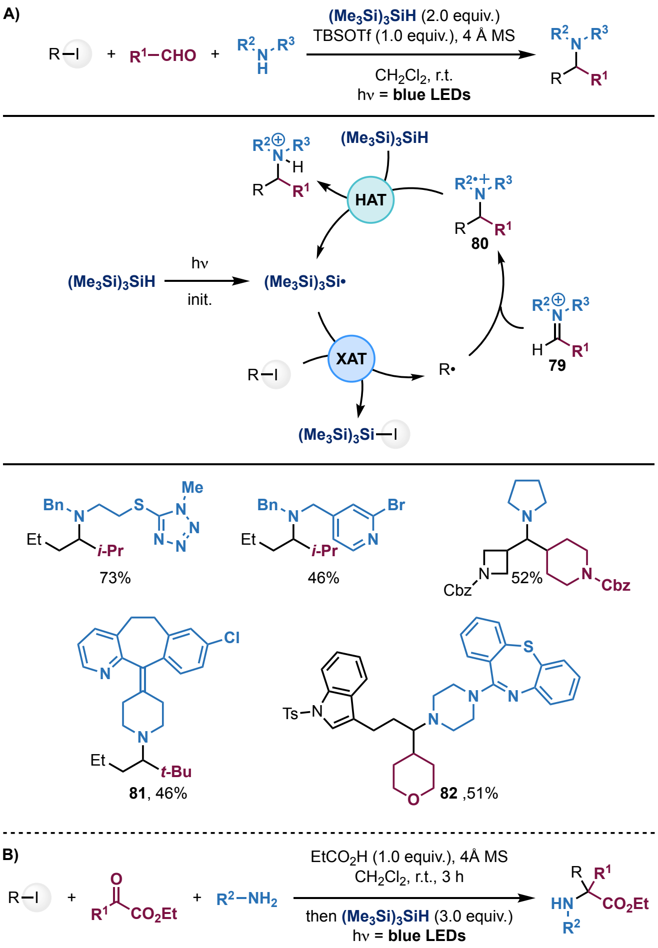
Scheme 34. (A) Photoinduced Reduction of Various Alkyl Halides with TTMSS (B) Photoinduced Silicon-Mediated 5-exo-trig Cyclisation of Various Aryl Halides



More recently, Gaunt employed the direct irradiation of TTMSS with blue LEDs to achieve the three-component coupling between alkyl iodides, aldehydes and secondary amines (Scheme 35A).[178] In this method, the alkyl radical (R•) is generated from the corresponding iodide by XAT with $(Me_3Si)_3Si$• while the aldehyde and the amine undergo condensation to the corresponding iminium ion **79**. Radical addition to **79** is probably reversible, but the resulting aminium radical **80** undergoes fast (polarity matched) and irreversible HAT from TTMSS thus enabling efficient chain propagation and product formation.[179] The exact nature of the initiation step could not be determined unambiguously, but the authors proposed it to result from a three-component interaction between the alkyl iodide, the iminium and TTMSS. Noteworthy, thermal conditions in the presence of AIBN were also able to initiate and sustain the radical chain delivering the products in good yields. A large array of alkyl amines and anilines as well as alkyl and benzyl aldehydes were successfully employed in this transformation. In some cases, TBSOTf (*t*-butyldimethylsilyl trifluorosulfonate) was identified as a beneficial additive to enhance the reaction yields. Regarding the alkyl iodides scope, unactivated primary, secondary and tertiary derivatives, as well as benzylic bromides and even iodomethane were engaged in generally high yields. Complex tertiary amines were rapidly assembled in a single step, as exemplified by the high-yielding formation of **81** and **82**.

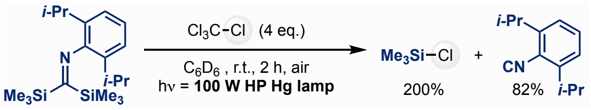
This reactivity was later extended to α-ketoesters and primary amines to give, upon addition of the alkyl radical to a preformed ketiminium ion, α-tertiary amino acid derivatives (Scheme 35B).[180]

Scheme 35. (A) Visible-Light Mediated Three-Component Reactions of Alkyl Iodides for the Synthesis of Tertiary Amines (B) Visible-Light Mediated Synthesis of Unnatural Aminoacids



Other silicon species have been reported to generate the corresponding silicon-radicals upon irradiation. In particular, acyl silanes display low-energy n–π* absorptions (λ = 380–420 nm) with relatively large extinction coefficients (ε = 100–300 M^{-1} cm^{-1})[181-183] and undergo Norrish type-I fragmentation across the C–Si bond.[184-186] This generates the corresponding silicon radicals and an undesiderably reactive acyl radical that however limits synthetic applications. Structurally related bis(organosilyl)imines have also been demonstrated to generate silyl radicals under photoirradiation (high-pressure Hg-lamp) and this has been used to achieve XAT reactivity with CCl_4, Et–I, *i*-Pr– I and Ph–I (Scheme 36).[187]

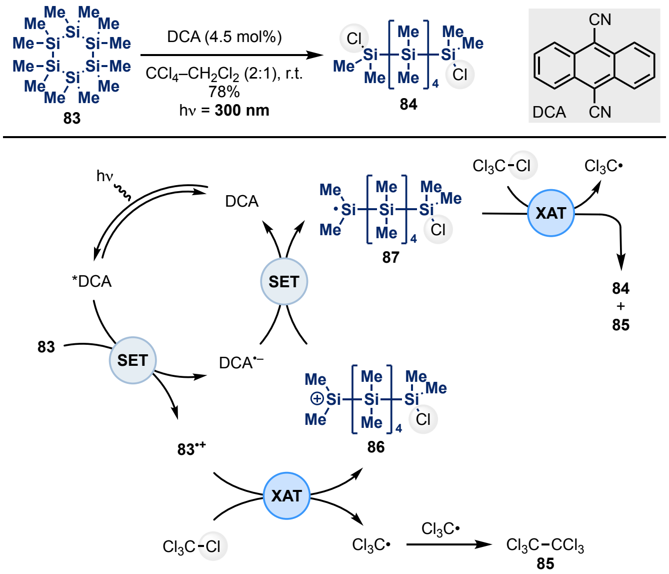
Scheme 36. Photogeneration of Silicon Radicals from Bis(organosilyl)imines and Its Application in Halogen Atom Transfer



Applications in Photoredox Catalysis. Strategies for silicon radical generation and XAT reactivity based on the use of photocatalysis with low-energy light sources have been significantly more adopted, especially through the use of photoredox manifolds.

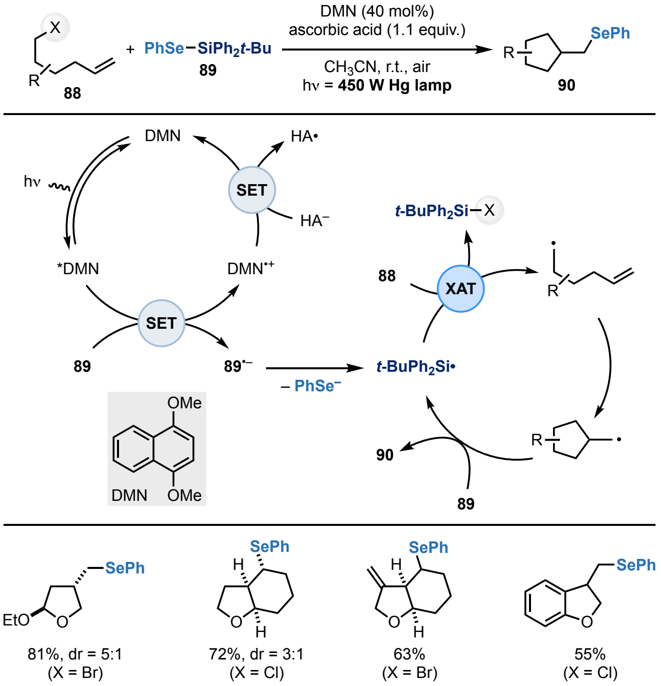
Historically, the first photocatalytic XAT reaction based on silicon radical reactivity has been reported by Sakurai in 1985.[188] In this early example, irradiation ($\lambda > 300$ nm) of dodecamethylcyclohexasilane **83** in CCl_4–CH_2Cl_2 using 9,10-dicyanoanthracene (DCA) as the photocatalyst, gave 1,6-dichlorohexasilane **84** and hexachloroethane **85**, which are products indicative of XAT on CCl_4 (Scheme 37). This process was rationalised on the basis of a reductive quenching photoredox cycle where the photoexcited DCA (*DCA) underwent SET with **83**. The resulting Si-based radical cation was proposed to react with CCl_4 (XAT) and generate Cl_3C• as well as the oxidized chlorinated polysilane **86**. At this point the authors envisioned a further SET between this species and the reduced DCA to generate the Si-radical **87**. This species might undergo another XAT step with CCl_4 yielding **84** and **85** (radical-radical recombination). Other photocatalytic approaches for silicon radical generation from disilanes have been reported but they have not been used in synthetic settings.[189-192]

Scheme 37. Photoredox Ring-Opening XAT-Chlorination of Dodecamethylcyclohexasilane



A distinct tactic for silicon radical generation via photoredox catalysis has been introduced by Pandey using the Se-containing reagent **89** (Scheme 38).[193] In contrast to classical silicon-based reagents that are competent electron donors (e.g. **83**, Scheme 37), **89** acted as electron acceptor and enabled radical generation via an oxidative quenching photoredox cycle based on 1,5-dimethoxynapthalene (DMN) as the photocatalyst and irradiation from a 450 W high-pressure Hg-lamp. Mechanistically, the photoexcited DMN (*DMN) underwent SET with **89** leading to the corresponding radical anion from which mesolytic cleavage of the Se–Si bond[194] gave the phenyl selenide anion and *t*-BuPh$_2$Si•. While the photoredox cycle was closed by SET between the oxidised DMN and ascorbic acid (additive used as sacrificial electron donor), the silicon radical established a radical chain propagation based on XAT activation of primary alkyl bromides and chlorides **88**, followed by cyclization onto the tethered olefin and final PhSe group-transfer with **89**. The method was demonstrated in the preparation of several Se-containing cyclic and bicyclic systems **90** in good yield.

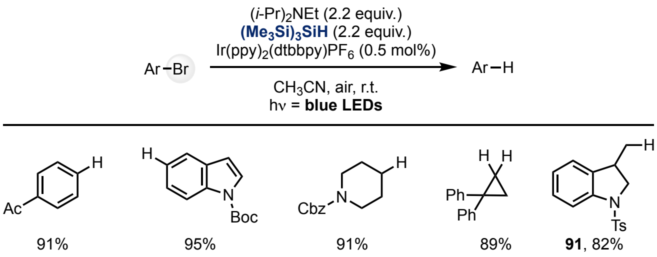
Scheme 38. Photoredox Tandem Radical Cyclisation/Phenylselenation of Various Alkyl Halides



Following these seminal reports, the generation of silicon radical via photoredox catalysis was not further developed until recently due to the renewed interest in methodologies harnessing low-energy visible light. The following discussion has been further organised on the basis of the overall transformation achieved.

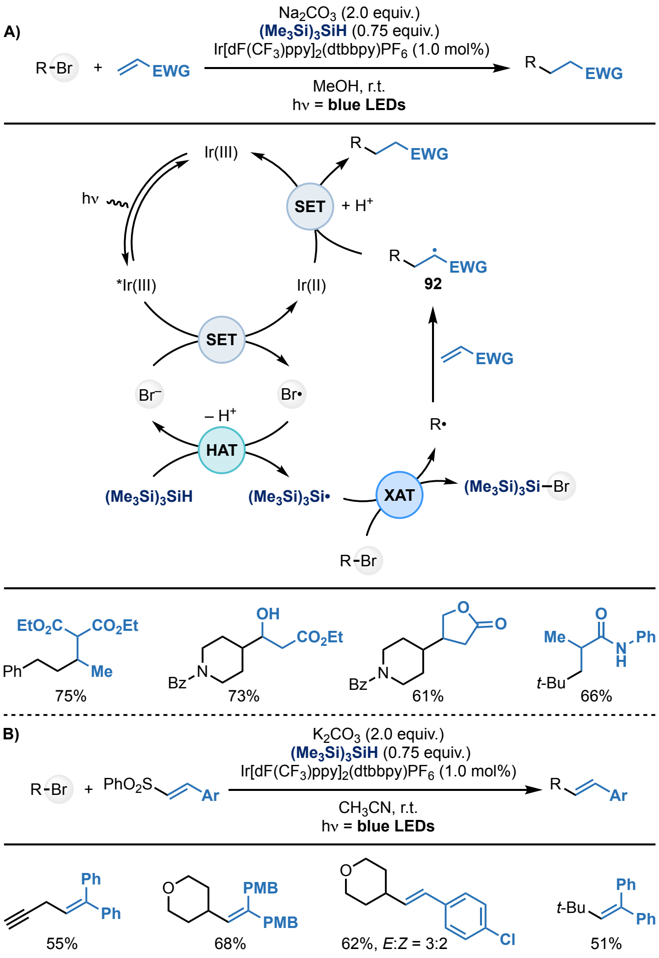
Dehalogenation reactions. In 2016, the Stephenson group reported the dehalogenation of unactivated alkyl and aryl bromides using TTMSS as the XAT reagent, [Ir(ppy)$_2$(dtbbpy)]PF$_6$ as the photocatalyst and (i-Pr)$_2$NEt as the base under blue light irradiation and air (Scheme 39).[195] This reaction was proposed to be initiated by the by oxidative quenching of the photoexcited Ir-photocatalyst by O$_2$. This step generated a peroxo radical that reacted via HAT with TTMSS. The resulting (Me$_3$Si)$_3$Si• then established a standard radical-chain process based on XAT on the halide and then carbon-radical reduction by HAT from the TTMSS. This protocol represents a powerful solution to achieve the general reduction of (hetero)aryl bromides spanning electron poor and electronic rich substituents in excellent yields. Unactivated alkyl bromides were also efficiently engaged and also implemented in *5-exo-trig* cyclisation processes (e.g. **91**).

Scheme 39. Photoredox Reduction of Various Organic Halides with TTMSS



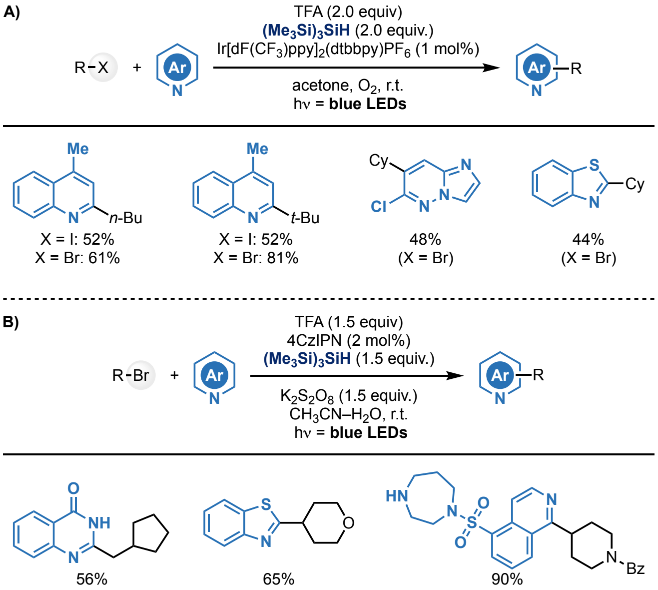
C–C and C–Heteroatom Bonds Formation. Silyl activators have been frequently exploited for the formation of C–C bonds through photoredox and XAT-based methodologies. An early example of this reactivity can be found in the work of ElMarrouni who developed the Giese addition of unactivated alkyl bromides to α,β-unsaturated carbonyl acceptors using TTMSS in combination with the Ir[dF(CF_3)ppy]$_2$(dtbbpy)PF_6 photocatalyst under blue light irradiation[196] (Scheme 40A).[197] The authors proposed the process to be initiated by SET oxidation of traces of bromide anion (E_{ox} = 0.71 V vs SCE)[198] by the photoexcited Ir catalyst (reductive quenching). The ensuing Br• could engage in HAT reactivity with TTMSS. XAT of the resulting silicon radical with the alkyl bromide was followed by Giese addition onto the acceptor. On the basis of the low quantum yield determined, $\Phi = 0.45$, the authors suggested that the electrophilic α-carbonyl radical **92** was reduced to the corresponding enolate by the Ir(II) and then protonated. This pathway was supported by the evidence that CD_3CN as the solvent led to deuterated products. During the reaction development, the use of 0.75 equiv. of TTMSS was identified as optimum to mitigate the direct reduction of the alkyl bromides. In terms, of scope, primary, secondary and tertiary alkyl bromides were reacted with a wide range of Giese acceptors in generally good yields and many functional groups were tolerated including free alcohol. Intermolecular reactions of alkyl bromides also using TTMSS and photoredox catalysis have been employed in combination with styrenyl sulfones to give Heck-type products as developed by König and Xiao (Scheme 40B).[199]

Scheme 40. (A) Silicon-Mediated Photoredox Giese Reaction of Alkyl Bromides (B) Photoredox Heck-Type Reaction of Alkyl Bromides with β-Phenylsulfonylstyrenes



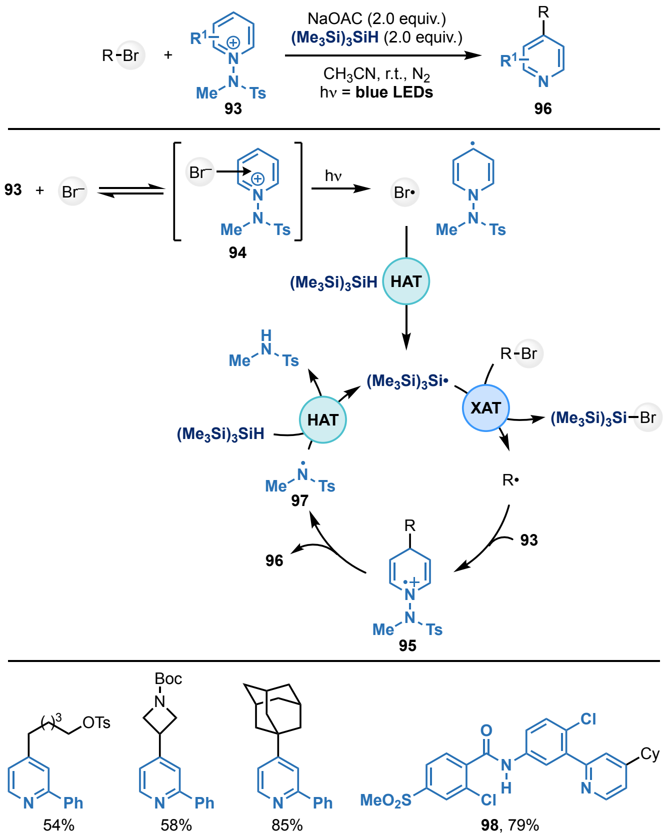
This photoredox approach for $(Me_3Si)_3Si$• generation by initial SET on a halide anion (X^- = bromide or iodide) followed by HAT between X• and TTMSS has also been used to achieve Minisci reactions of alkyl iodides and bromides as developed by Wang[200] and ElMarrouni[201] (Scheme 40, A and B respectively). The two methods differ in the type of photocatalyst used and they both require a terminal oxidant (O_2 and $S_2O_8^{2-}$, respectively) to close the photoredox cycle and/or re-aromatise the *N*-heterocycle after Minisci addition. It is worth noting that $(Me_3Si)_3Si$• is known to react with molecular oxygen (as well as other oxidants) to give various silyloxy species**,** which can potentially complicate the mechanistic picture.[157,202]

Scheme 41. (A) Silicon-Mediated Photoredox Minisci Reaction of Various Alkyl Iodides and Bromides (B) Silicon-Mediated Photoredox Minisci Reaction of Alkyl Bromides



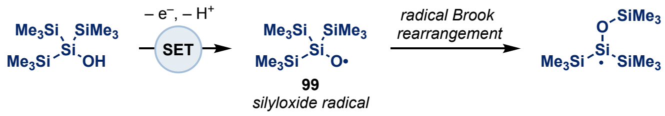
The generation of silicon radical via Br• mediated HAT does not necessarily require a photocatalyst manifold as demonstrated by Hong that developed C4-selective Minisci-type addition of unactivated alkyl bromides to *N*-amidopyridinium acceptors **93** (Scheme 42).[203] In this example, **93** and the bromide formed EDA complex **94** absorbing in the visible range (λ < 450 nm). Blue light irradiation at the charge-transfer band triggered a SET delivering Br• that initiated the chain by HAT on TTMSS. The alkyl radical, generated by XAT, reacted selectively at C4 on **93** and the aminium radical **95** fragmented across the weak N–N bond. This step released the C4-alkylated pyridine **96** and generated an electrophilic sulfonaminyl radical **97**, which propagated the chain process by polarity matched HAT on the silane. In contrast to standard Minisci reactions, this method does not require a Brønsted acid as the pyridine system is already activated. The chemistry was compatible with both primary secondary and tertiary alkyl bromides and also enabled the functionalization of complex and densely functionalised pyridine derivatives (e.g. vismodegib, **98**).

Scheme 42. EDA-Mediated C4-Selective Alkylation of *N*-amidopyridinium



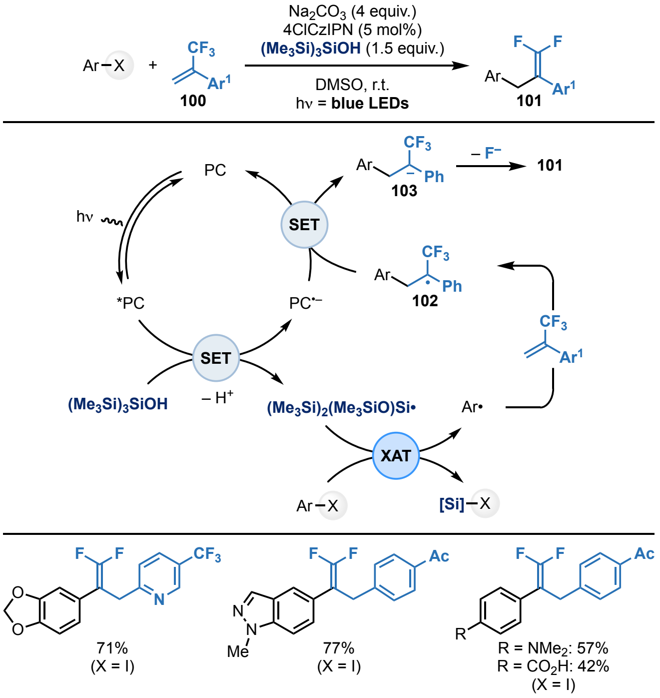
Despite TTMSS being a powerful reagent for application in XAT reactivity, it still suffers from the common pitfall associated to most tin and silicon hydrides, which is their ability to serve as HAT donors. HAT efficiency is not necessarily a virtue as this can be problematic when attempting the development of cascade reactions where the C-radical (generated by XAT) needs to undergo further steps that operates at slower rates than direct reduction. Furthermore, the generation of the $(Me_3Si)_3Si$• from TTMSS generally requires the identification of an appropriate HAT mediator which can potentially make optimisation more difficult and increase the number of undesired reaction pathways. A versatile solution addressing these issues has been the implementation of tris(trimethylsilyl)silanol ($(Me_3Si)_3SiOH$, TTMSSOH, often referred as “supersilanol”)[204] which, since the seminal report from MacMillan (see below),[205] has found broad application in photoredox manifolds (Scheme 43). Despite its somewhat elevated price, this reagent offers the mechanistic advantage that the silicon radical is generated by SET oxidation and deprotonation of TTMSSOH (E_{ox} for = +1.54 V vs SCE)[205]. This provides the silyloxy radical **99** that undergoes a radical Brook-type rearrangement to $(Me_3Si)_2(Me_3SiO)Si$•.[118,206] Crucially, this species displays a XAT reactivity similar to the one of $(Me_3Si)_3Si$• but the strong nature of the O–H bond in TTMSSOH eliminates any potential HAT to C-radical intermediates.

Scheme 43. Generation of Silicon Radicals from $(Me_3Si)_3SiOH$



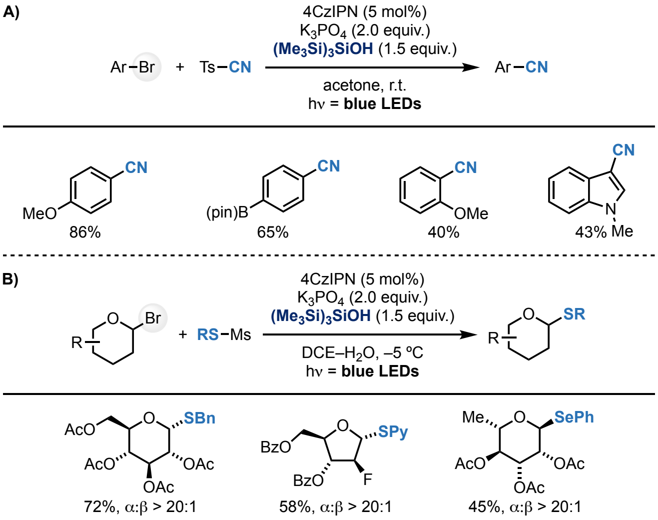
Molander utilised this reagent to convert aryl halides into the corresponding radicals that were used for the preparation of α-aryl-β,β'-difluorostyrenes **101** (Scheme 44).[207] This process proceed via a reductive quenching photoredox cycle (4ClCzIPN photocatalyst,[208] blue light irradiation) and upon oxidation → deprotonation → Brook rearrangement of TTMSSOH, the corresponding silicon radical underwent XAT with aryl iodides and bromides. The resulting aryl radicals reacted with α-trifluoromethylstyrene coupling partners **100** and the resulting benzylic radicals **102** were reduced to the anion **103**, owing to the inductive effect offered by the neighbouring CF_3 group. This reductive radical-polar crossover reaction[209] was concluded by fluoride elimination, which provided the desired products. In terms of substrate scope, both electron rich and electron poor (hetero)arenes reacted in good yields and the process demonstrated compatibility with a large variety of functional groups. In the case of precursors containing both a sp^2 C–I and C–Br bonds, the C–I was selectively activated. Noteworthy, despite the highly oxidizing 4ClCzIPN photocatalyst used, styrenes containing easily oxidized groups such as tertiary amines, aryl methyl sulphide or electron-rich aromatic cores were smoothly converted into their corresponding products.

Scheme 44. Reductive Radical-Polar Crossover Reaction of Alkyl Halides with α-Trifluoromethylstyrene



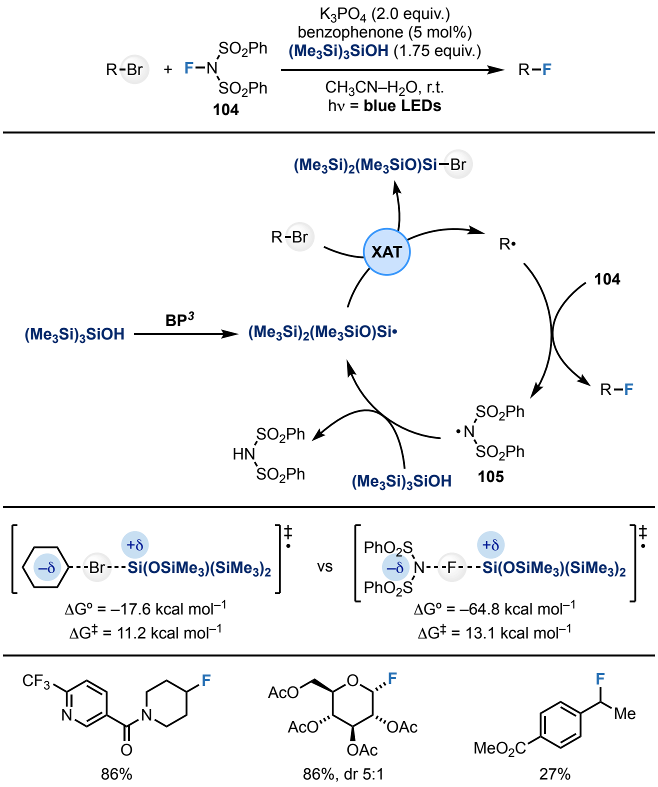
A related reactivity was then employed by the same authors to achieve the metal-free cyanation of aryl bromides using TsCN as the radical trap (Scheme 45A), and to convert anomeric alkyl bromides into thio- and seleno-glycosides using S/Se-sulfonates acceptors (Scheme 45B).[210]

Scheme 45. (A) Photoredox Cyanation of Aryl Bromides with Tosyl Cyanide (B) Synthesis of Thio- and Seleno-Glycosides from Bromosugars



The introduction of a fluorine atom is a sought-after modifications in MedChem.[211] MacMillan and Houk recently reported a strategy for the fluorination of alkyl bromides using NFSI (*N*-fluorobenzenesulfonimide, **104**) and photocatalysis (Scheme 46).[212] This process required the use of benzophenone (BP), which upon photoexcitation to the triplet carbonyl (^{3}BP) engaged with TTMSSOH by either HAT or SET. The resulting sillicon radical generated the alkyl radical from the bromide which was fluorinated upon reaction with **104**. This step provided the reaction products and generated the electrophilic *N*-radical **105**. The authors proposed this species to be able to sustain radical-chain propagation by reaction with TTMSSOH (either HAT or SET). Mechanistically it is interesting to note that despite the N–F bond in NFSI being weaker than a standard sp^3 C–Br bond (BDE$_{\text{N–F}}$ = 63 kcal mol^{-1} vs BDE$_{\text{C–Br}}$ = 71 kcal mol^{-1})[21,213] and the $(PhSO_2)_2N$ unit's ability to stabilise an incoming negative character, the silicon radical does not undergo fluorine-atom transfer. This is in line with XAT reactions responding to the polarizability of the halide[37] which, in this case, favours abstraction of the bromide as also determined by the authors' DFT studies. Primary, secondary and tertiary alkyl bromides were fluorinated in good yield. Furthermore, a *gem*-dibromide derivative was converted into the corresponding *gem*-difluoride is a carbonyl bioisosteres.[214,215]

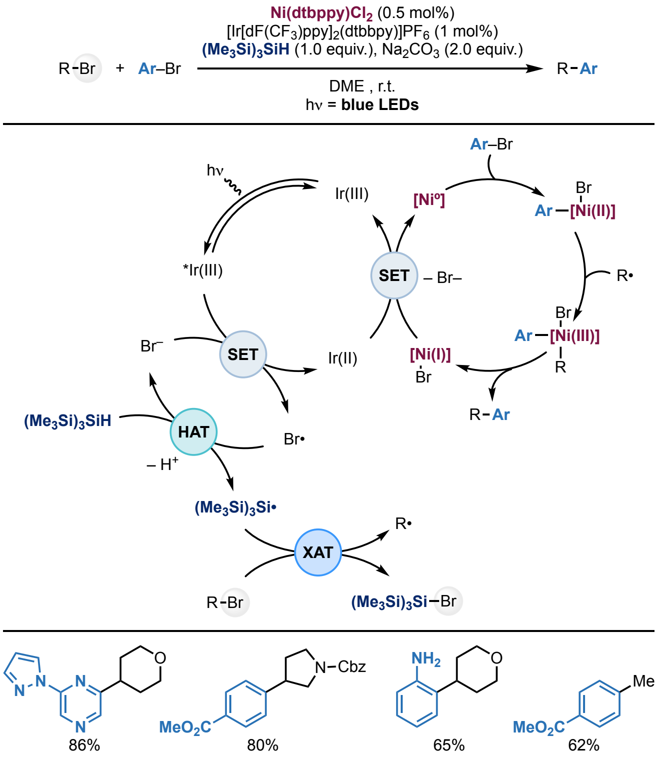
Scheme 46. Benzophenone-Initiated Fluorination of Alkyl Bromides and Related Mechanistic Considerations



Applications in Metallaphotoredox Catalysis. Metallaphotoredox catalysis, which encompasses the merger of photoredox with transition metal catalysis, has been a topic of intense research over the last decade.[16] This approach has had a great impact towards the exploration of radical reactivity in the presence of transition metals thus enabling the development of novel C–C and C–heteroatom bond-forming cross-coupling-type strategies. The integration of silicon radical-mediated activation of alkyl and aryl halides has provided a powerful solution to the "oxidative addition problem", whereby difficulties in the two-electron addition of organic halides to metal centers are eluded via their prior activation into the corresponding radicals. The following discussion has been divided on the basis of the metal utilised.

Nickel catalysis. The first example describing the integration of XAT in metallaphotoredox catalysis was reported by MacMillan in 2016 with the development of a reductive strategy for the sp^2–sp^3 cross-coupling between aryl and alkyl bromides (Scheme 47).[216] In this pioneering example, photoredox catalysis was used to generate a Br• in order to generate a silicon radical from TTMSS by HAT. The resulting $(Me_3Si)_3Si$• engaged in XAT with the alkyl bromide giving the corresponding radical. At the same time, the [Ni^0] co-catalyst underwent oxidative addition into the aryl bromide to provide the Ar–[Ni(II)]–Br complex, that was intercepted by the carbon radical. This step generated an alkyl,aryl–[Ni(III)] species from which facile reductive elimination gave the coupling product and a [Ni(I)] intermediate. As commonly hypothesized in metallaphotoredox strategies, both the photoredox and nickel cycles were closed by SET between the low-valent [Ni(I)] complexes and the reduced Ir(II) photocatalyst. An important feature of this reaction design is the complementary between the two activation pathways: the silicon radical selectively engages in XAT with the weaker sp^3 C–Br bond (see also Table 1), while the nickel catalyst preferentially undergo oxidative addition across the sp^2 C–Br bond.[217] In terms of scope, this protocol accommodates primary, secondary and tertiary alkyl bromides and even Me–Br (generated *in situ* by reaction of MeOTs with LiBr). Alkyl chlorides were also compatible but required to be activated (e.g. Cl–methyl methyl ether, MOMCl). Regarding the aryl bromide scope, *ortho*-, *meta*- and *para*-substituted derivatives of various electronic properties were engaged in good to excellent yields. Numerous *N*-heteroaromatic bromides, including pyridine, pyrazine, imidazole and pyrazole, reacted smoothly. Interestingly, Lei, almost simultaneously, reported a similar transformation but in the absence of the silane.[218] Using Et_3N as a terminal reductant together with $MgCl_2$, the role of which has not been fully elucidated, allowed both halide components to be activated and coupled together.

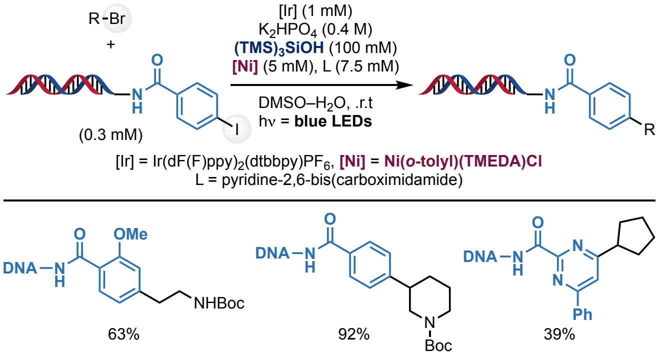
Scheme 47. Metallaphotoredox Ni-Catalysed Coupling of Aryl Bromides with Alkyl Bromides



The mildness of these reaction conditions and the high yields obtained, has made this process quickly adopted by the academic and industrial communities. For example, teams from Merck[219] and Abbvie[220] compared various sp^2–sp^3 cross-coupling methodologies and found this manifold to be general across a large range of alkyl and aryl bromides which makes it a valuable reaction in the MedChem toolkit to achieve rapid diversification. Indeed, this XAT-based approach outcompeted all modern non-photodriven methods with exception of the Negishi cross-coupling.

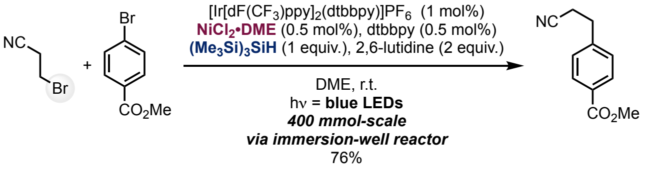
Further applications in MedChem was demonstrated by Flanagen and Kölmel that used this reaction for the generation of DNA-encoded libraries (Scheme 48).[221] In this case the reaction conditions had to be tailored to accommodate the aqueous environment required by DNA-tagged reactants, and the coupling was then demonstrated on a broad range of primary, secondary and tertiary alkyl bromides as well as numerous (hetero)aryl iodides. In this example, the TTMSSOH gave slightly superior yields than TTMSS, as the latter led to the formation of direct reduction by-products. Interestingly, the reaction could also be conducted in the absence of silane, albeit in a lower yield, suggesting that the nickel catalyst was able to activate simultaneously both the alkyl bromide and the aryl iodide.

Scheme 48. Application of Ni-Catalysed Photoredox Coupling of Alkyl Bromides with Aryl Iodides for the Generation of DNA-encoded libraries



A frequent challenge in photoredox catalysis is represented by the reaction scale-up that is often difficult to achieve in batch.[222] Candish recently demonstrated that immersion-well reactors are suitable for straightforward scale-up as demonstrated by the coupling of 4-bromobenzoate and 3-bromopropanenitrile on 400 mmol scale (Scheme 49).[223] In this case, partial re-optimisation of the process identified 2,6-lutidine as the most effective base.

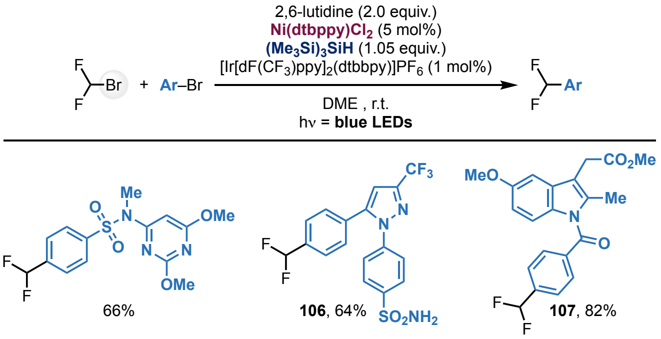
Scheme 49. Large Scale Ni-Catalysed Metallaphotoredox Coupling of Alkyl Bromides with Aryl Bromides using an Immersion-Well Reactor



Flow chemistry is usually the prime method for scale-up of photochemical reaction, because the set-up can be easily modified to ensure good light penetration. In particular, heterogeneous reactions like the ones using poorly soluble inorganic bases or metal complexes can sometimes be problematic for direct translation into photo-flow technology. This challenge has been addressed with the development of novel reactors like the Continuous Stirred-Tank Reactor (CSTR)[224] and the oscillatory plug flow photoreactor (COSTA)[225] that can be used for running these metallaphotoredox XAT-based cross-couplings on scale.

The ability of silicon radicals and metallaphotoredox catalysis to assemble sp^3-sp^2 C–C bond was then extended by MacMillan to the use of $BrCHF_2$ as the alkyl halide to enable highly sought-after but still challenging arene difluoromethylation (Scheme 50).[226] This process represents a powerful example where both enthalpic and polar effects facilitate XAT: the weak $F_2HC–Br$ bond (BDE = 69 kcal mol^{-1})[21] combined with the ability of the *gem*-difluoro methylene unit to stabilise an incoming negative charge in the TS, makes the process thermodynamically and kinetically very favourable. However, the activated nature of $BrCHF_2$ also means that this species can outcompete the aryl bromide for oxidative addition with the low-valent nickel catalyst.[227,228] This undesired pathway becomes particularly evident in the case of electron rich aryl bromides that display slower rates of reaction. In the endeavour to demonstrate this reactivity on a large scope, the authors found that tuning the equivalent of $BrCHF_2$ depending on the nature of the aryl bromide was effective in minimising the undesired side reactivity. This enabled the use of both electron poor and electron rich aryl bromides as well as heteroaryl derivatives. The method was also used in late-stage functionalisation as demonstrated by the modification of celecoxib and indomethacin (**106** and **107**).

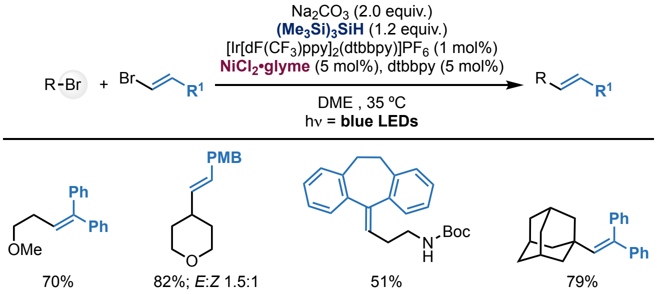
Scheme 50. Metallaphotoredox Difluoromethylation of Aryl Bromides



Scheme 50.

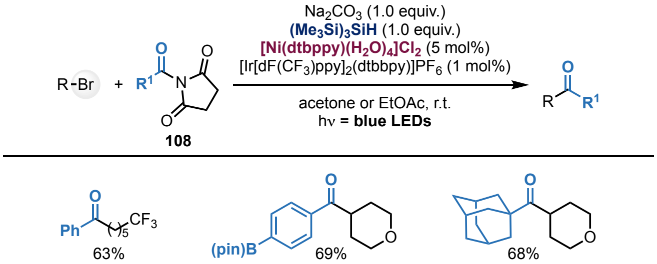
Vinyl bromides have also been employed as coupling partners in conjunction with alkyl bromides by exploiting the related concept of preferential XAT on the sp^3 electrophile and oxidative addition on the sp^2 one (Scheme 51).[199,229] Primary, secondary and tertiary alkyl bromides were coupled with α-substituted or α,α’-disubstitued vinyl bromides to deliver disubstituted and trisubstituted olefins, respectively, although with moderate *E* stereocontrol. Free alcohol, carbamate and alkyl chloride were well tolerated under the reaction conditions.

Scheme 51. Silicon-Mediated C(sp3)–C(sp2) coupling of Alkyl Bromides with Vinyl Bromides



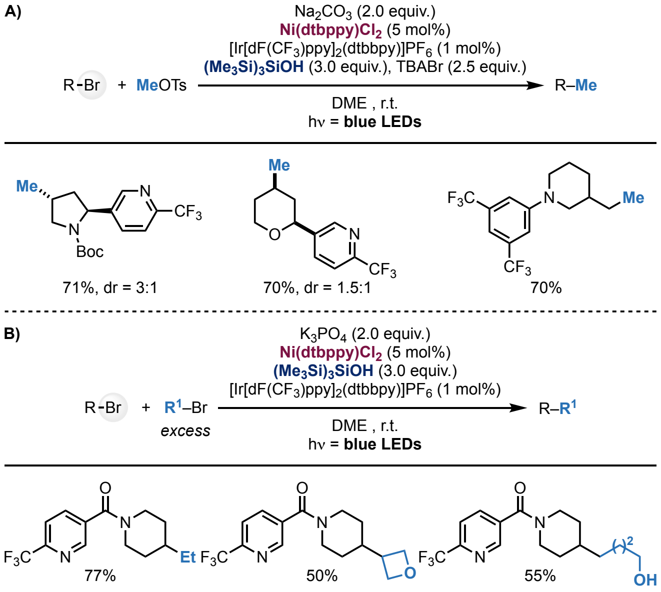
XAT and metallaphotoredox catalysis have also found application in the mild acylation of unactivated alkyl bromides for the preparation of ketone products. Several cross-electrophile couplings with various acyl donors have been reported over the years but alkyl bromides remained an elusive class of substrates for these purposes.[230-237] Amgoune demonstrated that acyl succinimides **108** could be activated by a low-valent nickel catalyst[232,235] and coupled with alkyl bromides using silicon-radical mediated XAT under dual photoredox settings (Scheme 52).[238] The reaction was amenable to primary, secondary and even benzylic bromides while the tertiary 1-bromoadamantane and alkyl chlorides failed to react. On the acyl side, both aryl and alkyl amides were successfully engaged in generally high yields.

Scheme 52. Silicon-Mediated Metallaphotoredox Ketone Synthesis from N-Acylsuccinimides



The possibility to merge silicon radical-mediated XAT reactivity with dual photoredox–nickel catalysis was then used by MacMillan to achieve the methylation of primary and secondary alkyl bromides and therefore obtain a rare example of sp^3–sp^3 cross-electrophile coupling (Scheme 53A).[239] The key reaction design of this process is similar to the one discussed before (see Scheme 47) as the silicon radical undergoes preferential Br-abstraction from the secondary alkyl bromides. Me–Br (formed *in situ* by the reaction of MeOTs with TBABr) is a challenging substrate for XAT but it is highly activated for oxidative addition with the nickel catalyst and this subtle interplay between radical and metal reactivity enabled selective sp^3–sp^3 C–C bond assembly. TTMSSOH was identified as optimum while TTMSS led to significant reduction by-product. The methylation of secondary and primary alkyl bromides was achieved in moderate to good yields and accommodated various protected amine and alcohol functionalities as well as several basic *N*-heterocycles (e.g. pyridine and piperidine). The alkyl bromide coupling partner, which had to be used in excess, could contain valuable polar functional group like free alcohol and epoxide. This approach for sp^3–sp^3 cross-coupling became more problematic when attempting the coupling between two unactivated alkyl bromides as a distinction based on preferential XAT or oxidative addition is challenging. Nevertheless, the authors successfully overcame this challenge by using an excess amount of the cheaper building block thus statistically favouring the formation of the desired heterocoupling product (Scheme 53B).

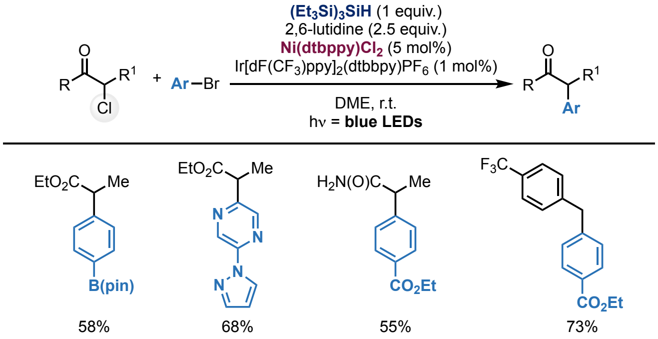
Scheme 53. (A) Silicon-Mediated Metallaphotoredox Methylation of Aryl Bromides (B) Silicon-Mediated Metallaphotoredox C(sp$_3$)–C(sp$_2$) Coupling of Alkyl and Aryl Bromides



So far, XAT chemistry has been mostly applied to organic iodides and bromides while chlorides are a desirable (they are cheaper and more available) but still challenging class of substrates.[240] Nonetheless, methodologies able to accommodate their use in fragment couplings have been reported.

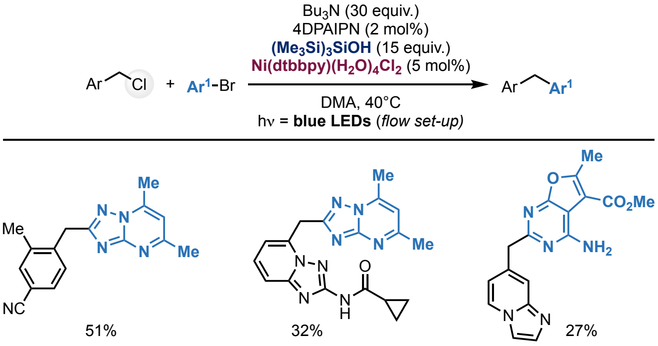
α-Chloro carbonyls are a class of activated substrates for XAT owing to their weak sp^3 C–Cl bond (BDE$_{C\text{–}Cl}$ ~ 72–77 kcal mol^{-1})[21] (enthalpic effect) and the ability of the carbonyl group to stabilize an incoming negative charge in the TS (polar effects). Using conditions similar to the ones identified for the coupling of alkyl bromides (see Scheme 47), MacMillan was able to translate the dual Ir–Ni approach to realise the general arylation of α-chloro carbonyls (Scheme 54).[241] Although the mechanism is similar to the one discussed for the coupling of alkyl bromides, one difference was the use of $(Et_3Si)_3SiH$ in place of TTMSS as this proved to be more efficient. The authors proposed this improved reactivity to occurred on the basis of a slower rate of Cl-transfer by the $(Et_3Si)_3Si$• with respect to $(Me_3Si)_3Si$•, which could allow better integration with the Ni-cycle. This mechanistic hypothesis was supported by the quantitative dehalogenation observed when 2-Br-propionate was used in place of 2-Cl-propionate under standard conditions. Alternatively, there could be a synergistic effect whereby the sterically more hindered $(Et_3Si)_3SiH$ reagent undergoes the undesired HAT with the α-carbonyl radical at a slower rate and this might contribute to a better integration of XAT with the dual photoredox-nickel manifold. Regarding the scope of the process, α-chloro acids, esters, amides, as well as benzylic chlorides (BDE_{C-Cl} = ~72 kcal mol^{-1})[21] could be coupled with aryl bromides of various electronics and steric properties in good yields. Sensitive and polar functional groups were tolerated and valuable *N*-heteroaryl chlorides were demonstrated to be feasible coupling partners.

Scheme 54. (Et3Si)3SiH-Mediated Metallaphotoredox Arylation of α-Chloroesters and Benzyl Chlorides



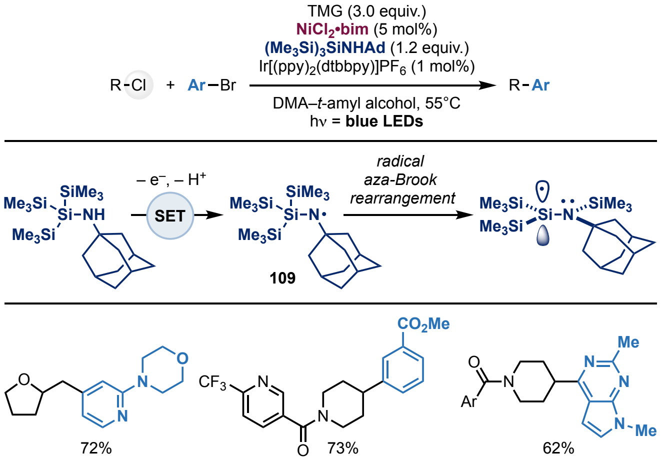
A more extensive exploration on engaging benzylic chlorides in XAT and metallaphotoredox catalysis was then reported by Brill that utilized these building blocks for the synthesis of di(hetero)arylmethanes in a flow setup (Scheme 55).[242] In this case, the Cl-transfer step was mediated by TTMSSOH [$(Me_3Si)SiOH$] as TTMSS led to considerable amounts of reduction by-products. The procedure provides the corresponding products in moderate yields, and the short reaction time associated with the structural diversity makes it a powerful tool to generate "hits" in drug discovery programs (only 1-2 mg of compounds are needed for pharmacological assays).

Scheme 55. Metallaphotoredox Coupling of Benzyl Chlorides and Aryl Bromides for the Synthesis of Diarylmethanes



While the examples mentioned before deal with the utilization of activated alkyl chlorides, unactivated substrates are still a remarkable challenge owing to their strong sp^3 C–Cl bonds (BDE ~82–86 kcal mol^{-1})[21] that makes the abstraction process significantly difficult. MacMillan tackled this challenge by designing the novel silicon-based reagent $(Me_3Si)_3SiNHAd$ that was successfully utilised in the cross-electrophile coupling between alkyl and aryl chlorides (Scheme 56).[243] The element of design for this species was based on the idea of introducing π-donating substituents at the Si to increase the nucleophilic character of its corresponding radical (captodative effect) and therefore maximise charge-transfer stabilization in the XAT TS. In analogy with TTMSSOH, $(Me_3Si)_3SiNHAd$ can be readily oxidised (E_{ox} = 0.86 vs SCE) and deprotonated to the aminyl radical **109** that transposes by radical aza-Brook rearrangement to the $(Me_3Si)_2[(Me_3Si)AdNH]Si\bullet$.[118,244,245] Using this highly nucleophilic α-amino silyl radical, the authors were able to engage secondary and even primary alkyl chlorides with *N*-heteroaryl chlorides under dual photoredox–nickel catalysis (T = 55 °C). No reaction was observed with TTMSSOH while TTMSS resulted in starting material consumption but did not lead to product formation. Furthermore, the lower oxidation potential of $(Me_3Si)_3SiNHAd$ meant that the milder photocatalyst $Ir(ppy)_2(dtbbpy)PF_6$ could be used in place of $Ir[dF(CF_3)ppy]_2(dtbpy)PF_6$ which usually employed in conjunction with TTMSSOH.

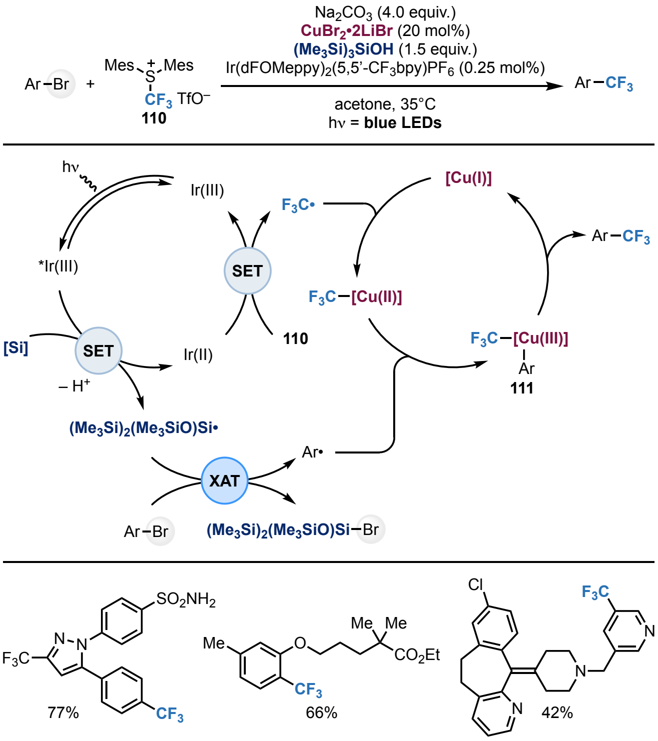
Scheme 56. $(Me_3Si)_3SiNHAd$-Enabled Coupling of Alkyl Chlorides and Aryl Bromides



Cu-catalysis. Copper is a cheap and abundant transition metal that is widely employed in cross-coupling strategies mostly due to the ease of reductive eliminations occurring from high-valent organyl–Cu(III) species.[246] However, copper catalysis can suffer from the poor ability of Cu(I) to undergo oxidative addition on aryl halides,[247,248] with the exception of activated electrophiles like aryl iodides or electron poor aryl bromides.[249,250] Metallaphotoredox catalysis has therefore been very useful in providing an alternative approach to overcome this oxidative addition challenge.

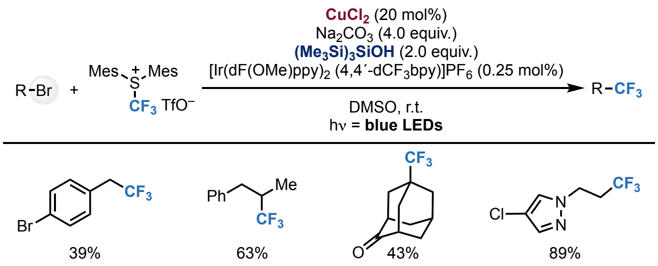
MacMillan has developed a dual photoredox–copper catalytic approach for the direct trifluoromethylation of aryl bromides where silicon radical-mediated XAT is used to activate the aromatic building block (Scheme 57).[205,251] In line with previous reports on dual photoredox-nickel catalysis, TTMSSOH was oxidized by the excited state of the Ir-photocatalyst to generate $(Me_3Si)_2(Me_3SiO)Si\bullet$ via deprotonation and radical Brook rearrangement. This silicon radical engaged in XAT with the bromide thus leading to the corresponding aryl radical species. Meanwhile, a $[Cu(II)]–CF_3$ complex was generated via SET reduction of **110**, which closed the photoredox cycle generating the F_3C•. This species was intercepted by the [Cu(I)] catalyst and the resulting [Cu(II)]–CF_3 species further reacted with the aryl radical to give the key high-valent Ar–[Cu(III)]–CF_3 complex **111**. Facile reductive elimination provided the trifluoromethylated product and regenerated the catalytically active [Cu(I)] species. Overall, this approach circumvented the difficult $2e^-$ oxidative addition of [Cu(I)] to the aryl bromide with two fast radical captures. In terms of substrate scope, electron-poor and electron-rich (hetero)aryl bromides were converted to the corresponding CF_3-containing products in yields.

Scheme 57. $(Me_3Si)_3SiOH$-Mediated Copper-Catalysed Trifluoromethylation of Aryl Bromides



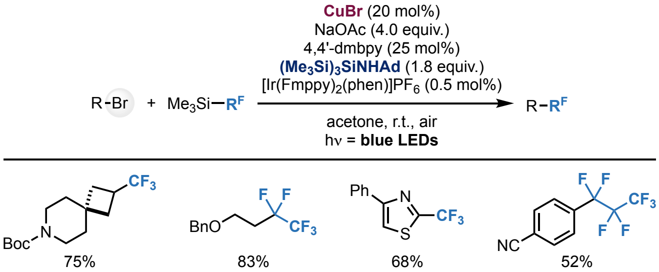
This approach was then translated to achieve the trifluoromethylation of unactivated alkyl bromides, a class of substrates which is typically out of reach for most copper-catalysed processes (Scheme 58).[252] Primary, secondary and tertiary derivatives delivered the products in average to high yields. When 4-bromobenzyl bromide was engaged, selective activation of the benzylic C–Br bond was observed, furnishing the 1-bromo-4-(2,2,2-trifluoethylbenzene) in 39% yield, owing to its lower BDE compared to sp^2 C–Br bonds (55.1 kcal mol^{-1} vs. 83.5 kcal mol^{-1}). The mild reaction conditions allowed base-sensitive homobenzylic bromide to be efficiently converted to their corresponding products, bypassing the undesired elimination pathway.

Scheme 58. $(Me_3Si)_3SiOH$-Mediated Copper-Catalysed Trifluoromethylation of Alkyl Bromides



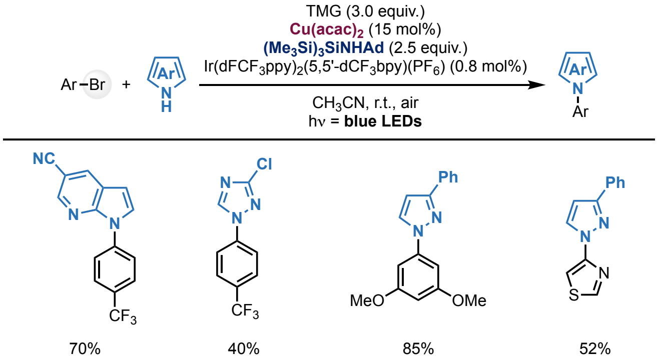
While the trifluoromethyl moiety is frequently used in MedChem programs, the introduction of high-order perfluoroalkyl groups is also of interest, especially to increase molecular properties like lipophilicity and electronegativity.[253,254] Complementing Pd- and Ni–based approaches,[255,256] MacMillan extended the previous metallaphotoredox manifold to achieve the general perfluoroalkylation of alkyl and aryl bromides using commercially available Ruppert–Prakash-type reagents ($Me_3Si–C_nF_{2n+1}$) (Scheme 59).[252] The nucleophilic character of these species required the presence of an external oxidant to turnover both catalytic cycles, running the reaction under air was found to sufficient to achieve high yields. Also in this case TTMSS and TTMSSOH performed poorly while $(Me_3Si)_3SiNHAd$ was identified as optimum. Under these conditions, primary and secondary alkyl bromides as well as (hetero)aryl bromides were successfully perfluoroalkylated in generally good yields.

Scheme 59. Silicon-Mediated Metallaphotoredox Copper-Catalysed Perfluoroalkylation of Alkyl and Aryl Bromides



This oxidative reaction manifold has also been extended to achieve Ullmann-Goldberg-type[257,258] cross-couplings between aryl bromides and nucleophilic *N*-heteroatomatics.[259] Using the same blueprint for the dual photoredox–copper perfluoroalkylation process (see Scheme 59) employing TTMSSOH as the XAT reagent, enabled the general coupling of a broad range of both *N*-heteroaromatics and (hetero)aryl bromides (Scheme 60). Very recently, this approach has also been extended to achieve the amination of alkyl bromides and chlorides building blocks.[260]

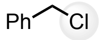
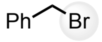
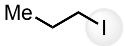
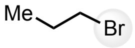
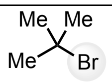
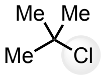
Scheme 60. Silicon-Mediated Metallaphotoredox Copper-Catalysed Arylation of Azoles



3.1.3. Germanium Radicals

Organogermanium hydrides are isoelectronic to silanes and stannanes and have found use in radical chemistry mostly to achieve hydrodefunctionalization processes.[261,262] Germanium radicals and their ability to abstract halogen atoms were first observed in 1970 by Brook while studying the photolysis of acyl–$GePh_3$ species in CCl_4.[263] Under these conditions, homolytic sp^2 C–Ge bond homolysis took place, generating Ph_3Ge•, which abstracted a chlorine atom from the solvent. In 1978 Tedder studied the Cl-atom abstraction from alkyl chlorides using alkyl germanium radicals in the gas phase.[264] Interestingly, the authors observed a stronger interplay of polar effects in comparison to analogous reactions of tin radicals under similar conditions. Fundamental studies in XAT reactivities were then reported by Hayashi, Mochida and Scaiano[23] in which several absolute rate constants for XAT processes were measured (Table 4). Overall, Bu_3Ge• displays a halogen-abstracting profile like that of Bu_3Sn• and about one order of magnitude slower in comparison with Et_3Si•.

Table 4. Comparison of XAT Rates using Ge-, Sn- and Si-radicals (all k_{XAT} are in M^{-1} s^{-1}).[a]

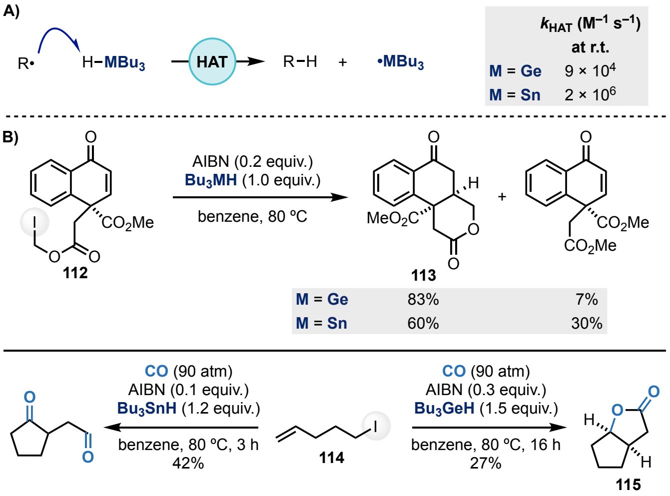
	k_{XAT} (M^{-1} s^{-1})		
Substrate	**Bu_3Ge•**	**Bu_3Sn•**	**Et_3Si•**
$Cl_3C{-}Cl$	3×10^8		5×10^9
	2×10^6	1×10^6	2×10^7
	8×10^8	1×10^9	2×10^9
	$>3 \times 10^7$		4×10^9
	5×10^7	3×10^7	5×10^8
	9×10^7	1×10^8	1×10^9
	$<5 \times 10^4$	3×10^4	3×10^6

[a] The rate constants for XAT (k_{XAT}) have been approximated to the near integral number.

In analogy to tin and silicon radicals, the high reactivity of germanium radicals in XAT settings is also rooted on their ability to stabilize charge separation in the transition state (polar effects). However, the H-donor ability of germanes is attenuated in comparison with stannanes (the HAT between primary alkyl radicals and Bu_3GeH is ~20 times slower than for Bu_3SnH, Scheme 61A),[265] which is a favorable aspect for the development of radical cascade processes. These reactivity features, together with their reduced toxicity, make germanes interesting alternatives to tin hydrides.[261,262]

The utilization of germanium radicals in organic synthesis has been generally achieved under thermal conditions using the decomposition of AIBN as the initiation mechanism as pioneered by Hershberger in 1985.[266] A discussion of these processes is beyond the scope of this review, but relevant examples can be found in the work of Beckwith,[267] and Ryu[268] in which germane reagents have been demonstrated to be superior to Bu_3SnH for the realization of challenging cyclizations (e.g. **112** → **113**) and intermolecular reactions (e.g. **114** → **115**) (Scheme 61B).

Scheme 61. (A) Rates of HAT for the Generation of Germanium and Tin Radicals.[a] (B) Comparison in the REactiivty of Alkyl Iodides Using Germanium and Tin Radicals.

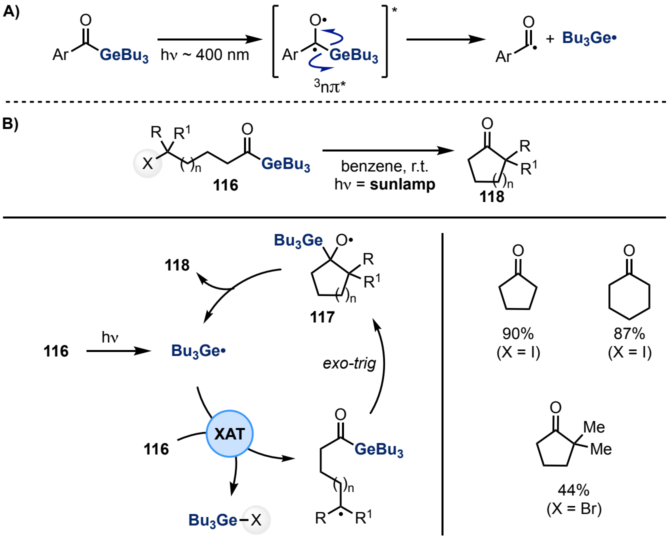


[a] The rate constants for XAT (k_{XAT}) have been approximated to the near integral number.

The photochemical fragmentation of acyl germanes has represented one of the most convenient methods for the generation of germanium radicals via Norrish type I reactivity from their triplet (n,π*) excited state (Scheme 62A).[263,269,270] In contrast to classical carbonyl photochemistry where high-energy UV light is generally required for photoexcitation, the red-shifted absorption of acyl germanes allows the use of low-energy visible light (>380 nm).[271,272] This photochemical reactivity has been used as an initiation mechanism in polymerization processes and its application in biomedical settings (e.g. dental filling) retains a high interest in view of the low toxicity of germanes, and the low-energy light required for their activation.[273]

Synthetic application of Norrish type 1 fragmentation of acyl germanes has been demonstrated by Curran to achieve the intramolecular cyclization of alkyl iodides under both thermal (AIBN) and photochemical conditions (Scheme 62B).[274] This process was based on a radical chain initiated by the Norrish type I fragmentation of **116**. This photochemical step generated the Bu_3Ge• that underwent XAT with the alkyl iodide followed by intramolecular cyclization onto the acyl germanium moiety. The resulting α-Ge O-radical **117** underwent β-scission across the weak C–Ge bond thus giving the cyclic ketone **118** and chain-carrying Bu_3Ge•. Later studies from the same authors extended this reactivity to related cyclizations of secondary and tertiary alkyl bromides.[275-277]

Scheme 62. (A) Photochemistry of Acyl Germanium Species. (B) Synthetic applications of Acyl Germanium-Containing Alkyl Halides.

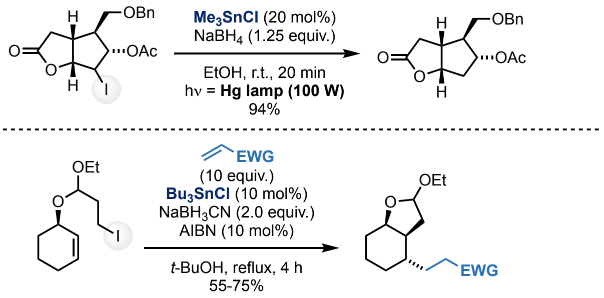


Other photochemical approaches for the generation of germanium radicals are direct HAT by *t*-BuO•,[278] or UV-C decomposition of digermoxanes $(R_3Ge)_2O$,[279] although these have mostly found use in laser-flash photolysis and not in synthetic settings.

3.1.4. Boron Radicals

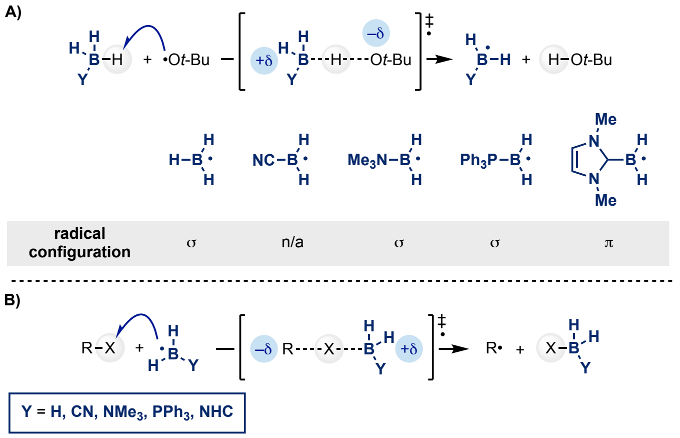
Borohydrides have found broad utilization in radical chemistry due to their ability to convert $R_3Sn–X$ species into the corresponding hydrides $R_3Sn–H$.[280,281] This has been frequently employed to develop transformations utilizing sub-stoichiometric amounts of tin reagents as pioneered by Corey[93] and Stork[282] under both photochemical and thermal activation (Scheme 63).[283]

Scheme 63. Radical Reactions of Alkyl Iodides with Sub-stoichiometric Amounts of Tin Reagents.



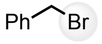
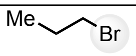
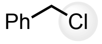
A different avenue is the use of boron radicals (boryl) as halogen-abstracting reagents (Scheme 64). These open-shell species are usually generated by HAT from the corresponding borohydrides and Lewis base–BH_3 complexes (Lewis base = HCN, Me_3N, Ph_3P, NHC) owing to their relatively low B–H BDEs.[284] The hydridic nature of the H-atom in these boronates means that electrophilic radicals (e.g. *t*-BuO•, triplet benzophenone, $^{-}O_3S$–O•) are required to maximize polar effects in the HAT step (Scheme 64A).[285,286] The corresponding boryl radicals are metalloid radicals of σ-configuration (bar the NHC–BH_2•, in which the unpaired electron is delocalized into the NHC π-system)[287] and with a formal negative charge, which provides them with distinct nucleophilic character (Scheme 64B).[288] XAT reactivity of boryl radicals follows the same mechanistic features discussed in Section 2: the strong nature of the resulting B–X bonds renders the reactions exothermic while the boryls' nucleophilic character stabilizes the interplay of polar effects in the abstraction TS.[289]

Scheme 64. (A) Generation and Properties of Boryl Radicals Generated by HAT. (B) Charge Transfer in XAT Using Boryl Radicals.



The ability of boryl radicals to take part in XAT reactivity has been amply demonstrated by the mechanistic EPR and FLP studies from Roberts, Ingold and Lalevée.[27,290] As shown in Table 5, the rate constants for XAT determined in these pioneering works, indicates that Me_3N–BH_2• and H_3B• have a reactivity comparable to the one of Et_3Si•, while NHC–BH_2• has a slower profile which is in line with its attenuated nucleophilic character.

Table 5. Rates of XAT from B- and Si-Radicals.[a]

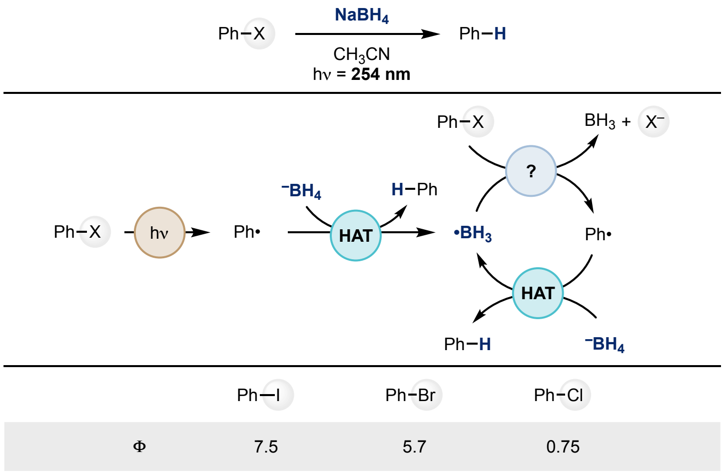
	k_{XAT} (M^{-1} s^{-1})			
Substrate	**Et_3Si•**	**$Me_3N–BH_2$•**	**H_3B•**	**NHC–BH_2•**
Cl_3C-Cl	5×10^9	5×10^9	2×10^9	2×10^7
	2×10^9	2×10^9	5×10^8	
	5×10^8	1×10^8	1×10^8	
	2×10^7	1×10^7	3×10^7	

[a] The rate constants for XAT (k_{XAT}) have been approximated to the near integral number.

Despite the versatility of boryl radicals in XAT settings, efforts towards their utilization in synthetic photochemistry are scarce as they are usually generated under thermal conditions (e.g. decomposition of AIBN) and their reactivity has been reviewed elsewhere.[291,292]

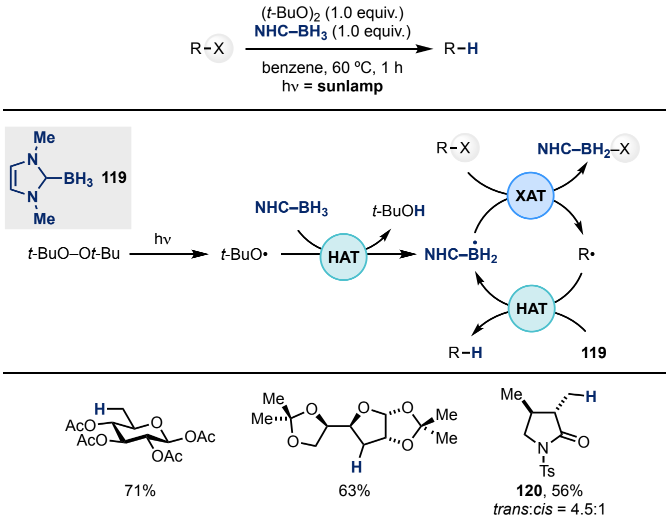
The first use of boryl radicals in XAT using photochemistry can be found in the pioneering works of Barltrop,[293] Groves,[294] Ohashi,[295] Beckwith[296] and Epling[297] on the photochemical dehalogenation of aryl halides using $NaBH_4$ under high-energy light (hν = 254 nm) irradiation (Scheme 65).[298] These processes are initiated upon homolysis of the sp^2 C–X bond followed by HAT between the Ph• and the borohydride. This event generated the boryl radical •BH_3 which acted as chain-carrier for the reduction of the aryl halide. Although a distinction between XAT and SET was not advanced to rationalize the key reaction between Ph–X and •BH_3, a good correlation was obtained between the quantum yields (Φ) of the processes and the various sp^2 C–X BDEs.

Scheme 65. Photochemical Dehalogenation of Aryl Halides Using $NaBH_4$.



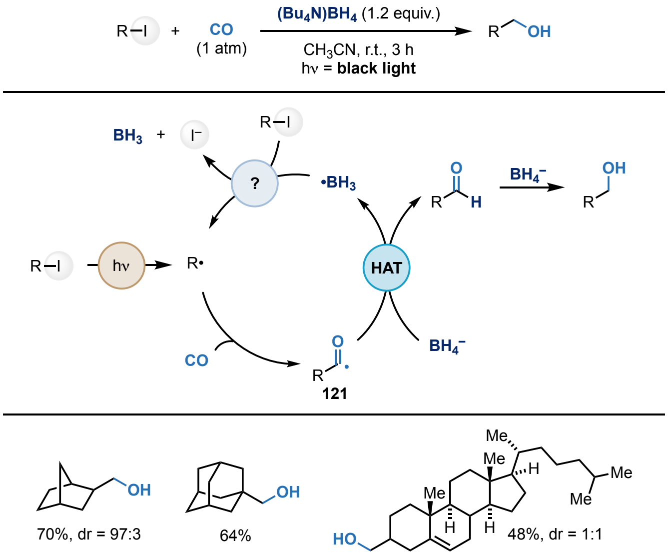
An example of photochemical dehalogenation mediated by NHC–BH_3 was reported by Fensterbank, Lacôte, Malacria and Curran in 2011 (Scheme 66).[299] In this case, the authors took advantage of the ability of standard sun lamps to promote the homolytic O–O bond cleavage of (t-BuO)$_2$. The resulting *t*-BuO• was used to generate NHC–BH$_2$• by HAT on **119** (BDE$_{B–H}$ = 79 kcal mol^{-1}). This step initiated a radical chain propagation based on XAT and HAT, which enabled the homolytic activation of alkyl iodides and bromides and was also applied to radical cyclization cascades (e.g. **120**).[300,301]

Scheme 66. Photochemical Dehalogenations of Alkyl Halides Using NHC–Boryl Radicals.



A powerful use of boryl radicals can be found in the work of Ryu on the hydroxymethylation of unactivated primary, secondary and tertiary alkyl iodides and tertiary alkyl bromides with CO (Scheme 67).[302,303] In these examples, the alkyl halides were engaged in photo-initiated radical-chain propagations where the alkyl radical (generated upon photochemical homolysis of the sp^3 C–X bond) intercepted CO thus providing the corresponding acyl radical **121**. This species reacted with the borohydride to give the aldehyde product that was further reduced to the alcohol. This HAT step provided the key chain-carrying H$_3$B• that engaged in a following reaction with the halide. The authors rationalized this process on the basis of SET due to the low reduction potential of •BH$_3$, but XAT was not excluded.

Scheme 67. Boryl Radical-Mediated Carbonylation of Alkyl Iodides.

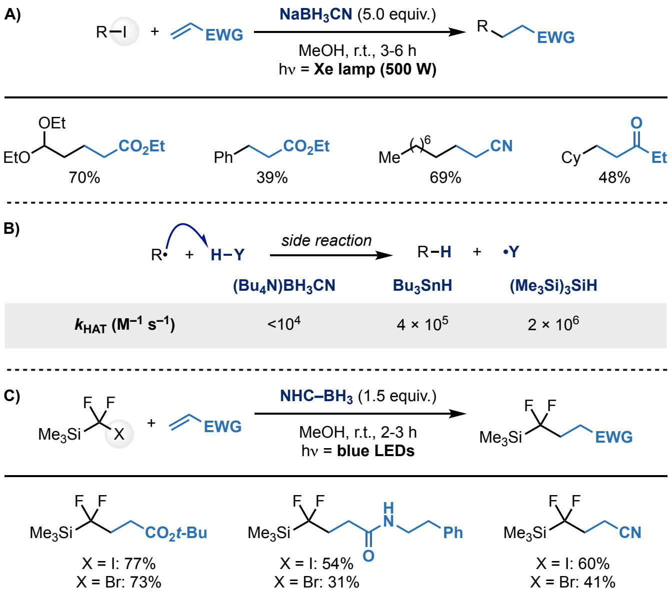


In 2014, the same group demonstrated a related photochemical strategy for the Giese alkylation of acrylates and other α,β-unsaturated acceptors with alkyl iodides (Scheme 68A).[304] This approach used $NaBH_3CN$ as boryl radical precursor and required irradiation from a 500 W Xe lamp. In analogy to the reactivity discussed above, photochemical homolysis of the sp^3 C–I bond generated the alkyl radical that underwent Giese addition to the acrylate. This step provided an α-ester radical that gave the desired product upon HAT with the borohydride. In this way, the chain-carrying boryl radical was regenerated for the subsequent activation of the iodide.

The utilization of a borohydride as XAT reagent precursor and HAT donor has a significant mechanistic advantage over the use of tin and silicon hydrides. Indeed, while $(CN)BH_2$•, Bu_3Sn• and $(Me_3Si)_3Si$• all display similar XAT reactivity on alkyl iodides, borohydrides are much slower at HAT with alkyl radicals (Scheme 68B). This means that the frequent side reactions caused by direct reduction can be minimized, facilitating the implementation of multicomponent processes. Despite this, functional group compatibility with borohydride reagents can sometimes be lower.[305]

More recently, a similar photochemical approach was exploited by Dilman to achieve the silyl-difluoromethylation of Giese acceptors (Scheme 68C).[306] In this case the NHC–BH_3 reagent was identified as optimum and a broad range of acceptors spanning esters, amides, ketones, sulfones and nitriles was engaged. The activated nature of the starting silyl-difluoromethyl halides was beneficial in terms of reaction set-up as simple irradiation from blue LEDs is sufficient to initiate the process and sustain the boryl radical chain reactivity.

Scheme 68. (A) Boryl Radical-Mediated Giese Reactions of Alkyl Iodides. (B) Comparison of the Rate Constants for HAT to Generate Boryl, Tin and Silicon Radicals.[a] (C) Photochemical Boryl Radical-Mediated Giese Reactions of Silyl-difluoromethyl Halides.

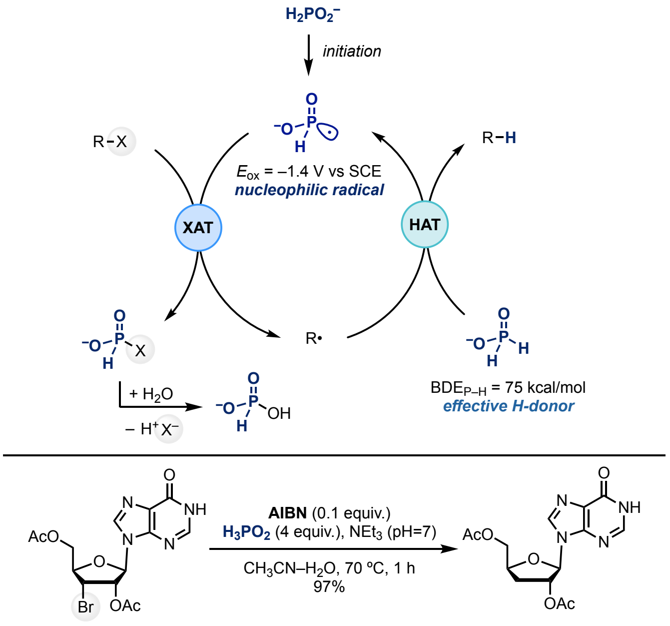


[a] The rate constants for XAT (k_{XAT}) have been approximated to the near integral number.

3.1.5. Phosphorous Radicals

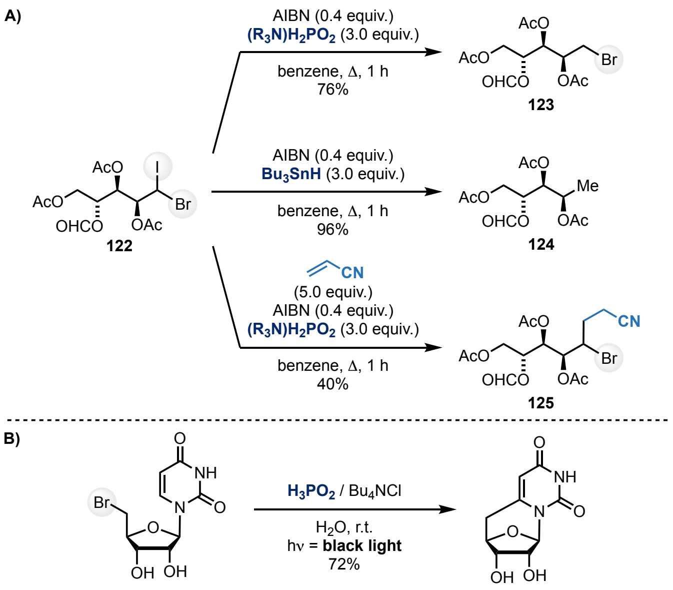
Phosphorous radicals derived from phosphates and hypophosphites can be generated by HAT or SET from their corresponding phosphoric and hypophosphorous acids.[307-309] In particular, hypophosphorous acid, H_3PO_2, and its salts (e.g. 1-ethylpiperidine hypophosphite) have found frequent application in radical chemistry as (i) the hypophosphinyl radical anion ($HPO_2^{\bullet-}$) is a nucleophilic species ($E_{\text{ox}} \sim -1.4$ V vs SCE),[310] capable of halogen abstraction, and (ii) H_3PO_2 contains a relatively weak P–H bond (BDE = 75 kcal mol^{-1}),[311] which makes it a good HAT donor. These features are optimal for application in radical chain dehalogenation and deoxygenation reactions where hypophosphites have been used as a water-soluble, non-toxic and inexpensive alternative to tin hydrides (Scheme 69).[312-315] It is important to note that phosphorous radicals are however less effective at XAT that tin and silicon reagents and often engage in competitive addition to olefins (hydrophosphination).[312,316] Indeed, mechanistic work carried out by Ingold on $(EtO)_2(O)P\bullet$ demonstrated that bromine abstraction with this species is 2 orders of magnitude slower than with $Bu_3Sn\bullet$.[317] Further study on different phosphorous radicals demonstrated that their reactivity towards XAT decreases with the radical planarization, which translates into a lower spin density at the P-atom.[316,318-320]

Scheme 69. Dehalogenation of Alkyl Bromides by the Hypophosphinyl Radical Anion.



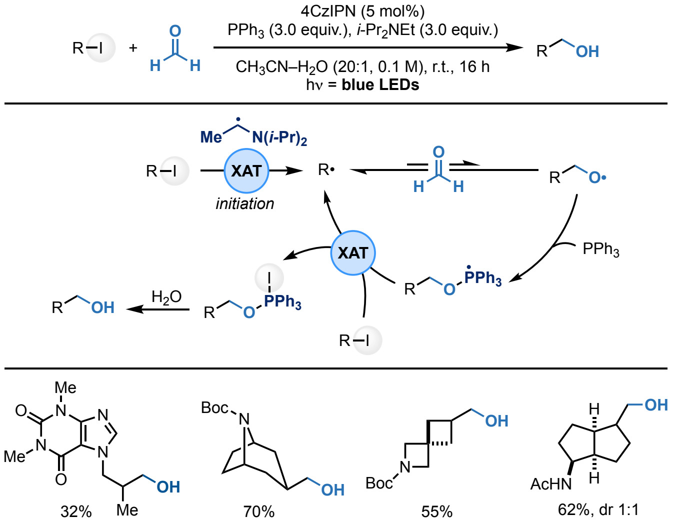
The utilization of phosphorous radicals in synthetic XAT strategies has mostly relied on thermal activation since the introduction of these reagents in atom-transfer processes by Barton 1982.[321,322] As mentioned before, phosphorous radicals undergo XAT at slower rates than other species (e.g. tin and silicon radicals) and although this can be perceived as a limitation, it can provide opportunities for the development of chemoselective reactions. This has been demonstrated by Suarez when studying the reactivity of 1-deoxy-1-iodo-1-halo-alditols (Scheme 70A).[323] In these examples, hypophosphite-based XAT was used to selectively deiodinate **122** to **123**, in contrast to the use of Bu_3SnH which gave complete bis-dehalogenation (**124**). This chemoselective sp^3 C–I bond activation protocol was also applied to the addition of the resulting 1-bromo-alkyl radical to Giese acceptors (e.g. **125**). More recently, Perchyonok described the use of black light (near UV) to initiate the cyclization of bromo-nucleosides (Scheme 70B).[324]

Scheme 70. (A) Hypophosphinyl Radical Anion-Mediated Reactions of Alkyl Halides. (B) Cyclization of Alkyl Bromides.



More recently phosphoranyl radicals have been proposed to be involved in the activation of alkyl iodides as part of hydroxymethylation reactions (Scheme 71).[325] The process enabled the use of formadehyde as C1 synthon in radical chemistry and was based on a radical chain mechanism based on XAT reactivity for both the initiation and the propagation step. The use of photoredox generated α-aminoalkyl radicals (see Section 3.3.1) was used to convert the secondary alkyl iodides into the corresponding alkyl radical that intercepted formaldehyde. While this thype of radical addition is reversible, the presence of a stoichiometric phosphine additive ensured the immediate trapping of the oxygen radical. The resulting phosphoranyl radical was determined to be strongly nucleophilic but not highly reducing, which led the authors to proposed iodine abstraction as the most likely chain carrying mechanism.

Scheme 71. Photochemical Hydroxymethylation of Alkyl Iodides via Phosphoranyl Radicals.



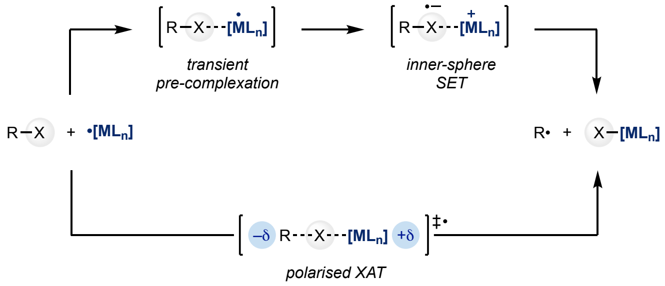
The underutilization of light activation for this purpose is notable, considering the vast amount of literature applying photoredox conditions as a mild way to generate related P-radicals via HAT or SET oxidation.[326-333] This blueprint, in contrast, has been implemented in many P-radical additions to olefins but, to the best of our knowledge, not in XAT reactivity.

3.2. Metal-Based XAT Reagents

In this Section we describe the use of open-shell metal complexes (i.e. metalloradicals) in photochemical XAT processes. These are commonly paramagnetic 17e$^-$ complexes, characterized by a SOMO based on a highly directional, singly-occupied d orbital. As a result, they display strong tendency towards atom abstraction to give a more stable 18e$^-$ closed-shell complex.[334,335] This reactivity profile has fundamental implications not just in XAT chemistry but in transition-metal catalysis as a whole since the activation of alkyl halides in cross-coupling reactions catalyzed by first-row transition metals (e.g. Ni, Co and Fe) is often proposed to occur via halogen transfer.[336-341] Considering the rise of metallaphotoredox approaches in recent years, particularly using nickel catalysis, metal-mediated XAT activation steps might be occurring although they are not explicitly discussed in the mechanistic proposals.

Accordingly, this section will not cover examples of metallaphotoredox catalysis[16,342] and will focus on representative examples of photochemical processes in which the metalloradical is a well-defined species and displays a role restricted to XAT. In some cases, *inner-sphere* SET processes to activate C–X bonds will also be discussed, considering the strong similarities they share with polarized XAT and the difficulties in discerning between these two processes (Scheme 72).[343]

Scheme 72. Mechanistic for XAT Reactions Involving Metal Complexes.



3.2.1. Dimeric Carbonyl Complexes Displaying Photo-Cleavable Metal–Metal Bonds

Low-valent metal carbonyl complexes (e.g. Mn, Fe, Co, W or Re) featuring a metal–metal bond have been extensively studied in the last 50 years and are considered nowadays archetypal complexes in the field of organometallic chemistry.[344-347] These species display interesting photochemistry and upon light absorption they undergo metal–metal bond homolysis to give a 17e$^-$ metalloradical pair (Scheme 73A).[348] The majority of carbonyl-metalloradicals recombine at almost diffusion controlled-rates but upon continuous light irradiation other processes can take place such as XAT from organic halides.[343]

The halogen abstraction is a thermodynamically favorable process by virtue of the fulfillment of the $18e^-$ rule and results in the formal $1e^-$ oxidation of the metal center together with the coordination of the halide ion.[334,343]

Dimeric carbonyl complexes with a metal center in oxidation state [M^0] (e.g. Mn, Re, Co) are usually homoleptic (bearing 8 or 10 CO ligands), although examples of heteroleptic complexes have been described with some of the CO ligands substituted by phosphines. Complexes based on metals in oxidation state [M^{+1}] (e.g. Fe, Cr, Mo, W) usually contain an additional anionic η^6-cyclopentadienyl ligand. The structures of the most representative examples are depicted in Scheme 73B.

The reactivity of these species is mainly governed by either CO dissociation or homolytic metal–metal bond cleavage, both of which can be triggered using thermal or photochemical conditions.[348-352] Upon light irradiation, the prevalence of CO dissociation vs metal–metal bond homolysis is wavelength-dependent, with high-energy (UV light) irradiation generally leading to CO loss and low-energy irradiation (visible light) resulting in metal–metal bond homolysis. In the latter case, light absorption at σ-σ^* transitions result in the weakening of the metal–metal bond which, upon cleavage, generates two metalloradicals with a single electron in a non-bonding d-orbital (Scheme 73C).

The relatively long lifetime and low-energy absorption profile of most metalloradical species make them suitable for laser-flash photolysis studies and a large number of rate constants for their XAT reaction with different halide donors are available (Table 6).[349,353-359] In addition, by performing experiments with mixed metal dimers (i.e. [M–M']), Wrighton determined a XAT reactivity scale for the abstraction of both 1-iodopentane and CCl_4 (Scheme 73D).[360,361]

Scheme 73. Photochemistry of Carbonyl Metal Dimers. (A) Photochemical Generation of 17e⁻ Metalloradicals and Their XAT Reactivity. (B) Representative Examples of Carbonyl Dimers Containing [M–M] Bonds. (C) Structure, Bonding and Primary Photochemical Process. (D) Reactivity Scale of Metalloradicals toward XAT.

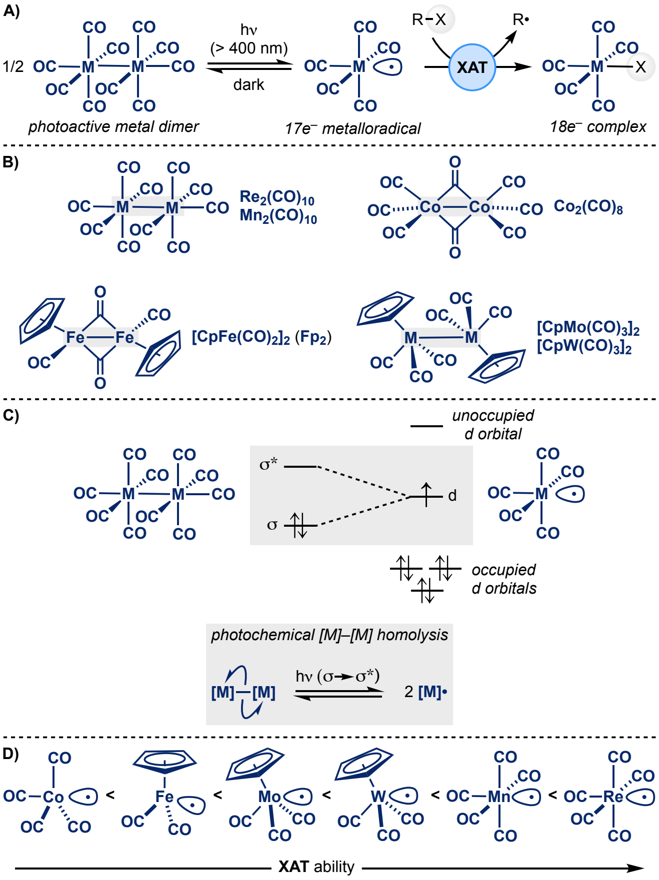
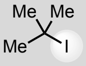
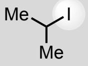
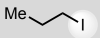
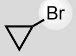
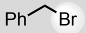


Table 6. Rates of XAT from Various Metalloradicals.[a]

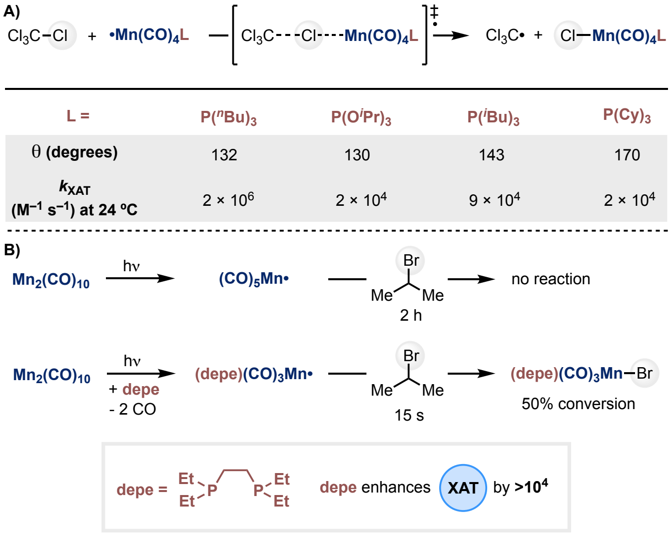
	k_{XAT} (M^{-1} s^{-1})							
[M]•	Cl_3C-Cl	Br_3C-Br	BrH_2C-Br					
$(CO)_4Co•$	$<2 \times 10^3$							
$Cp(CO)_2Fe•$	4×10^3							
$Cp(CO)_3Mo•$	1×10^4	2×10^8			1×10^5	7×10^3	4×10^4	8×10^4
$Cp(CO)_3W•$	3×10^4	4×10^8	4×10^2	6×10^6	3×10^5	1×10^4	9×10^4	9×10^4
$(CO)_5Mn•$	1×10^6	1×10^9	7×10^3					5×10^5
$(Bu_3P)(CO)_5Mn•$	2×10^6							
$(CO)_5Re•$	4×10^7							

$(EtPh_2P)(CO)_4Re$•	6×10^8		1×10^7					
$(Me_3P)(CO)_4Re$•	2×10^9	5×10^9	8×10^8					1×10^9

[a] The rate constants for XAT (k_{XAT}) have been approximated to the near integral number.

Beyond enthalpic factors associated with the strength of the forming metal–halogen bond, polar and steric effects are also important, as demonstrated by Brown's work on the reactivity of manganese metalloradicals $(L)(CO)_4Mn$• with CCl_4 (Scheme 74A).[362] In these examples, the XAT profile of the corresponding Mn-metalloradical was largely influenced by the nature of the phosphine ligand (L), for example, when L = PBu_3 the Cl-abstraction was two orders of magnitude faster than when L = $P(O\textit{i}\text{-}Pr)_3$. As these two ligands have similar sizes, this effect was rationalized on the basis of an increase in the nucleophilicity of the metalloradical bound to the more electron donating PBu_3. Steric effects were also demonstrated when evaluating the reactivity of Mn-complexes with bulky phosphine ligands. In these cases, the increase of steric hinderance of the overall metalloradical species (indirectly evaluated using the Tolman angle of the ligand, ϑ) translated into slower XAT reactivity. A similar trend based on the interplay of both polar and steric effects was observed for related $(L)(CO)_4Re$• species.[354,363] Along the same lines, it was observed that irradiation of $Mn_2(CO)_{10}$ in the presence of the electron-rich and small disphosphine ligand depe [1,2-bis(diethylphosphino)ethane] generated the highly reactive metalloradical $(depe)(CO)_3Mn$•, capable of undergoing XAT with unactivated alkyl and aryl bromides (Scheme 74B).[363]

Scheme 74. (A) Impact of Phosphine Ligands on the XAR Rate Constant with Mn-Metalloradicals.[a] (B) Polar and Steric Effects in Mn-Mediated XAT Reactions.



[a] The rate constants for XAT (k_{XAT}) have been approximated to the near integral number.

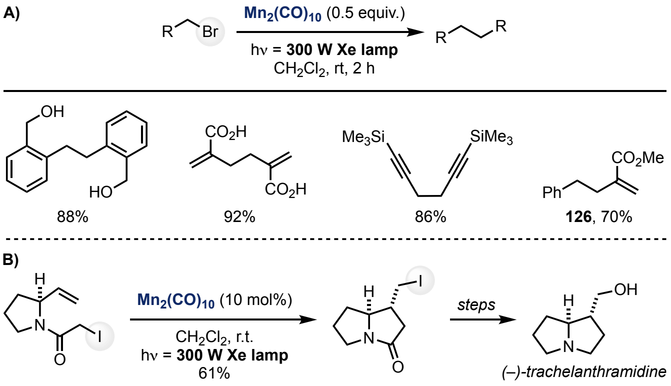
The modular reactivity and ease of generation, together with the many in-depth mechanistic studies have facilitated the implementation of metalloradical-based XAT processes in organic synthesis. However, despite the number of photoactive species based on Re, W, Mo, Co and Cr, synthetic photochemistry has thus far been performed almost exclusively with $Mn_2(CO)_{10}$ and, to a lesser extent, Fp_2.

Dimanganese decacarbonyl, $Mn_2(CO)_{10}$.

$Mn_2(CO)_{10}$ is a commercially available, bench-stable, low-valent dimeric complex that has shown applications in organic synthesis for more than half a century.[364] The ease of generation of $(CO)_5Mn•$ by visible-light irradiation has facilitated mechanistic studies on its reactivity as well as synthetic applications in XAT processes.[348,362,365] Historically, the photochemical reaction between $Mn_2(CO)_{10}$ and CCl_4 was reported by Bamford in 1965 who proposed it to be based on a chlorine transfer[366] and has found application in the initiation of polymerization processes (vide infra).

Although reactivity with alkyl halides was reported before,[362,367] the utilization of Mn-metalloradicals in organic synthesis started in 1999 when Parson used them for the photochemical dimerization of allylic, propargylic and benzylic bromides (Scheme 75A).[368] This method provided a mild alternative to obtain Wurtz-type coupling products without the need of sodium metal or other highly reactive organometallic reagents. The mild reaction conditions allowed broad functional group compatibility, including alcohol, esters and free carboxylic acids. In addition, the cross-coupling of two different substrates (e.g. **126**) was achieved in synthetically useful yields when one of the partners was used in two-fold excess. Shortly after, the same group extended this photochemical strategy using catalytic $Mn_2(CO)_{10}$ to achieve the cyclization of *N*-allyl-α-iodoamides[369,370] and the ATRC between Cl_3CBr and divinylated ethers and tosylamides. The synthetic value of this Mn-based photocatalytic process was further demonstrated in the synthesis of the alkaloid (–)-trachelanthamidine (Scheme 75B).[371-373] The use of biphasic CH_2Cl_2/NaOH(aq) conditions in the presence of a quaternary ammonium salt as phase-transfer agent was found to be beneficial in many cases, simplifying the removal of metal byproducts and allowing the use of $Mn(CO)_5Br$ as precursor.[373]

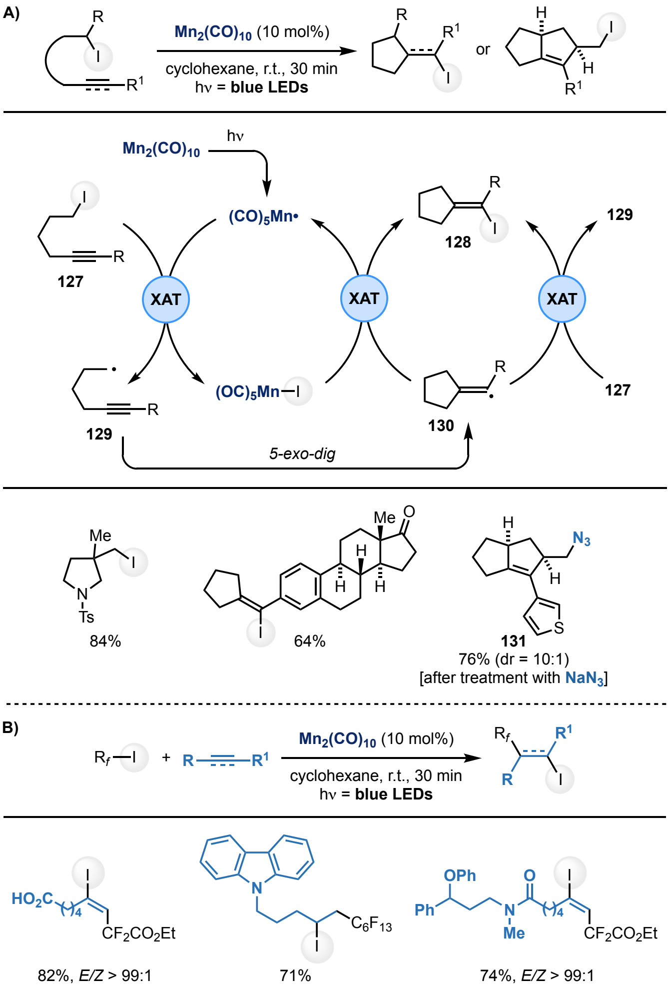
Scheme 75. (A) Photochemical Dimerization of Alkyl Bromides Using $Mn_2(CO)_{10}$. (B) Photochemical ATRC Reaction of Alkyl Iodides Using $Mn_2(CO)_{10}$.



More recently, the use of $Mn_2(CO)_{10}$ in photocatalytic ATRC processes has been further explored by Zhang in the development of *5-exo-dig* and *5-exo-trig* radical cyclizations of alkyl iodides to access the corresponding alkenyl and alkyl iodides (Scheme 76A).[374] The authors reported a fast reaction with a quantum yield (Φ) of 1.5, thus suggesting the presence of radical chain propagations sustaining the reactivity. Using the ATRC reaction of iodide **127** to give **128** as an example, blue LEDs irradiation enabled photochemical metal–metal bond homolysis thus generating the resultant Mn-metalloradical. This species underwent XAT with the alkyl iodides to give the C-radical **129** and the $(CO)_5Mn–I$ complex. Upon *5-exo-dig* cyclization, the vinyl radical **130** delivered product **128** by XAT with either $(CO)_5Mn–I$ (Mn-based catalytic cycle) or with the starting iodide **127** (radical chain propagation). This protocol exhibited good functional group tolerance as well as an array of structural variations in the alkene/alkyne acceptor, representing a convenient method to build complex alkyl/alkenyl iodides for further elaboration.

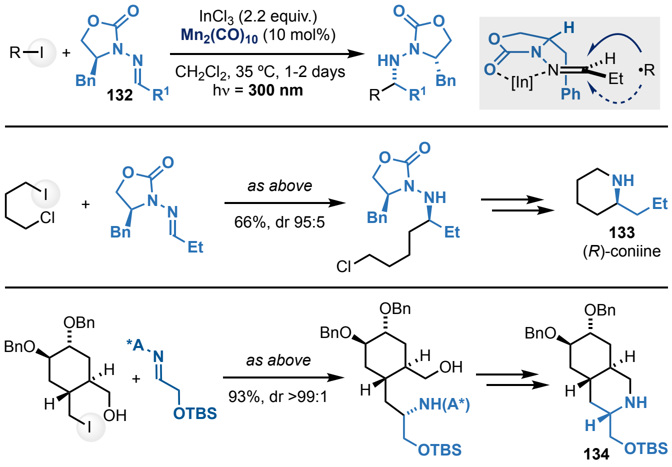
Further work from the same authors focused on the intermolecular ATRA–fluoroalkylation of alkenes and alkynes with activated α-difluoroesters and perfluoroalkyl iodides to give the desired alkyl and alkenyl iodides in good yield and high levels of *E* selectivity (Scheme 76B).[375]

Scheme 76. Application of $Mn_2(CO)_{10}$ in Photochemical Reactions of Iodides. (A) ATRC Reactions. (B) ATRA Reactions.



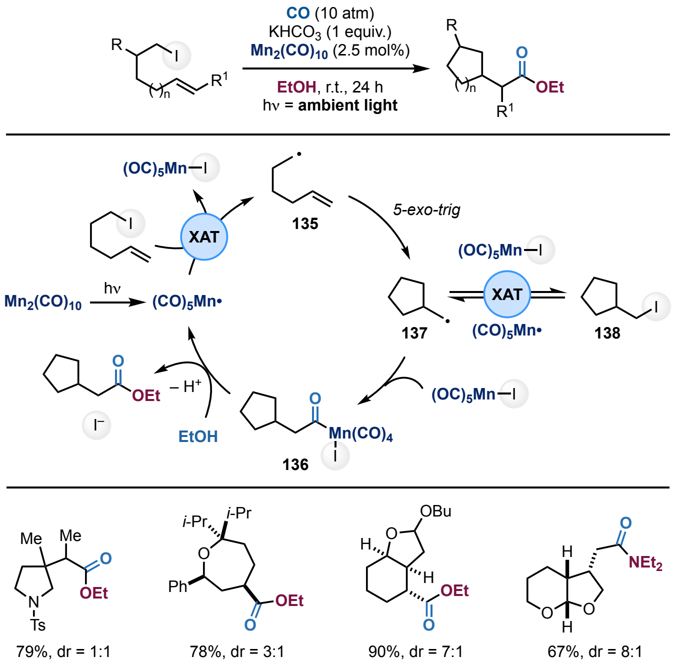
A powerful example of Mn-metalloradicals in synthetic photochemistry was demonstrated by Friedstad with the development of diasteroselective additions of alkyl iodides to chiral *N*-acylhydrazones **132** (Scheme 77).[376-378] This approach enabled the use of primary iodides which are difficult to engage using strategies based on Et_3B/O_2[379] or Bu_3SnH[380,381] owing to competitive Et• addition to **132** or premature radical hydrogenation, respectively. The chiral oxazolidinone-based auxiliary allowed the radical addition to occur with high levels of diasteroselectivity (generally > 95:5) which was used to access, upon N–N bond reduction, enantioenriched α-branched amines. This methodology has found many applications and, for example, was used in the asymmetric synthesis of alkaloids (e.g. (*R*)-coniine, **133**),[382,383] α- and γ-aminoesters,[384,385] perhydroisoquinolines (e.g. **134**)[386,387] and several intermediates for the preparation of tubulysin antibiotics.[388]

Scheme 77. Photochemical Enantionselective Radical Additions to Hydrazones.



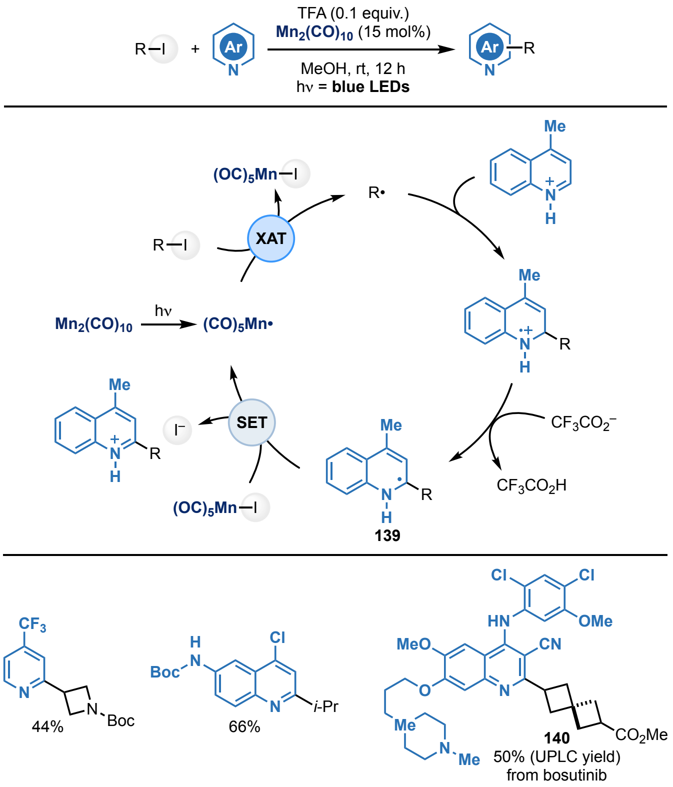
In 2016 Alexanian reported the carbonylative cyclization of alkyl iodides using catalytic amounts of $Mn_2(CO)_{10}$ under CO atmosphere (10 atm) (Scheme 78).[389] This approach combined the ability of $(CO)_5Mn•$ to undergo XAT with the activation of CO by OC→Mn coordination, which enabled a subsequent radical carbonylation. Although the use of powerful light sources was not required, the reactivity was completely suppressed when the reaction was conducted in the dark, thus suggesting that ambient light was enough to initiate and sustain the process. Regarding the mechanism, after Mn-metalloradical generation and XAT, the resulting C-radical **135** underwent *exo-trig* cyclization followed by carbonylation with $Mn(CO)_5I$ to give the acyl complex **136**. Nucleophilic addition of the alcohol solvent (e.g. EtOH) provided the corresponding α-cyclic esters and regenerated $(CO)_5Mn•$. It is interesting to note that intermediate **137** could also react with $Mn(CO)_5I$ via XAT thus giving the ATRC iodide product **138**. This reactivity was proved experimentally as this species accumulated at low conversion. However, this pathway is reversible [$(CO)_5Mn•$ can regenerate **137** by XAT on **138**] which eventually channels the reaction back into the final carbonylation manifold. Overall, this methodology allowed the replacement palladium catalysts, which are normally used in carbonylative processes of organic halides, with an inexpensive, first-row metal catalyst under relatively low CO pressure. Amine nucleophiles could be used as demonstrated by formation of amides in high yield.

Scheme 78. Photochemical Cyclization–Carbonylation of Alkyl Iodides.



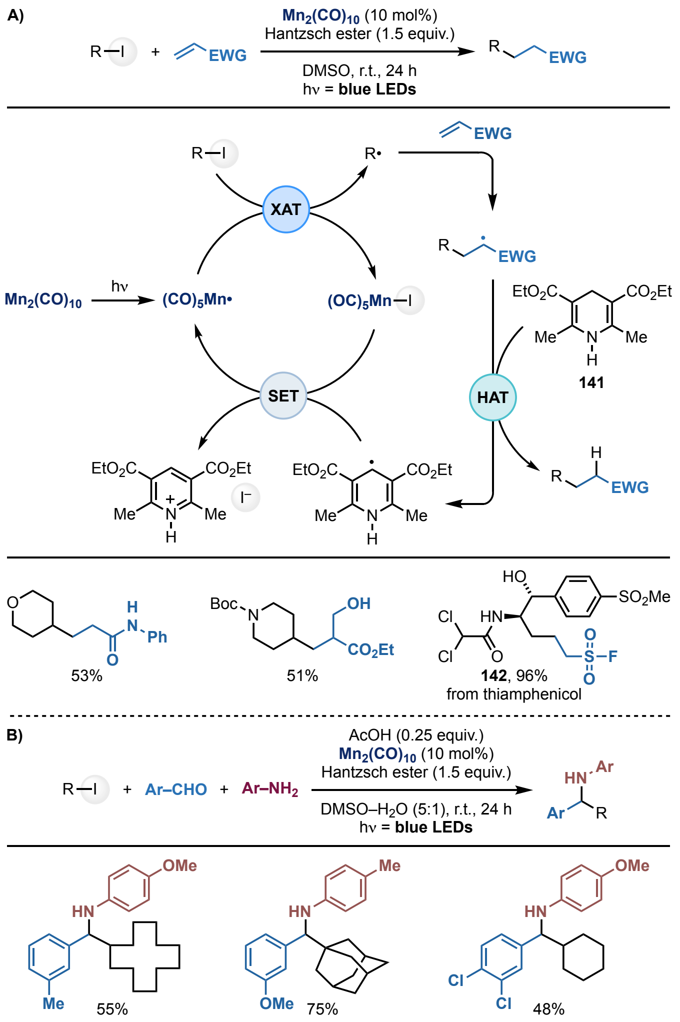
In 2017, Pfizer scientists in collaboration with the group of Frenette applied Mn-based XAT to use alkyl iodides in Minisci alkylation of several *N*-heterocycles (Scheme 79).[390] The proposed mechanism, supported by laser-flash photolysis measurements and DFT calculations, involved a Mn-catalytic cycle initiated by photochemical Mn–Mn bond homolysis. The resulting (CO)$_5$Mn• underwent XAT from an alkyl iodide to give the corresponding C-radical and Mn(CO)$_5$I. Minisci addition to the azine and deprotonation provided the α-*N*-radical **139** that was proposed to undergo SET with Mn(CO)$_5$I to close the catalytic cycle and deliver the product. This practical protocol enabled facile coupling between two electrophilic species and led to the installation of primary, secondary and tertiary alkyl fragments tolerating many functionalities (e.g. free alcohols, *N*-Boc protected amines, sugars) as well as small (hetero)cyclic and spirocyclic motifs. The robustness of the method was further demonstrated by the late-stage C–H alkylation of several drugs (e.g. bosutinib, **140**).

Scheme 79. Photochemical Minisci Reaction of Alkyl Iodides.



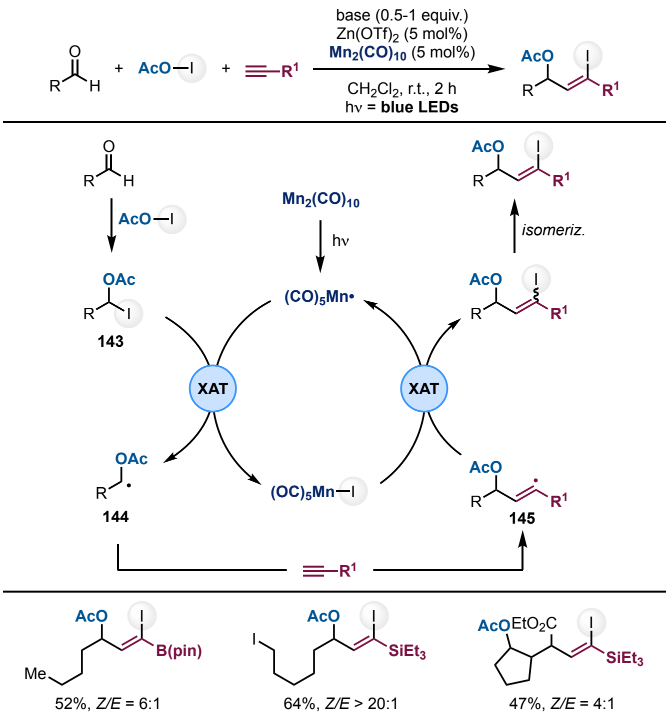
Further application in cross-electrophile couplings was demonstrated by Wang in reports on the addition of alkyl iodides to Giese-acceptors and β-ester-allyl sulfones (Scheme 80A).[391,392] The key mechanistic aspect in this transformation was the use of stoichiometric Hantzsch ester **141** to act as H-atom donor for the reduction of electrophilic α-EWG radical (HAT) and then reduce $Mn(CO)_5I$ (SET) to enable chain-propagation. This protocol engaged primary, secondary and tertiary alkyl iodides, while alkyl bromides and chlorides and aryl iodides remained unreactive. This approach for Giese-type alkylations with alkyl iodides has then be applied to the synthesis of alkyl sulfonyl fluorides (e.g. **142**), which are important targets in MedChem owing to their sulfur fluoride exchange (SuFEx) reactivity.[393] Conventional Ru- or Ir-based photocatalysts failed to provide the desired product, showcasing the benefits of the XAT approach, while the robustness of the method was demonstrated in the engagement of densely-functionalized bioactive compounds and drugs. Finally, the photocatalytic use of $Mn_2(CO)_{10}$ using Hantzsch ester as reductant has recently been applied to the multicomponent reductive carboamination between benzaldehydes and anilines (Scheme 80B).[394]

Scheme 80. (A) Photochemical Giese Reactions of Alkyl Iodides. (B) Photochemical Three-Component Reactions for Amine Synthesis.



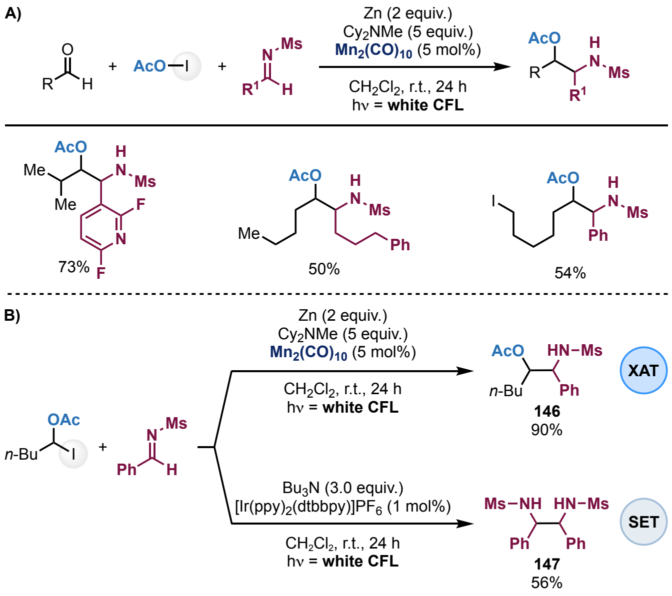
In 2018, Nagib introduced the use of Mn-metalloradicals for the generation and exploitation of ketyl radicals from aldehydes (Scheme 81).[395] This strategy required the *in situ* generation of α-acetoxy-iodides **143** by treatment of aliphatic aldehydes with acetyl iodide. These intermediates are (i) easier to reduce than the corresponding aldehyde ($E_{\mathrm{red}} = -1.1$ V vs SCE vs $E_{\mathrm{red}} < -2.2$ V vs SCE respectively) and (ii) suitable for efficient XAT activation by the Mn-metalloradicals. The proposed mechanism started with the blue light-mediated Mn–Mn bond homolysis to give the $(CO)_5Mn•$ which activated **143** via XAT to give $(CO)_5MnI$ and the ketyl radical **144**. This species underwent selective addition to the alkyne partner and the resulting vinyl radical **145** reacted with $(CO)_5MnI$. This second iodine-atom transfer process was determined to be very fast ($k_{\mathrm{XAT}} > 1 \times 10^{8}$ M^{-1} s^{-1} at r.t.) and provided the desired product while enabling catalytic turnover. This reactivity was used to achieve the general three component ATRA addition between aldehydes, Ac–I and terminal alkynes and obtain valuable vinyl iodides with high *Z*-selectivity. Compatibility with functional groups that are not tolerated under the highly reducing conditions required in classical methods for ketyl radical generation further underscore the synthetic utility of the protocol.

Scheme 81. Photochemical Three-Component Reactions for Vinyl Iodide Synthesis.



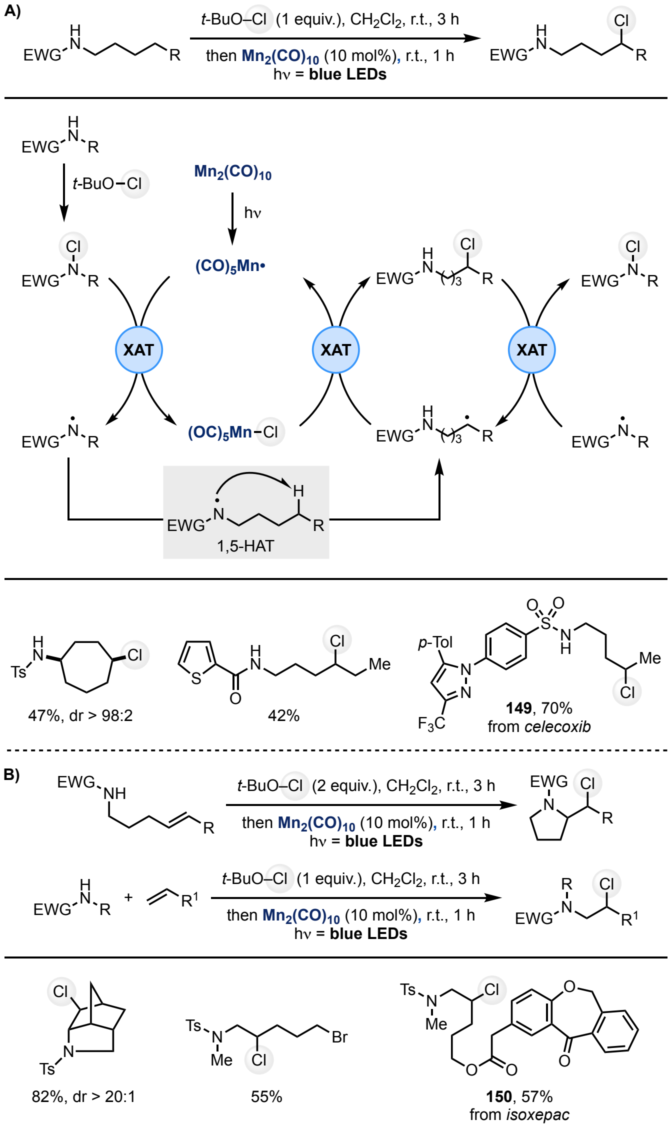
Recently, the same authors have applied this strategy for ketyl radical generation to achieve cross-selective aza-pinacol couplings of aldehydes with *N*-Ms-imines as radical acceptors (Scheme 82).[396] The net reductive character of this transformation still required a sacrificial reductant, which was achieved by combining Zn as an SET reductant, and a tertiary amine (Cy_2NMe) as an H-atom donor. The authors demonstrated how this XAT-based approach provided wide functional group compatibility (e.g. nitriles, ketones, alkyl and aryl halides) and crucially overcame the formation of imine homocoupling by-products (e.g. **146** vs **147**) that are usually obtained in SET-based methods. The methodology was also extended to other reductive transformations of ketyl radicals like hydroalkylation of electron-deficient alkynes and olefins, pinacol cross-coupling and ATRA reactivity on [1.1.1]propellane.

Scheme 82. (A) Mn-Mediated Three-Component Reactions. (B) Mechanistic Experiments to Probe the Alkyl Iodide Activation Pathway.



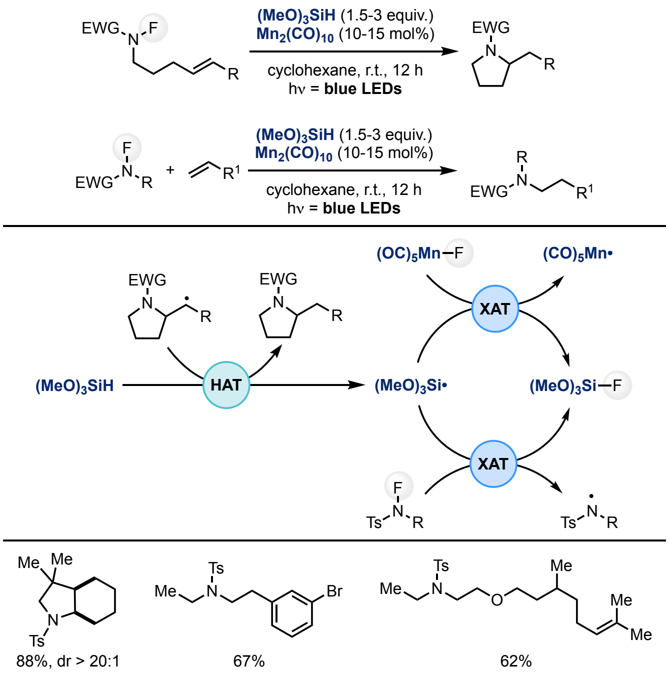
Beyond the formation of C-radicals, XAT reactivity of Mn-metalloradicals has also been used to access N-radicals as demonstrated by Zhang, Li and Qu through the development of photochemical remote sp^3 C–H chlorination of amides and sulfonamides (Scheme 83A).[397] This strategy required *in situ* (sulfon)amide *N*-chlorination followed by Cl-abstraction by (CO)$_5$Mn• to give the corresponding (sulfon)amidyl radical **148**. This species started a radical chain propagation ($\Phi = 22$) based on 1,5-HAT followed by C-radical chlorination, which could take place with the *N*-chloro(sulfon)amide or the (CO)$_5$MnCl species. Secondary and tertiary sp^3 C–H bonds in both linear and cyclic residues were chlorinated and the methodology was applied to the late stage modification of medicinally relevant compounds (e.g. celecoxib derivative **149**). This approach was then extended to achieve both intermolecular and intramolecular olefin amino-chlorination (Scheme 83B). Several chlorinated pyrrolidine scaffolds and secondary N-tosyl-amines containing different functional groups and substitution patterns were assembled using this method, as demonstrated by its application in the synthesis of drug derivatives (e.g. **150**).

Scheme 83. Photochemical Generation of Nitrogen Radicals by XAT on N–Cl Bonds. (A) Remote sp^3 Chlorinations. (B) Cyclization–Chlorination Cascades.



A related approach was then explored by the same authors using *N*–fluoro-(sulfon)amides as N-radical precursors (Scheme 84).[398] In this case, by using $(MeO)_3Si$-H as a HAT donor/XAT acceptor, the classes of radical cascades could be expanded to include intra- and intermolecular hydroamination and carboamination – enabled by the slower nature of the sp^3 C-radical fluorination step. This process was based on the ability of $(CO)_5Mn$• to undergo fluorine-atom abstraction with the *N*–fluoro-(sulfon)amide and the authors' DFT studies demonstrated this step to be feasible and with a low barrier ($\Delta G^\ddagger = 5.6$ kcal mol^{-1}). Furthermore, the stoichiometric silane reagent was crucial to (i) reduce the C-radical generated by N-radical cyclization or addition to olefin (HAT) and (ii) aid chain propagation acting as a fluorine atom acceptor from either the *N*–fluoro-(sulfon)amide and/or the $(CO)_5Mn$–F species. Mono- and disubstituted olefins could be used and 3-component reactions are possible when involving an *N*-fluoro-sulfonamide, an enol ether and a Giese acceptor.

Scheme 84. Photochemical Generation of Nitrogen Radicals by XAT on N–F Bonds.



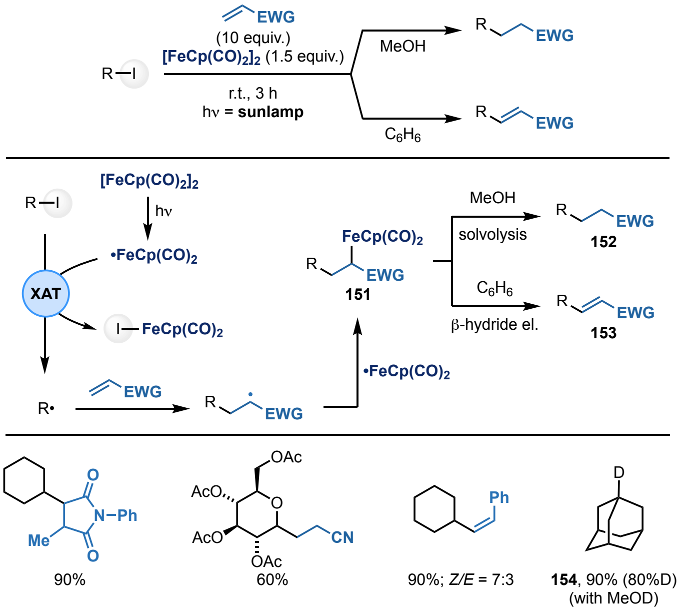
Since Bamford's early report,[399] $Mn_2(CO)_{10}$ has found many applications in polymer chemistry, most notably in photoinduced atom transfer radical polymerization (photo-ATRP, see section 3.4). Mn-based two-component photoinitiating systems (PISs) have been used in conjunction with an alkyl halides for the synthesis of telechelic,[400] block,[401] graft[402,403] and hyperbranched[404] polymers and have also been applied to the polymerization of fluorinated monomers.[405-407] $Mn_2(CO)_{10}$-based PISs have also been exploited in light-induced cationic,[408] living[409-411] and step-growth[412] polymerizations. In these systems, $Mn_2(CO)_{10}$ is usually employed in combination with activated organic halides, such as polyhalomethanes (e.g. CCl_4, $CHCl_3$, CCl_3Br), perfluoroalkyl iodides and bromides as well as benzyl bromides. Unactivated alkyl iodides (e.g. Me–I, *n*-hex–I) have been used as part of the Mn-based PIS for the free radical polymerization of vinylidene fluoride,[406] while unactivated alkyl bromides have been identified as suitable initiators for the formation of hyperbranched polymers.[404] Since an in dept discussion of these processes and their features is outside the scope of this review, the readers are referred to excellent resources on Mn-based PISs for radical polymerization.[413,414]

Iron cyclopentadienyldicarbonyl dimer, $[FeCp(CO)_2]_2$.

$[FeCp(CO)_2]_2$, known as Fp_2 (where Fp = $CpFe(CO)_2$) is an inexpensive, commercially available organometallic compound that has been the object of countless studies with different applications in synthesis and catalysis since its first report by Piper and Wilkinson in 1955.[415-417] This species undergoes efficient Fe–Fe bond homolysis upon visible light irradiation but the corresponding $Cp(CO)_2Fe$• (Fp•) metalloradical displays a smaller XAT profile than related Mn species.[418-422] Indeed, in many of the methodologies discussed before using $Mn_2(CO)_{10}$, Fp_2 has frequently been shown to be a competent but less effective mediator of XAT.[375,390,395]

The use of Fp_2 in XAT chemistry has however been fundamental to the development of synthetic radical chemistry as it was the system used by Giese in his pioneering studies demonstrating the radical addition of alkyl halides to electron poor olefins.[423,424] A general mechanistic picture for these reactions is shown in Scheme 85. After irradiation with a sun lamp, the Fe–Fe bond in Fp_2 was homolyzed generating the metalloradical Fp•. This species underwent XAT with the organic halide and the resulting alkyl radical added to the olefin acceptor. This step generated an electrophilic radical (α to an EWG) that was intercepted by another molecule of Fp• (persistent metalloradical), thus giving the iron alkyl complex **151**. When the reactions were run in protic media (e.g. MeOH) protodemetalation occured giving the hydroalkylation products (**152**), but when the reactions were run in benzene a β-hydride elimination gave Heck-type products (**153**). This combination of XAT ability by Fp• with the organometallic chemistry of Fp-alkyl products represents an interesting platform for the functionalization of alkyl halides. Reactivity in the absence of an olefin acceptor was also demonstrated and used as a powerful tool for dehalogenation (deuteration) reactivity (e.g. **154**).

Scheme 85. Fe-Mediated Reactions of Alkyl Iodides with Giese Acceptors.



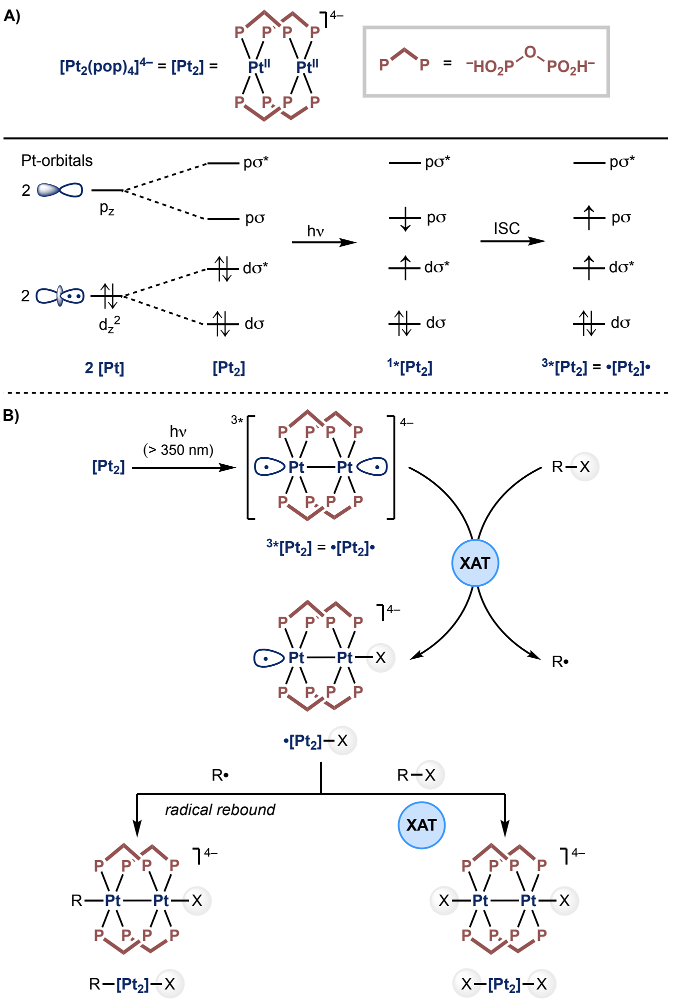
Consistently with its lower XAT reactivity, Fp_2 has found limited applications in photoinduced polymer synthesis. In contrast to many other metal carbonyl complexes (e.g. $Mn_2(CO)_{10}$), Fp_2 is not able to initiate the radical polymerization of vinylidene fluoride. However, it was able of activating the chain ends of the corresponding polymers, thus enabling the synthesis of well-defined ABA triblock polymers.[407] Furthermore, Fp_2 provided the best control over ATRP of 1,4-butadiene among different Fe-based complexes.[425] Fp_2 and ethyl 2-bromopropanoate have been used as a two-component PIS in the radical-initiated cationic and RAFT (reversible addition-fragmentation chain transfer) polymerization of vinyl ethers and acrylate derivatives.[426] Taking advantage of the wide absorption profile of Fp_2, near infra-red light was used to initiate the polymerization, thus improving light penetration in the media which enabled application in 3D printing by stereolithography.[427]

3.2.2. Dimeric Complexes Without Formal Metal–Metal Bonds

Tetrakis(μ-pyrophosphito)diplatinum(II) Tetraanion

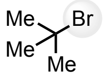
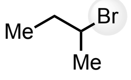
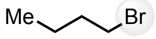
$[Pt_2(pop)_4]^{4-}$ (pop = $P_2O_5H_2^{2-}$), also known as "platinum pop", has been the subject of many studies since the 1980s owing to its intense ($\Phi = 0.52$) and long-lived ($\tau = 9.8$ μs) yellow phosphorescence in aqueous solution and its rich photochemistry.[428,429] While evaluating the reactivity of luminescent d^8-d^8 complexes, Gray studied the absorption and emission properties of $[Pt_2(pop)_4]^{4-}$ and assigned the electronic configuration of both ground and excited states.[430] A schematic representation of the orbital diagram of this metal complex is shown is Scheme 86A. In the ground state, the two occupied orbitals with higher energy are the dσ and dσ*, arising from a weak metallophilic interaction between the filled d_z^2 orbitals of each Pt(II) unit. This results in a Pt–Pt bond bond order = 0.[346,431] Upon light absorption, one of the electrons of the dσ* orbital (HOMO) is promoted to the LUMO, which is of pσ character. The resulting singlet excited state $^1[d\sigma^*p\sigma]$ has a bond order = 1, which can be considered a formal Pt–Pt bond. The long-lived phosphorescent emission of $[Pt_2(pop)_4]^{4-}$ arises from $^3[d\sigma^*p\sigma]$ states, resulting from the same $d\sigma^* \rightarrow p\sigma$ transition and fast ISC. Interestingly, this triplet excited state displays metalloradical character, as shown by the topology of the spin density determined by DFT calculations.[432] From a simplified MO perspective, the excited state of $[Pt_2(pop)_4]^{4-}$ can be seen as a dimeric complex with a Pt–Pt bond and a diradical character, *i.e.* •[Pt–Pt]•.[346] The "double metalloradical" •[Pt–Pt]• displays a large d_z^2 character, which makes it localized towards the exterior of the [Pt–Pt] unit. This morphology, together with its high energy, is responsible for the strong tendency of this species to participate in atom- (HAT[433] and XAT[434,435]) as well as group-transfer reactions.[436] Accordingly, $[Pt_2(pop)_4]^{4-}$ is a powerful reagent for photoinduced halogen-atom abstraction from alkyl and aryl halides giving the Pt(II)–Pt(III) intermediate •[Pt–Pt]–X, which has been detected and characterized by laser-flash photolysis (Scheme 86B).[435] Depending on the situations, this intermediate can engage in a following XAT event to give X–[Pt–Pt]–X species or recombine with the organic radical R• to generate the organometallic complex R–[Pt–Pt]–X.

Scheme 86. (A) Structure, Bonding and Photophysics of $[Pt_2(pop)_4]^{4-}$. (B) Photochemical XAT Reactivity of Pt-Metalloradicals.



The measured rates for XAT reactions involving photoexcited $[Pt_2(pop)_4]^{4-}$ place it among the most active organometallic reagents for this type of reactivity, capable of abstracting bromine atoms from aryl residues with high efficiency (Table 7).[437] With respect to the mode of C–X bond activation, Roundhill and Che elegantly proved that XAT and not SET is operating.[434,437] Despite these promising features, the use of $[Pt_2(pop)_4]^{4-}$ for applications in organic synthesis remains largely unexplored.[438]

Table 7. Rates of XAT using $[Pt_2(pop)_4]^{4-}$. [a]

Substrate	k_{XAT} (M^{-1} s^{-1}) at 25 °C	Substrate	k_{XAT} (M^{-1} s^{-1}) at 25 °C
	$> 10^9$	Cl_2HC-Cl	6×10^7
	2×10^8	Ph–I	2×10^9
	4×10^7	Ph–Br	4×10^6
Cl_3C-Cl	2×10^9	Ph–Cl	$<10^4$

[a] The rate constants for XAT (k_{XAT}) have been approximated to the near integral number.

Bis(diphenylphosphino)methane Gold(I) Dimer

Dimeric μ-diphosphino-gold(I) complexes of the type $[Au_2(P\text{^}P)_2]^{2+}$ (where P^P is a bidentate phosphine, bridging two Au(I) units) have retrieved significant interest owing to their interesting photophysical properties and their impact in aurophilic interactions (weak Au•••Au contacts).[346,439] The most representative example of this class of compounds is $[Au_2(dppm)_2]^{2+}$ (dppm: bis(diphenylphosphino)methane), which displays a long-lived phosphorescence ($\tau = 21$ μs, $\Phi = 0.31$) upon irradiation in the UV-A region (315-400 nm).[440] As depicted in Scheme 87A, the orbital diagram and primary photophysics of μ-phosphino-gold dimers resemble those previously discussed for $[Pt_2(pop)_4]^{4-}$. Upon light absorption, an electron is promoted from a fully occupied dσ* orbital to an empty pσ orbital and, after fast ISC, the $^3[d\sigma^*p\sigma]$ excited state is generated which has a covalent Au–Au bond with a formal bond order = 1. Excited state Au(I) dimers ($^{3*}[Au_2]$) present a remarkable tendency to increase their coordination number by either atom-transfer chemistry or by coordinating $2e^-$ donors as incoming ligands.[441] This behavior was studied by time-resolved ultrafast spectroscopy by Che in two different solvents, CH_2Cl_2 and CH_3CN (Scheme 87B).[442] In analogy to the reactivity of the triplet excited $[Pt_2(pop)_4]^{4-}$, $^{3*}[Au_2]$ readily participates in XAT reactions with halogenated solvents such as CH_2Cl_2. However, when CH_3CN was used as the solvent, an even faster reactivity was observed, which was ascribed to the formation of the exciplex $^*[Au_2$---NC–Me). Although no similar exciplex could be detected when the reactions were run in CH_2Cl_2, the formation of $^*[Au_2$----X–R] have been proposed to play a critical role in the photochemical reactivity of dimeric gold compounds with organic halides (see below).

In their pioneering studies, Che and Yam proposed XAT as the most probable mechanism for carbon–halogen bond cleavage after coordination of the organic halides to the excited $[Au_2]^*$,[443] but inner-sphere SET followed by halide abstraction was also considered.[444,445] Albeit, the exact nature of this process has not be ascertain, (see Scheme 72 for a comparison and parallelisms between inner-sphere SET and XAT) it enables these species to activate substrates of very negative reduction potentials (E_{red} < –2 V vs SCE), which should not react by standard outer-sphere SET mechanisms (for $[Au_2(dppm)_2]^{2+}$ $^*E_{ox} = -1.6$ V vs SCE).[446] To illustrate the fast reactivity of $[Au_2]^*$ with organic halides, the rates of XAT for some representative alkyl halides are shown in Table 8.[440]

Scheme 87. (A) Structure, Bonding and Photophysics of $[Au_2(dppm)_2]^{2+}$. (B) Photochemical Reactivity of of $[Au_2(dppm)_2]^{2+}$: XAT and exciplex formation.

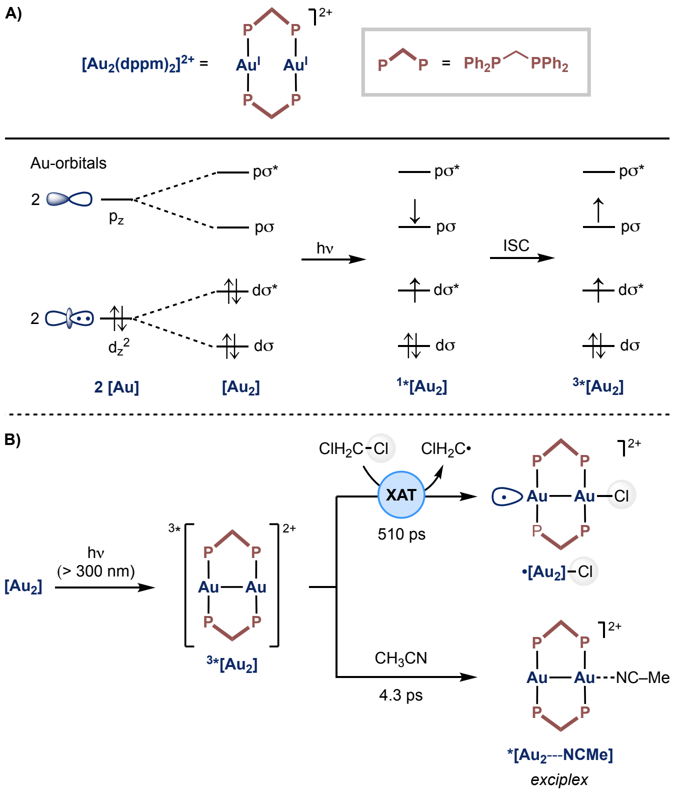
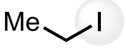
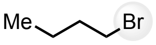
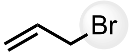
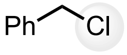


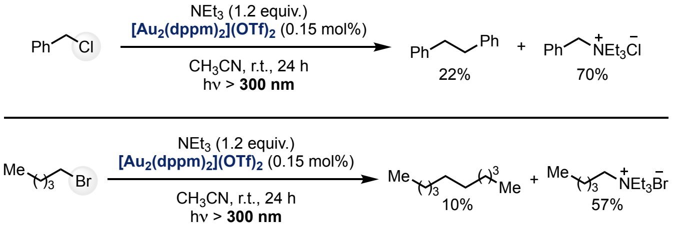
Table 8.[a] **Rates of XAT Using $[Au_2(dppm)_2]^{2+}$**

Substrate	k_{XAT} (M^{-1} s^{-1}) at 25 °C	Substrate	k_{XAT} (M^{-1} s^{-1}) at 25 °C
$Me{-}I$	1×10^9	$Br_3C{-}Br$	9×10^9
	2×10^9	$Cl_3C{-}Cl$	3×10^9
	3×10^6	$Cl_2HC{-}Cl$	5×10^7
	8×10^8		2×10^6

[a] The rate constants for XAT (k_{XAT}) have been approximated to the near integral number.

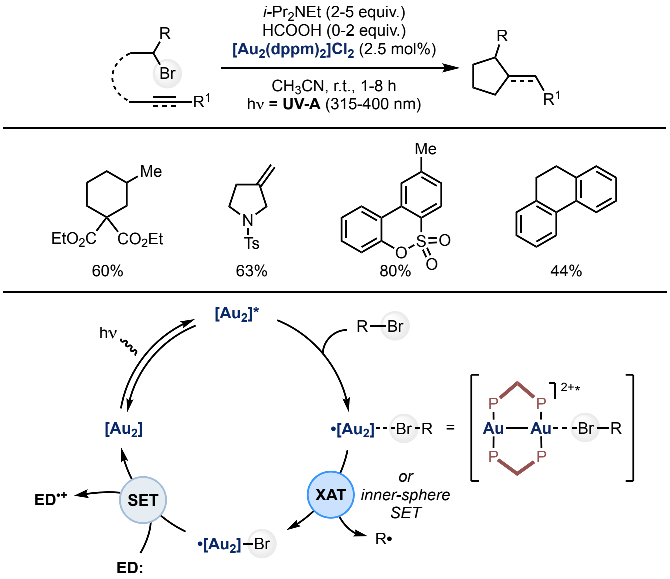
In contrast to $[Pt_2(pop)_4]^{4-}$, the use of $[Au_2(dppm)_2]^{2+}$ under photochemical conditions has found several applications in organic synthesis. In 1992, Che and Yam showed the first photocatalytic use of phosphino-Au(I) dimers for the homodimerization of benzyl chloride and 1-bromopentane, using NEt_3 as a sacrificial reductant (Scheme 88).[443] While the yields obtained were low due to competitive thermal quaternarization of the amine (S_N2 reactivity) useful turnover numbers >170 were obtained, paving the way for future catalytic applications.

Scheme 88. Photochemical Radical Dimerization of Benzylic Chlorides and Alkyl Bromides using $[Au_2(dppm)_2]^{2+}$.



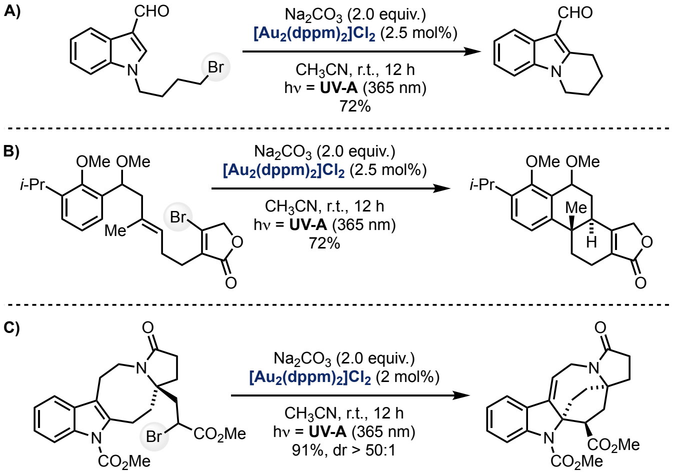
In 2013 Barriault succeeded in exploiting this photochemical approach for alkyl and aryl radical generation in synthetic settings (Scheme 89).[447] Using *i*-Pr_2NEt as both electron and H-atom donor, dehalogenation, cyclization and intermolecular reactions of alkyl and aryl bromides were achieved. Importantly, the authors demonstrated how standard photoredox catalysts, including the highly reducing $Ir(ppy)_3$, failed to engage in outer-sphere SET reduction of most of these unactivated bromides due to their negative reduction potentials ($E_{red} < -2.0$ V vs SCE). The most commonly-proposed mechanism in reactions catalyzed by $[Au_2(dppm)_2]^{2+}$ is depicted in Scheme 89 and proceeds via an oxidative quenching cycle. Upon irradiation, ^{3}*$[Au_2]$ is able to convert unactivated alkyl and aryl bromides into the corresponding radicals. Since an outer-sphere SET reduction is thermodynamically not feasible, this process was proposed to take place via the formation of a pre-coordination complex between^3*$[Au_2]$ and the organic bromide followed by an inner-sphere SET to give [Au–Au–Br] and a carbon radical. Given the close resemblance between inner-sphere SET and XAT, the exact mechanism of the carbon–halogen activation step operating in these reactions has not be unambiguously ascertained. For simplicity, in following discussions we will note this step as inner-sphere SET, as proposed by Barriault. The reduction of [Au–Au–Br] to $[Au_2]$ is generally proposed to close the catalytic cycle and requires either a stoichiometric electron donor (ED, e.g. a tertiary amine or an easy-to-oxidize carbon radical).

Scheme 89. Photochemical Dehalogenative Cyclization of Alkyl Bromides Using a Au₂-Dimer Catalyst.



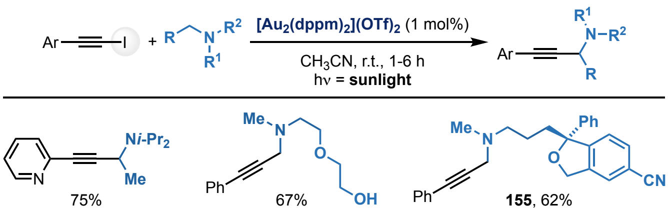
The Barriault group later used this approach in the cyclization of *N*-bromoalkyl-indoles[448] and also in the development of radical cascades based on vinyl radicals (Scheme 90A).[449] This latter development proved powerful for the assembly of complex natural products as demonstrated by the same authors in the preparation of intermediates for the total synthesis of (±)-triptolide[449] (Scheme 90B) as well as several pyrroloazocine indole alkaloids by Echavarren (Scheme 90C).[450] In all these cases, an inorganic base was used in place of the tertiary amine to minimize the direct reduction of the alkyl/vinyl bromides.

Scheme 90. Application of Au₂-Dimer in Photocatalysis. (A) Cyclization Onto Aromatic Rings. (B) and (C) Applications in Total Synthesis.



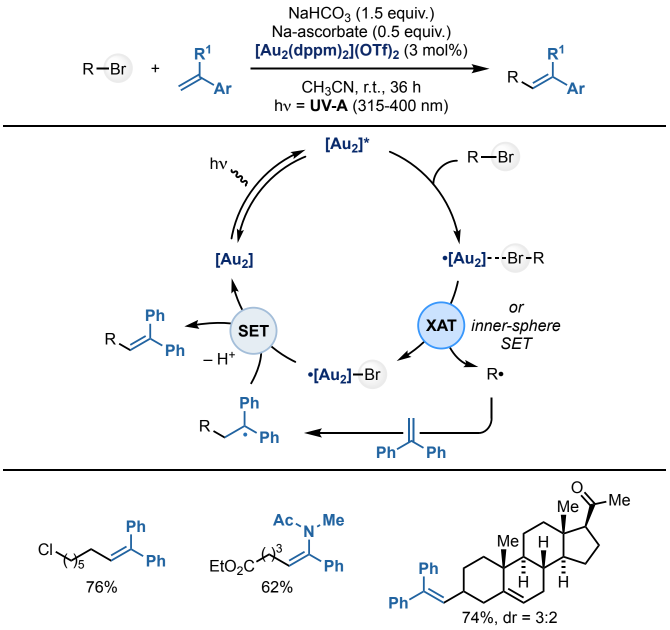
Shortly after, Hashmi unveiled the use of alkynyl iodides for the sp^3 C–H alkynylation of tertiary amines (Scheme 91).[451] A variety of iodoalkynes were efficiently coupled with structurally different tertiary amines, which included the antidepressant drug citalopram (**155**). The authors proposed a mechanism based on a radical-radical coupling between an α-aminoalkyl radical and an alkynyl radical, however since these species have short lifetime, alternative pathways might be operating. This approach was then expanded by Chan who developed the coupling of alkynyl bromides with tetrahydroisoquinolines under similar photochemical conditions.[452]

Scheme 91. Application of Au_2-Dimer in the Photocatalytic Amine sp^3 C–H Alkynylation.



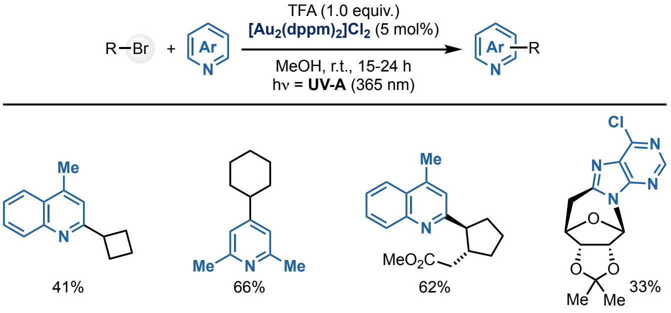
In 2016 Hashmi used [Au_2] to achieve the Heck-type coupling between alkyl bromides and 1,1-diarylalkenes (Scheme 92).[453] The authors proposed a mechanism where, upon irradiation, the ^{3}*[Au_2] generated the alkyl radical from the corresponding bromide and this species was then trapped by olefin. The resulting stabilized and electron rich benzylic radical was oxidized as part of the gold photoredox cycle, and the resulting carbocation deprotonated to give the olefin product. This redox-neutral reaction showed broad compatibility with many functionalities like free alcohol, nitriles, alkynes and was demonstrated on primary, secondary and tertiary alkyl bromides. With respect to the alkene acceptors beyond 1,1-diarylalkene acceptors, standard styrenes did not perform well, but aromatic silyl enol ethers and enamides underwent sp^2 C–H alkylation in good yields.

Scheme 92. Application of Au_2-Dimer in the Photocatalytic Heck-Type Olefination of Alkyl Bromides.



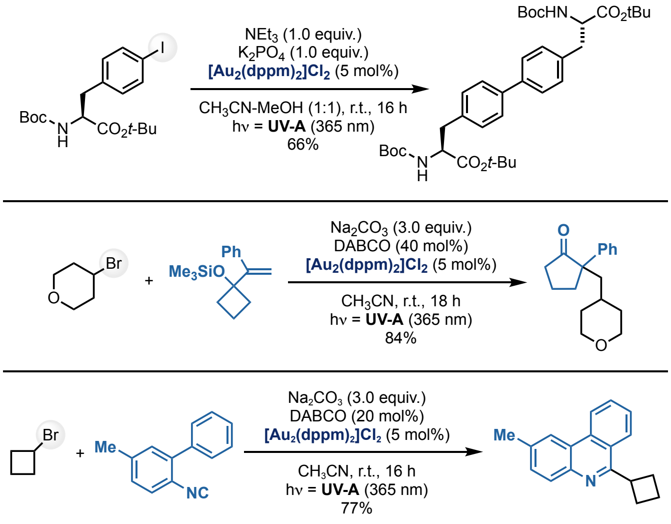
In the same year, Barriault targeted the implementation of gold photocatalysis to enable the use of unactivated alkyl bromides for the alkylation of heteroarenes in a Minisci-type reaction (Scheme 93).[454] This approach is based on a redox-neutral reactivity, thus obviating the use of sacrificial oxidants required by other methods and only requires TFA to activate the heteroarene. Primary, secondary and tertiary alkyl bromides were engaged in combination with different heteroarenes, while electron-deficient alkyl radicals were also shown to participate in a tandem olefin addition and subsequent Minisci-type reactivity.

Scheme 93. Application of Au$_2$-Dimer in Photocatalytic Minisci Reaction of Alkyl Bromides.



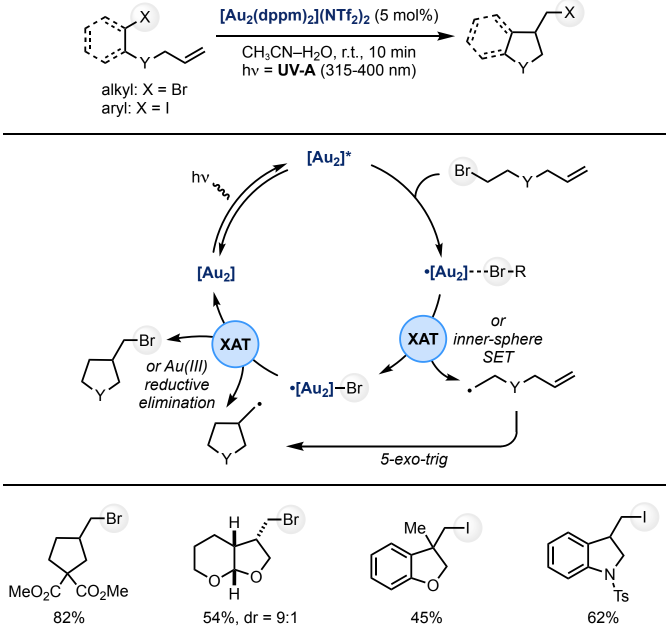
In subsequent years, the use of alkyl/aryl bromides in [Au$_2$]-based photocatalysis has been applied to many other transformations like radical-radical homocouplings,[455] cascades of radical addition–semipinacol rearrangements on cyclobutyl silyl ether derivatives[456] and addition to isonitriles to construct phenanthridines and amides (Scheme 94).[457]

Scheme 94. Au-Mediated XAT Reaction of Aryl Iodides and Alkyl Bromides.



In 2020 the same group reported the ATRC of unactivated alkyl bromides and aryl iodides (Scheme 95).[458] In general, ATRA and ATRC strategies require the use of electron-deficient substrates (e.g. α-halocarbonyls, perfluoroalkyl halides) as standard alkyl halides are challenging due to their poor ability to sustain chain propagations by XAT. This methodology has therefore addressed a relevant synthetic and mechanistic challenge in the area. The authors proposed a mechanism where the photoredox [Au_2]-cycle was responsible for Br-abstraction which was followed by fast *5-exo-trig* cyclization. The resultant exocyclic radical then reacted with the [Au–Au–Br] species to provide the ATRC product and regenerate the ground state [Au_2]. This bromination step can occur by either XAT or radical addition to gold followed by carbon–halogen reductive elimination. This fast reaction, occurring in less than 10 minutes, enable the intramolecular ATRC of aryl bromides and iodides as well as primary and secondary alkyl bromides.

Scheme 95. Application of Au_2-Dimer in Photocatalytic ATRA Reaction of Alkyl Halides.



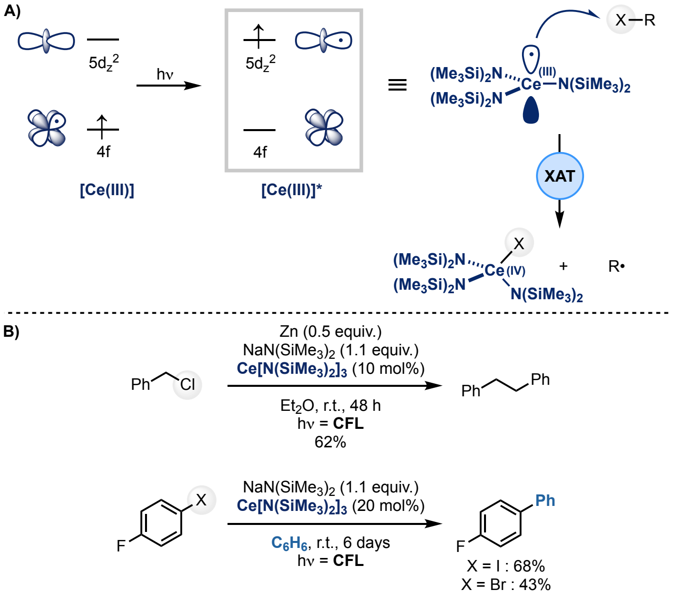
Finally, XAT mediated by photoexcited [$Au_2(dppm)_2]^{2+}$ has also found application in polymer chemistry as demonstrated by Laleveé, Fensterbank and Goddard, in the atom-transfer radical polymerization (ATRP) of methacrylates and acrylates using ethyl α-bromophenylacetate as the initiator.[459]

3.2.3. Metalloradicals Generated From Monomeric Species

Cerium(III) Amidato Complexes.

Ce(III)-amidato complexes display interesting excited-state properties as recently demonstrated by Schelter.[460] Upon visible-light irradiation these species undergo 4f→5d transitions resulting in a long-lived (τ = 25-70 ns), metal-centered $5d^1$ excited state characterized by a singly-occupied d_{z^2} orbital (Scheme 96A). In terms of XAT reactivity, photoexcited Ce(III) metalloradicals have been demonstrated to efficiently abstract halogen atoms and form strong Ce(IV)–halogen bonds. Remarkably, Ce(III) sensitizers have been used in chlorine abstraction as shown by the conversion of Bn–Cl to Bn_2, a transformation that cannot occur via outer-sphere SET according to the redox potential of BnCl (E_{red} = –2.24 V vs SCE) and excited Ce(III) complexes ($^{*}E_{ox}$ = –1.47 V vs SCE) (Scheme 96B). Addition of $NaN(SiMe_3)_2$ and/or metals (e.g. Zn) as sacrificial reductants rendered the process catalytic in Ce, which was also applied in the arylation of 4-fluorophenyl iodide/bromide with benzene as the solvent.[460] Interestingly, in a subsequent work, Schelter showed that in sterically congested Ce(III)-complexes the inner-sphere reactivity is switched off, and only outer-sphere SET is possible.[461]

Scheme 96. (A) XAT Reactivity of Photoexcited Ce(III) Species. (B) Synthetic Examples.

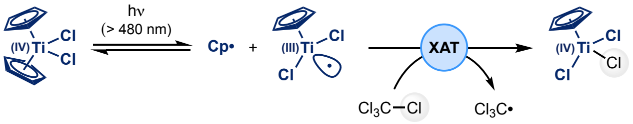


Titanium(III) Complexes.

Ti(III) metalloradicals are powerful intermediates in synthetic chemistry. The radical ring-opening of epoxides is one of their archetypal and most studied transformation as exemplified by the extensive utilization of titanocene(III) chloride (Cp_2TiCl, Cp = cyclopentadienyl) in synthesis.[462-464] These species are also efficient at abstracting halogen atoms,[465-467] and while their application in XAT-based transformations is largely based on thermal manifolds requiring stoichiometric reductants (e.g. Zn or Mn), applications in photochemistry and photocatalysis are receiving an increasing attention.[468-470]

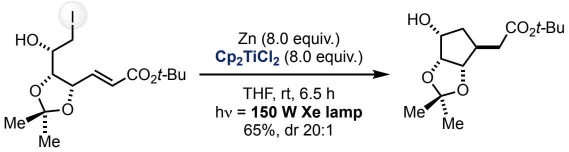
As shown in pioneering studies by Gray, visible-light irradiation of Cp_2TiCl_2 leads to the population of ligand-to-metal charge-transfer (LMCT) states, due to the transition of one electron from a MO localized on a Cp ligand to an empty d orbital of [Ti(IV)]. This event results in the homolysis of the Ti–Cp bond which forms a [Ti(III)]•/Cp• radical pair (Scheme 97). While radical recombination is fast, when photolysis was carried in CCl_4 or $CHCl_3$, the formation of $CpTiCl_3$ was observed, which is indicative of XAT reactivity.[471] Following work from Tyler demonstrated that the bond that is homolyzed under irradiation can change when stronger σ-donors ligands are used instead of chloride.[472-474] Therefore, when Cp_2TiX_2 (X = I, Me) are irradiated, the reactivity of the lowest-energy LMCT excited state involves the cleavage of Ti–X bonds, resulting in the formation of Cp_2XTi• which is also capable of abstracting halogen atoms from halogenated solvents.

Scheme 97. Photochemical Reactivity of Titanocenes.



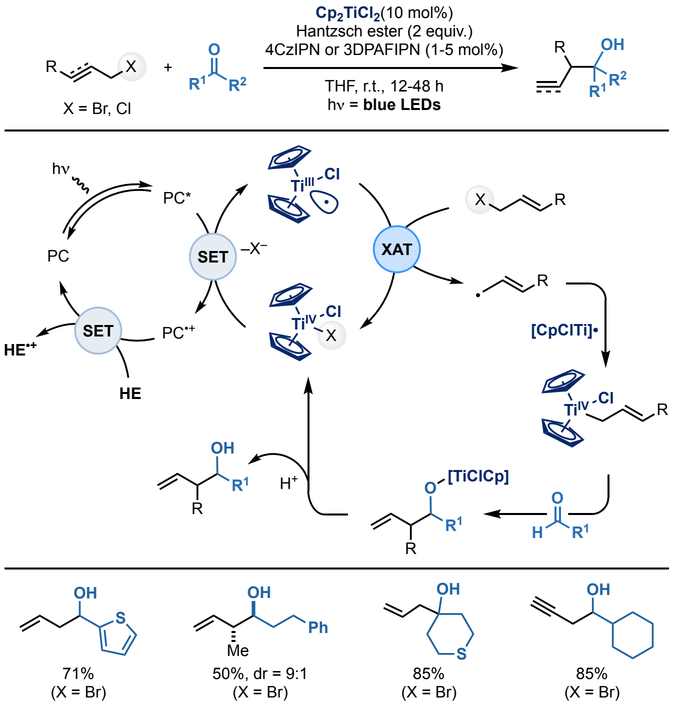
Application of Ti-metalloradicals in photochemical XAT strategies was first reported by Bennet to achieve *5-exo-trig* cyclization of alkyl iodides using Cp_2TiCl, albeit, no mechanistic hypotheses were advanced (Scheme 98).[475]

Scheme 98. Photochemical Intramolecular Cyclization of Alkyl Iodides Mediated by Cp_2TiCl_2.



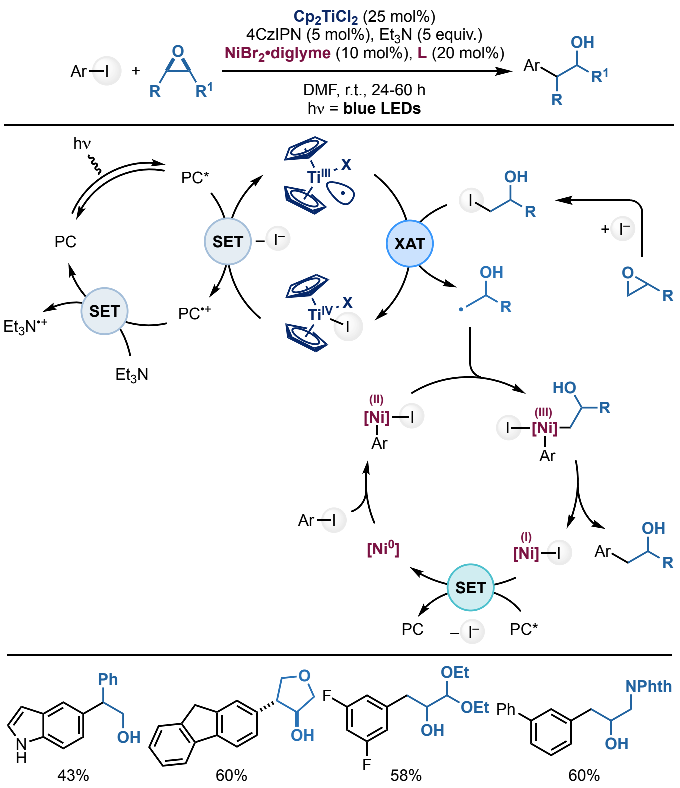
Inspired by previous reports on the generation of Ti(III) via photoredox catalysis (4CzIPN or 3DPAFIPN photocatalysts),[470,476] the groups of Gualandi, Bergamini and Cozzi and the one of Shi simultaneously reported the photoinduced Barbier-type allylation of aldehydes under dual photoredox-titanium catalysis (Scheme 99).[476-478] These methods enabled the transformation of aromatic and aliphatic aldehydes and ketones into the corresponding homoallylic alcohols by using allylic, propargylic and benzylic bromides and chlorides as coupling partners. Furthermore, this photoredox manifold bypasses the need for activated metal reductants (e.g. Zn or Mn) as simple Hantzsch esters are used as electron-donors. According to mechanistic studies conducted by the authors, this process started with the generation of the Ti(III) metalloradical by SET reduction of Cp_2TiCl_2 by the excited photocatalyst. XAT on the alkyl halides delivered the stabilized allyl/propargylic/benzylic radicals that were intercepted by another molecule of [Ti(III)]• to provide the desired allyl/propargyl/benzyl–[Ti(IV)] organometallic intermediates. Polar addition of these species to the carbonyl electrophiles gave, after hydrolysis, the desired products. Several functional groups such as nitriles or ketones, as well as heterocycles like thiophene and indole are well tolerated, while the functionalization of derivatives of the drugs indomethacin or probenecid were successfully applied.

Scheme 99. Allylation of Aldehydes via Dual Photoredox–Ti Catalysis.



In 2020 Doyle merged nickel, photoredox and titanium catalysis in a triple-catalytic system for the reductive ring opening of epoxides with (hetero)aryl iodides (Scheme 100).[479] Styrene oxides and aliphatic epoxides were reacted, giving β-arylated alcohols in good yields and regioselectivities with an excellent tolerance to diverse functional groups and structures. Mechanistic experiments suggested the intermediacy of iodohydrins, formed by nucleophilic ring opening of epoxides, which are responsible for the linear regioselectivity in the case of aliphatic epoxides. The proposed mechanism involves the generation of Cp_2ClTi• by SET with 4CzIPN* and subsequent XAT with iodohydrins generating a primary alkyl radical. This C-radical is then trapped by an aryl-Ni(II) complex, generated by oxidative addition of the aryl iodide into Ni(0), that leads to the β-arylated alcohol product after reductive elimination. The SET reduction of Ni(I)–I to Ni(0) would close the nickel catalytic cycle and generate the iodide required to form the iodohydrins, with Et_3N acting as the overall reductant to allow turnover of the photoredox cycle.

Scheme 100. Application of Cp_2TiCl_2 in Metallaphororedox Epoxide Opening With Aryl Iodides.



3.3. Carbon-Based XAT Reagents

In the reactions described thus far, XAT has been orchestrated by heteroatom/metal-based radicals as they synergistically form strong bonds with the halogen atom and maximize the interplay of polar effects in the abstraction TS. In contrast to these classical reaction types, recent work has focused on developing carbon-radical reagents for application in photochemical XAT methodology. Reactions in this category do not generally have a direct enthalpic benefit and therefore hinge on the use of nucleophilic radicals to provide the crucial kinetic acceleration resulting on charge transfer stabilization in the TS.

It is worth pointing out that the ability of carbon radicals to undergo XAT is the key feature enabling all ATRC- and ATRA-based reactions like the highly exploited olefin halo-functionalization protocols.[24] A discussion of these processes is beyond the scope of the present review but can be found in the recent excellent resources.[480-482] This section will also not discuss the synthetic strategies based on XAT reactivity of aryl radicals as these have, to the best of our knowledge, been achieved so far, under thermal settings.[483-486]

3.3.1. α-Aminoalkyl Radicals

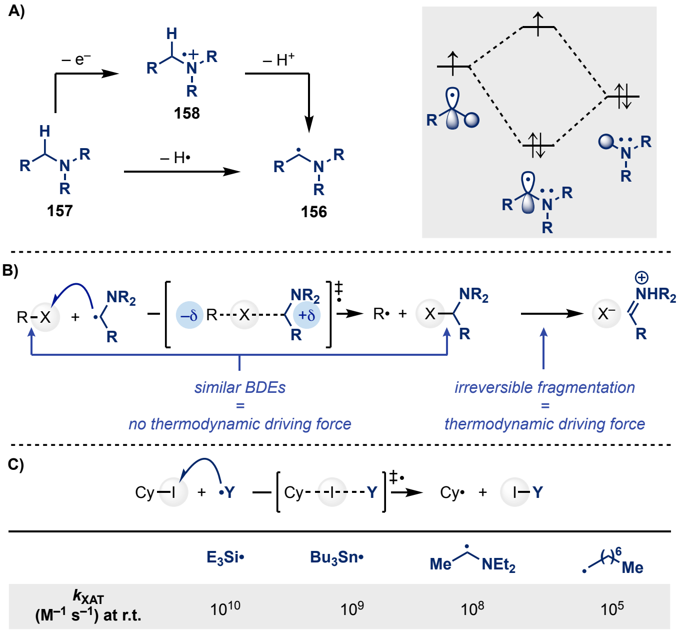
The conversion of amines into the corresponding α-aminoalkyl radicals has been a major avenue to accomplish α-*N* sp^3 C–H functionalization in photochemistry and photoredox catalysis.[487-490] Pioneering works of Lalevée demonstrated that these open-shell species, generated via HAT with *t*-

BuO•, are able to abstract halogen atoms from polyhalomethanes.[491,492] More recently these open-shell species have been demonstrated to be competent XAT reagents with a reactivity profile similar to the one of tin radicals.[28,492-494]

In general, α-aminoalkyl radicals **156** are easily accessible from the corresponding alkylamines **157** by SET oxidation to the aminium radical **158** (Scheme 101A).[495,496] This event lowers the p*K*a of the α-*N* protons and enables **158** to be readily deprotonated giving **156**.[497,498] Alternatively, site-selective HAT using electrophilic radicals (e.g. *t*-BuO•, thiyl radicals, quinuclidine$^{\bullet+}$) can be used to directly generate **156** from **157**.[499,500] The interaction of the radical centre with the adjacent *N*-lone pair provide significant stabilization to the "2-centers-3-electrons" **156**, and therefore displays strong nucleophilic character.[501,502] This hyperconjugation is responsible for the excellent reactivity of α-aminoalkyl radicals towards electrophilic radical acceptors (e.g. Giese acceptors,[41] organometallic intermediates in metallaphotoredox catalysis with nickel[16]) and also means that they can effectively stabilize charge separation in the TS of XAT reactions.[28] This polar effect provides the required kinetic acceleration for the abstraction to take place even if there are no significant enthalpic gains (i.e. the C–X BDE values in the starting material and the α-halo-amine are similar). As mentioned in Section 2, this reactivity is nevertheless facile due the fast and irreversible collapse of the α-haloamine into the corresponding iminium ion which is the overall driving force for the process (Scheme 101B).[28]

The rates of XAT by α-aminoalkyl radicals have not been studied in details like the ones for other systems, however our recent flash laser photolysis studies demonstrated that the radical derived from Et_3N (generated by HAT using the *t*-BuO•) undergoes XAT with Cy–I with $k_{XAT} = 10^8$ M^{-1} s^{-1} at room temperature, which is just one order of magnitude slower than Bu_3Sn• (Scheme 101C).[28]

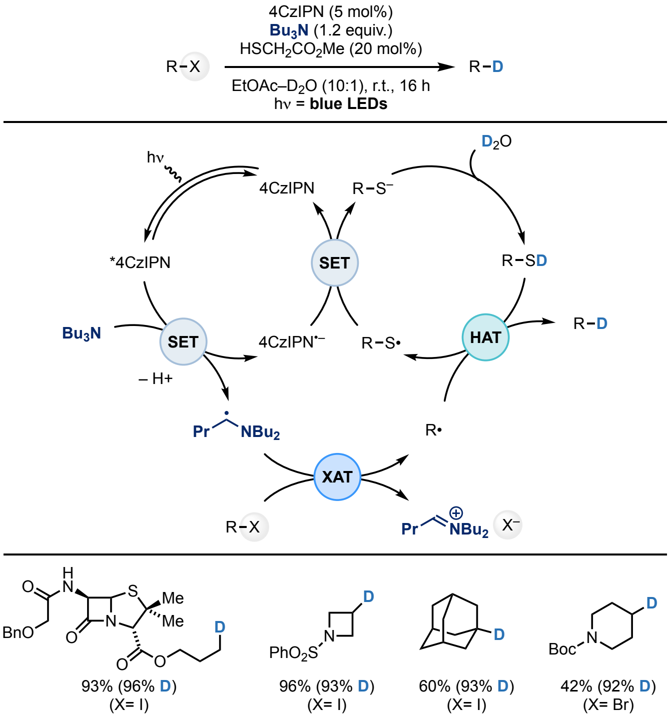
Scheme 101. (A) Mechanistic Pathways for the Generation of α-Aminoalkyl Radicals. (B) Profile of XAT Reactions Mediated by α-Aminoalkyl Radicals. (C) Comparison of Rates for XAT on Cyclohexyl Iodide.[a]



[a] The rate constants for XAT (k_{XAT}) have been approximated to the near integral number.

As competent halogen abstractors, α-aminoalkyl radicals can be used to accomplish a wide variety of XAT-based processes using both alkyl and aryl halides as recently demonstrate by our group (Scheme 102).[28] For instance, SET reduction of unactivated alkyl halides (E_{red} < –2 V vs SCE) using the photoredox catalyst 4CzIPN ($^*E_{ox}$ = –1.04 V vs SCE; E_{red} = –1.1 V vs SCE)[503] is highly disfavoured while oxidation of Bu_3N (E_{ox} = +0.71 V vs SCE) is facile. This leads to the formation of the key α-aminoalkyl radical that can be used in the homolytic activation of alkyl iodides/bromides as well as aryl iodides. The corresponding carbon-radicals can then be deuterated by using catalytic methyl thioglycolate and D_2O as the stoichiometric D-source.[504,505] This reactivity goes via a dual photoredox–HAT cycle that leads to the X→D exchange tolerating many organic functionalities.

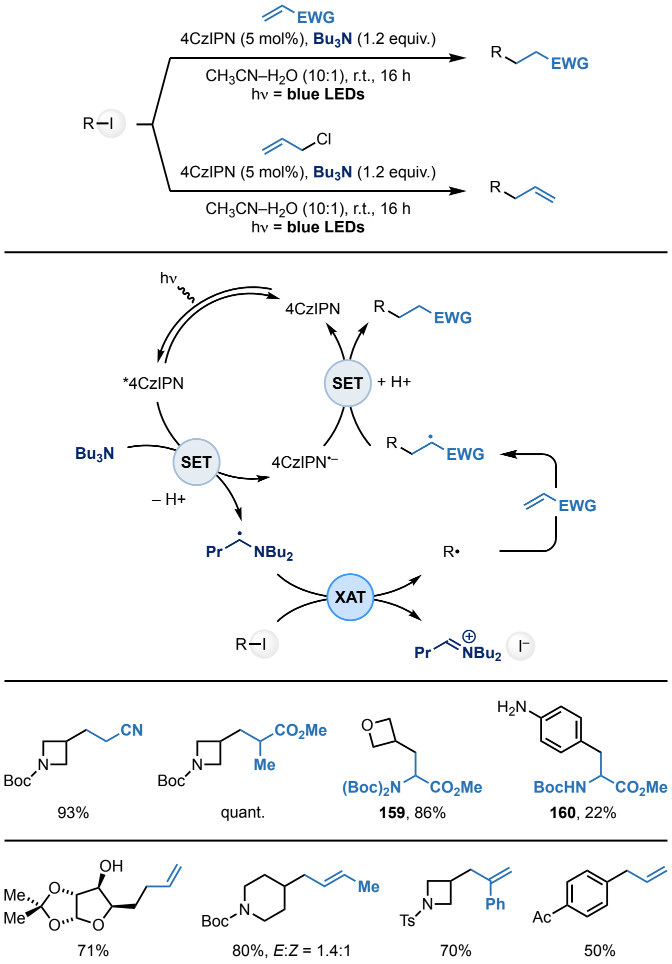
Scheme 102. Photochemical Dehalogenation–Deuteration of Alkyl Iodides and Bromides via α-Aminoalkyl Radicals.



The use of a reductive quenching photoredox cycle for α-aminoalkyl radical generation followed by XAT means that alkyl/aryl halides can be converted into their corresponding radicals without the need of strongly reducing photocatalysts. Furthermore, and in analogy to the examples with silicon radicals, this mechanistic feature enables the use of these building blocks in redox cross-electrophile couplings. From this perspective organic halides can then be used in transformations usually possible only with alkyl carboxylic acids,[506] trifluoroborates/silicates[507] and Hantzsch dihydropyridines.[507,508]

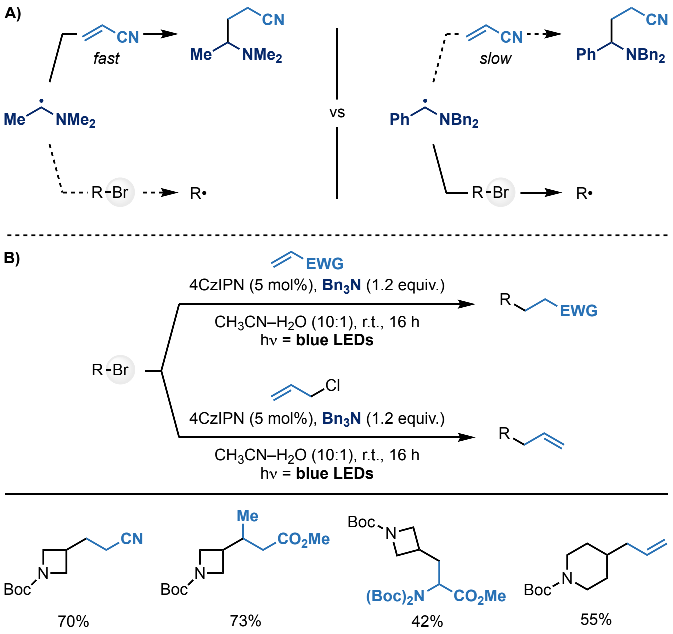
As an example, our group demonstrated photoredox Giese alkylation and allylation of alkyl and aryl iodides using Et_3N as the XAT reagent and 4CzIPN as the photocatalyst (Scheme 103). As in the dehalogenation chemistry, reductive quenching of *4CzIPN by the tertiary amine led the key α-aminoalkyl radical that achieved the iodine-abstraction reaction. The formed alkyl/aryl radicals were readily intercepted by Giese acceptors (i.e. α,β-unsaturated esters, amides, acids, ketones, nitriles, sulfones, phosphonates) or allyl chlorides, thus enabling the formation of sp^3–sp^3 or sp^2–sp^3 C–C bonds. This approach was also applied to the preparation of several unnatural amino acids (e.g. **159**) using dehydroalanine derivatives.[28]

Scheme 103. Photochemical Giese Reaction and Allylation of Alkyl Iodides via α-Aminoalkyl Radicals.



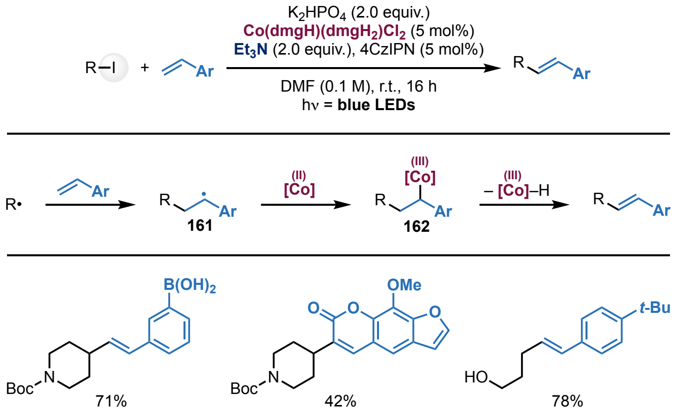
Something that needs to be considered when using α-aminoalkyl radicals in XAT-based processes is that these nucleophilic species might also participate in standard radical C–C bond-forming processes, like Giese addition or allylation, thus leading to unwanted α-*N* functionalization. Therefore, there is a requirement for XAT to kinetically outcompete any other radical reactivity. In the first report on the application of α-aminoalkyl radical-mediated XAT, our group noticed that while dehalogenation of unactivated secondary alkyl bromides using Bu_3N could proceed, extension of this activation mode to Giese and allylation reactivity was not possible. In this case, as XAT on alkyl bromides is slow ($<10^5$ M^{-1} s^{-1} at room temperature), the nucleophilic α-aminoalkyl radical underwent direct addition to the various acceptors thus hampering sp^3 C–Br bond activation (Scheme 104A). Nevertheless, the desired XAT-Giese/allylation manifold was achieved by changing the nature of the amine reagent. In particular, Bn_3N was found very effective as its corresponding α-aminoalkyl radical does not undergo Giese addition ($k_{Giese} < 10^4$ M^{-1} s^{-1} at r.t.)[491] and this minimizes the unwanted reactivity. Another example where amine modulation was crucial to enable XAT over other pathways was demonstrated on primary alkyl iodides activated towards S_N2. In this case, while Et_3N led to *N*-quaternarization, the use of hindered pentamethylpiperidine (PMP) meant that the ionic reactivity was retarded thus enabling α-aminoalkyl radical formation following XAT. Overall, the great structural diversity of commercial amine reagents can offer the potential to modulate both electronic and steric parameters around the α-aminoalkyl radicals and this should be considered when optimizing their XAT-based transformations (Scheme 104B).[28]

Scheme 104. (A) Reactivity Profile Displayed by α-Aminoalkyl Radicals Based on Their Substitution Pattern. (B) Photochemical Giese Reaction and Allylation of Alkyl Bromides via α-Aminoalkyl Radicals.



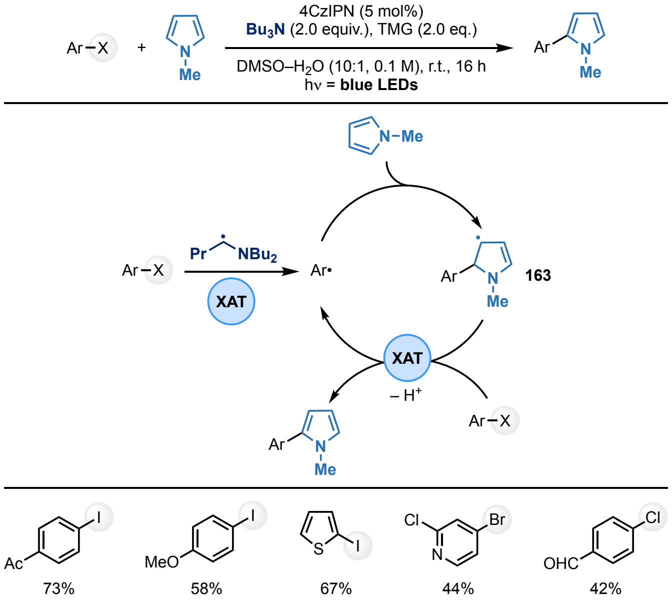
Oxidative photocatalysis for α-aminoalkyl radicals has also been used in combination with cobalt catalysis to achieve challenging Heck-type olefination of styrene acceptors with primary, secondary and tertiary alkyl iodides (Scheme 105). In this case, following α-aminoalkyl radical generation and XAT, the corresponding radical underwent selective addition to the styrene providing the corresponding benzylic radical **160**. This stabilized species was trapped by the [Co(II)] co-catalyst (diffusion-controlled reaction), which generated the alkyl–[Co(III)] species **161**. Photoinduced desaturation took place providing the desired Heck-type products in high *E*-selectivity and with broad functional group compatibility.[28]

Scheme 105. Photochemical Heck-Type Olefination of Alkyl Iodides via α-Aminoalkyl Radicals and Cobalt-Catalysis.



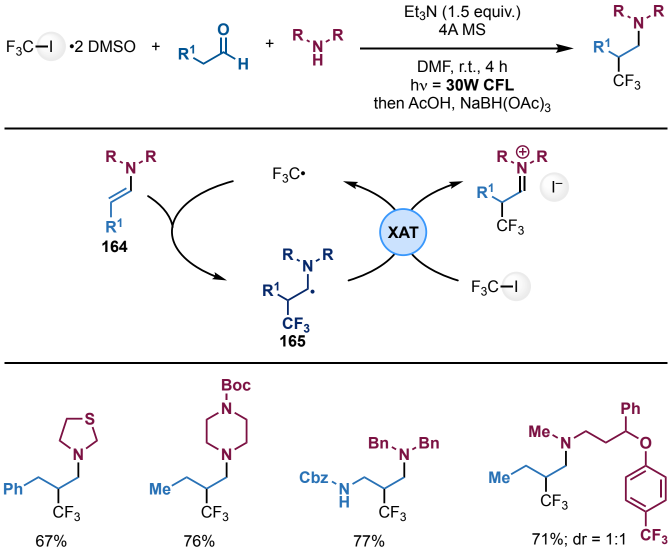
The application of α-aminoalkyl radical-mediated XAT in photocatalysis is not restricted to closed photoredox systems and can also be used as initiating mechanism as part of radical-chain propagations. This has been recently used to accomplish the transition metal-free sp^2–sp^2 coupling between aryl halides and pyrrole derivatives (Scheme 106).[509] In this case, the α-aminoalkyl radical derived from photoredox oxidation of Bu_3N underwent XAT on the halide to generate the corresponding aryl radical. This species reacted with the pyrrole at the most activated C2 position. The resulting vinylogous α-aminoalkyl radical-type intermediate **163** was then proposed to act as chain-carrier by regenerating the aryl radical by XAT (or SET in the case of highly electron poor derivatives). This reactivity was applied to both electron poor and electron rich aryl iodides as well as activated aryl bromides and chlorides but was restricted to pyrrole acceptors since furans and thiophens were not able to sustain radical-chain propagation, due to the lower nucleophilicty of the intermediate vinylogous radical. Other radical traps were used and for examples phosphites enabled sp^2 C–P bond formation, which generated chain carrying alkyl radicals upon β-scission.

Scheme 106. Photochemical Arylation of Pyrroles via α-Aminoalkyl Radicals.



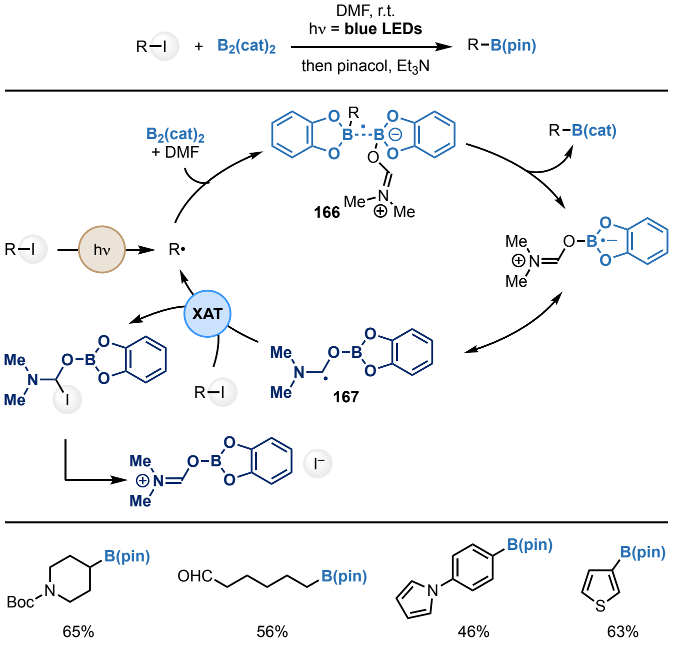
More recently, α-aminoalkyl radical-mediated XAT has also been proposed as part of an ATRA-type addition of CF_3–I to enamines for the preparation of β-CF_3 alkylamines (Scheme 107).[510] In this case, the condensation of a secondary amine with an enolizable aldehyde led to the corresponding enamine **164** that was intercepted by the electrophilic F_3C•. This polarized radical addition[29,511] provided the α-aminoalkyl radical **165** that was proposed to regenerate the F_3C• by XAT with CF_3–I.

Scheme 107. Photochemical Three-Component Reaction for the Preparation of β-CF3 alkylamines.



XAT reactivity of α-aminoalkyl radicals has also been proposed by Studer as part of a photochemical borylation of aryl and alkyl iodides using $B_2(cat)_2$ under blue LEDs irradiation (Scheme 108).[512] This reactivity requires the use of DMF as the solvent and also the source of α-aminoalkyl radical for halide activation. The authors proposed a radical chain process where the C-radical R• (generated by photochemical C–I bond homolysis) was trapped, in the presence of DMF, $B_2(cat)_2$ to give a **166**, which can be described as a weak B–B 1e– σ-bond. This would drive B–B bond homolysis to give the borylated product and the DMF-complex boryl radical **167**, that has considerable α-aminoalkyl radical character. Computational studies demonstrated XAT between this species and Me–I to be facile, thus supporting the last step of the propagating manifold. This practical process enabled the borylation of primary, secondary and tertiary alkyl iodides as well as several (hetero)aryl iodides. Final treatment with pinacol and Et_3N was used to convert *in situ* the unstable B(cat) boronic esters into the corresponding B(pin) derivatives that are easy to handle.

Scheme 108. Photochemical Borylation of Alkyl and Aryl Iodides.

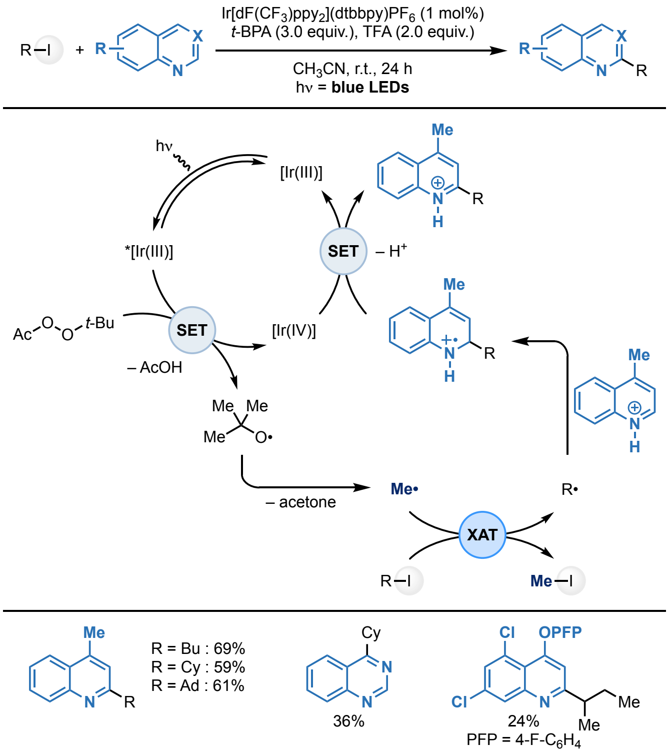


3.3.2. Methyl Radical

The use of Me• and Et• as initiators to engage alkyl/aryl halides in radical chain processes has had a profound synthetic impact with applications spanning dehalogenation, borylation and C-functionalization.[2] As these are unstabilised radicals,[502,513] XAT with organic halides is both favourable when using alkyl and aryl iodides mostly due to enthalpic effects.[513] So far, this reactivity mode has been mostly exploited under thermal or aerobic conditions[514,515] and limited applications in photochemistry and photocatalysis exist.[516]

In a recent example, Wang demonstrated the utilization of Me• in a photoredox approach for the Minisci[517,518] functionalization of azines using alkyl iodides (Scheme 109).[519] In this case, a reductive quenching photoredox cycle was used to reduce, under acidic conditions, the perester which provided the electrophilic *t*-BuO•.[520] This species underwent β-scission[521] to acetone and the Me•, which was used to enable homolytic activation of primary, secondary and tertiary alkyl iodides. The corresponding alkyl radicals were then engaged in standard Minisci reactivity with the protonated azines.

Scheme 109. Methyl Radical-Mediated Photochemical Minisci Reaction of Alkyl Iodides.

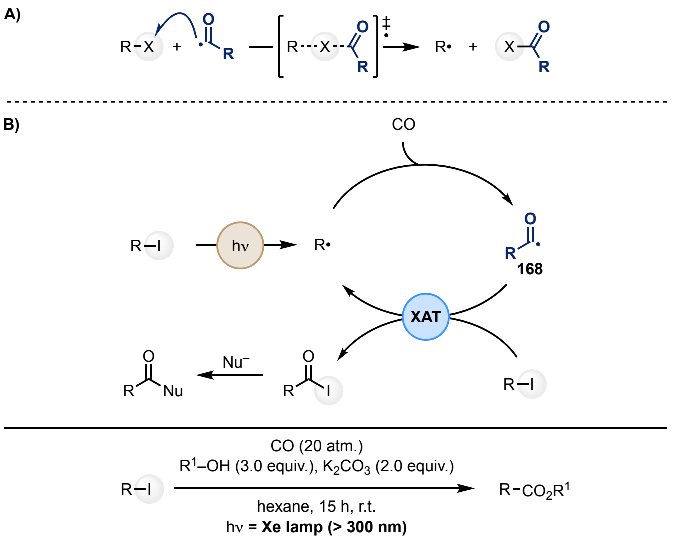


3.3.3. Acyl Radicals

Acyl radicals are powerful intermediates for the preparation of carbonyl containing building blocks.[522,523] These σ-radicals are highly nucleophilic and undergo efficient XAT reactions with alkyl iodides and, at higher temperature, alkyl bromides (Scheme 110A).[524] These processes are, however, reversible and therefore a subsequent ionic reaction on the acyl iodide/bromide is required.

While acyl radicals can be accessed by a number of precursors by either HAT[525] (aldehydes) or SET (ketoacids[526,527] and/or activated ketoesters,[528] Hantzsch dihydropyridines[529]), the most exploited approach for acyl radical generation and utilization in photochemical XAT methodologies has been via the reaction of alkyl radicals with CO (Scheme 110B).[530-532] This chemistry has been recently reviewed elsewhere[533] and follows a general mechanism where photochemical sp^3 C–I bond homolysis is used to generate the alkyl radical (initiation). This event starts a chain process where R• traps CO to provide the key acyl radical **168**. This species propagates the process by XAT. The formed acyl iodides have successfully used in a number of ionic transformations like esterification, amidation and lactonization.

Scheme 110. (A) XAT Using Acyl Radicals. (B) Photochemical Carbonylation of Alkyl Iodides.



More recently, this reactivity has been extended to the use of Pd(II) catalysts that provides crucial acceleration to these atom-transfer carbonylation reactions.[533-535] The mechanism of these processes is not based on XAT but on SET between the photoexcited Pdº complex and the alkyl halide.

3.4. XAT in Photochemical Atom Transfer Radical Polymerization (photo-ATRP)

The aim of this Section is to give some context about XAT reactivity in photochemical atom transfer radical polymerization (photo-ATRP).[536] As a detailed discussion of these processes and their relevance to material science is outside the aim of this review, the reader is directed to excellent resources in the field.[537-546]

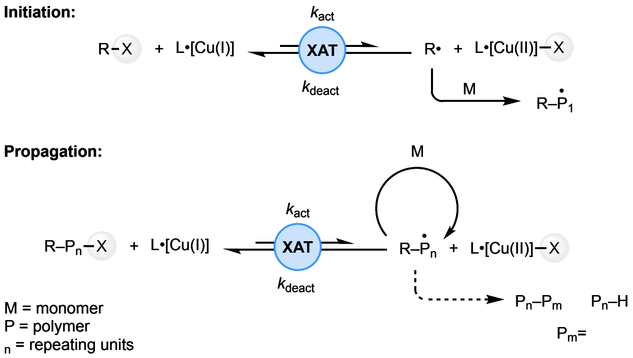
Radical polymerization is defined by the IUPAC as "*a chain polymerization in which the kinetic-chain carriers are radicals*". These processes proceed via chain mechanisms based on four elementary steps: (i) initiation by generation of radical species (e.g. XAT); (ii) propagation or chain growth by radical addition to unsaturated monomers; (iii) chain transfer which can take place by atom transfer (e.g. XAT) and (iv) termination by either radical-radical coupling or disproportionation.

Processes based on free-radical polymerization (FRP) offer limited control over the molecular weight and/or the architecture of the resulting polymer because the chain growth is uninterrupted until termination occurs. ATRP belongs to the class of reversible deactivation radical polymerization (RDRP) processes where the polymer chains can be temporarily put in a "dormant state",[547] which can then interconvert back to the active (growing) state. This means that at any given time, only a marginal fraction of the chains is active, while most are in their dormant state. This mechanistic approach leads to a much better control over the chain growth which results in well-defined polymers and low dispersity (see below).

ATRP processes have been developed in 1995,[548-550] and they are based on fundamental ATRA reactivity between alkyl halides and olefin monomers promoted by low valent metals Cu(I) or Fe(II)

(Scheme 111). In these processes, the metal acts as the initiator converting the alkyl halide into the corresponding alkyl radical via XAT (although in some cases, outer-sphere SET activation has been proposed)[551]. The oxidised metal–halide species generated as part of the halogen transfer acts as deactivator and control over polymerization is achieved through an equilibrium between the low valent and the oxidised metal species. The alkyl radical starts the polymerization by adding to several monomer units and the corresponding growing chain can be put into its dormant state by XAT reaction with the metal–halide. This process is repeated over several cycles, allowing for a controlled, uniform growth of the polymer chains. Although unavoidable, termination events are rare (typically, less than 10% of all chains undergo termination).

Scheme 111. Key Elementary Steps in ATRP.



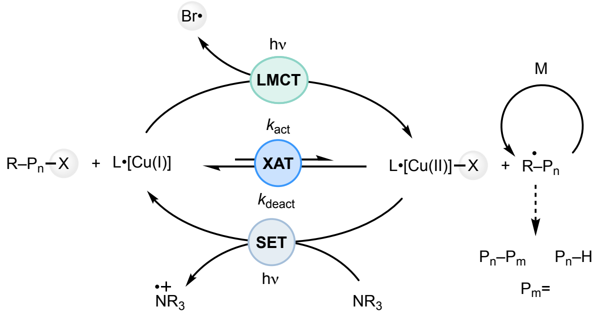
A typical ATRP system includes the olefin monomer and the initiator which consists in an alkyl halide, a metal catalyst and often a ligand. Although alkyl iodides are the most reactive class of substrates for XAT activation, alkyl bromides and chlorides are generally used since they lead to higher levels of control over the polymerization process.[552,553] As a rapid initiation is generally required in ATRP chemistry, activated derivatives like polyhalomethanes,[554] benzylic halides,[555] α-haloesters[556] or α-halonitriles,[557] or a combination of those categories[558-560] are generally employed.

The metal species needs to have two accessible oxidation states [M(n) and M(n+1)] displaying opposite reactivity in radical halogenation chemistry. The low valent metal [M(n)] needs to have strong affinity towards halogen atoms to ensure XAT activation of the alkyl halide; while the oxidised species [M(n+1)] needs to be an efficient halide donor for C-radical functionalization. This reactivity interplay is required to (i) establish an ATRP equilibrium and (ii) rapidly deactivate the growing chains providing the dormant species. In this way efficient control over polymerization can be achieved as, for example, a catalyst that deactivates the growing chains faster (smaller k_p/k_{deact} ratio) will result in polymers with lower dispersity.

The role of the ligand is generally to chelate the metal and therefore improve its solubility, which ensures fast activation and deactivation reactivity. The judicious choice of the ligand has sometimes been demonstrated to be critical to shift the ATRP equilibrium ($K_{ATRP} = k_{ac}/k_{deact}$). As an example, in Cu(I)/(II) mediated ATRP processes, the use of tris(dimethylaminoethyl)amine (M_6TREN) or pentamethyldiethylenetriamine (PMDTA) shift the K_{ATRP} equilibrium toward Cu(II) more strongly than bipyridine, which results in narrow dispersity of the corresponding polymers.[561]

The utilization of photochemical conditions in polymerization setting has been reported in 2000 on the ATRP of methyl methacrylate promoted by CuCl•bpy system and 2,2-dichloroacetophenone. Interestingly these processes were demonstrated to have faster kinetics and higher monomer conversions with respect to the same polymerizations run in the dark.[562] In line with what discussed before, the chain deactivation step is based on XAT reactivity of the polymer chain radical (P_n•) with the [Cu(II)]–X species to give the halogenated derivative P_n–X. The mechanism for chain re-activation was however dependant to the wavelength of the irradiation used to perform the polymerization. UV-based processes (λ = 335 nm) enabled irradiation at the bpy•Cu(II)–halide ligand-to-metal-charge-transfer band and this resulted in an "inner-sphere" SET leading to Cu(II)→Cu(I) with the concomitant formation of a X• radical.[563-565] Processes using lower energy sources (λ = 392 nm) required the addition of an external tertiary amine (e.g. M_6TREN, Et_3N) as this enabled [Cu(I)] regeneration by photoinduced SET.[566-569]

Scheme 112. Mechanisms of [Cu(I)] regeneration in photo-ATRP processes.



Regardless of the mechanistic pathway operating, the continuous photo-regeneration of the low valent metal species,[570] enables metal and ligand loadings to be reduced to ppm range,[564,571-573] while maintaining a good control over both the molecular mass and the dispersity of the resulting polymer. Indeed, polymerization control has been demonstrated by the often strictly linear increase in M_n as a function of the monomer conversion and narrow dispersity (typically Đ ⩽ 1.20).[562,570,574,575] Furthermore, high levels of control on the polymer architecture can be obtained as demonstrated by the preparation of ABCDE,[576] ABACADAEFG[577] block copolymers as well as nanocylinders based on graft block copolymers.[578]

Photo-ATRP is not limited to Cu-based systems and processes based on Fe(II)/Fe(III),[579-583] transition metal-based photocatalysts,[584-586] organic dyes[587-590] as well as previously mentioned systems (e.g. Fp_2, $Mn_2(CO)_{10}$) (see above) have been developed. These processes typically operates under milder conditions than standard ATRP (r.t. vs typically 70–120 °C) and it is worth noting that polymerizations using sunlight[410,591] and low energy near-infrared light have also been developed.[571,592]

4. CONCLUSION AND OUTLOOK

In this Review, we have summarized the use of halogen-atom transfer in photochemistry and photocatalysis. This reactivity mode represents a powerful strategy to exploit the chemistry of alkyl and aryl radicals using the corresponding halides, which are a class of readily available materials. Compared with strategies based on single-electron transfer, XAT allows synthetic chemists to activate these building blocks selectively without the need for strong reductants. The unique ability of XAT to engage unactivated halides and its incorporation into dual catalytic strategies has increased the number of retrosynthetic disconnections amenable through radical reactivity.

Despite the vast precedence and recent interest in the area, there are many opportunities for future research. For example, the development of novel XAT reagents based on readily available, inexpensive and non-toxic materials will be highly desirable; especially if they can fully mirror the rich reactivity of tin and silicon radicals. Novel systems enlarging the scope of halides amenable to XAT activation (e.g. aryl chlorides) and their integration in new dual catalytic manifolds will be beneficial to increase current synthetic capacity.

Developing novel radical species able to abstract halogens will also provide further fundamental knowledge and might better unveil the interplay of enthalpic/polar/steric factors operating in these processes. From this perspective, the impact that early mechanistic work has had on shaping the XAT field cannot be understated. The availability of accurate rate constants for XAT reactions has solved challenging problems in synthesis, so the continuance of physical organic chemistry studies will be crucial to the advancement of the field. Furthermore, methods in which the XAT mediator can be used as a catalyst are rare but would provide interesting opportunities over classical systems based on toxic or expensive materials. Metal complexes as well as C-based XAT systems are promising candidates to achieve this, but their synthetic potential is still underutilised.

Finally, as XAT belongs to the large class of atom-transfer reactions, it is difficult not to draw a comparison with the far more established field of H-atom transfer. Achieving selectivity in XAT reactions is still in its infancy but might be in reach following a deeper understanding of the underlying principles. Full harnessing polar, steric and stereoelectronic effects to target specific halogen atoms on polyhalogenated materials, or to desymmetrise *meso*-compounds may at present look unrealistic, but could be achievable with the design of bespoke reagents. We hope this Review will further stimulate the interest of the audience towards the exploration and the development of new paradigms in XAT reactivity for application in synthetic chemistry.

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Notes

The authors declare no competing financial interest.

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Timothée Constantin received his B.Sc. (2016) M.Sc. (2018) in Chemistry from Ecole Nationale Supérieure de Chimie de Montpellier. He then moved to the University of Manchester to pursue a PhD under the supervision of Prof Daniele Leonori. His research focuses on the activation of carbon–halogen bonds.

Daniele obtained his PhD at the University of Sheffield under the supervision of Prof Iain Coldham in 2010. After postdoctoral studies with Prof Magnus Rueping (RWTH Aachen University) and with Prof Peter H. Seeberger (Max Planck Institute of Colloids and Interfaces) he joined the group of Prof Varinder K. Aggarwal FRS as Research Officer (University of Bristol). In 2014 he commenced his independent career at the University of Manchester where is now Professor of Organic Chemistry.

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