

**Olefinic C-H functionalization through radical alkenylation**

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TUTORIAL REVIEW

Olefinic C-H functionalization through radical alkenylation

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Direct olefinic C-H functionalization represents the ideal way of introducing alkenyl group into organic molecules. The well-known process is the Heck reaction, which goes through transition metal involving alkene insertion and β -hydride elimination. However, traditional Heck reaction mainly deals with the alkenylation of aryl or vinyl electrophiles. Recent developments have revealed that alkenylation can also be achieved through radical addition to alkene and following SET oxidation/elimination. The radical alkenylation pathway allows the alkenylation with a variety of carbon-centered radicals and even heteroatom-centered radicals. This *Tutorial Review* gives an overview of recent advances in this emerging field.

Key learning points:

- (1) Olefinic C-H functionalization being achieved through radical processes
- (2) Single electron transfer processes in transition metal catalysis
- (3) Alkenyl functionality recovery from carbon-centered radicals after radical addition to alkenes
- (4) Radical generation under reductive and oxidative conditions
- (5) Both carbon-carbon bond and carbon-heteroatom bond being constructed through radical alkenylation

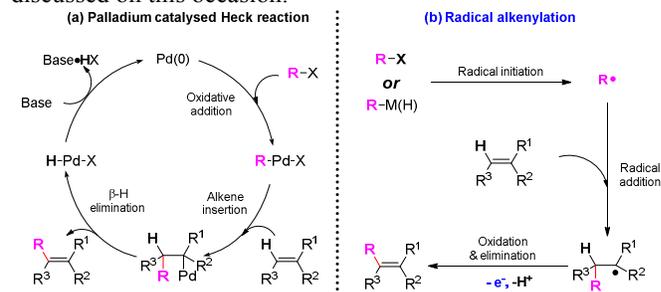
1. Introduction

Substituted alkenes are among the most useful and important structures in natural products, pharmaceuticals, materials and agrochemicals. Construction of substituted alkenes has long attracted the attention of the chemistry community.¹ Among the developed methods, direct olefinic C-H functionalization represents the most straightforward way of introducing alkenyl groups into organic molecules. The well-known process is the palladium-catalysed Heck reaction, which has now become a fundamental synthetic transformation.² However, the transition metal catalysed Heck reaction mainly deals with the alkenylation of aryl or vinyl electrophiles. Generally, it is known to go through transition metal involving alkene insertion and β -hydride elimination (Scheme 1, (a)).² Due to the decreased rates of oxidative addition and following facile β -hydride elimination, it is usually difficult for alkyl electrophiles to achieve alkenylation through traditional Heck reaction pathway.³ To solve this problem, radical processes have been gradually developed in recent years.

Addition of radicals to unsaturated bonds is a well-known process in radical reactions.⁴ However, radical addition to alkenes usually ends up with reductive addition or difunctionalization since there are a lack of elimination protocols. Recent achievements have revealed that the carbon

radical generated from radical addition can go through an SET oxidation/elimination step to recover the alkenyl functionality (Scheme 1, (b)). In those processes, radicals can be generated from both the SET reduction of organic halides (R-X) and SET oxidation of organometallic compounds (R-M) or hydrocarbons (R-H). This reaction type has been applied to a variety of carbon centered radicals and even heteroatom centered radicals. Thus, a lot of synthetically useful substituted alkenes can be constructed. This reaction pathway provides a new sight for the construction of substituted alkenes.

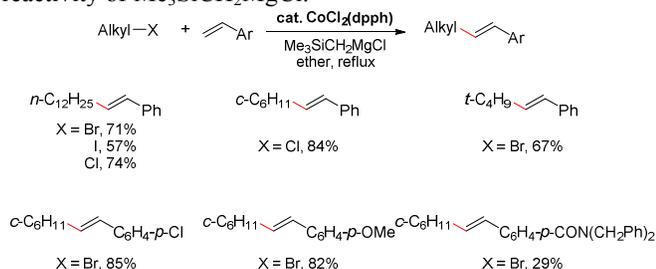
Over the past decade, various catalytic systems were developed for the olefinic C-H functionalization through radical processes. Spectacularly, developments in the transition metal catalysed radical alkenylation reactions opened a door for the alkenylation with alkyl electrophiles.⁵⁻⁸ Transition metals including Co, Pd, Ni and Cu, have subsequently been applied as catalysts in radical alkenylation processes. Moreover, radical alkenylation under transition metal free conditions has also been developed in recent years. Due to the novel breakthroughs in this area, we herein provide an overview which covers the recent development of this emerging field. Since this review focuses on the olefinic C-H functionalization processes, radical alkenylation with other functionalized alkenes such as cinnamic acids⁹, vinyl bromides¹⁰ and vinyl sulfones^{11, 12} will not be discussed on this occasion.



Scheme 1. Mechanism of alkenylation reactions

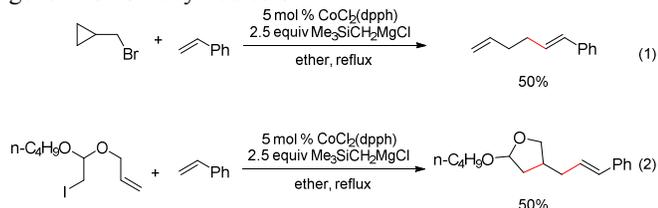
2. Cobalt catalysed radical alkenylation

In 2002, Oshima and co-workers demonstrated - a pioneering work of intermolecular cross-coupling between unactivated alkyl halides with styrenes through cobalt catalysis (Scheme 2).⁵ $\text{CoCl}_2(\text{dpph})$ was used as the catalyst and trimethylsilylmagnesium chloride was applied as an additive. Significantly, primary, secondary and even tertiary alkenyl halides were all suitable in this transformation. Moreover, less reactive alkyl chlorides also showed similar reactivity to alkyl iodides and bromides. A good functional group tolerance of styrene was achieved because of the low reactivity of $\text{Me}_3\text{SiCH}_2\text{MgCl}$.

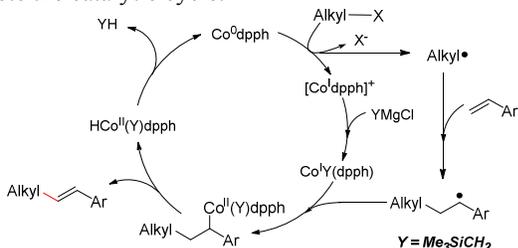


Scheme 2. Cobalt-catalysed radical alkenylation of unactivated alkyl halides.

The mechanism of this cobalt-catalysed reaction turned out to be quite different from the palladium-catalysed Heck reaction. In this reaction system, the reaction with cyclopropylmethyl bromide furnished a ring opening product (eqn. (1)) while the reaction with an iodoacetal afforded a tetrahydrofuran derivative (eqn. (2)). The features indicated the generation of alkyl radicals.



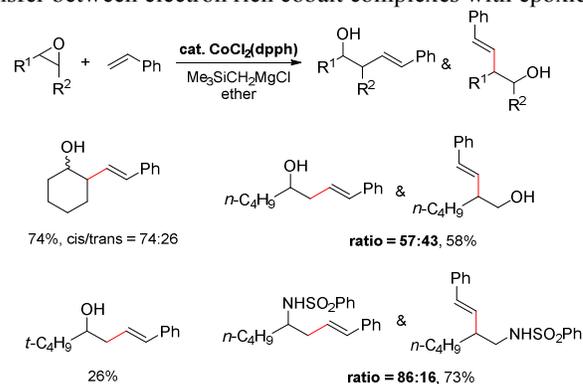
After the preliminary mechanistic study, a cobalt-catalysed single electron transfer mechanism was put forward by the authors (Scheme 3).¹³ Co(II) complex could be reduced to a Co(0) complex in presence of $\text{Me}_3\text{SiCH}_2\text{MgCl}$ (Y-H). The proposed catalytic cycle is initiated from the single electron transfer between the generated Co(0) complex and alkyl halides. An alkyl radical is generated along with a Co(I) complex. Afterwards, radical addition to styrene by the alkyl radical will generate a benzyl radical. The $\text{Co(I)}(\text{Me}_3\text{SiCH}_2)\text{dpph}$ captures this radical to form a C-Co(II) bond formation complex.¹⁴ β -Hydride elimination of the Co(II) complex furnishes the final product. Finally, reductive elimination of $\text{HCo(II)}(\text{Me}_3\text{SiCH}_2)\text{dpph}$ regenerates the Co(0) complex to complete the catalytic cycle.



At the same time, Oshima and co-workers also extended this reaction to an intramolecular version (Scheme 4).¹⁵ Under similar condition with the intermolecular reaction, 6-halo-1-hexene derivatives could be transformed into methylenecyclopentanes through cobalt catalysis.

Scheme 4. Cobalt-catalysed intramolecular radical alkenylation of 6-halo-1-hexene derivatives.

It is known that alkyl radical can be generated from epoxides by single electron transfer reduction of electron-rich metal complex.¹⁴ In 2004, the former cobalt radical alkenylation protocol was introduced into the alkenylation with epoxides (Scheme 5).¹⁶ Moderate to good yields could be obtained while the generated product, homocinnamyl alcohol, was obtained as a mixture of regioisomers. Aziridines were also suitable in this transformation to furnish homocinnamylamines. Mechanistically, the authors believed that the reaction might be initiated from ring opening of the epoxide by reacting with magnesium chloride instead of the direct single electron transfer between electron rich cobalt complexes with epoxides.

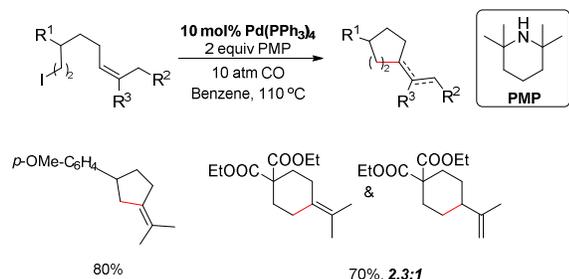


Scheme 5. Cobalt-catalysed radical alkenylation of epoxide with styrene.

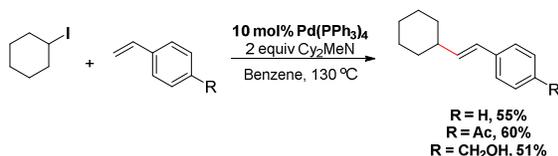
3. Palladium catalysed radical alkenylation

As early as 1998, Meijere and Waegell demonstrated a direct alkenylation of bridgehead adamantyl bromides with styrenes. They mentioned that the reaction might proceed through a radical or cationic mechanism, or a competition between those and a Heck-type mechanism was conceivable.³ More recently, Alexanian *et al.* developed a palladium catalysed radical process to achieve the intramolecular alkenylation with unactivated alkyl iodides (Scheme 6).⁸ Importantly, $\text{Pd}(\text{PPh}_3)_4$ was used as the catalyst under 10 atm pressure of CO. A suitable organic base was also important in this transformation. Both 5-membered and 6-membered ring could be synthesized through this process. However, the reaction afforded alkene isomerization product in most cases. The presence of CO was important for minimizing the formation of alkene isomers for the intramolecular alkenylation products. In a radical trapping experiment, the cyclization reaction was totally shut down and alkyl radical was trapped by TEMPO. This result clearly supported a radical alkenylation pathway under palladium catalysis. Besides the intramolecular reaction, the intermolecular cross coupling between unactivated iodides and styrenes afforded moderate results.

Intramolecular reaction:

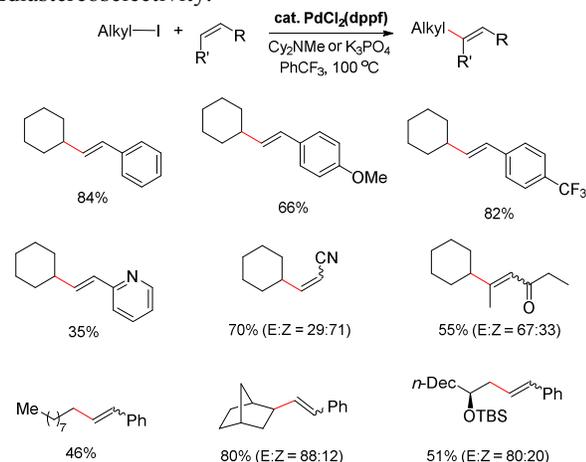


Intermolecular reaction:



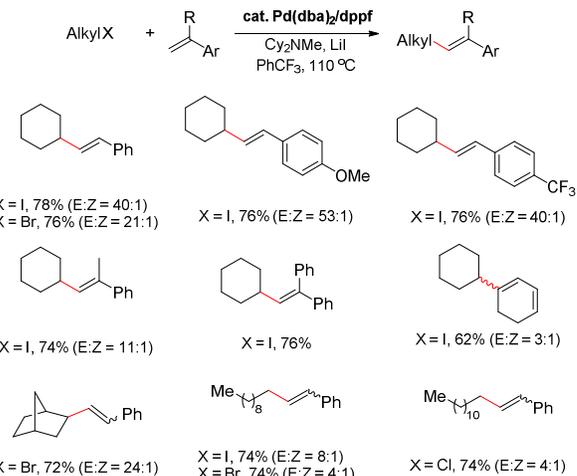
Scheme 6. Palladium-catalysed intramolecular and intermolecular radical alkenylation of unactivated alkyl iodides.

Until 2014, Alexanian and Zhou independently and simultaneously made improvements to the intermolecular alkenylation reaction of alkyl halides.^{17, 18} In Alexanian's study, the alkene substrates were expanded to non-styrenyl substrates (Scheme 7).¹⁷ PdCl₂(dppf) was used as the pre-catalyst instead of Pd(PPh₃)₄. In the case of electron deficient olefins, K₃PO₄ was found to be the optimized base. Importantly, electron-poor alkenes including vinyl ketones and acrylonitriles were firstly applied in radical alkenylation reactions. Both primary and secondary alkyl iodides were suitable in this system. The reaction showed a good functional group tolerance on styrenyl substrates. However, the reaction demonstrated moderate *E/Z* diastereoselectivity.



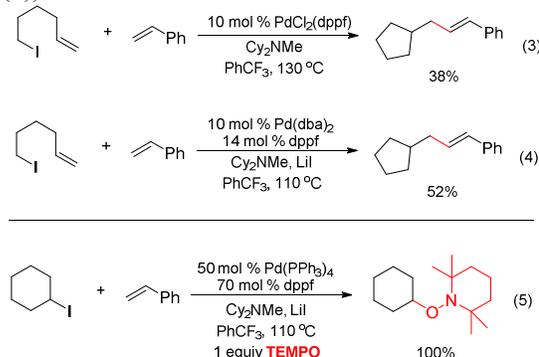
Scheme 7. Palladium-catalysed intermolecular radical alkenylation of unactivated alkyl iodides.

A significant development was made by Zhou in the same year.¹⁸ With the help of LiI, other alkyl halides including alkyl bromides and alkyl chlorides were applied in this Pd-catalysed radical alkenylation since they might generate alkyl iodides *in situ*. Dppf was proved to be the most efficient ligand, which was similar to that of Alexanian's work. While this reaction showed better diastereoselectivity than that of Alexanian's work (Scheme 8).

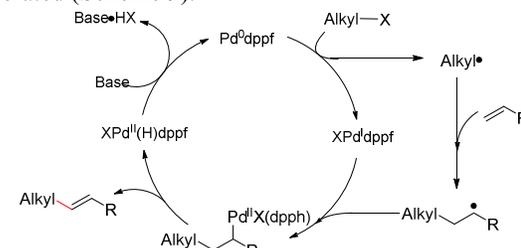


Scheme 8. Palladium-catalysed intermolecular radical alkenylation of unactivated alkyl halides.

Both in the works of Alexanian and Zhou, a radical-clock substrate 6-iodo-1-hexene selectively afforded the ring-closed alkenylation product with no linear coupling product observed (eqn. (3) and (4)). Furthermore, the alkyl radical could be trapped by a commonly used radical trapping reagent TEMPO. These results are consistent with a single-electron pathway (eqn. (5)).



A single electron transfer mechanism was proposed by both authors. In this mechanism, the Pd(0)/Pd(I)/Pd(II) catalytic cycle is quite similar to the Co(0)/Co(I)/Co(II) catalytic cycle. Compared with the mechanism through cobalt catalysis, the major difference is that there is no Grignard reagents participation, which allows base-sensitive functional groups to be tolerated (Scheme 9).

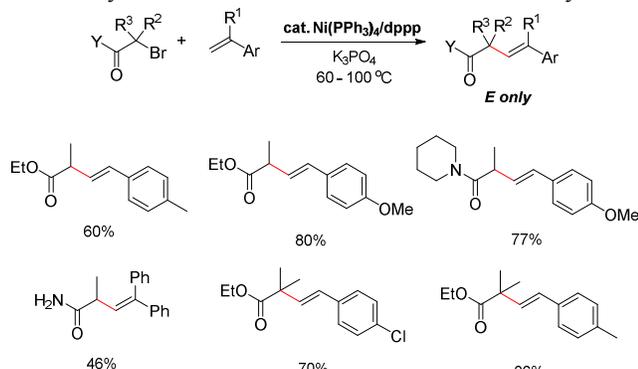


Scheme 9. Proposed mechanism for the palladium-catalysed radical alkenylation of unactivated alkyl halides.

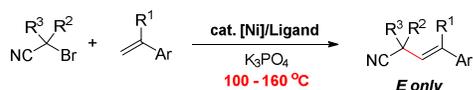
4. Nickel catalysed radical alkenylation

In 2012, Lei and co-workers described a Nickel-catalysed radical alkenylation reaction for the alkenylation of α -carbonyl alkyl halides with styrenes (Scheme 10).⁶ Ni(PPh₃)₄ was used

as the pre-catalyst and dppp was the optimized ligand. In this reaction system, only α -carbonyl alkyl bromides were applied as the alkyl halide source. Both secondary and tertiary alkyl bromides were suitable in this transformation while primary alkyl bromides were ineffective. Interestingly, amides bearing free NH groups were tolerated in this transformation. Higher temperature and an additive were both applied to ensure the reaction with non-electron-rich styrenes. However, electron deficient styrenes were still unsuitable in this reaction system.

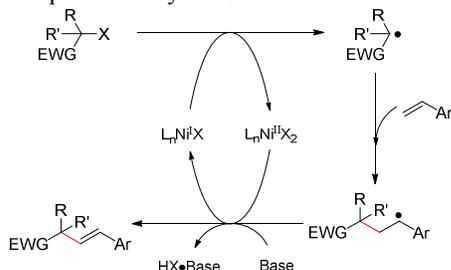


Scheme 10. Nickel-catalysed radical alkenylation of α -carbonyl alkyl bromides.



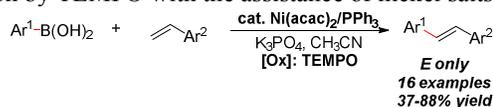
Scheme 11. Nickel-catalysed radical alkenylation of α -cyano alkyl bromides.

In the next year, the author extended the reaction to α -cyano alkyl bromides for the synthesis of β , γ -unsaturated nitriles (Scheme 11).¹⁹ During this study, the author demonstrated that high temperature was crucial to selective alkenylation with non-electron-rich styrenes. Primary α -cyano alkyl bromides were suitable while tertiary α -cyano alkyl bromides were too sensitive to be tolerated in this system. The authors explored the electron transfer process between the catalyst and alkyl bromides through EPR analysis. The reaction of α -cyano alkyl bromides with Ni(0) generates the active Ni(I) species. The reaction was believed to go through a single electron transfer process. Different from the mechanism proposed by Oshima, a Ni(I)/Ni(II) catalytic cycle was brought out by Lei and co-workers (Scheme 12). Since the reaction exhibited an excellent regioselectivity, it is believed that no C-M bond was formed in this reaction system. The carbon-carbon double bond recovery was proposed to go through a direct radical oxidation to generate a benzyl cation intermediate and a following deprotonation promoted by the base.



Scheme 12. Proposed mechanism for the Nickel-catalysed radical alkenylation of alkyl bromides.

Actually, arylboronic acids can be oxidized to generate aryl radicals in the presence of transition-metal salts and oxidants. Addition of aryl radical to alkenes has also been demonstrated in previous studies. In 2013, Lei and co-workers achieved an oxidative alkenylation between arylboronic acids and styrenes (Scheme 13).²⁰ Ni(acac)₂/PPh₃ was applied as a catalyst and K₃PO₄ was still the best choice of base. A single electron oxidant TEMPO was found to be the ideal oxidant. A variety of functional groups were well tolerated and moderate to good yields were obtained. It is noteworthy that electron deficient styrenes were well tolerated in this reaction system. Mechanistically, aryl radical was believed to be generated via oxidation by TEMPO with the assistance of nickel salts.



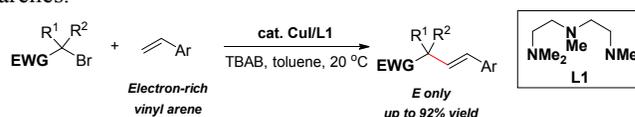
Scheme 13. Nickel-catalysed oxidative radical alkenylation of arylboronic acids.

5. Copper catalysed radical alkenylation

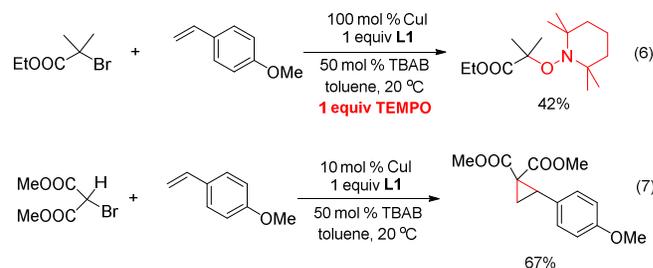
Copper catalysed radical alkenylation has been extensively studied over the past few years. A lot of radicals involving carbon centered radicals and even heteroatom centered radicals were subsequently applied in direct radical alkenylation reactions. In this part, the recent achievements of the copper catalysed radical alkenylation from different radical precursors will be discussed.

5.1 Alkyl radical

5.1.1 Reductive generation of alkyl radical In 2013, Nishikata and co-workers developed a copper/triamine catalyst system for the radical alkenylation of activated tertiary alkyl bromides with styrenes (Scheme 14).⁷ TBAB was used as an additive. The reaction showed a good reactivity with various tertiary alkyl bromides at room temperature. However, the alkene substrates were strictly limited to electron-rich vinyl arenes.

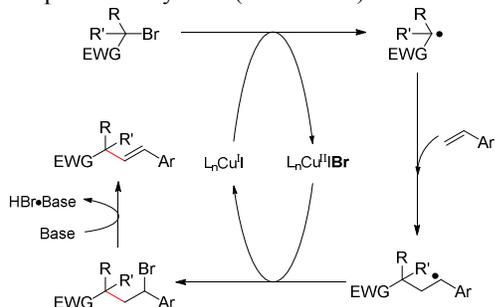


Scheme 14. Copper-catalysed oxidative radical alkenylation of tertiary activated alkyl bromides.



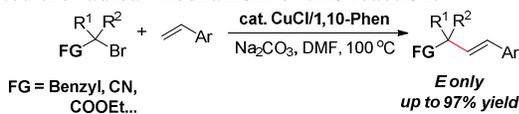
When TEMPO was added, the α -carbonyl carbon radical could be trapped under the standard condition (eqn. (6)). On the other hand, the reaction with secondary alkyl bromide afforded a cyclopropanation product, which was important for understanding the mechanism of this copper catalytic system (eqn. (7)). Based on these experiment results, the author proposed a Cu(I)/Cu(II) catalysed mechanism for this reaction. Different from the previous reports, the carbon-carbon double bond recovery was proposed to go through an atom transfer to

generate a brominated intermediate and a following HBr elimination promoted by base (Scheme 15).



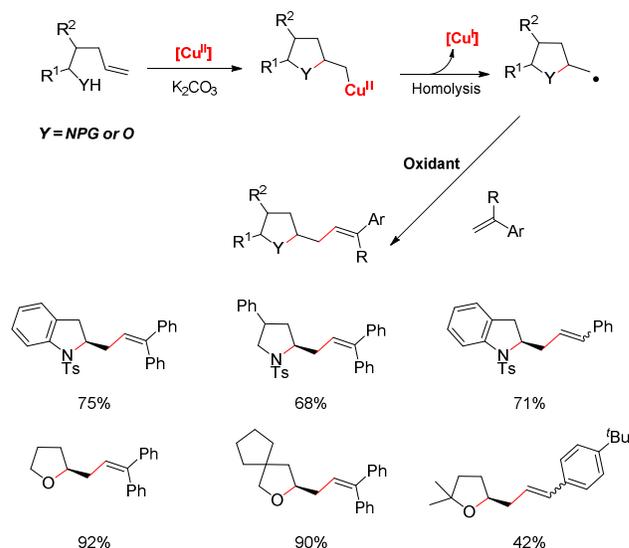
Scheme 15. Proposed mechanism for the copper-catalysed radical alkenylation of tertiary alkyl bromides.

In the next year, Lei and co-workers demonstrated their discovery of the copper-catalysed radical alkenylation between activated alkyl bromides with styrenes (Scheme 16).²¹ CuCl was used as the catalyst and 1,10-phenanthroline (1,10-phen) was applied as the ligand. The reaction was performed at 100 °C. Both benzyl bromides and α -carbonyl alkyl bromides were suitable substrates in this system. Primary, secondary and tertiary alkyl bromides were all reactive substrates for furnishing the alkenylation product. The alkene substrate was limited to electron-neutral and electron-rich styrenes. Mechanistically, EPR experiments observed the single electron transfer between Cu(I) and 2-(bromomethyl)benzotrile, which suggested the radical mechanism of this reaction.



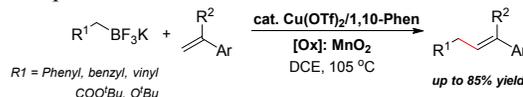
Scheme 16. Copper-catalysed oxidative radical alkenylation of activated alkyl bromides.

5.1.2 Oxidative generation of alkyl radical Actually, alkyl radical could also be generated from organometallic compounds (R–M) or aliphatic hydrocarbons (R–H) under oxidative conditions. In 2012, Chemler and co-workers reported that a chiral β -aminoalkyl radical could be generated from an enantioselective aminocupration of a γ -aminoalkene followed by C–Cu(II) homolysis (Scheme 17).²² The generated radical could undergo direct alkenylation under oxidative conditions. Cu(OTf)₂ in combination with a chiral bisoxazoline was applied as the catalyst system and MnO₂ was used as the oxidant. Two years later, the same group discovered that chiral β -alkoxy radicals could also be generated from enantioselective oxycupration of a γ -hydroxylalkene followed by C–Cu(II) homolysis.²³ In both of the processes, the substrate scope of alkenes was limited to 1,1-diarylethylenes and electron rich styrenes. Mono-substituted styrenes gave lower yields than that of 1,1-diphenylethylene.



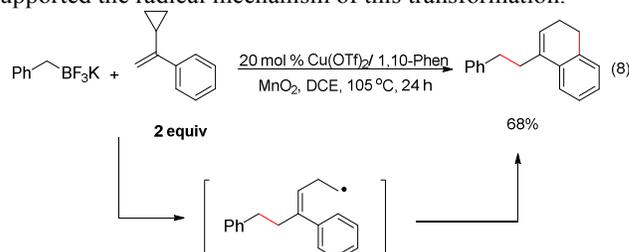
Scheme 17. Copper-catalysed oxidative radical alkenylation of γ -aminoalkene or γ -hydroxylalkene.

As mentioned in the nickel catalysed radical alkenylation, aryl radical could be generated from the oxidation of arylboronic acids. Chemler and co-workers also applied their copper catalytic system to the oxidative radical alkenylation of alkyltrifluoroborates with vinyl arenes (Scheme 18).²⁴ Various alkyltrifluoroborates could couple with 1,1-diphenylethylene in moderated to good yields. Unfortunately, this reaction suffered from a similar substrate scope on the vinyl arenes from their previous reports.



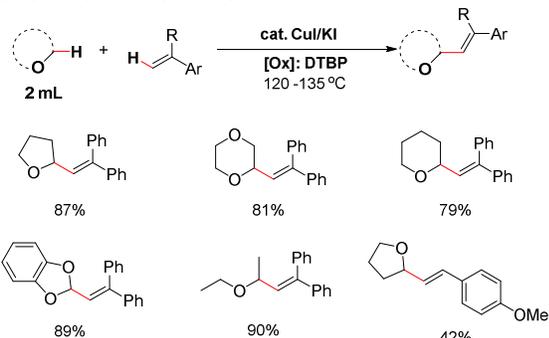
Scheme 18. Copper-catalysed oxidative alkenylation of alkyltrifluoroborates.

The reaction with 1-phenylvinylcyclopropane gave a ring expansion product in a 68% yield, supporting the addition of a benzyl radical to the alkene (eqn. (8)). This result strongly supported the radical mechanism of this transformation.

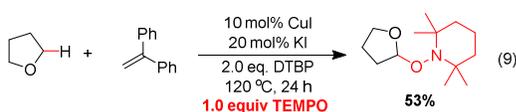


Compared with the radical generation from organic halides and organoboron compounds, the direct utilization of hydrocarbons to achieve alkenylation is an environmentally friendly pathway.^{25–27} Recent attention has been paid to the radical alkenylation with simple hydrocarbons. In this year, Lei and coworkers achieved the direct radical alkenylation of ether derivatives.²⁸ CuI was used as the catalyst and *di-tert*-butylperoxide (DTBP) was the most effective oxidant. The utilization of KI as an additive was positive for improving the yield of the desired product. It is worthy of noting that the ethers need to be used as solvents in this transformation. Various ether derivatives including ethyl ether were suitable coupling partners in this transformation (Scheme 19). However, for the alkene substrates, only 1,1-diarylethylenes were suitable

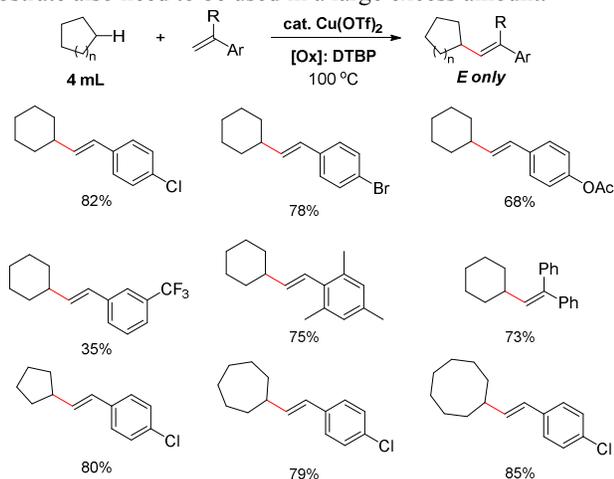
for generating the alkenylation product, which might be due to the fact that the corresponding generated radical is relatively easy to be oxidized to recover the alkene functionality. These types of olefins are usually good radical trapping reagents. Furthermore, the THF radical was captured by TEMPO in a 53% yield (eqn. (9)). These results obviously exhibited a radical process of this transformation.



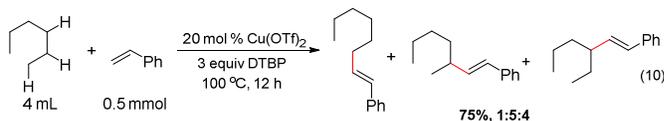
Scheme 19. Copper-catalysed oxidative alkenylation of different ethers.



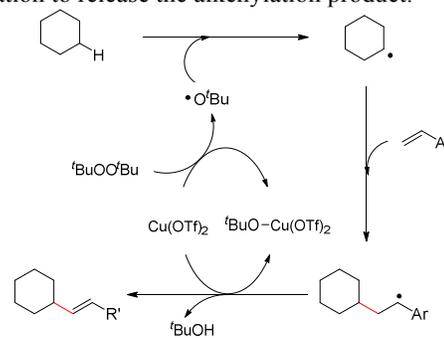
Almost at the same time, Wei and co-workers reported a copper catalysed oxidative alkenylation of unactivated alkanes with styrenes (Scheme 20).²⁹ Similar to the work by Lei, DTBP was utilized as the oxidant. The copper catalyst $\text{Cu}(\text{OTf})_2$ was crucial in this transformation. The substrate scope of styrenyl substrates was better than that of Lei's work. Both electron deficient and electron rich functional groups were tolerated on the styrenyl substrates. Strong electron deficient styrenes were still unreactive in this transformation. Various cyclic alkanes demonstrated good reactivity in this transformation. Significantly, even hexane was effective substrate in this transformation though a poor regioselectivity was obtained (eq. (10)). The major drawback of this systems is that the alkane substrate also need to be used in a large excess amount.



Scheme 20. Copper-catalysed oxidative radical alkenylation of unactivated cyclic alkanes.



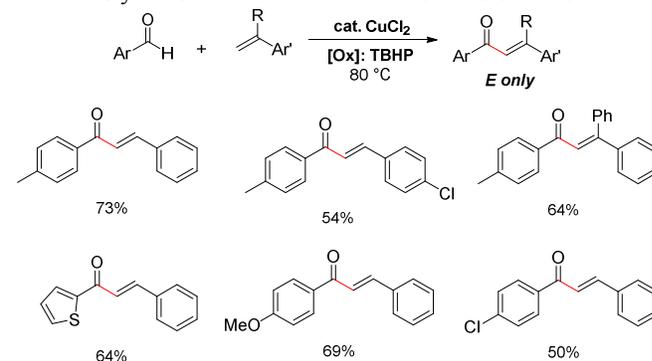
A $\text{Cu}(\text{II})/\text{Cu}(\text{III})$ catalysed oxidative radical alkenylation mechanism was proposed by the authors (Scheme 21). The major difference from the previous radical alkenylations is that the radical is initiated from a C-H SET oxidation pathway. Firstly, $\text{Cu}(\text{OTf})_2$ was oxidized by DTBP to generate $\text{Cu}(\text{III})$ species and a *tert*-butoxy radical. The *tert*-butoxy radical would abstract a hydrogen atom from the unactivated alkane to generate the alkyl radical. The radical addition to the alkene gives a benzyl radical, which is believed to undergo direct oxidation by the *in situ* generated $\text{Cu}(\text{III})$ complex and deprotonation to release the alkenylation product.



Scheme 21. Proposed mechanism for the copper-catalysed oxidative radical alkenylation of unactivated alkanes.

5.2 Acyl radical

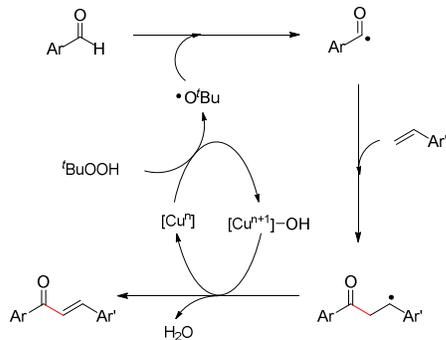
α,β -Unsaturated carbonyl compounds are extremely fascinating owing to their versatility for further synthetic transformations. Aldehyde has been shown to be facile to generate its corresponding acyl radical in the presence of peroxides. In 2013, Lei and co-workers realized the direct alkenylation of aryl acyl radicals under copper-catalysed oxidative conditions (Scheme 22).³⁰ Utilization of $\text{CuCl}_2/\text{TBHP}$ as the catalyst and oxidant combination was effective for the generation of alkenylation product. The reaction was conducted under a solvent-free condition. Only aromatic aldehydes and styrenes were suitable in this transformation. Strong electron deficient styrenes were ineffective in this transformation.



Scheme 22. Copper-catalysed oxidative radical alkenylation of aromatic aldehydes.

Addition of a radical inhibitor BHT in the reaction system completely shut down the generation of the coupling product, indicating that a radical process is most likely involved. This

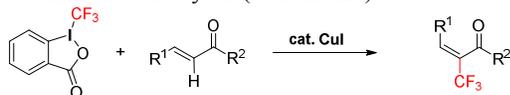
reaction was also proposed to go through an oxidative radical alkenylation pathway (Scheme 23). A Cu(I)/Cu(II) catalytic cycle was brought out by the authors. Firstly, TBHP is reduced by Cu(I) to generate a *tert*-butoxyl radical. Then an acyl radical can be generated after a hydrogen abstraction step by *tert*-butoxyl radical. The following radical addition to styrene furnishes a benzyl radical. Finally, the benzyl radical is oxidized by the Cu(II) complex to afford the alkenylation product.



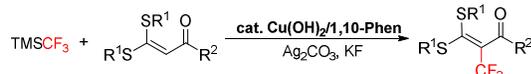
Scheme 23. Proposed mechanism for the copper-catalysed oxidative radical alkenylation of aldehydes.

5.3 Trifluoromethyl radical

It is known that electrophilic trifluoromethylation reagents (CF_3^+) can undergo single-electron-transfer (SET) reduction by a Cu(I) catalyst to generate trifluoromethyl radical. Alkynyl C-H trifluoromethylation utilizing Togni's reagent as the CF_3 radical precursor has been developed over the past years (Scheme 24).^{31, 32} However, only electron deficient internal alkenes were suitable in these transformations. Alternatively, CF_3 radical could also be generated from the oxidation of nucleophilic trifluoromethylation reagents (CF_3^-) by oxidants. The oxidative trifluoromethylation of internal olefinic C-H bonds from TMSCF_3 through copper catalysed radical process was also achieved in this year (Scheme 25).³³



Scheme 24. Copper-catalysed radical trifluoromethylation of internal alkenes from Togni's reagent.

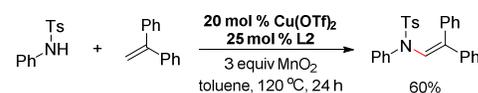


Scheme 25. Copper-catalysed oxidative radical trifluoromethylation of internal alkenes from TMSCF_3 .

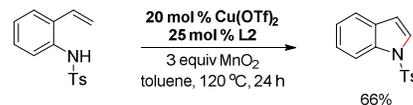
5.4 Amidyl radical

In 2013, Chemler and co-workers described a copper-catalysed direct alkenylation of amidyl radical. MnO_2 was used as the stoichiometric oxidant (Scheme 26).³⁴ Intermolecular reaction provided a method for the synthesis of enamines while the intramolecular reaction would furnish nitrogen containing heterocycles. The reaction showed rather limited substrate scope on the alkene substrates. The intermolecular reaction was mainly suitable for 1,1-diarylethylenes. Importantly, the existence of amidyl radical was proved by a radical clock experiment. The reaction with 1-phenylvinylcyclopropane gave a ring expansion product in a 33% yield (eqn. (11)). Thus, this reaction is most likely to proceed through an oxidative radical alkenylation pathway.

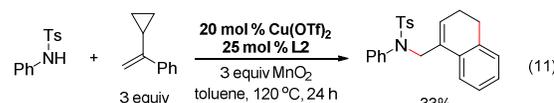
Intermolecular



Intramolecular

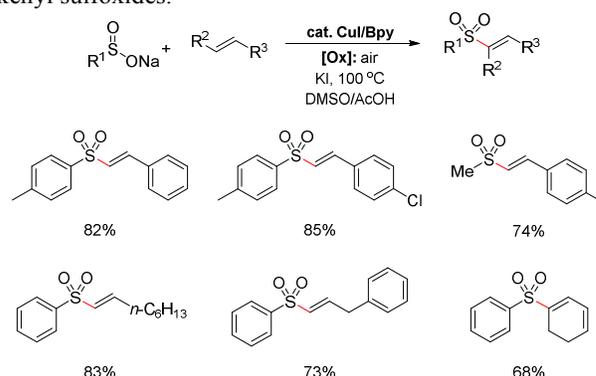


Scheme 26. Copper-catalysed intermolecular and intramolecular oxidative radical alkenylation of amides.



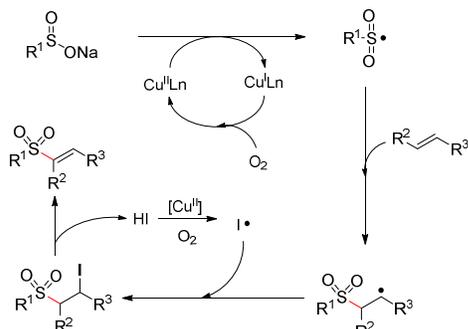
5.5 Sulfonyl radical

In 2011, Taniguchi reported a copper catalysed aerobic oxidative alkenylation of sodium sulfonates (Scheme 27).³⁵ Importantly, KI was used as an additive. Both styrenyl substrates and aliphatic olefins were suitable in this transformation. At the same time, both alkyl and aryl sodium sulfonates showed good reactivity in this transformation. This reaction provides a convenient approach for the preparation of alkenyl sulfoxides.



Scheme 27. Copper-catalysed aerobic oxidative radical alkenylation of sodium sulfonates.

Mechanistically, the reaction was believed to initiate from the copper-catalysed aerobic SET oxidation of sodium sulfonates. The generated sulfonyl radical would undergo radical addition to alkene to generate a carbon radical. The author thought that this carbon radical would be trapped by iodine radical generated from the oxidation of iodide. At last, a HI elimination step furnishes the alkenylation product (Scheme 28).



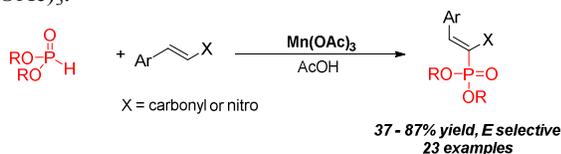
Scheme 28. Proposed mechanism for the Copper-catalysed aerobic oxidative radical alkenylation of sodium sulfonates.

6. Other radical alkenylations

Nowadays, more and more transition metal involved and transition metal free systems have been developed to achieve the alkenylation of certain radicals. Among these studies, different radical elimination protocols were discovered for the alkenyl functionality. Importantly, catalysis systems including photoredox catalysis and small molecular catalysis show great potential in radical alkenylation reaction. These reaction protocols open a door for further expanding the scope of radical alkenylation reactions. Herein, we would like to have a brief discussion on these new findings.

6.1 Mn mediated radical alkenylation

In 2010, Zhang and Zhou reported a $\text{Mn}(\text{OAc})_3$ -promoted phosphonations of internal alkenes (Scheme 29).³⁶ Under the oxidation of $\text{Mn}(\text{OAc})_3$, dialkylphosphonyl radical could be generated from dialkylphosphite. Since dialkylphosphonyl radicals are electrophilic and the α -position of the arylalkene has a high electron density, they envisioned that the reaction selectivity might be improved if an electronwithdrawing group was attached to the α -position of the arylalkene. The authors also discovered that ceric ammonium nitrate (CAN) could be used as an alternative oxidant for $\text{Mn}(\text{OAc})_3$ in this transformation, which supported the single electron transfer in the reaction processes. Recently, the Mn-mediated radical alkenylation strategy has also been applied to a Csp^2 -H radical trifluoromethylation of coumarins.³⁷ CF_3 radical can be generated from NaSO_2CF_3 through the oxidation by $\text{Mn}(\text{OAc})_3$. In both processes, the alkenyl functionality recovery is believed to come from the direct oxidation of the generated radical by $\text{Mn}(\text{OAc})_3$.



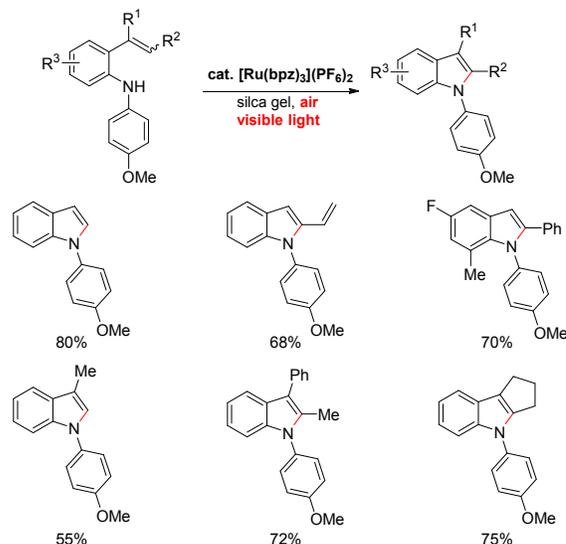
Scheme 29. Manganese-mediated radical alkenylation.

6.2 Visible-light photocatalytic radical alkenylation

In recent years, the photo-chemistry has drawn many chemists' attention and then many reactions have been accomplished with the help of photocatalyst.³⁸ The reactions often start with the excitation of the photocatalyst by visible light, which has a high oxidation ability and can serve as the oxidant to get only one electron from the reagents. Visible-light

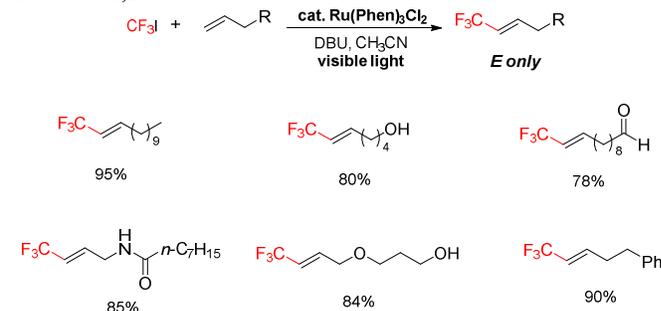
photocatalysis is now believed to be an environmentally friendly alternative choice for simple transition metal catalysis.

In 2012, Zhang and co-workers utilized a photocatalyst system to accomplish the intramolecular oxidative C-N bond formation for preparing *N*-arylindoles from styrenyl anilines (Scheme 30).³⁹ $[\text{Ru}(\text{bpz})_3](\text{PF}_6)_2$ was used as the photocatalyst and O_2 was utilized as terminal oxidant in this transformation. A number of alkenes containing various functional groups were applied with moderate to good yields.

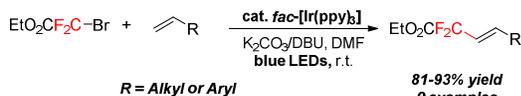


Scheme 30 Intramolecular radical alkenylation for the synthesis of indoles through visible-light photocatalysis.

At the same year, the direct trifluoromethylation of alkenes with high regioselectivity was developed by employing visible light photoredox catalysis with CF_3I , $\text{Ru}(\text{Phen})_3\text{Cl}_2$ and DBU (Scheme 31).⁴⁰ The mild reaction conditions allowed trifluoromethylation of alkenes containing a wide range of functional groups, including unprotected alcohol, aldehyde, ketone, ester, carbamate, amide, silyl ether, sulfonates, and aryl halides such as aryl bromide and aryl chloride. Notably, aromatic systems appeared to be inactive under the reaction conditions. Mechanistically, the reaction was believed to proceed through an ATRA pathway.⁴¹ A HI elimination of the iodotrifluoromethylation product with the help of the base DBU was the key step for alkenylation. More recently, Cho and co-workers introduced the visible light-induced process to the direct olefinic difluoroalkylation reactions (Scheme 32).⁴² With $\text{fac-}[\text{Ir}(\text{ppy})_3]$ as the photocatalyst, both aliphatic and aromatic olefins could afford corresponding alkenylation products with 2-bromo-2,2-difluoroacetate.

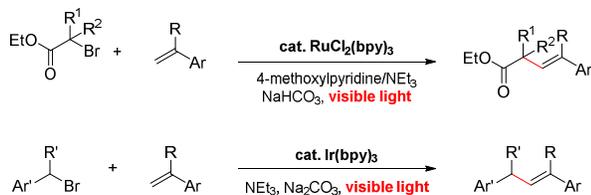


Scheme 31 Visible-light photocatalytic radical alkenylation with CF_3I .



Scheme 32 Visible-light photocatalytic radical alkenylation with 2-bromo-2,2-difluoroacetate.

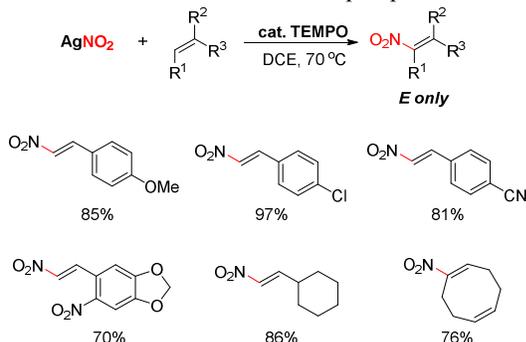
As an alternative catalysis system to nickel and copper, Lei and co-workers also introduced the visible-light photocatalytic system to the radical alkenylation of various α -carbonyl alkyl bromides and benzyl bromides to furnish α -vinyl carbonyls and allylbenzene derivatives through the use of $[\text{Ru}(\text{bpy})_3\text{Cl}_2]$ and $[\text{Ir}(\text{ppy})_3]$ as photocatalysts (Scheme 33).⁴³ This transformation is regioselective and can tolerate primary, secondary, and even tertiary alkyl halides that bear β -hydrides. Electron deficient styrenes were also unsuitable in this transformation.



Scheme 33. Visible-light photocatalytic radical alkenylation of α -carbonyl alkyl bromides and benzyl bromides.

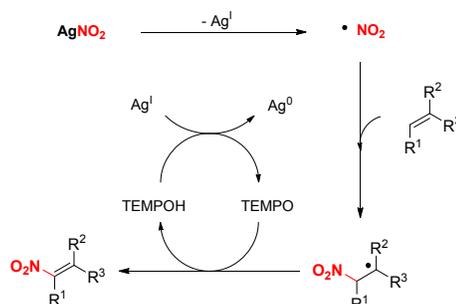
6.3 TEMPO as the catalyst

In 2013, Maiti and co-workers demonstrated that silver nitrite (AgNO_2) along with TEMPO could promote the regioselective nitration with a broad range of olefins (Scheme 34).⁴⁴ Aromatic and aliphatic olefins of different complexity could all be applied in the reaction. Both mono-substituted and di-substituted alkene showed good results in this transformation. An excellent functional group tolerance on the alkene substrates was also observed. Specifically, all these reactions exclusively formed (*E*)-nitro product in moderate to good yields. Among the radical alkenylation reactions developed, this reaction has demonstrated the broadest substrate scope up to now.



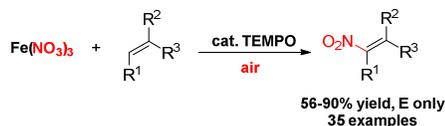
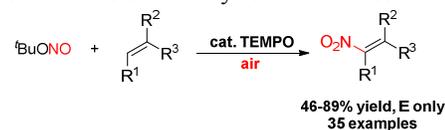
Scheme 34. Radical alkenylation with AgNO_2 and TEMPO to synthesize nitroolefins.

A plausible mechanism for the highly efficient radical alkenylation reaction was shown in Scheme 35. Firstly, nitro radical might be generated from AgNO_2 , which would undergo facile radical addition to afford a carbon-centered radical. TEMPO played a crucial role in the regeneration of the alkenyl functionality. The author provided two possible pathways for the generation of nitroolefin. TEMPO would either capture the carbon centered radical or directly abstract a hydrogen atom in the next step. Overall, both of the pathways led to the generation of TEMPOH which would be oxidized by $\text{Ag}(\text{I})$ complexes to regenerate TEMPO.



Scheme 35. Proposed mechanism for the radical alkenylation with AgNO_2 and TEMPO to synthesize nitroolefins.

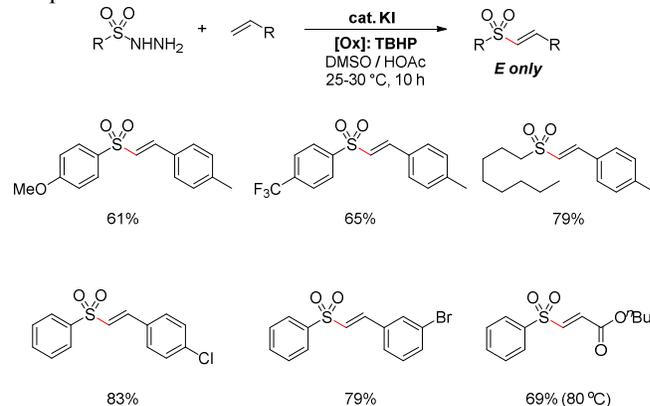
In the same year, the same group made improvements to the nitration by the replacement of the AgNO_2 with other cheaper reagents. Under aerobic condition, $\text{Fe}(\text{NO}_3)_3$ ⁴⁵ and $^t\text{BuONO}$ ⁴⁶ were subsequently applied as the nitro radical source for the synthesis of nitroolefins (Scheme 36). TEMPO used as the catalyst is believed to be the key for the success of the reactions.



Scheme 37 Radical alkenylation with $\text{Fe}(\text{NO}_3)_3$ and $^t\text{BuONO}$ to synthesize nitroolefins.

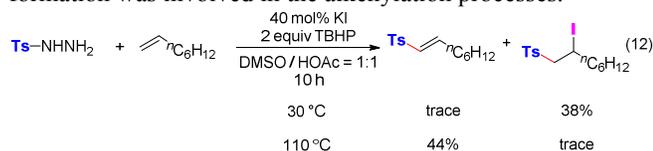
6.4 Iodine as the catalyst

Sulfonyl hydrazides have been shown to generate their corresponding sulfonyl radicals under oxidative conditions. In 2014, Lei and co-workers described an iodide-catalysed radical alkenylation of sulfonyl hydrazides (Scheme 37).⁴⁷ KI in combination with TBHP was found to be an effective oxidation system for the selective radical alkenylation. This reaction demonstrated a good functional group tolerance on both sulfonyl hydrazides and styrenes. Importantly, electron deficient styrenes were well tolerated. Significantly, even acrylates could afford the alkenylation product at a higher temperature.

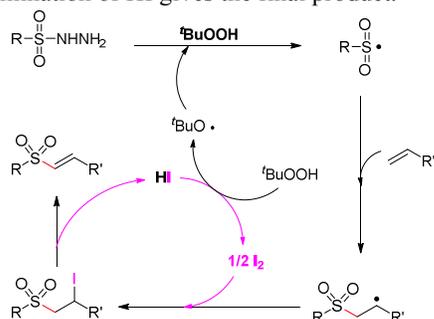


Scheme 37. Selected examples of iodine-catalysed oxidative alkenylation of sulfonyl hydrazides.

Interestingly, an iododisulfonation product was obtained instead of the desired alkenylation product at the standard condition when 1-octene was applied as the substrate (eqn. 12 at 30 °C). When the reaction temperature was raised up to 110 °C, the alkenylation product was obtained as the only product (eqn. 12 at 110 °C). These results indicated that C–I bond formation was involved in the alkenylation processes.



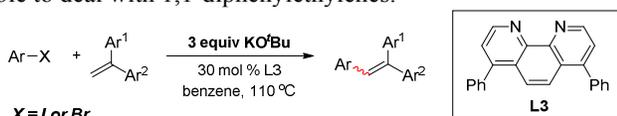
Therefore, a plausible mechanism is illustrated in Scheme 38. Sulfonyl radical is generated by the oxidation of sulfonyl hydrazide with TBHP, followed by radical addition to olefin to afford a new carbon centered radical. Next, this radical is captured by I₂ to afford an iododisulfonation intermediate. Further elimination of HI gives the final product.



Scheme 38. Proposed mechanism of iodine-catalysed oxidative alkenylation of sulfonyl hydrazides.

6.5 KO^tBu as the mediator

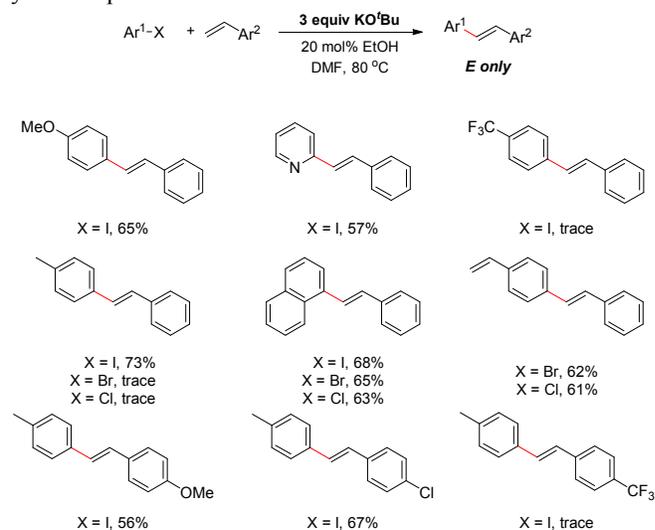
In 2011, Shi and co-workers described a KO^tBu-promoted cross-coupling between aryl halides and 1,1-diphenylethylene (Scheme 39).⁴⁸ No transition metal was used in this reaction system. Catalytic amount of a phenanthroline derivative was found to be crucial in the reaction system. Benzene was chosen as the solvent. Unfortunately, this reaction system was mainly able to deal with 1,1-diphenylethylenes.



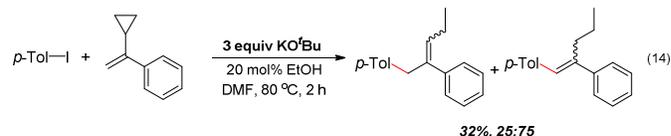
Scheme 39. KO^tBu-promoted alkenylation of aryl halides with styrenes

In the same year, Shirakawa and Hayashi reported a similar KO^tBu promoted Mizoroki–Heck reaction of aryl halides with styrenes (Scheme 40).⁴⁹ Different from the work by Shi, no dinitrogen ligand was needed. The solvent DMF was crucial in this transformation. Addition of catalytic amount of ethanol was beneficial for improving the yield of the desired product. Aryl and heteroaryl iodides were both suitable in this transformation. Phenyl iodides bearing electron-withdrawing groups could not give the desired products. Simple *p*-tolyl bromide or chloride could not furnish the alkenylation product while substitution by a conjugating group enhanced the reactivity of aryl bromides and chlorides. This reaction also demonstrated similar substrate limitations on styrenyl substrates. Electron deficient styrenes were unreactive in this reaction. Moreover, the reaction of alkyl-substituted alkenes, acrylic acid

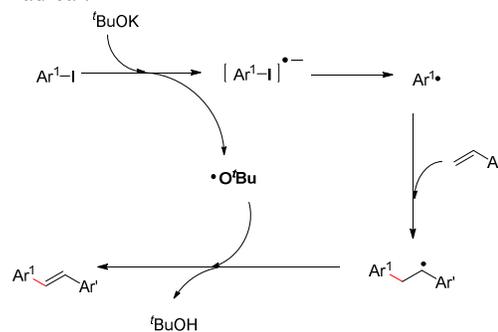
derivatives, or vinyl ethers did not give synthetically significant yields of products.



Scheme 40. KO^tBu-promoted alkenylation of aryl halides with styrenes.



Mechanistically, the reaction of *p*-tolyl iodide with *α*-cyclopropylstyrene gave a mixture of ring opening product (eqn. (14)). This result supports the reaction pathway that includes addition of aryl radicals to styrenes. One plausible reaction pathway is shown in Scheme 41. Firstly, single electron transfer between aryl iodide and ^tBuOK gives the radical anion [Ar-X]^{•-} and a *tert*-butoxyl radical. The radical anion subsequently releases a halide anion to generate an aryl radical. Following radical addition to styrenes will generate a benzyl radical, which will then be oxidized to afford the alkenylation product with the help of the *in situ* generated *tert*-butoxyl radical.



Scheme 41. Proposed mechanism for KO^tBu-promoted alkenylation of aryl halides with styrenes.

7. Conclusions

During the last decade, significant advances were made in the area of direct olefinic C–H functionalization through radical processes. Various radicals including both carbon-centered radicals and heteroatom-centered radicals have been applied in radical alkenylation reactions. Radical alkenylation offers an opportunity for the construction of substituted alkenes from readily available materials. The radicals in those reactions can be generated from organic halides, organometallic compounds

(R–M) and even hydrocarbons (R–H). Different classes of substituted alkenes can be synthesized since both carbon-carbon bond and carbon-heteroatom bond can be constructed through radical alkenylation. Hopefully, this reaction type will be a useful tool for the construction of substituted alkenes in the near future.

In most cases, the substrate applicability of alkene in radical alkenylation reactions is limited. Current studies mainly deal with aromatic alkenes. Only isolated examples are able to deal with aliphatic alkenes. Moreover, only limited categories of radicals have been utilized in alkenylation reactions. The major challenge for these issues is to find a suitable radical oxidation/elimination protocol for recovering the alkenyl functionality. Obviously, discovering highly efficient and selective catalytic systems for radical alkenylation remains to be a promising research area.

Acknowledgements

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Notes and references

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