

Recent Advances of Transition-Metal Catalyzed Radical Oxidative Cross-Couplings

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CONSPECTUS: Oxidative cross-coupling reactions between two nucleophiles are a powerful synthetic strategy to synthesize various kinds of functional molecules. Along with the development of transition-metal-catalyzed oxidative cross-coupling reactions, chemists are applying more and more first-row transition metals (Fe, Co, etc.) as catalysts. Since first-row transition metals often can go through multiple chemical valence changes, those oxidative cross-couplings can involve single electron transfer processes.

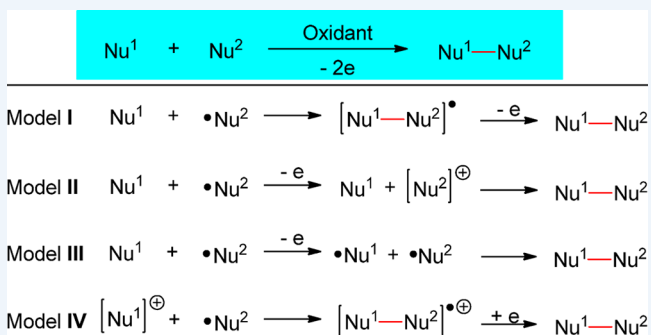
In the meantime, chemists have developed diverse mechanistic hypotheses of these types of reactions. However, none of these hypotheses have led to conclusive reaction pathways until now.

From studying both our own work and that of others in this field, we believe that radical oxidative cross-coupling reactions can be classified into four models based on the final bond formations. In this Account, we categorize and summarize these models.

In model I, one of the starting nucleophiles initially loses one electron to generate its corresponding radical under oxidative conditions. Then, bond formations between this radical and another nucleophile create a new radical, $[\text{Nu}^1\text{---}\text{Nu}^2]^{\bullet}$, followed by a further radical oxidation step to generate the cross-coupling product. The radical oxidative alkenylation with olefin, radical oxidative arylation-annulation, and radical oxidative amidation are examples of this model.

In model II, one of the starting nucleophiles loses its two electrons via two steps of single-electron-transfer to generate an electrophilic intermediate, followed by a direct bond formation with the other nucleophile. For example, the oxidative C–O coupling of benzylic sp^3 C–H bonds with carboxylic acids and oxidative C–N coupling of aldehydes with amides are members of this model group.

For model III, both nucleophiles are oxidized to their corresponding radicals. Then, the radicals combine to form the final coupling product. The dioxygen-involved radical oxidative cross-couplings between sulfinic acids and olefins or alkynes belong to this bond formation model. Lastly, in model IV, one nucleophile loses two electrons to generate an electrophilic intermediate, while the other nucleophile loses one electron to generate a radical. Then, a bond forms between the cation and the radical to generate a cationic radical, followed by a one-electron reduction to afford the final coupling product. The oxidative coupling between arylboronic acids and simple ethers was classified in this model. At the current stage, there are only a few examples presented for models III and IV, but they represent two types of potentially important transformations. More and more examples of these two models will be developed in the future.



1. INTRODUCTION

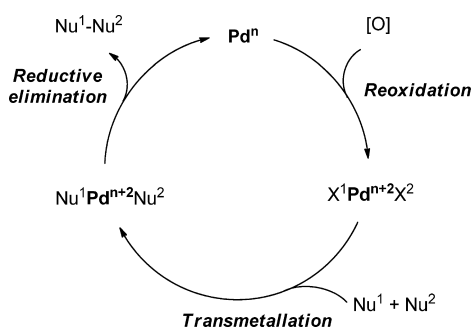
Since its initial discovery, transition metal catalyzed cross-couplings have emerged as a powerful tool for constructing various new chemical bonds and also have been widely applied in both academia and industry.¹ These classic cross-couplings normally occur between an electrophile and a nucleophile in the presence of a transition metal catalyst. Along with the development of synthetic methodology, new bond formation modes are reported. The oxidative cross-coupling between two different nucleophiles in the presence of a proper oxidant is one of the most extensively studied topics during the past ten years, in which utilization of hydrocarbons as the nucleophiles has been considered to be an ideal approach.^{2,3} During the past several years, palladium catalysis has dominated this research

area for achieving various chemical bond formations between two nucleophiles.^{2–5} For the mechanistic aspect of palladium catalysis in oxidative cross-couplings, a general catalytic cycle could be emphasized, in which reductive elimination is usually the key step for the final bond formations. As shown in Scheme 1, the catalytic cycle usually starts from a high valent Pd species. Then, the sequential transmetalation of two different nucleophiles with the Pd species generates a $\text{Nu}^1\text{---}\text{Pd}\text{---}\text{Nu}^2$ intermediate, followed by reductive elimination to afford the coupling product $\text{Nu}^1\text{---}\text{Nu}^2$, and releases a low valent palladium species $[\text{Pd}^n]$ which is oxidized by a proper oxidant to

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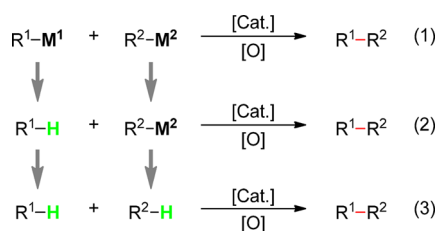
Scheme 1. General Catalytic Cycle of Palladium-Catalyzed Oxidative Couplings



regenerate the $[\text{Pd}^{n+2}]$ species. Most of those palladium-catalyzed reactions are not supposed to be radical processes. Along with the development of oxidative cross-couplings, more and more first-row transition metal catalysis has been discovered, in which single-electron transfer (SET) processes are usually dominating.^{6–9}

Since its foundation in 2005, our research group has focused on palladium-catalyzed oxidative cross-couplings between two different nucleophiles (Scheme 2).¹⁰ Our initial study focused

Scheme 2. Development of Our Research Programs on Oxidative Cross Coupling Reactions



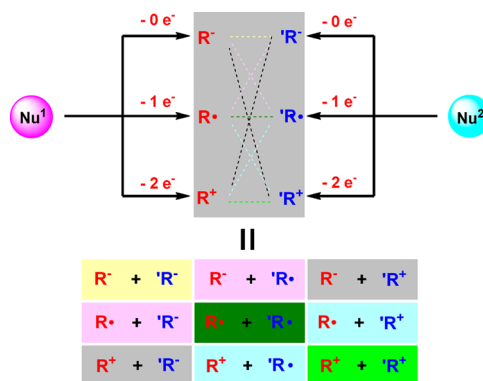
on the cross-coupling between two organometallic reagents in the presence of a Pd catalyst with desyl chloride as the oxidant (Scheme 2, eq 1).¹¹ The key achievement of this transformation is that it shows the possibility of high selectivity for cross-coupling of two different nucleophiles over their homocoupling products. However, problems still remain, since the utilization of two organometallic reagents does not meet the requirement of modern sustainable chemistry. In the following several years, we directed our efforts to replace those organometallic reagents with various simple C–H or X–H nucleophiles for achieving greener oxidative cross-couplings. Therefore, oxidative $\text{R}^1\text{-H}/\text{R}^2\text{-M}^2$ and $\text{R}^1\text{-H}/\text{R}^2\text{-H}$ cross-couplings are the major research topics in our group (Scheme 2, eqs 2 and 3). During the mechanistic studies of each transformation, we realized that radical processes are involved in many reactions, especially in those reactions that involve first-row transition metal catalysts and O_2 -involved organic transformations. In this Account, those radical oxidative cross-couplings from our group will mainly be summarized.

2. MODELS FOR RADICAL OXIDATIVE CROSS-COUPPLINGS

To achieve bond formations between two nucleophiles, two electrons need to be removed from the system. For each nucleophile in oxidative cross-couplings, there are three possible forms to participate in the bond formation step: anion, radical, and cation (Scheme 3). Therefore, there are nine

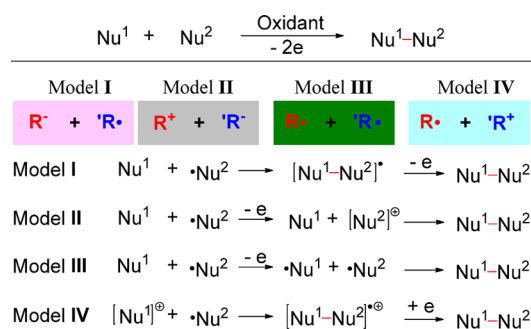
theoretical combinations for bond formations. Obviously, the R^-/R^- and R^+/R^+ combinations are not possible for direct bond formations.

Scheme 3. Combinations of Possible Bond Formation Modes between Two Nucleophiles



Based on those combinations, theoretically, there are four models for the final bond formations for radical oxidative cross-couplings (Scheme 4). In model I, one of the starting

Scheme 4. Four Models for the Final Bond Formations in Radical Oxidative Cross Couplings



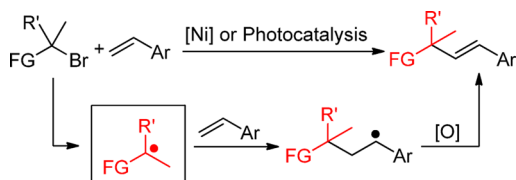
nucleophiles initially loses one electron to generate its corresponding radical under oxidative conditions. Then, bond formations between this radical and another nucleophile to afford a new radical $[\text{Nu}^1\text{-Nu}^2]^\bullet$, followed by a further radical oxidation to generate the cross-coupling product. In model II, one of the starting nucleophiles loses its two electrons via two steps to generate an electrophilic intermediate followed by a direct bond formation with the other nucleophile. In model III, both nucleophiles are oxidized to their corresponding radicals. Then, the radicals combine to form the final coupling product. In model IV, one nucleophile loses two electrons to generate an electrophilic intermediate, while the other nucleophile loses one electron to generate a radical. Then, bond formation between the cation and the radical to generate a cationic radical is followed by a one-electron reduction to afford the final coupling product. Our studies show the possibility of those four models in different reaction systems. Examples will be discussed in detail in this Account.

3. MODEL I IN RADICAL OXIDATIVE CROSS-COUPPLINGS

3.1. Radical Oxidative Alkenylation with Olefins

Alkenylation with olefin is a fundamental transformation in organic synthesis. It can easily introduce C=C functionality into various organic molecules.¹² Our research started from the alkenylation of alkyl halides with olefins. Initially, a nickel catalysis and a photocatalysis were found to be effective for the alkenylation of activated alkyl halides such as α -carbonyl alkyl bromides and benzylic bromides.^{13,14} Different from the Pd-catalyzed Heck reaction for alkenylation, this alkenylation occurs via a radical process by the reductive initiation of the alkyl halides (Scheme 5). These achievements provide us a

Scheme 5. Radical Alkenylation of Activated Alkyl Halides Utilizing Nickel Catalysis or Photocatalysis

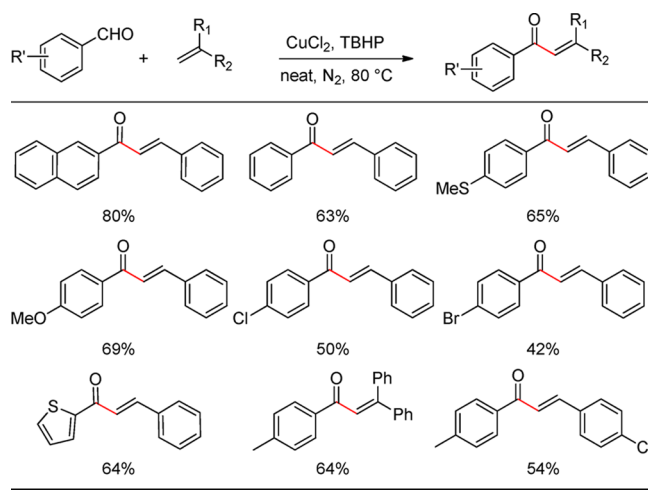


concept for achieving alkenylation of various organic molecules with olefin via a radical pathway. If we can find ways to generate proper radicals, various types of radical alkenylations will be achieved.

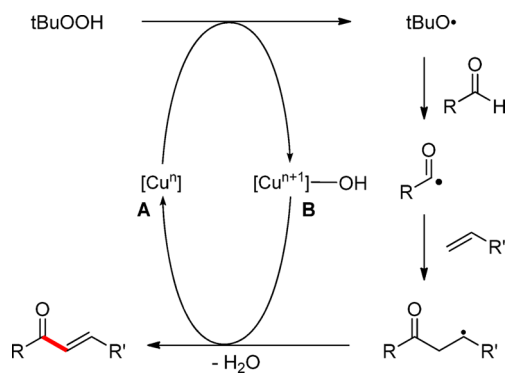
Compared with organohalides, direct utilization of hydrocarbons as the radical precursor under oxidative condition would be more appealing and highly atom-economic. Consequently, various radical oxidative cross-couplings between hydrocarbons and olefins were developed.

3.1.1. Alkenylation of Aldehyde with Olefin. α,β -Unsaturated carbonyl compounds are important building blocks owing to their versatility for further synthetic transformations. Aldehyde has been shown to easily generate its corresponding acyl radical in the presence of peroxides.¹⁵ Therefore, based on the previous design, the radical oxidative cross-coupling between aldehyde and olefin was investigated for the direct synthesis of α,β -unsaturated ketones by using peroxides combined with transition metal salts as the catalytic system (Scheme 6).¹⁶ With *t*-butyl hydroperoxide (TBHP) as the oxidant, CuCl₂ was found to be effective for the generation of alkenylation product, while other transition metal salts such as FeCl₂, CoCl₂, and NiCl₂ did not afford the alkenylation product. Addition of a radical inhibitor, butylhydroxytoluene (BHT) in the reaction system completely shut down the generation of the coupling product, indicating that a radical process is most likely involved. The transformation is believed to occur via the following pathway (Scheme 7). Initially, the low valent copper species, A, donates an electron to TBHP to generate copper species B and an alkoxy radical, which then abstracts a hydrogen atom from aldehyde to generate an acyl radical. The addition of acyl radical to alkene generates a benzylic radical. The next step is believed to be accomplished through the direct oxidation of this benzylic radical by copper species B and the deprotonation to release the final alkenylation product. Meanwhile, the low valent copper species A was generated to restart the catalytic cycle. Therefore, this transformation meets with model I of radical oxidative cross-coupling shown in Scheme 4.

Scheme 6. Copper Catalyzed Radical Oxidative Alkenylation of Aldehydes with Olefins

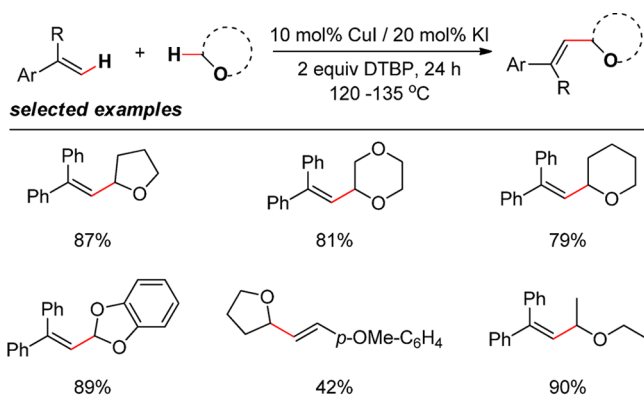


Scheme 7. Proposed Mechanism of Copper Catalyzed Radical Oxidative Alkenylation

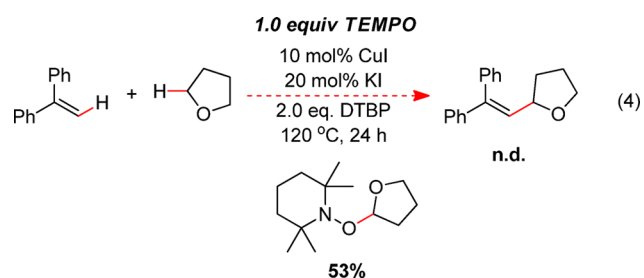


3.1.2. Alkenylation of Ethers with Olefin. The direct alkenylation of α -C-H of ethers with olefin would represent an ideal approach for the synthesis of allylic ethers. Usually, the α -C-H bonds have relatively low bond dissociation energy (BDE). Therefore, the homolytic cleavage of those C-H bonds in the presence of a hydrogen abstractor easily generates their corresponding carbon-centered radicals. Indeed, it has been shown that tetrahydrofuran (THF) could generate its corresponding carbon-centered radical in the presence of a peroxide.¹⁷ Consequently, THF was tested to couple with olefin in the presence of a peroxide and a transition metal catalyst.¹⁸ Condition screening showed that the combination of di-*tert*-butyl peroxide (DTBP) with CuI is effective for this transformation. The utilization of KI as an additive is positive for improving the yield of the alkenylation product. Ether derivatives such as THF, dioxane, and even diethyl ether were all suitable coupling partners (Scheme 8). For the olefin substrates, 1,1-diaryllkene derivatives were suitable for generating the alkenylation product. These types of olefins are usually good radical trapping reagents. We assume that the requirement for 1,1-diaryls might be because the corresponding generated radical is relatively easy to oxidize to recover the alkene functionality. Almost at the same time, Wei and co-workers reported a copper-catalyzed oxidative alkenylation of unactivated alkanes, in which a similar radical pathway was proposed.¹⁹

Scheme 8. Copper Catalyzed Radical Oxidative Alkenylation of Ethers with Olefins



When a radical trapping reagent, 2,2,6,6-tetramethylpiperidin-1-yl)oxy (TEMPO), was added in the reaction system, the alkenylation was totally inhibited. Meanwhile, the THF radical was captured by TEMPO to generate the captured product in a 53% yield (eq 4). These results obviously exhibited a radical process for this transformation.

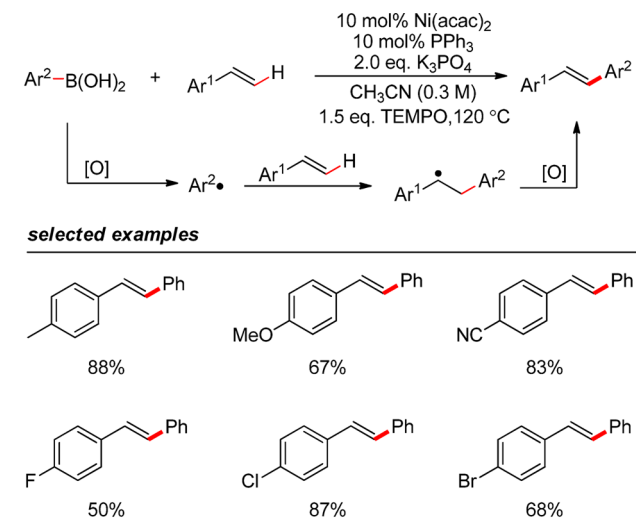


3.1.3. Alkenylation of Arylboronic Acids with Olefins.

The alkenylation of arylboronic acids with olefins is extensively studied under palladium catalysis, which has been defined as oxidative Heck reaction.²⁰ Those transformations were not normally proposed to involve radical processes. Actually, it has been shown that arylboronic acids can be oxidized to generate aryl radicals in the presence of transition-metal salts and oxidants.^{21–23} Addition of aryl radical to alkenes has also been demonstrated.²⁴ Therefore, a radical pathway for the alkenylation of arylboronic acids was designed (Scheme 9).²⁵ Our initial study on the oxidative cross-coupling of arylboronic acids with ethers showed that Ni(acac)₂ combined with an oxidant could promote the generation of aryl radical from arylboronic acid (see section 6, model IV).²⁶ Therefore, Ni(acac)₂/PPh₃ was applied as a catalyst to test the radical oxidative alkenylation of arylboronic acids. Condition screening showed that TEMPO was a proper oxidant for achieving selective alkenylation. K₃PO₄ was the best choice of additive, and CH₃CN was the proper solvent. A variety of functionalities were well tolerated, such as Me, F, Cl, Br, CN, and OMe groups (Scheme 9).

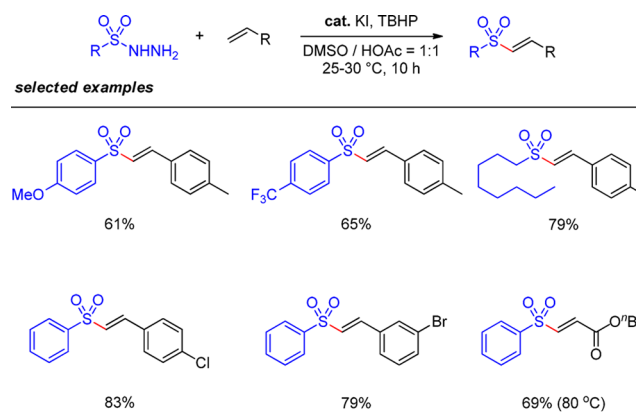
3.1.4. Alkenylation of Sulfonyl Hydrazides with Olefins. Sulfonyl hydrazides have been shown to generate their corresponding sulfonyl radicals under oxidative conditions.^{27–29} This provides us a possibility for the synthesis of alkenyl sulfones via the radical oxidative alkenylation of sulfonyl hydrazides. With TBHP as the oxidant, KI was found to be an optimal catalyst for the direct alkenylation process at room

Scheme 9. Nickel-Catalyzed Radical Oxidative Alkenylation of Arylboronic Acids with Olefins



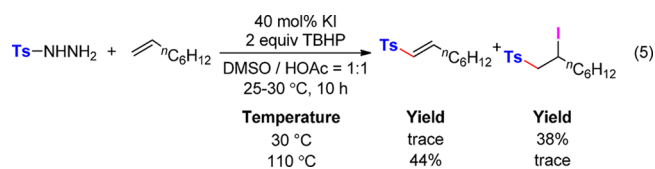
temperature (Scheme 10).³⁰ No product was observed without the addition of KI.

Scheme 10. Iodide Catalyzed Oxidative Alkenylation of Sulfonyl Hydrazides with Olefins

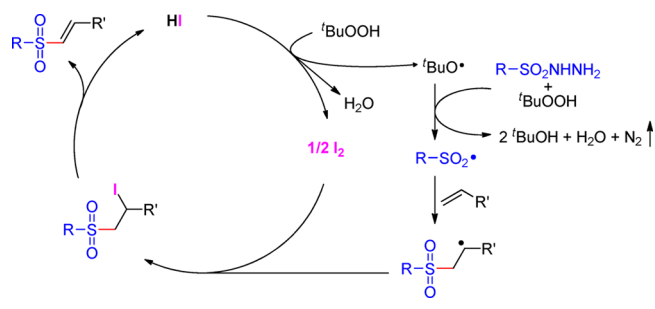


Iodine was believed to assist the elimination process with the generation of HI. Also, iodide helps to initiate the *tert*-butoxyl radical generation. I₂ was likely to be generated during reaction process, because the reaction system turned purple rapidly after the addition of KI. *In situ* IR monitoring exhibited that TBHP could not initiate the reaction between sulfonyl hydrazide and styrene. As long as KI was added, the starting sulfonyl hydrazide and styrene decreased rapidly along with the generation of the alkenylation product. Furthermore, iodosulfonylation product was obtained instead of the desired alkenylation product at room temperature when 1-octene was applied as the substrate, indicating the possible formation of C–I bond in this transformation. When the reaction was conducted at 110 °C, the desired alkenylation product was solely obtained, indicating that HI elimination might be the key to alkenylation.

Therefore, a plausible mechanism was illustrated (Scheme 11). Sulfonyl radical was generated by the oxidation of sulfonyl hydrazide with TBHP, followed by radical addition to olefin to afford a β -sulfonyl carbon-centered radical. Next, this radical



Scheme 11. Plausible Mechanism of Iodide Catalyzed Radical Oxidative Alkenylation

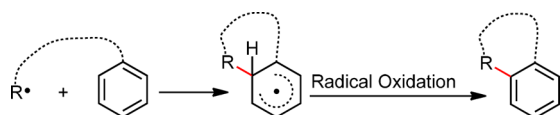


was captured by I_2 to afford an iodosulfonation intermediate. Further elimination of HI gives the final product. Herein, iodine behaves as a transition metal catalyst and is the key to the success of this transformation.

3.2. Radical Oxidative Arylative Annulation

Direct utilization of arenes as nucleophiles in oxidative cross-couplings is considered one of the most appealing topics in organic transformations.^{2,3,31} Usually, the C–H activation occurs via electrophilic metalation followed by further transformations. During our and others' investigations on aromatic C–H activations, a radical pathway has shown to be a nice alternative.^{32–35} Usually, the addition of a radical to an aromatic ring at a specific site is easily achieved to generate a π -radical. Then, oxidation of the generated π -radical recovers the aromatic system together with the loss of a proton. Meanwhile, a new chemical bond is formed (Scheme 12). Therefore, if a proper R radical could be generated under oxidative conditions, the corresponding radical oxidative coupling will be rationally achieved.

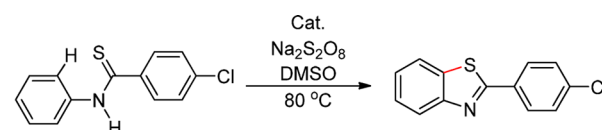
Scheme 12. Aromatic C–H Activation via Radical Pathway



3.2.1. Radical Oxidative Annulation for Benzothiazole

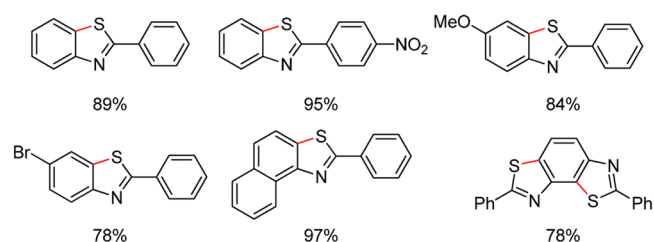
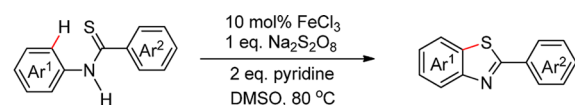
Synthesis. Sulfur radical has shown to be easily generated under oxidative conditions.³⁶ In 2012, we demonstrated an intramolecular C–S bond formation via an oxidative C–H sulfuration for the synthesis of various benzothiazole derivatives.³⁷ Our study showed that the C–H sulfuration product benzothiazole could be generated from arylthioamide via an intramolecular radical cyclization (Scheme 13). $\text{Na}_2\text{S}_2\text{O}_8$ could solely promote the transformation, although the yield was very low. The addition of catalytic amount of FeCl_3 increased the yield of the cyclization product to 68%. Two equivalents of pyridine could further enhance the yield to 87%. The reaction was general for a variety of arylthioamides (Scheme 14). The reaction was believed to occur via the oxidation of arylthioamide to a thioyl radical, followed by a radical addition

Scheme 13. Iron-Catalyzed Oxidative C–H Sulfuration from Arylthioamides



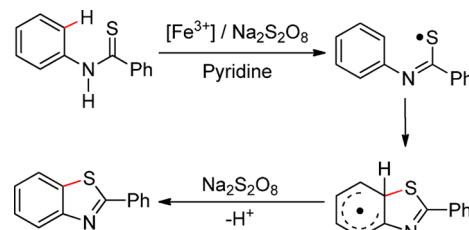
Entry	Cat. (10 mol %)	Additive (2 equiv)	Yield [%]
1	-	-	16
2	FeCl_3	-	68
3	FeCl_3	Pyridine	87

Scheme 14. Iron-Catalyzed Oxidative Intramolecular C–S Bond Formations for the Synthesis of Benzothiazoles



to the aromatic ring. Further radical oxidation afforded the final benzothiazole product (Scheme 15).

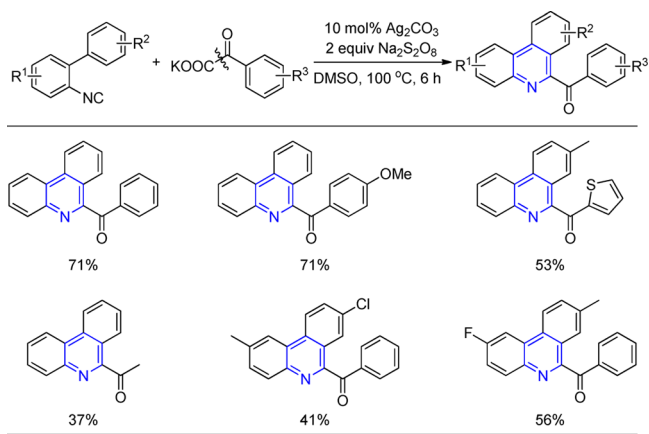
Scheme 15. Proposed Mechanism of Iron Catalyzed Oxidative C–H Sulfuration



3.2.2. Radical Oxidative Decarboxylation–Cyclization.

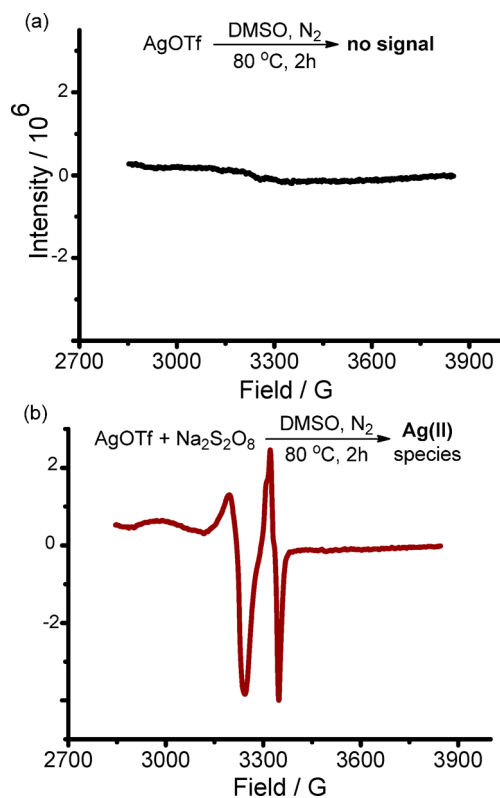
Radical addition with a C1 linker has been mainly dominated by radical insertion with CO to generate an acyl radical.¹⁵ As an isoelectronic species of CO, isocyanides can also act as a C1 linker to generate an imidoyl radical followed by further transformations.³⁸ In 2012, Chatani and Tobisu reported an oxidative cyclization of 2-isocyanobiphenyls with organoboron reagent as the radical precursor.³⁹ Later on, alkyl halides,⁴⁰ CF_3 reagents,^{41,42} aldehyde,⁴³ and diphenylphosphine oxide⁴⁴ were subsequently utilized as radical precursors for the same cyclization. Recently, we developed a protocol using α -oxocarboxylates as acyl radical precursors for the oxidative cyclization with 2-isocyanobiphenyls (Scheme 16).⁴⁵ Ag_2CO_3 was found to be the proper catalyst with $\text{Na}_2\text{S}_2\text{O}_8$ as the oxidant in DMSO solvent. A variety of 2-isocyanobiphenyls and α -oxocarboxylates were suitable substrates in this transformation. Radical inhibitors TEMPO and BHT completely shut down the reaction. Moreover, EPR analysis showed that Ag(I) could be

Scheme 16. Silver-Catalyzed Radical Oxidative Decarboxylation–Cyclization To Construct Phenanthridines



easily oxidized by $\text{Na}_2\text{S}_2\text{O}_8$ at 80 °C in DMSO (Scheme 17). These results suggested a single electron pathway for this

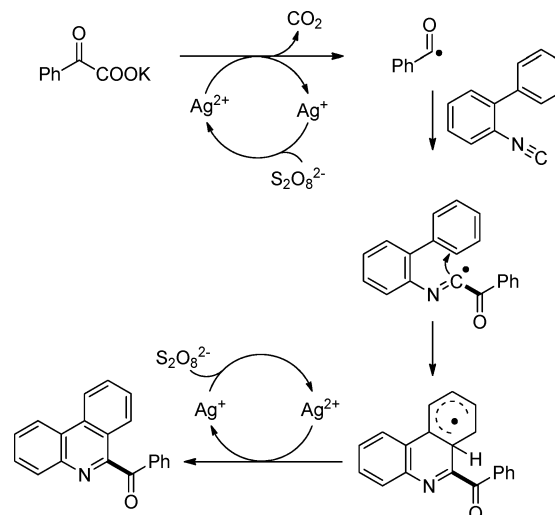
Scheme 17. EPR Study of the Oxidation of Silver(I) by $\text{Na}_2\text{S}_2\text{O}_8$



transformation and a plausible mechanism was illustrated (Scheme 18). Acyl radical was generated from the oxidative decarboxylation of α -oxo-carboxylate under a $\text{Ag(I)}/\text{Ag(II)}$ catalysis. Then, the intermolecular radical addition was followed by an intramolecular addition and radical oxidation to afford the final product.

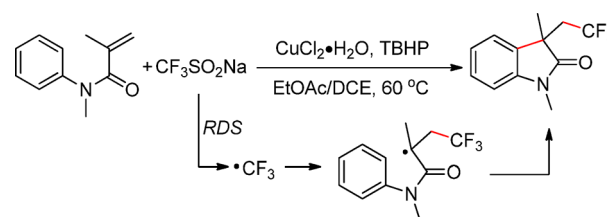
3.2.3. Radical Oxidative Annulation toward the Oxindole Synthesis. Comparatively, $\text{C}=\text{C}$ bonds can be considered as a C2 linker in oxidative cross-couplings. Furthermore, the addition of radicals to $\text{C}=\text{C}$ bonds is a fundamental transformation of a radical process.⁴⁶ We recently

Scheme 18. Proposed Mechanism of Silver-Catalyzed Radical Oxidative Decarboxylation–Cyclization



developed an oxidative trifluoromethylation with a $\text{C}=\text{C}$ bond as a C2 linker for the synthesis of oxindoles (Scheme 19).⁴⁷

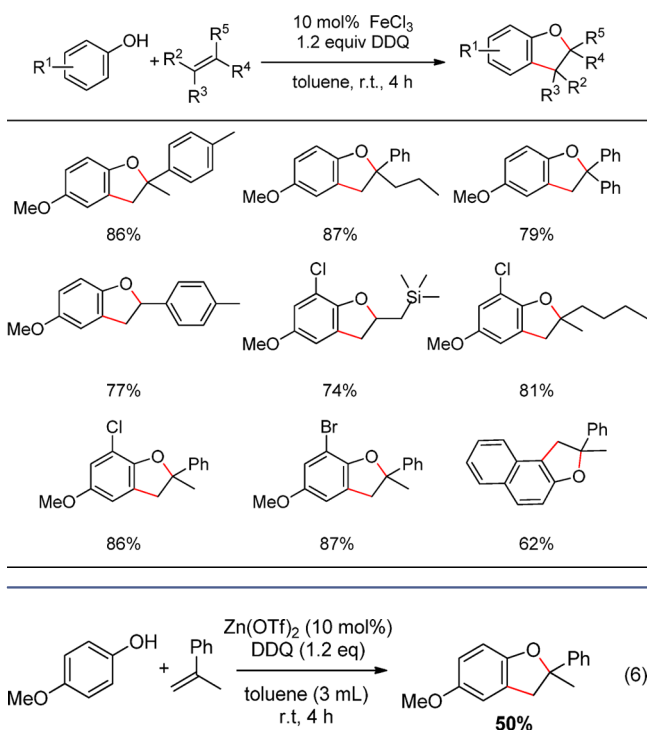
Scheme 19. Copper-Catalyzed Radical Oxidative Annulation for the Synthesis of Oxindoles



$\text{CF}_3\text{SO}_2\text{Na}$ was utilized as the CF_3 radical precursor. With acrylamide derivatives as the radical acceptor, the radical addition followed by cyclization proceeded well to generate the oxidative coupling product. The generation of CF_3 radical was demonstrated to be a facile step.

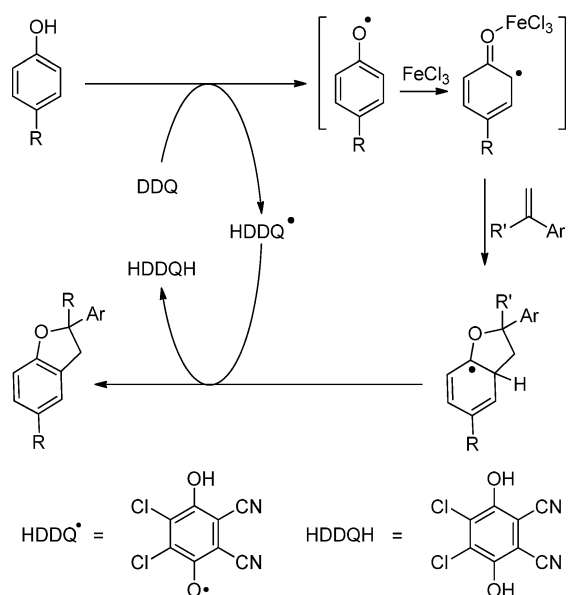
3.2.4. Radical Oxidative Cross-Coupling between Phenol and Olefin. Phenol derivatives have proven to be easily oxidized to their corresponding phenoxy radicals in the presence of various oxidants. With olefin as the C2 linker, we recently developed a radical oxidative coupling of phenol to generate dihydrobenzofuran in the presence of FeCl_3 as the catalyst and DDQ as the oxidant at room temperature.⁴⁸ The transformation was suitable for *para*-methoxy phenol derivatives and naphthols (Scheme 20). EPR spectroscopy was applied to study the radical species in the transformation, which indicated that FeCl_3 could not oxidize phenol under the reaction conditions, while 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) could oxidize the phenol substrate, and an EPR signal was possibly assigned as the HDDQ radical. Further monitoring of the catalytic system by both EPR and operando IR showed that FeCl_3 played a key role in promoting the selective product generation, although it could not oxidize phenol. By using Zn(OTf)_2 as a comparison (eq 6), FeCl_3 was considered to act as a Lewis acid in the transformation to promote the transfer of O-radical to the C-radical resonance.⁴⁹ Then, the C-radical addition to the olefin double bond was followed by cyclization and radical oxidation to afford the final

Scheme 20. Iron-Catalyzed Radical Oxidative Cross-Coupling between Phenols and Olefins



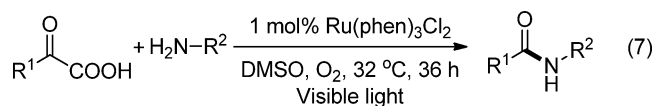
product. Overall, olefin could be considered as a C2 linker between the phenol OH and the *ortho*-CH (Scheme 21).

Scheme 21. Proposed Mechanism of Iron-Catalyzed Radical Oxidative Cross-Coupling



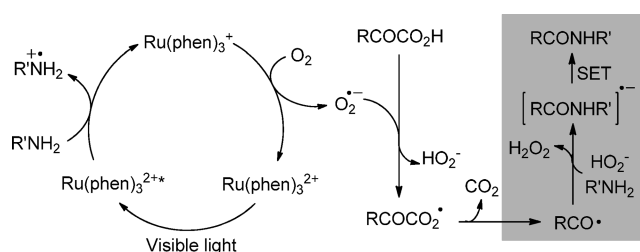
3.3. Radical Oxidative Amidation of α -Keto Acids with Amines

Photoredox catalysis has been shown to be a powerful tool for promoting radical transformations in recent years.^{50–52} With O₂ as the sole oxidant, we demonstrated a radical oxidative decarboxylative coupling of α -keto acids with amines under photocatalysis (eq 7).⁵³ α -Keto acids were shown to be precursors of acyl radicals. The bond formation was proven to



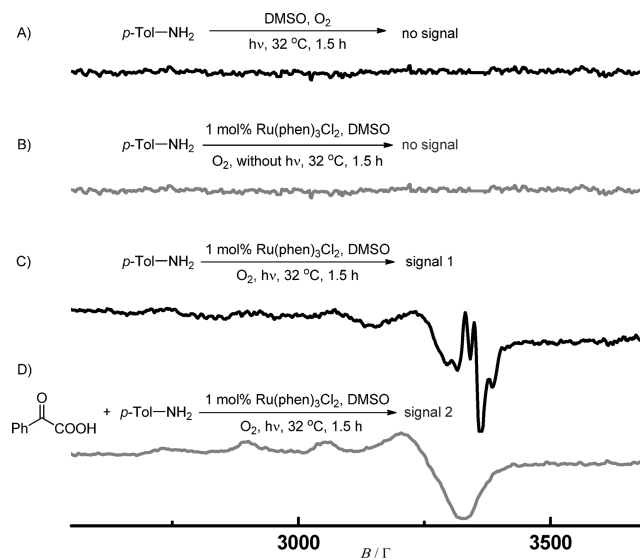
be achieved by the coupling between this acyl radical and amine to generate a radical anion followed by further radical oxidation to afford the final product. Amine initially acted as a sacrificial reagent to reduce the excited [Ru(bpy)₃]²⁺ to [Ru(bpy)₃]^{•+}, which further activated O₂ to a radical anion (Scheme 22).

Scheme 22. Proposed Mechanism of Visible-Light-Mediated Decarboxylation/Oxidative Amidation of α -Keto Acids with Amines



EPR analysis proved the SET oxidation of amine under photocatalysis and showed that O₂ activation by [Ru(phen)₃]⁺ was possibly involved in the rate-determining step, because the stable species detected by EPR is the resting state of photocatalyst in this transformation (Scheme 23). DFT

Scheme 23. EPR Study of Visible-Light-Mediated Decarboxylation/Oxidative Amidation



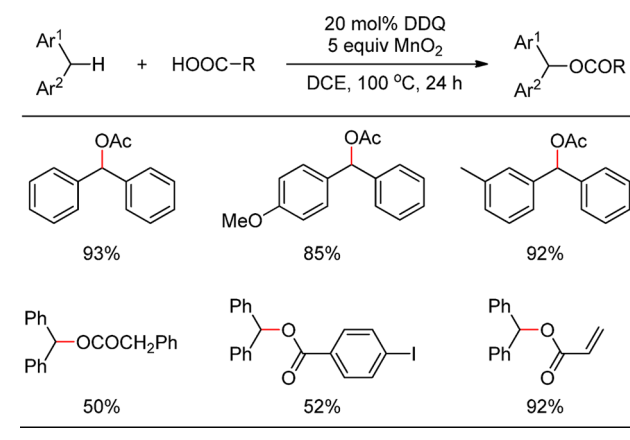
calculation results also supported that the formation of the radical anion [RCONHR'] was a facile process in this reaction. Different from the radical addition to olefin and arenes, this example shows the electron acceptor property of an acyl radical.

In all, the examples of model I in radical oxidative cross-coupling exhibit that the two redundant electrons were lost in two separate steps. It allows more transformations between the two steps.

4. MODEL II IN RADICAL OXIDATIVE CROSS-COUPPLINGS

In model II of radical oxidative cross-couplings between two nucleophiles, one of the nucleophiles loses two electrons consequently to afford an electrophilic umpolung followed by nucleophilic attack with another nucleophile to form a new chemical bond. The cross-dehydrogenative coupling (CDC) reactions developed by Li and co-workers are believed to occur via this model.⁵⁴ Among various tested oxidative cross-couplings between two nucleophiles in our group, several examples could also be classified in model II of radical oxidative cross-coupling. One of the examples is the oxidative C–O coupling of benzylic sp^3 C–H bonds with carboxylic acids.⁵⁵ A catalytic amount of DDQ was found to be a superior choice in the presence of MnO_2 as the terminal oxidant. Different diphenylmethane derivatives, even cinnamyl acetate, cross-coupled well with various kinds of carboxylic acids, generating the corresponding C–O bond formation products in good yields (Scheme 24). The addition of a radical inhibitor TEMPO

Scheme 24. DDQ-Catalyzed Oxidative C–O Coupling of Benzylic sp^3 C–H Bonds with Carboxylic Acids

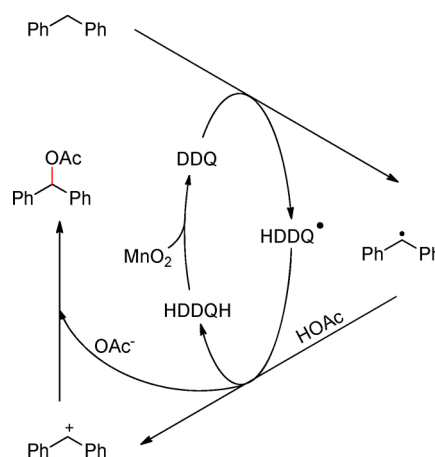


totally shut down this reaction, and reaction conversion was reduced to 25% in the presence of 2 equiv of 1,1-diphenylethane, indicating that a radical intermediate is most likely involved.

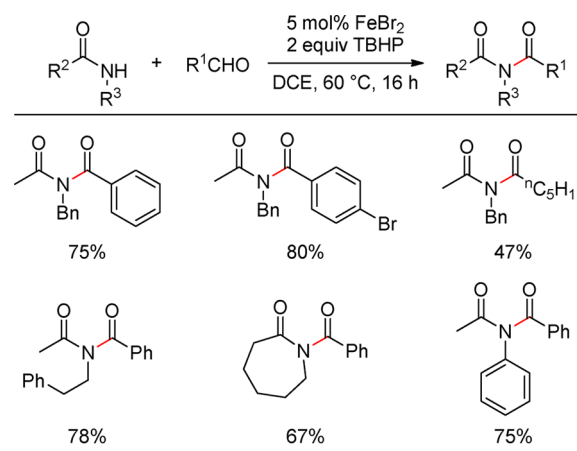
A proposed mechanism is depicted in Scheme 25. The oxidation of benzylic C–H by DDQ occurs via two SET steps to generate its corresponding benzylic cation and $DDQH^-$ anion. A subsequent nucleophilic attack by carboxylic acids affords the C–O coupled product. Meanwhile, the hydroquinone $DDQH_2$ was released. The catalyst DDQ is regenerated by the oxidation of $DDQH_2$ using MnO_2 as the oxidant.

Another example is the radical oxidative cross-coupling between aldehyde and amide for the synthesis of imide.⁵⁶ With the combination of a catalytic amount of $FeBr_2$ and TBHP as the oxidant in dichloroethene (DCE) at 60 °C for 16 h, the reaction of aldehyde and amide was found to proceed smoothly to afford imide. The substrate scope was fairly good (Scheme 26). The results revealed that aldehyde could be converted to the corresponding acyl chloride in the presence of $FeCl_2$ and TBHP, which demonstrated an oxidative umpolung process. Furthermore, addition of an equivalent amount of TEMPO as the radical inhibitor totally shut down this reaction and the acyl radical capture product was isolated in a 78% yield, providing

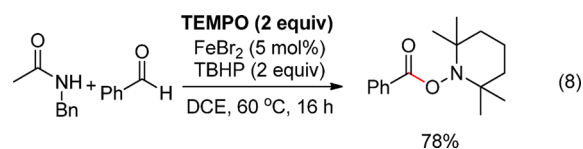
Scheme 25. Proposed Mechanism of DDQ Catalyzed Oxidative C–O Coupling



Scheme 26. Iron-Catalyzed Radical Oxidative Cross-Coupling between Aldehydes and Amides

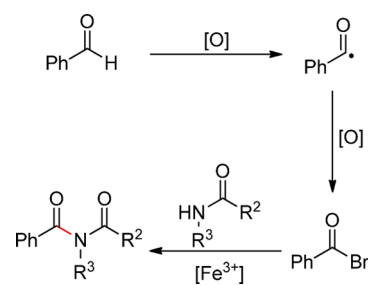


good evidence for the formation of acyl radical under the reaction conditions (eq 8).



A plausible pathway was proposed for this transformation (Scheme 27). Acyl radical was generated from aldehyde by hydrogen abstraction with butoxyl radical, which was generated

Scheme 27. Plausible Pathway of Iron-Catalyzed Radical Oxidative Cross-Coupling

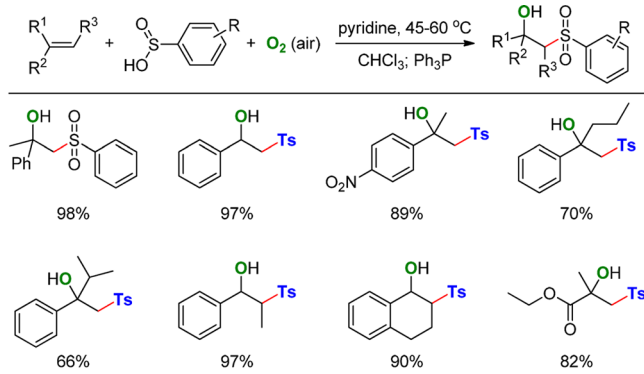


from TBHP in the presence of iron bromide. Subsequently, acyl radical was further oxidized to acyl bromide under the reaction conditions. The reaction of an amide with acyl bromide in the presence of iron salt afforded the desired product. In the product generation step, bond forms between acyl electrophile and nitrogen nucleophile, which meets with model II of radical oxidative cross-couplings.

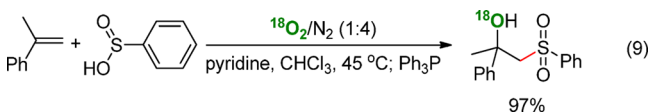
5. MODEL III IN RADICAL OXIDATIVE CROSS-COUPPLINGS

Forming a chemical bond between two radicals is reasonable, since both radicals tend to form a pair. However, it is still a challenge for achieving selective cross-couplings between two different radicals. Usually, two radicals obey a radical rule that forming a chemical bond is facile between a persistent radical and a transient biradical.^{57,58} Dioxygen is considered to be a persistent biradical. Therefore, achieving radical cross-couplings of dioxygen is highly desirable. We recently demonstrated a radical cross-coupling between dioxygen and sulfinic acid with olefin as a C2 linker to synthesize secondary and tertiary β -hydroxysulfones under transition-metal-free conditions (Scheme 28).⁵⁹ Although O₂ is not a nucleophile, the reaction

Scheme 28. Transition-Metal-Free Radical Oxidative Cross-Coupling between Dioxygen and Sulfinic Acid with Olefin as a C2 Linker

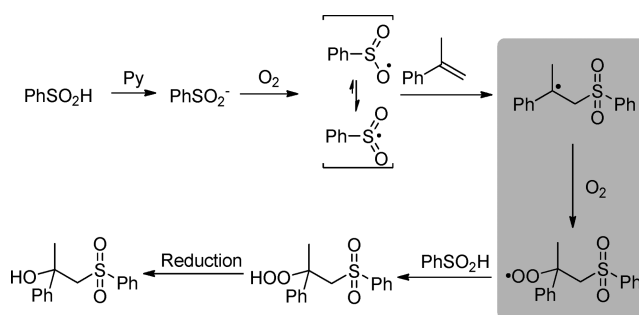


could be considered as a radical/radical cross-coupling. Therefore, it is classified here in model III. It has been shown that sulfinic acid could be oxidized by dioxygen to generate a sulfonyl radical in the presence of a base.⁶⁰ Condition screening showed that pyridine as the base in CHCl₃ solvent at 45 °C with PPh₃ workup gave the β -hydroxysulfones. Without PPh₃ workup at room temperature, β -peroxylsulfone could be readily isolated in an excellent yield. ¹⁸O isotope labeling experiments revealed that oxygen atom in the product came from dioxygen (eq 9).

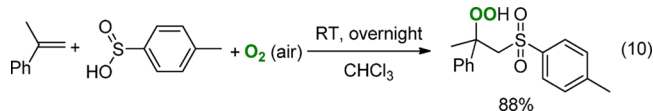


The reaction was believed to proceed via a radical pathway (Scheme 29). Initially, benzenesulfinic acid was easily oxidized to its corresponding radical by O₂ under basic conditions. Subsequent radical addition to alkenes affords a β -sulfonyl carbon-centered radical, which undergoes radical coupling with O₂ to produce an alkylhydroperoxy radical intermediate. Then

Scheme 29. Proposed Radical Pathway of Transition-Metal-Free Oxidative Cross-Coupling



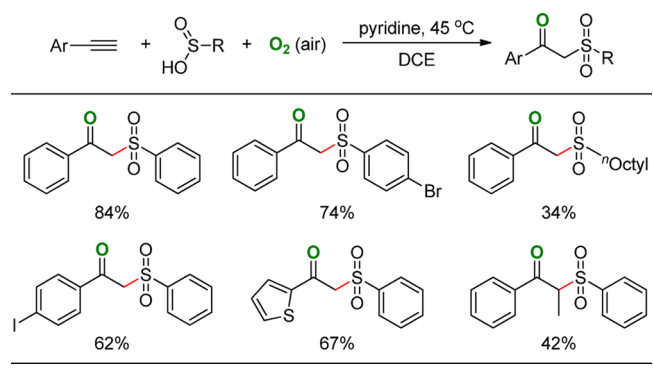
hydrogen abstraction generates β -peroxylsulfone, which has been isolated by changing the reaction conditions to room temperature (eq 10). Subsequent reduction of the β -



peroxylsulfone by benzenesulfinic acid or workup by PPh₃ gives the oxysulfonylation product. O₂ behaves as both an oxidant and a reactant in this transformation.

Similarly, a carbon–carbon triple bond can also be utilized as a C2 linker. Then, alkynes were utilized instead of alkenes under similar reaction conditions.⁶¹ A variety of β -keto sulfones were obtained (Scheme 30). The vinyl peroxide intermediate was generated, which undergoes subsequent reduction and isomerization to furnish the final product.

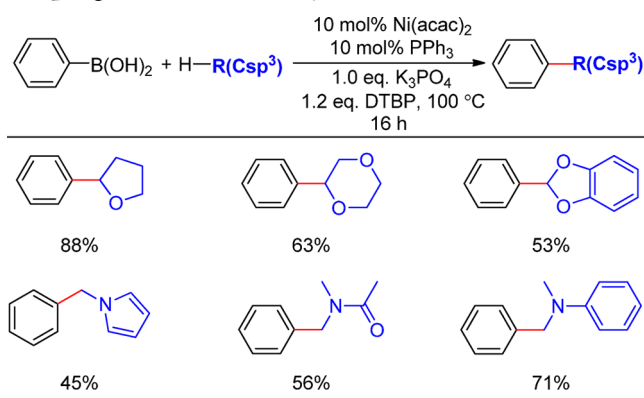
Scheme 30. Transition-Metal-Free Radical Oxidative Cross-Coupling between Dioxygen and Sulfinic Acid with Alkyne as a C2 Linker



6. MODEL IV IN RADICAL OXIDATIVE CROSS-COUPPLINGS

In model IV of radical oxidative cross-couplings, the bond formation occurs at the interaction between a radical and a cation, both of which are generated from the two starting nucleophiles. Our recent research on nickel-catalyzed oxidative cross-coupling of arylboronic acids with ethers might demonstrate the possibility of this reaction pathway.²⁶ The transformation achieves α -C–H arylation of THF or dioxane with arylboronic acids in the presence of Ni(acac)₂ as the catalyst with DTBP as the oxidant (Scheme 31). Notably, this transformation not only is suitable for THF and dioxane but

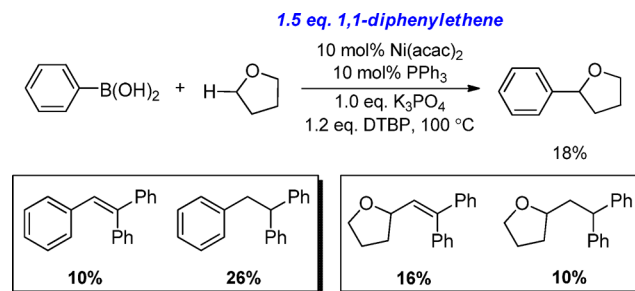
Scheme 31. Nickel-Catalyzed Radical Oxidative Cross-Couplings of Ethers with Arylboronic Acids



also is suitable for other C_{sp³}-H compounds such as the *N*-methyl group of *N,N*-dimethylaniline, *N,N*-dimethylacetamide, and *N*-methyl pyrrole, which were arylated smoothly to afford the desired products in moderate to good yields.

As demonstrated above, the α -C-H bonds are easily able to generate their corresponding carbon-centered radical through homolytic cleavage by a hydrogen abstractor.¹⁷ And also arylboronic acids could generate their relevant aryl radicals in the presence of oxidant.^{21–23} Both radicals were trapped by adding 1,1-diphenylethane in the reaction system, indicating the participation of both radicals (Scheme 32). However, both

Scheme 32. Radical-Trapping Experiments of Nickel-Catalyzed Oxidative Cross-Couplings

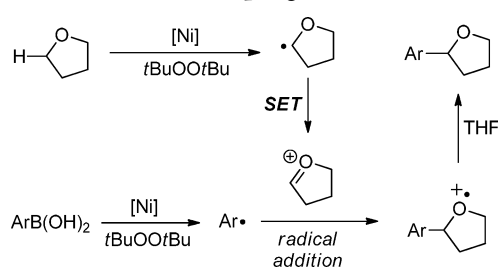


aryl and THF radicals are considered to be transient radicals. It is challenging for selectively forming a chemical bond between the two radicals. Furthermore, the α -carbon-centered radical easily loses the single electron to generate a carbon cation.⁶² Therefore, a possible pathway involves the formation of aryl radical with the aid of nickel catalyst and DTBP, and subsequent addition of aryl radical to the generated carbon cation generating an oxygen-centered radical cation is proposed. Final hydrogen abstraction from THF released the desired product (Scheme 33). At the current stage, another possible mechanism, such as the metal-assisted radical–radical cross-coupling or the formation of arylnickel species followed by the interaction with THF radical, could not be ruled out.

7. SUMMARY AND CONCLUSION REMARKS

In this Account, we have summarized our recent research on radical oxidative cross-couplings. Two redundant electrons were lost according to four models for the final bond formations between two nucleophiles. Several examples were demonstrated accordingly in each model. Most of the examples

Scheme 33. Proposed Mechanism of Nickel Catalyzed Radical Oxidative Cross-Couplings



were classified into models I and II. Although there are only few examples presented for models III and IV, they represent two types of potentially important transformations. More and more examples will be developed in the future. Along with the development of transition metal catalyzed oxidative cross-couplings, especially of those with no noble transition metal catalysis system, the radical process becomes dominant in this research area. There are still many unexplored methods and unknown insightful mechanisms left. Therefore, chances and challenges still remain, such as finding milder reaction conditions and proper ways to control the reactivity and chemoselectivity of radical species. We are continuously working on developing new, green, and efficient radical oxidative cross-couplings in our research group.

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Notes

The authors declare no competing financial interest.

Biographies

Chao Liu (1985) obtained his Ph.D. at Wuhan University (2012) under the supervision of Prof. Aiwen Lei. He spent one year (October 2008 to October 2009) as a visiting Ph.D. student in Prof. Todd B. Marder's group at Durham University, U.K. He is now a faculty member at College of Chemistry and Molecular Sciences, Wuhan University. In 2013, he spent three months (June–August) visiting in the group of Prof. Yoshihiro Uozumi at IMS, Japan. He was selected as a Hong Kong Scholar in the same year (Prof. Fuk-Yee Kwong's group at Hong Kong Polytechnic University).

Dong Liu (1989) obtained his B.S. degree (2012) at Wuhan University. He joined Prof. Aiwen Lei's group during his second year undergraduate study and started his Ph.D. study from September 2012 at the same group. He is currently a second year Ph.D. student and focused on transition metal catalyzed cross-couplings.

Aiwen Lei (1973) obtained his Ph.D (2000) while supervised by Prof. Xiyuan Lu at Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences (CAS). He then moved to Pennsylvania State University, U.S.A., and worked with Prof. Xumu Zhang as a postdoctoral fellow. He joined Stanford University (2003), working with Prof. James P. Collman as a research associate. He then became a full professor (2005) at College of Chemistry and Molecular Sciences, Wuhan University, China. His research focuses on novel approaches and understanding toward bond formations.

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