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Literature Review of Radical-Polar Crossover Reaction

Sen Zhang
senzhan@sas.upenn.edu, senzhan@sas.upenn.edu

Gary A. Molander
University of Pennsylvania, gmolandr@sas.upenn.edu

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Abstract
Described are Radical-Polar Crossover (RPC) reactions, which have played an important role in the organic synthesis, but very few review articles previously mentioned this concept. Using both photoredox catalysis and non-photoredox catalysis can achieve the RPC transformation within a one-pot mechanism under very mild condition. Besides this, RPC reactions provide many practical advantages such as rapid increasing in molecular complexity and good functional group tolerance. Therefore, this potentially valuable reaction can provide a lot of research opportunities.

Overall, the comparison of different authors' views, critical analyses of the methods, and an overall summary of the literature will be described in this review. The purpose of this work is to narrate both photoredox RPC reactions and non-photoredox RPC reactions in a systematic fashion and to grasp the valuable point of view from different authors. Applications of RPC reactions to the pharmaceutical sciences and industry will be presented at the end.

Keywords
radical-polar crossover, RPC, photoredox, non-photoredox

Disciplines
Chemistry

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Supervisors: Prof. Gary A. Molander and Dr. Ana-Rita Mayol
Secondary Reader: Prof. Madeleine M. Joullie
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Abstract approved:

Prof. Gary Molander

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LITERATURE REVIEW OF RADICAL-POLAR CROSSOVER REACTIONS

by

Frank Zhang

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APPROVED:

Professor Gary A. Molander, Organic Chemistry

I understand that my Document of Literature Review will become part of permanent collection of the University of Pennsylvania Master of Chemical Science Program. My signature below authorizes release of my final report to any reader upon request.

Sen Zhang

Frank Zhang, Author

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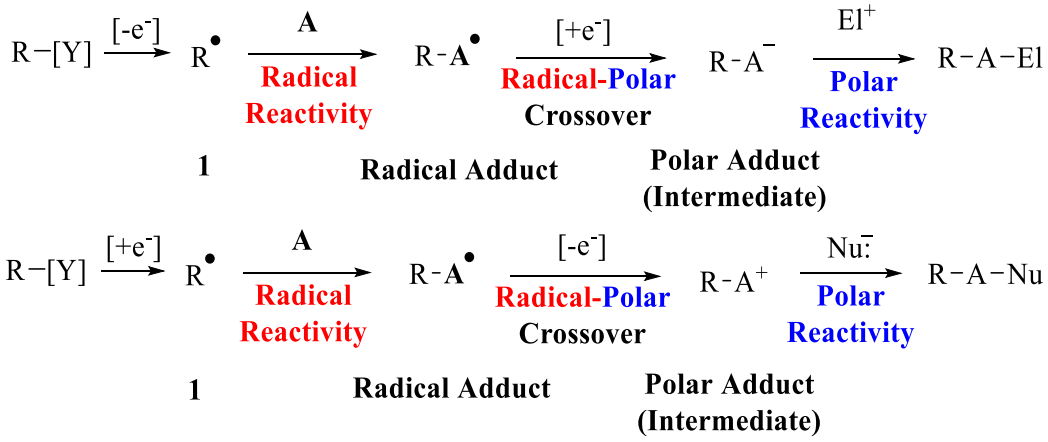
Literature Review of Radical-Polar Crossover Reactions

Chapter 1. Introduction

Radical-Polar Crossover (RPC) reactions played an important and ever-increasing role in organic synthesis. The novel feature of these reactions is that they are one-pot transformations that can accommodate both radical and polar reactivity, demonstrating step-economical properties. Such transformations attracted the attention of organic chemists to develop new reactions, but only few review articles mentioned the concept of RPC reactions.

Scheme 1 outlines two generic RPC reaction pathways. Radical **1**, which can be formed from homolytic cleavage of the covalent bond of a radical precursor (R-[Y]), is a high energy intermediate that can be incorporated into a variety of productive reactions. With the appropriate use of light, heat, and the assistance of catalysts, radicals can be easily formed from various radical precursors. Upon reaction with a suitable radical acceptor (**A**), a radical adduct (R-A•) will be generated. This radical adduct will experience **radical-polar crossover**, converting the initial intermediate to a polar adduct by single electron transfer (SET). The polar adduct (either an anion or a cation, depending on the transformation involved) can engage in further transformations to afford the final products via polar reactivity.[1] The polar reactivity might include addition, elimination, or even rearrangement reactions, among others.[1] The overall process of radical reactivity, transformation to a polar intermediate, and polar reactivity was defined as Radical-Polar Crossover Reactions.

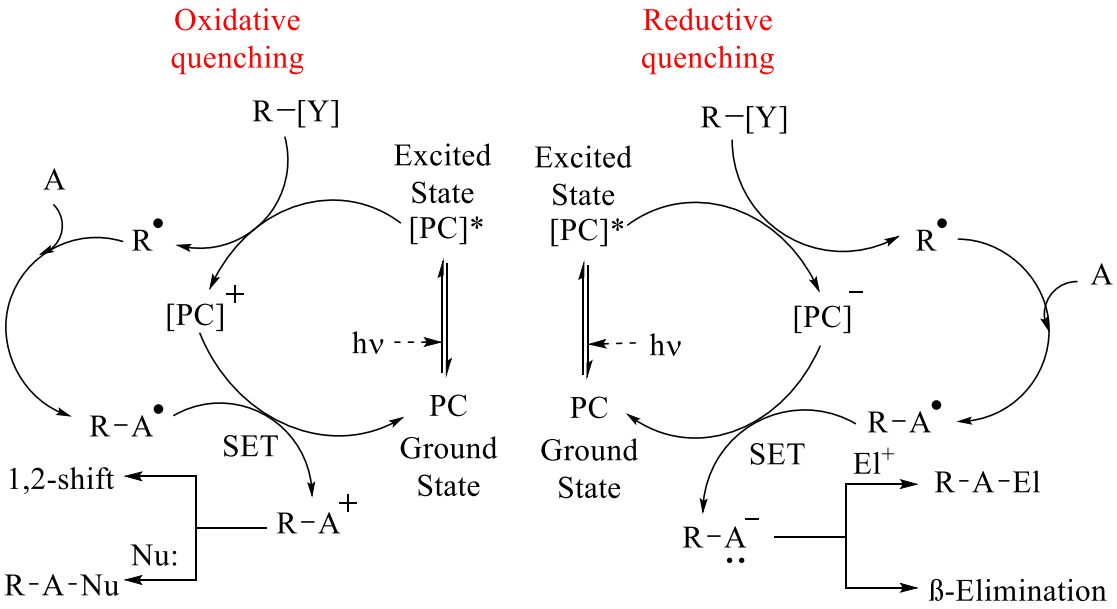
Scheme 1. Generic Reaction Pathway of Radical-Polar Crossover Reactions



Photoredox catalysis will be one of the most important aspects of this review because it enables radical initiation and the transformation of the radical adduct to a polar adduct. Under the irradiation of visible light, a photocatalyst [PC] will be transformed to its excited state [PC]*, which can act as either a reductant (oxidative quenching) or an oxidant (reductive quenching).[2, 3] As depicted in Scheme 2, in the oxidative quenching cycle, the excited state [PC]* is donating an electron to R-[Y] to generate the radical R•, and the ground state of the oxidized photocatalyst $[PC]^+$ will have a high enough oxidation potential to transform the resulting radical adduct R-A• to a cation (RPC step) by Single

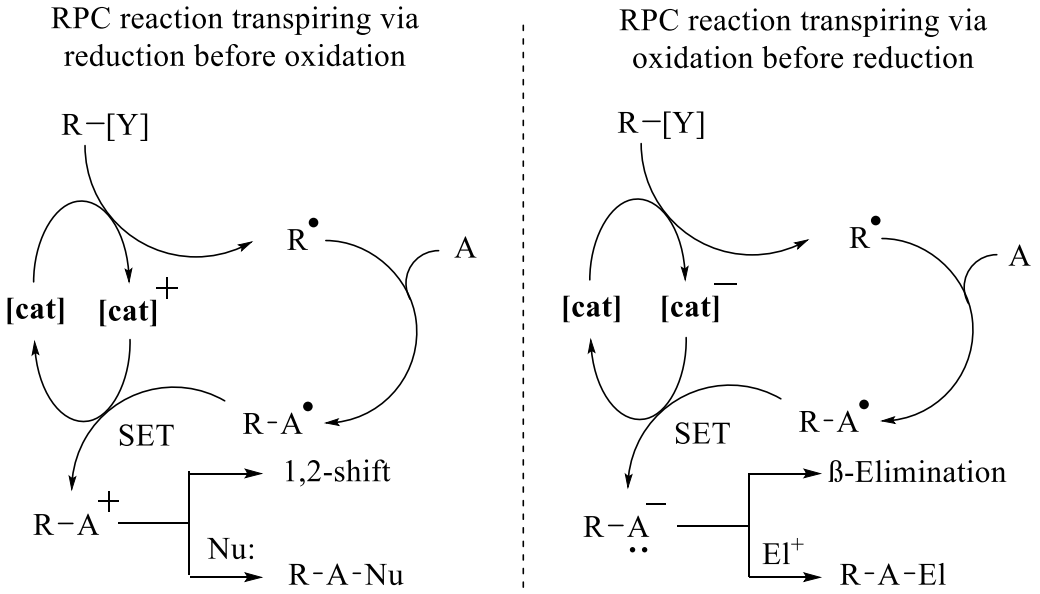
Electron Transfer (SET). Subsequent polar steps may include reactions with appropriate nucleophiles or rearrangements. Conversely, in the reductive quenching process, [PC]* is quenched by accepting an electron from the substrate R-[Y] to form R•, and the ground state $[PC]^-$ will have a high enough reduction potential to transform the incoming R-A• to an anion (RPC step) by SET. Further polar steps may occur by reaction with electrophiles, or, β-elimination when suitably substituted systems. Thus, under photoredox catalysis, the transformations may transpire via oxidation before reduction in reductive quenching cycle, or vice versa, reduction before oxidation in oxidative quenching cycle. A detailed mechanism depicting both oxidative quenching and reductive quenching was presented in a recent review article.[2, 3]

Scheme 2. The Photoredox Catalytic Cycle for RPC Reaction[2]

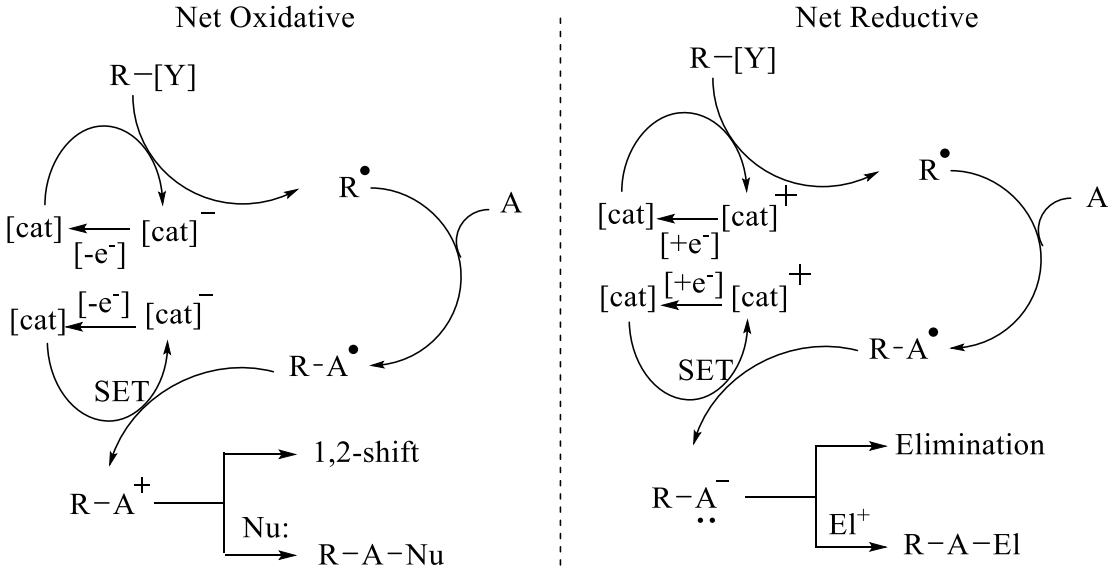


In addition to photoredox-catalyzed RPC reactions, non-photoredox-catalyzed RPC reactions will be reviewed. The non-photoredox-mediated RPC reaction are generally divided into four main categories: net redox-neutral (two different modes), net oxidative, or net reductive. In the net redox-neutral category, the selected non-photoredox catalyst, which denoted as ([cat]), participates in the catalytic cycle to mediate radical formation and transforms the generated radical adduct to a polar adduct via either reduction before oxidation, or oxidation before reduction (Scheme 3). Therefore, the series of net redox-neutral RPC reaction can be categorized as RPC reaction transpiring via oxidation before reduction, or vice versa. Conversely, in net oxidative or net reductive reactions, the selected catalyst requires a stoichiometric oxidant or reductant, respectively, to turn over the catalyst to achieve overall oxidative or reductive transformations (Scheme 4).

Scheme 3. The Catalytic Cycle for Net Redox-Neutral RPC Reaction



Scheme 4. The Catalytic Cycle for Net Oxidative and Reductive RPC Reaction

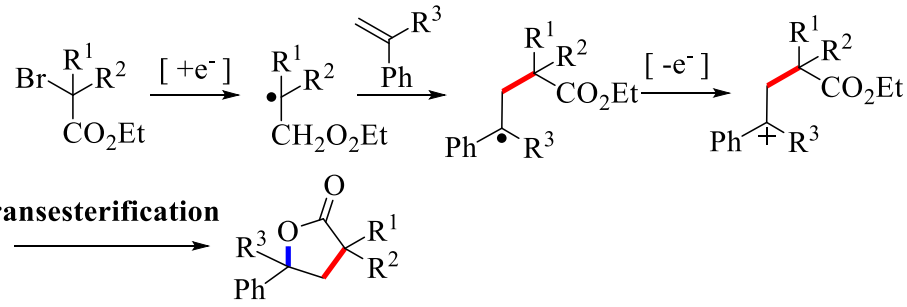


The RPC reaction is generally mediated by photoredox catalysis or non-photoredox catalysis, and both sorts of RPC reactions can be applied to either intramolecular or intermolecular transformations, resulting in either cycloadducts, coupling products, or ring-closed adducts. The nucleophile is frequently internal, resulting in a cyclized product, but intermolecular transformations can sometimes occur via cycloadditions and carbon-carbon or carbon-heterocyclic bond [C-C(X)] constructions. Therefore, the substrate scope of the reaction is relatively wide, and to date [4+2] cycloadditions, [3+2] cycloadditions, 5-membered ring formation, intermolecular C-C bond construction, and even the formation of heterocycles were developed. In Scheme 5, representative examples of [3+2] and [4+2] cycloadditions and cyclizations are displayed, and these examples will be further discussed in the later chapters. In this review article, bonds formed through the RPC process were

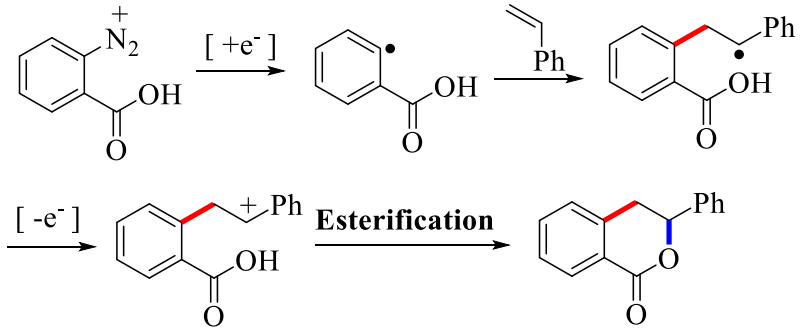
emboldened, and all the bonds were colored in red (indicating radical bond formation) or blue (indicating polar bond formation). In this review, the detailed [3+2] cycloaddition, [4+2] cycloaddition, and non-cycloaddition reactions, including ring closure, ring expansion, and C-C (heterocyclic) bond formation, will be presented in a systematic fashion.

Scheme 5. Cycloaddition and Non-Cycloaddition RPC Reactions[4-6]

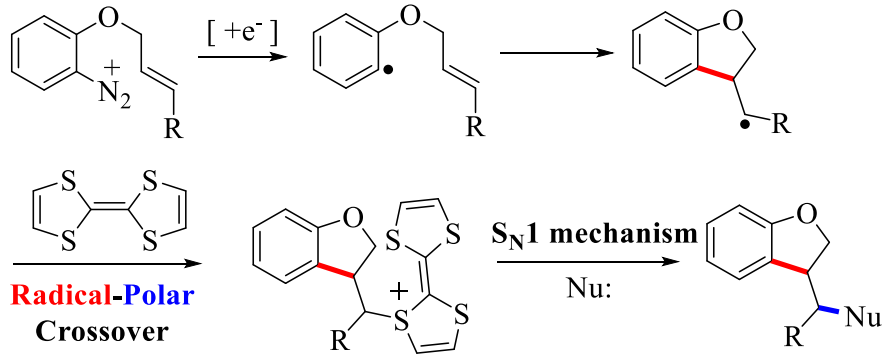
[3+2] cycloaddition reaction



[4+2] cycloaddition reaction



Cyclization



The construction of two or more bonds in a single operation increases efficiency in synthesis, and RPC reactions thus enable such processes to provide a rapid increase in

molecular complexity as well. The RPC reaction can be mediated by two main techniques; photoredox and non-photoredox, and most processes allow the RPC reaction to transpire under very mild conditions. Briefly, this review article will outline the use of both photoredox and non-photoredox catalysis in RPC reactions, as well as practical pharmaceutical applications.

Chapter 2. Photoredox-Mediated Radical-Polar Crossover Reaction

This chapter will address the current and state-of-the-art in photoredox-mediated RPC reactions, and the information will be presented taking into account the mechanistic pathway. First RPC Reactions Transpiring via Oxidation before Reduction will be presented followed by RPC Reactions Transpiring via Reduction before Oxidation. Moreover, the [3+2] and [4+2] cycloaddition reactions are still under investigation in the RPC reactions that transpires via oxidation before reduction, so these are potential opportunities that can provide valuable researches.

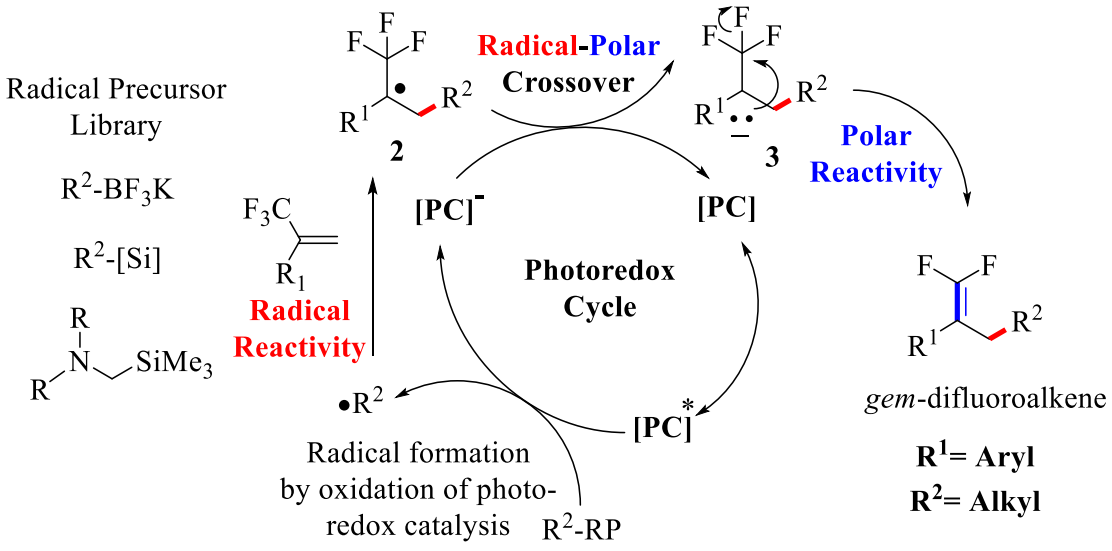
2.1 RPC Reactions Transpiring via Oxidation before Reduction

2.1.1 Non-Cycloaddition (Including Cyclization, Ring Expansion, or C-C(X) Formation)

2.1.1.1 Construction of 1,1-Difluoroalkene Carbonyl Mimics

Molander and co-workers pioneered a reaction pathway to the generation of *gem*-difluoroalkenes, with the idea that the $C{=}CF_2$ unit can serve as a mimic for the carbonyl group.[7] This work is worth highlighting because the group initiated a reaction pathway to generate the $C{=}CF_2$ unit, successfully achieving this construction through the RPC mechanism by photoredox catalysis. Using catalytic quantities of $Ru(bpy)_3(PF_6)_2$ as a photocatalyst, this research demonstrated that a library of trifluoromethylated alkenes can be accommodated in the transformation to achieve the $C{=}CF_2$ bond construction with uniformly good yields.[7]

Scheme 6. Proposed Mechanism of the 1,1-Difluoroalkenes Generation[7]



Scheme 6 outlines the mechanism of this access to *gem*-difluoroalkenes. Under irradiation by visible light, the photocatalyst is converted to its excited state. Subsequently, R• was generated by the SET oxidation of the radical precursors including $R\text{-}BF_3K$, $R_2NCH_2SiMe_3$, and alkyl silicate, which is denoted as R-[Si].[7] R• then reacts with the CF_3-

functionalized olefin to form a new α-CF_3 radical **2**. The α-CF_3 radical then undergoes SET reduction by the reduced photocatalyst (PC^-) to afford a carbanion **3**. Carbanion **3** undergoes an E1Cb-type fluoride elimination, even though protonation is also viable. Ultimately, the desired *gem*-difluoroalkene was generated by RPC reaction process under mild conditions.[7]

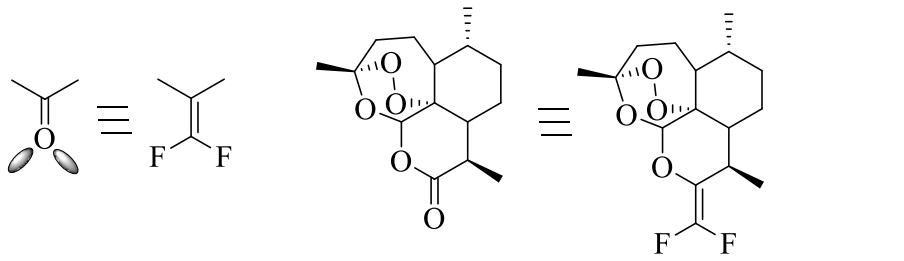
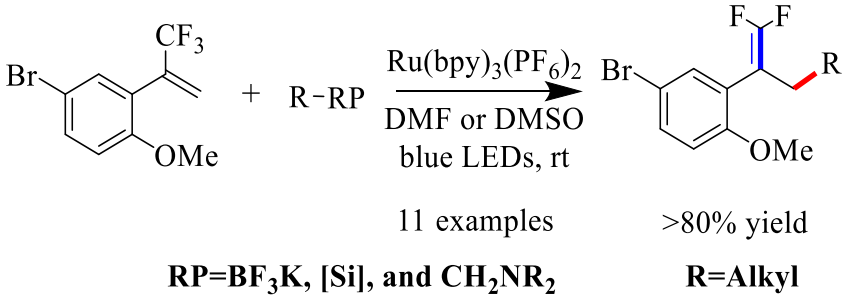


Figure 1. Representative Application of 1,1-Difluoroalkenes Carbonyl Mimics[10, 11]

The carbonyl bond presented in natural products may diminish the biological activity because of its low hydrophilicity and lipophilicity.[7, 8] "The *gem*-difluoroalkene moiety was shown to engage in analogous hydrogen bonding as the carbonyl bond, and the replacement of a carbonyl bond to *gem*-difluoroalkene was proven to result in unaffected recognition and improved biological activity (Figure 1)."[7-9] Thus, Molander, Begue, and Liu argued that the replacement of a carbonyl group to the $C{=}CF_2$ subunit would be worthwhile because of the favorable biological activity of this carbonyl mimic.[7, 8] In an examination of the mechanism of the traditional radical or polar pathway proposed by Begue in France, relatively good yields were obtained, and the technique was successfully applied to two commonly used pharmaceutical reagents -Artemisinin and gluconolactone.[8] However, the conditions needed to achieve these transformations were non-ideal, transpiring under extremely low temperature and strongly acidic conditions.[8] Conversely, in the presence of 2.5 mol % of photocatalyst, the transformation occurs at room temperature.[7] As a result, a wider range of radical precursors could be employed to participate in the reaction, and a broader scope was discovered. Of note, almost all products were isolated free CF_3-containing side products because of the rate of SET reduction and fluoride elimination, and yields in this transformation were uniformly acceptable (Scheme 7).[7]

Scheme 7. Representative Transformation of Molander's Protocol[7]



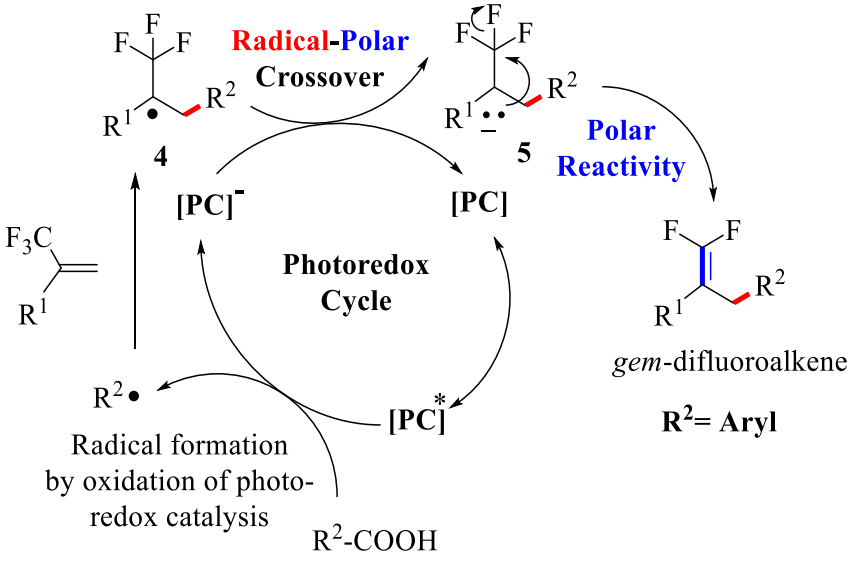
This RPC-catalyzed process has many benefits, such as the use of affordable photocatalysts, mild reaction conditions, and incorporation of a wide range of functional

groups.[7] Therefore, a library of biologically active molecules can be synthesized through this approach. In addition, the RPC reaction combines the mechanism of a radical process and fluoride elimination in a single mechanism, so it efficiently saves energy compared to stoichiometric processes.[7, 8] Another transformation discovered by Zhou and co-workers in China combined the mechanisms of a radical process, defluorination, and decarboxylation in a one-pot fashion.[12] The next section will thoroughly narrate the protocol designed by Zhou, and the comparison between two methods will be thoroughly provided in Section 2.2.3.2.[12]

2.1.1.2 A Photocatalytic Decarboxylative/Defluorinative RPC Reaction

Zhou developed an analogous method as Molander's method for synthesis of the $C=CF_2$ subunit, which can serve as a mimic of the carbonyl group in a variety of biologically active molecules.[12] The access to *gem*-difluoroalkenes in Zhou's protocol was depicted in Scheme 8. Under irradiation with visible light, the photocatalyst is converted to its excited state, and subsequently, R• is generated by SET oxidation of the radical precursor. R• then reacts with CF_3-functionalized olefin to form a new α-CF_3 radical **4**, which undergoes SET reduction by the reduced photocatalys (PC^-) to afford carbanion **5**. Anion **5** undergoes an E1Cb-type fluoride elimination, and ultimately, the desired *gem*-difluoroalkene is generated by RPC reaction under mild conditions.[12]

Scheme 8. The Mechanism of $C=CF_2$ Subunit Generation[12]



Molander and Zhou designed their protocols to accomplish the synthesis of *gem*-difluoroalkenes around the same reaction time, and both reactions occur at room temperature under visible light irradiation, employing photoredox catalysis.[7, 12] By contrast, their substrates, reaction conditions, and further synthetic applications are slightly different. Molander selected a radical precusors library, which includes $R\text{-}BF_3K$, alkyl silicate, and $R_2NCH_2SiMe_3$, to demonstrate that a wide range of radical precursors can be selected to participate in the RPC reaction.[7] Conversely, carboxylic acid was selected as a radical precursor by Zhou, and it did not show advantages in this synthesis.[12] More importantly, even though carboxylates were frequently used as radical precursors, because

stoichiometric base (2 equivalents of LiOH) is used for their generation, they might not be optimal radical precursors.[7, 12] In Molander's protocol, R-BF_3K, R-[Si], and $R_2NCH_2SiMe_3$ do not require harsh conditions such as strong base or high temperature, and all three radical precursors are either commercially available or simple to be prepared.[7]

Zhou and co-workers confirmed that the RPC reaction can enable the combination of both a radical process and defluorination step in a single mechanism, so it efficiently saves energy compared to the stoichiometric processes proposed by Bugue.[8]

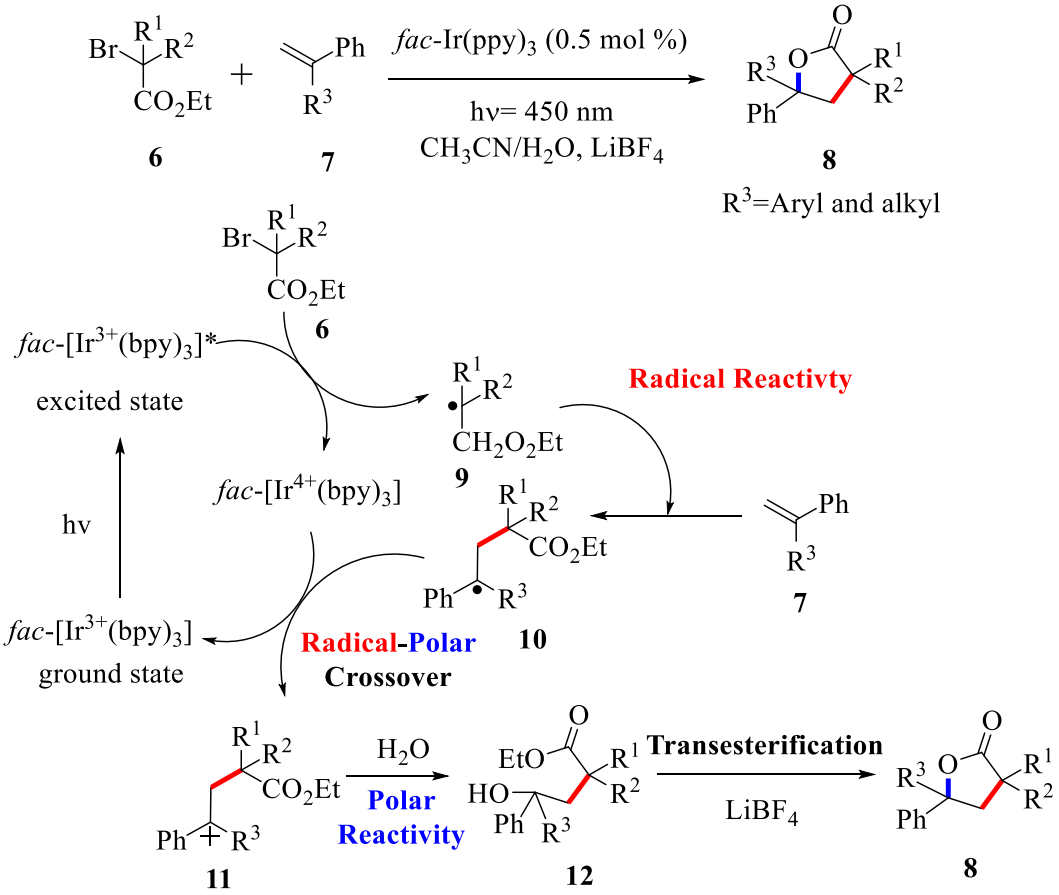
2.2 The RPC Reactions Transpiring via Reduction before Oxidation

2.2.1 [3+2] Cycloaddition

2.2.1.1 An Intermolecular Synthesis of γ-Lactones via Photoredox RPC Reaction

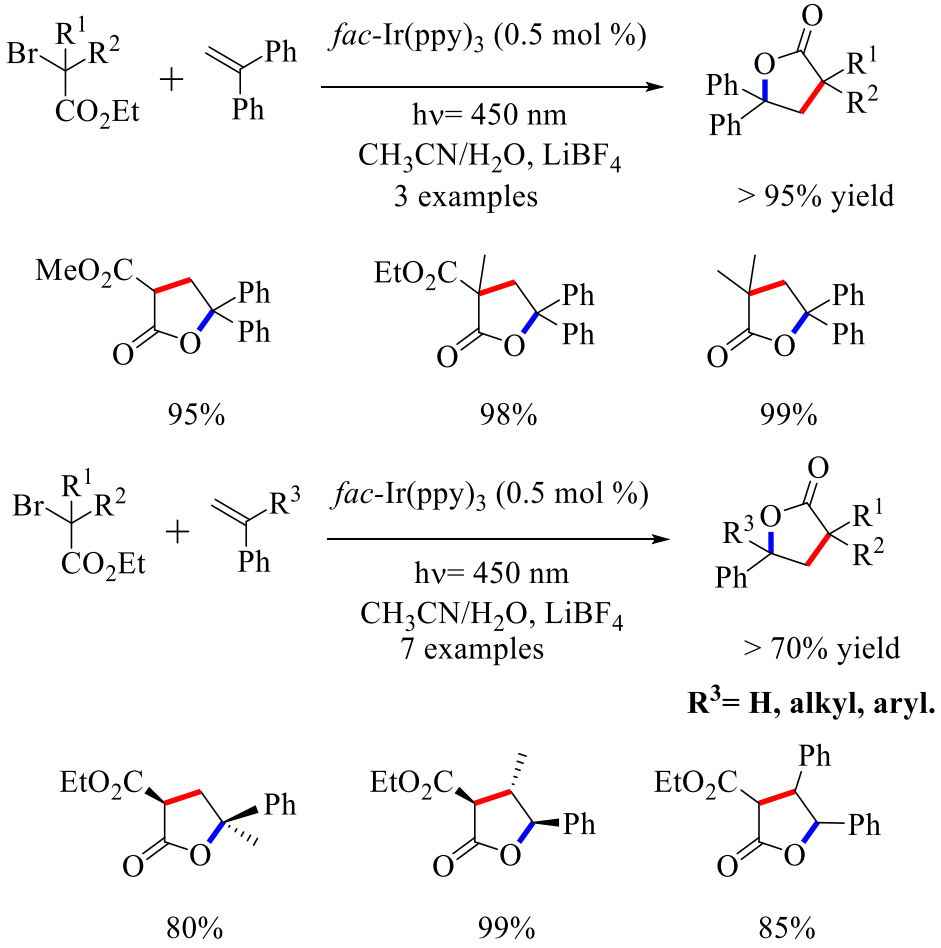
Lactones were utilized as building blocks in pharmaceutical and organic materials.[13] Liu and Fagnoni envisioned that photoredox catalyzed RPC reaction can be applied to the construction of highly substituted lactones, so they both employed photoredox catalyzed RPC reaction to construct γ- and δ- lactones, respectively.[4, 5] This method is highly efficient, because with a small amount of loading *fac*-$Ir(ppy)_3$, a number of γ-lactone derivatives can be synthesized.[4]

Scheme 9. Generic Reaction Pathway and Mechanism of γ-lactone Synthesis[4]



Scheme 9 depicts the mechanism of this designed route to γ-lactones. Under irradiation by visible light, the photocatalyst is transformed to its excited state. Subsequently, radical **9** was generated by oxidation of the photoexcited photocatalyst. Intermolecular π-addition of radical **9** to olefin **7** produced a new radical, **11**, which then undergoes SET oxidation by $Ir^{4+}(bpy)_3$ to afford a carbocation **11**. Nucleophilic attack by H_2O affords 1**2**. Ultimately, a spontaneous intramolecular transesterification was catalyzed by $LiBF_4$ and γ-lactones **8**.

Scheme 10. Scope of γ-Lactones Synthesis via Photoredox Catalysis[4]



The previous approaches to γ-lactones usually employed harsh reaction conditions and stoichiometric oxidants to achieve activation of the alkenyl moieties and radical initiation, but with the loading of 0.5 mol % of *fac*-$Ir(ppy)_3$, diphenylethylene and a variety of bromo-acetates were demonstrated to undergo RPC process efficiently to generate a variety of γ-lactones at room temperature.[4] Scheme 10 summarized that yields in this transformation were excellent, with most yields above 90%, and several select examples presented in Scheme 10 take place in >95% yield. In addition, the substrate scope with respect to substituted styrenes was examined (Scheme 10). Of note, the results indicated that both styrene and its derivatives could interact with bromoacetate to obtain the γ-lactones, with most yields above 70%.[4] However, a critical point that is worth addressing

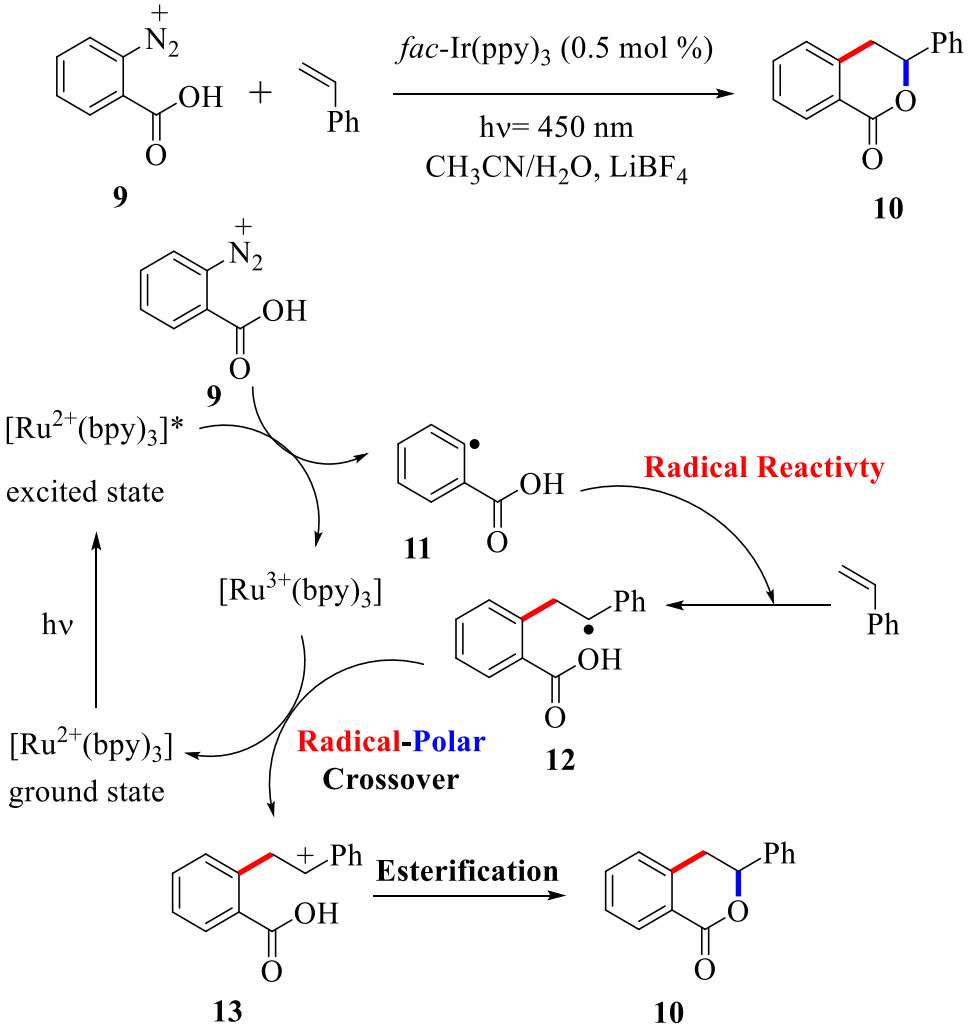
is that further extension of this method to construct δ-lactones via [4+2] cycloaddition reaction is yet to be realized.[4]

2.2.2 [4+2] Cycloaddition

2.2.2.1 The Synthesis of Isochromanones and Isochromenones via Photoredox RPC

Meerwein arylation was first published by Meerwein in 1939.[14] Under the catalysis of copper salts, an aryl diazonium salt (ArN_2X) will react with an electron-poor alkene to afford an alkylated arene product upon the reduction of Cu(II) to Cu(I).[14] However, the limitation of this method was shown in its poor yield and the high loading of stoichiometric copper salt (20 mol %).[14] Taking the Meerwein arylation concept further, Heinrich and Fagnoni envisioned that a tandem reaction pathway that could successfully combine Meerwein arylation and RPC might achieve expand the scope of the reaction, increasing molecular complexity.[5, 15]

Scheme 11. Proposed Mechanism of the Isochromanone Moiety Construction[5]



The catalytic cycle of photoredox Meerwein arylation proposed by Fagnoni is outlined in Scheme 11.[5] In this transformation, the photoexcited catalyst reduces the aryldiazonium salt **9** to the aryl radical **11** via single electron transfer, generating $Ru^{3+}(bpy)_2(PF_6)_2$ in the process. Subsequently, **11** reacts with styrene to yield radical **12**, affording cation **13** through the oxidation by $Ru^{3+}(bpy)_3(PF_6)_2$. Rearrangement of the cation occurs subsequently to achieve the ring expansion, providing the final product **10**. The final product was obtained by ring closure of intermediate **13**.

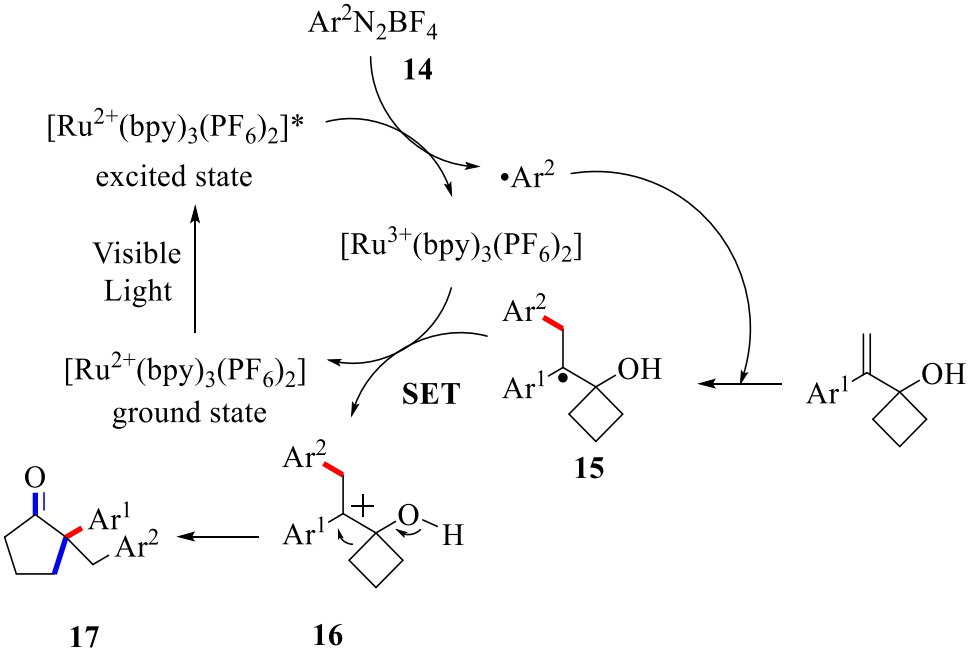
With the optimal catalyst loading of $[Ru(bpy)_3]^{2+}$ (2 mol %), phenylethylene and a variety of bromoacetates were demonstrated to undergo the RPC process to generate a variety of δ-lactones at room temperature.[5] This method is valuable in the preparation of structures in many biological active compounds, such as isochromanone and isochromenone moieties, and because of its pharmaceutical applicability, its practical applications will be presented in Chapter 4.[5] In addition to the photocatalytic Meerwein approach, a non-photoredox-mediated Meerwein approach was designed by Heinrich, which will be discussed in Section 3.2.2.1.[15]

2.2.3 Non-Cycloaddition including C-C(X) Formation or Ring Expansion

2.2.3.1 Arylative Ring Expansion Catalyzed by Photoredox Catalysis

A novel and environmentally benign process for photoredox-catalyzed ring expansion was discovered through the catalysis of $Ru(bpy)_3(PF_6)_2$, and it can be an efficient way to accomplish the synthesis of functionalized cyclic ketones.[16] Toste and co-workers reported an analogous ring expansion using a dual Au/photoredox catalysis method.[17] Kim's group envisioned that to achieve this transformation more efficiently, visible light-mediated photocatalytic ring expansion could be employed without gold catalysis.[16]

Scheme 12. Mechanism of Arylative Ring Expansion[16]

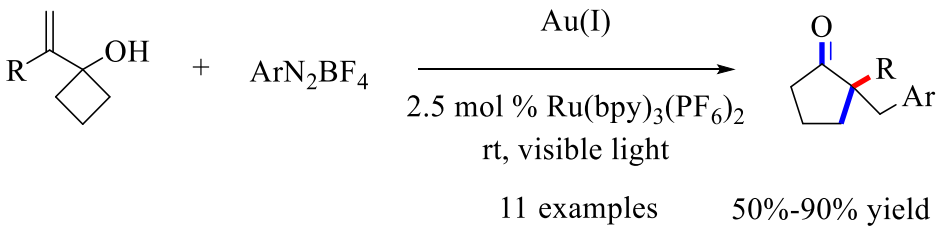


The catalytic cycle developed is outlined in Scheme 12. In this transformation, the photoexcited catalyst reduces the aryldiazonium salt **14** to the aryl radical •Ar^2 via single electron transfer, generating $Ru^{3+}(bpy)_2(PF_6)_2$ in the process. Subsequently, the •Ar^2 radical reacts with 1-(1-arylvinyl)-cyclobutanol to yield radical **15**, affording cation **16** through the oxidation by $Ru^{3+}(bpy)_3(PF_6)_2$. Rearrangement of the cation occurs subsequently to achieve the ring expansion, providing the final product **17**.

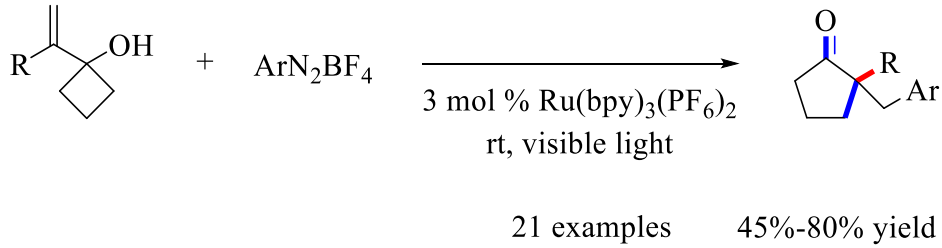
Compared to the method developed by Toste, this set of reaction conditions appears more efficient, and the scope of this reaction is relatively broad (Scheme 13).[16, 17] Therefore, without employing Au(I) catalyst, many advantages were provided such as mild reaction conditions and good functional group tolerance.[16] However, the current limitation of this reaction is that the overall yield of this reaction was not significantly increased, even though the photocatalyst loading of $Ru^{3+}(bpy)_2(PF_6)_2$ was increased from 2.5 mol % to 3 mol % compared to Toste's protocol (Scheme 13).[16, 17]

Scheme 13. Ring Expansion of 1-(1-Arylvinyl) Cyclobutanol[16, 17]

Dual/Gold Photoredox Calalysis:



Photoredox Catalysis:



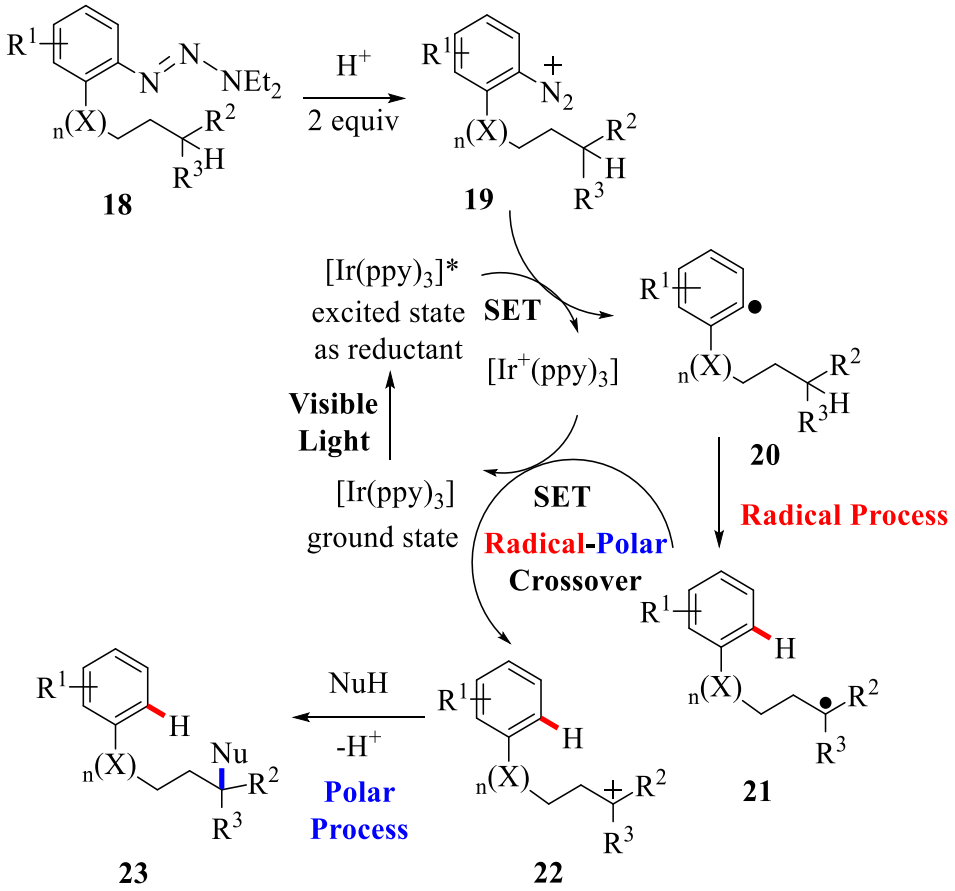
2.2.3.2 Remote Hydroxylation through Radical Translocation and RPC

"Radical translocation was applied to the intramolecular abstraction of a hydrogen atom or a group with a radical center, and this results in a repositioning of the site of the unpaired electron, which can lead to functionalization at positions that are unreactive."[18] A remote hydroxylation process that combined both radical translocation and RPC was discovered by Ragains and co-workers.[19] This process was viewed exemplary because it provided an efficient way to employ photoredox catalysis to achieve site-selective replacement of C-H bonds to useful C-OH functional groups.[19] Ragains designed this excellent process, and he indicated that remote hydroxylation is a key step in the mechanism, with photoredox catalysis efficiently promoting the RPC reaction.[19]

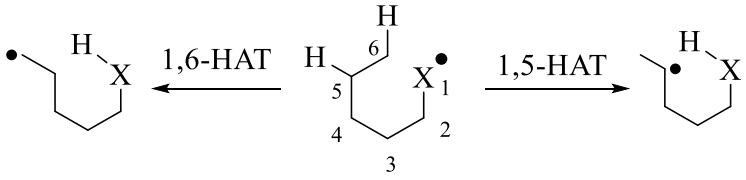
As shown in Scheme 14, the addition of a proton can initially transform **18** to **19**, and radical **20** is generated by the excited state of $Ir^+(ppy)_3$* as a reductant. The radical transformation subsequently transpires to produce a new radical **21**, which is subsequently

oxidized by the ground state Ir^+ to afford carbocation **22**. Finally, product **23** is generated by nucleophilic addition.

Scheme 14. Mechanism of Radical Translocation and RPC[19]



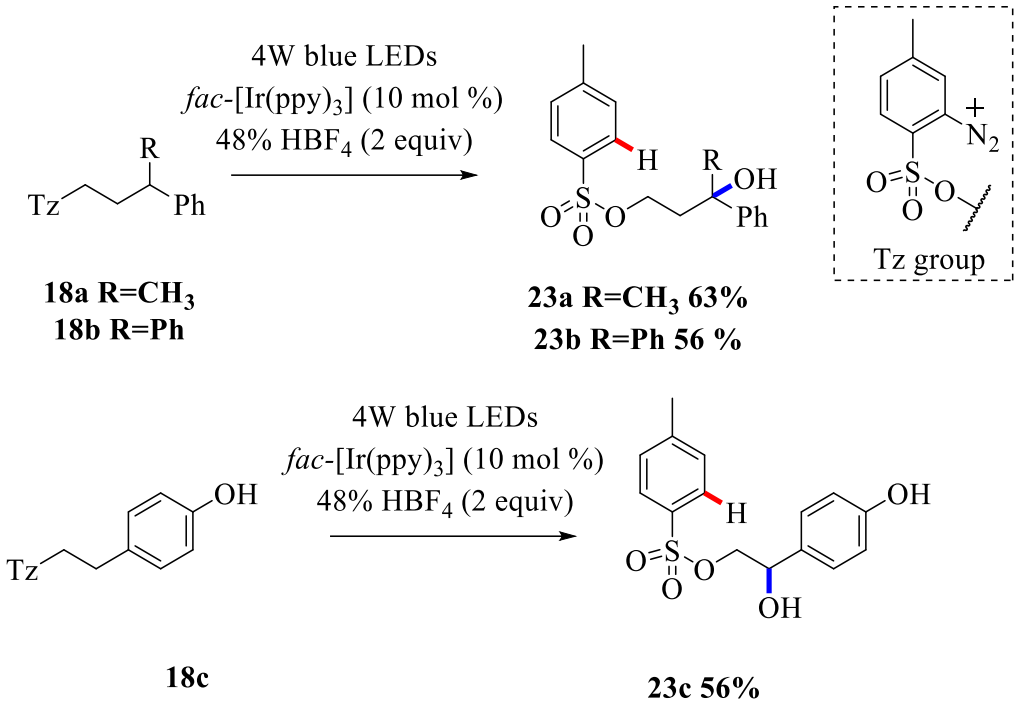
Scheme 15. Radical Translocation by 1,5- and 1,6- Hydrogen Atom Abstraction[18]



Hydrogen atom transfer (HAT) occurring intramolecularly is considered a radical translocation, and 1,5- and 1,6-HAT translocations are the most common (Scheme 15).[18] Comparatively, from a bond angle point of view, 1,5-HAT is much more favored in the competition between 1,5-HAT and 1,6-HAT (even 1,7 HAT). The X—H—C bond angle that is very close to 180 degree (typically 150-160 degree) makes the bond length shortest.[18] However, Regains used their protocol to demonstrate that 1,6- and 1,7-HAT can be predominantly achieved instead of 1,5-HAT.[19] They determined Tz group as the starting point, and under the trace of strong acid and visible light irradiation, the Tz ester was successfully converted into the corresponding alcohol.[19] The yielding of the products are uniformly good to excellent with a small amount of olefin side product. Most products

from the scope were afforded via 1,7-HAT, but one representative product **23c** from the scope proved that with the 1,6-HAT can be achieved via this remote hydroxylation (Scheme 16).[19] In this work, the reason why this remote hydroxylation was successful in replacing 1,6-HAT or 1,7 HAT (Tz group) was ambiguously presented, but the inferred reason is that the substrate selected for this transformation can minimize the entropy barrier.[19, 20] Therefore, it is noteworthy that 1,6-HAT and 1,7-HAT is favored in this case.

Scheme 16. Scope of Radical Translocation[19]



Even though Ragains pioneered the first process that involved both RPC and radical translocation, the current limitations were shown to be narrow in scope and low yielding (Scheme 16).[19] Furthermore, the only tested nucleophiles currently are H_2O, methanol, and ethanol, so to expand and further develop this research, a library of nucleophile selections would need to be tested.

2.2.3.3 The Photochemical Alkylation of Vinyl Boronate Complexes

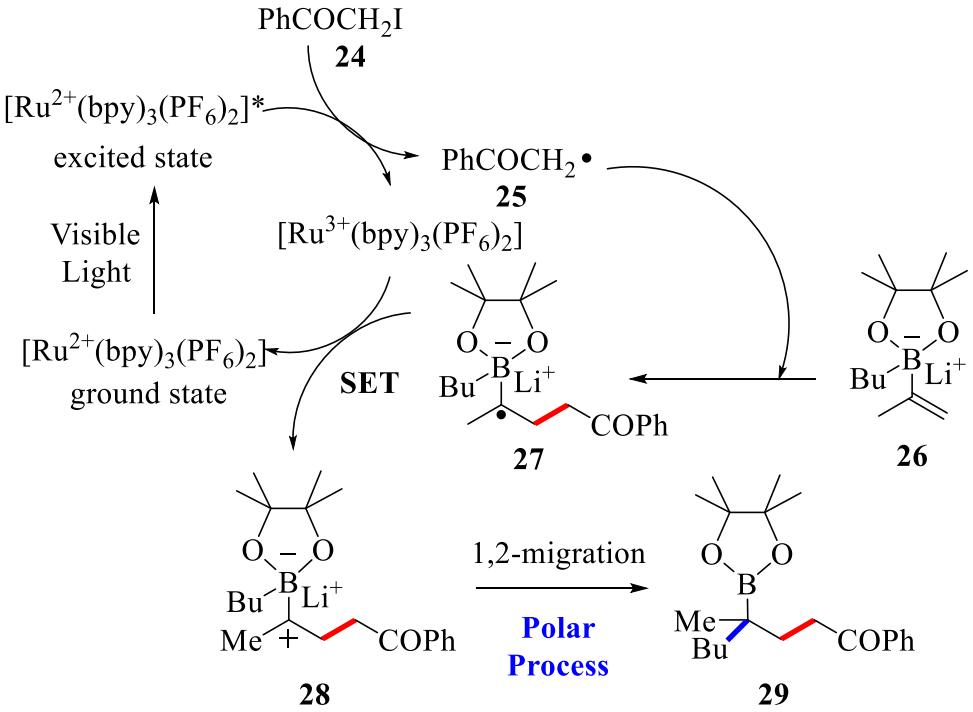
Organoboronates became key reagents in organic synthesis, attracting much attention in the organic synthesis community, and for instance, Suzuki coupling became one of the most well-known reactions using organoboron chemistry.[21] Suzuki coupling reaction has its undeniable advantages including its scalability, commercial availability, functional group tolerance, and its environmental friendliness.[21] Therefore, Suzuki coupling became the most frequently employed coupling reaction in the pharmaceutical industry.[21] However, recent research emanating from the groups of Aggarwal and Studer demonstrated that organoboronates can be used in RPC reactions.[22] Thus, organoboronates was used to conduct a 1,2-metalate rearrangement with a RPC step, and very mild conditions were employed.[23] Aggarwal and Studer differed in their approach, in that Aggarwal employed photoredox catalysis to achieve this transformation, while Studer

achieved this transformation stoichiometrically that will be mentioned in Section 3.2.1.1 of non-photoredox catalysis section.[22, 23]

In Aggarwal's protocol, outlined in Scheme 17, radical **25** was generated from **24** by reduction of excited state of Ru^{2+}, and the new radical **27** was produced by the π-addition to olefin **26**. The formed new radical **27** is subsequently oxidized by Ru^{III} to form a carbocation **28**, and 1,2-migration occurs as the last step to afford product **29**.

Compared to the method developed by Studer's group, which will be discussed later, the limitation of this method is that only C-C bond formation was investigated, and hypothetically, this method should be able to accommodate [3+2] cycloaddition reactions.[23] Therefore, one aspect for future development of this method is broadening the scope by designing a protocol to accomplish the synthesis of the cycloaddition adduct. Furthermore, the final product retains the boron functional group, and the alkylboronic esters can be very valuable for a variety of further chemistry for functional group installation.[23] Overall, this research is exemplary because it successfully broadened the application of organoboron chemistry to RPC reactions.[22, 23] It demonstrated that it is possible to enable a transformation to employ organoboron reagents without harsh conditions.[22]

Scheme 17. Plausible Mechanism of Merging Photoredox with 1,2-Metalate Rearrangements[22]



2.2.3.4 Photoredox-Catalyzed C-H Difluoroalkylation

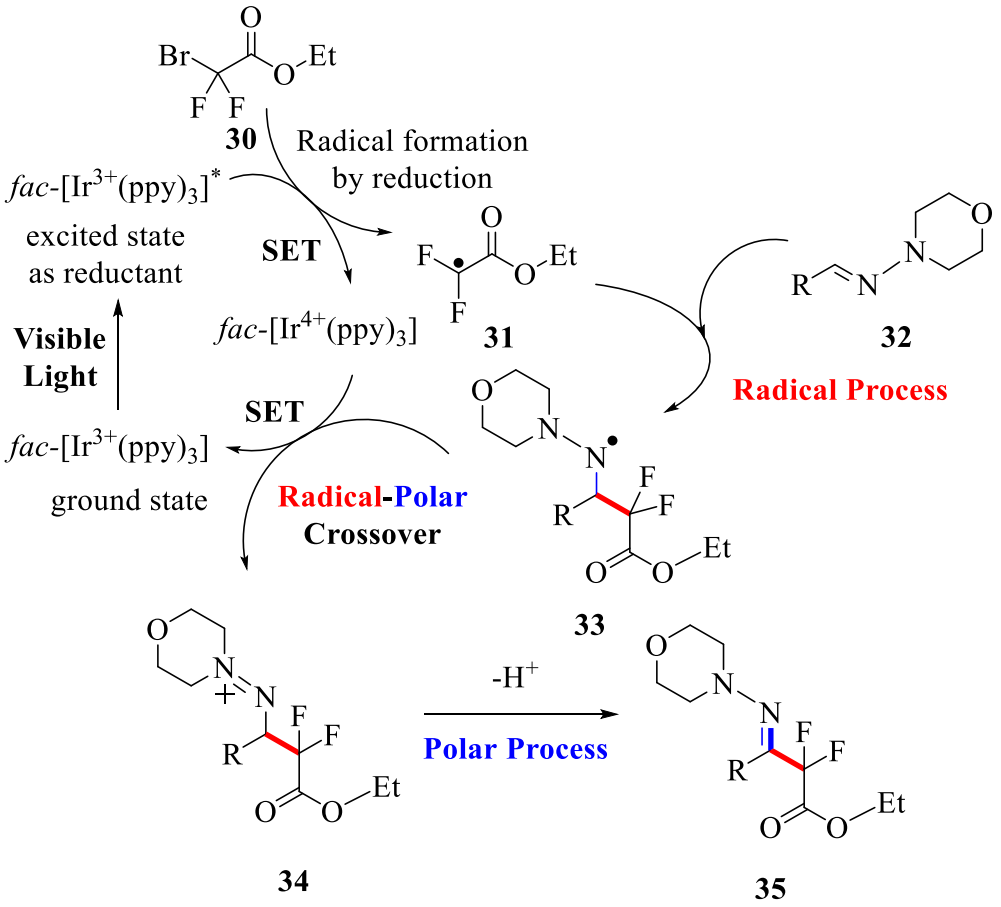
The first method for C-H bond functionalization of imino compounds was discovered by Zhu and collaborators.[10] Zhu and Song demonstrated that RPC reactions can be used to achieve meaningful C-H bond functionalization of imino compounds, and both scientists employed mild conditions in their protocol.[10, 24] However, Zhu and Song differed in their research, in that Zhu employed photoredox catalysis to achieve this $C(sp^2)$–H

difluoroalkylation, while Song achieved this C(sp^2)–H difluoroalkylation by a process that was mediated by a copper complex.[10, 24]

In the mechanism shown in Scheme 18, the photocatalyst $Ir^{3+}(ppy)_3$ was transformed to its excited state under irradiation, and subsequently, **30** was reduced to afford radical **31**. Addition of radical **31** to olefin **32** formed a new radical **33**, which was oxidized by SET from Ir^{4+} to afford carbocation **34**. Ultimately, product **35** was formed by 1,2-migration in a polar transformation.

Using only 2 mol % of *fac*-$Ir(ppy)_3$ as the photooxidant and weak base Na_2HPO_4 in DMF, the reaction could be carried out at room temperature.[10] The construction of the N=C-CF_2 moiety was proven useful to access biologically active materials. Section 3.2.3.5 will outline the copper-mediated C(sp^2)-H functionalization using aminyl RPC.[24, 25]

Scheme 18. Proposed Mechanism of Photoredox-Catalyzed Difluoroalkylation[10]

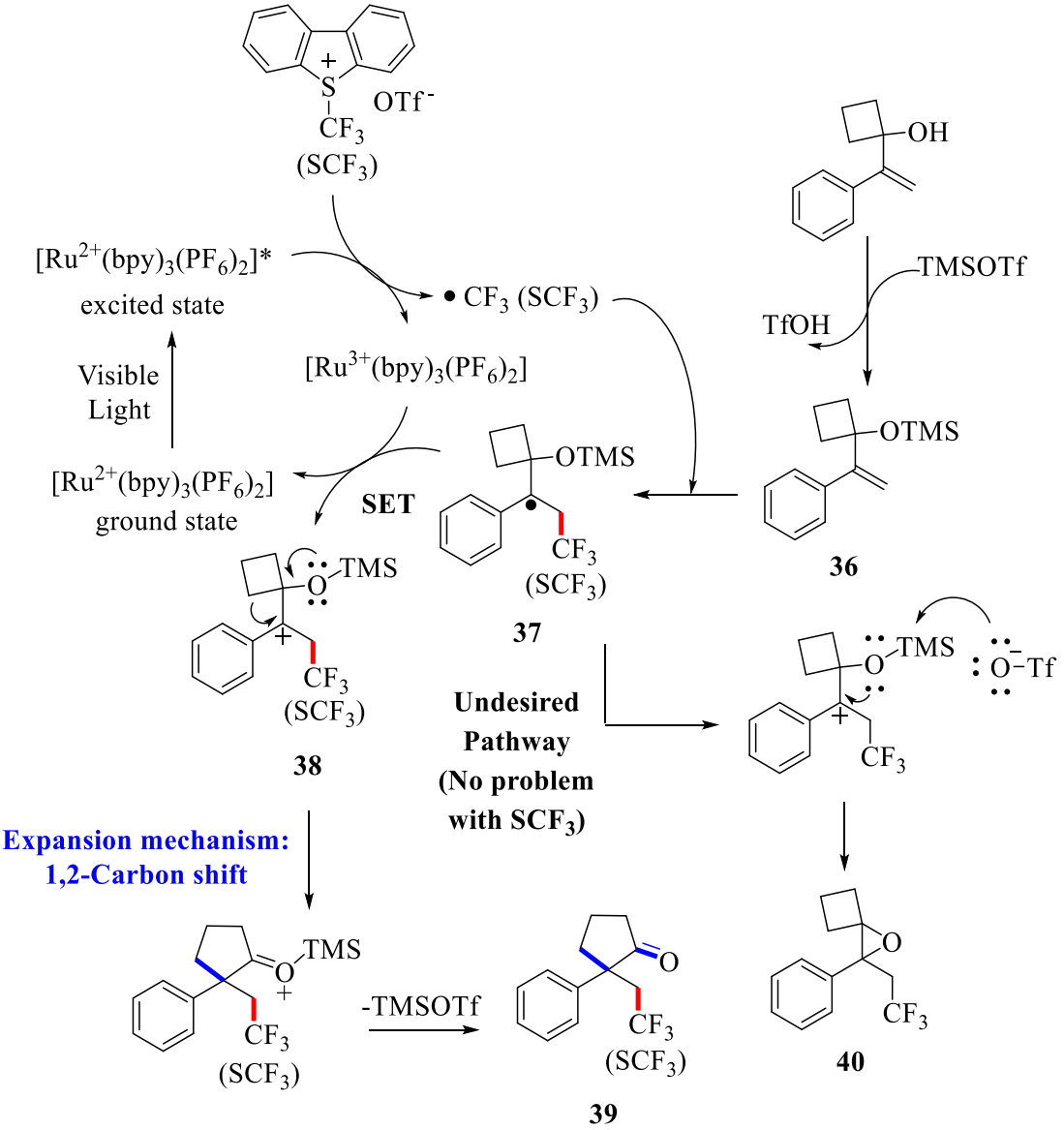


2.2.3.5 Photoredox-Catalyzed Semipinacol-type Rearrangement: Trifluoromethylation or Trifluoromethylthiolation/Ring Expansion by RPC

Glorius and co-workers designed a transformation proceeding via RPC reaction for the installation of –CF_3 and –SCF_3 groups with a subsequent ring expansion from a four-membered ring to a five-membered ring.[26, 27] In 2015, this effort resulted in a semipinacol-type rearrangement with trifluoromethylation and ring expansion through RPC mechanism, and the results were proven fruitful.[27] Scheme 19 outlines the mechanism proposed by Glorius regarding the installation of the –CF_3(–SCF_3) group. Scheme 19 depicts the

formation of the trifluoromethyl or trifluoromethylthiol radical, which denoted as •CF_3(•SCF_3) radical, by reduction of excited state *$[Ru(bpy)_3]^{2+}$. Subsequently, addition of •CF_3(•SCF_3) onto the double bond of olefin **36** affordeds radical **37**. At this point, RPC occurs to oxidize radical **37** to carbocation **38**, thereby simultaneously regenerating the photocatalyst. Ultimately, the 1,2-carbon shift occurs to achieve the ring expansion from a four-membered ring to a five-membered ring, and therefore, product **39** is generated. The reaction provided a relatively wide scope. Glorius' ongoing studies on the development of this catalyzed semipinacol type rearrangement resulted in trifluoromethythiolation/ring expansion in a one-pot process as indicated in Scheme 19.[26]

Scheme 19. Plausible Mechanism of Photoredox-Catalyzed Trifluoromethylation/ Trifluoromethylthiolation Ring Expansion by RPC[26, 27]



Side product **40** was detected in the trifluoromethylation process outlined in Scheme 19, which details the trifluoromethylation/ring expansion by RPC reaction.[26, 27]

The trifluoromethylthiolation/ring expansion does not have side products formed at the end of the synthesis.[26, 27] Therefore, to improve this ring expansion process, avoidance of side products becomes very critical.

Glorius developed a protocol to combine semipinacol-type rearrangement, RPC reaction, and functional group installation (i.e., $–CF_3$ and $–SCF_3$) simultaneously under photoredox catalysis.[26, 27] The reason why the construction of $–CF_3$ and $–SCF_3$ was mentioned is that both functional groups can be introduced into lead compounds of pharmaceutical targets to improve their chemical and physical properties.[26, 27] Compared to Zhu's work, this method was improved by incorporation of $-SCF_3$ group into the scope.[10]

2.3 Photoredox Conclusion

A series of photoredox-mediated RPC reactions are outlined in this Chapter. The RPC reaction under the photoredox catalysis provided fruitful results in both ring expansion and C-C(X) bond formation, but gaps still exist, such as the cycloaddition reaction that transpires under oxidation before reduction. Therefore, future research can be focused on more investigations of RPC cycloaddition reactions that transpire via oxidation before reduction.

The RPC reaction under photoredox catalysis has many advantages, including its step-economy and mild condition reaction conditions. Most of the reactions selected above were processed under mild condition and with low loading amount of catalyst, and molecular complexity was achieved in the reactions mentioned above. Noteworthy, a few products generated from photoredox mediated RPC reaction can be valuable as pharmaceutical reagents or in materials chemistry, in particular, the γ- and δ- lactones.[4, 5] The pharmaceutical applications of γ- and δ- lactones and comparison between the RPC pathway and previous approaches will be thoroughly narrated in Chapter 4.[4, 5]

In addition, many discoveries and innovations were outlined and discussed in non-photoredox catalyzed RPC reactions (Chapter 3). As stated in Chapter 1, this review article will outline the use of both photoredox and non-photoredox catalysts in RPC reactions, and therefore, the RPC reaction catalyzed by non-photoredox catalysis is going to be thoroughly reviewed in the next chapter.

Chapter 3. Radical Polar Crossover Reaction by Non-Photoredox Protocols

Many representative examples of photoredox catalyzed RPC reactions detailed in Chapter 2 provided insight to understand how the photoredox catalysis can be applied to RPC reactions, and the current limitations and advantages were described. Conversely, this chapter will address the current and state-of-the-art non-photoredox-mediated RPC reactions, and the subchapters are going to be divided into RPC Reactions transpiring via oxidation before reduction, RPC reactions transpiring via reduction before oxidation, RPC reactions transpiring via oxidation, and RPC reactions transpiring via reduction.

3.1 RPC Reaction Transpiring under Oxidation before Reduction

3.1.1 [3+2] Cycloaddition Reaction

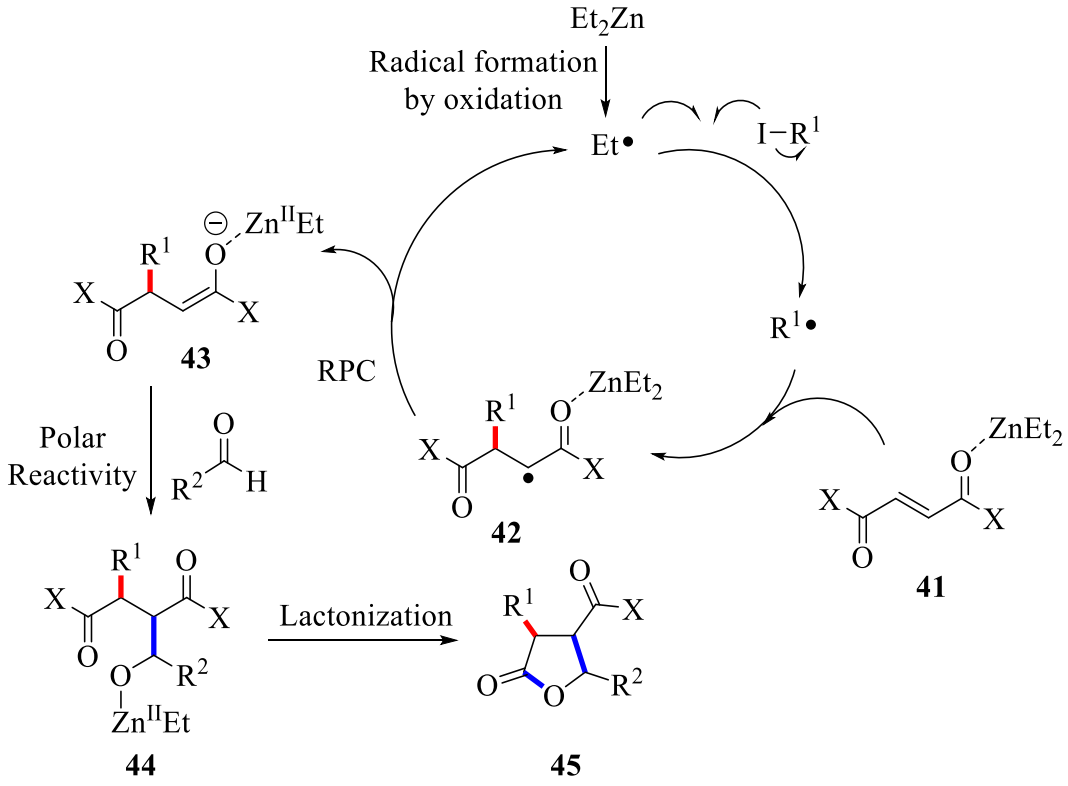
3.1.1.1 Dialkylzinc-Mediated Tandem Radical Addition/Aldol Condensation.

As stated in Section 2.3.1.1, Liu initiated his protocol to synthesize a variety of highly substituted γ-lactones via RPC reaction.[4] A method to achieve the same transformation was pioneered most extensively by Bertrand and Chemla, who introduced organozinc complexes as direct radical precursors to a variety of radicals.[28, 29] They demonstrated that the so-formed radical could either participate directly in the mechanism or participate in the mechanism after a radical exchange. With the growing interest in using dialkylzinc reagents as radical mediators, Bertrand contributed a review article describing the use of dialkylzinc reagents in radical reactions and mentioned that dialkylzincs reagents are air-sensitive organometallic species that can provide a radical species by exposure to oxygen.[30] Taking the concept further, both Bertrand and Chemla employed alkylzinc reagents as radical precursors in their RPC reactions even though their synthesis goals were aimed to different substances.[28, 29] In this Section, the synthesis of highly substituted λ-lactones designed by Bertrand will be discussed.[28]

In the protocol designed by Bertrand, Et_2Zn was utilized as the radical initiator that is oxidized by O_2 to generate an ethyl radical, and subsequently, the so-formed ethyl radical undergoes atom transfer with R-I to produce R•. A new radical **42** was afforded by the interaction between molecule **41** and R• and was simultaneously reduced to afford intermediate **43** and Et•. Afterward, the intermediate undergoes an aldol condensation to afford a new intermediate **44**, and intramolecular lactonization ultimately occurs to produce the final product, trisubstituted γ-lactone **45**. Overall, this transformation successfully involves four elementary steps, which are radical addition, homolytic substitution, aldol condensation, and lactonization (Scheme 20).[28]

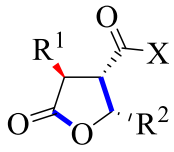
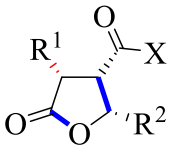
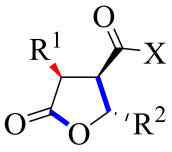
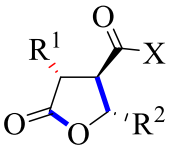
Most importantly, this dialkylzinc-mediated RPC reaction described herein successfully enabled the synthesis of trisubstituted γ-lactones in a remarkably step-economical manner. Bertrand succeeded in the synthesis of γ-lactones, but he did not realize the application of his method to δ-lactones.[28] To improve this strategy further, the synthesis of δ-lactone could be attempted. Overall, this work is valuable to accommodate a wider scope of product. Chemla carried out this work to demonstrate the accomplishment on the synthesis of functionalized tetrahydrofurans, which will be discussed in Section 3.1.3.1.[29] Thus, the scope of the Et_2Zn-mediated RPC reaction was proven to be expanded.

Scheme 20. Plausible Mechanism of Et_2Zn-Mediated RPC Reaction[28]



Chemla and Bertrand simultaneously demonstrated that alkylzinc complexes can follow a RPC mechanism, and in the meanwhile, they both designed their own protocol.[28, 29] This simple access to trisubstituted lactones was accomplished with high diastereoselectivity, and induced Bertrand to continue his investigation into the scope of the process in a series of di- or trisubstituted lactones (Table 1).[28] The results indicated that both the yields and scopes in this transformation were uniformly acceptable.

Table 1. Diastereomeric Ratios and Scope of **45**[28]

	 **45a**	 **45b**	 **45c**	 **45d**
R^1= *t*-Bu, R^2= *n*-Bu	19	0	0	81
R^1=Et, R^2=Ph	6	2	4	88
R^1= *i*-Pr, R^2= Ph	25	7	trace	68
R^1=Me, R^2=$C_{11}H_{23}$	15	0	0	85

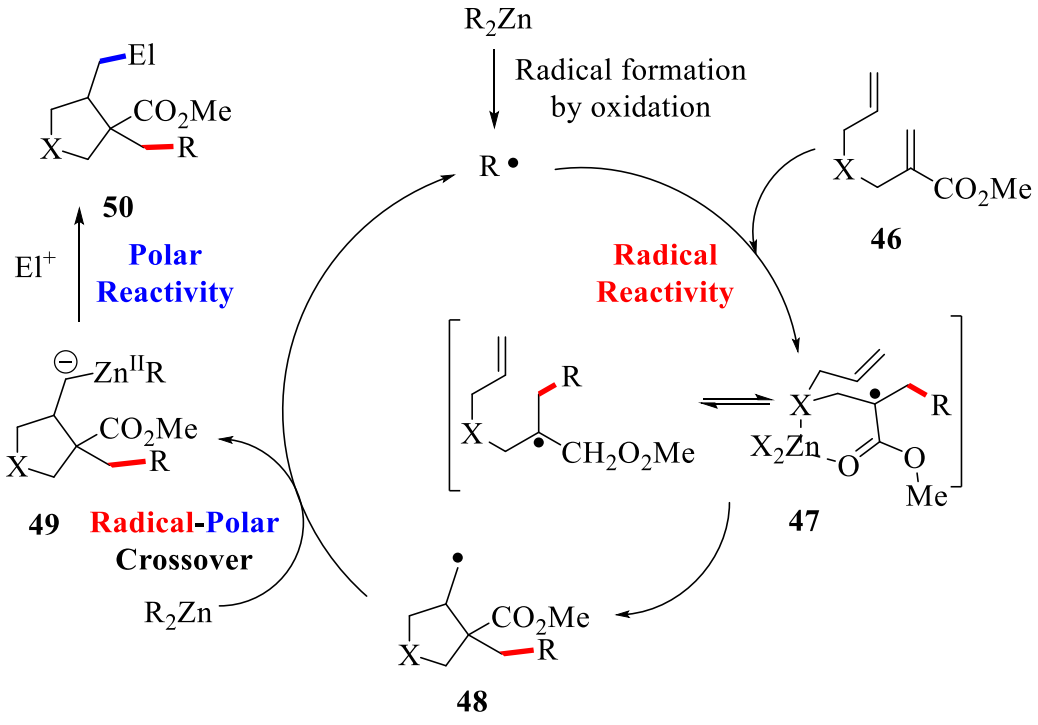
3.1.2 Non-Cycloaddition Reaction

3.1.2.1 Synthesis of Cyclized Ether Catalyzed by Zn-Mediated RPC Reaction

The organozinc catalysis applied to RPC reactions attracted much attention from the organic synthesis community, and recent advances provided by Chemla and Fabrice demonstrate that dialkylzinc reagents can be used successfully radical precursors in the RPC reactions.[28, 29] Even though both scientists shared the common motif to have dialkylzinc reagents, their proposed protocol and targets are different.[29]

Chemla and co-workers applied the R_2Zn-mediated RPC reaction to the synthesis of functionalized tetrahydrofurans in a multicomponent fashion.[29] Relatively good yields and wide scope were achieved in this transformation. The mechanism of the RPC reaction catalyzed by R_2Zn in Chemla's protocol is depicted in Scheme 21.[29] With a trace of O_2, the selected radical initiator R_2Zn is oxidized to produce R_2•. Different from Bertrand's protocol, the so-formed radical does not undergo radical exchange, and instead, the addition of Et• onto **46** occurs so that new radical **47** is formed. 5-*exo-dig* Cyclization then occurs to afford **48**, and subsequently, the **48** is reduced by Et_2Zn to afford intermediate **49** with C-Zn ionic bond formation. Attack by an incoming electrophile ultimately affords final product **50**.

Scheme 21. Proposed Mechanism of ZnR_2-Mediated RPC Reaction[29]



Different from the Bertrand-proposed, R_2Zn-mediated RPC reaction, the so-formed R_2• from R_2Zn participated in the reaction instead of exchanging to afford another radical.[28, 29] Overall, Fabrice and Chemla illustrated that dialkylzinc reagents can be successfully applied to RPC reaction, but their synthesis goals were aimed to different kinds of substances.[28, 29] Therefore, these results demonstrated that the alkylzinc complexes can follow a RPC mechanism and enable a one-pot reaction in building a variety of compounds

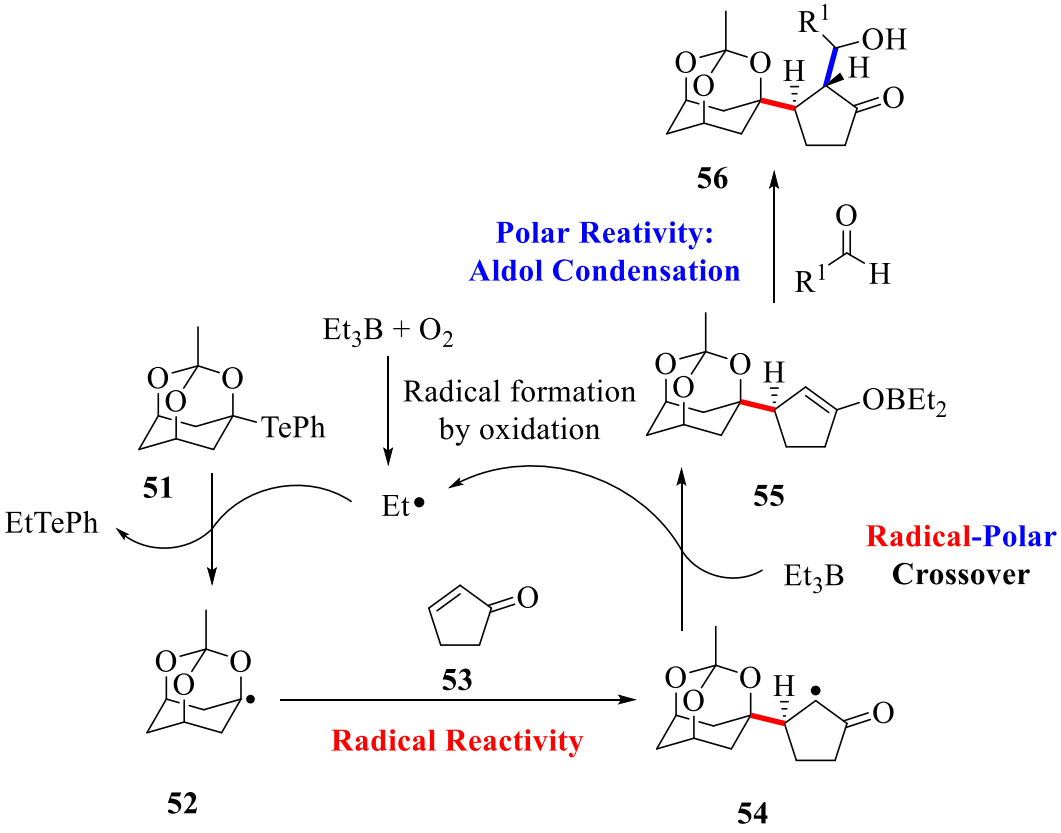
(δ-lactones and cyclic ethers), and in both protocols, the molecular complexity was increased.[28, 29]

3.1.2.2 Et_3B-Mediated RPC Reaction

RPC is a unique reaction that can facilitate three-component, one-pot coupling, and this feature was confirmed in a work reported by Inoue.[31] In 2013, Inoue achieved a three-component coupling by either ionic or radical processes,[32] with his innovation being inspired by combining radical and polar processes in one pot. Inoue and co-workers aimed to construct molecule terpenoid **56** in a one-pot reaction that successfully accommodated radical reactivity (including radical exchange and radical propagation), RPC, and polar reactivity (aldol condensation) within a single mechanism.[33]

Inoue designed this mild RPC reaction by making connections of hindered linkages between three units: α,β-unsaturated ketones, aldehydes/ketones, and O-Te acetals. The mechanism of this RPC reaction is illustrated in Scheme 22.[33] Et_3B, which has the same radical-generating property as Et_2Zn, can produce ethyl radical by exposure to an O_2 atmosphere.[30, 31] The so-formed ethyl radical induces the hemolytic cleavage of the C-Te bond of **51** to afford an α-alkoxy bridgehead radical **52**.[33] The so-formed α-alkoxy radical **52** interacts with **53** to afford **54**, and subsequently, Et_3B reduces **54** to afford an anionic intermediate **55**, with concomitant ejection of Et•. Ultimately, aldol condensation occurs between the anionic intermediate **55** and the carbonyl group of an incoming aldehyde to produce **56**.

Scheme 22. Proposed Mechanism of Et_3B-Mediated RPC Reaction[31]



Of note, previous research employed O-Se acetals because the C-Se bond can also work as the radical precursor, but the homolytic cleavage of the C-Se bond requires higher energy, and transpires slowly at 110°C.[34] Thus, the reaction conditions were optimized, in that the C-Se bond was replaced by a weaker C-Te bond as the alternative radical donor so that the transformation transpired under a mild condition at 0°C to afford a coupling product in modest yields.[31]

This work is notable because it was the first to pioneer the RPC reaction that can accommodate three complex components in a single mechanism. This reaction provided a broad scope for product **56**.[31] Additional advantages were provided including a transition metal-free procedure, mild conditions, and high efficiency. Because of these many advantages, this three-component, one-pot RPC reaction provided valuable strategy for the synthesis of functionalized terpenoids.[33, 35]

3.2 RPC Reaction Transpiring under Reduction before Oxidation

3.2.1 [3+2] Cycloaddition

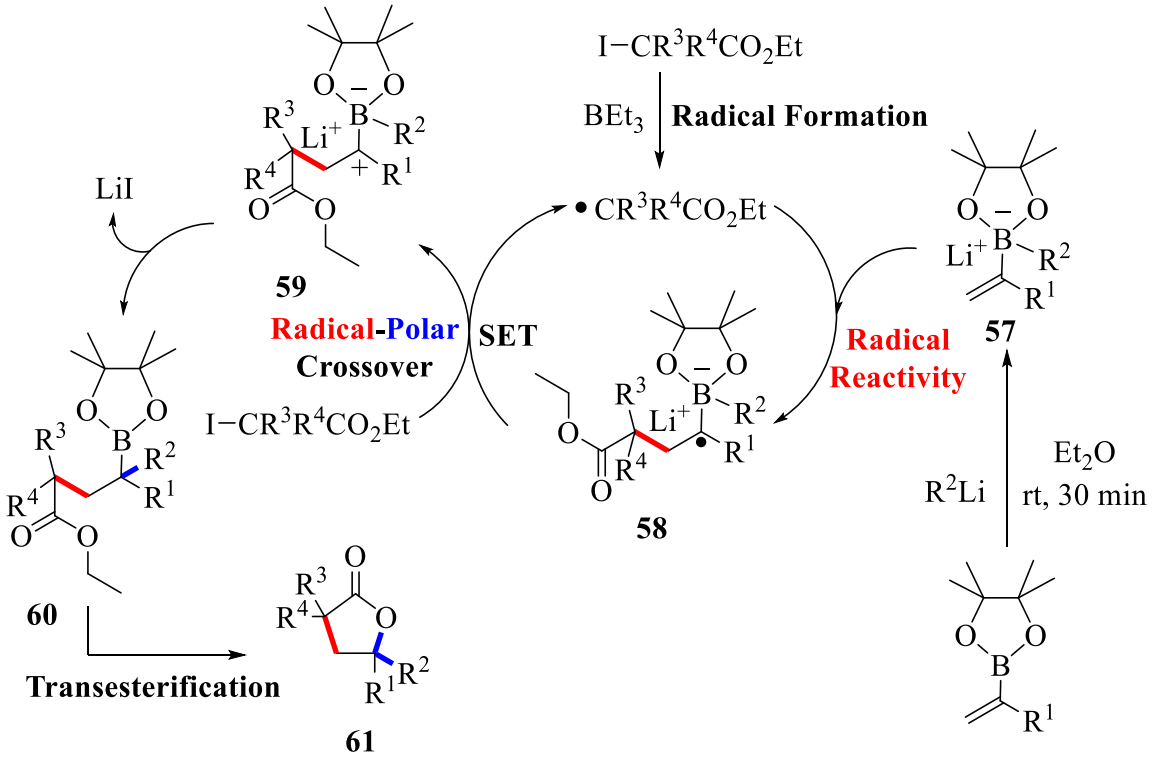
3.2.1.1 RPC Reactions of Vinylboronate Complexes

As described in Section 2.3.3.3, Aggarwal and Studer envisioned that organoborates can be used in RPC reactions, and the results were proven fruitful using Aggarwal's protocol.[22] As stated previously in Aggarwal's protocol, a photoredox-mediated RPC reaction was designed.[22] Conversely, Studer commenced his investigation of organoboron RPC reactions by employing vinylBpin, perfluoroalkyl iodide (R_f-I), and Li-R as the core reaction components, with BEt_3 as the radical initiator.[23] Remarkably, this transformation was carried out without the assistance of a transition metal, and this protocol provided uniformly good yields and broad scope.[23]

Compared to Aggarwal's protocol, Studer achieved this transformation without photoredox catalysis, and the first focal point is that his method successfully accommodated [3+2] cycloaddition reaction into the scope (Scheme 23).[22, 23] As Scheme 23 depicts, the R^2Li works as a reductant to afford new boronate ester **57**, and subsequently, the $\bullet CR^3R^4CO_2Et$ reacts with ester **57** to afford radical **58**. The newly formed radical is afterward oxidized by $I\text{-}CR^3R^4CO_2Et$ to form a carbocation **59**, and 1,2-migration occurs to afford **60** that retains the boron functional group. The final cycloaddition product **61** is afforded by transesterification under strong basic hydrogen peroxide conditions, and a variety of mono- and disubstituted λ-lactones were afforded, which illustrates that this protocol is tolerant of many functional groups (Scheme 24).[23]

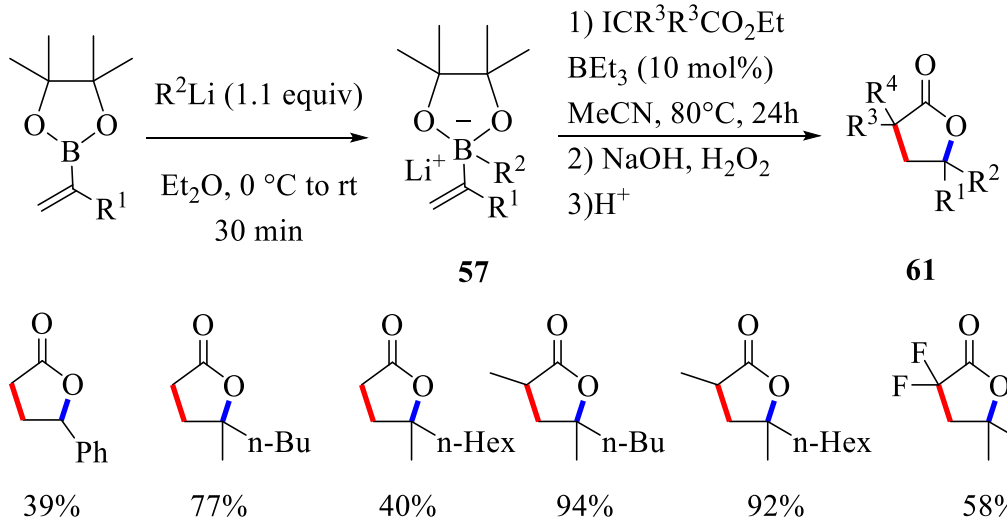
Aggarwal demonstrated that the application of boronate ester chemistry can be broadened to RPC reaction, but his method had several shortcomings with respect to retention of boron-containing product.[22] The alkylboronate ester can be very valuable for a variety of further chemistry for functional group installation.[36] Taking it further, Studer developed his protocol, which resulted in functional group installation, and three kinds of functional groups were introduced to replace the alkylboronate functional group.[23] As a result, the functional group installation was achieved. A later chapter outlining C-C(X) bond formation that employs this method will be discussed in Section 3.2.3.2.

Scheme 23. Plausible Mechanism of Vinylboronate RPC Reaction[23]



Aggarwal and Studer are in agreement that organoboron complexes can be used in RPC reactions, and they respectively proved this in their individual protocols.[22, 23] Their common advantage is that all reagents are commercially available relatively inexpensive, and both methods afford moderate to good yields (35-95%). Most importantly, the overall cost was reduced in the method developed by Studer because the radical process does not require the presence of a transition metal.[23]

Scheme 24. Scope of Vinylboronate RPC Reaction in [3+2] Cycloaddition[23]



3.2.1.2 [3+2] Cycloaddition of Azide with Aldehyde through an Aminyl RPC Strategy

Tetrazole have great biological activity because of its resistance to biological degradation.[37] For instance, TAK-456 demonstrated its strong biological activity and worked as an antibiotic (Figure 2).[37] Because of the biological activity of tetrazoles, they attracted attention from the organic synthesis community, and they were successfully synthesized by a few groups of chemists.[38, 39] However, previous analogous approaches of tetrazoles were achieved by Jiao and Narender, but both methods employed either harsh conditions or precious metals.[38-40] The aminyl radical polar crossover (ARPC) strategy achieved tremendous development in the synthesis of tetrazoles, and Zhu's group envisioned that the construction of tetrazole can be efficiently achieved under ARPC without harsh conditions or gold catalyst (Scheme 25).[38-40]

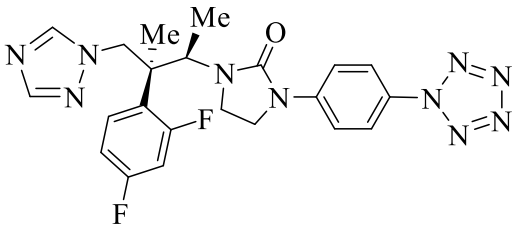
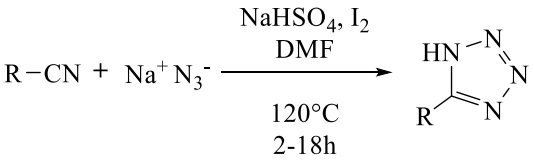


Figure 2. The Structure of TAK-456[37, 41]

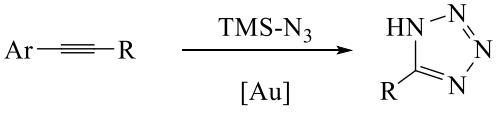
The mechanism of this transformation is outlined in Scheme 26.[41] In this transformation, the azide radical was generated from **62** via **63**, and subsequently, reacts with incoming olefin **64** to yield radical **65**, affording cation **66** through SET oxidation by Cu(II). Ultimately, ring closure occurs to achieve the cycloaddition, providing the final product **67**.

Scheme 25. Synthesis of Tetrazole [38, 40, 41]

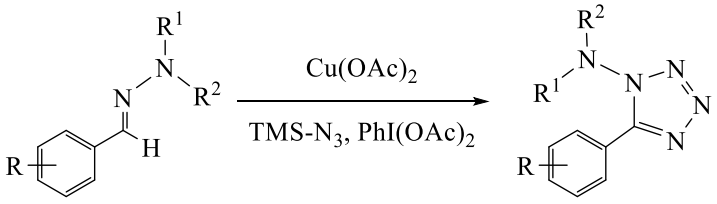
a) Cycloaddition of azide and nitrile to afford tetrazole



b) Cycloaddition of azide and alkyne to form tetrazole

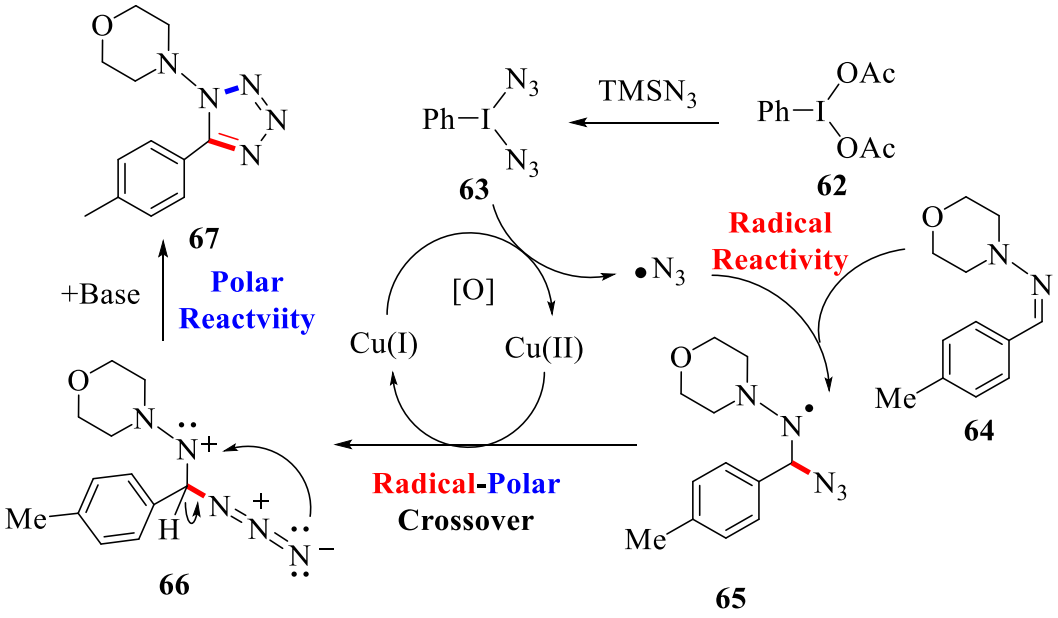


c) This work: ARPC



Zhu and co-workers reported mild conditions for the preparation of tetrazoles utilizing copper complexes. This method provided significant advantages in terms of ease of performance, broad scope, and mild conditions.[41] Thus, ARPC demonstrated its ability improve the reaction scope, tolerate a number of functional group, take place under mild reaction conditions, and allow successful scale-up.[41]

Scheme 26. Plausible Mechanism of ARPC Reaction[41]



3.2.2 [4+2] Cycloaddition

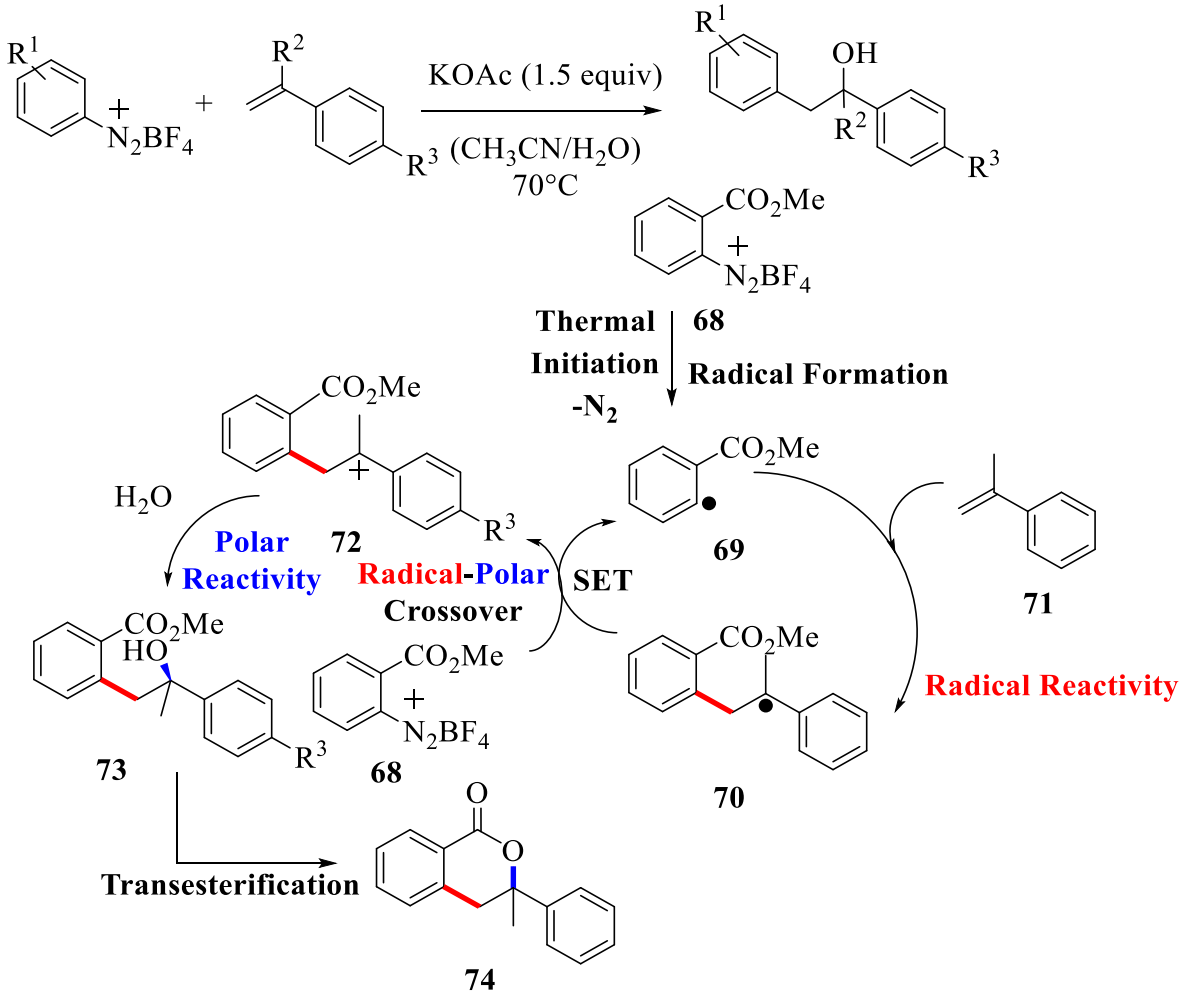
3.2.2.1 Thermally Induced Carbohydroxylation of Styrenes with Aryldiazonium Salts.

Fagnoni and Heinrich designed protocols to a reaction pathway that successfully combined Meerwein arylation and RPC, but they differ in their research in that Fagnoni constructed δ-lactones under photoredox catalysis.[5, 15] Heinrich employed a non-metal-mediated RPC reaction to afford a larger product scope, including the construction of C-C bonds and one representative [4+2] cycloaddition reaction. Overall, the yields were uniformly acceptable, and the δ-lactone was successfully synthesized.[15]

δ-Lactone **74** is a representative molecule from the scope of this transformation, and it demonstrated that [4+2] cycloaddition reaction was achieved in this transformation. The generic scheme and mechanisms were depicted in Scheme 27. Diazonium ion **69** acted as a self-reductant and to generate radical **68** via thermal initiation, and a new radical **69** was formed by the addition to olefin **71**. The so-formed radical **70** was subsequently oxidized by an incoming diazonium ion to form carbocation **72** as well as a new radical **69**. H_2O then acted as a nucleophile to attack the carbocation to afford **73**. Ultimately, the product δ-lactone **74** was produced by transesterification under moderately basic conditions (KOAc).

Of note, this transformation was successfully carried out without assistance of a transition metal, and it is environmentally sustainable and economical.[15] Furthermore, this method achieved the combination of Meerwein arylation and RPC, resulting in a broad product scope (Section 3.2.3.6).

Scheme 27. Mechanism of Meerwein Arylation in [4+2] Cycloaddition[15]



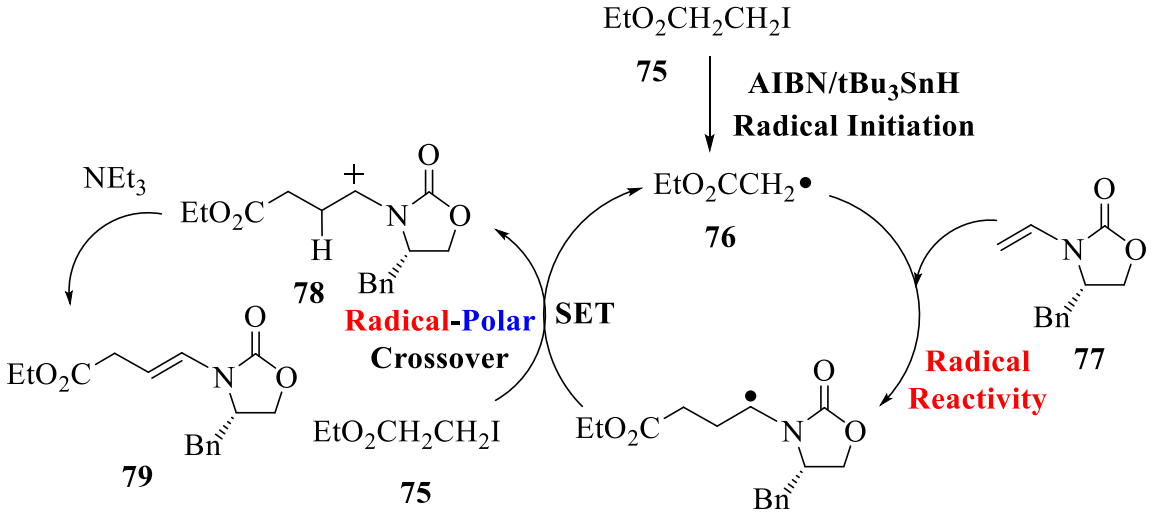
3.2.3 Non-cycloaddition

3.2.3.1 Intermolecular Nonreductive Alkylation of Enamides via RPC

Carbon-carbon bond construction via RPC reactions offer practical advantages in ease of performance. Friestad envisioned a process in which AIBN/tBu_3SnH, the former acting as a radical initiator, can initiate an RPC reaction that transpires under mild conditions to allow the alkylation of enamides.[42] This RPC reaction successfully enabled the construction of C-C bonds in a remarkably step-economical manner, and perhaps most impressively, this set of reactions and its corresponding results are reminiscent of the Heck reaction.[42]

In Friestad's protocol, outlined in Scheme 28, radical **76** was generated by AIBN/tBu_3SnH from **75**. A new radical was formed by the interaction between radical **76** and olefin **77** and subsequently oxidized by **75** to afford carbocation **78**. Ultimately, the incoming base NEt_3 neutralizes the reaction so that the Heck-like product **79** is formed.

Scheme 28. Proposed Mechanism of Enamides Alkylation[42]



One drawback of this protocol is that the RPC reaction transpires using AIBN/tBu_3SnH as the radical initiator.[42] Because of the toxicity of tin compounds, a tin-free process would be desirable.[43] In the RPC reaction developed by Studer (Section 3.2.3.2), only a small loading of BEt_3 was required to act as a radical initiator to transform R-I to R•, which indicates that the conversion of R-I to R• does not require AIBN/tBu_3SnH.[23] Therefore, to further improve this method, radical initiator AIBN/tBu_3SnH could perhaps be replaced by more environmentally friendly substances.

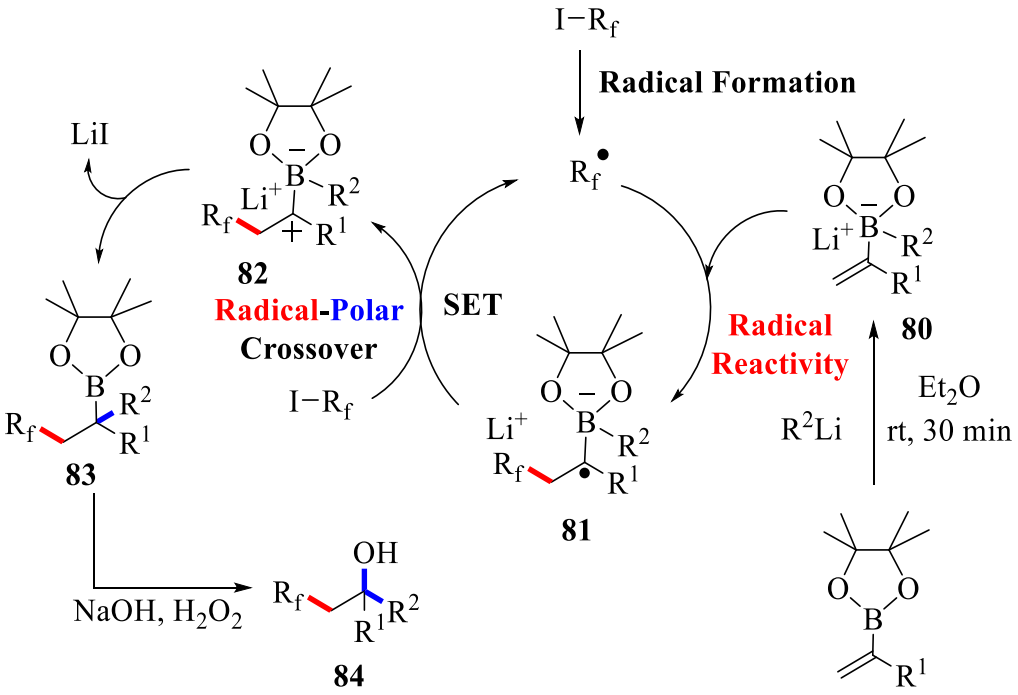
3.2.3.2 RPC Reactions of Vinylboronate Complexes

As stated in Section 3.2.1.1, the RPC reactions of vinylboronate complexes can accommodate [3+2] cycloadditions as well as C-C intermolecular bond construction.[23] In this section, the mechanism of C-C bond construction will be depicted, and further chemistry of the boronic acids will also be discussed.

The mechanism of C-C bond construction is slightly different from [3+2] cycloaddition reactions because of the replacement of the transesterification step to functional group installation.[23] The mechanism is depicted in Scheme 29. Due to the importance of Fluorine substituents in pharmaceutical chemistry, the predominant radical employed in the Studer's protocol is perfluoroalkyl radical, which was denoted as $•R_f$. Because of the low electronegativity of iodine, only 5 mol % of BEt_3 was used as a radical initiator to transform R_f-I to R_f• via homolytic cleavage of the covalent bond. Subsequently, the R_f• adds to the alkenylborate **80** to afford radical **81**, which then undergoes SET oxidation by an incoming R_f-I to produce carbocation **82**. A 1,2-alkyl shift from boron to the α-carbon (sp^2 center) generates the alkylboronate **83**, and ultimately, the alkylboronate was oxidized by $NaOH/H_2O_2$ to form alcohol **84**.

In contrast to Aggarwal's protocol, Studer demonstrated the organoboronate ester can be treated in RPC reaction under a non-photoredox catalysis without the presence of a transition metal.[22, 23] Additionally, Aggarwal demonstrated a wide scope of functional group transformations from the boronate.[22] For the initial studies, Studer oxidized the resulting boronate ester with $NaOH/H_2O_2$.[23] They found that all the targets were accessed smoothly with a uniformly acceptable yield (Scheme 30). To demonstrate that a wider

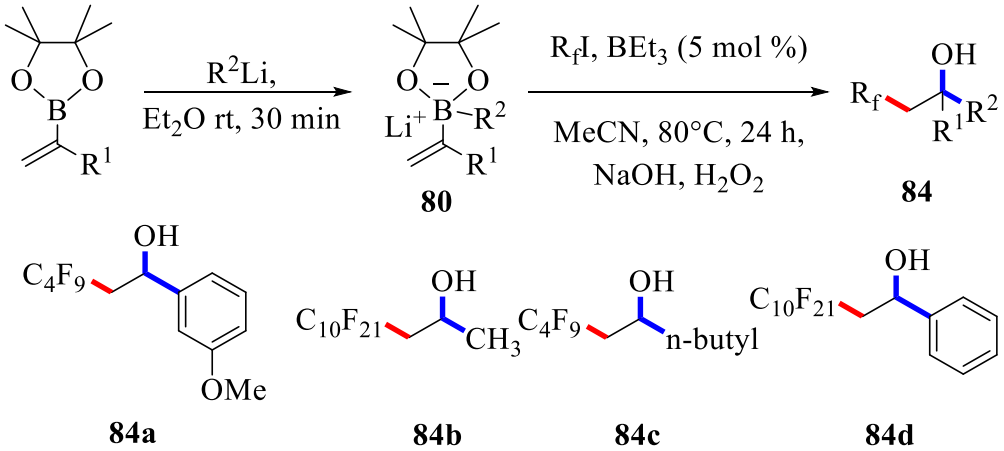
Scheme 29. Proposed Mechanism of C-C Bond Construction via Vinylboronate RPC Reaction[23]



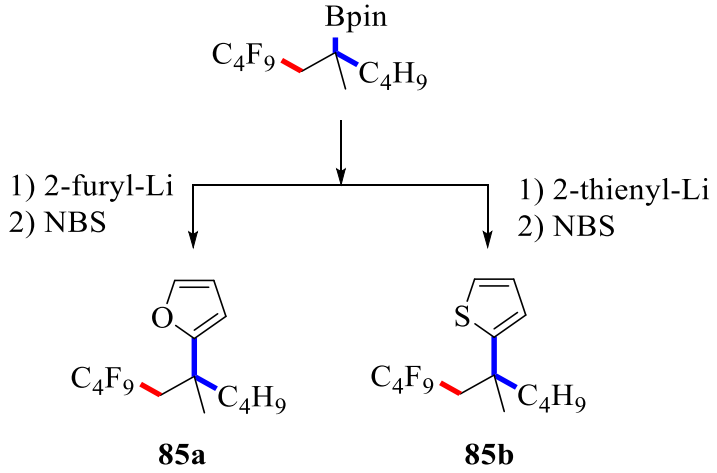
scope of functional groups can be installed, Studer continued to introduce 2-furyllithium and 2-thienyllithium, respectively to the organoboronate, and heterocyclic compounds **85a** and **85b** were formed (Scheme 31).[23] Overall, Studer pioneered a reaction pathway employing boronic acid in an RPC reaction, and the broad scope of further coupling was demonstrated.[23]

Scheme 30. Follow-up Chemistry of Alkylboronate by Installation of –OH Group[23]

Hydroxylation:



Scheme 31. Follow-up Chemistry of Alkylboronates[23]



85a **85b**

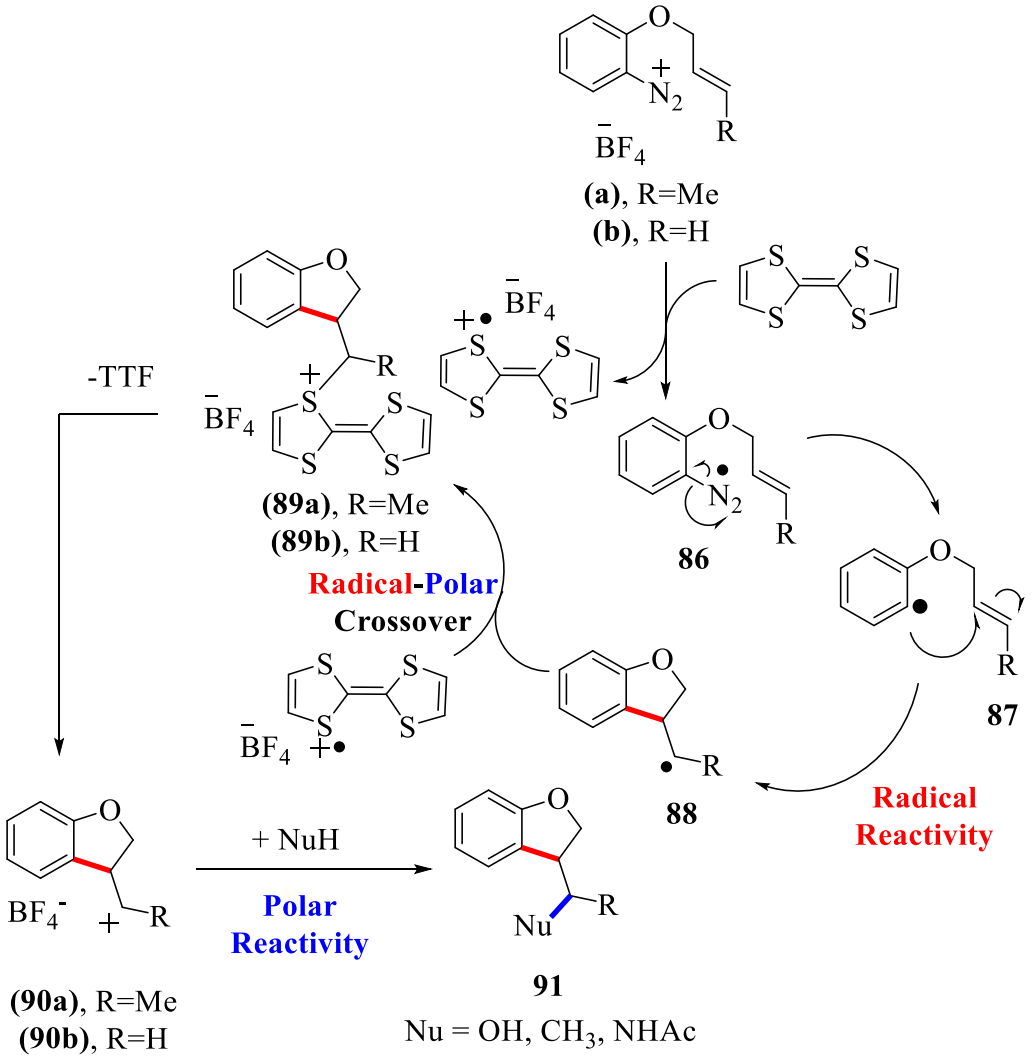
3.2.3.3 TTF-Mediated RPC Reaction

The tetrathiafulvalene (TTF) was first prepared by Perlstein in 1973, and TTF and its derivatives were extensively investigated by both the organic synthesis community and materials science community with a particular focus on new conductors and semiconductors.[44, 45] The most extensive research of TTF-chemistry was recently focused on its single electron donating property, and Murphy and co-workers published a very practical use of RPC reaction mediated by TTF in 1993.[46] In contrast to SmI_2-mediated RPC reactions, which will be discussed in Section 3.4.1, Murphy and co-workers demonstrated that the TTF-mediated RPC cyclization might transpire via reduction before oxidation, and an S_N1 reaction ultimately occurs to finalize the reaction cycle.[47] Overall, this work is notable because of the absence of transition metals in the protocol, and a relatively good yield and a broad scope were achieved (Scheme 32).[6]

The TTF-catalyzed RPC reaction was mostly applied to aryl diazonium salts, and the initial radical participating in the catalyzed cyclization is an aryl radical (Scheme 32). As depicted in Scheme 32, radical **87** is derived from **86** by loss of N_2, and a subsequent radical cyclization occurs to afford new radical **88**, which then undergoes SET oxidation by TTF. The intermediate **89** undergoes an S_N1 reaction with an incoming nucleophile after departure of TTF to generate carbocation **90**, providing **91** as the final product.

Murphy commenced the discovery of the scope of TTF-mediated RPC reaction by installing a variety of functional groups, which includes –OH, -OMe, and –NHCOMe group (Scheme 31).[45, 48] He realized that the TTF-mediated RPC reaction can produce alkaloids by employing an intramolecular nucleophile. Thus, in research performed in the same laboratory, a TTF-mediated RPC reaction was applied to the total synthesis of Aspidospermidine, which is a typical biological active reagent isolated from Aspidosperma tree (Section 4.1). [48, 49]

Scheme 32. Proposed Mechanism of TTF-Mediated RPC Reaction[45]



3.2.3.4 Copper-Catalyzed RPC Reaction to Achieve C(sp^2)-H Difluoroalkylation

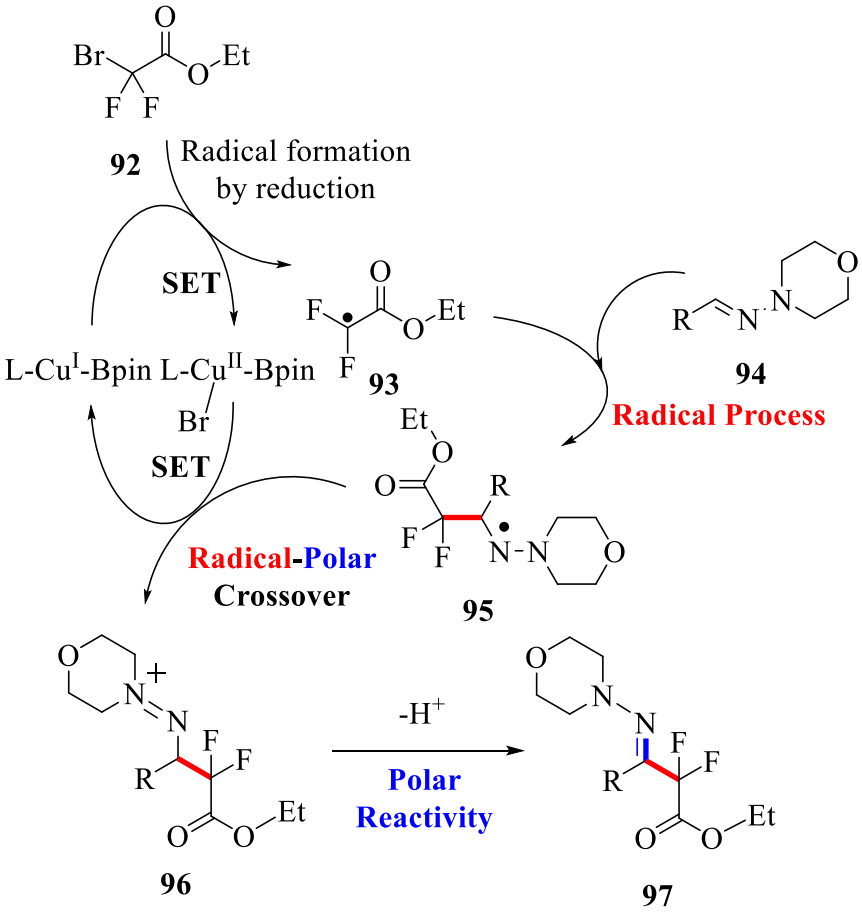
Difluoroalkylation of aldehyde-derived hydrazones was developed by Zhu and co-workers under visible-light photoredox catalysis. This work accomplished a C-H functionalization within a one-pot protocol.[10, 24] Conversely, Song and co-workers developed their own protocol to achieve the analogous C-H difluoroalkylation of aldehyde-derived hydrazones, and the N=C-CF_2 subunit is the core synthesized in the final product. Both groups of scientists envisioned the strong biological activity of N=C-CF_2 subunit.[10, 24] Song achieved the functionalization of C(sp^2)-H bonds under copper-mediated RPC reactions (using Cu/B_2pin) instead of using photoredox catalysis with low loading of B_2pin resulting more freedom in molecular complexity generation.[24]

Copper-mediated C(sp^2)-H difluoroalkylation of aldehydes was exclusively researched by Song and co-workers. According to the proposed mechanism depicted in Scheme 33, the radical **93** was afforded by the reduction of **92** by a Cu^I-Bpin complex. Subsequent addition of radical **93** to olefin **94** provided a new radical **95**, which was

oxidized by SET from Cu^{II}-Bpin to afford carbocation **96**. Ultimately, product **97** was formed by loss of a proton from intermediate **96**.

Coincidently, Monteiro and co-workers reported an analogous C-H difluoroalkylation of aldehyde-derived hydrazones, but in analyzing this method and protocol, the overall yield of the reaction is low, and vigorous reaction conditions and expensive materials, including both metals and ligands, needs to be used to afford the desired product (Scheme 33).[50] In a further coincidence, both Monteiro and Song synthesized aliphatic aldehyde-derived *N*,*N*-dimethyl hydrazines, but Song used his protocol under mild conditions to obtain a much higher yield than Monteiro's protocol.[24, 50] These results illustrate that RPC improved the method by employing mild conditions with an increase in the yield of product.[24] Overall, this transformation demonstrated that C-H difluoroalkylation of aldehyde-derived hydrazones is achievable under Cu-Bpin catalysis.

Scheme 33. Proposed Mechanism of Copper-Catalyzed RPC Reaction[24]



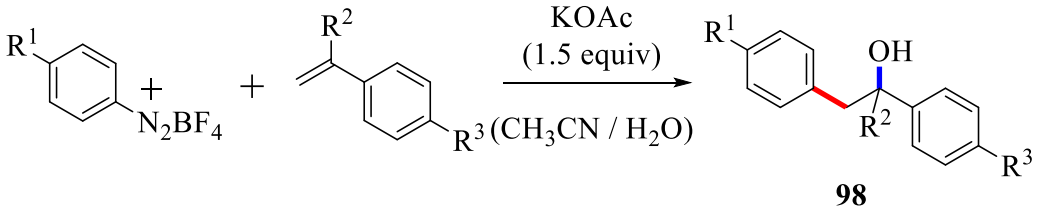
3.2.3.5 Thermally Induced Carbohydroxylation of Styrenes with Aryl diazonium Salts

Heinrich demonstrated that Meerwein arylation can be applied to RPC reactions in a one-pot fashion, and he successfully tested his protocol in the synthesis of δ-lactones

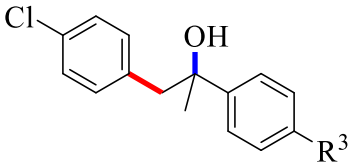
stated in Section 3.2.3.2.[15] This transformation afforded a broad scope of product via both [4+2] cycloaddition and C-C bond construction.

Scheme 34. Scope of Thermally Induced Carbohydroxylation of Styrenes with Aryl Diazonium Salts[15]

Synthesis of corresponding alcohol:

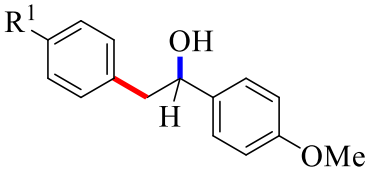


98



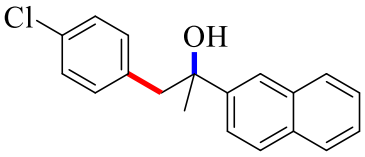
98a. R^3 = OMe 68%

98b. R^3 = NO_2 10%

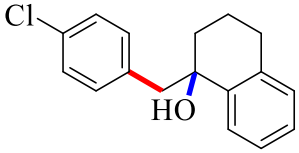


98c. R^1 = Cl 78%

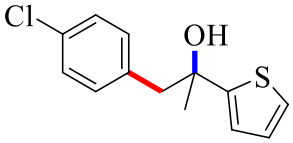
98d. R^1 = NO_2 55%



98e. 65%

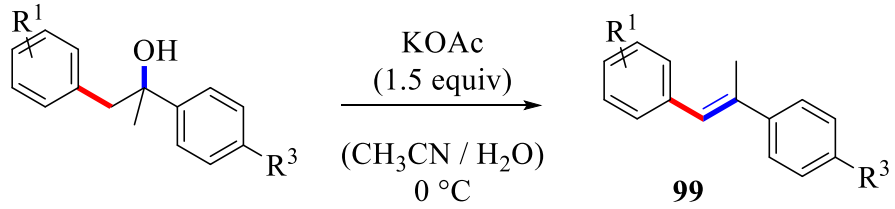


98f. 83%

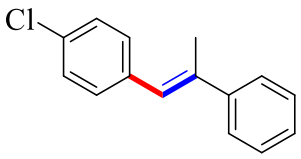


98g. 62%

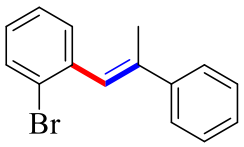
Synthesis of stilbenes:



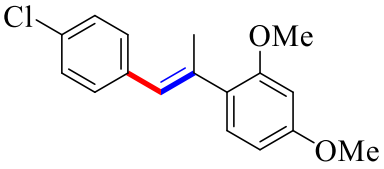
99



99a 70%



99b 95%



99c 85%

The method provided significant advantages in terms of ease of performance and wide product scope.[15] At room temperature, a variety of compounds can be afforded under the condition of KOAc and CH_3CN.[15] Several representative examples from the scope of transformation are outlined in Scheme 34, and overall, good to excellent yields of product **98** were achieved in this RPC transformation. Afterward, Heinrich lowered the reaction

temperature from room temperature to 0°C, and a variety of stilbene derivatives **99** were afforded with good to excellent yield (Scheme 34).[15]

In summary, it is feasible to apply the Meerwein arylation to RPC reactions under mild thermal reaction conditions, and through addition of water, this transformation afforded the corresponding alcohol at room temperature.[15] In addition to this discovery, the scope can be extended to achieve carboetherification or the synthesis of stilbene derivatives, and it was demonstrated by Heinrich (Scheme 34).[15]

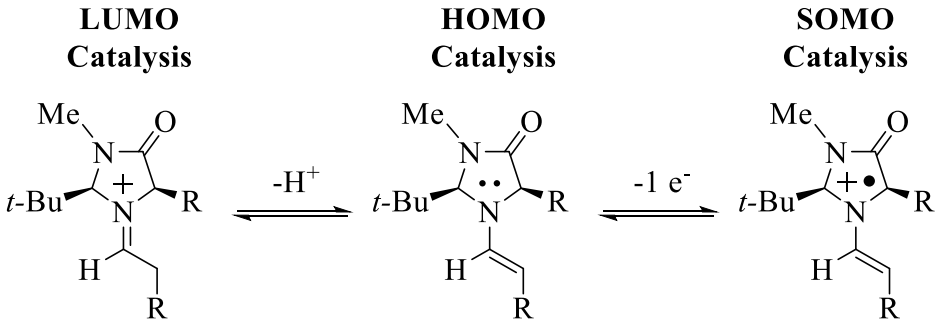
3.3 Net-Oxidative RPC Reaction

3.3.1 [3+2] Cycloaddition

3.3.1.1 SOMO Catalysis.

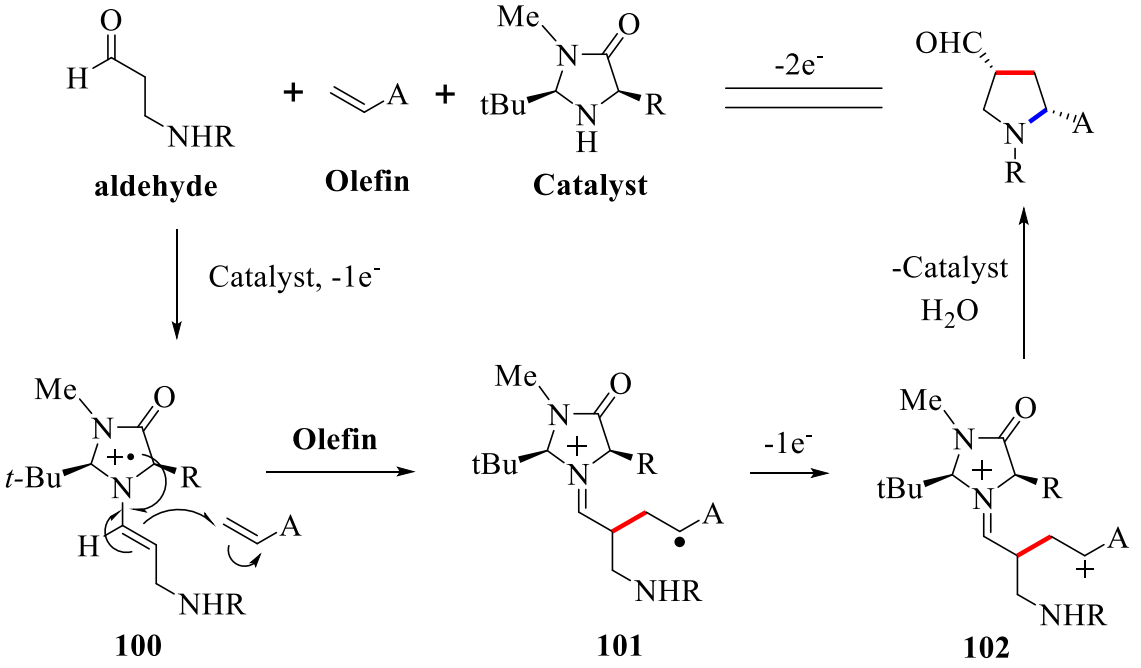
Singly Occupied Molecular Orbital (SOMO) catalysis was most extensively developed by the MacMillan group.[51] The concept of SOMO catalysis was unambiguously demonstrated by activation modes, and once the selected catalyst interacts with the carbonyl group on an aldehyde, the HOMO activation level is approached with a 4π system (Scheme 35).[52] With the presence of oxidant $[Fe(phen)_3]\bullet(SbF_6)_3$, the HOMO species is oxidized with loss of one electron to afford the SOMO catalysis species, and subsequently, the radical is successfully generated.

Scheme 35. Illustration of Both LUMO- and SOMO-Catalysis Activation Modes[52]



SOMO-catalyzed RPC reactions demonstrated their applicability in both [3+2] and [4+2] cycloaddition reactions.[53] SOMO catalysis is based on single-electron oxidation of electron-rich enamines, which generate radicals that can be oxidized to afford electrophiles.[51, 52] Subsequently, the lone pair on the nitrogen donates its electron pair to various electrophiles to form cycloadducts as the observed products of the reactions. Scheme 36 depicts one example of SOMO catalysis used in the RPC reaction. In this transformation, an aldehyde and an olefin are the main participants in a [3+2] cycloaddition reaction. The catalyst first interacts with the aldehyde to afford **100** as a radical cation intermediate, and a radical reaction then ensues to generate **101** followed by oxidation of the resulting radical by $Fe(phen)_3(PF_6)_3$ to afford electrophile **102**. The polar cyclization reaction affords the cyclized intermediate to complete the catalysis, with hydrolysis of the iminium ion providing the final product, regenerating the organocatalyst.[51, 52]

Scheme 36. Mechanism of SOMO Catalysis in [3+2] Cycloaddition[51, 52]



The combination of SOMO organocatalysis mode, RPC mechanism, and cycloaddition (including [3+2] and [4+2]) were achieved and employed to serve as a pathway to a variety pyrrolidines and piperidines, respectively.[51] Good to high yields were afforded under the SOMO catalysis with the same set of reaction conditions, and in addition to [3+2] cycloaddition, the [4+2] cycloaddition can provide the synthesis to piperidines, which will be discussed in Section 3.3.2.1.

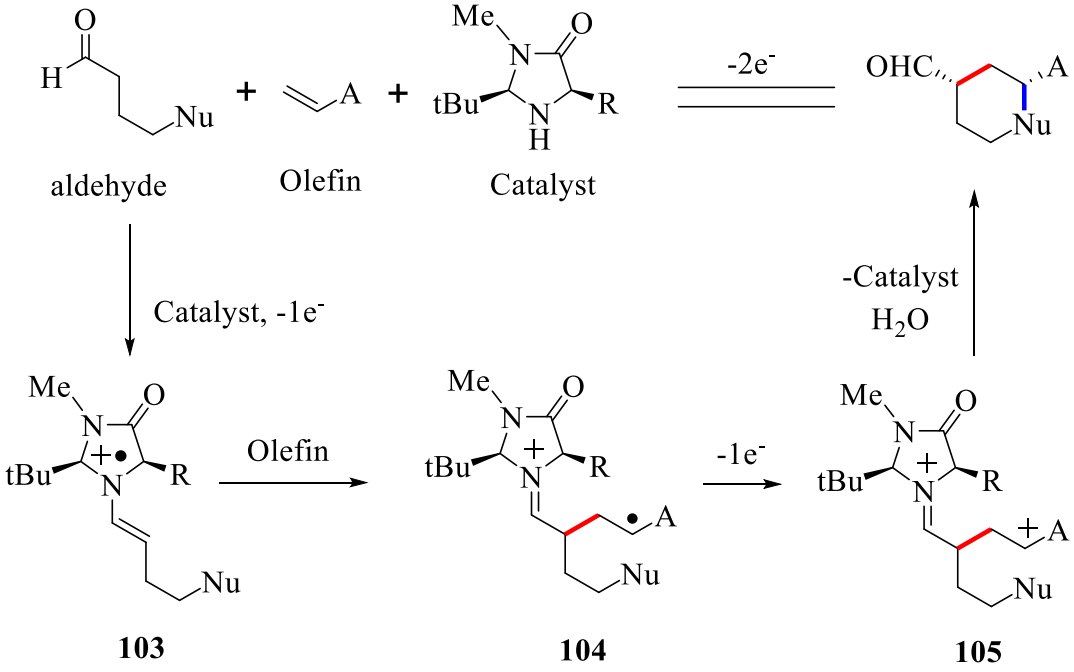
3.3.2 [4+2] Cycloaddition

3.3.2.1 SOMO Catalysis.

SOMO catalysis can be used to perform [4+2] cycloadditions as well as [3+2] cycloadditions.[51, 52] The Diels-Alder reaction became central in the development of six-membered ring systems, and prior to the development of radical-polar [3+2] cycloadditions, [4+2] cycloadditions were carried out by SOMO catalysis, enabling the direct, enantioselective allylic alkylation, nitro-alkylation, and vinylation reactions of aldehydes.[53, 54]

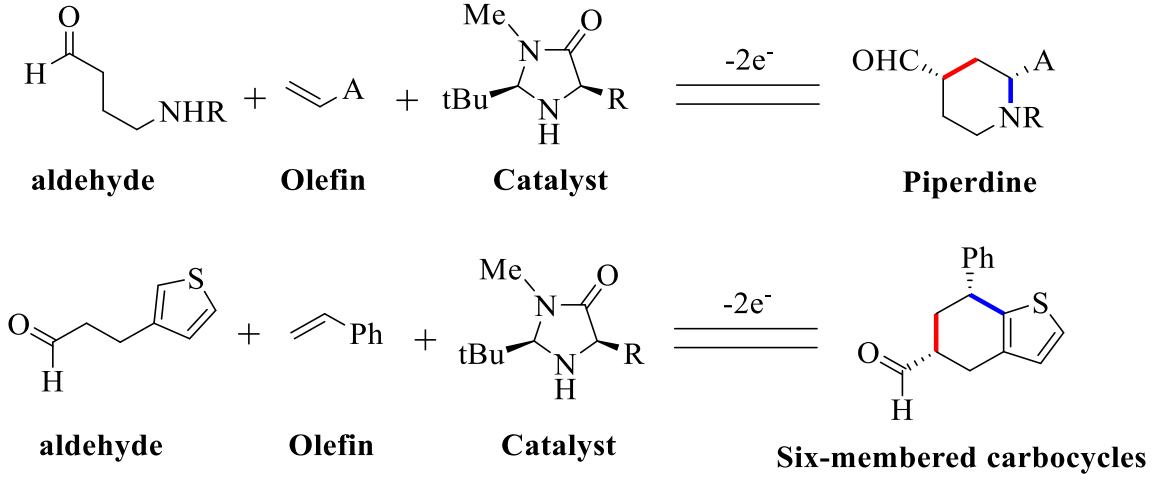
To achieve [4+2] cycloaddition reaction under SOMO catalysis, the aldehyde shown in Scheme 37 has an additional -CH_2- unit, and the interaction between the aldehyde and catalyst affords **103** with loss of one electron.[54] Subsequently, the olefin participates in the reaction, and the radical **104** is formed by an intermolecular 6-exo radical addition process. The resulting radical is oxidized by $IrCl_3$ to form the El^+ **105**. The polar process finalizes the transformation to afford the final six-membered ring as the product. Slightly different from the SOMO [3+2] cycloaddition reaction, MacMillan accomplished the [4+2] cycloaddition reaction in both carbocyclic and heterocyclic fashion, and cyclohexyl ring and piperidines are constructed.[53]

Scheme 37. SOMO Catalysis in [4+2] Cycloaddition[51-53]



Of note, the development of SOMO catalysis allowed access to six-membered heterocyclic and carbocyclic frameworks via RPC reactions, and piperidines were generated (Scheme 38). MacMillan published a series of articles of SOMO catalysis, and they demonstrated that the RPC reaction can successfully enable the reaction pathway toward both pyrrolidines and piperidines.[51, 53]

Scheme 38. The Synthesis of Piperidines and Six-Membered Carbocycles[53]



3.3.3 Non-cycloaddition reaction

3.3.3.1 Ceric Ammonium Nitrate (CAN) Mediated Oxidative RPC Reaction

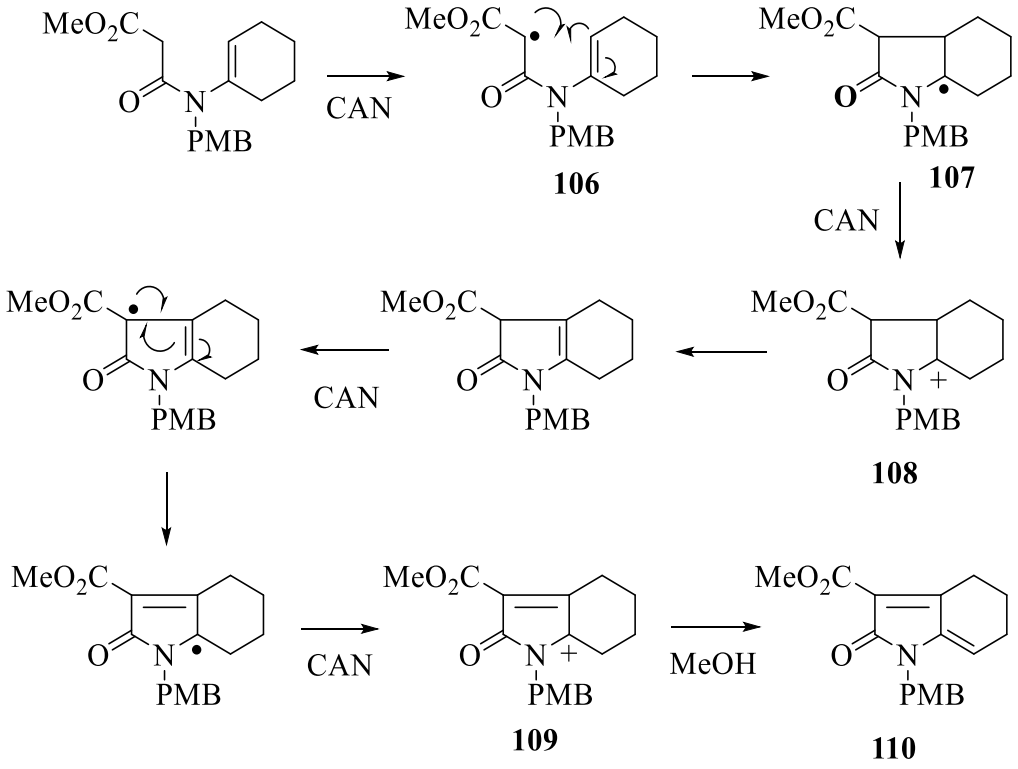
Cerium(IV) compounds, and in particular, ceric ammonium nitrate (CAN), are among the most useful oxidants in general.[55] In 1992, Molander composed a review article

demonstrating that the development of mild and convenient procedures were found in CAN-mediated reactions instead of using stoichiometric CAN.[55] Afterward, Mawdsley and co-workers discovered the CAN-mediated RPC cyclization, which can produce a number of biologically active products, for instance, Quinolacticin C.[56]

The mechanism of this transformation is depicted in Scheme 39.[56] The radical **106** is generated by SET oxidation of CAN, and radical cyclization occurs to form a new radical **107**, which is afterward oxidized by CAN to afford an iminium ion **108**. An elimination occurs, followed by an iterative radical generation and oxidation process to afford an iminium ion **109**. Subsequent interaction with solvents (MeOH) ultimately generates the final product **110**.

Mawdsley and co-workers developed this transformation to demonstrate that CAN-mediated RPC reactions are feasible under milder conditions compared to $Mn(OAc)_3$-catalyzed reactions.[56, 57] However, this reaction showed its disadvantage in the extremely high loading of CAN catalyst (1:4), and the oxidant CAN was not recyclable in the catalytic cycle. It is noteworthy that CAN-mediated RPC reactions afforded a number of valuable drug-like molecules, such as Quinolacticin C, L-755,807, and PI-091.[56]

Scheme 39. Proposed Mechanism of CAN-Mediated RPC Reaction[56]



3.4 Net-Reductive RPC Reaction

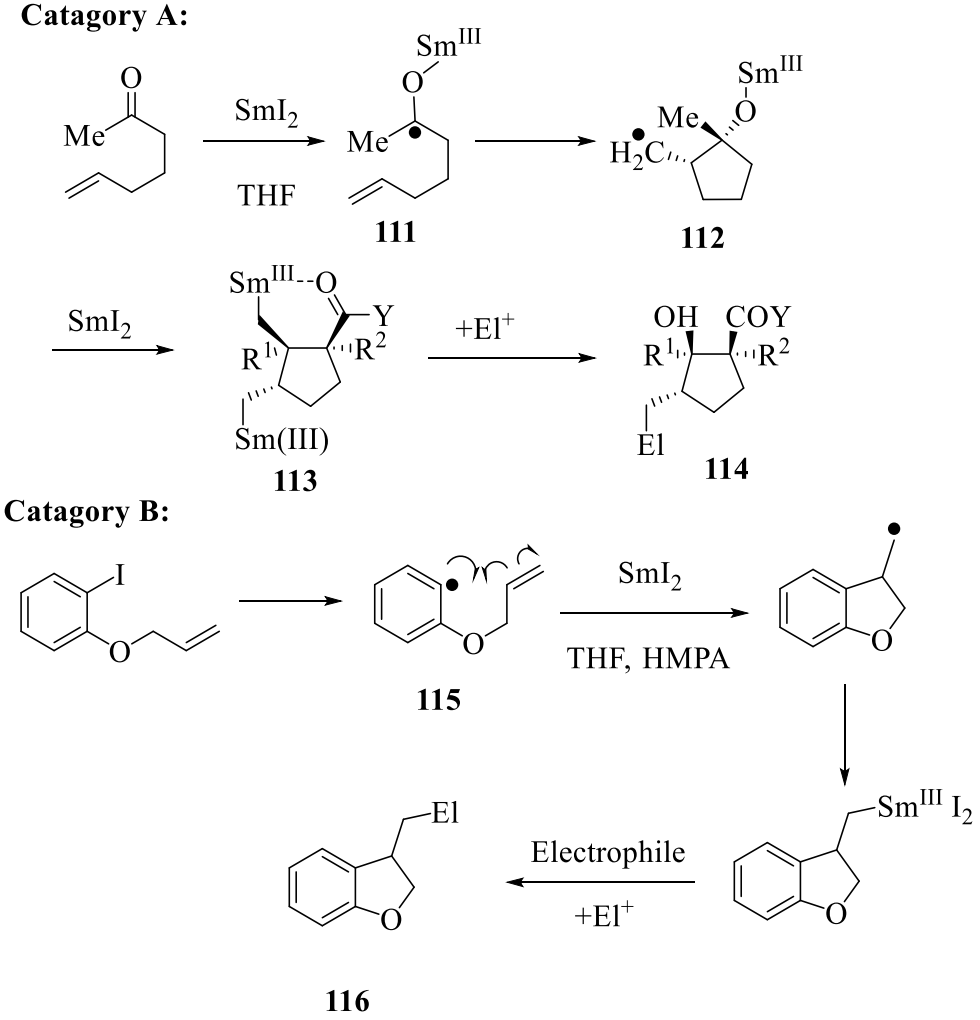
3.4.1 Samarium (II) Iodide (SmI_2)-Mediated RPC Reactions.

As stated in Section 3.3.1.1, mild and convenient procedures were promoted by lanthanide reagents.[55] A reductive cyclization was first reported by Molander, who envisioned that samarium(II) iodide (SmI_2) could provide significant advantages in terms

of its one electron reducing property and in applications to many organic transformations. [58] Taking the concept further, SmI_2-mediated RPC reactions were first developed by Molander and his former coworkers in 1991, and the whole transformation was carried out under reductive conditions.[58] Moreover, the SmI_2-mediated RPC reaction can be classified by category ketyl radical precursors (Category **A**) and aryl radical precursors (Category **B**) (Scheme 40).

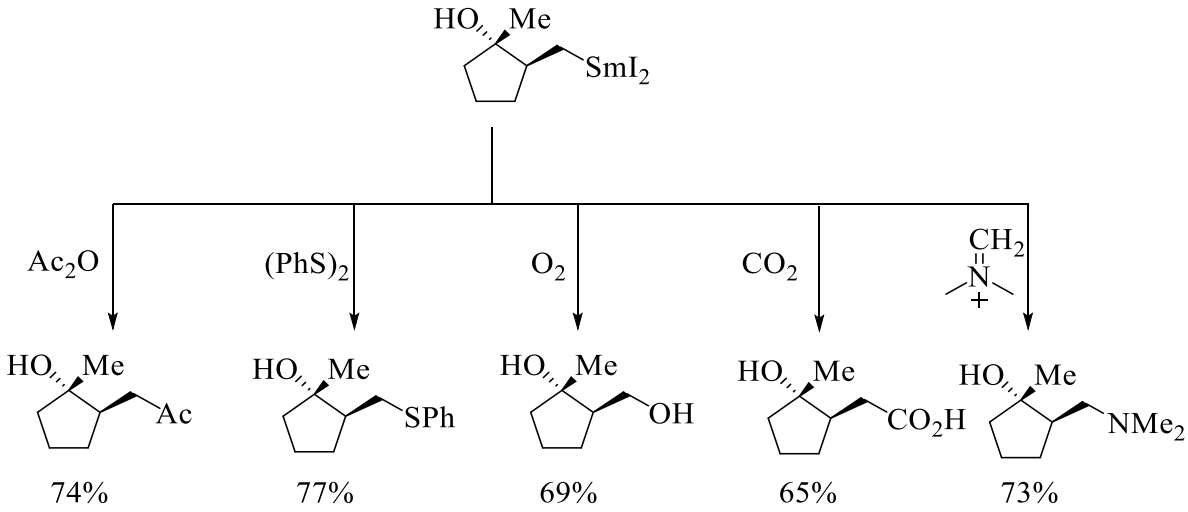
From 1991 to 1997, Molander and co-workers reported efforts on a series of publications outlining the SmI_2-mediated RPC reaction, and his discovery proved to be fruitful.[59] Scheme 40 outlines the mechanism of SmI_2-mediated RPC reaction in category A and B as mentioned above. In category A, radical **111** was initiated by reduction of SmI_2, and cyclization occurred to produce a new radical **112**, which then undergoes SET reduction by SmI_2 to afford carbanion **113**. Ultimately, addition of an electrophile finalizes this RPC transformation to afford product **114**. In category B, the step of radical initiation differs from category A, in that the radical **115** was initiated by SmI_2 via reduction of an aryl-iodide, and a series of analogous steps are followed toward the formation of final product **116**.

Scheme 40. Proposed Mechanism of SmI_2-Mediated RPC Reaction[58]



In the SmI_2-mediated ketyl RPC reaction, a variety of electrophile were used in the polar reactivity, and the installation of several representative functional groups are illustrated in Scheme 41 with a good yield (60-80%).[58, 59] In addition, the technique outlined in Category B was successfully applied to a total synthesis to of Penitrem D, which was developed by Curran.[60] The applicability of SmI_2-mediated RPC to the total synthesis of Penitrem D will be reviewed in Chapter 4.[60]

Scheme 41. Scope of Samarium (II) Iodide (SmI_2)-Mediated RPC Reactions[58, 59]



3.5 Non-Photoredox Conclusion

A series of non-photoredox-mediated RPC reactions were outlined in this chapter. The RPC reaction under non-photoredox conditions compounds provided fruitful results in [3+2] and [4+2] cycloadditions and C-C(X) bond construction. Compared to the photoredox-mediated RPC reaction, any protocol presented in non-photoredox afforded the cycloadduct as the product.

Different from photoredox mediated RPC reactions, a few cases of non-photoredox promoted RPC reactions transpire by adding stoichiometric reagents such as SmI_2 and cerium(IV).[55, 58] The stoichiometric reagents can make the transformation transpire under entirely oxidative or reductive conditions. The stoichiometric oxidant CAN cannot be recycled. Therefore, each RPC reaction promoted under stoichiometric conditions needs to have a catalyst to regenerate the oxidant/reductant for sustainability.

The RPC reaction has many foreseen advantages, including its step economy and mild reaction conditions, and this statement was confirmed in this chapter. The same can be said for photoredox-catalyzed reactions; mild conditions are predominantly employed in the non-photoredox-mediated RPC reaction, and many products generated from non-photoredox catalyzed reaction were applied to pharmaceutical chemistry, which will be described in Chapter 4. Overall, achievement of tin-free procedures and improvement by the absence of transition metals were achieved in state-of-the-art RPC reactions.

Chapter 4. Pharmaceutical Applications

A number of pharmaceutical agents can be synthesized using RPC reactions. RPC reactions might provide many practical advantages such as efficiency, good functional group tolerance, and avoidance of toxic side products. Therefore, this chapter will address the current representative pharmaceutical applications that employed photoredox- or non-photoredox-mediated RPC reactions.

4.1 Aspidospermidine

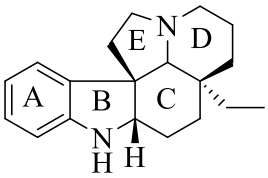
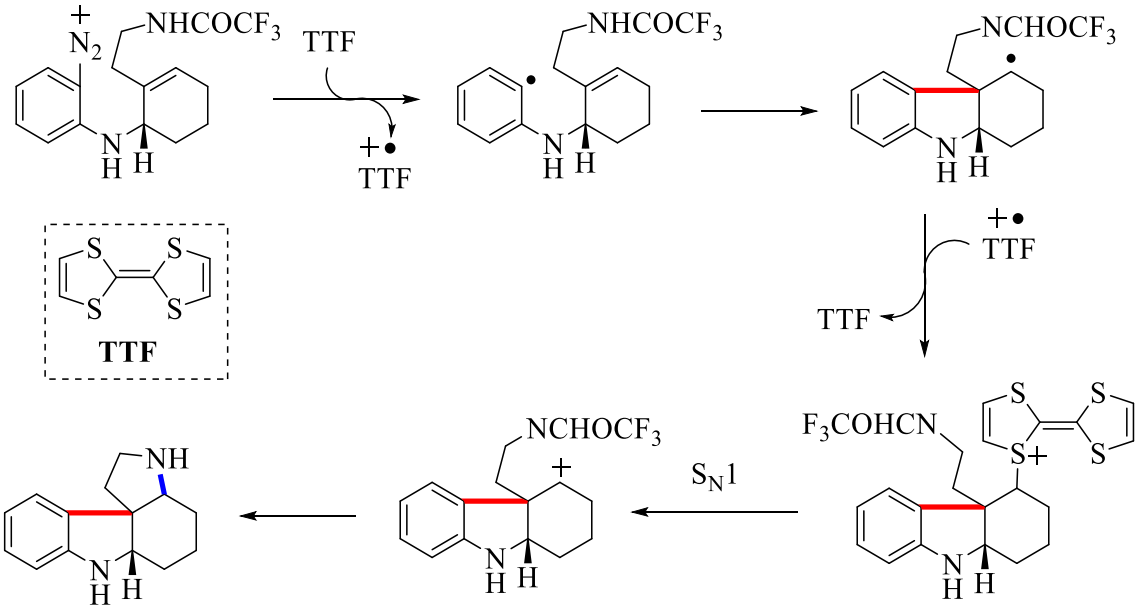


Figure 3. Structure of Aspidospermidine[62]

Aspidospermidine was first isolated from Aspidosperma, and because of its important bioactivity, it became an attractive parent structure for total synthesis.[61] In 1998, a total synthesis of the DCE-ring system of Aspidospermidine was carried out by Murphy and co-workers employing a TTF-mediated RPC reaction with an axially chiral substrate to induce enantioselectivity (Figure 3).[61] Murphy realized that among the five ring system of the parent structure Aspidospermidine, ring BCE system can be synthesized by a RPC reaction.

Scheme 42. The Construction of BCE Ring on Aspidospermidine[61]



In the work carried by Murphy, the construction of ring BCD was accomplished in a one-pot fashion at the first step of the total synthesis (Scheme 42).[61] The main catalyst chosen for this synthesis is TTF, which initiated the radical and transformed the radical adduct to a polar adduct during the synthesis.[45] The RPC reaction, which was proposed and

performed by Murphy, was successfully applied to the synthesis of aspidorspermidine with 51% yield.[61]

With the optimal conditions in hand, the synthesis of aspidorspermidine has the potential to allow scientists to synthesize a number of targets that can provide enormous pharmaceutical and clinical value, such as Vinorelbine (Figure 4), which can be targeted to treat lung cancers.[61, 63]

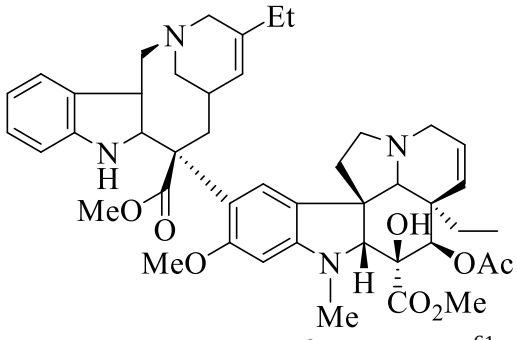


Figure 4: Structure of Vinorelbine[61]

4.2 A Highly Efficient Synthesis of the BCD-Ring System of Penitrem D

A total synthesis of the DEFG-ring system of Penitrem D was accomplished by Curran.[60] Penitrem D (Figure 5) is a molecule that has eight ring systems, and Curran and co-workers realized that the BCD ring on the molecule could be constructed by a SmI_2-mediated RPC reaction.[60]

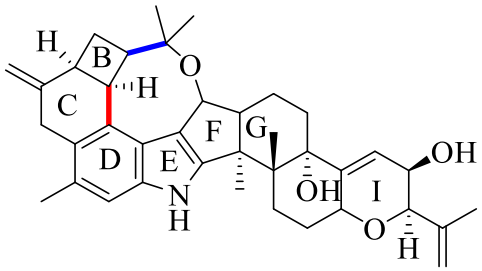
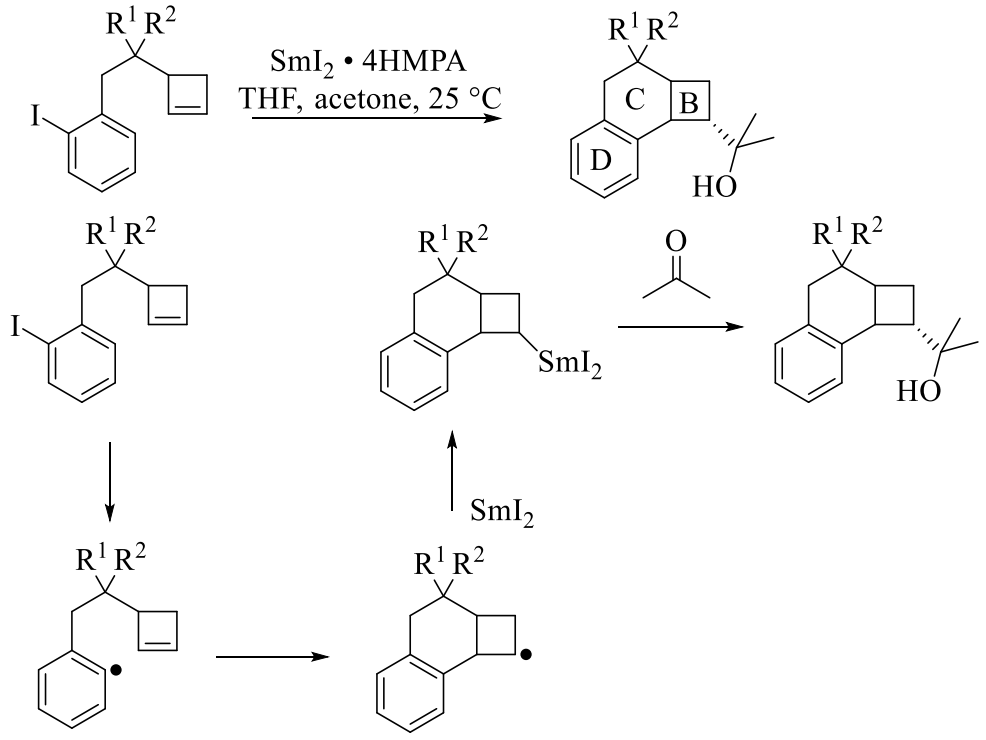


Figure 5: Structure of Penitrem D[60]

In the work designed by Curran, the construction of BCD ring become the last step of the total synthesis (Scheme 43).[60] SmI_2 was employed as the RPC reagent, and two equivalents of SmI_2 were required for the transformation. With the optimal conditions in hand, Curran examined the functional group tolerance of this method, which led to good to moderate yields of the target structures (40%-60%).[60]

Scheme 43. The Construction of BCD Ring on Penitrem D[60]



4.3 A Synthetic Pathway to Achieve the Synthesis of Lactones.

Lactones and their derivatives were extensively synthesized by the organic synthesis community, but in most methods, this sort of construction requires stoichiometric oxidants and harsh conditions.[4, 5] Therefore, a method that can enable the construction of highly substituted lactones in an efficient and environmentally friendly fashion was targeted. Liu and Fagnoni envisioned that under photoredox catalysis, many moieties with δ- and γ-lactones could be synthesized with excellent yields, high selectivities, and good functional group tolerance.[4, 5]

Because of the pharmaceutical applicability of γ-lactones as basic structural elements, Liu employed photoredox-mediated RPC reactions to achieve the construction of a variety of γ-lactones.[4] The optimal conditions selected to conduct this reaction were *fac*-Ir(ppy)$_3$, *hv* = 450 nm in CH_3CN. Under the optimal conditions, the γ-lactone moiety can be constructed in a [3+2] cycloaddition reaction via reduction before oxidation. Good to excellent yields were achieved, even as high as 99%. This process enabled the transformation to functionalized γ-lactones under mild conditions. A current limitation of Liu's protocol is that the functional group tolerance is still not high.[4] (Scheme 44)

With only 2 mol % loading of $[Ru(bpy)_3]^{2+}$, Fagnoni enabled a novel intermolecular synthesis of two typical δ-lactone moieties; isochromanone and isochromenone (Figure 6). The optimal conditions involved $[Ru(bpy)_3]Cl_2$ (2 mol %) as photocatalyst in dry MeCN. With the optimal conditions in hand, the scope of the reaction was investigated by employing a number of different substituted diazonium salts and a variety of styrenes.

Scheme 44. Synthesis of γ-and δ-lactones via Photoredox RPC Reactions[4, 5]

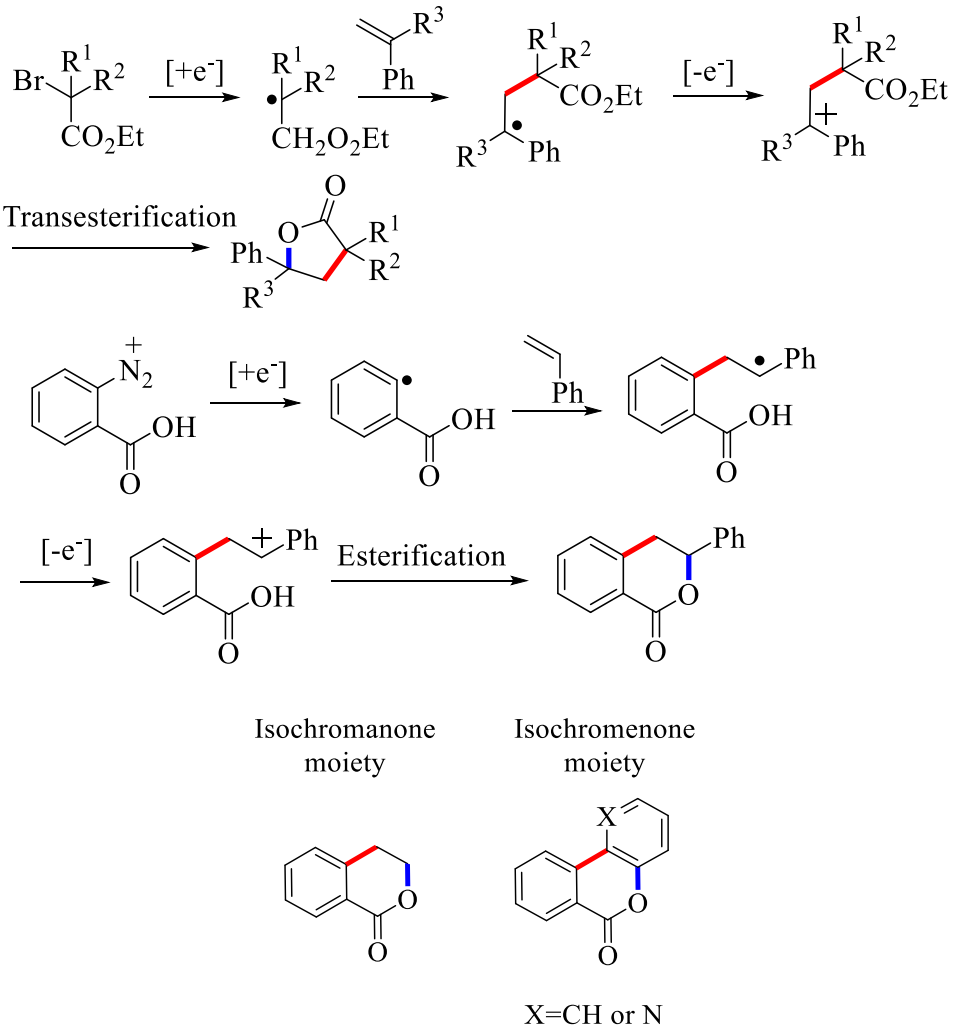


Figure 6. The Structure of Isochromanone and Isochromenone[5]

Amicoumacin A (Figure 7) is an antibiotic that can target bacterial ribosomes, and it can affect translocation and results an additional contact interface between ribosomal RNA and mRNA.[64] As a result, it may cause the death of cancer cell. Many scientists already envisioned that development of amicoumacin A and its derivatives can provide clinical value, and with the photoredox-mediated RPC reaction in hand, the construction of amicoumacin A will be achieved under mild condition and with low catalyst loading.

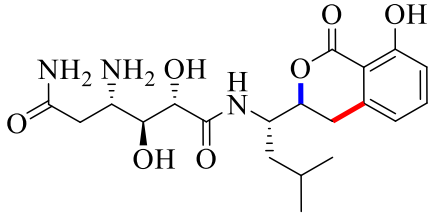


Figure 7. The Structure of Amicoumacin A[64]

Chapter 5. Conclusion

Over the past 25 years, radical-polar crossover reactions experienced an increasing role in the organic synthesis, and a number of natural product syntheses was carried out by such processes. RPC reactions provided a number of practical advantages, such as the ability to employ mild condition, increase molecular complexity, tolerate functional groups, and process in a one-pot operation.

A series of photoredox and non-photoredox catalyzed RPC reaction were investigated, and the overall results proved fruitful. The comparison of different authors' views, critical analysis of the methods, and an overall summary of literature were all described in a systematic fashion.

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