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An Asian Tiger Indeed

The Republic of Korea has become a global leader in chemistry innovation and has made significant contributions to green chemistry. The country has invested heavily in research and development (4.81% of GDP was spent on R&D in 2020 according to The World Bank) and created a supportive environment for scientists and entrepreneurs to innovate and bring new technologies and products to market. Attracted by the Republic of Korea's strong economy, highly skilled workforce, and government support, we are partnering with many universities and research institutions to support the growth of chemical-related industries. In 2016, we established the M Lab™ Collaboration Center in Songdo, providing a platform for life science customers to collaborate, and offering technical guidance and education through this center.

The country excels in many scientific fields, particularly in the development of new materials—driven by world-class research institutions and companies working on electronics, energy storage, and medical breakthroughs. We are looking forward to the Republic of Korea's innovative materials continuing to be introduced across a range of applications, from lightweight car parts to cutting-edge medical devices.

The Republic of Korea's innovative contributions in chemistry are helping to drive global progress and improve the quality of life and health for people around the world. We look forward to continuing our strong collaborations with the country's leading scientists and institutions to accelerate the transformation of the laboratory market.

Sincerely yours,

Jean-Charles Wirth
Head of Science & Lab Solutions
Global Business Unit

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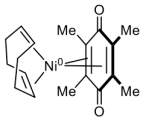
Dear Fellow Chemists,
Professor Keary M. Engle of the Department of Chemistry at The Scripps Research Institute, La Jolla, CA, kindly suggested that we offer Ni(COD)(DQ) (**912794**). This 18-electron complex is remarkably stable to heat, air, protic solvents including water, and silica gel. It serves as an excellent precatalyst in a number of classical transformations that can now be conducted outside of a glovebox. Such transformations include the Suzuki–Miyaura cross-coupling of aryls and heteroaryls, amination of aryl chlorides with secondary amines, aryl halide borylation, alkyne annulation, directed hydroarylation of unactivated alkenes, and decarboxylative cycloaddition. The products in each reaction type are obtained in generally good-to-high yields.

Tran, V. T.; Li, Z.-Q.; Apolinar, O.; Derosa, J.; Joannou, M. V.; Wisniewski, S. R.; Eastgate, M. D.; Engle, K. M. *Angew. Chem., Int. Ed.* **2020**, *59*, 7409, DOI: 10.1002/anie.202000124.



912794
Ni(COD)(DQ)

912794	Ni(COD)(DQ) [(1,5-cyclooctadiene)(duroquinone) nickel(0)], ≥95%	250 mg, 1g

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Rajeev Nair
Global Head of the Chemistry Franchise

TABLE OF CONTENTS

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Holding a Drinking Party (*주사거배*; 1805; ink on paper; 28.2 x 35.6 cm) is one of several paintings by famed Korean painter of the late Joseon era, Shin Yun-bok (신윤복; pen name Hyewon, 1758–early 19th century). Hyewon came from a family of court painters and his true-to-life depictions of ordinary Koreans—townsfolk, shamans, gisaengs—going about their daily lives offers us a window on the customs and lifestyles of the not-so-distant past that have greatly influenced modern-day Korean culture.

With this issue that highlights research from three prestigious institutions and four well-known research groups, we are raising a glass in celebration of the spectacular achievements in technology and science that The Republic of Korea has made in the past half-century, and which have turned it into one of the four Asian Economic Tigers.

Detail from ***Holding a Drinking Party.*** Photo courtesy the Kansong Art Museum, Seoul, The Republic of Korea. © Kansong Art Museum.

This painting is part of the Hyewon Pungsokdo (혜원풍속도) album at the Kansong Art Museum in Seongbuk-gu, Seoul, The Republic of Korea.

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Visible-Light-Mediated Reactions under Mild Conditions

온화한 조건의 가시광 반응

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Keywords. visible light; organo-photocatalysis; radical reaction; singlet oxygen; aerobic oxidation; oxidative bond cleavage reaction; electron donor–acceptor (EDA) complex; bioactive compound; selective synthesis; small molecule.

키워드. 가시광; 유기광촉매반응; 라디칼 반응; 활성 산소; 호기성 산화; 산화적 결합 해리 반응; 전자 주개-받개 복합체; 생리활성 화합물; 선택적 합성법; 저분자 화합물.

Abstract. Visible-light-mediated reactions have been incorporated into various organic synthesis schemes. Recently, owing to the important focus on environmental issues, the development of an environmentally friendly and mild synthetic methodology has become urgently needed. In this review, we summarize our recent approaches to developing the green mode of visible-light-mediated reactions that are available under mild reaction conditions without the use of toxic transition-metal-based catalysts or harsh reaction conditions. Relevant applications in the synthesis of valuable small molecules, including bioactive compounds, have also been highlighted.

초록. 가시광을 이용한 반응은 다양한 유기 화학 반응에 활용되고 있다. 최근, 환경 이슈의 중요성으로 인하여, 친환경적이며 온화한 반응법의 개발이 요구되고 있다. 본 리뷰에서는 최근에 본 연구실에서 개발한 온화한 조건의 가시광 반응을 이용한 합성법을 소개하고자 한다. 이와 같은 반응법은 독성이 강한 전이금속 기반의 촉매 사용을 배제하거나 가혹한 반응 조건을 최소화하여 반응을 진행하는 것을 특징으로 한다. 또한, 온화한 반응 합성법을 기반으로, 생리활성 물질과 같은 유용한 저분자 화합물 합성 응용 예시 또한 소개하고자 한다.

Outline

1. Introduction

The use of visible light to effect chemical transformations has been a long-term challenge for chemists. As an example, in 1912, Giacomo Ciamician reported "The Photochemistry of the Future" in *Science*.[1] Afterward, Kellogg provided a basis for modern photoredox catalysis by reporting a reductive amination reaction in 1978.[2] Interestingly, however, not many studies were reported until the 2010s. Recently, the visible-light-mediated photoredox catalysis has attracted a great deal

of attention in organic synthesis.[3] In these types of reactions, visible light is converted into chemical energy by engaging in single-electron transfer (SET) with substrates to generate reactive intermediates. Based on the unique reaction mode of visible-light-mediated transformations, a wide range of reactions have been developed over the past several years.

In recent years, green activation modes have been explored in this field owing to the growing interest in the development of environmentally benign synthetic methods. The most common and general approach to green photoredox catalysis is the use of organic photocatalysts. Various organo-photocatalysts, including newly developed catalysts and traditional organic dyes, such as rose bengal, eosin Y, and 4CzIPN (2,4,5,6-tetrakis(9*H*-carbazol-9-yl)-isophthalonitrile) (**Figure 1**), have been employed in numerous reactions.[3b,4]

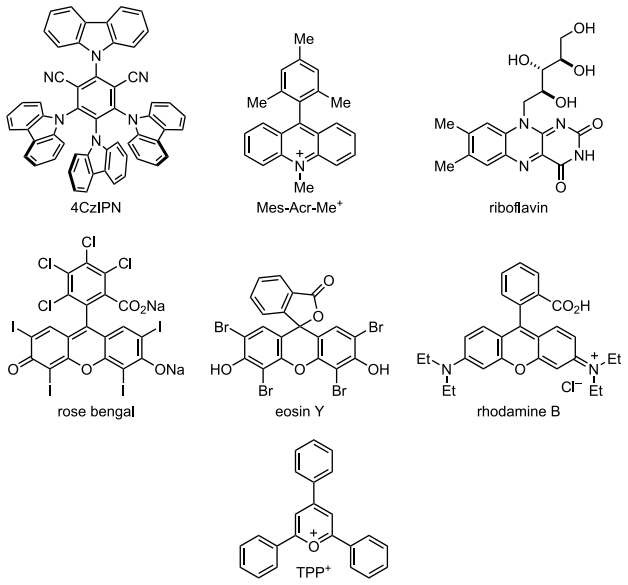


Figure 1. Examples of Common Organic Photocatalysts.

Recently, many research groups have focused on the advantages of organic photocatalysts because their structures can be modified by a rational approach to realize unprecedented reactivity or improve the catalytic activity. As an alternative green approach, catalyst-free reactions have been developed. These latter types of reaction modes include the use of photoactive starting compounds or in situ excitation of the substrates under visible-light irradiation. The substrates thus activated form electron donor–acceptor (EDA) complexes, obviating the need for photoredox catalysts.[5] This strategy relies on associating electron-donor with electron-acceptor substrates, such as Lewis bases and acids, respectively. The EDA complex can absorb visible light, undergoing an excitation process, which triggers a single-electron transfer (SET) that can generate radical intermediates. In addition to the above-mentioned approaches, green synthetic methods using natural substances such as molecular oxygen have also been studied. Our group has focused on the development of novel, visible-light-mediated reactions under mild reaction conditions. Herein, we summarize our approaches for realizing the green mode of visible-light-mediated reactions (**Figure 2**).

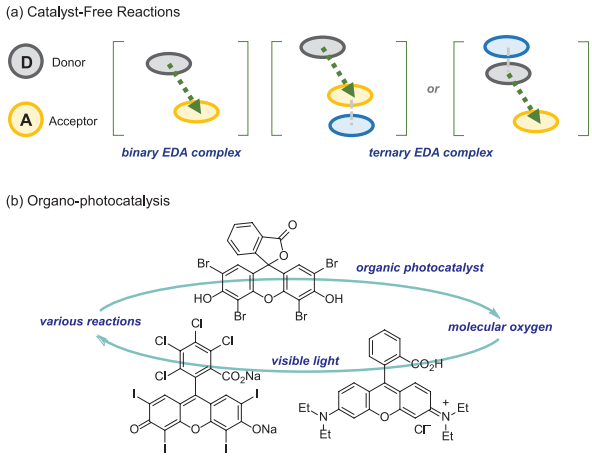


Figure 2. Our Green Approaches for the Development of Mild, Visible-Light-Mediated Reactions.

2. Development of Mild, Visible-Light-Mediated Reactions

2.1. Oxygen-Mediated Reactions

2.1.1. Aerobic Oxidation

Oxidation is one of the most important transformations in organic synthesis and often provides a facile route for the preparation of various types of building blocks. Therefore, many synthetic oxidation reactions have been reported, of which the ones that use molecular oxygen (O_2) are considered as green methods because oxygen is abundant and readily available and no by-products are formed during the reactions.[6] In general, two types of oxidation mechanisms using molecular oxygen are known: (i) direct oxidation using singlet oxygen ($^1O_2$) generated in situ via an energy transfer process, and (ii) the use of superoxide radical anion ($O_2^{\bullet-}$) species via an electron transfer process (**Figure 3**).[7] Our group has focused on the development of visible-light-mediated aerobic oxidation reactions through both reaction pathways under mild reaction conditions.

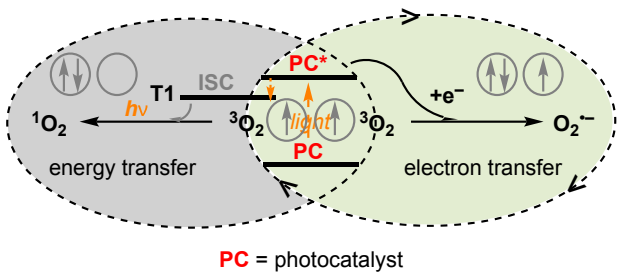


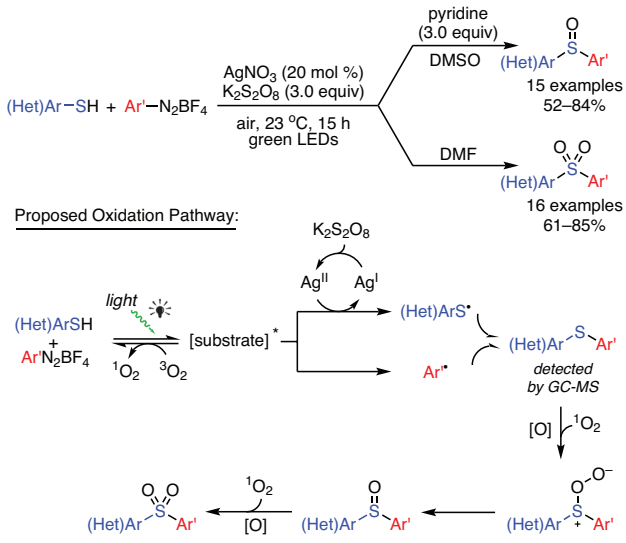
Figure 3. Aerobic Oxidation Pathways. *(Ref. 7)*

2.1.2. Aerobic Oxidation via Energy Transfer

To develop an aerobic oxidation reaction via an energy transfer pathway, we envisioned a mild, one-pot method for the selective

synthesis of diaryl sulfoxides and diaryl sulfones from aryl thiols via visible-light-induced aerobic oxidation.[8] The diaryl sulfoxide and diaryl sulfone functional groups are found in numerous bioactive compounds and drug candidates. Previously, a multistep procedure, including the stepwise oxidation of disulfides, was usually employed to prepare these compounds. Disulfide synthesis was necessary to perform the oxidation procedure in these cases. Moreover, stoichiometric quantities of oxidant are required. Recently, one-pot methods for the synthesis of aryl sulfones have been developed using organometallic reagents and iodonium salts or palladium catalysts.[9] However, toxic or sensitive catalysts and/or reagents are required.

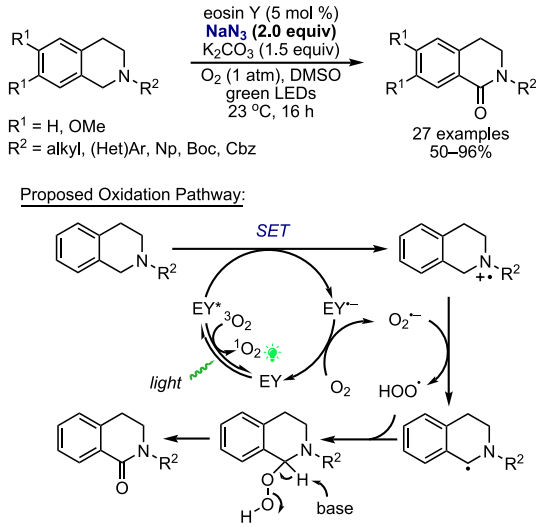
For our synthesis of diaryl sulfoxides and sulfones, we hypothesized that the oxidation process could be controlled via the generation of singlet oxygen in different chemical environments under visible-light irradiation. To test our hypothesis, we employed aryl diazonium salts and aryl thiols as starting compounds in the presence of silver nitrate as the catalyst. The silver catalyst was employed to generate thiyl radicals from thiols leading to disulfide intermediates, which could be oxidized to aryl sulfoxides or aryl sulfones via a one-pot process.[10] In this study, we found that diaryl sulfoxides were formed in the presence of pyridine in DMSO, whereas diaryl sulfones were obtained in DMF through further oxidation (**Scheme 1**).[8] Moreover, diaryl sulfides were formed as intermediates and singlet-oxygen-induced oxidation provided the desired products. The fact that the rate of singlet-oxygen deactivation depends on the chemical environment, such as solvents or additional radical sources, could explain the selective formation of sulfoxides in DMSO and sulfones in DMF.[11] Furthermore, amines are well-known single-electron reservoirs used in many radical-mediated reactions.[12] Therefore, the addition of pyridine proved beneficial for this selective oxidation process.



Scheme 1. Selective Aerobic Oxidation for the Synthesis of Diaryl Sulfoxides and Diaryl Sulfones. *(Ref. 8)*

2.1.3. Aerobic Oxidation via Electron Transfer

We took advantage of the electron-transfer pathway in the aerobic α-oxidation of N-substituted tetrahydroisoquinolines to dihydroisoquinolones by using eosin Y as an organic photocatalyst.[13] Dihydroisoquinolones possess several important biological characteristics and have been valuable precursors in organic synthesis. Interestingly, we found that the generation of singlet oxygen in this transformation led to the formation of byproducts. Therefore, the addition of a singlet-oxygen quencher (NaN_3)[14] was beneficial for suppressing the formation of byproducts and improving yields. The generation of superoxide radical anions was confirmed by EPR[15] studies in which the radical trapping agent DMPO (5,5-dimethyl-1-pyrroline *N*-oxide) was added. Moreover, based on additional mechanistic studies, such as catalyst quenching experiments, we proposed the mechanism depicted in **Scheme 2**.[13] Under visible-light irradiation, eosin Y (EY) produces an excited species of the catalyst (EY*). The aminyl cation radical and $EY^{\bullet -}$ are generated via a single-electron transfer (SET) from tetrahydroisoquinolines to the excited state of eosin Y (EY*). A subsequent reaction between oxygen and $EY^{\bullet -}$ provides the superoxide radical anion ($O_2^{\bullet -}$), which would react with the aminyl cation radical. Following reaction with the hydroperoxyl radical ($HOO^{\bullet}$) and proton abstraction by base yields the dihydroisoquinolone product. The examples in this and the previous sections show that the generation or suppression of singlet oxygen is critical for controlling the overall aerobic oxidation pathway.

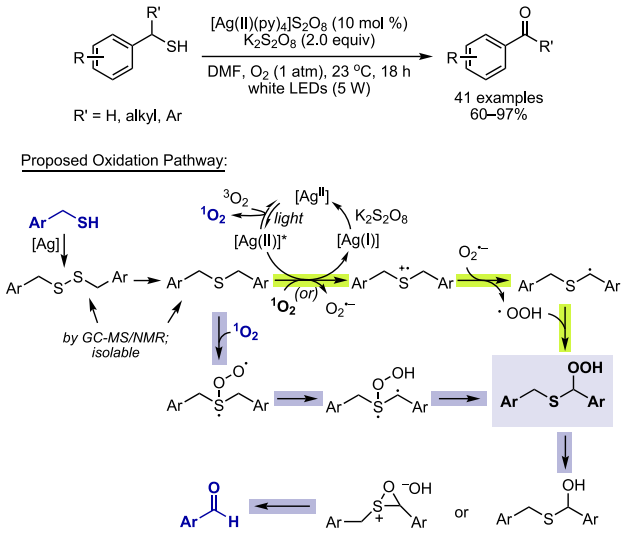


Scheme 2. Electron-Transfer Aerobic α-Oxidation of N-Substituted Tetrahydroisoquinolines to Dihydroisoquinolones. *(Ref. 13)*

2.1.4. Oxidative Bond Cleavage

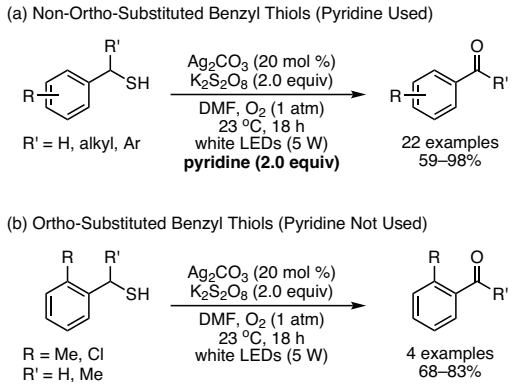
While the most common application of singlet oxygen in organic reactions is oxidation, its use has been extended to other organic transformations such as oxidative bond-cleavage reactions.[16] In 1976, Corey and Ouannès reported the first C–S bond cleavage using singlet oxygen.[17] Other research groups have also reported C–S bond-cleavage reactions with singlet oxygen starting from sulfides.[18] However, these reactions were

challenging: the reaction yields were low and various side products were observed. The main reason for this failure is the difficulty in controlling the singlet oxygen species during the reaction. Thus, we focused on developing a mild, oxidative bond-cleavage reaction under visible-light irradiation by utilizing Ag(II)–ligand complexes. Remarkably, Ag(II)–ligand complexes have rarely been employed as catalysts in organic synthesis despite the well-established syntheses of silver complexes in inorganic chemistry.[19] Our investigations showed that Ag(II) complexes can catalyze the oxidative C–S bond cleavage of benzyl thiols to selectively afford the desired products in good-to-excellent yields under irradiation with white LEDs (5 W).[20] We also found that disulfide and sulfide were subsequently formed as intermediates, followed by further oxidative cleavage pathways to afford the desired carbonyl compounds. Based on our experimental results, we proposed the reaction mechanism depicted in **Scheme 3**.[20]



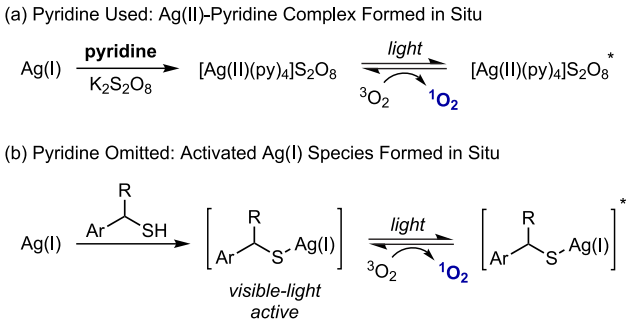
Scheme 3. Oxidative C–S Bond Cleavage Reaction. *(Ref. 20)*

In this study, the preparation of Ag(II)–ligand complexes was necessary. However, we were curious if we could further improve the reaction by forming the silver catalyst in situ. Therefore, we developed an in situ activated reaction system to generate C–S bond cleavage products under mild conditions.[21] After experimenting with various reaction conditions, we found that the Ag(II) complex was best generated in situ in the presence of silver carbonate, potassium persulfate, and pyridine. EPR studies were performed to confirm the formation of the Ag(II)–ligand complex. Most benzyl thiols readily underwent this transformation under these reaction conditions. Interestingly, unexpected reaction pathways and results were also observed, depending on the structure of the substrate as in the case of ortho-substituted benzyl thiols for which no desired products were obtained. In contrast, *ortho*-substituted benzyl thiols provided the desired carbonyl products in better yields in the absence of pyridine. In the case of ortho-substituted benzyl thiols, the addition of pyridine suppressed the formation of disulfides, which are key intermediates in this transformation. Therefore, two different optimized conditions were employed for the reaction, depending on the structure of the substrate (**Scheme 4**).[21]



Scheme 4. Oxidative C–S Bond Cleavage under Mild Conditions through an in Situ Activation Strategy. *(Ref. 21)*

In the absence of pyridine, we proposed that the Ag(I) catalyst generates a thiyl radical from thiol to form a disulfide and sulfide. These intermediates then react with singlet oxygen, which is generated by visible light from dioxygen and activated silver(I) thiolate, to provide the desired products (**Scheme 5**, conditions (b)).[21]



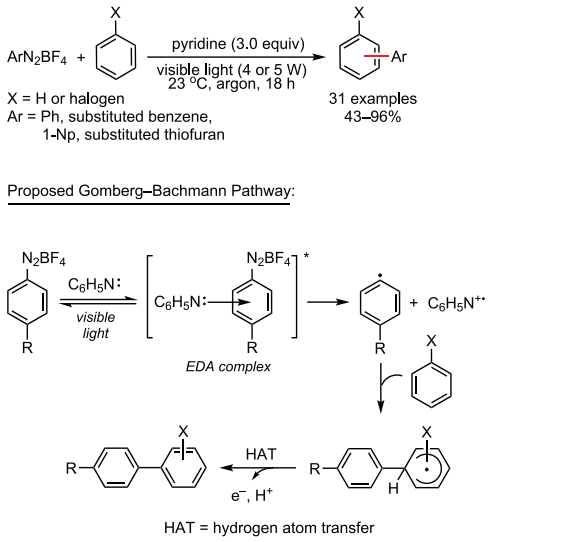
Scheme 5. Proposed in Situ Visible-Light Activation of the Catalyst in the Oxidative C–S Bond Cleavage Reaction. *(Ref. 21)*

Similarly, Jain's group recently reported a singlet-oxygen-mediated tandem C–C and C–N bond cleavage reaction under visible light irradiation using eosin Y.[22]

2.2. Catalyst-Free Reactions via Electron Donor–Acceptor Complex Formation

One approach for implementing an environmentally benign visible-light-mediated transformation may include methods that use organic photocatalysts or mild metal catalysts. However, the ultimate goal would be to develop a method that minimizes the use of a catalyst or reagent. The visible-light-mediated reaction could be performed without a photocatalyst by taking advantage of the excited state of the substrate. In such a method, the substrate acts as a photocatalyst through the formation of an

electron donor–acceptor (EDA) complex as in our synthesis of biaryl compounds,[23] which our group synthesized via a novel visible-light-promoted Gomberg–Bachmann reaction.[24] The reaction does not require a photocatalyst or any metal reagent and takes place through the formation of an EDA complex to give the desired biaryls in moderate-to-high yields **(Scheme 6)**.[23,]



Scheme 6. Catalyst-Free Gomberg–Bachmann Reaction. *(Ref. 23)*

To understand the reaction mode, we carried out a variety of mechanistic studies. The stoichiometry of the donor–acceptor complex was investigated by constructing a Job plot.[25] In this study, we found that the ratio of aryl diazonium salt to pyridine was 1:1 in the EDA complex (**Figure 4**, Part (a)). In addition, the association constant, K_{EDA} (K_{EDA} = 18.01), for the formation of the EDA complex was determined using the Benesi–Hildebrand method (Figure 4, Part (b)).[26]

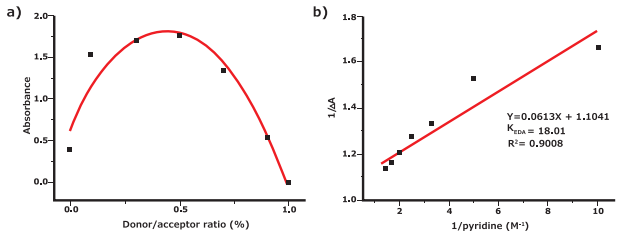
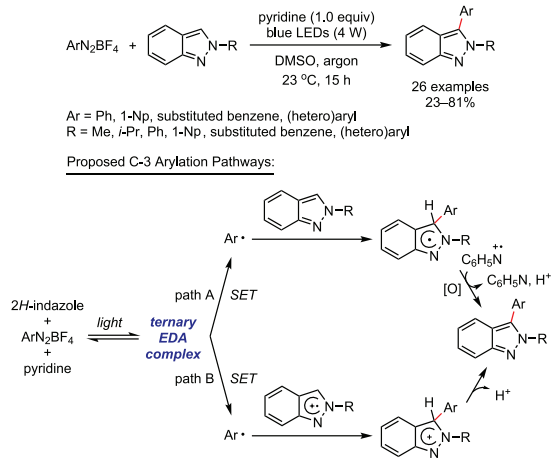


Figure 4. Mechanistic Studies of the Gomberg–Bachmann Reaction. Reproduced with permission from ref 23. Copyright 2019 American Chemical Society.

In this study, the EDA complex was a representative binary system that involved one electron donor and one electron acceptor. More complicated EDA complexes such as ternary or quaternary systems also exist.[27] However, there exist some challenges and limitations in proving the formation of a more complex EDA system. Thus, reactions via multiplex EDA complexes have rarely been reported, even though a substantial number of reactions may proceed by such a pathway. To overcome such limitations, we developed the arylation of 2*H*-indazoles via a visible-light-induced process in the absence of a photocatalyst through the formation of a ternary EDA complex **(Scheme 7)**.[28]



Scheme 7. Direct C-3 Arylation of 2*H*-Indazoles in the Absence of a Photocatalyst and through the Intermediacy of a Ternary EDA Complex. *(Ref. 28)*

To confirm the formation of the ternary EDA complex in the reaction, we carried out various mechanistic studies. UV–vis spectra confirmed that pyridine, aryl diazonium salts, and 2*H*-indazoles were involved in the formation of the EDA complex. For example, when a solution of aryl diazonium salt in DMSO was treated with 2*H*-indazole, the color of the mixture changed to yellow, and a clear bathochromic shift was observed in the UV–vis spectrum, which is characteristic of an EDA complex. A significant bathochromic shift was also observed for a mixture of 2*H*-indazole and pyridine in DMSO. Interestingly, a mixture of the aryl diazonium salt, 2*H*-indazole, and pyridine showed a further bathochromic shift, thereby suggesting the formation of a ternary EDA complex **(Figure 5)**.[28]

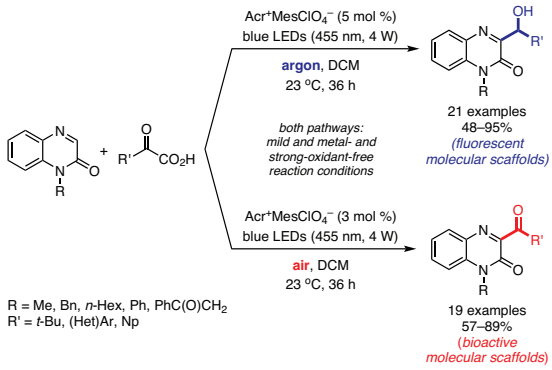
Furthermore, a Job plot showed that the ratio of pyridine to aryl diazonium salt was 1:1, and the ratio of 2*H*-indazole to aryl diazonium salt was 1:1. Therefore, we assumed that these components (aryl diazonium salt, 2*H*-indazole, and pyridine) comprise the EDA complex in a 1:1:1 ratio. Further NMR studies, including NOESY and DOSY, were also performed. We observed the interaction between 2*H*-indazole and aryl diazonium salt, and between aryl diazonium salt and pyridine by NOESY. In the DOSY studies, the diffusion coefficient (D value) decreased when we measured the mixture of 2*H*-indazole/aryl diazonium salt, aryl diazonium salt/pyridine, and 2*H*-indazole/aryl diazonium salt/pyridine. In contrast, the D value did not decrease in the mixture of 2*H*-indazole and pyridine. This led to the conclusion that pyridine and 2*H*-indazole acted as electron donors and did not form an EDA complex. Nevertheless, further studies that measure multiplex EDA complexes directly are required to gain a deeper insight into this phenomenon.

3. Synthesis of Valuable Small Molecules under Visible-Light Irradiation

3.1. Selective Synthesis of C-3 Functionalized Quinoxalin-2(1*H*)-ones

Applying our green approaches, we synthesized valuable small molecules under visible-light irradiation. For example, quinoxalin-2(1*H*)-ones derivatized at the C-3 position demonstrate interesting bioactivity, such as antitumor and pteridine reductase inhibitory properties. Various methods have been proposed for the synthesis of C-3 functionalized quinoxaline-2(1*H*)-ones. However, mild and efficient approaches are still required for the synthesis of these compounds. In addition, despite the availability of various protocols for the synthesis of acylated quinoxalin-2(1*H*)-ones, the direct synthesis of hydroxyl-containing quinoxalin-2(1*H*)-ones has rarely been reported. Moreover, the photophysical properties of these derivatives have been overlooked, even though hydroxyl-containing quinoxalin-2(1*H*)-ones could exhibit important fluorogenic properties **(Figure 6)**.[29]

Encouraged by the preceding observations, we developed a switchable, visible-light-mediated synthesis of C-3 functionalized quinoxalin-2(1*H*)-ones by employing 9-mesityl-10-methylacridinium perchlorate as an organic photocatalyst **(Scheme 8)**.[29] We demonstrated that the selective synthesis of hydroxyl- and acyl-containing quinoxalin-2(1*H*)-ones under mild reaction conditions was possible—without the use of any metal catalysts or toxic reagents—by controlling the atmosphere (argon vs air) under which the reaction is carried out.



Scheme 8. Selective Synthesis of C-3 Functionalized Quionxalin-2(1*H*)-ones. *(Ref. 29)*

We anticipated that the hydroxyl-containing products could be utilized as fluorophores for non-fluorescent compounds. To this end, product **A (Scheme 9)** was covalently attached to carvacrol, a non-fluorescent antibacterial natural product.[29] The resulting product, **B**, showed strong fluorescence as expected. This proof-of-concept demonstrated that hydroxyl-containing quinoxalin-2(1*H*)-ones could be employed as effective fluorescent

Figure 5. Mechanistic Studies of the Direct C-3 Arylation of 2*H*-Indazoles. Adapted with permission from ref 28. Copyright 2019 Royal Society of Chemistry.

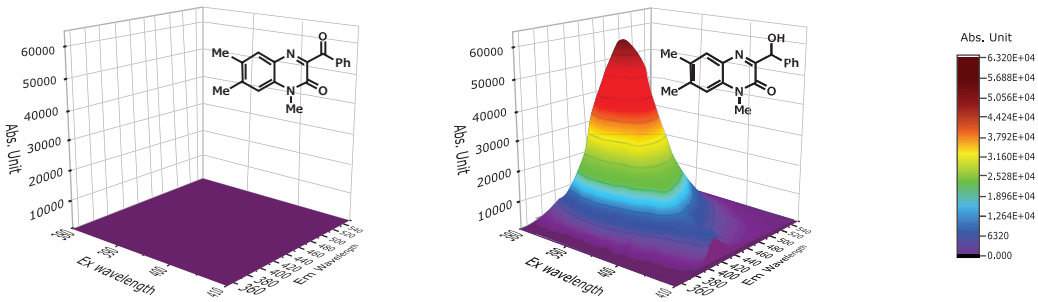
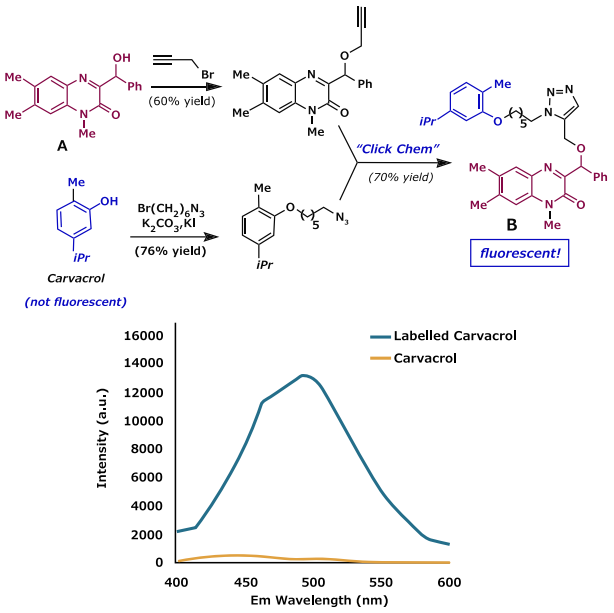
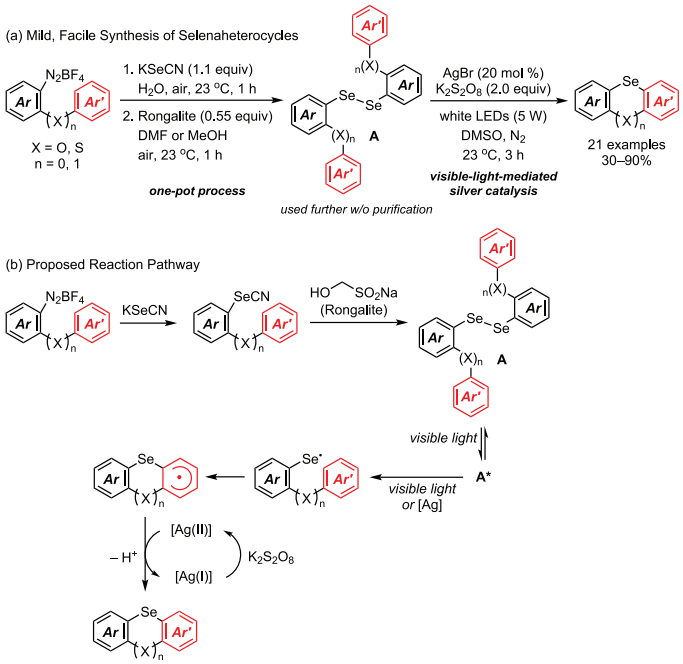


Figure 6. Fluorescent Property of Hydroxy-Containing Quinoxalin-2(1*H*)-ones. Reproduced with permission from ref 29. Copyright 2021 Wiley-VCH GmbH.

labels for a variety of non-fluorescent bioactive molecules.



Scheme 9. Fluorescent Labeling Experiments. Reproduced with permission from ref 29. Copyright 2021 Wiley-VCH GmbH.



Scheme 10. A Novel and Green Method for the Synthesis of Selenaheterocycles. *(Ref. 30)*

3.2. Synthesis of Selenaheterocycles via Intramolecular Radical Cyclization

The preparation of organoselenium compounds is an important topic in organic synthesis because these compounds possess significant biological activities such as antitumor, antiviral, antioxidant, and antimicrobial properties. Moreover, because of the unique electronegativity of the selenium atom, organoselenium compounds can be employed as electron donors or hydrogen-bond acceptors in materials chemistry. Most of the previously reported methods require the use of toxic and/or sensitive catalysts or reagents under sensitive and/or harsh reaction conditions. The main reason for this might be that diselenides have traditionally been utilized as starting materials. In addition, the synthesis of diselenides is challenging and generally requires sensitive or harsh reaction conditions. Based on this research background, we envisioned that selenaheterocycles could be synthesized using aryl diazonium salts as starting compounds in a one-pot process. In this regard, we showed that a one-pot process for generating the diselenide intermediates from aryl diazonium salts is possible. Moreover, we demonstrated that, in the presence of a silver catalyst, the visible-light-mediated intramolecular cyclization of diselenides affords the desired selenaheterocycles in generally good yields (Scheme 10).[30]

Based on mechanistic studies, we proposed the reaction pathway in Scheme 10. The reaction between the aryl diazonium salt and potassium selenocyanate generates the aryl selenocyanate in situ. Reaction of the latter with Rongalite forms the diselenide intermediate (**A**). Following formation of the selenyl radical by the silver catalyst or visible-light irradiation, an intramolecular radical cyclization and oxidation sequence takes place to afford the desired selenaheterocyclic product.

4. Conclusion and Outlook

The development of green synthetic methods is an important goal in the field of visible-light-mediated reactions. In this short review, we introduced our approaches for carrying out valuable organic transformations under mild reaction conditions such as visible-light-mediated aerobic oxidations using molecular oxygen. Additionally, we expanded the scope of singlet-oxygen-mediated reactions by developing oxidative C–S bond cleavage reactions. Moreover, using EDA complex-based synthetic strategies, we developed catalyst-free reactions through the intermediacy of binary or ternary EDA complexes. Various mechanistic studies have been conducted to understand the reaction mechanisms. However, further studies are required to directly analyze EDA complexes. In this review, applications of these approaches to the synthesis of valuable small molecules were also highlighted. Further studies are in progress in our laboratory to develop novel visible-light-mediated syntheses based on green approaches. Future directions would include the structural modification of organic photocatalysts and the development of novel visible-light-active starting compounds to expand the range of available reactions in this field.

5. Acknowledgments

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About the Author

Anna Lee received her Ph.D. degree in 2012 from the Max-Planck-Institut für Kohlenforschung in Germany under the supervision of Professor Benjamin List. After completing two years of postdoctoral research with Professor Karl A. Scheidt at Northwestern University in the United States (2013–2014), she started her independent research as an assistant professor at Myongji University in Korea. In 2020, she accepted an associate professor position at Jeonbuk National University in Korea. Her current research interests include the development of novel organic reactions and catalysis under mild conditions.

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Asymmetric Catalysis with Chiral Oxazaborolidinium Ions (COBIs): from Cyclization to Radical Reactions

카이랄 옥사자보롤리디늄 이온 (COBI)을 이용한 비대칭 촉매반응: 고리화반응부터 라디칼 반응까지


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Keywords. Lewis acid; asymmetric catalysis; COBI; dipolar cycloaddition; cyclopropanation; rearrangement; epoxidation; radical addition; photochemical reaction; electron donor–acceptor complex.

키워드. 루이스산; 비대칭 촉매반응; 코비; 쌍극자 고리부가반응; 삼각고리화반응; 재배열; 에폭사이드화반응; 라디칼 첨가반응; 광화학반응; 전자 주개-받개 복합체.

Abstract. Chiral Lewis acid catalysts are some of the most powerful and efficient catalysts for asymmetric synthesis. Among the various Lewis acid catalysts known, the chiral oxazaborolidinium ion (COBI) has proven widely applicable to a variety of asymmetric transformations, such as the Diels–Alder reaction, nucleophilic additions, and cycloadditions. In this review, we introduce our recent work on COBI-catalyzed asymmetric reactions, including cyclopropanation, epoxidation, and radical reactions.

초록. 카이랄 루이스산촉매들은 비대칭 촉매 반응을 위해 개발 되어진 가장 강력하고 효율적인 촉매들이다. 알려진 다양한 루이스산 촉매 중 카이랄 옥사자보롤리디늄 이온 (COBI)는 딜스-알더 반응, 친핵체 첨가반응과 고리부가반응들을 포함한 여러가지 종류의 비대칭 변환들에 광범위하게 적용되어져왔다. 이 리뷰에서는 COBI 촉매를 이용한 삼각고리화반응, 에폭사이드화 반응 그리고 라디칼 반응 등을 포함한 최근에 응용된 비대칭 반응들에 대해 소개하고자 한다.

Outline

1. Introduction

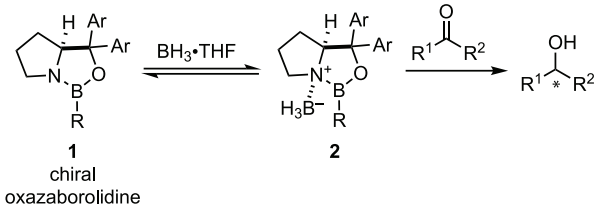
Asymmetric synthesis is one of the most important types of organic synthesis, because the majority of therapeutic compounds and bioactive natural products exist in one enantiomeric form.[1] The utilization of chiral auxiliaries or chiral reagents can be a good strategy for the asymmetric synthesis of chiral compounds,[2] but suffers from the need to

use stoichiometric amounts of the auxiliary or reagent. For this reason, asymmetric catalysis is an attractive and advantageous alternative for accessing enantiomerically enriched/pure compounds.[3]

Lewis acids have a long history of being employed as catalysts in the field of organic synthesis.[4] However, their true power and relevance as highly efficient asymmetric catalysts have only been recognized in the past several decades. Consequently, a large number of chiral Lewis acid catalysts have been developed and cover almost all the metals in the periodic table.[5]

In particular, after the first report in 1976 of an enantioselective catalytic Diels–Alder reaction with a chiral boron complex,[6] numerous chiral boron complexes have been designed and used extensively for catalyzing various cycloadditions, cyclizations, carbonyl reductions, and rearrangement reactions.[7]

The asymmetric reduction of prochiral ketones catalyzed by proline-derived chiral oxazaborolidines of type **1** was developed independently by Itsuno and Corey in 1981 and 1987, respectively **(Scheme 1)**.[8,9] This process, commonly referred to as the Corey–Itsuno reduction or Corey–Bakshi–Shibata (CBS) reduction, has proven effective in a large number of synthetic applications that have been reported in subsequent decades.[10,11]

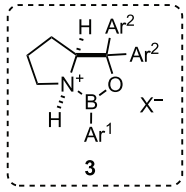


Scheme 1. Corey–Itsuno or Corey–Bakshi–Shibata (CBS) Reduction. *(Ref. 8,9)*

Since it was first reported by Corey in 2002,[12,13] the chiral oxazaborolidinium ion (COBI) has been used as a strong Lewis acid. COBI catalysts activated by Brønsted[12,14] or Lewis acids,[15]—referred to as combined acid catalysts[13c]—exhibit higher catalytic activity and stereoselectivity than the individual acid catalysts through enhancement of their acidity by attachment of the Brønsted or Lewis acid. Representative structures of COBI catalysts that we discuss in this review are shown in **Figure 1.**

A large number of enantioselective Diels–Alder reactions were developed using cationic oxazaborolidines to produce enantioenriched cyclized products, and these results were reviewed in 2002 and 2009 by E. J. Corey.[13a,b] In addition, various asymmetric nucleophilic 1,2- or 1,4-additions to carbonyl compounds have been developed with COBI catalysts, and the results were reviewed in 2019 by our group.[16] In this review, we highlight recent advances in the use of COBI catalysts to carry out the asymmetric formation of cyclic compounds (excluding Diels–Alder adducts) as well as enantioselective radical reactions.

All asymmetric reactions in this review have been shown to proceed via one of three pretransition-state assembly models of the COBI catalyst with carbonyl compounds **(Figure 2)**.[16] Thus, the stereochemistry of the asymmetric reactions can be rationalized based on one of these assembly models.



3	Ar^1	Ar^2	X
a	Ph	3,5-$Me_2C_6H_3$	TfO
b	Ph	2,3-$Me_2C_6H_3$	TfO
c	2-MeC_6H_4	3,5-$Me_2C_6H_3$	TfO
d	2-$F_3CC_6H_4$	3,5-$Me_2C_6H_3$	TfO
e	2-(*i*-PrO)C_6H_4	3,5-$Me_2C_6H_3$	TfO
f	1-Np	3,5-$Me_2C_6H_3$	TfO
g	1-Np	2-Np	TfO
h	1-Np	2,3-$Me_2C_6H_3$	TfO
i	Ph	Ph	Tf_2N
j	Ph	3,5-$Me_2C_6H_3$	Tf_2N
k	2-(*i*-Pr)C_6H_4	3,5-$Me_2C_6H_3$	Tf_2N
l	4-$F_3CC_6H_4$	2,3-$Me_2C_6H_3$	Tf_2N

Figure 1. Representative Known COBI Catalysts.

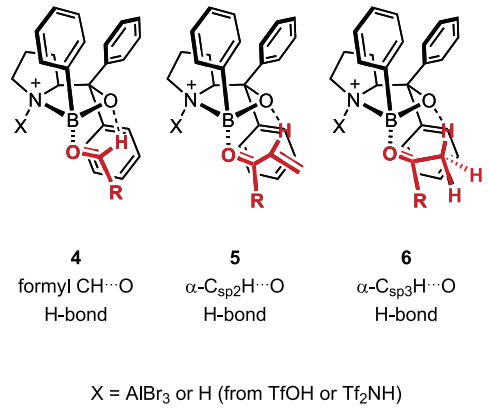


Figure 2. Pretransition-State Assembly Models for Reactive Complexes of COBI and Carbonyl Compounds. *(Ref. 16)*

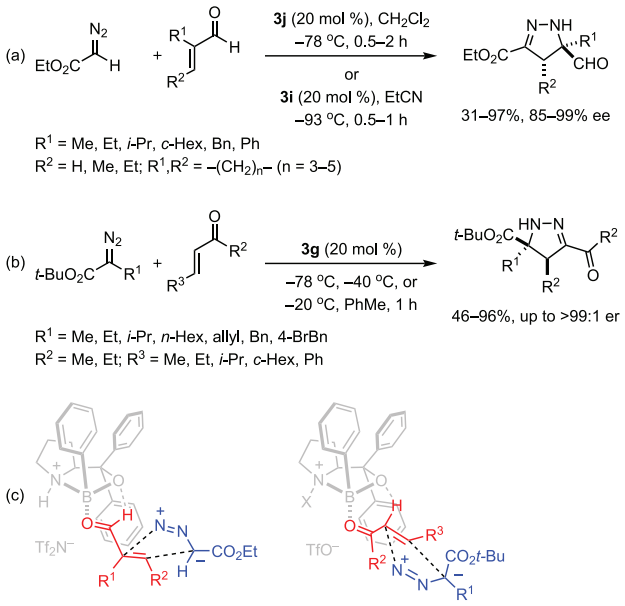
Complexes of COBI with carbonyl compounds are proposed to possess a Lewis base–acid interaction between the carbonyl oxygen and boron atom of the COBI catalyst. Synergistically, the formyl CH···O (**4**) and α-CH···O (**5** and **6**) hydrogen bonding restricts rotation of the bond between the boron atom and the carbonyl oxygen atom, which results in more rigid COBI-carbonyl complexes.[17] In the pretransition-state models, the electron-deficient carbonyl carbon or the β-carbon of the α,β-unsaturated carbonyl compound is positioned above one of the geminal aromatic groups of COBI through a π–π donor–acceptor interaction. Moreover, the pseudoaxial aromatic ring of the catalyst effectively shields the rear face of the carbonyl compound from attack by nucleophiles and directs addition of the nucleophile to the front face.

2. Asymmetric Synthesis of Chiral Cyclic Compounds with the COBI Catalyst

Cyclic compounds, including aromatic and non-aromatic ring systems, exist in nearly all natural products, therapeutic candidates, and medicinal drugs. Consequently, the construction of different types of cyclic compounds has been a central theme in organic synthesis, and has received great attention over several decades.[18] In particular, the enantioselective assembly of chiral cyclic compounds has become one of the most important topics in modern organic synthesis because of the prevalence of chiral cyclic skeletons in natural products and pharmaceuticals.[19] However, since not all sizes of cyclic compounds are equally accessible because of enthalpic and entropic effects, a large number of asymmetric synthetic strategies have been developed for forming chiral cyclic compounds, including ring-closing metathesis (RCM),[20] cycloaddition,[21] Diels–Alder reaction,[13a,b,22] Nazarov cyclization,[23] and radical cyclization.[24] Our research group has focused on developing COBI-catalyzed asymmetric synthetic methods for synthesizing various chiral carbocycles and heterocycles of different ring sizes.

2.1. 1,3-Dipolar Cycloadditions

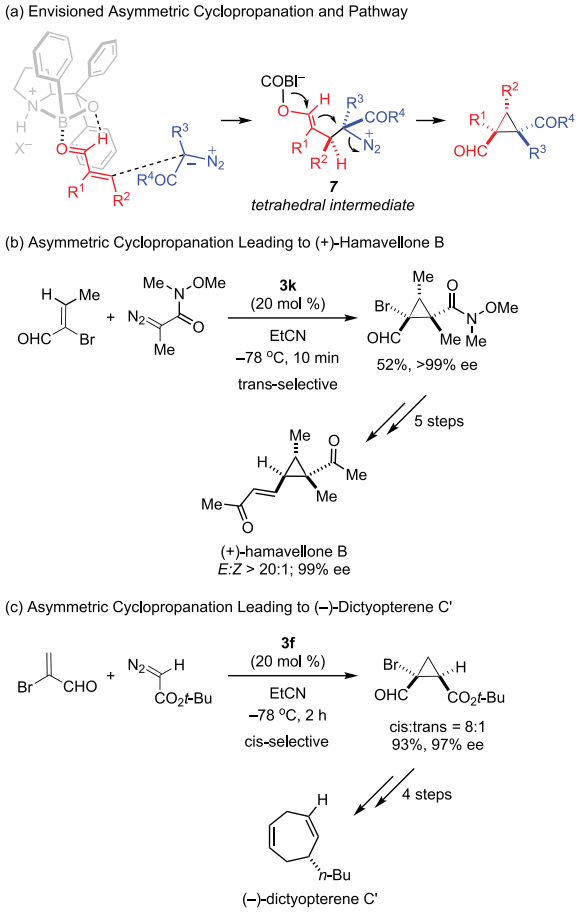
Pyrazolines are highly valuable heterocyclic scaffolds, and a variety of pyrazoline-containing molecules exhibit a broad spectrum of biological activity and some are clinically approved drugs.[25] Since Kanemasa and Kanai's first report of chiral Lewis acid catalyzed asymmetric formation of pyrazolines in 2000,[26] a few asymmetric synthetic methods using Lewis acid catalysts have been developed to generate chiral pyrazolines via a 1,3-dipolar cycloaddition.[27] However, these methods suffer from limited substrate scope and poor atom economy. Therefore, we envisioned utilizing COBI catalysis for the synthesis of chiral pyrazolines via an asymmetric 1,3-dipolar cycloaddition of alkyl diazoacetates to α,β-unsaturated aldehydes (acroleins) (**Scheme 2**, Part (a)).[28] This catalytic route provided highly functionalized chiral 2-pyrazolines in high yields (up to 97%) and excellent enantioselectivities (up to 99% ee). Furthermore, we considered whether α,β-unsaturated ketones (enones), which form pretransition-state complexes with COBI catalysts that are distinct from that of acrolein, could be used as dipolarophiles to construct chiral 2-pyrazolines. We found that the asymmetric cycloaddition with enones worked well in the presence of COBI **3g**, producing enantioenriched products in good yields (up to 96%) and ee's (up to > 99:1 er) (Scheme 2, Part (b)).[29] The observed stereochemistry of these reactions can be rationalized by formation of rigid COBI complexes with acrolein or enones (as described in **4** and **5** in Figure 2) and 1,3-dipolar cycloaddition of the diazo compounds to the front face of the α,β-unsaturated carbonyl compound (Scheme 2, Part (c)).



Scheme 2. COBI-Catalyzed Asymmetric 1,3-Dipolar Cycloaddition of Alkyl Diazoacetates to α,β-Unsaturated Carbonyls. *(Ref. 28,29)*

2.2. Cyclopropanations

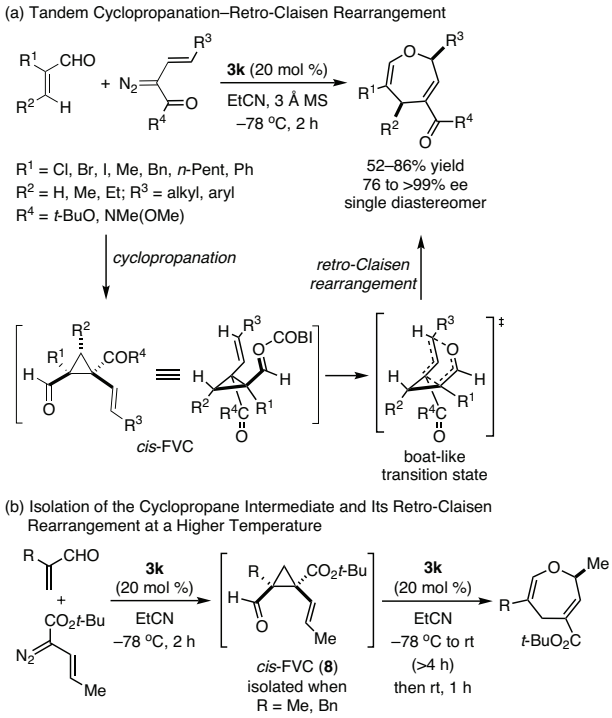
Following Corey's seminal work on the asymmetric 1,4-addition of silyl ketene acetals to enones,[30] we hypothesized that COBI could catalyze the asymmetric 1,4-addition of diazo compounds to α,β-unsaturated carbonyl compounds, generating tetrahedral intermediate **7**, which could give rise to chiral cyclopropanes via Michael-initiated ring closure (MIRC) (**Scheme 3**, Part (a)).[31] On the basis of this hypothesis, we successfully developed a COBI-catalyzed highly enantioselective cyclopropanation of α,β-substituted acroleins and α-aryl diazo esters.[31] This method provides highly functionalized tetrasubstituted cyclopropanes in moderate-to-high yields (up to 93% yield) with excellent enantioselectivities (up to 95% ee). Subsequently, we expanded the structural diversity of the chiral cyclopropane products by utilizing α-alkyl diazo esters or α-alkyl diazo Weinreb amides.[32] It is notable that virtually complete trans-diastereoselectivity (> 20:1) and excellent enantioselectivities were achieved, but yields were only moderate-to-good (45–76%) due to a competing β-hydride shift pathway,[33] which was not observed in the reaction of α-aryl diazo esters. The synthetic utility of this method was demonstrated by the total synthesis of the natural product (+)-hamavellone B (Scheme 3, Part (b)). In addition, our group recently found that the asymmetric reaction of α-bromoacrolein with *tert*-butyl diazoacetate selectively gave the cis-cyclopropane in excellent yield and ee (Scheme 3, Part (c)).[34] By utilizing this chiral cis-cyclopropane, total synthesis of the natural product (–)-dictyopterene C′ was accomplished efficiently. The coordination mode of acrolein is the same as that for the asymmetric 1,3-dipolar cycloaddition depicted in Scheme 2, Part (c). The 1,4-addition of α-substituted diazo compounds to the β carbon of acrolein occurs from the acrolein's *si* face (front), with the ester group situated away from the aldehyde due to the dipole-dipole interaction between the two carbonyl groups. Then, cyclization generates the chiral trans-cyclopropane (in which the aldehyde and ester carbonyl groups are situated trans to each other) as the major enantiomer (Scheme 3, Part (a)).



Scheme 3. Applications of the Enantioselective Cyclopropanation with the COBI Catalysts. *(Ref. 31,32,34)*

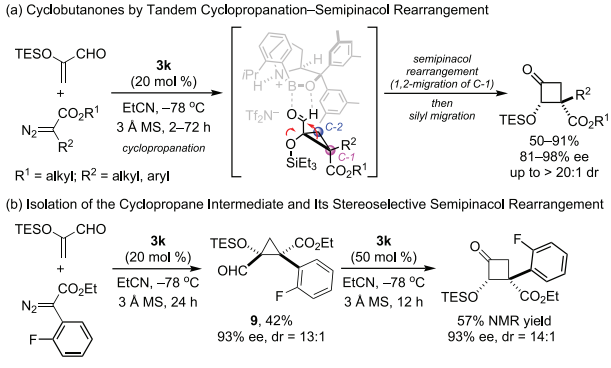
2.3. Rearrangement of Cyclopropanes

Since it is well known that 2,5-dihydrooxepines can be easily prepared via a retro-Claisen rearrangement of the cyclopropanes possessing vinyl and formyl groups in a cis relationship,[35] we hypothesized that *cis*-1-formyl-2-vinylcyclopropanes (*cis*-FVCs) could be prepared from α-vinyl diazo compounds and substituted acroleins and then rearranged into 2,5-dihydrooxepines. Based on this hypothesis, we successfully obtained chiral 2,5-dihydrooxepines in the presence of COBI catalyst **3k**. Under the optimized conditions highly enantioenriched, single diastereomeric 2,5-dihydrooxepines were prepared in moderate-to-high yields and high-to-excellent enantioselectivities (52–86%, 76–99% ee) (**Scheme 4**, Part (a)).[36] Interestingly, we were able to isolate intermediate *cis*-FVC **8** at –78 °C when methacrolein and α-benzyl acrolein were used as electrophiles. NOE experiments confirmed that the FVC intermediates possessed a cis relationship between the formyl and vinyl groups. In the presence of the same COBI catalyst, the FVCs were rearranged to the corresponding 2,5-dihydrooxepines at a higher temperature (Scheme 4, Part (b)). This result supported the plausible tandem cyclopropanation–retro-Claisen rearrangement mechanism for this transformation.



Scheme 4. Asymmetric Formation of *cis*-FVCs and Their Tandem Retro-Claisen Rearrangement to 2,5-Dihydrooxepines. *(Ref. 36)*

Our success in the tandem cyclopropanation–retro-Claisen rearrangement prompted us to consider utilizing COBI to catalyze the enantioselective synthesis of chiral cyclobutanones via the semipinacol rearrangement of α-silyloxycyclopropanes prepared from α-silyloxyacroleins and diazo compounds. Consequently, we successfully developed a catalytic enantioselective synthesis of cyclobutanones through a tandem enantioselective cyclopropanation–semipinacol rearrangement (**Scheme 5,** Part (a)).[37] With α-silyloxyacrolein as an electrophile, both α-alkyl and α-aryl diazoesters were good substrates for this reaction that produced optically active cyclobutanones (50–91% yields, 81–98% ee's, up to > 20:1 dr). Surprisingly, only the 1,2-alkyl

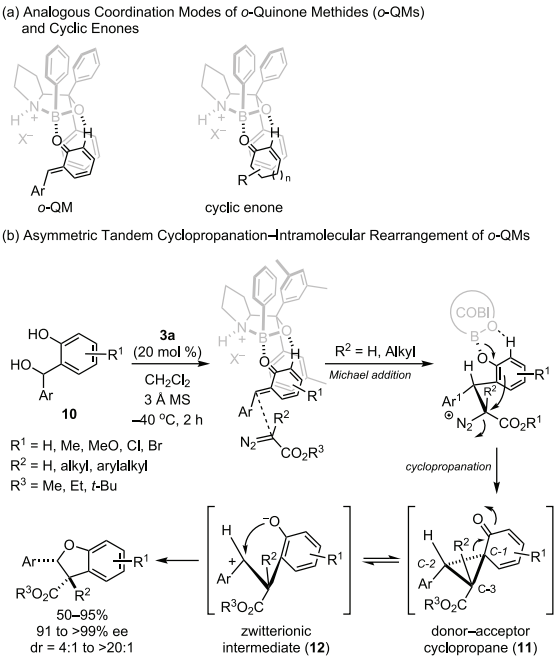


Scheme 5. Asymmetric Synthesis of Cyclobutanone via Tandem Cyclopropanation–Semipinacol Rearrangement. *(Ref. 37)*

shift of C-1 bearing electron-withdrawing group(s) occurred and no C-2 migration products were detected in all cases. This observation can likely be attributed to the anionic character of C-1, which is more stable than that of C-2, due to the electron-withdrawing group(s) effectively stabilizing the negative charge of the migrating carbon in the transition state.

Notably, chiral 2-flurophenyl-substituted cyclopropane intermediate **9** was isolated when the reaction was carried out at –78 °C for 24 h with COBI catalyst **3k**. When **9** (93% ee) was exposed to the same catalytic system with 50 mol % of COBI **3k** for 12 h at –78 °C, it was converted into the chiral cyclobutanone (93% ee) without loss of enantiopurity (Scheme 5, Part (b)). These experimental results suggest the asymmetric formation of the cyclopropane and its subsequent stereoselective semipinacol rearrangement under the COBI catalytic system.

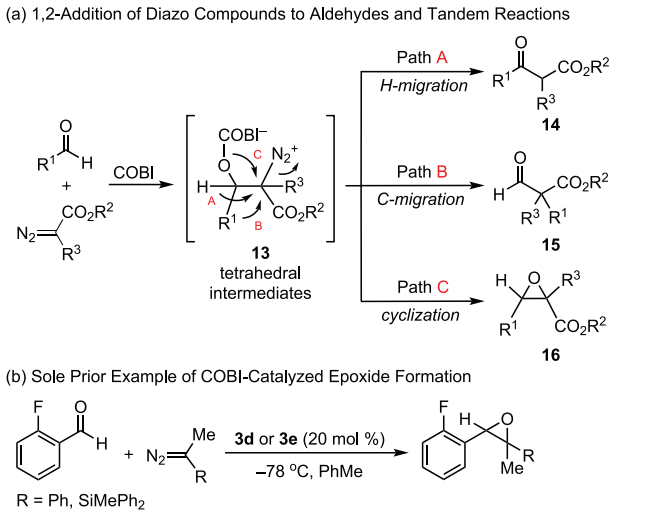
The successful utilization of acroleins as Michael acceptors for cyclopropanation and tandem rearrangements encouraged us to investigate the viability of using *ortho*-quinone methides (*o*-QMs) as Michael acceptors. We envisioned that *o*-QMs could be activated toward 1,4-addition by COBI through a coordination mode similar to those of cyclic α,β-unsaturated ketones (enones) (**Scheme 6**, Part (a)).[38] Based on this idea, we initiated our studies with *ortho*-hydroxybenzyl alcohols **10** since they can generate *o*-QMs in situ with the loss of H_2O. We found that treatment of *ortho*-hydroxybenzyl alcohols **10** with diazo compounds provided chiral 2-aryl-2,3-dihydrobenzofurans in 50–95% yields and 91 to >99% ee's under COBI catalysis.[38] Mechanistically, this sequence begins with a dehydration of *ortho*-hydroxybenzyl alcohols **10** to give *o*-QMs, followed by coordination to the COBI catalyst (Scheme 6, Part (b)). Next, Michael addition of diazo compounds to *o*-QMs and subsequent cyclization lead to donor–acceptor cyclopropane intermediate **11**. The resulting cyclopropane induces polarization of the C_1–C_2 bond with an electron-donating group (Ar) and is in equilibrium with the zwitterionic intermediate **12**. Finally, ring closure by formation of the C–O bond yields 2-aryl-2,3-dihydrobenzofurans.



Scheme 6. COBI-Catalyzed Asymmetric Synthesis of Dihydrobenzofurans from *o*-QMs. *(Ref. 38)*

2.4. Epoxidation

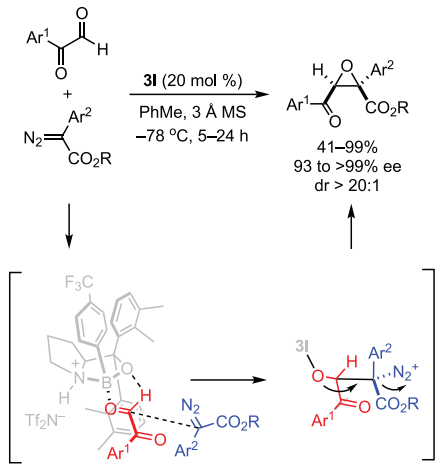
A number of COBI-catalyzed tandem asymmetric 1,2-addition reactions of diazo compounds to aldehydes have been developed in our laboratory.[16] These include the formation of β-keto esters **14** (via H-migration and Roskamp reaction, Path (A)) and all-carbon quaternary aldehydes **15** (via C-migration, Path (B)). However, epoxide products **16**, which can be generated through direct cyclization of an oxygen atom in tetrahedral intermediate **13** have not been observed (via Darzens reaction, Path (C)) (**Scheme 7**).[39–41] In prior studies, however, we observed that the electron-poor *o*-fluorobenzaldehyde provided epoxide side products.



Scheme 7. COBI-Catalyzed 1,2-Addition of Diazo Compounds to Aldehydes. *(Ref. 16,39–41)*

Based on this observation, we envisaged that electron-poor glyoxals would yield epoxides as major products through a Darzens-type direct cyclization pathway. After extensive exploration, we found that COBI catalyst **3l**—with sterically bulky geminal aryl groups and an electron-deficient aryl group at the boron center—in toluene generated single diastereomeric, trisubstituted chiral epoxides in high yields and with excellent enantiopurities (up to 99%, up to >99% ee, > 20:1 dr, **Scheme 8**).[41] NMR analysis of the pretransition state assembly suggested a monodentate coordination mode of glyoxal to COBI. Subsequently, several factors, such as the steric hindrance of bulky aryl groups in the COBI skeleton, dipole–dipole interaction

between the aldehyde group of glyoxal and the ester group of the diazoester, and π–π interaction between the aryl groups of glyoxal and the diazoester, guided the orientation of the diazo compound for 1,2-addition. Subsequent direct O-ring closure with extrusion of N_2 yielded chiral epoxide products. However, in some cases, all-carbon quaternary aldehyde products such as **15** in Scheme 7 were obtained as side products in significant quantities (32–58%).



Scheme 8. COBI-Catalyzed Asymmetric Epoxidation of Glyoxals. *(Ref. 41)*

3. Visible-Light-Induced, COBI-Catalyzed Enantioselective Radical Reactions

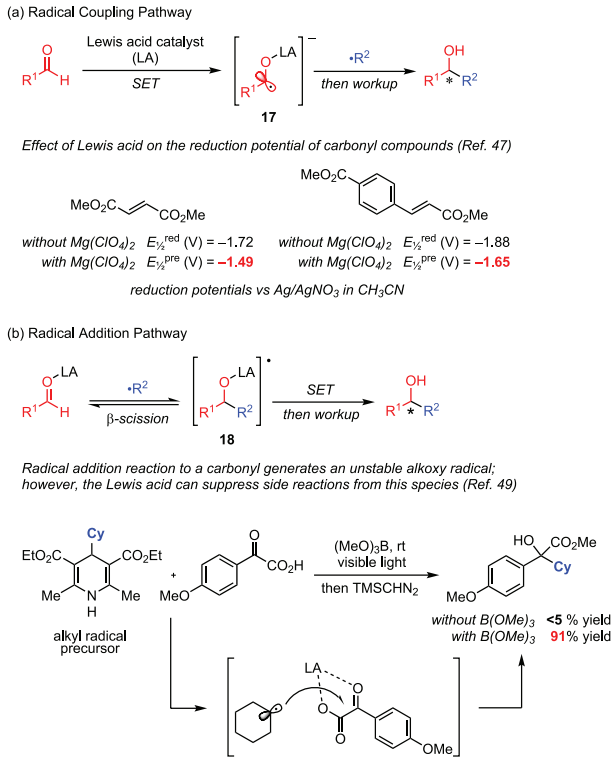
A wide variety of visible-light-promoted radical reactions have recently been developed.[42] Moreover, the development of enantioselective versions of radical reactions has proven quite challenging due to the high energy involved and the instability of the radical species.[42a,b] Recently, some research groups have successfully developed catalytic asymmetric radical reactions by introducing photosensitizers[42d] or metal catalysts that can stabilize the radical intermediates.[42e] Their results inspired our research group to solve the instability problem of radical species by utilizing synergistic catalysis—COBI catalyst and a photosensitizer[42e]— and to develop visible-light-induced enantioselective radical reactions.

When Lewis acids coordinate with Lewis bases, such as aldehydes or ketones, the photochemical properties such as extinction coefficient, triplet energy, or absorbance are changed.[43] Therefore, we expected that Lewis acid–base complexes between COBI and carbonyl compounds could induce a bathochromic shift that would cause them to absorb visible light, which could be followed by visible-light-induced enantioselective radical reactions. Recently, Schwinger and Bach[44] and Yoon's group[45,46] developed enantioselective [2+2] photocycloadditions by changing photochemical properties, such as extinction coefficient and triplet energy, in the presence of COBI catalysts. In this section, we shall describe our recently developed visible-light-induced asymmetric radical addition reactions of carbonyl compounds using COBI catalyst. The reactions proceed via a single-electron-transfer (SET) process.

3.1. Possible Radical Reaction Pathways of Carbonyl Compounds in the Presence of Lewis Acids

For the radical reaction of aldehydes in the presence of COBI catalysts, one can envision two possible reaction pathways that proceed through different mechanisms: radical coupling reaction and radical addition reaction (**Scheme 9**).

For the radical coupling reaction, acyl radical **17** is generated from the aldehyde by single-electron transfer (SET) and couples with other radical species (•R^2). On the other hand, in the radical addition reaction, the aldehyde couples with other reactive radical species (•R^2) to generate alkoxy radical intermediate **18** (Scheme 9). In the case of the radical coupling reaction, it is difficult to generate the active acyl radical species **17** selectively because of the high reduction potential of the aldehyde. However, it has been reported that Lewis acids can decrease the reduction potential of carbonyl compounds (Scheme 9, Part (a)).[47] Therefore, COBI catalyst would likely facilitate the radical coupling pathway by decreasing the reduction potential of the aldehydes. In contrast, the radical addition pathway would generate the thermodynamically unstable alkoxy radical intermediate **18**, and thus would not be the favored pathway.[48] However, Chen's group reported that radical addition can be facilitated by boron-based Lewis acid catalysts (Scheme 9, Part (b)),[49] so we envisaged that COBI



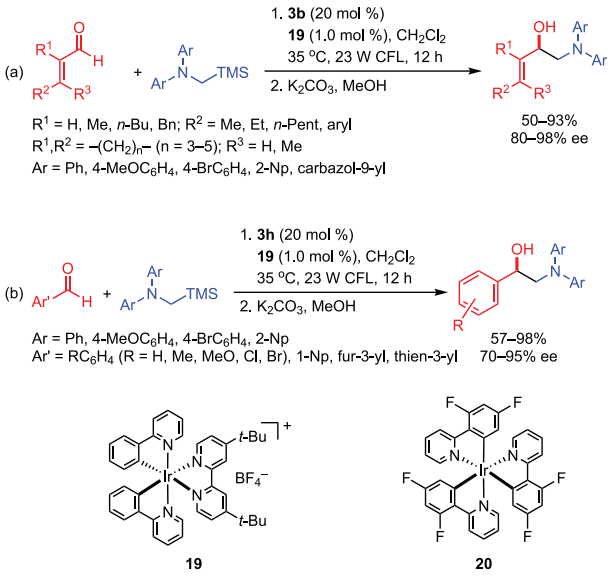
Scheme 9. Possible Radical Reaction Pathways of Aldehydes.

could also promote radical addition reactions by stabilizing unstable alkoxy radical species.

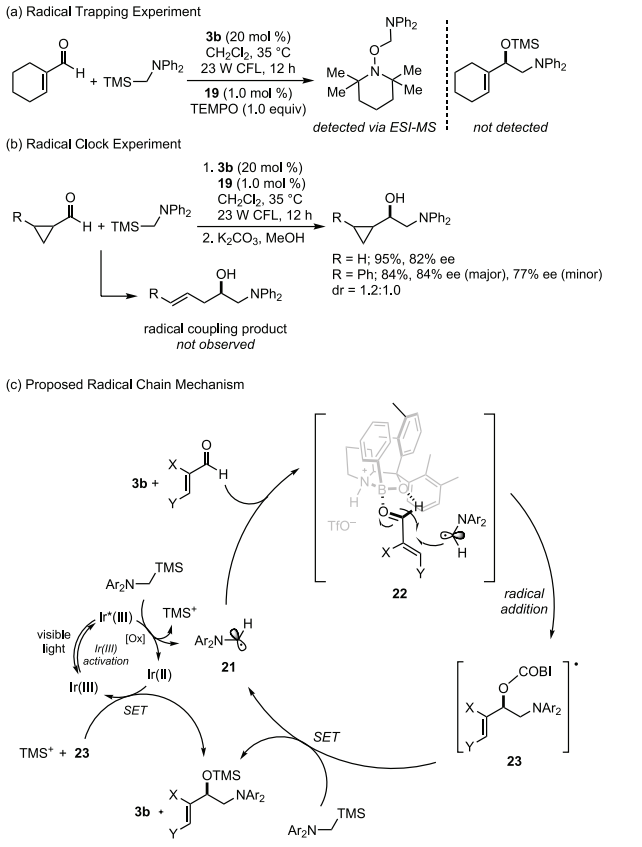
3.2. Radical Addition Reaction to Aldehydes

Based on the preceding observations and our hypothesis, we proceeded to react α,β-unsaturated aldehydes and α-silylamines in the presence of COBI catalyst **3b** and iridium-based photosensitizer **19** (**Scheme 10**, Part (a)).[50] In contrast to results from Yoon's group that yielded 1,4-addition products under analogous conditions,[51] we obtained unexpected 1,2-addition products in good-to-excellent yields (up to 99%) and with high enantioselectivities (up to 98% ee's). Furthermore, we successfully applied this methodology to various aromatic and aliphatic aldehydes, obtaining the desired chiral β-amino benzylic alcohols in high yields and enantioselectivities (Scheme 10, Part (b)).[50]

We then performed various mechanistic experiments to understand the mechanistic details of this reaction (**Scheme 11**).[50] With a radical trapping experiment, we found that the α-aminoalkyl radical was an active radical species by observation of its TEMPO adduct (Scheme 11, Part (a)). We also performed radical clock experiments with cyclopropyl-substituted aldehydes and discovered that ring-opened products that could be formed from the corresponding acyl radicals were not detected (Scheme 11, Part (b)). Therefore, we ruled out the radical coupling mechanism for this methodology and concluded that this reaction proceeded via the radical addition pathway. Furthermore, light on/off experiments and quantum yield measurements were performed. A high quantum yield (Φ = 30)[52] suggested that this process proceeds via a radical chain mechanism (Scheme 11, Part (c)). In this mechanism, the active α-aminoalkyl radical **21** is generated by an iridium-based photosensitizer.[53] This is followed by attack on the COBI-coordinated aldehyde from the *si*-face to generate radical intermediate **23**. Reaction of **23** with the α-silyldiarylamine substrate yields the silyl-protected optically active 1,2-amino alcohol product and regenerates the active α-aminoalkyl radical **21** by SET.



Scheme 10. Enantioselective Radical Addition of α-Aminoalkyl Radicals to Aldehydes. *(Ref. 50)*



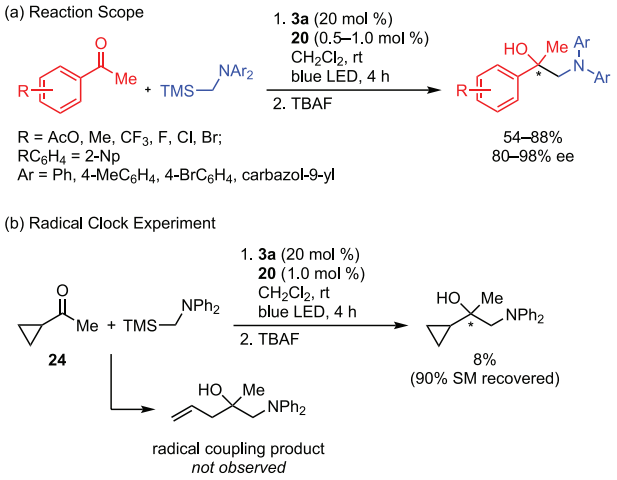
Scheme 11. Mechanistic Experiments and Proposed Reaction Mechanism. *(Ref. 50)*

3.3. Radical Addition Reaction to Acetophenone Derivatives

Because the reactivity of ketones is lower than that of aldehydes, the radical reactions of ketones with α-aminoalkyl radicals have rarely been reported, and their enantioselective versions remain particularly underdeveloped.[54] Previously, enantioselective hydro- and cyanosilylations of ketones have been described in the presence of COBI catalysts.[55] Prompted by these reports, we developed a analogous visible-light-induced enantioselective addition of α-aminoalkyl radicals to acetophenones to generate optically active tertiary alcohols.

We reacted acetophenone derivatives and α-silyl amines in the presence of COBI catalyst **3a** and iridium-based photosensitizer **20** (see Scheme 10) under irradiation by blue

LEDs to produce optically active tertiary alcohols in high yields (up to 88%) and high enantioselectivities (up to 98% ee) (**Scheme 12**, Part (a)).[56] Mechanistic experiments, such as radical trapping and radical clock experiments (Scheme 12, Part (b)), and quantum yield measurements were performed, which verified that the α-aminoalkyl radical was generated and that the reaction involves a radical chain mechanism and proceeds via a radical addition pathway.

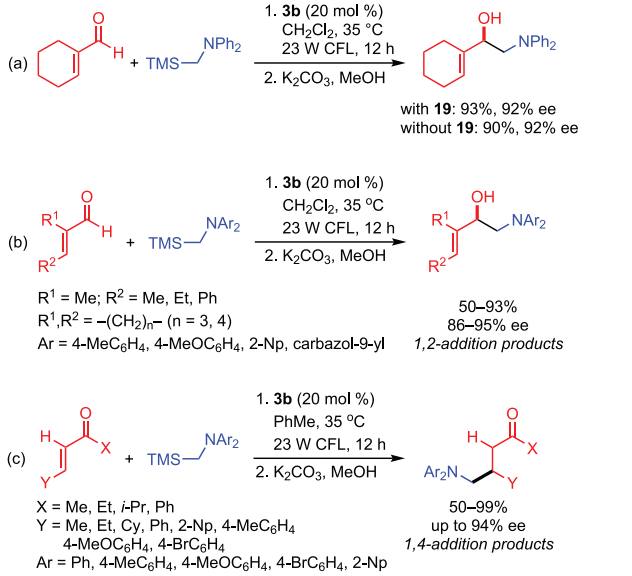


Scheme 12. Enantioselective Addition of α-Aminoalkyl Radicals to Acetophenones. *(Ref. 56)*

3.4. Ternary Electron Donor–Acceptor Complex with COBI

Previously, we observed that the enantioselective radical addition reaction between α,β-unsaturated aldehydes and α-silylamines proceeds without the iridium-based photosensitizer (**Scheme 13**, Part (a)).[57] While 1,4-addition products were not observed, 1,2-addition products were obtained in 50–90% yields and with 86–95% enantioselectivities (Scheme 13, Part (b)). Interestingly, compared to the catalytic reactions of α,β-unsaturated aldehydes which result in 1,2-addition products, 1,4-addition products are obtained in high yields (up to 99%) and enantioselectivities (up to 94% ee) from the catalytic reactions of α,β-unsaturated ketones without any photosensitizer (Scheme 13, Part (c)).

To elucidate how this reaction proceeds in the absence of a photosensitizer, we prepared four COBI catalysts with different L-prolinol backbone structures (**Figure 3**, Part (a)). Surprisingly, COBI catalyst **3m, 3n**, and **3o**, which have two hydrogen atoms or one phenyl substituent at the C-3 position, failed to catalyze the reaction (Figure 3, Part (a)). We acquired UV-Vis absorption spectra to verify the generation of electron donor–acceptor (EDA) complexes, because EDA complexes can catalyze photoredox reactions in the absence of additional photosensitizers.[58] First, we measured the individual UV-Vis absorption spectrum of aldehyde **25**, α-silyl amine **26**, COBI **3a**, COBI complex **27** (with aldehyde) and COBI complex **28** (with α-silyl amine) (Figure 3, Part (b)). Alone, aldehyde **25**, α-silyl amine **26**, and COBI **3a** did not show absorption in the visible region (Figure 3, Part (b)). Since Ooi's group reported the generation of an EDA complex between α-silylamine and a Lewis acid,[59] we expected that an EDA complex could be generated between the α-silylamine and the COBI catalyst. However, the absorption spectrum of the COBI complex **28** did not exhibit any absorption in the visible region, which indicates that an EDA complex was not generated (Figure 3, Part (b), pink line). Similarly, an EDA complex was not generated between the aldehyde and the COBI catalyst (Figure 3, Part (b), blue line). In addition, we observed a bathochromic shift[43] with the COBI catalyst and aldehyde, but this shift was not observed in the visible region, suggesting that this bathochromic shift was not a main factor in facilitating the reaction in the absence of photosensitizer (Figure 3, Part (b), blue line). When α-silyl amine **26** was added to the mixture of aldehyde and COBI catalyst, however, we observed a charge-transfer (CT) band around 425 nm (Figure 3, Part (c), blue line). This observation verifies that the ternary EDA complex is generated by the combination of **3p**, aldehyde, and α-silyl amine. In contrast, absorption in the visible region was not observed when COBI **3n** and **3o** were used instead of COBI **3p** (Figure 3, Part (c)). Therefore, two-aryl substituents at the C-3 position of the COBI catalyst are required to generate an EDA complex in this reaction. Furthermore, a Job's plot analysis was performed to observe the 1:1 ratio between the electron donor (α-silylamine **26**) and acceptor (COBI–carbonyl complex **27**) (Figure 3, Part (d)).



Scheme 13. Ternary EDA Complex Initiated Radical Addition Reactions between α,β-Unsaturated Carbonyls and α-Aminoalkyl Radicals. *(Ref. 57)*

Mechanistic studies, such as radical trapping, radical clock reaction, and deuterium labeling experiments led to the proposed mechanism for this reaction (**Scheme 14**).[57] Irradiation with visible light and desilylation produces α-aminoalkyl radical **21**,

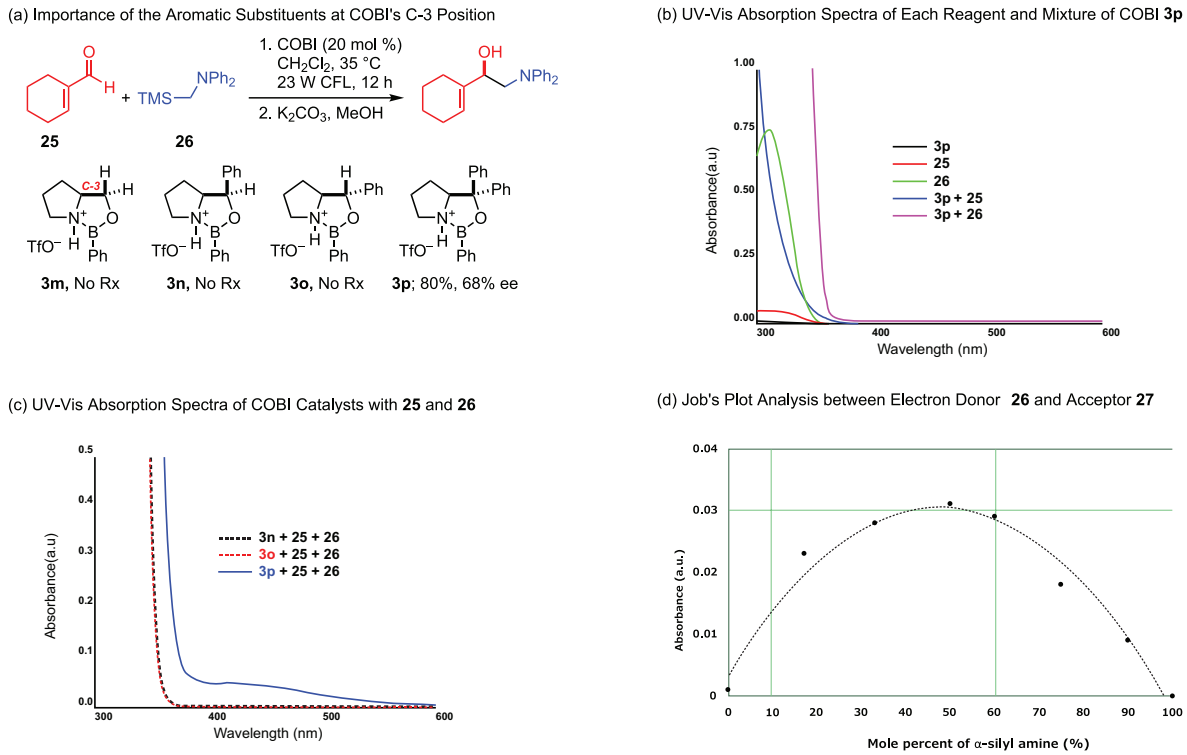
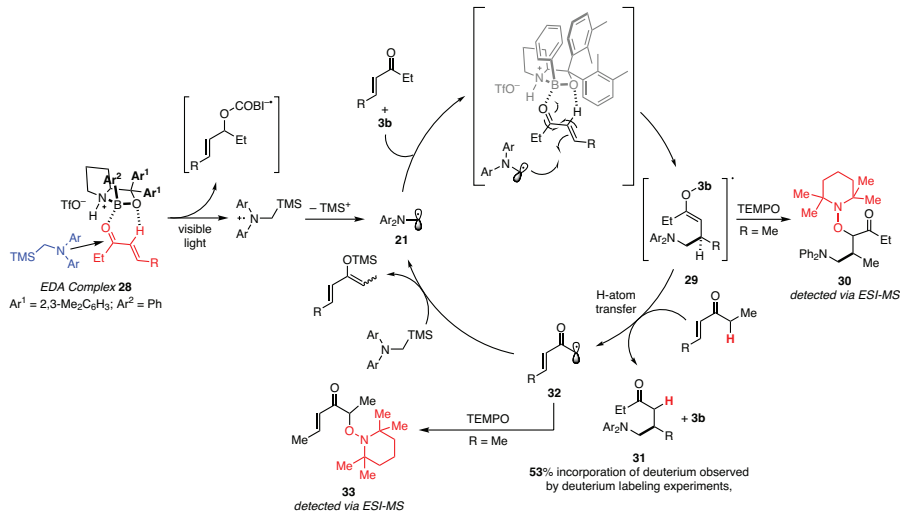


Figure 3. UV-Visible Absorption Spectra and Job's Plot Analysis Used in Determining the EDA Composition. Adapted with Permission from ref 57. Copyright 2021 American Chemical Society.

which adds to the α,β-unsaturated ketone coordinated with COBI catalyst **3b**. This step generates radical intermediate **29**, which is supported by the detection of TEMPO adduct **30**. As determined by deuterium labeling experiments, hydrogen-atom transfer then takes place from the α,β-unsaturated ketone to radical intermediate **29**, leading to the desired product, **31**, and regenerating COBI catalyst **3b** and radical species **32**. Furthermore, the high quantum yield (Φ = 296) obtained supports the hypothesis that this enantioselective radical reaction initiated by the ternary EDA complex is a radical chain reaction, whereby **32** extracts one electron from the α-silylamine to regenerate the active α-aminoalkyl radical **21**.



Scheme 14. Mechanistic Studies and Proposed Catalytic Cycle for the Ternary EDA Complex Induced Enantioselective Radical Addition Reaction. *(Ref. 57)*

4. Conclusion

Asymmetric catalysis has been an important tool in organic synthesis. In particular, chiral Lewis acid catalysts have been applied to various synthetic methodologies and the total synthesis of natural products and pharmaceuticals. Among the chiral Lewis acid catalysts reported, chiral oxazaborolidinium ions (COBIs) are some of the most efficient catalysts for the activation of carbonyl compounds in such asymmetric reactions as dipolar cycloadditions, cyclopropanations, epoxidations, and visible-light-induced radical additions. We aimed in this review to, not only introduce various enantioselective methodologies that employ COBIs, but also provide a deeper understanding of the details of their catalytic action such as in pretransition state models or ternary EDA complexes. Further studies utilizing COBIs are underway in our laboratory to develop novel catalytic asymmetric methodologies for different types of nucleophilic addition reactions, rearrangements, radical reactions, and total syntheses.

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Single-Electron Oxidation-Induced Chemical Transformations: Carbon–Carbon Bond Formation and Selective Oxaziridine Rearrangement

단일 전자 산화 유도 화학 변환: 탄소-탄소 결합 형성 및 선택적 옥사지리딘의 재배열


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Keywords. visible light; photoredox catalysis; single-electron transfer (SET); silicon-based radical precursor; Giese reaction; oxaziridine rearrangement; PMP deprotection.

키워드. 가시광선; 광산화환원 촉매작용; 단일 전자 이동 (SET); 실리콘 기반 라디칼 전구체; Giese 반응; 옥사지리딘 재배열; PMP 탈보호.

Abstract. Visible-light photoredox catalysis is an important and growing research area in the field of green and sustainable organic synthesis. One of the main mechanisms involved in photoredox catalysis is single-electron transfer (SET), which has been extensively investigated in our group for the development of greener carbon–carbon bond forming reactions and oxaziridine rearrangement. In this review, we highlight our results on the development and application of neutral silicon radical precursors for the generation of alkyl radicals and the selective rearrangement of oxaziridines into nitrones or amides.

초록. 가시광선 광산화환원 촉매작용은 녹색 및 지속 가능한 유기 합성 분야에서 중요한 연구 분야입니다. 광산화환원 촉매작용에서 주요 메커니즘 중 하나는 단일 전자 전달(SET) 이며, 우리 그룹에서는 이를 활용해 친환경적인 탄소-탄소 결합 형성 반응과 옥사지리딘 재배열을 개발하였습니다. 본 리뷰에서 우리는 알킬 라디칼 생성 위한 중성 실리콘 라디칼 전구체의 개발 및 적용과 옥사지리딘의 나이트론 또는 아마이드로의 선택적 재배열을 대한 결과를 설명합니다.

Outline

1. Introduction

In the past decade, visible-light photoredox catalysis has received significant attention in the field of sustainable organic synthesis because of its inexpensive, abundant, and clean light sources and mild reaction conditions, which have led to the development of many organic reactions that are facilitated by

visible-light photocatalysts.[1] Single-electron transfer (SET), in which radical species are produced, is one of the main mechanisms by which photoredox catalysis takes place. The SET mechanism can be classified into oxidative and reductive quenching cycles according to the redox state of the catalyst in the catalytic cycle (**Figure 1**, Part (a)).[1b,f,2] The spontaneity of the SET mechanism can be easily predicted from the Gibbs energy of a photoinduced electron transfer ($\Delta G_{PET} = -F[E_{red}(A/A^{\bullet-}) - E_{ox}(D^{\bullet+}/D)] - w - \Delta E_{0,0}$), where the redox potentials of catalysts and substrates can be obtained from the literature or determined through cyclic voltammetry. Our research has focused on the use of SET in photoredox catalysis for carbon–carbon bond forming reactions and oxaziridine rearrangement using transition-metal-based and organic photocatalysts such as $Ru(bpz)_3(PF_6)_2$, $Ir(dF(CF_3)ppy)_2(dtbpy)PF_6$, Fukuzumi's acridinium salt (Acr^+–Mes), 2,4,5,6-tetrakis(9*H*-carbazol-9-yl)-isophthalonitrile (4CzIPN), and 2,4,5,6-tetrakis(3,6-dichloro-9*H*-carbazol-9-yl)isophthalonitrile (Cl-4CzIPN), which are good oxidizers (Figure 1, Part (b)). In particular, we have favored organic photocatalysts because of their low cost and easy preparation. In this review, we present the results of our investigations of neutral silicon-based radical precursors for the generation of alkyl radicals via SET and the selective rearrangement of oxaziridines into nitrones or amides.

2. Development and Application of Neutral Silicon-Based Radical Precursors

In classical radical chemistry, alkyl radicals are generally generated from alkyl halides, organoselenium compounds, or organostannane compounds in the presence of a radical initiator and heat or light. However, classical methods require vigorous reaction conditions, such as a high temperature and a high energy source, and generate toxic wastes (e.g., organic tin compounds). Therefore, intense research efforts have been devoted to the development of greener methods for the generation of alkyl radicals. As a result, visible-light photocatalysis has emerged as a promising green and sustainable method to generate and utilize radicals. In photoredox catalysis, radical precursors are widely employed to generate alkyl radicals through the SET mechanism.[1i] The most commonly used alkyl radical precursors are electron-rich alkyl trifluoroborates,[3] carboxylate anions,[4] alkyl bis(catecolato)-silicates,[5] and alkyl-substituted dihydropyridines,[6] which generate radicals through single-electron oxidation reactions (**Figure 2**, Part (a)). On the other hand, radical precursors that generate radicals through single-electron reduction due to a lack of electrons; including alkyl halides, alkyl pyridinium salts,[7] and NHPI esters[8] (Figure 2, Part (b)); are widely used; however, they are utilized in their salt form and have low atom economy. Therefore, the development of a neutral radical precursor characterized by high atom economy is still needed. In this context, we envisioned that the introduction of a trimethylsilane (TMS) group into the alkyl groups of ethers, alcohols, and alkenes would decrease their oxidation potential by the β-silicon effect, which involves the stabilization of a cation radical intermediate as a result of the overlap of the

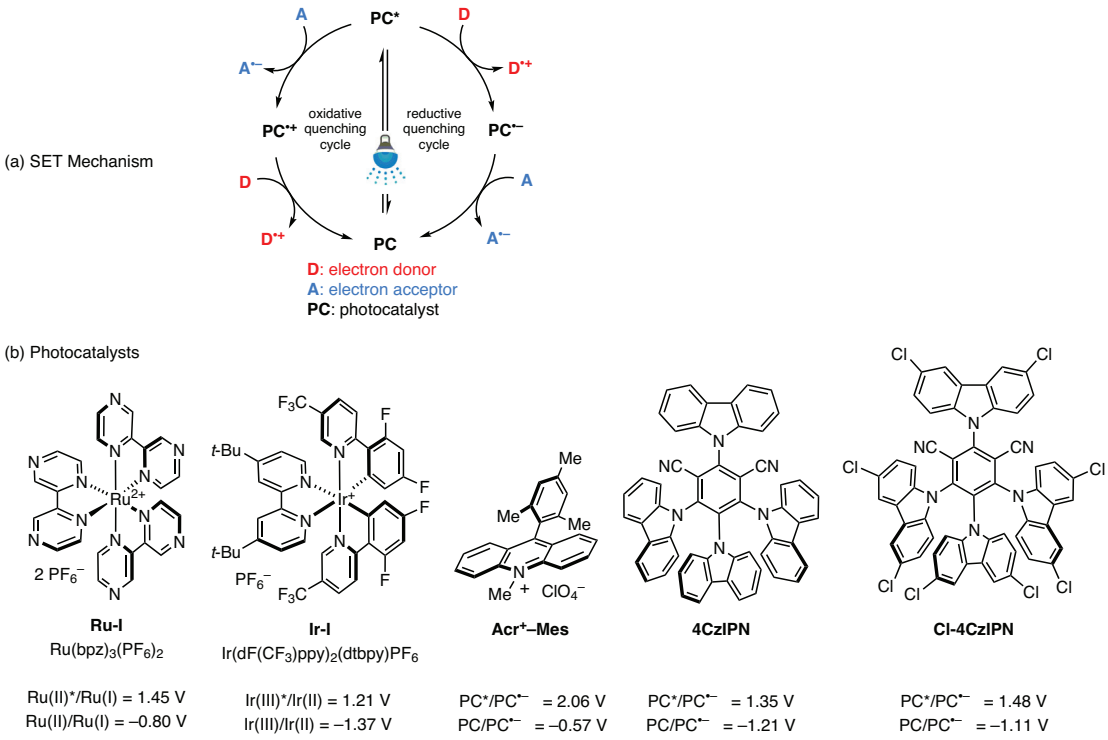


Figure 1. (a) Single-Electron Transfer (SET) Mechanism. (b) Popular Oxidizer Photocatalysts. *(Ref. 1)*

filled carbon–silicon bond with the half-vacant 2p orbital when silicon is adjacent to an oxygen atom or a π-bond.[9] Thus, we developed neutral, silicon-based alkyl radical precursors of alkoxymethyl, hydroxymethyl, and allylic nucleophilic radicals that can react with electron-deficient alkenes or imines to form new carbon–carbon bonds (Figure 2, Part (c)).

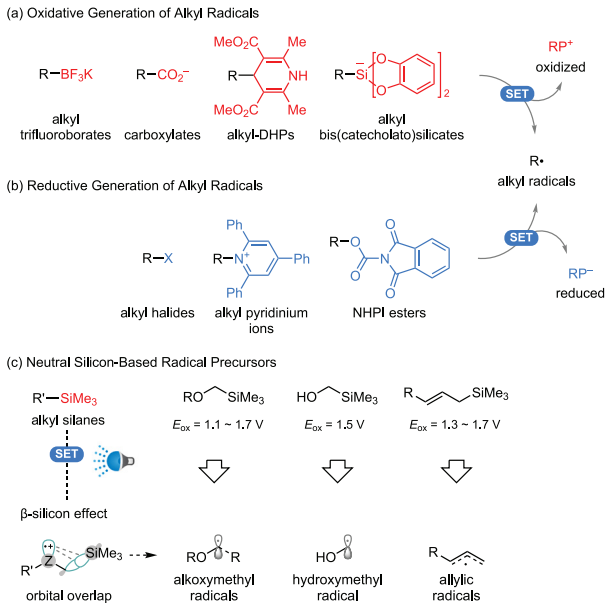
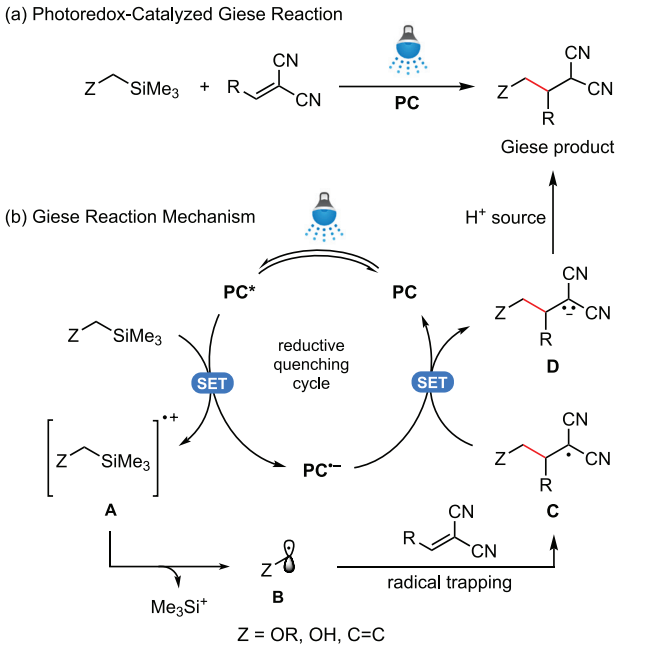


Figure 2. (a) and (b) Commonly Used Alkyl Radical Precursors and (c) Newly Developed Neutral, Silicon-Based Radical Precursors.

2.1. Photoredox-Catalyzed Giese Reaction

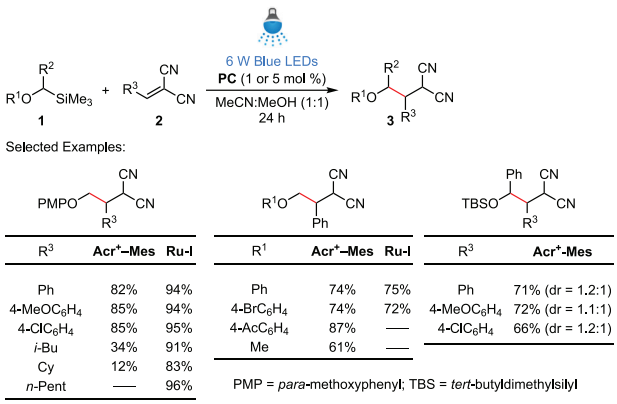
We initially explored the use of silicon-based radical precursors in the photoredox-catalyzed Giese reaction. The Giese reaction[10] consists of the overall addition of a nucleophilic alkyl radical[11] to an electron-deficient alkene to form a new carbon–carbon bond (**Scheme 1**, Part (a)). Examples of suitable nucleophilic alkyl radicals are the alkoxymethyl, hydroxymethyl, and allylic radicals generated from the corresponding, silicon-based precursors. In the general mechanism of the photoredox-catalyzed Giese reaction employing neutral, silicon-based alkyl radical precursors (Scheme 1, Part (b)), irradiation with blue light moves the photocatalyst (**PC**) from the ground state to an excited state, **PC***. Subsequently, single-electron oxidation of the silicon-based alkyl radical precursor by **PC*** generates radical cation **A**, which undergoes desilylation to produce alkyl radical species **B**. Alkyl radical **B** is then trapped by the electron-deficient alkene to afford intermediate radical **C**. Afterward, **C** undergoes single-electron reduction by the reduced photocatalyst ($PC^{\bullet-}$) to regenerate the ground-state photocatalyst (**PC**) and furnish the Giese adduct product after protonation.

α-Alkoxyalkyl radicals are useful reaction intermediates in the formation of carbon–carbon bonds to form ethers, which is a functional group found in many biologically active compounds, drugs, and natural products.[12] However, the direct generation



Scheme 1. Photoredox Catalyzed Giese Reaction and Mechanism.

of α-alkoxyalkyl radicals from alkyl ethers via single-electron oxidation is challenging because ethers have a high oxidation potential (e.g., E_{ox} > +2.4 V vs SCE for THF, THP, and diethyl ether) and can be overoxidized under oxidative conditions.[13] Owing to the β-silicon effect, alkoxymethylsilanes ($ROCH_2TMS$, **1**) have lower oxidation potentials (+1.1 ~ +1.7 V vs SCE in MeCN) than the corresponding alkyl ethers. In 2018, we developed a visible-light, photoredox-catalyzed hydroalkoxymethylation of electron-deficient alkenes **2** by utilizing alkoxymethylsilanes **1** as α-alkoxyalkyl radical precursors (**Scheme 2**).[14] Acr^+–Mes (E_{red} = +2.06 V vs SCE) or $Ru(bpz)_3(PF_6)_2$ (E_{red} = +1.46 V vs SCE) served as the photocatalyst in this transformation, which showed good tolerance toward various substituents and



R^3	Acr^+–Mes	Ru-I
Ph	82%	94%
4-$MeOC_6H_4$	85%	94%
4-ClC_6H_4	85%	95%
i-Bu	34%	91%
Cy	12%	83%
n-Pent	—	96%

R^1	Acr^+–Mes	Ru-I
Ph	74%	75%
4-BrC_6H_4	74%	72%
4-AcC_6H_4	87%	—
Me	61%	—

R^3	Acr^+-Mes
Ph	71% (dr = 1.2:1)
4-$MeOC_6H_4$	72% (dr = 1.1:1)
4-ClC_6H_4	66% (dr = 1.2:1)

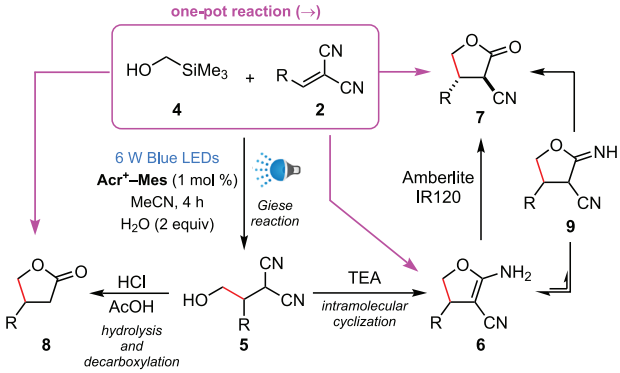
PMP = *para*-methoxyphenyl; TBS = *tert*-butyldimethylsilyl

Scheme 2. Visible-Light, Photoredox-Catalyzed Hydroalkoxymethylation of Alkenes under Mild Conditions. *(Ref. 14)*

functional groups in alkenes **2**, including alkyl, aryl, methoxy, halogen, and ester groups. Various primary α-silyl ethers and TBS-protected secondary α-silyl ethers were competent reaction partners, generating the corresponding alkyl radicals and furnishing the functionalized ethers **3** under mild conditions.

Next, we developed α-hydroxymethylsilane ($HOCH_2TMS$, **4**) as an α-hydroxymethyl radical equivalent having a lower oxidation potential (E_{ox} = +1.5 V vs SCE in MeCN) than methanol (E_{ox} > +2.5 V vs SCE in MeCN). Compared with α-alkoxymethyl radicals, the α-hydroxymethyl radical has a nucleophilic hydroxyl group that can be elaborated further after carbon–carbon bond formation. Consequently, we designed a controllable, photoredox-catalyzed one-pot reaction of the α-alkoxymethyl radical with alkenes, which is particularly attractive in organic synthesis because it reduces the overall reaction time and cost. The one-pot approach provides access to a diverse range of products and is known as the diversity-oriented synthesis protocol.[15] Valuable scaffolds such as alcohols **5** (Giese reaction), 2,3-dihydrofurans **6**, α-cyano-γ-butyrolactones **7**, and γ-butyrolactones **8** were obtained by this approach (**Scheme 3**).[16] These scaffolds serve as very useful building blocks for synthesizing natural products and biologically active pharmaceutical agents.[17] 2,3-Dihydrofurans **6** were formed by intramolecular cyclization under weak basic conditions, whereas α-cyano-γ-butyrolactones **7** were obtained under acidic conditions by the direct hydrolysis of cyclic imine **9** (the tautomer of **6**) in a one-pot fashion. Furthermore, alcohols **5** were converted into γ-butyrolactones **8** through hydrolysis and decarboxylation in the presence of HCl and acetic acid under reflux. Products **5**–**8** were also selectively synthesized in a one-pot fashion by controlling the reaction conditions. This reaction showed good tolerance toward a variety of substituted benzalmalononitrile derivatives and alkylidene malononitriles, affording the corresponding products in good-to-excellent yields.

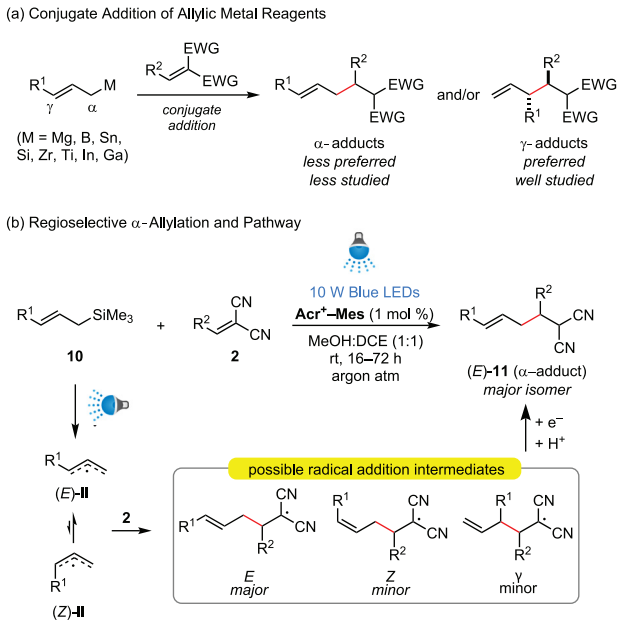
The regioselective conjugate addition of allyl groups to α,β-unsaturated carbonyl, nitro, and nitrile compounds is important in organic synthesis because allyl moieties can be easily converted into various functional groups. When utilizing allyl metal reagents, γ-addition is preferred over α-addition (**Scheme 4**, Part (a)).[18] For instance, allyl silanes are used as allylic metal reagents in the Hosomi–Sakurai reaction, which involves a carbocation intermediate stabilized by the β-silicon effect and generally affords the γ-adduct. Other studies found that allyl silanes can also be utilized to generate allyl radicals. Interestingly in this case, the α-adducts are the most favored products due to steric effects during the addition of the allylic radicals to the activated alkenes.[19] In 2020, we developed a highly α-regioselective conjugate allylation (Scheme 4, Part (b)[20] by employing allyltrimethylsilanes **10** that are easily prepared from allylic alcohols. The oxidation potential of allyltrimethylsilanes **10** ranges from +1.39 to +1.61 V (vs SCE in MeCN), which is suitable for the photoredox-catalyzed generation of *E* or *Z* allylic radicals **II** upon addition of **Acr⁺–Mes** (E_{red} = +2.06 V vs SCE).



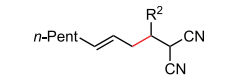
Selected Examples:

R	5	6	7
Ph	90%	90%	78% (dr = 3:1)
4-$MeOC_6H_4$	91%	91%	64% (dr = 4.4:1)
4-$MeO_2CC_6H_4$	89%	89%	70% (dr = 3.6:1)
i-Pr	75%	75%	54% (dr = 5:1)
Cy	83%	83%	not detected

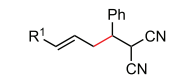
Scheme 3. Hydrohydroxymethylation of Alkenes and Further Elaboration of the Initially Formed Primary Alcohols. *(Ref. 16)*



Selected Examples:



R^2	Yield	α:γ	*E*/*Z*
Ph	79%	>20:1	16:1
4-MeC_6H_4	74%	>20:1	10:1
i-Pr	76%	>50:1	16:1
Cy	69%	>50:1	13:1



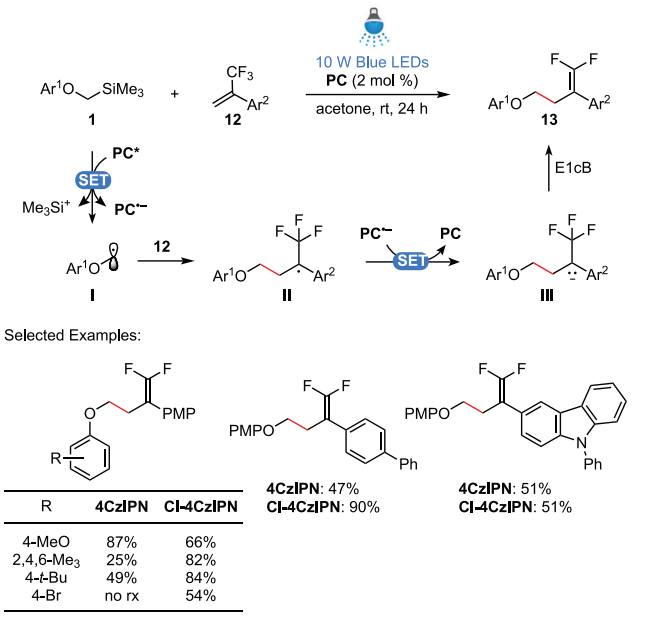
R^1	Yield	α:γ	*E*/*Z*
Cy	87%	>50:1	13:1
Bn	70%	>20:1	13:1

Scheme 4. Regioselective α-Allylation of Activated Alkenes and Reaction Pathway. *(Ref. 20)*

Allylic radical (*E*)-**II** is in equilibrium with (*Z*)-**II**, with (*E*)-**II** being the thermodynamically dominant isomer.[21] The addition of **II** to benzal- and alkylidene malononitrile derivatives **2** can give rise to three possible radical addition intermediates, among which the α-adduct obtained from (*E*)-**II** is the major isomer and furnishes (*E*)-**11** as the major product. The α terminus in allyl radical **II** selectively adds to the activated alkene to reduce steric repulsion. Various benzal- and alkylidene malononitriles **2** gave the corresponding products with allyltrimethylsilanes in good yields, high α-regioselectivities, and (*E*)-stereoselectivities.[20]

2.2. Radical–Polar Crossover (RPC) Reaction for the Synthesis of *gem*-Difluoroalkenes

RPC reactions have recently emerged as valuable and powerful tools to overcome the limitations of both radical and traditional polar chemistry.[22] RPC reactions are classified into oxidative RPCs and reductive RPCs according to the redox properties of the generated radicals. The anion intermediates produced via the reductive RPC reaction are utilized as nucleophiles in various reactions. *gem*-Difluoroalkenes are widely known in medicinal and pharmaceutical chemistry as mimics of carbon and esters, serving as carbonyl bioisosteres to improve the pharmaceutical performance of drugs and drug candidates.[23] Moreover, *gem*-difluoroalkenes can be transformed into other fluorine-containing scaffolds of interest. To date, the radical addition reaction of 1-trifluoromethylalkenes using various radical precursors under visible-light photocatalysis is well-developed. For our part, we recently reported the synthesis of *gem*-difluoroalkenes **13** from alkoxymethylsilanes **1** and 1-trifluoromethylalkenes **12** under mild reaction conditions by using 4CzIPN and Cl-4CzIPN as photocatalysts (**Scheme 5**).[24]



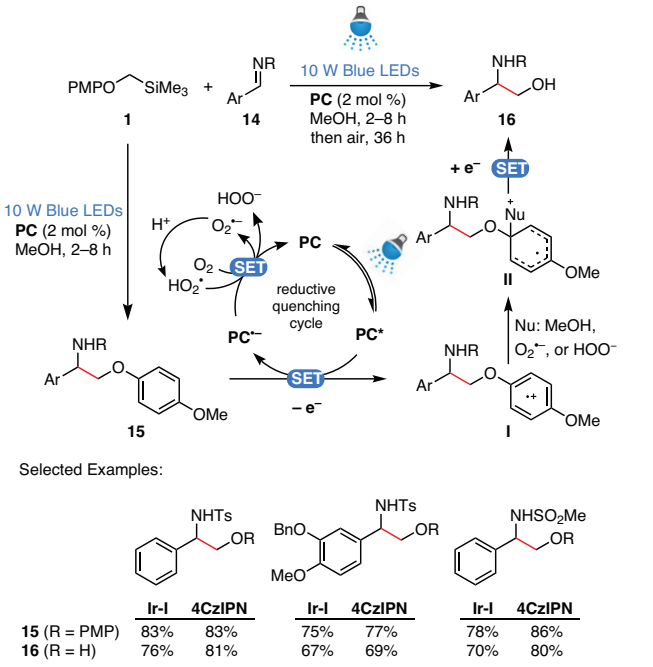
R	4CzIPN	Cl-4CzIPN
4-MeO	87%	66%
2,4,6-Me$_3$	25%	82%
4-*t*-Bu	49%	84%
4-Br	no rx	54%

Scheme 5. Synthesis of *gem*-Difluoroalkenes by a Radical–Polar Crossover Reaction under Mild Conditions. *(Ref. 24)*

In particular, and since Cl-4CzIPN (E_{red} = +1.48 V vs SCE) is a stronger oxidant than 4CzIPN (E_{red} = +1.35 V vs SCE), we have used Cl-4CzIPN for the generation of alkoxymethyl radicals from silyl ethers **1** containing less-electron-rich arenes. Several examples including heteroaromatics and substituted arenes provided moderate-to-good yields. In the proposed mechanism for the reaction, α-aryloxymethyl radicals **I** are formed via single-electron oxidation in the presence of **PC*** through a desilylation process (Scheme 5). The addition of **I** to trifluoromethylalkenes **12** generates stable α-trifluoromethyl radicals **II**. Subsequently, the single-electron reduction of **II** by **PC**$^{\bullet-}$ leads to nucleophilic carbanions **III** and regenerates the ground-state photocatalyst **PC**. Finally, fluorine elimination through E1cB furnishes products **13**.

2.3. Imine Addition and Sequential One-Pot Deprotection of *para*-Methoxyphenyl (PMP) Ether

β-Amino alcohols are important intermediates and building blocks in organic synthesis.[25] However, the hydroxymethylation of imines with α-hydroxymethyl radicals to prepare β-amino alcohols has rarely been reported because the generation of α-hydroxyalkyl radicals from carbonyl compounds or alcohols via reduction or oxidation, respectively, is a challenging task. To utilize the developed neutral, silicon-based precursors of the α-hydroxymethyl radical, we selected TMSCH$_2$OPMP (**1**, R^1 = PMP, R^2 = H) as a synthetic equivalent coupled with an in situ PMP group deprotection strategy. This strategy enables the simultaneous synthesis of β-amino alcohols and β-amino ethers, which are valuable motifs, and permits the use of



	Ir-I	4CzIPN	Ir-I	4CzIPN	Ir-I	4CzIPN
15 (R = PMP)	83%	83%	75%	77%	78%	86%
16 (R = H)	76%	81%	67%	69%	70%	80%

Scheme 6. Mild, One-Pot β-Amino Alcohol Synthesis by α-((*para*-Methoxyphenyl)oxy)methyl Radical Addition to Imines Followed by PMP Deprotection. *(Ref. 27)*

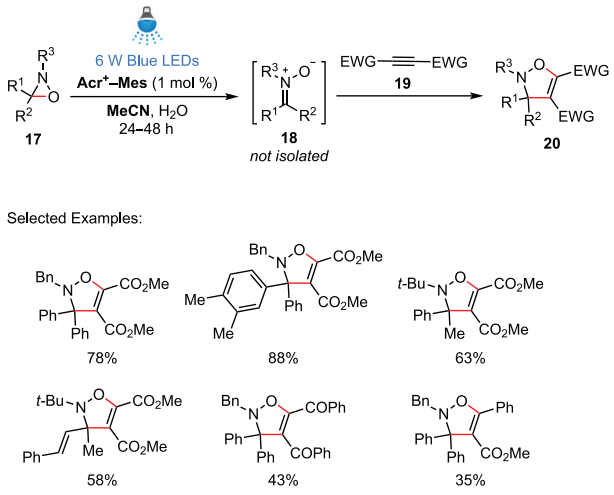
weaker photooxidants compared with $TMSCH_2OH$ (**4**). β-Amino ethers **15** were readily prepared via the alkoxymethylation of imines under mild photoredox catalysis conditions. We had also developed a strategy for the deprotection of the *para*-methoxybenzyl (PMB) protective group via visible-light photoredox catalysis under mild conditions using air and peroxodisulfate as terminal oxidants.[26] Inspired by this PMB deprotection work, we successfully deprotected the PMP group in β-amino ethers **15** using air as a terminal oxidant, which had not been reported before, furnishing β-amino alcohols **16**.[27] A wide range of β-amino ethers **15** and β-amino alcohols **16** were explored using $Ir(dF(CF_3)ppy)_2(dtbpy)PF_6$ (Ir-I) and 4CzIPN as photocatalyst, affording the corresponding products in moderate-to-good yields (**Scheme 6**).[27] In the proposed mechanism, β-amino ethers **15**, which are formed by the addition of the α-alkoxymethyl radicals to imines, are oxidized by **PC*** to form radical cation **I** at the PMP group. In the coupled catalytic cycle steps, oxygen is reduced by $PC^{\bullet-}$ to generate the superoxide anion ($O_2^{\bullet-}$) and a hydrogen peroxide anion. Subsequently, radical cation **I** reacts with nucleophiles (e.g., superoxide anion, hydrogen peroxide anion, or methanol) to form adduct **II** via a nucleophilic aromatic substitution (S_NAr) pathway.[28] Finally, single-electron reduction of adduct **II** by $PC^{\bullet-}$ regenerates the ground-state photocatalyst **PC** and furnishes β-amino alcohols **16**.[27]

3. Selective Rearrangement of Oxaziridines into Nitrones and Amides

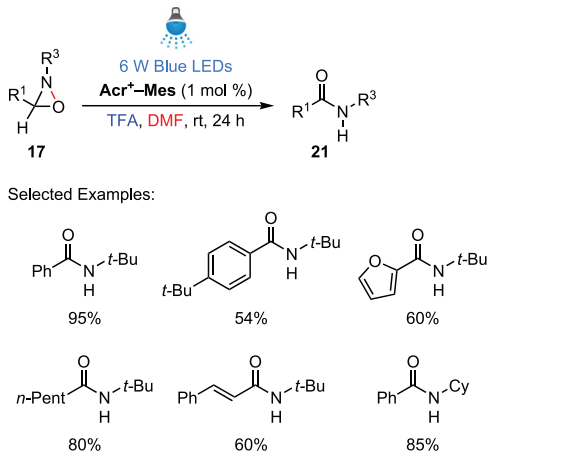
The reactivity of oxaziridines stems from the presence of a strained three-membered ring containing two electronegative heteroatoms, nitrogen and oxygen.[29] Oxaziridines, which are generally synthesized via oxidation of imines, can act as oxygen and nitrogen atom transfer reagents to various nucleophiles and can rearrange to nitrones and amides. The selective rearrangement of oxaziridines into nitrones and amides under photocatalytic reaction conditions is of interest because of its ecofriendly nature, high atom economy, and mild reaction conditions. Controlling the N–O or C–O bond cleavage is an important factor in the selective rearrangement of oxaziridines. One way that control over the ring opening can be exerted is through the use of different solvents.

We initially examined the selective rearrangement of oxaziridines into nitrones. Although cleavage of the C–O bond (to give nitrones) of photooxidized oxaziridines is preferred over that of the N–O bond (to give amides), the examples reported suffer from low yields and narrow substrate scope.[30] However, by taking advantage of the reactivity of nitrones as 1,3-dipoles,[31] this obstacle can be overcome. When oxaziridines are subjected to photocatalytic reaction conditions in the presence of electron-deficient alkynes, the initially formed nitrones can undergo [3 + 2] cycloaddition to provide 4-isoxazolines under mild conditions (**Scheme 7**).[32] The 4-isoxazoline products are obtained in moderate-to-good yields with high functional-group tolerance both in the oxaziridine and alkyne substrates. 4-Isoxazolines are of interest as building blocks and as structural components in a variety of biologically active compounds.

Next, we explored the selective rearrangement of oxaziridines to amides. In this context, reversing the selectivity of the ring opening is challenging, because the N–O bond cleavage of single-electron-oxidized oxaziridines **I** has a higher transition state energy than the corresponding C–O bond cleavage owing to the required hydride shift.[33] Inspired by previous studies demonstrating the conversion of oxaziridines into amides through deprotonation of the C–H bond with strong bases,[34] we facilitated the selectivity reversal by reducing the acidity of the C–H bond in oxaziridines via single-electron oxidation. The acidity of the C–H bond in single-electron-oxidized oxaziridines **I** is lower than that in neutral oxaziridines **17**, allowing their conversion into amides under weak base conditions. Using trifluoracetate anion ($CF_3CO_2^-$) and dimethylformamide (DMF) as weak bases, we



Scheme 7. Selective Rearrangement of Oxaziridines into Nitrones Followed by Trapping of the Nitrone by a [3 + 2] Cycloaddition. *(Ref. 32)*

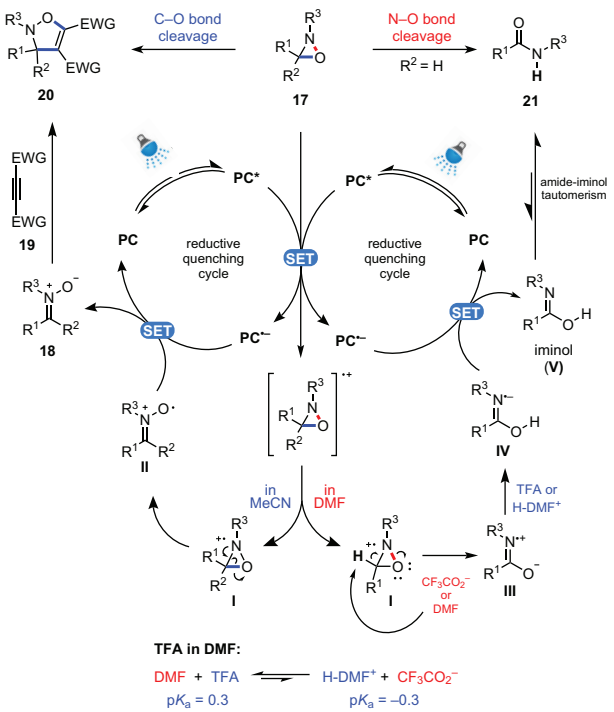


Scheme 8. Selective Rearrangement of Oxaziridines into Amides. *(Ref. 35)*

synthesized a variety of amides with broad substrate scope (**Scheme 8**).[35] Aryl-substituted oxaziridines with electron-donating or electron-withdrawing groups were found to afford the corresponding products in good-to-excellent yields. Similarly, oxaziridines containing heteroarenes, alkyl, or allyl groups readily formed the corresponding amides in moderate-to-good yields.

The selective rearrangement of oxaziridines to nitrones occurs in MeCN, ethyl acetate, or acetone as solvent. In the proposed mechanism, **PC*** oxidizes the oxaziridine to a radical cation, which then undergoes selective C–O bond cleavage to give nitrone radical **II**. Simultaneously, the photocatalyst returns to its reduced state $PC^{\bullet-}$ and reduces nitrone radical **II** to nitrone **18**. [3 + 2] Cycloaddition of **18** with alkyne **19** provides the corresponding cyclization product **20** (**Scheme 9**).[32,35] It is worth noting that nitrone **18** can be isolated by column chromatography.

The proposed mechanism for the conversion of oxaziridines to amides is depicted in Scheme 9.[35] Trifluoracetic acid and DMF are in equilibrium with $CF_3CO_2^-$ and protonated DMF (H-DMF$^+$) based on their pK_a values. DMF and $CF_3CO_2^-$ act as weak bases in the oxaziridine rearrangement. When R^2 = H, single-electron oxidized oxaziridines **I** are deprotonated by DMF and $CF_3CO_2^-$, enabling the selective cleavage of the N–O bond to generate intermediates **III**, which are then converted to intermediates **IV** via protonation by acid species. Then, single-electron reduction of **IV** followed by amide–iminol tautomerism furnish amides **21**. We verified our proposed mechanism by performing DFT calculations, which revealed that DMF and $CF_3CO_2^-$ reduce the energy of the transition state from single-electron oxidized oxaziridines **I** to intermediates **III** compared with MeCN.



Scheme 9. Solvent-Dependent and Divergent Visible-Light Photocatalyzed Ring-Opening of Oxaziridines. *(Ref. 32,35)*

4. Conclusion

In this review, we have summarized our contributions to the development of greener and more sustainable reactions proceeding via a SET mechanism in photoredox catalysis for the formation of carbon–carbon bonds and the rearrangement of oxaziridines. We have developed neutral, silicon-based precursors of alkoxymethyl, hydroxymethyl, and allylic radicals and used them in Giese reactions, RPC reactions, and imine addition reactions to form new carbon–carbon bonds. These reactions provide access to a wide range of valuable scaffolds such as ethers, alcohols, 2,3-dihydrofurans, α-cyano-γ-butyrolactones, γ-butyrolactones, allylic compounds, *gem*-difluoroalkenes, β-amino ethers, and β-amino alcohols. We have also demonstrated the selective rearrangement of oxaziridines into nitrones and amides under photocatalytic conditions. The rearrangement of oxaziridines to nitrones was selectively observed in acetonitrile, ethyl acetate, and acetone as solvents, while amides were formed through a weak-base–promoted rearrangement that utilizes weak bases such as $CF_3CO_2^-$ and DMF. Our ongoing research efforts aim to further improve silicon-based alkyl radical precursors for the generation and utilization of various alkyl radicals and to further explore the chemical conversion of oxaziridines. It is our sincere hope that our research will contribute to the expansion of ecologically friendly organic synthesis.

5. Acknowledgments

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Shafrizal Rasyid Atriardi received his B.Sc. degree in 2018 from the University of Indonesia, where he conducted research under the supervision of Professor Tribidasari A. Ivandini on the electrochemical reduction of CO_2 using metal-modified, boron-doped diamond. In the winter of 2017, he became a visiting researcher in Professor Yasuaki Einaga's group at Keio University (Tokyo, Japan), where he worked on the electrochemistry of boron-doped diamond before resuming his studies back in Indonesia. He then moved to the University of Ulsan in the fall of 2018 to pursue a doctoral degree under the supervision of Professor Sang Kook Woo. He is currently working on the development of visible-light-photocatalyzed reactions.

Sang Kook Woo received a B.S. degree in chemistry from Yeungnam University (Gyeongsan, Republic of Korea) and a Ph.D. in organic chemistry from Seoul National University under the supervision of Professor Eun Lee. He then carried out postdoctoral studies on the catalytic enantioselective carbonyl propargylation and total synthesis of polyketide natural products at the University of Texas at Austin under the guidance of Professor Michael J. Krische. In 2013, he joined the faculty at the University of Ulsan as an assistant professor of chemistry and became professor in 2023. His research focuses on the development of synthetic methodology and the synthesis of biologically active compounds.

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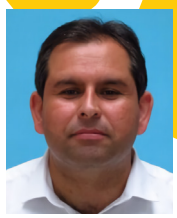
Recent Advances in the Catalytic Transformations to Access Alkylsulfonyl Fluorides as SuFEx Click Hubs

서펙스 클릭 허브를 합성하기 위한 알킬설포닐 플루오라이드로의 촉매변환에 관한 최근의 발전


Mr. B. J. Koo


Mr. S. B. Lee


Mr. W. H. Kim


Dr. M. Israr


Prof. H. Y. Bae

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Keywords. sulfur(VI) fluoride exchange (SuFEx); click chemistry; alkylsulfonyl fluoride; photoredox catalysis; electrocatalysis; transition-metal catalysis; organocatalysis.

키워드. 황(VI) 불화물 교환(SuFEx); 클릭 화학; 알킬설포닐 플루오라이드; 광산화환원촉매반응; 전기촉매반응; 전이금속촉매반응; 유기촉매반응.

Abstract. The search for new and efficient methods to access sulfonyl fluorides is of considerable research interest owing to the widespread application of these molecules in different fields. In this context, sulfur(VI) fluoride exchange (SuFEx) click chemistry is emerging as one of the most prominent such methods. The development of competent new catalytic methodologies for preparing alkylsulfonyl fluorides has become an area of special interest in organic synthesis. Compared with the substantial progress already made in the synthesis of arylsulfonyl fluorides, approaches for preparing aliphatic sulfonyl fluorides remain less explored. In this review, we summarize recent advances in four different strategies for synthesizing alkylsulfonyl fluorides: (i) photoredox catalysis, (ii) electrocatalysis, (iii) transition-metal catalysis, and (iv) organocatalysis. These reactions result in different sulfonyl fluorides that can act as bioactive molecules and building blocks suitable for further SuFEx transformation.

초록. 알킬설포닐 플루오라이드는, 새로운 클릭화학으로 주목받고 있는 '황(VI) 불화물 교환(SuFEx: 서펙스)' 를 위한 허브로서 중요한 역할을 한다. 공유결합성 의약품 및 소재과학에서 사용되는 매우 중요한 작용기임에도 불구하고, 이들은 합성하기 까다로운 물질으로 알려져 있다. 본 리뷰에서, 우리는 알킬설포닐 플루오라이드를 합성하기 위한 최근의 촉매반응개발의 노력에 관하여 정리하고자 한다. 전이금속촉매반응, 광산화환원촉매반응, 그리고 유기촉매반응이 활용되었으며, 특히 우리는 생체모방의 "on-water" 조건에서 수월하게 작동되는 유기촉매반응을 통해 이들을 성공적으로 개발하였다.

Outline

1. Introduction

Sulfonyl fluorides are important building blocks in chemical synthesis and have a diverse range of applications in materials science, chemical biology, and drug discovery.[1–3] Beginning in 2014, Sharpless and co-workers demonstrated that the sulfur(VI) fluoride exchange (SuFEx) reaction is an emerging new click reaction possessing the inimitable reactivity and stability of organosulfur fluorides.[4–6] The first-generation click reaction, the Huisgen azide–alkyne cycloaddition, has become a useful tool owing to the ligation ability of the azide and alkyne and to the utilization of mild copper catalysis.[7–10] Click reactions can work under aqueous and oxygen-tolerant conditions, resulting in excellent yields of products. Sulfonyl fluoride is more robust under acidic and basic conditions than the well-known sulfonyl chloride.[11]

Sulfur(VI)-containing compounds have been widely used in pharmaceuticals,[12–15] materials science,[16] and polymer science.[17] Interesting applications of sulfonyl fluorides in biochemistry have included the inhibition of proteases and as biological probes (**Figure 1**, Part (a)).[18–20] The SuFEx reaction between di(arylsulfonyl fluorides) and di(aryl silyl ethers) that affords polysulfonate–SuFEx polymers has unique applications in polymer science[21–24] because of its efficiency. To synthesize the functional molecules of interest, multistep processes are required in conventional approaches (Figure 1, Part (b)). Moreover, well-designed and readily available precursors are needed to apply the catalytic processes. For example, ethenesulfonyl fluoride (ESF, $H_2C{=}CHSO_2F$) has been introduced as a good Michael acceptor for the preparation of various nitrogen-, oxygen-, and carbon-based nucleophiles that can be utilized in the synthesis of functionalized alkylsulfonyl fluorides (Figure 1, Part (c)).[25–27]

In this review, we highlight new methodologies; including photoredox catalysis, electrocatalysis, transition-metal catalysis, and organocatalysis; that have been developed for the synthesis of alkylsulfonyl fluorides (Figure 1, Part (d)).

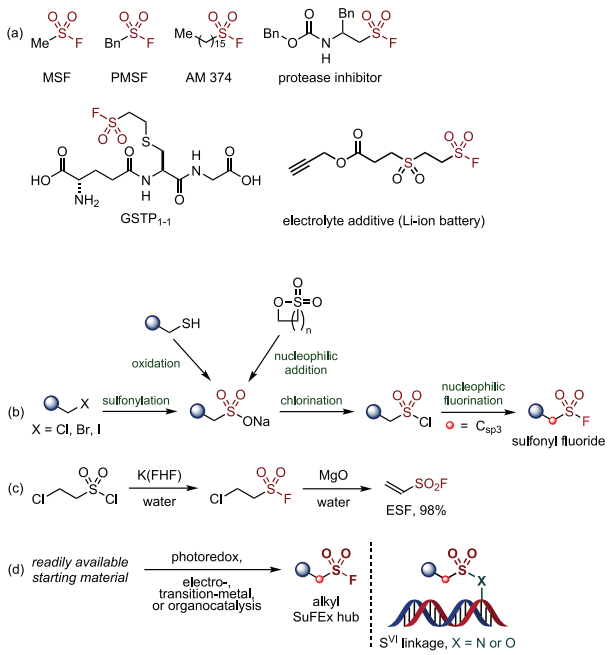
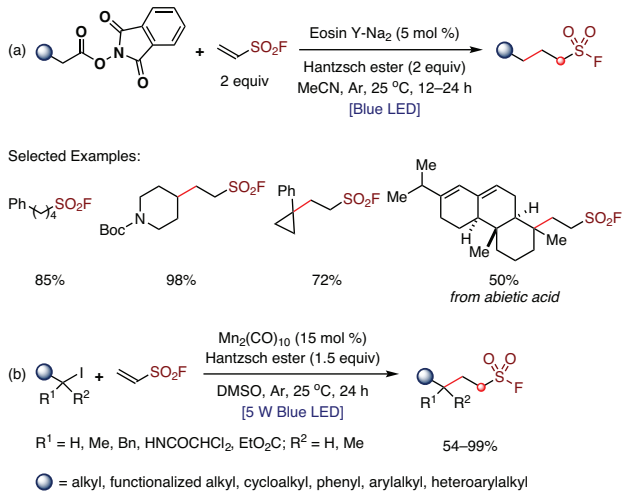


Figure 1. (a) Chemical Structures of Representative Biologically Active Alkylsulfonyl Fluorides. (b) Conventional Methods Used for the Synthesis of Alkylsulfonyl Fluorides. (c) Sharpless's Kilogram-Scale Synthesis of ESF. (d) Catalytic Synthetic Methods Highlighted in This Review.

2. Photoredox Catalysis

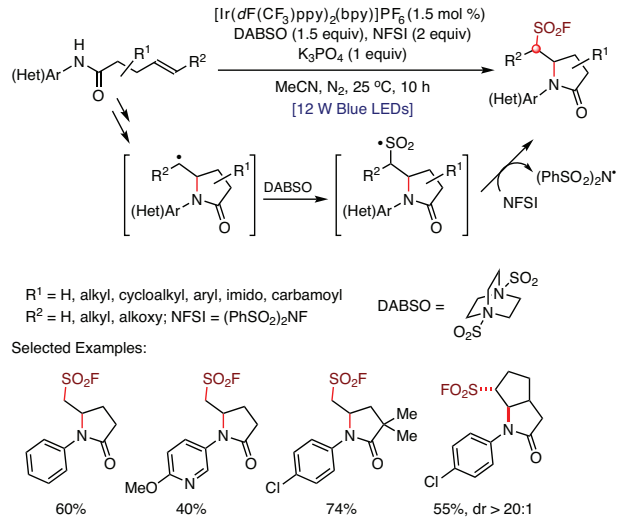
In recent decades, visible-light-mediated photocatalysis has become a valuable tool for the synthesis of functionalized and complex molecules from simple starting materials. Harnessing light to produce reactive radical intermediates is an important aspect of this strategy, providing novel bond-forming procedures that are not readily possible under thermal conditions. In general, photoredox catalysis requires very mild reaction conditions, which allows its application in the late-stage modification of highly functionalized complex polar molecules. Moreover, photoredox catalysis offers organic chemists the option of using safer, more economical, and readily accessible reagents. In 2019, Liao and co-workers reported a visible-light-mediated decarboxylative reaction for the synthesis of aliphatic sulfonyl fluorides that employs *N*-hydroxyphthalimide (NHPI) as the radical precursor and ESF as the acceptor.[28] Various aliphatic sulfonyl fluorides were synthesized from readily available alkyl carboxylic acids (primary, secondary, and tertiary), amino acids, and peptides (**Scheme 1**, Part (a)).[28] In addition, the diversification of the resulting sulfonyl fluorides was also investigated by using intramolecular cyclizations and SuFEx reactions to access different pharmaceutically important functional groups such as sultams, sulfonates, and sulfonamides. Qin's group reported a photo-catalyzed reductive addition reaction of primary, secondary, and tertiary alkyl iodides to ESF using Hantzsch ester as a hydrogen source (Scheme 1, Part (b)).[29] The synthetic utility of this latter process was achieved upon further derivatization of the aliphatic sulfonyl fluorides via SuFEx reactions to provide different sulfonates and sulfonamides that are important molecular motifs in medicinal chemistry. The reaction occurs via homolytic cleavage of the Mn–Mn bond to provide the [·$Mn(CO)_5$] radical. Subsequent reaction of [·$Mn(CO)_5$] with the alkyl iodide generates $Mn(CO)_5I$ and a nucleophilic alkyl radical that reacts with the double bond in ESF to deliver the target product. Recently, Qin's lab

reported the same approach that employs $Mn_2(CO)_{10}$ as the photocatalyst in reactions of alkyl and benzyl iodides with 2-chloroprop-2-ene-1-sulfonyl fluoride (CESF).[30]



Scheme 1. Photocatalyzed Coupling of Ethenesulfonyl Fluoride with Redox-Active Carboxylic Acid Esters and with Alkyl Iodides. *(Ref. 28,29)*

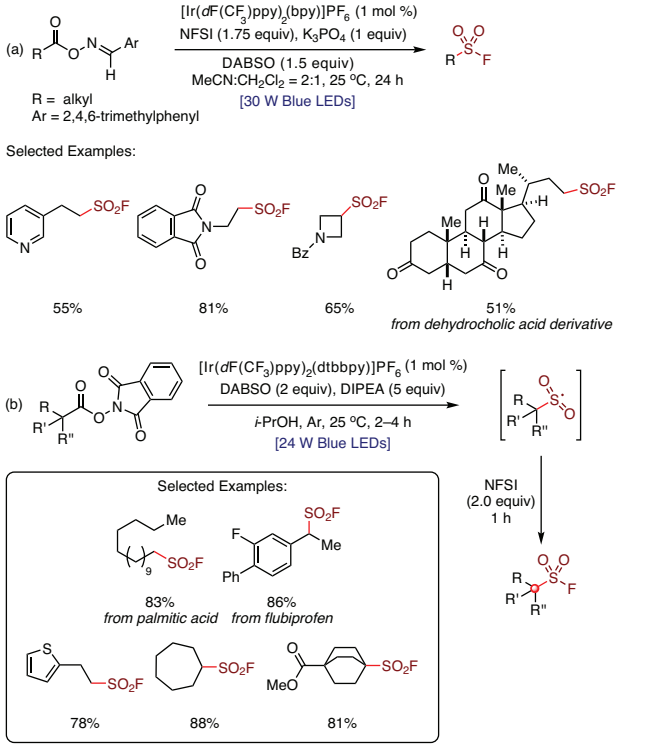
Weng and co-workers have described a three-component aminofluorosulfonylation of unactivated olefins with *N*-fluorobenzenesulfonimide (NFSI) by combining photoredox-catalyzed, proton-coupled electron transfer (PCET) activation with a radical relay pathway (**Scheme 2**).[31] Different aliphatic sulfonyl fluorides, incorporating a privileged 5-membered heterocyclic core (pyrrolidinone, oxazolidinone, and imidazolidinone), were efficiently prepared under mild conditions with good functional group tolerance. The synthetic utility of the resulting sulfonyl fluorides was investigated in a variety of transformations, including SuFEx



Scheme 2. Aminofluorosulfonylation of Unactivated Olefins. *(Ref. 31)*

reactions, transition-metal-catalyzed cross-couplings, and cascade reactions. Mechanistic experiments and Stern–Volmer studies suggested that proton-coupled electron transfer (PCET) based activation is crucial to the formation of amidyl radicals, followed by intramolecular addition to ESF, giving the γ-lactam-bearing alkyl radical intermediate. Finally, the alkyl radical is trapped with SO_2 resulting in the corresponding alkyl sulfonyl radical. This is followed by fluorine atom transfer from *N*-fluorobenzenesulfonimide (NFSI) to afford the desired sulfonyl fluoride product.

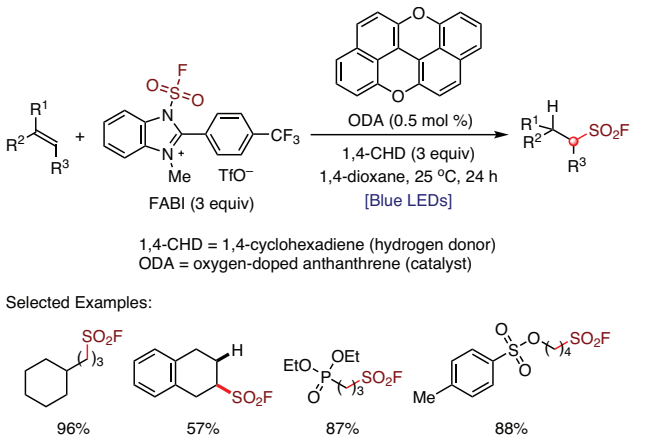
Very recently, Weng and co-workers reported the first catalytic decarboxylative fluorosulfonylation of simple aliphatic carboxylic acids to the corresponding sulfonyl fluorides. This transformation involved a simple preactivation of the carboxylic acid to the corresponding aldoxime ester followed by an energy-transfer-mediated transformation using [Ir(*d*F(CF_3)ppy)$_2$(bpy)]PF_6 as the photocatalyst (**Scheme 3**, Part (a)).[32] The same year, Nie's group disclosed another example of visible-light-mediated decarboxylative radical fluorosulfonylation via an SO_2 insertion–fluorination of NHPI esters, which are easily obtained from the corresponding aliphatic carboxylic acids.[33] This method is applicable to various aliphatic carboxylic acids (including primary, secondary, and tertiary acids), affording the desired alkyl sulfonyl fluorides (Scheme 3, Part (b)),[33] which are important intermediates in different fields of chemistry, biology, and materials science. Furthermore, the synthetic utility of the obtained sulfonyl fluorides was demonstrated by



Scheme 3. Decarboxylative Fluorosulfonylation of Aliphatic Carboxylic Acids via Their Oxime and NHPI Ester Derivatives. *(Ref. 32,33)*

their direct conversion to the corresponding sulfonyl azides and sulfonate esters.

Radical fluorosulfonylation has evolved as an attractive approach for the synthesis of highly functionalized sulfonyl fluorides. Song, Liao, and co-workers have reported the radical photocatalytic hydrofluorosulfonylation of unactivated alkenes and alkynes.[34] The transformation was enabled by 1-fluorosulfonyl-2-arylbenzoimidazolium triflate (FABI) salts as the redox-active fluorosulfonyl radical precursors along with 1,4-cyclohexadiene (1,4-CHD) as the hydrogen donor[35] to trap the key radical intermediate (**eq 1**).[34] Liao's group also employed a new radical fluorosulfonylation precursor, sulfuryl chlorofluoride (FSO_2Cl),[36] for the synthesis of aromatic and cyclic ESF. In contrast to the known radical reagents, FABI salts are bench-stable, easy to handle, and allow the radical fluorosulfonylation of terminal alkenes under photoredox conditions, resulting in high yields in the radical fluorosulfonylation reactions of challenging substrates.[37,38]

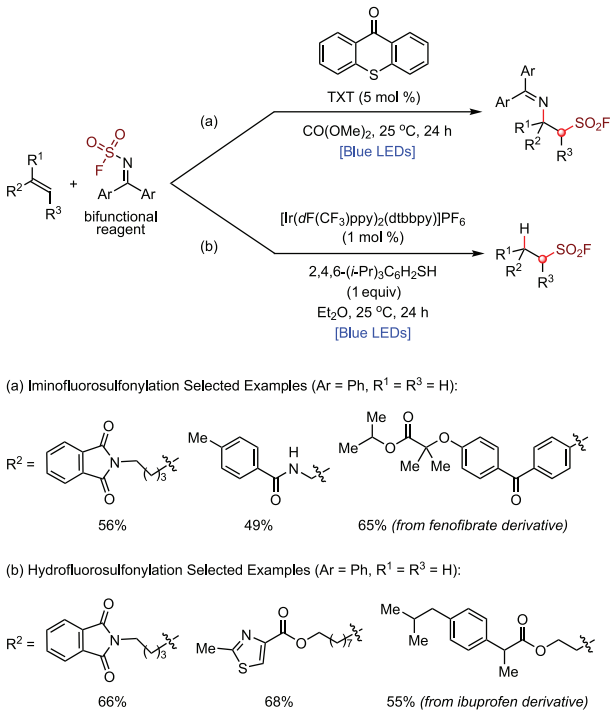


eq 1 *(Ref. 34)*

Glorius and co-workers recently reported a new bench-stable sulfamoyl fluoride reagent for preparing protected β-amino sulfonyl fluorides from functionalized alkenes (**Scheme 4**).[38] The reagent goes through N–S sigma-bond homolysis via an energy transfer (EnT)-mediated process under the influence of thioxanthone (TXT) photocatalyst (Scheme 4, Part (a)). Alternative conditions such as using $[Ir(dF(CF_3)ppy)_2(dtbbpy)]PF_6$ as photocatalyst with 2,4,6-triisopropylbenzenethiol (TripSH) as hydrogen-atom transfer agent provided a broad range of functionalized aliphatic sulfonyl fluorides (Scheme 4, Part (b)).

3. Electrocatalysis

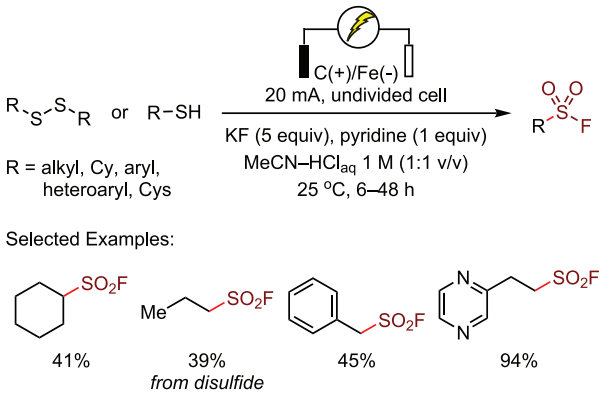
Electrochemistry utilizing a redox system is an environmentally friendly protocol that can reduce energy consumption and eliminate the need for hazardous and toxic redox reagents by replacing them with an electric current.[39] Although the electrochemical step is typically part of a multistep sequence, it gives rise to a wide range of reactive intermediates and



Scheme 4. Glorius's Photocatalytic N–S Homolysis of Sulfamoyl Fluoride Reagent to Access Functionalized Aliphatic Sulfonyl Fluorides from Alkenes. *(Ref. 38)*

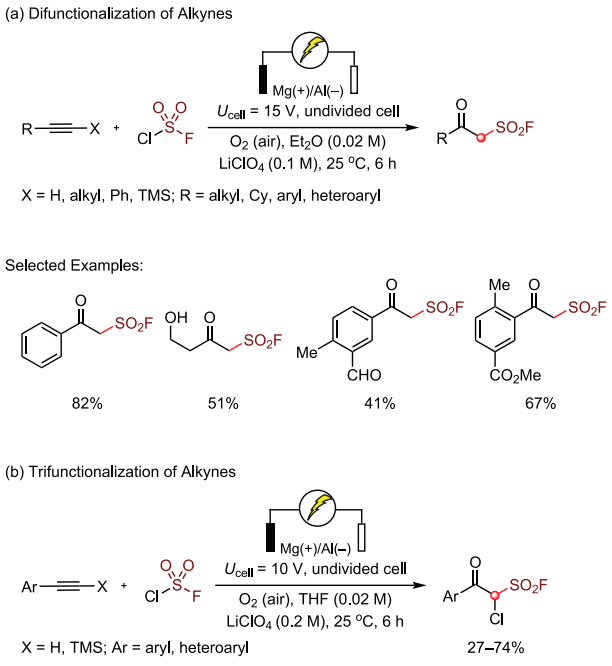
provides interesting and valuable alternatives to conventional synthetic approaches.[40,41] As redox chemistry has grown, diverse attempts have been made to directly prepare sulfonyl fluorides using electrochemistry. In 2019, Noël and co-workers reported a new electrochemical approach for the direct conversion of thiols into sulfonyl fluorides using KF as an ideal fluoride source.[42] The reaction showed a broad substrate scope, including different alkyl, benzyl, aryl, and heteroaryl thiols or disulfides, which can be converted into their corresponding sulfonyl fluorides in moderate-to-excellent yields (**eq 2**).[42] KF is considered the best fluoride source in terms of its availability, cost, and safety when compared to other fluorine sources.[43] A mechanistic study validated these redox-mediated transformations through radical trapping, while the thiol intermediate, generated from the disulfide precursor via anodic oxidation, is converted into the desired sulfonyl fluoride in the batch electrochemical system.

β-Keto sulfonyl fluorides and derivatives have showed remarkable antifungal activities against pathogenic fungi. Huang, Liao, and co-workers have reported a new method for the preparation of β-keto sulfonyl fluorides by oxo-fluorosulfonylation of alkynes using air as oxidant and sulfuryl chlorofluoride (FSO_2Cl) as the radical source.[44] A suitable electrochemical system was required to produce $FSO_2^{\bullet}$ radicals by the cathodic reduction of FSO_2Cl under continuous electron-reductive conditions. Employing Mg(+)/Al(−) electrodes and $LiClO_4$ as the electrolyte was crucial for obtaining high



eq 2 *(Ref. 42)*

yields. Solvent switching also plays a significant role in the chemoselectivity of the reaction (**Scheme 5**).[44] The reaction performed under a nitrogen atmosphere did not proceed, and a H_2O^{18} labeling study showed that the carbonyl oxygen atom of the product was derived from air. Later on, the same laboratory reported the electrochemical synthesis of β-keto sulfonyl fluorides by the radical fluorosulfonylation of vinyl triflates.[45] The main features of this reaction were the transition-metal-free conditions and the utilization of inexpensive graphite felt as the electrode.

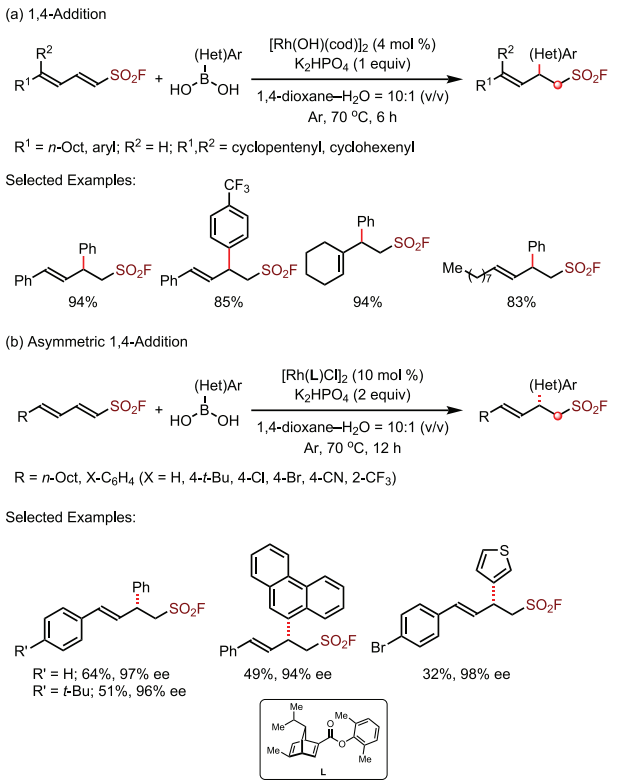


Scheme 5. β-Keto Sulfonyl Fluorides Prepared via Electrochemical Oxo-Fluorosulfonylation of Alkynes. *(Ref. 44)*

4. Transition-Metal Catalysis

The introduction of the -SO_2F functionality with inexpensive reagents such as olefins to prepare aliphatic sulfonyl fluoride bearing motifs constitutes an area of interest in molecular catalysis research. Notably, the best-known method for preparing aliphatic sulfonyl fluorides involves a transition-metal-catalyzed (asymmetric) conjugate addition reaction. Examples of the reaction include: (i) the Cu-catalyzed conjugate addition of carboxylic acids to ethenesulfonyl fluoride,[46] (ii) the zinc-mediated intermolecular reductive radical fluoroalkylsulfination of unsaturated C–C bonds with fluoroalkyl bromides and sulfur dioxide,[47] (iii) the palladacycle-promoted enantioselective hydrophosphination of α,β-unsaturated sulfonyl fluorides,[48] and (iv) the three-component reactions used to construct indolizine-containing aliphatic sulfonyl fluorides.[49]

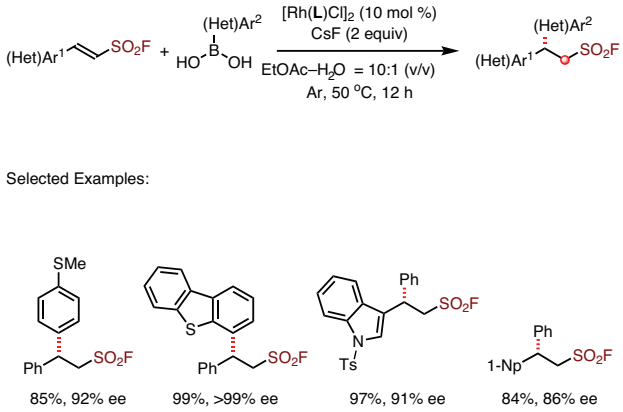
The transition-metal-catalyzed Michael addition reaction is typically used to activate C=C bonds in modern organic chemistry.[50,51] However, the addition of organometallic reagents to activated conjugated dienes is challenging due to the control required over the regioselectivity of the reaction (1,2-substitution vs 1,4-addition vs 1,6-addition). In view of the significance of the Michael addition reaction, Qin and co-workers reported a Rh(I)-catalyzed Michael addition of arylboronic acids to α,β,γ,δ-dienesulfonyl fluorides. A perfect 1,4-selectivity was observed with significant improvement over the mixture of 1,4- and 1,6-addition products obtained with conjugated dienes activated by conventional electron-withdrawing groups (**Scheme 6**).[52] The 1,4-selectivity results from the stabilization originating from the significant Coulombic attraction between



Scheme 6. Rh-Catalyzed Michael Addition of Arylboronic Acids to 1,3-Dienylsulfonyl Fluorides. *(Ref. 52)*

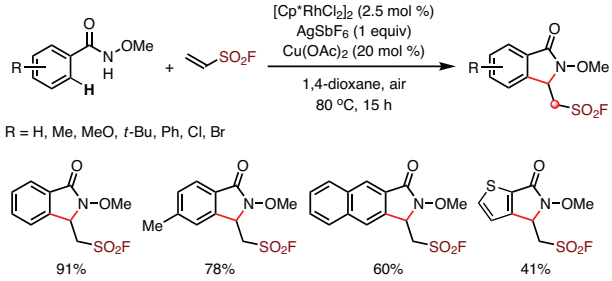
the large partial positive charge on the SO_2F-bound Rh(I) and the large partial negative charge on the C_α that is bound by a covalent bond that displays a large degree of ionic character.

The asymmetric 1,4-conjugate additions to alkenes using organoboron reagents and Rh-based catalysts[53] are useful and robust methods for forming new C–C bonds. In 1998, Hayashi reported a Rh-catalyzed asymmetric 1,4-addition of arylboronic acids to conjugated enones.[54] Moreover, Wu, Sharpless, and co-workers developed a new palladium-catalyzed method for preparing a library of diverse β-arylethenesulfonyl fluorides,[55] and the broader technology was reviewed by Barrow et al.[56] Qin's laboratory has described the first example of a Rh-catalyzed enantioselective synthesis of aliphatic SO_2F compounds made possible by the asymmetric 1,4-addition of (hetero)arylboronic acids to (*E*)-2-(hetero)arylethenesulfonyl fluorides (**eq 3**).[57] The method enabled the synthesis of previously inaccessible chiral β,β-disubstituted aliphatic sulfonyl fluorides, which could have applications in drug discovery and development research.



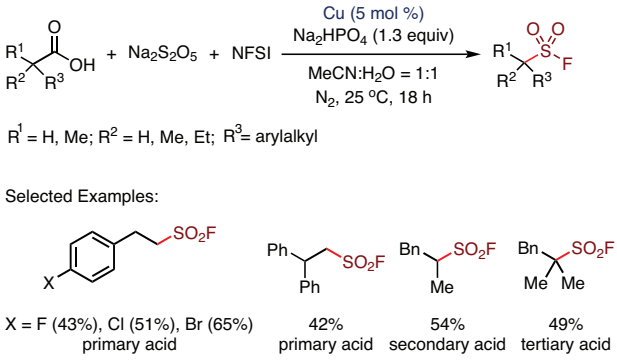
eq 3 *(Ref. 57)*

The transition-metal-catalyzed direct C–H functionalization is an excellent and proven method for constructing carbon–carbon (C–C) and carbon–heteroatom (C–X) bonds.[58] Numerous transition metals have been evaluated for the directing-group-assisted selective C–H functionalization.[59] Moreover, *N*-methoxybenzamides have inherent synthetic utility[60] and have been successfully employed as directing groups in transition-metal-catalyzed C–H alkenylation reactions with conjugated systems.[61] In 2018, Qin and co-workers developed a Rh-catalyzed oxidative coupling reaction of *N*-methoxybenzamides with ESF using a C–H bond activation approach for the synthesis of 2-arylethenesulfonyl fluorides and γ-lactams possessing a sulfonyl fluoride functional group (**eq 4**).[62] The reaction pathway was completely temperature-dependent: When the reaction was performed at 100 °C, only the ortho C–H activation products were obtained, while at 80 °C the reaction afforded the γ-lactam product resulting from an intramolecular aza-Michael addition. Furthermore, this protocol enhances the usefulness of ESF and enriches the SuFEx reaction toolbox.



eq 4 *(Ref. 62)*

Very recently, Lu, Weng, and co-workers reported a direct decarboxylative fluorosulfonylation of aliphatic carboxylic acids to prepare the corresponding sulfonyl fluorides. This copper-catalyzed process represents the first use of a Cu/NFSI combination (where NFSI is instantaneously used as a fluorine source and the N-centered HAT reagent is utilized for the cleavage of the O–H bond in the carboxylic acid) for a selective decarboxylative functionalization rather than the well-studied benzylic C–H bond functionalization. Different carboxylic acids; including primary, secondary, and tertiary acids; underwent the reaction to afford a range of structurally diverse sulfonyl fluorides in moderate-to-excellent yields (**eq 5**).[63]

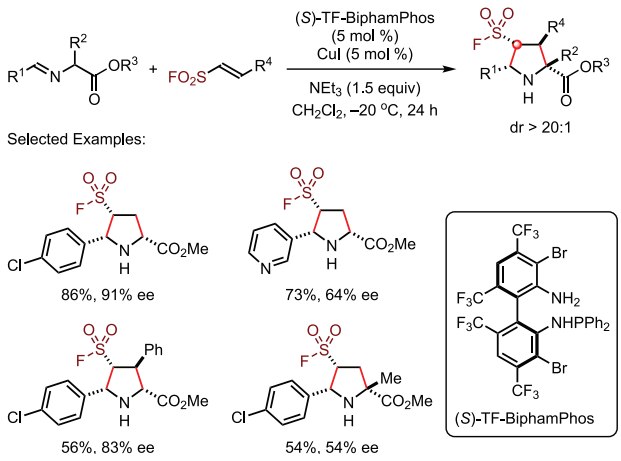


eq 5 *(Ref. 63)*

Dong, Wang, and collaborators have disclosed a Cu-catalyzed, endo-selective, and enantioselective 1,3-dipolar cycloaddition of azomethine ylides with ESFs. A library of chiral pyrrolidine-3-sulfonyl fluorides was accessed in good-to-excellent yields, diastereoselectivities, and enantioselectivities (**eq 6**).[64] Pyrrolidine-3-sulfonyl fluorides are valuable substrates in a range of synthetic applications and can be readily transformed in good yields into other useful chiral sulfonyl derivatives such as sulfonamides and sulfonates.

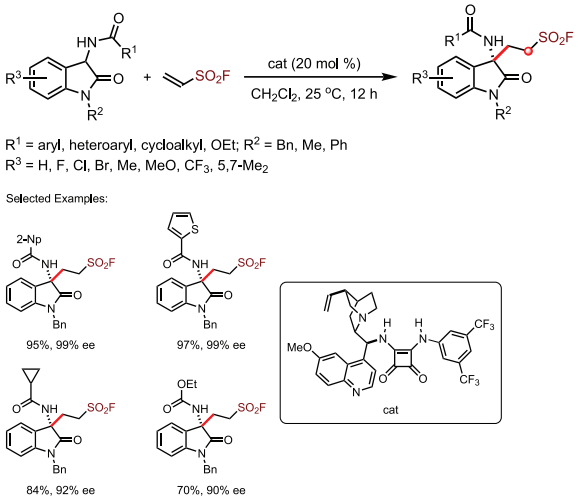
5. Organocatalysis

The 2021 Noble Prize in Chemistry was awarded for research breakthroughs in asymmetric organocatalysis. Moreover, in the last two decades, the functionalization of simple alkenes has been deemed a powerful tool for the generation of



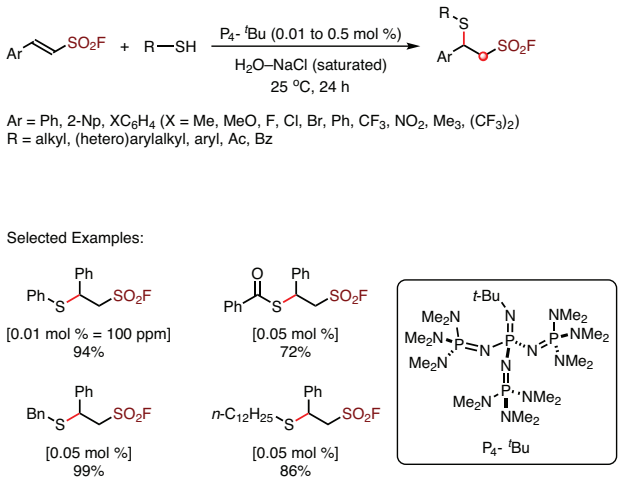
eq 6 *(Ref. 64)*

highly functionalized skeletons in organic synthesis, and has prompted chemists to develop new functionalization strategies. In addition to simple olefin C–C bond forming reactions, the Michael addition of simple nucleophiles to sulfonyl fluoride electrophiles has attracted significant interest in recent years. Moreover, organocatalysis has enabled the Michael addition of readily accessible starting materials, such as 4-amido-5-hydroxypyrazoles,[65] *N*-2,2,2-trifluoroethylisatin ketimines,[66] and azlactones[67] (Michael donors) to ESF. In 2019, Yan's group reported the asymmetric Michael addition of ethylene sulfonyl fluorides to 3-amido-2-oxindoles efficiently catalyzed by quinine-derived squaramides.[68] Mechanistic studies by the authors established that the reaction proceeds through a bifunctional activation pathway. A variety of 3-amido-2-oxindolesulfonyl fluorides were formed under mild conditions in excellent yields and enantioselectivities (**eq 7**).[68] Further elaboration of the sulfonyl fluorides to optically active sulfamides, sulfonates, and spirocyclic oxindole γ-sultams was also accomplished.



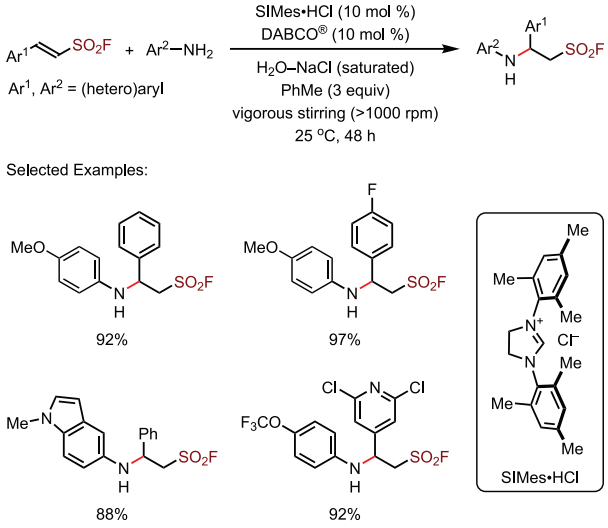
eq 7 *(Ref. 68)*

In 2022, our group reported a novel thia-Michael addition reaction catalyzed by a phosphazene superbase and utilizing substantial "on-water" hydrophobic amplification to obtain β-aryl-β-sulfidosulfonyl fluorides with excellent chemo- and site-selectivity.[69] Different thiols and β-arylated ESFs were successfully converted into the corresponding thia-Michael adducts in excellent yields (**eq 8**).[69] Furthermore, a protected chiral amino acid, *N*-Boc-L-cysteine methyl ester, was transformed into the corresponding thia-Michael product in >99% yield. Preliminary mechanistic investigations suggested that the reaction proceeds via a typical Michael addition pathway. When compared to conventional organic solvents, this thia-Michael addition reaction showed a rapid rate acceleration under "on-water (saturated NaCl)" conditions. This substantial rate acceleration might be ascribed to the "hydrophobic hydration" of the reaction components.[70]



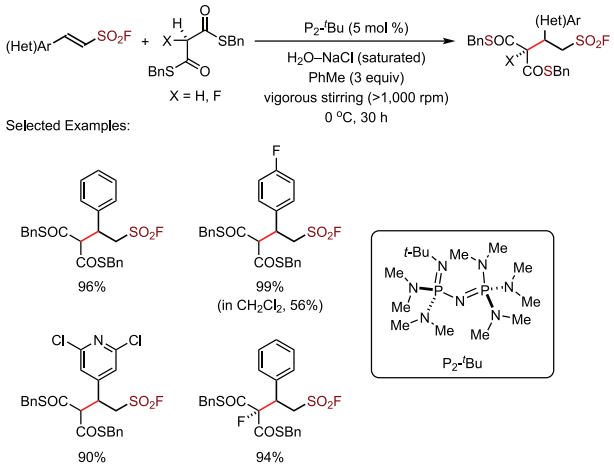
eq 8 *(Ref. 69)*

The N-heterocyclic carbene (NHC) catalyzed, water-promoted synthetic approaches have received considerable interest in recent years.[71] However, the use of water as a solvent in NHC-catalyzed, polarity-inversion reactions is still limited. Very recently, our research group reported a water-accelerated, NHC-catalyzed aza-Michael addition reaction that delivers a variety of β-amino sulfonyl fluorides.[72] The gram-scale synthesis, annulation to sultam molecules, and more interestingly, the SuFEx reaction of phenolic bioactive molecules were achieved. Water plays a significant role in enhancing the reaction rate with excellent chemo- and site-selectivity (up to >99:1) when compared to organic solvents. Control experiments and mechanistic and computational studies support non-covalent activation over NHC catalysis under "on-water" conditions (**eq 9**).[72] Consequently, we posited that the typical hydrophobic amplification[73] derived from biphasic hydrophobic solvation[74] may increase the reaction rate. The generated and confined water-embraced organic cages may have a high-pressure-like effect when the reaction mixture is vigorously stirred (>1,000 rpm).



eq 9 *(Ref. 72)*

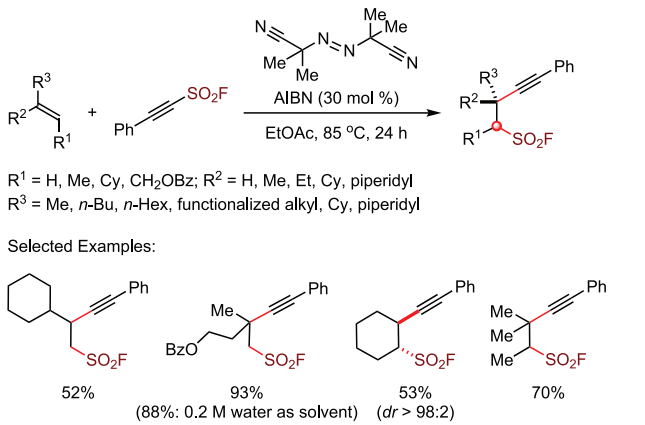
Our group recently reported an efficient synthesis of γ-geminal dithioester-functionalized alkylsulfonyl fluorides by a Michael addition reaction catalyzed by a phosphazene superbase, P_2-^{t}Bu (**eq 10**).[75] The reaction utilizes benzyl dithiomalonates (DTM) as the enolate donors and β-arylated ESFs as the Michael acceptors, resulting in significant reactivity enhancement under the aqueous reaction conditions. Intermolecular SuFEx click reactions with bioactive molecules such as carvacrol and estrone were also achieved using this approach. Density functional theory was a powerful tool for investigating the formation of the desired γ-geminal dithioesters through the hydrogen-bonded C_{sp3}–C_{sp3} bond-forming transition state preorganization that was facilitated by the P_2-^{t}Bu catalyst in the Michael addition step.



eq 10 *(Ref. 75)*

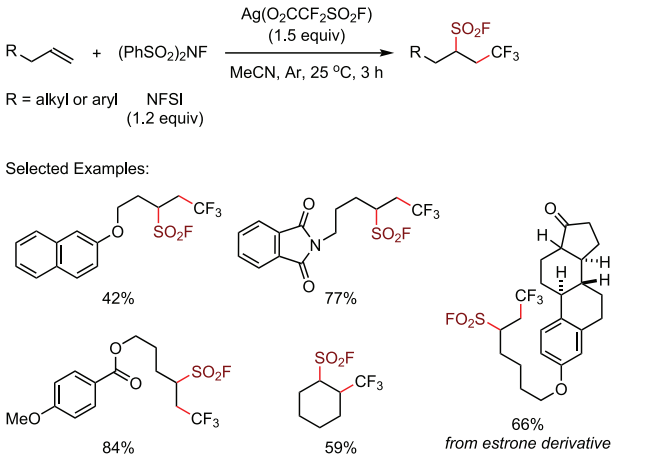
6. Miscellaneous Reactions

Recently, Studer and co-workers developed a radical-mediated 1-fluorosulfonyl-2-alkynylation of unactivated alkenes for the synthesis of β-alkynyl-fluorosulfonylalkanes.[76] In this method, 2-substituted alkynyl-1-sulfonyl fluorides (SASF) were employed as FSO_2 radical donors, while azobisisobutyronitrile (AIBN) was utilized as a radical initiator. The developed protocol shows excellent functional group tolerance and offers an easy way to synthesize several aliphatic sulfonyl fluorides (**eq 11**).[76] The β-alkynyl-fluorosulfonylalkanes can be further transformed using established SuFEx click chemistry to access different sulfonates and sulfonamides.



eq 11 *(Ref. 76)*

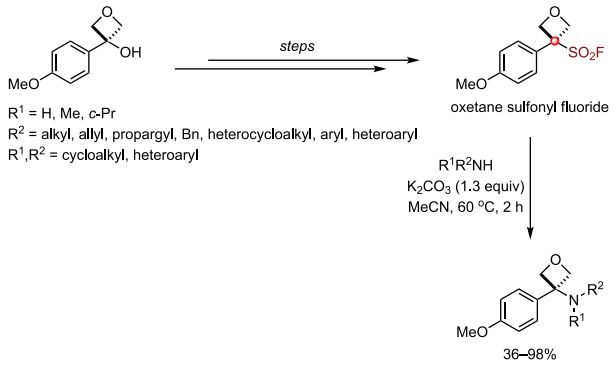
Fluorination of the SO_2 group is a crucial process for directly accessing sulfonyl fluorides. Therefore, NFSI is widely used as an electrophilic fluorination reagent. In 2016, Shavnya et al. developed a one-pot synthesis of unsymmetrical sulfones and sulfonamides using a combination of alkyl halides and rongalite (sodium hydroxymethylsulfinate).[77] Furthermore, this efficient method enabled the synthesis of some representative aliphatic sulfonyl fluorides by treating the alkylated rongalite intermediate with NFSI. In 2017, Chen, Liu, and co-workers reported a novel, radical-based intermolecular trifluoromethylfluorosulfonylation



eq 12 *(Ref. 78)*

of unactivated olefins with readily accessible $Ag(O_2CCF_2SO_2F)$ and NFSI as electrophilic fluorine sources (**eq 12**).[78] A detailed mechanistic study showed that $Ag(O_2CCF_2SO_2F)$ decomposed in situ to form SO_2 and $AgCF_3$, with the latter species serving as the source of the CF_3 radical. Reaction of the CF_3 radical with the alkene substrate generates an alkyl radical, which, upon reaction with SO_2 and subsequent electrophilic fluorination with NFSI affords the corresponding sulfonyl fluoride product. In the absence of the alkene, the radicals are prone to self-coupling, leading to CF_3SO_2F as a byproduct. Therefore, the simultaneous introduction of the reagents is required to obtain the desired trifluoromethyl-substituted alkyl sulfonyl fluorides.

Subsequently, the same group developed an intermolecular oxidative fluoroalkylfluorosulfonylation reaction of unactivated alkenes by using NFSI and 1,4-diazabicyclo[2.2.2]octane-bis(sulfur dioxide), DABSO, as the SO_2 radical donor source.[79] In this process, silver fluoroalkyl (AgR_F) complexes were generated from the combination of AgF and TMS—R_F. Furthermore, the same lab reported a new direct route for preparing aliphatic sulfonyl fluorides via reductive decarboxylative fluorosulfonylation of aliphatic carboxylic acid NHPI esters and NFSI.[80] Several aliphatic carboxylic acids, including primary, secondary, and tertiary acids, along with various natural and pharmaceutically important acids, were transformed into different biologically active aliphatic sulfonyl fluorides under aqueous conditions. Inspired by these results, Tang, Wang, and co-workers developed an "on-water" and catalyst-free fluorination reaction of sulfonyl hydrazides in the presence of NFSI to afford aryl- and alkylsulfonyl fluorides.[81] Sharpless demonstrated the fluorination of aliphatic sulfonyl chloride with KHF_2 in water as a cornerstone for the synthesis of ESF.[27] Talko and Barbasiewicz developed an advanced method utilizing KHF_2 and $(n\text{-Bu})_4NCl$ as a phase-transfer catalyst for long-alkyl-chain sulfonyl chlorides.[82] This phase-transfer-catalyzed fluorination reaction provides enhanced synthetic reactivity under environmentally benign conditions. Recently, Bull and co-workers described the synthesis of amino-oxetanes by a defluorosulfonylative coupling of sulfonyl fluorides catalyzed by inorganic base.[83] This method allowed the synthesis of a library of oxetanesulfonyl fluorides, which underwent extrusion of sulfonyl fluoride and coupling with an amine to generate the amino-oxetanes. Moreover, direct electrophilic fluorination using Selectfluor® is required because some lipophilic sulfinate salts are unstable. The prepared oxetanesulfonyl fluorides can be converted into the corresponding amino-oxetanes via a defluorosulfonylative amine coupling rather than forming the SuFEx adduct. The introduction of K_2CO_3 prevents nucleophilic fluorination due to the decomposition of sulfonyl fluoride through production of KF, resulting in a quarantined insoluble organic medium. This methodology represents a breakthrough for the extremely limited direct access to amino acids (**Scheme 7**).[83] A Li-catalyzed, chemoselective thiol alkylation with oxetanols, also developed by Bull's group, generates oxetane sulfides via C–OH activation by $Li(NTf_2)$.[84] The subsequent oxidation to sulfone using *m*CPBA proceeds with sulfinate elimination.



Scheme 7. Synthesis of Oxetanesulfonyl Fluorides and Amino-Oxetanes by a Defluorosulfonylative Coupling Reaction of the Sulfonyl Fluorides. *(Ref. 83)*

7. Conclusions and Outlook

We have surveyed the synthesis of alkylsulfonyl fluorides via carbon–carbon or carbon–heteroatom bond formation and their fluoride exchange (SuFEx) reaction with suitable coupling partners. Reactions of the SO_2F functional group provide access to a wide variety of carbo- and heterocycles upon activation through photoredox catalysis, electrocatalysis, transition-metal catalysis, and organocatalysis. We believe that these methods will contribute to the expansion of sulfonyl fluoride containing compound libraries for pharmaceutical and agrochemical research.

8. Acknowledgment

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(†) These two authors contributed equally to this work.

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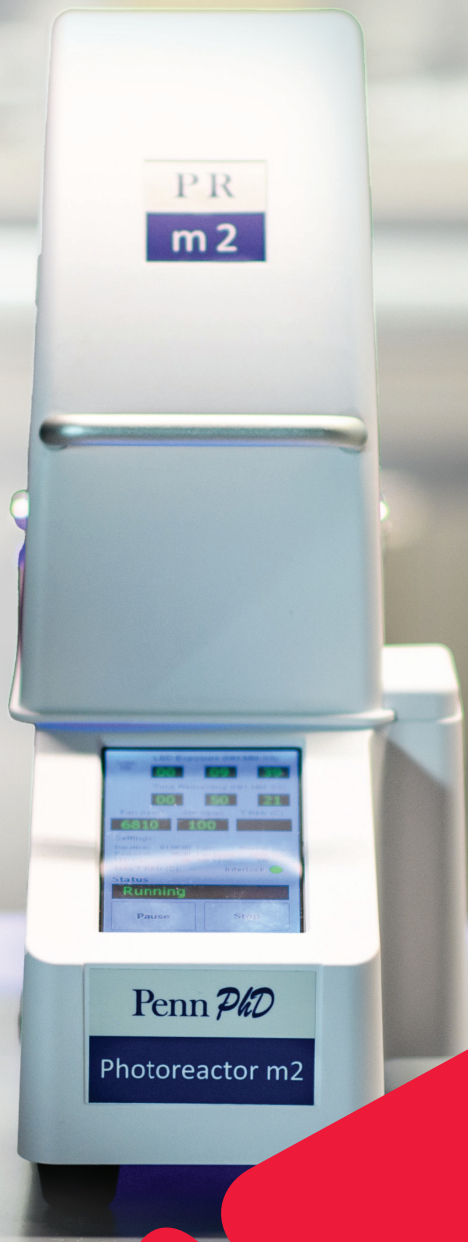

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