Catalyst-Free Reactions under Biocompatible Conditions

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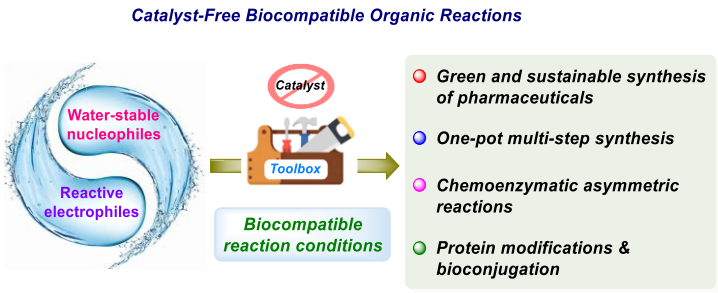

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Abstract Catalyst-free biocompatible reaction is a class of green chemical processes that are also applicable to the field of chemical biology. In this account, we detailed our journey in this exciting area of research since 2000. Various types of catalyst-free biocompatible reactions such as the Mukaiyama-aldol reactions and thiol-specific 'click' reactions, and their applications to the functionalization of proteins are described. These reactions worked well without destroying the 3-dimensional structures of the proteins. Other reactions include the C-SO_2 and C-N bond forming reactions were also discussed. These reactions work in a truly green manner where organic solvents can be totally avoided. This toolbox of green chemical processes will certainly facilitate researchers working in the pharmaceutical industries.

Key words catalyst-free, biocompatible, Mukaiyama-aldol, allenic amide, antibody-drug conjugates, green chemistry

1 Introduction

The development of catalyst-free reactions that can work under biocompatible reaction conditions (aqueous media, pH 7.0, rt, etc.) is one of the most important goals in green chemistry and chemical biology.[1] Furthermore, performing catalyst-free reactions in water have many other advantages.[2] In contrast to the commonly used toxic, expensive and flammable organic solvents, water is cheap, abundant and safe. Reactions carried out in water can avoid the need to protect-deprotect reactive functional groups such as hydroxyl group, therefore significantly increasing the overall efficiency of the synthetic route. Water-soluble substrates such as hydrates of aldehydes, carbohydrates etc. can be used directly without the need for pretreatment.[3] Unfortunately, there are also challenges when carrying out reactions in water. For example, most of the organic compounds are not soluble in water, therefore making it extremely difficult for the reactions to occur in many cases. Although the addition of a green co-organic solvent such as ethanol, etc. can help to alleviate some of these problems, the need to use organic solvents for workout and purification after completion of the reactions also defeat the purpose of using water as a green solvent. Moreover, many organometallic reagents and Lewis acid catalysts are also not stable in water. In recent years, water-tolerant variants have emerged but have yet found wide applications due to their high cost and disposal problems. In addition, water-waste is also difficult to treat in many cases. To overcome these problems, the development of highly atom-economical reactions that produce minimum or no wastes is highly important and desirable.

Despite these challenges, the push to develop greener and safer chemical processes in the chemical and pharmaceutical industries have spurred researchers to develop green synthetic methodologies that can work in water.[4] Catalyst-free water-based reactions that can work under biocompatible reaction conditions are not only green but also applicable to the functionalization of biomolecules such as peptides and proteins. They also have the benefits of carrying out one-pot multistep reactions including chemo-enzymatic asymmetric transformations and may also be performed in the living systems. As such, many groups including our research group since the early 90s have been focusing on the development of a toolbox of green synthetic methods, and applying them to the synthesis of complex natural products and biologics.[5]

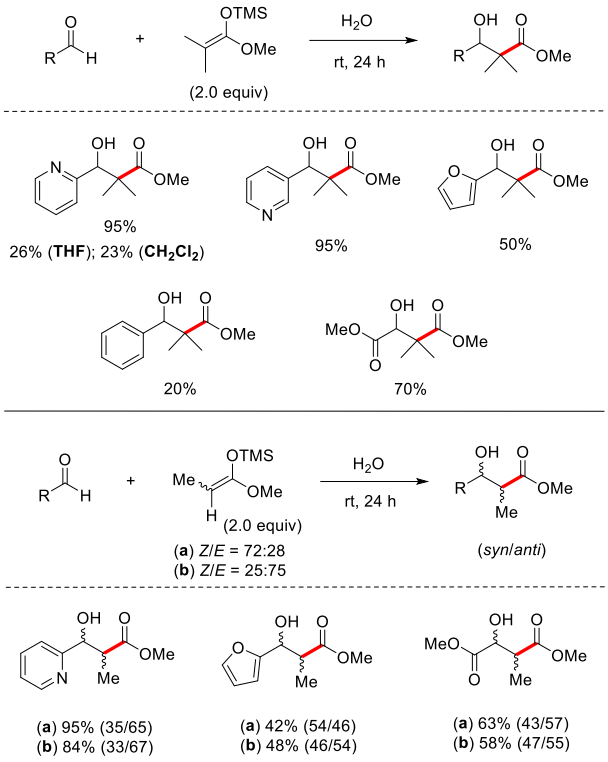
As mentioned earlier, there are many research groups that have contributed to the advancement in this fascinating area. One of the earliest examples include the catalyst-free Diels-Alder reaction in water which was later popularized by Breslow.[6] Breslow has shown that Diels-Alder reaction proceeded faster in water than in organic solvents. It was proposed that the hydrophobic effect due to preference for organic compounds to aggregate together in water is one of the major reasons for the faster reaction.[7] This seminal discovery has spurred extensive research interests in the development of new water-based reactions. In 2005, Sharpless reported that water-insoluble substrates tend to react on water.[8] Other reactions include the 2022 Nobel-Prize winning Huisgen click reactions reported by Sharpless,[9] Meldal,[10] and Bertozzi,[11] the multicomponent Ugi reaction,[12] and many native amino acid (cysteine, lysine, tyrosine, tryptophane, etc.) bioconjugation methods.[5] Despite these advances, catalyst-free organic reactions in water are still rather limited.

We envisage that reactions using highly reactive electrophiles such as aldehydes, *α,β*-unsaturated carbonyls, activated allylic alcohols, etc. with water-stable nucleophiles such as silyl enols, indoles, arenes, alkenes, thiols, amines, etc. may lead to the discovery of novel catalyst-free reactions in water. In order to make sure that the reactions developed are truly catalyst-free in nature, it is important to take the following precautions when working on catalyst-free water-based reactions: new reaction flasks and stirring bar must be used to avoid the reactions catalyzed by trace amount of metal leftover from previous experiments. Moreover, reactions must also be carried out in plastic or Teflon flasks to alleviate reactions catalyzed by silicates, and it is also important to make sure that substrates used in the reaction is free from metal contamination that may catalyze the reaction.[1]

In this personal account, we would like to detail our continuous efforts and latest achievements in this fascinating area of research. This account will be summarized according to the type of reactions.

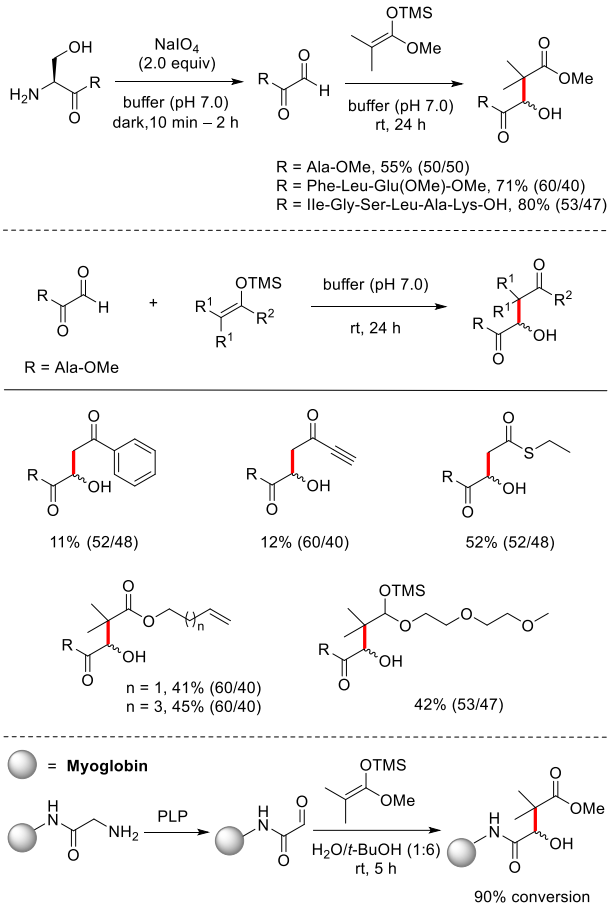
2 C-C Bond Formation Reactions: The Mukaiyama-Aldol Reactions

Due to the importance of C-C bond in organic synthesis, many different types of catalyst-free C-C bond forming reactions have been reported.[13] Among these C-C bond forming reactions, the aldol reaction is one of the most important C-C bond forming reactions in organic synthesis due to their ability to construct synthetically useful β-hydroxy carbonyl compounds. The direct Aldol reactions using reactive aldehydes with carbonyl compounds containing α-carbon acidic hydrogen have been reported. Unfortunately, the need to use strong acid or base may pose problems during some of their applications. The Mukaiyama-aldol variant is an attractive alternative but it is commonly carried out under anhydrous inert atmosphere in the presence of Lewis-acids.[14] The first Mukaiyama aldol reactions in water without the use of Lewis acid catalyst has been reported by Lubineau.[15] Unfortunately, the reactions carried out in water without activation afforded the desired products in low yields. Early in 2000, we reported a catalyst-free Mukaiyama-aldol reaction that worked in water without any special activation (Scheme 1).[16] This reaction worked well with reactive aldehydes such as glyoxylates, furfural aldehydes, etc. Various silyl enol ethers and silyl ketone acetals were found to be effective nucleophiles for the reactions.



Scheme 1 Water-accelerated Mukaiyama-aldol reactions of ketene silyl acetals with aldehydes

Later in 2010, we applied this water-accelerated Mukaiyama-Aldol reaction for the functionalization of *N*-terminal proteins (Scheme 2).[17] The feasibility of this reaction with protein was first demonstrated using myoglobin which contain a *N*-terminal glycine amino acid. Using both the chemical or biological method, the terminal amino group could be easily converted to the aldehyde. The biological method using PLP reported by Francis was preferred as it provided the desired aldehyde in better purity.[18] Reactions of this protein aldehyde with various silyl ketone acetals proceeded smoothly to afford the β-hydroxy carbonyl compounds in moderate to good yields. The reactions were relatively fast and highly efficient. The incorporation of additional functional groups such as alkyne for "click" reaction was also successful. Most importantly, the protein adducts were obtained with the 3-dimensional structures intact and the enzymatic activities of the proteins were also preserved. The successful applications of this type of reaction for protein functionalization will open up new avenues to label protein as well as access protein conjugates via metal-free chemical functionalization.



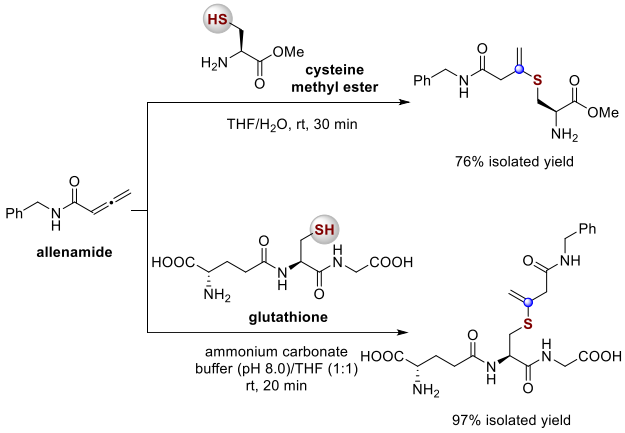
Scheme 2 Water-based Mukaiyama-aldol reactions of ketene silyl acetals with peptide aldehydes

3 C-S Bond Formation Reactions: Allenic Amide as the Electrophiles

As mentioned earlier, click reactions involving Huisgen-type reaction have been used widely in chemical biology.[9,10] The biorthogonality of this reaction makes it especially attractive for chemical biology applications.[11] Unfortunately, the difficulty to introduce the azide or alkyne moiety into biomolecules substantially increases the cost of the process. In our efforts to develop new bioconjugation technology that target a specific native amino acid such as cysteine in the protein, we investigated the thiol-click reaction using allenic amide as the electrophile.[19]

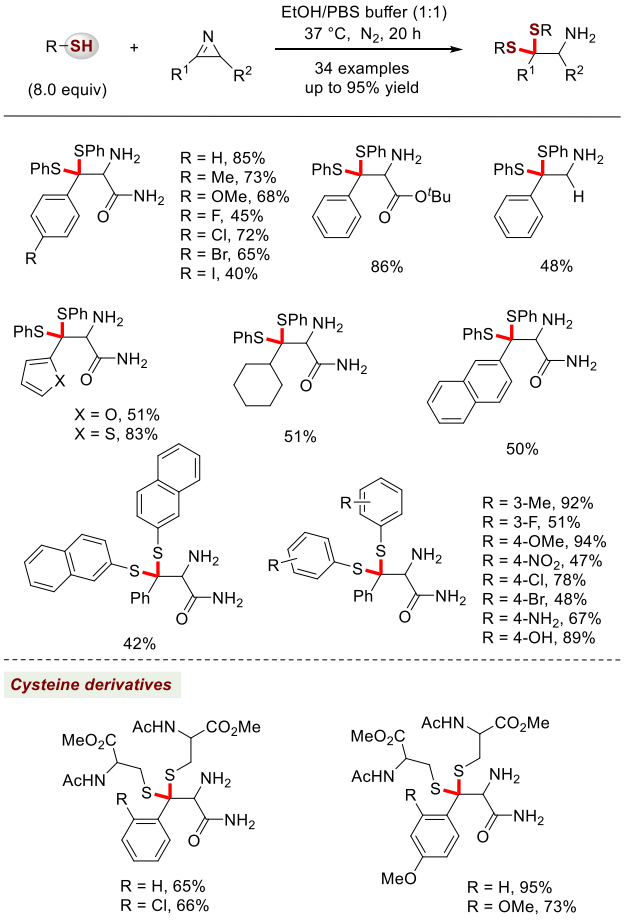
In 2014, we reported an efficient and highly chemoselective C-S bond forming reaction using allenic amide as the electrophile (Scheme 3).[20] The reaction is highly selective, reacting selectively with cysteine moieties in unprotected peptides and proteins. The reaction between allenic amide and cysteine proceeded smoothly in aqueous buffer with excellent chemselectivity in almost quantitative yields, forming a

stable conjugate. The allenic amide used in this strategy were proven to be a powerful and multifaceted linker for cysteine bioconjugation and could be employed for the synthesis of antibody-drug-conjugates (ADCs). This reaction was easy to handle and extremely fast, usually completing in less than 10-20 mins. Comparing with the classical thiol-maleimide click reaction, our allenic amide-thiol click reaction can even be carried out in amine buffer. In contrast with the maleimide thiol product, the allenic thiol products did not readily undergo *retro*-Micheal reaction.



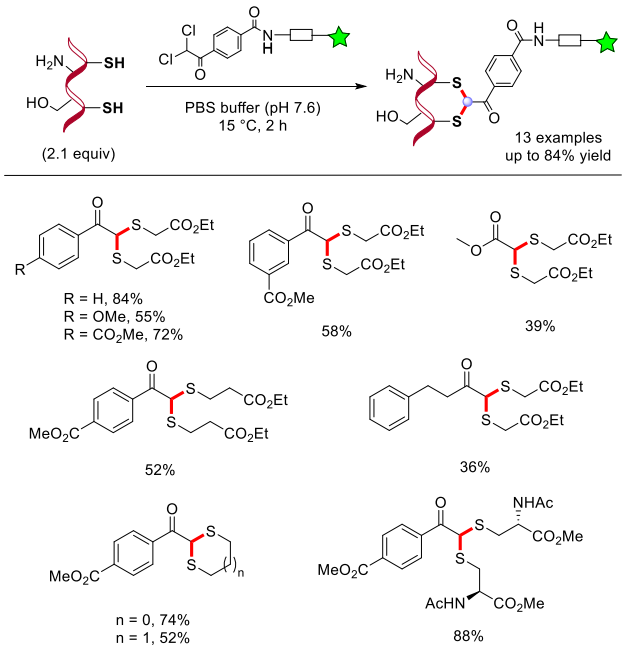
Scheme 3 Highly selective modification of cysteine in peptides and proteins under biocompatible conditions

With the current focus in biologics and antibody-drug conjugates research, many of these established conjugation strategies will need to have excellent drug-to-antibody ratio (DAR) control as it is important in the biological activities of antibody-drug conjugates. Many of the antibody-drug conjugates currently approved by FDA have 3-4 S-S groups in the antibody delivery system. Reduction of the S-S groups resulted in 6-8 free thiol groups that may participate in the conjugation with the payload. On the other hand, DAR 3-4 gave the most active compounds. Therefore, the development of a conjugation technology that can bind one payload with 2 thiol groups conjugation may solve this problem. In 2020, our group reported 2*H*-azirine as a novel type of linker for cysteine residues under biocompatible reaction conditions (Scheme 4).[21] Under the conditions, the C=N double bond was cleaved to generate an amino amide molecule in situ via the addition of the thiol groups, thereafter opening the azirine ring in the process. The reaction exhibited a broad substrate scope under catalyst-free and ambient conditions. Interestingly, peptides bearing cysteine moieties also worked effectively under a phosphate buffer system.

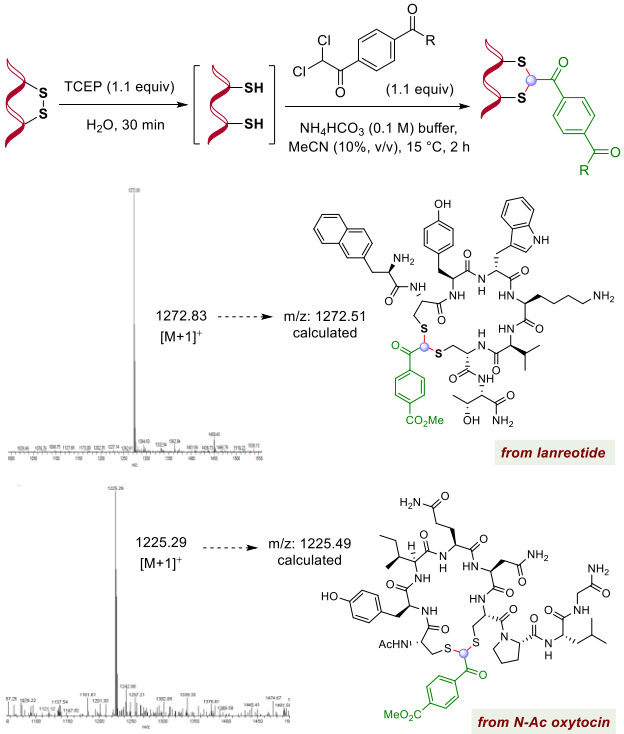


Scheme 4 2*H*-Azirines as bifunctional chemical linkers of cysteine residues

In the same year, our group also developed a disulfide bridging in peptides by elegantly employing dichloroacetophenones as chemical linkers (Scheme 5).[22] This strategy is extremely selective, highly atom-economic and operates under benign and biocompatible conditions. These two technologies will be applicable to ADC synthesis with a more controlled DAR. In addition, they also provided efficient methods for the protection of carbonyl compounds to form dithiane. In this work, we also demonstrated the application of this strategy in disulfide bridging of commercially available peptides lanreotide and *N*-Ac-oxytocin (Scheme 6).



Scheme 5 Dichloroacetophenones as a new class of bioconjugation reagents



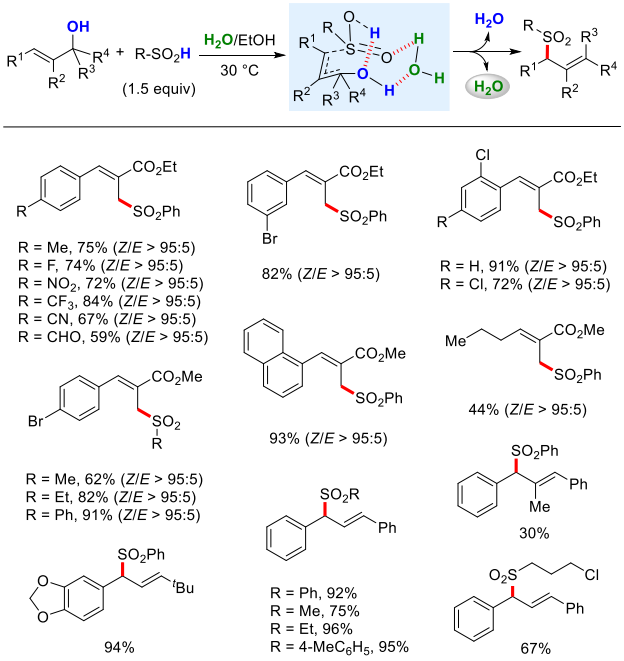
Scheme 6 Disulfide bridging of lanreotide and *N*-Ac oxytocin

4 C-SO_2R Bond Formation Reactions

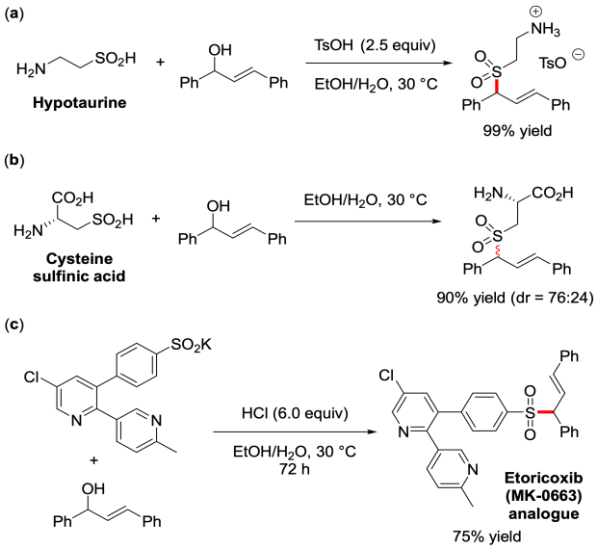
4.1 Allylic Alcohols as the Electrophiles

Allylic sulfones are key fragments that are featured widely in a variety of synthetic building blocks and anti-cancer agents.[23] Unfortunately, classical methods to access this class of compounds usually involve the use of metal catalysts under acidic or basic conditions.

In 2018, we reported a water-based C-SO_2R bond formation reaction using activated allylic alcohols as the electrophiles (Scheme 7).[24] This reaction proceeded through a dehydrative cross-coupling of sulfinic acids and allylic alcohols under metal-free conditions. The reaction was found to be highly effective and useful due to its environmentally-friendly conditions (metal-free, neutral, aqueous solvent, ambient temperature) and especially noteworthy is that the desired allylic sulfones can be easily isolated by simple filtration without the need for other purification techniques such as liquid-liquid extraction or column chromatography. The mild reaction conditions, using green water as the solvent, highly atom-economy with water as the byproduct and totally avoiding the use of organic solvent in the reaction, make this process an ideal green chemical process in organic synthesis. More interestingly, water was found to be crucial for this dehydrative transformation. On the basis of DFT calculations, water was found to act as a promoter via intermolecular hydrogen bonding. Hypotaurine and cysteine sulfinic acid were also compatible substrates for this dehydrative coupling, affording the corresponding dehydrative products in excellent yields (Schemes 8a and b). Moreover, we also applied this strategy for the synthesis of etoricoxib (MK-0663) analogue (Scheme 8c).



Scheme 7 Catalyst-free water-promoted C-S bond formation reactions

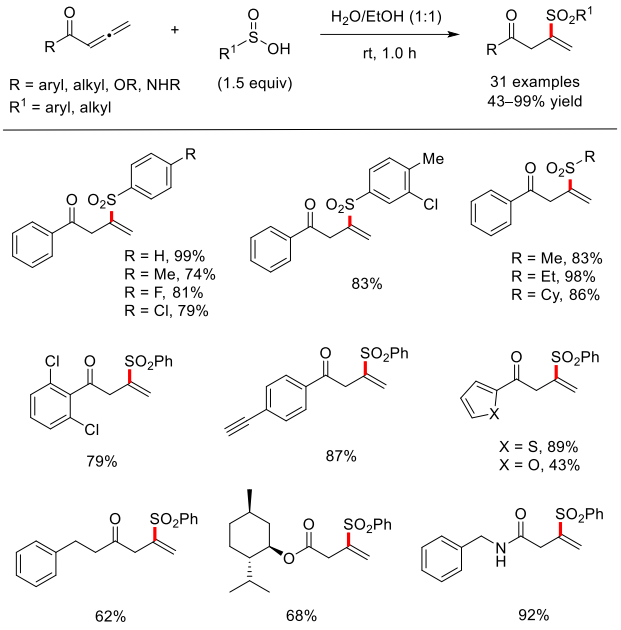


Scheme 8 Synthetic applications of catalyst-free C-S bond formation reactions

4.2 Allenic Carbonyl Compounds as the Electrophiles

Vinylic sulfones are important moieties featured widely in a myriad of biologically and pharmaceutically active molecules (such as anticancer agents, cysteine protease inhibitors, antibacterial agents, and TSH receptor antagonists).[25] They are also synthetically useful building blocks in modern organic synthesis and have also been widely used as linkers in protein and material science. However, many of the reported methods suffer from various setbacks including the need to use toxic reagents/solvents, metal catalysts, and harsh reaction conditions and their poor atom-economy. A well-developed green synthetic methodology to synthesize vinylic sulfones can potentially supplement or replace existing strategies, thereby significantly reducing chemical waste and offering an alternative approach to access this crucial class of compounds.

In 2021, we reported an efficient method to effect vinylic sulfination of allenic carbonyl compounds in an environmentally friendly manner (Scheme 9).[26] Remarkably, the reaction can be performed in water/ethanol solvent mixture under metal-free conditions where solid vinylic sulfones can be isolated without chromatography. In this protocol, an excess amount of sulfinic acid improves the yield of the reaction. The reaction worked with a wide variety of sulfinic acids and allenic ketones. With this newfound protocol, we have increased the reactions in the toolbox of green synthetic methods.



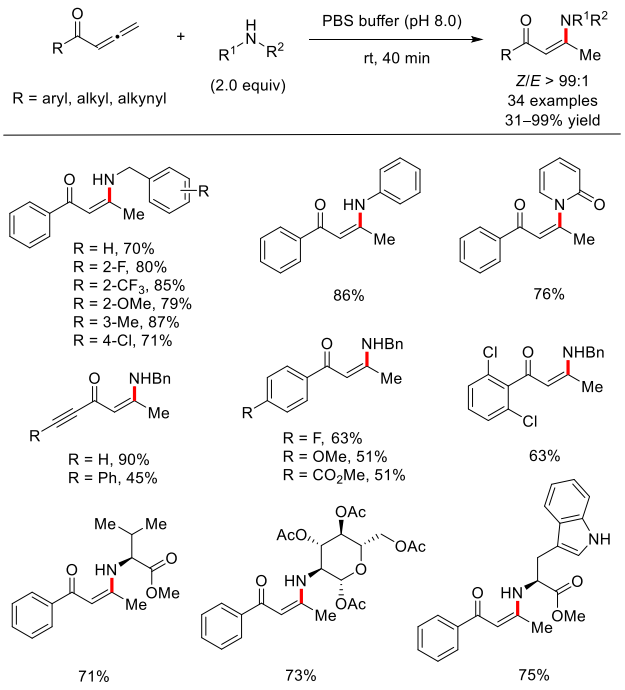
Scheme 9 Catalyst-free synthesis of vinylic sulfones in aqueous media

5 C-N Bond Formation Reactions

Nitrogen containing compounds are found widely in a variety of pharmaceuticals and bioactive natural products. Therefore, there is much interest directed toward the development of catalyst-free C-N bond forming reactions. Furthermore, reactions that work under biocompatible conditions will allow the functionalization of biomolecules such as peptides and proteins. In our continuous effort to develop a green method to construct amine compounds as well as to develop new methods for amine conjugation, we explored the reaction of amines with allenic ketones as the electrophiles under biocompatible reaction conditions.

As mentioned earlier, we have shown that allenic amide reacted selectively with thiol compounds. No reaction was observed with amino compounds. To react with the less reactive amines, we utilized the more reactive allenic ketones, and this strategy proven to be successful. In 2022, we reacted a wide variety of amines with diverse allenic ketones under biocompatible reaction conditions (Scheme 10).[27] This method works well with a wide variety of amines including amino acid derivatives, affording synthetically useful enaminones in modest to excellent yields (31–99%). In this work, the enaminone products were formed by the initial regioselective *aza*-Michael attack at the *β*-position of allenic ketones, producing an enol intermediate. The enol intermediate was proposed to be stabilized through

a six-membered ring transition state via intramolecular hydrogen bonding, which readily tautomerized to generate thermodynamically favored enaminones as the exclusive products.



Scheme 10 Catalyst-free C–N bond formation under biocompatible reaction conditions

6 Conclusion and Outlook

The development of practical and environmentally green processes using sustainable starting materials is one of the most important areas in organic synthesis. In recent years, we have witnessed ever-increasing awareness among researchers to include green and environmental considerations when developing new chemical processes. Moreover, the concept of a circular' economy has also emerged in many governments' overall developmental plans. One such focus is the development of green chemical processes. Among them, the catalyst-free water-based reactions that can work under mild reaction conditions and avoid the use of toxic metals, flammable and toxic organic solvents, etc. is one of the most important goals. To achieve this goal, a toolbox of different types of green organic reactions should be developed so that industrial scale process chemists can adopt these processes for the green synthesis of pharmaceuticals and functional materials. Unfortunately, the number of these methods in the green synthetic toolbox is still rather limited.

It is important that we continue to develop different types of new and practical green synthetic transformations such as C-C, C-N, C-O, C-P bonds forming reactions. The application of these methods for the green and one-pot multi-step synthesis of natural products and pharmaceuticals will be a fascinating area to pursue. Synthesis of pharmaceuticals should try to incorporate these features (atom-economy, metal- and organic solvent-free, mild reaction conditions, use of sustainable starting materials, etc.) as much as possible. As these conditions are biocompatible, there are also applicable in the area of chemical biology such as bioconjugation chemistry. Therefore, new catalyst-free bioconjugation technologies especially for native amino acids such as cysteine, lysine, tyrosine, etc. would be another interesting area that will help to expand the green synthetic method toolbox. The applications of these reactions in the living system and the development of new and practical asymmetric versions are research areas of interest. We believe that this relatively untapped territory of reaction carried out under biocompatible conditions without the use of metal complex and organic solvent is an area that will continue to grow.

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Conflict of Interest

The authors declare no conflict of interest.

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Biosketches

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	**Teck-Peng Loh** is a distinguished university professor of chemistry at Nanyang Technological University, Singapore. Under the tutelage of Professor E. J. Corey, he obtained his PhD (1994) from Harvard University. He has been awarded outstanding researcher awards from both National University of Singapore and Nanyang Technological University. In 2017 he received the Yoshida Prize (Japan) and the prestigious President's Science Award (individual) Singapore. He has been elected Fellow, Academia of Sciences, Singapore (2018) and Fellow of Academia of Sciences, Malaysia since 2010. His research work mainly focuses on the development of new synthetic methodology, green chemistry, and synthesis of natural products.