Development and Applications of Water-Compatible Reactions: A Journey to Be Continued

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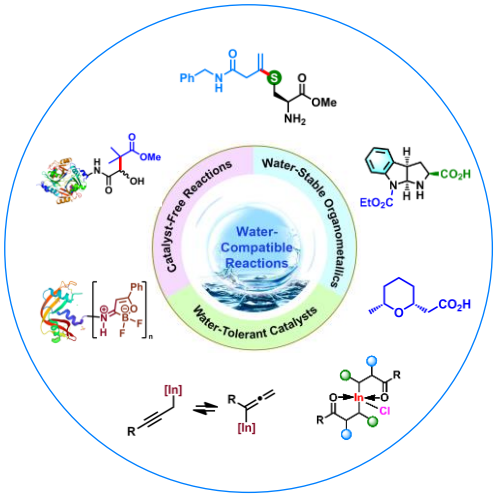

CONSPECTUS: The pursuit of novel and eco-friendly methods in organic synthesis is gaining prominence, with a strong emphasis on green transformations using renewable and sustainable resources. Among these environmentally conscious approaches, water-compatible reactions stand out for their many advantages. Water, as a solvent, offers unmatched abundance, cost-efficiency, and environmental compatibility compared to organic solvents. Its use eliminates the need for complex protection and deprotection steps for reactive functional groups in multi-step synthesis and enables the use of water-soluble substrates like proteins and carbohydrates. Water-compatible reactions also provide opportunities to combine with enzymes, resulting in chemoenzymatic transformations that can increase efficiency. Additionally, these reactions facilitate site-specific modification and bioconjugation of biomolecules, leading to bioconjugate therapeutics.

Over nearly three decades, our research group has been dedicated to developing innovative water-compatible methodologies and concepts. This Account provides a comprehensive overview of our contributions since 1994. Our central strategy revolves around integrating green

chemistry principles into our methods, focusing on: (i) Developing reactions that can operate under mild conditions, including room temperature, atmospheric pressure, and physiological pH. (ii) Designing atom-economical reactions that minimize waste production. (iii) Replacing toxic and flammable organic solvents with eco-friendly alternatives like water and ethanol. (iv) Reducing reliance on metals or halogenated compounds in specific reactions.

In this Account, we detail our achievements in developing efficient methodologies in aqueous media, highlighting their scope, limitations, asymmetric control, and applications for the synthesizing complex molecules and functionalizing peptides and proteins. Mechanistic investigations underlying these developments are also discussed when applicable. Furthermore, we offer insights into the reasoning behind our work and address future opportunities and challenges in this fertile area of research. We hope that this Account will inspire continuous interest and foster new breakthroughs. By exploring innovative and broadly applicable strategies that expand the water-compatible synthetic toolbox, we aim to pave the way for truly green and sustainable synthesis of complex molecules and pharmaceuticals.

■ KEY REFERENCES

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1. INTRODUCTION

Over the past few decades, the field of organic synthesis has seen remarkable advancements in practical and innovative methods. As global awareness shifts towards environmental protection and sustainability, the need to integrate green principles into these methodologies becomes increasingly evident. Emphasizing the use of renewable carbon sources and eco-friendly reaction media goes beyond mere efficiency and practicality. The United States Environmental Protection Agency (EPA) has laid out the 12 principles of green chemistry to guide researchers in designing environmentally responsible methods. Inspired by the elegance and sustainability of biological processes in water, our group has undertaken a dedicated three-decade-long journey towards developing water-compatible reactions.

Despite our biological system's seamless utilization of water as a reaction medium, organic chemists have long harbored apprehensions due to the limited solubility of most organic compounds and the instability of commonly used organometallic reagents in its presence. However, the unique properties of water make it an ideal solvent for sustainable chemistry, as it is abundant, inexpensive, non-toxic, non-flammable, and readily available. By focusing on water as a reaction medium, chemists seek to minimize the environmental impact associated with hazardous organic solvents and toxic waste generation.[5] Despite challenges, water-compatible conditions offer significant advantages, streamlining reactions without elaborate precautions, allowing the direct use of water-soluble compounds, and eliminating laborious protection and deprotection steps. The potential for hydrogen bonding and hydrophobic effects in water-accelerated reactions opens doors to novel reaction concepts not commonly observed in organic solvents, enabling an array of successful transformations, including the Diels-Alder reaction and click reactions.[6]

Our overarching research goal is to develop a comprehensive toolbox of green synthetic methods compatible with water. This Account presents a detailed chronicle of our tireless endeavors in exploring water-compatible reactions since the early 1990s. We focus on three categories: i) water-tolerant organometallic reactions and their versatile applications, ii) water-tolerant catalysts and their innovative uses, and iii) catalyst-free biocompatible reactions and their applications (Figure 1). Within each category, we explore the scope, and limitations, examining various stereochemical studies and their applications in the synthesis of complex molecules and functionalization of peptides and proteins. Through this Account, we hope to share our journey and contribute to the collective effort in building a more sustainable future for chemical research and practice.

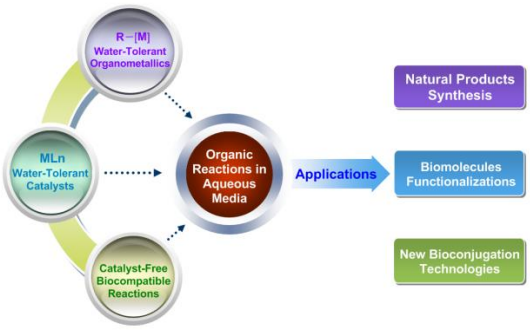


Figure 1. General overview of water-compatible reactions and their applications.

2. WATER-TOLERANT ORGANOMETALLIC REACTIONS AND THEIR VERSATILE APPLICATIONS

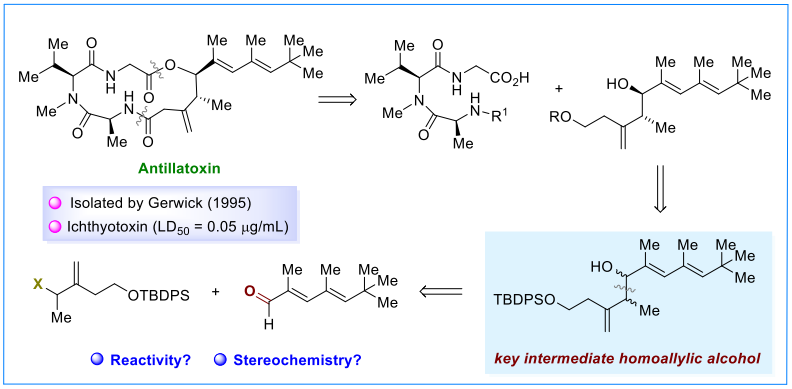
Organometallics represent a significant category of compounds extensively employed in organic synthesis. These reagents have revolutionized organic synthesis with their nucleophilic prowess and capability for carbon-carbon bond formation. However, their vulnerability to water, which can cause rapid decomposition, significantly hampers broader application. Their high nucleophilic reactivity also limits their applications in the direct functionalization of molecules containing reactive groups, such as proteins and carbohydrates. These challenges not only underscore the imperative to create water-resilient versions but also highlight a persisting gap in broadening the scope and applications of current methods. Guided by our dedication to develop eco-friendly and efficient catalytic processes, we have intensely focused on designing and deploying water-tolerant organometallics. For clarity, this section will be demarcated into four key segments: (1) water-tolerant allylic metals; (2) homoproargylic vs allenic metals; (3) alkyl indium reagents; (4) indium homoenolates. We will provide insights into their preparation, scope, limitations and their applications in the synthesis of complex natural products. However, it should be noted that “water-tolerant” in this Account refers to nucleophiles like organometallics that do not react with water directly but with the electrophiles of choice, while “water-compatible” describes reaction systems that can operate effectively in the presence of water.

2.1. Water-Tolerant Allylic Metals

Among the organometallics, the Barbier reaction is a robust method for coupling carbonyl compounds (such as aldehydes, ketones, and esters) with alkyl halides. This reaction utilizes metals like magnesium, reminiscent of the Grignard reaction, and others including zinc and indium. These metals facilitate the formation of an organometallic intermediate, which then reacts with carbonyl compounds.[7]

In the early 1990s, our group recognized the potential of water-compatible metal-mediated allylation reactions in organic synthesis, since it furnishes versatile homoallylic alcohols and therefore used widely in constructing complex molecules. Our particular interest lay in the efficient synthesis of the advanced intermediate homoallylic alcohol, pivotal for the total synthesis of antillatoxin, a scarcely available ichthyotoxin (Scheme 1).[8] The anticipated intermediate, possessing a homoallylic fragment, could originate from a conjugated aldehyde in combination with intricate allylic metal reagents such as indium, zinc and tin in aqueous media. However, scant literature was available on the employment of this reaction with complex allylic bromides or unreactive conjugated aldehydes. Furthermore, little has been done on the relative and stereochemical studies.

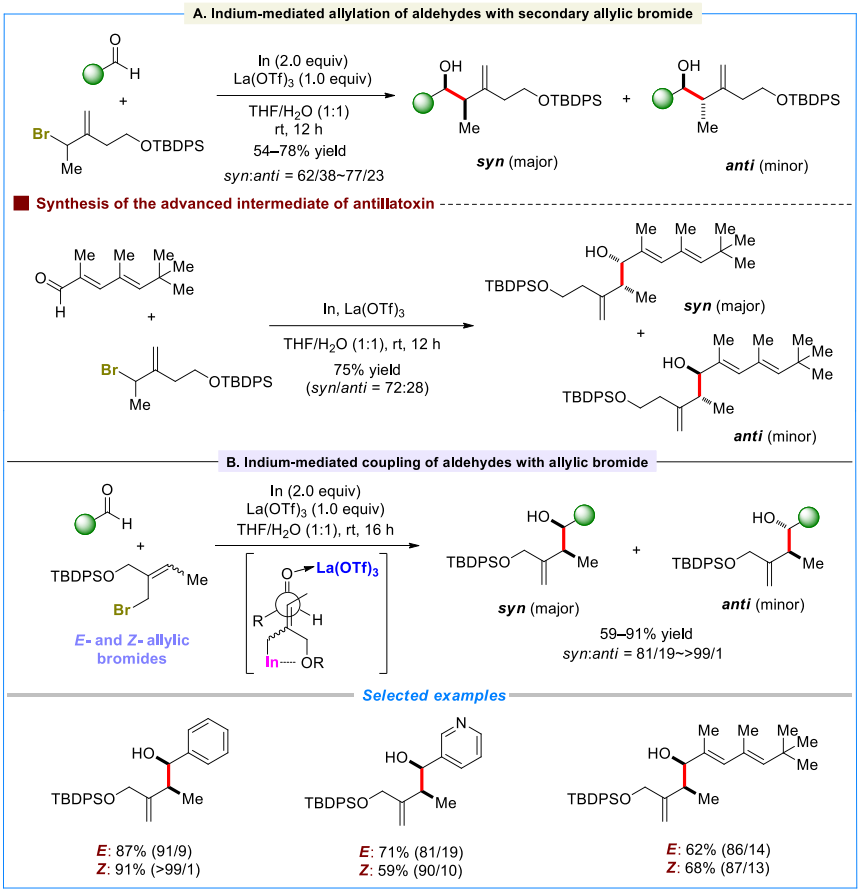
Scheme 1. Retrosynthetic Analysis Towards Total Synthesis of Antillatoxin



Despite these challenges, we began our studies using allylic metals in water-compatible allylation reactions for these complex substrates. Our aim was twofold: to create a reliable and efficient method, and to address the critical stereochemical considerations inherent in the total synthesis of complex molecules like antillatoxin.[9] Our initial efforts, while rooted in established literature, were met with obstacles. Standard conditions, using different metals such as Sn and Zn, etc. failed to yield the desired products. However, through perseverance, we discerned that incorporating water-compatible Lewis acids, such as $La(OTf)_3$, could spur the indium-mediated allylation reactions (Scheme 2A).[10] Indeed, the reactions predominantly afforded the 1,2-addition product, with the 1,4-addition product being conspicuously absent. Interestingly, irrespective of the geometry of the allylic indium used, the resultant *syn*-diastereoselectivity was markedly different from established literature (Scheme 2B).[11] Prior research indicated that *E*-allylic indium yielded an *anti*-product, while the *Z*-indium reagent produced a *syn*-product. Contrarily, our findings suggested an alternative mechanism at play. This realization led us to hypothesize a shift in the reaction mechanism due to the inclusion of the Lewis acid. Instead of the conventionally accepted cyclic transition state, we proposed that our reaction followed an open-

chain *anti*-periplanar transition state. Bolstered by these new findings and the unprecedented diastereoselectivities observed, we ventured further into the detailed studies of the indium-mediated allylation reactions.

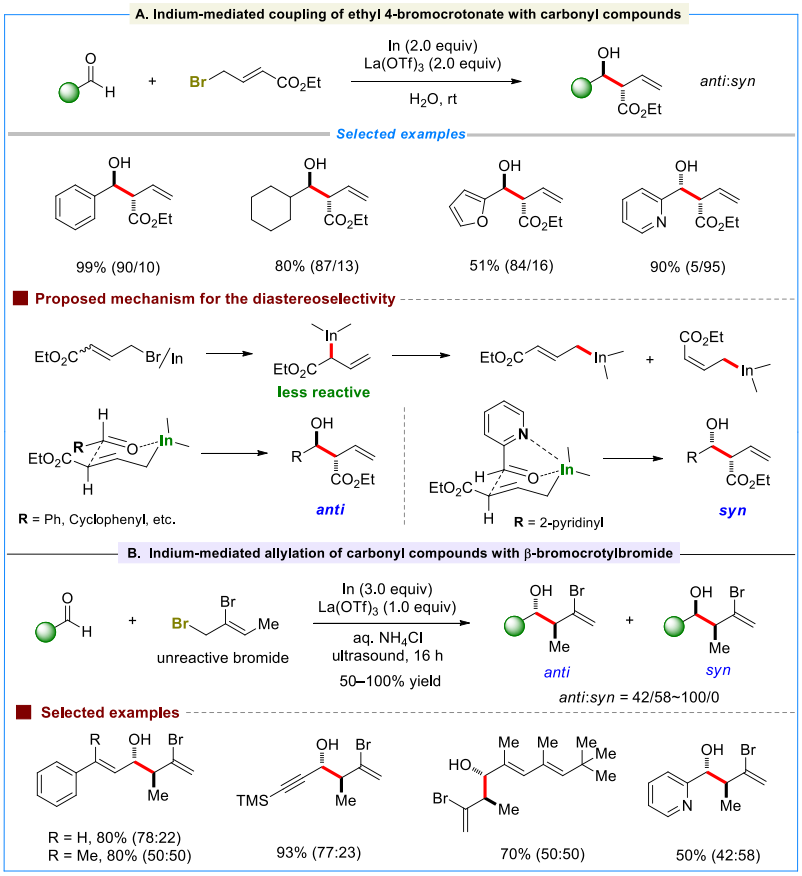
Scheme 2. Indium-Mediated Allylation of Aldehydes with Allylic Bromides



2.1.1. Simple Diastereoselectivity Studies. The reactions of aldehydes with β-substituted allylic indium create two new stereogenic centers. As mentioned in the antillatoxin case, we found that *syn*-selectivities were obtained regardless of the geometry of the allylic bromides used in the reaction.[11] Previous studies by Chan,[12a] Paquette[12b] *et al.* have revealed that bulky groups such as phenyl, ester, etc on the γ-site of the allylic indium led to high *anti*-diastereoselectivities while smaller groups such as methyl resulted in no selectivity. A cyclic transition state has been proposed to account for the observed selectivities. Similar results were observed in our studies using crotonyl allylic bromide (Scheme 3A)[13] and β-bromocrotylbromide (Scheme 3B).[14] Reversed selectivities could be observed when aldehyde containing an extra coordinating group such as 2-pyridinyl aldehyde was used in the reactions. It is noteworthy that even with the use of

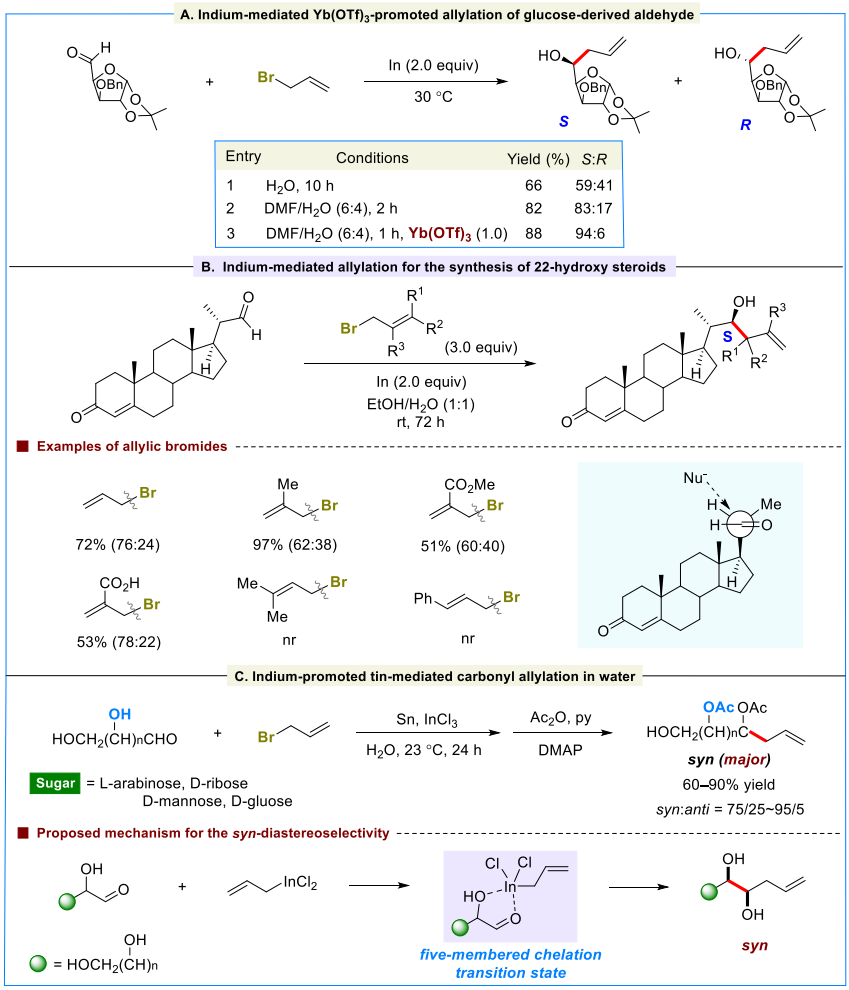
secondary bromide, the same *anti*-product was obtained since the allylic indium can undergo 1,3-shift to the most stable linear *E*-homoallylic indium species.

Scheme 3. Indium-Mediated Allylation Reactions of Carbonyl Compounds



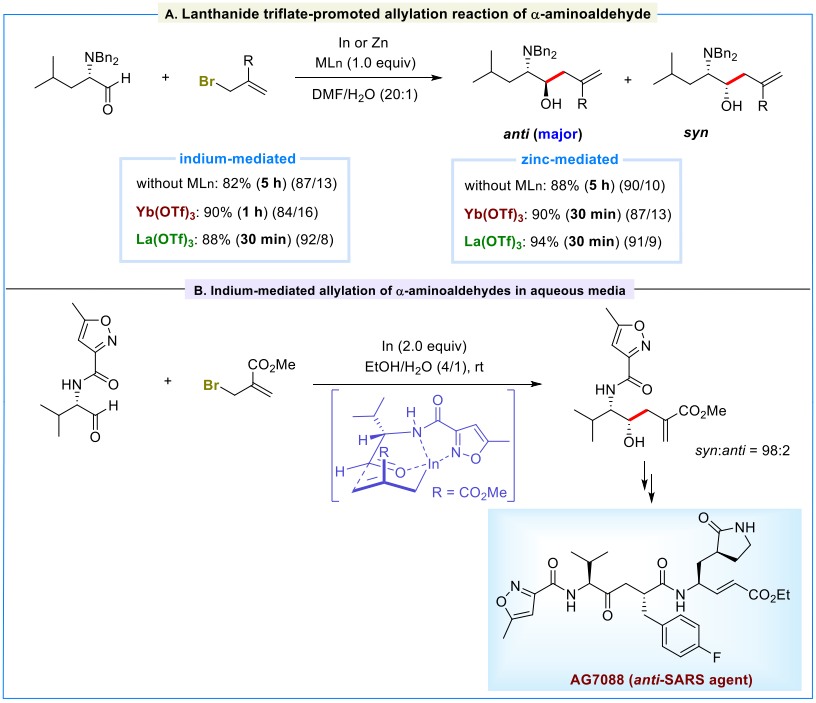
2.1.2. Diastereofacial Selectivity Studies. Like many other reactive allylic metals, allylic indium reactions proceeded smoothly with chiral aldehydes, yielding high *syn* or *anti*-facial selectivity depending on the substrates and conditions employed. We found that moderate to excellent selectivity in non-chelation (Cram's) reactions could be achieved when sugar-derived aldehydes (Scheme 4A)[15] or steroidal aldehydes (Scheme 4B)[16] were used as substrates. Moreover, chelation 1,2-*syn* products were obtained with high selectivity when α-hydroxy aldehydes were used (Scheme 4C).[17]

Scheme 4. Indium Trichloride-Promoted Tin-Mediated Allylation Reactions



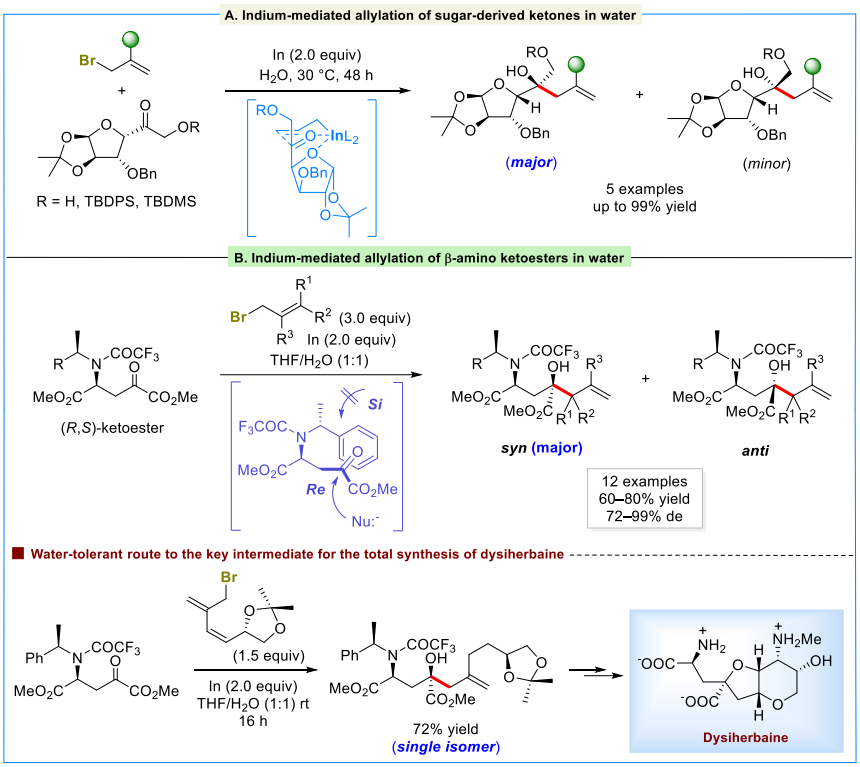
Moreover, we explored the use of lanthanide triflate as an efficacious Lewis acid to promote the In- or Zn-mediated allylation reactions of α-aminoaldehyde (Scheme 5A).[18] By the judicious choice of the α-*N*,*N*′-dibenzylamino-protecting group, excellent yields and high *anti*-diastereofacial selectivity were observed. This lanthanide triflate-promoted reaction was extremely fast, typically completed within 30 mins, providing rapid access to chiral β-aminoalcohols. In an effort to the synthesis of *anti*-SARS agent AG7088 and its analogues, we also investigated the chelation-assisted allylation of isoxazoloyl-containing α-aminoaldehyde in aqueous ethanol, giving rise to a key intermediate for synthesizing AG7088 with excellent *syn*-selectivity (Scheme 5B).[19]

Scheme 5. Indium-Mediated Allylations of α-Aminoaldehydes



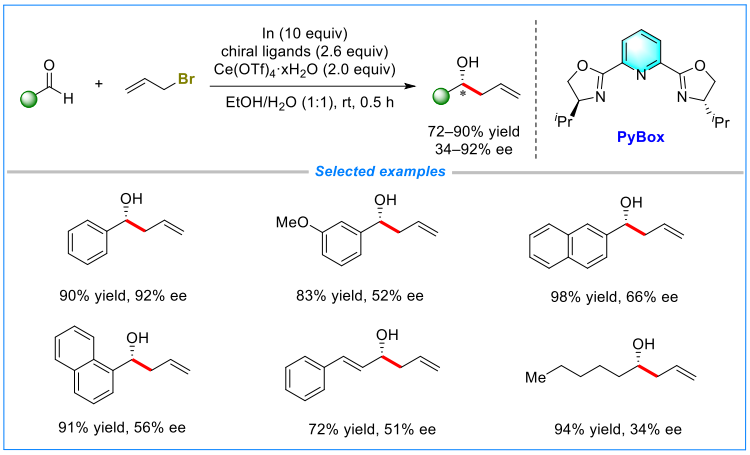
During our studies on the total synthesis of zaragozic acid, we explored the allylation of sugar-derived ketones to generate chiral tertiary alcohols (Scheme 6A).[20] We noted that the preferential orientation of the ketone largely determined the stereochemistry of the newly formed tertiary alcohol. A similar observation was also made in our studies towards the total synthesis of dysiherbaine, where allylation of amino acid-derived ketoesters led to intriguing stereochemical control (Scheme 6B).[21] This ketoester also refers to adopt a special conformation where the phenyl ring from the benzylic group helps to shield one of the faces, leading to high stereoselectivities.

Scheme 6. Indium-Mediated Allylation of Sugar-Derived Ketones and β-Amino Ketoesters



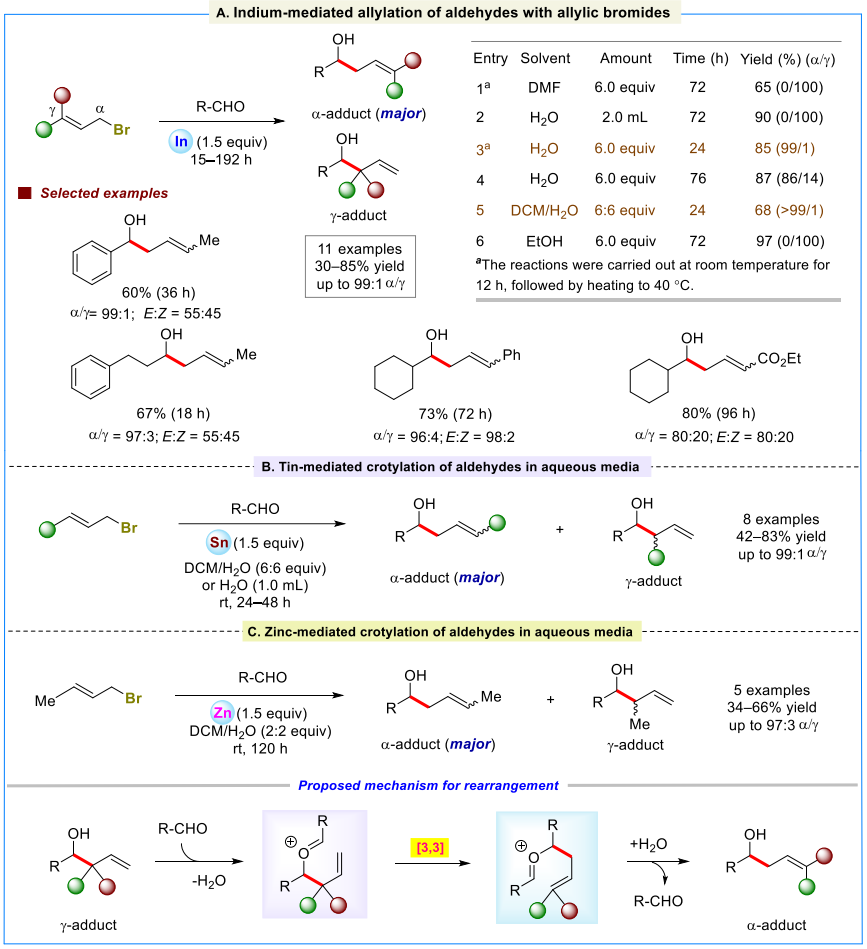
2.1.3. Enantioselectivity Studies. Prior to our investigations, studies on indium-mediated enantioselective allylation reactions remained largely uncharted. The challenges arise due to the multiple indium species that could be present under varying reaction conditions, such as the metallic indium (In^0), organoindium sesquihalide and other indium(III) species. Each of these species can have different reactivities and selectivity patterns, making the development of an enantioselective process especially difficult. After screening a myriad of chiral ligands and Lewis acids, we found that the combination of a chiral bis(oxazoline) ligand (PyBox), with a cerium trifluoromethanesulfonate hydrate $Ce(OTf)_4 \cdot xH_2O$ proved particularly effective (Scheme 7).[22] This combination not only activated the indium reagent but also provided the necessary chiral environment for the substrate to approach in a stereoselective manner. Under optimized conditions, a range of carbonyl compounds underwent allylation with decent yields and modest to good enantioselectivities (34−92% ee). This methodology paves the way for the water-compatible synthesis of enantioenriched homoallylic alcohols, which can serve as highly valuable intermediates in the synthesis of chiral molecules of medicinal and material interest.

Scheme 7. Indium-Mediated Enantioselective Allylation Reaction of Aldehydes



2.1.4. Regioselectivity Studies: α- vs γ-Selectivies. The exploration of α- vs γ-selectivity in metal-mediated allylation holds significant intrigue, particularly considering the widespread presence of both linear and branched homoallylic alcohols in natural products and pharmaceuticals. γ-Selectivity is prevalent in most metal-mediated allylation reactions, especially when less bulky γ-substituted allylic bromides are employed. However, there's a great demand for highly efficient α-selective methods due to the prominence of linear homoallylic alcohols in many compounds. Our initial experiments of indium-mediated allylation reactions, using 6.0 equivalents of water, afforded the branched homoallylic alcohol but upon prolonged stirring transformed it into its linear counterpart, highlighting the possibility of another reaction at play (Scheme 8).[23] Interestingly, we consistently detected a trace amount of aldehyde in the crude NMR despite adding less than 1.0 equivalent in the reaction, suggesting its possible influence on the reaction pathway. Further experiments employing pure branched homoallylic alcohol with a Lewis acid, the corresponding aldehyde yielded the linear variant in appreciable amounts. Notably, control experiments using optically pure branched homoallylic alcohol resulted in the linear form but with inverted stereochemistry. Such results indicate the likely involvement of an oxocarbenium ion, followed by a 3,3-sigmatropic rearrangement. The overall mechanism leading to the α-selective product is proposed as shown in Scheme 8 (bottom). Interestingly, we also found that tin and zinc could proceed via a similar mechanism in this α-regioselective allylation reactions with good selectivities.

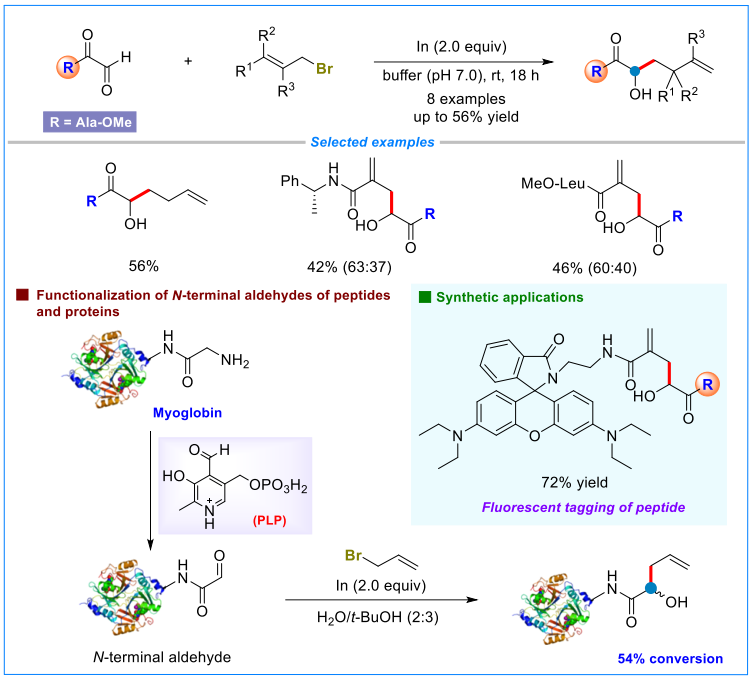
Scheme 8. Highly α-Regioselective Allylation Reactions



The success of obtaining the α-allylated product and understanding of the underlying mechanism pave the way for the discovery of novel allyl or α-prenyl group transfer reactions, including the asymmetric versions. This research not only presents a novel methodology in the domain of indium-mediated allylation but also reveals broader mechanistic avenues, which might be valuable for tackling other synthetic challenges.

2.1.5. Other Applications. One of the benefits of conducting water-compatible reactions is the ability to directly use water-soluble substrates such as proteins and hydrate forms of reactive aldehydes. For example, alkyl glyoxylate hydrate can be directly employed in indium-mediated allylation reactions to produce homoallylic alcohols. This approach is also applicable to myoglobin aldehyde (Scheme 9).[24] When reacted with allylic indium reagents, this protein-aldehyde yielded homoallylic alcohols. Notably, the 3-dimensional structure of the protein, partially disrupted during the reaction, could be readily restored through reconstitution experiments.

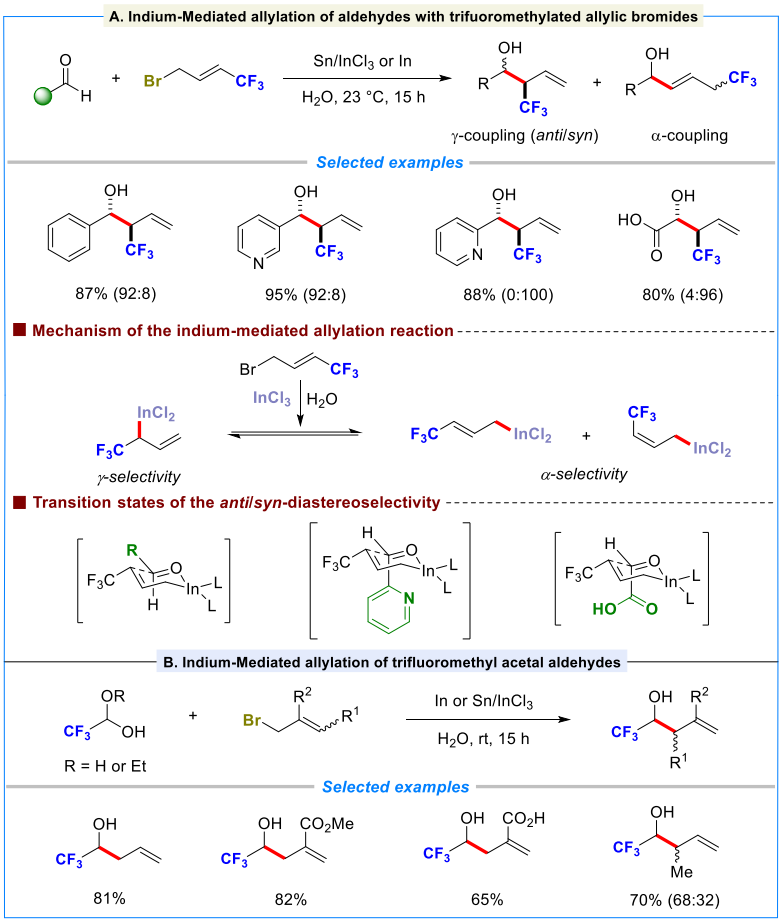
Scheme 9. Functionalization of *N*-Terminal Aldehydes of Peptides and Proteins



When trifluoromethyl γ-substitiuted allylic bromides were used in the reactions, the desired *anti*-selective trifluoromethylated products could be obtained in high yields (Scheme 10A).[25] This protocol offers easy access to a broad range of trifuoromethylated homoallylic alcohols. Similarly, reversed selectivities were also observed when aldehyde bearing a coordinating group such as glyoxylate or 2-pyridinyl aldehyde was employed.

Moreover, commercially available trifluoromethyl acetal aldehyde which prefers to exist in its more stable hydrate or hemiacetal form can be directly reacted with various allylic reagents, leading to a wide range of trifluoromethylated alcohols (Scheme 10B).[26] The significance of these fluorinated compounds cannot be understated, as they play a crucial role in fields such as pharmaceuticals, agrochemicals, and materials science due to their unique chemical properties.

Scheme 10. Synthesis of α-Trifluoromethylated Homoallylic Alcohols

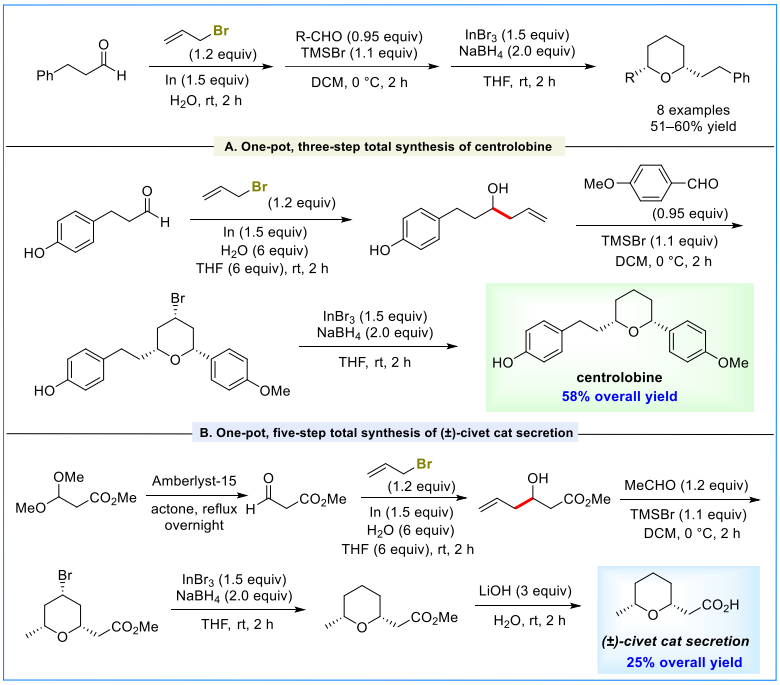


The concept of "pot-economy," originally coined by Hayashi,[27] stands as a foundational principle in the realm of efficiently synthesizing complex molecules. This innovative approach eliminates the necessity for intermediary purifications, reduces waste generation, and ultimately saves both time and costs. While not devoid of challenges, the success of one-pot strategies hinges on the ability to harmonize various reactions seamlessly. In our research, we embraced this paradigm, culminating in the attainment of a remarkable feat: a streamlined one-pot, three-step synthesis yielding centrolobine, and a five-step synthesis yielding (±) civet cat secretion with yields of 58% and 25%, respectively (Scheme 11).[28] In this one-pot process, each reaction component was sequentially added to the crude mixture without any intermediate purification steps. Moreover, it is crucial to emphasise that no extra indium reagent was introduced during this process.

At the heart of this methodology lies an intriguing pivotal role indium assumes throughout these syntheses, performing three crucial functions. Foremost, indium serves as a mediator for allylation; secondly, the generated indium complex byproduct further acts as a proficient Lewis acid, facilitating the intricate Prins reaction. Finally, transformating the indium salt to an indium

hydride, achieved through $NaBH_4$, plays an indispensable role in effecting bromide elimination within an aqueous medium. The essence of this integrated approach underscores the paramount importance of compatibility in reaction conditions across diverse stages. Leveraging the recyclable indium complex byproduct as a catalyst further amplifies its significance. This synergy underscores the extraordinary efficiency and potency of the pot-economy principle and water-compatible reactions in orchestrating complex molecular syntheses. Moreover, it paves the way for the broader application of water-compatible pot-synthesis in crafting other complex molecules containing THP moieties.

Scheme 11. Indium-Mediated One-Pot Synthesis of Tetrahydropyrans

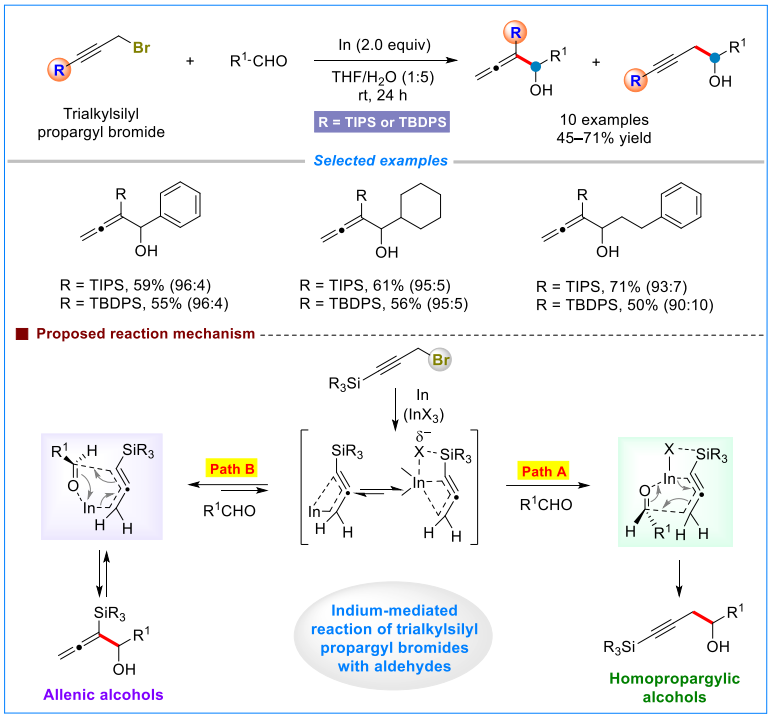


2.2. Homopropargylic vs Allenic Metals

The synthesis of either allenic or homopropargylic indium reagents frequently produces a mixture of these two reagents. Therefore, a primary challenge has been controlling the regioselectivity of the reaction between homopropargylic/allenic metal and carbonyl compounds to obtain either allenic or homopropargylic alcohols, respectively. To address this issue, we employed trialkylsilyl propargyl bromides into indium-mediated reactions with various aldehydes (Scheme 12).[29] This approach was informed by the ability of indium complex to chelate with silicon groups and the difference in indium complex species in organic versus aqueous media. Changing the silyl group and the reaction conditions enabled the formation of both the allenic and homopropargylic alcohols in good regioselectivities. We found that when we

use the smaller trimethylsilyl group, the homopropargylic alcohol prefers to adopt the allenic indium structure when the reaction was performed in THF in the presence of a catalytic amount of $InBr_3$ or InF_3. The process is faster with InF_3 and demands two equivalents of indium for optimal regioselectivity. On the contrary, the more bulky triisopropyl silyl group, due to steric repulsion, prefers to adopt the homopropargylic indium species when carried out in water, yielding the allenic alcohols in high selectivities.

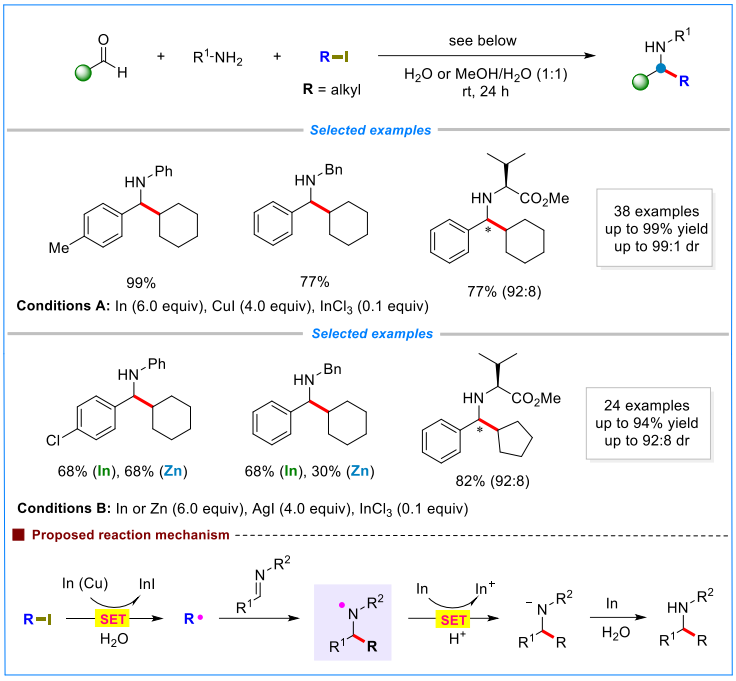
Scheme 12. Indium-Mediated Reaction of Trialkylsilyl Propargyl Bromides with Aldehydes



2.3. Alkyl Indium Reagents

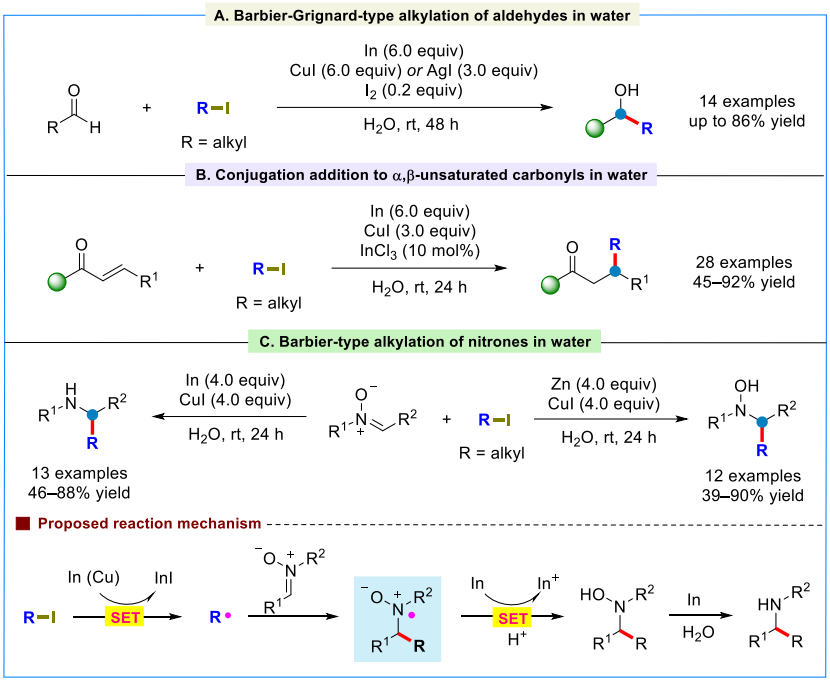
The Barbier–Grignard-type reaction has traditionally employed moisture-sensitive reagents, notably Grignard reagents (RMgX). Although some progress has been made in adapting the reaction to aqueous media using various metals, a major challenge has been to perform the alkylation of carbonyls in water with unactivated alkyl halides. Through extensive investigations, a novel water-compatible method has been developed using an $In/CuI/I_2$ or $In/AgI/I_2$ catalytic system, which enables the Barbier–Grignard-type alkylation reaction of imines with unactivated alkyl halides (Scheme 13).[30] This new approach, characterized by mild conditions and consistent yields, highlights the importance of water both in activating indium and scavenging the resultant alkoxide anion, making this method viable for larger scale applications.

Scheme 13. Barbier-Grignard-Type Alkylation Reaction of Imines



Then, we sought to expand the application of alkyl indium reactions to other electrophiles. Gratifyingly, the reactions of alkyl halides with aldehydes (Scheme 14A),[31] α,β-unsaturated carbonyls (Scheme 14B)[32] and nitrones (Scheme 14C)[33] have also proven to be applicable. Mechanistically, alkyl radical was probably involved through a single-electron transfer (SET) process from In (Cu) to alkyl iodides.

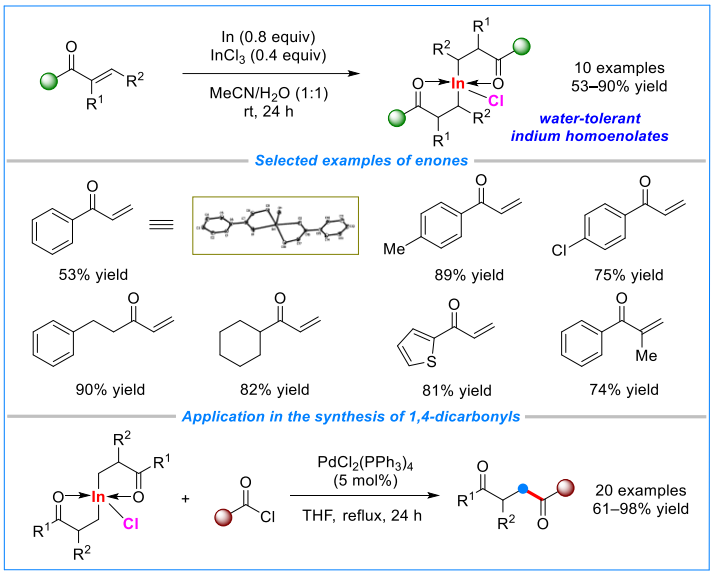
Scheme 14. Indium-Mediated Barbier-Type Alkylation Reactions



2.4. Indium Homoenolates

Homoenolates represent a crucial class of reactive intermediates, enabling a myriad of elegant transformations.[34] These species, characterized by an enolate functionality that's removed from the carbonyl or imine by an extra carbon, offer unique regioselectivity in reactions, leading to the generation of distinct products compared to conventional enolates. While traditional homoenolate chemistry often requires anhydrous conditions due to high sensitivity towards water, recent advances have resulted in water-tolerant versions. In 2010, we first prepared the ketone-type indium homoenolates via oxidative addition of In/$InCl_3$ or InCl to enones in aqueous media (Scheme 15).[35] We also demonstrated the utility of these water-tolerant indium homoenolates via Pd-catalyzed cross-coupling with acyl chlorides, giving rise to a variety of 1,4-dicarbonyl compounds in 61−98%yields. These homoenolates are a significant stride forward, permitting reactions to be conducted in aqueous environments or under conditions where complete exclusion of water is challenging. Such an adaptation not only makes the processes more environmentally benign but also broadens the scope of reactions by allowing the integration of water-sensitive substrates and reagents.

Scheme 15. Synthesis of Water-Tolerant Indium Homoenolates and Their Applications



Overall, our investigations into water-compatible metal-mediated reactions have shown great promise, underscoring the efficacy of water-tolerant organometallic reagents in executing complex synthetic transformations.[36] We have primarily focused on organoindium reagents, exploring their use in various types of reactions including allylic, homopropargylic/allenic, and alkyl metal reactions, as well as in the formation of homoenolates. Comprehensive studies have been carried out to determine the preparation protocols, scope, limitations, and stereochemical outcomes, yielding results that have overcome previous limitations in the field. Importantly, these advances have been successfully applied to practical applications such as protein functionalization, the synthesis of fluorinated compounds, and the one-pot total synthesis of complex natural products. We anticipate that our work will provide invaluable insights for researchers interested in leveraging these reagents in organic synthesis. Looking forward, we aim to expand our research focus to explore the capabilities of non-metal-based reagents, such as boron-based compounds, to achieve comparable transformations, thereby continuing to extend the range and applicability of these water-compatible synthetic methods.

3. WATER-TOLERANT CATALYSTS AND THEIR INNOVATIVE USES

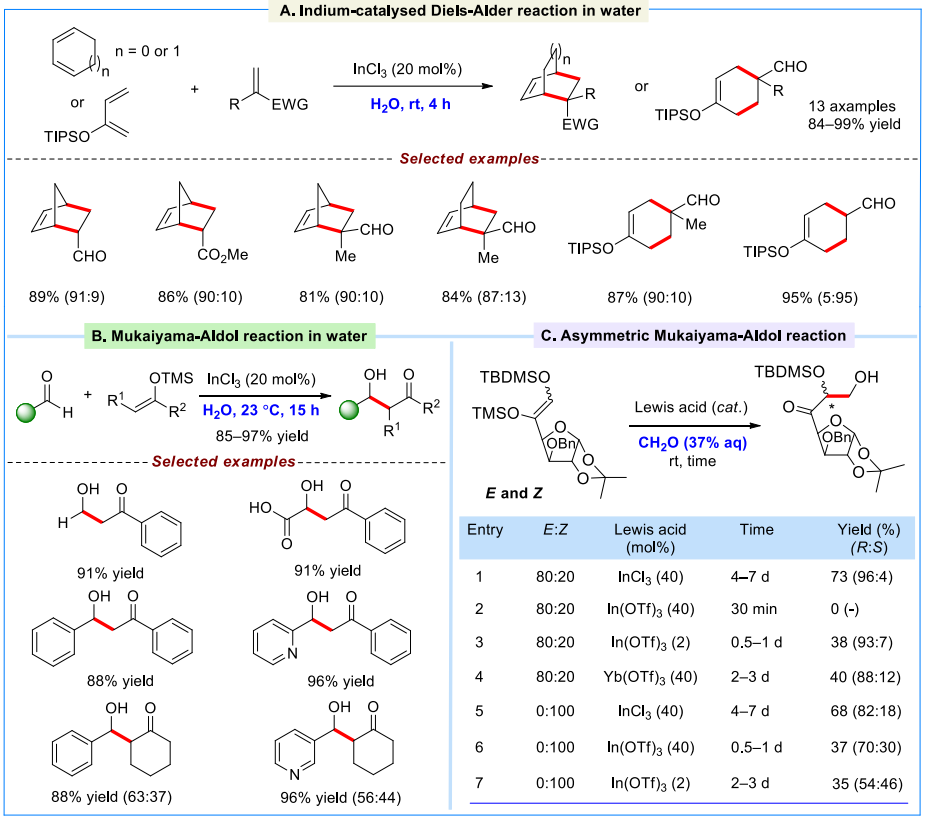
The development of new water-tolerant catalysts is of paramount importance in the field of green chemistry and sustainable technologies. Inspired by enzymes that are highly efficient at catalyzing a myriad of chemical transformations in water, researchers have been actively exploring novel water-tolerant catalysts that can facilitate diverse organic transformations under aqueous conditions. Among the available approaches, there are several categories of water-tolerant catalysts, including metal complexes, organocatalysts, Bronsted acids, ion-pair catalysts,

etc. For the purpose of this discussion, we would group them into three main categories: water-tolerant Lewis acids, organocatalysts, and ion-pair catalysts.

3.1. Water-Tolerant Lewis Acids

The development of water-tolerant catalysts holds significant promise for a more sustainable approach to chemical synthesis and manufacturing processes, as water is abundant, non-toxic, and often considered as the ideal solvent for chemical reactions.[37] A notable achievement in this field comes from our early studies on the transmetallation reactions of allylic stannane with a catalytic amount of indium trichloride in water to generate allylic indium. This approach has been successfully implemented in water, leading to the discovery of indium complexes as water-tolerant Lewis acids.[17] This progress is part of a broader shift from single-use, sensitive catalysts to reusable and highly tolerant catalysts. Despite the strides made, achieving truely green methodologies that exclude organic solvents in every step remains a great challenge.[38] Indium salts, chosen for their low-toxicity and high stability in air and water, have been central to our group's efforts in developing water-compatible reactions.[39] We have successfully employed water-tolerant indium salts in diverse carbon-carbon bond formation reactions, such as Diels-Alder reaction (Scheme 16A) and Mukaiyama-aldol reactions (Scheme 16B and C).

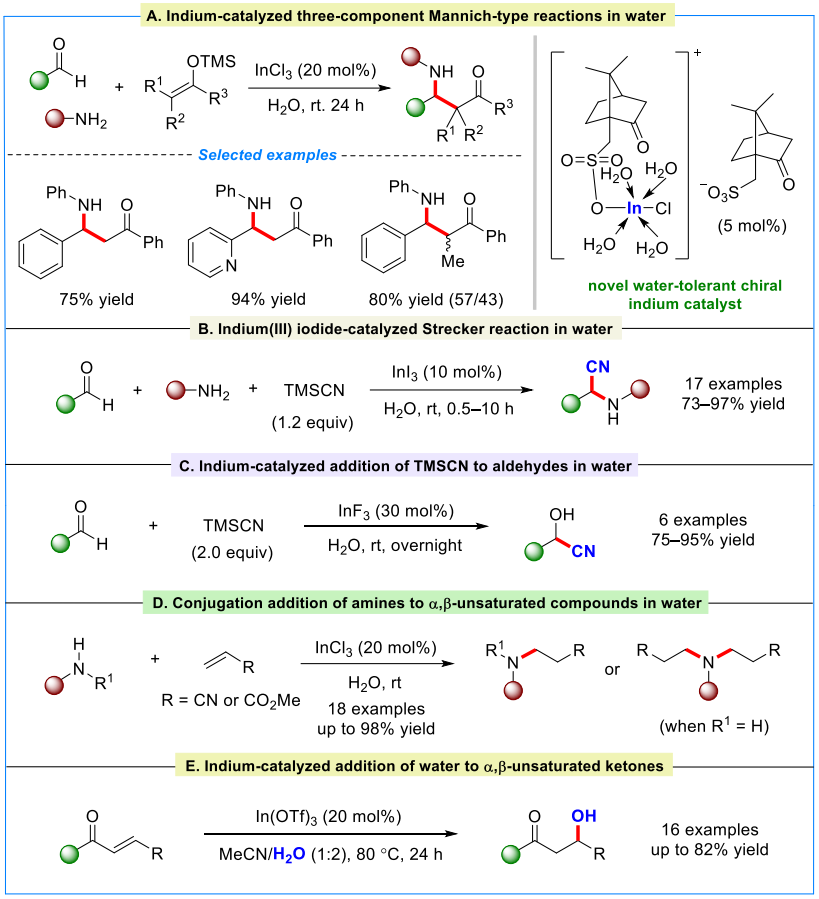
Scheme 16. Indium-Catalyzed Diels-Alder and Mukaiyama-Aldol Reactions



Entry	*E*:*Z*	Lewis acid (mol%)	Time	Yield (%) (*R*:*S*)
1	80:20	$InCl_3$ (40)	4–7 d	73 (96:4)
2	80:20	$In(OTf)_3$ (40)	30 min	0 (-)
3	80:20	$In(OTf)_3$ (2)	0.5–1 d	38 (93:7)
4	80:20	$Yb(OTf)_3$ (40)	2–3 d	40 (88:12)
5	0:100	$InCl_3$ (40)	4–7 d	68 (82:18)
6	0:100	$In(OTf)_3$ (40)	0.5–1 d	37 (70:30)
7	0:100	$In(OTf)_3$ (2)	2–3 d	35 (54:46)

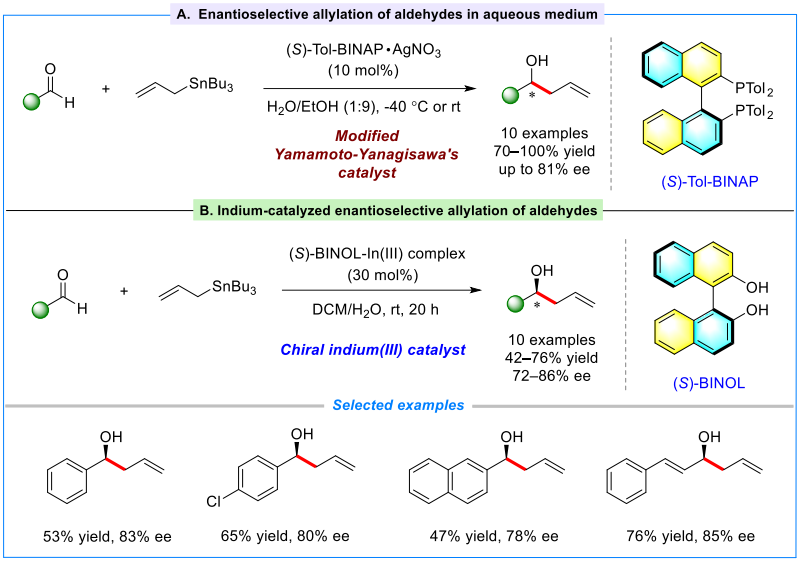
Indium catalysts have proven to be highly effective, facilitating diverse organic transformations in aqueous environments.[39,40] Continuing with our interests in water-compatible reactions, we further applied these catalysts to a broad range of reactions, including Mannich-type reactions (Scheme 17A),[41] Strecker reactions (Scheme 17B),[42] TMSCN addition to aldehydes (Scheme 17C),[43] amine addition to α,β-unsaturated compounds (Scheme 17D)[44] and water addition to α,β-unsaturated ketones (Scheme 17E).[45] It is worthwhile to note that we also discovered a new water-tolerant chiral indium(III) camphorsulfonate complex as an efficient Lewis acid for the one-pot three-component Mannich-type reactions (Scheme 17A, right).[46] Notably, these catalysts can be recycled and reused for up to five cycles without significant drop in product yields. It has been truly gratifying to see the extensive applicability of these catalysts in various water-compatible organic transformations, as demonstrated by researchers around the world.[36]

Scheme 17. Indium-Catalyzed Organic Reactions in Water



In 2000, we realized a catalytic version of asymmetric allylation reaction of aldehydes with allyltributylstannane using a slightly modified Yamamoto-Yanagisawa's catalyst (*S*)-Tol-BINAP•$AgNO_3$ (Scheme 18A).[47] Later in 2005, we successfully prepared a chiral (*S*)-BINOL-In(III) catalyst for the enantioselective allylation of carbonyl compounds and enantioselective Diels-Alder reactions. With this moisture-tolerant chiral indium(III) catalyst, we further investigated the indium(III)-catalyzed asymmetric allylation of various aldehydes in aqueous media. With optimal 7.4 equiv of H_2O relative to the chiral indium(III) catalyst, the allylation of both aliphatic and aromatic aldehydes with allyltributylstannane proceeded smoothly to give homoallylic alcohols with good enantioselectivities (Scheme 18B).[48]

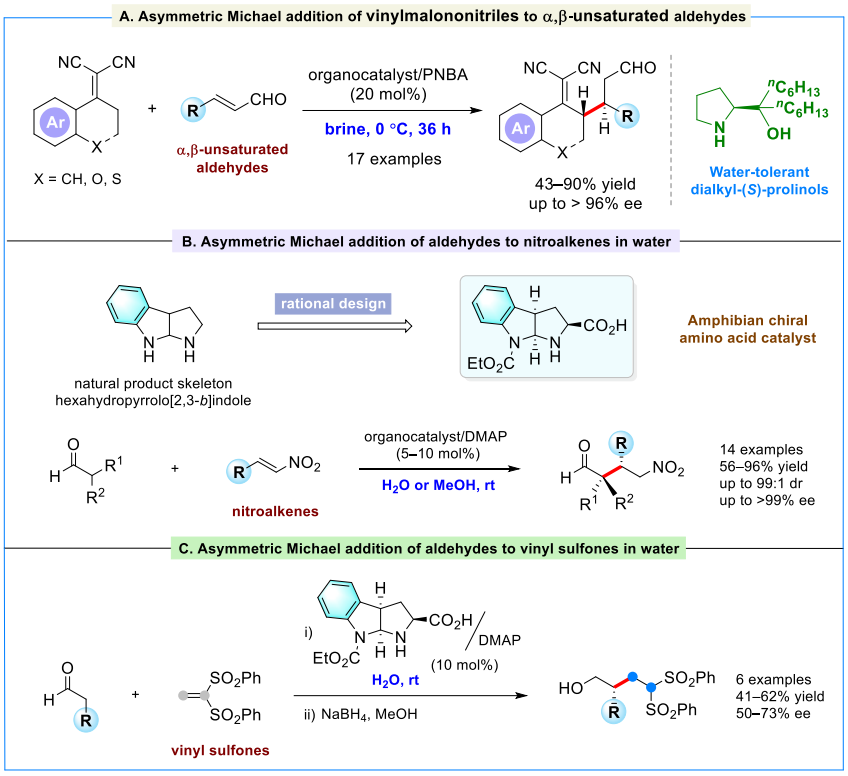
Scheme 18. Enantioselective Allylation Reactions of Aldehydes



3.2. Organocatalysts

The development of metal-free catalysts for water-compatible reactions represents a groundbreaking area of research, addressing both economic and environmental challenges associated with traditional metal-based catalysts.[49] Initially, we designed a new water-compatible chiral organocatalyst, namely dialkyl-(*S*)-prolinols, which exhibited remarkable efficiency in asymmetric Michael addition of dicyanoolefins to various α,β-unsaturated aldehydes in brine (Scheme 19A).[50] This proline-derived organocatalyst afforded the corresponding *anti*-Michael addition products with good to excellent enantioselectivity, significantly demonstrating its potential for highly stereoselective organic transformations. We further designed a novel type of chiral organocatalyst based on the privileged hexahydropyrrolo[2,3-*b*]indole skeleton (Scheme 19B).[51] This amphibian organocatalyst features a structurally rigid tricyclic skeleton and a chiral pocket, offering an excellent chiral environment for the enantioselective Michael addition of aldehydes to nitrostyrenes. With this water-tolerant organocatalyst, we explored the more challenging asymmetric Michael addition of aldehydes to vinyl sulfones in H_2O (Scheme 19C),[52] furnishing the products with modest enantioselectivities (50−73% ee).

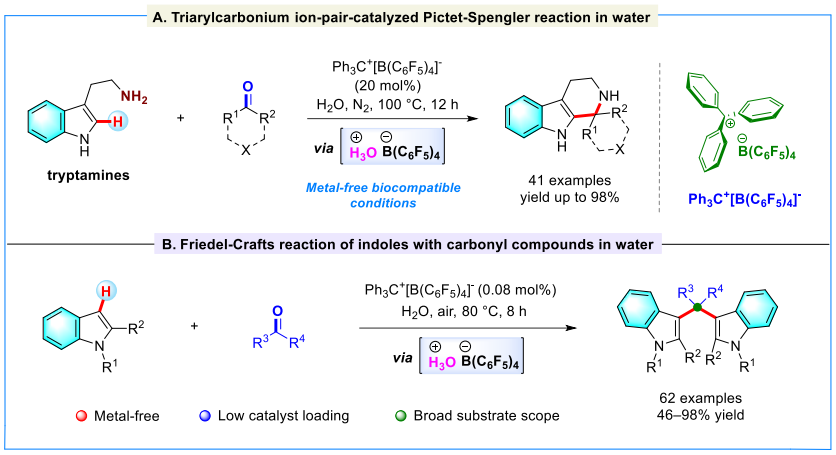
Scheme 19. Asymmetric Michael Addition Reactions



3.3. Water-Tolerant Ion-Pair Catalysts

Building on this success, we explored the use of trityl tetrakis(pentafluorophenyl)borate $[Ph_3C]^+[B(C_6F_5)_4]^-$ as a water-tolerant catalyst for the reactions in water, further broadening the scope of metal-free catalysis. Specifically, we reported the metal-free Pictet−Spengler reaction in water using trityl tetrakis(pentafluorophenyl)borate as a superacidic precatalyst, leading to tetrahydro-β-carbolines and spirocyclic tetrahydro-β-carbolines in satisfactory yields (Scheme 20A).[53] Late-stage diversification of complex natural products and pharmaceutically relevant molecules illustrated the potential of this strategy. Mechanistic investigations revealed that the superacidic species ($H_3O^+[B(C_6F_5)_4]^-$) was probably involved in this water-compatible reaction. With this catalyst, we further disclosed the Friedel–Crafts reaction of indoles with carbonyl compounds in water (Scheme 20B).[54] This protocol features a remarkably low catalyst loading of 0.08 mol% and broad substrate scope. Interestingly, unprotected sugars could be directly converted into the 3,3′-bisindolylmethanes in good yields, without the need for pre-treatment.

Scheme 20. Water-Compatible Pictet−Spengler and Friedel–Crafts Reactions



The urgency for metal-free alternatives lies in the scarcity and rising costs of metal catalysts, as well as their environmental toll. Looking ahead, our future work is geared towards developing chiral versions of these water-tolerant catalysts and advancing into new territories such as asymmetric chemoenzymatic reactions. By doing so, we aim to offer sustainable, efficient, and cost-effective options for both industrial and academic research, thereby contributing to green chemistry initiatives globally.

4. CATALYST-FREE BIOCOMPATIBLE REACTIONS AND THEIR APPLICATIONS

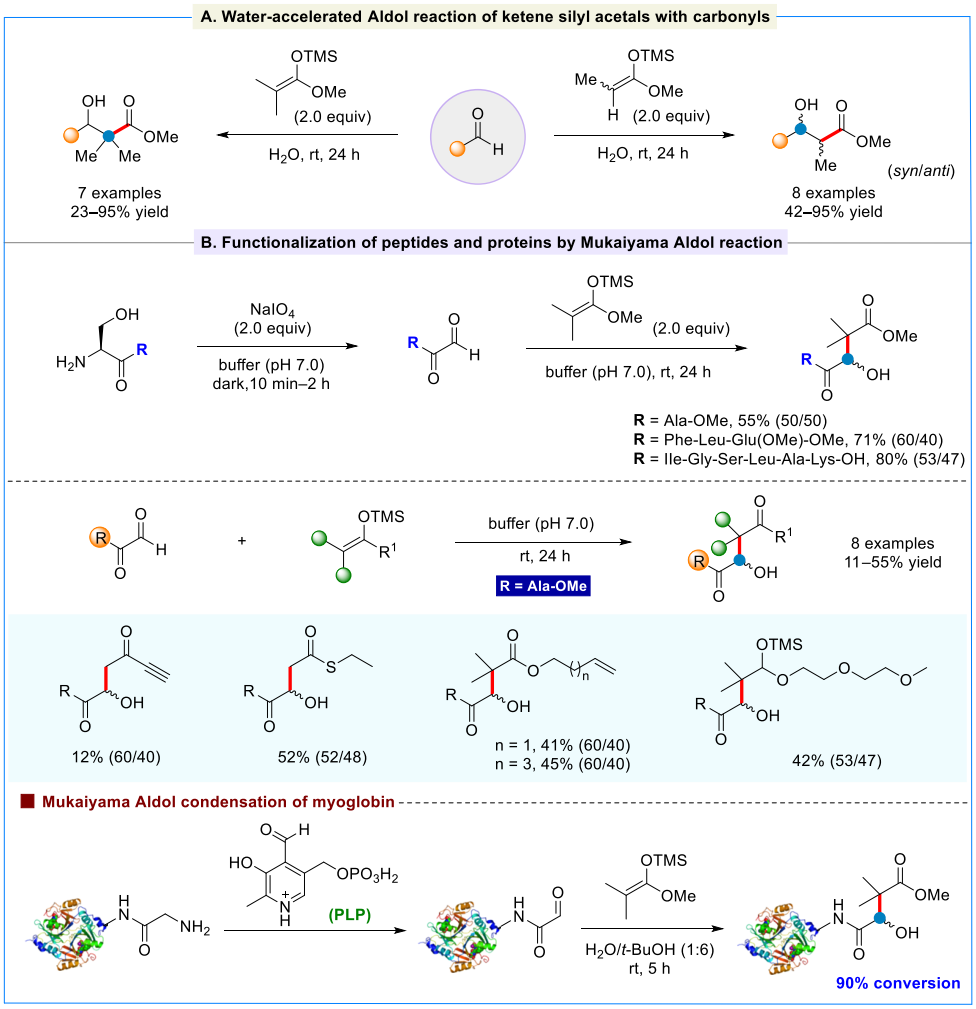
With the concept of sustainable chemistry, the development of water-compatible reactions that can work under catalyst-free, biocompatible conditions (aqueous media, room temperature, pH 7.0, etc.) is highly sought-after, especially in chemical biology. These reactions are not only green but also could be applied to the site-specific modification of biomolecules, thus enabling the development of bioconjugate therapeutics such as antibody-drug conjugates (ADCs). They also provide opportunities for performing one-pot multi-step reactions including chemo-enzymatic transformations. Most importantly, these catalyst-free biocompatible reactions could be carried out in the living systems. Considering these advantages, our group has been focusing on the development of a catalyst-free, biocompatible toolbox for nearly three decades.[55] For clarity, we summarized this part according to the type of reactions.

4.1. C–C Bond Formation Reactions

At the outset of our research, we envisaged that the employment of reactive electrophiles with diverse water-stable nucleophiles such as silyl enols, thiols, sulfinic acids, amines, etc. may result in the development of biocompatible reactions. In our initial efforts, we embarked on developing a highly efficient catalyst-free, water-compatible Mukaiyama-aldol reaction. Lubineau *et al.* first realized the feasibility of water-compatible Mukaiyama-aldol reaction of

silyl enol ethers with carbonyl compounds.[56] Unfortunately, the reaction afforded the aldol products in remarkably low yields. In 2000, we found that using reactive 2-pyridine carboxaldehyde, the Mukaiyama-aldol condensation with various ketene silyl acetals occurred smoothly in water at ambient temperature, giving rise to the products in high yields. Notably, methyl glyoxylate, which prefers to exist in its hydrate form in aqueous media, was also an effective substrate for this reaction (Scheme 21A).[57]

Scheme 21. Mukaiyama-Aldol Reaction of Ketene Silyl Acetals with Aldehydes



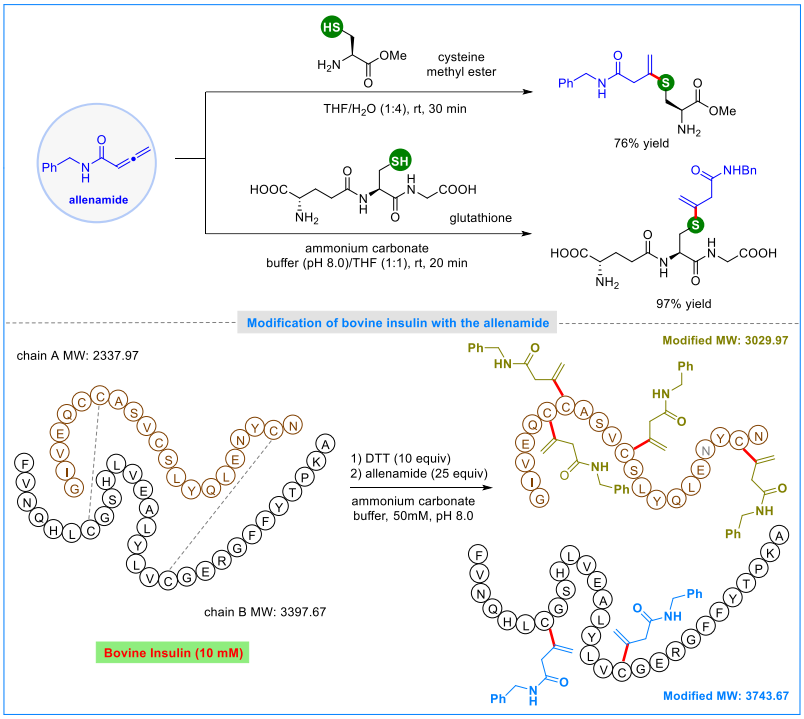
The ability to chemoselectively modify peptides and proteins is of continuous interest in both chemical biology and synthetic biology. Given that these conditions are typically biocompatible, we further applied this newfound catalyst-free Mukaiyama-aldol condensation for the site-selective functionalization of N-terminal aldehydes of biomolecules (Scheme 21B).[1] Gratifyingly, both protected and unprotected short peptides containing serine at the N-terminus reacted

uneventfully with silyl ketone acetal, leading to β-hydroxy carbonyl compounds in decent yields. Both silyl enol ethers and silyl ketone acetals could be readily converted into the products. The reaction with protein aldehyde myoglobin which contains a N-terminal glycine amino acid proceeded smoothly with 90% conversion. Notably, the tertiary structures of the protein adducts remained totally intact, and the enzymatic activities of the functionalized proteins were preserved as well. This site- and chemoselective modification of proteins opens new access to protein labeling and protein conjugates via catalyst-free targeted functionalizations.

4.2. C–S Bond Formation Reactions

The carbon–sulfur bond formation reactions under catalyst-free, biocompatible conditions are highly sought-after, especially in chemical biology.[58] Our group has pursued developing new linker technology that can directly target a specific native amino acid in peptides and proteins.[59] In this regard, we reported a thiol-click reaction using allenamides as efficient orthogonal handles for the thiol-selective functionalization of cysteine-containing biomolecules such as peptides and proteins (Scheme 22).[2] The catalyst-free reaction between allenamide and cysteine residues worked smoothly in buffer, leading to allenic thiol products. As a particular highlight, the obtained products do not readily undergo the *retro*-Micheal reaction, which is significantly in contrast to the classical maleimide thiol adducts. This thiol-based bioorthogonal reaction proceeded extremely fast, typically finished within 30 mins. Moreover, the thiol groups, generated from the DTT treatment of bovine insulin, could also be fully modified in $(NH_4)_2CO_3$ buffer (pH 8.0). The high reaction rates, almost quantitative yields, exclusive selectivity towards thiols, and remarkably high stability of the adducts, should make them an attractive linker for cysteine bioconjugation as well as the synthesis of antibody-drug-conjugates (ADCs).

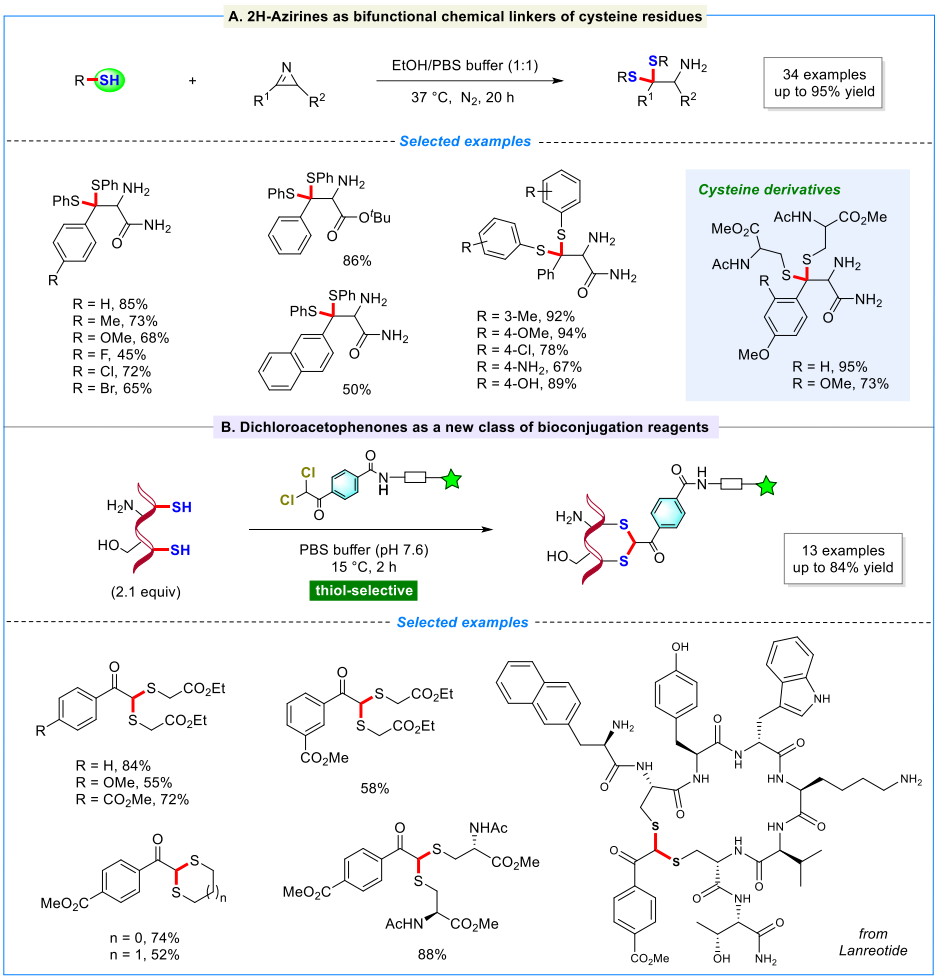
Scheme 22. Allenamides as Orthogonal Handles for Modification of Cysteines



The development of a bifunctional linker that can bind one payload with two thiols is of great importance, as it could reduce the amount of precious payloads and significantly decrease the risk of off-target toxicity of drugs from antibodies. With our interest in biologics and antibody-drug conjugates, we continued to investigate new bioconjugation linkers, and reported a new class of bifunctional linker based on 2*H*-azirines to target dithiols of cysteine residues under catalyst-free, biocompatible conditions (Scheme 23A).[60] The substrate scope was impressive as a variety of thiols with different substitution patterns were compatible. Moreover, cysteine-containing peptides also reacted effectively in buffer. Mechanistically, this bioconjugation reaction proceeded through the thiol addition onto 2*H*-azirines to produce an aziridine, followed by a ring-opening process.

Next, we expanded to report another thiol-reactive bifunctional linker to target cysteine residues (Scheme 23B).[61] Successfully, we employed α,α-dichloroacetophenones as a new type of chemical bioconjugation reagents for disulfide bridging. This class of bioconjugation linker was highly chemoselective to target thiol groups, no N- or O-addition products were observed. Complex peptides such as lanreotide and *N*-Ac-oxytocin reacted cleanly to afford the disulfide bridging products. Given that the reaction conditions are typically mild, catalyst-free and biocompatible, these two newly developed target-specific bioconjugation reagents are excellent linker candidates for ADC synthesis with a more controllable drug-to-antibody ratio.

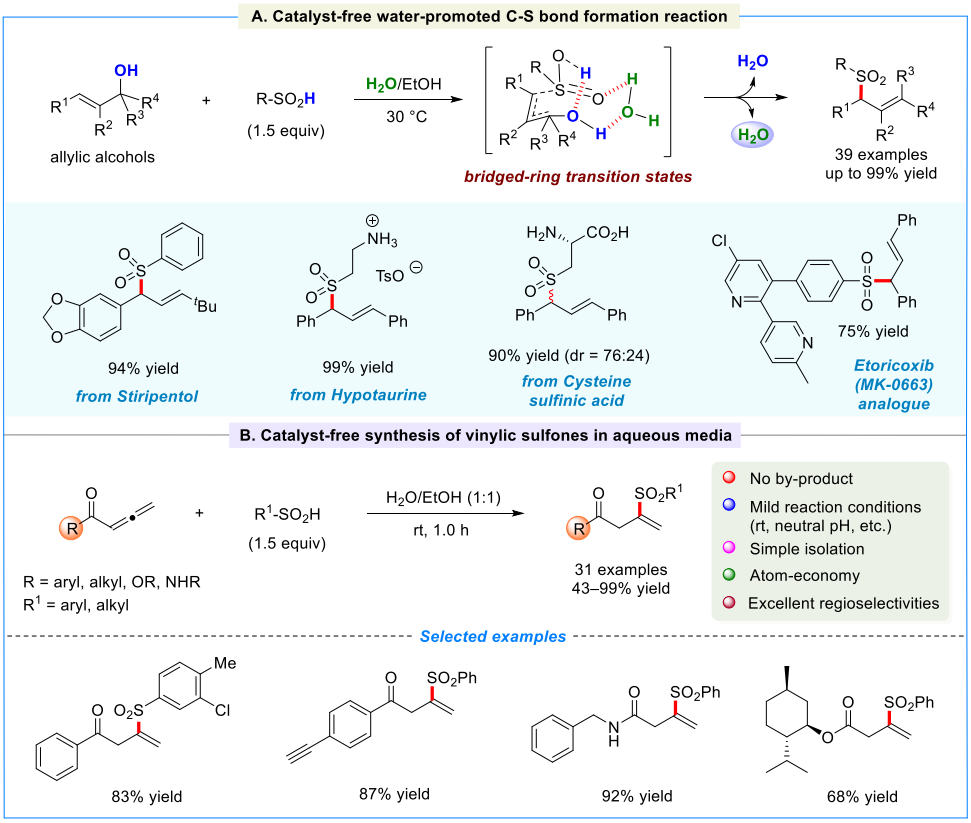
Scheme 23. Bifunctional Chemical Linkers for the Bioconjugation of Cysteine Residues



4.3. C–SO_2 Bond Formation Reactions

Next, we directed our attention to the C–SO_2 bond formation reactions. In 2018, we disclosed the use of sulfinic acids as water-stable nucleophiles to couple with activated allylic alcohols under catalyst-free conditions (Scheme 24A).[3] This sulfinic acids ligation strategy proceeded in co-solvent water/ethanol through an atom-economical dehydrative cross-coupling, with water as the only byproduct. Both aliphatic and aromatic sulfinic acids were suitable, efficiently producing a variety of allylic sulfones. Complex sulfinic acids such as hypotaurine and cysteine-containing sulfinic acid were tolerable, remarkably showcasing the capability of this strategy. With this approach, we also achieved the facile synthesis of etoricoxib (MK-0663) analog. The role of water in this reaction was rationalized by DFT calculations, which indicated that water acts as a promoter for this dehydrative coupling via intermolecular multi-hydrogen bonds. It is noteworthy that the obtained solid vinylic sulfones could be readily isolated by simple filtration, totally avoiding the use of any organic solvent.

Scheme 24. Synthesis of Allylic and Vinylic Sulfones in Aqueous Media



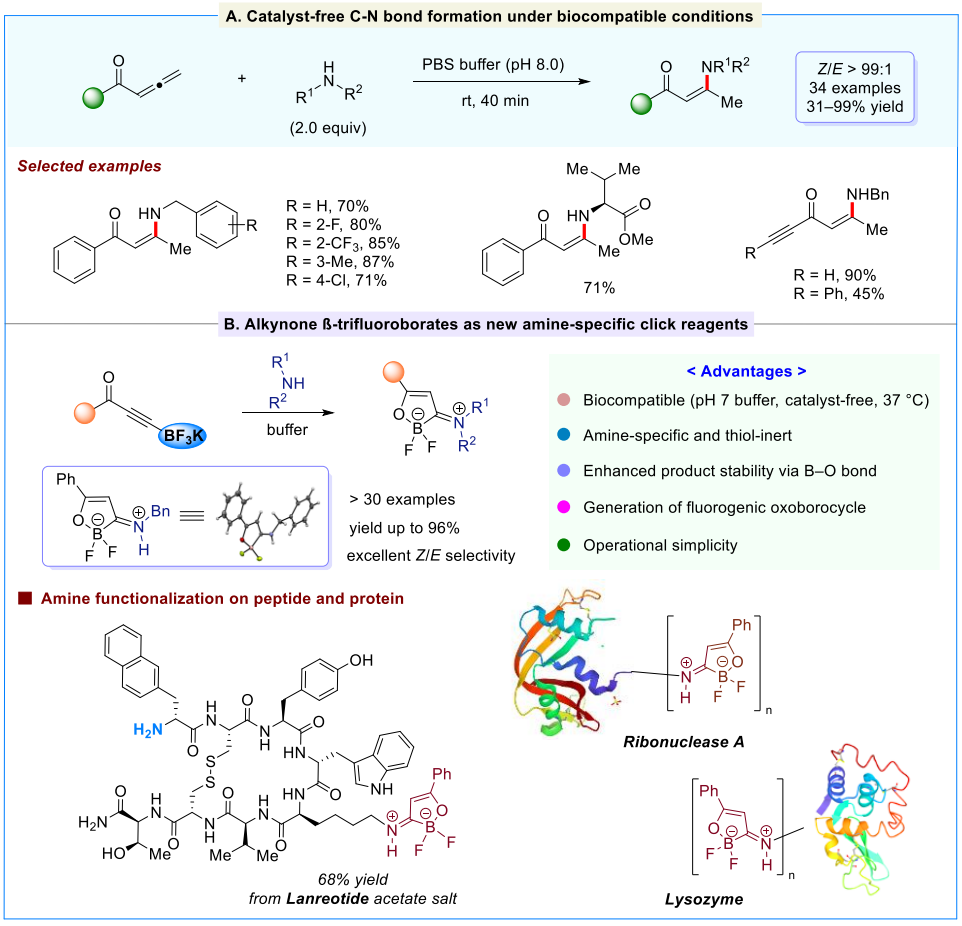
Encouraged by this success, we expanded to disclose the water-compatible reactions using allenic carbonyl compounds as the electrophiles under slightly modified conditions (Scheme 24B).[62] Similarly, this catalyst-free reaction was performed in co-solvent H_2O/EtOH at room temperature. The substrate scope turned out to be quite broad, as a variety of allenic carbonyl compounds including allenic ketones, esters and amides worked well with both aryl and alkyl sulfinic acids, affording diverse vinylic sulfones in satisfactory yields.

4.4. C–N Bond Formation Reactions

With our long-term goal to develop new strategies for amine bioconjugation of native amino acids, we explored the reaction of amines with water-tolerant electrophiles under catalyst-free biocompatible conditions (Scheme 25A).[63] As mentioned above, allenamides targeted thiols exclusively, showing great inertness towards less reactive amine nucleophiles.[2] To achieve amino-specific conjugation strategies, we employed more reactive allenic ketones as the electrophiles, and reported the amination reaction of allenic ketones with a broad array of amines. This finding led to the establishment of efficient strategies for amine-reactive bioconjugation. Specifically, the reaction proceeded rapidly, and was typically finished within 40 min in PBS

buffer (pH 8.0), giving rise to highly useful enaminones. Complex chiral amines such as glucosamine derivative and amino acid/peptide esters were tolerable, albeit with a prolonged reaction time.

Scheme 25. Development of Amine Bioconjugation Technologies



Recently, we also disclosed a practical amine conjugation technology using boron-based alkynone β-trifluoroborates as the electrophiles (Scheme 25B).[4] This new class of amine-specific bioconjugation reagents exhibited exclusive chemoselectivity toward amines over thiols. Under the conditions, both aromatic and aliphatic amines could be effectively converted into the products with excellent *Z*/*E*-selectivity. A series of alkynone β-trifluoroborates were compatible with this amine-conjugation process, affording five-membered oxaboracycle products. Remarkably, aliphatic alkynones furnished iminium trifluoroborates as the major products. A modular approach for late-stage derivatization of diverse N-terminal amino acids and peptides illustrated the potential of this strategy. Of note, the reaction with cyclic peptide antitumor lanreotide acetate, which contains a lysine residue and a branched α-amino group, selectively

afford the linear conjugated adduct, while the branched amino acid residue remained totally intact. We eventually implemented this amine conjugation technology through incubation of proteins such as lysozyme and ribonuclease A with alkynone β-trifluoroborates in NH_4OAc buffer, efficiently producing the adducts with multiple functionalities. Combined experimental studies and DFT calculations suggested that water acts as a proton shuttle in the reaction.

With these newfound catalyst-free water-compatible methods, the toolbox of green synthetic methodologies has been significantly expanded. We hope that these strategies will provide new avenues for the truly green synthesis of complex natural products and pharmaceuticals.

5. SUMMARY AND OUTLOOK

In conclusion, over nearly three decades, our research group has significantly advanced the field of green, water-compatible reactions. We have focused on building a comprehensive toolbox of sustainable synthetic methods, anchored in three key areas: water-tolerant organometallics, water-tolerant catalysts, and catalyst-free biocompatible reactions. These methods have been instrumental in enabling the efficient total synthesis of complex molecules, facilitating one-pot multi-step synthesis, and driving advances in protein functionalization, including the bioconjugation of native amino acids. Looking forward, we aim to expand this toolbox with innovative approaches such as metal-free organometallic equivalents, organic solvent-free reactions, new chiral water-tolerant catalysts, and environmentally friendly water waste treatment methods. We are also delving into new applications, including catalyst-free bioconjugation of additional native amino acids like tyrosine group of protein, protecting group free synthesis of carbohydrate conjugates and chemo-enzymatic multistep one-pot synthesis for pharmaceuticals. Through these endeavors, we aspire to inspire greater environmental responsibility and innovation in the realm of organic synthesis.

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Notes

The authors declare no competing financial interest.

Biographies

Ming-Zhu Lu was born in Huaian, Jiangsu province of the P. R. of China. In 2015, he obtained his Ph.D. degree from the University of Science and Technology of China under the guidance of Professor Teck-Peng Loh. Then, he carried out postdoctoral research with Professor Jin-Quan Yu (2015–2017) at Shanghai Institute of Organic Chemistry. He worked as a senior research fellow in the group of Professor Teck-Peng Loh at Nanyang Technological University, Singapore. He is currently a professor at Henan University of Technology, where his research interest focuses on C–H functionalization reactions and their applications in organic synthesis.

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 Ph.D. (1994) from Harvard University. 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 and unnatural products.

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