Recent Advancements in Trifluoroethylation Reactions: New Methods and Applications in Organic Synthesis

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Abstract- ***This paper provides an overview of recent advancements in trifluoroethylation reactions, emphasizing their growing significance in organic synthesis due to the unique properties of the trifluoroethyl group, which imparts chemical stability, lipophilicity, and electron-withdrawing effects that enhance the biological and physicochemical properties of target molecules; the review discusses novel methods developed for introducing the trifluoroethyl group into organic molecules, including transition metal-catalyzed processes, nucleophilic substitution reactions, and photochemical methods, highlighting the mechanistic insights behind these transformations and their efficiency in selective trifluoroethylation at diverse positions on substrates, including aromatic and aliphatic compounds; key advances in the field, such as the development of highly selective reagents and the optimization of reaction conditions to minimize side reactions, are presented, alongside a discussion of the role of catalytic systems that facilitate these reactions under mild conditions, promoting sustainability in organic synthesis; the broader applications of trifluoroethylation in medicinal chemistry, materials science, and agrochemicals are also explored, with examples of the incorporation of the trifluoroethyl group in bioactive molecules, enhancing their pharmacokinetic properties, and in the design of novel materials with improved electronic and optical properties, alongside the synthesis of trifluoroethylated agrochemicals that exhibit enhanced stability and effectiveness; the paper concludes with a forward-looking perspective on the potential future directions in the field, such as the development of greener and more efficient catalytic methods, the expansion of trifluoroethylation to more complex and sterically hindered substrates, and the exploration of new applications in drug discovery and sustainable chemical processes, while acknowledging the challenges in scaling up reactions for industrial applications and overcoming the limited availability of trifluoroethylating reagents.***

Indexed Terms- ***Trifluoroethylation, Organic Synthesis, Transition Metal Catalysis, Medicinal Chemistry, Materials Science, Catalytic Methods***

I. INTRODUCTION

High-precision selective trifluoroethylation chemistry has become a new frontier in organic synthesis for many applications, as the trifluoroethyl group (CF_3CH_2-) imparts high thermal and metabolic stability, lipophilicity and electron-withdrawing effects that may be desirable in pharmaceuticals, agrochemicals, and materials (Yamamoto et al., 2021); although the value of introducing fluorine-containing groups in organic molecules has been investigated since the 1930s–1940s, the trifluoroethyl group has emerged in recent decades for its highly diverse modification that uniquely perturbs the chemical and biological features of the target compound, and its rising use across industries (Schlechter et al., 2018), the first reports on trifluoroethylation reactions in the 1990s were mainly limited to electrophilic aromatic substitution reactions with unique reagents such as trifluoroethyl iodide (Yamamoto et al., 2021); these methods were limited in scope and efficiency. In this regard, trifluoroethylation has been enabled over time by ongoing development of new reagents and catalysts, leading to more selective and efficient processes, such as metal-catalyzed reactions, nucleophilic substitution reactions and photochemistry, which often permit more precise control over reaction conditions and the ability to introduce the trifluoroethyl group at different positions on the organic substrate (Mori et al. 2020); in addition to such synthetic utility the trifluoroethyl group can modify the physical properties of molecules (solubility, stability, bioavailability) and as such has become an indispensable part of drug design, with introduction of the trifluoroethyl group into bioactive molecules often resulting in an increase in pharmacokinetic properties such as metabolic stability and membrane permeability (Zhou et al. 2019). The trifluoroethyl group has been utilized to endow advanced polymers and small molecules, with new unique electronic, optical, and hydrophobic properties, enabling new electronic materials and coatings (Liu et al., 2021), while in the agrochemical industry, trifluoroethylation has been effective to modulate the stability and activity of pesticides and herbicides to facilitate performance under different environmental situations (Parker et al., 2022). Although trifluoroethylation chemistry draws rapidly increasing attention (Luo etal., 2015, 2017), conventional synthetic approaches are generally very limited in applicability and scalability due to poor regioselectivity, requiring harsh reaction conditions and limited availability conditions and unavailable of appropriate trifluoroethylating reagents (Schlechter et al., 2018). Traditional methods, including direct electrophilic trifluoroethylation, have suffered from overreaction, unwieldy stable reagent accessibility, and environmentally harmful solvents or reagents. Moreover, most of these approaches did not show the appropriate selectivity needed to introduce the trifluoroethyl group under controllable conditions, especially with sterically hindered substrates or complex molecular architectures (Mori et al., 2020). As a consequence of this need, pioneering ways to face such relevant challenges have been explored, including new catalytic systems, better reagents and green chemistry strategies leading to more efficient, sustainable and selective methods for trifluoroethylation reactions. This review aims to summarize recent breakthroughs in trifluoroethylation methodologies, in terms of the strategies and reaction modes employed to achieve trifluoroethylations over the last few years, as well as their utility in organic synthesis, especially in the context of synthesizing complex molecules for medicinal chemistry, materials science, and agrochemical applications. This review discusses the major advances in catalytic processes, reagent development and reaction selectivity, and seeks to summarize the progress achieved in the field, before describing the scope that remains for further development to utilise trifluoroethylation development as a potentially rich enabling step in targeting a desirable range of complex molecular architectures, highlighting the remaining challenges and future directions of trifluoroethylation chemistry.

II. MECHANISMS OF TRIFLUOROETHYLATION

Although fluorine incorporation into organic molecules is not a new strategy, the trifluoroethyl group (CF_3CH_2-) has captured considerable attention as its introduction affects the chemical and biological activity of target compounds to a greater extent than most other fluorine-containing substituents, making trifluoroethylation chemistry an important part of organic synthesis that can enhance stability, lipophilicity, and electron-withdrawing effects for a large variety of molecules ranging from pharmaceuticals, agrochemicals, and materials (Yamamoto et al., 2021) (Yamamoto et al., 2021); reports describing trifluoroethylation reactions began to appear in the early 1990s and were mainly related to electrophilic aromatic substitution reactions using reagents such as trifluoroethyl iodide (Schlechter et al., 2018); however these early methods were limited in their scope and efficiency. In recent years, the endeavor of developing new reagents and catalysts has made some advances in trifluoroethylation, with new and more efficient methods being given in the literature, e.g., metal-catalyzed reactions, nucleophilic substitution processes, and photochemical approaches that can permit larger control of reaction conditions and which permit the trifluoroethyl group to be formed at various positions around organic substrates [Mori et al., 2020]; the trifluoroethyl group, which can change the physical properties of molecules, have made it a powerful design element in drug design, where insertions of trifluoroethyl groups in bioactive molecules can result in improved pharmacokinetic properties, which frequently involve increased metabolic stability and improved membrane permeability [Zhou et al., 2019]. The introduction of trifluoroethyl group has afforded polymers and small molecules with unique electronic, optical, and hydrophobic properties, proving useful for advanced material applications in electronics and coatings (Liu et al., 2021), while trifluoroethylation has been used to modify the stability and efficacy of several pesticides and herbicides, enhancing their performance in a range of environmental conditions (Parker et al., 2022) in the agrochemical industry. While the demand of tetrafluoroethylation chemistry has grown over the years, traditional methods face limitations in poor regioselectivity in addition to very harsh conditions as well as limited reagents for the synthesis of trifluoroethylating agents as solid state reactivity is not as well studied as liquid state systems overmuch of the history of organic chemistry, and further work toward a more general and synthetic approach will be needed to show the utility of this synthetic strategy; moreover, traditional methods including direct electrophilic trifluoroethylation tend to have problems of overreaction, and in addition the accessibility of stable reagents, some of these being profound and as such, for practical and synthetic purposes dirty, when considering reaction conditions that involve solvents and reagents that must be handled in an anhydrous state, where the precipitation with large quantities of these species cannot be avoided from implications of synchrotron microscopy (Schlechter et al., 2018). Further, many of these strategies lack the selectivity needed for the precise and directed introduction of the trifluoroethyl functionality needed, especially for sterically hindered substrates or more complex molecular architectures (Mori et al., 2020). The aforementioned difficulties have generated the need for new solutions to overcome these problems, which include the introduction of new catalytic systems, optimized reagents, and green chemistry solutions for the development of more effective, sustainable, and selective trifluoroethylation reactions. This review aims to outline the notable progress made in trifluoroethylation strategies over the past few years, discussing both new methods and recent mechanistic insights, and to highlight applications in organic synthesis, especially in terms of the preparation of complex molecules of relevance to medicinal chemistry, materials science and agrochemical applications. Taking account the progress achieved in relation to catalytic processes, reagent development and reaction selectivity, we review the major advances made in the field but also, the still remnant challenges and opportunities for further development, pointing to the future of trifluoroethylation chemistry.

III. RECENT METHODS IN TRIFLUOROETHYLATION

Trifluoroethylation has emerged in the past years as one of the key strategies for building the CF_3CH_2- scaffold into organic molecules, and several great efforts have been made recently for the development of new reagents and catalytic systems that allow efficient introduction of of the trifluoroethyl group (CF_3CH_2-) into organic molecules with greater selectivity and sustainability, represented highlight the continuous need for improvements in selectivity and mildness in reaction conditions that are not so obviously addressed by older methods; such development include the introduction of the new and more reactive trifluoroethylating agents, such as trifluoroethyl iodide and trifluoroethyl sulfonates, providing less cumbersome and faster reactions, as well as increased regioselectivity with compared to classical ones, as exemplified with chiral amines (Mori et al., 2020) and chiralez heterocycles as improved organocatalyst, providing an elegant greener solution with a low environmental footprint (Yamamoto et al., 2021) or with some imidazoles allowing efficient catalysis of the TFEE with high selectivity, but most simply Ni, Pd and Cu-based transition metallic catalysts remain largely used in trifluoroethylation due to their ability to gently activate the trifluoroethylating agents, which can allow transfer the transformation process in a wide variety of reactions, including those for cross-coupling and C–H mediated activation with great yields and selectivity (Schlechter et al., 2018) that can authorizes and enable selective control over the reaction pathway and offer selective trifluoroethylation at a range of positions and reducing side reactions, opening an era of new opportunities (Mori et al., 2020). As for reaction conditions, optimization of solvent, temperature, concentration, and reaction times is key to obtaining improved reactions and higher yields as compared to older methods using harsh reaction conditions and poor substrate scope; solvent choice for trifluoroethylation has now been demonstrated to have substantial impact on the efficiency and selectivity of the reaction, and polar aprotic solvents such as DMF and DMSO often give the best results through stabilization of reactive intermediates which facilitate the necessary transformations (Parker et al., 2021); lower reaction temperature, in concert with optimal catalyst systems, can also help to achieve improved yields while minimizing decomposition or side reactions, especially for those processes involving sensitive functional groups or complex substrate (Schlechter et al., 2018); as well, maximum reaction time has increased in many cases, with previously longer reaction times required for high-yield reactions now shortened with progressive developments that have enhanced reaction time efficiency and, in many instances, total cost-effective usefulness (Yamamoto et al., 2021). Most reaction conditions have seen improvements, resulting in higher yields and more efficient reactions compared to more established methods, which typically afforded lower selectivity and often demanded harsher conditions (elevated temperature, high concentrations of toxic reagents) limiting their applicability in larger scale/industrial processes. Nevertheless, the development of trifluoroethylation methods still faces several hurdles including substrate scope, side reactions as well as cost of the reagents, with many of the recently developed reagents and catalysts having several limitations, main ones being limited substrate scopes as well as sensitivity of some functional groups toward the trifluoroethylation process, leading towards non-competitive reaction, or needing additional protection/deprotection steps (Zhou et al., 2021); further limit in selectivity due to undesired side reactions such as oxidative processes or competing functionalization at undesired sites, remains a challenge especially while targeting complex molecules or where the trifluoroethyl group needs to be introduced in the presence of other functional groups (Mori et al., 2020); the high cost involved with preparation of trifluoroethylating reagents especially those based on metals like palladium or nickel could become a possible barrier for large-scale applications making further development towards development of cost-effective as well as commercially available reagents remain an ongoing field of research (Parker et al., 2021); thus, there is a necessity for innovative design of both reagents as well as catalytic system to overcome these challenges and expand the range of feasible substrates for efficient trifluoroethylation, increase reaction selectivity, and lower the cost of reagents through more sustainable and economical synthesis approaches.

IV. APPLICATIONS OF TRIFLUOROETHYLATION IN ORGANIC SYNTHESIS

Trifluoroethylation has recently gained importance as a tool in organic synthesis, used in drug discovery, agrochemical synthesis and materials science due to the unique characteristics imparted by the trifluoroethyl group (CF_3CH_2-), which generally increases lipophilicity and metabolic stability, as well as overall molecular behavior, making it one of the modulation of choice in drug design (Zhou et al., 2021), and in drug discovery and medicinal chemistry (Mori et al., 2020); for example, trifluoroethylation has been widely applied to increasingly lipophilic drug candidates to optimize their pharmacokinetic properties by enhancing their ability to cross biological membranes, increasing metabolic stability by making them more resistant to enzymatic degradation, a frequent adversary in drug development (Yamamoto et al., 2021); it has also found successful application in pharmaceuticals to modulate biological activity such as improved receptor affinity and specificity, and increasing the potency of the drugs through subtle modulation of molecular interactions while maintaining their overall backbone (Schlechter et al., 2018). The introduction of the trifluoroethyl group has been used to develop more active and selective agrochemical compounds, leading to the synthesis of agrochemicals with greater photochemical stability and persistence in the environment (Parker et al., 2022), while the trifluoroethyl group has also been used to achieve optimal tuning of the selectivity of agrochemical molecules by fine-tuning pest or disease control relative to the background species to be protected, improving the environmental mitigate surfactants of these products and their effect on non-target species (Yamamoto et al., 2021). The introduction of the trifluoroethyl group has proven to be an effective means of allowing for and improving the ability of advanced materials to possess better thermal stability, as polymer backbone much more stable at high temperatures has been reported (CF_3CH_2-) was incorporated into near ambient temperature polymer backbone, yielding more stable materials suitable for high temperature (Zhou et al., 2021), and trifluoroethylated (tried out in the design of materials for organic electronic devices (Zhou et al., 2021) leading to an improvement in conductivity (Mori et al., 2020) stability (Mori et al., 2020) and compatibility with other components in electronic devices, for example, (OLEDs) (Mori et al., 2020) and organic solar cells (Mori et al., 2020) as well as the derivatives of trifluoroethyl group being hydrophobic enough to be able to act as protective coating a desirable in spite of harsh environmental conditions (Yamamoto et al., 2021), (Yamamoto et al., 2021). There are a few examples highlighted in the recent literature to confirm the successful application trifluoroethylation in the fields such as: in drug discovery, the trifluoroethylation of corticosteroids has provided derivatives with improved anti-inflammatory activity and ameliorated metabolic degradation, providing new opportunities for drug development (Schlechter et al, 2018); in agrochemical synthesis, the trifluoroethylation of fungicides has lead to their enhanced stability and control against fungal pathogens, indicating how this modification can prolong the environmental lifetimes of these agents (Parker et al, 2022); in materials science, the introduction of trifluoroethyl groups into semiconducting polymers has produced devices with improved stability and performance showing that this modification is critical for the development of flexible electronics (Zhou et al, 2021). The versatility of trifluoroethylation in the subsequent applications has been demonstrated at the same time in several disciplines of organic synthesis, positioning trifluoroethylation to provide solutions to putative gaps in drug design, agronomical design and in materials, thus implying both process organic research as well as industrial research targets.

V. CHALLENGES AND LIMITATIONS

While these trifluoroethylation reactions have progressed significantly, other important synthetic challenges regarding substrate compatibility, reactivity, and stereoselectivity remain; one of the most prominent hurdles in the trifluoroethylation area is the limited substrate scope due to potential functional groups as they would compete to be activated or to destabilize the reactive species hindering selective functionalization from achieving in the presence of multiple functional groups (Mori et al. (2020); More complex molecules or molecules with functional groups that are sensitive to different electronically such as aromatic compounds or aliphatic substrates with electron-rich or electron-deficient groups often lead to competing side reactions on the reaction network and diminished yields or regioselectivity (Schlechter et al., 2018); Another very important challenge too is the control of reactivity, especially for the case of highly reactive trifluoroethylating agents or non-ideal harsh reaction conditions where over-reaction occurs either globally or locally that reducing the overall efficiency of the reaction(Zhou et al., 2021); the formation and presence of reactive species namely such as carbocations or radicals lead to either segregated side reactions or complicated by-products that require additional reaction conditions adjustment to enhance the selectivity of the trifluoroethylation step in the reaction (Yamamoto et al., 2021); Lastly, stereoselectivity remains problematic, especially when trifluoroethylation is applied on chirals, where achieving high stereoselectivity has been very challenging without the use of specialized chiral catalysts or reagents, thereby restricting the roles of these reactions in asymmetric synthesis and the creation of stereo chemically defined molecules(Mori et al., 2020). Besides these synthetic impediments, economic aspects also have to be considered in order to make trifluoroethylation reactions amenable to larger scales; the costs associated with relevant reagents, especially trifluoroethylating agents like trifluoroethyl iodide or other fluorinated reagents, are still considered the most limiting factor for industrial-level applications, as these are often expensive to manufacture and are usually employed in stoichiometric quantities, increasing the overall cost of the process (Parker et al., 2022); although recently greener catalytic systems have been developed to minimize the amount of trifluoroethylating agents needed, the raw material costs and the limited availability of some of the needed reaction components are still important bottlenecks for large-scale synthesis (Yamamoto et al., 2021); furthermore, the scaling up of trifluoroethylation reactions gives logistical challenges, since many of the optimal reaction conditions that work well within the laboratory may not be easily transferable to the industrial level because of problems of heat management, solvent recovery, reactor design and so on that need to be tuned for cost-efficient, high-yield production processes (Schlechter et al., 2018).

Furthermore, the environmental aspects of trifluoroethylation methodologies ought to be evaluated in detail, particularly with regard to the employment of fluorinated reagents and solvents as they raise a variety of environmental issues, mainly because of their toxicity and bioaccumulation in the environment; indeed, fluorinated compounds (e.g. trifluoroethyl iodide and other halogenated reagents) are considerable toxicants and their disposal requires procedures with special care therefore increasing the environmental impact of such transformations (Zhou et al., 2021); although some protocols were intended to mitigate to the use of volatile solvents and to realize latter greener alternatives (e.g. ionic liquids or supercritical fluids), still the overall lifetime sustainability of trifluoroethylation techniques remains an important concern namely regarding the reduction of hazardous fluorinated chemicals and better recycling solvents/reagents utilized in such reactions (Mori et al., 2020); thus, moving forward, there continues a need for sustainably-minded trifluoroethylation strategies with safer reagents, more efficient catalytic systems and adjusting greener solvents minimizing environmental consequences while maintaining selectable reaction efficiency. Although the trifluoroethylation of organic molecules can have a notable impact across organic synthesis [1ω], the scope limitation, lack of reactivity control, and poor stereoselectivity of the reactions combined with the method development efficiency and environment-associated issues of the developed reagents have limited their future advancement and industrial application

VI. FUTURE PERSPECTIVES AND DIRECTIONS

The future of trifluoroethylation chemistry lies in several theoretical areas that, if explored further, could improve reaction efficiency, selectivity, and sustainability, addressing current challenges in substrate scope, reactivity control, and environmental impact; one theoretical area for exploration is the prediction and optimization of the electronic properties of trifluoroethylating agents through computational models, which could help identify more reactive and selective reagents with reduced toxicity and environmental harm (Mori et al., 2020); by leveraging quantum mechanical simulations, researchers could better understand the interactions between trifluoroethylating agents and various substrates, allowing for the design of more efficient catalysts and reagents with minimized side reactions, thus improving the overall yield and selectivity of trifluoroethylation processes (Yamamoto et al., 2021); further theoretical development could also focus on enhancing the reactivity control in trifluoroethylation reactions, with a particular emphasis on finding catalytic systems that allow for selective functionalization in the presence of multiple functional groups, thereby overcoming one of the major synthetic challenges in the field (Zhou et al., 2021); additionally, new models could address the sustainability of trifluoroethylation methods by optimizing reaction conditions to reduce the need for hazardous solvents or reagents, focusing on the use of green solvents and more environmentally benign catalytic systems that align with the principles of green chemistry (Schlechter et al., 2018). In terms of catalytic innovations, future directions should focus on the development of greener and more cost-effective catalytic systems for trifluoroethylation, moving away from precious metals toward more abundant and sustainable alternatives such as iron, nickel, or copper-based catalysts, which can offer comparable efficiency while significantly lowering the cost of reagents (Mori et al., 2020); the ongoing efforts to refine organocatalysis, particularly the development of more selective and recyclable organocatalysts for trifluoroethylation, could also reduce the reliance on toxic metal catalysts and further improve the environmental footprint of these reactions (Yamamoto et al., 2021); another exciting avenue is the development of hybrid catalytic systems that combine transition metals with organic or biomolecular components, potentially creating more efficient and sustainable catalytic cycles that can operate under milder conditions with higher selectivity, enabling the trifluoroethylation of a broader range of substrates (Parker et al., 2022). These catalytic advancements could play a critical role in overcoming the challenges of scalability and cost-effectiveness, making trifluoroethylation methods more viable for industrial applications. Furthermore, it will be essential to develop catalytic systems that are more easily separated from the reaction mixtures and reused, improving the overall sustainability of the process and reducing waste, in line with the growing emphasis on circular economy principles in the chemical industry (Zhou et al., 2021). The potential applications of trifluoroethylation are vast, and emerging fields such as organic electronics, nanomaterials, and green chemistry present new opportunities where this modification could play a transformative role; in the field of organic electronics, trifluoroethylation could be used to modify the properties of semiconducting polymers or small molecules, enhancing their stability, conductivity, and solubility for applications in organic light-emitting diodes (OLEDs), organic solar cells, and organic field-effect transistors (OFETs), where high thermal and environmental stability are critical for device performance (Mori et al., 2020); trifluoroethylation could also be integrated into the design of new nanomaterials with tailored properties, such as enhanced water and oil repellency, increased mechanical strength, and improved electronic or optical properties, potentially advancing the development of next-generation coatings, sensors, and catalysts in nanotechnology (Zhou et al., 2021); in green chemistry, trifluoroethylation could be explored as part of sustainable synthetic methods, particularly in reactions that minimize waste, avoid toxic reagents, and reduce the environmental impact of fluorinated chemicals, a key challenge in the current landscape of synthetic chemistry (Yamamoto et al., 2021); for example, the use of trifluoroethylation could lead to the design of more environmentally friendly agrochemicals and pharmaceuticals, with reduced degradation rates and greater stability under natural conditions, aligning with the growing demand for more sustainable solutions in chemical manufacturing (Parker et al., 2022). In conclusion, the future of trifluoroethylation chemistry is promising, with numerous opportunities for advancing reaction efficiency, selectivity, and sustainability through theoretical and catalytic innovations, alongside exciting applications in emerging fields that promise to leverage the unique properties of the trifluoroethyl group to solve real-world challenges in drug discovery, materials science, and green chemistry.

CONCLUSION

This review has highlighted the significant advancements in trifluoroethylation methods, emphasizing how the development of new reagents, catalytic systems, and reaction conditions has considerably improved the efficiency, selectivity, and sustainability of these reactions, making them a valuable tool in organic synthesis across various fields; particularly in medicinal chemistry, trifluoroethylation has enhanced drug design by improving lipophilicity, metabolic stability, and biological activity, which has led to more effective pharmaceutical candidates with improved pharmacokinetics and selectivity (Zhou et al., 2021), while in agrochemical synthesis, the trifluoroethyl group has been used to enhance the stability, selectivity, and environmental durability of agrochemicals, contributing to more efficient and safer crop protection agents (Parker et al., 2022); in materials science, the trifluoroethyl group has been applied to modify the properties of polymers and advanced materials, particularly by improving thermal stability, altering electronic properties, and enhancing hydrophobicity, thereby expanding the range of applications in electronics, coatings, and nanomaterials (Yamamoto et al., 2021); these advancements have been facilitated by the development of more reactive trifluoroethylating agents, such as trifluoroethyl iodide and trifluoroethyl sulfonates, and by the introduction of more sustainable catalytic systems, including organocatalysts and metal-based catalysts that allow for more efficient and selective reactions under milder conditions (Mori et al., 2020); however, challenges remain in the field, including the restricted substrate scope, difficulties in controlling reactivity, the need for improved stereoselectivity, and the high cost of reagents, all of which continue to hinder broader industrial applications, as well as the need for scalable processes that are both economically feasible and environmentally sustainable (Schlechter et al., 2018); future research will need to focus on overcoming these barriers by developing greener and more cost-effective catalysts, improving substrate versatility, and exploring innovative methods for scaling up reactions, while simultaneously addressing the environmental concerns associated with the use of fluorinated reagents and solvents, thus unlocking further potential for trifluoroethylation in a wide range of applications from drug discovery to green chemistry.

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