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GREEN CHEMISTRY ISSUE • **B. H. LIPSHUTZ**, GUEST EDITOR

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ABOUT OUR COVER

Detail from ***Wivenhoe Park, Essex***. Photo courtesy National Gallery of Art, Washington, DC.

A self-sustaining country estate*—what a fitting subject for the cover of our *Acta* issue that is dedicated to the topic of Green Chemistry and sustainability in chemical synthesis! ***Wivenhoe Park, Essex*** (oil on canvas, 56.1 × 101.2 cm) was painted in 1816 by John Constable (1776–1837), one of the great British landscapists of the 19th century, who is credited with elevating the status of this genre. Constable's interest in painting started early, but faced initial disapproval from his family; nevertheless, he was able to eventually enroll at London's Royal Academy of Art, where he received his formal training. While he never traveled abroad, he had the opportunity to study the works of earlier Dutch and French landscapists. He struggled in his early years to get recognition from the British art establishment, which he did not receive until he was into his forties. His artistic influence was greatest after his death and outside of England, particularly in France.

Constable's delight in, and profound connection to, nature is obvious in his many paintings of the countryside of his native Suffolk and other counties in southeast and southwest England. Nowhere is this more apparent than in this painting with its almost photographic quality. Here, Constable aims to capture on canvas a fleeting moment in the life of this idyllic setting and to convey to the viewer the same sensation of balance and harmony between man and nature that it evoked in him. The precise and crisp brushwork, attention to detail, and the use of billowing, brightly lit clouds to communicate movement, are characteristic of Constable's style.

This painting is part of the Widener Collection at the National Gallery of Art, Washington, DC.

** Wivenhoe Park was a working, self-sustaining country estate when Constable painted it. Can you identify some of the elements in the painting that indicate this sustainability? To find out, visit* ***Aldrich.com/acta481***

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Green Chemistry Next: Moving from Evolutionary to Revolutionary

A View from the Co-Author of the 12 Principles of Green Chemistry

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The Past

Green Chemistry was launched as a field of endeavor in 1991, and has since evolved significantly while remaining true to its bedrock foundations.[1] From the beginning, the field was about inventions and innovations, rather than limitations and restrictions, and has been based on the premise that proactive design is essential and far more desirable than reacting to problems after they arise.[2] Green Chemistry considers as its appropriate scope the entire life cycle of a chemical or material,[3] rather than simply one aspect or stage in the life cycle—as outlined in the *Twelve Principles of Green Chemistry*.[4]

Green Chemistry originally manifested in ways that focused on efficiencies. Trost's atom-economy metrics[5] and Sheldon's E factor[6] were important early contributions that enabled quantification of the inherent material performance of a reaction or of an entire manufacturing process. Further refinements of the metrics included Wender's step-economy[7] for chemical syntheses. Additionally, other metrics have been developed to include energy and water utilization.[8]

Much of the earliest work in Green Chemistry used these metrics as drivers for new synthetic methodologies[9] and new solvent systems[10]. These new green alternatives were significant improvements in terms of quality of the chemistry and in terms of cost-effectiveness. This was especially pertinent in complex syntheses such as those in the pharmaceutical industry.[11] Over the past two decades, similar techniques have been employed to discover new materials,[12] new molecules, new catalysts,[13] new solvents,[10,14] and new synthetic transformations[15]. These have proved to be of tremendous benefit to a variety of industry sectors including agriculture,[16] energy,[17] chemicals,[9] personal care,[18] transportation,[19] electronics,[20] paints and coatings, and much more.

The Future

The successes of Green Chemistry since 1991 notwithstanding, its greatest achievements still lie in the future. To attain these achievements, Green Chemistry needs to transform this evolution into a revolution with significant changes in the way we conceive and design our chemistry. Some of these revolutionary aspects are already being explored and demonstrated by some leading thinkers in the field.

More Systematic

In order to derive the maximum benefit from the *Twelve Principles of Green Chemistry*, they will need to be regarded not as twelve independent principles, but rather as a multiparameter system to optimize. Understanding that achieving the synergies of one principle (e.g., renewable feedstock) can and should enable achieving the goals of other principles (e.g., ready degradability) is important to the development of greener chemistry in the future. It has, of course, always been antithetical to the *Twelve Principles* that you would achieve the goals of one principle (e.g., waste reduction) by violating another (e.g., by using toxic reagents). While it is often stated that "there are always trade-offs", it should be noted that there is no data to suggest that there is any *intrinsic* conflict between any of the principles. This means that it is simply a design challenge—albeit daunting and difficult, but possible—to optimize the system.

More Nexus

Many Green Chemistry technologies are being developed not only to be inherently sustainable, but also to address key sustainability challenges such as renewable energy, sustainable food production, water purification, and pollutant elimination. All of these challenges are important and, in the future, Green Chemistry will need to develop approaches that accomplish multiple goals simultaneously. Instead of merely reducing waste, for instance, Green Chemistry technologies would convert and utilize the "waste" material for value-added applications. Examples exist of sewerage bio-solids waste being utilized to generate energy and provide purified water. Other examples are emerging of how to split seawater to use in energy storage and then reclaim the purified water.[21–23] The energy–water–etc. nexus should be an essential target for Green Chemistry in the future.[24]

More about Inventing than Improving

While improving existing chemical products and processes has served Green Chemistry and the chemicals industry well, one of the great challenges of the future will be to shift from improving to inventing. While there are many logistical and economic impediments to introducing entirely new molecules and production schemes,[25] it is also the only way to be truly transformative. In addition, this type of transformative innovation is likewise the only way for Green Chemistry to bring maximum economic value. Existing members of the chemical enterprise across many sectors may embrace these disruptive technologies. In other cases, new small companies with these leapfrog Green Chemistry technologies will disrupt the less agile companies. While the question for many Green Chemistry researchers over the past twenty years has been, "How do we supply what industry is saying it needs?"; the question in the future will be, "How do we supply what a future sustainable industry needs, whether or not current industry recognizes it as necessary?"

More Focus on Function and Performance than on the Molecule

No one has ever paid for a chemical. That provocative statement is mostly if not absolutely true. People pay for function; for the performance that a chemical provides. So, while we often ask how to make a flame retardant or a solvent or a catalyst, what we need to be asking in the future is how to provide the function of flame retardancy, solvency, or catalysis. The difference between the two questions is that the latter opens up new degrees of design freedom that can result in new products—such as clothes that remain clean rather than inventing a new detergent, or polymers that are inherently fire resistant rather than needing additives. Clark et al. have recently proposed a new F Factor that would measure the amount of function you get per kg of product.[26] This concept leads one to want as much function in the numerator of the ratio with minimal mass needed in the denominator.

More Working Toward the Ideal

Pursuing function and performance leads to the logical conclusion of wanting to get all of the function with the needed chemicals or materials to achieve that function. In other words, how do we move toward the ideal? If it is true that no one ever buys a chemical—they buy a function; they buy performance—this raises great challenges that are being met every day and some that are just beginning to be enunciated such as: (i) How do you get color without pigments or dyes? (ii) How do you get adhesion without adhesives? (iii) How do you get flame retardancy without flame retardants? (iv) How do you get catalysis without catalysts? (v) How do you get 'transformation' without a chemical reaction?

Fusion with Engineering

For over two hundred years of creative chemistry, new molecules have been invented with new functions, and then they were transferred to engineering to make them work on a commercial scale. Often, the transfer to engineers and other users was not only for scale-up or process manufacturing, but rather for the engineering required for the end utilization or application of the product. This transfer has not brought about optimal results for chemistry nor engineering from the perspectives of cost, functionality, or utilization. DesignBuild is a concept that is widely accepted at the architecture/construction interface, where the critical parties are sitting at the same design table. In order to have the highest functioning—and greenest molecules—reach their highest performance potential and not be regarded as unscalable, the fusion of green chemistry and green engineering[27] must become seamless wherever possible.[28]

Fusion with Toxicology

Chemists understand how to make molecules, and toxicologists know which molecules are toxic and what makes them this way. Until such time when chemists are routinely trained in the fundamentals of toxicology and/or toxicologists are trained how to synthesize molecules, these two disciplines need to create mechanisms and frameworks that permit them to accomplish their synergistic goals of designing the next generation of molecules to be inherently less capable of manifesting hazards to humans and the environment.[29–32]

Fusion with Biology

As the field of synthetic biology builds upon the foundations of genetic engineering, there will be even greater challenges of design at the molecular level. It will be important to remember that the goal of Green Chemistry is, to the highest level of our knowledge and foresight, not to minimize change no matter how disruptive, but to minimize hazard and adverse consequence. By using fundamental principles of what can ultimately cascade into unintended consequences rather than the tools of simple current testing of manifested hazard, Green Chemistry, as the approach of molecular design, is just as applicable to molecular/chemical biology as it is to traditional systems regardless of the added complexity. If the potential benefits of synthetic biology and biological chemistry generally are to be realized, the perspectives of Green Chemistry are essential to ensure that they are realized safely and without the undesirable and undersigned impacts.

Conclusion

The accomplishments of the field of Green Chemistry thus far have ranged from scientific discoveries and advances, to industrial innovations in new products and processes, and to benefits to human health and the environment. The ability to align environmental and economic goals through Green Chemistry has been demonstrated.

However, the most important achievements of Green Chemistry clearly lie in the future, where, through systems thinking and design that strive toward the ideal, unimagined transformative innovations will take place at the interface of numerous disciplines. While the word “green” has many connotations, some of the most relevant for the future of Green Chemistry are “fresh, new, emerging, and growing”.

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Taking a Measure of Green Success

A Science Journalist's Perspective on Green Chemistry

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In a guest editorial in *Chemical & Engineering News* (*C&EN*) in 2013, Dow Chemical chairman and CEO, Andrew N. Liveris, commented that, despite the benefits of the products and technologies the chemical industry creates, the industry "is still misjudged, misaligned, and misrepresented…."[1] That disconnect is partially the industry's own fault, Liveris added, because it "has not done enough to operate with transparency and to lead on matters such as sustainability…."

In that regard, the chemical industry has evolved through what Liveris calls the four Ds—(i) defiance of those who call attention to problems concerning safety and pollution; (ii) denying their claims; (iii) debating them; and (iv) now, finally, engaging them in a dialogue. This observation might be a shock to anyone who was expecting to read a glowing review on the success of Green Chemistry.

Green Chemistry is a great concept, and it has been wildly successful around the globe; but, Green Chemistry isn't close yet to addressing all of the health, safety, and environmental concerns that are typically associated with the use of chemicals. Perhaps some historical perspective will help to explain.

Green Chemistry thinking started appearing in *C&EN* by the mid-1970s, just as protective health and environmental laws such as the Toxic Substances Control Act were being passed. Awareness of the environmental impacts of unfettered use of industrial and agricultural chemicals was growing. Trevor A. Kletz of Imperial Chemical Industries, who helped develop the idea of inherently safer design of chemical processes, was quoted in a story from the 1975 American Institute of Chemical Engineers conference. Kletz was reflecting on the deadly caprolactam plant explosion at Nypro UK's facility in Flixborough, Scotland, from the year before.[2]

"So often we keep a lion and build a strong cage to keep it in. Our cages are usually very strong, and only rarely, as at Flixborough, does the lion break loose. I am sure that by good design and operation one can make the chance of it breaking loose acceptably low. But before we keep a lion, we should perhaps ask if a lamb will do instead."[2]

Kletz's ideas percolated over the years, and inherently safer design is now one of the pillars of Green Chemistry. Other events, such as the lethal methyl isocyanate leak in Bhopal, India, in 1984, and interest in global sustainable development, increased concerns over the adverse effects of man-made chemicals in our daily lives. The chemical industry, however, was doing little on its own to curb these problems.

Enter the Pollution Prevention Act of 1990. It was the first environmental law to focus on preventing pollution during manufacturing rather than dealing with remediation or capture of pollutants after the fact. The new law led the Environmental Protection Agency to establish its Green Chemistry Program in 1991 to unify chemists around a common goal of designing chemical products and processes that reduce or eliminate the use and generation of hazardous substances.

The first "Green Chemistry" story published in *C&EN* appeared in the September 6, 1993, issue.[3] The article reported on a symposium organized by EPA's Carol A. Farris and Paul T. Anastas on alternative synthetic design for pollution prevention, which was held at the 206th ACS National Meeting in Chicago (August 1993). It was Anastas, an organic chemist who is now a chemistry professor and director of the Center for Green Chemistry & Green Engineering at Yale University, who had coined the term "Green Chemistry."

Organic chemists at the time were largely trained to identify reaction pathways that provided highest yields and best selectivity at a reasonable cost, pointed out symposium speaker Kenneth G. Hancock, who was director of the National Science Foundation's Chemistry Division at the time. Hancock said that chemists generally proceeded without regard to potential environmental problems stemming from hazardous feedstock, solvents, and waste. But he predicted that, through the lens of Green Chemistry, synthesis routes of the future would be designed by making informed choices about which reactants, solvents, and conditions to use to reduce resource consumption and waste.[4]

As an incentive, EPA established the Presidential Green Chemistry Challenge Awards in 1996. The awards were created as a competitive effort to promote and recognize environmentally friendly chemical products and manufacturing processes. At about the same time, ACS's Green Chemistry Institute® (GCI) was created as a grassroots effort to facilitate industry–government partnerships with universities and national laboratories.

In 1998, Anastas and Polaroid's John C. Warner, who is now head of the Warner Babcock Institute for Green Chemistry, published a molecular-level how-to book that included the *12 Principles of Green Chemistry*.[5] Their framework of intuitive concepts included using less hazardous reagents and solvents, simplifying reactions and making them more energy efficient, using renewable feedstock, and designing products that can be easily recycled or that break down into innocuous substances in the environment.

"Green Chemistry is the mechanics of doing sustainable chemistry," Warner once told *C&EN*.[6] "By focusing on green chemistry, it puts us in a different innovative space. It presents industries with an incredible opportunity for continuous growth and competitive advantage."

Yet, in the early years, Green Chemistry seemed only to resonate with academic scientists and with environmentally minded advocacy groups. Chemical companies were reluctant to speak with reporters about their new and improved chemistry technologies. In fact, some Green Chemistry Award winners asked *C&EN* not to report on their award-winning technology. Although they coveted the award, they did not in any way want to suggest that they had developed a better product or process because there was something wrong with the existing one.

That mindset is changing, however, as Dow's Liveris alluded to. One example is GCI's Pharmaceutical Roundtable,[7] a collaborative effort by pharmaceutical companies to work together on common research and development issues such as solvent selection and streamlining process chemistry. This development is natural, because pharmaceutical production to make complex molecules with a high demand for product purity is the least green among all chemical manufacturing sectors.

As part of the green evolution, more chemists and most companies are now taking life-cycle thinking more seriously. Life-Cycle Analysis (LCA) allows scientists to peel back the layers of their processes to see how subtle changes in sourcing raw materials, selecting solvents and catalysts, controlling water usage, making process equipment more energy efficient, managing distribution supply chains, and designing products for end-of-life reuse or recycling can make a difference. LCA gives executives and marketing departments leverage with their upstream suppliers and downstream customers, as well as with their stockholders and with consumers. No company today can realistically expect to succeed without life-cycle thinking.

Nonprofit research organizations have also made a difference in driving chemical innovation. For example, GreenBlue was one of the first sustainable nonprofits to work in collaboration with industry. Its business-to-business database, called CleanGredients®, assists companies in selecting alternative surfactants, solvents, fragrances, and chelating agents for their household cleaning products.

Helping to communicate Green Chemistry research, ACS's *Organic Process Research & Development* and RSC's *Green Chemistry* are both first-class journals. They have inspired creation of other fine journals, such as Wiley-VCH's *ChemSusChem* and *ACS Sustainable Chemistry & Engineering*. Nowadays, each ACS meeting has substantial Green Chemistry research and education programming. Moreover, *C&EN*'s coverage of the 18th Green Chemistry & Engineering Conference held in June 2014 and of the 2014 Presidential Green Chemistry Challenge Awards shows that Hancock's vision of Green Chemistry is coming true, and then some.[8]

For reporters, there's still no shortage of press releases from politically motivated think tanks, industry trade groups, and environmental advocacy groups announcing policy positions that either support or rebut research findings and regulatory decisions regarding chemicals and the chemical industry. Some label Green Chemistry a conspiracy that involves alarmist tactics to promote a ridiculous antichemicals agenda. Others take the position that many chemicals used in commerce disrupt hormone signals and cause cancer, and argue that the chemical industry surreptitiously exploits loopholes in laws to duck regulations and subvert EPA efforts to restrict the use of unsafe chemicals.

Although much of that rhetoric is stretching the truth, it does make a point that Green Chemistry's job is incomplete. Warner has estimated that, of all chemical products and processes in existence, perhaps only 10% of them are already environmentally benign, meaning that their production, use, and end-of-life disposal have little environmental impact and little drag on sustainability. Maybe another 25% could be made environmentally benign relatively easily, he says. "But we still need to invent or reinvent the other 65%," Warner points out. "Green chemistry is how we can do it."[9]

The question remains, when will it be done? A panel discussion on Green Chemistry held during the 247th ACS National Meeting in Dallas (March 16–20, 2014) discussed the challenges for pursuing Green Chemistry and the barriers that seem to be impeding broader adoption of green practices.[10] The panelists suggested that as academics go about teaching students and writing journal articles, and as industrial chemists help mentor their junior colleagues, they need to take the time to explain why a certain reaction pathway is selected and why one solvent was chosen over another. They should also provide tangible numbers to show how beneficial a green process can be. These explanations are necessary, even if they seem obvious or simplified, because chemists too often assume everyone knows and understands the nuances of Green Chemistry, when actually many still don't.

Anastas, always the optimist, has often said that Green Chemistry "is a direction, not a destination." From the beginning, Green Chemistry was intended to become so systematic that every student would know its tools and principles, Anastas has explained, and every practitioner would know its power for efficiency, effectiveness, and innovation. Green chemistry will be successful, Anastas observes, "when the term fades away because it is simply what we, as chemists, do."[11]

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Moving Toward a Green Chemistry and Engineering Design Ethic

Insight from the Head of the ACS Green Chemistry Institute® (GCI)

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As someone who has been working since the mid-1990s to better understand and promote sustainable and Green Chemistry and Engineering, it's been interesting to think about how the field has and hasn't developed over nearly 20 years. It's also interesting to consider how little, on balance, sustainable and Green Chemistry and Engineering has penetrated everyday activities of the rank-and-file chemists working in academic chemistry and engineering departments and those working in industry. This lack of uptake amongst the chemistry and chemical engineering community has been a frequent topic amongst sustainable and Green Chemistry devotees for as long as I have been associated with the field and generally has resulted in a considerable amount of navel-gazing and handwringing.

I think that one reason for this dilemma is the very human tendency to fight change of any kind; we're very comfortable with the way things are. Perhaps another reason is that we are very bad at addressing problems until our backs are against the wall and we absolutely must change. And perhaps it is just that most chemists don't see any problem with the way they do chemistry. It has also been my experience that the educational system, the people who are teaching and doing research, the infrastructure which supports it, and its rewards and benefits do not appreciate that integrating green chemistry and engineering into the routine work of research is worthy of academic pursuit. In fact, I could write a considerable amount outlining a variety of reasons, barriers and potential solutions, but I would not be the first person to do that.

To me, sustainable and Green Chemistry and Engineering is simply a way of thinking about chemistry and engineering. *It is not the end, but the means to an end*; and if one considers the endpoint to be a product (a molecule all the way to a consumer product), service or a function, the endpoints are not really so different than the endpoints chemists and engineers are already working on. For example, I want to create a novel molecule for any one of a variety of purposes. I can go to the literature and perhaps find what I may think are several different potentially interesting precedents for adding functionality to one of maybe 120 or so commonly used framework molecules based on petroleum that will get me to my target. The chemistries, the chemical process, the reagents, the solvents, the catalysts, etc., can generally be selected in a more systematic or perhaps a less mindful fashion to just "get it done"; or they can, with a little practice, just as easily be selected in a manner that causes the least harm to people and the environment, uses the least energy, and takes the least amount of time and the least amount of non-renewable resources.

In essence, what I am referring to is a design ethic; i.e., the choices that one makes when making something. Since it's close to lunch as I'm writing this, I'll use the analogy of making something for lunch. A person may claim that what one eats doesn't matter as long as one's hunger is satisfied. So, suppose one person takes some white bread, grabs some lunchmeat, throws on a slice of cheese, squirts a little mustard or mayonnaise on top, eats a bag or two of potato chips, a double fudge brownie, and washes it all down with a large diet soda. Another person may say that a meal like I've just described doesn't sound very healthy, doesn't eat meat because it has too great an impact on the environment, and feels it is better to eat a salad with some beans, almonds, and a bunch of different vegetables. Both people are likely to have satisfied their hunger, but they've made different choices about what they eat for potentially a variety of reasons, or perhaps they ate what they ate out of habit.

I think it is fair to say that the field of Green Chemistry and Engineering got off the ground based on a concern about chemical toxicity and waste, as well as potential harm to humans and the environment associated with each. These concerns and others, in turn, are likely to inform and influence a person's design ethic. If this is true—and any given person's choice to do greener chemistry or engineering is values-based, and because doing greener chemistry and engineering requires chemists and engineers to learn a few things they are generally not taught on their way to becoming a chemist, and because most things chemists and engineers use and do in chemistry and chemical engineering entails some handling of toxic materials—a person's choice to do green chemistry and engineering will generally require a thoughtful change in what they are doing. As chemists and chemical engineers, most of us can't imagine doing what we do in too many other ways. So perhaps the problem is a failure of discipline, imagination, and innovation, in addition to exercising a different set of values.

I would suggest to you that what the world needs from chemists and engineers is for each of us to adopt a different design ethic. I would also suggest that the time for resisting or ignoring design principles of green chemistry and engineering is over; the earth is simply not able to sustain chemistry and chemical engineering practices as we know them. Please take the time to investigate for yourself the myriad ways in which the earth is being adversely impacted by the global chemistry enterprise and consider what you can do to reimagine chemistry and chemical engineering for a sustainable future.

Practical Aerobic Alcohol Oxidation with Cu/Nitroxyl and Nitroxyl/NO_x Catalyst Systems

An Update from a Pioneer of Greener Methods for Industrially Relevant Oxidations

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Introduction

Aldehydes and ketones are common functional groups in pharmaceutical, agrochemical, and fine chemical products and intermediates, and they are often prepared by oxidation of the corresponding alcohols. Classical oxidation routes generally suffer from large amounts of toxic waste and poor functional group compatibility. Due to the importance of these functional groups, significant effort has been made to develop synthetically more appealing oxidation routes, and aerobic oxidation methods have received considerable attention in recent years.[1]

TEMPO (2,2,6,6-tetramethylpiperidine 1-oxyl) is a stable organic nitroxyl that has found widespread application in alcohol oxidation reactions. This topic is the focus of a recent comprehensive review by Bobbitt, Brückner, and Merbouh.[2,3] The use of inexpensive stoichiometric oxidants, such as sodium hypochlorite (NaOCl), bromine, or $PhI(OAc)_2$, often enables TEMPO to be used in catalytic quantities, and one of the most common protocols features stoichiometric NaOCl in combination with catalytic TEMPO and bromide in a buffered organic–aqueous biphasic solvent mixture (the "Anelli oxidation").[4] An important recent development in this area is the recognition that less sterically hindered bicyclic nitroxyls, such as ABNO (9-azabicyclo[3.3.1]nonane *N*-oxyl), AZADO (2-azaadamantane *N*-oxyl), and related derivatives, often significantly improve the efficiency and scope of the alcohol oxidation reactions (**Figure 1**).[5]

The development of nitroxyl-catalyzed alcohol oxidations that employ O_2 as the terminal oxidant has been achieved by using a variety of co-catalysts, including transition-metal salts, polyoxometallates, or metalloenzymes (laccase).[6] Cu/nitroxyl catalyst systems have emerged as the most versatile and effective among this group.The mechanism of these reactions is believed to involve cooperative one-electron redox chemistry at Cu and the nitroxyl (**Scheme 1,** Part (a)). Alternative transition-metal-free protocols have been identified that employ nitrogen oxide (NO_x) co-catalysts to achieve alcohol oxidation with O_2 as the terminal oxidant. The mechanism of the latter reactions is believed to involve a NO/NO_2 redox cycle coupled to a hydroxylamine/oxoammonium cycle, which resembles the mechanism of the NaOCl/nitroxyl-catalyzed alcohol oxidation methods mentioned above (Scheme 1, Part (b)).[6]

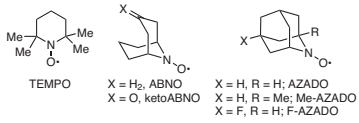
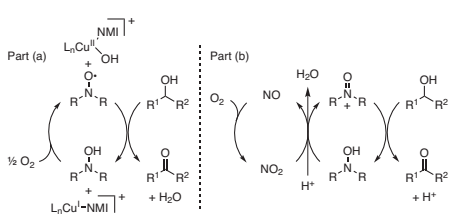


Figure 1. Nitroxyl Derivatives Employed in Aerobic Alcohol Oxidations. *(Ref. 5)*



Scheme 1. (a) Mechanism of Cu/Nitroxyl-Catalyzed Alcohol Oxidation via a Cooperative Pathway. (b) NO_x-Coupled Hydroxylamine–Oxoammonium Mechanism for Aerobic Alcohol Oxidation. *(Ref. 6)*

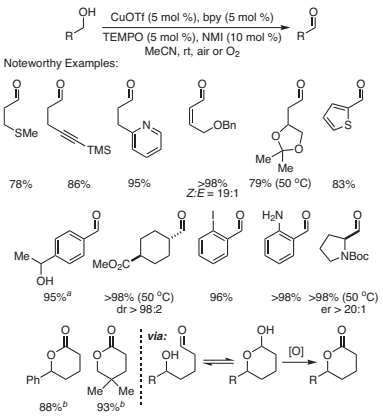
Whereas aerobic alcohol oxidation reactions have historically been the focus of attention, they are rarely used in organic chemical synthesis. Widespread adoption of aerobic alcohol oxidations will require a number of specific issues to be addressed. For example, the methods must exhibit high functional-group tolerance and chemoselectivity, feature simple reaction setup, have short reaction times, and employ low-cost reagents and/or catalysts. The present article describes the development and synthetic scope of a series of Cu/nitroxyl- and nitroxyl/NO_x-based aerobic alcohol oxidation methods that meet all or most of these criteria.

Cu/Nitroxyl-Catalyzed Aerobic Oxidation of Alcohols

Semmelhack was the first to explore the synthetic scope of Cu/TEMPO-catalyzed aerobic alcohol oxidation.[7] CuCl and TEMPO were identified as effective cocatalysts for the aerobic oxidation of activated alcohols. Stoichiometric quantities of copper and TEMPO were required to oxidize less reactive aliphatic alcohols. This CuCl/TEMPO oxidation method has been employed in a number of synthetic routes to prepare complex molecules, especially for the oxidation of allylic alcohols.[6] Knochel and co-workers reported in 2000 the first Cu/TEMPO-based catalyst system that is effective for the aerobic oxidation of aliphatic alcohols.[8] However, the use of fluorous biphasic reaction conditions and a perfluoroalkyl-substituted bipyridine ligand for the Cu catalyst probably limited the widespread adoption of this method. Subsequently, Sheldon and co-workers demonstrated that a simple catalyst system (5 mol % of each of $CuBr_2$/bpy/TEMPO/KO*t*-Bu; bpy = 2,2'-bipyridine) enabled the efficient oxidation of activated (allylic and benzylic) alcohols in acetonitrile–water, and it could also oxidize aliphatic alcohols at somewhat higher temperatures and for longer reaction times.[9] A Cu/salen catalyst system reported by Punniyamurthy and co-workers successfully oxidized aliphatic alcohols, but required more forcing reaction conditions (100 °C).[10] In 2009, Kumpulainen and Koskinen reported a catalyst composed of Cu^{II}/bpy/TEMPO with DBU (1,8-diazabicyclo[5.4.0]-undec-7-ene) and/or NMI (*N*-methylimidazole) that exhibited excellent reactivity towards unactivated aliphatic alcohols at room temperature.[11]

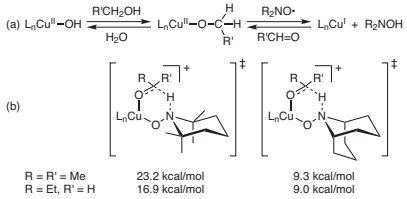
Hoover and Stahl developed a CuOTf/bpy/TEMPO/NMI catalyst system that was effective in the oxidation of benzylic, allylic, propargylic, and aliphatic alcohols under ambient air (**Scheme 2**).[12] A significant improvement in catalytic activity was associated with the use of a copper(I), rather than a copper(II), source. Cu^{I} salts with non-coordinating anions (e.g., CuOTf) were especially effective. The mild reaction conditions were compatible with numerous functional groups, including aryl halides, anilines, nitrogen and sulfur heterocycles, and sulfides. This method is compatible with base-sensitive substrates owing to the lack of stoichiometric or strongly basic additives. For example, (*Z*)-allylic alcohols were successfully oxidized to (*Z*)-enals without alkene isomerization, and *N*-Boc-prolinol was oxidized to the aldehyde without epimerization. As observed with other Cu/TEMPO catalyst systems, secondary alcohols did not undergo effective oxidation. The chemoselectivity for primary over secondary alcohols was exploited in the oxidation of diols that contained both primary and secondary alcohols. Reactions of 1,5-diols led to efficient lactonization in high yields (Scheme 2). A subsequent study by Root and Stahl demonstrated the feasibility of implementing these reactions on a large scale by employing continuous-flow reaction conditions.[13] Short reactor residence times (≤5 min) were demonstrated for activated alcohols, with somewhat longer times (30–45 min) required for aliphatic alcohols.

Several recent mechanistic studies of Cu/TEMPO-catalyzed alcohol oxidation show that the higher reactivity of allylic, benzylic, and other activated alcohols relative to aliphatic alcohols arises from a change in the turnover-limiting step.[14] In the case of activated alcohols, the turnover-limiting step is the oxidation of Cu^{I} by O_2 (Scheme 1, Part (a)), whereas aliphatic alcohols feature turnover-limiting cleavage of a Cu^{II}–alkoxide C−H bond (**Scheme 3**, Part (a), Step 2).



[a] Using $CuBr_2$ instead of CuOTf and DBU instead of NMI. [b] From unprotected 1,5-diols.

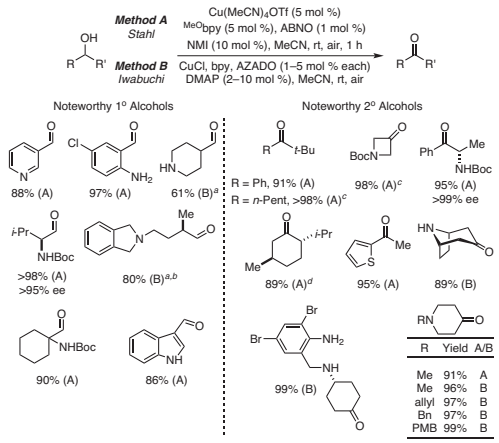
Scheme 2. Stahl's Aerobic Oxidation of Aliphatic Alcohols and Diols with CuOTf/bpy/TEMPO/NMI. *(Ref. 12)*



Scheme 3. (a) Mechanism of the Substrate Oxidation Half-Reaction in the Cu/Nitroxyl-Catalyzed Alcohol Oxidation. (b) Transition-State Structures for Step 2 in the Substrate Oxidation Half-Reaction for Cu/TEMPO and Cu/ABNO Catalyst Systems. *(Ref. 14)*

The mechanistic observations noted above prompted Steves and Stahl to test nitroxyl derivatives other than TEMPO, with the hope of achieving faster rates and/or broader substrate scope in the catalytic reactions.[15] The fastest reaction rates were observed with the bicyclic nitroxyls ABNO, keto-ABNO, and AZADO; and subsequent studies were performed with ABNO due to its commercial availability. The Cu/ABNO catalyst system exhibited nearly identical oxidation rates with essentially all classes of alcohols, including 1° and 2° benzylic and 1° and 2° aliphatic alcohols. This universal scope of reactivity contrasts the Cu/TEMPO system, which is effective only with 1° benzylic and aliphatic alcohols. A recent in-depth experimental and computational study of the mechanism of Cu/nitroxyl-catalyzed alcohol oxidations showed that both catalysts proceed via an Oppenauer-type six-membered-ring transition state (Scheme 4, Part (b)).[14c] The hydrogen-transfer transition state is much lower in energy for Cu/ABNO relative to Cu/TEMPO as a result of the decreased steric profile of this bicyclic nitroxyl. This observation explains the much higher reactivity and broader substrate scope of the Cu/ABNO catalyst system.

Optimization studies showed that 4,4′-dimethoxy-2,2′-bipyridine (^{MeO}bpy) was superior to bpy as a ligand, and the resulting Cu/ABNO catalyst system was tested with an array of 1° and 2° aliphatic and benzylic alcohols. A broad range of functional groups was tolerated, including ethers, thioethers, heterocycles, amines, alkenes, and alkynes (**Scheme 4**). Alcohols bearing adjacent stereocenters underwent oxidation without epimerization. Excellent yields were obtained at room temperature with ambient air as the oxidant and reaction times of ≤ 1 h.



[a] 1-Me-AZADO was utilized instead of AZADO. [b] Aldehyde product was isolated as the ethyl ester after treatment with a Wittig reagent. [c] 60 °C. [d] 70 °C, O_2 balloon.

Scheme 4. Effective Primary and Secondary Alcohol Oxidation with Cu/Bicyclic Nitroxyl Systems under Ambient Conditions. *(Ref. 15,16)*

Iwabuchi and co-workers subsequently reported a complementary catalyst system that employed AZADO as a bicyclic nitroxyl co-catalyst in a study that focused on the oxidation of unprotected amino alcohols.[16] Such reactions are typically challenging due to competitive oxidation of the alcohol and amine groups and/or unfavorable interaction of the electron-rich amine with the oxidant. Synthetic methods to access carbonyl products bearing unprotected amines typically require the protection of the amino group. The Cu/AZADO catalytic method was shown to be superior to several conventional oxidation methods (e.g., with pyridinium chlorochromate, Swern, Dess–Martin periodinane, and tetrapropylammonium perruthenate oxidants). The advantage of the Cu/AZADO catalyst system relative to traditional oxidation methods was showcased in synthetic routes to two small alkaloid targets, (–)-mesembrine and myosmine.

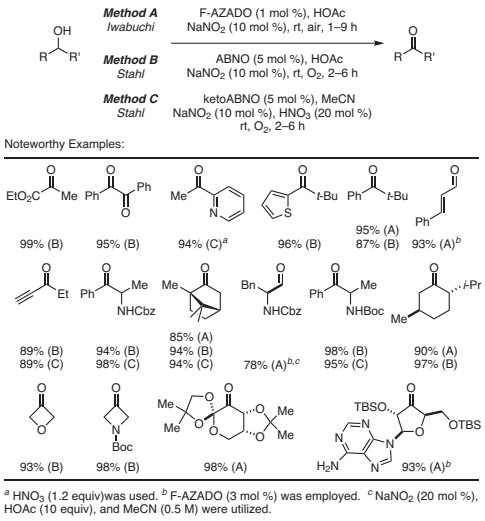
Iwabuchi's method tolerated substrates with aliphatic 1°, 2°, and 3° amines; those with ester and cyano groups; and N-heterocyclic substrates (see Scheme 4). Some carboxylic acid formation was observed in the oxidation of primary aliphatic alcohols; however, the authors demonstrated that this complication could be minimized by using the slightly more sterically demanding bicyclic nitroxyl, 1-Me-AZADO. No desired oxidation was observed with acyclic vicinal amino alcohols [e.g., $Et_2NCH_2CH(OH)Me$].

Nitroxyl/NO_x-Catalyzed Aerobic Oxidation of Alcohols

Transition-metal-free aerobic alcohol oxidation methods developed in recent years complement the Cu/nitroxyl methods described above. The former methods operate under mildly acidic conditions. The utility of NO_x-based co-catalysts with nitroxyl radicals in aerobic alcohol oxidation was first demonstrated by Hu and Liang.[17,18] The catalyst components included TEMPO, $NaNO_2$, and Br_2, and the reactions were effective with ambient air as the oxidant. A related halogen-free system that employed *tert*-butyl nitrite as the NO_x source required heat and higher pressures of oxygen.[19] These aerobic oxidations require longer reaction times (typically 24 h), and have a more limited substrate scope (benzylic and simple aliphatic alcohols) relative to traditional TEMPO/NaOCl methods. Nevertheless, these early catalyst systems established the viability of aerobic oxidative transformations with nitroxyl/NO_x.

Iwabuchi and co-workers developed the bicyclic nitroxyl F-AZADO, and demonstrated its excellent reactivity in aerobic alcohol oxidations with a NO_x-based co-catalyst.[20] They proposed that the higher redox potential and lower steric profile of the nitroxyl underlies the improved alcohol oxidation reactivity. Higher yields and shorter reaction times were achieved during optimization of the oxidation of menthol. The reactivity was shown to correlate with the steric profile of the nitroxyl, following the trend AZADO > 1-Me-AZADO > TEMPO. Comparison of AZADO derivatives revealed that incorporation of electron-withdrawing groups into the

backbone of AZADO leads to higher reactivity and enables the oxidation reactions to proceed under ambient air. Primary unactivated alcohols and 1° and 2° benzylic and allylic alcohols were oxidized efficiently using 1 mol % F-AZADO and 10 mol % $NaNO_2$ in acetic acid under ambient air (**Scheme 5**, Method A). Nucleic acid derivatives as well as compounds bearing alkenes, which are challenging substrates for NaOCl-based oxidations, were also oxidized readily.



[a] HNO_3 (1.2 equiv)was used. [b] F-AZADO (3 mol %) was employed. [c] $NaNO_2$ (20 mol %), HOAc (10 equiv), and MeCN (0.5 M) were utilized.

Scheme 5. Substrate Scope for Nitroxyl/NO_x-Catalyzed Aerobic Oxidation of Alcohols. *(Ref. 20,22)*

The F-AZADO catalyst system represents a significant advance in aerobic alcohol oxidation; however, F-AZADO is not commercially available and is difficult to synthesize.[21] As a result, Lauber and Stahl pursued related alcohol methods capable of using more accessible bicyclic nitroxyl sources.[22] The less sterically encumbered bicyclic nitroxyls ABNO (Method B) and keto-ABNO (Method C) were especially effective for the oxidization of secondary alcohols. Method B was the more versatile of the two methods, and provided good-to-excellent yields of the desired carbonyl products bearing diverse functional groups, including thiophenes, pyridines, terminal alkynes, ethers, esters, and Boc- and Cbz-protected amines. Pyridine-containing substrates can be challenging for transition-metal-based oxidation methods due to metal coordination, but substrates of this type were oxidized readily with Method C. A requirement for excess acid probably reflects the need to protonate the pyridine nitrogen. Very sterically demanding alcohols could be oxidized in good yields. Reactions with substrates bearing a primary aniline were not successful due to formation of a diazonium species under the reaction conditions.

Conclusions and Outlook

The alcohol oxidation methods described above represent some of the first practical and synthetically useful aerobic oxidation methods available to synthetic organic chemists. The Cu/nitroxyl and nitroxyl/NO_x catalyst systems match or exceed the scope and utility of many widely used conventional oxidation methods. Preliminary results suggest that these laboratory-scale methods will also be amenable to large-scale industrial application wherein the "green" features of these reactions could have a more profound impact.

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Toward a Sustainability Mindset in the Practice of Pharmaceutical Chemistry—from Early Discovery to Manufacturing

A Perspective on Green Chemistry Spanning R&D at Novartis

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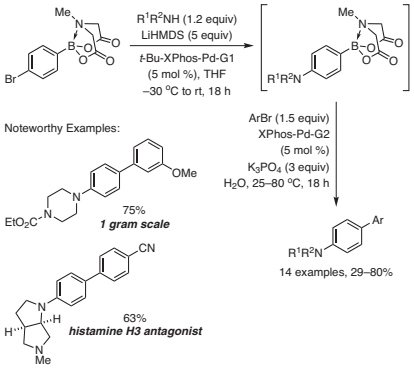
The so-called first rule of medicine, "primum non nocere" (Latin, meaning "first, do no harm"), contained in the Hippocratic Oath, describes an ethos that should also stand as an aspirational goal in the conduct of research and development activities within the pharmaceutical sector. Scientists devoted to such endeavors for the betterment of human health have both the major responsibility of bringing innovative products to market for the benefit of patients suffering from disease, and to conduct such pursuits with a respectful and constant concern for society and the environment as a whole. The work done to help some should not come at the cost of harm to all. Tremendous technological advances in synthetic chemistry over the past several decades, combined with a greatly increased level of awareness of the principles of sustainability, are contributing to our present ability to embrace these more environmentally benign practices in the course of our efforts to produce new medicines. In this article, we wish to raise awareness—and enhance the social consciousness and recognition of the impact of chemists and of pharmaceutical companies—by encouraging the pharmaceutical and biotechnology chemistry community to evolve strategic thinking in planning syntheses for medicinal and process chemistry. We highlight what we believe to be our critical responsibilities as chemists and point to future opportunities. The illustrative examples herein are not intended to be exhaustive, but rather to provide a basis for stimulating further interest and discussion among practitioners in this field.

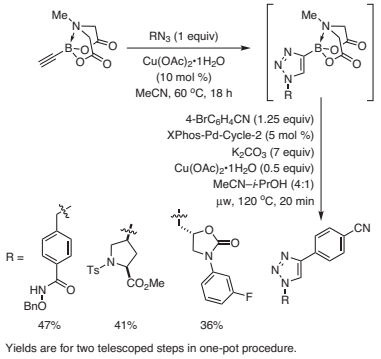
Chemists play a pivotal role in delivering innovative drugs to patients—their impact extending from the research stage, where new biologically active compounds are identified and optimized for efficacy and safety, to the development stage, where suitable manufacturing syntheses and processes are developed. At each step of the way, conscious choices are made in designing the next analogue and enabling its synthesis through an efficient route. Increasingly, such choices are both aimed at achieving the desired scientific results with respect to physicochemical and pharmacological properties, and doing so in a more environmentally responsible manner, and so come both with tremendous opportunity and responsibility. Much has been written in the arena of sustainable chemistry practices, first epitomized by the *12 Principles of Green Chemistry* by Anastas and Warner.[1] Moreover, significant progress is being made every day in several key relevant research areas such as catalysis; atom- and step-economy; the design and adoption of safer chemicals, chemical routes, and environmentally benign solvents; and the development of renewable feedstock. The incorporation of sustainable chemistry practices into the everyday mindset and workflow of chemists in biomedical research is gaining significant traction as well, especially where these very same practices also provide more efficient and technologically improved methods to achieving key target molecules.[2]

There have also been tremendous strides made in the past few years to reduce waste in the fine and specialty chemicals industry, mostly by replacing antiquated technologies. For example, catalytic substitutes to the use of stoichiometric reagents is being evaluated and embraced by most companies in the quest to identify greener, more efficient alternatives. Although there is still considerable room for further improvement, catalysis will undoubtedly be a centerpiece for achieving the objective of providing large quantities of complex molecules, including natural products, with a minimum amount of labor and material expense. To some extent, the goal of organic chemists has become to achieve degrees of regio- and stereoselectivities that are usually observed in biochemical processes with their inherently more atom-economical and catalytic transformations.[3]

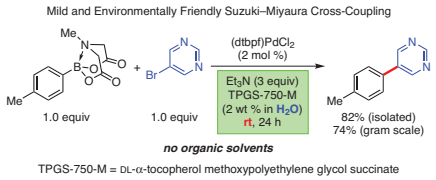
Among such technologies, some of the most versatile and broadly applicable synthetic transformations employed in the construction of pharmaceutical agents are transition-metal-catalyzed cross-coupling reactions. In the context of such methodologies, the efficiency of the cross-coupling step (catalyst loading, temperature, yield, and ease of purification) is of paramount importance when it comes to overall mass efficiency, as reduction of the stoichiometry to a 1 to 1 ratio for a coupling reaction can have a profound effect on sustainability considerations. This is all the more relevant where the coupling partners are complex, and increased selectivities and efficiencies minimize post-reaction purification operations that are both time- and material-intensive. Such a convergent synthetic strategy is one of the most efficient and widely used within the industry as it allows for rapid and modular elaboration of complex products. For example, we have recently developed mild conditions for a variety of telescoped one-pot sequences including Suzuki–Miyaura cross-couplings of historically difficult-to-access and/or poorly stable boron species. These tandem reaction sequences, C–N/C–C cross-couplings and cycloaddition/C–C cross-coupling are made possible by the use of methyliminodiacetic acid (MIDA) boronates,[4] bearing one of the most efficient functional groups for rendering even unstable 2-heteroarylboronic acids as competent cross-coupling partners. The telescoped one-pot sequences allow rapid buildup of structural complexity while dramatically reducing solvent use for workup and purification (**Schemes 1 and 2**).[5]



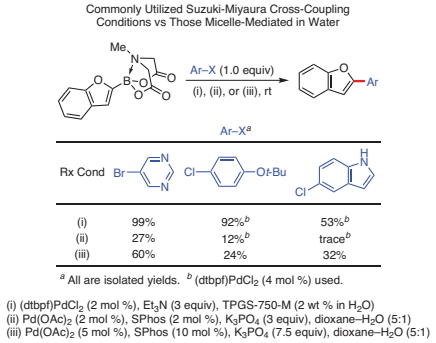
Scheme 1. Tandem C–N/C–C Cross-Couplings. *(Ref. 5a)*



Scheme 2. Tandem [2 + 3] Cycloaddition/Suzuki–Miyaura Cross-Coupling. *(Ref. 5b)*



eq 1 *(Ref. 6)*



eq 2 *(Ref. 6)*

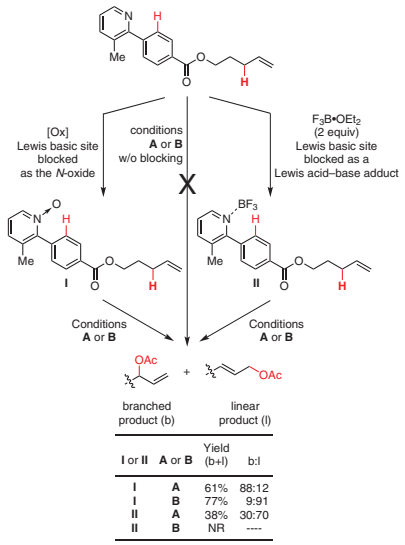
This approach was subsequently refined to incorporate the use of surfactants for mediating the transformation in water at very mild temperatures (rt up to 40 °C, vs the commonly employed elevated temperatures in polar aprotic solvents), thus permitting the routine use of the aspirational 1:1 stoichiometry (**eq 1**).[6] Furthermore, such reaction conditions allow minimization or even complete avoidance of the use of organic solvents in some cases, thus resulting in high selectivities (**eq 2**).[6] Such methods are amenable to scaling up and to recycling of the reaction medium and catalyst—further enhancing synthetic efficiency and minimizing waste.

Martin Burke's research group, pioneers in the use of MIDA boronates, has very recently disclosed a particularly conceptually elegant example of the application of iterative cross-couplings of MIDA boronate derived building blocks to the realm of entire families of natural products, perhaps presaging the ultimate potential of such catalytic sequences.[7]

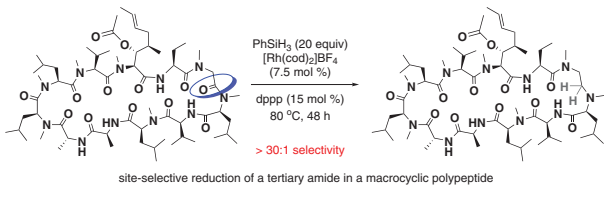
The direct, selective functionalization of readily available C–H bonds, inherently atom-economical, has been a topic of major interest in the last decade, with significant advances made in particular in directed C–H functionalization.[8] However, the identification of non-directed C–H functionalization alternatives, especially in the presence of competent directing groups, is still lagging behind and is a requirement to unleash the full potential of the technology. Recently, we reported preliminary progress in enabling non-directed allylic C–H acetoxylation of various homoallylic substrates in the presence of Lewis basic heterocycles—a feature commonly found in pharmaceutical compounds and one which has always been a vexing challenge in C–H functionalization (**Scheme 3**).[9]

The development of increasingly selective reactions opens up a variety of options for combinations of chemistry and biology, especially in the field of natural products. Modifications and/or derivatization of polypeptides allow for modulating structure to regulate a variety of biological processes and for the potential creation of novel drug candidates. This process is naturally done biocatalytically with outstanding selectivity and efficiency. Historically, examples of non-biocatalytic processes for post-modification of peptides are very rare, and generally rather limited to sterically driven derivatizations[10]—the key issue being the proper control of the chemo- and regioselectivity. In our continuing studies of the chemistry of cyclosporins, we identified novel, highly attractive and selective transformations that enable rapid and significant advances in generating new derivatives of very complex scaffolds obtained by fermentation (**eq 3**).[11] While the results are somewhat preliminary, one can readily imagine how such methods may realize their potential through further development that fully unleashes the power of readily available feedstock from Mother Nature.

The development of Green Chemistry and Engineering based technologies requires a conscious and deliberate effort in order to radically change our approaches and evolve beyond current practices. The accelerated uptake and rapid implementation of such advances from the earliest stages of research on through manufacturing will be key to continued progress toward more sustainable and environmentally sound processes in this field. It is incumbent upon industry to identify with a sense of urgency focus areas to reach such objectives, and, in so doing, help define the challenges and stimulate interest from the academic community. As in other fields of science, the goals of developing a Green Chemistry toolbox will be best served through a shared vision and cooperation between practitioners in both academia and industry.[12,13] The new paradigm will require a new breed of pharma industry leaders, who can champion education and awareness within their respective organizations, and who create opportunities to redirect efforts towards innovative sustainability research and development enterprises. It will also require engaged participation in consortia comprised of thought leaders in academia, industry, and government in order to foster sharing of best practices among members.



Scheme 3. Regiodivergent Pd(II)-Catalyzed Allylic C–H Acetoxylation. *(Ref. 9)*



eq 3 *(Ref. 11a)*

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Catalytic C–C Bond Formation and the Hendricksonian Ideal: Atom- and Redox-Economy, Stereo- and Site-Selectivity

Update from a Recipient of a Presidential Green Chemistry Challenge Award

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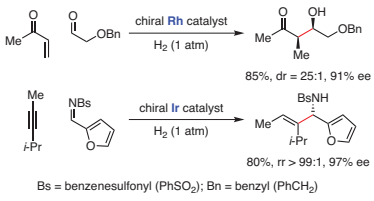
"*The ideal synthesis creates a complex skeleton… in a sequence only of successive construction reactions involving no intermediary refunctionalizations, and leading directly to the structure of the target, not only its skeleton but also its correctly placed functionality.*"[1]

The Hendricksonian view of synthetic efficiency[1] tacitly recognizes the importance of merged redox-construction events ("redox-economy");[2] regio-, chemo- (site-), and stereoselectivity;[3] protecting-group-free chemical synthesis;[4] and the minimization of pre-activation: the degree of separation between reagent and feedstock.[5] Guided by these principles, it can be posited that stereo- and site-selective methods for the assembly of organic molecules that occur with the addition, acceptorless removal or redistribution of hydrogen are natural endpoints in the advancement of methods for process-relevant chemical synthesis.[6,7]

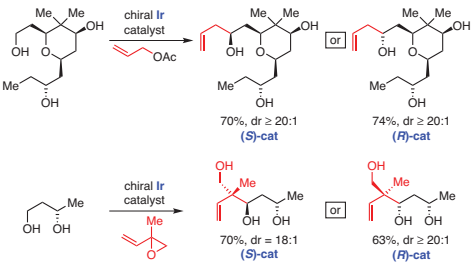
Hydrogenation and hydroformylation represent two of the largest-volume applications of homogeneous metal catalysis. Merging the chemistry of hydrogenation and carbonyl addition, we have developed a broad new family of "*C–C bond forming hydrogenations*"—processes wherein two or more reactants are hydrogenated to form a single, more complex product in the absence of stoichiometric byproducts (**Scheme 1**).[7a,b,8] Unlike classical carbonyl additions, such transformations bypass the use of premetallated reagents and cryogenic conditions, and are completely atom-efficient.

By folding hydrogen into the carbonyl reactant, one can exploit the native reducing ability of alcohols in the related "*C–C bond forming* ***transfer*** *hydrogenations*." Here, redox-triggered carbonyl addition is achieved upon hydrogen exchange between alcohols and π-unsaturated reactants to generate transient aldehyde–organometal pairs that combine to form products of alcohol C–H functionalization.[7c,d] Remarkably, certain chiral iridium catalysts display a pronounced kinetic preference for primary alcohol dehydrogenation, enabling enantio- and site-selective C–C coupling of diols and triols (**Scheme 2**).[9] Such site-selectivity streamlines chemical synthesis, as it precludes protecting group installation and removal, as well as discrete alcohol-to-aldehyde redox manipulations.

As illustrated in the total syntheses of diverse polyketide natural products (**Figure 1**),[7c] the ability to engage polyfunctional molecules in a redox-economic, stereo- and site-selective manner has induced a shift in retrosynthetic paradigm and a step-function change in synthetic efficiency. More broadly, the hydrogen-mediated C–C couplings we have developed suggest other processes that traditionally employ premetallated reagents can now be conducted catalytically in the absence of stoichiometric metals.



Scheme 1. Byproduct-Free Carbonyl and Imine Addition via C–C Bond-Forming Hydrogenation. *(Ref. 8)*



Scheme 2. Catalyst-Directed Diastereo- and Site-Selectivity via C–C Bond-Forming Transfer Hydrogenation. *(Ref. 9)*

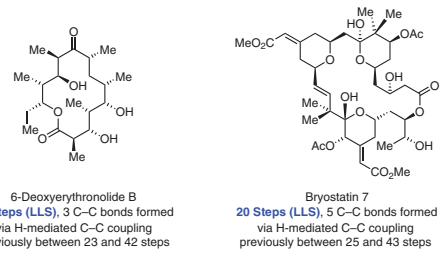


Figure 1. Polyketide Natural Products Prepared via Direct Alcohol C–H Functionalization. *(Ref. 7c)*

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Pharmaceutical Green Chemistry at Amgen: Seeing with New Eyes

Co-Chair of the ACS Green Chemistry Institute® Pharmaceutical Roundtable

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An astounding level of achievement has been reached toward the goal of greater sustainability in the pharmaceutical industry through the application of Green Chemistry principles. These principles have served to inspire a plenitude of chemical and engineering innovations that have delivered superior science, reduced environmental impact, provided for greater safety, and concomitantly improved the economics of pharmaceutical manufacture. As demands for "right first time" and "reduced cost and time to market" become ever more critical, Green Chemistry practices have provided a true differentiator with regard to competitive success in the ever-evolving pharmaceutical industry. Consequently, many pharmaceutical companies today integrate Green Chemistry into core development activities, and the exemplification of Green Chemistry principles by generic firms continues to expand. Firms, such as Amgen, that have built a corporate culture of Green Chemistry are now harvesting the fruits of their commitment and investment.

Amgen develops human therapeutics by unlocking the potential of biology and making use of multiple modalities to provide the best products, including small molecules and biologics. Motivated and talented scientists, with a strong concern for the environment and holistic efficiency, are impassioned to deliver safe and efficacious medicines for patients. Green Chemistry teams ensure that Amgen remains at the cutting edge of pharmaceutical development and manufacture while minimizing environmental impact.

Creating Awareness

The effort at Amgen began with presentations highlighting the concepts of Green Chemistry, including examples of application to pharmaceutical targets. SHAREPOINT® sites were created and theme articles published in the internal *Amgen News*. Academic Green Chemistry experts; such as Professors Robert Grubbs, Bruce Lipshutz, and Steven Ley; were invited to present in a Green Chemistry lecture series. Scientists were provided visual reminders such as magnets on fume hoods describing the principles of Green Chemistry and the Amgen solvent guide for reference. Marcel Proust stated that *"The real voyage of discovery consists not in seeking new landscapes but in having new eyes"*.[1] These efforts greatly enhanced awareness to perceive Green Chemistry opportunities with new eyes.

Quantifying Impact

Soon, E-factor metrics were captured across the portfolio, confirming marked reductions in environmental impact as Green Chemistry principles were applied. It became apparent that awareness of these principles enabled scientists to seize upon opportunities previously overlooked. Real-time E-factor calculations were incorporated into our electronic notebooks, enabling quick assessment of the impact of process changes, and providing focus upon chemical steps that were large E-factor contributors. Greener processes were proving to be scientifically and environmentally superior, and demonstrated financial benefit for Amgen repeatedly. A consistent reduction in the cost of manufacturing has been a result of improvements in process E factor, substantiating that a Green Chemistry mindset and culture can drive the innovation required for greater sustainability and lower cost.

New Technologies

Investment in new technology expanded during our Green Chemistry efforts to become transformative, and resulted in our first large-scale enzymatic process to synthesize a chiral small molecule and in our first continuous-flow ozonolysis being carried out safely at the kilogram scale. New interfaces germinated between chemistry and biology, delivering hybrid products with the help of the combined skill sets of small- and large-molecule experts. Innovation thrived, and each success provided momentum for further inspiration.

Rewarding Green Chemistry

To acknowledge these innovations, an annual Green Chemistry award program was initiated. The awards recognize and share superior science throughout the organization, and clearly demonstrate management's commitment to, and appreciation of the importance of, Green Chemistry. This serves to further encourage scientists, reaffirming that Green Chemistry is a key deliverable within the organization.

External Education and Collaboration

Amgen is an active member of the scientific community, sponsoring invited lectures at local universities and providing company site tours for students. Amgen is also a member of the IQ Consortium and the ACS GCI Pharmaceutical Roundtable (where I serve as co-Chair). Among other benefits, pre-competitive consortia provide tools for solvent and reagent selection as well as life-cycle analysis, help drive the research agenda through academic grants and industrial–academic partnerships, and provide insight into successful Green Chemistry approaches. A recent publication[2a] and webinar[2b] highlighted the "Seven Important Elements for an Effective Green Chemistry Program." An additional joint IQ/FDA document describes the "Regulatory Strategies to Enable Green Chemistry."[3] These cooperative interactions provide opportunities to address complex areas of impedance to Green Chemistry through greater communication, transparency, enhanced education, support of new technologies and tools, and engagement with academic researchers and regulators. Firms that have yet to participate in Green Chemistry consortia should consider the multifaceted benefits of joining in this combined effort. Gratifyingly, it is clear that a commitment to Green Chemistry and sustainability is becoming more apparent and recognizable by organizations outside of the pharmaceutical industry. Amgen was recognized by the 2012 Pacific Sustainability Index as the top-ranked pharmaceutical company in North America,[4] and, in 2013, became a member of the Dow Jones Sustainability™ Index.[5] Amgen was also recognized as a 2012 sustainability mover by Sustainable Asset Management,[6] a firm that directs investment toward companies that have a vision for sustainability.

Looking Forward

Green Chemistry has reached a new level of adoption in the pharmaceutical industry. The metrics collected have overwhelmingly confirmed advantages for the environment accompanied by greater process efficiencies and lower manufacturing costs. It embodies a differentiating approach that provides a competitive advantage in pharmaceutical development and manufacture. To achieve a future of greater sustainability, Amgen has invested in and built a robust and active Green Chemistry program and culture, which has been exciting and rewarding, and continues to drive innovation and achievement for the organization.

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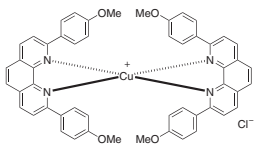
PRODUCT HIGHLIGHT

Visible Light Photocatalysis

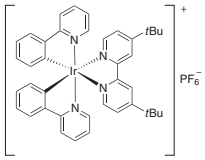
The application of radical chemistry in organic synthesis is well-developed and far-reaching, though often hampered by a dependence on stoichiometric toxic radical initiators. Alternatively, the burgeoning field of photocatalysis has provided a number of transition-metal complexes and organocatalysts capable of initiating radical formation in the presence of visible light.

- Activated by visible light
- Used in catalytic amounts
- Ever-growing applications in organic synthesis

Learn more about this important new field. Visit our website's Corey Stephenson and Tehshik Yoon pages:
Aldrich.com/prof-prod-portal



L511803
Cu(dap)$_2$ chloride



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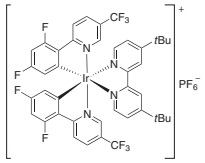

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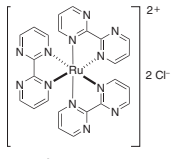

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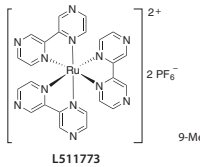

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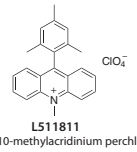

L511811
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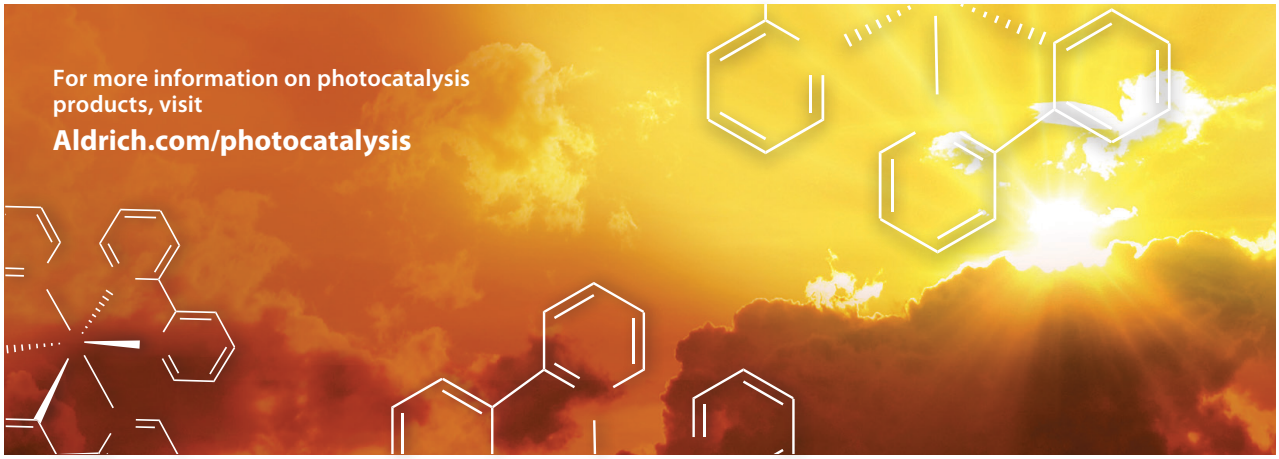

Switchable Solvents as Media for Synthesis and Separations

An Update from the Co-Creator of GreenCentre Canada

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Introduction

The greenest solvent for any process is the solvent that makes the process the greenest. Green chemists and chemical engineers should choose the solvent that causes the process or product to have the lowest possible environmental impact. Thus, a solvent that has, on its own, very little environmental impact, but makes a process very inefficient and wasteful, would not be a green solvent for that process. Given that the vast majority of the environmental impact of chemical syntheses is often the post-reaction separation, then the researcher trying to design or select a green solvent needs to find one that will make the post-reaction separation efficient in energy and materials.

Many of the environmental impacts of solvents and of processes using solvents; including flammability, smog formation, and inhalation risks to workers; happen because of the use of volatile solvents. Despite their many disadvantages, however, volatile solvents are still widely employed. Practitioners choose volatile solvents either because they plan to remove the solvent from the product by distillation, or because they plan to recycle their solvents using a distillation step. The choice of a volatile solvent is therefore directly determined by post-reaction separation needs.

Therefore, there is a need for solvents that (i) have very low volatility, and (ii) can be easily removed from the product without the help of volatile organic compounds. While ionic liquids and liquid polymers address the first need, they are difficult to separate from the product without the help of a volatile solvent.

It was to address this need that my students and I first developed switchable solvents. These solvents, also known as "reversible" or "smart" solvents, change their properties as soon as a trigger is applied, and change back again when that trigger is removed or another trigger is applied. Waste CO_2 gas, at 1 atmosphere, is a particularly inexpensive and green trigger because it is nontoxic, nonflammable, and easily removed. A switchable solvent, by changing its properties upon command, can facilitate post-reaction separations without the solvent being volatile.

This very brief review will summarize the three classes of CO_2-responsive switchable solvents and their use in reactions and separations. A more detailed review was published in 2012,[1] although much work has been done since that review was written.

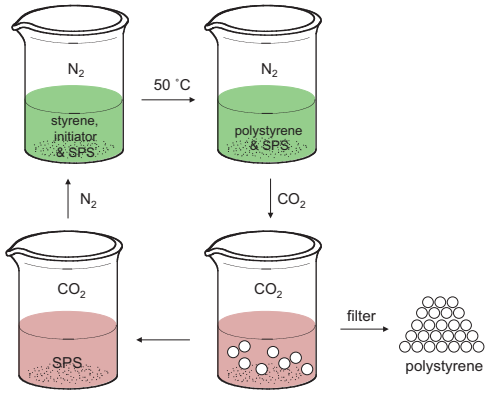
Switchable-Polarity Solvents (SPS's)

Switchable-Polarity Solvents (SPS's) change from having a low polarity to having a high polarity, with the result that the solubility of many solutes is dramatically changed. Thus, precipitation of a solute from the solvent can be effected by simply changing the solvent's polarity.

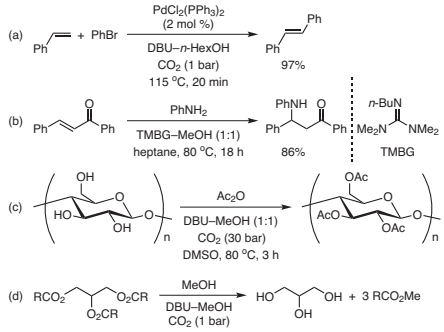
There have been many SPS's reported to date. The first SPS was a low-polarity liquid mixture of 1-hexanol and an amidine called DBU (1,8-diazabicyclo[5.4.0]undec-7-ene), which when exposed to CO_2 gas became a much more polar ionic liquid {***n*-HexOH + DBU (molecular liquid) + CO_2(g) = [DBU•H$^+$][*n*-HexCO$_3^-$] (polar ionic liquid)**}.[2] Fortunately, the reaction is easily reversed simply by removing the CO_2 from the system. Since that original paper, my group, the Eckert/Liotta group, and others have reported many new examples of SPS's; including other binary liquid mixtures such as glycerol–amidine,[3] alcohol–guanidine,[4] or amidine–primary amine mixtures;[5–8] and single-component SPS's such as diamines,[9] hydroxyamidines,[9] hydroxyguanidines,[9] secondary amines {**2R$_2$NH (molecular liquid) + CO_2(g) = [R$_2$NH$_2^+$][R$_2$NCO$_2^-$] (polar ionic liquid)**},[10] and primary amines.[11]

SPS's have been employed as media for many reactions, including the polymerization of styrene (**Scheme 1**),[4] Claisen–Schmidt condensation, cyanosilylation, Michael addition, and the Heck reaction (**Scheme 2**).[12–14] They have also been used as solvent for the post-reaction separation of catalysts from products in some of those reactions and in the copolymerization of epoxide and CO_2.[10] In biomass conversion, they have been utilized in the acylation of cellulose,[14] activation of microcrystalline cellulose toward hydrolysis,[15] transesterification of soybean oil and other triacylglycerides,[16–19] and in the delignification of wood.[20] In some cases, the reaction was performed in the absence of CO_2 and then CO_2 was added to trigger the separation of the product. In other cases, the reverse procedure was used.

SPS's have been employed in other applications, including CO_2 capture (reviewed in detail in 2012)[1] and especially extractions. Anugwom and co-workers[21] found that DBU–*n*-BuOH SPS selectively extracts hemicellulose from wood, while DBU–H$_2$N(CH$_2$)$_2$OH SPS extracts both hemicellulose and lignin.[20,22] Other extractions, reported by other researchers, include algae oil from algae[23,24] and crude oil or bitumen from oil sands or oil shale.[13,25]



Scheme 1. Use of an SPS (DBU–*n*-PrOH) for Facile Post-Reaction Separation of Polystyrene Product from the Solvent and Recycling of the Solvent. Green Indicates the Low-Polarity Form and Pink the High-Polarity Form, Respectively. *(Ref. 4)*



Scheme 2. Examples of Reactions That Have Been Performed in SPS. *(Ref. 12,14)*

Switchable-Hydrophilicity Solvents (SHS's)

Switchable-Hydrophilicity Solvents (SHS's) are liquids that reversibly convert between a hydrophilic state that is miscible with water and a hydrophobic state that forms a biphasic mixture when mixed with water {**solvent (hydrophobic form) + H_2O + CO_2 = [solvent•H^+][HCO_3^-] (hydrophilic form)**}.[26,27] The solvent in its hydrophobic form is typically an amidine, a tertiary amine, or a bulky secondary amine; whereas, in its hydrophilic form, the solvent is the corresponding bicarbonate salt.

The solvent in its hydrophobic state can be employed to dissolve or extract organic compounds or materials such as crude oil, bitumen,[28] algae oil,[29–31] polystyrene,[32] and lignin pyrolysis oil.[33] Once the desired product has been extracted, the solvent can then be washed away from the product using carbonated water, into which the solvent (as its bicarbonate salt) readily dissolves. The solvent can be recovered from the carbonated water by removing CO_2 from the solution: the solvent reverts to its hydrophobic form and forms a second phase above the water.

This process has significant advantages over normal extractions using conventional solvents like hexane, toluene, or acetone, because such solvents are flammable, smog forming, and pose inhalation risks to workers. SHS's, because they do not require a distillation step during their use or recycling, do not need to be volatile. In fact, some SHS's have so little volatility that they have no odor and have predicted flash points approaching 200 °C.[34] Because several dozen SHS's have been identified,[27,34–36] and thousands are possible, it is possible to select an SHS that is appropriate for any desired performance, safety, or environmental criteria. For instance, low water solubility is a desirable attribute of an SHS for the extraction of lipids from wet algae; thus, new examples of SHS's have been designed with that in mind.[30] Particular efforts have been dedicated to finding "green" SHS's, meaning those with minimized health and environmental impacts. This has been done either (i) by screening small numbers of synthesized SHS's[34] or (ii) by employing a chemical informatics approach that uses software to generate very large numbers of possible structures. QSAR (quantitative structure–activity relationship) predictions are then employed to narrow down the choices to those which are likely to be the greenest.[37]

Almost any amine having a pK_{aH} (the pK_a of the protonated amine) in the range 9.5–11.0, and a logK_{ow} (K_{ow} = octanol–water partition coefficient) between 1.2 and 2.5, is an SHS (**Figure 1**).[34] SHS's are found in these narrow ranges due to the reaction and partitioning equilibria;[38] if a change in miscibility had not been required, less basic amines would have sufficed.

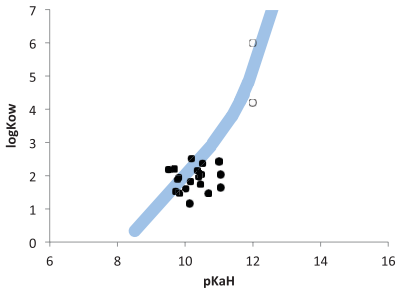
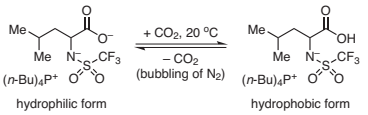


Figure 1. The Amines (●) and Amidines (○) That Function as SHS's All Fall Very Close to the Theoretical Line (Shown in Blue) of Maximum Effectiveness for an SHS (Assuming a 1:1 Water:SHS Ratio by Volume, 25 °C, and a Pressure of 1 bar CO_2; and Assuming That Peralkylated Amidines Have a pK_{aH} of 12). Other Amines Can Function as SHS's If the Volume Ratio or Conditions Are Changed. *(Ref. 34,38)*

Secondary amines are more biodegradable and have faster rates of reaction with CO_2, but most of them form carbamate salts, a reaction which is enthalpically harder to reverse. Fortunately, secondary amines with one, but not two, bulky substituents have the same elevated rate of reaction with CO_2 without the problematic formation of carbamate salts.[34]

Kohno et al.[39] reported an ionic liquid SHS (**Scheme 3**) that is miscible with water at 20 °C in the absence of CO_2, but separates from water when CO_2 is added.

So far, there have not been any reports of SHS's being utilized as media for chemical syntheses, but that situation will likely change in the near future.



Scheme 3. Ionic Liquid SHS Reported by Ohno's Group. *(Ref. 39)*

Switchable Water

The expression "Switchable Water" (SW) describes a stimulus-responsive aqueous solution, where application of a trigger causes the properties, including especially the ionic strength, of the solution to dramatically change. For example, in an aqueous solution containing an amine or polyamine (the ionogen), addition of CO_2 at one atmosphere causes a large increase in the ionic strength of the solution {**B + $n$$H_2O$ (low-ionic-strength solution) + $n$$CO_2$ = [BH_n]$^{n+}$ + n[HCO_3^-] (high-ionic-strength solution)**}.[40–44] The final ionic strength is ½m(n^2+n), where m is the molality of the ionogen (B) and n is the average number of protons accepted per molecule of B when CO_2 is present. This change is accompanied by other changes such as a decrease in the ability of the solution to dissolve organic compounds, an increase in the conductivity of the solution, and an increase in the osmotic pressure of the solution.

While the low-ionic-strength solution is a good solvent for organic compounds, because the ionogen is a hydrotrope, the high-ionic-strength form of the SW is a much worse solvent for organic compounds. The reduction in solubility of organic solutes can be as high as 95%, depending on the choice of solute.[45] Thus, low-ionic-strength SW can be used to extract a desirable product from a matrix and then, after CO_2 is added to switch the SW to high ionic strength, the product will precipitate. The SW can then be switched back to low ionic strength by removal of CO_2 and re-used. A wide range of organic solutes can be expelled from the SW solution, including molecules as hydrophobic as capsaicin[45] or as hydrophilic as ionic liquids.[46,47]

Similarly, if SW is employed as a medium for chemical synthesis, then addition of CO_2 after the synthesis would trigger the separation of the product. This technique was utilized for a hydroformylation: post-reaction addition of CO_2 triggered the separation of the aldehyde product, while the water-soluble catalyst remained dissolved in the aqueous phase (**Figure 2**).[48]

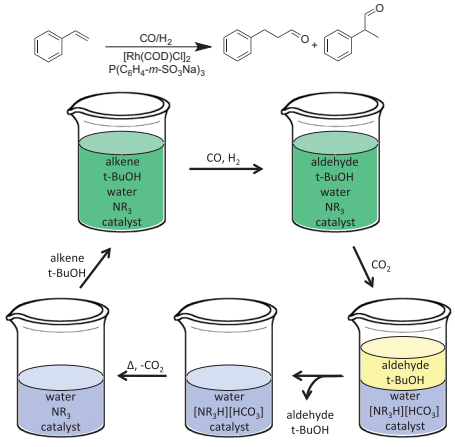


Figure 2. Use of SW as a Medium for Hydroformylation, with Post-Reaction Separation of the Product in *t*-Butanol Triggered by CO_2. *(Ref. 48)* [Reproduced by Permission of The Royal Society of Chemistry (RSC).]

The ionogen can be a small-molecule monoamine, a small-molecule polyamine, or a polymeric amine, depending on the application. Polyamines in which the carbon linker between two nitrogens has only two carbons tend to perform poorly because protonation of one nitrogen renders the other nitrogen less basic, so that it is not protonated in the carbonated water.[43] Employing a three- or four-carbon linker ensures that all of the N atoms have a chance to be protonated. Using a very long linker (over 6 carbons) is not recommended, because the hydrophobicity of the linker tends to enhance the solubility of organic solutes in the solution even when CO_2 is present.[43,49]

SW is a very versatile technology; it can be utilized for many applications other than simply as a medium for syntheses or extractions. For example:

- Polymeric amines, combined with CO_2, are potent flocculants for causing the settling of clay suspensions in water. However, when CO_2 is removed, the flocculants can be "switched off", which is advantageous if the water containing the flocculant is to be re-used.[44] The amount of ionogen required is very low, on the order of 10 ppm by mass.
- While most commercially available ionic surfactants are not CO_2-responsive in normal aqueous solutions, they are CO_2-responsive in switchable water.[50] Thus, these surfactants can be employed to stabilize emulsions or suspensions and then can be "switched off" by the addition of CO_2, causing the emulsions to be broken or the suspensions to settle. For example, if styrene is polymerized in an emulsion stabilized by sodium dodecylsulfate, then the resulting latex can be coagulated by the addition of 1 bar of CO_2 if a SW ionogen is present in the solution.
- A concentrated solution of an amine in carbonated water can be employed as a draw solution for forward osmosis to obtain fresh water from wastewater or seawater. The draw solution on one side of a membrane draws water from the seawater or wastewater on the other side of the membrane, because the draw solution has the higher osmotic pressure (**Figure 3**). The seawater or wastewater is thus concentrated while the draw solution is diluted. The remaining seawater can be discarded into the ocean or the remaining wastewater can be more cheaply processed now that its volume has been reduced. The water drawn into the draw solution can be used once the amine and CO_2 have been removed. First, the CO_2 is removed, leaving behind an aqueous solution of amine with a greatly reduced osmotic pressure. The amine is then removed from the water either by evaporation (if it is a gas), decantation (if the amine is an SHS), filtration (if the neutral amine is an insoluble solid), or by reverse osmosis. This idea was invented by our group and made the subject of patent applications filed in 2010.[41,42] The technology has been further developed at GreenCentre Canada with a focus on polymeric amines such as PDEAEMA and on small amines such as trimethylamine (Me_3N). A new company, Forward Water Technologies, was created to commercialize the idea. The trimethylamine option has also been explored by Ikeda and Miyamoto of Fujifilm in Japan.[51] After this flurry of initial reports, the various options began to be studied by many groups. Elimelech's group further studied the trimethylamine option,[52] while Wilson's group focused on the use of SHS as the ionogen,[35,36,53] and Hu's team concentrated on the filtration option using the polymeric amine PDMAEMA.[54] The theoretical osmotic pressure, assuming a dilute ideal solution, is mRT in the absence of CO_2 and $(n+1)m$RT in its presence. Thus, if the amine is soluble when CO_2 is absent, then an increase in osmotic pressure of n+1 fold is expected when CO_2 is added. In practice, the solutions are neither dilute nor ideal, so the ratio of osmotic pressures varies considerably. In the literature, the osmotic pressures have generally not been observed directly, and have been calculated from freezing point osmometry measurements.[35,36,53] However, when direct measurements of osmotic pressure of such solutions were carried out, the osmotic pressure increase for polymeric amines varied from 1.2 - to over 15-fold.[55]
- Aqueous solutions of switchable viscosity can be created with SW using either of two approaches: (i) In the first approach, a SW ionogen is employed to effect the micelle formation of a non-switchable surfactant. The groups of Jessop and Cunningham have reported that a solution of sodium octadecylsulfate surfactant in switchable water (dimethylaminoethanol or a diamine as the ionogen) had a high viscosity in the absence of CO_2 due to the formation of worm-like micelles, which were destroyed when CO_2 was added.[56] The result was a reversible change in viscosity of 5 orders of magnitude. Feng's group obtained similar viscosity changes combining sodium dodecylsulfate and a diamine.[57] (ii) The second approach is the use of a SW polymer that can self-associate when neutral but not when charged. By employing this approach, Zhao's group showed that aqueous solutions of polymeric tertiary amines could reversibly transition from solutions to gels or the reverse when exposed to CO_2.[58,59] Su et al. reported that a star polymer containing tertiary amine functional groups formed a viscous solution in the absence of CO_2 and a nonviscous solution in the presence of CO_2, with the change in viscosity being 100-fold in water or 10,000-fold in NaCl solution.[60]

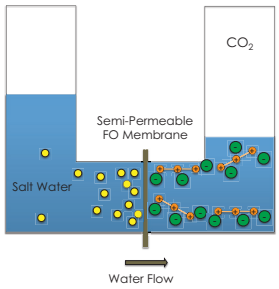


Figure 3. Forward Osmosis Using a CO_2-Switchable Draw Solution (on the Right), with the Natural Direction of Flow of Water from the Low-Osmotic-Pressure Side (The Seawater or Wastewater) to the High-Osmotic-Pressure Side (- Draw Solution). *(Ref. 55)*

Conclusions and Prospects

The concept of switchable solvents, which was introduced in 2005, has now blossomed into a very active field of research. Of the references cited in this review, 83% are from 2010 onwards. The field has changed during that time from focusing on solvents for extractions or reactions to a far more wide-ranging consideration of many possible applications as diverse as mining (using SW for clay settling) or water purification (using SW for forward osmosis). There has also been a shift from the early steps of making the first switchable solvents actually work, to making far more practical, inexpensive, and greener switchable solvents. The focus on greener switchable solvents has progressed the furthest for SHS's[34,37] although it is desirable that this effort progress further for all three classes of switchable solvents.

An obvious question raised by all of this work is whether CO_2 must be the only trigger. There have been some examples of switchable solvents using SO_2 as a trigger,[61–64] but there have not been, to my knowledge, any examples in which a solvent can be reversibly switched using light or voltage as a trigger. While many light-responsive molecules are so large that they are necessarily solids, it is only a matter of time before someone finds an example that is liquid at a usable temperature.

The first industrial application of switchable solvents has not yet happened, probably because switchable solvents are so very new. At present, it appears that the most promising application is forward osmosis, but extractions using SHS's and many of the other applications of SW have great potential.

Acknowledgments

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The Leading Edge of Green Chemistry at Genentech

From the Editor of the 2013 Monograph, Scalable Green Chemistry

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Recent decades have seen a great reduction in the environmental footprint of small-molecule pharmaceutical manufacturing. This shift has taken place largely due to the incorporation of green chemistry principles and practices by process chemists in designing more efficient chemical routes that use sustainable components. Expanding on this success, Genentech is applying sustainable-science paradigms to small-molecule drug discovery (and other areas of development), as well as large-molecule discovery and development to foster further innovation. Sustainability is a valuable new dimension for improving R&D efficiency, but it requires a change in mindset to reap the full rewards.

Genentech was founded as a large-molecule biotechnology company, but has since developed a thriving small-molecule organization. In 2009, the company became a member of the Roche Group in one of the largest acquisitions in pharma history. Through the melding of organizations, Genentech process chemists formalized Roche's small-molecule Green Chemistry approach to produce its clinical candidates more sustainably.[1] This advance led to a growing interest in eco-friendly practices, and became a catalyst for the formation of internal teams to expand these concepts to other scientific areas.

In small-molecule drug discovery, the onus is on the chemist to rapidly synthesize a large set of compounds for preliminary evaluation within a limited timeframe. Historically, there has been little incentive to introduce Green Chemistry at this stage as time-to-candidate was the most critical factor. However, with the realization that the chemistry chosen at this early stage can have a disproportionate impact on development timelines, along with growing pressures to improve overall R&D efficiency, it has become clear that prudent selection of the initial chemical route provides long-term benefits. By integrating green principles and practices early in the drug discovery process, efficiencies can be built into each program and accelerate time-to-clinic.[2] The Genentech program continues to evolve through affiliation of internal teams with the medicinal chemistry subgroup of the ACS Green Chemistry Institute® Pharmaceutical Roundtable (GCIPR).

Of highest priority in the quest for sustainable drug discovery is a general adoption of the *12 Principles of Green Chemistry*.[3] Beyond this basic evolution in mindset, there are several practices that can help realize innovation: (i) In terms of reaction setup and execution, the investigation of atom-economy (C–H activation chemistry, protecting-group-free syntheses, etc.) and step-economy (telescoping, flow chemistry, etc.); and the consideration of reagent (amenable to scale-up, enantioselective, non-rare-earth–metal- and biocatalysis) and solvent guides (circumventing toxic media, evaluating aqueous and surfactant chemistry, etc.) are becoming more mainstream. (ii) The avoidance of chromatography by utilizing precipitation or crystallization techniques and, when chromatography is necessary, judicious choices in mobile phase (to avoid dichloromethane and hexanes) can also greatly impact the environmental footprint of drug discovery.[4] (iii) Sharing best practices with partner Contract Research Organizations (CROs), and (iv) collaborating with academics to pursue both eco-friendlier methods and training of chemists are helping ensure that the changes within drug discovery are felt even further than the clinic.

Large molecules have traditionally been viewed as environmentally benign since they are produced by organisms in aqueous systems, yet it is now clear that these advanced therapeutics require vast amounts of raw materials and leave a large ecological footprint.[5] As the industry shifts to a greater proportion[6] of products in this realm (including bridging the divide with small-molecule bioconjugates[7]), sustainability becomes a critical consideration. Genentech established a Green BioPharma program with the mission of leading our industry in innovations that minimize the environmental impact of the research, development, and manufacturing.[8] The program encourages adoption of eco-friendlier methods for biologics through innovative, metric-based impact analyses, employee engagement, and supplier relationships. Early successes have included partnering with technical development to research innovative approaches to cell culture methods and reuse of resins for the purification of multiple large molecules.[9]

To accelerate progress within the industry, Genentech worked with the GCIPR to launch a biopharma focus group, a non-competitive collaboration with other member companies. This group has set out to craft widely applicable tools and techniques for biologics to complement what has been achieved in the small-molecule space. Initial projects include a biopharma process mass-intensity metric that will allow companies to benchmark the amount of water, raw materials, and consumables used in a typical production run. Member companies are also sharing best practices in facilities management, cleaning techniques, and, where applicable, unit operations—creating an atmosphere of collaboration to reduce the environmental footprint of biopharma.

With its history of rigorous and groundbreaking science, Genentech is focused on discovering and developing innovative new medicines to treat serious unmet medical needs.[10] This commitment to excellent science includes the incorporation of sustainability practices and principles to guide R&D productivity, and lessening the environmental impact of our medicines. Genentech is expanding Green Chemistry beyond the manufacture of small molecules to medicinal chemistry and to large-molecule discovery and development to boost overall efficiency.

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Green Chemistry in the Introductory Organic Laboratory

Working toward the Future of Organic Chemistry Labs: No Organic Solvents

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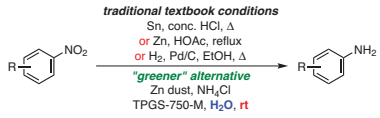
Today, and for as long as one is likely to remember, introductory organic chemistry has been taught at the collegiate level. Textbooks, many being practically works of art, present material using representative reactions that, for the most part, are run in a variety of organic solvents. The corresponding laboratory courses, oftentimes taken concurrently, likewise, tend to favor experiments that correlate with theory taught in the lecture hall. Hence, both the nature and practice of the chemistry of life are presented perhaps as nothing more than a matter of record, as chemistry in organic media. This is unfortunate, as Nature has opted since the beginning of time to provide the wonders of life based on one reaction medium—water, in which chemistry not only takes place but does so under milder conditions than many of those reactions learned by students in lab or lecture. Thus, as part of our research program in Green Chemistry, we are focused on providing experiments for introductory organic laboratories that can be carried out in water at ambient temperatures. These provide all the pedagogy characteristic of traditional lab manuals, but offer a perspective that encourages students to consider the impact of an equivalent reaction, performed in organic solvent, on the environment. It is now recognized that 80+% of organic waste generated by chemistry done worldwide is attributable to organic solvents.[1] There is every reason, therefore, to train our students to appreciate the importance of getting organic solvents out of organic reactions. Realization of this goal will be challenging and will take time, but we have the perfect model that guarantees eventual success: Nature.

As was described in late 2013 in the *Journal of Chemical Education*, two experiments involving "click" and olefin cross-metathesis chemistry were developed and extensively tested with considerable success in the organic labs at the Claremont Colleges in Los Angeles.[2] A third experiment is now offered herein that addresses a fundamental textbook reaction: reduction of a nitroaromatic compound to the corresponding aniline derivative (**eq 1**). According to most undergraduate texts, this conversion is performed in a variety of ways including Sn/HCl or Zn/HOAc as reducing agents, or by using H_2 over Pd/C. While these time-honored processes accomplish the intended transformation, from a Green Chemistry perspective it seems fair to ask: at what cost to the environment?

To achieve the same net reduction at ambient temperature, but in a fashion that entirely avoids organic solvents as the reaction medium, Zn can be used as the source of electrons in an aqueous environment.[3] The omnipresent issue of substrate solubility is addressed—as in the case of 4-nitroacetophenone (**1**) as a model substrate (**eq 2**), and as with the "click" and olefin metathesis chemistry (vide supra)—by the presence of nanoreactors composed of the "designer" surfactant TPGS-750-M.[4] These nanomicellar arrays form spontaneously when the surfactant is present above its critical micelle concentration (CMC; ca. 10^{-3} M). In these reactions, as with most involving this amphiphilic species, a mere two *weight* percent is sufficient. The makeup of TPGS-750-M consists of three innocuous components: racemic vitamin E, succinic acid, and MPEG-750. Each of these ingredients is both safe for human consumption and environmentally benign. The reduction is commenced by simply adding the substrate to this aqueous solution containing either NH_4Cl or TMEDA ($Me_2NCH_2CH_2NMe_2$), followed by introduction of inexpensive Zn dust. With vigorous stirring, complete reduction to the aniline occurs. Neither nitroso nor hydroxylamine intermediates are found to complicate product workup. Such a process is very clean, safe, and tolerant of a wide variety of functionality.

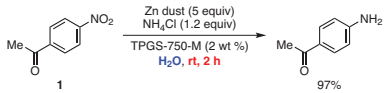
Product isolation is very simple: an "in-flask" extraction involving gentle stirring requires a minimum amount of an organic solvent (e.g., EtOAc, ether, MTBE, hexanes, toluene). The aqueous medium retained in the reaction vial can be reused.[5] Since the overall process requires three of five equivalents originally added of zinc, the amount of zinc needed for each recycle can be adjusted to achieve full conversion.

The choice of experiment, i.e., $ArNO_2$ to $ArNH_2$, was predicated on the importance of the $-NH_2$ residue within the pharmaceutical arena. This is a timely topic, in general, and one that requires at the process level a safe, inexpensive, and green alternative to existing methodologies; and while the technology illustrated herein may meet both goals of undergraduate education with prospects for industrial use, it should also be noted that this chemistry has an important limitation. That is, it may come as a surprise to many practitioners that zinc is an "endangered" metal, meaning that its global supply is dropping, and at a pace that even exceeds that of the platinoids![6] With such a situation, however, comes a new opportunity, as is true for many of the experiments employed in the introductory organic labs, to develop alternatives that maximize adherence to the *12 Principles of Green Chemistry*,[7] and in doing so, increase environmental awareness and sustainability on planet Earth.



TPGS-750-M = DL-α-tocopherol methoxypolyethylene glycol succinate
Traditional vs Green Conditions for the Reduction of Nitroaromatic Compounds

eq 1



Zn-Mediated Reduction of 4-Nitroacetophenone in Water at Room Temperature

eq 2

Reduction of 4-Nitroacetophenone by Zn in Aqueous Nanoparticles (eq 2)

Finely ground 4-nitroacetophenone (0.826 g, 5 mmol) and ammonium chloride (0.33 g, 6 mmol) were added to a 50 mL round-bottom recovery flask equipped with a PTFE-coated egg-shaped magnetic stir bar (1 in × ½ in). This was followed by introduction via syringe of a solution of 2 wt % TPGS-750-M in H_2O (10 mL, 0.5 M) into the flask. The mixture was stirred for ca. 1 min before adding zinc dust (1.63 g, 25 mmol) in a single batch. The resulting mixture was stirred *vigorously* at rt for 2 h. It was then diluted with EtOAc (20 mL), and filtered quickly through a 3 cm silica gel (230–400 mesh size) plug in a sintered glass Büchner funnel (40 mm diameter) to remove water and zinc solids. The plug was rinsed with a minimum volume of EtOAc. The combined organic filtrates were concentrated in vacuo, affording 4-aminoacetophenone as a faint yellow solid (0.655 g, 97%). Thin-layer chromatography (TLC): R_f = 0.32 (EtOAc–hexanes, 1:1; UV254). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.81 (d, J = 7.2 Hz, 2H, aromatic H's), 6.65 (d, J = 7.2 Hz, 2H, aromatic H's), 4.16 (br s, 2H, NH_2), 2.51 (s, 3H, CH_3). The spectral data matched those reported in the literature for 4-aminoacetophenone.[8]

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Fluorous Chemistry Meets Green Chemistry: A Concise Primer

An Overview from an Authority on Recoverable and Recyclable Catalysts and Organometallic Chemistry

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Basic Concepts

Perhaps you have been drawn to this issue of the *Aldrichimica Acta* by an interest in Green Chemistry, and seek from this article a feel for what fluorous chemistry can do to advance it. But first, what does this term "fluorous", now only twenty years old,[1] mean? It can be defined as "*of, relating to, or having the characteristics of highly fluorinated saturated organic materials, molecules or molecular fragments.*"[2] Stated differently, think "perfluorinated sp^3 segments" that consist of at least 4–5 carbon atoms. However, sp^2 systems such as hexafluorobenzene, which have a much different polarity footprint, are *not* fluorous. In contrast, ether oxygen and amine nitrogen atoms *are* "allowed", as the lone pairs in $–(CF_2)_nO(CF_2)_n–$, $–(CF_2)_nN(CF_3)(CF_2)_n–$, or similar moieties are "sucked dry" by the highly electronegative perfluoromethylene segments.

Fluorous chemistry offers a myriad of ways of recycling reagents and catalysts,[1,3] as detailed below, as well as many other useful applications such as catalyst activation protocols[4] and strategic separations (e.g., compound libraries).[5] At the same time, there are some well-defined categories of fluorous compounds that are environmentally persistent and in some cases bioaccumulative.[6,7] Although space limitations preclude an in-depth analysis, strides are being made in the design and synthesis of substitute materials that remain fluorous, but are not sequestered into living tissue or undergo facile biodegradation.[8,9] It has furthermore been shown that vitamin B_{12} can serve as a catalyst for the Ti(III)-citrate promoted reductive defluorination of perfluorooctane sulfonate.[10] This has raised hopes that microorganisms will eventually be found that are capable of degrading molecular species with $-(CF_2)_8-$, $-(CF_2)_{10}-$, and similar segments.

Three major classes of orthogonal phases are recognized: organic, aqueous, and fluorous (**Figure 1**, left side). Fluorous phases are both lipophobic and hydrophobic, per the proverbial expression about the fluoropolymer Teflon® "not sticking to anything". There is no significant enthalpic attraction between fluorous molecules,[11] but they are commonly expelled from organic or aqueous phases into their own domain so that the molecules in the non-fluorous phase can enthalpically interact more effectively. In other words, the overall enthalpic interactions are stronger when the fluorous molecules "get out of the way".

Nonetheless, many fluorous–organic, liquid–liquid biphase systems become monophasic upon warming (Figure 1, right side), with entropy being the major driving force. Typical temperatures to effect this transition range from 40 to 100 °C, but exact values are solute-dependent. Some of the more common fluorous solvents in use include perfluorohexanes (FC-72), perfluoromethylcyclohexane ($CF_3C_6F_{11}$, PFMC), perfluoro-2-butyltetrahydrofuran (FC-75), and perfluorotributylamine (FC-43). Many reviews categorize these as green solvents.[12]

Compounds or materials can be made fluorophilic by adding sufficient numbers of fluorous "tags" or phase labels of sufficient lengths (**Figure 2**).[13] These are often termed "ponytails", with groups of the type $(CH_2)_m(CF_2)_{n-1}CF_3$ (abbreviated $(CH_2)_mR_{fn}$) most often employed. The $(CH_2)_m$ spacer serves to modulate the electron-withdrawing effect of the perfluoroalkyl group. This effect is still substantial when $m = 2$ or 3, which can be desirable when enhanced Lewis acidity is sought.[14] Some strategies for reducing the environmental persistence of ponytails include alternating spacer/fluorous/spacer/fluorous segments, and the use of multiple *t*-C_4F_9 substituents.[8]

When catalogs of vendors who specialize in fluorinated chemicals are examined, many interesting future directions for ponytail design are apparent. Some of the numerous potential building blocks that are commercially available are (i) the branched terminal alkenes $R_{f3}C(CF_3)_2CH=CH_2$ and $R_{f3}OCF(CF_3)CF_2OCF=CF_2$; (ii) the branched carboxylic acid chlorides $(CF_3)_3CC(CF_3)_2OCH_2C(=O)Cl$ and $R_{f3}OCF(CF_3)C(=O)Cl$; (iii) the alcohols $(CF_3)_3CCF_2CF(CF_3)CF_2CH_2OH$, $R_{f4}O(CF_2)_2OCF_2CH_2OH$, and $R_{f3}O[CF(CF_3)CF_2O]_4CF(CF_3)CH_2OH$; and (iv) the α,ω-diol $HOCH_2CF_2O–(CF_2)_2O(CF_2)_2OCF_2CH_2OH$. These can be easily elaborated into a variety of other functional groups.

The most common way of assaying the fluorophilicity of a molecule is by a liquid–liquid biphase partition coefficient.[15] These are most often measured in mixtures of perfluoromethylcyclohexane and toluene, but a variety of other fluorous–organic solvent combinations can be found in the literature. However, one should keep in mind that many commercial fluorous solvents are mixtures of isomers or stereoisomers. Computational algorithms for predicting fluorophilicities have also been developed.[16] A so-called "heavy fluorous" solute has a partition coefficient of >90:<10, and in general there is no particular difficulty attaining values of >99:<1. Nonetheless, there are many applications, particularly in compound libraries, for "light fluorous" molecules, with partition coefficients of <50:>50.

Applications in Catalyst Recycling

Liquid–Liquid Biphase Systems

Per the seminal publication by Horvath and Rabai in 1994,[1] the primary motivation for the development of fluorous chemistry was for catalyst recycling via liquid–liquid biphase protocols. **Figure 3** depicts the general procedure and one specific example. The idea is to synthesize a fluorous analogue of an established catalyst with a very high fluorous–organic partition coefficient. One begins with a fluorous solution of the catalyst and an organic solution of the reactants (Figure 3, **I**). Typical organic reactants and products partition almost exclusively into the organic phase (>98%). The sample is warmed to establish one phase homogeneous conditions, where the reaction can proceed at a convenient rate (Figure 3, **II**). The

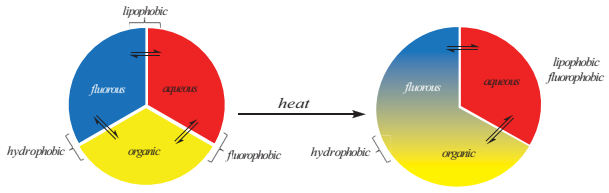

Figure 1. Left: Orthogonal Phases (Room Temperature); Right: Miscible Fluorous–Organic Phases (Heating).

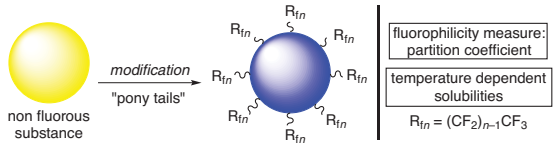

Figure 2. Generation of Fluorous Compounds or Materials. *(Ref. 13)*

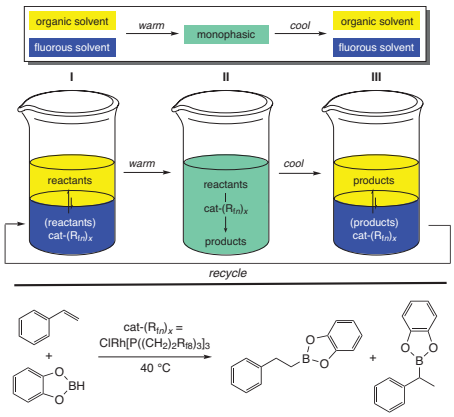

Figure 3. Protocol 1: Fluorous–Organic, Liquid–Liquid Biphase Catalysis. *(Ref. 17)*

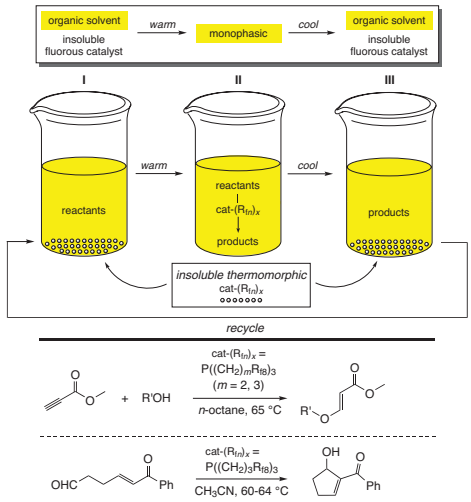

Figure 4. Protocol 2: Fluorous–Organic, Solid–Liquid Biphase Catalysis without Fluorous Solid Support. *(Ref. 20,21)*

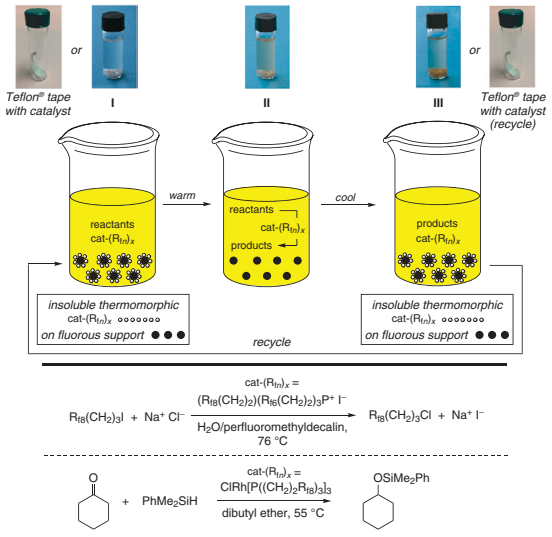

Figure 5. Protocol 3: Fluorous–Organic, Solid–Liquid Biphase Catalysis with Fluorous Solid Support. *(Ref. 20–24)*

sample is then cooled, re-establishing two-phase conditions (Figure 3, **III**). Simple separation of the fluorous and organic phases yields a product solution (organic) and a catalyst solution (fluorous). The latter, which should be thought of more accurately as containing the catalyst resting state, can be recycled.

A number of fluorous phosphines are readily available, and rhodium catalysts of the formula $ClRh[P((CH_2)_mR_{fn})_3]_3$ ($m = 2, 3$; $n = 6, 8$) have been used to effect olefin hydroborations and ketone hydrosilylations according to Figure 3.[17,18] Related rhodium catalysts have been employed for olefin hydroformylations.[1] Actually, the hydroborations usually proceed at temperatures lower than those required to obtain one-phase conditions; and, if reactions are sufficiently fast under two-phase conditions, all the better. The hydrosilylations and hydroformylations are conducted under one-phase conditions. Such protocols carry many of the caveats of biphase catalysis such as catalyst leaching, catalyst decomposition, etc. However, these problems can be minimized by careful attention to partition coefficients and other design elements. In conclusion, this solvent-intensive procedure has now largely been superseded, but remains a reader-friendly starting point.

Liquid–Solid Biphase Systems without Fluorous Solid Support

As researchers gained more and more experience with fluorous compounds, they recognized that many such compounds had highly temperature-dependent solubilities.[19] Of course, the solubility of small-molecule solutes commonly increases with temperature. However, the concentration gradient with fluorous molecules, in both organic and fluorous solvents, is commonly much greater.[20] Hence, a fluorous molecule may have very little or no solubility in an organic solvent at room temperature, but appreciable solubility at 100 °C. This was recognized as a way to do fluorous catalysis *without* fluorous solvents.

Thus, one can take the protocol in Figure 3, and simply omit the fluorous solvent; the temperature-dependent solubility of the fluorous catalyst is then exploited (**Figure 4**). Given that catalysts are often employed at very low loadings, only a relatively small mass of the catalyst must dissolve under the higher-temperature homogeneous conditions (Figure 4, **II**). When the reaction is complete and the mixture cooled (Figure 4, **III**), the product–catalyst separation is effected by a simple liquid–solid phase separation. The amount of catalyst leaching will be bounded by the residual solubility under the separation conditions.

Some specific examples of such protocols, both involving phosphine catalysts, are shown in Figure 4 (bottom).[20,21] Many other examples have been described by other research groups, as tabulated elsewhere.[3,22] Interestingly, for liquid reactants and products, it is possible to conduct some of these reactions in the absence of *any* solvent! Liquid–solid phase separations are considered to have many advantages from an engineering standpoint. However, in the cases of highly active transition-metal catalysts, it can be difficult to efficiently recover a few milligrams from a gram-scale reaction. This prompted the refinements described in the following section.

Liquid–Solid Biphase Systems with Fluorous Solid Support

Given the difficulties noted in recycling small quantities of solids by the protocol shown in Figure 4, analogous experiments were conducted in the presence of fluorous solid phases (**Figure 5**). As noted above, enthalpic interactions involving fluorous molecules or molecules and surfaces are very modest. Still, the precipitating catalyst or reagent only has two choices: (1) solidify as its own phase, or (2) coat the support. Interestingly, the latter almost always occurs. Supports that have been employed include various forms of Teflon®, Gore-Tex® fibers, and fluorous silica gel.[3,22] For the first cycle, the catalyst can be added either in its supported or (as depicted in **I**) unsupported state.

The vials (Figure 5, top) illustrate the use of Teflon® shavings to recycle the phosphine catalyst in Figure 4 (bottom).[20] The cyclization in Figure 4 was also studied using Gore-Tex® fibers, which can be viewed as a porous version of Teflon®.[21] In accord with their greater surface area, the fibers gave superior results. The other examples in Figure 5 (bottom) employed Teflon® tape for the support.[23,24] The tapes could, if desired, be pre-coated by allowing a solution of the catalyst to evaporate.

Of course, NaCl has no solubility in fluorous solvents. Thus, the Finkelstein-type reaction in Figure 5 is noteworthy for being a rare example of an ionic displacement reaction that proceeds in a very nonpolar fluorous phase (perfluoromethyldecalin). The NaCl originates from an aqueous solution, with the fluorous phosphonium salt serving as a phase-transfer catalyst, the cation of which transports the chloride ion into the fluorous phase. Since the fluorous phosphonium salt is white, there is not a dramatic visual difference when it precipitates onto the tape upon cooling. However, the rhodium catalyst used for the hydrosilylation reaction is orange, and coats the tape yellow-orange. For both reactions, rates are reasonably constant from cycle to cycle, which is the optimum measure of recyclability.[25]

Other Types of Application

Caution: Once one starts, it's easy to get hooked on fluorous chemistry, and a sampling of recent results from a collaboration of the authors with Professor H. Bazzi (Texas A&M-Qatar) is highlighted in the following figures. Catalyst *activation* was mentioned above. There are many metal-based catalysts from which a ligand must initially dissociate. With the resulting intermediate, there is a competition between binding the substrate and reattaching the ligand (except when the initial dissociation is rate-determining). In many cases, if the ligand could somehow be trapped or scavenged, faster rates would ensue. Thus, we have explored a strategy we term "phase transfer activation".[4,26]

Figure 6 shows an analogue of Grubbs' third-generation metathesis catalyst. The pyridine or 3-bromopyridine ligands have been replaced by a fluorous pyridine ligand that is quite fluorophilic ($CF_3C_6F_{11}$:PhMe, 93.9:6.1).[27] However, the catalyst or catalyst precursor itself remains predominantly lipophilic ($CF_3C_6F_{11}$:PhMe, 39.8:60.2). Thus, under fluorous–organic, liquid–liquid biphase conditions, the scenario in Figure 6 is realized. Ring-closing metatheses take place at rates much faster than in organic monophase conditions that use analogous catalyst concentrations.

Figure 7 depicts exploratory research involving di-anionic, redox-active Fe_4S_4 clusters that closely model Fe_4S_4 units found in many metalloenzyme cofactors.[28] Both the iron thiolate ligands and the accompanying cations can be rendered fluorous. The idea here is to both phase-shift and redox-shift (e.g., $E°$ values) these systems. Indeed, with fluorous cations (Q_F^+), these salts become fluorophilic. One idea behind the phase shift is to take advantage of the high solubility of small nonpolar gases in fluorous liquid phases, apropos to their use as blood substitutes.[29] The same factors responsible for enhanced O_2 solubility also lead to enhanced N_2 and H_2 solubility.[30] Thus, in view of the key role such Fe_4S_4 moieties play in nitrogenaese proteins, fluorous solvents could present intriguing possibilities for abiological nitrogen fixation.

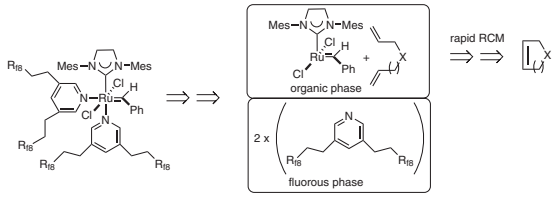

Figure 6. Catalyst Activation under Fluorous–Organic, Liquid–Liquid Biphase Conditions. *(Ref. 27)*

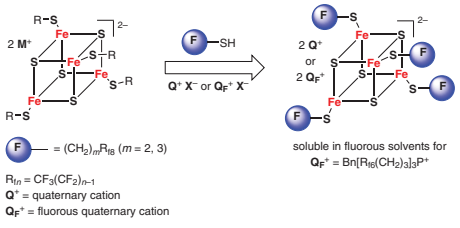

Figure 7. Fluorous Analogues of Metalloenzyme Cofactors—Ionic Compounds That One Can Fine-Tune to Be Lipophilic or Fluorophilc, Depending upon Fluorous Content. *(Ref. 28)*

In an inverse sense, various types of hydrophilic or lipophilic polycations such as $[Co(en)_3]^{3+}$ or $[Ru(bpy)_3]^{2+}$ can be rendered soluble in fluorous solvents by using fluorophilic anions.[31] The most accessible fluorophilic anion would be "fluorous BAr_f", or $[3,5\text{-}C_6(R_{f6})_2H_3]_4B^-$.[31]

Prospective

This brief overview has attempted to capture some of the contemporary excitement regarding fluorous chemistry, while at the same time treating the key underlying principles and concepts in sufficient detail. Due to length constraints, nearly all of the examples were taken from the author's laboratories. However, readers are referred to the reviews and compendia cited for a broader range of specific applications.[3,25,32] From a Green Chemistry standpoint,[12] fluorous chemistry provides protocols extraordinaire for catalyst recycling. However, there remain a number of frontiers for optimization. Probably the most critical is the design and application of effective ponytails that do not persist in the environment, or at least avoid bioaccumulation. These and other objectives are under active investigation in a number of research groups worldwide.

Acknowledgment

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Where We Should Focus Green Chemistry Efforts

Insight from the Co-Author of the 12 Principles of Green Chemistry

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I am often asked to identify what I feel are the most important technologies that need to be improved from a Green Chemistry perspective. I am sure that I am not alone in receiving this type of question. One can understand why this question is so prevalent. It is certainly no secret that today's funding resources for scientific research are scarce. It makes sense to want to make progress in a fewer number of focused areas, rather than be spread too thin making imperceptible headway across too many pathways. It is logical to want to identify the technologies that have the most negative impact on human health and the environment, and cross-reference them with the most promising early-stage ideas. In so doing, the assumption follows that these early successes will provide confidence and momentum to expand and take on more difficult challenges.

My reaction to this question is to become quite uncomfortable: who am I to be so presumptuous as to pick what is most important? In choosing the focus areas, should we identify classes of materials: phthalates, brominated flame retardants, parabens, or plastics? Perhaps we should identify negative impacts: endocrine disruption, global climate change, carcinogenesis, or fossil fuel consumption? Maybe we should focus on areas of research: catalysis, solvents, nanotechnology, or feedstock? It seems like we need help in every area. But there isn't really any "one size fits all" winner. I would imagine different industry sectors have different top priority needs. What the petroleum industry needs is probably different from what the pharmaceutical industry needs; and people working on the front lines of patient care at a cancer hospital will likely see different needs than farmers working in the fields of a vegetable farm.

And then there is the question of how innovation should be "caused to happen" in any given area once it is selected. I often say that Green Chemistry has three long-term requirements: (i) It must have less impact on human health and the environment than some incumbent technology. But this is not enough. (ii) It also must perform better than the incumbent technology in order to be successful in replacing it. No one is going to use a cleaner that doesn't clean, just because it is greener. (iii) It also must have appropriate costs. Society has not demonstrated an overwhelming willingness to pay too much of a premium for a green technology. Reflecting upon this, Green Chemistry really provides a "holy grail" of sorts: better performance, better cost, and "Oh, by the way… it is better for human health and the environment." Given these criteria, what market barrier exists for adopting a greener product save its invention in the first place?

So the question then becomes, how does identifying a focus area that "needs improvement" catalyze innovation? How do scientists learn how to "make better products"? The United States Environmental Protection Agency has given out 5 Presidential Green Chemistry Challenge awards every year since 1996. Other international organizations have various award programs as well. Exemplifying and disseminating case studies of successful discoveries and implementations of Green Chemistry is critical. But is it enough? Does listening to a symphony teach someone to play a musical instrument? Does watching the Boston Marathon train someone how to run 26.2 miles? While illustrative examples are important, something deeper is necessary.

We really need to get at the roots of how we train chemists in the first place. We need to reflect upon the words and semantics we use in our scientific "disciplines". We have a body of knowledge called "organic chemistry". We have another body of knowledge called "physical chemistry". There is "analytical chemistry", "inorganic chemistry", and several other subdisciplines. But, it is important to realize that these subdisciplines are merely intellectual constructs. They allow us to apply the reductionist approach while learning and growing the body of knowledge. We place boundaries on a given subdiscipline for bureaucratic reasons: in order to define the scope of a journal, the syllabus of a class, or the table of contents of a textbook. But, at the end of the day, there really is no such thing as an "organic chemist". One cannot possibly function in the world of chemistry doing "only" organic chemistry. Organic chemists function simultaneously as analytical, physical, theoretical, and other types of chemist. They choose to identify organic chemistry as their "specialty"; but, in no way could they restrict themselves to doing "only" organic chemistry. All of the other subdisciplines work in the same way. It is an illusion to believe that any of these subdisciplines have any independent reality of their own. In my opinion, Green Chemistry should work the same way; and the field is growing as such. There now are many journals, classes, and textbooks in Green Chemistry. The only problem is that Green Chemistry is still seen as something of an "elective" in chemistry. Can you imagine having a student graduate with a degree in chemistry after only being shown "illustrative examples" of physical chemistry? It is inconceivable that a chemistry degree program at a university suggest that, instead of having several semester-long classes in organic chemistry, the initiated should look at examples of papers in the *Journal of Organic Chemistry*. While these hypothetical examples are laughable, we are still at a point in our evolution where Green Chemistry is treated as such. This must change.

Of course, there are moral and ethical issues surrounding this. It is an inescapable truth that the field of chemistry has a certain obligation to society to make sure that future practitioners learn some fundamental principles regarding the making of materials and products that have reduced impact on human health and the environment. But, this is also about innovation and economic competitiveness. Chemists need to treat Green Chemistry as simply a part of the fundamentals of chemistry—nothing more, and nothing less.

This is where the Green Chemistry Commitment program of the nonprofit organization Beyond Benign (www.beyondbenign.org) comes into play. Obviously, it is difficult to introduce Green Chemistry into the basic chemistry curriculum. If no one has had these classes before, who is going to teach them? Beyond Benign seeks to create a community of chemistry departments to share best practices for what uniquely works for them. If a chemistry department wants to develop a standalone class in Green Chemistry, it should do so. If a department wants to integrate it across various existing classes, it should do so. If a department wants to address Green Chemistry in the labs, it should do so. By sharing best practices, the community can grow and move from illustrative examples to basic pedagogy.

So when I am asked to identify what I feel are the most important technologies that need to be improved from a Green Chemistry perspective, my answer is instantaneous: ***education***. Imagine a world where all chemists had fundamental training in how to design technologies that had reduced impact in human health and the environment. Instead of merely picking the technologies, materials, and endpoints that we need to improve upon, let's focus on how we train the scientists in the first place; and we can consequently improve ***all***.

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A Practical Overview of Organic Synthesis in Ionic Liquids

A Synopsis from a Leader of Research into Sustainable Biomaterials and Green Manufacturing

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Since the discovery of the use of ambient-temperature 1-ethyl-3-methylimidazolium chloroaluminate melts in Friedel–Crafts reactions,[1] low-melting salts, which have come to be known as ionic liquids (ILs), have attracted a lot of attention as replacements for traditional solvents and catalysts in organic synthesis. This body of work, which is in fact so large that entire books have been devoted to it,[2–4] is far too broad to receive anything close to a comprehensive treatment in this mini-review. The recent IL literature is not only vast in terms of the number of publications, but also the range of fields to which they are applied (even if one limits the area to organic synthesis, where they can be employed in almost any class of reaction).

The most recent and highly cited reviews in the area of organic reactions and catalysis in ILs are on the properties of ILs as solvents or reaction media.[5,6] However, one finds in searching the literature that many reactions are not conducted using the IL as the reaction medium, but rather as the catalyst in the presence of some other supporting solvent. A major reason for this is that many newly discovered ILs, particularly those with functional moieties, are not actually liquid at convenient temperatures.[7] Additionally, the most commonly studied ILs that are liquid at room temperature are considerably more expensive than common laboratory solvents and incompatible with evaporation-based techniques for product isolation. For many chemists working at the bench scale and seeking to incorporate ILs into their research, the answer to these problems has been to adapt ILs to be utilized with more typical techniques.

The real technological breakthroughs based on ILs, however, are likely to stem from research that recognizes and uses all of the unique properties of these materials. For instance, in the year 2000, major rate enhancements were discovered for palladium-catalyzed Suzuki coupling reactions carried out in a dialkylimidazolium-based IL,[8] and were attributed to the unusual ability of dialkylimidazolium ILs to act as reservoirs of N-heterocyclic carbenes[9,10] that ligate the Pd centers.[11] This finding is considered to have opened an entire subfield in cross-coupling reactions,[12] and represents a contribution by this particular class of ILs that could not have been possible in any other solvent. However, with so much new work being generated in so many directions, even using the literature as a guide is difficult for researchers from other areas seeking to apply ILs to their fields. This mini-review is therefore intended to serve as a short and practical overview of what sort of problems organic chemists are facing in choosing which ILs are suited to their needs and the options for using ILs as reaction media despite—or better yet, taking advantage of—their unusual properties.

The key to using ILs is to recognize that they are neither universally better nor worse than molecular solvents; they are different and have corresponding advantages and disadvantages. For instance, a small controversy erupted in the past over the heavy promotion of ILs as green replacements for solvents. ILs were assumed by many authors to be universally non-volatile, non-flammable, and non-hazardous, which prompted a critical look at the life-cycle analysis of ILs,[13,14] as well as reports of hazards such as toxicity,[15] explosiveness,[16] and hazardous decomposition products.[17] Despite the existence of ILs that are hazardous (including many that are commonly used), ILs can in fact have an intrinsic advantage over molecular compounds for green chemical applications. There is a virtually unlimited range of ion combinations with which to make ILs, and many innocuous and renewable compounds have been incorporated into ILs.[18,19] By contrast, there are only so many molecular liquids out there that have suitable properties and are inexpensive enough to be used as solvents, and many of these happen to be toxic or nonrenewable in origin.

In addition to this structural variability, ILs generally have sets of properties that distinguish them from molecular liquids. The most important of these from a synthetic standpoint is probably the wide liquid range, which allows experimental excursions into conditions that cannot be obtained with most molecular solvents. ILs can usually be heated to the decomposition temperatures of their ions without boiling, and many ILs are liquid or can be supercooled to temperatures below the freezing point of water. Unlike most molecular solvents, ILs are intrinsic electrolytes and open new possibilities for organic electrochemistry.[20] The chemical effects of ILs as solvents tend to vary depending on the ions, and are discussed thoroughly in a recent review by Hallet and Welton.[5] Many ILs also differ from organic solvents in that a combination of charge ordering and segregation of polar and nonpolar regions lead to nanoscale structuring and heterogeneity, which are hypothesized to affect reaction rates by, for instance, decreasing the activation energy of solvent reorganization.[21]

As mentioned earlier, many researchers are likely deterred from employing commercially available ILs as solvents due to their high cost compared to conventional solvents. The most common approach to cutting down on the volume of the IL used is simply to do the reaction under solventless conditions, using only as much IL as is needed to catalyze the reaction. The use of ILs immobilized on solid supports (supported ionic liquid phases, or SILPs) deserves special mention here due to its widespread success in a number of applications.[22,23] SILPs are often utilized as heterogeneous catalysts in gas-phase reactions, but the actual chemical reactions usually occur between chemicals dissolved in the thin film of supported IL.[24] In this sense, the IL affects the reaction as though it were a bulk solvent even though it is used in catalytic amounts relative to the feedstock. Solventless reactions in general, however, are not the same as reactions conducted in solution in IL as the amount of IL is too small to truly solvate the other components of the system. Furthermore, if control over the thermodynamics of the system by controlling the volume concentration of reactants is required, this is most easily done by using a bulk solvent.

Even if they are used in bulk, ILs do not have to be more expensive or exotic than any other molecular solvents. Many common acids and bases form salts that are liquid even at room temperature,[25–27] and the range of usable ions increases greatly if melting points up to the reflux temperatures of higher boiling solvents are considered. Solvent replacement in the related field of deep eutectic solvents (fluids which are similar to ILs and typically form when combinations of a solid salt and a neutral compound form very low-melting mixtures across a composition range)[28] has been very successful, and this is likely because the most commonly used deep eutectic solvents are made from easily prepared and very inexpensive compounds.[29] However, even dialkylimidazolium ILs can be prepared in bulk using simple procedures and inexpensive starting materials.[30] It should be cautioned though that, while ILs are inexpensive to make, they are often difficult to purify and can be strongly affected by trace impurities.[31] Even those that are made by combining a neat acid and base can have complex speciation.[32] *ILs (synthesized or purchased) should be characterized thoroughly to ensure reproducible results*.

ILs cannot usually be removed effectively by distillation, and, while organic solvents can be used in liquid–liquid extractions with ILs, this may be contrary to their application as organic solvent replacements in some

cases. Instead, the unusual solubility and dissolving power of ILs (which have themselves fueled a thriving research area in IL-based separations[33]) can be exploited in alternative product workups. Many ILs can dissolve water-insoluble compounds yet dissolve in water themselves; so, water can often be utilized as a viable alternative to organic solvents for recovering both the product and the IL.[34] Some ILs form liquid clathrates with organic liquids, where the IL is not fully miscible with the organic solute but does dissolve it in significant quantities.[35] This strategy can be employed to allow a liquid clathrate-forming product to be precipitated as the reaction proceeds. Aqueous solutions of ILs also form immiscible phases with aqueous solutions of chaotropic molecules such as poly(ethylene glycol), allowing for strictly aqueous liquid–liquid extractions.[36] The nonvolatility of ILs can also be exploited to allow volatile products to simply be distilled out, which is especially useful when working with nonvolatile starting materials such as raw biomass.[37] Crystallization from ILs is less well explored than in molecular solvents, but it has been used for the crystallization of unusual organic solutes.[38]

The field of ILs has at times been derided as a fad, where their application was promoted in spite of their disadvantages, and tentative applications of ILs to a known methodology was considered new science. However, ILs are poised in many cases to live up to the claims made about them as green, tunable, and effective solvents and reaction media when their unusual properties are embraced and used instead to boldly change the usual approach of a field. They are a complex and immense class of materials, which will probably defy any generalizations beyond the one implied by the name—liquids composed of ions—but if there is one property which ties the field together, it is the adaptability of ILs to almost any problem. The key is to avoid inappropriate preconceptions about particular ILs based on their membership in a class and, instead, characterize their properties individually to find out how each might be employed to one's advantage.

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Biocatalysis and Biomass Conversion in Ionic Liquids

Update from an Authority on Green Chemistry and Catalysis and the Developer of the E-Factor Concept

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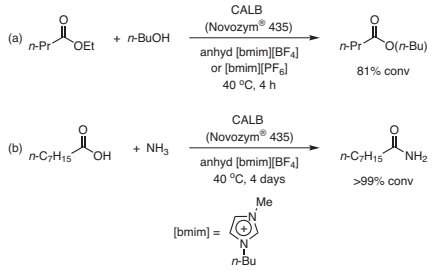
Introduction

Enzymes are Nature's sustainable catalysts—biocompatible, biodegradable, and derived from renewable resources—and enzymatic processes are generally more step-economic, generate less waste, and are more energy-efficient, cost-effective, and, ultimately, more sustainable than conventional chemical processes.[1,2] Conventional wisdom dictates that enzymes function properly only in an aqueous environment, which is generally perceived as an important benefit. However, it can be a serious shortcoming when the organic substrate is only sparingly soluble in water. Sporadic reports of the use of enzymes in organic media stem from the advent of the last century,[3] but it was the seminal paper, published in 1984 by Zaks and Klibanov[4] on enzymatic catalysis in organic media at 100 °C, that heralded the era of "nonaqueous enzymology".[5] Their observation that many enzymes were actually more thermally stable in organic solvents, such as toluene, than in water was nothing short of a revelation. It led, in the following decades, to the adoption of biocatalysis as a mainstream synthetic tool, with a broad industrial scope. The benefits of biocatalysis in nonaqueous media[6] include easier product recovery from low-boiling organic solvents and elimination of microbial contamination. Furthermore, certain transformations, such as esterification and amidation, which are difficult to perform in water owing to equilibrium limitations and/or competing hydrolytic side reactions, are readily conducted in organic media.

However, these benefits come at a cost: enzymes can function as suspensions in organic solvents, but their catalytic efficiencies are two or more orders of magnitude lower than those observed with the enzyme dissolved in water. The activity of enzymes in organic solvents can be increased, however, by lyophilization in the presence of relatively large amounts of salts,[7] such as potassium chloride. This led us to speculate that a suspension of an enzyme in a room-temperature ionic liquid (IL), with its salt- and water-like character, would afford significant rate enhancements compared to organic solvents. Ionic liquids (ILs) are substances that are composed entirely of ions and are liquid at, or close to, ambient temperature. Interest in their use as reaction media,[8] in particular for catalytic processes,[9] has increased exponentially over the last two decades. Indeed, they have been widely advocated as green alternatives to volatile organic solvents (VOCs) based on their negligible vapor pressure, coupled with their good thermal stability and widely tunable properties such as polarity, hydrophobicity, and solvent miscibility. One can distinguish between whole-cell biotransformations—in which a water phase contains the suspension of whole cells and the IL functions as a reservoir for the substrate and/or product—and reactions with isolated enzymes. In the latter case, the enzyme may be dissolved in a second, water phase or in a one-phase mixture of a hydrophilic IL and a water-miscible solvent, or it can be suspended in a water-free IL. Strictly speaking, only the latter constitutes a biotransformation in an IL, since, in the presence of water, we are dealing with an *ionic solution*, just as we would refer to a solution of sodium chloride in water.

Biocatalysis in Ionic Liquids (ILs)

The first example of whole-cell biocatalysis in a two-phase system comprising water and the hydrophobic IL, [bmim][PF_6], involved a nitrile hydrolysis catalyzed by whole cells of *Rhodococcus* sp. strain R312.[10] The system avoids the toxicity and flammability issues associated with the use of the more conventional toluene–water. Moreover, the cells were better dispersed and more stable toward disruption, and higher product yields were observed. Similarly, Erbeldinger and co-workers[11] reported an ester amidation catalyzed by the protease thermolysin in [bmim][PF_6] containing 5 vol % water. They observed excellent enzyme stabilities, as well as activities and yields that are comparable to those achieved in conventional water–organic solvent mixtures. We reported the same year the first example of biocatalysis in an anhydrous IL, namely transesterifications and amidations catalyzed by a suspension of *Candida antarctica* lipase B (CALB) in anhydrous [bmim][PF_6] or [bmim][BF_4] (**Scheme 1**).[12] Both the IL and the enzyme were dried over phosphorus pentoxide prior to use to eliminate any traces of water. Following these initial reports in 2000, biocatalysis in ionic liquids has been widely studied over the last decade.[13]



Scheme 1. CALB-Catalyzed Reactions in Anhydrous ILs. *(Ref. 12)*

First- and Second-Generation ILs: How Green Are They?

In order to have practical utility there must be definite economic and/or environmental benefits associated with the use of enzymes in ILs. Our original motivation was based on the expectation that it would lead to higher activities, but the rates observed in ILs were at best slightly better than those observed in the best organic solvents such as toluene or *tert*-butanol. Conformational changes of enzymes in IL media might be expected to lead to changes in their selectivity and/or stability, and there have been many reports of enhanced enantioselectivities[14] and remarkable increases in storage and operational stabilities in ILs containing non-coordinating anions.[15] However, a major driver for conducting biocatalysis in ILs is the possibility of replacing volatile, environmentally undesirable organic solvents with nonvolatile and greener ILs. Initial studies were conducted mostly in water-miscible [bmim][BF_4] or water-immiscible [bmim][PF_6], but these anions are not completely stable toward hydrolysis. Hence, other weakly coordinating anions, such as trifluoroacetate, triflate bis-triflamide, and methylsulfate, have been introduced. In the context of biotransformations, we refer to such salts as first-generation ILs (**Figure 1**). The use of simple, less expensive anions such as chloride and acetate is not feasible, because such coordinating anions cause dissolution and accompanying deactivation of the enzymes.

As noted above, the use of ILs was motivated by the possibility of replacing volatile organic solvents with nonvolatile, low flammability ILs, thereby reducing air pollution. However, ILs have significant solubility in water, and first-generation dialkylimidazolium ILs, such as [bmim][BF_4] and [bmim][PF_6], and tetraalkylammonium ILs are poorly biodegradable[16] and exhibit aquatic ecotoxicity.[17] Furthermore, their preparation involves circuitous, high E-factor processes, making them prohibitively

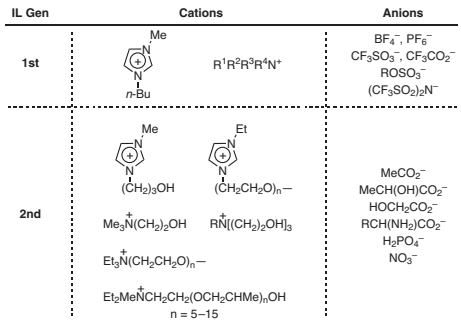


Figure 1. First- and Second-Generation ILs.

expensive.[18] Consequently, second-generation ILs have been developed that contain more biocompatible cations and anions—often derived from relatively inexpensive and more eco-friendly natural products[19] such as carbohydrates[20,21] and amino acids[22,23] (Figure 1). For example, ILs containing the cholinium cation $[HO(CH_2)_2(Me)_3N^+]$, are prepared by reaction of inexpensive choline hydroxide with a (naturally occurring) carboxylic acid affording the corresponding carboxylate salt and water as the only byproduct.[24,25] Similarly, 2-hydroxyethylammonium lactate consists of a cation closely resembling that of the natural cation choline, and a natural, readily biodegradable anion.[26] Indeed, ILs lend themselves to fine-tuning of their properties by appropriate selection of cation and anion, and the current trend is toward the rational design of task-specific ILs that can be employed for particular biotransformations while maintaining a low environmental footprint.

The search for inexpensive ILs that exhibit reduced ecotoxicity and biodegradability and are compatible with enzymes recently led to the use of protic ionic liquids (PILs) as solvents for CALB-catalyzed transesterifcations.[27] PILs are exquisitely simple to prepare by mixing a tertiary amine with an acid, such as a carboxylic acid, and are known[28,29] to exhibit better biodegradability and lower toxicity than the corresponding quaternary ammonium salts. Moreover, they have suitable H-bond donating properties for interaction with, and stabilization of, enzymes, and are self-buffering when combined with alkanoate anions.

Deep Eutectic Solvents (DES's): An Alternative to ILs

In addition to the second-generation ILs, another class of interesting neoteric solvents has emerged in recent years: the so-called deep eutectic solvents (DES's),[30] which are formed by mixing certain solid salts with a hydrogen-bond donor such as urea and glycerol (**Table 1**). For example, combining choline chloride (mp 302 °C) with urea (mp 132 °C) in a 1:2 molar ratio affords a DES that is liquid at room temperature (mp 12 °C). Although DES's are, strictly speaking, not ILs since they contain uncharged moieties, they have properties resembling those of ILs.

Table 1. Deep Eutectic Solvents (DES's)

Salt	H-Bond Donor	Molar Ratio	Result
$[HO(CH_2)_2NMe_3]^+Cl^-$	$(H_2N)_2C{=}O$	1:2	DES
$[HO(CH_2)_2NMe_3]^+Cl^-$	$(HOCH_2)_2CHOH$	1:2	DES
$[HO(CH_2)_2NMe_3]^+Cl^-$	$MeCH(OH)CO_2H$	1:1	DES
$[HO(CH_2)_2NMe_3]^+Cl^-$	$MeCH(OH)CO_2^-$	1:1	IL

Interestingly, many primary metabolites can form DES's, and it is known from NMR-based metabolomics studies[31] that certain relatively simple molecules—some sugars, amino acids, choline, and organic acids (e.g., malic, citric, lactic, and succinic)—are always present in high concentrations in all living cells. This suggests that these molecules serve some basic function in cellular metabolism, and it was shown that various combinations of these molecules can form DES's. This led to the postulation that such natural deep eutectic solvents (NADES) constitute a missing link in understanding cellular metabolism and physiology, and play a role in phenomena such as cryoprotection and drought tolerance. It was further suggested that DES's and ILs formed from primary metabolites may serve as reaction media for the intracellular biosynthesis of sparingly water soluble compounds such as flavonoids and steroids.[32] Indeed, NADES are being touted as solvents for the 21st century.[33] Hydrolases such as CALB[34] and *Penicillium expansum* lipase (PEL)[35] show good catalytic activity in DES's, and choline-based DES's have been used as solvents for lipase-catalyzed biodiesel production.[36]

Maintaining Activity of Enzymes Dissolving in ILs

Hydrophilic ILs containing anions such as chloride, acetate, and nitrate, are able to dissolve polysaccharides and proteins by breaking the intermolecular hydrogen bonds. However, this can lead to inactivation of enzymes by disrupting intramolecular hydrogen bonds that are essential for their activity.[37] There are basically two strategies for maintaining the activity of the enzyme: (i) designing enzyme-compatible ILs, or (ii) modifying the enzyme to make it more resistant to denaturation by the IL. The first example of the former approach was reported by Walker and Bruce,[38] who studied the enzymatic oxidation of codeine catalyzed by the NADP-dependent morphine dehydrogenase. The low solubility of the substrate in both water and common organic solvents led the authors to the idea of using an IL as the reaction medium. To this end, they designed an IL containing a hydroxyl functionality in both the cation and the anion, based on the assumption that the enzyme would be stable in an IL that more closely resembled an aqueous environment. This proved to be the case. An IL consisting of 1-(3-hydroxypropyl)-3-methylimidazolium cation ([hpmim]) and glyoxylate anion ($HOCH_2CO_2^-$) dissolved the substrate, product, enzyme, and cofactor; and the dissolved enzyme was more active, even at a water content of 100 ppm, than as a suspension in other ILs. An example of the second approach is the reported transesterifications catalyzed by suspensions of cross-linked enzyme aggregates ($CLEA^†$) of CALB[39] in ILs that completely deactivated the free enzyme. Similarly, feruloyl esterase CLEAs were active and stable in the enzymatic esterification of glycerol in ILs,[40] and various lipase CLEAs displayed better activities than the corresponding free enzymes in transesterifications,[41,42] including biodiesel production.[43]

Biomass Conversion in ILs and DES's

Water is the first choice of solvent for carbohydrate conversions, but some reactions such as (trans)esterifications cannot be performed in water, and conducting such reactions in common organic solvents is challenging owing to the very low solubility of carbohydrates in these solvents. Polar aprotic solvents; e.g., dimethyl formamide (DMF), dimethyl sulfoxide (DMSO), and pyridine; can be used, but they are environmentally unacceptable and/or are incompatible with enzymes. Consequently, increasing attention has been focused on the design of ILs that can dissolve large amounts of carbohydrates and are suitable as nonaqueous media for biocatalytic reactions of carbohydrates.[44–47] Fatty acid esters of sugars, such as sucrose, are commercially important products with a wide variety of applications in food, cosmetics, and pharmaceutical formulations. In addition to being derived from renewable raw materials, they are tasteless, odorless, nontoxic, non-irritating, biodegradable, and have a hydrophilic–lipophilic balance (HLB) that is tunable by a suitable choice of fatty acid and carbohydrate. They are currently manufactured by chemical processes at elevated temperatures, resulting in low selectivities and the formation of colored impurities. Hence, there is increased interest[48] in enzymatic alternatives that can be conducted under milder conditions with higher selectivities and higher product qualities. Zhao and co-workers[49] have designed a series of ILs consisting of acetate anions and an imidazolium cation containing an oligoethylene glycol side chain, that are both enzyme-compatible and dissolve more than 10 wt % cellulose and up to 80 wt % glucose. Free CALB dissolved in these ILs with retention of activity, thus providing the possibility of conducting homogeneous enzymatic reactions such as the acylation of glucose and the steroid betulinic acid.[50]

The emergence of the bio-based economy that is founded on the use of renewable biomass as raw material, particularly lignocellulose, for the production of biofuels and commodity chemicals, has drawn attention to the utilization of ILs and DES's as reaction media for enzymatic conversions of polysaccharides such as starch,[51] chitin,[52] and cellulose.[53,54] Currently, much attention is focused on the use of ILs and DES's as reaction media for lignocellulose pretreatment[55,56] in combination with enzymatic hydrolysis of the cellulose to fermentable sugars.[57] In order to be economically and ecologically viable, the ILs or DES's should be very inexpensive, efficiently recyclable, and environmentally attractive. What could be better than employing biomass-derived solvents[58] and choline-based ILs and DES's?[59] Choline chloride is a feed additive, and glycerol is a byproduct of biodiesel production, both costing < $1/kg, which leads one to conclude that the DES formed by mixing them in a 1:2 molar ratio would cost $1/kg or less. Similarly, an IL containing a cholinium cation and a lactate anion is likely to be inexpensive and to have a small environmental footprint.

Conclusions and Prospects

In the last decade, considerable research has focused on biocatalysis in ILs. For example, second-generation ILs based on renewable raw materials and protic ionic liquids (PILs) have been developed that are less expensive, more environmentally benign, and more compatible with enzymes. The use of immobilized enzymes in the form of insoluble cross-linked enzyme aggregates (CLEAs) can provide for their efficient separation and reuse. Conducting biotransformations in ILs is particularly beneficial with highly polar substrates, such as carbohydrates, that are sparingly soluble in common organic solvents. Furthermore, the current interest in the production of fuels and platform chemicals from renewable biomass has stimulated interest in the development of biotransformations of polysaccharides in ILs or DES's. In short, we believe that biocatalysis in ILs has much untapped potential to be exploited in industrial-scale applications in the future.

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(†) CLEA is a trademark of CLEA Technologies B.V., registered in the Benelux countries.

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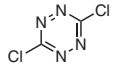

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ABOUT OUR COVER

Detail from ***A Royal Party Admiring the Sunset atop the Hesselberg Mountain***. Photo courtesy National Gallery of Art, Washington, DC.

Johann Georg von Dillis (1759–1841), a German master painter of the late 18th and early 19th centuries, painted and signed ***A Royal Party Admiring the Sunset atop the Hesselberg Mountain*** in 1801. He received his first drawing lessons while attending the Gymnasium in Munich. He then studied art at the Munich Zeichnungsakademie under the guidance of F. I. Oefele and J. J. Dorner the Elder. His art career began ca. 1786 and, until his retirement in the late 1830s, consisted of official appointments by the courts of Maximilian I and Ludwig I, commissioned sketches and drawings, and a professorship of landscape painting at the Munich Royal Academy of Fine Arts. He travelled frequently and widely throughout Europe on Bavarian State business, and it was during these travels that he became acquainted with, and influenced by, the work of P.-H. de Valenciennes, S. Denis, J.-J.-X. Bidauld, W. Allston, and, especially, J. M. W. Turner. His artwork influenced such artists as C. E. F. Blechen, and his gallery work had a profound influence on the world of art in Germany, especially in Bavaria.

Von Dillis excelled at landscapes, and was instrumental in moving the genre from the classical tradition of idealized pastorals to a new, realistic form, whereby the artist draws from life, not only what he perceives with his eyes upon close examination of nature, but also what he feels within himself. This romantic approach to landscape painting values emotions, which are aroused nowhere better than in the countryside with its powerful pull on the artist, as this work demonstrates. Not only is the average person drawn to nature, but even sophisticated, urban dwellers such as this elegantly attired group of royals* and their aides can appreciate the wonders of nature. This composition (watercolor, gouache, and pen and gray ink over graphite on laid paper) measures 37 x 42.7 cm and is von Dillis's best-known work. With its crisp colors, decidedly finished look, and the artist's meticulous attention to detail, it clearly highlights von Dillis's complete immersion in the work.

This painting is part of the Wolfgang Ratjen Collection at the National Gallery of Art, Washington, DC.

** Who could the "royals" depicted in this painting be? To help solve the mystery, visit* ***Aldrich.com/acta482***

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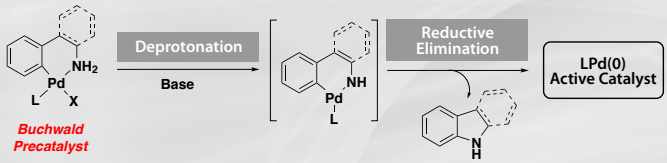

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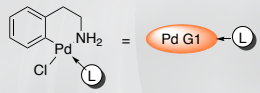

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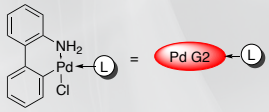

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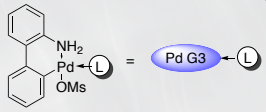

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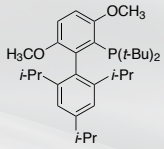

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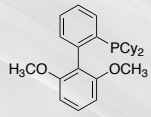

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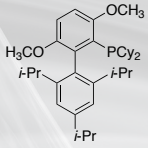

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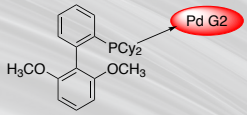

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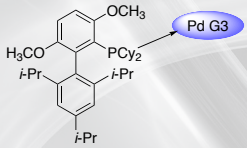

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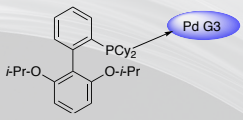

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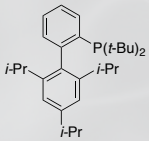

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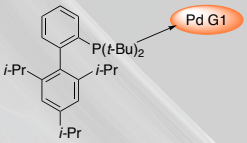

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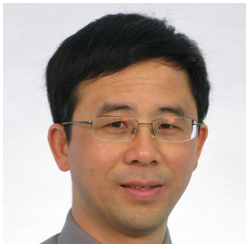

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Abstract. The catalytic asymmetric hydrogenation of racemic α-substituted aldehydes or ketones via dynamic kinetic resolution (DKR) affords a highly efficient method for the preparation of chiral alcohols with one or more stereogenic centers. This review presents and discusses recent advances and applications of this approach.

Outline

1. Introduction

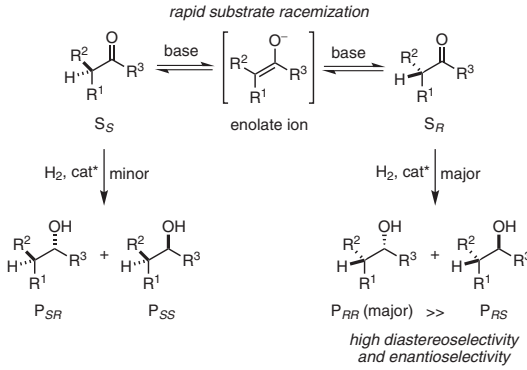
The catalytic asymmetric hydrogenation of α-substituted ketones via dynamic kinetic resolution (DKR) is a highly efficient method for obtaining optically active alcohols with two or more contiguous stereogenic centers in a single operation.[1] This method was first disclosed in 1996 by Noyori and co-workers, who reported the hydrogenation of racemic α-isopropylcyclohexanone with chiral $RuCl_2$[diphosphine]-[diamine] complexes as catalysts.[2] Soon thereafter, Matsumoto et al. applied this approach to the synthesis of the tricyclic β-lactam antibiotic sanfetrinem, highlighting the synthetic utility of the reaction.[3] Nevertheless, the application of the reaction in organic synthesis remained limited because only conformationally rigid substrates such as α-substituted cycloalkanones could provide the corresponding chiral alcohols with high enantioselectivity and diastereoselectivity.[1b] The challenge has been to find catalysts that selectively catalyze the hydrogenation of only one of the two enantiomers of the substrate, which can rapidly racemize via the corresponding enolate ion under the reaction conditions (**Scheme 1**).

We have explored the application of chiral spiro ruthenium complexes as catalysts for the asymmetric hydrogenation of racemic α-substituted aldehydes and ketones via DKR for the purpose of synthesizing optically active chiral alcohols. We found that $RuCl_2$[SDPs]-[diamine] complexes (**Figure 1**)[4] efficiently catalyze the reaction of both conformationally rigid and flexible substrates. This work led to the development of several new methods for the preparation of optically active primary alcohols with one stereocenter[5] and secondary alcohols with two or three contiguous stereocenters.[6] These methods not only provide a practical and environmentally benign route to chiral alcohols, but they also facilitate the enantioselective synthesis of chiral pharmaceuticals and biologically active natural products. This review focuses on recent progress in the enantioselective synthesis of diverse chiral alcohols and their applications in the enantioselective synthesis of chiral pharmaceuticals and natural products.

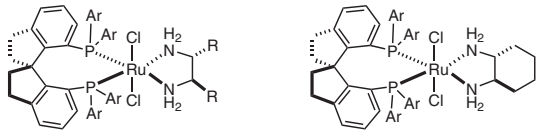
2. Asymmetric Hydrogenation via DKR

2.1. α-Substituted Aldehydes to Chiral Primary Alcohols

Although the catalytic asymmetric hydrogenation of prochiral ketones is a powerful method for the synthesis of chiral secondary alcohols, the asymmetric hydrogenation of racemic α-substituted aldehydes to form chiral primary alcohols had remained a challenge until recently. This has been the case mainly because no new stereogenic center is generated in the hydrogenation of α-substituted aldehydes, which makes enantiocontrol of the reaction extremely difficult. In this respect, the ideal synthesis of chiral primary alcohols would involve asymmetric hydrogenation of racemic α-substituted aldehydes via DKR. In 2007, we reported the first examples of such a reaction catalyzed by chiral spiro ruthenium catalysts.[7] For example, in the presence of $RuCl_2$[(S_a)-DMM-SDP][(*R*,*R*)-DACH] (**2a**, 0.1 mol %) and a base (KO*t*-Bu, 20 mol %) under 50 atm of hydrogen, various racemic α-aryl aldehydes were hydrogenated to chiral primary alcohols with 100% conversion and 78–96% enantiomeric excess (ee) (**eq 1**).[7] Substrates with a bulky α-alkyl group in addition to the α-aryl group gave higher enantioselectivities.



Scheme 1. Asymmetric Hydrogenation of Racemic Ketones and Aldehydes via DKR.



$RuCl_2[(S_a)\text{-SDP}][(R,R)\text{-DPEN}]$ (**1**)

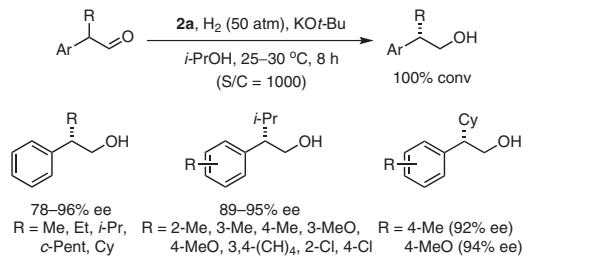
R	Ar	No
H	3,5-Me_2-4-$MeOC_6H_2$ (DMM)	**1a**
Ph	4-Tol (Tol)	**1b**
Ph	Ph	**1c**
Ph	3,5-$Me_2C_6H_3$ (Xyl)	**1d**

$RuCl_2[(S_a)\text{-SDP}][(R,R)\text{-DACH}]$ (**2**)

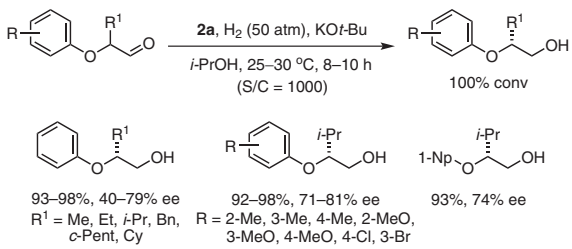
Ar	No
3,5-Me_2-4-$MeOC_6H_2$ (DMM)	**2a**
3,5-$Me_2C_6H_3$ (Xyl)	**2b**

SDP = spiro diphosphine; DPEN = 1,2-diphenylethylenediamine;
DACH = *trans*-1,2-diaminocyclohexane

Figure 1. Chiral Spiro Ruthenium Complexes Employed as Effective Catalysts of the Asymmetric Hydrogenation of Racemic α-Substituted Aldehydes and Ketones via DKR. *(Ref. 4–6)*



eq 1 *(Ref. 7)*



eq 2 *(Ref. 8)*

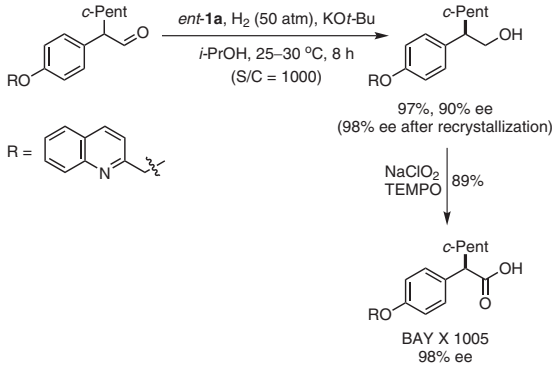
However, the location and the electronic nature of the substituent on the aromatic ring of the substrate has little impact on the enantioselectivity.

With the same catalyst, **2a**, racemic α-aryloxy aldehydes could also be hydrogenated to the corresponding chiral β-aryloxy primary alcohols with moderate-to-good enantioselectivities (**eq 2**).[8] As was the case for α-aryl aldehydes, α-aryloxy aldehydes with a bulky α-alkyl group, such as isopropyl, resulted in higher enantioselectivities.

List[9] and Lin[10] have achieved highly efficient and enantioselective hydrogenations of racemic α-aryl aldehydes to chiral primary alcohols via DKR by employing Noyori BINAP catalysts $RuCl_2[(S_a)$-Xyl-BINAP$][(S,S)$-DACH] and $RuCl_2[(R_a)$-Xyl-BINAP$][(R,R)$-siloxy-DACH]. The chiral primary alcohols produced by this reaction are highly useful for organic synthesis. For example, (*S*)-2-(4-methoxyphenyl)-3-methylbutan-1-ol is a key intermediate in the preparation of (1*S*,4*S*)-*cis*-7-methoxycalamenene,[11] and (*S*)-2-(4-chlorophenyl)-3-methylbutan-1-ol can be easily converted into (*S*)-2-(4-chlorophenyl)-3-methylbutanoic acid, which is a building block for the pyrethroid pesticide (*S*,*S*)-fenvalerate.[12] We have used this reaction to synthesize BAY X 1005, a leukotriene receptor antagonist and a potent inhibitor of lipoxygenase activating protein,[13] in only a few steps (**Scheme 2**).[7]

2.2. Alkyl Ketones with an α-Aryl Substituent to Chiral Secondary Alcohols with Two Stereogenic Centers

The catalytic asymmetric hydrogenation via DKR of racemic alkyl ketones possessing an α-aryl substituent is an efficient method for the synthesis of chiral secondary alcohols with two adjacent stereogenic centers. Because cycloalkanones are more conformationally rigid than acyclic alkanones, the asymmetric hydrogenation of racemic α-aryl cycloalkanones via DKR has received more attention than similar reactions of acyclic ketones. For example, in 2003, Scalone and Waldmeier reported an efficient asymmetric hydrogenation of dibenzylpiperidin-3-one catalyzed by $RuCl_2[(S_a)$-3,5-^{i}Pr-MeOBIPHEP$]$-$[(R,R)$-DPEN]. The reaction afforded chiral *cis*-1,4-dibenzylpiperidin-3-ol with 96% ee and 99% cis-selectivity. These investigators applied this method to the synthesis of Ro 67-8867, an NMDA 2B receptor antagonist that has potential for the treatment of acute ischemic stroke.[14] In 2004, Noyori and co-workers reported the hydrogenation of racemic α-arylcycloalkanones catalyzed by $RuCl_2[(S_a)$-Tol-BINAP$]$-$[(S,S)$-DPEN] to give chiral *cis*-β-arylcycloalkanols with excellent enantioselectivities (up to 99.7% ee) and cis:trans selectivities (≥98:2).[15]



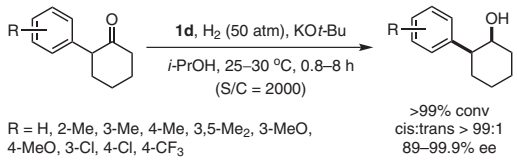
Scheme 2. Application of the Enantioselective Hydrogenation of Racemic α-Aryl Aldehydes via DKR to the Enantioselective Synthesis of BAY X 1005. *(Ref. 7)*

We have also studied the asymmetric hydrogenation of racemic α-arylcyclohexanones for the purpose of developing new strategies for the asymmetric total synthesis of chiral natural products. We found that $RuCl_2[(S_a)$-Xyl-SDP][(*R*,*R*)-DPEN] (**1d**) efficiently catalyzed the asymmetric hydrogenation of racemic α-arylcyclohexanones, yielding *cis*-β-arylcyclohexanols in 89–99.9% ee and cis:trans selectivities of >99:1 (**eq 3**).[16] An electron-donating or withdrawing group at the meta or para position of the benzene ring of the substrate has little influence on the enantioselectivity, but a substrate with an ortho substituent gave lower enantioselectivity. This catalyst could also be used for cycloalkanones possessing a five- or seven-membered ring, although the resulting enantioselectivities were lower.

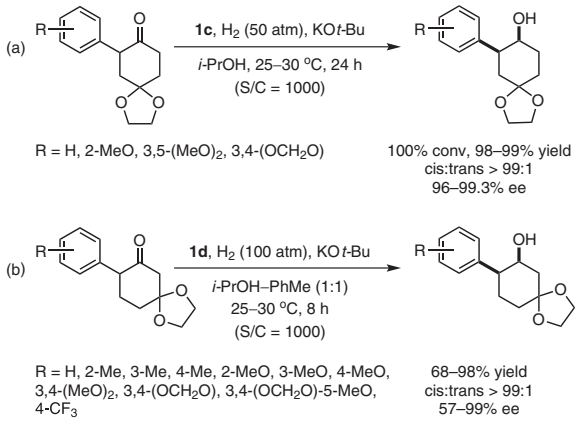
These results encouraged us to study the asymmetric hydrogenation of racemic α-arylcyclohexanones with a bulky ethylene ketal group attached to the cyclohexanone ring. The ketal-functionalized chiral β-arylcyclohexanols that would result are potential chiral building blocks for the synthesis of bioactive natural products and chiral drugs. The hydrogenation proceeded well in the presence of $RuCl_2[(S_a)$-SDP][(*R*,*R*)-DPEN] (**1c**) as catalyst, and led to the corresponding chiral *cis*-β-arylcyclohexanols in excellent yields and up to 99.3% ee (**Scheme 3**, Part (a)).[17] One exception was the cyclohexanone with a 2,6-dimethoxyphenyl substituent at C2, which gave only 5% conversion. In contrast, substrates with the ketal group at the 5 position gave nearly quantitative yields of 3-isopropoxy-2-cyclohexenones instead of the desired products. However, after careful optimization of the reaction conditions, we found that these base-sensitive α-arylcyclohexanones could be catalytically hydrogenated with $RuCl_2[(S_a)$-Xyl-SDP][(*R*,*R*)-DPEN] (**1d**) (in a 1:1 (v/v) mixture of isopropanol and toluene under 100 atm of H_2) to afford chiral *cis*-β-arylcyclohexanols in good-to-excellent yields (68–98%), high enantioselectivities (up to 99% ee), and very high cis:trans selectivities (>99:1) (Scheme 3, Part (b)).[18]

The asymmetric hydrogenation of racemic α-arylcyclohexanones via DKR is a highly efficient method for the construction of chiral, aryl-substituted cyclohexane motifs, and has been applied to the asymmetric total syntheses of various natural products and pharmaceuticals (**Scheme 4**). For example, the cannabinoids (–)-Δ^8-THC and (–)-Δ^9-THC, isolated from *Cannabis sativa* L.,[19] share a chiral hexahydro-6,6-dimethyl-6*H*-benzo[*c*]chromene motif, which can be constructed by the catalytic asymmetric hydrogenation of racemic 7-aryl-1,4-dioxaspiro[4.5]decan-8-one and subsequent intramolecular S_NAr cyclization. We have synthesized these two aromatic terpenoids in 35% and 30% overall yields in 13 and 14 steps, respectively, from commercially available starting materials.[20] Similarly, (–)-CP-55940, a potent nonselective cannabinoid (CB) receptor agonist for human recombinant CB1 and CB2 receptors,[21] has been synthesized in 14% yield over 14 steps.[17] Furthermore, by employing the product of the hydrogenation of racemic 8-aryl-1,4-dioxaspiro[4.5]decan-7-one as a key chiral intermediate, we have synthesized (–)-α-lycorane, a pentacyclic alkaloid isolated from plants of the amaryllidaceae family, in 19.6% yield over 13 steps from commercially available 1,4-dioxaspiro[4.5]decan-7-one.[18]

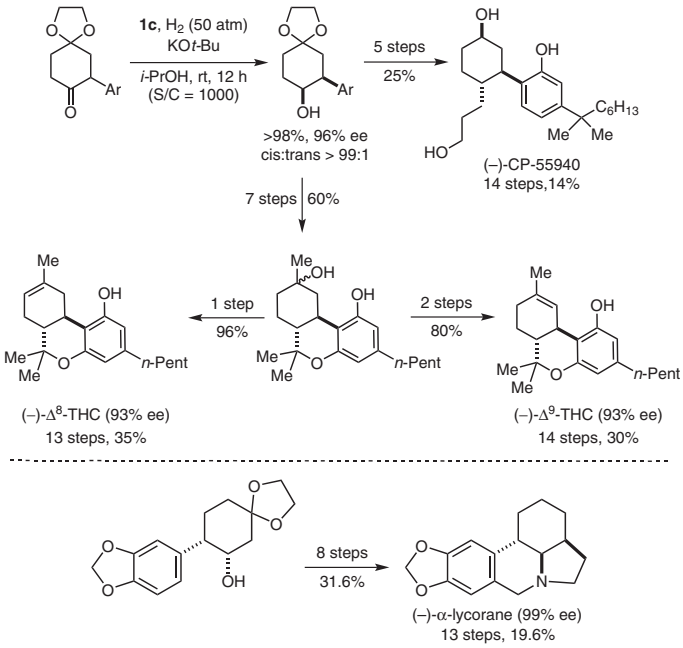
Chiral 1-alkyl-1-aryl-2-propanols are important building blocks for the preparation of chiral drugs. In 2007, Chen and co-workers reported that chiral $RuCl_2$[diphosphine][diamine] complexes efficiently catalyze the hydrogenation of racemic 1-alkyl-1-aryl-2-propanones via DKR to afford chiral alcohols.[22] For example, the asymmetric hydrogenation of racemic 3-(3-bromophenyl)-4-(4-chlorophenyl)-2-butanone catalyzed by $RuCl_2[(S_a)$-Xyl-BINAP][(*S*)-DAIPEN] (DAIPEN = 1-isopropyl-2,2-bis(4-methoxyphenyl)ethylenediamine) yielded the corresponding chiral alcohol with 95% ee but with lower diastereoselectivity



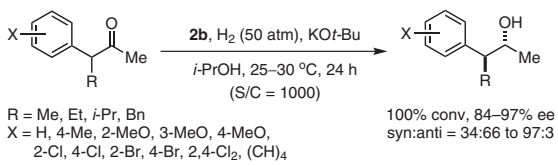
eq 3 *(Ref. 16)*



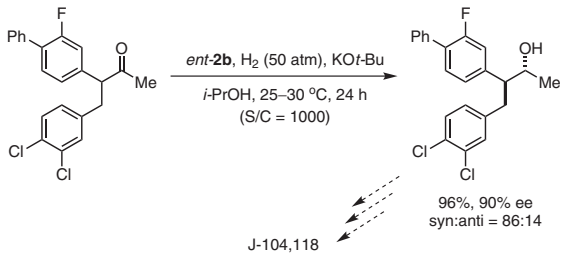
Scheme 3. Enantioselective Hydrogenation of Racemic 7-Aryl-1,4-dioxaspiro[4.5]decan-8-ones and 8-Aryl-1,4-dioxaspiro[4.5]decan-7-ones. *(Ref. 17,18)*



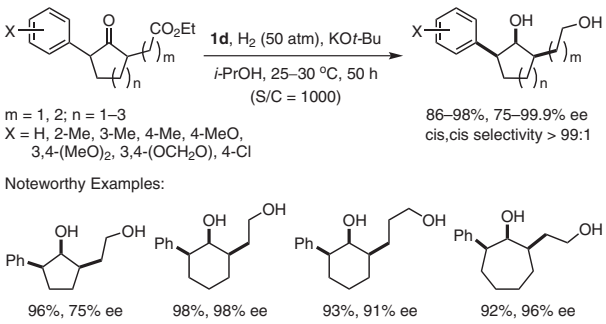
Scheme 4. Application of the Catalytic Asymmetric Hydrogenation of α-Substituted Ketones to the Enantioselective Synthesis of (–)-CP-55940, (–)-Δ^8-THC, (–)-Δ^9-THC, and (–)-α-Lycorane. *(Ref. 17,18,20)*



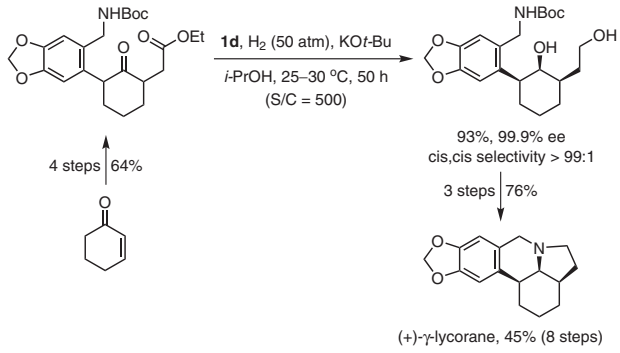
eq 4 *(Ref. 24)*



Scheme 5. Enantioselective Synthesis of Key Intermediate in the Synthesis of Squalene Synthase Inhibitor J-104,118. *(Ref. 24)*



eq 5 *(Ref. 6)*



Scheme 6. Enantioselective Synthesis of the Amaryllidaceae Alkaloid (+)-γ-Lycorane. *(Ref. 6)*

(syn:anti = 8:1). Higher diastereoselectivity (syn:anti up to 23:1) could be achieved with $RuCl_2[(R_a)$-Xyl-PhanePhos][(*S,S*)-DPEN] (Xyl-PhanePhos = 4,12-bis(di-3,5-xylylphosphino)[2.2]paracyclophane), but the enantioselectivity was lower (88% ee). Although this method has been employed in the synthesis of MK-0346, an oral inverse agonist for the CB1 receptor,[23] the asymmetric hydrogenation of conformationally flexible, racemic, and acyclic α-substituted dialkyl ketones via DKR has remained a challenge.

We have investigated the use of $RuCl_2$[SDP][diamine] catalysts for the asymmetric hydrogenation of conformationally flexible racemic dialkyl ketones via DKR.[24] After careful evaluation of various catalysts, $RuCl_2[(S_a)$-Xyl-SDP][(*R,R*)-DACH] (**2b**) was found to be the best choice for the hydrogenation of racemic 1-alkyl-1-aryl-2-propanones via DKR, producing chiral 1-alkyl-1-aryl-2-propanols in high yields, good-to-excellent enantioselectivities (84–97% ee), and diastereoselectivities (syn:anti up to 97:3) (**eq 4**).[24] The α-alkyl group strongly influenced the enantioselectivity and diastereoselectivity: higher enantioselectivities and diastereoselectivities were obtained with α-benzyl ketones. The electronic nature of the substituent on the phenyl ring had no obvious effect on either the enantioselectivity or the diastereoselectivity. However, benzylic substrates with ortho substituents on the phenyl ring gave relatively higher enantioselectivity and diastereoselectivity.

The asymmetric hydrogenation of a fluorinated racemic α-benzyl 1-aryl-2-propanone catalyzed by $RuCl_2[(R_a)$-Xyl-SDP][(*S,S*)-DACH] (*ent*-**2b**) was utilized to prepare a key intermediate in the synthesis of squalene synthase inhibitor J-104,118[25] (**Scheme 5**).[24]

Many natural products, such as γ-lycorane,[26] hexahydroapoerysopine,[27] and lycorine-type alkaloids,[28] contain a cyclic alcohol featuring three contiguous stereocenters. The asymmetric hydrogenation of racemic α,α'-disubstituted ketones via DKR offers a potential synthetic approach to this unit. However, since these ketones have four stereoisomers, controlling the enantio- and diastereoselectivity of their hydrogenation is extremely difficult. To address this challenge, we have investigated the asymmetric hydrogenation of racemic cycloalkanones containing an α-alkoxycarbonylmethyl or ethyl group and an α-aryl group. Fortunately, $RuCl_2$[SDP][diamine] complexes efficiently catalyzed the hydrogenation of these substrates, with $RuCl_2[(S_a)$-Xyl-SDP][(*R,R*)-DPEN] (**1d**) leading to the desired product from racemic 2-ethoxycarbonylmethyl-6-phenylcyclohexanone with 98% ee and >99:1 cis,cis selectivity. Interestingly, the ester group in the substrate was hydrogenated to the corresponding alcohol at room temperature during the reaction. Various α-ethoxycarbonylalkyl-α′-arylcycloalkanones were hydrogenated with this catalyst in high yields (86–98%) and with good-to-excellent enantioselectivities (75–99.9% ee) (**eq 5**).[6] Both the side-chain ester group and the aryl group of the substrate were necessary for high enantioselectivity; changing the ester group to an alkyl group led to lower enantioselectivities (Me, 73% ee; Bn, 27% ee). Good-to-high enantioselectivities were also observed when the ester group was replaced with the *N,N*-dimethylaminocarbonyl group ($CONMe_2$, 92% ee), the *N*-benzylaminocarbonyl group (CONHBn, 79% ee), or the benzyloxymethyl group ($BnOCH_2$, 84% ee).

Using this highly efficient method for constructing a cyclic alcohol with three contiguous stereocenters, we synthesized the amaryllidaceae alkaloid (+)-γ-lycorane in 45% overall yield from commercially available 2-cyclohexenone in 8 steps (**Scheme 6**).[6]

Chung et al. recently employed the asymmetric hydrogenation via DKR of racemic 1,2-diaryl-1-pentanone—using $RuCl_2[(S_a)$-Xyl-SEGPHOS®][*S*)-DAIPEN] (Xyl-SEGPHOS® = 5,5′-bis(di-3,5-xylylphosphino)-4,4′-bi-1,3-benzodioxole) as catalyst (0.02 mol %)—

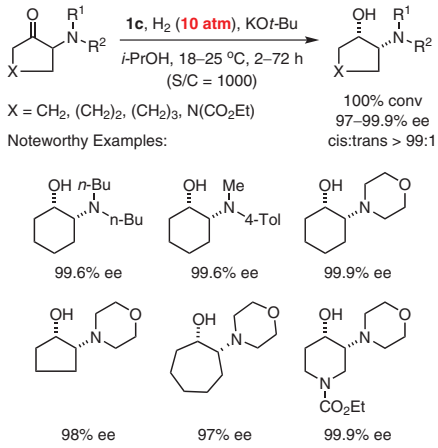
in the synthesis of a glucagon receptor antagonist on a kilogram scale (110 kg) with 98.5% ee and 99% syn-selectivity.[29]

2.3. α-Aminoalkanones to Chiral 1,2-Amino Alcohols

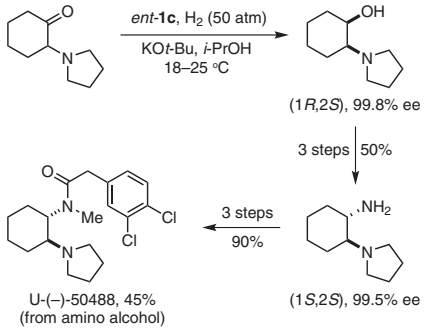
Chiral 1,2-amino alcohols are present in various natural products and are a key functional group in biologically active molecules; optically pure amino alcohols have also been employed as chiral ligands and auxiliaries in asymmetric synthesis.[30] Noyori and co-workers reported in 2000 the first example of the asymmetric hydrogenation via DKR of racemic α-amino ketones, specifically 2-(*tert*-butoxycarbonylamino)-cyclohexanones, to chiral 1,2-amino alcohols with two stereogenic centers; the reaction, however, was only moderately enantioselective (82% ee).[31] In 2007, we reported that $RuCl_2[(S_a)$-SDP][(*R*,*R*)-DPEN] (**1c**) efficiently catalyzed the hydrogenation of racemic *N*,*N*-disubstituted α-aminocycloalkanones to the corresponding chiral *cis*-β-aminocycloalkanols in 97–99.9% ee, >99:1 cis:trans selectivity, and with turnover numbers of up to 30,000 (**eq 6**).[32] The reaction was highly tolerant of substituents on the dialkylamino group with respect to enantioselectivity and diastereoselectivity, whereas the reaction rate was sensitive to the nature of the dialkylamino group. Substrates with benzyl- or aryl-substituted amino groups required longer reaction times or higher hydrogenation pressures for complete reaction. The enantioselectivity of the reaction was slightly lower for substrates with a five- or seven-membered ring. An aza analogue of α-dialkylaminocyclohexanone underwent the hydrogenation reaction with excellent enantioselectivity (99.9% ee) and cis:trans selectivity (>99:1).[32]

An advanced intermediate for the synthesis of U-(−)-50488, a highly selective κ-opioid agonist,[33] was synthesized by this method (**Scheme 7**).[32] Asymmetric hydrogenation of 2-(pyrrolidin-1-yl)-cyclohexanone led to the corresponding (1*R*,2*S*) amino alcohol in 99.8% ee. Mesylation of the hydroxyl group, followed by treatment with NaN_3 and Pd/C-catalyzed hydrogenation led to chiral *trans*-2-(pyrrolidin-1-yl)cyclohexanamine in 99.5% ee. This result suggests that substitution of the mesyl group occurred by a mechanism that did not involve the formation of an aziridinium intermediate,[34] with the cis relationship between the pyrrolidino and mesyl groups being unfavorable for the formation of an aziridinium ion. The chiral *trans*-1,2-diamine was transformed into U-(−)-50488 in 90% yield over three steps.

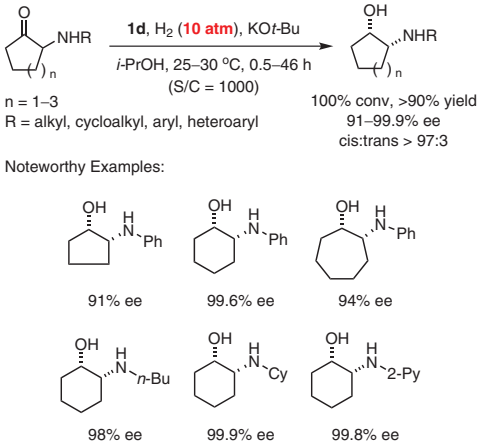
$RuCl_2[(S_a)$-Xyl-SDP][(*R*,*R*)-DPEN] (**1d**) was the best catalyst for the asymmetric hydrogenation of racemic α-aminocycloalkanones with a secondary amino group, providing a series of chiral β-*N*-alkylamino- and β-*N*-arylaminocycloalkanols with 91–99.9% ee and >97:3 cis:trans diastereoselectivities (**eq 7**).[35] The enantioselectivity and diastereoselectivity of the reaction were unaffected by the nature of the substituent on the *N*-phenyl ring of the substrate. However, owing to their low solubility in 2-propanol, substrates with a *para*-bromo atom or an *ortho*-methoxy group on the *N*-phenyl ring required longer reaction times to undergo complete hydrogenation. Substrates with an *N*-alkylamino group also underwent the reaction with excellent enantioselectivities (98–99.9% ee) and cis:trans diastereoselectivities (>98:2). α-Aminocyclopentanones and α-aminocycloheptanones were also hydrogenated to the desired chiral *cis*-β-(*N*-arylamino)-cycloalkanols with high enantioselectivities (91% and 94% ee, respectively) and high diastereoselectivities (cis:trans = 98:2 and 99:1, respectively). These results demonstrate that the rigidity and steric bulk of the spiro diphosphine ligand could be preventing coordination of the NH group of the substrates and products with the metal of the catalyst. Such coordination has previously been reported to be the major reason for catalyst deactivation.[36]



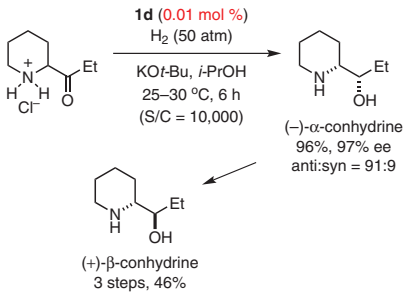
eq 6 *(Ref. 32)*



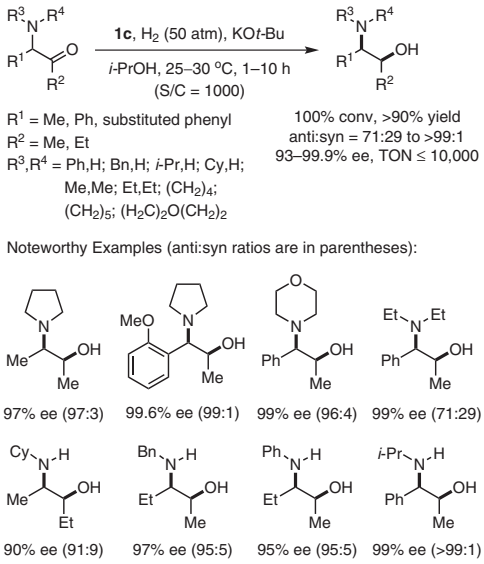
Scheme 7. Enantioselective Synthesis of U-(–)-50488, a Highly Selective κ-Opioid Agonist. *(Ref. 32)*



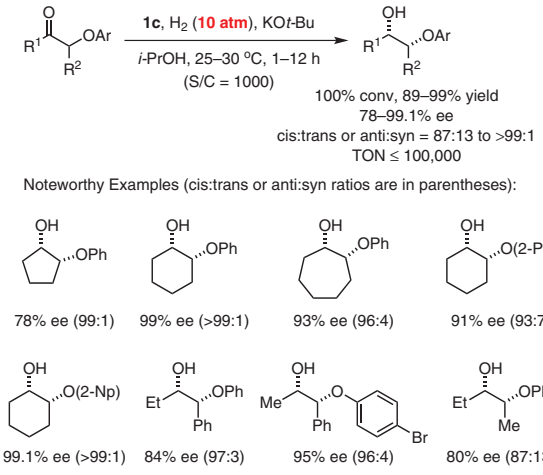
eq 7 *(Ref. 35)*



Scheme 8. Enantioselective Synthesis of the Alkaloids (–)-α- and (+)-β-Conhydrines. *(Ref. 35)*



Scheme 9. Asymmetric Hydrogenation of Racemic, Acyclic α-*N*-Alkylamino- and α-*N*-Arylaminoalkanones. *(Ref. 38)*



eq 8 *(Ref. 43)*

With $RuCl_2[(S_a)$-Xyl-SDP][(*R*,*R*)-DPEN] (**1d**) as catalyst, 1-(piperidinyl)-1-propanone was hydrogenated—in 96% yield, 97% ee, and 91:9 anti:syn selectivity at a remarkable catalyst loading of only 0.01 mol % and TON = 10,000—to the chiral amino alcohol *anti*-1-(piperidinyl)-1-propanol,[35] also known as (–)-α-conhydrine, which is an alkaloid isolated from the seeds and leaves of hemlock (*Conium maculatum L.*).[37] Treatment of optically active (–)-α-conhydrine with sulfuryl chloride (SO_2Cl_2) afforded a cyclic sulfate, which underwent ring-opening acetylation with NaOAc; subsequent hydrolysis with K_2CO_3 in MeOH gave (+)-β-conhydrine in 46% overall yield (**Scheme 8**).[35]

Conformationally flexible substrates, such as racemic acyclic a-substituted aliphatic ketones, are more difficult to hydrogenate enantioselectively and diastereoselectively. In an investigation of the asymmetric hydrogenation of conformationally flexible, acyclic aliphatic α-*N*,*N*-dialkylamino ketones, we found that $RuCl_2[(S_a)$-SDP][(*R*,*R*)-DPEN] (**1c**) was an efficient catalyst, affording the corresponding chiral amino alcohols with 93–99.9% ee and 71:29 to >99:1 anti:syn selectivities (**Scheme 9**).[38] The α-dialkylamino group of the substrates strongly influenced the diastereoselectivity of the reaction: Generally, ketones with a small dialkylamino group, such as dimethylamino or pyrrolidino, provided high diastereoselectivities. However, when the bulkier diethylamino group was present, the diastereoselectivity decreased. It is worth noting that the catalyst loading for this hydrogenation reaction could be lowered to 0.01 mol % without an obvious decrease in enantioselectivity or diastereoselectivity. The related α-amino ketones with a secondary amino group afforded the corresponding chiral β-amino alcohols with high enantioselectivities (90-99% ee) and high anti:syn selectivities (91:9 to >99:1) (Scheme 9).[38]

Ohkuma and co-workers reported that $RuCl_2[(S_a)$-Tol-BINAP]-[(*R*)-DMAPEN] (DMAPEN = *N*,*N*′-dimethyl-2-phenylethane-1,2-diamine) catalyzed the hydrogenation of racemic 2-amino-1-phenyl-1-propanone to the corresponding chiral 1,2-amino alcohol, which is an intermediate in the synthesis of the widely used nasal decongestant pseudoephedrine,[39] as well as a useful chiral auxiliary in synthetic organic chemistry.[40] High enantioselectivity and high syn-selectivity were obtained under the optimal reaction conditions. Itsuno and co-workers achieved excellent enantioselectivity and syn-selectivity in the hydrogenation of 2-(*N*-benzoyl-*N*-methylamino)propiophenone by employing polymer-immobilized $RuCl_2[(R_a)$-BINAP][(*S*,*S*)-DPEN], and the catalyst could be recycled five times without any loss in enantioselectivity.[41] Hibino et al. reported that nickel complexes with chiral diphosphine ligands catalyzed the asymmetric hydrogenation of racemic aromatic α-amino ketones, although a high catalyst loading (10 mol %) and high hydrogen pressure (100 atm H_2) were required.[42]

2.4. α-Aryloxyalkanones to β-Aryloxy Alcohols

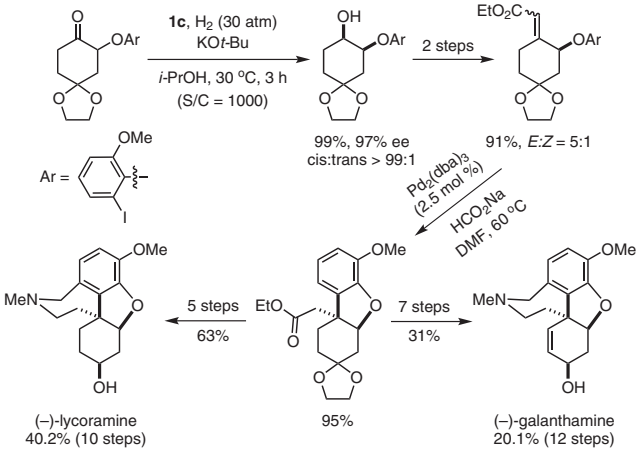
Chiral β-aryloxy alcohols are common structural units in pharmaceuticals and bioactive natural products. We have developed a highly efficient method for the preparation of optically active secondary β-aryloxy alcohols with two adjacent stereocenters that relies on the asymmetric hydrogenation of racemic, aliphatic α-aryloxy ketones via DKR in the presence of $RuCl_2[(S_a)$-SDP][(*R*,*R*)-DPEN] (**1c**) (**eq 8**).[43] Conformationally rigid substrates, such as racemic cyclic α-aryloxy ketones, gave higher enantioselectivities (>91% ee) and higher cis:trans selectivities (>93:7), except for cyclopentanones (78% ee, cis:trans = 99:1). Good-to-high enantioselectivities (80–96% ee) and anti:syn selectivities (87:13 to 98:2) were achieved with conformationally flexible acyclic α-aryloxy ketones. The catalyst

was highly efficient with TONs of up to 100,000. This reaction has been employed to prepare the key intermediate in the synthesis of nonsteroidal glucocorticoid modulators.[44]

The alkaloid (–)-galanthamine,[45] which has been employed in the early treatment of Alzheimer's disease, contains a unique tricyclic tetrahydrodibenzofuran core structure and a chiral arylated quaternary carbon center. Encouraged by our successful synthesis of chiral β-aryloxy alcohols, we developed a new strategy for the total synthesis of (–)-galanthamine by employing the asymmetric hydrogenation of an α-aryloxycyclohexanone as a key step (**Scheme 10**).[46] In the presence of $RuCl_2$[(S_a)-SDP][(*R*,*R*)-DPEN] (**1c**), the hydrogenation yielded the corresponding chiral β-aryloxycyclohexanol in high yield (99%) and with excellent enantioselectivity (97% ee) and cis:trans selectivity (>99:1). The hydrogenation product was converted into (–)-galanthamine in 20% yield over 12 steps, including a Pd-catalyzed intramolecular reductive Heck cyclization to install the chiral arylated quaternary carbon center. Employing the same strategy, (–)-lycoramine,[47] an acetylcholinesterase inhibitor and an allosteric potentiating ligand, was synthesized in 10 steps with a 40% overall yield.[46]

3. Summary and Outlook

Our ongoing search for efficient methods to prepare chiral alcohols for the eventual synthesis of natural products and chiral pharmaceuticals, has led us to investigate the ruthenium-catalyzed asymmetric hydrogenation via DKR of racemic α-substituted alkanones and aldehydes. Racemic α-aryl and α-aryloxy aldehydes; α-aryl, aryloxy, and aminoalkanones; and α,α′-disubstituted alkanones were hydrogenated to the corresponding chiral primary and secondary alcohols with excellent enantioselectivities and diastereoselectivities by employing chiral spiro ruthenium complexes as catalysts. These highly efficient methods were successfully utilized to synthesize chiral pharmaceuticals and natural products. Perhaps most importantly, we have demonstrated that the catalytic asymmetric hydrogenation of racemic α-substituted alkanones and aldehydes via DKR is a promising method for the preparation of diverse chiral alcohols possessing one, two, or even three stereogenic centers. Moreover, we have shown that natural products can inspire the design and development of new reactions, such as the catalytic asymmetric hydrogenation of racemic aldehydes and ketones via DKR. Efficient synthetic methods are still lacking for many bioactive molecules, in particular, complex natural products. We plan to continue to develop highly efficient methods for the synthesis of diverse chiral alcohols with the goal of offering new approaches for the synthesis of pharmaceuticals and natural products.



Scheme 10. Enantioselective Synthesis of (–)-Galanthamine and (–)-Lycoramine. *(Ref. 46)*

4. Acknowledgments

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Jian-Hua Xie was born in 1968. He received his Ph.D. degree in 2003 under the supervision of Professor Qi-Lin Zhou at the Institute of Elemento-organic Chemistry, Nankai University. He then worked in the same institute, and was promoted to Associate Professor in 2005 and to Full Professor in 2010. In 2007, he spent one year as a postdoctoral fellow in Prof. Michael Doyle's group at Maryland University. His research interests focus on asymmetric catalysis and the asymmetric synthesis of natural products and chiral drugs.

Qi-Lin Zhou obtained his Ph.D. degree in 1987 from the Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences. After several years of postdoctoral research (with Professors Klaus Müllen, Andreas Pfaltz, and Michael Doyle), he started his independent research in 1996 at East China University of Science and Technology, Shanghai, China. In 1999, he moved to the Institute of Elemento-Organic Chemistry, Nankai University, as Cheung Kong Scholar. His research interests include organometallics, synthetic methodology, and asymmetric catalysis.

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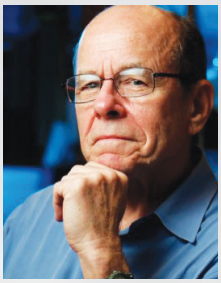

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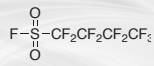

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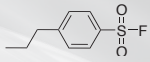

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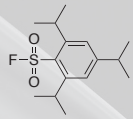

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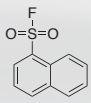

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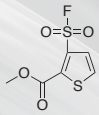

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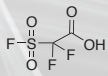

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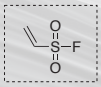

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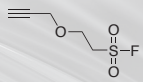

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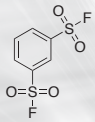

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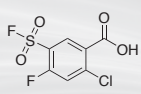

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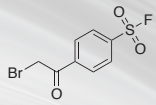

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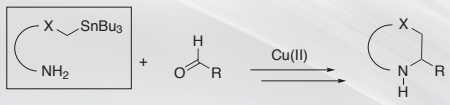
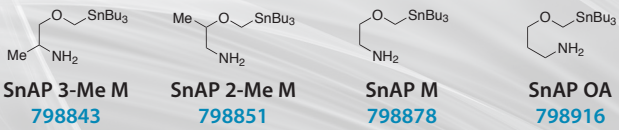
Left to right: Mr. Michael U. Luescher, Dr. Paula L. Nichols, Professor Dr. Jeffrey W. Bode, and Dr. Kimberly Geoghegan



SnAP Reagent | Aldehyde | Saturated N-Heterocycle

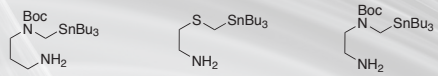


SnAP 3-Me M 798843

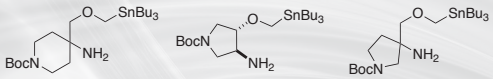
SnAP 2-Me M 798851

SnAP M 798878

SnAP OA 798916



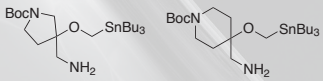
SnAP DA† **SnAP TM**† **SnAP Pip**†



SnAP 3-Spiro-(4-Pip) M†

SnAP 2,3-Bicyclo-(3,4-Pyr) M†

SnAP 3-Spiro-(3-Pyr) M†



SnAP 2-Spiro-(3-Pyr) M†

SnAP 2-Spiro-(4-Pip) M†

† Available soon

References:

(1) Vo, C.-V. T.; Luescher, M. U.; Bode, J. W. *Nat. Chem.* **2014,** *6,* 310.
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SnAP Reagents for a Cross-Coupling Approach to the One-Step Synthesis of Saturated N-Heterocycles


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Dr. P. L. Nichols


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Keywords. SnAP reagents; saturated N-heterocycle synthesis; cross-coupling methodology; medium-size rings.

Abstract. Saturated N-heterocycles can be found with increasing frequency in bioactive molecules, despite their limited commercial availability and challenging synthetic routes. A direct extension of aromatic cross-coupling methods to include saturated N-heterocycles remains elusive. However, the coupling of commercially available, or easily accessible, SnAP reagents with a wide range of aldehydes and ketones offers an alternative, practical, and versatile approach to saturated N-heterocycles.

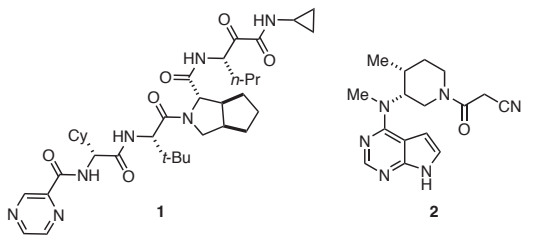
Outline

1. Introduction

Following the extraordinary success of metal-catalyzed cross-coupling reactions in organic chemistry over the last few decades, the number of easily appended aromatic groups in bioactive molecules has increased dramatically. However, a high aromatic-ring count often leads to development-limiting problems associated with poor solubility, pharmacokinetics, and bioavailability.[1] Such issues are now well recognized, and much effort has been directed toward reducing the number of aromatic rings by incorporating alternative groups such as saturated N-heterocycles (**Figure 1**). The incorporation of saturated N-heterocycles introduces solubilizing features, such as ionizable moieties, and a greater diversity of shapes, including chiral elements. It also allows the biological relevance of larger ring systems to be explored, while maintaining a greater degree of control over the overall physicochemical properties of the molecule.

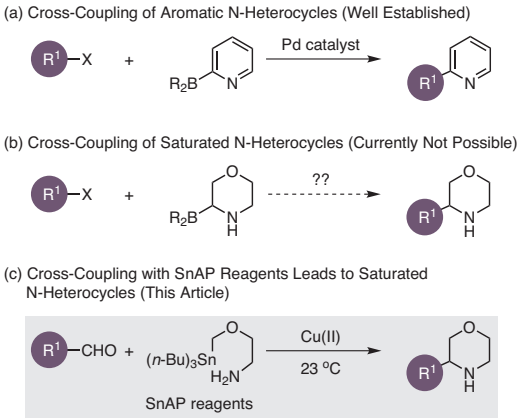
Despite the growing importance of such saturated N-heterocyclic motifs in drug discovery, their installation has been challenging due to poor commercial availability of precursors and the often long and laborious synthetic routes needed to form these ring systems. This stands in contrast to the impressive repertoire of methods for the facile and predictable introduction of N-heteroaromatics, as exemplified by the palladium-catalyzed cross-coupling of stable, and often commercially available, aromatic halides with boronic acids and derivatives (**Scheme 1**, Part (a)).

Unfortunately, a direct extension of the metal-catalyzed cross-coupling to saturated N-heterocycles has been elusive (Scheme 1, Part (b)). Recent efforts to address this well-known limitation have provided promising new methodologies for the derivatization of simple N-heterocycles; but these methods still have considerable shortcomings, including harsh reactions conditions, restricted substrate scope, and intractable N-protecting groups.[2]

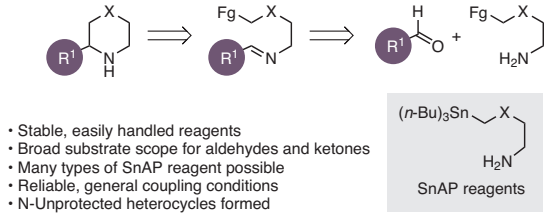


No	Generic Name	Trade Name(s)	FDA Approval	For Treating
1	Telaprevir	Incivek®, Incivo®	2011	Hepatitis C
2	Tofacitinib	Xeljanz®	2012	Rheumatoid arthritis
3	Alogliptin	Nesina®	2013	Type 2 diabetes
4	Suvorexant	Belsomra®	2014	Insomnia

Figure 1. Bioactive Molecules Incorporating Saturated N-Heterocycles.



Scheme 1. Employing the Metal-Catalyzed Cross-Coupling Reaction in the Formation of Saturated N-Heterocycles.



Scheme 2. Genesis of the SnAP Reagent Concept. *(Ref. 3)*

As an alternative to traditional cross-coupling approaches, our group has recently introduced "**SnAP**" [**Sn (tin) Amine Protocol**] as a versatile, predictable methodology for the synthesis of saturated N-heterocycles from widely available aromatic, heteroaromatic, aliphatic, and glyoxylic aldehydes (Scheme 1, Part (c).[3–7] This review will highlight how, since the first report on SnAP reagents in 2013,[3] an increasing number of readily accessible reagents are now available for the convenient synthesis of medium-ring (six- to nine-membered) saturated N-heterocycles. Many of the SnAP reagents are now commercially available, and custom-made reagents for specific applications or targets can be prepared from simple starting materials.

2. SnAP Reagents for N-Heterocycle Synthesis

2.1. Development of SnAP Reagents

Our development of SnAP reagents for the synthesis of N-heterocycles relied on our recognition that an aldehyde could serve as a readily introduced and identified functional group for cross-coupling and as the source of one of the carbon atoms in the ring (**Scheme 2**).[3] This approach would allow coupling of the two starting materials to take place via imine formation—a generally facile and chemoselective process—which is followed by intramolecular cyclization. After considerable experimentation, we identified tin-based reagents as ideal reaction partners in terms of ease of use, substrate scope, and the preparation and stability of the reagents.

Following our first report on SnAP reagents for the preparation of thiomorpholines,[3] we have extended the line of SnAP reagents to include ones suitable for the synthesis of morpholines and piperazines,[4a] a variety of bi- and spirocycles,[5,6] and other medium-size rings.[7] These reagents are easy-to-handle, air- and moisture-stable liquids, and can be synthesized on a multigram scale by employing a straightforward synthetic sequence (**Figure 2**).

Widely available aliphatic, aromatic, and heteroaromatic aldehydes and cyclic ketones are converted into various N-heterocycles using an operationally simple and general reaction protocol (**eq 1**). This process has outstanding substrate scope and functional-group tolerance, and displays an easily recognizable retrosynthetic disconnection. It offers the unprecedented advantage of delivering N-unprotected products directly, which obviates the need to cleave the often difficult-to-remove aryl or benzylic protecting groups that are utilized in traditional C–H functionalization approaches to substituted N-heterocycles.

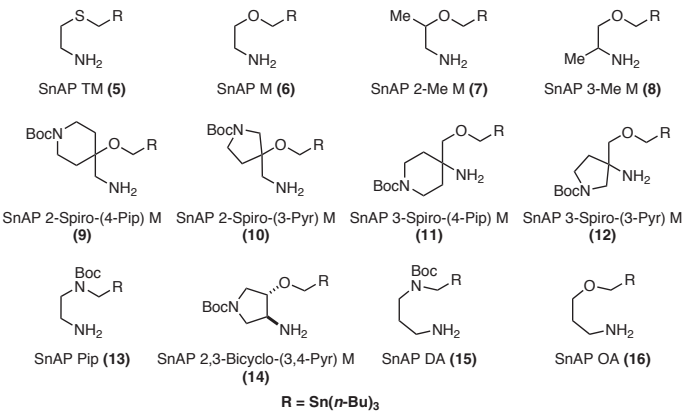


Figure 2. Commercially Available SnAP Reagents for the Synthesis of Unprotected, Saturated N-Heterocycles from Aldehydes and Ketones. *(Ref. 3–7)*

2.2. Synthesis of SnAP Reagents

The easily handled, air- and moisture-stable SnAP reagents can be stored neat at –10 °C for months without notable decomposition. They can be prepared on a multigram scale from inexpensive starting materials by straightforward and efficient routes. Tributyl(iodomethyl)-stannane [$(n\text{-Bu})_3SnCH_2I$; can be stored neat at –10 °C for 1–2 weeks, but decomposes slowly at room temperature] is commercially available or can be synthesized from cheap starting materials in 50–100 g batches in two steps, with only one purification needed.[4a,7]

2.2.1. Morpholine and Thiomorpholine SnAP Reagents and Analogues

Morpholines and thiomorpholines are prepared from amino alcohols and amino thiols, respectively.[3,4a] In general, all amino thiols and amino alcohols with a substituent in the α position to the nitrogen are S- or O-alkylated with tributyl(iodomethyl)stannane in a simple, one-step reaction to afford the desired SnAP reagents.

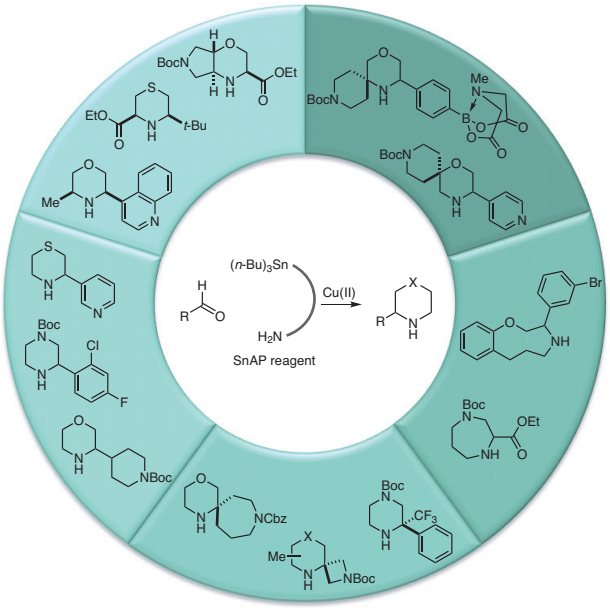
SnAP reagents for morpholines and their medium-size analogues without a substituent in the α position to the amine functionality, or no substituents at all in the backbone, are synthesized in a three-step, two-pot procedure involving protection, O-alkylation, and deprotection steps (**Scheme 3**).[4a,7]

2.2.2. Piperazine SnAP Reagents and Analogues

Piperazine SnAP reagents and their medium-size-ring analogues are synthesized starting either from the amino alcohols or the diamines, depending on the desired substitution pattern on the backbone of the requisite SnAP reagent (**Scheme 4**).[4a,7]

3. Applications of SnAP Reagents

SnAP reagents can be utilized in a simple and effective protocol to prepare a diverse range of saturated, substituted N-heterocycles as exemplified in **Scheme 5**.[4]



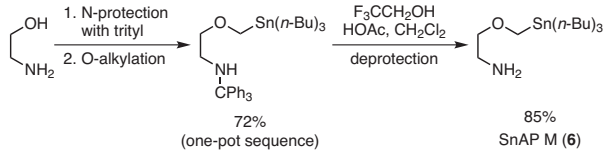
Unprotected, Saturated N-Heterocycles from Aldehydes and Ketones through the Use of Commercially Available SnAP Reagents

eq 1 *(Ref. 3–7)*

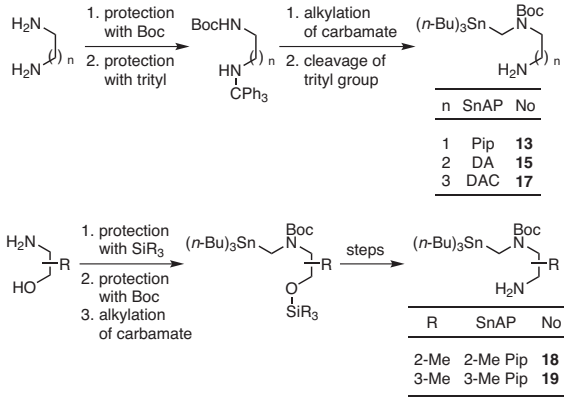
3.1. Synthesis of Six-Membered Rings

Unprotected, substituted morpholines, piperazines, and thiomorpholines prepared with SnAP reagents **5**–**8**, **13**, **18**, **19**, and **20** were obtained in good-to-excellent yields by employing electronically and sterically diverse aromatic, heteroaromatic, and aliphatic aldehydes—one of the most widely available classes of starting material (**eq 2**).[3,4a] A single reaction protocol was employed in all of the cyclization reactions, and we anticipate that substrate-specific optimization should be possible if higher yields and/or faster reaction times are necessary.

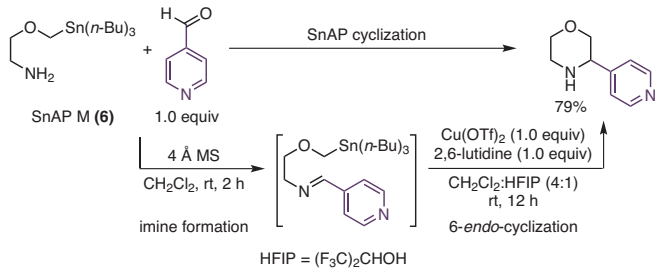
In general, the formation of six-membered rings tolerates a variety of functional groups such as esters, organohalides, amines, and a variety of heterocycles; and the cyclization step takes place under mild conditions at room temperature. For the most challenging substrates, larger amounts of protodestannylated side-products were observed.



Scheme 3. Example of the Preparation of SnAP Reagents Lacking a Substituent α to the Amine Group. *(Ref. 4a)*



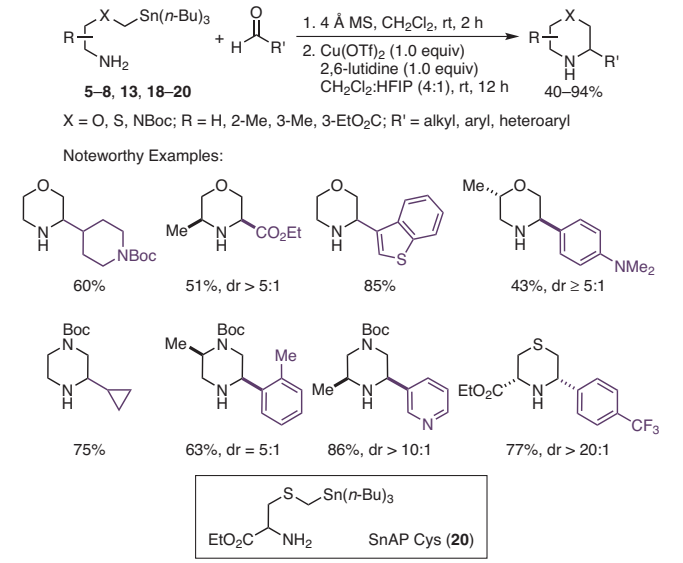
Scheme 4. Synthesis of Piperazine SnAP Reagents and Analogues. *(Ref. 4a,7)*



Scheme 5. Example of the Application of SnAP Reagents in N-Heterocycle Synthesis. *(Ref. 4a)*

3.2. Synthesis of Medium-Size Rings

SnAP reagents can also be utilized to prepare more challenging medium-size rings.[7] Reagents suitable for the synthesis of saturated seven-, eight-, and nine-membered-ring N-heterocycles, including diazepanes and oxazepanes, have been designed and synthesized. The substrate scope and functional group tolerance were similar to those observed in the synthesis of the six-membered-ring analogues, albeit with somewhat lower yields due to increased protodestannylation. It is remarkable, however, that this process can easily access medium-size rings, even in cases where the SnAP reagents do not contain any backbone elements that would favor cyclization (**Figure 3**).[7]



eq 2 *(Ref. 3,4a)*

3.3. Spirocycles from Ketones

Saturated, spirocyclic N-heterocycles[8] are regarded as promising scaffolds for drug discovery and development.[9] However, relatively few multifunctional saturated spirocycles are actually available for use due to the scarcity of methods for their synthesis. A major challenge in this area is the preparation of diverse spirocycles by the union of two discrete components.[10,11] The reaction of cyclic and α-CF_3-substituted ketones with SnAP reagents **6–8**, **13**, **18**, and **19** affords saturated, spirocyclic and α-CF_3-substituted N-heterocycles under operationally simple reaction conditions (**Scheme 6**).[6]

3.4. Customized SnAP Reagents for C-Substituted Spirocycle Formation

We envisaged the preparation of customized SnAP reagents as cross-coupling partners for aldehydes and ketones in order to form more elaborate C-substituted bicyclic and spirocyclic structures. These new SnAP reagents proved compatible with a variety of aldehydes and ketones. The cyclization using our standard SnAP conditions provided the desired C-substituted bicyclic and spirocyclic morpholines and piperazines. Coupling partners containing functional groups such as esters, aldehydes, and a MIDA ester provided scaffolds suitable for further functionalization (**Figure 4**).[5]

3.5. SnAP Reaction Limitations

The main drawback of this methodology is the dependence on tin and its related toxicity.[12] However, the large difference in polarity between the tin byproducts and the desired N-heterocycles simplifies the purification by column chromatography, and most of the tin byproducts

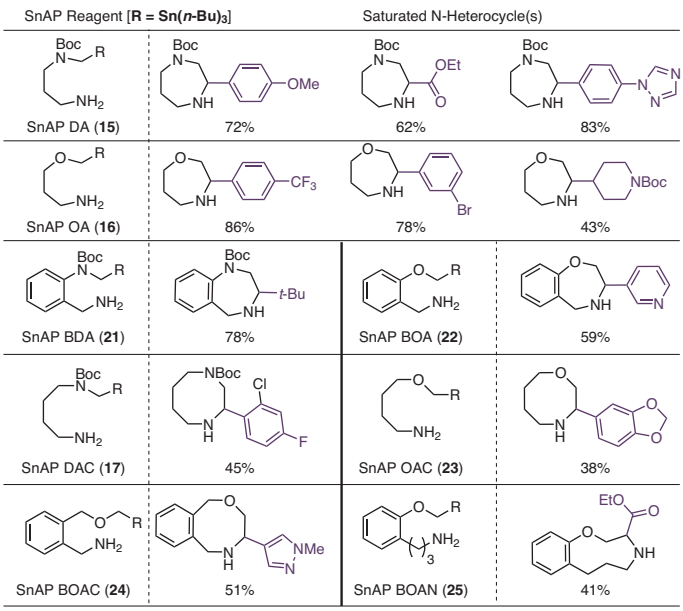
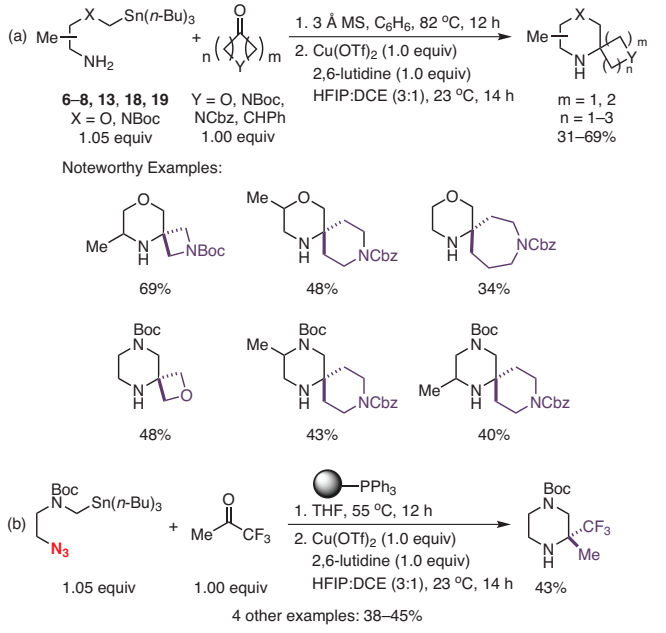


Figure 3. SnAP Reagents and Substrate Scope for Saturated, Medium-Size N-Heterocycles. *(Ref. 7)*



Scheme 6. Synthesis from SnAP Reagents and Ketones of (a) Saturated, Spirocyclic N-Heterocycles and (b) α-Trifluoromethyl N-Heterocycles. *(Ref. 6)*

can be removed prior to purification by simple extraction with mixtures of acetonitrile and hexanes.[13] Furthermore, the unprotected N-heterocycles can be converted into their salts to remove any last traces of tin impurities. The use of aliphatic aldehydes and ketones involves intermediate imines that readily undergo enamine tautomerization; for example, 3-pyrrolidinone and 3-piperidinone. In these cases, along with the desired N-heterocycles, larger amounts of protodestannylation byproducts are typically observed. Efforts toward improving the utility of this class of substrates are currently ongoing.

3.6. Mechanistic Considerations

Our investigation to date implicates a radical-based process initiated by a copper-mediated oxidation of the carbon–tin bond to form a stabilized primary carbon radical (**Scheme 7**).[3,7] Although radical cyclizations onto alkenyls typically proceed via exo-bond formation, the SnAP reagents, as aza analogues, prefer formation of the endo products due to thermodynamic and kinetic factors.[14] In principle, the cyclization should be catalytic in copper, but coordination of the unprotected N-heterocycles to Cu(II) might lead to catalyst inhibition. Efforts to render this process catalytic are yielding encouraging results.

3.7. Catalytic Variant

Preliminary results from the elaborate screening of the reaction conditions—including solvent, ligands, and additives—appear promising. In the presence of a commercially available bisoxazoline ligand and using hexafluoroisopropanol (HFIP) as the sole solvent, the amount of $Cu(OTf)_2$ needed can be lowered to 10 mol %, and the reaction still affords the desired unprotected N-heterocycles with a broad substrate scope (**eq 3**).[15]

4. Conclusion

SnAP reagents are a stable, easy-to-handle, and rapidly expanding class of reagents that offer a convenient and general approach to the synthesis of small-to-medium-size N-heterocycles, bicycles, and spirocycles. They have an outstanding substrate scope, and their coupling with widely available aliphatic, aromatic, and heteroaromatic aldehydes and ketones provides access to a large variety of N-heterocycles that are challenging to prepare using existing synthetic methods. SnAP reagents and their products should be of great interest in drug discovery, since they can provide ready access to differentially substituted analogues for structure–activity relationship (SAR) studies, and since they greatly expand the availability of saturated N-heterocycles.[16,17]

5. References and Notes

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(3) Vo, C.-V. T.; Mikutis, G.; Bode, J. W. *Angew. Chem., Int. Ed.* **2013**, *52*, 1705.

(4) (a) Luescher, M. U.; Vo, C.-V. T.; Bode, J. W. *Org. Lett.* **2014**, *16*, 1236. (b) The SnAP reagent and the aldehyde are stirred in CH_2Cl_2 in the presence of molecular sieves to afford the corresponding imine. The solution containing the imine intermediate is filtered through a sintered-glass funnel and evaporated to ensure clean and full conversion before being subjected to the cyclization conditions. Separately, a solution of $Cu(OTf)_2$ and 2,6-lutidine in HFIP (hexafluoroisopropanol) is stirred at rt for one hour, during which a heterogeneous suspension is formed. The solution of the imine in CH_2Cl_2 is added in one portion to this suspension, and the resulting reaction mixture is stirred at rt for 12 hours. Alternatively,

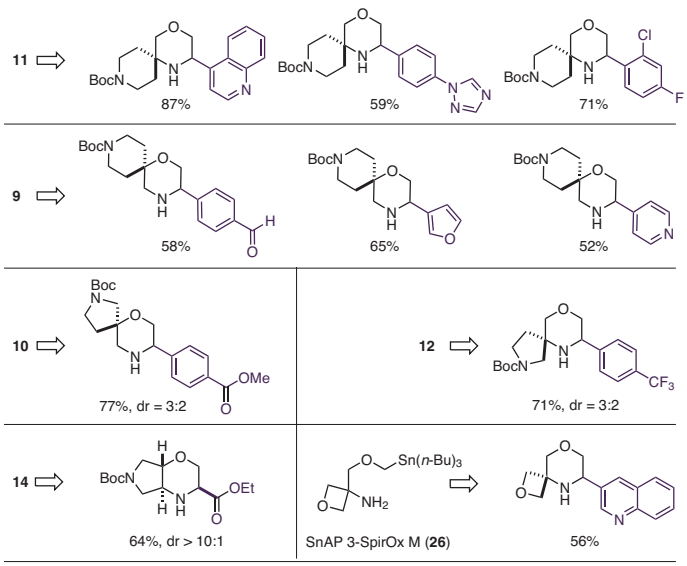
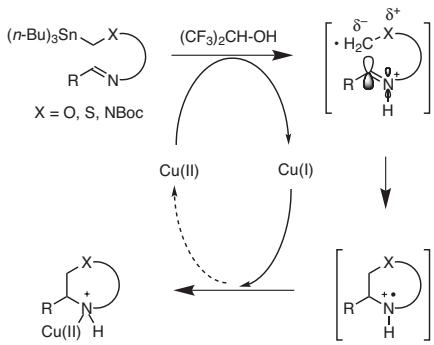
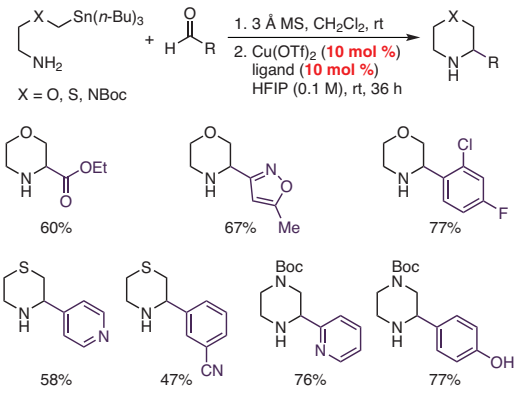


Figure 4. Synthesis of C-Substituted Bicyclic and Spirocyclic Morpholines by Employing Customized SnAP Reagents. *(Ref. 5)*



Scheme 7. Proposed Mechanism for the Second Step of the Reaction of SnAP Reagents with Carbonyl Compounds. *(Ref. 3,7)*



eq 3 *(Ref. 15)*

the imine can be diluted with additional CH_2Cl_2 and transferred to the heterogeneous suspension using a filter-syringe to remove the molecular sieves. Stirring at room temperature for 2–15 h, followed by aqueous workup and purification, affords the desired N-heterocyclic compound.

(5) Geoghegan, K.; Bode, J. W. *Org. Lett.* **2015**, *17*, 1934.

(6) Siau, W.-Y.; Bode, J. W. *J. Am. Chem. Soc.* **2014**, *136*, 17726.

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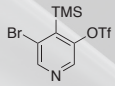

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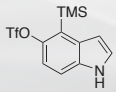

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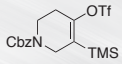

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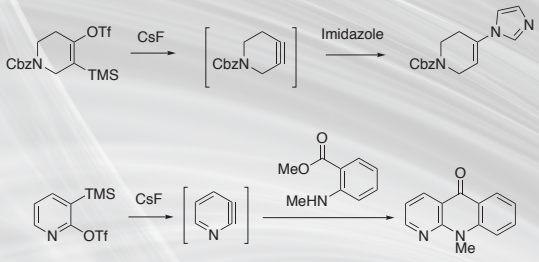

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246654	Heptane, anhydrous, 99%	Hexane, pentane	Reaction, Purification[3]
673277	2-Methyltetrahydrofuran, anhydrous, ≥99%, inhibitor-free (2-MeTHF)	DCM, THF, diisopropyl ether, diethyl ether	Reaction[4]
414247	2-Methyltetrahydrofuran, anhydrous, ≥99.0%, contains 250 ppm BHT as stabilizer (2-MeTHF)	DCM, THF	Reaction[4]
791962	Cyclopentyl methyl ether, anhydrous, ≥99.9%, inhibitor-free (CPME)	THF, MTBE, 1,4-dioxane and other ether solvents	Reaction,[5] Purification[6]
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270989	Ethyl acetate, anhydrous, 99.8%	DCM, DCE	Reaction, Purification[7]
517127	Dimethyl carbonate, anhydrous, ≥99% (DMC)	DMF, DCM, DME	Reaction[8]
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271004	Acetonitrile, anhydrous, 99.8%	DMF, DMA, NMP	Reaction[7]

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Development of Solvent Selection Guides


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Abstract. A review of the development of solvent selection guides that focuses on the efforts of major pharmaceutical companies and several academic groups to provide guides that facilitate the selection of more benign solvents for use in synthetic chemistry.

Outline

1. Introduction

The sustainability of chemical processes is of increasing importance within the chemical industry and is becoming a key concern for a wider range of practitioners.[1] Historically, process chemists have been the leading proponents of sustainable chemistry practices and, while this does remain integral to chemical development operations, sustainability is now becoming a significant consideration earlier on in the discovery phase of industrial, as well as academic, research.[2]

In this regard, solvent is one of the largest overall components used in chemical reactions. For example, solvent has been estimated to account for over half of the total material utilized to manufacture active pharmaceutical ingredients.[3] Based on this knowledge, and perhaps unsurprisingly, solvent was identified very early on in the sustainable chemistry revolution as a priority area for research because of the direct and substantial impact that a change in this area may have.

Consequently, over approximately the past 15 years, efforts have been made to identify existing solvents that exhibit undesirable properties from an environment, health, and safety (EHS) perspective such that, wherever possible, solvents with an unacceptable profile may be avoided. In addition, considerable research has been invested in identifying replacements for solvents that are less favorable from a sustainability perspective. These efforts have resulted in a series of solvent selection guides that helpfully describe the alignment of a broad range of widely used solvents with sustainable chemistry principles.

2. Development of Solvent Selection Guides

Two principal approaches have been taken toward providing guidelines to assist with solvent selection. The first helps the practitioner select a priori a more sustainable solvent for a reaction, while the second approach allows an existing less favorable solvent to be supplanted with a more benign alternative. A series of reports have emerged over the past 15 years from leading pharmaceutical companies detailing their assessment of what solvents they consider to be favorable or unfavorable (and anywhere in between). Their evaluations were based on a range of criteria encompassing EHS considerations and considerations that relate to operational costs and impact on life-cycle management.[4–8] In a more applied approach, several industrial and academic groups have published task-specific guides to help facilitate the replacement of an unfavorable solvent within widely used processes or reactions such as chromatographic purification,[9,10] amide-bond formation,[11] reductive amination,[12] and olefin metathesis.[13]

2.1. General Solvent Selection Guides

As stated above, the development of solvent selection guides has been driven principally by industry, in particular, by several large pharmaceutical companies.[4–8] Accordingly, the guidance delivered is broadly similar, with typically only small variations in the perceived environmental impact of a particular solvent, and these variations are generally related to the nature and number of the variables being

employed in the assessment. The use of a traffic-light-type guide to facilitate solvent selection is also common. This familiar representation is broadly accessible for practitioners and is designed to facilitate movement to a more sustainable solvent choice. Over the years, the depth of analysis relating to the sustainability credentials of a given solvent has increased markedly and in parallel with the best guidance available at the time (**Table 1**). In 1999, GlaxoSmithKline (GSK) published the first solvent selection guide,[5a] which has been subsequently embellished with follow-up publications in 2005[5b] and 2011.[5c] In 1999, the level of scrutiny a solvent was subjected to was four-fold: waste, environmental impact, health, and safety. Life-Cycle Analysis (LCA)[14] was included in the analysis by 2005, and a further series of considerations in 2011. The most recent guide, from Sanofi in 2013,[7] employed an extensive range of factors in the analysis, with at least 11 components constituting this new analysis.

Table 1. Development of Solvent Selection Guides by Pharmaceutical Companies: Chronological Escalation of Analysis Detail

Year	Company	Factors Considered in Determining the Sustainability Credentials of a Given Solvent
1999	GlaxoSmithKline	Waste, environmental impact, health, safety
2005	GlaxoSmithKline	Waste, environmental impact, health, safety, LCA
2008	Pfizer	Environmental/regulatory considerations, worker safety
2011	GlaxoSmithKline	Waste, environmental impact, health, safety, LCA, flammability/explosion, reactivity/stability, legislation flag, physical properties
2013	Sanofi	Environmental hazard bands, health, safety, physical properties, water miscibility, source, industrial/legal constraints, ICH limits, biodegradability, resistivity, cost

LCA = life-cycle analysis. ICH = International Conference on Harmonization (of Technical Requirements for Registration of Pharmaceuticals for Human Use).

The desire to transition away from harmful solvents to more favorable alternatives on an industrial scale was clearly demonstrated by GSK in an analysis of its pilot plant operations.[3] For example, undesirable dichloromethane ranked #3 for usage in 1999, but dropped to #8 in 2005, a positive movement away from the use of this solvent. Conversely, the more favorable isopropyl alcohol increased in usage from #5 to #1 in the same period of time, while heptane (a hexane replacement) increased from #12 to #5, again demonstrating positive movements toward solvents that, following the available guidance, were considered more benign.

The perspective of precisely how well aligned a particular solvent is with the ethos of sustainability has closely correlated with the available guidance, and this perspective has evolved as the guidance has developed and matured. An analysis of the evolution of GSK's solvent guide over 12 years (through the three published iterations) provides an interesting snapshot of how perspectives changed as a function of time (**Figure 1**).[5] For example, taking a subset of 12 common solvents and tracking the average sustainability score (as a percentage of the total possible score) arising from GSK's analysis using selected available variables from 1999 (4), 2005 (5), and 2011 (6) illustrate the change in perceived sustainability over this time period (note that legislation issues are not taken into account). In particular, this analysis demonstrates that the impact of the introduction of a larger range of analyzed variables serves to generally increase the sustainability score of the solvent. Reasons for this are unclear but may be due to the introduction of additional variables that tend to score highly for most solvents, such as reactivity/stability (GSK 2011: >75% of solvents scored ≥8/10 for this criterion), which may lead to a skewed average sustainability score.

Taking the information available in all of these published guides, a more holistic solvent selection guide is shown in **Table 2**, along with suggested alternatives to assist in supplanting a range of less desirable solvents (**Table 3**). A point to note is that some suggested alternatives

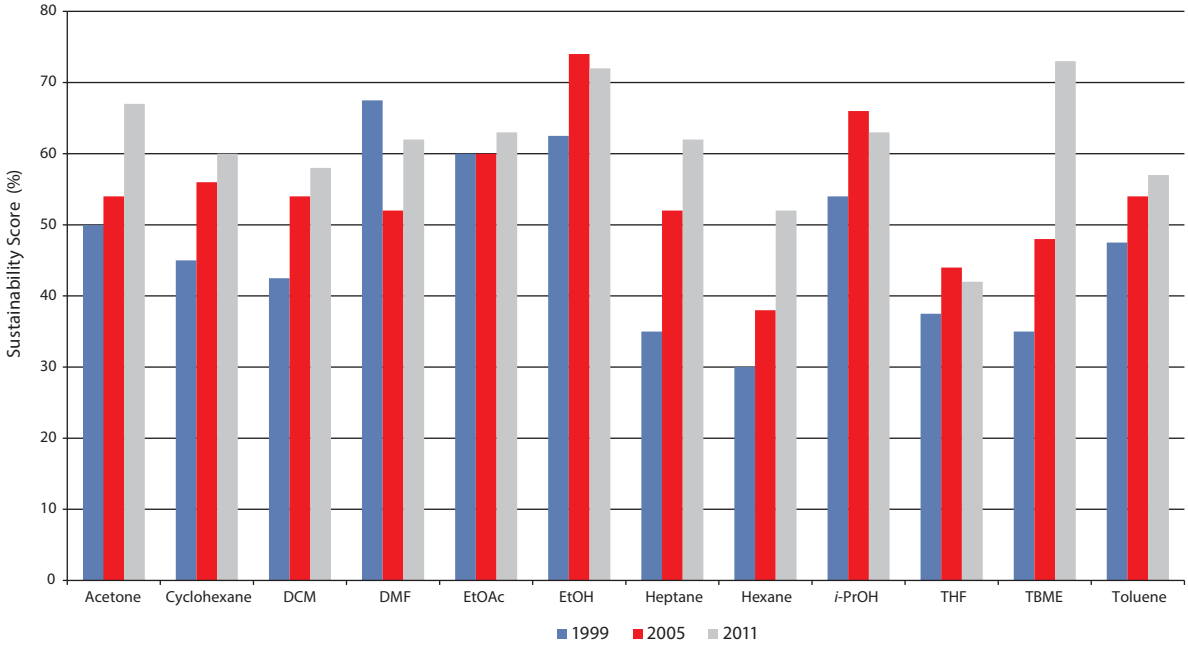
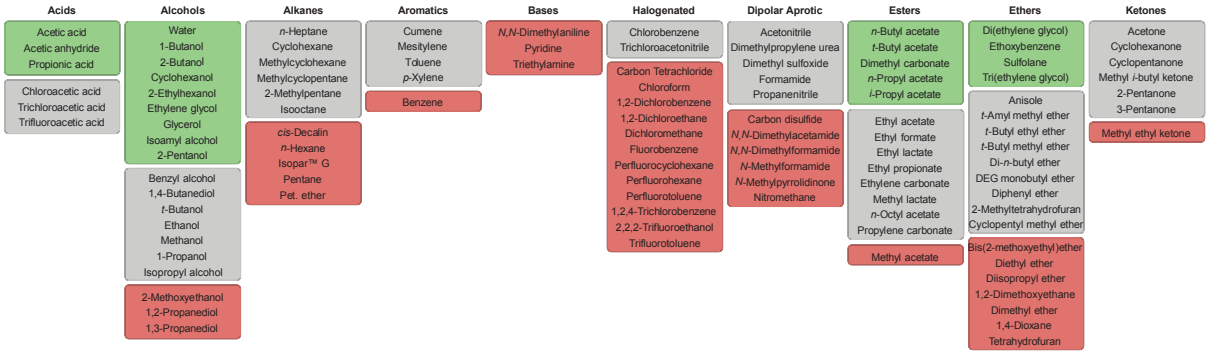


Figure 1. Evolution of GSK's Sustainability Score of 12 Selected Solvents from 1999 to 2011. *(Ref. 5)*

Table 2. A Summarized Solvent Selection Guide Based on the Analyses by GSK, Pfizer, and Sanofi. (Color key: red, solvents that should be avoided where possible; gray, solvents with some issues; green, solvents that are preferred.)



are not necessarily desirable themselves, but are preferred relative to the progenitor system for which a replacement is sought. For example, CH_2Cl_2 should be used as a replacement for $CHCl_3$, CCl_4, or DCE only where no other options are available.

2.2. Task-Specific Solvent Selection Guides

2.2.1. Chromatography

Chromatographic purification has been identified as the largest consumer of solvent within common synthetic processes.[3] Accordingly, adopting green chemistry principles within chromatography could have a significant impact on the overall sustainability of a chemical process without requiring substantial investment in terms of reaction development or optimization. In the 1960s, Neher published the first widely used equielutropic series that assisted in the identification of equipolar eluent systems for chromatographic purification.[15] Sustainability, however, was not necessarily a prevailing concern at the time, and this series was largely based upon solvents that are not in keeping with current green chemistry principles (for example, chlorinated solvents, hexane).

In the past few years, two studies—one from a group of industrial chemists at Amgen[10a] and the other from a collaboration between an academic group at the University of Strathclyde, GlaxoSmithKline (GSK), and Sigma-Aldrich (SA)[9]—sought to provide some guidance toward improving solvent selection in this area. These studies specifically targeted the replacement of CH_2Cl_2, which is commonly used in conjunction with MeOH as a modifier for the purification of relatively polar compounds.

The Amgen study focused on the use of alcohol- (MeOH, EtOH, *i*-PrOH) and additive-modified (AcOH, NH_4OH) mixtures of heptanes, EtOAc, and *tert*-butyl methyl ether (TBME) for the purification of a range of 26 drug-like molecules on silica, and helpfully presented a modern equielutropic series based on these mixtures in comparison to MeOH–CH_2Cl_2.

The Strathclyde/GSK/SA group adopted a slightly different approach and focused on establishing a direct replacement for CH_2Cl_2 while retaining MeOH as the modifier. Ultimately, cyclopentyl methyl ether (CPME) was identified as a potential greener surrogate for CH_2Cl_2, providing comparable and, in some cases improved, chromatographic results on normal silica gel. Similarly to the Amgen approach, this study also evaluated their suggested replacement solvent system on a 95-member library of drug-like and fragment compounds.

Both of these studies provided the first guidance for identifying eluents that can be used in a practical sense to replace CH_2Cl_2 in chromatography (i.e., utilizing a broad range of real examples). A summary of this guidance is provided in **Table 4**.[9]

Table 3. Suggested Alternatives to Undesirable Solvents

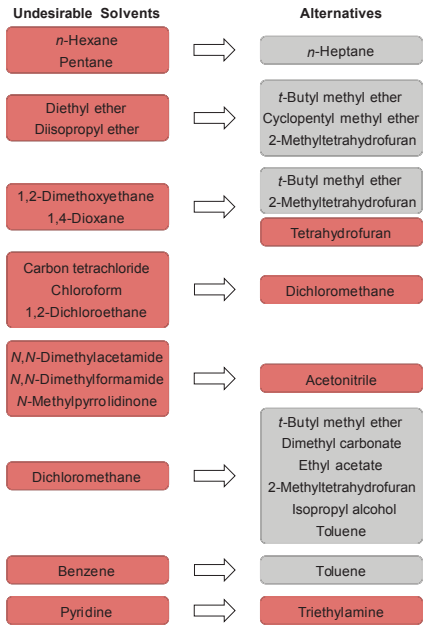
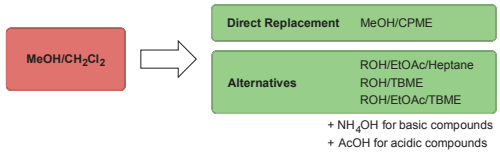


Table 4. Replacement of Dichloromethane in Chromatographic Purification *(Ref. 9)*

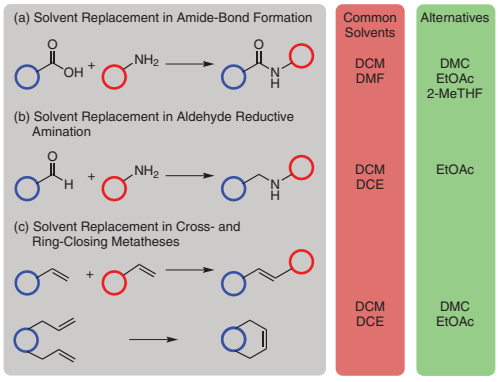


2.2.2. Reaction-Specific Solvent Selection Guides

Over the past few years, several studies have emerged that evaluate the performance of a range of established or emerging alternative solvents within widely used chemical transformations.[11–13] Many of the most common organic reactions employ solvents that have considerable issues from the sustainability perspective—DMF and chlorinated solvents in particular. As such, the primary aim of these reaction-specific investigations has been to establish the best alternative media without compromising the chemistry either from an efficiency perspective (i.e., yield) or from a practical viewpoint (i.e., setup, temperature, time, etc.).

Amide-bond formation is one of the most widely practiced organic reactions.[16,17] Indeed, a 2011 survey of the types of reaction used by industrial practitioners found that amidation accounted for approximately 16–17% of all transformations carried out in a medicinal chemistry environment.[16,17] In addition, DMF remains the solvent of choice for the majority of amide-bond-forming processes, and, for this reason, an effort was undertaken to provide a general alternative to DMF (as well as CH_2Cl_2) for amide-bond-forming reactions. The resulting comprehensive survey of eight alternative solvents within four benchmark reactions (aryl acid–aryl amine, aryl acid–alkyl amine, alkyl acid–aryl amine, and alkyl acid–alkyl amine) and using five common amidation reagents found that dimethyl carbonate (DMC), EtOAc, and 2-MeTHF are viable alternatives (**Scheme 1**, Part (a)).[11] This study also compared the reaction time in order to demonstrate the utility of the proposed replacements, alongside CH_2Cl_2 and DMF, in a representative application using amines and carboxylic acids that displayed the functionality common to Discovery Phase Medicinal Chemistry.

A similar analysis from the same research team was performed on another staple of industrial organic synthesis—reductive amination.[12] Similarly to amidation processes, reductive amination is broadly utilized[16,17] but has a heavy reliance on the use of chlorinated solvents, such as CH_2Cl_2 and DCE.[12] A thorough investigation of 12 benchmark reactions—employing representative examples of 12 amine classes in reductive amination with both alkyl and aryl aldehydes and using three different reductants and 10 solvents—found EtOAc to be a suitable replacement solvent in these reactions (Scheme 1, Part (b)).[12] Once more, the generality of these alternative conditions was exemplified through application to a set of 21 amine syntheses with an indication of reaction efficiency.



Scheme 1. Solvent Replacement in Common Organic Reactions. *(Ref. 11–13)*

The replacement of chlorinated solvents within key reactions continues to be a strong theme for research. Olefin metathesis is another key organic transformation that routinely employs chlorinated solvents. It was recently shown that CH_2Cl_2 could be replaced, once more, with EtOAc and DMC for cross-metathesis and ring-closing metathesis reactions (Scheme 1, Part (c)).[13]

3. Conclusions and Outlook

Over the past 15 years, a combination of industrial and academic research has provided a series of guides that have been designed to assist the practitioner with the selection of a more sustainable solvent for synthetic transformations. Of particular interest has been the replacement of solvents that are viewed as particularly problematic from a sustainability perspective—especially DMF and chlorinated solvents. As new guidance emerges and new alternative solvents researched and discovered, the identification of alternative solvents suitable for supplanting other problematic media will no doubt continue.

Indeed, beyond the guides described above, Grignard additions have recently been shown to be effective using deep eutectic solvents as a replacement for conventional ethereal solvents, as well as requiring a less stringent reaction setup: at room temperature and using air as the atmosphere.[18] Moreover, a series of specific guides and more general information on the selection of greener *reagents* for reactions are beginning to emerge, allowing facile selection not only of greener solvents for reactions but also of the reagents needed.[6,19]

4. Acknowledgments

We thank Dr. Helen F. Sneddon, GlaxoSmithKline, and Dr. Jane Murray, Sigma-Aldrich, for their support of our sustainable chemistry program.

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Harry Eastman was born in 1992 in Portsmouth, England, U.K. He studied chemistry at the University of Surrey, working for a year with Professor A. M. P. Koskinen at Aalto University, and completed an M.Sci. degree in Chemistry program in 2014. He began his Ph.D. studies with Dr. Allan Watson in 2014, and is currently focused on the development of new methods for organic synthesis.

Craig Jamieson earned his B.Sc. (Hons) in Chemistry degree at the University of Glasgow in 1996. His Ph.D. studies were carried out under the direction of Professor R. Ramage at the University of Edinburgh (1999). Following postdoctoral research under the supervision of Professor S. V. Ley at the University of Cambridge, he was appointed in 2001 as Principal Scientist in GlaxoSmithKline's Discovery Medicinal Chemistry group, where he worked on a range of exploratory medicinal chemistry programs. In 2004, Craig joined Organon Laboratories (later Merck Research Labs) as a Group Leader in the Medicinal Chemistry Department, with responsibility for hit-to-clinical candidate optimization. In August 2010, he accepted an appointment as John Anderson Research Lecturer in Chemical Biology in the Department of Pure and Applied Chemistry at the University of Strathclyde.

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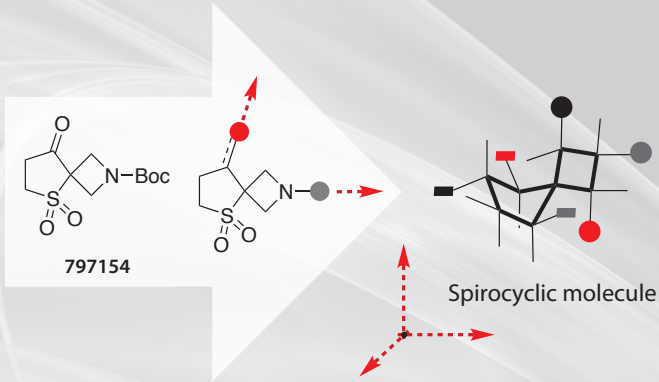

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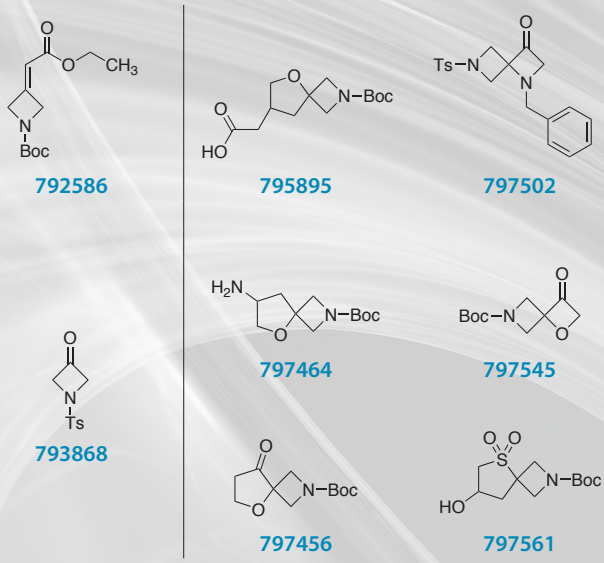

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Detail from ***Tamaca Palms***. Photo courtesy National Gallery of Art, Washington, DC.

Tamaca Palms (oil on canvas, 67.9 × 91.3 cm) was painted in 1854 by the famed American landscape artist Frederic Edwin Church (1826–1900). Born to a wealthy family, Church took up art studies at an early age and apprenticed for two years with the renowned British landscape painter Thomas Cole, who had relocated to the U.S. and co-founded the Hudson River School of landscape painting. Church began his artistic career soon after by painting scenes from the northeastern U.S. in the style of the Hudson River School. He won artistic acclaim and achieved commercial success early in his career and, unlike many posthumously famous artists, had assembled a small fortune from the sale of his works by the time he died.

Inspired by the writings of the distinguished naturalist and explorer Alexander von Humboldt, Church travelled extensively in South America, Jamaica, the North Atlantic, the Middle East, Italy, and Greece. It was upon his return from a trip to Colombia in 1853 that Church painted ***Tamaca Palms*** in his New York studio based on meticulous sketches and observations he had made during the trip.* He often painted stunning, large, brightly lit, and detailed panoramas that documented the natural features, plants, and animals of exotic locales. Reminiscent of the romantic tradition in European art, Church's awe of the beauty and majesty of the natural world is unmistakable in his works, where natural features and phenomena are given prominence over the human element.

This painting is part of the Corcoran Collection at the National Gallery of Art, Washington, DC.

** Could Church have used the sketches that he based* ***Tamaca Palms*** *on as an inspiration for later compositions, especially in his later years? To find out, visit* ***Aldrich.com/acta483***

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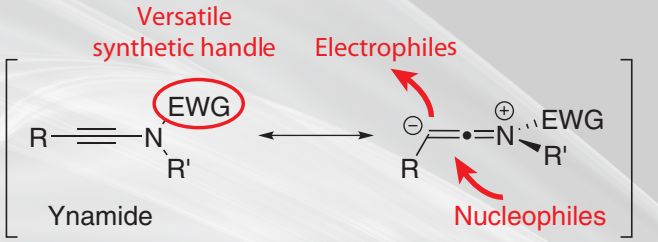

Despite their huge potential, the inaccessibility and instability of highly reactive nitrogen-substituted alkynes such as ynamines impede numerous synthetic routes.

In collaboration with Professor Gwilherm Evano, Aldrich offers a selection of ynamides—stable surrogates for ynamines due to the presence of the electron-withdrawing group (EWG). These strikingly reactive yet stable building blocks are ideal for a multitude of chemo-, regio-, and stereoselective transformations. Their utility is extended since the EWG furnishes a versatile chelating or directing site. Significant scaffolds and reagents in total synthesis and medicinal chemistry, ynamides are also excellent precursors of highly reactive keteniminium ions, carbenoids, and many other useful intermediates for the development of new and innovative chemical transformations.

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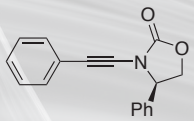
- Medicinal chemistry
- Heterocyclic chemistry
- Functionalization
- Asymmetric synthesis
- Organometallic chemistry



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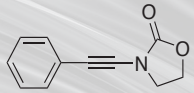

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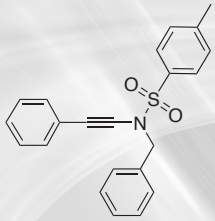

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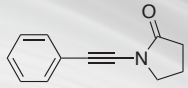

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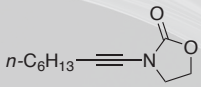

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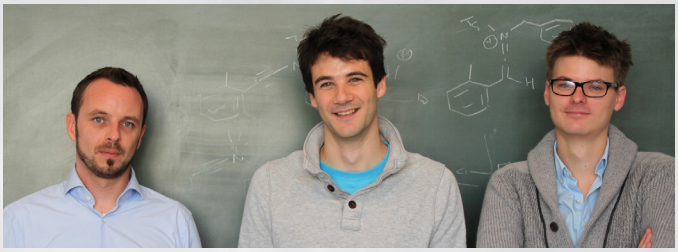

Professor Gwilherm Evano, Cédric Theunissen, and Morgan Lecomte (left to right)

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Ynamides: Powerful and Versatile Reagents for Chemical Synthesis


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Mr. C. Theunissen


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Keywords. ynamides; alkynes; organic synthesis; heterocyclic chemistry; reactivity; reactive intermediates.

Abstract. Ynamides have recently emerged as particularly useful building blocks for chemical synthesis. Their remarkable reactivity has been exploited in the design of a number of novel synthetic processes and for the generation of otherwise inaccessible reactive intermediates. The state of the art of the chemistry of ynamides and its impact on organic synthesis are highlighted in this review, which has been structured according to the nature of both the reactive intermediates generated and the types of reaction they undergo.

Outline

1. Introduction

Organic synthesis is today clearly a central science with significant contributions to, and impact on, various other scientific disciplines such as biology, medicine, and materials science. As a consequence, the high and growing demand for efficient synthetic routes to assemble complex molecules or pharmaceuticals from simple building blocks, as well as the quest for molecular diversity, will continue to challenge the resourcefulness of organic chemists for years to come. In this context, the development of original and versatile starting materials, together with the design of new strategies, will contribute to the selective syntheses of ever larger and more complex systems with increased efficiency.

The need for cleaner, environmentally benign, and more sustainable chemical practices also poses new challenges and requires new ways of carrying out chemical synthesis. Hence, in addition to the development of new reactions, reagents, and catalysts, novel ways to assemble molecules in a more sustainable manner are presently an important factor to consider.

The chemistry of ynamides clearly falls into this category: they display an exceptionally fine balance of stability and reactivity, offer unique and multiple opportunities for the inclusion of nitrogen-based functionalities into organic molecules,[1] and have recently emerged as especially useful and versatile building blocks.[2,3] Indeed, the electron-donating ability of the ynamide nitrogen strongly polarizes the triple bond, which allows for exceptionally high levels of reactivity and regio- and/or stereoselectivities. This reactivity is yet tempered by the electron-withdrawing group, which provides enhanced stability when compared to the highly sensitive ynamines,[4,5] and can also act as an efficient directing group, chiral auxiliary, or can even participate in the reaction (**Figure 1**). These characteristics, coupled with recent breakthroughs in their synthesis,[6–16] have allowed for the increased application of ynamides in synthesis and for their involvement in new and remarkably efficient sequences that are difficult to accomplish otherwise.

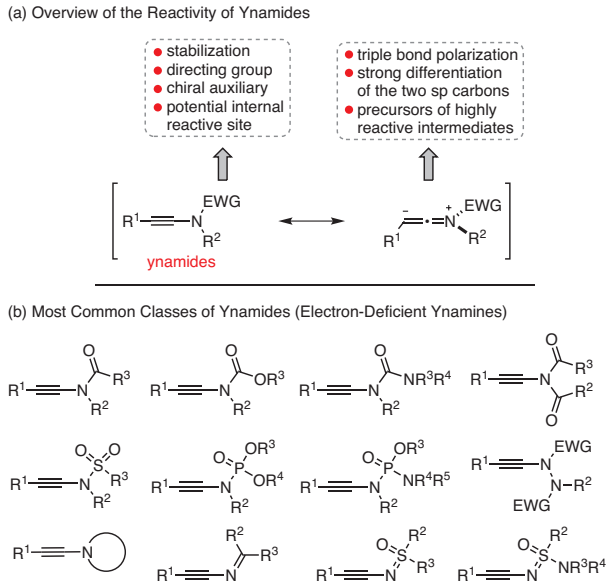


Figure 1. "Ynamides": Structural Types and Chemical Properties.

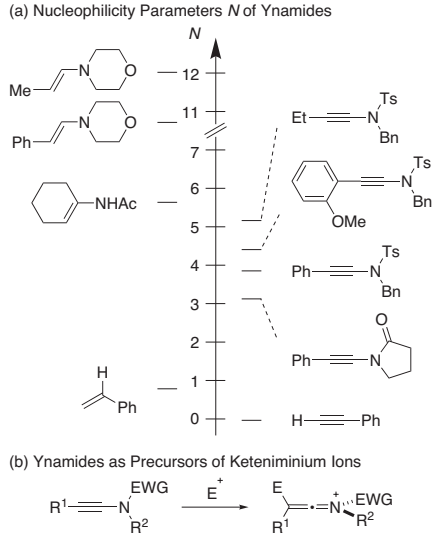


Figure 2. (a) Comparison of the Nucleophilicity Parameters *N* of Ynamides with Those of Related π-Nucleophiles (Mayr Reactivity Scale). (b) Generation of Keteniminium Ions from Ynamides. *(Ref. 18)*

This short review highlights the remarkable reactivity of these building blocks through selected and representative examples of new reactions that have been designed on the basis of the unique behavior of ynamides and other electron-deficient ynamines,[17] which are now also commonly referred to as "ynamides".

2. Ynamides as User-Friendly Precursors

2.1. Of Otherwise Inaccessible Keteniminium Ions

Two characteristic features that are crucial to the reactivity of ynamides are the activation of the triple bond and its strong polarization due to the conjugation of the amine group with the alkyne. Recent studies have shown that ynamides react with electrophiles between 10^3 to 10^5 times faster than regular alkynes (**Figure 2**).[18] The resulting keteniminium ions can participate in a number of transformations including the trapping of these highly reactive and otherwise inaccessible intermediates with nucleophiles. Many electrophile–nucleophile combinations have been employed to access diverse building blocks from ynamides; selected examples will be presented in the next paragraphs.

2.1.1. By Protonation

Brönsted acids have been widely utilized for the generation of keteniminium ions by protonation of ynamides. Depending on the type of acid used and the presence or absence of an additional nucleophile, the conjugated base can act as a nucleophile that traps the keteniminium ion. This yields polysubstituted enamides in a highly stereocontrolled manner, which are valuable building blocks in chemical synthesis and medicinal chemistry. The regio- and stereoselective hydrohalogenation of ynamides is certainly the most representative example of this type of reactivity (**Scheme 1**, Part (a)).[19–21]

Provided that a strong acid is utilized for the protonation of ynamides—which allows the generation of keteniminium ions associated with weakly nucleophilic counterions—additional nucleophiles such as arenes can be used to trap the intermediate keteniminium intermolecularly (Scheme 1, Part (b))[22] or even intramolecularly (which would correspond to a keteniminium version of the Pictet–Spengler cyclization), as exemplified in Scheme 1, Part (c).[23] The generation of highly reactive keteniminium ions by protonation of ynamides, followed by their reaction with a nucleophile, has also been employed to generate intermediate species which can then undergo a [3,3]-sigmatropic rearrangement. Indeed, the protonation of chiral ynamides with *para*-nitrobenzenesulfonic acid, followed by addition of allylic alcohols and subsequent rearrangement of the intermediate allyl vinyl ethers, yields highly substituted homoallylic amides with good levels of diastereoselectivity, which illustrates well the use of chiral ynamides in asymmetric synthesis (Scheme 1, Part (d)).[24] In a similar fashion, the use of arylsulfoxides instead of allylic alcohols provides an efficient (excellent yields within minutes at room temperature) entry into α-arylamides, when catalytic amounts of triflic acid are utilized (Scheme 1, Part (e)).[25]

2.1.2. By Reaction with Electrophiles

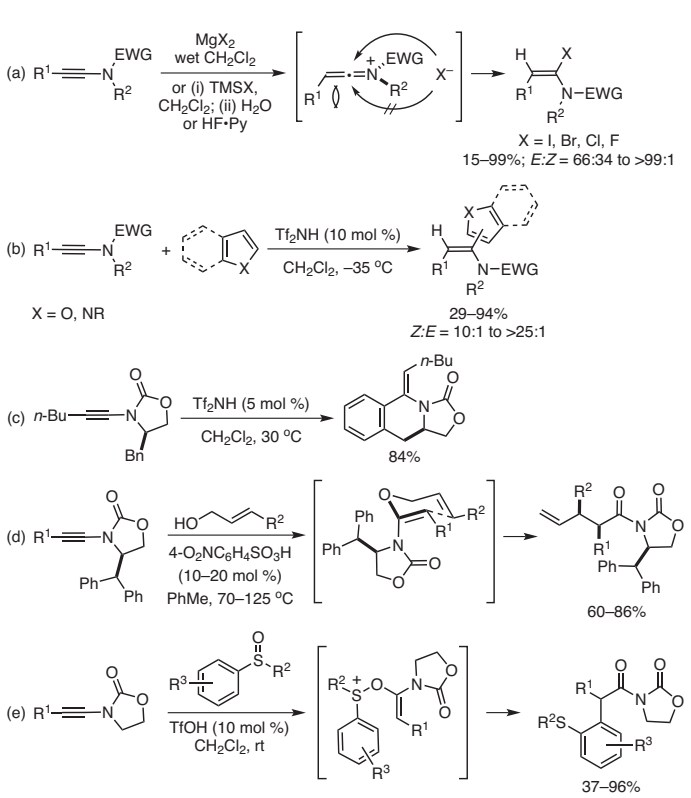
The use of other electrophilic reagents for the generation of keteniminium ions from ynamides is much more challenging since they need to selectively react with the triple bond and not the electron-withdrawing group, which would result in a loss of the stabilization of the ynamides. In addition, the counteranion needs to be a weak nucleophile to avoid trapping the keteniminium ion, which can be circumvented by using an internal nucleophile. The halo-[26] and carbocyclizations[27] of *ortho*-anisole-substituted ynamides yielding highly substituted benzofurans (**Scheme 2**, Part (a)) are representative of this strategy. Other examples that nicely illustrate both the synthetic potential of ynamides and the exceptional reactivity of keteniminium ions generated from these building blocks include the reaction of ynamides with aldehydes, ketones, or enones in the presence of a Lewis acid catalyst. Indeed, upon activation with boron trifluoride or a combination of $CuCl_2$ and $AgSbF_6$, the activated carbonyl derivatives are electrophilic enough to react with ynamides to give intermediate keteniminium ions which can be converted into conjugated amides (Scheme 2, Part (b))[28,29] or into formal [2 + 2] cycloaddition products (Scheme 2, Part (c)).[30] An enantioselective version of the last reaction, now commonly known as the Ficini cycloaddition, has been reported recently.[31]

2.1.3. By Reaction with Electrophilic Metal Complexes

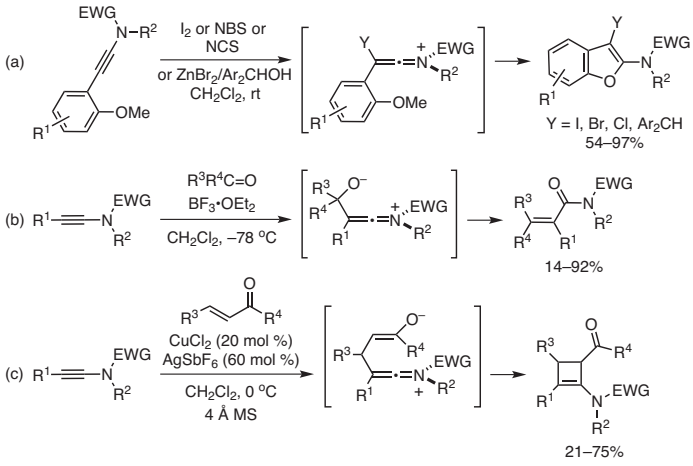
Besides strong acids and other electrophiles; such as halonium ions, carbocations, or activated carbonyl derivatives; electrophilic metal complexes can also be employed for the generation of transient keteniminium ions that can then be trapped by a nucleophile, generally in an intramolecular fashion. In this respect, electrophilic Pd^{II} and Cu^{III} complexes—generated by (formal) oxidative addition of Pd^0 or Cu^I precursors to aryl triflates and diaryliodonium salts respectively—react readily with ynamides, as exemplified by the palladium-catalyzed arylative cyclization of hydroxy-ynamides (**Scheme 3**, Part (a))[32] and the copper-catalyzed carbocyclization of homobenzylic ynamides (Scheme 3, Part (b)).[33]

In addition to these electrophilic palladium and copper complexes, the metal that is probably the most suitable for the activation of the triple bond of ynamides is gold. Indeed, gold complexes have been shown over the years to be excellent electrophilic catalysts for the activation of alkynes, and their use with ynamides, which are more electron-rich than regular alkynes, is therefore ideal. In addition, the polarization of the triple bond ensures high levels of chemoselectivity, as demonstrated by the gold-catalyzed hydroamination of ynamides which proceeds readily at room temperature (Scheme 3, Part (c)).[34]

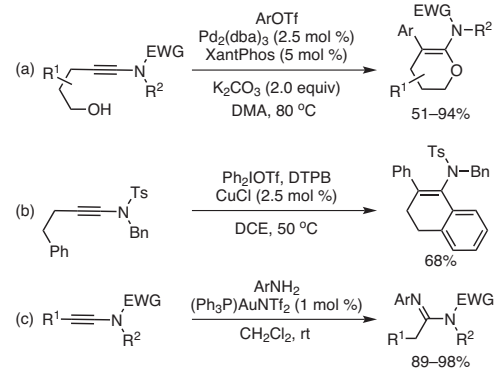
Perhaps more importantly than its use for the regioselective addition of nucleophiles to ynamides, this exceptional affinity between gold complexes and ynamides has found a number of applications in the design of new reactions based on the interception of the auro-keteniminium ions with certain nucleophiles, giving rise to intermediates that can be further elaborated into carbenoid species. Representative examples of such transformations will be discussed in the next section.



Scheme 1. Keteniminium Ions by Protonation of Ynamides and Their Subsequent Transformations. *(Ref. 19–25)*



Scheme 2. Remarkably Reactive Keteniminium Ions by Reaction of Ynamides with Electrophiles. *(Ref. 26–30)*

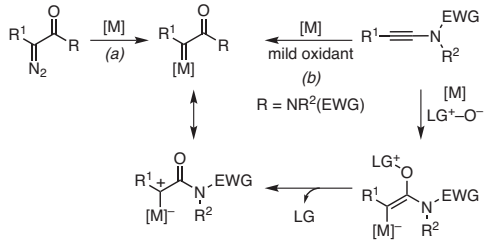


Scheme 3. Cyclization and Functionalization of Ynamides via Keteniminium Ions Promoted by Electrophilic Metal Complexes. *(Ref. 32–34)*

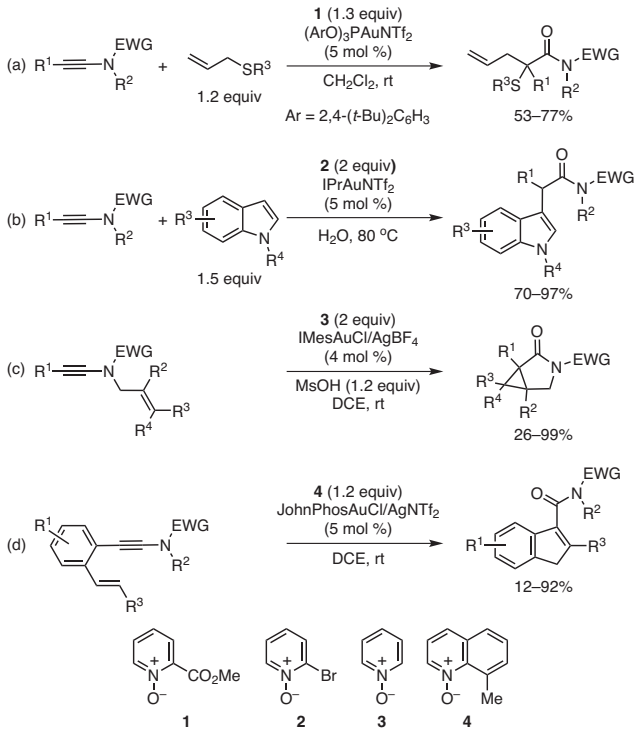
2.2. Of α-Oxo- or α-Imidocarbenes and Carbenoids

α-Oxocarbenes and carbenoids are versatile intermediates that are extensively employed for the development of a wide array of useful transformations. They are, however, typically generated by metal-promoted decomposition of the corresponding potentially hazardous diazo derivatives, which is clearly a severe limitation in terms of efficiency, flexibility, and safety (**Scheme 4**, Part (a)). In an attempt to address this drawback, recent studies have shown that such carbenoids can be readily generated by metal-promoted activation of ynamides in the presence of a suitable mild oxidant. This approach provides an interesting and user-friendly alternative to the use of diazo derivatives (Scheme 4, Part (b)).

Both the inherent reactivity of ynamides and the nature of the oxidant are critical in this approach, since the polarization of the triple bond of the ynamide ensures a total regiocontrol of the π-acidic activation by the metal, and therefore the addition of the nucleophilic external oxidant (LG^+-O^-) α to the nitrogen atom, while the presence of a leaving group in the oxidant enables the generation of the carbenoid.



Scheme 4. Ynamides as Precursors of α-Oxocarbenoids.



Scheme 5. Gold α-Oxocarbenoids from Ynamides and Their Subsequent Inter- and Intramolecular Reactions. *(Ref. 35–38)*

2.2.1. α-Oxocarbenes by Gold-Catalyzed Reaction of Ynamides with Mild Oxidants

This strategy turned out to be especially fruitful by allowing the generation of α-oxocarbenoids under remarkably mild conditions (gold complexes as catalysts and pyridine *N*-oxides as oxidants) from readily available starting materials. In addition, these transformations proceed with impressive levels of chemoselectivity, since the ynamide can be selectively activated in the presence of a wide number of potentially oxidizable functional groups such as alkenes, alkynes, or even sulfides.

Once generated, the α-oxocarbenoids can participate in a number of inter- and intramolecular transformations. Representative examples involving an intermolecular reaction of α-oxocarbenoids include their trapping with allylic sulfides followed by a [2,3]-sigmatropic rearrangement, which leads to highly functionalized α-thioamides (**Scheme 5**, Part (a)),[35] or their reaction with indoles (Scheme 5, Part (b)).[36] Alternatively, the presence of an internal functional group which can react with the intermediate carbenoid can be utilized to access various cyclic and polycyclic molecules. For example, intramolecular cyclopropanation of an appended alkene provides a straightforward entry to fused cyclopropyl-lactams (Scheme 5, Part (c)),[37] while a *5-exo-dig* cyclization involving an internal styryl group yields functionalized indenes (Scheme 5, Part (d)).[38] In all cases, the advantage of using ynamides rather than the corresponding diazo compounds as precursors of carbenoids is quite obvious. Following these studies, the use of other oxidants such as sulfoxides[39] or nitrones[40] and the use of rhodium complexes instead of gold catalysts have been reported.[41]

2.2.2. α-Imidocarbenes by Gold-Catalyzed Reaction of Ynamides with Pyridine *N*-Aminidines and Isoxazoles

In all examples mentioned in the previous paragraphs, the pyridine *N*-oxide derivatives only transfer their oxygen atom to generate the oxocarbenoid that is then trapped by a nucleophile, either intramolecularly or intermolecularly. An extension of this strategy relies on the use of nitrogen nucleophiles possessing both a leaving group and a nucleophilic site, masked or not, enabling the generation of electrophilic gold α-imidocarbenes that can react with the internal nucleophile. The gold-catalyzed, formal [3 + 2] cycloaddition between ynamides and pyridine *N*-aminidines is a remarkable application of this reactivity: Reaction of the ynamides with dichloro(pyridine-carboxylato)gold triggers the addition of the pyridine *N*-aminidine ylide to the ynamide. This is followed by cleavage of the pyridine *N*-aminidine N–N bond—generating the key α-imidocarbene—and cyclization involving the *N*-acyl group to yield highly substituted oxazoles (**Scheme 6**, Part (a)).[42] Similarly, isoxazoles can be employed in place of the pyridine *N*-aminidine ylide to give 2-aminopyrroles that result from a formal [3 + 2] cycloaddition (Scheme 6, Part (b)).[43]

As evidenced by all the examples described up to this point, ynamides have evolved as remarkably useful building blocks which act as efficient precursors of highly reactive intermediates such as keteniminium ions or carbenoids that can hardly be accessed from other reagents. This exceptional reactivity, which has ultimately led to the design of original reactions, is mostly based on the electron-rich nature of the ynamides and the polarization of the alkyne. Another facet of their reactivity that has been explored recently is based on their anionic chemistry and, here too, ynamides act as unique building blocks, notably as substrates for carbometallation reactions. These reactions, and the impressive input of ynamides in this chemistry, will be presented in the next section.

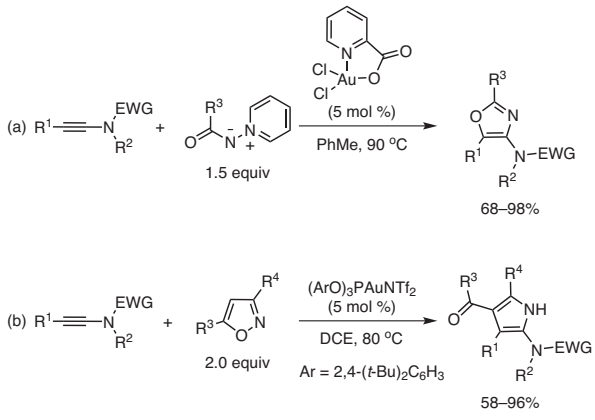
3. Carbometallation of Ynamides: New Paradigms in Asymmetric Synthesis and Heterocyclic Chemistry

The carbometallation of ynamides is certainly the most straightforward way to generate, with high levels of regio- and stereoselectivities, metallated enamides. Except in the case where the metal employed is palladium, the presence of the electron-withdrawing group (EWG)—which is also an excellent coordinating group—usually overcomes the polarization of the triple bond (the two effects acting in opposite ways), and controls the regioselectivity of the carbometallation. This results in the selective formation of α-metallated enamides rather than their β-metallated isomers, regardless of the inter- or intramolecular nature of the reaction.

3.1. Intermolecular Carbometallation: Easy Access to Metallated Enamides and Beyond

Various organometallic reagents have been employed for the carbometallation of ynamides in the presence or absence of a catalyst. For example, the carbocupration[44,45] and rhodium-catalyzed carbozincation[46] of these building blocks afford straightforward entries to α-metallated enamides, which can be trapped by an array of electrophiles, with total control of both the regio- and stereoselectivities. The carbometallation of ynamides with organoboron reagents is a good illustration of the switch of regioselectivity that can be achieved by the proper choice of the catalytic system. Indeed, while the use of a rhodium catalyst provides the β-functionalized enamides resulting from a cis carbometallation that places the metal next to the nitrogen atom (**Scheme 7**, Part (a)),[47] switching to palladium catalysts reverses both the regio- and stereoselectivity of the reaction (Scheme 7, Part (b)).[48]

Besides providing one of the most efficient entries to multisubstituted enamides, the carbometallation of ynamides has had a dramatic impact in asymmetric synthesis. One of the most striking examples is the carbocupration of chiral ynamides and oxidation of the resulting vinylcopper species. This sequence, the success of which is clearly based on the unique reactivity of ynamides, enables the generation of stereodefined trisubstituted enolates—compounds that are especially challenging to generate otherwise—which are then trapped with aldehydes to yield aldol adducts possessing all-carbon quaternary stereocenters (Scheme 7, Part (c)).[49]

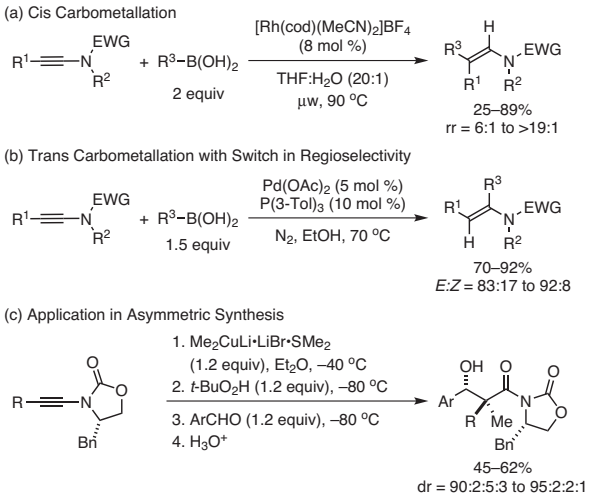


Scheme 6. Gold-Catalyzed, Formal [3 + 2] Cycloaddition of Ynamides via α-Imidocarbenoids. *(Ref. 42,43)*

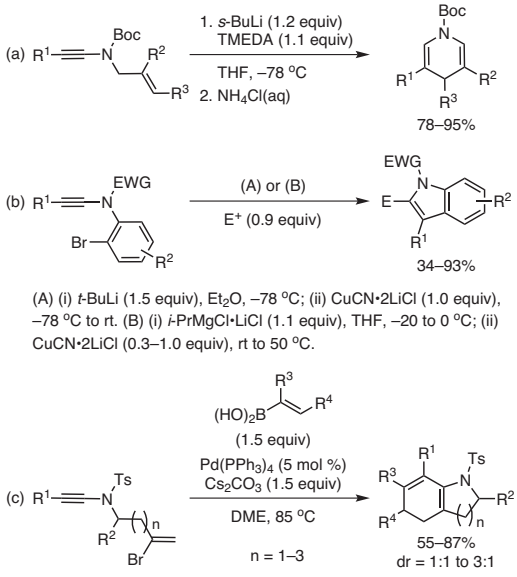
3.2. Intramolecular Carbometallation: New Perspectives in Heterocyclic Chemistry

The unique reactivity of ynamides towards organometallic reagents has also been exploited for the design of new syntheses in heterocyclic chemistry based on intramolecular carbometallation reactions. In this context, the capacity of the electron-withdrawing group to control the regioselectivity of an intramolecular carbolithiation has been used to prepare highly functionalized 1,4-dihydropyridines from *N*-allylynamides by a totally selective deprotonation and 6-*endo*-*dig* cyclization sequence (**Scheme 8**, Part (a)).[50]

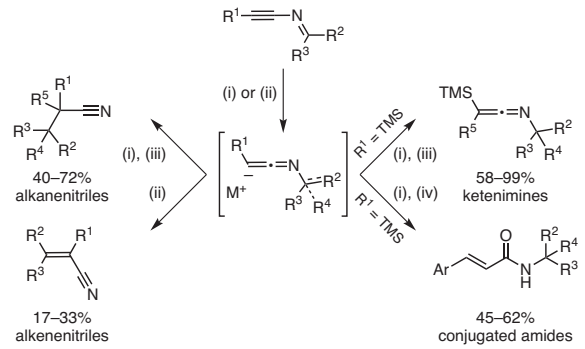
Other heterocycles that can be readily prepared by intramolecular carbometallation of ynamides include functionalized indoles—easily



Scheme 7. Intermolecular Carbometallation of Ynamides, Highlighting Control of the Regioselectivity and Remarkable Application in Asymmetric Synthesis. *(Ref. 47–49)*

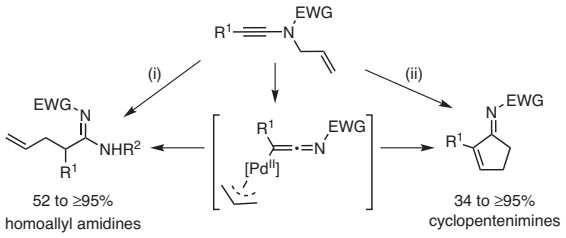


Scheme 8. Synthesis of Heterocycles by Intramolecular Carbometallation of Ynamides. *(Ref. 50–53)*



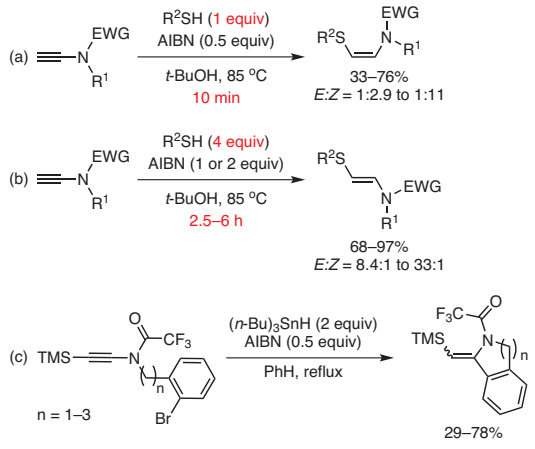
(i) R^4Li, THF, –78 °C. (ii) KHMDS, THF, –78 °C.
(iii) R^5X, –78 °C to rt. (iv) ArCHO, –78 °C to rt.

Scheme 9. Generation and Reactivity of Metallated Ketenimines from Ynimines. *(Ref. 54)*



(i) $Pd(PPh_3)_4$ (5 mol %), K_2CO_3 (1.0 equiv), R^2NH_2 (3.0 equiv), THF, 65 °C
(ii) $Pd(PPh_3)_4$ (5 mol %), PhMe, 70 °C

Scheme 10. Generation and Reactivity of Palladated Ketenimines from *N*-Allylynamides. *(Ref. 55,56)*



Scheme 11. Ynamides as Excellent Radical Acceptors. *(Ref. 59–61)*

obtained by carbocupration of readily available *N*-arylynamides (Scheme 8, Part (b))[51,52]—or their tetrahydro derivatives. Higher ring systems can be accessed from bromoenynamides by a palladium-catalyzed cyclization–cross-coupling–electrocyclization sequence (Scheme 8, Part (c)).[53]

4. Ynamides as Precursors of Metallated Ketenimines

If organometallic reagents and palladium catalysts can be utilized to generate metallated enamides from ynamides, as discussed in the previous paragraphs, they can also be employed to generate metallated ketenimines in situ, another useful class of reactive intermediates that are quite challenging to prepare despite their interesting reactivity.

The first strategy to generate these metallated ketenimines involves either the addition of an organolithium to ynimines or the deprotonation of the latter with a strong base. The metallated ketenimines can then be trapped with electrophiles, which provides a highly divergent and efficient entry to various building blocks, including highly substituted alkanenitriles, alkenenitriles, ketenimines, and conjugated amides (**Scheme 9**).[54]

The second strategy for the generation of metallated ketenimines is based on the palladium-catalyzed oxidative addition to the C–N bond of *N*-allylynamides. The products resulting from this oxidative addition are in equilibrium with the palladated ketenimine, which can then proceed down a number of reaction pathways including reductive elimination and reaction with amines yielding homoallyl amidines,[55] or an aza-Rautenstrauch rearrangement affording cyclopentenimines[56] (**Scheme 10**). The reductive elimination represents a straightforward and efficient entry to ketenimines, while the intermediate palladated ketenimines have found various elegant applications in the synthesis of complex heterocyclic systems.[57,58]

5. Ynamides as Radical Acceptors

Ynamides are also excellent radical acceptors and their use in free radical reactions provides many opportunities for the synthesis of nitrogen-containing molecules. There are still only few examples of intermolecular addition of radical intermediates to ynamides, the most notable being the addition of the electrophilic thiyl radicals. One equivalent of thiol in *tert*-butyl alcohol in the presence of AIBN as the radical initiator provides within 10 minutes the corresponding *Z* β-thioenamide—a moiety that is found in various natural products—as the main product. Employing an excess of thiol and longer reaction times affords mainly the *E* isomer (**Scheme 11**, Parts (a) and (b)).[59]

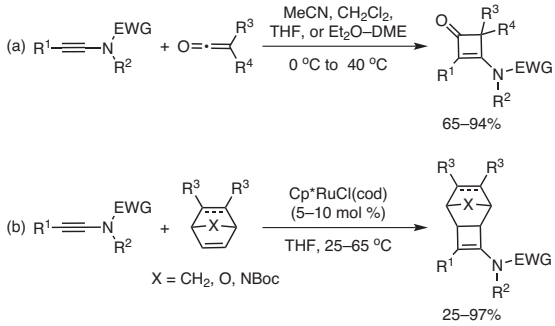
The beneficial use of ynamides as radical acceptors is even more evident in the intramolecular counterparts, since they afford efficient and original entries to nitrogen heterocycles of various sizes. The size of the heterocyclic ring is controlled simply by the length of the tether between the radical center and the ynamide (Scheme 11, Part (c)).[60,61]

6. Ynamides in Cycloaddition Reactions: Diversity-Oriented Syntheses of Heterocycles

The main problem of cycloadditions involving alkynes is that they often yield mixtures of regioisomers due to a poor differentiation of the two sp carbon atoms of the triple bond. This issue can be easily overcome by using ynamides since the inherent polarization of the triple bond ensures that high levels of regioselectivity are typically reached. Another clear advantage of ynamides in cycloaddition reactions lies in the intramolecular variants, which lead to the direct assembly of a wide range of heterocyclic scaffolds. These reactions are efficiently catalyzed by various metals, and representative examples are covered in this section.

6.1. [2 + 2] Cycloadditions

The most notable example of a formal [2 + 2] cycloaddition involving ynamides is the Ficini cycloaddition, which is actually a stepwise process involving the generation of an intermediate keteniminium ion followed by ring closure as described in Section 2.1.2 (Scheme 2, Part (c)). [2 + 2] cycloadditions with ynamides, which efficiently yield aminocyclobutenes, also include their highly regioselective thermal reaction with ketenes (**Scheme 12**, Part (a)).[62] This variant was recently extended to the use of ynesulfoximines,[63] iodoynamides,[64] and vinylketenes,[65] and is now a robust method for the synthesis of 3-aminocyclobutenones. Other examples of [2 + 2] cycloadditions with ynamides are the Ru- or Rh-catalyzed reactions with bicyclic alkenes (Scheme 12, Part (b))[66] and nitrostyrenes.[67]



Scheme 12. [2 + 2] Cycloadditions with Ynamides. *(Ref. 62,66)*

6.2. [3 + 2] Dipolar Cycloadditions

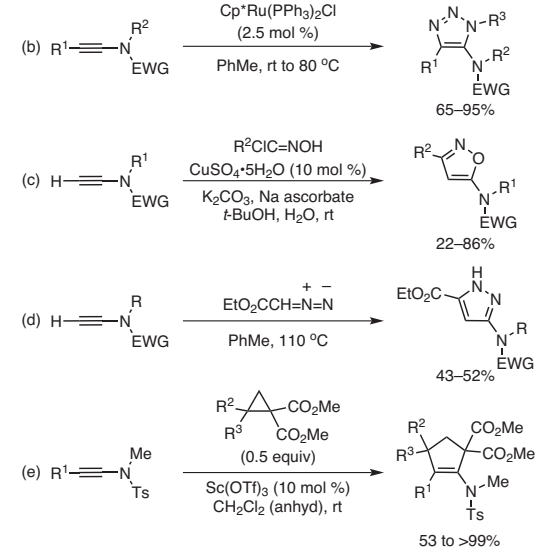
While most alkynes typically afford mixtures of regioisomers in dipolar [3 + 2] cycloaddition reactions, cycloadditions of ynamides with dipoles usually proceed with high levels of regioselectivity, and can therefore be employed for the preparation of an array of amino-substituted carbocycles and heterocycles (**Scheme 13**).[68–71] In addition, terminal ynamides are also remarkably efficient reaction partners for the copper-catalyzed Kinugasa reaction, an iconic route to β-lactams in which the first step involves a [3 + 2] cycloaddition with a nitrone. The use of an ynamide in this reaction offers two main advantages: it can introduce a nitrogen atom on the final β-lactam, or it can control the stereochemistry of the two stereocenters formed by starting from chiral ynamides.[72]

6.3. [4 + 2] Cycloadditions

The intramolecular [4 + 2] cycloadditions of ynamides can be a straightforward entry to various nitrogen heterocycles, and can be conducted either in the presence of a cationic rhodium catalyst from diene-ynamides (**Scheme 14**, Part (a)),[73] or thermally from enyne-containing ynamides (Scheme 14, Part (b)).[74,75]

An interesting extension—which increases the range of heterocyclic systems that can be conveniently synthesized from ynamides using a [4 + 2] cycloaddition strategy—was recently reported, and is based on a hexadehydro-Diels–Alder reaction of diyne-ynamides. This reaction, which can be performed either thermally[76] or in the presence of catalytic amounts of silver triflate (Scheme 14, Part (c)),[77] generates an intermediate aryne which can then be trapped by various nucleophiles to generate highly functionalized indolines.

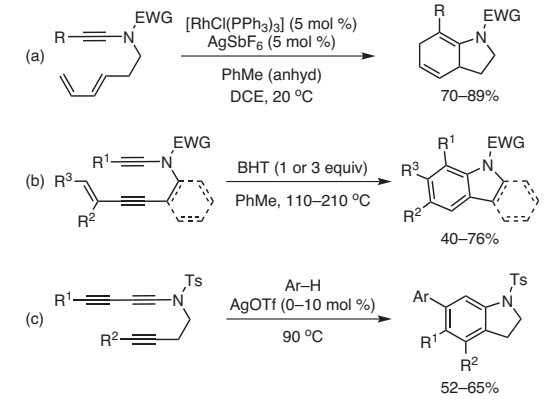
In addition to their remarkable [2 + 2], [3 + 2], and [4 + 2] cycloaddition reactions, ynamides have been elegantly utilized in [2 + 2 + x] reactions, providing entries to other molecular architectures. Here again, the success and the high levels of selectivity of these processes lie in most cases in the exceptional reactivity of ynamides. These reactions will be described in the following paragraphs.



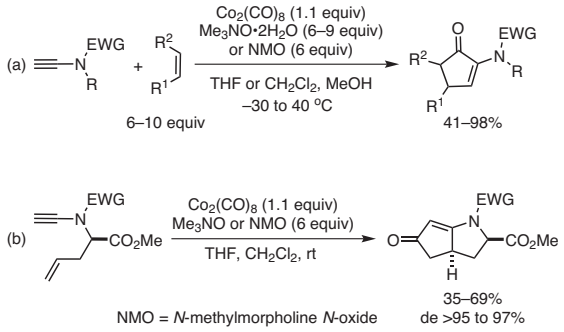
Scheme 13. Formal, [3 + 2] Dipolar Cycloadditions with Ynamides. *(Ref. 68–71)*

6.4. [2 + 2 + 1] Pauson–Khand Cycloadditions

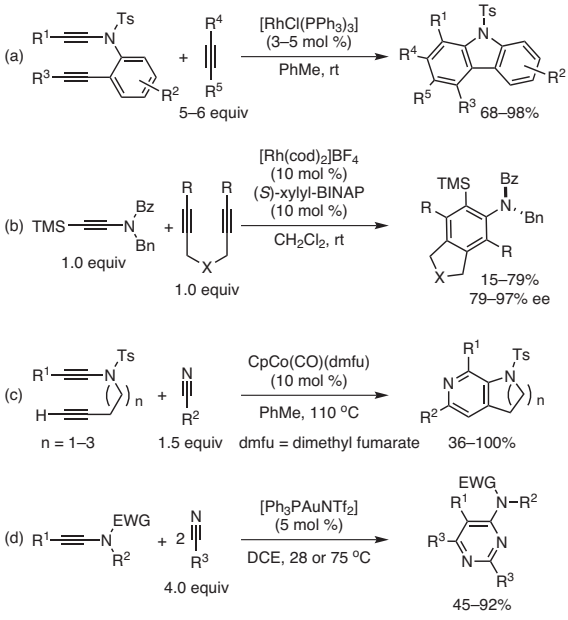
[2 + 2 + 1] reactions of ynamides are mostly associated with the Pauson–Khand reaction. As a gross simplification, the use of ynamides in this venerable reaction can be beneficial mostly in two cases: either in an intermolecular reaction in which the ynamide is utilized to introduce an exocyclic amine (**Scheme 15**, Part (a)),[78] or in intramolecular processes in which the nitrogen is incorporated into one of the rings formed during the cycloaddition. This latter case results in the diastereoselective formation of cyclopentapyrrol-5-one derivatives (Scheme 15, Part (b)).[79] In both cases, the reaction conditions are based on Schreiber's protocol and rely on the use of $[Co_2(CO)_8]$ and trimethylamine *N*-oxide.



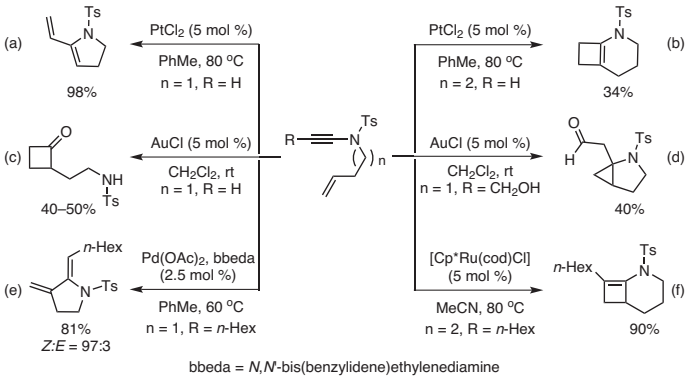
Scheme 14. [4 + 2] Cycloadditions with Ynamides. *(Ref. 73,74,77)*



Scheme 15. Pauson–Khand Reactions with Ynamides. *(Ref. 78,79)*



Scheme 16. [2 + 2 + 2] Cyclotrimerizations with Ynamides. *(Ref. 80–83)*



Scheme 17. Examples of Cycloisomerizations of Enynamides. *(Ref. 84,86,87)*

6.5. [2 + 2 + 2] Cycloadditions

The metal-catalyzed [2 + 2 + 2] cycloaddition of ynamides with alkynes and/or nitriles provides original entries to polysubstituted anilines, aminopyridines, and aminopyrimidines. These reactions have been extensively studied over the past decade and, in most cases, at least two reactants are tethered to ensure high levels of selectivity. Representative examples include the rhodium-catalyzed reaction of yne-ynamides with alkynes yielding polysubstituted carbazoles (**Scheme 16**, Part (a)),[80] the enantioselective cyclization of ynamides with diynes leading to axially chiral anilides (Scheme 16, Part (b)),[81] and the cobalt-catalyzed cyclotrimerization of yne-ynamides with nitriles affording bicyclic 3-aminopyridines (Scheme 16, Part (c)).[82]

While monomolecular versions of these reactions where all reactants are tethered together—which leads to the formation of one additional cycle—have also been reported, the corresponding trimolecular processes, in which serious issues with selectivity often arise, are still rare. One isolated example of such cyclotrimerization was reported in 2014, and is based on the gold-catalyzed, formal [2 + 2 + 2] cycloaddition of an ynamide with two equivalents of a nitrile (Scheme 16, Part (d)).[83] 4-Aminopyrimidines, which are commonly found in many bioactive molecules, are formed in high yields and with remarkable efficiency. The selectivity of this reaction was attributed to the electron-rich nature of the ynamide triple bond, which can be selectively activated by the gold catalyst.

7. Cycloisomerization of Ynamides: Rapid Approaches to Diverse Nitrogen Heterocycles

Heterocyclic scaffolds that are at the core structures of various natural and/or biologically relevant molecules can be accessed by cycloisomerization of ynamides possessing other reactive moieties such as an alkene or an allene. The cycloisomerization of homoallylic ynesulfonamides and their higher homologues is quite representative of the advances recently made in this area, and showcases the dramatic effect that both the metal catalyst and the substitution pattern of the starting ynamide can have on the outcome of the reaction. Indeed, upon reaction with a catalytic amount of $PtCl_2$, a 1,6-enynamide produced a vinyl-substituted dihydropyrrole (**Scheme 17**, Part (a)),[84] a compound which can also be obtained from the same enynamide using a ring-closing metathesis reaction.[85] Under the exact same conditions, a 1,7-enynamide exhibited a different behavior and led to the selective formation of a strained 2-azabicyclo[4.2.0]oct-1(6)-ene (Scheme 17, Part (b)).[84] A skeletal rearrangement of the 1,6-enynamide to an aminoethylcyclobutanone was promoted by a gold catalyst (Scheme 17, Part (c)).[86] The presence of a propargylic alcohol in the starting enynamide had a dramatic influence on the cycloisomerization reaction pathway, which led to the formation of a fused cyclopropylpyrrolidine (Scheme 17, Part (d)).[86] The combination of a 1,6-enynamide and a palladium(II) catalyst resulted in a cycloisomerized product possessing both a five-membered-ring heterocyclic core and an exocyclic diene (Scheme 17, Part (e)).[87] The ruthenium-catalyzed cycloisomerization of the 1,7-analogue afforded a 2-azabicyclo[4.2.0]oct-1(8)-ene (Scheme 17, Part (f)).[87] Since the outcome of these cycloisomerizations is now well understood, they clearly provide excellent opportunities for diversity-oriented synthesis in heterocyclic chemistry.

If enynamides clearly are ideal substrates in cycloisomerization reactions, the cycloisomerizations are not restricted to this subclass of ynamides. Other functional groups on the starting ynamides can be employed to access other types of cycloisomerization products. The silver-catalyzed cycloisomerization of allenynamides (**Scheme 18**,

Part (a))[88] and the gold-catalyzed transformation of furanyl-ynamides (Scheme 18, Part (b))[89] are two examples of this approach.

The reliability of the ynamide reactions described up till now, and the possibility of predicting the regioselectivity in most of them, have recently led to the design of more complex processes in which more than one cycle are formed in a single operation. These efficient polycyclization reactions from ynamides will now be briefly discussed.

8. Polycyclizations of Ynamides: Straightforward Routes to Complex Nitrogen Heterocycles

Most reactions involving ynamides can be taken one step further by carefully tuning the nature and position of substituents to promote cascade processes, leading to the selective formation of complex heterocyclic frameworks. In most cases, the activation of the ynamide triggers the polycyclization, and its presence typically controls the regioselectivity of the process.

The first cationic cascade involving ynamides was reported in 2014, and is based on a keteniminium ion initiated cascade polycyclization of *N*-benzyl- or *N*-allyl-*ortho*-tolylynamides. Upon reaction with excess triflic acid or catalytic amounts of bistriflimide, these ynamides are transformed into the corresponding highly reactive keteniminium ions. This induces a [1,5]-shift of hydrogen, an electrocyclization, and a Friedel–Crafts-type reaction (**Scheme 19**, Part (a)).[90] Polycyclic nitrogen heterocycles possessing up to three stereocenters and seven fused cycles can be easily obtained in a single operation: the comparison of this route with previously reported ones for accessing similar molecular architectures in more than ten steps clearly demonstrates the advantages of using ynamides.

The gold-catalyzed activation of ynamides can also be employed to promote polycyclization reactions via gold carbenoids. Treatment of an *N*-styryl *ortho*-azidophenyl ynamide with a cationic gold catalyst at room temperature generates the key carbenoid (by activation of the ynamide, nucleophilic attack of the azide, and extrusion of dinitrogen), which is trapped by the appended alkene to generate a cyclopropanindoloquinoline with remarkable efficiency (Scheme 19, Part (b)).[91]

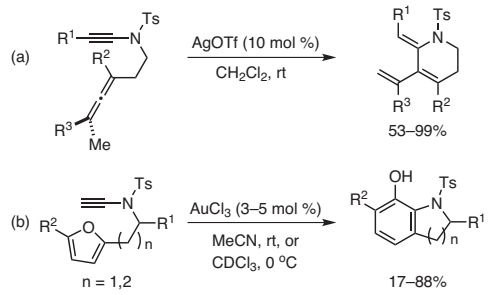
The vinylpalladium complex formed after an initial oxidative addition–carbopalladation sequence of a bromoenynamide (see Scheme 8, Part (c)) can also be utilized in a cascade polycyclization by further intramolecular carbopalladation of a second alkyne group in the starting acyclic precursor (Scheme 19, Part (c)).[92] Reactive aryne intermediates—which are conveniently generated by a silver-catalyzed formal [4 + 2] cycloaddition from diyne-ynamides as discussed in Section 6.3 (see Scheme 14, Part (c))—can also trigger a second cyclization by insertion into a C(sp^3)–H bond, affording multisubstituted cyclopentaindoles in excellent yields (Scheme 19, Part (d)).[93]

9. Ynamides as Building Blocks for the Synthesis of Natural Products: Enabling New and Original Bond Disconnections

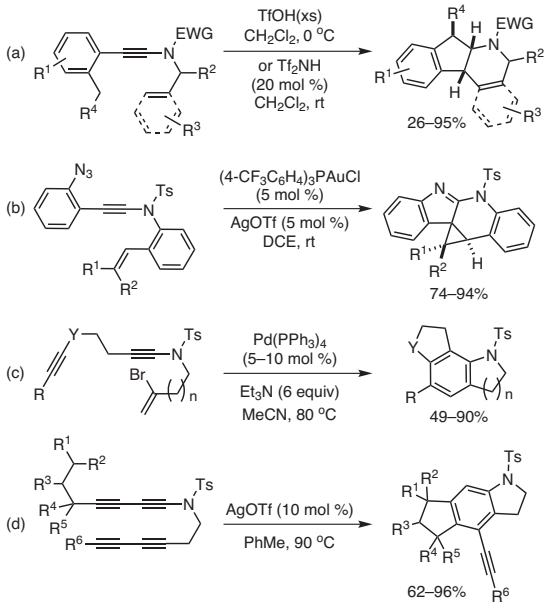
Previous sections demonstrated the tremendous advances recently reported in the chemistry of ynamides. Capitalizing on the remarkable reactivity of ynamides, a number of robust, reliable, and efficient processes have been developed over the past 15 or so years. Simple building blocks, heterocycles, reactive intermediates, as well as complex molecular architectures can efficiently be obtained from various ynamides. The attractiveness and reliability of some of these processes, which often also provide shorter and more efficient synthetic routes as compared to other approaches, have been exploited in the synthesis of various natural products, an area of chemistry where only the most robust and reliable methods can be employed.[94] **Figure 3** showcases a few of the natural and/or biologically relevant molecules that are readily obtained using an ynamide in a key step of the synthesis.[23,95–104] Importantly, ynamides are not only utilized for the introduction of a nitrogen atom, they can also be employed to access key intermediates in a synthetic sequence or to control the regio- and/or stereoselectivity of a reaction. In this latter case, the nitrogen atom of the starting ynamides can be sacrificial and does not necessarily have to be incorporated into the target molecule.

10. Conclusion and Outlook

The unique reactivity of ynamides has made them into powerful reagents for chemical synthesis. They are convenient precursors of highly reactive intermediates such as keteniminium ions or carbenoid species. They offer general, reliable, and often straightforward routes to many molecules ranging from simple building blocks and heterocycles to complex polycyclic structures and natural products. Chiral ynamides offer new opportunities in asymmetric synthesis, and various long-



Scheme 18. Other Cycloisomerizations of Ynamides. *(Ref. 88,89)*



Scheme 19. Cascade Polycyclizations of Ynamides. *(Ref. 90–93)*

standing synthetic challenges—such as the generation of stereodefined trisubstituted enolates,[49] the catalytic and stereocontrolled generation of dienolates,[105] and the preparation of an azacyclohexyne derivative[106]—have been, at least partially, solved by taking advantage of ynamide chemistry. In most cases, they do not only react as "nitrogen-substituted alkynes" or "*N*-alkynylamides", but their reactivity is in fact a subtle combination of both functional groups, and the ynamide moiety should in general be considered as a whole. Ynamides have been used recently in coordination chemistry, where they behave as stable equivalents of unstable oxazol-4-ylidenes.[107] Ynamides are also starting to find applications in medicinal chemistry. In spite of the widespread studies of ynamides, many aspects of their reactivity remain largely unexplored. Further understanding and quantification of the exact influence of the electron-withdrawing groups and other substituents on the reactivity of ynamides will facilitate the choice of a class of ynamides for a given application. In any case, this field is anticipated to continue to rapidly expand and mature, and interesting breakthroughs can be expected.

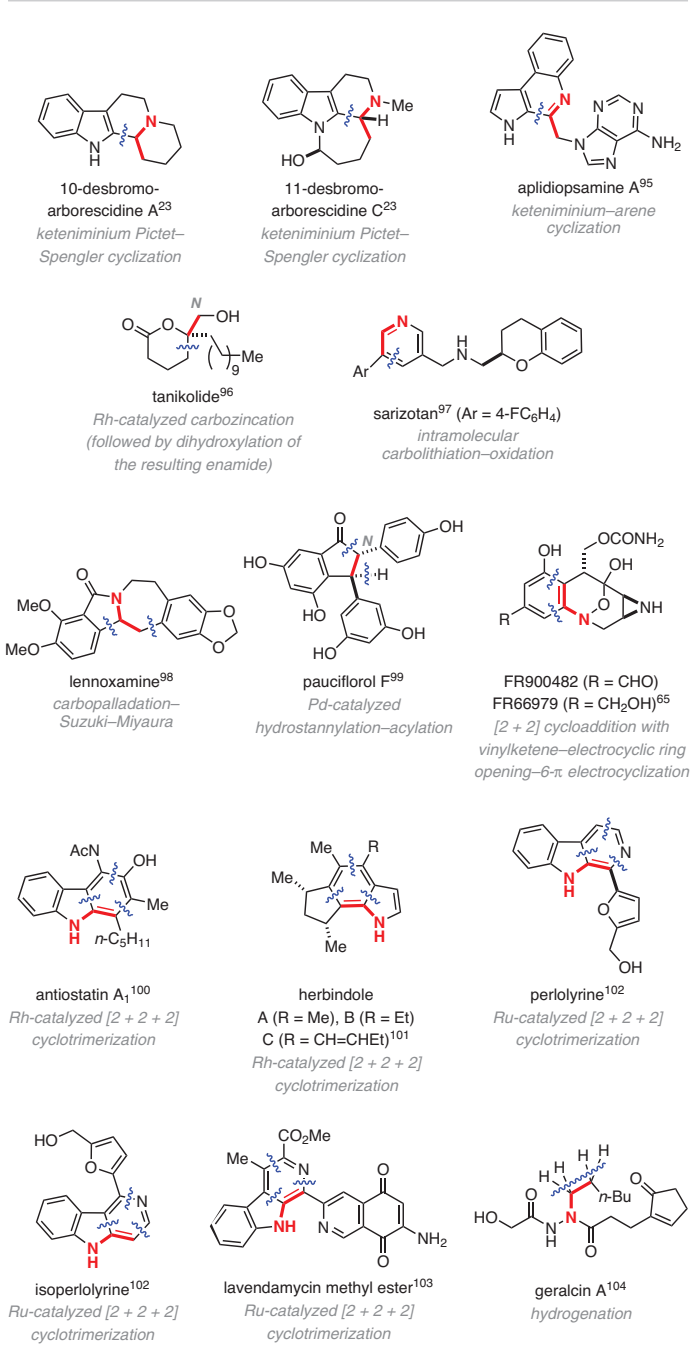


Figure 3. Natural and/or Biologically Relevant Molecules Synthesized from Ynamides (Bonds and Atoms Shown in Red Were Initially Part of the Starting Ynamides. In the Case Where the Nitrogen Atom of the Ynamide Was Not Incorporated in the Final Product, Its Initial Position Is Indicated by a Grey, Italic, and Upper-Case *N*. Key Bond Disconnections Involving the Ynamides Are Shown in Blue).

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Morgan Lecomte was born in 1988 in Arlon, Belgium, and studied chemistry at the Université Libre de Bruxelles. In 2012, he joined the Laboratory of Organic Chemistry as a master's student, working under the supervision of Professors Ivan Jabin and Gwilherm Evano on the use of hetero-substituted alkynes for the selective functionalization of calixarenes. He obtained an F.R.I.A. fellowship in 2013 to work toward his Ph.D. degree in the group of Prof. Gwilherm Evano, where he focuses on the study of the reactivity of ynamides and other hetero-substituted alkynes and on the development of new reactions and processes from these building blocks.

Cyclic Sulfamidate Enabled Syntheses of Amino Acids, Peptides, Carbohydrates, and Natural Products


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Keywords. regiospecific; stereospecific; ring-opening; unnatural amino acid; chiral building block; natural product; cyclic sulfamidate.

Abstract. This article reviews the emergence of cyclic sulfamidates as versatile intermediates for the synthesis of unnatural amino acids, chalcogen peptides, modified sugars, drugs and drug candidates, and important natural products.

Outline

1. Introduction

Cyclic sulfamidates are synthetic intermediates that are readily accessible from both amino acids and amino alcohols, and form a versatile set of electrophiles that can undergo facile and regiospecific nucleophilic substitution at the O-bearing carbon center. Synthetically, five- and six-membered-ring sulfamidates are equivalent to aziridines and azetidines. However, cyclic sulfamidates have several advantages over aziridines and azetidines in terms of reactivity and selectivity (**Figure 1**, Part (a)). The present article reviews exciting recent advances in organic synthesis enabled by cyclic sulfamidates.

2. Structural Analysis and Reactivity of Cyclic Sulfamidates

Cyclic sulfites (1,3,2-dioxathiolane 2-oxides, **1**) and cyclic sulfates (1,3,2-dioxathiolane 2,2-dioxides, **2**) are the sulfite and sulfate esters of diols, and are the synthetic equivalents of epoxides. Cyclic sulfamidites (1,2,3-oxathiazole 2-oxide, **3**) and sulfamidates (1,2,3-oxathiazole 2,2-dioxides, **4**) are the corresponding sulfite and sulfate esters of amino alcohols, and are the synthetic equivalents of aziridines (Figure 1, Part (b)). Although compound classes **1**–**4** have been known for a long time,

their general application in synthesis became possible only after the development of efficient methods for their synthesis. Derivatives **3** and **4** can be better alternatives to aziridines, since they are not encumbered with regioselectivity issues; sulfamidates (**4**), an activated form of sulfamidites (**3**), have a great potential as nitrogenous electrophiles for regioselective ring-opening under mild conditions.

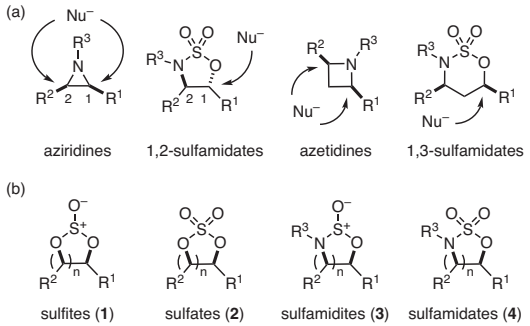
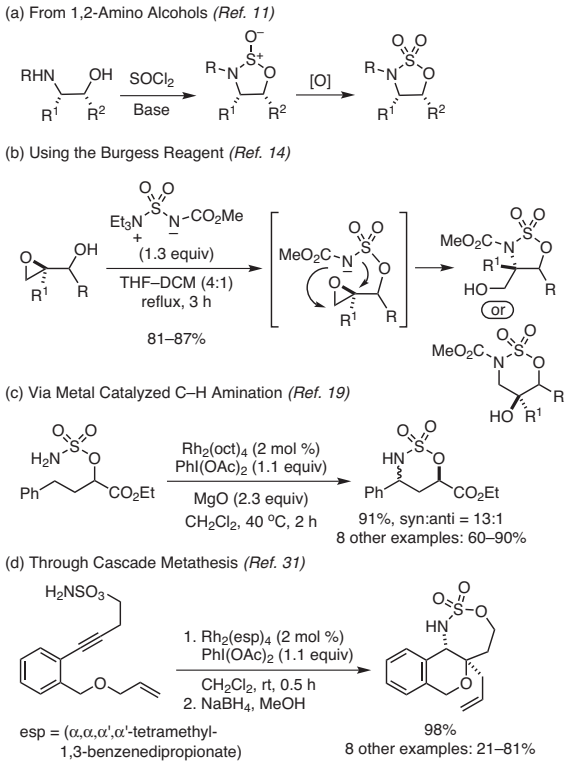


Figure 1. (a) Preferred Sites of Nucleophilic Attack in Aziridines, Azetidines, and Cyclic Sulfamidates. (b) Cyclic Sulfite and Sulfate Derivatives of Diols and Amino Alcohols.



Scheme 1. Syntheses of Cyclic Sulfamidates.

3. Synthesis of Cyclic Sulfamidates

McCombie and Parkes discovered cyclic sulfamidites by accident in 1912.[1] However, they remained little used until 1969, when Deyrup and Moyer's unsuccessful attempt to prepare aziridines from 1,3-amino alcohols led to the formation of cyclic sulfamidites instead.[2] While this became thereafter a practical method for their synthesis,[3] the sluggish reactivity of sulfamidites, and the need to employ drastic conditions in their reactions, prevented their wider use in organic synthesis.[4] The sluggish reactivity of sulfamidites has been overcome by converting them into the corresponding sulfamidates.[5–7]

3.1. From 1,2-Amino Alcohols

Cyclic sulfamidates can be prepared directly in one step from 1,2-amino alcohols by treatment with SO_2Cl_2 or SO_2Im_2.[8] This method, however, found limited success in the case of conformationally constrained 1,2-amino alcohols, such as 2-aminophenols and prolinols,[9] and cannot be utilized as a general preparative method due to competitive aziridination and/or azitidation. Consequently, a two-step approach that mirrors the synthesis of cyclic sulfates[10] has been developed, whereby treatment of 1,2- or 1,3-amino alcohols with $SOCl_2$ leads to the efficient formation of cyclic 1,2- and 1,3-sulfamidites[2] that are then oxidized to the sulfamidates (**Scheme 1**, Part (a)).[11]

3.2. From Diols and Epoxides Using the Burgess Reagent

The Burgess reagent is prepared from chlorosulfonyl isocyanate and triethylamine in a simple, two-step procedure.[12] Nicolaou and co-workers have shown that this reagent can be utilized to synthesize cyclic sulfamidates from diols via a double alcohol activation mechanism,[13] and applied this approach to the synthesis of functionalized chiral sulfamidates from allyl epoxides (Scheme 1, Part (b)).[14] This method allows the direct conversion of diols (1,2-diols, 1,3-diols, etc.) into the corresponding sulfamidates, with the regioselectivity being dependent on the stereoelectronic preferences of the diols. Hudlicky and co-workers have also demonstrated that cyclic sulfamidates can be accessed from epoxides by treatment with the Burgess reagent.[15]

3.3. Via Metal-Catalyzed C–H Amination

Capitalizing on the discovery by Breslow and Gellman,[16] Che and co-workers demonstrated that intermolecular nitrogen insertion into an unactivated C–H bond is possible via Ru- or Mn-catalyzed nitrene insertion.[17] This strategy was applied to cyclic sulfamidates by using the enantioselective intramolecular amidation of saturated C–H bonds catalyzed by a Ru-porphyrin chiral complex.[18] Du Bois and co-workers reported a similar protocol using a Rh-catalyzed reaction (Scheme 1, Part (c)).[19] Che's and Du Bois's methods involved intramolecular cyclization of sulfamate ester wherein the cyclization results most of the time in the formation of six-membered-ring cyclic sulfamidates.[20,21] Some sluggish substrates give five- or even seven-membered-ring sulfamidates.[20] This study led to the development of a modular method for the synthesis of sulfamidates from sulfamate esters.[22] Cui and He have employed silver metal in combination with phenyliodonium acetate for the intramolecular cyclization of sulfamate esters.[23] There have been other strategies utilizing Rh, Cu, and Au metal salts or complexes for the formation of seven-membered-ring sulfamidates, where the nitrogen is also a part of an aziridine ring system.[24–25] Although the metal-catalyzed synthesis of cyclic sulfamidates has been well established using C–H activation, the asymmetric variant has not been generalized. Che[26] employed chiral manganese(III) Schiff-base complexes, while Müller[27,28] attempted the use of rhodium chiral complexes as catalysts for the enantioselective synthesis of

cyclic sulfamidates. However, moderate asymmetric inductions were observed in both cases. In contrast, Du Bois's use of a chiral rhodium carboxamidate complex[29] and Blakey's demonstration of cationic ruthenium(II)-pybox systems[30] have provided a reasonable, practical synthesis of chiral cyclic sulfamidates.

3.4. Through Cascade Metathesis

Blakey and co-workers disclosed an unconventional method for the synthesis of cyclic sulfamidates using a cascade metallonitrene–alkyne metathesis process.[31] Their study was based on the hypothesis that the metallonitrene species would react with an alkyne, leading to a zwitterionic intermediate; this would be followed by a metal shift that precipitates a cascade cyclization coupled with a concerted imine reduction. The method has been very useful for the synthesis of six- and seven-membered-ring sulfamidates (Scheme 1, Part (d)).[31–32]

3.5. By Hydrogenation and Transfer Hydrogenation

Treatment of α-hydroxy ketones with sulfamoyl chloride (H_2NSO_2Cl) affords the corresponding cyclic imines which can be hydrogenated to sulfamidates. The asymmetric variant gives direct access to enantioenriched cyclic 1,2-sulfamidates as in the case of the Pd/binaphane one (**Scheme 2**, Part (a)).[33] The reaction proceeds efficiently and gives quantitative yields in almost all cases. Lee and co-workers, reported that RhCl(*R,R*)-TsDPEN]Cp* catalyzes an asymmetric transfer hydrogenation using formic acid and triethyl amine as the hydrogen source.[34,35]

3.6. By Arylation of Cyclic N-Sulfamidate Alkylketimines

Feng, Lin, and co-workers developed a new route for the enantioselective synthesis of sulfamidates by 1,2-arylation of cyclic *N*-sulfamidate alkylketimines with arylboronate esters. A range of enantiomerically pure substituted cyclic sulfamidates have been prepared in 19–99% yield by this method in the presence of a chiral rhodium–diene complex as a catalyst (Scheme 2, Part (b)) These sulfamidates provide access to biologically interesting and enantiomerically pure β-alkyl-β-aryl amino alcohols.[36]

3.7. Through Aminohydroxylation of Sulfamate Esters

Inspired by the intramolecular aminohydroxylation of carbamates derived from allylic alcohols,[37] Kenworthy and Taylor employed the aminohydroxylation of sulfamate esters derived from homoallylic alcohols for the synthesis of six-membered-ring sulfamidates (Scheme 2, Part (c)).[38]

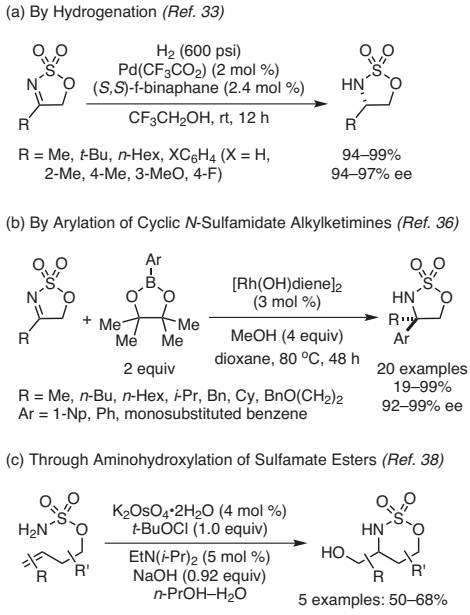
4. Ring-Opening Reactions of Cyclic Sulfamidates

The main driving force in aziridine and azetidine chemistry comes from the ring strain, which is lacking in five- and higher-membered-ring nitrogen heterocycles. In contrast, the reactivity in sulfamidate ring-opening reactions is attributed to the activation of the C–O bond by the SO_2 group, which makes them good electrophiles that can react with a variety of heteroatom and carbon nucleophiles. Moreover, their ability to undergo regioselective ring-opening reactions augments their synthetic value.

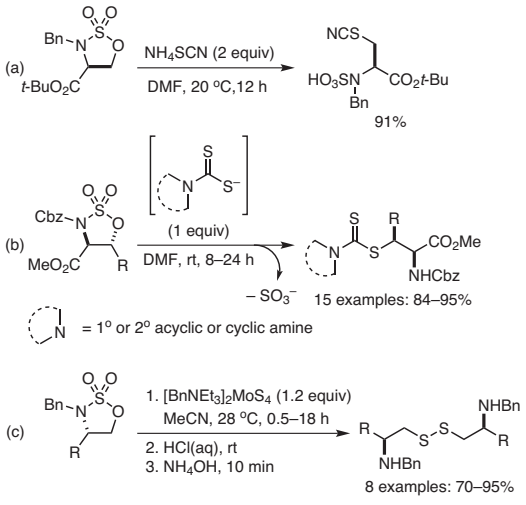
4.1. Heteroatom Nucleophiles

4.1.1. Sulfur Nucleophiles

The ring-opening of sulfamidates with ammonium thiocyanate gives 3-thiocyanate alanine derivatives (**Scheme 3**, Part (a)).[39,40] Lubell and co-workers were able to confirm that the stereoselectivity of the reaction is not compatible with an elimination–addition mechanism which would result in racemization.[3–5] The free thiol group is not a suitable nucleophile for the opening of five-membered-ring sulfamidates bearing an α-carbonyl group; in combination with a base it leads to the formation of dehydro amino acids. Thioacetates, a stabilized form of thiol nucleophiles, serve as masked thiols in reactions with sulfamidates to give amino thioacetate derivatives.[41] Our group has demonstrated the usefulness of in situ generated dithiocarbamates, another type of stabilized sulfur nucleophile, in sulfamidate chemistry (Scheme 3, Part (b)).[42] The addition of in situ generated dithiocarbamate anion to cyclic sulfamidates leads to stereo- and regioselective ring-opening to form



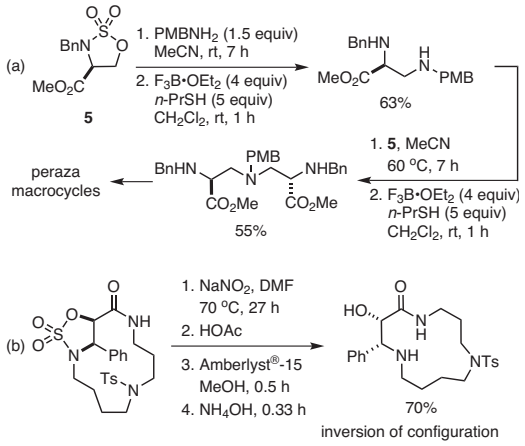
Scheme 2. Additional Syntheses of Cyclic Sulfamidates.



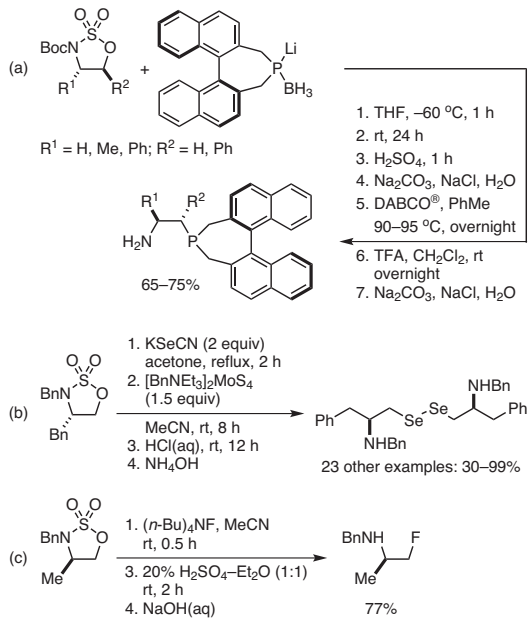
Scheme 3. Ring-Opening of Sulfamidates with Sulfur Nucleophiles. (*Ref. 39,40,42,43*)

the optically pure products in high yield (84–95%). Chandrasekaran and co-workers have effected the ring-opening of sulfamidates using $[BnEt_3N]_2MoS_4$, which acts as a sulfur-transfer reagent via disulfide bond formation. The reaction proceeds efficiently in acetonitrile to give the *N*-alkyl-β-amino disulfides directly (Scheme 3, Part (c)).[43]

Interestingly, $[BnEt_3N]_2MoS_4$ exhibited anomalous behavior in the reaction with sulfamidates derived from diols by using the Burgess reagent. Its reaction with sulfamidates under conditions similar to those shown in Scheme 3, Part (c), resulted in the formation of β-amino thiols instead of β-amino disulfides.[44] This regio- and stereoselective ring-opening of sulfamidates provides an efficient, direct, and altenative route to conventional methods for the synthesis of β-amino thiols via the acid-catalyzed ring-opening of aziridines with hydrogen sulfide or with the sodium or potassium salt of thioacetic acid, followed by deprotection of masked thiols.[45] Five-membered-ring sulfamidates give β-amino thiols, whereas the reaction of six-membered-ring sulfamidates forms γ-amino thiols.[44]



Scheme 4. Ring-Opening of Cyclic Sulfamidates with (a) Nitrogen and (b) Oxygen Nucleophiles. *(Ref. 47,51)*



Scheme 5. Ring-Opening of Cyclic Sulfamidates with (a) Phosphorus, (b) Selenium, and (c) Halogen Nucleophiles. *(Ref. 54–56)*

4.1.2. Nitrogen Nucleophiles

The nucleophilic nitrogen can be that of a primary amine, secondary amine, azide, or even that of a heterocyclic system such as imidazole or related scaffold. Sodium azide reacts with cyclic sulfamidates to give the corresponding amino azide derivatives, with no apparent restriction on substrate structure and substituents.[46] Primary and secondary amines react efficiently with cyclic sulfamidates to give the corresponding diamine derivatives (**Scheme 4**, Part (a)).[47] The ring-opening with a heterocyclic system nitrogen has been employed effectively to prepare chiral 2,3-diaminopropanoate derivatives.[48]

4.1.3. Oxygen Nucleophiles

The ring-opening of sulfamidates has been unsuccessful with most strong oxygen nucleophiles (e.g., sodium methoxide). The possible hydrolysis of serine- or threonine-derived cyclic sulfamidates with sodium bicarbonate in deuterated water (D_2O) has been disappointing,[49] and the ring-opening of α-methylserine-derived sulfamidates gave a very poor yield of ring-opened products.[40] The first successful ring-opening of sulfamidates was achieved with weakly basic oxygen nucleophiles, and was further exemplified using stabilized phenoxy ions.[50] Khanjin and Hesse utilized $NaNO_2$ for the ring-opening of sulfamidates, which was followed by hydrolysis to give macrocyclic alcohols (Scheme 4, Part (b)).[51]

4.1.4. Phosphorus Nucleophiles

The introduction of phosphorus has been very difficult due to its sensitivity to the reaction conditions and substrate structure. Although many N–P chiral ligands have been synthesized, severe problems have been encountered in terms of byproduct formation and purification.[52] Chiral 1-isopropylamino-2-(diphenylphosphino)ethanes can be synthesized through ring-opening of chiral, cyclic sulfamidates with potassium diphenylphosphide ($KPPh_2$).[53,54] This method has been extended to the synthesis of protic aminophosphines with multiple chiral centers by the nucleophilic ring-opening of N-protected cyclic sulfamidates. The introduction of another chiral center into the aminophosphine backbone using nucleophilic phosphide—derived from the reaction of butyllithium and the respective phosphine–borane—was a significant finding that was extended to the synthesis of a wide range of multicenter phosphine ligands (**Scheme 5**, Part (a)).[53,54]

4.1.5. Selenium Nucleophiles

Chandrasekaran and co-workers reported the synthesis of chiral *N*-benzyl-β-aminodiselenides in moderate-to-good yields via a regio- and steroselective ring-opening of sulfamidates with potassium selenocyanates (Scheme 5, Part (b)).[55] The reaction proceeds through selenocyanate intermediates, which, on dimerization with tetrathiomolybdate, afford the *N*-benzyl-β-aminodiselenide products.

4.1.6. Halogen Nucleophiles

Among halogens, fluoride ion has been employed for the nucleophilic ring-opening of sulfamidates to afford, in the case of five-membered-ring

sulfamidates, β-amino fluorides. KF/CaF_2 or ammonium fluorides have been used as sources of nucleophilic fluorines (Scheme 5, Part (c)).[56]

4.2. Carbon Nucleophiles

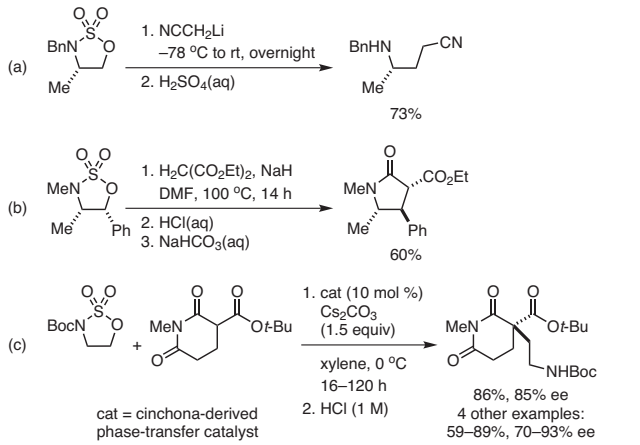
4.2.1. Hard Carbon Nucleophiles

The ring-opening of sulfamidates with aryllithium reagents (e.g., phenyl-, 3,4-dimethoxyphenyl-, and 2-thienyllithium) has been reported.[57] While the reaction of cyclic sulfamidates with alkyllithiums failed initially,[58] the reaction of alaninol-derived sulfamidates with alkyllithiums such as di(*n*-butyl)lithium cuprate, lithiated acetonitrile, and lithiated 1,3-dithiane afforded the corresponding amines (**Scheme 6**, Part (a)).[59] The same reaction with PhLi or *n*-BuLi gave a mixture of products, presumably due to competitive attack at the electrophilic C-5 and S centers. Similarly, the reaction of hard carbon nucleophiles (such as alkyllithium, Grignard reagents, etc.) with serine- and threonine-derived sulfamidates consistently led to mixtures of products due to competitive attack at the reactive carbonyl group.

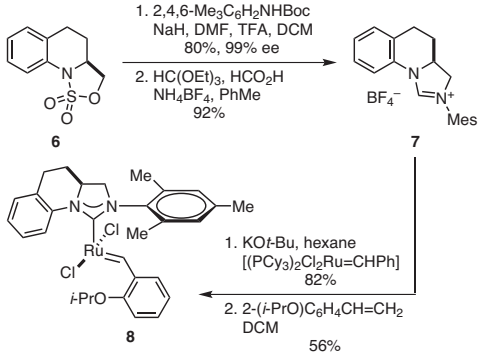
4.2.2. Soft (Stabilized) Carbon Nucleophiles

It is believed that the softening of carbon nucleophiles through conjugation or stabilization would result in increased selectivity. Cyanide ion is the most stable of carbon nucleophiles; it can react with any type of sulfamidates to give the corresponding aminonitrile derivatives.[60] Cyclic sulfamidates react with most of the stabilized carbon nucleophiles (e.g. β-keto esters, diethyl malonates, aryl-substituted enolates, and phosphonate-stabilized enolates) to give the cyclized product in the presence of a proximate ester, ketone, or amine functional group (Scheme 6, Part (b)).[61]

Many natural products bearing aminoethylene and aminopropylene scaffolds at a quaternary stereocenter are known in the literature.[62] These aminoalkenes can be incorporated at quaternary centers through the enantioselective ring-opening of aziridines and azetidines. However, these electrophiles require activation at nitrogen, and, typically, a wide range of activating groups need to be screened along with asymmetric induction. In contrast, the reaction of cyclic sulfamidates with *tert*-butyl 1-methyl-2,6-dioxopiperidine-3-carboxylate in the presence of a cinchona-derived phase-transfer catalyst readily gives the ring-opened product (Scheme 6, Part (c)). The variation in ring size and protecting group at the nitrogen atom in the sulfamidates does not alter the reaction outcome.[63]



Scheme 6. Ring-Opening of Cyclic Sulfamidates with (a) Hard Carbon Nucleophiles and (b, c) Soft Carbon Nucleophiles. *(Ref. 59,61,63)*



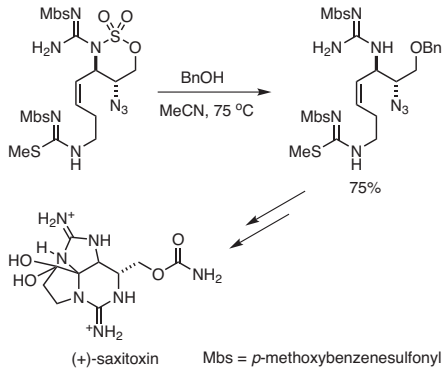
Scheme 7. Cyclic Sulfamidates for the Synthesis of Asymmetric Ligands of Chiral Olefin-Metathesis Catalysts. *(Ref. 64)*

5. Applications of Cyclic Sulfamidates in Heterocycle and Natural Product Synthesis

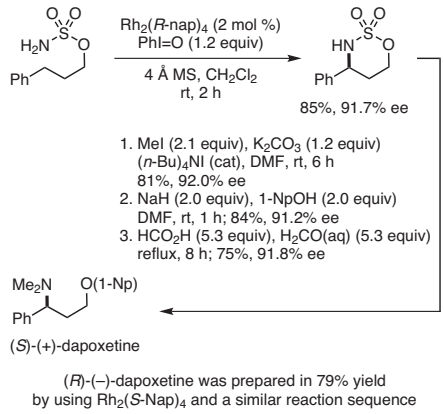
Blechert and co-workers utilized cyclic sulfamidates for the synthesis of asymmetric ligands that are incorporated into highly active, chiral olefin-metathesis catalysts (**Scheme 7**).[64,65] Cyclic sulfamidate **6** was converted into chiral diamine **7**, in high yield and with high enantioselectivity, through a regioselective ring-opening with Boc-mesidine. Chiral diamine **7** was then elaborated into chiral ruthenium catalyst **8** in two straightforward steps.

5.1. (+)-Saxitoxin

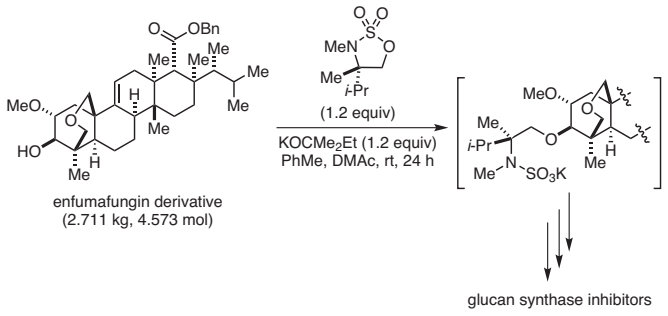
Neurotoxic agents are important pharmacological scaffolds used for understanding protein function associated with the ionic mechanisms of electrical transmission in cells. The guanidinium toxins such as (+)-saxitoxin and (–)-tetrodotoxin are exemplary in this regard, and have been employed for the study of voltage-gated sodium channels along with their identification and characterization. The basic saxitoxin skeleton was assembled from cyclic sulfamidate, and converted into (+)-saxitoxin and its derivatives (**Scheme 8**).[66]



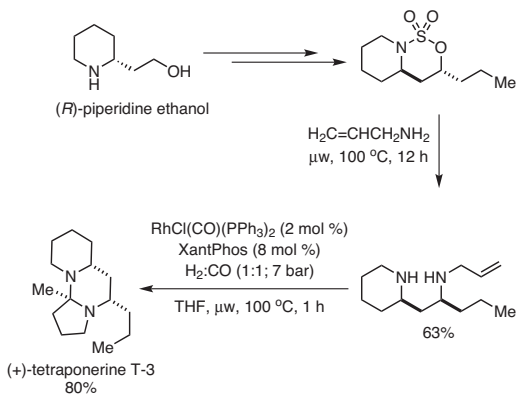
Scheme 8. Cyclic Sulfamidate Ring-Opening as a Key Step in the Synthesis of (+)-Saxitoxin. *(Ref. 66)*



Scheme 9. (*S*)-(+)- and (*R*)-(–)-Dapoxetines from Cyclic Sulfamidates. *(Ref. 67)*



Scheme 10. Cyclic Sulfamidate Allows a Direct and Milder Incorporation of the Side Chain en Route to a Large-Scale Semisynthesis of Enfumafungin Derivatives. *(Ref. 70)*



Scheme 11. Cyclic Sulfamidate as Key Intermediate in the Synthesis of (+)-Tetraponerine T-3 Alkaloid. *(Ref. 71)*

5.2. (S)-(+)- and (R)-(–)-Dapoxetines

(*S*)-(+)-Dapoxetine hydrochloride is a potent and selective serotonin reuptake inhibitor, and is used specifically for the treatment of premature ejaculation. It is obtained from racemic dapoxetine by tartaric acid promoted chiral resolution, or from chiral amino alcohols through enzymatic synthesis. In contrast, Du Bois's method, employing Rh_2(*S*-nap)$_4$ or Rh_2(*R*-nap)$_4$, provides both enantiomers of the cyclic 1,3-sulfamidate precursors, which are easily converted into (*S*)-(+)- and (*R*)-(–)-dapoxetines using a straightfoward reaction sequence (**Scheme 9**).[67]

5.3. Antifungal Glucan Synthase Inhibitors

Enfumafungin, isolated from a fermentation of a *Hormonema* species, is capable of inhibiting fungal glucan synthase, and two novel enfumafungin derivatives have been identified as potent glucan synthase inhibitors.[68] The installation of the side chain was accomplished by S_N2 ring-opening of an N-tosylated aziridine by the in situ generated potassium alkoxide of the starting material.[69] The replacement of aziridine with its synthetic equivalent, a five-membered-ring sulfamidate, allows the direct incorporation of the side chain under milder condition (**Scheme 10**).[70]

5.4. (+)-Tetraponerine T-3

The tetraponerines constitute a family of alkaloids that pseudomyrmecine ants of the genus *Tetraponera* deploy as paralyzing venoms in chemical warfare. Their challenging tricyclic skeleton and biological activities make them attractive targets for total synthesis.[71] Mann and co-workers reported the synthesis of (+)-tetraponerine T-3 starting from chiral (*R*)-piperidine ethanol and using sulfamidate as a key intermediate en route to the strategically important diamine. The diamine was directly converted into (+)-tetraponerine T-3 in a one-pot hydroformylation and cyclization process (**Scheme 11**).[71]

5.5. Pyrrolidinones and Piperidinones

The reactions of five- and six-membered-ring sulfamidates with enolates derived from malonate afford access to C–3 carboxylated lactams, such as pyrrolidinone and piperidinone derivatives, in excellent yields.[61,72] It is important to note that the lactamization is dependent on the ring size: formation of six-membered rings is slower than that of five-membered rings. The reaction of cyclic sulfamidates with phosphonate-stabilized enolates gives α-phosphono lactams,[73] which are amenable to double-bond installation through a Wadsworth–Emmons olefination. Elevated temperatures are required to achieve C–O bond cleavage, which leads to the competitive decomposition of the enolate component possibly due to nucleophilic attack on phosphorus.[74] Gallagher and co-workers have demonstrated the use of α-sulfinyl-substituted nucleophiles in sulfamidate ring-opening reactions, which lead upon hydrolysis to the lactamization product.[75] The strategy could not be extended to other cyclic sulfamidates due to competing sulfoxide elimination at higher temperatures, leading to the formation of complex mixtures. Switching to the α-phenylsulfenyl group [PhS(=O)–] on the enolate component helped generate an array of α-sulfenylated lactams in good-to-excellent yields. The sulfenylated lactams can be easily converted into unsaturated lactams by a Pummerer rearrangement. The strategy was employed for the synthesis of alkylidene pyrrolidines and piperidines starting with cyclic sulfamidates, which undergo ring-opening with the dianion of ethyl acetoacetates, followed by in situ *N*-sulfate hydrolysis and intramolecular condensation onto the intermediate ketone.[76] The most important application of sulfamidate chemistry in this regard has been the enantioselective total synthesis of (–)-paroxetine (**Scheme 12**, Part (a))

and (+)-laccarin.[76] Gallagher also utilized sulfamidates in the synthesis of (–)-aphanorphine, a natural product isolated from the freshwater blue-green algae, *Aphanizomenon flos-aquae* (Scheme 12, Part (b)).[77–81] These syntheses proceed through pyrrolidinone or piperidinone intermediates, which have also been utilized in the synthesis of natural products and their heterocyclic analogues.[76–81]

5.6. Thiomorpholinones and Piperazinones

Cyclic 1,2-sulfamidates, even sluggish ones possessing both primary and secondary electrophilic centers, react with methyl thioglycolate to give chiral thiomorpholinones in excellent yields (**Scheme 13**, Part (a)).[79] Gallagher's group extended this methodology to the synthesis of piperazinones, wherein phenylalanine-derived cyclic sulfamidates provide the corresponding piperazinones (Scheme 13, Part (b)).[79] Bicyclic systems such as praziquantel can be constructed by employing different amino-based nucleophiles;[6] a phenylalanine-derived cyclic sulfamidate reacts efficiently with enantiotopic proline ethyl esters to afford bicyclic piperazinones.[79] The ring-opening of an enantiopure cyclic sulfamidate with the indole nitrogen of indolecarboxylic acid methyl ester provides the corresponding pyrazino-indole with 98% ee.[80]

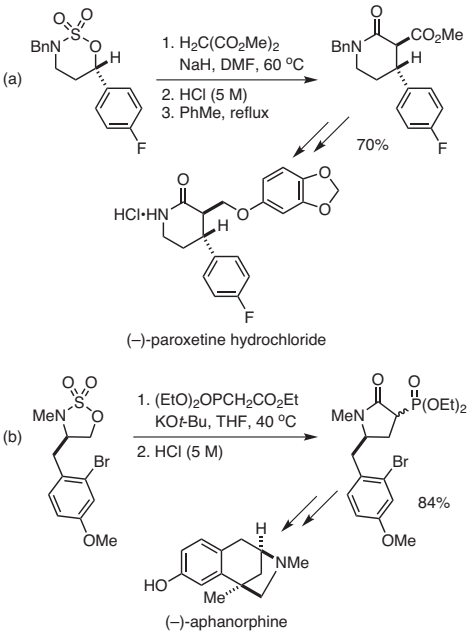
5.7. 1,4-Benzoxazines, Benzothiazines, and Quinoxalines

The ring-opening of sulfamidates with aromatic amines, phenols, or thiophenols under basic conditions, in combination with a Pd-catalyzed Buchwald-type amination, opens a new avenue for the synthesis of 1,4-benzoxazines, benzothiazines, and quinoxalines. For example, when the ring-opening of cyclic sulfamidates with 2-bromophenols is followed by *N*-sulfate hydrolysis and Pd-catalyzed amination, substituted and enantiopure 1,4-benzoxazines are obtained in good-to-high yields (**Scheme 14**, Part (a)).[81]

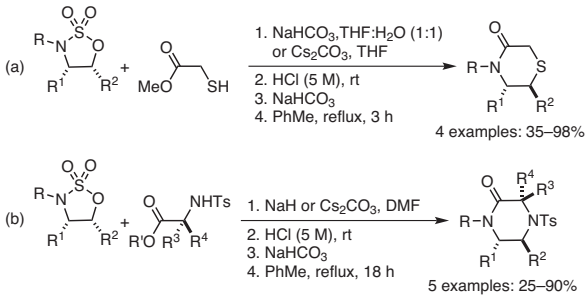
(–)-Levofloxacin is one of the major antibiotic drugs used to treat a wide range of infections, and is active against both gram-positive and gram-negative bacteria. The crucial step in its preparation was the asymmetric synthesis of the chiral benzoxazine core from the sulfamidate. The benzoxazine intermediate was then easily converted into (–)-levofloxacin in a few simple steps.[81,82] The seven-membered-ring variants of benzoxazine are important in pharmaceutical applications.[83] Tetrahydro-1,4-benzothiazepines S107 and JTV519 are being evaluated for treating conditions linked to the stabilization of cardiac ryanodine receptors (RyR1) that leak Ca^{2+} when subjected to stress.[84,85] The usefulness of cyclic sulfamidates in this area was proven by the synthesis of relevant seven- and eight-membered-ring heterocycles (Scheme 14, Part (b)).[85]

5.8. Carbohydrates

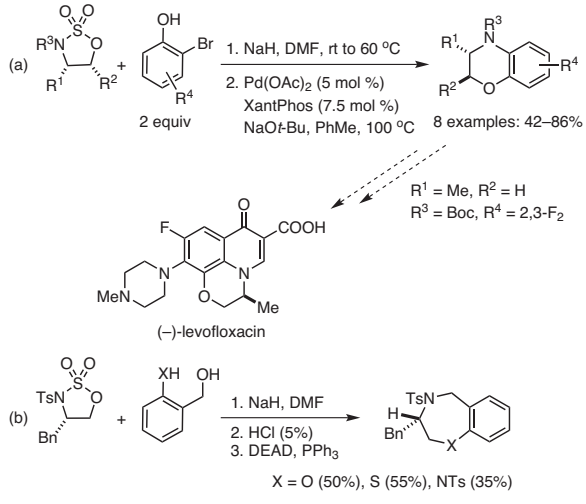
A wide range of diols on different carbohydrate scaffolds (e.g., D-Glc, D-Gal, L-Rha, D-Rib, etc.) can be converted into the corresponding sulfamidates by using the Burgess reagent.[86] Nucleophilic ring-opening of these sulfamidates with sodium azide permits the synthesis of α-glycosylamines.[86] The ring-opening of carbohydrate-derived sulfamidates with non-carbon strong nucleophiles of low basicity proceeds efficiently, while the use of carbohydrate-derived soft



Scheme 12. Cyclic Sulfamidates in the Synthesis of Piperidinones and Pyrrolidinones en Route to (–)-Paroxetine and (–)-Aphanorphine. *(Ref. 76,77)*



Scheme 13. Thiomorpholinones and Piperazinones by Ring-Opening of Cyclic Sulfamidates. *(Ref. 79)*



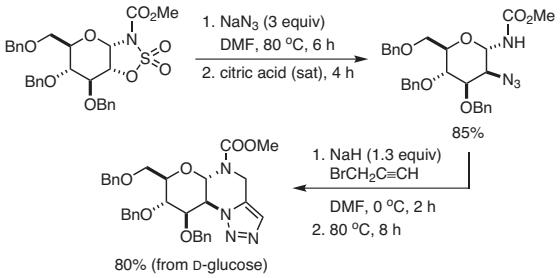
Scheme 14. Cyclic Sulfamidates as Convenient Precursors of 1,4-Benzoxazines, Benzothiazepines, and Benzodiazepines. *(Ref. 81,85)*

nucleophiles results in the successful synthesis of di- and trithiosaccharide analogues.[87] Chandrasekaran and co-workers effected the synthesis of carbohydrate-fused triazole heterocycles in a one-pot tandem process. The reaction proceeds via azido ring-opening propargylation and subsequent intramolecular cycloaddition of the alkyne and azide to deliver the carbohydrate-fused triazole derivative (**Scheme 15**).[46] The same group also reported that the reaction of D-glucose-derived sulfamidates with bis(benzyltriethylammonium) tetrathiomolybdate $\{[BnNEt_3]_2MoS_4\}$ results in the formation of 2-thiolglucosamine derivatives.[44,88]

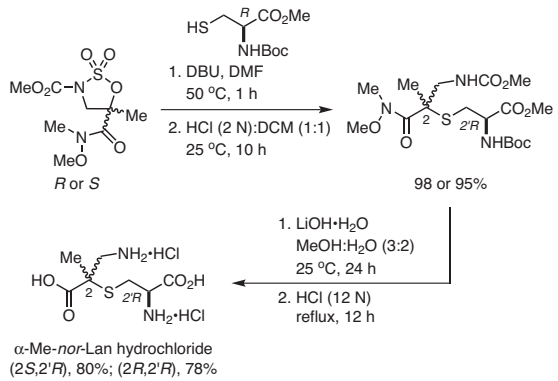
5.9. Unnatural Amino Acids

Interest in unnatural amino acids has been growing due to their application in peptide research.[89] Cyclic sulfamidates provide a unique opportunity to modify natural amino acids into a wide range of unnatural analogues by simple reaction sequences and in fewer steps. Chandrasekaran's group converted serine and threonine derivatives into unnatural cystine and selenocystine amino acids via cyclic sulfamidate intermediates.[43,55] Our group has demonstrated that the reaction of cyclic sulfamidates with in situ generated dithiocarbamate anions can be used for the synthesis of unnatural amino acids containing dithiocarbamate side chains.[42a] We have also utilized sulfamidates for the synthesis of triazole-modified unnatural amino acids in 71–86% yields through the nucleophilic ring-opening of sulfamidates with azide, followed by azido–alkyne cycloaddition.[89]

Lubell and co-workers synthesized *N*-(9-(9-phenylfluorenyl))-homoserine-derived cyclic sulfamidates, and showed that they could be used for the synthesis of functionalized, enantiopure γ-amino acids. The reactions were successful with nitrogen, sulfur, and stabilized oxygen nucleophiles, providing the corresponding unnatural, γ-substituted amino acids in >97% ee's.[90] Peregrina's group reported that the five-membered-ring, α-methylisoserine-derived (*R*)-sulfamidate could be used as an excellent chiral building block that undergoes ring-opening with sulfur nucleophiles at the quaternary carbon.[91] They developed a protocol for the synthesis of (2*S*,2'*R*)- and (2*R*,2'*R*)-α-methylnorlanthionines (α-Me-*nor*-Lan) in diastereomerically pure forms by using the corresponding α-methylisoserine-derived cyclic sulfamidate as a chiral building block (**Scheme 16**).[92]



Scheme 15. Carbohydrate-Derived Fused Heterocycles Through the Intermediacy of Cyclic Sulfamidates. *(Ref. 46)*



Scheme 16. Diastereomerically Pure (2*S*,2'*R*)- and (2*R*,2'*R*)-α-Methylnorlanthionines (α-Me-*nor*-Lan) from Chiral Cyclic Sulfamidates. *(Ref. 92)*

6. Conclusion

This review highlighted the important role cyclic sulfamidates are playing in natural product synthesis and method development. Their reactions are highly regioselective and stereospecific with inversion of configuration at the reaction center. Even though cyclic sulfamidates had not been extensively studied because of their reactions with carbon nucleophiles had led to complex mixtures and/or decomposition products, recent investigations have overcome most of these limitations by softening the carbon nucleophiles. This approach has resulted in new synthetic strategies in organic chemistry with no limitations in terms of reactivity. We believe that cyclic sulfamidates offer a unique synthetic potential, and can provide practical solutions to the synthesis of challenging drug targets that are sought after by both academia and industry.

7. Acknowledgments

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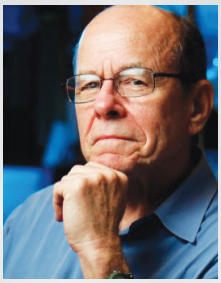

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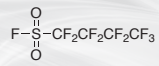

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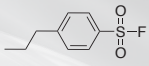

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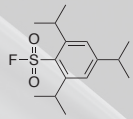

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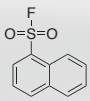

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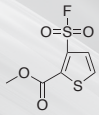

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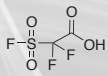

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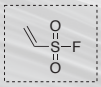

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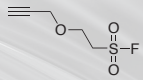

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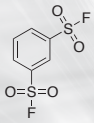

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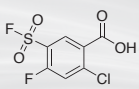

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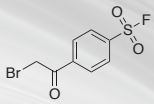

ALD00364

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(2) Dong, J.; Krasnova, L.; Finn, M. G.; Sharpless, K. B. *Angew. Chem., Int. Ed.* **2014,** *53*, 9430.

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